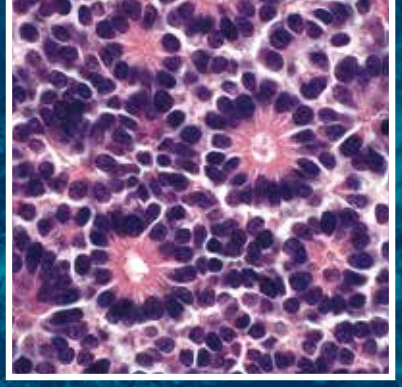

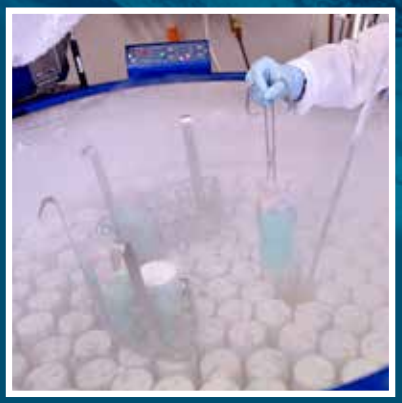

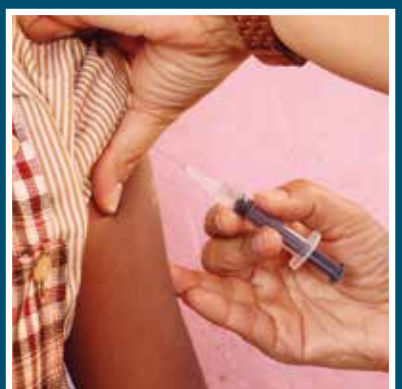

World Cancer Report

Cancer research for cancer prevention

Edited by CHRISTOPHER P. WILD, ELISABETE WEIDERPASS, and BERNARD W. STEWART

International Agency for Research on Cancer

World Health Organization

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Cancer research for cancer prevention

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Contents

Foreword

Cancer is the second most common cause of death globally, accounting for an estimated 9.6 million deaths in 2018.

At the United Nations General Assembly in 2018, world leaders agreed to take responsibility for preventing and treating cancer and other noncommunicable diseases, including fiscal measures to protect people from cancer-causing products, to promote evidence-based treatment, and to work towards universal health coverage.

We have no time to lose. The cancer burden is rising globally – but not equally. The greatest impact of cancer and the fastest increase in the cancer burden over the coming decades is projected to be in low- and middle-income countries, many of which already face difficulties coping with the current burden. There are massive social inequalities in cancer, with large variations in incidence, survival, and mortality between social groups.

We have learned that many cancer cases can be prevented, and even when prevention is not possible, early diagnosis saves lives. By using evidence-based and feasible interventions and adapting them to low- and middle-income countries where most new cancer cases will occur, a large proportion of those cases can be prevented. There is much that can be done to reduce social inequalities in cancer globally.

Robust, independent scientific evidence is critical, focused on the scale and patterns of cancer and its causes, prevention, and early detection. The high-quality research produced by the International Agency for Research on Cancer (IARC), working with researchers around the world, is essential for the development of evidence-based guidelines and policy by WHO, and for regulatory decisions by national institutions to protect the health of their populations.

This new IARC *World Cancer Report* presents the most comprehensive, up-to-date science on cancer prevention, including statistics, causes, and mechanisms, and how this can be used to implement effective, resource-appropriate strategies for cancer prevention and early detection. It also includes examples of successful prevention strategies. This book is a useful reference for researchers, cancer professionals, public health workers, and policy-makers.

The 2017 World Health Assembly requested WHO, in collaboration with IARC, to provide a global perspective on all measures that are recognized to limit the burden of cancer. The outcome of this charge – the *WHO Report on Cancer: Setting priorities, investing wisely and providing care for all* – complements the IARC *World Cancer Report* by synthesizing evidence to translate the latest knowledge into actionable policies to support governments. These two publications provide a solid foundation for effective cancer policies, and bring us closer to our goal of changing the trajectory of cancer for communities around the world.

Dr Tedros Adhanom Ghebreyesus

Director-General
World Health Organization

Preface

The objective of the International Agency for Research on Cancer (IARC) is to promote international collaboration in cancer research. The Agency is interdisciplinary, bringing together skills in epidemiology, laboratory sciences, and biostatistics to identify the causes of cancer so that preventive measures may be adopted and the burden of disease and associated suffering reduced. A significant feature of IARC is its expertise in coordinating research across countries and organizations; its independent role as an international organization facilitates this activity. As part of its wide dissemination of information about cancer, the Agency produces *World Cancer Report*.

The previous *World Cancer Report*, published in 2014, identified a foreseeable increase in the global burden of cancer, with a particularly heavy burden projected to fall on low- and middle-income countries. This new *World Cancer Report* is focused on the only consideration that will credibly decrease that burden: prevention. This volume addresses cancer research for cancer prevention.

IARC routinely coordinates specialist assessments in which multiple individual research studies – typically hundreds or thousands of articles – are assessed by international groups of expert scientists. The results are published as volumes of publications series, and each series is widely recognized as providing authoritative determinations. These series include the *IARC Monographs on the Identification of Carcinogenic Hazards to Humans*, which address the causes of cancer; the volumes of *Cancer Incidence in Five Continents*, which present population-based data on cancer occurrence; the *IARC Handbooks of Cancer Prevention*, which evaluate cancer prevention strategies; and the *WHO Classification of Tumours* series (also known as the WHO Blue Books), for the histological and genetic classification of human tumours. Typically, a particular volume in each of these series is focused on some aspect of cancer causation, prevention, pathology, and so on. This approach is not amenable to the provision of broad perspectives.

For broad perspectives, *World Cancer Report* is the relevant publication. *World Cancer Report* is not a digest of assessments made by IARC or any other authority. *World Cancer Report* is based on purpose-made assessments, prepared by recognized investigators worldwide and published after undergoing peer review.

A broad perspective – and, where possible, a “bottom line” – is crucial in several respects. First, it ensures that all relevant findings are taken into account. For example, for ultraviolet radiation in sunlight, evidence of tissue injury from low-level exposure must be considered together with known biological benefits, including production of vitamin D. Second, although knowledge of biological mechanisms provides valuable insights, it may not necessarily account for human circumstances. For example, in preventing exposures to known human carcinogens, inequalities between populations may contribute to marked variations in health outcomes. Third, although investigative design may be constrained to parameters that can be readily determined, human behaviour is never restricted in such a way. For example, the incidence of obesity-related cancers is critically affected by dietary composition, physical activity, and sedentary practices, because these vary between communities. Finally, factors that influence cancer causation and prevention may have markedly different outcomes when implemented across communities or countries that differ environmentally, sociologically, climatically, and economically.

IARC is uniquely placed to encompass a broad spectrum of knowledge while presenting the results in manageable terms. The production of *World Cancer Report* is achieved by engaging the Agency's scientific staff to collaborate in the development of the publication at every level. This includes ensuring that the planned contents address all relevant knowledge; identifying distinguished authors and reviewers from across the globe; ensuring that differing perspectives are offered in a balanced, evidence-based manner; and considering circumstances that my restrict implementation of cancer-preventive interventions.

Cancer can be prevented by avoiding exposure to a known carcinogen. However, this fundamental concept cannot always encompass why different tumour types are particularly prevalent in some populations and not others, or how genomics and related technologies may reveal individual susceptibility and new methods of early diagnosis. Nor can a simplistic understanding of cancer prevention explain why health service-related and other inequalities differentially determine the degree of success of preventive initiatives in different communities. Smoking cessation remains the most widely established means of cancer prevention, and new insights are offered in this *World Cancer Report*. However, efforts to reduce the burden of cancer cover a broad range, from contending with tumour types that essentially have no known causative agents all the way through to the prospect of cervical cancer being eliminated by the use of vaccines, which have been developed because of research on particular cancer-causing viruses.

Accordingly, this new *World Cancer Report* provides investigators with detailed information across a multidisciplinary spectrum. Equally, *World Cancer Report* provides people in the wider community, no matter where they are located worldwide, with insights into how the cancer types that have for so long affected their communities may now have a lesser impact than was previously thought.

Dr Elisabete Weiderpass

Director
International Agency for Research on Cancer

Introduction

World Cancer Report is an initiative of the International Agency for Research on Cancer (IARC) and is published about every 5 years. Since the inception of *World Cancer Report*, in 2003, the editorial policy has been to provide a concise, multidisciplinary assessment of current research, made as accessible as possible through a high illustrative content and a minimum of scientific jargon. For every chapter included, authority is achieved in the first instance by engaging experts worldwide, who then face the challenge of presenting information covering broad fields in a few thousand words. All chapters are subject to peer review.

The scope of this *World Cancer Report*

The breadth of knowledge addressed in each *World Cancer Report* has varied to meet the needs of the time. In 2003, when the availability of concise overviews across all aspects of cancer causation, prevention, and treatment in a single volume was unprecedented, a comprehensive approach was taken. Although a section on cancer treatment was included in the first *World Cancer Report*, since then there has been an explosive increase in research on precision therapy, and coverage of this proved to be impracticable if *World Cancer Report* were to remain of manageable size. The fact that *World Cancer Report* is concise is a central consideration and one that readers collectively value. This may be one reason why *World Cancer Report 2014* has been downloaded more than 35 000 times.

As explained in the Preface, this *World Cancer Report* is focused on cancer research for cancer prevention. This focus has necessitated the inclusion of a new section, so that the scope of available research can be adequately recognized: a section on inequalities that affect cancer prevention. This section has not appeared in any previous *World Cancer Report*.

Section 4, on inequalities that affect cancer prevention, is the antithesis of, for example, Section 3, on biological processes in cancer development. The chapters in Section 3 concern human biology, largely without reference to geography or community, whereas the chapters that discuss inequalities must involve references to particular communities and their circumstances. The need to address what is particular to various communities also underpins the content of Section 1, about the global cancer burden.

Another first for this *World Cancer Report* is the inclusion of a chapter on sporadic cancer. On the basis of current research, an attainable reduction in the incidence of cancer worldwide depends primarily on reducing exposure to known carcinogens. However, currently available research on several cancer types, including prostate cancer, brain cancer, and leukaemias, does not allow a clear proportion of these malignancies to be attributed to particular exogenous factors. So, in such cases, is the development of sporadic cancer due to “bad luck”, and is prevention no longer a consideration? Not at all! Indeed, in such situations particularly, genomics and other technologies are key to further investigations of etiology and to delivering new or improved procedures for early diagnosis and screening; these matters are covered in Section 6.

What information is provided in *World Cancer Report*?

World Cancer Report is designed to provide cancer researchers, health-care professionals, regulators, and policy-makers with current findings about the causes of cancer, its prevention, and other matters tending to reduce the burden of cancer. In particular, this volume provides insights into fields of investigation that may be adjacent to those with which a particular reader may be familiar. Broader professional engagement with cancer control and a need for information by journalists, governments, and community-based cancer-oriented authorities and the teaching profession is also recognized.

As cancer research scientists, we, the editors of this *World Cancer Report*, readily acknowledge the need to provide information about cancer causes and prevention to the wider community with as few barriers as are compatible with an accurate understanding. In the past, such a commitment to immediate comprehension has involved providing explanations for technical terms and/or including a glossary. We have not adopted such options, for several reasons: to avoid interrupting the flow of information, because most of the text is immediately accessible, and considering that search engines are available to provide access to specifics.

In providing insight to those who are not necessarily undertaking research in a particular field, some background information must be specified. This is an important but secondary consideration. Indeed, this *World Cancer Report* is not intended to be a textbook that provides a comprehensive overview of well-established key knowledge. Therefore, given the overall constraints on length, the authors of each chapter have provided a separate set of statements covering the Fundamentals (presented in a shaded sidebar). The information provided in the Fundamentals is axiomatic to the field of research covered in the chapter, but, unlike the points given in the chapter's Summary, is not necessarily addressed in the main text of the chapter.

To meet the immediate needs of professionals for contemporary data, the authors of each chapter were asked to focus on research results achieved during the past 5 years. This determinant of content is not the same as summarizing current knowledge. For example, the chapters in Section 2, on the causes of cancer, are not necessarily comprehensive. Tobacco smoking continues to be the major preventable cause of death from cancer, and indeed from multiple other diseases, but this long-held knowledge does not, in our view, require reiteration at the expense of describing the latest research findings, including the latest approaches to smoking cessation.

A feature of this volume, as in all previous *World Cancer Reports*, is that the largest single section (Section 5) is that devoted to particular cancer types: 20 chapters. In numerical terms, 20 is small compared with the hundreds of tumour types as documented in the *WHO Classification of Tumours* series (also known as the WHO Blue Books; http://whobluebooks.iarc.fr). However, the 20 types of cancer that are covered here, when taken together, account for the overwhelming majority of cancer cases worldwide and, of greater importance, account for almost all initiatives aimed at cancer prevention.

The volumes of *Cancer Incidence in Five Continents* (http://ci5.iarc.fr/) and the associated GLOBOCAN database document data on incidence, prevalence, mortality, and trends for multiple cancer types across hundreds of communities. These findings are summarized and made readily accessible online through the IARC Global Cancer Observatory (https://gco.iarc.fr). Therefore, the epidemiological information in chapters in Section 5 is not documented systematically. Rather, authors were invited to give priority to recent epidemiological findings that have contributed to an increased understanding of etiology or, in some rare cases, prevention. As a result, there are marked differences between the chapters with respect to the amount of epidemiological data presented. Similarly, information about exogenous causes or population-based screening varies markedly between cancer types, from comprehensive data to nothing relevant, and such circumstances account in large part for differences between chapters in Section 5.

Where to from here?

All the research described in this *World Cancer Report* is calculated, directly or indirectly, to reduce the burden of cancer, whether globally or in particular communities or for certain categories of people at risk. Typically, such outcomes occur as a result of the adoption of certain policies, either by governments or by other competent authorities. Then, many cancer-preventive options depend on individual decision-making and commitment. All such matters are themselves amenable to research.

There is no generally operative procedure that determines the transition from cancer research findings to cancer prevention policies. When such a pathway is charted for a particular innovation, the ease of its implementation will be determined by many factors as they operate in particular countries or communities. In this context, *World Cancer Report* is not designed as a vehicle for advocacy: research needs are not listed as such, nor are priorities specified.

The key role of cancer research in cancer prevention, as a record of achievement, is clear and unequivocal on a global scale. Since the publication of *World Cancer Report 2014*, the burden of cancer attributable to obesity and – separately – to pollution has been made clearer than ever before. More immediately in terms of the ultimate goal of prevention, there is global progress in reducing tobacco-attributable cancers, at least in some countries. And where once there was the goal of increased screening for cervical cancer, there is now, through vaccination, the prospect of eliminating cervical cancer as a public health concern.

In short, “cancer research for cancer prevention” is not simply a way to describe a particular field of investigation. Far more importantly, these words identify a pathway that may materially reduce the acknowledged burden of cancer faced by humanity. There is, in fact, no other way.

Christopher P. Wild, Elisabete Weiderpass, and Bernard W. Stewart (Editors)

1 The global cancer burden

As far as we know, cancer has always afflicted humans, although for centuries its relative impact was overshadowed by early death from infectious diseases. Until recently, information on the global distribution of cancer was limited for certain communities and countries. We now have a reasonable basis for estimating the global cancer burden. For several tumour types – colorectal, prostate, and breast cancer – high incidence rates were once restricted to North America, western Europe, and Australia, but now incidence rates are rising in many other countries. Lung cancer, for which high incidence was initially restricted to high-income countries, has long been recognized as a global scourge. Previously, low-income countries primarily had a relatively high incidence of stomach, liver, and cervical cancer, but changes in incidence over time for these and other cancer types illustrate variation between countries. Finally, there are marked differences between countries or regions in cancer mortality, with an increasing burden in low- and middle-income countries, attributable both to less-than-optimal implementation of preventive measures and to diagnosis at a later stage, rather than an early stage, of cancer development.

1.1 The burden and prevention of premature deaths from noncommunicable diseases, including cancer: a global perspective

Bochen Cao
Isabelle Soerjomataram
Freddie Bray
Bernard W. Stewart (reviewer)
Elisabete Weiderpass (reviewer)
Christopher P. Wild (reviewer)

SUMMARY

- Cancer is the first or second leading cause of premature death (i.e. at ages 30–69 years) in 134 of 183 countries, and it ranks third or fourth in an additional 45 countries.
- Of the 15.2 million premature deaths from noncommunicable diseases worldwide in 2016, 4.5 million (29.8%) were due to cancer.
- The United Nations, within the Sustainable Development Goals agenda, has set a target to reduce the total premature mortality from noncommunicable diseases by one third by 2030.
- Mortality rates from noncommunicable diseases, and cancer in particular, are declining in most higher-income countries, but such progress is lacking in lower-income countries, posing challenges in meeting the Sustainable Development Goals target.
- Attaining the goal of a reduction by one third in premature mortality from the four major types of noncommunicable diseases would increase the average expected years lived in the target age group (30–69 years) by 0.64 years worldwide, with larger gains foreseen in countries with low or medium levels of the Human Development Index (HDI).
- Feasible, affordable, and cost-effective interventions that reduce exposure to the key causes and other risk factors for cancer and for other noncommunicable diseases, increase access to essential health-care services, and ensure the availability of effective and affordable essential medicines and vaccines are crucial for disease control globally.

This chapter reviews the burden and trends of premature mortality (i.e. deaths at ages 30–69 years) from noncommunicable diseases (NCDs), with a focus on cancer, based on the WHO Global Health Estimates that are available nationally by cause and year of death [1].

When studying cancer patterns and trends, it is important to consider what constitutes human development, and how it may be measured. The Human Development Index (HDI) is a composite index of three basic dimensions of human development: a long and healthy life (based on life expectancy at birth), education (based on average and expected years of schooling), and a decent standard of living (based on gross national income per capita). The development levels of countries can be considered according to four tiers of HDI: low, medium, high, and very high HDI.

NCDs have become the leading cause of death worldwide and pose a major threat to healthy ageing, accounting for 72% of all deaths globally in 2016 [1]. The total of 40.5 million deaths from NCDs globally in 2016 is a sharp increase from the corresponding figure of 31.6 million deaths in 2000. In 2016, about one third (15.2 million) of all deaths from NCDs occurred at ages 30–69 years. Of these premature deaths, 6.2 million (40.8%) were due to cardiovascular diseases, 4.5 million (29.8%) to cancer, 1.1 million (7.0%) to chronic respiratory diseases, and 0.7 million (4.5%) to diabetes [1].

These increasing trends in mortality from NCDs accompany the decline in mortality from infectious diseases, but they also result from the demographic and epidemiological transitions that are taking place.

Demographic transition refers to population-level shifts from a pattern of high birth (fertility) rates and high death (mortality) rates to one of low birth rates and low death rates. This shift increases the number of older adults, who are more susceptible to ageing-related diseases, including cancer, particularly in countries in transition [2].

Epidemiological transition refers to changes in mortality rates and causes of death that reflect underlying changes in exposure to risk factors. During the past century, a pattern of dominance of infectious diseases has gradually been

replaced with one in which chronic or degenerative diseases, such as NCDs, predominate. Within this diverse group of NCDs, the relative contribution to overall deaths has evolved with trends in mortality rates. For example, there have been greater reductions in mortality rates for cardiovascular diseases than in those for cancer in many populations with medium or high HDI, and the absolute and relative reductions in cancer mortality rates have been considerably larger in populations with very high HDI (Fig. 1.1.1) [3,4].

Cancer as a leading cause of death worldwide

In the past 60 years, better sanitation and the development of vaccines and antibiotics have brought about dramatic declines in mortality from infectious diseases. With improving primary and secondary prevention for cardiovascular diseases, changing demographic and risk factors have led to today's observation that cancer is the first or second leading cause of premature death (i.e. at ages 30–69 years) in 134 of 183 countries, and it ranks third or fourth in an additional 45 countries (Fig. 1.1.2) [1]. Specifically, cancer is currently the leading cause of premature death in most of the countries with high or very high HDI, including Canada and the USA in North America, Argentina and Chile in South America, most countries in Europe (including France, Germany, and the United Kingdom), Australia and New Zealand in Oceania, and Japan, the Republic of Korea, and Singapore in Asia. Cancer also ranks first in Thailand and Viet Nam. Cancer is the second leading cause of premature death, after cardiovascular diseases, in Brazil, China, and many countries in eastern Europe (including the Russian Federation and Ukraine), as well as Algeria and Egypt. In most countries in sub-Saharan Africa, cancer ranks third or fourth, and there are only a few countries in this region in which cancer ranks fifth or sixth [1].

Cancer is a complex disease, for which the patterns and trends in mortality vary markedly between countries and across specific cancer types. These variations are due to differences in changing lifestyles and in local exposures to known or putative determinants, as well as an altering built environment (e.g. synthetic changes to the physical environment, including structural conditions that have impacts on mobility and recreation, diet, and exposure to environmental pollutants). The inherent disparities and widening gaps between and within countries in levels of medical practice and health infrastructure also influence the diverging patterns and trends in cancer mortality [5–10].

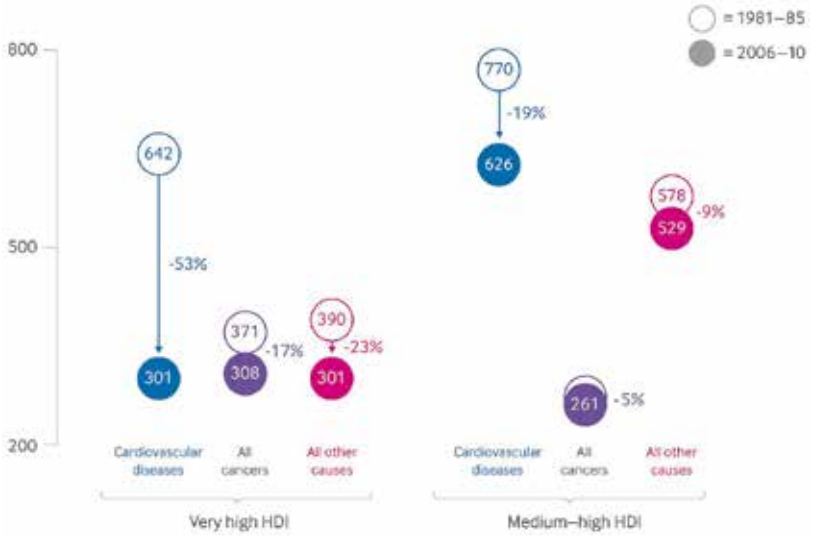
In most countries with high HDI, cancer mortality rates are declining, primarily as a result of recent successes in combating common cancer types through effective interventions for prevention, early detection, and treatment. In contrast, in countries in transition, mortality rates are still increasing, or at best stabilizing, for many cancer types, including breast cancer, prostate cancer, and colorectal cancer [5,9,10].

The Sustainable Development Goals target for combating noncommunicable diseases

In response to the major threat that NCDs pose to sustainable human development, and to curb the rapid rise in NCDs worldwide, the United Nations, within the Sustainable Development Goals agenda, has set an overarching target (Target 3.4) to reduce the total premature mortality from NCDs by one third by 2030 [11,12]. For the successful realization of Target 3.4, a set of health targets have been proposed to reduce the exposure to risk factors for NCDs and to improve the prevention and treatment of NCDs. A subsequent reduction in premature deaths from NCDs would have a profound effect on population longevity and an economic impact (see Chapter 6.9).

If the goal of a reduction by one third in premature mortality from the four major types of NCDs is attained in 2015–2030, the average expected years lived in the target age group (30–69 years) could potentially increase by 0.64 years worldwide [13]. This figure ranges from 0.44 years in countries with very high HDI to about

Fig. 1.1.1. Changes between 1981–1985 and 2006–2010 in age-standardized mortality rates per 100 000 people, for ages 40–84 years in men and women combined, in populations with very high Human Development Index (HDI) and medium or high HDI.



0.70 years in countries with low or medium HDI (Fig. 1.1.3). Extending the one third reduction in premature mortality to all NCDs would lead to a further gain of 20% in average expected years lived [13]. These are significant gains when considered in light of the increases in life expectancy over the last three decades of the 20th century: 2.5–3.7 years in countries with very high HDI and 1.1–1.4 years in countries with medium or high HDI.

Although attaining Target 3.4 of the Sustainable Development Goals is a promising prospect for population longevity in the long run, it is debatable whether countries will indeed meet this target. Using the historical trends in premature mortality from the four major types of NCDs in the 15-year period between 2000 and 2015 as a reference, one observes that higher-income countries are well on track to meeting the target between 2015 and 2030, whereas lower-income countries

Fig. 1.1.2. Global map of cancer as a leading cause of premature death (i.e. at ages 30–69 years), indicating the rankings, with the numbers of countries in parentheses.

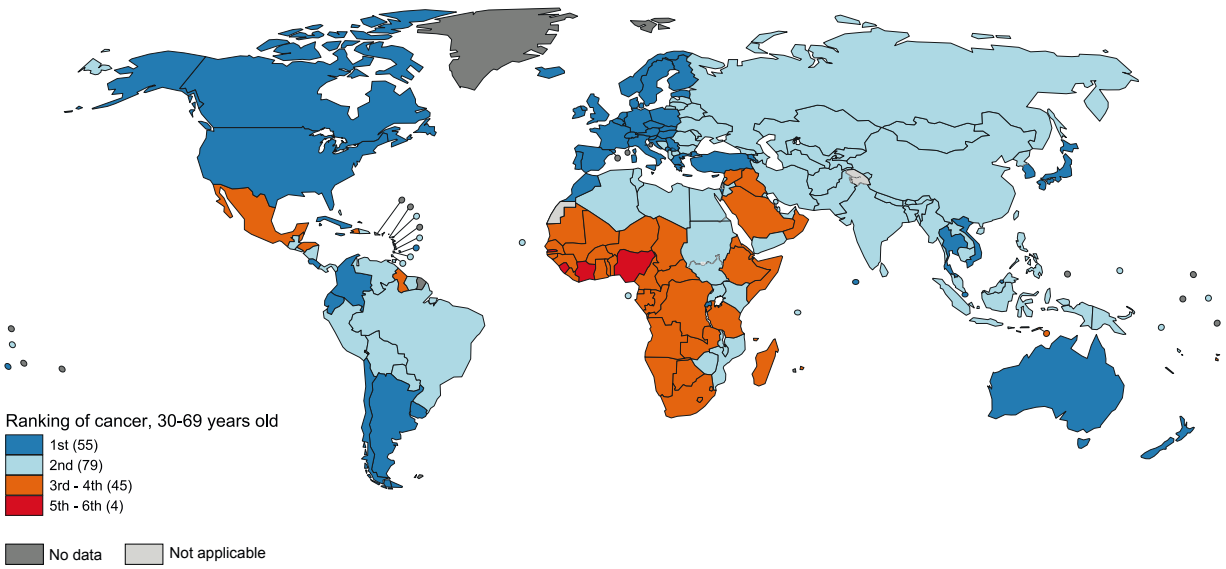
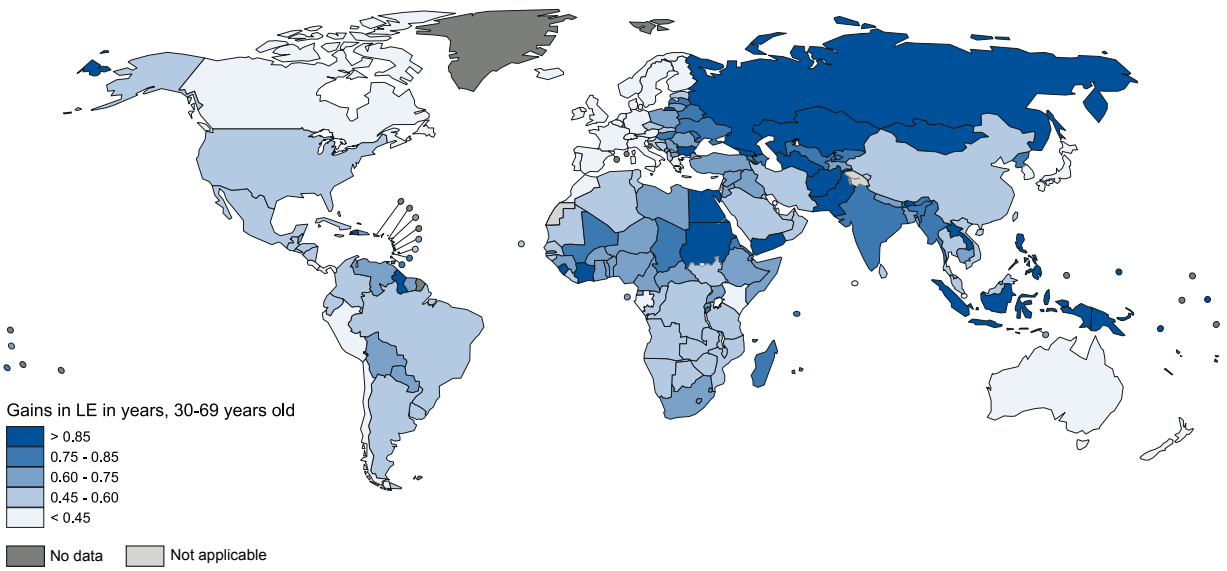


Fig. 1.1.3. Global map of estimated gains in average expected years lived (LE) between ages 30 years and 69 years if the Sustainable Development Goals target of a reduction by one third in premature mortality from the four major types of noncommunicable diseases is attained in 2015–2030.



still face considerable challenges. A similar picture is seen for cancer. In higher-income countries, a large part of the targeted reduction has generally been attained. In contrast, in low- and middle-income countries the achievements are more limited (Fig. 1.1.4) [13]. It should be noted that the lack of progress in lower-income countries in 2000–2015 does not necessarily predict future failings in attaining the target in such populations in the longer term, given that many NCDs can still be successfully prevented, treated, and managed.

The distinct patterns of causes of death help to prioritize approaches to reduce mortality from specific major causes in a given country. Specifically, cancer has surpassed cardiovascular diseases as the leading cause of death in countries with high or very high HDI. In contrast, cardiovascular diseases remain the leading cause of death in lower-income countries, largely because of inadequate and ineffective implementation of the available prevention and treatment modalities for cardiovascular diseases. There is a clear need to prioritize prevention strategies at the national level and to structure health systems accordingly to manage the imminent epidemic of NCDs worldwide.

A key and effective measure in the prevention of cancer and other NCDs is to reduce the exposure to modifiable causes of NCDs, including several risk factors that contribute significantly to the occurrence of these diseases, such as behavioural factors (e.g. tobacco use [see Chapter 2.1], harmful alcohol consumption [see Chapter 2.3], unhealthy diet, and physical inactivity [see Chapter 2.7]), metabolic factors (e.g. high blood pressure, overweight and obesity, and high cholesterol level), and environmental factors (e.g. air pollution [see Chapter 2.9]), [12,14]. In many middle-income countries, risk factors for NCDs continue to prevail. For example, the highest levels of smoking prevalence, harmful alcohol consumption, and high blood pressure globally are observed in countries of the former Soviet Union and other countries in central and eastern Europe [12,15–17], leading to high rates of premature mortality from NCDs, including cancer.

However, lower-income countries face the additional burden of poverty-related NCDs, such as infection-related cancers (including stomach cancer [see Chapter 5.4], liver cancer [see Chapter 5.6], and cervical cancer [see Chapter 5.10]), cardiovascular diseases due to fetal and childhood malnutrition, and respiratory diseases that are correlated with a poor living environment [18,19]. As countries progress societally and economically, and epidemiological transitions continue, the reduction in NCDs linked to poverty-related factors is expected to be offset by increasing exposure to many behavioural, environmental, and occupational risk factors linked with industrialized settings, including tobacco use, harmful alcohol consumption, and physical inactivity [20–26]. The path towards attaining Target 3.4 of the Sustainable Development Goals will be particularly challenging for resource-constrained countries if

Fig. 1.1.4. Changes between 2000 and 2015 in the risk of dying from cancer at ages 30–69 years, for selected countries with low or medium Human Development Index (HDI) and high or very high HDI.

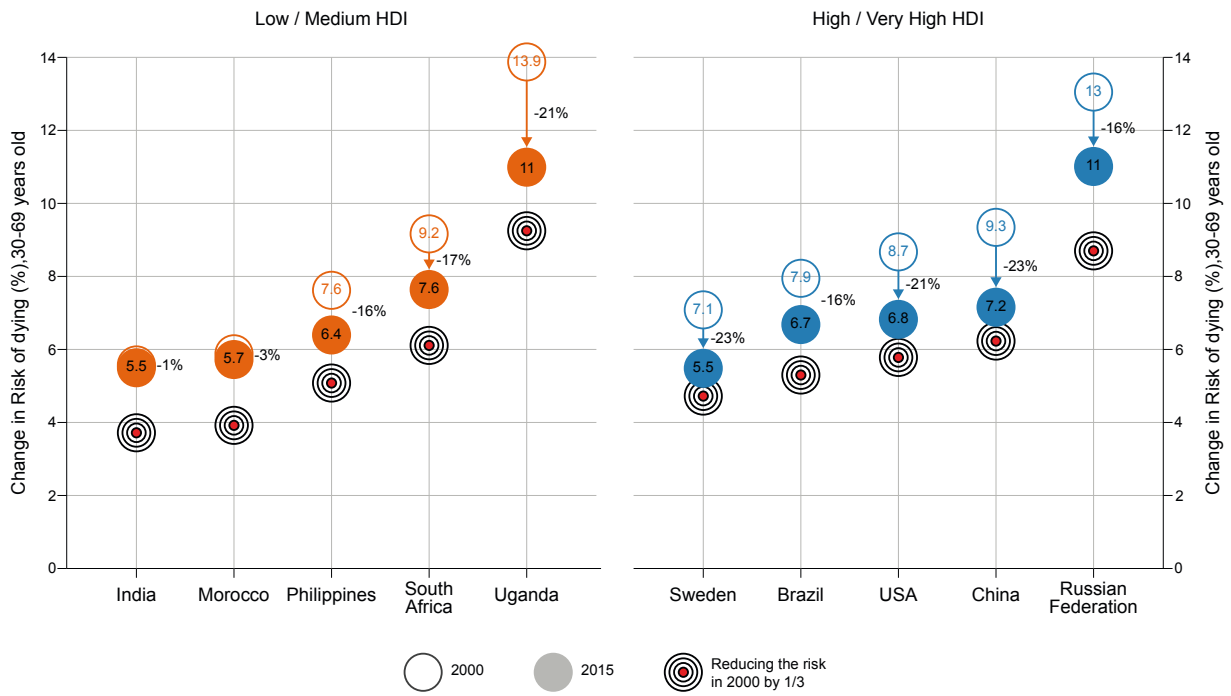


Fig. 1.1.5. Dancers in Ayquina, Chile, illustrate the diversity of communities affected by cancer. In Chile, the incidence rates of cancer of the gall bladder are among the highest in the world.

their adoption of unhealthy lifestyles and activities with high environmental impact is not halted. Therefore, in the coming decades it will be increasingly critical to mitigate the rise in NCDs in lower-income countries by preventing the adoption of unhealthy behaviours (see Chapter 6.1) and ensuring that environmental actions are sustainable [27,28].

To curb the rising burden of NCDs, WHO proposed a "best buys" package to facilitate interventions that are feasible, affordable, and cost-effective [12,29]. An extended list of options to reduce the prevalence of tobacco smoking, harmful alcohol consumption, unhealthy diet, and physical inactivity as well as environmental action, for example to reduce air pollution, are essential elements to control NCDs, including cancer. Furthermore, measures proposed by the WHO "best buys" and by the "essential package" of interventions presented in the third edition of *Disease Control Priorities* – including implementing vaccination programmes, extending the preventive and early detection measures for cancer at the primary care level, and improving access to services for cancer and other NCDs – are expected to contribute substantially to a reduction in premature deaths from NCDs by 2030 [30,31]. Finally, establishing high-quality surveillance systems for cancer and other NCDs is imperative to plan and evaluate national responses to the Sustainable Development Goals target [29].

The slow pace of progress in resource-limited countries that are undergoing major transitions, relative to the pace in higher-resource countries (Fig. 1.1.4) highlights the need for accelerated actions to achieve the Sustainable Development Goals target in these countries. However, inadequate access to affordable primary care, early detection, and treatment continues to be a barrier to effective prevention and treatment in these settings, leading to poorer survival outcomes in patients [12,17]. For example, whereas cancer surgery services are available in 95% of high-income countries, the equivalent rate is only about 25% in low-income countries [32], leading to substantially higher cancer case fatality in lower-income countries (70%) than in higher-income countries (45%) [33]. As part of the Sustainable Development Goals targets, achieving universal health coverage, including access to essential health-care services and access to effective and affordable essential medicines and vaccines for NCDs for all, is crucial to ensure a narrowing of the inequity gap and a reduction in mortality from NCDs globally.

The potential for health improvement is particularly striking in low- and middle-income countries, if the prompt adoption of "best buys" interventions leads to the Sustainable Development Goals target being met, because in these countries

Fig. 1.1.6. The disparities that are evident within many countries are illustrated in this view of Manila, Philippines.

NCDs commonly rank higher as a cause of death. A parallel impact across the four major types of NCDs is expected, with a marked reduction in cancer mortality rates, many of which have stagnated nationally. In addition to improved health outcomes, the additional societal and economic potential of these interventions for NCDs is large, because the targeted decline in mortality would bring about a substantial increase in the number of person-years lived in the most productive age groups, hence increasing workplace productivity and reducing costs of health care and social care. Ultimately, these potential benefits provide further arguments for implementing actions aimed at reducing the global burden of NCDs.

References

1. WHO (2018). Global health estimates 2016: deaths by cause, age, sex, by country and by region, 2000–2016. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/healthinfo/global_burden_disease/en/.
2. Caldwell JC (1976). Toward a restatement of demographic transition theory. Popul Dev Rev. 2(3/4):321–66. https://doi.org/10.2307/1971615
3. Kanavos P (2006). The rising burden of cancer in the developing world. Ann Oncol. 17(Suppl 8):viii15–viii23. https://doi.org/10.1093/annonc/mdl983 PMID:16801335
4. Omran AR (1971). The epidemiologic transition. A theory of the epidemiology of population change. Milbank Mem Fund Q. 49(4):509–38. https://doi.org/10.2307/3349375 PMID:5155251
5. DeSantis CE, Bray F, Ferlay J, Lortet-Tieulent J, Anderson BO, Jemal A (2015). International variation in female breast cancer incidence and mortality rates. Cancer Epidemiol Biomarkers Prev. 24(10):1495–506. https://doi.org/10.1158/1055-9965.EPI-15-0535 PMID:26359465
6. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015). Global cancer statistics, 2012. CA Cancer J Clin. 65(2):87–108. https://doi.org/10.3322/caac.21262 PMID:25651787
7. Torre LA, Siegel RL, Ward EM, Jemal A (2014). International variation in lung cancer mortality rates and trends among women. Cancer Epidemiol Biomarkers Prev. 23(6):1025–36. https://doi.org/10.1158/1055-9965.EPI-13-1220 PMID:24836468
8. Ferro A, Peleteiro B, Malvezzi M, Bosetti C, Bertuccio P, Levi F, et al. (2014). Worldwide trends in gastric cancer mortality (1980-2011), with predictions to 2015, and incidence by subtype. Eur J Cancer. 50(7):1330–44. https://doi.org/10.1016/j.ejca.2014.01.029 PMID:24650579
9. Siegel R, Desantis C, Jemal A (2014). Colorectal cancer statistics, 2014. CA Cancer J Clin. 64(2):104–17. https://doi.org/10.3322/caac.21220 PMID:24639052
10. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, et al. (2012). International variation in prostate cancer incidence and mortality rates. Eur Urol. 61(6):1079–92. https://doi.org/10.1016/j.eururo.2012.02.054 PMID:22424666
11. United Nations General Assembly (2015). Transforming our world: the 2030 Agenda for Sustainable Development. Available from: https://sustainabledevelopment.un.org/post2015/transformingourworld.
12. WHO (2014). Global status report on noncommunicable diseases 2014. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/148114.
13. Cao B, Bray F, Ilbawi A, Soerjomataram I (2018). Effect on longevity of one-third reduction in premature mortality from non-communicable diseases by 2030: a global analysis of the Sustainable Development Goal health target. Lancet Glob Health. 6(12):e1288–e1296. https://doi.org/10.1016/S2214-109X(18)30411-X PMID:30420032
14. GBD 2015 Risk Factors Collaborators (2016). Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 388(10053):1659–724. https://doi.org/10.1016/S0140-6736(16)31679-8 PMID:27733284
15. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ; Comparative Risk Assessment Collaborating Group (2002). Selected major risk factors and global and regional burden of disease. Lancet. 360(9343):1347–60. https://doi.org/10.1016/S0140-6736(02)11403-6 PMID:12423980
16. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, et al.; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Pressure) (2011). National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. Lancet. 377(9765):568–77. https://doi.org/10.1016/S0140-6736(10)62036-3 PMID:21295844
17. Di Cesare M, Khang Y-H, Asaria P, Blakely T, Cowan MJ, Farzadfar F, et al.; Lancet NCD Action Group (2013). Inequalities in non-communicable diseases and effective responses. Lancet. 381(9866):585–97. https://doi.org/10.1016/S0140-6736(12)61851-0 PMID:23410608
18. Ezzati M, Riboli E (2012). Can noncommunicable diseases be prevented? Lessons from studies of populations and individuals. Science. 337(6101):1482–7. https://doi.org/10.1126/science.1227001 PMID:22997325
19. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. (2012). Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 13(6):607–15. https://doi.org/10.1016/S1470-2045(12)70137-7 PMID:22575588
20. WHO (2017). WHO report on the global tobacco epidemic, 2017: monitoring tobacco use and prevention policies. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/255874.
21. Singh T, Arrazola RA, Corey CG, Husten CG, Neff LJ, Homa DM, et al. (2016). Tobacco use among middle and high school students – United States, 2011–2015. MMWR Morb Mortal Wkly Rep. 65(14):361–7. https://doi.org/10.15585/mmwr.mm6514a1 PMID:27077789

22. Samet JM, Yoon S-Y, editors (2001). Women and the tobacco epidemic: challenges for the 21st century. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/66799.

23. Guthold R, Louazani SA, Riley LM, Cowan MJ, Bovet P, Damasceno A, et al. (2011). Physical activity in 22 African countries: results from the World Health Organization STEPwise approach to chronic disease risk factor surveillance. Am J Prev Med. 41(1):52–60. https://doi.org/10.1016/j.amepre.2011.03.008 PMID:21665063

24. Pratt M, Sarmiento OL, Montes F, Ogilvie D, Marcus BH, Perez LG, et al.; Lancet Physical Activity Series Working Group (2012). The implications of megatrends in information and communication technology and transportation for changes in global physical activity. Lancet. 380 (9838):282–93. https://doi.org/10.1016/S0140-6736(12)60736-3 PMID:22818940

25. Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJF, Martin BW; Lancet Physical Activity Series Working Group (2012). Correlates of physical activity: why are some people physically active and others not? Lancet. 380(9838):258–71. https://doi.org/10.1016/S0140-6736(12)60735-1 PMID:22818938

26. WHO (2014). Global status report on alcohol and health – 2014. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/112736.

27. Preston SH (1976). Mortality patterns in national populations: with special reference to recorded causes of death. New York (NY), USA: Academic Press.

28. Salomon JA, Murray CJL (2002). The epidemiologic transition revisited: compositional models for causes of death by age and sex. Popul Dev Rev. 28(2):205–28. https://doi.org/10.1111/j.1728-4457.2002.00205.x

29. WHO (2013). Global action plan for the prevention and control of noncommunicable diseases 2013–2020. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/94384.

30. Gelband H, Jha P, Sankaranarayanan R, Horton S, editors (2015). Disease control priorities. 3rd ed. Vol. 3, Cancer. Washington (DC), USA: World Bank.

31. Gelband H, Sankarayanarayanan S, Gauvreau CL, Horton S, Anderson BO, Bray F, et al.; Disease Control Priorities-3 Cancer Author Group (2016). Costs, affordability, and feasibility of an essential package of cancer control interventions in low-income and middle-income countries: key messages from *Disease Control Priorities*, 3rd edition. Lancet. 387(10033):2133–44. https://doi.org/10.1016/S0140-6736(15)00755-2 PMID:26578033

32. WHO (2016). Assessing national capacity for the prevention and control of noncommunicable diseases: report of the 2015 global survey. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/246223.

33. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today.

1.2 Global trends in cancer incidence and mortality

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SUMMARY

- In men, lung cancer incidence and mortality rates vary across countries and are almost invariably correlated with the prevalence of tobacco smoking 20–30 years earlier. In women, the smoking epidemic typically began later, or – in some countries – not at all, and this is reflected in the corresponding rates.
- Rising breast cancer incidence rates are correlated with trends towards earlier ages at menarche, later ages at first birth, and lower parity. In many countries with high levels of the Human Development Index (HDI), incidence rates have stabilized and mortality rates are declining, whereas in countries in transition towards higher HDI levels, mortality trends have tended to parallel the increasing incidence trends.
- Incidence rates of colorectal cancer have increased in countries in transition, whereas in countries with high HDI, rates have either stabilized or decreased. However, incidence is increasing in younger age groups and in recent generations in a diverse set of countries. Mortality rates have decreased in countries with high HDI; mortality rates are increasing in many low- and middle-income countries.
- An increase in prostate cancer incidence rates followed by a decline, as observed in the USA, is attributable to prostate-specific antigen (PSA) testing. In several countries in Asia and Latin America, incidence rates increased substantially and then stabilized. Mortality rates have been declining in most countries.
- Worldwide, stomach cancer ranks fifth in terms of incidence and third in terms of mortality. Incidence and mortality rates of stomach cancer (predominantly the non-cardia type) are decreasing, whereas incidence of cancer of the cardia region of the stomach is increasing in several populations. Most cases of stomach cancer are attributable to infection with *Helicobacter pylori*.
- Cervical cancer incidence and mortality rates have declined in most countries in recent decades, as a result of the detection of precancerous lesions by screening, but increasing rates have been observed in younger generations of women in some countries. Global elimination of the disease – in terms of cervical cancer no longer being considered a public health problem – is attainable during this century through HPV vaccination and screening programmes.

This chapter reviews the incidence and mortality trends for the six most common cancer types worldwide (lung cancer, breast cancer, colorectal cancer, prostate cancer, stomach cancer, and cervical cancer) and the main determinants of these trends, including the role of the changing prevalence and distribution of key risk factors as well as the impact of preventive, screening, and therapeutic interventions.

IARC is responsible for the compilation, estimation, and reporting of cancer statistics generated through flagship projects and databases, including *Cancer Incidence in Five Continents* (http://ci5.iarc.fr) and GLOBOCAN, for which the resulting statistics are disseminated on the Global Cancer Observatory, an interactive, user-friendly, and data-driven online interface (http://gco.iarc.fr).

The primary source for this chapter is the cancer incidence trends from successive volumes of *Cancer Incidence in Five Continents*, the compendium of data sets from national or subnational high-quality population-based cancer registries. Equivalent data on cancer mortality trends were obtained from the national statistics compiled in the WHO Mortality Database (https://www.who.int/healthinfo/mortality_data/en/).

This chapter also makes reference to the current global burden of the six most common cancer types using the GLOBOCAN 2018 estimates of incidence and mortality, which are provided for 185 countries

or territories worldwide on the Cancer Today subsite of the Global Cancer Observatory (http://gco.iarc.fr/today).

Lung cancer

Lung cancer is the most common cancer type worldwide in terms of both incidence (2.1 million new cases in 2018) and mortality (1.8 million deaths in 2018). The key cause of lung cancer is tobacco smoking (see Chapter 2.1), which is responsible for 63% of overall global deaths from lung cancer and for more than 90% of lung cancer deaths in countries where smoking is prevalent in both sexes [1]. Therefore, trends in lung cancer incidence and mortality are determined largely by past exposure to tobacco smoking, reflecting the differential evolution of the smoking epidemic by sex in individual countries.

In men, the countries where the smoking epidemic first began (the United Kingdom and the USA, followed by Australia, New Zealand, and Canada), were also the first countries in which the prevalence of smoking decreased, followed about 20–30 years later by a decline in lung cancer incidence and mortality rates (Fig. 1.2.1). In world regions where lung cancer rates have historically been low (e.g. Costa Rica, Ecuador, and India) or intermediate (e.g. Japan and Turkey), lung cancer incidence in men appears to have recently stabilized or increased (e.g. Thailand).

In women, the tobacco smoking habit has commonly been acquired more recently, or – in some countries – not at all. Therefore, the most common trend is of rising lung cancer rates, as observed in Australia, Japan, the United Kingdom, and the USA, with a peak and a recent decline that are most evident in the United Kingdom and the USA (Fig. 1.2.2). In many countries with lower levels of the Human Development Index (HDI), trends in rates are largely stable over time, reflecting either that smoking is not being taken up or that the smoking epidemic is at too early a stage to be visible in the lung cancer trends.

The trends by histological subtype present a somewhat different picture. Incidence rates of squamous cell carcinoma of the lung are currently decreasing (at least in men), whereas rates of adenocarcinoma of the lung are rising in some populations (particularly in women) [2]. In men, squamous cell carcinoma was previously the most common lung cancer subtype, but by the end of the 1990s a shift had occurred and adenocarcinoma was the most common subtype. In women, this effect is delayed, meaning that in many countries with high HDI, incidence rates of adenocarcinoma of the lung are now decreasing in men and are still increasing in women (see Chapter 5.1).

Fig. 1.2.1. Age-standardized (World) (a) incidence rates and (b) mortality rates per 100 000 by year in selected countries for lung cancer in men, circa 1975–2012. Asterisks indicate regional registries (other registries are national).

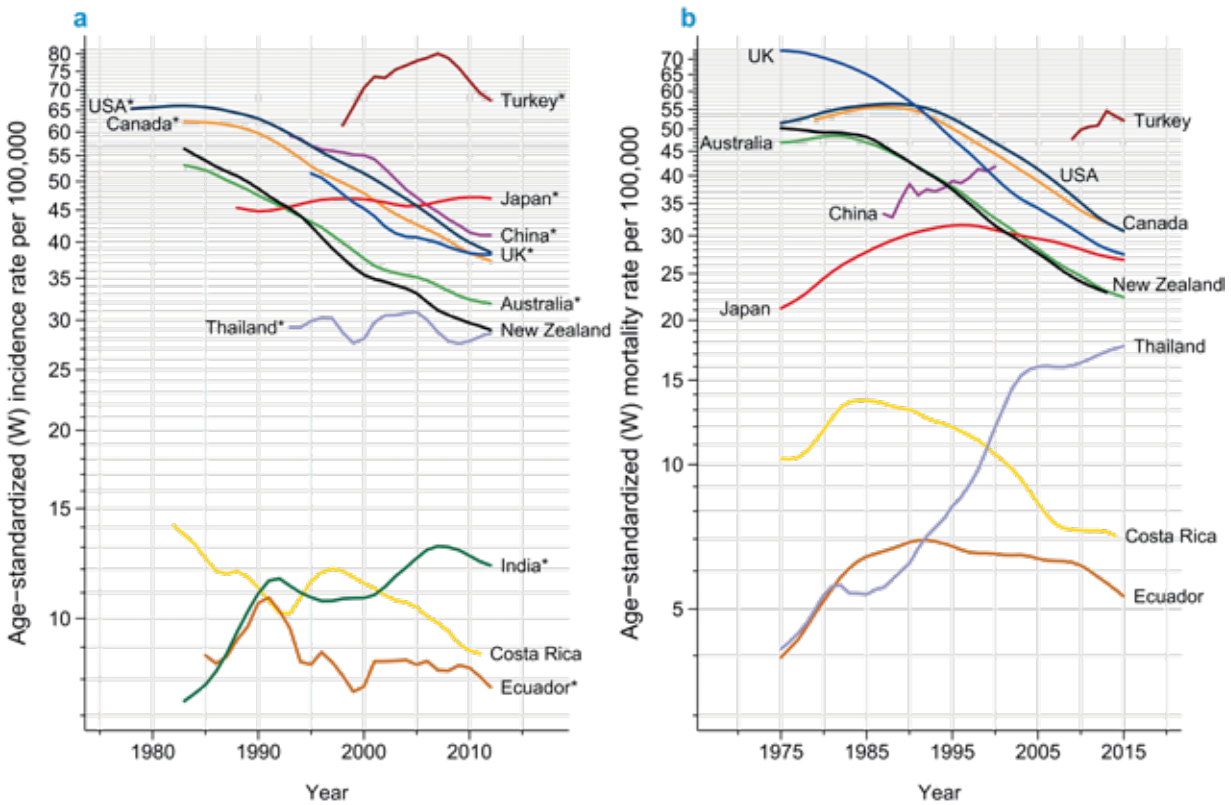
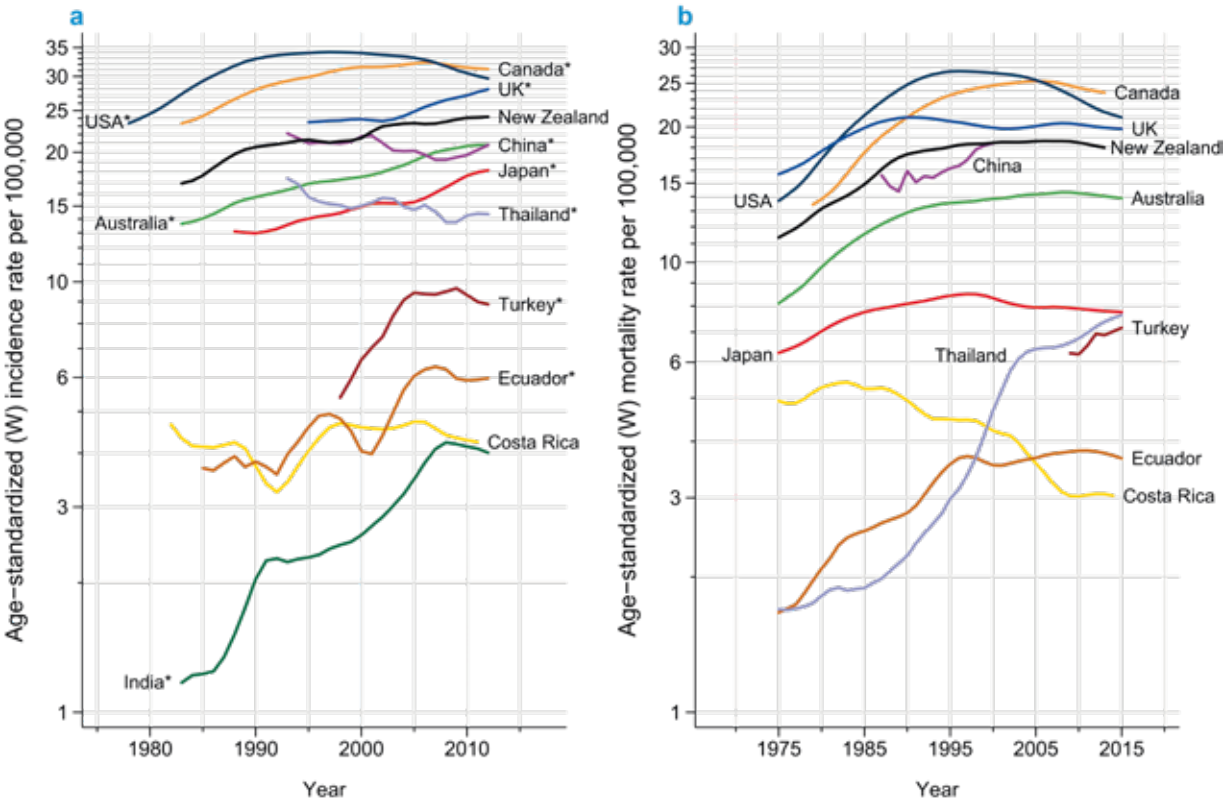


Fig. 1.2.2. Age-standardized (World) (a) incidence rates and (b) mortality rates per 100 000 by year in selected countries for lung cancer in women, circa 1975–2012. Asterisks indicate regional registries (other registries are national).



Lung cancer survival remains low globally. The fact that lung cancer is the leading cause of cancer death has motivated the assessment of the benefits of lung cancer screening, i.e. low-dose computed tomography (CT), among heavy smokers. A 16% reduction in lung cancer mortality among those screened in a large trial in the USA [3] has led to the recommendation of lung cancer screening in the USA, followed by similar recommendations in Europe [4]. However, controversy still exists, because the current short-term trials have not shown any beneficial impact on deaths [3]; further results and a complete assessment of the long-term costs, benefits, and harms are needed before the implementation of national programmes (see Chapter 6.6).

Given that tobacco smoking is a major contributor to the burden of multiple cancer types and chronic diseases, primary prevention to reduce the prevalence of tobacco smoking remains a key pillar in disease control.

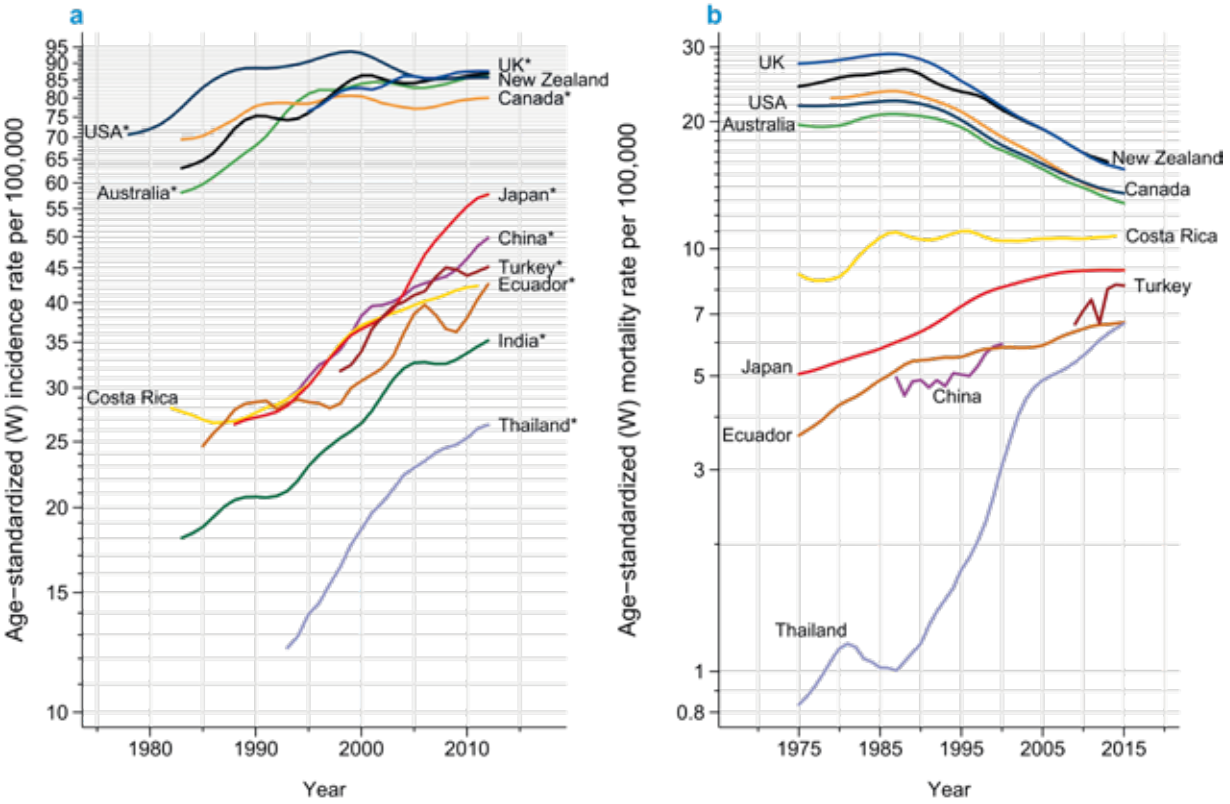
Breast cancer

Breast cancer is the most commonly diagnosed cancer in women (2.1 million new cases in 2018) and the leading cause of cancer death in women globally (627 000 deaths in 2018) (see Chapter 5.9) [5].

The rising incidence rates observed in many higher-income countries during the past five decades – and in lower-income countries more recently – can be attributed partly to the changing prevalence and distribution of several reproductive and hormonal factors (see Chapter 3.6), including a trend towards earlier ages at menarche, later ages at first birth, and lower parity [6]. These changes may partly explain the rapid rises in breast cancer incidence rates in several countries in Asia (e.g. India, Japan, Thailand, and Turkey) and in Latin America (e.g. Costa Rica and Ecuador) (Fig. 1.2.3a).

Artefactual factors may inflate incidence. Breast cancer screening captures prevalent cases for a few years after implementation of screening, and the reported increases in incidence in Brazil and Mexico of 2.9% and 5.9% per year, respectively, were greatest among women aged 55–64 years, the targeted screening age group [6]. In contrast, in countries with high HDI (e.g. Australia, Canada, the United Kingdom, and the USA), incidence rates have stabilized after a marked decline in incidence starting in about 2000, which is considered to result from the publication of two landmark studies that reported on the harmful effects of menopausal hormone replacement therapy on breast cancer risk (see Chapter 2.11) [7]. Dietary factors (including an increasing prevalence of alcohol

Fig. 1.2.3. Age-standardized (World) (a) incidence rates and (b) mortality rates per 100 000 by year in selected countries for breast cancer in women, circa 1975–2012. Asterisks indicate regional registries (other registries are national).



consumption in women), obesity, and physical inactivity (see Chapter 2.7) cannot be ruled out as potential contributors to the previous rising trends in these countries with high HDI, because rates also increased in women outside of the targeted screening age group [6].

In countries in transition towards higher HDI levels, breast cancer mortality trends have tended to parallel the increasing incidence trends; rising mortality rates have consistently been observed in countries in Asia and Latin America (Fig. 1.2.3b) [8], for all age groups and also for women in the targeted screening age group (which suggests an absence of effective screening programmes).

In contrast, a steady decline in breast cancer mortality has been observed in numerous countries with high HDI [8,9], including Australia, Canada, and the USA, where breast cancer mortality rates declined by 18–22% from 2002 to 2012. Although the earlier detection of breast cancer through earlier diagnosis and effective screening programmes may in part explain these favourable trends, the marked decline of rates in non-screened age groups indicates the

Fig. 1.2.4. Women in Peru wearing traditional dress. In Peru and in many other countries in transition, breast cancer mortality trends have tended to parallel the increasing incidence trends.

importance of multiple improvements in the management and treatment of the disease.

Colorectal cancer

Colorectal cancer is the third most common cancer in both sexes worldwide (1.8 million new cases in 2018). It ranks second in terms of mortality (880 000 deaths in 2018). The fact that mortality is considerably lower than incidence reflects the relatively good prognosis for cases on average (see Chapter 5.5).

In general, in countries in transition, where overall risk of colorectal cancer has typically been low, incidence rates have increased, whereas in countries with high HDI, where risk of colorectal cancer tends to be relatively high, incidence rates have either stabilized or decreased in both sexes (Fig. 1.2.5a and Fig. 1.2.6a) [10].

As an example, the declining incidence trends in Australia, Canada, the United Kingdom, and the USA are observed predominantly in older age groups (55 years and older); these populations are subject to early detection programmes that detect and remove precancerous colorectal polyps, leading to a decline in malignancies [11]. Other factors may have contributed, including the adoption of preventive therapies such as regular use of aspirin, postmenopausal estrogen therapy, or – as a matter of greater speculation – an increasing intake of vitamin D [12].

However, marked increases in incidence in younger age groups have been observed in countries with higher HDI and are now also observed in recent birth cohorts in Asia (e.g. in Japan, Thailand, and Turkey) and in Latin America (e.g. in Costa Rica and Ecuador). The rising risk is seen in successive generations, implying the importance of changing risk factors; these are still ill-defined but may include poor diet (characterized by low consumption of fruits, vegetables, and fibre and high consumption of red meat and processed meat [see Chapter 2.6]), a lack of physical activity, and an increasing prevalence of overweight and obesity (see Chapter 2.7).

Consistent with the declines in incidence, colorectal cancer mortality rates have decreased in countries with high HDI (e.g. Australia, Canada, the United Kingdom, and the USA) in both sexes (Fig. 1.2.5b and Fig. 1.2.6b). These decreases can be linked partly to improving survival through the adoption of best practices in cancer treatment and management, in addition to earlier detection of colorectal cancer in these countries [10]. The contrasting increases in mortality rates in several countries in Asia and Latin America may reflect the limited health infrastructure and poorer access to early detection and treatment [10].

Fig. 1.2.5. Age-standardized (World) (a) incidence rates and (b) mortality rates per 100 000 by year in selected countries for colorectal cancer in men, circa 1975–2012. Asterisks indicate regional registries (other registries are national).

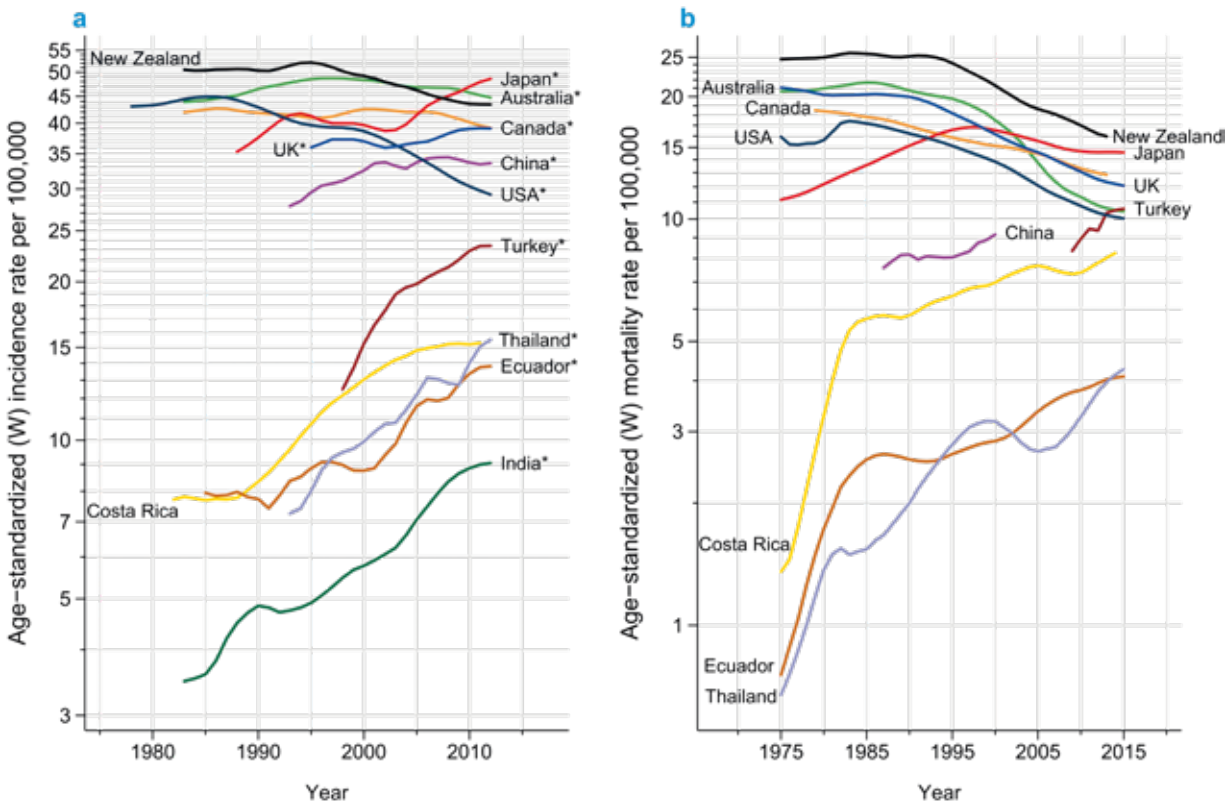
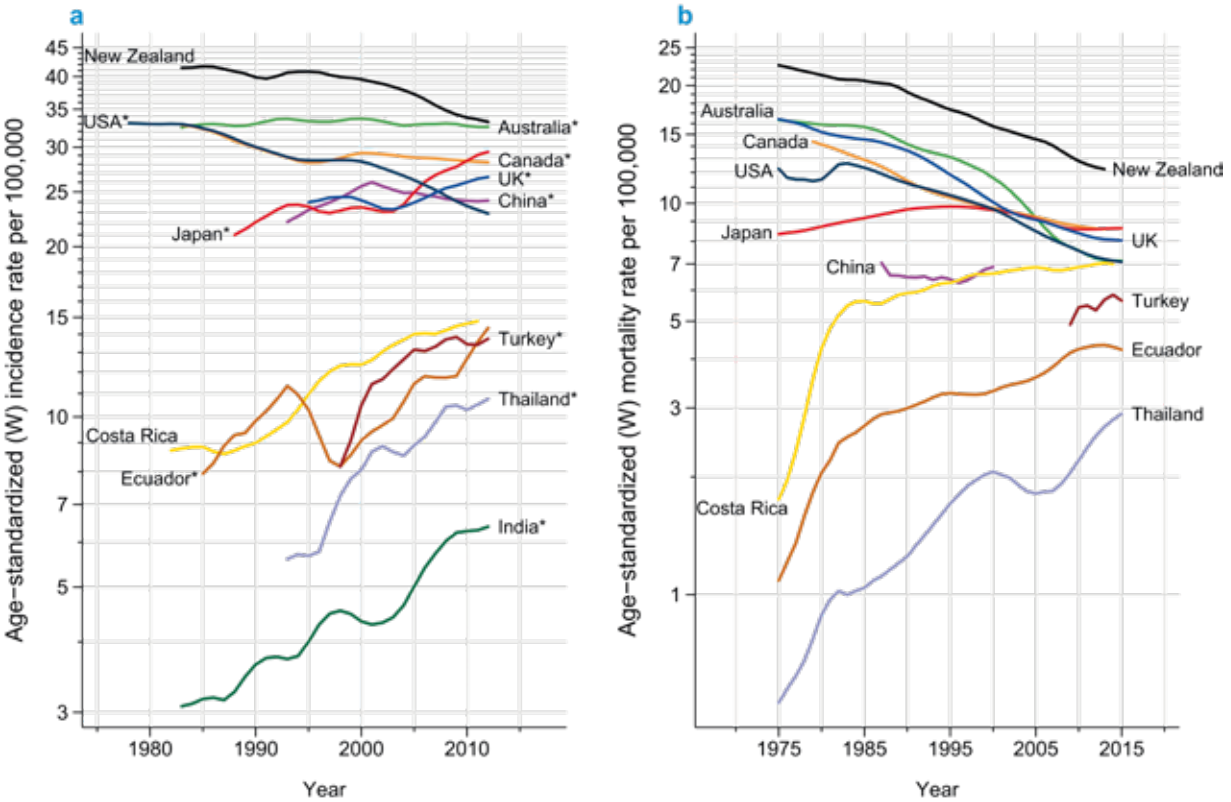


Fig. 1.2.6. Age-standardized (World) (a) incidence rates and (b) mortality rates per 100 000 by year in selected countries for colorectal cancer in women, circa 1975–2012. Asterisks indicate regional registries (other registries are national).



Cancer survival is highly dependent on the stage of cancer at diagnosis, and the unfavourable stage distribution of colorectal cancer partly explains the higher excess mortality from this cancer in a given region [13]. Furthermore, the complexity of treatment, which requires a combination of chemotherapy and radiotherapy (for rectal cancers) after major surgery, can further complicate adequate management of colorectal cancer. In the future, improved access to earlier cancer detection and treatment may decrease the evident inequalities in colorectal cancer survival globally.

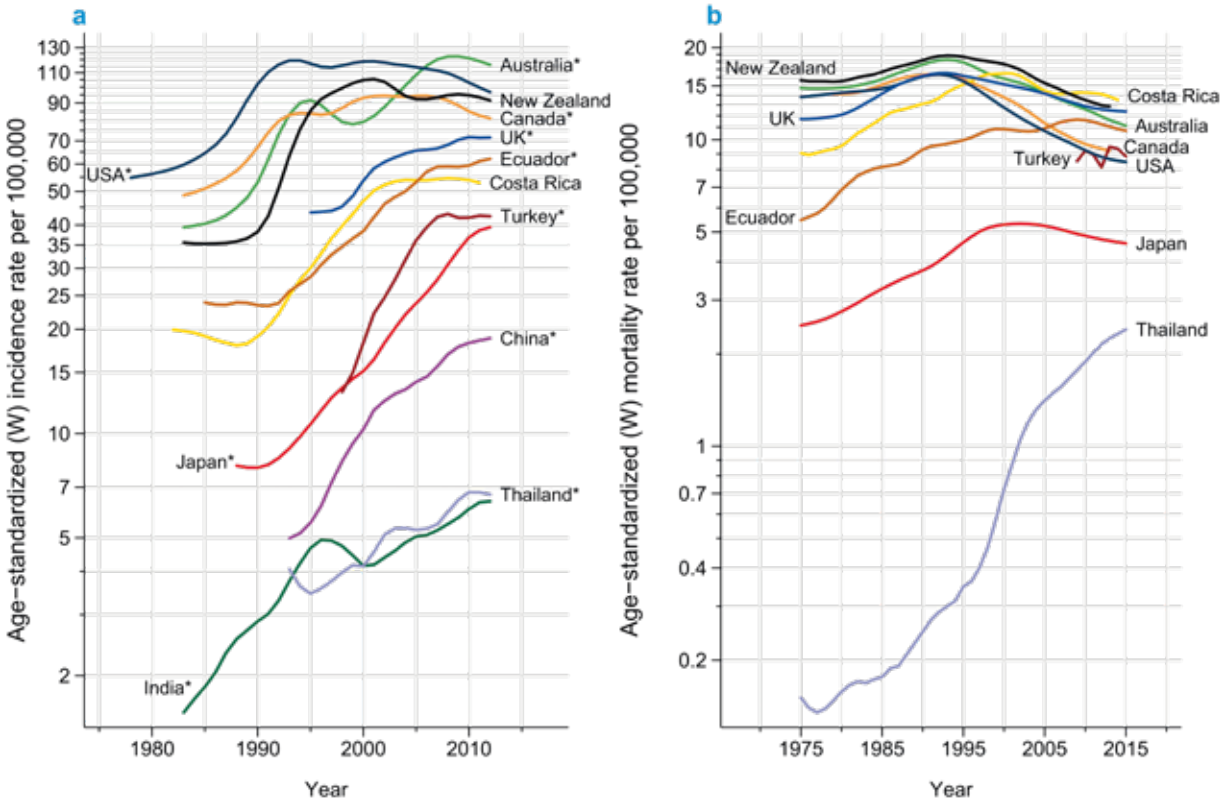
Prostate cancer

Prostate cancer is now the second most common cancer in men worldwide, with an estimated 1.3 million new cases in 2018, accounting for 13.5% of new cancer cases in men. It is a somewhat less important cause of cancer mortality, accounting for 360 000 deaths (6.7% of cancer deaths in men) in 2018 (see Chapter 5.13).

Until the mid-1990s, prostate cancer incidence rates in the USA were increasing substantially, which was largely attributed to the introduction of prostate-specific antigen (PSA) testing as a diagnostic test for asymptomatic prostate cancers [14]. This increase was followed by a peak and a subsequent decline by 2000. Similar time trends were observed in Australia and Canada, with a later decline in incidence rates (Fig. 1.2.7a). Similar trends of incidence rates that increased substantially and then stabilized were observed in several countries in Asia (e.g. Turkey) and Latin America (e.g. Costa Rica and Ecuador) [14,15].

Where incidence rates have decreased or stabilized, these trends may have resulted partly from a decline in PSA testing in general practice and among urologists after the publication of the results of two large randomized trials [16,17] and a broad consensus to cease the testing of men older than 75 years. Where increases in incidence rates have been observed, competing explanations may include greater population awareness of the disease, the diagnosis of small and latent cancers through PSA testing, or a genuine increase in the incidence rates of invasive prostate cancer. A changing lifestyle has been proposed as one of the drivers of trends, including an increased prevalence of obesity and increased consumption of dairy products and calcium, but these factors confer only a small or minimal increase in risk [14]. Prostate cancer incidence rates are much higher in Black populations, which points to a role of genetic factors, although it is unlikely that such factors explain much of the time trends observed in different populations.

Fig. 1.2.7. Age-standardized (World) (a) incidence rates and (b) mortality rates per 100 000 by year in selected countries for prostate cancer, circa 1975–2012. Asterisks indicate regional registries (other registries are national).



In contrast to incidence rates, prostate cancer mortality rates have largely been declining in most countries, with the exception of Thailand, where rates have consistently been low (Fig. 1.2.7b). The two main factors causing the observed decline in mortality rates are probably a stage shift in prostate cancer related to PSA testing (i.e. more cancers are detected at an earlier stage) and better management of patients diagnosed with the disease [18]. The rather short lead time from the observed decline in incidence and mortality has brought considerable controversy with regard to the beneficial impact of PSA testing on prostate cancer mortality. The causes of the decline are probably manifold, including earlier detection and improved treatment; also, greater specificity and less misclassification of earlier deaths from prostate cancer may have led to a slight downturn in prostate cancer mortality rates. A better understanding of the causes and factors that affect incidence is urgently needed to inform future prevention strategies.

Stomach cancer

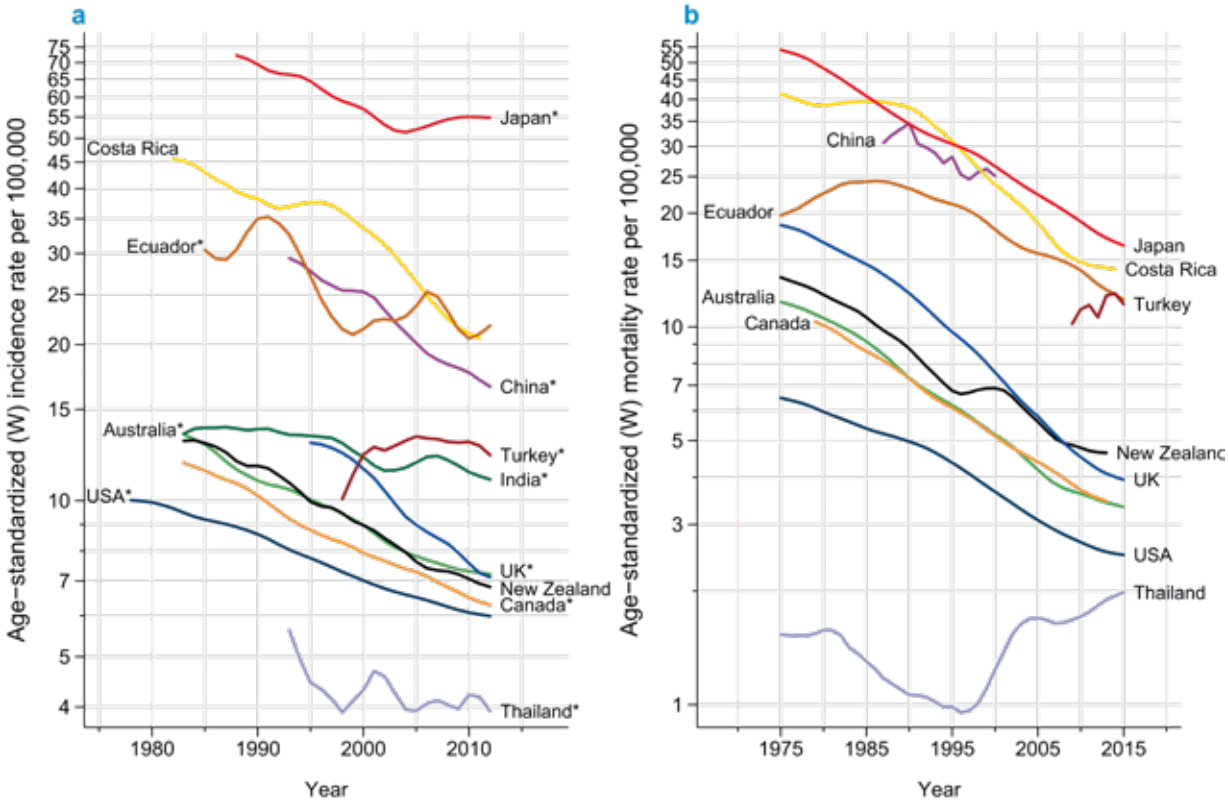
In the first systematic collation of global high-quality cancer incidence data, in the 1960s, stomach cancer was the most common cancer type worldwide [19]. Stomach cancer is now the fifth most common cancer type globally, with an estimated 1 million new cases in 2018 (5.7% of new cancer cases), but because survival is poor, stomach cancer ranks third in terms of mortality (783 000 deaths in 2018) (see Chapter 5.4) [5].

A key epidemiological finding is the steady decline in incidence and mortality rates of stomach cancer (predominantly the non-cardia type of stomach cancer) that has consistently been observed over more than five decades across all world regions (Fig. 1.2.8). Trends in women (not shown) are similar to those in men, but the rates are generally lower.

The risk of non-cardia stomach cancer is closely related to infection with *Helicobacter pylori*; 75–90% of all stomach cancer cases can be attributed to infection with this bacterium (see Chapter 2.2) [20]. *H. pylori* infection is generally acquired at a young age. The risk of infection is increased by overcrowding, and therefore stomach cancer is strongly associated with low socioeconomic status. The declining rates of stomach cancer have been attributed partly to improved living conditions, in particular among young cohorts. Furthermore, improved food preservation practices and better nutrition, including refrigeration for the transportation and storage of food, have been suggested as leading to a declining trend (see Chapter 2.8) [7].

In Japan and the Republic of Korea – countries that have some of

Fig. 1.2.8. Age-standardized (World) (a) incidence rates and (b) mortality rates per 100 000 by year in selected countries for stomach cancer in men, circa 1975–2012. Asterisks indicate regional registries (other registries are national).



the highest stomach cancer rates – part of the decline has been linked to the national screening programmes that have been implemented over the past few decades [21]. Randomized trials are under way to assess the impact of *H. pylori* eradication on non-cardia stomach cancer [21]. Within the next decade, results from these randomized trials may provide further insights to decrease the current uncertainties about *H. pylori* screening and treatment.

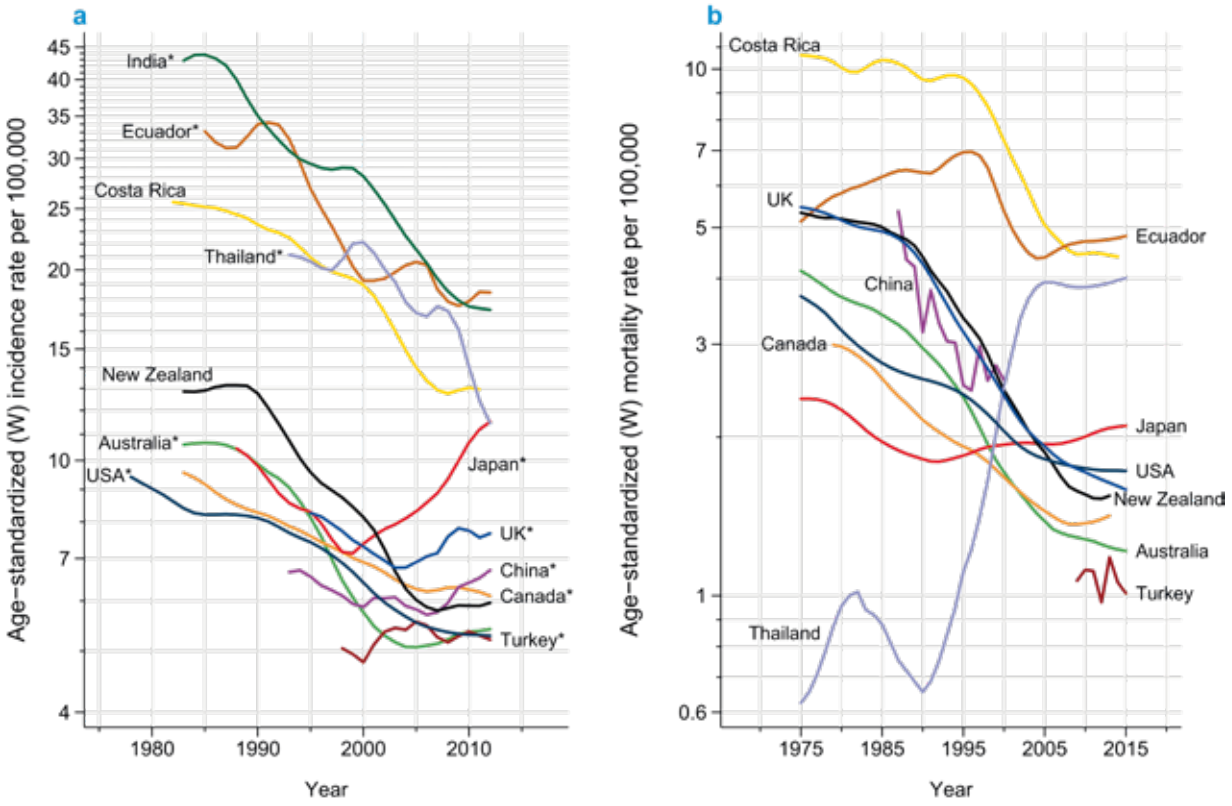
In contrast to the overall decline in rates of non-cardia stomach cancer, studies have indicated an increasing incidence of cardia stomach cancer (which accounted for 27% of all stomach cancer cases in 2012 [22]) in several populations [23]. This increase has been linked to the increased prevalence of Barrett oesophagus and adenocarcinoma of the lower third of the oesophagus, which are strongly associated with overweight and obesity. This double burden of infection-related and obesity-related stomach cancer calls for targeted public health actions that tackle the emerging divergence in the burden and trends observed across the world.

Fig. 1.2.9. Shibuya Crossing in Tokyo, Japan. Although incidence rates of stomach cancer are declining in almost all countries worldwide, Japan has one of the highest recorded rates.

Cervical cancer

Cervical cancer is the fourth most common cancer type in women worldwide in terms of both incidence and mortality, with an estimated 570 000 new cases and 311 000 deaths in 2018 [5]. Infection with human papillomavirus (HPV) — notably HPV types 16, 18, 31, and 45 —

Fig. 1.2.10. Age-standardized (World) (a) incidence rates and (b) mortality rates per 100 000 by year in selected countries for cervical cancer, circa 1975–2012. Asterisks indicate regional registries (other registries are national).



is an established cause of the disease and is estimated to cause all cases of cervical cancer (see Chapter 5.10) [24].

Incidence and mortality rates of cervical cancer have consistently declined in most countries in the past few decades (Fig. 1.2.10) [25,26], and rates appear to have stabilized in many countries with high HDI (e.g. Australia, Canada, the United Kingdom, and the USA), where declines have been ascribed to the success of cytology-based screening programmes [26]. However, several studies have shown that, within the overall decline in incidence and mortality rates, increases have been observed in the younger generations of women in some countries, such as Finland [27] and the Netherlands [28]. The general consensus is that these trends relate to changes in sexual behaviour and increased transmission of persistent HPV infection among birth cohorts. This applies to the Baltic countries, parts of eastern Europe and western Asia [29], and Japan, where the effect has been occurring for an extended period [30], in the absence of effective screening programmes. Other determinants have contributed to the declines in cervical cancer rates in countries without effective screening programmes, including improved genital hygiene and the impact of cofactors linked to progression of HPV infection to cervical cancer: parity, age at first birth, use of oral contraceptives, and tobacco use.

A recent WHO call to action seeks to overcome the multiple challenges to global cervical cancer prevention by scaling up HPV vaccination (see Chapter 6.3) and screening programmes in countries to eliminate cervical cancer as a public health concern during this century (https://www.who.int/reproductivehealth/cervical-cancer-public-health-concern/en/).

Conclusions

This brief overview of global incidence and mortality trends for six major cancer types in a subset of countries is based on the availability of recent data from national or subnational population-based cancer registries and/or national vital registration systems. Local high-quality cancer surveillance systems are needed to gain a reasonably accurate picture of how the cancer burden and risk are changing with time in different communities. The focus on rates for all ages has precluded a more detailed exposition of trends by age and birth cohort, which is needed to fully understand the underlying factors responsible for these time trends.

Evidently there are increasing global inequalities in cancer control planning and outcomes. Although there have been many triumphs in the prevention, early diagnosis, and management of these major cancer

types in recent decades, those benefits have occurred predominantly in countries with higher HDI, where health systems infrastructure and capacity are already in place. To ensure that the potential for prevention, cure, and alleviation of suffering from cancer becomes a reality in all countries of the world within the first half of this century, it is paramount that the existing evidence-based and cost-effective interventions – such as those listed in the updated Appendix 3 [31] of the WHO global action plan 2013–2020, in which interventions are rated with reference to "best buys" – are implemented and their success evaluated equitably in lower-resource settings.

References

1. GBD 2015 Risk Factors Collaborators (2016). Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 388(10053):1659–724. https://doi.org/10.1016/S0140-6736(16)31679-8 PMID:27733284

2. Lortet-Tieulent J, Soerjomataram I, Ferlay J, Rutherford M, Weiderpass E, Bray F (2014). International trends in lung cancer incidence by histological subtype: adenocarcinoma stabilizing in men but still increasing in women. Lung Cancer. 84(1):13–22. https://doi.org/10.1016/j.lungcan.2014.01.009 PMID:24524818

3. Coureau G, Salmi LR, Etard C, Sancho-Garnier H, Sauvaget C, Mathoulin-Pélissier S (2016). Low-dose computed tomography screening for lung cancer in populations highly exposed to tobacco: a systematic methodological appraisal of published randomised controlled trials. Eur J Cancer. 61:146–56. https://doi.org/10.1016/j.ejca.2016.04.006 PMID:27211572

4. Oudkerk M, Devaraj A, Vliegenthart R, Henzler T, Prosch H, Heussel CP, et al. (2017). European position statement on lung cancer screening. Lancet Oncol. 18(12):e754–66. https://doi.org/10.1016/S1470-2045(17)30861-6 PMID:29208441

5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593

6. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A (2017). Global cancer in women: burden and trends. Cancer Epidemiol Biomarkers Prev. 26(4):444–57. https://doi.org/10.1158/1055-9965.EPI-16-0858 PMID:28223433

7. Arnold M, Karim-Kos HE, Coebergh JW, Byrnes G, Antilla A, Ferlay J, et al. (2015). Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European Cancer Observatory. Eur J Cancer. 51(9):1164–87. https://doi.org/10.1016/j.ejca.2013.09.002 PMID:24120180

8. Carioli G, Malvezzi M, Rodriguez T, Bertuccio P, Negri E, La Vecchia C (2018). Trends and predictions to 2020 in breast cancer mortality: Americas and Australasia. Breast. 37:163–9. https://doi.org/10.1016/j.breast.2017.12.004 PMID:29246526

9. Carioli G, Malvezzi M, Rodriguez T, Bertuccio P, Negri E, La Vecchia C (2017). Trends and predictions to 2020 in breast cancer mortality in Europe. Breast. 36:89–95. https://doi.org/10.1016/j.breast.2017.06.003 PMID:28988610

10. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F (2017). Global patterns and trends in colorectal cancer incidence and mortality. Gut. 66(4):683–91. https://doi.org/10.1136/gutjnl-2015-310912 PMID:26818619

11. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al. (2017). Colorectal cancer statistics, 2017. CA Cancer J Clin. 67(3):177–93. https://doi.org/10.3322/caac.21395 PMID:28248415

12. Fidler MM, Bray F, Vaccarella S, Soerjomataram I (2017). Assessing global transitions in human development and colorectal cancer incidence. Int J Cancer. 140(12):2709–15. https://doi.org/10.1002/ijc.30686 PMID:28281292

13. Maringe C, Walters S, Rachet B, Butler J, Fields T, Finan P, et al.; ICBP Module 1 Working Group (2013). Stage at diagnosis and colorectal cancer survival in six high-income countries: a population-based study of patients diagnosed during 2000–2007. Acta Oncol. 52(5):919–32. https://doi.org/10.3109/0284186X.2013.764008 PMID:23581611

14. Zhou CK, Check DP, Lortet-Tieulent J, Laversanne M, Jemal A, Ferlay J, et al. (2016). Prostate cancer incidence in 43 populations worldwide: an analysis of time trends overall and by age group. Int J Cancer. 138(6):1388–400. https://doi.org/10.1002/ijc.29894 PMID:26488767

15. Sierra MS, Soerjomataram I, Forman D (2016). Prostate cancer burden in Central and South America. Cancer Epidemiol. 44(Suppl 1):S131–40. https://doi.org/10.1016/j.canep.2016.06.010 PMID:27678315

16. Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, et al.; PLCO Project Team (2009). Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 360(13):1310–9. https://doi.org/10.1056/NEJMoa0810696 PMID:19297565

17. Schröder FH, Hugosson J, Roobol MJ, Tammela TLJ, Ciatto S, Nelen V, et al.; ERSPC Investigators (2009). Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 360(13):1320–8. https://doi.org/10.1056/NEJMoa0810084 PMID:19297566

18. Wong MC, Goggins WB, Wang HHX, Fung FDH, Leung C, Wong SYS, et al. (2016). Global incidence and mortality for prostate cancer: analysis of temporal patterns and trends in 36 countries. Eur Urol. 70(5):862–74. https://doi.org/10.1016/j.eururo.2016.05.043 PMID:27289567

19. Doll R, Payne P, Waterhouse JAH, editors (1966). Cancer incidence in five continents: a technical report. Berlin, Germany: Springer.

20. Plummer M, Franceschi S, Vignat J, Forman D, de Martel C (2015). Global burden of gastric cancer attributable to *Helicobacter pylori*. Int J Cancer. 136(2):487–90. https://doi.org/10.1002/ijc.28999 PMID:24889903

21. IARC *Helicobacter pylori* Working Group (2014). *Helicobacter pylori* eradication as a strategy for preventing gastric cancer. Lyon, France: International Agency for Research on Cancer (IARC Working Group Reports, No. 8). Available from: http://publications.iarc.fr/391.

22. Colquhoun A, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I (2015). Global patterns of cardia and non-cardia gastric cancer incidence in 2012. Gut. 64(12):1881–8. https://doi.org/10.1136/gutjnl-2014-308915 PMID:25748648

23. Anderson WF, Rabkin CS, Turner N, Fraumeni JF Jr, Rosenberg PS, Camargo MC (2018). The changing face of noncardia gastric cancer incidence among US non-Hispanic Whites. J Natl Cancer Inst. 110(6):608–15. https://doi.org/10.1093/jnci/djx262 PMID:29361173

24. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S (2016). Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 4(9):e609–16. https://doi.org/10.1016/S2214-109X(16)30143-7 PMID:27470177

25. Vaccarella S, Laversanne M, Ferlay J, Bray F (2017). Cervical cancer in Africa, Latin America and the Caribbean and Asia: regional inequalities and changing trends. Int J Cancer. 141(10):1997–2001. https://doi.org/10.1002/ijc.30901 PMID:28734013

26. Vaccarella S, Lortet-Tieulent J, Plummer M, Franceschi S, Bray F (2013). Worldwide trends in cervical cancer incidence: impact of screening against changes in disease risk factors. Eur J Cancer. 49(15):3262–73. https://doi.org/10.1016/j.ejca.2013.04.024 PMID:23751569

27. Anttila A, Pukkala E, Söderman B, Kallio M, Nieminen P, Hakama M (1999). Effect of organised screening on cervical cancer incidence and mortality in Finland, 1963–1995: recent increase in cervical cancer incidence. Int J Cancer. 83(1):59–65. https://doi.org/10.1002/(SICI)1097-0215(19990924)83:1<59::AID-IJC12>3.0.CO;2-N PMID:10449609

28. de Kok IM, van der Aa MA, van Ballegooijen M, Siesling S, Karim-Kos HE, van Kemenade FJ, et al.; Working Group Output of the Netherlands Cancer Registry (2011). Trends in cervical cancer in the Netherlands until 2007: has the bottom been reached? Int J Cancer. 128(9):2174–81. https://doi.org/10.1002/ijc.25553 PMID:20626043

29. Bray F, Lortet-Tieulent J, Znaor A, Brotons M, Poljak M, Arbyn M (2013). Patterns and trends in human papillomavirus-related diseases in Central and Eastern Europe and Central Asia. Vaccine. 31(Suppl 7):H32–45. https://doi.org/10.1016/j.vaccine.2013.02.071 PMID:24332296

30. Utada M, Chernyavskiy P, Lee WJ, Franceschi S, Sauvaget C, de Gonzalez AB, et al. (2019). Increasing risk of uterine cervical cancer among young Japanese women: comparison of incidence trends in Japan, South Korea and Japanese-Americans between 1985 and 2012. Int J Cancer. 144(9):2144–52. https://doi.org/10.1002/ijc.32014 PMID:30474210

31. WHO (2017). Updating Appendix 3 of the WHO global NCD action plan 2013–2020. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/ncds/governance/appendix3-update/en/.

1.3 Transitions in human development and the global cancer burden

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SUMMARY

- The Human Development Index (HDI), with a four-tier categorization of countries as having low, medium, high, or very high HDI, provides a useful framework for assessing the global cancer burden geographically and over time.
- The average HDI values at the country level can be linked to the corresponding scale and profile of cancer to document the effect of transitions towards higher HDI levels, and this can serve as evidence for national cancer control priorities. Similar linkages to risk factors and cancer-related outcomes can help to further explain transitions and inequalities in the cancer burden.
- A high residual burden of infection-related cancers is observed in countries with low HDI. Several countries with medium and high HDI, which are often undergoing major social and economic transitions, have experienced marked declines in the burden of infection-related cancers. These declines have subsequently been offset by increasing rates of cancer types that are more frequently observed in industrialized countries.
- The predicted global cancer burden is expected to exceed 27 million new cancer cases per year by 2040, a 50% increase on the estimated 18.1 million cancers in 2018. The estimated increases in the cancer incidence burden from 2018 to 2040 using demographic changes will occur in all countries, but the predicted increases will be proportionately greatest in countries with low and medium HDI.
- Human development plays a critical role in understanding the shifting scale and profile of cancer globally. However, using the four-tier HDI to describe transitions has limitations, given that it de-emphasizes the diversity of cancer occurrence and can oversimplify the multifactorial influences, including sex, ethnicity, and cultural aspects, on a complex set of diseases.
- Although attention has been drawn to broad patterns of cancer incidence according to human development level, there are clear examples of national and regional cancer diversity of cancer occurrence that depart from this model. Also, because HDI indicates national averages, it does not reflect any inequalities in human development within countries.

Epidemiological transitions in cancer

Omran's theory of epidemiological transition described how changing health and disease patterns are influenced by demographic, economic, and societal factors [1]. In particular, Omran described how, in the third stage of the transition, infections become less important and chronic diseases become more important as the major causes of morbidity and mortality as life expectancy increases to more than 70 years and mortality – from "degenerative diseases" – is delayed. This late stage of the transition corresponds with the current rising prominence of noncommunicable diseases, which in the past decades have surpassed communicable diseases as the leading causes of death worldwide [2].

Among noncommunicable diseases, cancer has emerged as a particularly important health concern. Cancer is the first or second leading cause of premature mortality (i.e. deaths at ages 30–69 years) in more than 90 countries worldwide (see Chapter 1.1). An estimated 18.1 million new cancer cases and 9.6 million cancer-related deaths occurred worldwide in 2018, and 1 in 8 men and 1 in 10 women are likely to develop the disease during their lifetimes [3]. When coupled with the estimated cost of cancer care of US$ 1.16 trillion per year [4], this clearly makes cancer a public health priority. As a result, there has been a growing recognition of the need for action to reduce the cancer burden. This is exemplified by the World Health Assembly

resolution on cancer prevention and control, which was adopted unanimously by WHO Member States in May 2017 [5].

Although cancer was once considered to be a disease of rich people and of the highest-income countries, it is now a global problem that affects all countries. The increasing magnitude of the cancer burden is in part a consequence of declining fertility and increasing life expectancy, but it is also the result of societal, economic, and lifestyle changes associated with globalization.

In this chapter, the impact of transitions in human development on cancer occurrence worldwide is illustrated by the profound effects on the patterns and trends of cancer incidence, mortality, and prevalence at the national, regional, and global levels. The predicted increases in the cancer burden will be proportionately greatest in countries in transition towards higher levels of human development. Such findings have major implications for public health and cancer control planning, and therefore should alert the global community to the growing cancer burden and the need for action, particularly in countries that are currently ill-equipped to deal with the expected escalating numbers of cancer patients in coming decades.

The Human Development Index

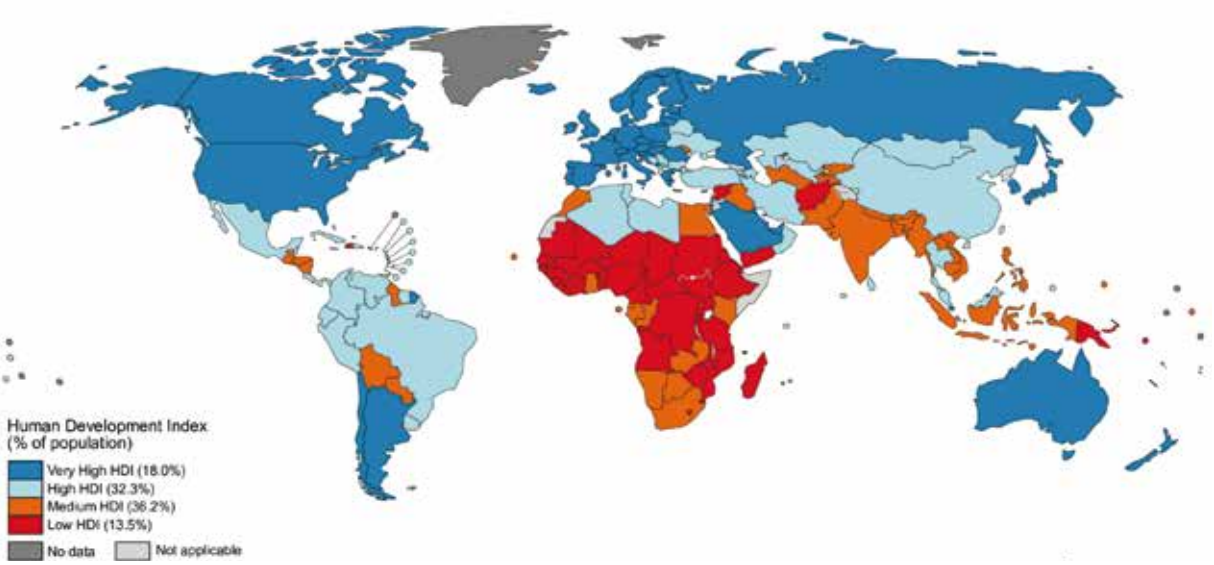
Human development focuses on two core dimensions: (i) directly enhancing human abilities, and (ii) creating conditions for human development [6]. Like the previous two chapters, this chapter uses the Human Development Index (HDI), a summary measure developed by the United Nations Development Programme. HDI is an indicator of national achievement in attaining a long and healthy life (based on life expectancy at birth), acquiring knowledge (based on average and expected years of schooling), and achieving a decent standard of living (based on gross national income per capita) [7]. HDI values range from 0 to 1; lower values indicate the least developed countries in terms of human development, and higher values indicate the most developed countries. Values are commonly presented, as in this chapter, according to four tiers of HDI (low, medium, high, and very high HDI), using the predefined cut-off points of the United Nations Development Programme. Because HDI is a composite indicator of national averages, it does not reflect any inequalities in human development within countries.

The global map of countries according to the HDI tiers is shown in Fig. 1.3.1. The low HDI tier includes countries that are largely concentrated in sub-Saharan Africa, although several countries in this region have now transitioned to the medium HDI level. The countries in the high and very high HDI tiers are geographically diverse, spanning across continents, although the very high HDI tier remains closest to the traditional view of "developed" countries in that it includes Europe and North America, Japan, and Australia and New Zealand. The very high HDI tier also includes several countries in Asia, the Eastern Mediterranean region, and South America. Most the world's population live in countries in the medium (36.2%) and high (32.3%) HDI tiers, followed by the very high (18.0%) and low (13.5%) HDI tiers.

Cancer burden by HDI level in 2018

When the cancer burden in 2018 was assessed by the four-tier HDI, a stepwise increase in the number of new cancer cases and in the age-standardized incidence rates was evident with each increase in HDI level

Fig. 1.3.1. Global map of the development levels of individual countries according to the four-tier Human Development Index (HDI), in 2015.

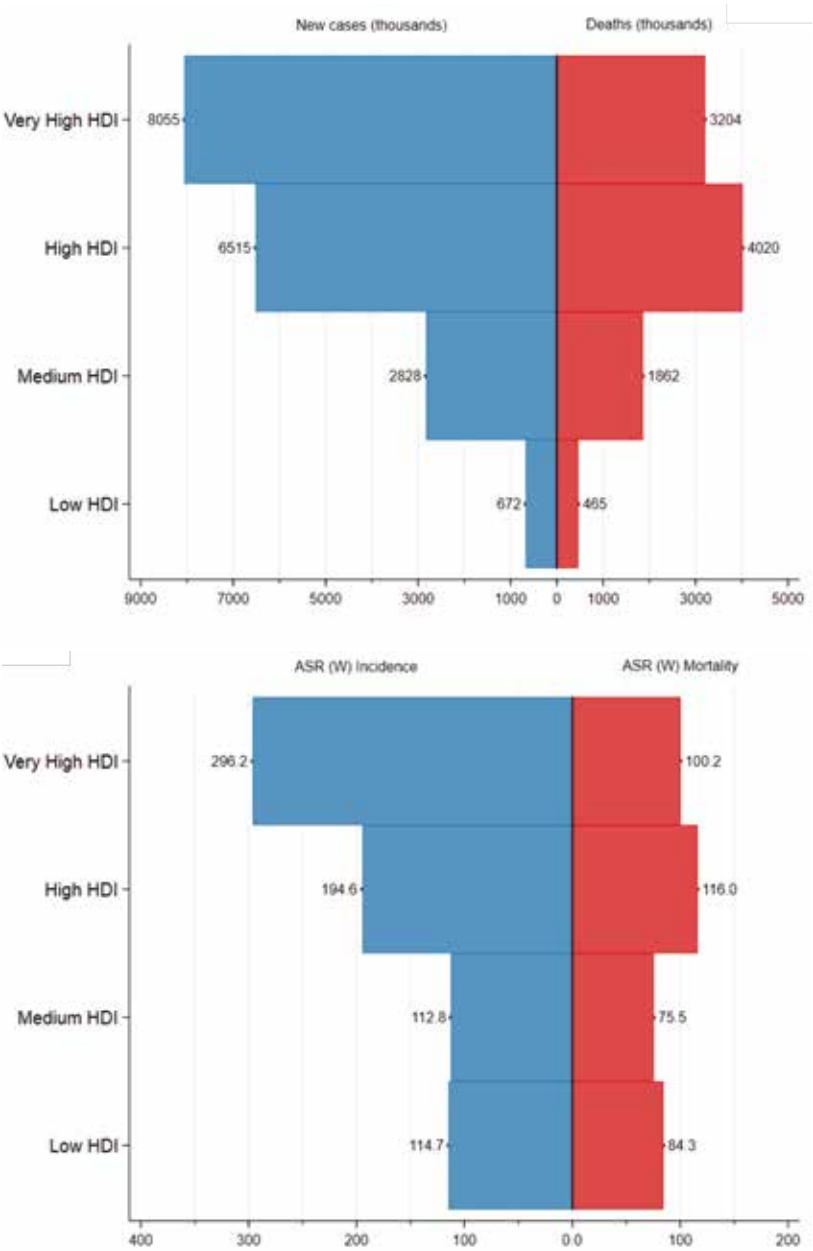


(Fig. 1.3.2). In 2018, 45% of the estimated new cancer cases occurred in countries with very high HDI, compared with 36%, 16%, and 4% in countries with high, medium, and low HDI, respectively. In contrast, the greatest number of cancer deaths occurred in countries with high HDI, driven by the 2.9 million cancer deaths that occurred in China. Age-standardized incidence rates indicate a slightly different pattern, in which countries in the low and medium HDI tiers have comparable burdens, although the burden is slightly higher in the low HDI tier. For age-standardized mortality rates, no correlation with HDI level is observed.

The age-standardized incidence and mortality rates for the top 15 cancer types in 2018 for each sex are shown in Fig. 1.3.3, which compares the burden in countries with high or very high HDI with that in countries with low or medium HDI. With the exception of rates of a few cancer types, the incidence rates were generally greater in countries with higher HDI; the age-standardized incidence rates in many of these countries were 2–3 times those in countries in transition towards higher HDI levels.

In contrast, the mortality rates were broadly comparable between the two groups of countries. For some cancer types, such as breast cancer and ovarian cancer, the mortality burden was greater in countries with low or medium HDI, although the incidence rates in those countries were lower than the rates in countries with high or very high HDI. The proportionately higher case fatalities in countries with low or medium HDI relates to the poorer survival prospects after diagnosis on average, for reasons that include a lack of access to timely diagnosis and treatment. For example, when the mortality-to-incidence ratio is used as a proxy of survival, the case fatality for breast cancer is 48% in countries with low or medium HDI, 4 times that in countries with high or very high HDI.

Fig. 1.3.2. The total burden of new cancer cases and cancer deaths (above) and the corresponding age-standardized (World) incidence and mortality rates per 100 000 (below) for each Human Development Index (HDI) tier, in 2018.



Cancer profile by HDI level in 2018

Cancer profiles by HDI level differ when assessed by incidence, mortality, and 5-year prevalence.

In women, the five major cancer types accounted for more than 50% of the burden in each of these three indicators (Fig. 1.3.4). Uniquely, breast cancer was the most common cancer type across all HDI tiers in terms of incidence, followed by cervical cancer in the low and medium HDI tiers and colorectal cancer in the high and very high HDI tiers.

Cervical cancer was the most common cause of cancer mortality in the low HDI tier and the second most common in the medium HDI tier, highlighting a residual burden of infection-related cancers in countries

Fig. 1.3.3. Bar charts of age-standardized (World) incidence and mortality rates per 100 000 for the top 15 cancer types in 2018 in countries with high or very high Human Development Index (HDI) compared with countries with low or medium HDI, in women (top) and men (bottom).

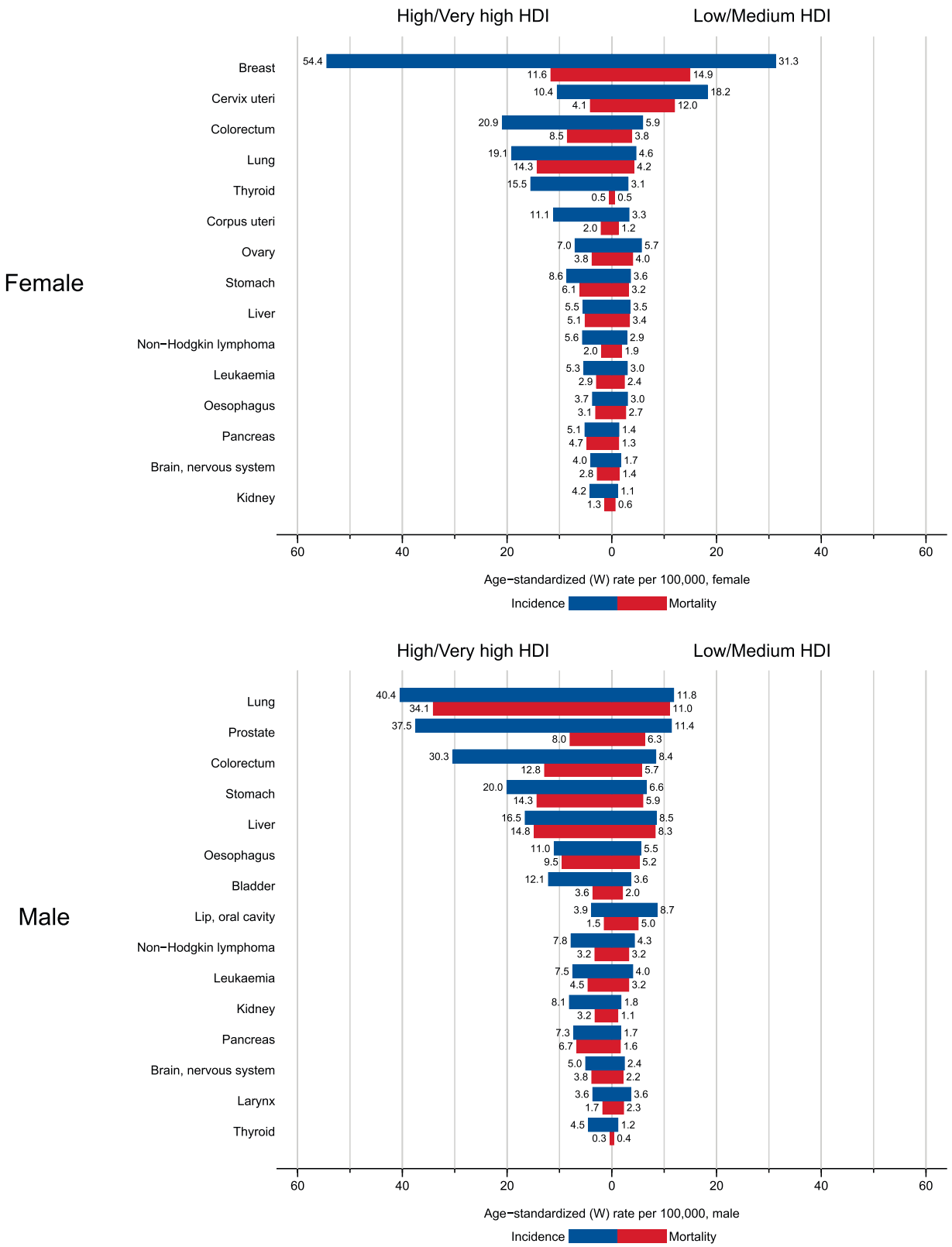


Fig. 1.3.4. The five leading cancer types in terms of incidence, mortality, and 5-year prevalence for each Human Development Index (HDI) tier in women in 2018.

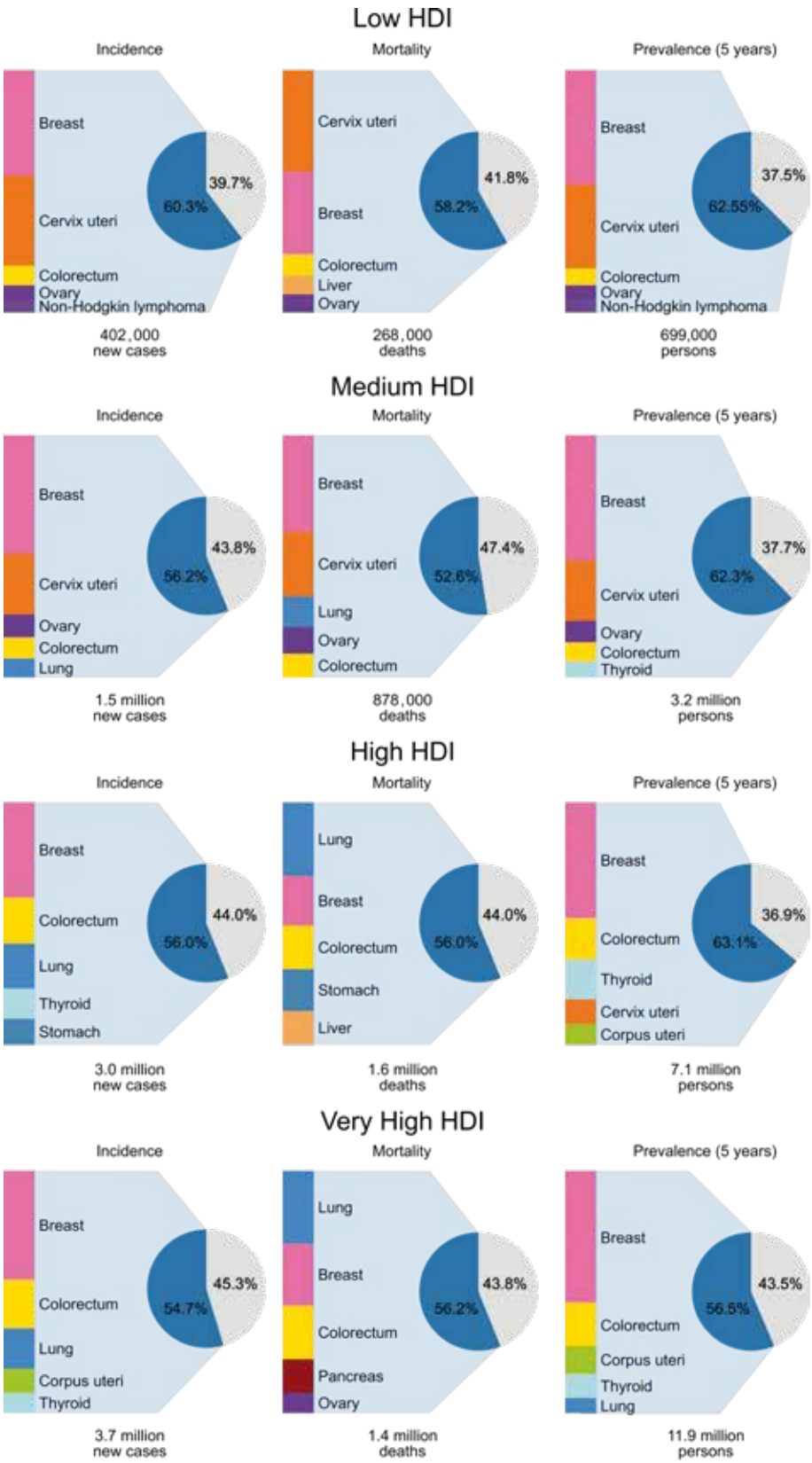
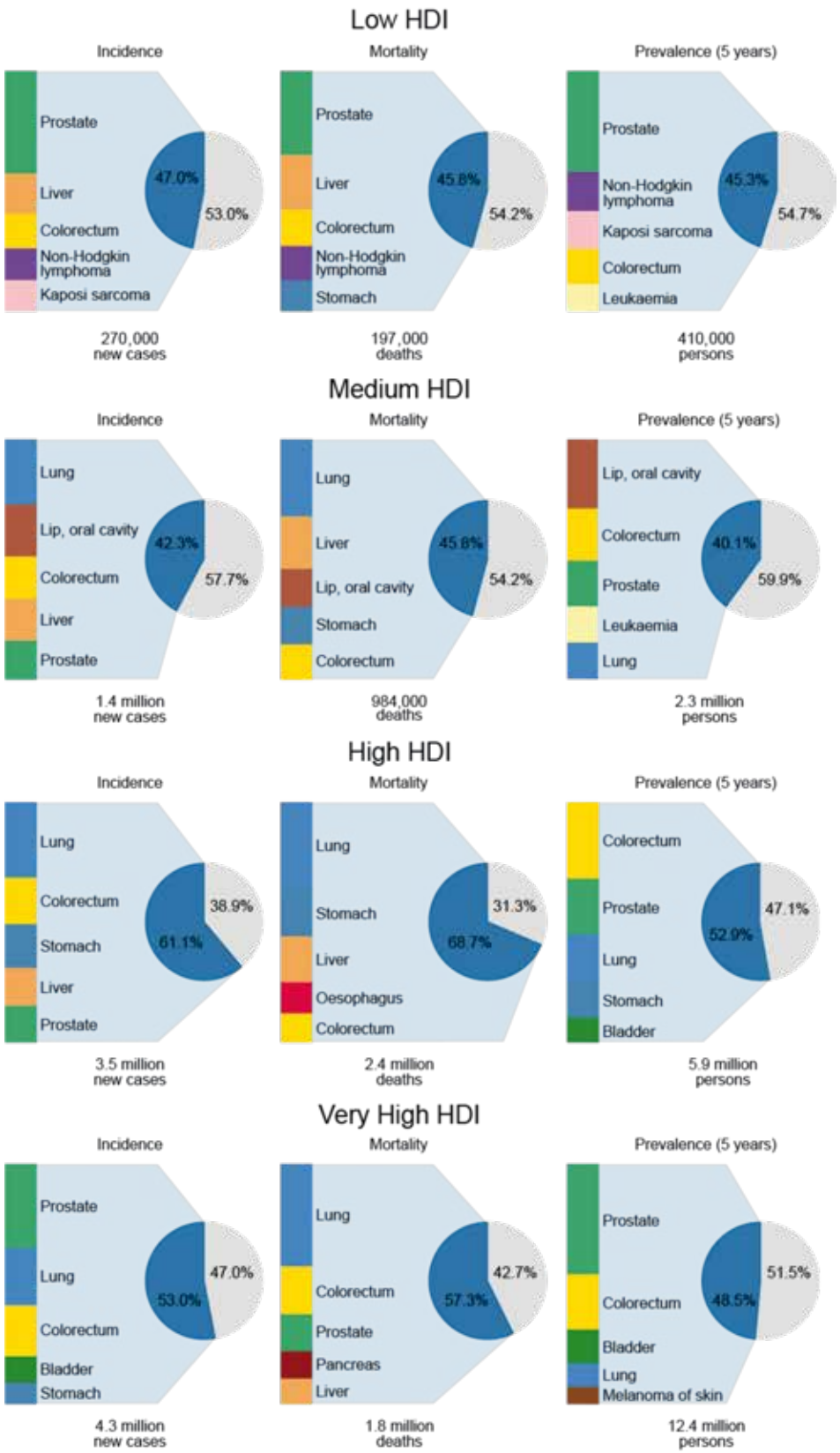


Fig. 1.3.5. The five leading cancer types in terms of incidence, mortality, and 5-year prevalence for each Human Development Index (HDI) tier in men in 2018.



in these tiers. In contrast, in both the high and very high HDI tiers, infection-related cancers (see Chapter 2.2) have been displaced by lung cancer, breast cancer, and colorectal cancer; these cancer types, which are associated with behaviours and lifestyles that are more typical of industrialized societies, have become the leading causes of cancer mortality in the high and very high HDI tiers.

In women, the 5-year prevalence burden in each HDI tier generally had a similar profile of cancer types to that observed for incidence.

In 2018, the cancer profile by HDI level varied more substantially in men than in women. In men, the top five cancer types were different in each HDI tier (Fig. 1.3.5). In terms of incidence, lung cancer was the most common type in the medium and high HDI tiers, whereas prostate cancer was the most common type in the low and very high HDI tiers; this pattern may relate to ethnic and underlying genetic predispositions in the low HDI tier and to prostate-specific antigen (PSA)-related diagnosis of latent cancers in the very high HDI tier. Although the burden of infection-related cancers, such as liver cancer and Kaposi sarcoma, is higher in countries in transition, there remains a large burden of liver cancer in the high HDI tier; this is due to the nearly 393 000 new cases in China in 2018, which accounted for 84% of the liver cancer cases in the high HDI tier.

Prostate cancer was the leading cause of cancer mortality in the low HDI tier, whereas lung cancer was the leading cause in the medium, high, and very high HDI tiers. Liver cancer and colorectal cancer were also among the most common causes of cancer mortality in all four HDI tiers. The cancer types contributing to the remaining mortality burden varied by HDI level.

In men, the 5-year prevalence burden in each HDI tier had a similar profile of cancer types to that observed for incidence, except that the ranking was higher for cancer types associated with better survival prospects after diagnosis.

Future cancer burden by HDI level

The predicted global cancer burden is expected to exceed 27 million new cancer cases per year by 2040, a 50% increase on the estimated 18.1 million new cancer cases in 2018. Although the predicted cancer incidence burden is highest in countries with high and very high HDI, the predicted increases will be proportionately greatest in countries with low and medium HDI: the estimated increase from 2018 to 2040 using demographic changes alone is 100% for the low HDI tier and 75% for the medium HDI tier (Fig. 1.3.6).

Because countries with low and medium HDI levels are currently the least equipped to deal with the impending increase in the cancer burden, these findings underscore the necessity for investment in targeted, resource-dependent, effective, and cost-effective interventions that can reduce the burden of the disease [5,8].

Cancer risk factors by HDI level

Despite the broad associations between cancer and HDI described above, there remain a large number of carcinogenic hazards, including tobacco use and alcohol consumption [9,10], infectious agents [11], obesity [12], diet [13–15], radiation [16], solar radiation [17,18], and air pollution [19,20]. Of these, obesity and infectious agents are particularly interesting to examine according to HDI, because of their relative importance in the cancer burden in countries with higher HDI (obesity) and lower HDI (infectious agents).

Obesity

Excess body fatness (see Chapter 2.7) is considered to cause the following cancer types: cancers of the oesophagus (adenocarcinoma), gastric cardia, colon and rectum, liver, gall bladder, pancreas, breast (in postmenopausal women), endometrium, ovary, kidney (renal cell carcinoma), and thyroid, and meningioma and multiple myeloma [12]. When the relationship between excess weight – or obesity – and cancer was assessed by HDI, the attributable fractions in countries with very high and high HDI (~5% each) were 2–3 times those in countries with medium HDI (1.6%) or low HDI (1.0%) [21]. When the relationship was assessed by sex, the number of cancer cases attributable to obesity was observed to

Fig. 1.3.6. The estimated number of new cancer cases in 2018 and the predicted increase in the number of new cancer cases from 2018 to 2040, assuming only a demographic effect, by Human Development Index (HDI) tier.

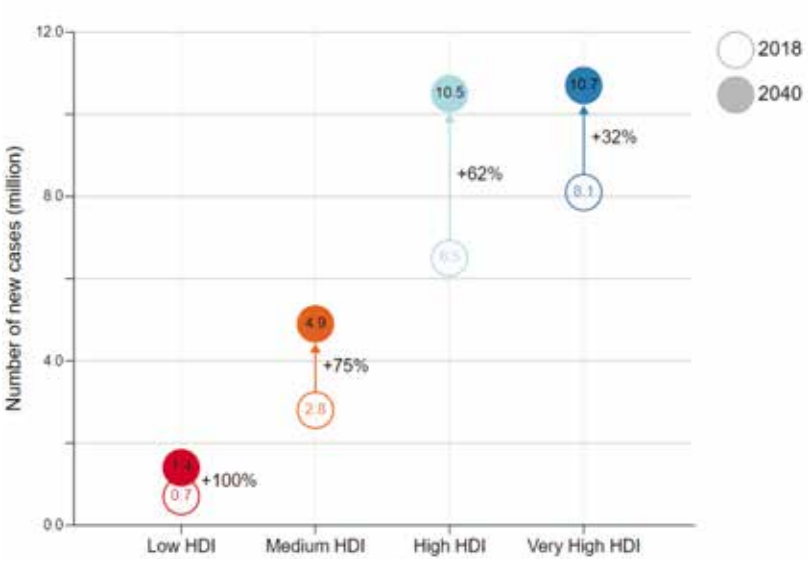
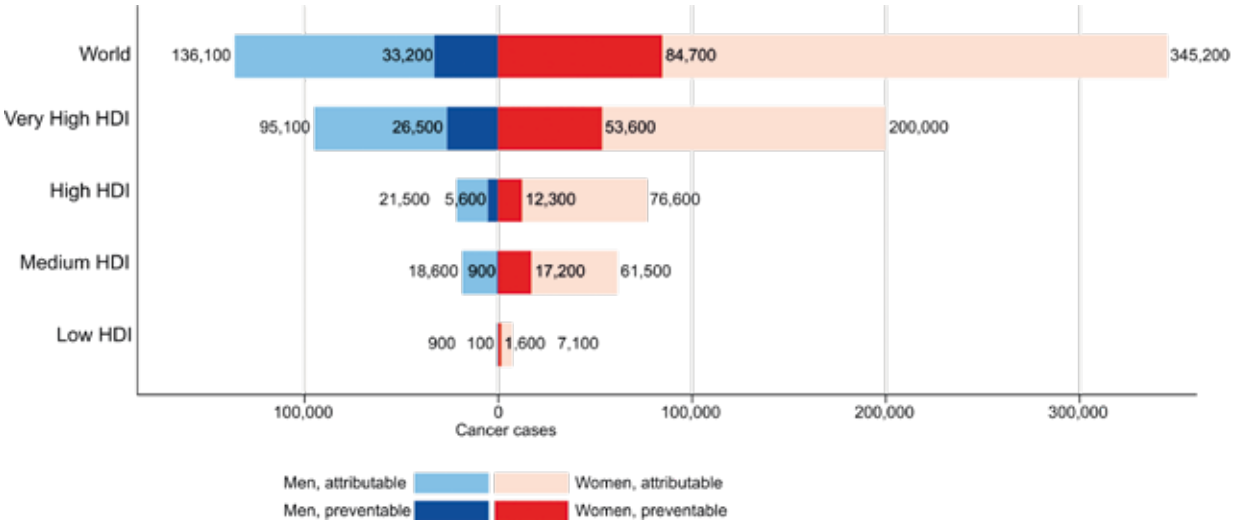


Fig. 1.3.7. The number of cancer cases attributable to high body mass index (BMI) and the number of preventable cancers if BMI scores remained the same in 2012 as in 1982, by sex and Human Development Index (HDI) tier.



increase with HDI level in both men and women (Fig. 1.3.7).

When the number of preventable cancers was assessed, the number increased with HDI level in men. This relationship was less consistent in women; the number of preventable cancers was greatest in the very high and medium HDI tiers [21]. Therefore, although prevention programmes that seek to control weight gain are clearly needed in the most developed countries, these findings also emphasize the need for a global effort to reduce the number of people with high body mass index, because the continuation of current patterns of population weight gain will increase the future cancer burden across all HDI tiers [21].

Infections

In 2012, approximately 15% of new cancer cases worldwide were attributable to infections (see Chapter 2.2) [22]. When the proportion of cancers attributable to infections was assessed by HDI tier, a gradient was observed: the attributable fractions were 25%, 22%, 13%, and 8%, respectively, in the low, medium, high, and very high HDI tiers [22].

Infection with human papillomavirus (HPV) caused approximately half of all infection-attributable cancers in the low HDI tier, and the proportion of infection-related cancers attributable to HPV decreased with increasing HDI [22]. In contrast, infection with *Helicobacter pylori* contributed substantially to the cancer burden in countries in the high and very high HDI tiers [22].

Because two thirds of infection-attributable cancer cases occurred in less-developed countries, effective population-based vaccination and screen-and-treat programmes should be prioritized and implemented in a cost-effective manner to combat the disproportionately high burden in these countries.

Cancer outcomes by HDI level

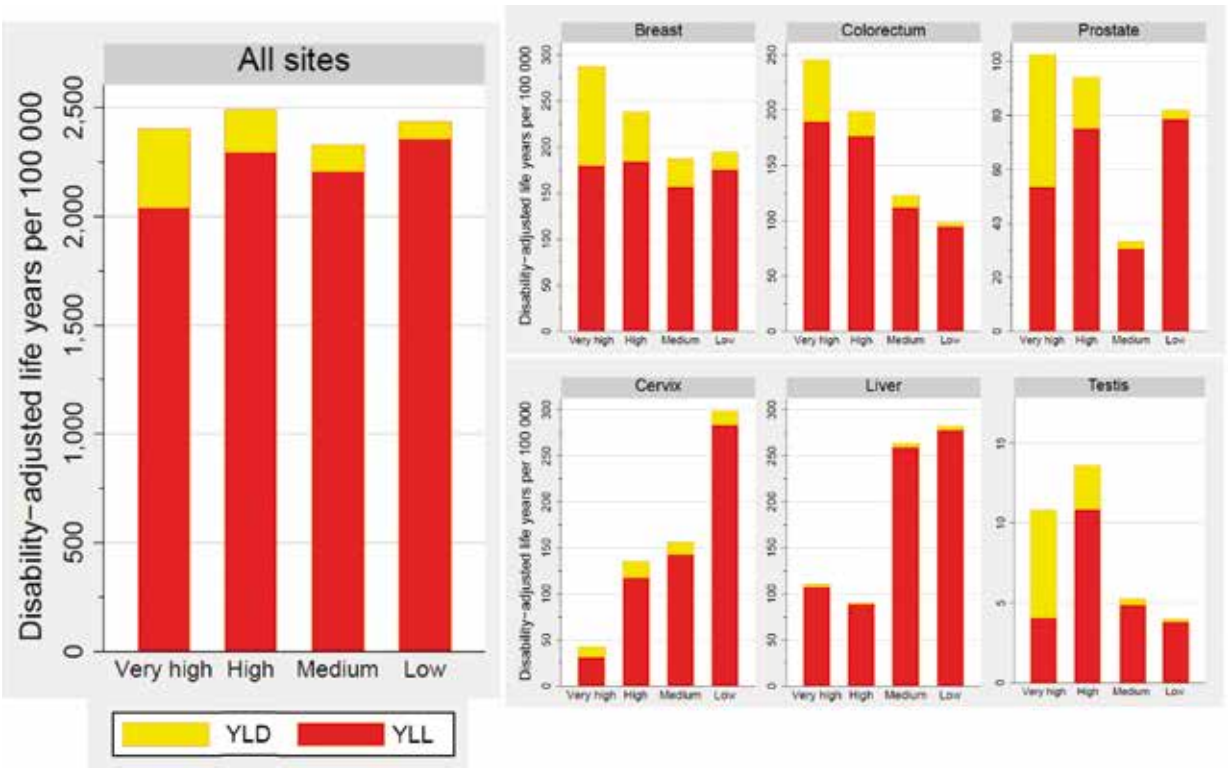
Given that cancer contributes substantially to morbidity and mortality globally, it is important to assess the implications of cancer and the extent of cancer-related sequelae. To determine the impact of fatal and non-fatal cancer outcomes, disability-adjusted life years (DALYs) are often used as a measure. DALYs combine the degree of illness and disability in patients and long-term survivors (years of healthy life lost due to disability [YLD]) and the burden of cancer mortality (years of life lost due to premature mortality [YLL]), to quantify the number of years of healthy life lost.

Soerjomataram et al. assessed DALYs globally by the four-tier HDI and found the total DALYs to be similar across HDI tiers (Fig. 1.3.8) [23]. However, the contribution of YLL and YLD to the total DALYs varied substantially by HDI tier: in general, the number of years lived with disability (YLD) was greater in countries with higher HDI levels, and the burden of premature mortality (YLL) was greater in countries with lower HDI levels.

The relationship between DALYs and HDI level varied depending on the cancer site being assessed. In particular, for cancer types more commonly attributable to obesity (e.g. breast cancer and colorectal cancer), DALYs were greater in countries with higher HDI levels, whereas for infection-related cancer types (e.g. cervical cancer and liver cancer), DALYs were greater in countries with lower HDI levels [23]. YLL was consistently the main contributor to DALYs across HDI tiers, but the fraction of DALYs due to YLL in the lowest HDI tier was generally the same as or larger than the fraction in the highest HDI tier, reflecting the poorer average prognosis of patients with cancer in low-resource settings.

In another study, the impact of cancer on changes (increases or decreases) in life expectancy was

Fig. 1.3.8. Age-adjusted disability-adjusted life years (DALYs) per 100 000 population by Human Development Index (HDI) tier for all cancer sites combined and selected cancer sites. YLD, years of healthy life lost due to disability; YLL, years of life lost due to premature mortality.



assessed worldwide for the period 1981–2010 [24]. The findings suggested that countries with very high HDI had larger gains in life expectancy compared with countries with medium or high HDI. In particular, declines in cancer mortality were responsible for the increases in life expectancy for individuals aged 40–84 years by 0.8 years for men and 0.5 years for women in countries with very high HDI, whereas the corresponding gains were less in countries with medium or high HDI: 0.2 years for both men and women [24].

Similar inequalities in life expectancy gains were observed for the hypothetical situation of eliminating all deaths from cancer. The resulting increase in life expectancy for individuals aged 40–84 years for the period 2006–2010 was 2.5 years for men and 1.9 years for women in countries with very high HDI, whereas the increases were only modest in countries with medium or high HDI: 1.6 years for men and 1.5 years for women [24]. These results provide evidence of disproportionate improvements in cancer outcomes according to HDI level, leading to widening gaps in life expectancy between more-developed and less-developed countries.

Evidence of diversity within HDI levels

Evidently, the marked differences in the scale and profile of cancer incidence and mortality by HDI level result from a myriad of factors, which will dictate whether, in the longer term, gains in societal and economic development will reduce the widening gap between countries with low versus very high HDI in the risk of developing or dying from cancers that are preventable or treatable. Some of the determinants are systems-related, including the extent to which cancer control initiatives are implemented, and others link to risk directly, such as the changing prevalence and distribution of specific reproductive, dietary, and metabolic factors.

Using the four-tier HDI to describe transitions has limitations, given that it de-emphasizes the diversity of cancer occurrence worldwide and the extent to which it varies between and within countries. Although attention has been drawn to broad patterns of cancer incidence according to human development level, there are clear examples of national and regional diversity of cancer occurrence that depart from this model.

For example, although there have been systematic declines in cervical cancer incidence rates in countries with medium or high HDI, the 40-year trends in incidence rates indicate recent increases in countries with high or very high HDI (e.g. Belarus and Japan) (Fig. 1.3.9). Such increases are likely to be due to changes in sexual behaviour that, in the absence of effective screening

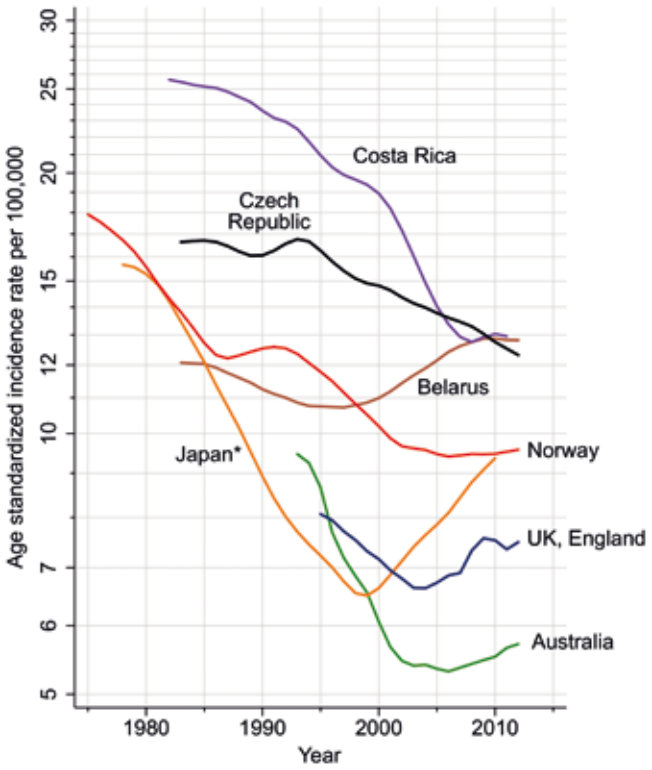
programmes, have led to an increasing risk of persistent infection with high-risk HPV subtypes and subsequent increases in the occurrence of cervical cancer (see Chapter 1.2).

Conclusions

Despite inherent diversity in the cancer burden within a given HDI level, HDI provides a useful framework to map out continuing transitions in cancer incidence, risk factors, and outcomes. In particular, HDI serves as an exploratory tool to monitor shifts in the profile of cancer types, as clearly demonstrated by the displacement of infection-related cancers by cancers associated with behaviours and lifestyles that are more typical of industrialized societies, and with increasing societal and economic development.

Although the cancer incidence burden is currently highest in countries with very high HDI, the predicted increases in the cancer burden will have the greatest impacts on countries with low and medium HDI. Because cancer outcomes are already poorer in countries in transition, appropriate scaling up of resources for effective strategies in primary and secondary prevention in these countries is critical to effectively control the prevalence of adverse lifestyle factors, to ultimately reduce the cancer burden.

Fig. 1.3.9. Age-standardized (World) incidence rates per 100 000 for cervical cancer by year in selected countries with high and very high Human Development Index (HDI) levels, circa 1975–2012. Asterisks indicate regional registries (other registries are national).



References

1. Omran AR (1971). The epidemiologic transition. A theory of the epidemiology of population change. Milbank Mem Fund Q. 49(4):509–38. https://doi.org/10.2307/3349375 PMID:5155251
2. WHO (2016). Global Health Observatory (GHO) data repository. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/gho/en/.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593
4. Seventieth World Health Assembly (2017). Resolution WHA70.12. Cancer prevention and control in the context of an integrated approach. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/275676.
5. WHO (2017). Seventieth World Health Assembly update, 30 May 2017. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/news-room/detail/30-05-2017-seventieth-world-health-assembly-update-30-may-2017.
6. UNDP Human Development Report Office (2015). What is human development? New York (NY), USA: United Nations Development Programme. Available from: http://hdr.undp.org/en/content/what-human-development.
7. UNDP (2015). Human development report 2015: work for human development. New York (NY), USA: United Nations Development Programme. Available from: http://hdr.undp.org/en/content/human-development-report-2015-work-human-development.
8. WHO (2017). Updating Appendix 3 of the WHO global NCD action plan 2013–2020. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/ncds/governance/appendix3-update/en/.
9. IARC (2010). Alcohol consumption and ethyl carbamate. IARC Monogr Eval Carcinog Risks Hum. 96:1–1428. Available from: http://publications.iarc.fr/114 PMID:21735939
10. IARC (2004). Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum. 83:1–1438. Available from: http://publications.iarc.fr/101 PMID:15285078
11. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al.; WHO International Agency for Research on Cancer Monograph Working Group (2009). A review of human carcinogens – Part B: biological agents. Lancet Oncol. 10(4):321–2. https://doi.org/10.1016/S1470-2045(09)70096-8 PMID:19350698
12. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group (2016). Body fatness and cancer – viewpoint of the IARC Working Group. N Engl J Med. 375(8):794–8. https://doi.org/10.1056/NEJMsr1606602 PMID:27557308
13. Armstrong B, Doll R (1975). Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer. 15(4):617–31. https://doi.org/10.1002/ijc.2910150411 PMID:1140864
14. Grant WB (2013). A multicountry ecological study of cancer incidence rates in 2008 with respect to various risk-modifying factors. Nutrients. 6(1):163–89. https://doi.org/10.3390/nu6010163 PMID:24379012
15. Bouvard V, Loomis D, Guyton KZ, Grosse Y, Ghissassi FE, Benbrahim-Tallaa L, et al.; International Agency for Research on Cancer Monograph Working Group (2015). Carcinogenicity of consumption of red and processed meat. Lancet Oncol. 16(16):1599–600. https://doi.org/10.1016/S1470-2045(15)00444-1 PMID:26514947
16. IARC (2012). Radiation. IARC Monogr Eval Carcinog Risks Hum. 100D:1–437. Available from: http://publications.iarc.fr/121 PMID:23189752
17. Fleischer AB Jr, Fleischer SE (2016). Solar radiation and the incidence and mortality of leading invasive cancers in the United States. Dermatoendocrinol. 8(1):e1162366. https://doi.org/10.1080/19381980.2016.1162366 PMID:27195056
18. Hrushesky WJM, Sothern RB, Rietveld WJ, Du Quiton J, Boon ME (2005). Season, sun, sex, and cervical cancer. Cancer Epidemiol Biomarkers Prev. 14(8):1940–7. https://doi.org/10.1158/1055-9965.EPI-04-0940 PMID:16103441
19. Gharibvand L, Shavlik D, Ghamsary M, Beeson WL, Soret S, Knutsen R, et al. (2017). The association between ambient fine particulate air pollution and lung cancer incidence: results from the AHSMOG-2 Study. Environ Health Perspect. 125(3):378–84. https://doi.org/10.1289/EHP124 PMID:27519054
20. Yang W-S, Zhao H, Wang X, Deng Q, Fan W-Y, Wang L (2016). An evidence-based assessment for the association between long-term exposure to outdoor air pollution and the risk of lung cancer. Eur J Cancer Prev. 25(3):163–72. https://doi.org/10.1097/CEJ.0000000000000158 PMID:25757194
21. Arnold M, Pandeya N, Byrnes G, Renehan PAG, Stevens GAG, Ezzati PM, et al. (2015). Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol. 16(1):36–46. https://doi.org/10.1016/S1470-2045(14)71123-4 PMID:25467404
22. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S (2016). Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 4(9):e609–16. https://doi.org/10.1016/S2214-109X(16)30143-7 PMID:27470177
23. Soerjomataram I, Lortet-Tieulent J, Ferlay J, Forman D, Mathers C, Parkin DM, et al. (2012). Estimating and validating disability-adjusted life years at the global level: a methodological framework for cancer. BMC Med Res Methodol. 12(1):125. https://doi.org/10.1186/1471-2288-12-125 PMID:22901001
24. Cao B, Bray F, Beltrán-Sánchez H, Ginsburg O, Soneji S, Soerjomataram I (2017). Benchmarking life expectancy and cancer mortality: global comparison with cardiovascular disease 1981–2010. BMJ. 357:j2765. https://doi.org/10.1136/bmj.j2765 PMID:28637656

Known causes of human cancer by organ site

Agents classified as carcinogenic to humans (Group 1) by the IARC Monographs programme (*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volumes 1–125), listed by organ site with sufficient evidence.

Organ site	Agent
All cancer sites (combined)	2,3,7,8-Tetrachlorodibenzo-*para*-dioxin
Anus	Human immunodeficiency virus type 1 Human papillomavirus type 16
Biliary tract	1,2-Dichloropropane *Clonorchis sinensis* *Opisthorchis viverrini*
Bladder	Aluminium production 4-Aminobiphenyl Arsenic and inorganic arsenic compounds Auramine production Benzidine Chlornaphazine Cyclophosphamide Magenta production 2-Naphthylamine Painter (occupational exposure as) Rubber production industry *Schistosoma haematobium* Tobacco smoking *ortho*-Toluidine X-radiation, γ-radiation
Bone	Plutonium Radium-224 and its decay products Radium-226 and its decay products Radium-228 and its decay products X-radiation, γ-radiation
Brain and central nervous system	X-radiation, γ-radiation
Breast	Alcoholic beverages Diethylstilbestrol Estrogen–progestogen contraceptives Estrogen–progestogen menopausal therapy X-radiation, γ-radiation
Cervix	Diethylstilbestrol (exposure in utero) Estrogen–progestogen contraceptives Human immunodeficiency virus type 1 Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 Tobacco smoking
Colon and rectum	Alcoholic beverages Consumption of processed meat Tobacco smoking X-radiation, γ-radiation

Organ site	Agent
Corpus uteri (endometrium)	Estrogen menopausal therapy Estrogen–progestogen menopausal therapy Tamoxifen
Endothelium (Kaposi sarcoma)	Human immunodeficiency virus type 1 Kaposi sarcoma herpesvirus
Eye	Human immunodeficiency virus type 1 Ultraviolet-emitting tanning devices Ultraviolet radiation from welding
Gall bladder	Thorium-232 and its decay products
Kidney	Tobacco smoking Trichloroethylene X-radiation, γ-radiation
Larynx	Acid mists, strong inorganic Alcoholic beverages Asbestos (all forms) Tobacco smoking
One or more subtypes of leukaemia or lymphoma	Azathioprine Benzene Busulfan 1,3-Butadiene Chlorambucil Cyclophosphamide Cyclosporine Epstein–Barr virus Etoposide with cisplatin and bleomycin Fission products, including strontium-90 Formaldehyde *Helicobacter pylori* Hepatitis C virus Human immunodeficiency virus type 1 Human T-cell lymphotropic virus type 1 Kaposi sarcoma herpesvirus Lindane Melphalan MOPP combined chemotherapy (vincristine, prednisone, nitrogen mustard, and procarbazine mixture) Pentachlorophenol Phosphorus-32, as phosphate Rubber production industry Semustine [1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea, or methyl-CCNU] Thiotepa Thorium-232 and its decay products Tobacco smoking Treosulfan X-radiation, γ-radiation
Liver (angiosarcoma)	Vinyl chloride
Liver (hepatocellular carcinoma)	Aflatoxins Alcoholic beverages Estrogen–progestogen contraceptives Hepatitis B virus Hepatitis C virus Plutonium Thorium-232 and its decay products Tobacco smoking (in smokers and in smokers' children)

Organ site	Agent
Lung	Acheson process (occupational exposures associated with) Aluminium production Arsenic and inorganic arsenic compounds Asbestos (all forms) Beryllium and beryllium compounds Bis(chloromethyl)ether; chloromethyl methyl ether (technical grade) Cadmium and cadmium compounds Chromium(VI) compounds Coal, indoor emissions from household combustion Coal gasification Coal-tar pitch Coke production Diesel engine exhaust Haematite mining (underground) Iron and steel founding MOPP combined chemotherapy (vincristine, prednisone, nitrogen mustard, and procarbazine mixture) Nickel compounds Outdoor air pollution Outdoor air pollution, particulate matter in Painter (occupational exposure as) Plutonium Radon-222 and its decay products Rubber production industry Silica dust, crystalline Soot Sulfur mustard Tobacco smoke, second-hand Tobacco smoking Welding fumes X-radiation, γ-radiation
Mesothelium (pleura and peritoneum)	Asbestos (all forms) Erionite Fluoro-edenite Painter (occupational exposure as)
Multiple sites (unspecified)	Cyclosporine Fission products, including strontium-90 X-radiation, γ-radiation (exposure in utero)
Nasal cavity and paranasal sinus	Isopropyl alcohol manufacture using strong acids Leather dust Nickel compounds Radium-226 and its decay products Radium-228 and its decay products Tobacco smoking Wood dust
Nasopharynx	Epstein–Barr virus Formaldehyde Salted fish, Chinese-style Tobacco smoking Wood dust
Oesophagus	Acetaldehyde associated with consumption of alcoholic beverages Alcoholic beverages Betel quid with tobacco Betel quid without tobacco Smokeless tobacco Tobacco smoking X-radiation, γ-radiation

Organ site	Agent
Oral cavity	Alcoholic beverages Betel quid with tobacco Betel quid without tobacco Human papillomavirus type 16 Smokeless tobacco Tobacco smoking
Ovary	Asbestos (all forms) Estrogen menopausal therapy Tobacco smoking
Pancreas	Smokeless tobacco Tobacco smoking
Penis	Human papillomavirus type 16
Pharynx (oropharynx, hypopharynx, and/or not otherwise specified)	Alcoholic beverages Betel quid with tobacco Human papillomavirus type 16 Tobacco smoking
Renal pelvis and ureter	Aristolochic acid, plants containing Phenacetin Phenacetin, analgesic mixtures containing Tobacco smoking
Salivary gland	X-radiation, γ-radiation
Skin (melanoma)	Polychlorinated biphenyls Solar radiation Ultraviolet-emitting tanning devices
Skin (other malignant neoplasms)	Arsenic and inorganic arsenic compounds Azathioprine Coal-tar distillation Coal-tar pitch Cyclosporine Methoxsalen plus ultraviolet A Mineral oils, untreated or mildly treated Shale oils Solar radiation Soot X-radiation, γ-radiation
Stomach	*Helicobacter pylori* Rubber production industry Tobacco smoking X-radiation, γ-radiation
Thyroid	Radioiodines, including iodine-131 (exposure during childhood and adolescence) X-radiation, γ-radiation
Tonsil	Human papillomavirus type 16
Upper aerodigestive tract	Acetaldehyde associated with consumption of alcoholic beverages
Vagina	Diethylstilbestrol (exposure in utero) Human papillomavirus type 16
Vulva	Human papillomavirus type 16

Group 1 agents with less than *sufficient* evidence in humans: 2,3,4,7,8-pentachlorodibenzofuran; polychlorinated biphenyls, dioxin-like, with a Toxicity Equivalency Factor (TEF) according to the World Health Organization (WHO); 4,4′-methylenebis(2-chloroaniline) (MOCA); α- and β-particle emitters; areca nut; aristolochic acid; benzidine, dyes metabolized to; benzo[*a*]pyrene; ethanol in alcoholic beverages; ethylene oxide; etoposide; ionizing radiation (all types); neutron radiation; *N*′-nitrosonornicotine (NNN) and 4-(*N*-nitroso-methylamino)-1-(3-pyridyl)-1-butanone (NNK); ultraviolet radiation.

2 Causes of cancer, including hazardous circumstances

At the community or national level, causes are established for a proportion of all cancers – a proportion that differs markedly between tumour types. Tobacco smoking was once prevalent mostly among men in high-income countries but is now much more prevalent, involving women in many countries, and tobacco use is highest in Asia, Africa, and South America. Cancers attributable to unhealthy diet and lack of exercise are often correlated with the increasing prevalence of overweight and obesity worldwide. Previously, the cancer types most common in low-income countries were those caused by human papillomavirus (HPV) infection or mediated by chronic inflammatory diseases caused by infectious agents. These patterns are changing, particularly with industrialization. The highest exposures are often those of workers near industrial sources of pollution. Emissions from factories and vehicles contribute to air pollution, a cause of lung cancer. Identifying the causes of cancer indicates a potential means of prevention.

2.1 Tobacco products
Massive and still growing causes of cancer worldwide

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SUMMARY

- Tobacco products have been studied for decades and are well known to cause cancer. Nevertheless, with larger epidemiological studies, longer follow-up, and better control for confounding, the number of types or subtypes of cancer known to be caused by tobacco products continues to increase.
- Worldwide, most tobacco is now consumed in low- and middle-income countries in the form of smoked products, chiefly as manufactured or hand-rolled cigarettes.
- Both smoked and smokeless products are widely used in South-East Asia.
- In North America and Europe, and increasingly elsewhere, non-cigarette products such as electronic nicotine delivery systems, heated tobacco products, water pipes, and cigars have become popular, particularly among young people.
- Progress in tobacco control is notable but far from sufficient. Worldwide, an estimated 2.4 million tobacco-related cancer deaths occur per year.
- Without dramatic declines in use, tobacco products are projected to cause 1 billion deaths worldwide this century, mostly in low- and middle-income countries.
- The introduction of electronic nicotine delivery systems, heated tobacco products, and other emerging nicotine and tobacco products challenges regulatory approaches to tobacco control. Their long-term impact is unknown and is, rightly, the subject of considerable debate.

Tobacco comes in many forms, and tobacco use has long been established to cause multiple types of cancer and other major noncommunicable diseases. Cigarette smoking causes at least 20 different types of cancer [1,2]. An estimated 1.3 billion people use tobacco products worldwide [3]. Together, cigarettes and other tobacco products are estimated to cause 2.4 million tobacco-related cancer deaths worldwide per year [4]. Moreover, tobacco use causes even more deaths from vascular conditions (3.1 million deaths per year) and respiratory conditions (606 000 deaths per year from respiratory infections and tuberculosis; 1.5 million deaths per year from chronic respiratory disease) than from cancer [4].

Previous comprehensive reviews have described the carcinogenicity of smoked and smokeless tobacco products [1,2], their impact on non-malignant diseases, the evolution of the tobacco epidemic, and the harmful effects of second-hand smoke [2,5]. This chapter focuses on selected recent developments that affect cancer risk and tobacco control.

Tobacco products

Commonly used tobacco products are listed in Box 2.1.1.

Electronic nicotine delivery systems (ENDS), of which e-cigarettes are the most common, are not considered as tobacco products by WHO. Some countries classify and regulate these products as tobacco products. According to the *Report of the Advisory Group to Recommend Priorities for the IARC Monographs during 2020–2024*, no data are available so far pertaining to the carcinogenicity of ENDS in humans. The Advisory Group assigned ENDS a high priority for evaluation by the IARC Monographs programme within 5 years.

Smoked/combustible products

Most of the tobacco consumed worldwide is in the form of smoked products, chiefly as manufactured

Fig. 2.1.1. A woman in Rajasthan, India, smoking a bidi.

Box 2.1.1. Commonly used tobacco products.

Smoked/combustible products

- Cigarettes (manufactured and hand-rolled)

  The most commonly used tobacco product worldwide
- Cigars (large and small)

  Tobacco that is wrapped in tobacco leaf
- Pipes

  The oldest tobacco product, in which tobacco is placed in a bowl and smoked through a stem
- Bidis

  Hand-rolled tobacco made of shredded tobacco leaves wrapped in dried temburni leaf and tied with a string
- Kreteks

  Clove- and coca-flavoured small cigarettes, used particularly in Indonesia
- Water pipes (hookah, shisha)

  Users draw smoke through a water chamber by use of a long hose

Other nicotine and tobacco products

- Smokeless tobacco

  Used in many forms worldwide (see Fig. 2.1.2)
- E-cigarettes and other electronic nicotine delivery systems (ENDS)

  An emerging product in which a nicotine-containing solution is heated to produce an aerosol
- Heated tobacco products

  An emerging product in which tobacco sticks are heated to produce an aerosol

or hand-rolled cigarettes but also as cigars, pipes, water pipes, kreteks, and bidis [6,7]. In high-income countries, manufactured cigarettes displaced other forms of tobacco by the mid-20th century. Since then, products that were not previously of concern, such as ENDS [8] and water pipes [9,10], have been introduced or more intensively marketed in high-income countries, and manufactured cigarettes have gained market share in low- and middle-income countries.

Cigars, which consist of tobacco that is wrapped in tobacco leaf, are available in many shapes and sizes, including small, filtered cigars, which often appear indistinguishable from cigarettes. Bidis, which are traditionally smoked in India and Pakistan, are a form of hand-rolled tobacco made of shredded tobacco leaves wrapped in dried temburni leaf and tied with a string. Kreteks are clove- and coca-flavoured small cigarettes, which are manufactured and used particularly in Indonesia. Both bidis and kreteks are now marketed worldwide.

Water pipes (also called hookah or shisha) were traditionally smoked in the Middle East but are now also marketed worldwide [10]. Users draw smoke through a water chamber by use of a long hose. The introduction of mu'assel (a molasses-soaked tobacco mix) and fruit flavourings in the early 1990s increased the appeal of water pipe smoking to younger people [10].

Cigars, pipes, and smokeless tobacco have all been determined to cause cancer [1,2]. Tobacco products other than cigarettes have

FUNDAMENTALS

- Tobacco use is the leading preventable cause of cancer worldwide. Cigarettes are the predominant form and have been determined to cause at least 20 different types or subtypes of cancer. Other forms of tobacco use are of growing importance worldwide, but they have been less studied than cigarettes.
- Although the prevalence of smoking has decreased in most regions of the world, an estimated 1.3 billion people use tobacco products worldwide, and an estimated 2.4 million tobacco-related cancer deaths occur per year.
- Reductions in smoking prevalence in high-income countries have substantially reduced the incidence rates of lung cancer and laryngeal cancer in men and younger women.
- However, about 80% of the world's smokers live in low- and middle-income countries, where the disease burden from tobacco use continues to increase as a result of population growth and the ageing of long-term, continuing smokers. Even if the age-specific death rates from tobacco-attributable cancers remain the same, the number of people affected by these cancers will increase dramatically because of these demographic changes.
- The WHO Framework Convention on Tobacco Control is a public health treaty that has been signed by 181 countries to protect their populations from the dangers of tobacco use. WHO Member States have also pledged to meet the target of a 30% relative reduction in the prevalence of tobacco use by 2025.
- Without accelerated progress, tobacco products are projected to cause 1 billion deaths this century, many from cancer.

Fig. 2.1.2. Examples of smokeless tobacco products, by country or region: South-East Asia: kiwam, zarda, gutka; USA: moist snuff, dry snuff, moist snuff (caffeinated), plug, twist tobaccos, dissolvables (orbs, strips, sticks, tobacco-coated toothpicks); Sweden: snus (pouch); Venezuela: chimó; Uzbekistan: nasway; Sudan: toombak; India: red toothpowder, mawa; Saudi Arabia: shammah; Brazil: rapé.

generally been much less studied than cigarettes, despite their growing importance.

Other nicotine and tobacco products

Other tobacco products also come in many forms (Fig. 2.1.2) [11]. Some traditional forms of smokeless tobacco include only tobacco, whereas others include flavours and other constituents. In South-East Asia, smokeless tobacco is widely used with areca nut, lime, wood, and ash. Another form of smokeless tobacco, naswar, is commonly used in central Asia. Naswar is frequently prepared by mixing lime and ground, powdered tobacco.

During the past decade, novel and emerging nicotine and tobacco products have rapidly transformed the tobacco market in Europe, North America, and elsewhere. ENDS heat a solution of nicotine without producing smoke [8]. ENDS were first sold by a pharmacist in China in 2003 and have been marketed in the USA since 2007. Although ENDS are supposedly marketed to adults, they often include flavours (such as strawberry and gummy bear) that are attractive to younger people. ENDS products are diverse and are rapidly evolving. For example, the Juul e-cigarette is a highly engineered product that delivers a high dose of nicotine and is a small, discreet device. Its use was uncommon a few years ago, but as a result of marketing campaigns through social media [12] and the absence of regulatory policies or underregulation, it now makes up about half of the ENDS market in the USA (Fig. 2.1.3). Heated tobacco products, which heat tobacco [13] rather than a nicotine solution, are available in selected countries [14].

The eventual impact of e-cigarettes and other putative harm-reduction products on health is not yet known, but there are substantial concerns. Although these products generally produce lower exposures to toxic and carcinogenic compounds than combusted tobacco does, users of these products may become addicted to nicotine and transition to more traditional forms of tobacco use, including cigarettes and other combustible products [15–18].

Biological impact of tobacco products

Cigarettes

Cigarette smoke contains more than 8000 compounds, including more than 70 carcinogens [19]. Certain carcinogens are thought to be particularly important, including tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, and aromatic amines. The molecular mechanisms linking cigarettes to cancer have been comprehensively reviewed [2,19,20]. Nevertheless, knowledge about the physiological and pathogenic consequences of cigarette smoking continues to expand (see Chapter 3.11). For example, over the past 5 years cigarette smoking has been linked to altered patterns of circulating inflammatory markers [21], altered DNA methylation patterns [22], altered airway gene expression patterns [23], an altered oral microbiome [24], specific mutational signatures [25], and Y chromosome loss [26]. It is plausible that non-cigarette tobacco products also cause many of these changes, but fewer molecular studies on the biological effects of these products have been published.

Other combustible tobacco products

Smokers of other combustible products, including bidis, cigars, and

pipes, are exposed to many, if not all, of the carcinogens found in cigarette smoke [27]. Although water pipe smoking is less studied, it also generates high levels of carcinogens and toxicants that are not removed by passage through water [28]. Water pipe smoking requires users to breathe very deeply and, by doing so, replace much of the air in the lungs with smoke, in contrast to the smaller puffs of cigarette smoke [9]. The charcoal used to ignite the tobacco in water pipe smoking seems to expose users to even higher levels of carbon monoxide and benzene compared with cigarette smokers [28].

Smokeless tobacco

Smokeless tobacco is available in many forms throughout the world [11]. The levels of specific carcinogens vary across the different products, but smokeless tobacco has been shown to contain at least 30 carcinogens [11] and to release high levels of tobacco-specific nitrosamines.

ENDS

Unlike other products described here, ENDS have emerged only during the past decade [8]. Typical ENDS products include nicotine, glycerine, propylene glycol, and flavours in a liquid solution, which is then vaporized into an aerosol. Laboratory studies indicate that ENDS devices generally heat to a lower temperature and have lower levels of most carcinogens than combusted cigarettes [29]. ENDS products also contain numerous different flavourings, such as fruit or caramel.

Heated tobacco products

Heated tobacco products use a similar ignition system but use tobacco instead of a liquid [13,14]. Because of the rapidly changing nature of these products [12–14], it is important that their composition and carcinogen content be monitored regularly by researchers independent of the industry.

Cancer types caused by tobacco use

Cigarettes

With larger epidemiological studies, longer follow-up, and better control for confounding, the number of sites or subsites of cancer known to be caused by cigarette smoking continues to increase. The IARC Monographs [1] and the United States Surgeon General [2] designate causal relationships with at least 20 types of cancer, including cancers of the lung, oral cavity, nasal cavity and accessory sinuses, nasopharynx, oropharynx, hypopharynx, larynx, oesophagus (adenocarcinoma and squamous cell carcinoma), stomach, pancreas, colorectum, liver, kidney (body and pelvis), ureter, bladder, cervix, and ovary (mucinous), and acute myeloid leukaemia (Table 2.1.1). This list is conservative, because it does not include breast cancer or advanced prostate cancer, two sites for which the evidence for causality has been

Fig. 2.1.3. Sales (in millions of United States dollars) of e-cigarettes in Nielsen-tracked retail channels in the USA in 2011–2017, by brand.

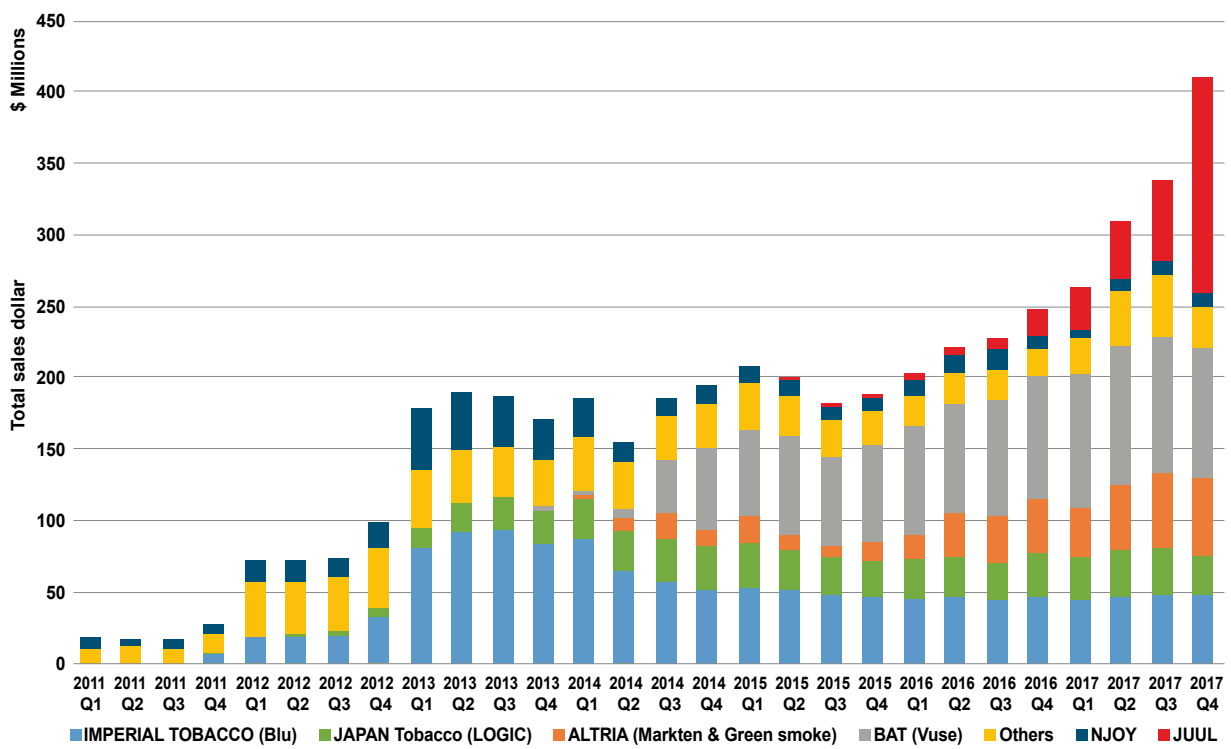


Table 2.1.1. Types of cancer caused by cigarette smoking

Cancer site or type	Year formally classified by the United States Surgeon General	Year formally classified by the IARC Monographs	Relative risk for current versus never smoking	
			Men	Women
Lip, oral cavity, pharynx	1964/1971[a]	1986	5.7	5.6
Oesophagus	1982	1986	3.9	5.1
Stomach	2004	2004	1.9	1.7
Colorectum	2014	2012	1.4	1.6
Liver	2014	2004	2.3	1.8
Pancreas	1982	1986	1.6	1.9
Larynx	1964	1986	13.9	103.8
Trachea, lung, bronchus	1964/1968[b]	1986	25.3	22.9
Cervix	2004	2004	–	3.5
Bladder	1979	1986	3.9	3.9
Kidney, other urinary tract	1982	2004	1.8	1.2
Acute myeloid leukaemia	2004	2004	1.9	1.1

[a] Lip cancer was classified as causal in 1964, and other oropharyngeal cancers in 1971.

[b] Lung cancer was classified as causal in men in 1964 and in women in 1968.

labelled suggestive but not conclusive. Recent meta-analyses and pooled analyses have supported possible associations with these sites [30,31].

Non-cigarette tobacco products and second-hand smoke

The IARC Monographs have also concluded that cigar smoking and pipe smoking are strongly related to cancers of the lung and upper aerodigestive tract, including the oral cavity, oropharynx, hypopharynx, larynx, and oesophagus [20]. Smokeless tobacco has been determined to be causally related to cancers of the oesophagus, oral cavity, and pancreas [1]. Exposure to second-hand smoke has been determined to cause lung cancer [1,2]; associations with other cancer types are less clear.

Surveillance of tobacco use and tobacco control

Population-based surveillance of tobacco use and tobacco control measures has expanded greatly in the past decade [32]. When the WHO Framework Convention on Tobacco Control [33] first entered into force in 2005, only a few predominantly high-income countries systematically collected data on the prevalence and determinants of tobacco use. These data were largely limited to smoked tobacco products. Since then, population-based surveillance of tobacco use and tobacco control has become a critical component of global tobacco control [34]. Several multirisk-factor health surveys provide nationally representative data on schoolchildren and adults from an increasing number of countries; examples are the WHO STEPwise approach to Surveillance (STEPS), the Global Youth Tobacco Survey (launched in 1999), and the Global Adult Tobacco Survey (begun in 2007) [32].

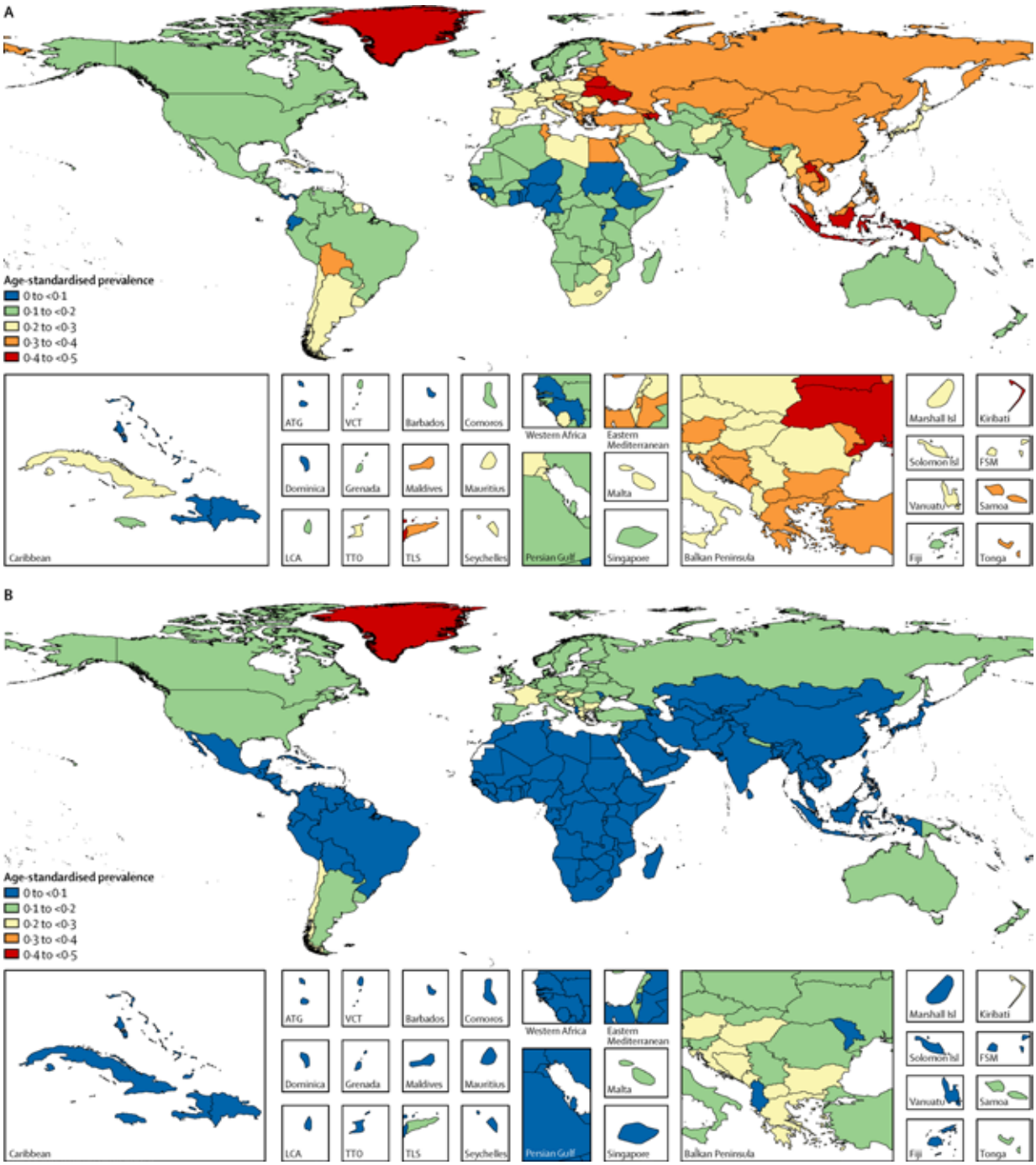
Six evidence-based measures in line with the WHO Framework Convention on Tobacco Control have been identified or defined in the WHO MPOWER package for tobacco control [35]. These are monitoring tobacco use and prevention policies (M), protecting people from tobacco smoke (P), offering help to quit tobacco use (O), warning people about the harms of tobacco (W), enforcing bans on tobacco advertising, promotion, and sponsorship (E), and raising taxes on tobacco (R). Since 2007, the number of people protected by at least one best-practice measure has more than quadrupled, from 1 billion to 5 billion people (nearly two thirds of the world's population) [34].

Patterns and trends in tobacco use

Descriptive studies of tobacco use have often grouped all smoked tobacco products together and focused on daily smoking, the most common pattern [32,36,37]. In 2015, an estimated 1.3 billion people worldwide used tobacco products [3] and 1.1 billion people smoked, of which more than 80% smoked daily [7]. The prevalence of smoking is higher in men than in women. About 25% of men in the world are daily smokers, compared with about 5% of women [37]. Geographical patterns of smoking prevalence also differ by sex (Fig. 2.1.4). Among men, the prevalence of daily smoking is highest in central and eastern Europe and South-East Asia; among women, the prevalence is highest in selected countries in eastern and western Europe (see the interactive maps at the WHO Global Health Observatory; http://gamapserver.who.int/gho/interactive_charts/tobacco/use/atlas.html).

Overall, the age-standardized prevalence of daily smoking decreased from 1990 to 2015 in both men and women. An analysis of 195 countries and territories by the

Fig. 2.1.4. Age-standardized prevalence of daily smoking for men (A) and women (B), in 2015.



Global Burden of Disease collaboration estimated reductions of 28% in men and 34% in women since 1990 [37]. Similar reductions in smoking prevalence have been reported in other studies [32,36].

From 2005 to 2015, 53 of 195 countries and territories in the Global Burden of Disease project had significant declines in the prevalence of smoking in men, and 32 had significant declines in the prevalence in women [37]. The reductions were largest in high-income countries and in Latin America [37]. Of the 10 countries with the greatest number of smokers in 2015, the largest reduction in smoking prevalence occurred in Brazil, where the prevalence dropped by more than half between 1990 and 2015 [37]. Pakistan, Panama, and India are also notable for implementing numerous tobacco control policies during the period

from 2005 to 2015 and having large declines in daily smoking prevalence since 2005 [37].

Despite this encouraging progress, the prevalence of tobacco use remains high worldwide, and progress has been uneven. Indonesia has the highest recorded prevalence of smoking in men (46.7%) [37]. It is also the only country in South-East Asia that has not signed the WHO Framework Convention on Tobacco Control. Four countries had significant increases in smoking prevalence from 2005 to 2015: Congo and Azerbaijan for men, and Kuwait and Timor-Leste for women [37].

There is concern about the future impact of tobacco use in Africa. Although the prevalence of tobacco smoking is currently relatively low in most African countries, the impact of tobacco use is projected to rise as a result of population growth, increasing affluence, relatively weak tobacco control measures, and greater tobacco marketing [37]. Only one region, the Americas, is predicted to reach the target of a 30% reduction in tobacco use in men and women by 2025 [32].

Analyses of daily tobacco smoking also have limitations. Combustible products other than cigarettes (pipes, cigars, bidis, etc.) predominate in some countries [38], and nearly 20% of smokers worldwide report occasional (non-daily) smoking [7], a pattern of exposure to tobacco that itself appears to cause disease [39]. The need for surveillance of dual use and use of novel and emerging nicotine and tobacco products (especially ENDS) is discussed below.

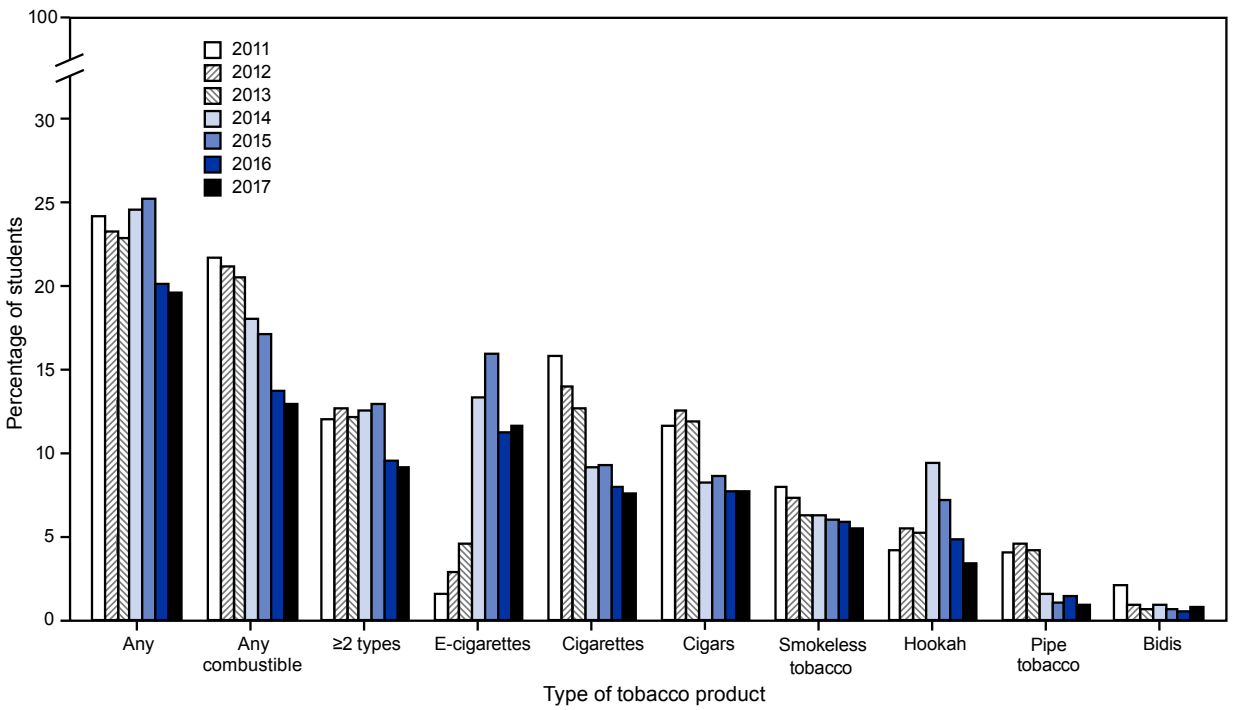
Smoking prevalence among young people

Current trends in smoking prevalence among young people are encouraging. In the Global Burden of Disease analysis, the prevalence of daily smoking among those aged 15–19 years decreased between 1990 and 2015, from 16.1% to 10.6% in males and from 4.8% to 3.0% in females [37]. The prevalence of cigarette smoking among young people is at historically low levels in the USA. According to the National Youth Tobacco Survey, the prevalence of any tobacco use in high school students fell from 24.2% in 2011 to 19.6% in 2017, and the prevalence of cigarette smoking fell from 15.8% in 2011 to 7.6% in 2017 (Fig. 2.1.5) [40]. However, the prevalence of smoking in adolescents remains high in other countries, including in Europe. In 2015, 22 countries had a smoking prevalence above 15% in young women, and 24 countries had a smoking prevalence above 20% in young men. Most of the countries with a high prevalence in young women are in Europe, whereas the countries with a high prevalence in young men are in many world regions [37].

Number of smokers

Although there have been clear declines in smoking prevalence worldwide, population growth has meant that trends in the absolute number of smokers worldwide are less clear. Conclusions about whether the number of smokers is increasing, decreasing, or staying the same

Fig. 2.1.5. Estimated percentage of high school students who currently use any tobacco product, any combustible tobacco product, two or more tobacco products, and selected tobacco products, from the National Youth Tobacco Survey, USA, in 2011–2017.



worldwide have differed in different reports. A Global Burden of Disease analysis published in 2014 concluded that despite a decline in smoking prevalence from 1980 to 2012, the number of daily smokers increased from 721 million to 967 million [36]. In contrast, the WHO global report on the prevalence of tobacco use in 2000–2025, which included both daily and occasional smoking, concluded that there was a modest decrease in the number of smokers, from 1.14 billion in 2000 to 1.11 billion in 2015 [32].

Tobacco smoking in low- and middle-income countries

About 80% of the world's smokers live in low- and middle-income countries. In addition, 64% of the world's daily smokers live in only 10 countries [37], and more than 50% of the world's male smokers live in three countries: China, India, and Indonesia [37]. Despite decreases in smoking prevalence, the disease burden from tobacco use continues to increase rapidly in low- and middle-income countries, because of the size and the growth of populations and the ageing of long-term, continuing smokers [7].

Involuntary smoking

Involuntary smoking is the inhalation of second-hand smoke by non-smokers. In most countries, an estimated 15–50% of the population is exposed to second-hand smoke (also called "environmental" tobacco smoke); in some countries, exposure to second-hand smoke affects as much as 70% of the population [7]. In China alone, an estimated 717 million people are exposed to second-hand smoke at home [6]. Exposure to second-hand smoke is estimated to cause more than 1.2 million deaths per year, of which 114 000 are deaths from cancer [4].

Use of smokeless tobacco products

WHO has estimated that worldwide there are more than 367 million smokeless tobacco users aged 15 years or older [32]. Use of smokeless tobacco is more common in men (237 million) than in women (129 million). Use of smokeless tobacco was estimated to cause more than 101 000 cancer deaths per year [41]. The Global Burden of Disease project published a comparable estimate, of 76 000 cancer deaths per year from use of smokeless tobacco [4]. Use of smokeless tobacco is common in every WHO region, each of which has at least 8 million users of smokeless tobacco [32]. An estimated 82% of users (301 million users) are in the WHO South-East Asia Region. The disease burden from smokeless tobacco use is substantial in that region. For example, it has been estimated that 87% of cancer deaths from smokeless tobacco occur in the South-East Asia Region [41]. Oral cancer is of particular concern in that region, reflecting the high prevalence of use of both smokeless tobacco and smoked tobacco (cigarettes and bidis) [42].

In much of the world, children use smokeless tobacco. In every WHO region except the European Region, there are at least 1 million young people aged 13–15 years who use smokeless tobacco [32]. The highest prevalence in this age group is in the South-East Asia Region (7.3% overall; 9.5% in boys and 4.8% in girls), which accounts for almost 60% of smokeless tobacco use in this age group worldwide [32].

Use of other nicotine and tobacco products

Longitudinal information on the use of other nicotine and tobacco products is still limited. The available data indicate that water pipe smoking is more common than cigarette smoking in many parts of the Middle East [10]; the highest reported prevalence (almost 40%) is in adolescent boys in Lebanon. Water pipe use has also become commonplace among young people worldwide. In the Eurobarometer survey, the prevalence of current water pipe smoking was 5% or higher in 11 European countries; the highest reported prevalence (11.5%) was in Latvia [38].

Use of ENDS products has increased rapidly over the past decade in many countries, although surveillance data are largely restricted to high-income countries. In the USA, ENDS products have become more popular than cigarettes among high school students aged 14–18 years: in 2017, 11.7% used ENDS and 7.6% used cigarettes (Fig. 2.1.5) [40]. It remains to be seen whether this pattern will emerge in other countries. Rapid

Fig. 2.1.6. Electronic nicotine delivery systems (ENDS) and the practice of vaping have emerged only during the past decade.

changes in the design, flavours, usage patterns, and names of these products challenge surveillance efforts, particularly among young people [8,12]. To date, a range of regulatory approaches to these products have been used in different countries [43].

Dual use and poly-use

A growing proportion of tobacco users worldwide use more than one product. For example, in Bangladesh, 22.5% of men who use tobacco use both cigarettes and smokeless tobacco. In India, 19.4% of men who use tobacco are dual users [6]. In a 2014 study including data from the 2008 to 2012 Global Adult Tobacco Survey and the Eurobarometer survey, at least 20% of current smokers also used another tobacco product in 28 of the 44 countries examined [38]. Among high school students in the USA, dual use (9.2%) is now more common than the use of cigarettes alone (7.6%) (Fig. 2.1.5) [40]. Among adults in the USA, most ENDS users also use cigarettes [44]. Determining the long-term implications of these behavioural changes on the burden of cancer and other diseases is a critical research and public health question.

Impact of continued smoking on cancer burden and smoking-attributable disease

Without dramatic global reductions in cigarette use, the burden of tobacco-related cancer and other diseases will be substantially higher in the future than it is now. In the USA and other high-income countries, declines in smoking prevalence have resulted in substantial decreases in incidence rates of lung cancer and laryngeal cancer [2,45]. Elsewhere, and especially in low- and middle-income countries, the cancer burden from smoking continues to increase as a result of population growth and the ageing of smokers [37]. The Global Burden of Disease collaboration has estimated that the number of cancer deaths caused by tobacco smoking increased from 1.5 million per year in 1990 to 2.4 million per year in 2017 [4]. Nevertheless, effective tobacco control could potentially prevent hundreds of millions of premature deaths [40].

As mentioned above, the ultimate impact of the shift towards ENDS and other emerging products and dual use on cancer remains to be determined. Laboratory studies can currently measure the carcinogen yield of novel products and biomarkers of exposure among users [29] but cannot yet determine the potential long-term effects of these products on cancer risk or on the use of more traditional tobacco products. For example, cigarette smokers may become dual users of cigarettes and ENDS rather than quitting smoking. Young people who become addicted to nicotine via ENDS may switch to cigarettes. The United States Food and Drug Administration Center for Tobacco Products is currently considering reducing the nicotine content in cigarettes, to encourage users to quit cigarette smoking [46]. Such a policy would be expected to increase cessation of cigarette smoking but would also be likely to encourage users to switch to other products. Global surveillance of the entire range of tobacco products is critical for understanding the future cancer and public health impact of emerging tobacco products.

Current and potential impact of tobacco control

Tobacco control policies have been demonstrated to save lives. It has been estimated that tobacco control resulted in 8 million fewer premature deaths in 1964–2012 in the USA [45]. Similarly, an estimated 22 million deaths were prevented in 2007–2014 in 88 countries that adopted at least one highest-level MPOWER policy [47]. Nevertheless, MPOWER and other tobacco control interventions are underutilized [7]. Accelerated implementation of tobacco control measures would have an enormous public health impact. For example, a 50% increase in cigarette prices in 13 middle-income countries in Asia and Latin America with a total of 2 billion men (500 million male smokers) in their populations would result in 450 million years of life gained from smoking cessation [48], with the largest gains among lower-income individuals.

Conclusions

Tobacco products are well-established causes of multiple types of cancer. Tobacco control is, rightly, a poster child for public health interventions that use policy measures and education to motivate behaviour change. However, despite progress, the global health and economic burden of tobacco use remains enormous and is increasingly borne by low- and middle-income countries. Unfortunately, most countries are not on track to achieve the global target of a 30% reduction in the prevalence of tobacco use by 2025, agreed to by WHO Member States.

Furthermore, emerging tobacco products challenge regulatory approaches to tobacco control and may undermine progress. Future research is needed to determine the disease risks of emerging tobacco products and to understand their effects on the use of established, and very harmful, traditional products. Continued tobacco and cancer surveillance will also be needed to track the impact of public health interventions and to chart cancer rates.

Without dramatic reductions in tobacco use, the number of cancer deaths per year caused by tobacco, which is already very large, is projected to increase further, reflecting demographic factors and the global maturation of the tobacco epidemic, and to cause 1 billion deaths worldwide this century [49]. Accelerated progress in tobacco control is urgently needed. Monitoring of trends in age-specific incidence or death rates from lung cancer at younger ages can be especially informative in this regard.

References

1. IARC (2012). Personal habits and indoor combustions. IARC Monogr Eval Carcinog Risks Hum. 100E:1–575. PMID:23193840. Available from: http://publications.iarc.fr/122.

2. U.S. Department of Health and Human Services (2014). The health consequences of smoking – 50 years of progress: a report of the Surgeon General. Atlanta (GA), USA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. Available from: https://www.ncbi.nlm.nih.gov/books/NBK179276/.

3. WHO (2019). WHO global report on trends in prevalence of tobacco use 2000–2025. 3rd ed. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/publications-detail/who-global-report-on-trends-in-prevalence-of-tobacco-use-2000-2025-third-edition.

4. GBD 2017 Risk Factor Collaborators (2018). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 392(10159):1923–94. https://doi.org/10.1016/S0140-6736(18)32225-6 PMID:30496105

5. U.S. Department of Health and Human Services (2006). The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Atlanta (GA), USA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. Available from: https://www.cdc.gov/tobacco/data_statistics/sgr/2006/index.htm.

6. Asma S, Mackay J, Song SY, Zhao L, Morton J, Palipudi KM, et al. (2015). The GATS atlas: Global Adult Tobacco Survey. Atlanta (GA), USA: CDC Foundation. Available from: http://gatsatlas.org/.

7. U.S. National Cancer Institute and World Health Organization (2016). Patterns of tobacco use, exposure, and health consequences. In: The economics of tobacco and tobacco control. NCI Tobacco Control Monograph 21. NIH Publication No. 16-CA-8029A. Bethesda (MD), USA: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; and Geneva, Switzerland: World Health Organization; pp. 23–70. Available from: https://cancercontrol.cancer.gov/brp/tcrb/monographs/21/index.html.

8. Grana R, Benowitz N, Glantz SA (2014). E-cigarettes: a scientific review. Circulation. 129(19):1972–86. https://doi.org/10.1161/CIRCULATIONAHA.114.007667 PMID:24821826

9. Cobb C, Ward KD, Maziak W, Shihadeh AL, Eissenberg T (2010). Waterpipe tobacco smoking: an emerging health crisis in the United States. Am J Health Behav. 34(3):275–85. https://doi.org/10.5993/AJHB.34.3.3 PMID:20001185

10. Maziak W, Taleb ZB, Bahelah R, Islam F, Jaber R, Auf R, et al. (2015). The global epidemiology of waterpipe smoking. Tob Control. 24(Suppl 1):i3–12. https://doi.org/10.1136/tobaccocontrol-2014-051903 PMID:25298368

11. National Cancer Institute and Centers for Disease Control and Prevention (2014). Smokeless tobacco and public health: a global perspective (NIH Publication No. 14-7983). Bethesda (MD), USA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, and National Institutes of Health, National Cancer Institute.

12. Huang J, Duan Z, Kwok J, Binns S, Vera LE, Kim Y, et al. (2019). Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. Tob Control. 28(2):146–51. https://doi.org/10.1136/tobaccocontrol-2018-054382 PMID:29853561

13. Simonavicius E, McNeill A, Shahab L, Brose LS (2019). Heat-not-burn tobacco products: a systematic literature review. Tob Control. 28(5):582–94. https://doi.org/10.1136/tobaccocontrol-2018-054419 PMID:30181382

14. Tabuchi T, Gallus S, Shinozaki T, Nakaya T, Kunugita N, Colwell B (2018). Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to second-hand heat-not-burn tobacco aerosol. Tob Control. 27(e1):e25–33. https://doi.org/10.1136/tobaccocontrol-2017-053947 PMID:29248896

15. Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, et al. (2017). Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: a systematic review and meta-analysis. JAMA Pediatr. 171(8):788–97. https://doi.org/10.1001/jamapediatrics.2017.1488 PMID:28654986

16. Stanton CA, Bansal-Travers M, Johnson AL, Sharma E, Katz L, Ambrose BK, et al. (2019). Longitudinal e-cigarette and cigarette use among US youth in the PATH study (2013–2015). J Natl Cancer Inst. 111(10):1088–96. https://doi.org/10.1093/jnci/djz006 PMID:30689915

17. Siddiqui F, Mishu M, Marshall AM, Siddiqi K (2019). E-cigarette use and subsequent smoking in adolescents and young adults: a perspective. Expert Rev Respir Med. 13(5):403–5. http://doi.org/10.1080/17476348.2019.1589371 PMID:30822173

18. Jenssen BP, Walley SC; Section on Tobacco Control (2019). E-cigarettes and similar devices. Pediatrics. 143(2):e20183652. http://doi.org/10.1542/peds.2018-3652 PMID:30835247

19. Hecht SS, Szabo E (2014). Fifty years of tobacco carcinogenesis research: from mechanisms to early detection and prevention of lung cancer. Cancer Prev Res (Phila). 7(1):1–8. https://doi.org/10.1158/1940-6207.CAPR-13-0371 PMID:24403288

20. IARC (2004). Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum. 83:1–1438. PMID:15285078. Available from: http://publications.iarc.fr/101.

21. Shiels MS, Katki HA, Freedman ND, Purdue MP, Wentzensen N, Trabert B, et al. (2014). Cigarette smoking and variations in systemic immune and inflammation markers. J Natl Cancer Inst. 106(11):dju294. https://doi.org/10.1093/jnci/dju294 PMID:25274579

22. Joehanes R, Just AC, Marioni RE, Pilling LC, Reynolds LM, Mandaviya PR, et al. (2016). Epigenetic signatures of cigarette smoking. Circ Cardiovasc Genet. 9(5):436–47. https://doi.org/10.1161/CIRCGENETICS.116.001506 PMID:27651444

23. Billatos E, Faiz A, Gesthalter Y, LeClerc A, Alekseyev YO, Xiao X, et al. (2018). Impact of acute exposure to cigarette smoke on airway gene expression. Physiol Genomics. 50(9):705–13. https://doi.org/10.1152/physiolgenomics.00092.2017 PMID:29932825

24. Wu J, Peters BA, Dominianni C, Zhang Y, Pei Z, Yang L, et al. (2016). Cigarette smoking and the oral microbiome in a large study of American adults. ISME J. 10(10):2435–46. https://doi.org/10.1038/ismej.2016.37 PMID:27015003

25. Alexandrov LB, Ju YS, Haase K, Van Loo P, Martincorena I, Nik-Zainal S, et al. (2016). Mutational signatures associated with tobacco smoking in human cancer. Science. 354(6312):618–22. https://doi.org/10.1126/science.aag0299 PMID:27811275

26. Dumanski JP, Rasi C, Lönn M, Davies H, Ingelsson M, Giedraitis V, et al. (2015). Mutagenesis. Smoking is associated with mosaic loss of chromosome Y. Science. 347(6217):81–3. https://doi.org/10.1126/science.1262092 PMID:25477213

27. Chen J, Kettermann A, Rostron BL, Day HR (2014). Biomarkers of exposure among U.S. cigar smokers: an analysis of 1999-2012 National Health and Nutrition Examination Survey (NHANES) data. Cancer Epidemiol Biomarkers Prev. 23(12):2906–15. https://doi.org/10.1158/1055-9965.EPI-14-0849 PMID:25380733

28. Jacob P 3rd, Abu Raddaha AH, Dempsey D, Havel C, Peng M, Yu L, et al. (2013). Comparison of nicotine and carcinogen exposure with water pipe and cigarette smoking. Cancer Epidemiol Biomarkers Prev. 22(5):765–72. https://doi.org/10.1158/1055-9965.EPI-12-1422 PMID:23462922

29. Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU, et al. (2017). Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: a cross-sectional study. Ann Intern Med. 166(6):390–400. https://doi.org/10.7326/M16-1107 PMID:28166548

30. Gaudet MM, Carter BD, Brinton LA, Falk RT, Gram IT, Luo J, et al. (2017). Pooled analysis of active cigarette smoking and invasive breast cancer risk in 14 cohort studies. Int J Epidemiol. 46(3):881–93. http://doi.org/10.1093/ije/dyw288 PMID:28031315

31. Islami F, Moreira DM, Boffetta P, Freedland SJ (2014). A systematic review and meta-analysis of tobacco use and prostate cancer mortality and incidence in prospective cohort studies. Eur Urol. 66(6):1054–64. https://doi.org/10.1016/j.eururo.2014.08.059 PMID:25242554

32. WHO (2018). WHO global report on trends in prevalence of tobacco smoking 2000–2025. 2nd ed. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/tobacco/publications/surveillance/trends-tobacco-smoking-second-edition/en/.

33. WHO (2003). WHO Framework Convention on Tobacco Control. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/fctc/text_download/en/.

34. WHO (2019). WHO report on the global tobacco epidemic, 2019: offer help to quit tobacco use. Geneva, Switzerland: World Health Organization. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/tobacco/global_report/en/.

35. WHO (2008). MPOWER: a policy package to reverse the tobacco epidemic. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/tobacco/mpower/mpower_english.pdf.

36. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, Thomson B, et al. (2014). Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. JAMA. 311(2):183–92. https://doi.org/10.1001/jama.2013.284692 PMID:24399557

37. GBD 2015 Tobacco Collaborators (2017). Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: a systematic analysis from the Global Burden of Disease Study 2015. Lancet. 389(10082):1885–906. https://doi.org/10.1016/S0140-6736(17)30819-X PMID:28390697

38. Agaku IT, Filippidis FT, Vardavas CI, Odukoya OO, Awopegba AJ, Ayo-Yusuf OA, et al. (2014). Poly-tobacco use among adults in 44 countries during 2008-2012: evidence for an integrative and comprehensive approach in tobacco control. Drug Alcohol Depend. 139:60–70. https://doi.org/10.1016/j.drugalcdep.2014.03.003 PMID:24685560

39. Inoue-Choi M, Liao LM, Reyes-Guzman C, Hartge P, Caporaso N, Freedman ND (2017). Association of long-term, low-intensity smoking with all-cause and cause-specific mortality in the National Institutes of Health-AARP Diet and Health Study. JAMA Intern Med. 177(1):87–95. https://doi.org/10.1001/jamainternmed.2016.7511 PMID:27918784

40. Wang TW, Gentzke A, Sharapova S, Cullen KA, Ambrose BK, Jamal A (2018). Tobacco product use among middle and high school students - United States, 2011-2017. MMWR Morb Mortal Wkly Rep. 67(22):629–33. https://doi.org/10.15585/mmwr.mm6722a3 PMID:29879097

41. Sinha DN, Suliankatchi RA, Gupta PC, Thamarangsi T, Agarwal N, Parascandola M, et al. (2018). Global burden of all-cause and cause-specific mortality due to smokeless tobacco use: systematic review and meta-analysis. Tob Control. 27(1):35–42. https://doi.org/10.1136/tobaccocontrol-2016-053302 PMID:27903956

42. Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F, et al. (2017). The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. CA Cancer J Clin. 67(1):51–64. https://doi.org/10.3322/caac.21384 PMID:28076666

43. Kennedy RD, Awopegba A, De León E, Cohen JE (2017). Global approaches to regulating electronic cigarettes. Tob Control. 26(4):440–5. https://doi.org/10.1136/tobaccocontrol-2016-053179 PMID:27903958

44. CDC (2016). *QuickStats:* Cigarette smoking status* among current adult e-cigarette users,† by age group – National Health Interview Survey,§ United States, 2015. MMWR Morb Mortal Wkly Rep. 65(42):1177. https://doi.org/10.15585/mmwr.mm6542a7 PMID:27787495

45. Holford TR, Meza R, Warner KE, Meernik C, Jeon J, Moolgavkar SH, et al. (2014). Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964-2012. JAMA. 311(2):164–71. https://doi.org/10.1001/jama.2013.285112 PMID:24399555

46. Apelberg BJ, Feirman SP, Salazar E, Corey CG, Ambrose BK, Paredes A, et al. (2018). Potential public health effects of reducing nicotine levels in cigarettes in the United States. N Engl J Med. 378(18):1725–33. https://doi.org/10.1056/NEJMsr1714617 PMID:29543114

47. Levy DT, Yuan Z, Luo Y, Mays D (2018). Seven years of progress in tobacco control: an evaluation of the effect of nations meeting the highest level MPOWER measures between 2007 and 2014. Tob Control. 27(1):50–7. https://doi.org/10.1136/tobaccocontrol-2016-053381 PMID:27956650

48. Global Tobacco Economics Consortium (2018). The health, poverty, and financial consequences of a cigarette price increase among 500 million male smokers in 13 middle income countries: compartmental model study. BMJ. 361:k1162. https://doi.org/10.1136/bmj.k1162 PMID:29643096

49. Jha P, Peto R (2014). Global effects of smoking, of quitting, and of taxing tobacco. N Engl J Med. 370(1):60–8. https://doi.org/10.1056/NEJMra1308383 PMID:24382066

2.2 Infectious agents
Missed opportunities for prevention

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SUMMARY

- Infectious agents are an important cause of cancer, particularly in low- and middle-income countries, which have limited ability to manage the disease; therefore, prevention is a priority.
- The bacterium *Helicobacter pylori* was estimated to be responsible for about 810 000 new cancer cases in 2018, including 89% of non-cardia gastric cancers (760 000 cases), 74% of gastric non-Hodgkin lymphoma (22 000 cases) and 29% of cardia gastric cancers in East Asia (36 000 cases). Treatment by a combination of anti-microbial drugs is potentially preventive.
- Thirteen sexually transmitted mucosal human papillomavirus subtypes are established human carcinogens. Together, they are responsible for all cervical cancer cases globally (570 000 cases) and a variable proportion of cases of other anogenital and oropharyngeal cancers (totalling 120 000 cases). Vaccination against human papillomaviruses occurs in more than 80 countries.
- Chronic infection with hepatitis B virus and hepatitis C virus resulted in about 360 000 cases and 140 000 cases, respectively, of hepatocellular carcinoma in 2018, amounting to about 76% of all cases of hepatocellular carcinoma.
- Preventive vaccines against hepatitis B virus have been available since 1982, and direct-acting antiviral agents have the potential to cure more than 95% of people with hepatitis C virus infection.

The IARC Monographs programme has classified 11 infectious agents, or groups of related agents, as carcinogenic to humans (Group 1) [1]. These include one bacterium, seven viruses, and three macroparasites. The bacterium is *Helicobacter pylori*. The viruses are human papillomaviruses (HPVs), 13 subtypes of which are classified as carcinogenic, hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein–Barr virus (EBV), Kaposi sarcoma-associated herpesvirus (KSHV), human T-cell lymphotropic virus type 1 (HTLV-1), and HIV-1. The macroparasites are *Schistosoma haematobium*, *Opisthorchis viverrini*, and *Clonorchis sinensis*. Each of these infectious agents causes at least one type of cancer, and some cause several cancer types (Table 2.2.1).

The burden of cancer associated with chronic infections is substantial. It is estimated that in 2018, out of a total of 18 million new cancer cases worldwide, 2.2 million – about one eighth of all new cases – were caused by infection [2] (Table 2.2.1). However, the proportion of cancer cases caused by infection varies markedly by geographical region and World Bank income group; it is substantially higher in East Asia and in the lowest-income regions of the world [3]. In many high-income countries in Australasia, Europe, and North America, fewer than 5% of cancer cases are attributable to infections. In countries in sub-Saharan Africa, the proportion is at least one third; this may be an underestimate, because there is limited cancer registration in many countries in this region, and almost none in rural areas.

Four infectious agents – *H. pylori*, HPVs, HBV, and HCV – were together responsible for about 2 million cancer cases in 2018 (Table 2.2.1). More than one third of infection-related cancer cases occurred in China, where 42% of all *H. pylori*-related cancers and 69% of all HBV-related cancers occurred. Among the other infectious agents, several, including HTLV-1 and the macroparasites, contribute little to the global cancer burden but are significant causes of cancer in endemic populations. (For a recent, extensive review of infections and cancer, see [4]).

Helicobacter pylori

The bacterium *H. pylori* was estimated to be responsible for about 810 000 new cancer cases in 2018, including 89% of non-cardia gastric cancers (760 000 cases), 74% of gastric non-Hodgkin lymphoma cases (22 000 cases), and 29% of cardia gastric cancers in East Asia (36 000 cases) [2]. In addition, *H. pylori* causes substantial morbidity and mortality from peptic ulcer disease. Millions of cases of duodenal

Table 2.2.1. Estimated numbers of new cancer cases in 2018 attributable to infectious agents

Infectious agent	Cancer types for which there is sufficient evidence of causality	Number of new cancer cases
Helicobacter pylori	Non-cardia gastric carcinoma, low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma	810 000
Human papillomavirus	Carcinomas of the cervix, vulva, vagina, penis, anus, oral cavity, oropharynx, and tonsil	690 000
Hepatitis B virus (chronic infection)	Hepatocellular carcinoma	360 000
Hepatitis C virus	Hepatocellular carcinoma, non-Hodgkin lymphoma	160 000
Epstein–Barr virus	Nasopharyngeal carcinoma, Burkitt lymphoma, immunosuppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin lymphoma	160 000
Kaposi sarcoma-associated herpesvirus	Kaposi sarcoma, primary effusion lymphoma	42 000
Human T-cell lymphotropic virus type 1	Adult T-cell leukaemia/lymphoma	3 600
HIV-1	Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, cervical cancer, anal cancer, conjunctival cancer	–[a]
Schistosoma haematobium	Bladder cancer	6 000
Opisthorchis viverrini *Clonorchis sinensis*	Cholangiocarcinoma	3 600

[a] Cancers attributable to HIV are included with the underlying causal infections.

and gastric ulcer diseases are diagnosed each year globally, although the proportion attributable to *H. pylori* is unclear (see Chapter 5.4) [5].

H. pylori is a highly adapted bacterium that is able to live in the acidic environment of the human gastric mucosa, where it causes chronic inflammation, which may slowly lead to fibrosis, atrophy, and ultimately cancer in a small proportion of infected individuals, usually after several decades. Infection often occurs during childhood, and in the absence of treatment by an effective combination of three or four antimicrobial drugs, the infection is lifelong.

H. pylori transmission occurs via oral–oral and faecal–oral routes within the family and is considerably more frequent among people with low socioeconomic status. In high-income countries, the prevalence of *H. pylori* infection has been declining in tandem with the occurrence of the diseases it causes, and is now rare in children and young adults. However, gastric cancer tends to occur at an advanced age (≥ 65 years) compared with other infection-related cancers. Because of global population growth and ageing, the total number of *H. pylori*-related gastric cancer cases is not expected to decrease for decades.

The treatment for *H. pylori* infection comprises a combination of antimicrobial drugs and a proton-pump inhibitor and is used widely in symptomatic individuals. Mass treatment provides a means of cancer prevention, although studies are bedevilled by the need for large numbers and lengthy follow-up; there may also be deleterious consequences in terms of drug

FUNDAMENTALS

- Eleven infectious agents, or groups of related agents, are established human carcinogens, including one bacterium, seven viruses, and three macroparasites.
- About 13% of cancers worldwide, or 2.2 million cases per year, are caused by chronic infections. This proportion varies by geographical region and World Bank income group; it is highest in the lowest-income regions, especially for cervical cancers caused by human papillomaviruses. In sub-Saharan Africa, at least one third of cancer cases are of infectious origin, and the proportion may be significantly underestimated, because there is limited cancer registration in many countries in this region.
- Four agents – *Helicobacter pylori*, human papillomaviruses, hepatitis B virus, and hepatitis C virus – contribute most to the burden of cancer caused by infections globally. Several carcinogenic infectious agents, including *H. pylori*, hepatitis B virus, hepatitis C virus, Epstein–Barr virus, HIV, and macroparasites, also cause substantial morbidity and mortality from non-malignant diseases.
- Some cancer-causing infections, such as infections with macroparasites, contribute little to the global cancer burden but are significant causes of cancer in endemic populations.
- Human papillomavirus and hepatitis B virus infections are amenable to primary prevention through vaccination. Infections with hepatitis C virus, *H. pylori*, and the macroparasites are curable. For HIV and hepatitis B virus, infections can be controlled by antiviral treatment to reduce the risk of cancer and of transmission to others.
- If existing strategies for prevention were more widely applied and new infection control strategies developed, the global cancer burden could be greatly reduced.

resistance and the unknown impact of changes to the microbiome. However, the evidence from seven published studies (reviewed in [4] and [6], with an additional study published more recently [7]) indicates that *H. pylori* eradication programmes can be effective. The adoption of further screen-and-treat strategies has been recommended, together with trials of screening for early disease using non-invasive pepsinogen testing. The recently initiated GISTAR study aims to test the impact of the combination of *H. pylori* eradication and screening for early disease on the gastric cancer burden, and has a 15-year follow-up period [8].

An effective prophylactic or therapeutic vaccine against *H. pylori* would provide a cheaper and more effective way to reduce disease risk, particularly in low- and lower-middle-income countries, which have limited health infrastructure. Vaccine-related activities are summarized in [9]; all of the vaccines currently under development are at an early stage, and there appears to be little, if any, investment from large pharmaceutical companies, without which progress is likely to be limited.

Human papillomaviruses

Thirteen sexually transmitted mucosal HPV subtypes have been classified as carcinogenic to humans. Together, they are responsible for all cervical cancer cases globally (570 000 cases) and a variable proportion of cases of other anogenital and oropharyngeal cancers (totalling 120 000 cases) [2]. The most affected region of the world is sub-Saharan Africa, where about 60% of all infection-associated cancer cases are caused by HPV (see Chapter 5.10).

In every world region, two subtypes, HPV16 and HPV18, are responsible for about 70% of cervical cancer cases. HPVs are responsible for more than half of all infection-associated cancers in women worldwide and for about half of all infection-associated cancers in both sexes in low- and lower-middle-income countries, where screening for early cervical disease is limited and where the prevalence of HPV infection and of risk factors such as early age at first sexual intercourse and co-infection with HIV is high.

The risk of cancer associated with HPV can be reduced with a combination of factors that limit either risk of infection or risk of disease: using safe sexual practices (including delayed start of sexual activity), male circumcision, and reduction in tobacco use, which is an important co-factor for cervical cancer and oropharyngeal cancers in particular. Cervical cancer screening, for detection of early disease, has resulted in substantial declines in cervical cancer mortality in high-income countries but is often unavailable in low- and lower-middle-income countries.

Over the past 10–15 years, safe and effective HPV vaccination, including bivalent, quadrivalent, and nonavalent vaccines, has been introduced in more than 80 countries. However, most of these are high- and upper-middle-income countries rather than low- and lower-middle-income countries, which have the highest burden of HPV-associated disease [10]. About 20 of these countries either already vaccinate boys in addition to girls or plan to do so. National vaccination programmes

Fig. 2.2.1. A woman and her baby daughter in Cochabamba, Bolivia. Like many other low- and middle-income countries, Bolivia has a high mortality rate for cervical cancer, which is caused by human papillomavirus (HPV) infection. Cervical cancer screening, which has resulted in substantial declines in mortality in high-income countries, is often unavailable in low- and lower-middle-income countries.

with more than 50% coverage of two- or three-dose schedules have been shown to have a big impact in decreasing HPV prevalence and persistence and rates of cervical intraepithelial neoplasia (a precursor of cervical cancer) [11]. The quadrivalent and nonavalent vaccines are also highly effective at preventing anogenital warts, caused by HPV6 and HPV11.

Although there has been considerable progress in the deployment of HPV vaccination, many years will need to go by before the impact on cancer will be fully evident (see Chapter 6.3). Therefore, cervical screening programmes, in particular using HPV-based point-of-care testing where available, will need to be maintained for the foreseeable future, to protect cohorts of unvaccinated women.

The barriers to HPV vaccination are greatest in those countries with the weakest health systems and the highest burden of HPV-associated disease. To maintain HPV vaccination as a key element of cancer control programmes globally, and to introduce it in other settings, will require major international commitment and funding. If current efforts to establish the efficacy of single-dose vaccination prove viable, this would remove some of the barriers to wider deployment in low- and lower-middle-income countries.

Fig. 2.2.2. A girl in Zambia receives a human papillomavirus (HPV) vaccination. Safe and effective HPV vaccination has been introduced in more than 80 countries.

Hepatitis B virus

Globally, more than 260 million people are estimated to be chronic carriers of HBV, of whom 1–2% per year will progress to liver disease; more than 90% are unaware of their status (see Chapter 5.6) [4]. Chronic HBV infection resulted in about 360 000 cases of hepatocellular carcinoma in 2018, amounting to about 55% of all cases of hepatocellular carcinoma. In addition, there is substantial mortality from non-malignant manifestations of infection, with about 890 000 HBV-related deaths, including those from cancer, per year [12]. The largest proportion of HBV-associated cases of hepatocellular carcinoma occur in Asia and in sub-Saharan Africa, reflecting the prevalence of the virus and the age at which infection commonly occurs.

The predominant modes of transmission of HBV infection are perinatal, parenteral, and sexual. The risk of chronic carriage, and hence of cancer, is related to the age at infection. The risk is highest among people infected as infants, of whom about 90% become chronic carriers; this is the predominant mode of transmission in Asia. The risk is intermediate among those infected during childhood, of whom 30–50% become chronic carriers; this is the predominant mode of transmission in sub-Saharan Africa. The risk is lowest among those infected as adults, of whom less than 5% become chronic carriers; this mode of transmission occurs mainly in high-income countries.

Safe and effective preventive vaccines against HBV have been available since 1982. Global coverage is thought to be about 84%, although there is evidence from rural sub-Saharan Africa that this may be an overestimate [13]. For adults with chronic infection and evidence of liver damage, a daily dose of antiviral therapy, using widely available drugs, is effective in most people at reducing complications and transmission to others, although treatment needs to be maintained for life. Prevention of mother-to-child transmission can be improved via a combination of routine antenatal screening, antiviral drugs during pregnancy, and HBV vaccination of the baby at birth; administration of HBV immunoglobulin can further reduce the risk of vertical transmission. Coverage of the birth dose of HBV vaccine is thought to be about 39% globally. However, with a latency period from infection to cancer of 30–40 years, it will be decades before the impacts of prevention efforts are felt, highlighting the need for screen-and-treat strategies in high-risk populations in the interim.

Hepatitis C virus

Approximately 200 million people worldwide are estimated to be infected with HCV. Chronic HCV infection resulted in about 160 000 new cancer cases in 2018, predominantly cases of hepatocellular carcinoma but also about 16 000 cases of

Fig. 2.2.3. A patient with liver cancer at the National Cancer Center of Mongolia, in Ulaanbaatar. Chronic infection with hepatitis B virus resulted in about 360 000 cases of hepatocellular carcinoma in 2018.

non-Hodgkin lymphoma [2]. In low- and middle-income countries, the predominant cause of hepatocellular carcinoma is HBV, but in high-income countries, 40% of cases are caused by HCV; in Japan, the proportion is up to 60% [1,2]. About 75–85% of infections become chronic, and in the absence of treatment approximately half of the chronic carriers will die of liver disease.

The prevalence of HCV infection varies widely; it is highest in Egypt, Pakistan, and Mongolia (up to 20%), intermediate in parts of Italy and China (10%), and relatively lower elsewhere, except in high-risk groups, such as intravenous drug users and people who received a transfusion before widespread HCV testing of blood donors was implemented. Transmission is mainly parenteral, although it can occur via sex and from mother to child, although rarely; many infected people have no clear risk factors.

HCV is highly variable, with many different genotypes. This significantly complicates vaccine development, and currently no vaccines are available. The introduction of direct-acting antiviral agents in 2014 has resulted in cure rates of greater than 90% in treated individuals, with minimal side-effects. However, the complexity of testing for HCV and the high cost of treatment mean that treatment is currently unavailable to most of the people who would benefit, even in high-income countries [14].

Epstein–Barr virus

In 2018, EBV was estimated to have caused 160 000 new cancer cases [2], including cases of African endemic Burkitt lymphoma, which is also associated with exposure to malaria, as well as nasopharyngeal cancer, Hodgkin lymphoma, some non-Hodgkin lymphomas, especially in immunocompromised people, and a still ill-defined fraction of gastric cancer cases. EBV is also the primary cause of infectious mononucleosis, which affects about half of people in whom EBV infection occurs in adult life and has been implicated as a cause of multiple sclerosis.

EBV infection is extremely common worldwide and affects about 90% of the population. In low- and middle-income countries, the peak prevalence of infection is within the first years of life, but in high-income countries, only about 45–50% of people are infected as infants. Transmission is mainly via saliva, although it can also occur via blood [1,2,4].

In 2007, a vaccine against the EBV gp350 antigen was shown in a phase 2 trial to prevent infectious mononucleosis, although it did not prevent infection with EBV (reviewed in [15]). However, since then, further work both on that vaccine candidate and on others has stalled, and currently no trials are under way. A vaccine to prevent EBV-related post-transplant lymphoma would provide an important proof of principle for the prevention of EBV-associated cancer. Trials to reduce the incidence of other EBV-associated cancers would be challenging, but feasible.

Kaposi sarcoma-associated herpesvirus

KSHV is a necessary but not sufficient cause of Kaposi sarcoma, primary effusion lymphoma, and probably also multicentric Castleman disease. KSHV caused about 42 000 cancer cases in 2018, predominantly in HIV-infected people, in whom the resulting immunosuppression facilitates the development of cancer [1,2].

KSHV is unique among the herpesviruses in that it is not ubiquitous in human populations, but rather shows marked geographical variation in prevalence; the prevalence of KSHV is highest in sub-Saharan Africa (50–95%), intermediate in Mediterranean countries (10%), and generally low in other parts of the world [1,16]. This distribution broadly reflects that of Kaposi sarcoma, even before the HIV epidemic.

Transmission of KSHV is via saliva in both high-risk and low-risk populations; in areas where the prevalence is high, such as sub-Saharan Africa, infection occurs throughout childhood and into adult life [4,16]. No vaccines or treatments for KSHV are available, but management of HIV

greatly reduces the risk of developing Kaposi sarcoma. Identification of the factors that sustain the high transmission in sub-Saharan Africa may provide opportunities for reducing the burden of associated cancer.

Human T-cell lymphotropic virus type 1

HTLV-1 caused about 3600 cases of adult T-cell leukaemia/lymphoma in 2018 [2]. It also causes progressive myelopathy and other inflammatory conditions [1]. Globally, an estimated 10–20 million people are infected, and 3–8 million of them are in sub-Saharan Africa. Although data from many parts of the world are sparse, the prevalence of infection appears to be highest in parts of Japan, Africa, the Caribbean, Central and South America, and northern Australasia. More than 90% of infections will remain asymptomatic.

The predominant route of transmission of HTLV-1 is via breastfeeding, and interventions that limit the duration of breastfeeding have prevented up to 90% of mother-to-child transmissions, in parts of the world where alternative feeding options are available. Surveillance of the blood supply has also reduced transfusion-related infections [4]. No vaccines or treatments are available.

HIV

Although HIV is not directly carcinogenic, HIV infection causes immunosuppression, thereby facilitating the development of cancers caused by other infections. The cancers associated with HIV have been attributed to those underlying infections mentioned above. These include Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, cervical cancer, anal cancer, and conjunctival cancer [1]. Perhaps of more relevance is the total morbidity and mortality associated with HIV: in 2017, 36.9 million people globally were living with HIV, 21.7 million people were accessing antiretroviral therapy, and 940 000 people died from AIDS-related illnesses, despite the success of antiretroviral therapy in treating the disease [17]. No vaccine is available, but several are under development.

Macroparasites

An estimated 200 million people worldwide are infected with one of six species of *Schistosoma*, which are prevalent to varying extents in tropical regions. All cause significant pathology and have been linked to several cancer types, but only for *Schistosoma haematobium* in relation to bladder cancer is the evidence sufficiently robust; *S. haematobium* infection caused about 6000 cancer cases in 2018 [2]. Infections occur after exposure to contaminated freshwater and are treatable. However, evidence that large-scale pharmacological interventions reduce the burden of cancer remains limited [1].

The liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis* affect up to 45 million people, primarily in South-East Asia. In endemic areas, they are an important cause of cholangiocarcinoma (bile duct cancer), causing about 3600 cases in 2018, although this number, which is based on imperfect statistics, is probably a gross underestimation [2]. Infection occurs via consumption of raw or undercooked contaminated fish, providing a key target for prevention.

Conclusions

Infections are an important cause of cancer, especially in Asia and sub-Saharan Africa. In 2018, more than one third of infection-related cancer cases occurred in China, where 42% of all *H. pylori*-related cancers and 69% of all HBV-related cancers occurred. Adequate infection control strategies, encompassing cheap and reliable point-of-care diagnostic assays for particular infectious agents for use in screening, effective treatments, and therapeutic and preventive vaccines, should all play a more widespread role in cancer control programmes. Substantial international investment is required to realize these aspirations. Further work is also justified to identify additional cancers with an underlying infectious cause.

References

1. IARC (2012). Biological agents. IARC Monogr Eval Carcinog Risks Hum. 100B:1–441. Available from: http://publications.iarc.fr/119 PMID:23189750
2. de Martel C, Georges D, Bray F, Ferlay J, Clifford G (2019). Global burden of cancers attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. [Epub ahead of print] https://doi.org/10.1016/S2214-109X(19)30488-7 PMID:31862245
3. Bray F, Jemal A, Grey N, Ferlay J, Forman D (2012). Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. Lancet Oncol. 13(8):790–801. https://doi.org/10.1016/S1470-2045(12)70211-5 PMID:22658655
4. Franceschi S, El-Serag HB, Forman D, Newton R, Plummer M (2018). Infectious agents. In: Thun MJ, Linet MS, Cerhan JR, Haiman C, Schottenfeld D, editors. Schottenfeld and Fraumeni cancer epidemiology and prevention. 4th ed. New York (NY), USA: Oxford University Press; pp. 433–60.
5. GBD 2013 Mortality and Causes of Death Collaborators (2015). Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 385(9963):117–71. https://doi.org/10.1016/S0140-6736(14)61682-2 PMID:25530442
6. IARC *Helicobacter pylori* Working Group (2014). *Helicobacter pylori* eradication as a strategy for preventing gastric cancer. Lyon, France: International Agency for Research on Cancer (IARC Working Group Reports, No. 8). Available from: http://publications.iarc.fr/391.
7. Pan KF, Zhang L, Gerhard M, Ma JL, Liu WD, Ulm K, et al. (2016). A large randomised controlled intervention trial to prevent gastric cancer by eradication of *Helicobacter pylori* in Linqu County, China: baseline results and factors affecting the eradication. Gut. 65(1):9–18. https://doi.org/10.1136/gutjnl-2015-309197 PMID:25986943
8. Leja M, Park JY, Murillo R, Liepniece-Karele I, Isajevs S, Kikuste I, et al. (2017). Multicentric randomised study of *Helicobacter pylori* eradication and pepsinogen testing for prevention of gastric cancer mortality: the GISTAR study. BMJ Open. 7(8):e016999. https://doi.org/10.1136/bmjopen-2017-016999 PMID:28801429
9. Sutton P, Boag JM (2019). Status of vaccine research and development for *Helicobacter pylori*. Vaccine. 37(50):7295–9. https://doi.org/10.1016/j.vaccine.2018.01.001 PMID:29627231
10. Gallagher KE, LaMontagne DS, Watson-Jones D (2018). Status of HPV vaccine introduction and barriers to country uptake. Vaccine. 36(32 Pt A):4761–7. https://doi.org/10.1016/j.vaccine.2018.02.003 PMID:29580641
11. Drolet M, Bénard É, Boily MC, Ali H, Baandrup L, Bauer H, et al. (2015). Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis. 15(5):565–80. https://doi.org/10.1016/S1473-3099(14)71073-4 PMID:25744474
12. O'Hara GA, McNaughton AL, Maponga T, Jooste P, Ocama P, Chilengi R, et al. (2017). Hepatitis B virus infection as a neglected tropical disease. PLoS Negl Trop Dis. 11(10):e0005842. https://doi.org/10.1371/journal.pntd.0005842 PMID:28981505
13. Asiki G, Newton R, Marions L, Seeley J, Kamali A, Smedman L (2016). The impact of maternal factors on mortality rates among children under the age of five years in a rural Ugandan population between 2002 and 2012. Acta Paediatr. 105(2):191–9. https://doi.org/10.1111/apa.13252 PMID:26503711
14. Kanwal F, El-Serag HB (2014). Hepatitis C virus treatment: the unyielding chasm between efficacy and effectiveness. Clin Gastroenterol Hepatol. 12(8):1381–3. https://doi.org/10.1016/j.cgh.2014.02.031 PMID:24607698
15. Cohen JI (2018). Vaccine development for Epstein-Barr virus. Adv Exp Med Biol. 1045:477–93. https://doi.org/10.1007/978-981-10-7230-7_22 PMID:29896681
16. Newton R, Labo N, Wakeham K, Miley W, Asiki G, Johnston WT, et al. (2018). Kaposi's sarcoma associated herpesvirus in a rural Ugandan cohort: 1992–2008. J Infect Dis. 217(2):263–9. https://doi.org/10.1093/infdis/jix569 PMID:29099933
17. UNAIDS (2018). Global HIV & AIDS statistics – 2018 fact sheet. Geneva, Switzerland: Joint United Nations Programme on HIV and AIDS. Available from: https://www.unaids.org/en/resources/fact-sheet.

2.3 Alcohol consumption
A leading risk factor for cancer

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SUMMARY

- In 2016, alcohol consumption was one of the leading risk factors for cancer development and cancer death globally, causing an estimated 376 200 cancer deaths, representing 4.2% of all cancer deaths, and 10.3 million cancer disability-adjusted life years lost, representing 4.2% of all cancer disability-adjusted life years lost.
- The impact of alcohol consumption on cancer in 2016 varied by age group; the proportion of cancer deaths attributable to alcohol consumption ranged from 13.9% of cancer deaths among people aged 30–34 years to 2.7% of cancer deaths among people aged 80–84 years.
- The burden of cancers caused by alcohol consumption might be decreased through (i) individual-level and societal-level interventions that reduce alcohol consumption, and (ii) measures that target those risk factors that interact with alcohol consumption to increase the risk of cancer or that directly affect the risk of alcohol-related cancers.

Alcohol consumption as a risk factor for cancer

The IARC Monographs [1] and the Continuous Update Project of the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) [2] have attributed the highest level of causal evidence to the association between consumption of alcoholic beverages and the development of cancer. IARC classified alcohol consumption as carcinogenic to humans (Group 1), and the WCRF/AICR Continuous Update Project concluded that there is convincing evidence that consumption of alcoholic beverages increases cancer risk.

Alcoholic beverages contain numerous carcinogenic compounds, but the majority of the risk relationship between alcohol consumption and the development of cancer is due to ethanol [3]. Although carcinogenesis due to alcohol is far from being fully understood, the main pathophysiological carcinogenic mechanisms of ethanol that have been postulated include its metabolism into the carcinogenic metabolite acetaldehyde, its inhibition of the one-carbon metabolism pathway and DNA methylation (especially among people with a low dietary intake of folate), and its effect on increasing serum levels of endogenous estrogens (see Chapter 3.11) [2]. Ethanol has also been hypothesized to increase the risk of cancer through the production of reactive oxygen species and polar metabolites, through the conversion of pro-carcinogens in the metabolic pathway of ethanol, by lipid peroxidation, by the production of prostaglandins, by altering the insulin-like growth factor 1 pathway, and by acting as a solvent for cellular penetration of environmental carcinogens (e.g. tobacco) [2]. The biological pathways involved, and the relative contributions of these pathways to carcinogenesis, differ by cancer site.

On the basis of the evidence from epidemiological studies in humans, studies in experimental animals, and mechanistic data, the IARC Monographs and the WCRF/AICR Continuous Update Project have reported that alcohol consumption causes cancers of the oral cavity, oropharynx, hypopharynx, oesophagus (squamous cell carcinoma), colon, rectum, liver and

Fig. 2.3.1. A farmer in Amani, Tanzania, drinks a cup of bamboo wine.

intrahepatic bile duct, larynx, and female breast (both premenopausal and postmenopausal as evaluated by IARC [1]; postmenopausal only as evaluated by the WCRF/AICR Continuous Update Project [2]). For all of these sites, there are dose–response relationships, with almost linear gradients of relative risks and no apparent lower risk threshold [4,5]. The risk relationships depend mainly on the level of lifetime exposure to alcohol [5,6]. However, for female breast cancer, in addition to the dose–response relationship between level of exposure and cancer incidence, patterns of alcohol consumption, especially episodic heavy drinking, may play an important role [7].

The risk relationships have been shown to differ by population. For example, Mendelian randomization studies have found genetic variations that affect the metabolism of acetaldehyde in humans (see Chapter 3.3). In particular, people with at least one copy of the aldehyde dehydrogenase *ALDH2*2* allele (with the Glu487Lys polymorphism), a variant that is prevalent in eastern Asian populations, have a higher risk of cancers of the upper aerodigestive tract and of colorectal cancer [8]. Variations in the alcohol dehydrogenase 1B (*ADH1B*) and 1C (*ADH1C*), cytochrome P450 2E1, and methylenetetrahydrofolate reductase (*MTHFR*) genes are also hypothesized to modify the relationship between alcohol consumption and the development of cancer [9,10].

The WCRF/AICR Continuous Update Project concluded that there is probable evidence that alcohol consumption is associated with the risk of non-cardia stomach cancer, and limited–suggestive evidence that alcohol consumption is associated with the risk of cancers of the lung, pancreas, and skin (basal cell carcinoma and malignant melanoma) [2]. However, alcohol consumption is associated with other risk factors, including diet and smoking, and therefore confounding may explain these associations. Furthermore, there are inconsistent epidemiological findings for a relationship between alcohol consumption and the development of cancers of the gall bladder and prostate [4]. In addition, there is no evidence that alcohol consumption affects breast cancer survival or recurrence [2].

The WCRF/AICR Continuous Update Project concluded that there is probable evidence that alcohol consumption is associated with a decreased risk of kidney cancer; this may be due to improved insulin sensitivity, improved blood lipid profiles, and higher adiponectin levels among people with light and moderate alcohol consumption [2]. Resveratrol (a substance found in red wine) has received attention for its hypothesized anticarcinogenic properties; however, based on the empirical evidence, for every cancer case that the resveratrol in wine might prevent, 100 000 cancer cases are caused by ethanol [5]. Inconsistent inverse associations between alcohol consumption and the development of thyroid cancer, Hodgkin lymphoma, and non-Hodgkin lymphoma also have been found in epidemiological studies, but there is currently not sufficient evidence to determine the causality of these relationships [1,2].

As a result of its effects on the propensity to engage in unprotected sex and its weakening of the immune system, alcohol also may indirectly increase the risk of infection with sexually transmitted viruses that potentially cause

FUNDAMENTALS

- Alcohol (ethanol), an addictive substance with carcinogenic properties, was consumed by 42.9% of adults globally in 2016 (yearly prevalence).
- A relationship between alcohol consumption and the development of cancer was first suggested by Lamy in 1910, when he noted that a high proportion of patients with either cancer of the oesophagus or cancer of the cardiac region of the stomach were alcohol misusers.
- The IARC Monographs and the Continuous Update Project have identified the contribution of alcohol to carcinogenesis at numerous cancer sites. Alcohol consumption has been found to be causally associated with the development of cancers of the oral cavity, oropharynx, hypopharynx, oesophagus (squamous cell carcinoma), colon, rectum, liver and intrahepatic bile duct, larynx, and female breast.

Fig. 2.3.2. Young women in Japan drinking beer at a barbecue.

cancer (including Kaposi sarcoma-associated herpesvirus and human papillomavirus) and of HIV-1; the immunosuppression caused by HIV-1 is thought to increase the carcinogenic effect of other infectious agents [5]. However, more research is needed to further establish and quantify any indirect effect of alcohol on an increased risk of cancers caused by infectious diseases.

The global cancer burden due to alcohol

In 2016, alcohol consumption caused an estimated 3.0 million deaths from all causes worldwide, representing 5.3% of all deaths [11]. A large proportion of the health burden caused by alcohol consumption stems from cancer. In 2016, alcohol caused an estimated 376 200 (95% uncertainty interval, 324 900–439 700) cancer deaths, representing 4.2% (95% uncertainty interval, 3.6–4.9%) of all cancer deaths, and an age-standardized rate (ASR) of 4.8 deaths (95% confidence interval, 4.2–5.7) per 100 000 people (Table 2.3.1). Here, the term "alcohol-attributable cancers" is used to refer to cancers caused by alcohol. The proportion of alcohol-attributable cancers is thus defined by the proportion of cancers that would not have occurred if there had been no alcohol exposure (for definitions of causality, see [12]; for alcohol-attributable fractions, see [13]).

Of the 245 million disability-adjusted life years (DALYs) lost in 2016 due to cancer, 10.3 million (95% uncertainty interval, 8.7 million–12.0 million) were due to alcohol consumption, representing 4.2% (95% uncertainty interval, 3.6–4.9%) of all cancer DALYs lost (Table 2.3.2). The majority (97.7%) of these alcohol-attributable cancer DALYs lost were due to years of life lost because of premature death resulting from high cancer fatality rates.

In 2016, cancers of the colorectum, liver, and oesophagus were the largest contributors to the alcohol-attributable cancer burden, responsible for 23.9%, 22.3%, and 19.3%, respectively, of all alcohol-attributable cancer deaths.

Among all cancers types, alcohol consumption had the largest impact on cancers of the upper aerodigestive tract. Alcohol was responsible for 26.4% of all cancers of the lip and oral cavity, 30.5% of all other pharyngeal cancers (excluding nasopharyngeal cancers), 21.6% of all laryngeal cancers, and 16.9% of all oesophageal cancers. These findings reflect the stronger associations – i.e. the higher gradients of the dose–response curves – between levels of alcohol consumption and cancers of the upper aerodigestive tract compared with cancers of the colorectum, liver, and breast [11].

Like with cancer deaths, in 2016 the largest contributors to the alcohol-attributable cancer DALYs lost were cancers of the liver, colorectum, and oesophagus, responsible for 22.5%, 20.6%, and 18.5%, respectively, of all alcohol-attributable cancer DALYs lost.

Fig. 2.3.3. Alcohol-attributable cancer deaths (top) and alcohol-attributable cancer disability-adjusted life years (DALYs) lost (bottom) in 2016, by age group.

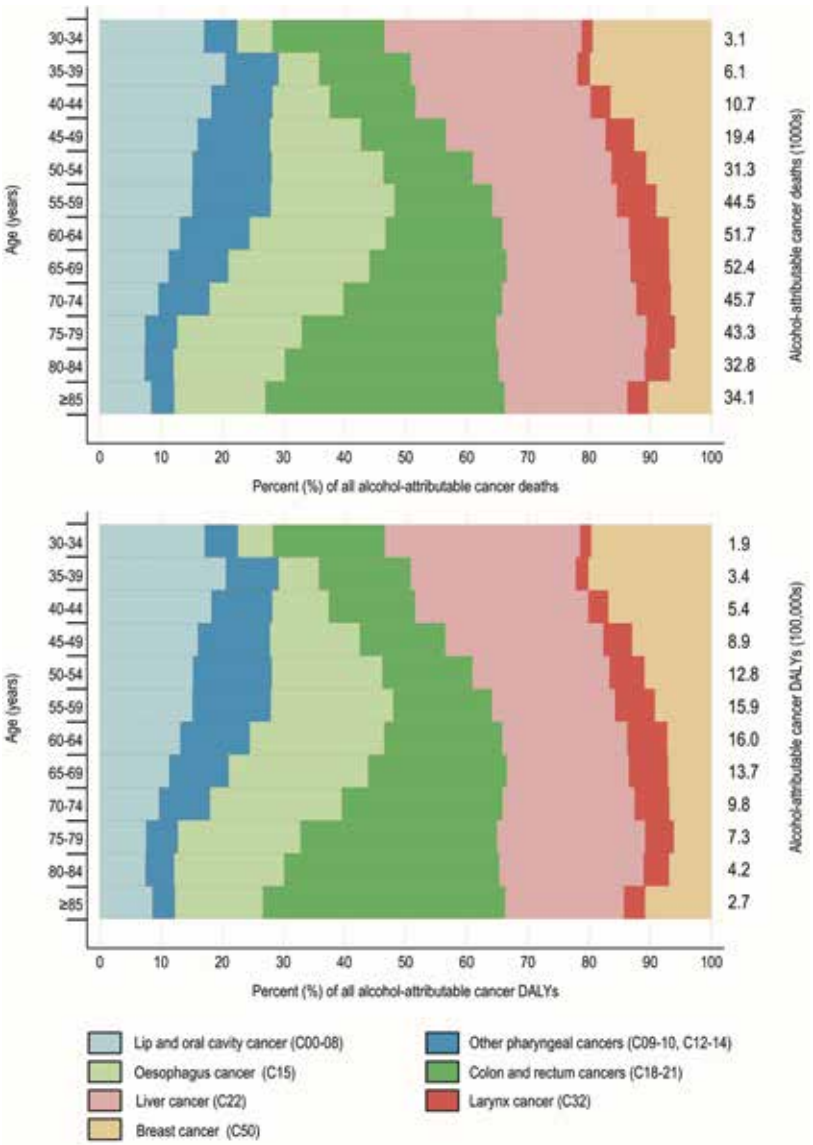


Table 2.3.1. Alcohol-attributable cancer deaths in 2016, by sex and cancer site

Outcome and cancer site	ICD-10 code	Number of alcohol-attributable deaths/1000 (95% uncertainty interval)			Percentage of deaths attributable to alcohol consumption (95% uncertainty interval)			Percentage of the total alcohol-attributable cancer deaths
		Men	Women	Both sexes	Men	Women	Both sexes	
Cancer	C00–97	297.6 (246.9–346.1)	78.6 (66–115.4)	376.2 (324.9–439.7)	5.8 (4.8–6.8)	2.0 (1.7–3.0)	4.2 (3.6–4.9)	100.0
Lip and oral cavity	C00–08	38.9 (30.4–46.0)	5.2 (3.8–7.3)	44.0 (35.3–52.3)	34.7 (27.1–41.0)	9.4 (7.0–13.3)	26.4 (21.2–31.4)	11.7
Other pharynx	C09–10, C12–14	31.7 (24.9–37.7)	2.1 (1.5–3.0)	33.8 (27.0–39.9)	35.3 (27.8–42.1)	9.9 (7.3–14.2)	30.5 (24.4–36.1)	9.0
Oesophagus	C15	66.9 (51.6–79.7)	5.8 (3.9–8.9)	72.7 (56.8–87.2)	21.7 (16.7–25.8)	4.8 (3.2–7.4)	16.9 (13.2–20.3)	19.3
Colorectum	C18–21	75.9 (61.5–89.6)	13.8 (6.6–25.2)	89.8 (73.1–107.4)	17.6 (14.3–20.7)	3.8 (1.8–6.9)	11.3 (9.2–13.5)	23.9
Liver	C22	65.1 (31.5–102.5)	18.9 (9.5–34.4)	84.0 (49.8–125.3)	11.1 (5.4–17.5)	7.8 (3.9–14.1)	10.1 (6.0–15.1)	22.3
Larynx	C32	19.1 (14.8–23.1)	0.8 (0.6–1.0)	19.9 (15.6–24.0)	23.7 (18.4–28.6)	6.7 (5.2–9.2)	21.6 (16.9–26.1)	8.5
Breast	C50	–	32.0 (26.8–51.1)	32.0 (26.8–51.1)	–	5.5 (4.6–8.8)	5.5 (4.6–8.7)	5.3
All causes	A00–Z99	2307.3 (1929.7–2720.1)	681.0 (536.4–990.7)	2988.3 (2596.8–3523.9)	7.7 (6.4–9.0)	2.6 (2.0–3.8)	5.3 (4.6–6.2)	–

ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision.

Table 2.3.2. Alcohol-attributable cancer disability-adjusted life-years lost in 2016, by sex and cancer site

Outcome and cancer site	ICD-10 code	Number of alcohol-attributable DALYs lost/100 000 (95% uncertainty interval)			Percentage of DALYs lost attributable to alcohol consumption (95% uncertainty interval)			Percentage of the total alcohol-attributable cancer DALYs lost
		Men	Women	Both sexes	Men	Women	Both sexes	
Cancer	C00–97	81.6 (67.0–95.9)	21.1 (18.0–31.4)	102.6 (87.3–120.0)	5.9 (4.9–7.0)	2.0 (1.7–2.9)	4.2 (3.6–4.9)	100.0
Lip and oral cavity	C00–08	12.2 (9.2–14.7)	1.4 (1.0–2.0)	13.6 (10.6–16.5)	33.2 (25.0–40.0)	8.6 (6.3–12.2)	25.7 (19.9–31.0)	13.3
Other pharynx	C09–10, C12–14	9.7 (7.6–11.6)	0.6 (0.4–0.9)	10.3 (8.2–12.3)	35.5 (27.6–42.5)	9.3 (6.8–13.4)	30.6 (24.1–36.5)	10.1
Oesophagus	C15	17.7 (13.8–20.9)	1.4 (0.9–2.1)	19.0 (15.0–22.6)	22.1 (17.2–26.1)	4.7 (3.2–7.2)	17.5 (13.8–20.7)	18.5
Colorectum	C18–21	18.0 (14.4–21.4)	3.2 (1.6–5.8)	21.2 (17.2–25.3)	16.7 (13.4–19.9)	3.8 (1.9–6.9)	11.1 (9.0–13.2)	20.6
Liver	C22	18.6 (8.9–29.7)	4.5 (2.3–8.2)	23.1 (13.2–35.0)	10.7 (5.1–17.0)	7.2 (3.7–13.1)	9.7 (5.6–14.8)	22.5
Larynx	C32	5.4 (4.2–6.5)	0.2 (0.2–0.3)	5.6 (4.4–6.7)	23.8 (18.5–28.8)	6.7 (5.2–9.0)	21.8 (17.0–26.3)	9.6
Breast	C50	–	9.9 (8.2–16.4)	9.9 (8.2–16.4)	–	5.2 (4.4–8.7)	5.2 (4.3–8.6)	5.4
All causes	A00–Z99	1065.4 (903.2–1240.8)	261.0 (234.4–331.5)	1326.4 (1164.1–1539.8)	7.6 (6.5–8.9)	2.2 (1.9–2.7)	5.1 (4.5–5.9)	–

DALYs, disability-adjusted life years; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision.

Similarly, alcohol consumption had the largest contributory impact on DALYs lost due to cancers of the upper aerodigestive tract. Alcohol was responsible for 25.7% of all lip and oral cavity cancer DALYs lost, 30.6% of all other pharyngeal cancer DALYs lost (excluding nasopharyngeal cancers), 21.8% of all laryngeal cancer DALYs lost, and 17.5% of all oesophageal cancer DALYs lost.

Based on different consumption levels by age [14], the impact of alcohol consumption on cancer in 2016 varied by age group (Fig. 2.3.3); the proportion of cancer deaths attributable to alcohol consumption ranged from 13.9% of cancer deaths among people aged 30–34 years to 2.7% of cancer deaths among people aged 80–84 years. At younger ages, cancers of the liver, breast, and colorectum were the leading contributors to the alcohol-attributable cancer burden, responsible for 32.2%, 19.4%, and 18.4%, respectively, of all alcohol-attributable cancer deaths among people aged 30–34 years. At older ages, cancers of the colorectum, liver, and oesophagus were the leading contributors to the alcohol-attributable cancer burden, responsible for 39.1%, 20.1%, and 14.9%, respectively, of all alcohol-attributable cancer deaths among people aged 80 years and older. The impact of alcohol on cancer deaths and DALYs lost among people aged 29 years and younger is unknown, because data are lacking and the etiology of these cancers is complex; however, the proportion of alcohol-attributable cancers among this age group is hypothesized to be relatively small [15].

In 2016, there were large variations between countries and geographical regions in the ASRs of alcohol-attributable cancer deaths (Fig. 2.3.4) and cancer DALYs lost (Fig. 2.3.5). Based on the regions as defined by the Institute for Health Metrics and Evaluation's Global Burden of Disease study, the burden of alcohol-attributable cancers was lowest in North Africa and the Middle East (ASRs of 0.8 cancer deaths and 24.2 cancer DALYs lost per 100 000 people) and highest in eastern Europe (ASRs of 12.0 cancer deaths and 360.4 cancer DALYs lost per 100 000 people).

Fig. 2.3.4. Global burden of cancer deaths caused by alcohol consumption in 2016: (top) age-standardized cancer deaths attributable to alcohol consumption per 100 000 people; (bottom) percentage of cancer deaths attributable to alcohol.

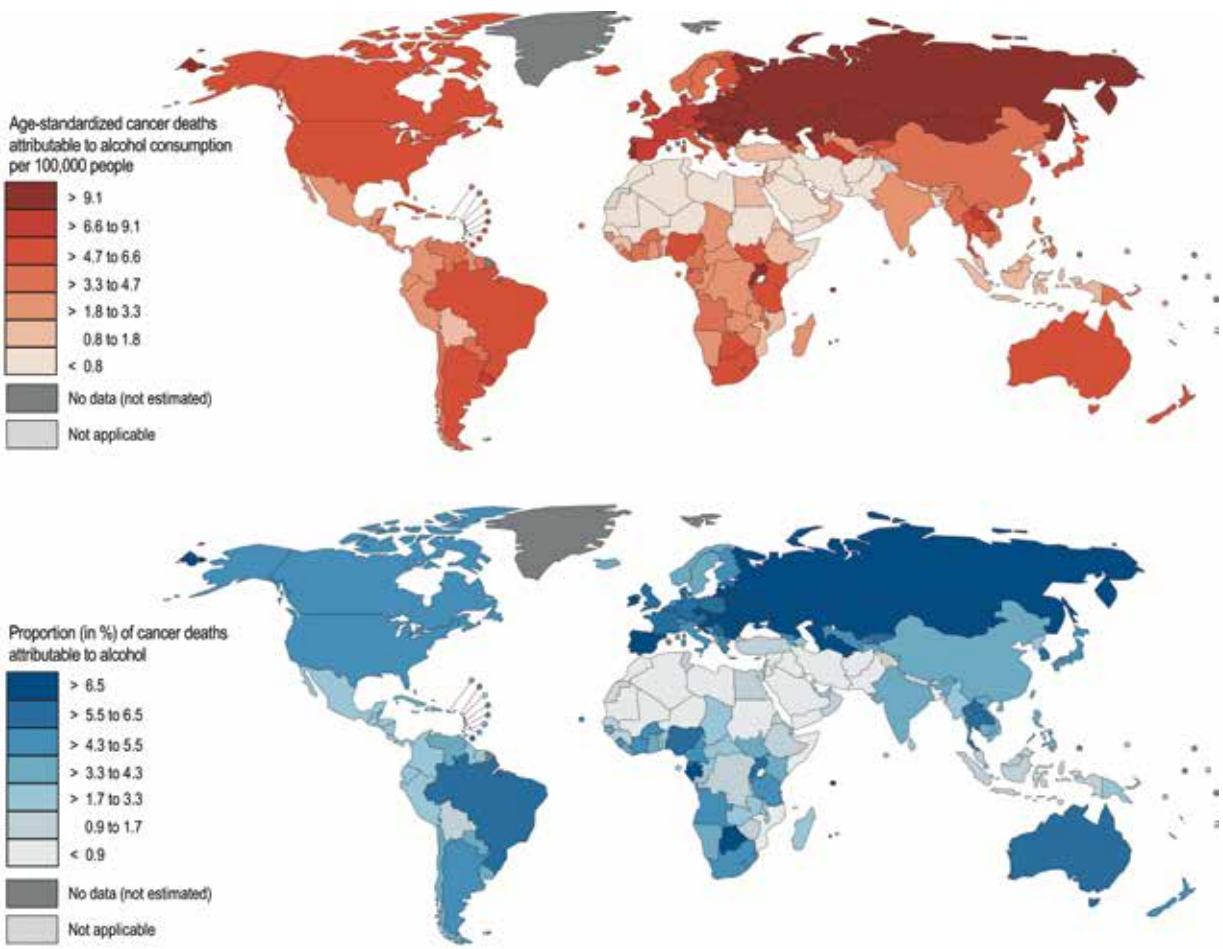
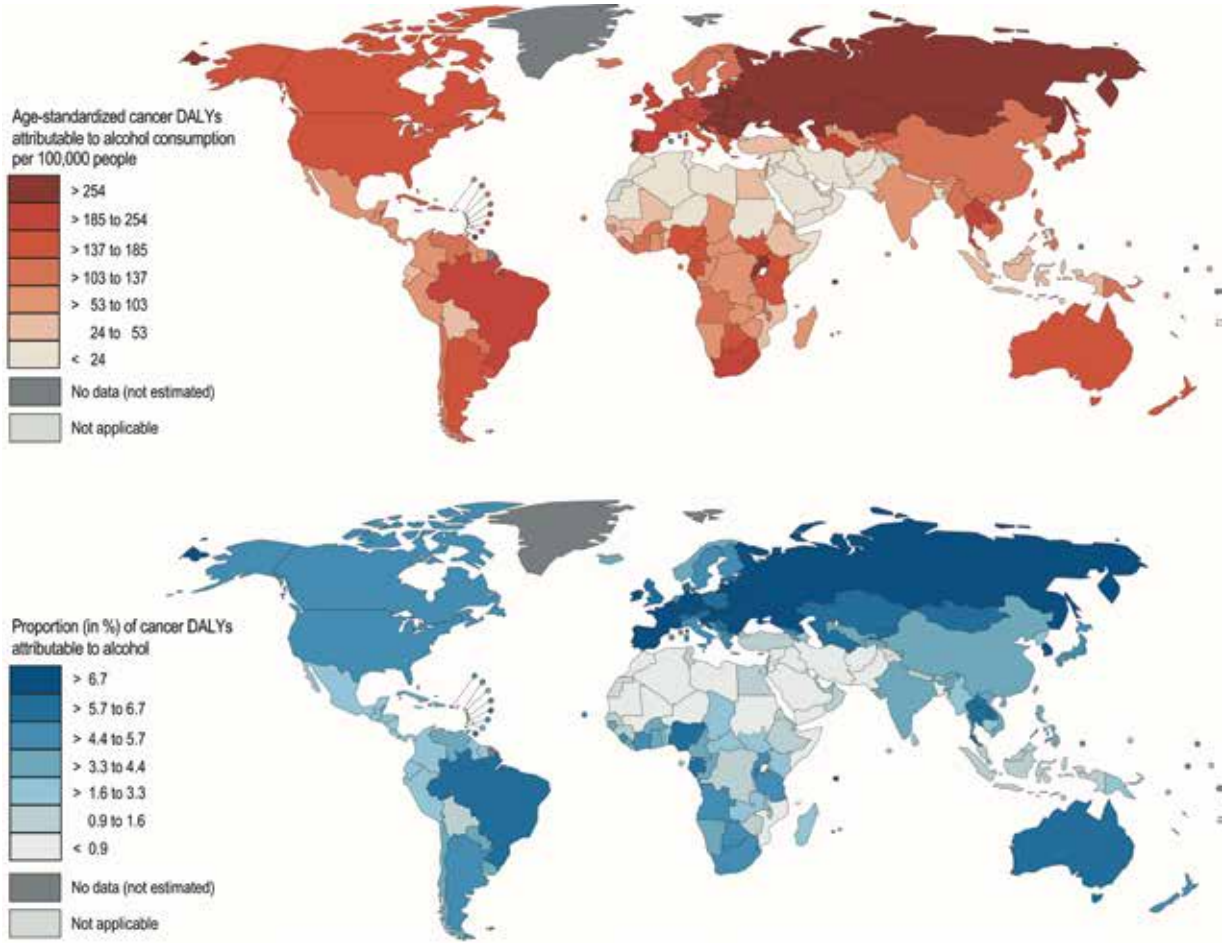


Fig. 2.3.5. Global burden of cancer disability-adjusted life years (DALYs) lost caused by alcohol consumption in 2016: (top) age-standardized cancer DALYs lost attributable to alcohol consumption per 100 000 people; (bottom) percentage of cancer DALYs lost attributable to alcohol.



Similarly, the proportion of alcohol-attributable cancer deaths and cancer DALYs lost also varied between countries and regions. The proportions were lowest in North Africa and the Middle East (0.8% of cancer deaths and 0.8% of cancer DALYs lost) and highest in eastern Europe (8.1% of cancer deaths and 8.6% of cancer DALYs lost).

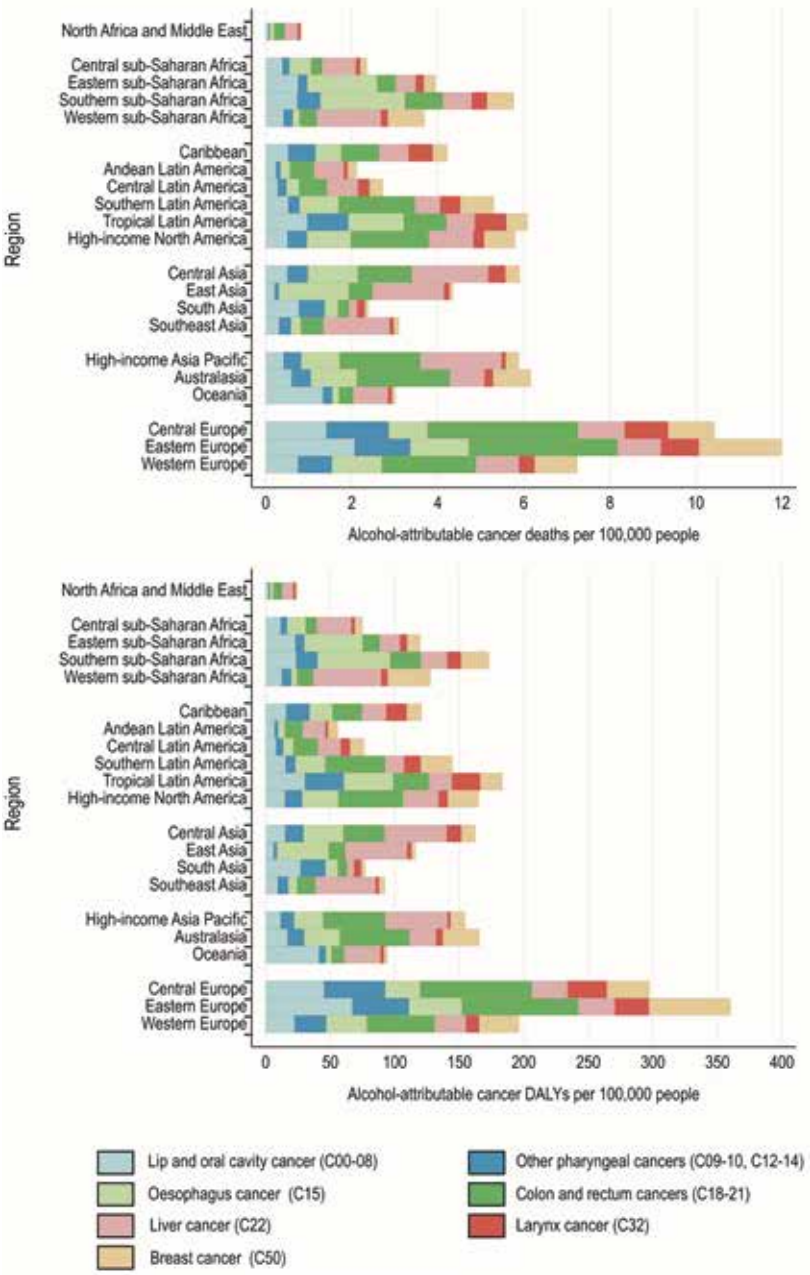
The burden of cancer by site also varied across geographical regions (Fig. 2.3.6). In particular, alcohol-attributable cancers of the colorectum (see Chapter 5.5) were prominent in southern Latin America, high-income North America, high-income Asia Pacific, Australasia, and central, eastern, and western Europe; all of these regions have countries with high or very high levels of the Human Development Index (HDI).

Both the consumption of alcohol and the burden of cancer increase as countries develop [11,16]. In 2016, the ASRs of the alcohol-attributable cancer burden were highest for countries with very high HDI (7.3 cancer deaths and 203.8 cancer DALYs lost per 100 000 people) and lowest for countries with medium HDI (2.5 cancer deaths and 78.8 cancer DALYs lost per 100 000 people) (Fig. 2.3.7). The site-specific alcohol-attributable cancer burden also varied by HDI. The largest contributors to the ASRs of alcohol-attributable cancer deaths were colorectal cancer in countries with very high HDI, liver cancer (see Chapter 5.6) in countries with low HDI and countries with high HDI, and cancers of the lip and oral cavity in countries with medium HDI.

The alcohol-attributable cancer deaths and cancer DALYs lost discussed above include only cancer sites for which sufficient causal evidence exists, as determined by the IARC Monographs, and do not include cancer sites for which there was insufficient evidence of carcinogenicity in humans [1]. However, an analysis conducted for France in 2015 found that the proportion of cancer incidence due to alcohol increased from 7.9% when limited to cancers for which sufficient causal evidence exists to 8.4% when including cancers for which at least limited evidence of a causal association exists [17].

Country- and region-specific analyses of the relative contributions of risk factors to the cancer burden in the USA [18], France [15], the United Kingdom [19], Australia [20], and the Nordic countries (Denmark, Finland, Iceland, Norway, Sweden, the Faroe Islands, and Greenland) [21] have shown that alcohol is a leading risk factor for cancer development and cancer death. In some analyses and countries, alcohol is the second most important risk factor for cancer development and cancer death after tobacco, for example in an analysis of nine behavioural and environmental risk factors for the Global Burden of Disease 2000 study [22] and in an analysis of 13 risk factors for France in 2015 [15].

Fig. 2.3.6. Age-standardized alcohol-attributable cancer deaths per 100 000 people (top) and alcohol-attributable cancer disability-adjusted life years (DALYs) lost per 100 000 people (bottom) in 2016, by geographical region.



Trends in the cancer burden due to alcohol from 2010 to 2016

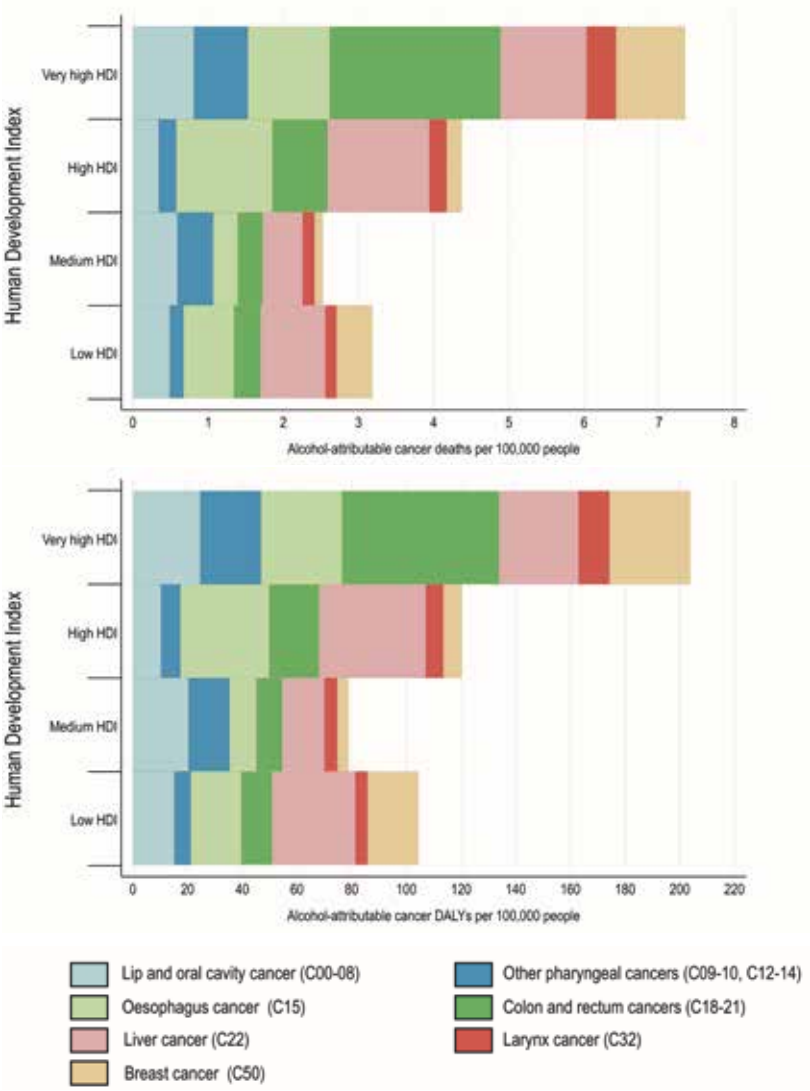
Trends in the alcohol-attributable cancer burden depend on changes in alcohol consumption as well as in cancer incidence, treatment, and mortality. As a result of population growth and ageing and the economic development of countries, the total number of cancer deaths worldwide increased from 8.1 million in 2010 to 9.0 million in 2016 [11]. However, the ASR of cancer mortality decreased by 6.0% (from 122.4 per 100 000 in 2010 to 115.0 per 100 000 in 2016), less than the 9.0% decrease in the ASR of overall mortality (from 791.3 per 100 000 in 2010 to 720.1 per 100 000 in 2016).

The ASRs of alcohol-attributable mortality decreased less than overall cancer mortality rates in general (by 4.8%, from 5.1 deaths per 100 000 in 2010 to 4.8 deaths per 100 000 in 2016), resulting in an increase of 1.5% in the proportion of cancer deaths attributable to alcohol consumption (from 4.1% in 2010 to 4.2% in 2016). Thus, the relative impact of alcohol on cancer mortality increased slightly from 2010 to 2016.

Trends in the ASRs of alcohol-attributable cancer mortality and in the proportion of cancers attributable to alcohol consumption showed heterogeneous patterns by cancer site. In particular, the ASR of mortality due to cancers of the lip and oral cavity was the only ASR to increase (from 2.1 deaths per 100 000 in 2010 to 2.2 deaths per 100 000 in 2016), and the ASR of mortality due to oesophageal cancer (see Chapter 5.3) decreased the most (from 6.2 deaths per 100 000 in 2010 to 5.5 deaths per 100 000 in 2016).

In the long term, increases in the economic wealth of countries are likely to lead to further increases in life expectancies, resulting in higher incidence of and mortality from cancer and a concomitant higher relative importance of cancer as a cause

Fig. 2.3.7. Age-standardized alcohol-attributable cancer deaths per 100 000 people (top) and alcohol-attributable disability-adjusted life years (DALYs) lost per 100 000 people (bottom) in 2016, by level of Human Development Index (HDI).



of death (http://www.healthdata.org/results/country-profiles), as well as to higher per capita alcohol consumption [11,14]. Furthermore, because the median latency between mean alcohol consumption and the diagnosis of cancer is 10 years [23], it is expected that alcohol-attributable cancer mortality will continue to increase in the countries that have had the most pronounced increases in alcohol consumption over the past few years. Examples of such countries are China and India, countries in which life expectancies have also increased ([11]; http://www.healthdata.org/results/country-profiles). Accordingly, whereas in high-income countries alcohol consumption, cancer mortality rates, and alcohol-attributable cancer mortality rates have declined, and may continue to decline, the overall global burden of alcohol-attributable cancers is not expected to decrease, and may increase in the long term.

The cancer burden due to alcohol is preventable

The current burden of cancers caused by alcohol consumption is large, and this burden is expected to increase in the future. Therefore, programmes designed to reduce alcohol consumption in the general population are an effective and cost-effective means of targeting and improving cancer control (see Chapter 6.1). The observed differences between countries and regions in alcohol-attributable fractions of cancer deaths and cancer DALYs lost provide an evidence base for how to reduce this burden through individual-level and societal-level programmes that reduce alcohol consumption, such as the WHO intervention strategies known as alcohol policy "best buys", which include increasing excise taxation of alcoholic beverages, restricting access to retailed alcoholic beverages, and limiting advertising and promotion of alcoholic products [24].

Furthermore, the burden of alcohol-attributable cancers could be reduced through measures that target those risk factors that interact with alcohol consumption to increase the risk of cancer or that directly affect the risk of alcohol-related cancers, such as tobacco smoking (see "Tobacco cessation: the WHO perspective"). In addition, early recognition of the signs and symptoms of cancer, as well as prompt diagnosis of precancerous lesions and tumours, are in many cases vital to patient survival, and therefore screening for colorectal cancer and breast cancer may also reduce the burden of alcohol-attributable cancers [25].

Finally, despite the evidence of the causal relationship between alcohol consumption and the development of cancer, the majority of the general population is unaware of this causal link [26]. Warning labels can be used to raise awareness of the link between alcohol and cancer; however, the effectiveness of these labels to reduce alcohol consumption is currently unknown [11]. In addition, explaining the causal link between alcohol and cancer could be part of brief interventions by medical professionals in primary care, to reduce alcohol consumption [27].

References

1. IARC (2012). Personal habits and indoor combustions. IARC Monogr Eval Carcinog Risks Hum. 100E:1–575. PMID:23193840. Available from: http://publications.iarc.fr/122.
2. WCRF/AICR (2018). Diet, nutrition, physical activity and cancer: a global perspective. Continuous Update Project Expert Report 2018. World Cancer Research Fund/American Institute for Cancer Research. Available from: https://www.wcrf.org/dietandcancer.
3. Pflaum T, Hausler T, Baumung C, Ackermann S, Kuballa T, Rehm J, et al. (2016). Carcinogenic compounds in alcoholic beverages: an update. Arch Toxicol. 90(10):2349–67. https://doi.org/10.1007/s00204-016-1770-3 PMID:27353523
4. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer. 112(3):580–93. https://doi.org/10.1038/bjc.2014.579 PMID:25422909
5. Rehm J, Gmel GE Sr, Gmel G, Hasan OSM, Imtiaz S, Popova S, et al. (2017). The relationship between different dimensions of alcohol use and the burden of disease – an update. Addiction. 112(6):968–1001. https://doi.org/10.1111/add.13757 PMID:28220587
6. Bergmann MM, Rehm J, Klipstein-Grobusch K, Boeing H, Schütze M, Drogan D, et al. (2013). The association of pattern of lifetime alcohol use and cause of death in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Int J Epidemiol. 42(6):1772–90. https://doi.org/10.1093/ije/dyt154 PMID:24415611
7. Liu Y, Nguyen N, Colditz GA (2015). Links between alcohol consumption and breast cancer: a look at the evidence. Womens Health (Lond). 11(1):65–77. https://doi.org/10.2217/WHE.14.62 PMID:25581056
8. Pierce BL, Kraft P, Zhang C (2018). Mendelian randomization studies of cancer risk: a literature review. Curr Epidemiol Rep. 5(2):184–96. https://doi.org/10.1007/s40471-018-0144-1 PMID:30034993
9. Druesne-Pecollo N, Tehard B, Mallet Y, Gerber M, Norat T, Hercberg S, et al. (2009). Alcohol and genetic polymorphisms: effect on risk of alcohol-related cancer. Lancet Oncol. 10(2):173–80. https://doi.org/10.1016/S1470-2045(09)70019-1 PMID:19185835
10. LoConte NK, Brewster AM, Kaur JS, Merrill JK, Alberg AJ (2018). Alcohol and cancer: a Statement of the American Society of Clinical Oncology. J Clin Oncol. 36(1):83–93. https://doi.org/10.1200/JCO.2017.76.1155 PMID:29112463
11. WHO (2018). Global status report on alcohol and health 2018. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/substance_abuse/publications/global_alcohol_report/en/.
12. Rothman KJ, Greenland S, Lash TL (2008). Modern epidemiology. 3rd ed. Philadelphia (PA), USA: Lippincott Williams & Wilkins.
13. Shield KD, Parkin DM, Whiteman DC, Rehm J, Viallon V, Micallef CM, et al. (2016). Population attributable and preventable fractions: cancer risk factor surveillance, and cancer policy projection. Curr Epidemiol Rep. 3(3):201–11. https://doi.org/10.1007/s40471-016-0085-5 PMID:27547696
14. Manthey J, Shield KD, Rylett M, Hasan OSM, Probst C, Rehm J (2019). Global alcohol exposure between 1990 and 2017 and forecasts until 2030: a modelling study. Lancet. 393(10190):2493–2502. https://doi.org/10.1016/S0140-6736(18)32744-2 PMID:31076174
15. Soerjomataram I, Shield K, Marant-Micallef C, Vignat J, Hill C, Rogel A, et al. (2018). Cancers related to lifestyle and environmental factors in France in 2015. Eur J Cancer. 105:103–13. https://doi.org/10.1016/j.ejca.2018.09.009 PMID:30445359
16. Bray F, Jemal A, Grey N, Ferlay J, Forman D (2012). Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. Lancet Oncol. 13(8):790–801. https://doi.org/10.1016/S1470-2045(12)70211-5 PMID:22658655
17. Shield KD, Marant Micallef C, Hill C, Touvier M, Arwidson P, Bonaldi C, et al. (2018). New cancer cases in France in 2015 attributable to different levels of alcohol consumption. Addiction. 113(2):247–56. https://doi.org/10.1111/add.14009 PMID:28833736
18. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. (2018). Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 68(1):31–54. https://doi.org/10.3322/caac.21440 PMID:29160902
19. Parkin DM, Boyd L, Walker LC (2011). 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 105(Suppl 2):S77–81. https://doi.org/10.1038/bjc.2011.489 PMID:22158327
20. Whiteman DC, Webb PM, Green AC, Neale RE, Fritschi L, Bain CJ, et al. (2015). Cancers in Australia in 2010 attributable to modifiable factors: summary and conclusions. Aust N Z J Public Health. 39(5):477–84. https://doi.org/10.1111/1753-6405.12471 PMID:26437735
21. Andersson TM, Engholm G, Pukkala E, Stenbeck M, Tryggvadottir L, Storm H, et al. (2018). Avoidable cancers in the Nordic countries – the impact of alcohol consumption. Eur J Cancer. 103:299–307. https://doi.org/10.1016/j.ejca.2018.03.027 PMID:29739641
22. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M; Comparative Risk Assessment collaborating group (Cancers) (2005). Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet. 366(9499):1784–93. https://doi.org/10.1016/S0140-6736(05)67725-2 PMID:16298215
23. Holmes J, Meier PS, Booth A, Guo Y, Brennan A (2012). The temporal relationship between per capita alcohol consumption and harm: a systematic review of time lag specifications in aggregate time series analyses. Drug Alcohol Depend. 123(1–3):7–14. https://doi.org/10.1016/j.drugalcdep.2011.12.005 PMID:22197480
24. Chisholm D, Moro D, Bertram M, Pretorius C, Gmel G, Shield K, et al. (2018). Are the "best buys" for alcohol control still valid? An update on the comparative cost-effectiveness of alcohol control strategies at the global level. J Stud Alcohol Drugs. 79(4):514–22. https://doi.org/10.15288/jsad.2018.79.514 PMID:30079865
25. Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, et al. (2018). Cancer screening in the United States, 2018: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 68(4):297–316. https://doi.org/10.3322/caac.21446 PMID:29846940
26. Scheideler JK, Klein WMP (2018). Awareness of the link between alcohol consumption and cancer across the world: a review. Cancer Epidemiol Biomarkers Prev. 27(4):429–37. https://doi.org/10.1158/1055-9965.EPI-17-0645 PMID:29615419
27. Babor TF, Higgins-Biddle JC (2000). Alcohol screening and brief intervention: dissemination strategies for medical practice and public health. Addiction. 95(5):677–86. https://doi.org/10.1046/j.1360-0443.2000.9556773.x PMID:10885042

2.4 Sunlight and ultraviolet radiation
Affecting skin cancer incidence in many countries

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SUMMARY

- Ultraviolet radiation directly and indirectly induces DNA lesions, which cause mutations and trigger inflammation and immunosuppression, which mediate tumour growth. Both ultraviolet radiation itself and ultraviolet-induced inflammation lead to the generation of reactive oxygen species. These reactive oxygen species also cause DNA lesions and increase the frequency of mutations. Furthermore, lipid peroxidation caused by ultraviolet radiation and reactive oxygen species also contributes to immunosuppression.
- The incidence of skin cancers is increasing worldwide, and especially in older people.
- The most effective way to reduce skin cancer incidence is to avoid unnecessary sun exposure, use protective measures when in the sun, and avoid tanning devices.
- Photocarcinogenesis is a complicated, multistep pathway, which is initiated by the formation of dipyrimidine photoproducts, which lead to the formation of mutations (the initiation phase). Sunburn and inflammation caused by the presence of persistent DNA lesions, including dipyrimidine photoproducts and oxidative DNA lesions, function as the promotion phase in photocarcinogenesis. Dipyrimidine photoproducts trigger ultraviolet-induced immunosuppression, which leads to the failure of immunosurveillance and enables the cancer cells to grow and progress.
- People who are taking immunosuppressants or some other kinds of medication, including voriconazole and hydrochlorothiazide, should be careful to protect themselves from exposure to sunlight.

Solar radiation encompasses a broad range of wavelengths of photon energy in the electromagnetic spectrum, including ionizing radiation, ultraviolet (UV) radiation, visible light, and infrared radiation (Fig. 2.4.1). UV radiation is conventionally classified into three types: UVA (wavelengths of 315–400 nm), UVB (280–315 nm), and UVC (100–280 nm). Solar UV radiation has beneficial biological effects, including enabling vitamin D synthesis, but its adverse effects include the induction of skin cancers (see Chapter 5.8).

Fig. 2.4.1. Schematic diagram of bands of solar radiation, classified by wavelength. UVR, ultraviolet radiation.

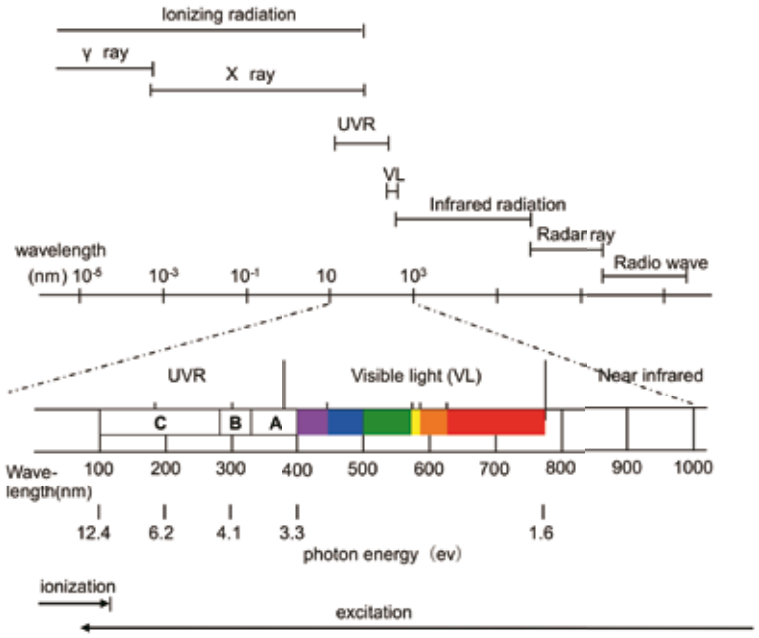
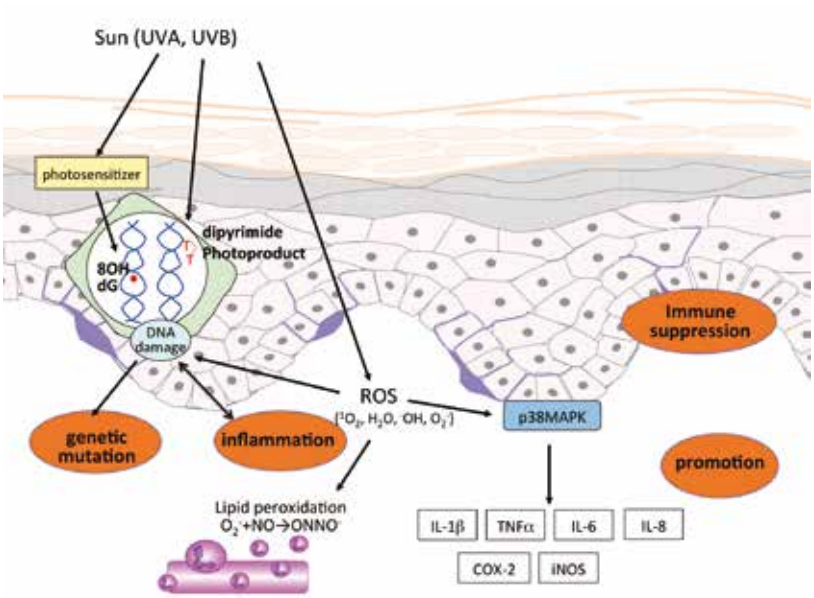


Fig. 2.4.2. Schematic summary of photocarcinogenesis as detailed in the text. COX-2, cyclooxygenase 2; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; 8-OHdG, 8-hydroxydeoxyguanosine; ROS, reactive oxygen species; TNF-α, tumour necrosis factor α.



FUNDAMENTALS

- Solar radiation encompasses a broad range of wavelengths of photon energy, including ionizing radiation, ultraviolet radiation, visible light, and infrared radiation. Ultraviolet radiation is conventionally classified into three types: UVA (wavelengths of 315–400 nm), UVB (280–315 nm), and UVC (100–280 nm).
- Solar ultraviolet radiation has beneficial biological effects, including enabling vitamin D synthesis, but its adverse effects include sunburn and the development of solar lentigines, immunosuppression, and skin cancers.
- Irradiating mice with ultraviolet radiation induces skin cancer, and the action spectrum in the mouse model of ultraviolet-induced photocarcinogenesis falls into the UVB range.
- Ultraviolet radiation generates DNA photolesions, and such dipyrimidine photoproducts include cyclobutane pyrimidine dimers and (6–4) photoproducts, which are mutagenic and contribute to cancer development.

A simple perspective is that UVB-induced DNA photolesions cause mutations, which may be equated with *initiation*, a term originally used to describe the first phase of chemically induced carcinogenesis in rodents; on the same basis, UVB-induced inflammation, and specifically sunburn, equates to the *promotion* phase of carcinogenesis. However, recent findings have revealed that the photocarcinogenesis pathway is more complex; each of these processes is mediated by various cellular, biochemical, and molecular changes, which are closely interrelated (see Chapter 3.11).

The accumulation of DNA photolesions caused by UV radiation in several cancer-related genes, which may still be regarded as the initiation phase, plays a crucial role in carcinogenesis. These DNA photolesions contribute to the development of skin cancers through specific mutations that lead to the upregulation or downregulation of signal transduction pathways of cell growth and cell-cycle dysregulation [1,2]. In addition, pyrimidine dimers play a role in UV-induced immunosuppression, which also plays an important role in photocarcinogenesis [3], partly by upregulation of interleukin 10 (IL-10), an immunosuppressive cytokine [4]. In skin cells, UV radiation also produces oxidative stress and oxidative DNA damage, which cause alteration of the genes involved in apoptosis and modification of cell signalling by redox regulation, resulting in inflammation (Fig. 2.4.2).

In this chapter, knowledge about photocarcinogenesis is summarized.

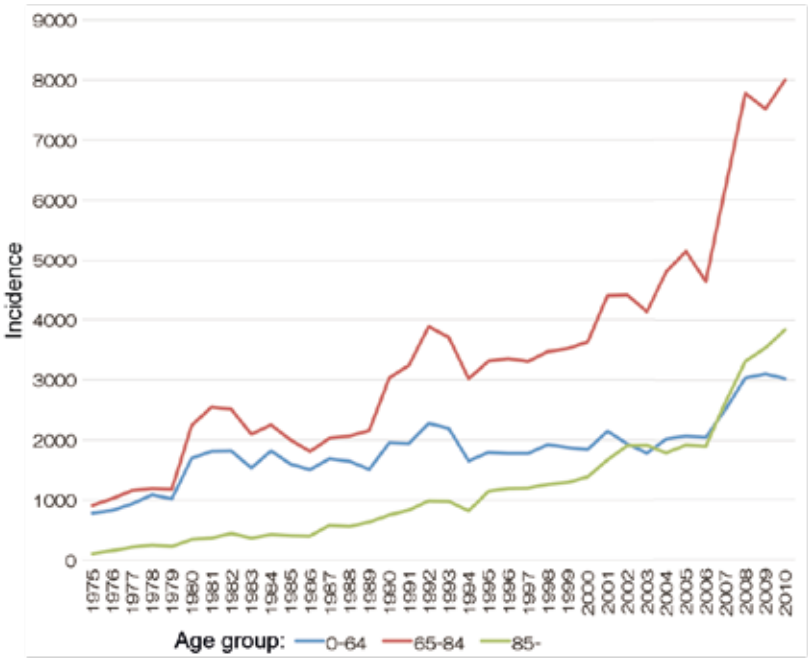
Sources of ultraviolet radiation

The main source of human exposure to UV radiation is solar radiation. In addition, many people have been exposed through the use of tanning devices (sunlamps and sunbeds), which are artificial sources of UV radiation; this warrants concern for human health (as discussed later).

In some occupational circumstances, UV lamps are used for the purpose of polymerization, typically in the course of hardening resin and coating. Modern factories have production processes designed so that employees are well protected, and therefore such lamps are rarely associated with harmful impacts on human health. Germicidal UV lamps are commonly used to disinfect rooms, the floors of laboratories, and sometimes public spaces, including hospitals, gymnasiums, and swimming pools.

Special UV lamps are used therapeutically to treat certain skin diseases, including vitiligo vulgaris, psoriasis, and atopic dermatitis. Currently, for therapeutic purposes,

Fig. 2.4.3. Incidence of skin cancers in Japan in 1975–2010 in different age groups.



narrow-band UVB sources that emit specifically radiation of wavelength 311 nm are widely used, to reduce exposure to wavelengths shorter than 305 nm, which are most harmful in relation to developing skin cancer.

During the welding process, UV radiation is emitted, and therefore welders should use personal protective equipment in the course of their work (see Chapter 2.10).

The ozone layer in the stratosphere absorbs solar UV radiation of wavelengths shorter than 300 nm. Therefore, only UVA radiation and UVB with wavelengths longer than 300 nm reach the Earth's surface. The radiation reaching the Earth's surface is largely composed of UVA (95%), with a small UVB component (5%).

The level of solar UV exposure at the Earth's surface varies with latitude, altitude, time of day and time of year, cloud cover, other atmospheric factors (specifically including pollution), and reflection from nearby surfaces. UV radiation is stronger at high altitudes than at ground level, because the thinner atmosphere blocks less UV radiation. About 80% of solar UVB penetrates thin cloud. UVB scatters in the air and is reflected by buildings and land surfaces. The reflection of solar UV radiation varies depending on the condition of the land surface. Snow, sand, and other surfaces reflect UV radiation to varying degrees: new snow reflects 80%, a sandy beach reflects 10–25%, concrete or asphalt reflects 10%, the surface of water reflects 10–20%, and a lawn or grassy plain reflects 10%. The intensity of solar UV radiation depends on the height of the sun in the sky; it is strongest at solar noon and during the summer months.

Some weather services provide daily forecasts of the intensity of solar UV radiation. Such information may be helpful as a rough indication, but caution should be exercised, because the intensity of solar UV radiation differs greatly between locations where relevant measurements are conducted. Although several UV dosimetry instruments are commercially available, not all of the equipment is accurate and reliable. The best way to protect oneself from the sun is to adopt multiple personal measures, such as wearing protective clothing, wearing a hat, applying sunscreen, and using shade.

Epidemiology of skin cancers

The incidence of both melanoma and non-melanoma skin cancers is increasing worldwide, not only in White populations [5] but also in Asian populations. In addition, there is marked variation in incidence by geographical location between and within countries. Epidemiological studies have demonstrated a negative correlation between the latitude of residence and the incidence and mortality rates of melanoma and non-melanoma skin cancers in homogeneous populations.

According to statistics from the Ministry of Health, Labour and Welfare of Japan, the incidence of skin cancers in Japan has increased dramatically over the past decades, especially in people older than 65 years (Fig. 2.4.3). A longer life expectancy contributes to this increase in risk, because non-melanoma skin cancer is more common in older people. Furthermore, the incidence of non-melanoma skin cancer in men is strikingly higher than that in women in Japan as well as in Australasia, Europe, and North America, probably because the effects of lifestyle factors are similar in different countries.

The IARC Monographs classified UV-emitting tanning devices (sunlamps and sunbeds) as carcinogenic to humans (Group 1). Although commercial use of tanning devices is prohibited in some states of the USA, in almost all states and territories of Australia, and in some other countries, many people continue to use them. The association of sunbed exposure with predicted increased risk of induction of squamous cell carcinoma has been confirmed [6], and people should be aware of the risk associated with use of tanning devices.

Ultraviolet-induced DNA photolesions

The photon energy of UV radiation is not capable of causing ionization but results only in excitation at the atomic level. Therefore, all the biological consequences of UV radiation are

attributable to excited chemical reactions in the molecules of the skin. DNA directly absorbs more energy from UVB photons than from UVA photons. UVB specifically acts on DNA by directly exciting the nucleobases, resulting in the instant formation of dimeric photoproducts at dipyrimidine sites. In contrast, UVA and visible light primarily exert a biological impact directly by participating in the formation of reactive oxygen species in the presence of photosensitizers, and indirectly produce oxidative DNA lesions. UVB produces dipyrimidine photoproducts by direct excitation, and also generates oxidative DNA lesions.

Studies have suggested that dipyrimidine photoproducts are the most important UV-induced DNA photolesions, because they are involved in cytotoxicity and mutagenesis [7]. Reactive oxygen species cause various biological effects via the redox signalling pathway and produce oxidative DNA lesions, which also play a role in carcinogenesis [8]. Among oxidative DNA lesions, 8-hydroxydeoxyguanosine (8-OHdG) has been established as a sensitive marker of oxidative DNA damage. The guanine base in genomic DNA is highly susceptible to oxidative stress, because guanine has the lowest oxidation potential of all the bases.

Recent work has shown that cyclobutane pyrimidine dimers are produced at higher yields than 8-hydroxyguanine (8-oxoG) after exposure to UVA in human skin cells and human skin in vivo [9]. The diuretic medication hydrochlorothiazide significantly increases the production of thymine dimers by UVA, independent of the presence of oxygen [10]. This indicates that excited hydrochlorothiazide molecules function as UVA-absorbing chromophores, which transfer energy to adjacent pyrimidines, thereby resulting in the formation of thymine dimers.

Ultraviolet-induced DNA lesions and mutations in skin cancers

The action spectrum for UV-induced carcinogenesis in animal experimental models is maximal within the UVB range, with the peak at 293 nm [11]. Formation of dipyrimidine photoproducts can lead to UV signature mutations in DNA. UV signature mutations are associated with transition-type mutations such as C:G → T:A at dipyrimidine sequences, where a transition is defined as a change from one pyrimidine (cytosine or thymine) or purine (guanine or adenine) to the other. The molecular changes observed in skin cancers have been analysed in many studies. In White people, *TP53* mutations are present at much higher frequencies (~50–90%) in non-melanoma skin cancers than they are in internal malignancies [1]. These mutations are predominantly C:G → T:A at dipyrimidine sites, the UV signature mutations.

In Asian people, the UV signature mutations are significantly more frequent in skin cancers at sun-exposed body sites than in those at non-sun-exposed sites [12], suggesting that UV radiation is also closely involved in the development of non-melanoma skin cancer in Asian people. Several other reports have demonstrated that the types of mutations that are not considered to be caused by dipyrimidine photoproducts are frequently observed in human skin cancers at sun-exposed body sites [13], thereby suggesting that oxidative DNA lesions may also play a role to some extent in photocarcinogenesis.

Inflammation caused by sunburn promotes carcinogenesis, and particular DNA lesions are implicated

The sunburn process is dependent on several factors, including UV dose, UV wavelength, and photoskin type. After cellular molecules absorb UV radiation, photochemical reactions occur, and these processes are responsible for biological changes that culminate in sunburn. The findings of Devary et al. suggested that the UV response is initiated at or near the cell membrane rather than in the nucleus, and that the response may be elicited by oxidative stress caused by UV radiation [14]. There is plenty of evidence that various antioxidants attenuate erythema or oedema induced by UVB radiation [15]. Low levels of oxidants can modify cell signalling via redox regulation, and these signal modifications have functional consequences [16].

UV radiation triggers sequential molecular responses, thereby activating cell-surface growth factors and pro-inflammatory cytokine receptors. Mice deficient in tumour necrosis factor α (TNF-α), a pro-inflammatory cytokine, are resistant to skin carcinogenesis, although both deficient and wild-type mice exhibited the same c-Ha-*ras* mutations after treatment with 7,12-dimethylbenz[*a*]anthracene [17]. In animal photocarcinogenesis studies, some antioxidant nutrition that suppresses UV-induced inflammation has been shown to suppress cancer development.

Earlier, it was reported that in this mouse photocarcinogenesis model, the accumulation of 8-oxoG, an oxidative DNA photolesion, increases the development of skin cancers; this result is attributable to the upregulation of genes related to the inflammatory response pathway, such as *Cxcl1* and *Il-6*, but not to the mutations caused by oxidative DNA lesions [8]. Rodier et al. reported that large doses of UV radiation, which cause irreparable damage to cells, induce DNA double-strand breaks and increase secretion of IL-6 [18].

Melanoma and ultraviolet-induced inflammation

Recently, much attention has been paid to melanoma formation and UV-induced inflammation. It is generally accepted that chronic inflammation increases the risk of cancer; this is consistent with the finding that excessive intense, intermittent sun exposure is one of the most important risk factors for melanoma.

In hepatocyte growth factor/scatter factor transgenic mice, a single dose of burning UV radiation to neonates, but not to adults, is necessary

Fig. 2.4.4. Crowds at Bondi Beach, Sydney, Australia. A relatively high incidence of melanoma and other skin cancers is attributable to exposure of fair-skinned populations to intense ultraviolet radiation in countries such as Australia. The incidence of both melanoma and non-melanoma skin cancers is also increasing in Asian populations, specifically including those in Japan.

and sufficient to induce melanoma with a high incidence [19]. This provides an experimental basis for the epidemiological evidence that childhood sunburn is a major risk factor for the development of melanoma [20].

Whether UVA or UVB radiation is more dangerous for the development of melanoma is still controversial. Both non-melanocytic skin cancers and melanomas are induced by solar UV radiation, but there are some differences. Melanocytes show resistance to UVB-induced apoptosis. Consequently, melanocytes survive after acute sunburn, while harbouring high levels of DNA lesions, whereas keratinocytes tend to undergo apoptosis after large doses of UV radiation. The most frequent body sites for the development of superficial spreading melanoma, which is the most common type of malignant melanoma in the White population, are the trunk and thigh; these anatomical regions are often particularly exposed to the sun when sunbathing. Eumelanin protects the skin against UV-induced damage, whereas pheomelanin acts as a photosensitizer and causes oxidative DNA damage in melanocytes.

Role of UVA in photocarcinogenesis

Until recently, studies on carcinogenesis induced by UV radiation have focused on UVB-induced DNA mutations. However, the role of UVA in photocarcinogenesis is now receiving much more attention. One reason for this is increasing awareness of the involvement of UVA-induced reactive oxygen species in the development of melanoma. Another reason is that many studies have revealed that UVA generates not only reactive oxygen species but also cyclobutane pyrimidine dimers in vivo.

Cyclobutane pyrimidine dimers are now known to be produced at higher yields than 8-oxoG after UVA irradiation in rodent and human skin cells [9], prompting a paradigm shift in the theory of photocarcinogenesis. A recent series of studies demonstrating that UVA induces thymine dimers at much higher levels than other types of pyrimidine dimers, and that UVA does not induce (6–4) photoproducts [9], explains the mutation spectrum of the relevant genes in cancers at sun-exposed areas of the skin in humans [2]. An in vivo study analysing the action spectrum for photocarcinogenesis in a mouse model revealed that UVA is partly responsible for photocarcinogenesis [11].

UVA seems to cause cancer-promoting biological changes apart from DNA lesions that result in genomic mutations. Many of the carcinogenic functions of UVA have been attributed to the production of reactive oxygen species and the subsequent induction of the inflammatory signalling pathway. Reactive oxygen species generated by UV radiation upregulate the expression of many signalling molecules, including inducible nitric oxide synthase (iNOS), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activator protein 1 (AP-1), signal transducer and activator of transcription (STAT), and cyclooxygenase 2 (COX-2), resulting in inflammation, which is followed, in turn, by generation of reactive oxygen species, depending on the strength of the inflammation.

Ultraviolet-induced immunosuppression

The immune system plays an important role in UV-induced carcinogenesis by contributing to host resistance to skin cancer development. However, UV radiation may circumvent immunosurveillance against skin cancers by modulating the immune response in a way that favours tumour development.

Skin cancers induced by UV radiation are highly antigenic, and can therefore be recognized by the immune system. This is evident from UV-induced murine skin cancers, many of which are immunologically rejected upon transplantation into normal syngeneic mice [3]. The exceptionally high incidence of skin cancers, particularly squamous cell carcinoma, in the sun-exposed skin of immunosuppressed renal transplant recipients or patients who received phototherapy together with an immunosuppressant [21] suggests that UV-induced human skin cancers are also highly antigenic.

However, despite the potential for immunological control, skin cancers

occur with a high frequency in susceptible, sun-exposed populations. Earlier studies, mainly those using mouse models, have provided an explanation for this paradox by demonstrating that UV radiation not only transforms cells by inducing mutations but also interferes with host immunity against the developing skin tumours. These studies demonstrated that UV irradiation of the skin produces both local immunosuppression, which inhibits immune functions within the irradiated skin, and systemic immunosuppression against antigens introduced at a critical time after exposure to UV radiation.

Modulation of immune responses initiated at non-irradiated sites is now known to involve soluble mediators. Among such soluble mediators, IL-10 is crucial in the photocarcinogenesis pathway [22]. IL-10 polymorphisms and susceptibility to squamous cell carcinoma have been reported in several studies in humans.

Failure of immunosurveillance is closely related in photocarcinogenesis, and in this context, the use of a Toll-like receptor agonist recently emerged as a new strategy for cancer treatment. Imiquimod, an agonist for Toll-like receptor 7, is now clinically used worldwide for the therapy of actinic keratosis, a precancerous lesion caused by sun damage that has the potential to progress to squamous cell carcinoma.

Prevention of damage from solar ultraviolet radiation

The most effective way to reduce skin cancer incidence is to avoid unnecessary sun exposure and adopt personal preventive measures for protection from sunlight, such as wearing protective clothing, wearing a hat, applying sunscreen, and using shade. Minimizing the time spent outdoors between the hours of 9:00 a.m. and 3:00 p.m. – the period when the intensity of sunlight is the strongest – markedly reduces the risk of sun damage.

Members of the public should be advised that the strength of UV radiation does not correlate with the temperature. For example, in March in the Northern Hemisphere, the intensity of UV radiation is strong even though temperatures may be low. Even on cloudy days, about 80% of the solar UV radiation reaches ground level. About 10% of solar UVB radiation passes through glass windows.

In relation to photocarcinogenesis, the heritable disease xeroderma pigmentosum should be kept in mind. Xeroderma pigmentosum is characterized by an extreme sensitivity to sunlight and a greatly increased risk of developing skin cancers at sun-exposed areas from early childhood, because of deficiency in the repair of DNA photolesions [2].

Recently, accelerated photoageing and development of skin cancer have been reported in patients who developed severe photosensitivity disorders after being treated with voriconazole, an antifungal agent [23]. Use of the diuretic antihypertensive medication hydrochlorothiazide was associated with increased risk of non-melanoma skin cancer in a nationwide case–control study in Denmark [24]. This epidemiological result is consistent with the finding that hydrochlorothiazide significantly increased the production of thymine dimers after exposure to radiation in the UVA range [10]. Taking account of these data and results from studies in animals and in humans, increased attention should be paid to any severe inflammatory lesions that are subject to UV radiation.

Fig. 2.4.5. Sun protection during play. Avoiding unnecessary sun exposure is critical to avoiding sunburn and the associated risk of skin cancer.

References

1. Ziegler A, Jonason AS, Leffell DJ, Simon JA, Sharma HW, Kimmelman J, et al. (1994). Sunburn and p53 in the onset of skin cancer. Nature. 372(6508):773–6. https://doi.org/10.1038/372773a0 PMID:7997263

2. Nishigori C, Hattori Y, Toyokuni S (2004). Role of reactive oxygen species in skin carcinogenesis. Antioxid Redox Signal. 6(3):561–70. https://doi.org/10.1089/152308604773934314 PMID:15130282

3. Kripke ML (1974). Antigenicity of murine skin tumors induced by ultraviolet light. J Natl Cancer Inst. 53(5):1333–6. https://doi.org/10.1093/jnci/53.5.1333 PMID:4139281

4. Nishigori C, Yarosh DB, Ullrich SE, Vink AA, Bucana CD, Roza L, et al. (1996). Evidence that DNA damage triggers interleukin 10 cytokine production in UV-irradiated murine keratinocytes. Proc Natl Acad Sci U S A. 93(19):10354–9. https://doi.org/10.1073/pnas.93.19.10354 PMID:8816804

5. Eisemann N, Waldmann A, Geller AC, Weinstock MA, Volkmer B, Greinert R, et al. (2014). Non-melanoma skin cancer incidence and impact of skin cancer screening on incidence. J Invest Dermatol. 134(1):43–50. https://doi.org/10.1038/jid.2013.304 PMID:23877569

6. Tierney P, de Gruijl FR, Ibbotson S, Moseley H (2015). Predicted increased risk of squamous cell carcinoma induction associated with sunbed exposure habits. Br J Dermatol. 173(1):201–8. https://doi.org/10.1111/bjd.13714 PMID:25645571

7. Ellison MJ, Childs JD (1981). Pyrimidine dimers induced in *Escherichia coli* DNA by ultraviolet radiation present in sunlight. Photochem Photobiol. 34(4):465–9. https://doi.org/10.1111/j.1751-1097.1981.tb09387.x PMID:7031709

8. Kunisada M, Sakumi K, Tominaga Y, Budiyanto A, Ueda M, Ichihashi M, et al. (2005). 8-Oxoguanine formation induced by chronic UVB exposure makes *Ogg1* knockout mice susceptible to skin carcinogenesis. Cancer Res. 65(14):6006–10. https://doi.org/10.1158/0008-5472.CAN-05-0724 PMID:16024598

9. Mouret S, Baudouin C, Charveron M, Favier A, Cadet J, Douki T (2006). Cyclobutane pyrimidine dimers are predominant DNA lesions in whole human skin exposed to UVA radiation. Proc Natl Acad Sci U S A. 103(37):13765–70. https://doi.org/10.1073/pnas.0604213103 PMID:16954188

10. Kunisada M, Masaki T, Ono R, Morinaga H, Nakano E, Yogianti F, et al. (2013). Hydrochlorothiazide enhances UVA-induced DNA damage. Photochem Photobiol. 89(3):649–54. https://doi.org/10.1111/php.12048 PMID:23331297

11. de Gruijl FR (1995). Action spectrum for photocarcinogenesis. Recent Results Cancer Res. 139:21–30. https://doi.org/10.1007/978-3-642-78771-3_2 PMID:7597292

12. Nishigori C (2006). Cellular aspects of photocarcinogenesis. Photochem Photobiol Sci. 5(2):208–14. https://doi.org/10.1039/B507471A PMID:16465307

13. Pierceall WE, Goldberg LH, Tainsky MA, Mukhopadhyay T, Ananthaswamy HN (1991). *Ras* gene mutation and amplification in human nonmelanoma skin cancers. Mol Carcinog. 4(3):196–202. https://doi.org/10.1002/mc.2940040306 PMID:2064725

14. Devary Y, Gottlieb RA, Smeal T, Karin M (1992). The mammalian ultraviolet response is triggered by activation of Src tyrosine kinases. Cell. 71(7):1081–91. https://doi.org/10.1016/S0092-8674(05)80058-3 PMID:1473146

15. Köpcke W, Krutmann J (2008). Protection from sunburn with beta-carotene – a meta-analysis. Photochem Photobiol. 84(2):284–8. https://doi.org/10.1111/j.1751-1097.2007.00253.x PMID:18086246

16. Sun Y, Oberley LW (1996). Redox regulation of transcriptional activators. Free Radic Biol Med. 21(3):335–48. https://doi.org/10.1016/0891-5849(96)00109-8 PMID:8855444

17. Moore RJ, Owens DM, Stamp G, Arnott C, Burke F, East N, et al. (1999). Mice deficient in tumor necrosis factor-alpha are resistant to skin carcinogenesis. Nat Med. 5(7):828–31. https://doi.org/10.1038/10552 PMID:10395330

18. Rodier F, Coppé JP, Patil CK, Hoeijmakers WA, Muñoz DP, Raza SR, et al. (2009). Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. Nat Cell Biol. 11(8):973–9. https://doi.org/10.1038/ncb1909 PMID:19597488

19. Noonan FP, Recio JA, Takayama H, Duray P, Anver MR, Rush WL, et al. (2001). Neonatal sunburn and melanoma in mice. Nature. 413(6853):271–2. https://doi.org/10.1038/35095108 PMID:11565020

20. Whiteman DC, Whiteman CA, Green AC (2001). Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control. 12(1):69–82. https://doi.org/10.1023/A:1008980919928 PMID:11227927

21. Naldi L (2010). Malignancy concerns with psoriasis treatments using phototherapy, methotrexate, cyclosporin, and biologics: facts and controversies. Clin Dermatol. 28(1):88–92. https://doi.org/10.1016/j.clindermatol.2009.03.003 PMID:20082957

22. Loser K, Apelt J, Voskort M, Mohaupt M, Balkow S, Schwarz T, et al. (2007). IL-10 controls ultraviolet-induced carcinogenesis in mice. J Immunol. 179(1):365–71. https://doi.org/10.4049/jimmunol.179.1.365 PMID:17579057

23. Sheu J, Hawryluk EB, Guo D, London WB, Huang JT (2015). Voriconazole phototoxicity in children: a retrospective review. J Am Acad Dermatol. 72(2):314–20. https://doi.org/10.1016/j.jaad.2014.10.023 PMID:25481710

24. Pedersen SA, Gaist D, Schmidt SAJ, Hölmich LR, Friis S, Pottegård A (2018). Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case-control study from Denmark. J Am Acad Dermatol. 78(4):673–681.e9. https://doi.org/10.1016/j.jaad.2017.11.042 PMID:29217346

2.5 Ionizing radiation and radiofrequency electromagnetic fields

Further clarification of particular risks

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SUMMARY

- Epidemiological studies involving people exposed to low levels of ionizing radiation from the environment (natural and artificial sources), occupations, or medical diagnostic procedures demonstrate that the risk of leukaemia and other cancers increases with radiation dose.
- The latency between exposure to ionizing radiation and occurrence of an excess risk of cancer varies from several years to several decades. In addition, host factors such as age at exposure, attained age, and sex modify the dose–risk relationship.
- Most of the epidemiological research does not support an association between mobile phone use and tumours occurring in the head, which is the body part with the highest exposure to radiofrequency electromagnetic fields. In studies reporting positive associations, it is difficult to exclude various forms of bias, such as recall bias in retrospective exposure assessment.

Ionizing radiation

Ionizing radiation is made up of electromagnetic waves on the high-energy end of the electromagnetic spectrum (X-radiation and γ-radiation) and energetic subatomic particles (neutrons, β-particles, and α-particles). This type of radiation carries enough energy to liberate electrons from atoms and thus is able to break chemical bonds.

Biological effects of ionizing radiation are determined by the amount of energy absorbed by the exposed organ or tissue. Low doses are generally defined as effective doses below 100 millisieverts (mSv).

Sources and exposures

Humans have always been exposed to ionizing radiation from natural sources. Natural radiation exposure comes from four main sources: cosmic radiation, terrestrial radiation, ingestion of radionuclides present in the soil and ground, and inhalation of radon. Exposure to cosmic radiation is higher at high altitudes. Exposure to natural radionuclides varies considerably from place to place according to geology. Radon is a gas that is formed during the decay of natural uranium in the soil. Exposure to indoor radon varies depending on the geology, building construction, and household lifestyle. Worldwide, inhalation of radon accounts for about half of the average exposure to natural radiation sources [1].

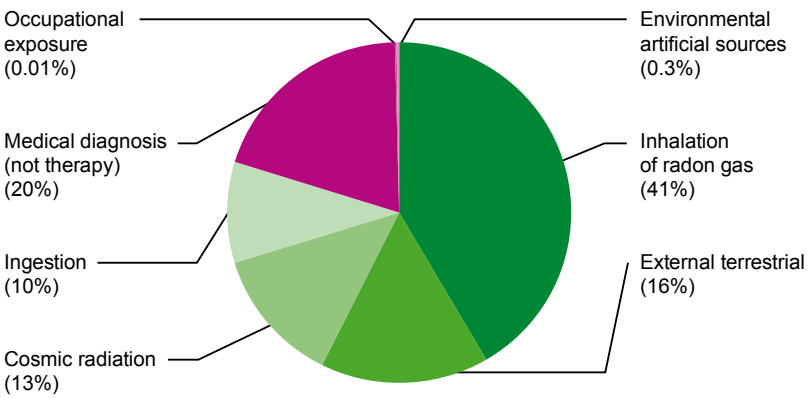
In addition, artificial sources of exposure have developed over the past century. Today, ionizing radiation is encountered in a wide variety of fields, such as medicine, nuclear power, research, manufacturing, and construction, and this can lead to environmental, occupational, or medical exposures. Environmental exposures include fallout from weapons testing, nuclear power plant accidents (such as those at Chernobyl and Fukushima), and routine releases from nuclear installations. Exposures to medical radiation provide a direct benefit to the exposed individuals. These exposures arise from some diagnostic procedures, such as radiography, nuclear medicine, and computed tomography (CT), or as a consequence of treatment, most commonly radiotherapy for cancer. Medical uses of radiation have increased rapidly as techniques have been developed and widely disseminated.

The contributions of the main components of average population exposure are detailed in Fig. 2.5.1. The worldwide average annual effective dose is about 3 mSv, and individual doses vary from tenths of millisieverts to several tens of millisieverts, according to place of residence and behaviour [1].

Cancer causation

Ionizing radiation is one of the most intensely studied carcinogens [2]. The mechanisms by which radiation may produce carcinogenic changes include mutations, alterations in the structure of genes or chromosomes (see Chapter 3.11), and changes in gene expression. Radiobiological research in recent decades has shown the biological complexity of

Fig. 2.5.1. Average annual doses of ionizing radiation by source. The worldwide average annual effective dose is about 3 millisieverts (mSv). Natural sources (2.4 mSv; 80%) are shown in green, and artificial sources (0.6 mSv; 20%) are shown in pink. Environmental artificial sources include atmospheric nuclear testing (0.2%), releases from the Chernobyl accident (0.1%), and routine releases from the nuclear fuel cycle (0.01%).



the carcinogenic impact of radiation, and many uncertainties still remain, especially at low doses.

Evidence that ionizing radiation can cause cancer in humans comes from epidemiological studies, especially from studies of patients irradiated for therapeutic reasons and from the follow-up of Japanese atomic bomb survivors. In recent decades, other studies have provided complementary results in populations exposed to lower doses, from environmental (e.g. natural exposure, consequences of nuclear accidents), occupational (e.g. miners, nuclear workers), or medical (e.g. diagnostic procedures) situations.

The latency between exposure to ionizing radiation and occurrence of an excess risk of cancer varies from several years to several decades. In addition, host factors such as age at exposure, attained age, and sex modify the dose–risk relationship.

Recent epidemiological results

Atomic bomb survivors

The follow-up of cancer mortality and incidence in the cohort of atomic bomb survivors exceeds 60 years after exposure. This large cohort includes more than 86 000 people of both sexes and all ages, with acute external radiation exposure. The range of doses was 0–4 Sv, but about 80% of the survivors received less than 100 mSv. Recent results confirmed the existence of a dose–risk relationship for a large variety of cancer types, such as leukaemia and cancer of the bladder, breast, colon, liver, lung, skin, stomach, and thyroid, and improved the estimation of how the risk varies with age at exposure and attained age. A statistically significant dose–response relationship was observed for incidence of solid cancers in the 0–100 mSv dose range [3].

Patients

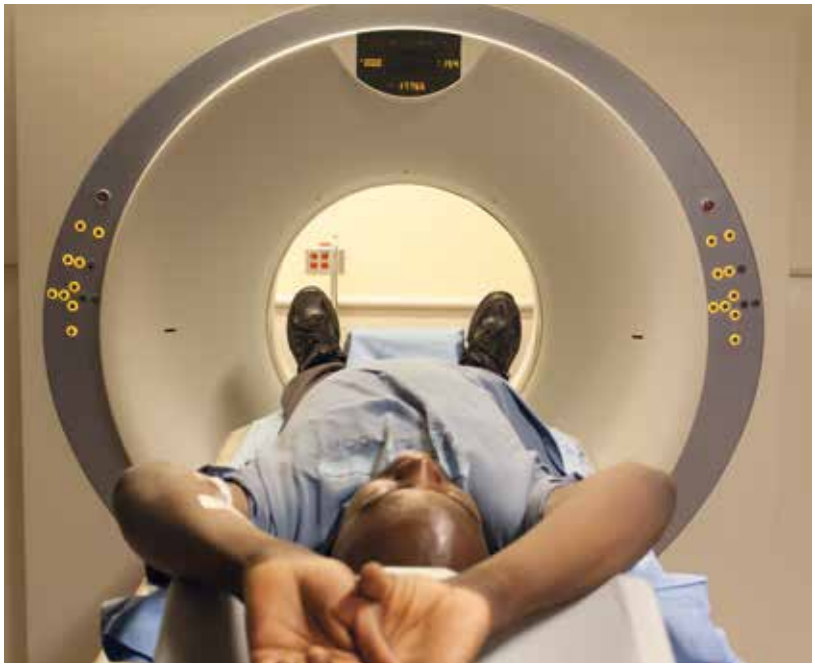
CT is a highly informative medical imaging technique, but it leads to much higher doses than conventional radiology. Therefore, the increasing use of CT scans in paediatric populations raised the question of a possible health impact of radiation exposure.

Cohort studies in Australia and the United Kingdom showed a statistically significant dose–response relationship between the dose to the red bone marrow due to CT examinations and the risk of leukaemia, and between the dose to the brain and the risk of brain tumours.

FUNDAMENTALS

- The electromagnetic spectrum is divided into non-ionizing and ionizing radiation.
- On average, natural sources contribute 80% to the average total dose of ionizing radiation in the population. The remaining 20% originates from artificial sources, such as medical diagnostic procedures, atmospheric nuclear testing, and nuclear power plant accidents. Inhalation of radon is the single highest source of exposure.
- Ionizing radiation is able to produce carcinogenic changes by mutations, alterations in the structure of genes or chromosomes, and changes in gene expression. Although considerable uncertainty still exists about the form of the dose–response relationship in the low-dose range, an increasing number of epidemiological studies indicate the carcinogenicity of ionizing radiation at relatively low dose levels.
- Most of the exposure to radiofrequency electromagnetic fields arises from people's own mobile phone calls, and thus the head is the most exposed body part.
- Despite considerable research efforts, no mechanism relevant for carcinogenesis of radiofrequency electromagnetic fields has been consistently identified to date. Also, most of the epidemiological research does not indicate carcinogenicity of radiofrequency electromagnetic fields. This implies that any potentially undetected risk is expected to be small from an individual perspective.

Fig. 2.5.2. A man undergoes a computed tomography (CT) scan, which involves exposure to ionizing radiation.



These results raised controversies about the impact of uncertainties in dosimetry and potential bias linked to underlying medical conditions (e.g. higher prevalence of predisposing factors, inverse causation). More recent studies tried to address these issues, and they suggest that these potential biases should be small [4]. The European EPI-CT project, which includes more than 1 million children, will provide new results on cancer risks associated with paediatric CT scans [5].

More information about thyroid cancer risks at low doses was provided by a pooled analysis of nine cohorts of more than 100 000 children (eight medical cohorts of children treated for benign and malignant diseases and the cohort of atomic bomb survivors). It showed a statistically significant linear dose–response relationship for thyroid doses of 0–100 mSv [6].

Workers

Nuclear industry workers are exposed to protracted low-dose radiation and are individually monitored for their occupational exposure. Several studies were published in recent years in France, Japan, Taiwan (China), the United Kingdom, and the USA, including results from the INWORKS project (see "INWORKS:

INWORKS: a pooled analysis of cancer risks associated with ionizing radiation among nuclear workers

The International Nuclear Workers Study (INWORKS) is a multinational research project coordinated by IARC. It evaluated the exposures of more than 300 000 workers in the nuclear industry in France, the United Kingdom, and the USA, with detailed individual monitoring data for external exposure to ionizing radiation.

Over an average follow-up duration of 27 years, there were 17 957 deaths due to solid cancers and 1791 deaths due to haematological cancers. The average individual cumulative external dose over the period 1945–2005 was 21 mSv to the colon and 16 mSv to the red bone marrow.

Analyses demonstrated a significant association between the dose to the red bone marrow and the risk of leukaemia (excluding chronic lymphoblastic leukaemia), and between the dose to the colon and the risk of solid cancers [1,2]. These associations were significant even when the analyses were restricted to a low-dose range of 0–300 mSv. The estimated dose–risk coefficients were very consistent with those derived from the cohort of atomic bomb survivors, which form the main basis for the system of radiological protection.

INWORKS is contributing to strengthening the scientific basis for the protection of adults from low-dose, low-dose-rate exposures to ionizing radiation.

References

1. Leuraud K, Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, et al. (2015). Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. Lancet Haematol. 2(7):e276–81. https://doi.org/10.1016/S2352-3026(15)00094-0 PMID:26436129
2. Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, Hamra GB, et al. (2015). Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS). BMJ. 351:h5359. https://doi.org/10.1136/bmj.h5359 PMID:26487649

a pooled analysis of cancer risks associated with ionizing radiation among nuclear workers"). These results strengthen the quantification of risks associated with external exposures to ionizing radiation at a low dose rate.

Other studies quantified a dose relationship for specific internal exposures. A recent analysis of cohorts of uranium miners confirmed the association between radon exposure and risk of lung cancer, even among miners with low levels of exposure [7]; the results were consistent with those from studies of indoor radon. Also, an analysis of the cohort of workers from the Mayak nuclear facility in the Russian Federation confirmed the existence of a relationship between lung dose due to plutonium and lung cancer risk, compatible with a linear model without threshold [8].

Fig. 2.5.3. Debris from the upper levels of unit 4 at the Fukushima Daiichi power plant in December 2012, 21 months after the nuclear accident.

Nuclear accidents

The largest nuclear accident in the world occurred on 26 April 1986 at the Chernobyl nuclear plant in Ukraine. This accident resulted in a large release of radionuclides, which were deposited over a very wide area; the greatest deposits were in Belarus, the western part of the Russian Federation, and Ukraine. Recent results confirmed the excess risk of thyroid cancer associated with exposure to iodine-131 among people exposed during childhood, and demonstrated the persistence of this excess risk among people who are now adults (see Chapter 5.18). About 25% of thyroid cancer cases in the contaminated area among people who were children or adolescents at the time of the accident have been attributed to this exposure [9].

The Fukushima Daiichi nuclear accident occurred on 11 March 2011 in Japan. Compared with the Chernobyl accident, this accident resulted in a much lower release of radionuclides, which were essentially deposited over some parts of Fukushima Prefecture. Furthermore, preventive measures, such as evacuation and food restrictions, resulted in much lower thyroid doses to the resident populations than after the Chernobyl accident. The estimated doses are low and are limited to a small population, and no observable radiation-induced excess risk of cancer is expected.

A large project has been launched, called the Fukushima Health Management Survey, which includes systematic thyroid examinations of children and adolescents. A large number of thyroid cancer cases have been recorded [10], but these are mostly attributable to the implementation of screening, which led to the detection of small, indolent cancers and to overdiagnosis [11].

Other environmental exposures

A case–control study in Great Britain that included more than 9000 cases of leukaemia and 18 000 cases of other childhood cancers observed a statistically significant dose–response relationship between leukaemia and the cumulative dose to the red bone marrow due to background radiation exposure, but found no clear evidence of a relationship for other childhood cancers [12]. A cohort of 2 million children in Switzerland, including 530 leukaemia cases and 1252 cases of other childhood cancers, suggested a positive relationship between exposure to background radiation and both leukaemia risk and cancer risk, at the limit of statistical significance [13].

Prevention

A comprehensive system of protection against ionizing radiation has been developed, based especially on recommendations from the International Commission on Radiological Protection. Recent studies have improved our knowledge of radiation-induced risks at low doses, down to a few hundreds of millisieverts for solid cancers [14] and a few tens of millisieverts for childhood leukaemia [15]; these results have contributed to the strengthening of the radiation protection system. In the medical field, the benefits of radiation applications for medical diagnostic procedures are undeniable, but recent results from epidemiology and the increasing use of CT scans highlight the need to enhance awareness among medical practitioners

and to reinforce prevention, through the use of dose optimization and procedure justification.

Radiofrequency electromagnetic fields

Sources and exposures

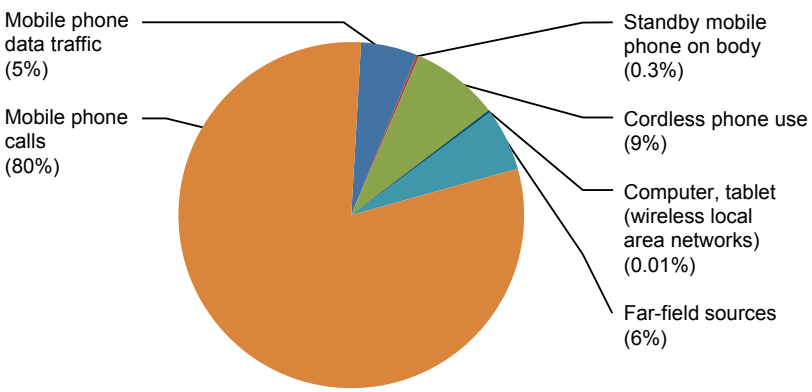
Radiofrequency electromagnetic fields (RF-EMF) are emitted from various sources. For the public, the most relevant sources in daily life are wireless communication devices and transmitters.

Wireless phones and other devices that are used close to the body produce a near-field exposure, which is characterized by the specific absorption rate (expressed in watts per kilogram of tissue weight) [16]. Transmitters that are further away, such as access points in wireless local area networks, base stations for mobile and cordless phones, broadcast transmitters, and other people's mobile phones, are far-field sources, and the most common exposure metric is the incident electric field (in volts per metre). Combining the two exposure measures into a single dose measure requires dosimetric calculations.

In a recent cohort study of adolescents in Switzerland, contributions of various RF-EMF sources to the dose to grey matter in the brain were estimated [17]. In this cohort of moderate users of mobile phones and cordless phones (with calls lasting on average 11 minutes and 6 minutes per day, respectively), mobile and cordless phone calls contributed 80% and 8%, respectively, to the average grey matter dose from RF-EMF (Fig. 2.5.4). The proportion from all far-field sources combined was 6%, including 3% from mobile phone base stations and 2% from other people's mobile phones.

As technology and knowledge advance, these dose estimates may change. One of the main uncertainties in such calculations is the adaptive power control of mobile phones in response to the network quality. For instance, the average output power for calls made on the Global System for Mobile Communications (GSM) network (2G) was shown to be 100–500 times that for calls on the Universal Mobile Telecommunications System (UMTS) network (3G) [18,19]. This implies that in new epidemiological research since the introduction of UMTS, one would expect a lower cumulative dose to the brain for the same amount of mobile phone use. The increased variability in the output power of mobile phones implies that in new studies, duration of mobile phone use has become a less valid surrogate of the RF-EMF exposure of the brain than in older studies. It is not yet known what the situation will be for the Long-Term Evolution (LTE) network (4G) or for 5G.

Fig. 2.5.4. Contribution of various sources that emit radiofrequency electromagnetic fields (RF-EMF) to the average daily dose to grey matter in the brain in a cohort of adolescents in Switzerland. The total average RF-EMF dose was 900 millijoules per kilogram (mJ/kg) per day. Mobile phone calls and data traffic contributed 85%. Far-field sources (6%) included mobile phone base stations (3.4%), other people's mobile phones (2.0%), access points in wireless local area networks (0.2%), broadcasting (0.2%), and cordless phone base stations (< 0.1%).



Cancer causation

Because RF-EMF belong to the non-ionizing part of the electromagnetic spectrum, the photon energy is too weak to ionize molecules [20] and thereby cause direct DNA damage. Absorption of RF-EMF is known to heat biological tissue, but a minimal temperature increase below the regulatory limits is not expected to increase the risk of cancer [16]. Despite considerable research efforts, no mechanism relevant for carcinogenesis has been consistently identified to date [21].

Recent epidemiological results

In the past 5 years, epidemiological research on mobile phone use and tumours occurring in the head has slowed down compared with the previous decade. Most new and previous case–control studies do not indicate an association between mobile phone use and risk of glioma, meningioma, acoustic neuroma, pituitary tumours, or salivary gland tumours [22]. Sporadic associations observed in a few case–control studies are inconsistent in terms of exposure–response associations. For example, in a new analysis of pooled case–control studies in Sweden, with cases diagnosed in 1997–2003 and 2007–2009, glioma risk was higher for people with at least 123 hours of cumulative use [23], whereas in a case–control study in France with 253 glioma cases and 504 controls, glioma risk was significantly higher for people with at least 339 hours of cumulative use [24]. In contrast, in the large international Interphone study, which included 2708 glioma cases, 2409 meningioma cases,

and 1105 acoustic neuroma cases, no indication of higher risk was observed for cumulative use up to 1640 hours [25]. Thus, there is concern that some studies are affected by recall bias, because cases may overestimate their previous mobile phone use as a potential cause of their disease.

A recent study followed up 806 glioma cases previously enrolled in a collaborative population-based case–control study in Denmark, Finland, and Sweden for survival and found no evidence of reduced survival in relation to mobile phone use [26]. Strikingly, this study found some indications that prodromal symptoms of the tumour may prevent cases from starting to regularly use mobile phones, which may explain some of the seemingly protective effects of mobile phone use observed previously in the Interphone study [25].

In summary, such kinds of reverse causality, recall bias, and selection bias are potential issues in a case–control study. The continuing prospective COSMOS study, which is using operator-recorded data for mobile phone use, is less vulnerable to such kinds of recall bias and exposure misclassification [27].

Nowadays it is common for a large proportion of the population to have used a mobile phone for a few hundred hours, and simple calculations demonstrate that some of the reported excess risks for brain tumours would have been noticed by now. For instance, the populations of the Nordic countries were among the first to use mobile phones regularly, and in Europe a 50% penetration rate was achieved in 2000. Thus, substantially more than 50% of the population in European countries are now long-term mobile phone users, and reported excess risks on the order of 60–70% for long-term users would produce an increase in the incidence of glioma of at least 30%, which is not the case in people younger than 70 years [22].

In addition, a very comprehensive analysis of global trends of tumours of the brain and central nervous system, which included data from 1993–2007 from 96 registries in 39 countries, did not find a pattern supporting the hypothesis of increasing incidence rates following, with some latency, the time period of mobile phone uptake in different populations [28]. This analysis is in line with the results of several other time trend studies [29], although a few studies [30,31] reported increases in the incidence of specific topographic or morphological subtypes of brain cancer. However, in the same studies, a decrease in the incidence of other subtypes of brain cancer was seen, suggesting that these time trends may be explained by changes in cancer coding practices over time.

Research on exposures from transmitters has not progressed much in the past 5 years, and the evidence base has not expanded. Several reported clusters of childhood cancer in the vicinity of individual transmitters could not be confirmed in large population-based studies on childhood cancer in relation to RF-EMF emissions from broadcast transmitters and mobile phone base stations [32]. For adults, even fewer studies have been conducted. However, RF-EMF from transmitters will rarely be a relevant exposure source for adults who at least occasionally use wireless communication devices.

Fig. 2.5.5. Women using mobile phones in Kolkata, India.

Prevention

The large amount of research on RF-EMF suggests that any potentially undetected risk is expected to be small from an individual perspective. To address such small risks needs high-quality research with accurate exposure assessment, taking into account that the duration of mobile phone calls alone is not expected to adequately reflect the RF-EMF exposure of the brain. In the meantime, for tumours of the head with few other risk factors, monitoring of incidence rates is a suitable approach to detect relevant changes in incidence rates possibly related to the use of wireless phones.

Given the research uncertainties, precautionary measures might be taken. Because mobile phones are the most relevant exposure source and because the strength of RF-EMF decreases rapidly with distance from the source, the simplest and most effective precautionary measure is to hold the mobile phone away from the body during transmission; this will result in a substantial reduction in exposure.

References

1. UNSCEAR (2010). Sources and effects of ionizing radiation. UNSCEAR 2008 Report to the General Assembly, with scientific annexes. Volume I: Sources. New York (NY), USA: United Nations Scientific Committee on the Effects of Atomic Radiation. Available from: http://www.unscear.org/unscear/publications/2008_1.html.

2. IARC (2012). Radiation. IARC Monogr Eval Carcinog Risks Hum. 100D:1–437. PMID:23189752. Available from: http://publications.iarc.fr/121.

3. Grant EJ, Brenner A, Sugiyama H, Sakata R, Sadakane A, Utada M, et al. (2017). Solid cancer incidence among the Life Span Study of atomic bomb survivors: 1958–2009. Radiat Res. 187(5):513–37. https://doi.org/10.1667/RR14492.1 PMID:28319463

4. Berrington de Gonzalez A, Salotti JA, McHugh K, Little MP, Harbron RW, Lee C, et al. (2016). Relationship between paediatric CT scans and subsequent risk of leukaemia and brain tumours: assessment of the impact of underlying conditions. Br J Cancer. 114(4):388–94. https://doi.org/10.1038/bjc.2015.415 PMID:26882064

5. Bernier MO, Baysson H, Pearce MS, Moissonnier M, Cardis E, Hauptmann M, et al. (2019). Cohort profile: the EPI-CT study: a European pooled epidemiological study to quantify the risk of radiation-induced cancer from paediatric CT. Int J Epidemiol. 48(2):379–81g. https://doi.org/10.1093/ije/dyy231 PMID:30388267

6. Lubin JH, Adams MJ, Shore R, Holmberg E, Schneider AB, Hawkins MM, et al. (2017). Thyroid cancer following childhood low-dose radiation exposure: a pooled analysis of nine cohorts. J Clin Endocrinol Metab. 102(7):2575–83. https://doi.org/10.1210/jc.2016-3529 PMID:28323979

7. Kreuzer M, Sobotzki C, Schnelzer M, Fenske N (2018). Factors modifying the radon-related lung cancer risk at low exposures and exposure rates among German uranium miners. Radiat Res. 189(2):165–76. https://doi.org/10.1667/RR14889.1 PMID:29215327

8. Gillies M, Kuznetsova I, Sokolnikov M, Haylock R, O'Hagan J, Tsareva Y, et al. (2017). Lung cancer risk from plutonium: a pooled analysis of the Mayak and Sellafield worker cohorts. Radiat Res. 188(6):645–60. https://doi.org/10.1667/RR14719.1 PMID:28985139

9. UNSCEAR (2018). Evaluation of data on thyroid cancer in regions affected by the Chernobyl accident: a white paper to guide the Scientific Committee's future programme of work. New York (NY), USA: United Nations Scientific Committee on the Effects of Atomic Radiation. Available from: http://www.unscear.org/docs/publications/2017/Chernobyl_WP_2017.pdf.

10. Yamashita S, Suzuki S, Suzuki S, Shimura H, Saenko V (2018). Lessons from Fukushima: latest findings of thyroid cancer after the Fukushima Nuclear Power Plant accident. Thyroid. 28(1):11–22. https://doi.org/10.1089/thy.2017.0283 PMID:28954584

11. IARC Expert Group on Thyroid Health Monitoring after Nuclear Accidents (2018). Thyroid health monitoring after nuclear accidents. Lyon, France: International Agency for Research on Cancer (IARC Technical Publications, No. 46). Available from http://publications.iarc.fr/571.

12. Kendall GM, Little MP, Wakeford R, Bunch KJ, Miles JC, Vincent TJ, et al. (2013). A record-based case-control study of natural background radiation and the incidence of childhood leukaemia and other cancers in Great Britain during 1980-2006. Leukemia. 27(1):3–9. https://doi.org/10.1038/leu.2012.151 PMID:22766784

13. Spycher BD, Lupatsch JE, Zwahlen M, Röösli M, Niggli F, Grotzer MA, et al.; Swiss Pediatric Oncology Group; Swiss National Cohort Study Group (2015). Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study. Environ Health Perspect. 123(6):622–8. https://doi.org/10.1289/ehp.1408548 PMID:25707026

14. Shore R, Walsh L, Azizova T, Rühm W (2017). Risk of solid cancer in low dose-rate radiation epidemiological studies and the dose-rate effectiveness factor. Int J Radiat Biol. 93(10):1064–78. https://doi.org/10.1080/09553002.2017.1319090 PMID:28421857

15. Little MP, Wakeford R, Borrego D, French B, Zablotska LB, Adams MJ, et al. (2018). Leukaemia and myeloid malignancy among people exposed to low doses (<100 mSv) of ionising radiation during childhood: a pooled analysis of nine historical cohort studies. Lancet Haematol. 5(8):e346–58. https://doi.org/10.1016/S2352-3026(18)30092-9 PMID:30026010

16. International Commission on Non-Ionizing Radiation Protection (1998). Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz). Health Phys. 74(4):494–522. PMID:9525427

17. Foerster M, Thielens A, Joseph W, Eeftens M, Röösli M (2018). A prospective cohort study of adolescents' memory performance and individual brain dose of microwave radiation from wireless communication. Environ Health Perspect. 126(7):077007. https://doi.org/10.1289/EHP2427 PMID:30044230

18. Gati A, Hadjem A, Wong M-F, Wiart J (2009). Exposure induced by WCDMA mobiles phones in operating networks. IEEE Trans Wirel Commun. 8(12):5723–7. https://doi.org/10.1109/TWC.2009.12.080758

19. Persson T, Törnevik C, Larsson LE, Lovén J (2012). Output power distributions of terminals in a 3G mobile communication network. Bioelectromagnetics. 33(4):320–5. https://doi.org/10.1002/bem.20710 PMID:22012866

20. Challis LJ (2005). Mechanisms for interaction between RF fields and biological tissue. Bioelectromagnetics. 26(Suppl 7):S98–106. https://doi.org/10.1002/bem.20119 PMID:15931683

21. Parham F, Portier CJ, Chang X, Mevissen M (2016). The use of signal-transduction and metabolic pathways to predict human disease targets from electric and magnetic fields using in vitro data in human cell lines. Front Public Health. 4:193. https://doi.org/10.3389/fpubh.2016.00193 PMID:27656641

22. Röösli M, Lagorio S, Schoemaker MJ, Schüz J, Feychting M (2019). Brain and salivary gland tumours and mobile phone use: evaluating the evidence from various epidemiological study designs. Annu Rev Public Health. 40:221–38. https://doi.org/10.1146/annurev-publhealth-040218-044037 PMID:30633716

23. Hardell L, Carlberg M (2015). Mobile phone and cordless phone use and the risk for glioma – analysis of pooled case-control studies in Sweden, 1997-2003 and 2007-2009. Pathophysiology. 22(1):1–13. https://doi.org/10.1016/j.pathophys.2014.10.001 PMID:25466607

24. Coureau G, Bouvier G, Lebailly P, Fabbro-Peray P, Gruber A, Leffondre K, et al. (2014). Mobile phone use and brain tumours in the CERENAT case-control study. Occup Environ Med. 71(7):514–22. https://doi.org/10.1136/oemed-2013-101754 PMID:24816517

25. INTERPHONE Study Group (2010). Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Int J Epidemiol. 39(3):675–94. https://doi.org/10.1093/ije/dyq079 PMID:20483835

26. Olsson A, Bouaoun L, Auvinen A, Feychting M, Johansen C, Mathiesen T, et al. (2019). Survival of glioma patients in relation to mobile phone use in Denmark, Finland and Sweden. J Neurooncol. 141(1):139–49. https://doi.org/10.1007/s11060-018-03019-5 PMID:30421160

27. Toledano MB, Auvinen A, Tettamanti G, Cao Y, Feychting M, Ahlbom A, et al. (2018). An international prospective cohort study of mobile phone users and health (COSMOS): factors affecting validity of self-reported mobile phone use. Int J Hyg Environ Health. 221(1):1–8. https://doi.org/10.1016/j.ijheh.2017.09.008 PMID:29056311

28. Miranda-Filho A, Piñeros M, Soerjomataram I, Deltour I, Bray F (2017). Cancers of the brain and CNS: global patterns and trends in incidence. Neuro Oncol. 19(2):270–80. PMID:27571887

29. Chapman S, Azizi L, Luo Q, Sitas F (2016). Has the incidence of brain cancer risen in Australia since the introduction of mobile phones 29 years ago? Cancer Epidemiol. 42:199–205. https://doi.org/10.1016/j.canep.2016.04.010 PMID:27156022

30. Philips A, Henshaw DL, Lamburn G, O'Carroll MJ (2018). Brain tumours: rise in glioblastoma multiforme incidence in England 1995–2015 suggests an adverse environmental or lifestyle factor. J Environ Public Health. 2018:7910754. https://doi.org/10.1155/2018/7910754

31. Hardell L, Carlberg M (2015). Increasing rates of brain tumours in the Swedish national inpatient register and the causes of death register. Int J Environ Res Public Health. 12(4):3793–813. https://doi.org/10.3390/ijerph120403793 PMID:25854296

32. Hauri DD, Spycher B, Huss A, Zimmermann F, Grotzer M, von der Weid N, et al.; Swiss National Cohort; Swiss Paediatric Oncology Group (2014). Exposure to radio-frequency electromagnetic fields from broadcast transmitters and risk of childhood cancer: a census-based cohort study. Am J Epidemiol. 179(7):843–51. https://doi.org/10.1093/aje/kwt442 PMID:24651167

2.6 Diet and nutrition
Understanding which factors are critical

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SUMMARY

- Multiple aspects of diet influence cancer risk, some adversely and some beneficially.
- Probably most important are the influences of diet on adiposity, a major risk factor for many cancer types. Avoidance of sugar-sweetened beverages and replacement of refined carbohydrates with whole-grain alternatives is particularly important.
- Limiting consumption of red meat and processed meat, especially of processed meat, may decrease risk of colorectal cancer.
- Generous consumption of fruits and vegetables has less impact on cancer risk than was thought earlier, but some benefits exist.
- An overall healthy dietary pattern that emphasizes low intake of red meat and processed meat, generous intake of fruits and vegetables, whole grains rather than refined grains, and plant sources of protein and fat will reduce risk of cancer as well as of cardiometabolic disease.
- Although data on the effects of diet after cancer diagnosis on overall and cancer-specific survival are sparse, recent findings support adopting a similar dietary pattern as for prevention.

For many decades, studies in animals and comparisons of cancer rates across countries have raised hypotheses that various aspects of diet might influence risk of cancer in humans. Recently, the results of long-term epidemiological studies have provided a wealth of information about the relationships between diet and risk of many cancer types. Some of the recent evidence has not supported earlier beliefs, for example that high total fat intake and low intake of fruits and vegetables are key cancer risk factors. Other factors related to nutrition, such as overweight (see Chapter 2.7) and alcohol consumption (see Chapter 2.3), have emerged as clearly important, and evidence for a role of overall healthy dietary patterns has strengthened.

Because dietary and other exposures many years before the diagnosis of cancer, including during childhood, can influence cancer risk, current evidence on diet and cancer remains incomplete, and continued research is needed. In addition, more research on diet and cancer is needed in countries undergoing the nutrition transition towards a lifestyle typical of industrialized countries, where the incidence of diet-related cancer types (e.g. colorectal cancer) is rising.

This chapter briefly describes the current state of knowledge, with an emphasis on findings during the past 5 years.

Dietary factors

Plant foods

Fruits, vegetables, nuts, legumes, and whole grains are naturally rich in vitamins, phytochemicals, and dietary fibre – constituents that are thought to inhibit carcinogenesis [1]. During the late 20th century, there was a great deal of research on the role that plant foods may play in reducing the risk of cancer, with initially promising findings originating primarily from case–control studies. Although the evidence that fruits and vegetables independently decrease cancer risk has weakened during recent decades, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) concluded that greater consumption of non-starchy vegetables or fruits probably protects against several cancers of the aerodigestive tract [1]. Emerging studies of molecularly defined tumour subtypes can identify different associations with plant foods and/or their constituents. For example, higher concentrations of β-carotene, α-carotene, and other carotenoids found in fruits and vegetables are associated with lower risk of more aggressive and deadly breast tumours [2], including estrogen receptor-negative breast tumours [3].

The evidence that consumption of whole grains (i.e. grains in which 100% of the original kernel is retained) decreases risk of colorectal

cancer was categorized by WCRF/AICR as *probable* [1]. Whole grains, which are rich in dietary fibre and phytochemicals, may decrease risk of colorectal cancer by diluting carcinogens in the colon, through production of short-chain fatty acids, and also by limiting growth of pro-inflammatory bacterial species [4]. WCRF/AICR also categorized as *probable* the evidence that consumption of dietary fibre, which is found in plant foods including whole grains, fruits and vegetables, nuts, and seeds, is associated with lower risk of colorectal cancer, weight gain, overweight, and obesity [1].

Red meat and processed meat

In 2015, IARC classified consumption of processed meat as carcinogenic to humans (Group 1), based on sufficient evidence in humans for colorectal cancer, and consumption of red meat as probably carcinogenic to humans (Group 2A), based on evidence for colorectal cancer, with strong mechanistic support [5]. Similarly, WCRF/AICR concluded that the evidence was *convincing* that consumption of processed meat increases risk of colorectal cancer [1], whereas the evidence for consumption of unprocessed red meat was classified as *probable* [1].

Processed meat is defined as meat that has been transformed through salting, smoking, curing, and/or fermentation to enhance flavour or for preservation (examples are frankfurters, bacon, salami, deli meats, and similar products), whereas red meat refers to unprocessed mammalian muscle meat (e.g. beef, veal, lamb, pork, and goat) [5]. For each 50 grams of processed meat consumed per day, the risk of colorectal cancer increases by approximately 16%, and for each 100 grams of red meat consumed per day, it increases by about 12% [1]. For colon cancer, these estimates are 23% and 22%, respectively [1].

Potential biological mechanisms underlying these associations include oxidative damage resulting from endogenous formation of *N*-nitroso compounds catalysed by haem iron, and genotoxic compounds formed during smoking or high-temperature cooking of meat [5] (see Chapter 2.8). Additional research is needed on the mechanisms involved and on mediating factors (e.g. cooking methods and concomitant dietary components).

Dietary fat

From the 1980s until recently, dietary fat intake was widely believed to be the most important cause of cancers of the breast, colorectum, and prostate and some other common cancer types in developed countries. This belief was based largely on correlations between national per capita fat intake and rates of these cancer types, which were potentially confounded by many aspects of diet and lifestyle. In subsequent large cohort studies with long follow-up, dietary fat has not been associated with risk of these cancer types [6], and in two large randomized trials, women assigned to low-fat diets did not have lower risks of breast cancer or other cancer types [7,8]. Also, the type of fat, whether assessed by diet or biomarkers, has not been clearly associated with risk of breast cancer, but more research is needed. Although excess body fatness, most commonly assessed as body mass index, increases risk of many cancer types (see Chapter 2.7), a higher percentage of energy intake from dietary fat is not a major factor in weight control; in randomized trials with balanced intensity of intervention, weight loss is somewhat greater in diets with higher fat intake and lower carbohydrate intake [9]. However, higher overall diet quality, including higher intakes of fruits, vegetables, nuts, and whole grains and lower intakes of red meat and refined starch, is associated with less overall weight gain [10].

Dairy products and calcium

The effects of intake of dairy products and calcium on cancer risk are complex. Intake of dairy products has been associated with increased risk of prostate cancer in many studies,

FUNDAMENTALS

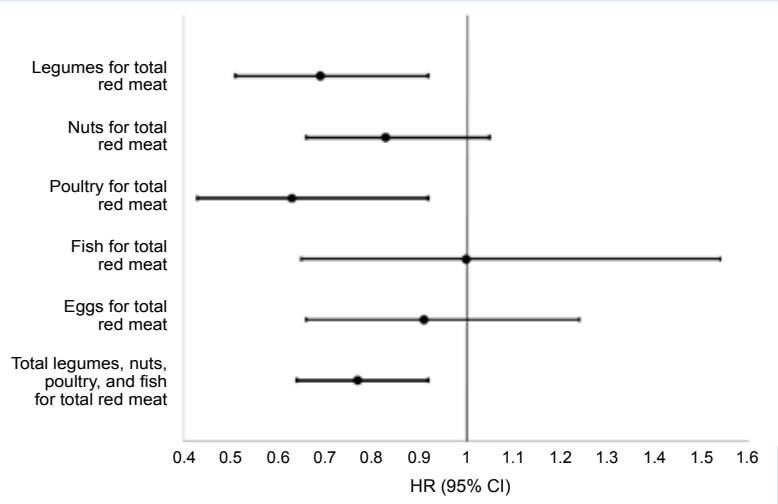
- Diets in childhood and throughout adult life can influence the carcinogenic process at various stages.
- Because dietary and other exposures many years before the diagnosis of cancer can influence cancer risk, various types of studies are needed, including long-term epidemiological studies, randomized trials, and shorter-term studies with cancer risk factors as the outcome.
- The available dietary assessment methods complemented by biomarkers of diet have proven value for the study of diet and cancer.
- Overweight and obesity are major risk factors for many cancer types and account for much of the impact of diet.
- Studies of specific nutrients and foods provide important insights on diet and cancer, but studies of overall dietary patterns may provide the most useful guidance for individuals and policies.
- A dietary pattern that emphasizes abundant intake of fruits and vegetables, whole grains rather than refined grains, and low intake of red meat and processed meat, sugar-sweetened beverages, and salt will reduce risk of cancer, as well as of cardiovascular disease, diabetes, and overall mortality.
- Although research on the relationship between diet after the diagnosis of cancer and survival is still limited, recent evidence supports a benefit on survival from the same dietary pattern recommended to lower risk, for at least some cancer types.

Diet and cancer across the life-cycle

Most cancers, especially adult-onset cancers, represent a multistage process that occurs over decades. Several well-established non-dietary risk factors demonstrate specific temporal associations with cancer. For example, breast tissue may be particularly susceptible to carcinogenic exposures during childhood, adolescence, and early adult life, as observed in women exposed to ionizing radiation. It is reasonable to anticipate that to the extent that dietary factors influence cancer risk, similar temporal associations exist. Importantly, emerging data suggest that early dietary exposures, particularly during adolescence, may influence risk of breast cancer (Fig. B2.6.1).

Some factors may act on early stages of carcinogenesis, so a time lag (latency period) may be required to elicit an effect on cancer. For example, from randomized trials and observational data, aspirin use lowers risk of sporadic colorectal cancer, but only after about a decade from onset of use. Notably, intake of micronutrients such as folate and calcium appears to be related to lower risk of colorectal cancer only after latency periods of more than a decade [1,2]. A randomized trial of multivitamin use with up to 14 years of follow-up did not show a significant reduction in the incidence of colorectal cancer, but intriguingly did suggest a possible decrease in risk after about a decade of use [3], consistent with observational studies.

Fig. B2.6.1. Dietary protein sources during adolescence in relation to risk of premenopausal breast cancer. The graph shows the hazard ratios (HR; circles) and 95% confidence intervals (95% CI; bars) for breast cancer in premenopausal women associated with replacement of adolescent intake of one serving per day of total red meat with other sources of dietary protein.



References

1. Lee JE, Willett WC, Fuchs CS, Smith-Warner SA, Wu K, Ma J, et al. (2011). Folate intake and risk of colorectal cancer and adenoma: modification by time. Am J Clin Nutr. 93(4):817–25. https://doi.org/10.3945/ajcn.110.007781 PMID:21270374
2. Zhang X, Keum N, Wu K, Smith-Warner SA, Ogino S, Chan AT, et al. (2016). Calcium intake and colorectal cancer risk: results from the Nurses' Health Study and Health Professionals Follow-up Study. Int J Cancer. 139(10):2232–42. https://doi.org/10.1002/ijc.30293 PMID:27466215
3. Gaziano JM, Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, et al. (2012). Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA. 308(18):1871–80. https://doi.org/10.1001/jama.2012.14641 PMID:23162860

including in a recent meta-analysis, possibly through increases in levels of insulin-like growth factor 1 [11]. Whether this association is attributable to the calcium in dairy products is unclear on the basis of the existing evidence.

WCRF/AICR categorized as *probable* the evidence that higher intake of calcium and dairy products decreases risk of colorectal cancer [1]. Calcium binds to potentially toxic secondary bile acids in the intestinal lumen. In addition, intraluminal calcium binds to the calcium-sensing receptor, a cell surface receptor that is expressed on colonocytes and increases expression of E-cadherin, p21, and p27, which have anticancer effects. The lower risk of colorectal cancer appears to be related specifically to calcium intake, because intakes of supplemental calcium and nondairy dietary sources of calcium are also related to lower risk [12].

Vitamins and minerals

Vitamin D

The potential role of vitamin D in lowering risk of cancer, particularly of colorectal cancer, is of great interest. An international consortium of 21 prospective cohorts (studies of breast cancer and colorectal cancer) reported that higher pre-diagnostic levels of circulating 25-hydroxyvitamin D (25(OH)D), the accepted measure of vitamin D status,

were associated with lower risk of colorectal cancer [13]. Compared with men and women with sufficient 25(OH)D concentrations (50–< 62.5 nanomoles per litre [nmol/L]), those with deficient 25(OH)D concentrations (< 30 nmol/L) had a 31% higher risk of colorectal cancer, whereas those with concentrations of 75–100 nmol/L had a 22% lower risk [13]. Mendelian randomization using four single-nucleotide polymorphisms associated with vitamin D to predict a 25 nmol/L increase in 25(OH)D concentrations in relation

Cancer survivors

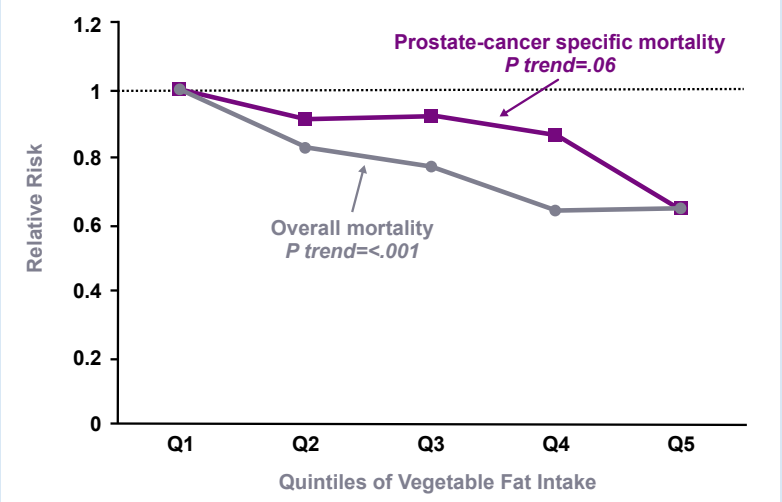
In recent decades, because of increases in the size of the population, ageing of the population, and enhanced use of screening techniques, the number of cancer survivors has skyrocketed. The role of dietary factors in the prognosis of cancer is just beginning to be studied. The specific role of diet is likely to differ by cancer type.

For cancer types with high long-term survival rates (e.g. early-stage colorectal, breast, and prostate cancer), deaths from other chronic diseases, such as cardiovascular diseases, diabetes, and second cancers, exceed those from the cancer itself. Therefore, general dietary guidelines for overall health (including cancer prevention) are likely to be most beneficial for the patient. For example, breast cancer survivors who follow healthy dietary patterns have a lower risk of mortality from outcomes other than breast cancer, such as death from cardiovascular disease [1].

Emerging evidence suggests potential benefits for cancer-specific mortality. A recent study of stage III colon cancer examined adherence to the American Cancer Society guidelines on nutrition and physical activity, which include maintaining a healthy body weight, being physically active, and eating a diet that includes ample amounts of vegetables, fruits, and whole grains, in relation to survival over a median follow-up period of 7 years, during which the majority of deaths were cancer-related. Compared with those who did not adhere to the guidelines, those who adhered to the combined guidelines had a 42% lower risk of death during the study period and a 31% improved disease-free survival. Consuming five or more servings per day of vegetables and fruits and choosing whole grains over refined grains were associated with a 35–40% lower mortality [2].

Among men with prostate cancer, replacing animal fat or carbohydrates with vegetable fat in the post-diagnostic period was associated with a reduced risk of all-cause mortality and possibly prostate cancer-specific mortality [3]. Fig. B2.6.2 illustrates the association of higher intake of vegetable fat (replacing animal fat and trans fat) with prostate cancer-specific and all-cause mortality among prostate cancer survivors [3].

Fig. B2.6.2. Relationship of higher intake of vegetable fat with prostate cancer-specific and overall survival among 4577 men with prostate cancer.



References

1. George SM, Ballard-Barbash R, Shikany JM, Caan BJ, Freudenheim JL, Kroenke CH, et al. (2014). Better postdiagnosis diet quality is associated with reduced risk of death among postmenopausal women with invasive breast cancer in the Women's Health Initiative. Cancer Epidemiol Biomarkers Prev. 23(4):575–83. https://doi.org/10.1158/1055-9965.EPI-13-1162 PMID:24493629

2. Van Blarigan EL, Fuchs CS, Niedzwiecki D, Zhang S, Saltz LB, Mayer RJ, et al. (2018). Association of survival with adherence to the American Cancer Society Nutrition and Physical Activity Guidelines for cancer survivors after colon cancer diagnosis: the CALGB 89803/Alliance Trial. JAMA Oncol. 4(6):783–90. https://doi.org/10.1001/jamaoncol.2018.0126 PMID:29710284

3. Richman EL, Kenfield SA, Chavarro JE, Stampfer MJ, Giovannucci EL, Willett WC, et al. (2013). Fat intake after diagnosis and risk of lethal prostate cancer and all-cause mortality. JAMA Intern Med. 173(14):1318–26. https://doi.org/10.1001/jamainternmed.2013.6536 PMID:23752662

to colorectal cancer risk was non-significant (relative risk, 0.92; 95% confidence interval, 0.76–1.10) [14] but overlapped with (and was consistent with) estimates from the consortium (relative risk, 0.87; 95% confidence interval, 0.82–0.92 per 25 nmol/L increase). In contrast, preliminary findings from the same pooling project showed no association of pre-diagnostic 25(OH) D levels with risk of breast cancer across a wide range of concentrations (< 20 nmol/L to > 125 nmol/L) (unpublished data). Although randomized trials would be desirable to confirm a protective effect of taking vitamin D for prevention of colorectal cancer, supplementation trials usually cannot achieve this wide range of 25(OH)D levels, and tend to include smaller numbers of cases followed up for limited time periods.

Vitamin D can be obtained by exposure to sunlight or consumption of fatty fish, fortified foods, and supplements [15]. However, excessive exposure to ultraviolet radiation is a strong risk factor for skin cancer (see Chapter 5.8) and should therefore be limited. Vitamin D intakes above 4000 international units per day are not recommended, because of potential adverse effects [15]. People at risk of vitamin D inadequacy include those living at high latitudes or in areas without vitamin D fortification, the elderly, obese individuals, those with dark skin, and those who cover most of their skin for cultural, religious, or other reasons.

Folate

Folate, which is found primarily in plant foods and is added to the food supply in certain countries as folic acid, is essential as a carrier of single-carbon units; as such, it is critical for DNA methylation and DNA biosynthesis and repair. It has been proposed that folate has a dual role in cancer, particularly colorectal cancer. Folate deficiency, particularly early in carcinogenesis, may increase risk, whereas at a late stage, excess folate (particularly in the form of folic acid) may enhance carcinogenesis in rapidly growing tumours that are reliant on DNA synthesis.

Epidemiological data have tended to support that higher folate intake is associated with a lower risk of colorectal cancer [16]. An analysis examining timing of folate intake in relation to risk found a protective association, but only after a latency period of at least 12–16 years [16]. Despite proven benefits of folic acid supplementation on incidence of neural tube defects and strokes, folic acid fortification efforts have been hindered in some countries because of concerns of higher cancer risk. Yet, reassuringly, no evidence of an increased risk of colorectal cancer or other cancer types was observed in an analysis of individual participant data of 50 000 subjects from all placebo-controlled trials of folic acid for prevention of cardiovascular disease or colorectal adenoma, with a mean follow-up of 5.5 years [17], or in a study of time trends and colorectal cancer incidence and death rates in the USA [18].

Vitamin supplementation

Cancer prevention trials of vitamin and/or mineral supplementation at high doses have mostly shown no benefit, and some have shown the potential for harm [1] (see Chapter 6.4). In contrast, multivitamin trials of multiple nutrients at recommended dietary amounts have not shown harm, and some have shown benefit in men [19]. Currently, cancer organizations recommend against taking supplements for cancer prevention, and recommend obtaining nutrients from food whenever possible [1,20].

Processed foods

Processing modifies food from its natural state for safety, convenience, palatability, or taste [21]. However, the term "processed foods" reflects a wide range of alterations, from washing, cutting, and freezing fresh produce to forming new products that do not exist in nature, such as sugar-sweetened beverages, chicken nuggets, and cheese puffs, items termed ultra-processed foods [22] or highly processed foods [23]. Moreover, fast foods are readily available convenience foods that tend to have a high energy density and be seductively flavoured, affordable, easy to access, aggressively marketed,

Fig. 2.6.1. Women eating together in Chhattisgarh, India. In many countries, the proportion of highly processed foods consumed has risen markedly as large numbers of people move from rural to urban areas, often with a transition from traditional diets to global industrial diets.

and consumed in large portions. Both fast foods and sugar-sweetened beverages are considered a cause of weight gain, overweight, and obesity [1]. Processed meats and foods preserved by salting (e.g. pickled vegetables and dried fish) increase the risk of gastrointestinal cancers [1,5].

In a large study in France, compared with men and women with less than 12% of energy intake from ultra-processed foods, those with more than 25% of energy intake from ultra-processed foods had a 23% higher risk of any cancer, a 23% higher risk of colorectal cancer, and a 38% higher risk of postmenopausal breast cancer [22]. Although it is unknown which aspects may be related to cancer risk, possible factors include excess sugar and energy, low dietary fibre and micronutrients, added preservatives and other ingredients, carcinogens formed during processing, and/or lifestyle correlates of highly processed foods, such as sedentary behaviours.

Over the past century, the global food system has shifted dramatically from that of consumption of local staple foods and home cooking to increasing intake of ready-to-consume, processed, and packaged foods, available globally. In 2012, highly processed foods comprised about 60% of per capita daily energy consumption in North America, and this percentage has remained stable since 2000 [23], whereas the proportion of food intake made up of highly processed foods has risen markedly since 2000 in several countries that are undergoing a transition from traditional diets to global industrial diets [23,24].

Dietary patterns

The study of overall dietary patterns and cancer risk has grown markedly in recent decades. Diet scores reflecting greater concordance with hypothesized healthy eating patterns, and with traditional and regional dietary patterns, are associated with lower cancer risk and mortality in many prospective studies [25,26]. Such diets tend to be rich in whole grains, fruits, vegetables, nuts, and unsaturated fats (e.g. monounsaturated and/or polyunsaturated fat) and contain lower amounts of processed meat, red meat, sugar, and saturated and/or trans fats [25,26]. In contrast, a dietary pattern typical of industrialized countries, high in meat, refined grains, fried potatoes, and sugar and low in fruits and vegetables, is associated with increased risk of colorectal cancer [27]. The Alternate Healthy Eating Index represents an overall healthy dietary pattern (see “Distribution of global diet quality”).

In the Prevención con Dieta Mediterránea (PREDIMED) trial in Spain [28], women were assigned to follow a Mediterranean diet supplemented with either extra virgin olive oil or nuts, or were advised to follow a low-fat diet (control group). Compared with controls, a 68% lower risk of invasive breast cancer was seen in women on the Mediterranean diet supplemented with olive oil, and a non-significant 41% lower risk was seen in the group on the Mediterranean diet supplemented with nuts [28]. It is unclear whether the lower risk of breast cancer among women in the arm with olive oil supplementation was due to the Mediterranean diet, the olive oil intervention, or chance, given the small number of breast cancer cases (n = 35).

Fig. 2.6.2. Traditional diets, such as those in India (left), tend to be rich in whole grains, fruits, vegetables, and nuts. In contrast, dietary patterns typical of industrialized countries, particularly in the context of fast foods (right), tend to be high in meat, refined grains, fried potatoes, and sugar, and low in fruits and vegetables.

Coffee

Studies conducted in the 1970s concluded that coffee consumption may increase risk of cancer, particularly of bladder cancer and pancreatic cancer. It is now thought that these early retrospective case–control studies had been largely confounded by tobacco use among coffee drinkers or other sources of bias. More recent research suggests that coffee consumption may lower the risk of liver cancer and endometrial cancer [1], and possibly other cancer types [29,30].

In a pooling project of nine cohorts in the USA including more than 1 million people, compared with not drinking coffee, drinking 3 cups of coffee per day was associated with a 27% lower risk of hepatocellular carcinoma [31]. Biologically active compounds in coffee, including chlorogenic acid, kahweol, and *N*-methylpyridinium, have been found to induce apoptosis, improve insulin sensitivity, and inhibit inflammation and angiogenesis, among other potential anticancer mechanisms [32].

Distribution of global diet quality

Diet has many components that ultimately need to be combined in an overall eating pattern. Fig. B2.6.3 shows the global distribution of scores in 2017 for the Alternate Healthy Eating Index [1], a measure of diet quality that has predicted lower risks of weight gain and major chronic disease in many populations. Higher scores are given to lower amounts of red meat, sugar-sweetened beverages, salt, and trans fat, and higher amounts of fruits, vegetables, whole grains, nuts and legumes, omega-3 fatty acids, and omega-6 polyunsaturated fatty acids (alcohol is not included).

Countries in the Mediterranean region, South-East Asia (e.g. Viet Nam), the Caribbean, and some parts of Africa tend to have relatively high scores, as do Brazil, the Islamic Republic of Iran, and Japan. These scores reflect relatively low consumption of red meat, sugar-sweetened beverages, and trans fat, and higher intakes of plant-sourced proteins, fruits, and vegetables.

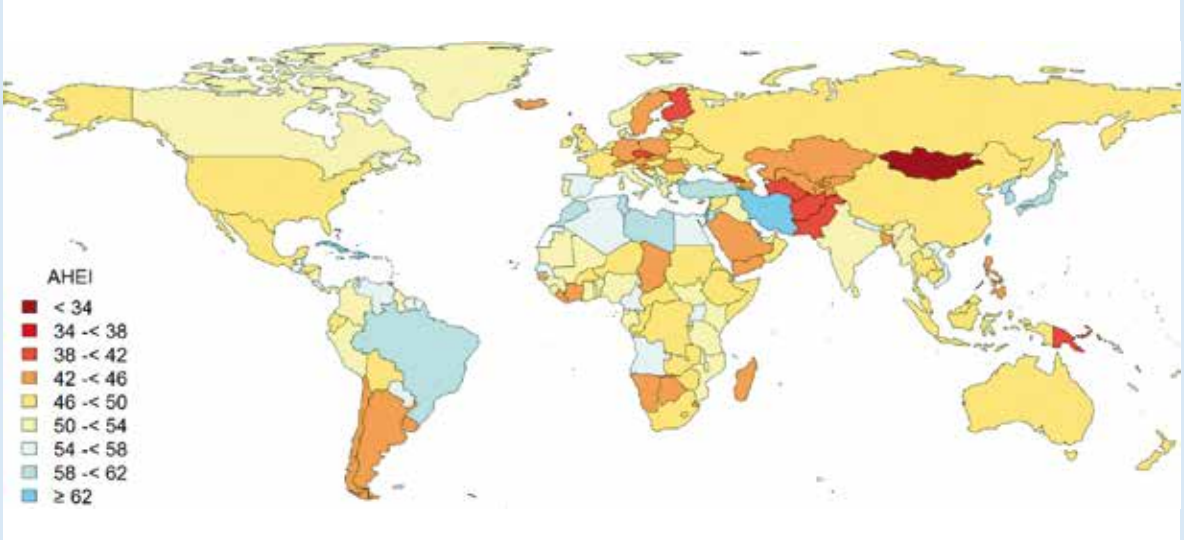
The high scores in some Mediterranean countries are consistent with the well-documented health benefits of the traditional diets of this region, although the region has generally experienced declines in dietary quality over time. The relatively high scores of countries in some parts of Africa reflect the positive aspects of many traditional diets and are consistent with low rates of chronic disease. However, in many of these same areas childhood mortality remains high, in part because of inadequate food availability and unmet nutrition needs of growing children. These countries are undergoing rapid economic and nutrition transitions, and it will be important to retain healthful aspects of traditional diets, because these are often lost with growing affluence and the industrialization of food systems. The low scores for Afghanistan, Argentina, Finland, Mongolia, Pakistan, Turkmenistan, and some parts of Africa and Europe in part reflect low intakes of fruits and vegetables and high intakes of red meat, processed meat, sugars, and refined grains; in some of these countries, intake of industrial trans fat remains high.

Although scores vary widely across the globe, even those countries with the highest scores (60–65) have considerable room for improvement, because the ideal diet would score 100. Many countries lacked current representative dietary surveys, requiring imputation of national food intakes and emphasizing the need for improved dietary surveillance.

Reference

1. Wang DD, Li Y, Afshin A, Springmann M, Mozaffarian D, Stampfer MJ, et al. (2019). Global improvement in dietary quality could lead to substantial reduction in premature death. J Nutr. 149(6):1065–74. https://doi.org/10.1093/jn/nxz010 PMID:31049577

Fig. B2.6.3. Geographical distribution of scores for the Alternate Healthy Eating Index (AHEI) in men and women aged 25 years and older in 190 countries or territories in 2017. The AHEI scores range from 0 (worst) to 100 (best). White areas indicate that dietary data were not available.



Mechanisms

Many pathways are thought to underlie a role of diet in carcinogenesis, including those involved in cell-cycle regulation, growth factors (e.g. insulin and insulin-like growth factors), inflammation, immunity, and angiogenesis. Potential, but as yet unproven, effects of the microbiome are currently a topic of great interest [33]. Contemporary research on diet and cancer, using tumour molecular pathology and –omics research, including genetics (see Chapter 3.2), metabolomics (see Chapter 3.7), and the microbiome (see Chapter 3.10), will continue to elucidate the role of diet in cancer etiology.

Population attributable fractions

Estimating the population attributable fraction for diet and cancer involves identifying relevant dietary factors, deriving a relative risk estimate from the literature for each risk factor and cancer, and estimating a population prevalence of each risk factor from the available data. Then, the percentage of cases of the cancer that are accounted for by that factor can be estimated. As science evolves and dietary exposures change, these figures will be updated.

For example, a recent analysis from the American Cancer Society relied on findings from WCRF/AICR to estimate the total numbers of cancer cases and deaths attributable to diet (independent of obesity) in the USA [34]. The risk factors identified included consumption of red meat, consumption of processed meat, and low intake of fruits and vegetables, dietary fibre, and dietary calcium. These factors were estimated to account for approximately 5.1% of cancer deaths in the USA. The largest proportion of these cancer deaths was from colorectal cancer. A previous analysis for the United Kingdom concluded that 9.2% of cancer cases are attributable to diet [34]. The higher estimate is mostly a result of a greater weight given to intake of fruits and vegetables, for which the estimates have trended downwards in recent years.

The range of estimates for population attributable fraction is approximately 5–10%. These estimates do not account for synergies among dietary factors, or for the important indirect effect of diet on obesity. Also, these estimates do not account for errors in measuring diet or the potential effect of diet during childhood or early adult life. Continued research on dietary assessment measures, uniform assessment of dietary patterns, and contemporary dietary exposures, as well as large harmonized pooled analyses, randomized trials (where feasible), and research across the lifespan, will continue to contribute information on the impact of diet on cancer risk.

References

1. WCRF/AICR (2018). Diet, nutrition, physical activity and cancer: a global perspective. Continuous Update Project Expert Report 2018. World Cancer Research Fund/American Institute for Cancer Research. Available from: https://www.wcrf.org/dietandcancer.
2. Eliassen AH, Liao X, Rosner B, Tamimi RM, Tworoger SS, Hankinson SE (2015). Plasma carotenoids and risk of breast cancer over 20 y of follow-up. Am J Clin Nutr. 101(6):1197–205. https://doi.org/10.3945/ajcn.114.105080 PMID:25877493
3. Bakker MF, Peeters PH, Klaasen VM, Bueno-de-Mesquita HB, Jansen EH, Ros MM, et al. (2016). Plasma carotenoids, vitamin C, tocopherols, and retinol and the risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition cohort. Am J Clin Nutr. 103(2):454–64. https://doi.org/10.3945/ajcn.114.101659 PMID:26791185
4. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K, et al. (2017). Influence of diet on the gut microbiome and implications for human health. J Transl Med. 15(1):73. https://doi.org/10.1186/s12967-017-1175-y PMID:28388917
5. Bouvard V, Loomis D, Guyton KZ, Grosse Y, Ghissassi FE, Benbrahim-Tallaa L, et al.; International Agency for Research on Cancer Monograph Working Group (2015). Carcinogenicity of consumption of red and processed meat. Lancet Oncol. 16(16):1599–600. https://doi.org/10.1016/S1470-2045(15)00444-1 PMID:26514947
6. Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, et al. (2001). Types of dietary fat and breast cancer: a pooled analysis of cohort studies. Int J Cancer. 92(5):767–74. https://doi.org/10.1002/1097-0215(20010601)92:5<767::AID-IJC1247>3.0.CO;2-0 PMID:11340585
7. Martin LJ, Li Q, Melnichouk O, Greenberg C, Minkin S, Hislop G, et al. (2011). A randomized trial of dietary intervention for breast cancer prevention. Cancer Res. 71(1):123–33. https://doi.org/10.1158/0008-5472.CAN-10-1436 PMID:21199800
8. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, et al. (2006). Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA. 295(6):629–42. https://doi.org/10.1001/jama.295.6.629 PMID:16467232
9. Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB (2015). Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 3(12):968–79. https://doi.org/10.1016/S2213-8587(15)00367-8 PMID:26527511

10. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB (2011). Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 364(25):2392–404. https://doi.org/10.1056/NEJMoa1014296 PMID:21696306

11. Aune D, Navarro Rosenblatt DA, Chan DS, Vieira AR, Vieira R, Greenwood DC, et al. (2015). Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am J Clin Nutr. 101(1):87–117. https://doi.org/10.3945/ajcn.113.067157 PMID:25527754

12. Keum N, Aune D, Greenwood DC, Ju W, Giovannucci EL (2014). Calcium intake and colorectal cancer risk: dose-response meta-analysis of prospective observational studies. Int J Cancer. 135(8):1940–8. https://doi.org/10.1002/ijc.28840 PMID:24623471

13. McCullough ML, Zoltick ES, Weinstein SJ, Fedirko V, Wang M, Cook NR, et al. (2019). Circulating vitamin D and colorectal cancer risk: an international pooling project of 17 cohorts. J Natl Cancer Inst. 111(2):158–69. https://doi.org/10.1093/jnci/djy087 PMID:29912394

14. Dimitrakopoulou VI, Tsilidis KK, Haycock PC, Dimou NL, Al-Dabhani K, Martin RM, et al.; GECCO Consortium; PRACTICAL Consortium; GAME-ON Network (CORECT, DRIVE, ELLIPSE, FOCI-OCAC, TRICL-ILCCO) (2017). Circulating vitamin D concentration and risk of seven cancers: Mendelian randomisation study. BMJ. 359:j4761. https://doi.org/10.1136/bmj.j4761 PMID:29089348

15. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium (2011). Dietary reference intakes for calcium and vitamin D. Washington (DC), USA: National Academies Press. PMID:21796828

16. Lee JE, Willett WC, Fuchs CS, Smith-Warner SA, Wu K, Ma J, et al. (2011). Folate intake and risk of colorectal cancer and adenoma: modification by time. Am J Clin Nutr. 93(4):817–25. https://doi.org/10.3945/ajcn.110.007781 PMID:21270374

17. Vollset SE, Clarke R, Lewington S, Ebbing M, Halsey J, Lonn E, et al.; B-Vitamin Treatment Trialists' Collaboration (2013). Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet. 381(9871):1029–36. https://doi.org/10.1016/S0140-6736(12)62001-7 PMID:23352552

18. Keum N, Giovannucci EL (2014). Folic acid fortification and colorectal cancer risk. Am J Prev Med. 46(3 Suppl 1): S65–72. https://doi.org/10.1016/j.amepre.2013.10.025 PMID:24512932

19. Gaziano JM, Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, et al. (2012). Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA. 308(18):1871–80. https://doi.org/10.1001/jama.2012.14641 PMID:23162860

20. Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, et al.; American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee (2012). American Cancer Society guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin. 62(1):30–67. https://doi.org/10.3322/caac.20140 PMID:22237782

21. Adams J, White M (2015). Characterisation of UK diets according to degree of food processing and associations with socio-demographics and obesity: cross-sectional analysis of UK National Diet and Nutrition Survey (2008-12). Int J Behav Nutr Phys Act. 12(1):160. https://doi.org/10.1186/s12966-015-0317-y PMID:26684833

22. Fiolet T, Srour B, Sellem L, Kesse-Guyot E, Allès B, Méjean C, et al. (2018). Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. BMJ. 360:k322. https://doi.org/10.1136/bmj.k322 PMID:29444771

23. Popkin BM (2017). Relationship between shifts in food system dynamics and acceleration of the global nutrition transition. Nutr Rev. 75(2):73–82. https://doi.org/10.1093/nutrit/nuw064 PMID:28395033

24. PAHO (2016). Pan American Health Organization Nutrient Profile Model. Washington (DC), USA: PAHO. Available from: http://iris.paho.org/xmlui/handle/123456789/18621.

25. Schwingshackl L, Schwedhelm C, Galbete C, Hoffmann G (2017). Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis. Nutrients. 9(10):E1063. https://doi.org/10.3390/nu9101063 PMID:28954418

26. Schwingshackl L, Bogensberger B, Hoffmann G (2018). Diet quality as assessed by the Healthy Eating Index, Alternate Healthy Eating Index, Dietary Approaches to Stop Hypertension score, and health outcomes: an updated systematic review and meta-analysis of cohort studies. J Acad Nutr Diet. 118(1):74–100.e11. https://doi.org/10.1016/j.jand.2017.08.024 PMID:29111090

27. Grosso G, Bella F, Godos J, Sciacca S, Del Rio D, Ray S, et al. (2017). Possible role of diet in cancer: systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk. Nutr Rev. 75(6):405–19. https://doi.org/10.1093/nutrit/nux012 PMID:28969358

28. Toledo E, Salas-Salvadó J, Donat-Vargas C, Buil-Cosiales P, Estruch R, Ros E, et al. (2015). Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: a randomized clinical trial. JAMA Intern Med. 175(11):1752–60. https://doi.org/10.1001/jamainternmed.2015.4838 PMID:26365989

29. Grosso G, Godos J, Galvano F, Giovannucci EL (2017). Coffee, caffeine, and health outcomes: an umbrella review. Annu Rev Nutr. 37(1):131–56. https://doi.org/10.1146/annurev-nutr-071816-064941 PMID:28826374

30. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J (2017). Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ. 359:j5024. https://doi.org/10.1136/bmj.j5024 PMID:29167102

31. Petrick JL, Freedman ND, Graubard BI, Sahasrabuddhe VV, Lai GY, Alavanja MC, et al. (2015). Coffee consumption and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma by sex: the liver cancer pooling project. Cancer Epidemiol Biomarkers Prev. 24(9):1398–406. https://doi.org/10.1158/1055-9965.EPI-15-0137 PMID:26126626

32. Bøhn SK, Blomhoff R, Paur I (2014). Coffee and cancer risk, epidemiological evidence, and molecular mechanisms. Mol Nutr Food Res. 58(5):915–30. https://doi.org/10.1002/mnfr.201300526 PMID:24668519

33. Arkan MC (2017). The intricate connection between diet, microbiota, and cancer: a jigsaw puzzle. Semin Immunol. 32:35–42. https://doi.org/10.1016/j.smim.2017.08.009 PMID:28870704

34. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. (2018). Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 68(1):31–54. https://doi.org/10.3322/caac.21440 PMID:29160902

2.7 Physical activity, sedentary behaviour, and obesity

Established and emerging modifiable risk factors

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SUMMARY

- Strong epidemiological evidence exists that being physically active reduces the risk of cancers of the bladder, breast, colon, endometrium, kidney, oesophagus, and stomach.
- Emerging evidence suggests that sedentary behaviour is associated with an increased risk of cancers of the breast, colon, endometrium, and lung.
- Strong evidence exists for an association between obesity and increased risk of cancers of the postmenopausal breast, colorectum, endometrium, kidney, liver, oesophagus, and pancreas, and moderate evidence exists for an association with cancers of the gall bladder, mouth, pharynx, larynx, ovary, prostate (advanced), and stomach.
- Several common biological mechanisms are likely to be involved in the association between physical activity, sedentary behaviour, and obesity and cancer risk, including an effect on endogenous sex and metabolic hormones, insulin resistance, and chronic inflammation.
- The population attributable fractions associated with physical inactivity, sedentary behaviour, and obesity are estimated to range, collectively, from 20% to 40% for all cancers associated with these risk factors.

Three main modifiable factors have emerged in the past 30–40 years that are associated with an increased risk of cancer at several sites: physical inactivity, sedentary behaviour, and overweight or obesity. This chapter reviews the observational epidemiological evidence that has been synthesized in systematic reviews and meta-analyses, and highlights the strength of the associations, evidence for dose–response relationships, and the biological plausibility of these associations. In addition, the prevalence of these exposures worldwide is discussed, as well as the population attributable fractions that have been estimated for these exposures. The efficacy of programmes to improve physical activity, decrease sedentary time, and control obesity that have been evaluated are highlighted.

Physical activity

More than 450 studies have been conducted that have examined some aspect of physical activity and its relationship to cancer risk, and dozens of meta-analyses and systematic reviews have been published that have examined the associations for specific cancer sites. Most recently, the scientific report of the 2018 Physical Activity Guidelines Advisory Committee (PAGAC) reviewed 45 meta-analyses and systematic reviews performed in 2008–2017, to assess the strength of the evidence for an etiological role for cancer risk [1]. The World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) 2018 Expert Report also provided an expert synthesis of the evidence [2]. These recent reports have concluded that there is strong evidence for an etiological role of physical activity associated with the incidence of several cancer types. In addition, a pooling project coordinated by the United States National Cancer Institute examined these associations for 26 cancer sites with data from more than 1 million study participants [3].

From these two main reviews and this large pooling project, the current state of the evidence is that physical activity is associated with a reduced risk of 13 cancer types. The PAGAC report provided the most recent and comprehensive review of the evidence on the association between physical activity and cancer as well as a standardized evidence grading system. Based on the PAGAC review, there is *strong* evidence that physical activity reduces the risk for cancers of the bladder, breast, colon, endometrium, kidney, and gastric cardia and for oesophageal adenocarcinoma. There is also *moderate* evidence for an association of physical activity with decreased risk of lung cancer, although confounding by smoking remains a concern for this cancer

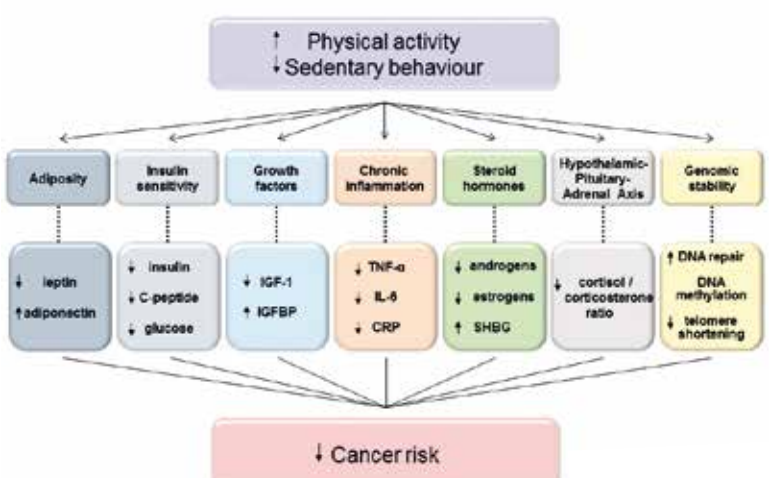
site (see Chapter 5.1). The evidence is classified as *limited* for a protective effect of physical activity against cancers of the ovary, pancreas, prostate, and mouth, pharynx, and larynx. There is *limited evidence of no effect* of physical activity on risk of cancers of the thyroid and rectum.

The magnitude of the risk reduction is approximately 10–20% for most of these cancer sites, with stronger reductions of about 25% for lung cancer, when the highest versus the lowest levels of physical activity are compared. There is evidence for a dose–response relationship between increasing levels of physical activity and decreasing cancer risk. However, the methods used to measure and categorize physical activity have been inconsistent across studies. Therefore, it is currently impossible to determine the exact levels of physical activity that are needed to provide benefits in reduced cancer incidence for any particular cancer site.

Currently, limited information is available on how the association between physical activity and cancer varies by cancer subtype. There is evidence that physical activity is equally beneficial for men and women for cancers of the colon and kidney, and there is limited evidence that effect modification by sex may exist for other cancers, such as those of the bladder, gastric cardia, lung, oesophagus, and pancreas. There is insufficient evidence to determine whether the association between physical activity and cancer incidence varies by age or socioeconomic status, and some limited information suggests that the benefits of physical activity appear to be equal for all racial and ethnic groups.

There are several hypothesized biological mechanisms involved in the association between physical activity and cancer risk, including an effect on adiposity, endogenous sex and metabolic hormones, chronic inflammation, oxidative stress, and genomic instability [4]. Randomized controlled trials have been investigating how these mechanisms are changed with year-long exercise interventions and have demonstrated direct effects on several mechanisms (see "Randomized exercise intervention trials of biological mechanisms between physical activity and cancer risk"). Not only were these trials able to demonstrate

Fig. 2.7.1. Potential biological mechanisms linking increased physical activity and decreased sedentary behaviour to reduced risk of cancer. (Inter-relationships between mechanisms are not shown.) CRP, C-reactive protein; IGF-1, insulin-like growth factor 1; IGFBP, insulin-like growth factor-binding protein; IL-6, interleukin 6; SHBG, sex hormone-binding globulin; TNF-α, tumour necrosis factor α.



FUNDAMENTALS

- Research on the association between physical activity and cancer risk began to emerge in the mid to late 1980s; early studies focused on athletes and their risk of cancer over a lifetime, as determined through long-term follow-up.
- During the past 30–40 years, more than 450 observational epidemiological studies have been published that have examined some aspect of physical activity – however that is defined – and the risk of developing cancer.
- In the past 10–15 years, there has been a focus on how sedentary behaviour, independent of physical activity, is associated with cancer risk, and evidence is now emerging on these associations for a few cancer sites.
- Some randomized controlled trials of exercise interventions have been conducted to investigate how physical activity influences several hypothesized biological mechanisms involved in the association between physical activity and cancer risk, and these studies are demonstrating an impact on adiposity, endogenous sex hormones, metabolic factors, insulin resistance, and chronic inflammation.
- Research on the association between obesity and cancer risk has accumulated over the past 40 years, and there is now strong evidence for an association between obesity and increased risk for several cancer sites.

Randomized exercise interventions trials of biological mechanisms between physical activity and cancer risk

Randomized controlled trials of exercise interventions [1–3] have been conducted using healthy populations to address the question of how aerobic exercise influences biomarkers hypothesized to be associated with cancer risk, with the main focus on breast cancer and colon cancer. These year-long randomized controlled trials have demonstrated that increased levels of aerobic activity do decrease the levels of endogenous sex hormones, insulin, glucose, insulin resistance as assessed by homeostatic model assessment of insulin resistance (HOMA-IR), inflammatory markers, and several measures of body fat. The exercise interventions have used varying volumes of aerobic activity, ranging from 150 minutes to 300 minutes per week of a combination of supervised and unsupervised activity.

The most recent of these trials was the Breast Cancer and Exercise Trial in Alberta (BETA) [4], which specifically examined the question of the optimal dose of activity needed for the most beneficial effect on these biomarkers. In BETA, 400 healthy postmenopausal women were randomized to a year-long intervention of either 150 minutes per week (moderate volume) or 300 minutes per week (high volume). The moderate-volume arm was selected because it represents the widely recommended level of physical activity for general health that is often prescribed by public health agencies worldwide. The high-volume arm was chosen because larger volumes of activity may provide more benefit for cancer prevention.

In BETA, participants in the high-volume arm had statistically significantly greater decreases in adiposity compared with the moderate-volume arm for all measures of body fat that were taken [4]. For the remaining biomarkers, there were similar decreases in both arms of the trial, but there was evidence for greater decreases in insulin resistance and in inflammatory markers for those participants who had the highest exercise adherence and spent a greater amount of their prescribed exercise in their heart rate zone, i.e. exercising at a higher intensity.

These studies have focused on aerobic exercise, and there remains a need to understand how resistance exercise influences these biomarkers. Additional potential pathways have been examined, with a focus on chronic stress, oxidative stress, genomic instability as assessed by DNA methylation, and leukocyte telomere length. The evidence for a direct effect of aerobic exercise on these additional pathways has been inconsistent to date.

Taken together, these trials have provided some evidence that regular aerobic activity at a moderate to vigorous intensity level for at least 150 minutes per week has beneficial effects on biomarkers associated with cancer risk.

References

1. Friedenreich CM, Woolcott CG, McTiernan A, Terry T, Brant R, Ballard-Barbash R, et al. (2011). Adiposity changes after a 1-year aerobic exercise intervention among postmenopausal women: a randomized controlled trial. Int J Obes (Lond). 35(3):427–35. https://doi.org/10.1038/ijo.2010.147 PMID:20820172

2. Irwin ML, Yasui Y, Ulrich CM, Bowen D, Rudolph RE, Schwartz RS, et al. (2003). Effect of exercise on total and intra-abdominal body fat in postmenopausal women: a randomized controlled trial. JAMA. 289(3):323–30. https://doi.org/10.1001/jama.289.3.323 PMID:12525233

3. Monninkhof EM, Velthuis MJ, Peeters PH, Twisk JW, Schuit AJ (2009). Effect of exercise on postmenopausal sex hormone levels and role of body fat: a randomized controlled trial. J Clin Oncol. 27(27):4492–9. https://doi.org/10.1200/JCO.2008.19.7459 PMID:19687339

4. Friedenreich CM, Neilson HK, O'Reilly R, Duha A, Yasui Y, Morielli AR, et al. (2015). Effects of a high vs moderate volume of aerobic exercise on adiposity outcomes in postmenopausal women: a randomized clinical trial. JAMA Oncol. 1(6):766–76. https://doi.org/10.1001/jamaoncol.2015.2239 PMID:26181634

the efficacy of the exercise interventions in increasing physical activity levels in the study participants, but they also clearly found that these interventions resulted in beneficial changes in these biological mechanisms. Hence, biological plausibility for the association between physical activity and cancer risk exists from efficacy trials.

In epidemiological studies, the intensity of physical activity is commonly expressed in metabolic equivalents (METs); 1 MET is the amount of energy expended at rest. Moderate activity is defined as any activity of 3–6 METs, and vigorous activity is 6 or more METs. The most recent WHO public health recommendations for physical activity are to achieve 150 minutes per week of moderate activity or 75 minutes per week of vigorous activity. The WCRF/AICR committee recommended that this target for weekly physical activity should be the minimum that is done for cancer prevention [2]. Physical inactivity is defined as an activity level that is insufficient to meet the current recommendations [5].

Globally, the prevalence of physical inactivity is high, with an estimated median prevalence of 24% (range, 4.1–65.0%) worldwide [6]. Estimates of the median

Fig. 2.7.2. Sedentary behaviour in the household includes sitting while watching television.

population attributable fractions for physical inactivity for cancers of the breast, colon, and endometrium range from 12% to 19% worldwide, and the highest estimates are more than 25% [7]. Hence, the global burden of cancer that could be prevented by regular physical activity is considerable (see Chapter 6.2).

Sedentary behaviour

Sedentary behaviour is defined as "any waking behaviour characterized by an energy expenditure less than or equal to 1.5 METs while in a sitting or reclining posture" [8]. Sedentary behaviour comprises sitting in the workplace, during leisure time, while commuting, and in the

Improvements in measurement of sedentary behaviour to improve understanding of the association between sedentary behaviour and cancer

Prolonged sedentary behaviour plays a potentially important role in cancer etiology. Despite considerable research progress in this area over the past years, the epidemiology of sedentary behaviour and cancer is still in its infancy. Numerous uncertainties and limitations persist [1], in part because of concerns that self-reported questionnaires and traditional accelerometers measure sedentary behaviour with too much error.

Early investigations used questionnaires, which proved useful for large-scale observational studies but may have introduced a certain degree of measurement error due to reporting bias. Subsequent investigations helped overcome some of the limitations of self-report assessments by deploying objective measures of sedentary behaviour in epidemiological studies. However, those studies mainly used waist-worn accelerometers, which are unable to determine posture and thus produce output that does not represent sedentary behaviour itself but rather lack of ambulatory movement.

Further progress in measurement technology has recently enabled advanced activity monitoring that distinguishes between sitting, lying down, and standing. Integrating this new generation of thigh-worn sensors or combinations of sensor placements on the thigh and the hip or lower back into new and continuing prospective epidemiological studies represents a major step forward in validly quantifying the volume and patterns of accumulation of daily sedentary time.

Ideally, such technology should be combined with self-reports to gather relevant information about the social and environmental contexts in which sedentary behaviour takes place (e.g. location and purpose). In addition, measurements should not be limited to a single time point – at study baseline – but should be performed repeatedly during follow-up to capture information about changes in sedentary behaviour over time and to identify potential time-sensitive effects of sedentary behaviour on cancer incidence.

Also, most of the available studies have examined sedentary behaviour in isolation, but activity behaviours do not occur independently of one another. Rather, time spent in one behaviour ultimately replaces time spent in another behaviour. Therefore, sophisticated statistical approaches such as isotemporal substitution modelling and compositional data analysis are required to appropriately handle the interdependent elements of daily energy expenditure within the 24-hour continuum to identify optimal combinations of sitting, standing, light activity, moderate to vigorous activity, and sleep. The joint capacity of these approaches will help to further develop the epidemiological evidence base that is needed to advance what is known about sedentary behaviour and cancer.

Reference

1. Schmid D, Jochem C, Leitzmann MF (2018). Limitations in sedentary behaviour research and future research needs. In: Leitzmann MF, Jochem C, Schmid D, editors. Sedentary behaviour epidemiology. Springer Series on Epidemiology and Public Health. Springer International Publishing; pp. 629–38. https://doi.org/10.1007/978-3-319-61552-3_28

household. Examples of sedentary behaviour include computer use, television viewing, reading, and sitting while commuting by car, bus, train, and airplane.

Data on sedentary behaviour in relation to risk of cancer are far less abundant than those on physical activity and cancer risk. However, a growing body of evidence demonstrates that prolonged sedentary behaviour is associated with increased cancer risk, independent of physical activity level. Specifically, a meta-analysis of 14 observational studies showed that high versus low levels of time spent sitting are related to a 24% higher risk of cancer incidence after adjustment for physical activity [9]. Another meta-analysis of prospective studies reported a 2% increase in risk of cancer mortality for each additional hour per day of television viewing when adjusted for physical activity [10]. A recent meta-analysis showed that physical activity modifies the relationship of sedentary behaviour to cancer mortality: increased risk associated with longer time spent sitting was noted only among individuals with low levels of physical activity, and no increased risk of cancer mortality with prolonged sedentary behaviour was noted in individuals with higher levels of physical activity [11].

Like for the above-mentioned data on total cancer risk, epidemiological evidence is sparse about the relationship of sedentary behaviour to risk of cancer at individual sites. The strongest evidence has been reported for cancers of the breast, colon, and endometrium. Weaker evidence has been found for lung cancer, a site for which associations are particularly prone to confounding by smoking. A meta-analysis of observational studies reported that each increment of 2 hours per day in time spent sitting was associated with an increase of 8% in risk of colon cancer, an increase of 10% in risk of endometrial cancer, and a borderline statistically significant increase of 6% in risk of lung cancer [12]. Another meta-analysis reported that sedentary behaviour is related to an increased risk of breast cancer [13]. There is insufficient evidence to determine whether the relationship of sedentary behaviour to cancer risk varies according to age, sex, race and ethnicity, or other factors.

Very little is known about whether prolonged sedentary behaviour affects biological pathways of cancer risk. One possible etiological mechanism involves obesity, which may contribute to cancer risk directly, or indirectly through enhanced circulating concentrations of sex and metabolic hormones and of adipokines, and chronic inflammation (see Chapter 3.5). Time spent in sedentary behaviour typically replaces time spent in light-intensity activity, which is associated with greater energy expenditure. However, data showing that sedentary behaviour leads to weight gain are inconsistent, and the relationship of sedentary behaviour to weight gain is potentially bidirectional [14].

Studies examining prolonged sedentary behaviour in relation to putative molecular markers of cancer risk have been restricted to cross-sectional study designs or small-scale interventions in selected populations and have produced partly inconsistent findings. Nevertheless, several experimental studies have demonstrated that interrupting prolonged bouts of sitting by standing or stepping has a beneficial impact on circulating levels of insulin and glucose [15], supporting a link between sedentary behaviour and type 2 diabetes, which is itself a risk factor for numerous cancer types.

Quantifying the global burden of cancer due to sedentary behaviour is challenging, because global surveillance programmes for sedentary behaviour have not yet been established. However, a study that estimated the population attributable fractions for sitting-related overall mortality from all causes (not cancer mortality specifically) for 54 countries found that time spent sitting accounted for 4% of mortality from all causes [16].

The volume and patterns of accumulation of daily sedentary behaviour related to the risk of cancer have not been determined. In addition, it remains unclear whether there are specific periods across the life-course during which an individual may be particularly susceptible to the adverse effects of prolonged sedentary behaviour. To date, there is inadequate evidence

Fig. 2.7.3. Most office work is characterized by prolonged sedentary time.

to formulate specific recommendations about restrictions on daily sedentary time or sitting breaks. Therefore, current guidelines from government organizations and cancer control agencies are limited to generic, non-quantitative reductions in sedentary behaviour [17].

Obesity

Overweight and obesity are generally assessed through various anthropometric measures. In population studies of cancer, the predominant measures used are body mass index (BMI), which is obtained by dividing the body weight (in kilograms) by the square of the height (in metres), and waist circumference. There is now considerable epidemiological evidence supporting an association between overweight and obesity and cancer risk (Table 2.7.1). This evidence has been systematically reviewed in dozens of meta-analyses based on hundreds of studies conducted worldwide, including by WCRF/AICR [2].

There is currently *convincing* evidence that being overweight or obese in adulthood is associated with increased risks of cancers of the postmenopausal breast, colorectum, endometrium, kidney, liver, oesophagus, and pancreas, and *probable* evidence for an association with cancers of the gall bladder, gastric cardia, mouth, pharynx, larynx, ovary, and prostate (advanced), and *limited suggestive* evidence for an association with cervical cancer [2]. For breast cancer, being overweight or obese as an adult before menopause decreases the risk of premenopausal breast cancer risk, but greater weight gain in adulthood increases the risk of postmenopausal breast cancer.

The IARC Handbooks volume that reviewed the evidence on obesity and cancer in 2016 concluded that there was *sufficient* evidence for an association between obesity and 13 cancer sites, and included thyroid cancer, multiple myeloma, and meningioma in this category along with the sites previously listed by WCRF/AICR [18].

Fig. 2.7.4. Children playing football in Pakistan.

The associations between obesity and cancer risk differ within subgroups of the population: stronger effects are observed for some cancers for women than men, and for older versus younger populations. There is also some evidence that the effect of obesity on cancer risk differs by race and ethnicity. For example, a stronger adverse effect of obesity on breast cancer risk was found for women of Asian ethnicity than for women of Hispanic, African, or non-Hispanic White ancestry [19]. The observed ethnicity-associated variation in cancer risk at similar levels of adiposity is thought to be, in part, related to differences in distribution of body fat. Larger waist circumference, as a measure of central adiposity, is now a recognized risk factor for several cancer sites independent of body size [2,18].

Other cancer risk factors are also being recognized as important effect modifiers of the association between obesity and cancer; the most important ones are smoking (see Chapter 2.1) and use of hormone replacement therapy (see Chapter 2.11). Meta-analyses have generally demonstrated an inverse association between obesity and smoking-related cancers (e.g. lung cancer and oesophageal cancer), which can be explained by null associations that are observed in the never-smoker category. Among ever users of hormone replacement therapy, there are no associations between BMI and postmenopausal breast cancer and ovarian cancer, and there is an attenuated association with endometrial cancer. However, for never-users of hormone replacement therapy, there are clearly increased risks associated with elevated BMI for these three cancer sites [20].

There are several plausible biological mechanisms that could explain the association between obesity and cancer risk. The main ones are an increase in endogenous sex hormones (see Chapter 3.6), insulin and insulin-like growth factors, circulating adipokines, and systemic inflammation [21].

WCRF/AICR reported that worldwide in 2016, 1.97 billion adults and more than 338 million children and adolescents were classified as overweight or obese [2]. Furthermore, the increase in the prevalence of obesity is being observed in both high-income countries and low- and middle-income countries, given the increased industrialization and the decrease in active occupations and active transport (e.g. walking and cycling) that have occurred globally. Over the next two decades, the largest proportional increase in overweight and obesity is projected

Table 2.7.1. Evidence on the relationships of physical activity, sedentary behaviour, and obesity to risk of cancer

Cancer site	Physical activity	Sedentary behaviour	Obesity
Colorectum	Strong evidence for decreased risk (colon)	Limited evidence for increased risk (colon)	Strong evidence for increased risk
Endometrium	Strong evidence for decreased risk	Limited evidence for increased risk	Strong evidence for increased risk
Breast (postmenopausal)	Strong evidence for decreased risk	Limited evidence for increased risk	Strong evidence for increased risk
Breast (premenopausal)	Strong evidence for decreased risk	Limited evidence for increased risk	
Oesophageal adenocarcinoma	Strong evidence for decreased risk		Strong evidence for increased risk
Kidney	Strong evidence for decreased risk		Strong evidence for increased risk
Bladder	Strong evidence for decreased risk		
Gastric cardia	Strong evidence for decreased risk		Strong evidence for increased risk
Liver			Strong evidence for increased risk
Lung	Limited evidence for decreased risk	Limited evidence for increased risk	
Prostate	Limited evidence for decreased risk		Strong evidence for increased risk (advanced)
Ovary	Limited evidence for decreased risk		Strong evidence for increased risk
Pancreas	Limited evidence for decreased risk		Strong evidence for increased risk
Gall bladder			Strong evidence for increased risk
Mouth, pharynx, and larynx			Strong evidence for increased risk
Cervix			Limited evidence for increased risk
Thyroid			Limited evidence for increased risk
Multiple myeloma			Limited evidence for increased risk
Meningioma			Limited evidence for increased risk

to occur in low- and middle-income countries [22]. Countries that are undergoing an economic transition are particularly relevant to investigate, because the impact of rapid weight gain on cancer risk can be evaluated. These trends in the prevalence rates of obesity are expected to result in a substantial increase in cancer incidence worldwide.

Globally, the median fraction of cancers that are attributable to overweight and obesity, as measured by BMI, has recently been estimated to range from less than 1% to 9.5%, depending on the cancer site and the country [23]. The highest fractions are found in North America, the Middle East, and Europe, and lower fractions are observed in sub-Saharan Africa and Asia, which corresponds to the prevalence of obesity in those regions. These population attributable fractions are generally similar for men and women, although variations by sex do occur, depending on the prevalence of obesity in those populations and the risks associated with obesity for specific cancer sites. At a global level, obesity is ranked the third most important risk factor for cancer, with respect to attributable fractions, after smoking and infections [20].

The determinants of overweight and obesity are complex and multifactorial, and it is now increasingly recognized that a multilevel approach is necessary to decrease the prevalence of obesity globally. Several initiatives are needed that target behaviour change not only at the individual level but also at the societal level. Policies are required that enable populations to achieve and maintain a healthy weight and that consider the food environment, food systems, and the built environment. WCRF/AICR has provided some recommendations on how these policy changes can be made at a governmental and societal level [2].

The recommendations of the WCRF/AICR report [2] for healthy weight are to keep weight within the healthy range of BMI for adults, which is 18.5–24.9 kg/m^2, and to avoid weight gain in adult life. To achieve this overall recommendation, three goals were provided: (i) to ensure that body weight during childhood and adolescence projects towards the lower end of the healthy adult BMI range; (ii) to keep weight as low as possible within the healthy range throughout life; and (iii) to avoid weight gain, measured as body weight or waist circumference, throughout adulthood.

References

1. 2018 Physical Activity Guidelines Advisory Committee (2018). 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington (DC), USA: U.S. Department of Health and Human Services. Available from: https://health.gov/paguidelines/second-edition/report/.
2. WCRF/AICR (2018). Diet, nutrition, physical activity and cancer: a global perspective. Continuous Update Project Expert Report 2018. World Cancer Research Fund/American Institute for Cancer Research. Available from: https://www.wcrf.org/dietandcancer.
3. Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, et al. (2016). Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Intern Med. 176(6):816–25. https://doi.org/10.1001/jamainternmed.2016.1548 PMID:27183032
4. Neilson HK, Conroy SM, Friedenreich CM (2013). The influence of energetic factors on biomarkers of postmenopausal breast cancer risk. Curr Nutr Rep. 3(1):22–34. https://doi.org/10.1007/s13668-013-0069-8 PMID:24563822
5. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT; Lancet Physical Activity Series Working Group (2012). Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 380(9838):219–29. https://doi.org/10.1016/S0140-6736(12)61031-9 PMID:22818936
6. Sallis JF, Bull F, Guthold R, Heath GW, Inoue S, Kelly P, et al.; Lancet Physical Activity Series 2 Executive Committee (2016). Progress in physical activity over the Olympic quadrennium. Lancet. 388(10051):1325–36. https://doi.org/10.1016/S0140-6736(16)30581-5 PMID:27475270
7. Whiteman DC, Wilson LF (2016). The fractions of cancer attributable to modifiable factors: a global review. Cancer Epidemiol. 44:203–21. https://doi.org/10.1016/j.canep.2016.06.013 PMID:27460784
8. Sedentary Behaviour Research Network (2012). Letter to the editor: standardized use of the terms “sedentary” and “sedentary behaviours”. Appl Physiol Nutr Metab. 37(3):540–2. https://doi.org/10.1139/h2012-024 PMID:22540258
9. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, et al. (2015). Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med. 162(2):123–32. https://doi.org/10.7326/M14-1651 PMID:25599350
10. Patterson R, McNamara E, Tainio M, de Sá TH, Smith AD, Sharp SJ, et al. (2018). Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. Eur J Epidemiol. 33(9):811–29. https://doi.org/10.1007/s10654-018-0380-1 PMID:29589226
11. Ekelund U, Brown WJ, Steene-Johannessen J, Fagerland MW, Owen N, Powell KE, et al. (2019). Do the associations of sedentary behaviour with cardiovascular disease mortality and cancer mortality differ by physical activity level? A systematic review and harmonised meta-analysis of data from 850 060 participants. Br J Sports Med. 53(14):886–94. https://doi.org/10.1136/bjsports-2017-098963 PMID:29991570
12. Schmid D, Leitzmann MF (2014). Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis. J Natl Cancer Inst. 106(7):dju098. https://doi.org/10.1093/jnci/dju098 PMID:24935969
13. Zhou Y, Zhao H, Peng C (2015). Association of sedentary behavior with the risk of breast cancer in women: update meta-analysis of observational studies. Ann Epidemiol. 25(9):687–97. https://doi.org/10.1016/j.annepidem.2015.05.007 PMID:26099193
14. Ekelund U, Brage S, Besson H, Sharp S, Wareham NJ (2008). Time spent being sedentary and weight gain in healthy adults: reverse or bidirectional causality? Am J Clin Nutr. 88(3):612–7. https://doi.org/10.1093/ajcn/88.3.612 PMID:18779275
15. Henson J, Dunstan DW, Davies MJ, Yates T (2016). Sedentary behaviour as a new behavioural target in the prevention and treatment of type 2 diabetes. Diabetes Metab Res Rev. 32(Suppl 1):213–20. https://doi.org/10.1002/dmrr.2759 PMID:26813615
16. Rezende LFM, Sá TH, Mielke GI, Viscondi JYK, Rey-López JP, Garcia LMT (2016). All-cause mortality attributable to sitting time: analysis of 54 countries worldwide. Am J Prev Med. 51(2):253–63. https://doi.org/10.1016/j.amepre.2016.01.022 PMID:27017420
17. Stamatakis E, Ekelund U, Ding D, Hamer M, Bauman AE, Lee IM (2019). Is the time right for quantitative public health guidelines on sitting? A narrative review of sedentary behaviour research paradigms and findings. Br J Sports Med. 53(6):377–82. https://doi.org/10.1136/bjsports-2018-099131 PMID:29891615
18. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group (2016). Body fatness and cancer – viewpoint of the IARC Working Group. N Engl J Med. 375(8):794–8. https://doi.org/10.1056/NEJMsr1606602 PMID:27557308
19. Bandera EV, Maskarinec G, Romieu I, John EM (2015). Racial and ethnic disparities in the impact of obesity on breast cancer risk and survival: a global perspective. Adv Nutr. 6(6):803–19. https://doi.org/10.3945/an.115.009647 PMID:26567202
20. Renehan AG, Soerjomataram I (2016). Obesity as an avoidable cause of cancer (attributable risks). Recent Results Cancer Res. 208:243–56. https://doi.org/10.1007/978-3-319-42542-9_13 PMID:27909911
21. Renehan AG, Zwahlen M, Egger M (2015). Adiposity and cancer risk: new mechanistic insights from epidemiology. Nat Rev Cancer. 15(8):484–98. https://doi.org/10.1038/nrc3967 PMID:26205341
22. Malik VS, Willett WC, Hu FB (2013). Global obesity: trends, risk factors and policy implications. Nat Rev Endocrinol. 9(1):13–27. https://doi.org/10.1038/nrendo.2012.199 PMID:23165161
23. Arnold M, Leitzmann M, Freisling H, Bray F, Romieu I, Renehan A, et al. (2016). Obesity and cancer: an update of the global impact. Cancer Epidemiol. 41:8–15. https://doi.org/10.1016/j.canep.2016.01.003 PMID:26775081

2.8 Dietary carcinogens
A continuing concern in various contexts

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SUMMARY

- Dietary carcinogens include single specific agents, such as aflatoxin and aristolochic acid, as well as complex mixtures, such as processed meat.
- Consumption of processed meat was recently classified as carcinogenic to humans (Group 1), joining the individual dietary contaminants aflatoxin and aristolochic acid in that category.
- Many cohort, case–control, and other observational studies have associated and causally linked exposures in the diet to a spectrum of human cancer types, including cancers of the breast, colorectum, liver, pancreas, and prostate.
- The acceleration of the obesity pandemic and the rising incidence of type 2 diabetes in many populations are changing the potential toxicological hazard from dietary carcinogens, which could, in turn, increase the incidence of several human cancer types.
- New technologies that use deep sequencing methods may reveal unique mutational signatures that can inform future risk analyses, providing evidence for the role of dietary carcinogens in cancer development.

Historical context

For nearly 50 years, the IARC Monographs have summarized the proportionate role that dietary carcinogens play in the development of the spectrum of cancer types in humans. Most of Volume 1 of the Monographs, published in 1972, was devoted to *N*-nitroso compounds formed in foods and their consumption, and natural products that contaminate dietary staples, such as aflatoxins, cycasin, safrole, and sterigmatocystin [1]. These dietary contaminants had been identified using the tools of epidemiology and experimental toxicology, as a result of their potency as initiating agents of the carcinogenic process. At that time, the mechanistic understanding of cancer biology, including DNA adduct formation and resultant mutations, the role of oncogenes and tumour suppressor genes in cancer development, and the multiple stages of cancer that span decades before diagnosis, was still in its infancy. Therefore, during that period only the most potent carcinogens, or those carcinogens with high exposure across the lifespan, were identified. This provided a clear focus for pursuing basic and population studies.

Most solid tumours, irrespective of their organ site, evolve through a 15–25-year period of biological development. The current understanding of these molecular processes is extensively reviewed in Section 3 of this volume. Within the context of dietary carcinogens, it is reasonable to assume that many tumours diagnosed today had their etiological roots in about 1975–1995. Therefore, it remains a significant issue whether those dietary carcinogen factors of 20–40 years ago will continue to be risk factors for the cancers that will be diagnosed 20–40 years from now [2]. This is a critical question for future risk assessment analysis and for the informed deployment of prevention strategies.

Some dietary carcinogens, such as aflatoxin, that were predominant in the past are still significant risk factors for many cancer types in different populations today. Furthermore, since 1972 some new dietary carcinogens, such as aristolochic acid, have been identified and formally classified as carcinogenic to humans (Group 1). In recent years, the pace of the discovery of new single potent agents in the diet as carcinogens has slowed down. Now, greater attention is being focused on dietary exposures from complex mixtures, such as red meat and processed meat as documented in Monographs Volume 114 [3].

Projecting future risk from dietary carcinogens will require knowledge of the dramatic change that is occurring in country after country with respect to population health and overall chronic disease burden (see [4]). Simply put, experimental toxicology models have explored the potency, biology, and mechanisms

Fig. 2.8.1. Harvested groundnuts lying on the ground are susceptible to fungal and mould growth and hence, among other things, aflatoxin contamination.

FUNDAMENTALS

- For nearly 50 years, naturally occurring, cooking-derived, and complex constituents of the diet have been determined to be risk factors for a wide variety of cancer types occurring at different organ sites in humans.
- Assessing dietary exposures and their roles in the development of cancer in humans has been a daunting task, because exposure assessment has proven to be challenging. The development of chemically specific and mechanistically justified biomarkers has been shown to be very important in the identification of several potent human carcinogens that contaminate dietary staples.
- The translation of basic science and mechanistic studies has proven to be essential for the development of risk models from dietary exposures.
- Knowledge gleaned from epidemiological studies of dietary exposures has been successfully used in cancer prevention, particularly with respect to aflatoxin and liver cancer development.
- The most challenging problem in the analysis of dietary carcinogens as risk factors remains the difficulty involved in exposure assessment, particularly across the lifespan.

of action based on single compounds and animal models that use balanced nutrition and growth management. Over the past 30 years, the average energy intake has been rising rapidly in many economically developing countries. This trend is dramatically changing the physiology, across the lifespan, of people who are chronically exposed to dietary carcinogenic agents. For example, by 2020 400 million people across all continents will have been diagnosed with type 2 diabetes [5]. This disease will contribute to an increase in the incidence of liver cancer (see Chapter 5.6) and is a sentinel for chronic disease resulting from the obesity pandemic.

From a regulatory and policy perspective, the current experimental models do not necessarily provide the data to judge whether carcinogenic risk from specific dietary carcinogens will be potentiated or antagonized by chronic diseases such as type 2 diabetes. Fortunately, when specific carcinogens or risk factors are identified, prevention can be successfully implemented. The targeted prevention programmes that have reduced the burden of lung cancer by decreasing the use of tobacco are a model for the future.

Naturally occurring dietary carcinogens

The potency of various naturally occurring dietary carcinogens has spurred many investigations, because these contaminants pose a hazard across the lifespan. Examples of this category of agents are aflatoxin, aristolochic acid, and fumonisins. These chemicals have in common the range of exposures from major staple grains and foodstuffs consumed worldwide. Therefore, prevention strategies will have to include source mitigation, primary and secondary prevention, and appropriate regulatory levels in commerce and trade.

Aflatoxin

Since the early 1970s, aflatoxin has been repeatedly examined as a human carcinogen, eventually resulting in its classification as carcinogenic to humans (Group 1) in Monographs Volume 56 [6]. Recently, an IARC Working Group Report summarized exposures and health consequences from aflatoxin in low- and middle-income countries [7]. Classic investigations have documented the greater-than-multiplicative interaction between aflatoxin and hepatitis B virus, which is important in liver cancer development in Africa and Asia [8].

More recently, as a result of the availability of aflatoxin-specific biomarkers, new investigations have been conducted to explore exposures in populations that consume very high levels of maize and maize

products. Some populations, particularly those in Central America, consume up to 500 grams of maize per day, and even low concentrations of aflatoxin in this food source can lead to substantial exposures on a daily basis.

A study in Guatemala that used the aflatoxin-specific serum albumin biomarkers found levels comparable to those detected during the 1980s in high-risk countries in Africa and Asia [9,10]. Remarkably, Guatemala has the highest liver cancer incidence rate in the Western Hemisphere [11], but preliminary studies have found low levels of hepatitis B virus and hepatitis C virus infection. Thus, the availability of sensitive and specific biomarkers is expanding the understanding of at-risk populations and communities in previously underinvestigated regions of the world.

In eastern China, the availability of serum samples collected over a 20-year period has enabled the measurement of changing aflatoxin exposure patterns by using the biomarker strategy described above. The population-based cancer registry in Qidong, China, documented a reduction of more than 50% in mortality rates from primary liver cancer across birth cohorts from the 1960s to the 1980s for people younger than 35 years; all were born before the universal vaccination of newborn babies against hepatitis B virus. Median levels of the aflatoxin biomarker decreased by more than 95% from 1989 to 2009. A population attributable benefit of 65% for reduced liver cancer mortality was estimated from a government-facilitated switch of dietary staple from maize to rice [12]. Thus, economic growth is leading to market basket diversity, which will help to reduce exposure to aflatoxin from a single source that is susceptible to high levels of contamination.

Aristolochic acid

A coalescence of epidemiological research – focused on the etiology of Balkan endemic nephropathy, an investigation of rare urothelial cancers in people who participated in certain weight-reduction interventions, and a unique mutational signature in *TP53* in tumours – led to the discovery of the role of aristolochic acids in human cancer [13,14]. Aristolochic acid emerged as a dietary carcinogen as a result of inadvertent contamination of staple grains as they grow in the field, because *Aristolochia* plants encroach on the fields. During harvest, the *Aristolochia* plant is harvested together with the foodstuff (such as wheat). Other widespread sources of human exposure to this carcinogen are herbal medicines that have been demonstrated to be contaminated with this group of compounds.

During the past 25 years, sufficient evidence has accrued for aristolochic acid to be classified as carcinogenic to humans (Group 1), as summarized in Monographs Volume 100A [15]. The specific mutational signature found in the *TP53* tumour suppressor gene that is a result of aristolochic acid–adenine adducts has formed a basis for biomarkers to explore this carcinogen as a risk factor in many populations [14].

A recent population-based case–control study involving nearly 6000 cases and about 23 000 controls investigated the linkage between history of prescription of medicines containing *Aristolochia*, cumulative consumption of aristolochic acid, and renal cell carcinoma in Taiwan, China. The presence and level of mutagenic aristolochic acid-derived DNA adducts were determined. Cumulative ingestion of more than 250 milligrams of aristolochic acid increased the risk of renal cell carcinoma, with an odds ratio of 1.25. Furthermore, the distinctive mutational signature described above was evident in 6 of 10 sequenced renal cell carcinoma exomes [16]. This study and others provide strong evidence implicating aristolochic acid in a significant fraction of renal cell carcinoma in Taiwan, China, and thus aristolochic acid may contribute more broadly to this cancer type in many other settings.

Fig. 2.8.2. An *Aristolochia* plant. These plants encroach on fields where staple grains are growing, and hence cause contamination of the grains during harvesting.

Fumonisin

The initial reports implicating fumonisins in human cancer were in association with high rates of oesophageal cancer in residents of Transkei, South Africa, in 1988 [8]. Mechanistically, fumonisin causes toxic effects through inhibition of ceramide synthase, an enzyme needed for sphingolipid metabolism.

Elevated levels of fumonisin in animal feed cause diseases such as leukoencephalomalacia

Fig. 2.8.3. Maize contaminated with fumonisin. Studies have supported a role for fumonisins in the development of a variety of human cancer types.

in horses and pulmonary oedema, reduced weight gain, and liver damage in swine. Fumonisin has also been shown to cause liver cancer and kidney cancer in rats and liver cancer in mice, as summarized in *World Cancer Report 2014* [17]. Collectively, studies in China and South Africa have supported a role for fumonisins in the development of a variety of human cancer types, and because of its widespread contamination of maize, this agent may also interact with other mycotoxins, amplifying their effect in the initiation of cancer [18,19].

Red meat and processed meat

Among the most significant recent advances in the understanding of the role of dietary carcinogens in cancer at several organ sites in humans was the evaluation published in Monographs Volume 114 [3] on the contribution of red meat and processed meat to cancer development (see Chapter 2.6) [20–22]. This evaluation reviewed numerous cohort, case–control, and other observational studies across many different populations. Consumption of red meat was classified as probably carcinogenic to humans (Group 2A), and consumption of processed meat was classified as carcinogenic to humans (Group 1).

Similarly to other Monographs evaluations that reviewed complex mixtures and culminated in the identification of carcinogenic hazards to humans, such as the evaluation of outdoor air pollution (Monographs Volume 109) [23], this evaluation of red meat and processed meat transcends traditional compound-by-compound approaches to hazard assessments. From a policy and regulatory perspective, this has enormous implications for the translation of these findings in both individual and population public health prevention.

Collectively, the findings in Monographs Volume 114 point towards major lifestyle factors that clearly underlie the development of many cancers that will be diagnosed throughout the rest of this century. Diets high in meat consumption also have impacts on the development of other chronic diseases, such as type 2 diabetes, further illustrating the complexity of multiple chronic diseases contributing to the development of cancers.

It is clear that consumption of red meat and processed meat plays a role in the development of cancers of the colorectum, pancreas, and prostate. These findings suggest opportunities for prevention, particularly for colorectal cancer and prostate cancer, for which screening methods exist and for which the incidence is rising as countries transition to higher levels of economic development. Furthermore, because pancreatic cancer is a major contributor to overall cancer mortality, these findings provide further justification for the development of biomarkers in early detection strategies for this cancer, which is nearly always fatal [24,25].

Although it has been revealed in numerous epidemiological investigations that consumption of red meat and processed meat contributes to the development of cancer in humans, the proportionate roles of individual agents or classes of chemical carcinogens in these products remain unresolved. Since the early 1970s, *N*-nitroso compounds have been evaluated for their carcinogenic hazard to humans. Controversy has surrounded the role that nitrates and nitrites play in a balance between preservation

Fig. 2.8.4. Frankfurters and other processed meats. Numerous epidemiological investigations have revealed that consumption of processed meat contributes to the development of cancer in humans.

of foods, bacteriological resistance, and general organoleptic presentation, given that many specific *N*-nitroso compounds are potent experimental carcinogens. Biomarkers have been developed to attempt to evaluate internal and biological effective dose from exposures to these agents. However, many different chemical compounds form identical adducts, and this has confounded the ability to obtain precise measurements of exposure or dose.

Various compounds are chemically formed during the cooking of red meat. These include acrylamide, many heterocyclic aromatic amines, and many different polycyclic aromatic hydrocarbons. Each group or class of these compounds has deleterious biological potency in experimental models, and the heterocyclic aromatic amines have been demonstrated to cause cancers of the breast, colon, and prostate in experimental models. Collectively, these agents represent intriguing hypotheses for their contribution to the development of cancer in humans. Similarly to the issue with nitrates and nitrites, there is a balance between the processes that lead to the formation of these chemical agents and the biological safety of the cooked product. This remains an unresolved issue that needs to be addressed in future research.

Future insights and strategies

Over the past several decades, there has been tremendous progress in the identification of single chemical carcinogens in the diet that are associated with – and, in some cases, causally linked to – the development of cancer in humans. Recent findings have shown that a reduction in exposure to aflatoxin, as documented by biomarker measurements, has produced a reduction in the incidence of liver cancer in a high-risk population. This reduction is similar in trajectory over time to the decrease in the risk of lung cancer seen in individuals who quit tobacco smoking [26]. These data provide a roadmap for translation to other agents that have been identified as being potent human carcinogens. However, recent analyses indicate that complex dietary situations, such as that found with red meat and processed meat, pose particularly challenging analytical strategies for eventual translation to prevention and interventions. The enormous variation on a day-to-day basis due to cooking practices and sources of these foods contributes to major uncertainty in exposure assessment for the compounds present or formed in different food components.

New technologies that use deep sequencing methods may reveal unique mutational signatures that can be used as integrative metrics for cancer risk assessment before a tumour diagnosis. Advances achieved with these new deep sequencing technologies and their attendant biostatistical approaches have shown mutational fingerprints for specific carcinogens, such as aflatoxin and aristolochic acid, and the patterns are also suggestive for oxidative damage [27,28]. Use of the accumulated damage that survives to a tumour diagnosis as a metric of the area under the curve for long-term dosages of carcinogens is an exciting prospect for future work. It will be a challenge to the cancer prevention community not only to develop these analytical strategies but also to validate them in investigations in human populations.

References

1. IARC (1972). Some inorganic substances, chlorinated hydrocarbons, aromatic amines, *N*-nitroso compounds, and natural products. IARC Monogr Eval Carcinog Risk Chem Man. 1:1–184. Available from: http://publications.iarc.fr/19.

2. Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, Allen C, et al.; Global Burden of Disease Cancer Collaboration (2018). Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol. 4(11):1553–68. https://doi.org/10.1001/jamaoncol.2018.2706 PMID:29860482

3. IARC (2018). Red meat and processed meat. IARC Monogr Eval Carcinog Risks Hum. 114:1–502. Available from: http://publications.iarc.fr/564.

4. WHO (2017). Evaluation of certain contaminants in food: eighty-third report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, Switzerland: World Health Organization (WHO Technical Report Series, No. 1002). Available from: https://apps.who.int/iris/handle/10665/254893.

5. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al.; GBD 2015 Obesity Collaborators (2017). Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 377(1):13–27. https://doi.org/10.1056/NEJMoa1614362 PMID:28604169

6. IARC (1993). Some naturally occurring substances: food items and constituents, heterocyclic aromatic amines and mycotoxins. IARC Monogr Eval Carcinog Risks Hum. 56:1–599. Available from: http://publications.iarc.fr/74.

7. Wild CP, Miller JD, Groopman JD, editors (2015). Mycotoxin control in low- and middle-income countries. Lyon, France: International Agency for Research on Cancer (IARC Working Group Reports, No. 9). Available from: http://publications.iarc.fr/535.

8. Wu F, Groopman JD, Pestka JJ (2014). Public health impacts of foodborne mycotoxins. Annu Rev Food Sci Technol. 5(1):351–72. https://doi.org/10.1146/annurev-food-030713-092431 PMID:24422587

9. Groopman JD, Egner PA, Schulze KJ, Wu LS-F, Merrill R, Mehra S, et al. (2014). Aflatoxin exposure during the first 1000 days of life in rural South Asia assessed by aflatoxin B_1-lysine albumin biomarkers. Food Chem Toxicol. 74:184–9. https://doi.org/10.1016/j.fct.2014.09.016 PMID:25308602

10. Smith JW, Kroker-Lobos MF, Lazo M, Rivera-Andrade A, Egner PA, Wedemeyer H, et al. (2017). Aflatoxin and viral hepatitis exposures in Guatemala: molecular biomarkers reveal a unique profile of risk factors in a region of high liver cancer incidence. PLoS One. 12(12):e0189255. https://doi.org/10.1371/journal.pone.0189255 PMID:29236788

11. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today.

12. Chen JG, Egner PA, Ng D, Jacobson LP, Muñoz A, Zhu Y-R, et al. (2013). Reduced aflatoxin exposure presages decline in liver cancer mortality in an endemic region of China. Cancer Prev Res (Phila). 6(10):1038–45. https://doi.org/10.1158/1940-6207.CAPR-13-0168 PMID:23963804

13. Aydin S, Ambroise J, Cosyns J-P, Gala J-L (2017). *TP53* mutations in p53-negative dysplastic urothelial cells from Belgian AAN patients: new evidence for aristolochic acid-induced molecular pathogenesis and carcinogenesis. Mutat Res. 818:17–26. https://doi.org/10.1016/j.mrgentox.2017.03.003 PMID:28477877

14. Hoang ML, Chen C-H, Sidorenko VS, He J, Dickman KG, Yun BH, et al. (2013). Mutational signature of aristolochic acid exposure as revealed by whole-exome sequencing. Sci Transl Med. 5(197):197ra102. https://doi.org/10.1126/scitranslmed.3006200 PMID:23926200

15. IARC (2012). Pharmaceuticals. IARC Monogr Eval Carcinog Risks Hum. 100A:1–437. Available from: http://publications.iarc.fr/118 PMID:23189749

16. Hoang ML, Chen C-H, Chen P-C, Roberts NJ, Dickman KG, Yun BH, et al. (2016). Aristolochic acid in the etiology of renal cell carcinoma. Cancer Epidemiol Biomarkers Prev. 25(12):1600–8. https://doi.org/10.1158/1055-9965.EPI-16-0219 PMID:27555084

17. Stewart BW, Wild CP, editors (2014). World cancer report 2014. Lyon, France: International Agency for Research on Cancer. Available from: http://publications.iarc.fr/396.

18. Pitt JI, Miller JD (2017). A concise history of mycotoxin research. J Agric Food Chem. 65(33):7021–33. https://doi.org/10.1021/acs.jafc.6b04494 PMID:27960261

19. De Ruyck K, De Boevre M, Huybrechts I, De Saeger S (2015). Dietary mycotoxins, co-exposure, and carcinogenesis in humans: short review. Mutat Res Rev Mutat Res. 766:32–41. https://doi.org/10.1016/j.mrrev.2015.07.003 PMID:26596546

20. Farinetti A, Zurlo V, Manenti A, Coppi F, Mattioli AV (2017). Mediterranean diet and colorectal cancer: a systematic review. Nutrition. 43–44:83–8. https://doi.org/10.1016/j.nut.2017.06.008 PMID:28935150

21. Domingo JL, Nadal M (2017). Carcinogenicity of consumption of red meat and processed meat: a review of scientific news since the IARC decision. Food Chem Toxicol. 105:256–61. https://doi.org/10.1016/j.fct.2017.04.028 PMID:28450127

22. Alexander DD, Weed DL, Miller PE, Mohamed MA (2015). Red meat and colorectal cancer: a quantitative update on the state of the epidemiologic science. J Am Coll Nutr. 34(6):521–43. https://doi.org/10.1080/07315724.2014.992553 PMID:25941850

23. IARC (2015). Outdoor air pollution. IARC Monogr Eval Carcinog Risks Hum. 109:1–448. Available from: http://publications.iarc.fr/538.

24. Abid Z, Cross AJ, Sinha R (2014). Meat, dairy, and cancer. Am J Clin Nutr. 100(Suppl 1):386S–93S. https://doi.org/10.3945/ajcn.113.071597 PMID:24847855

25. Jankovic N, Geelen A, Winkels RM, Mwungura B, Fedirko V, Jenab M, et al.; Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES) (2017). Adherence to the WCRF/AICR dietary recommendations for cancer prevention and risk of cancer in elderly from Europe and the United States: a meta-analysis within the CHANCES project. Cancer Epidemiol Biomarkers Prev. 26(1):136–44. https://doi.org/10.1158/1055-9965.EPI-16-0428 PMID:27793797

26. Jha P, Peto R (2014). Global effects of smoking, of quitting, and of taxing tobacco. N Engl J Med. 370(1):60–8. https://doi.org/10.1056/NEJMra1308383 PMID:24382066

27. Petljak M, Alexandrov LB (2016). Understanding mutagenesis through delineation of mutational signatures in human cancer. Carcinogenesis. 37(6):531–40. https://doi.org/10.1093/carcin/bgw055 PMID:27207657

28. Rosenquist TA, Grollman AP (2016). Mutational signature of aristolochic acid: clue to the recognition of a global disease. DNA Repair (Amst). 44:205–11. https://doi.org/10.1016/j.dnarep.2016.05.027 PMID:27237586

2.9 Contamination of air, water, soil, and food

The challenge is to characterize specific risks

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SUMMARY

- Exposures to environmental carcinogens are widespread, and include a large number of agents emitted by different sources to which human populations are exposed through various routes. Many people may be exposed to relatively low levels of environmental carcinogens, thus potentially accounting for a substantial number of excess cancer cases.
- Air pollution, both outdoor and indoor, is the most widely investigated and most important contributor to the environmental cancer burden in human populations. Air pollution alone was responsible for an estimated 350 167 deaths from lung cancer worldwide in 2017.
- The most consistent predictor of the carcinogenicity of air pollution is the concentration of airborne particulate matter with particles of aerodynamic diameter less than 2.5 μm. This complex mixture of pollutants originates mainly from fuel combustion for transportation, power generation, industrial activity, combustion of biomass, and domestic heating and cooking.
- Drinking-water, or water used for agricultural or recreational activities, can be polluted by naturally occurring carcinogenic contaminants (e.g. arsenic) or by anthropogenic pollutants (e.g. chlorinated agents, perfluorinated alkylated substances, and metals). Water pollution can be due to leaks from contaminated soils, and can result in contamination of the food chain.
- The prevention of exposure to carcinogenic environmental pollutants requires both regulatory action and community commitment. At the global level, the situation is currently improving in high-income countries and worsening in low- and middle-income countries.
- Exposome approaches to research on environment and cancer have been applied recently, based on extensive technological advances that opened up new opportunities to collect and analyse large data sets and promote effective preventive actions and policies. Exposome studies promote interdisciplinarity in research, encompass a wide spectrum of environmental exposures experienced by humans from conception onward, and integrate the external exposome with complex mechanistic interactions and cross-omics responses.

Throughout life, people are involuntarily exposed to a wide range of pollutants at home and in the general environment, and many of these pollutants are established or suspected carcinogens (Table 2.9.1).

Such environmental exposures have several common characteristics: (i) They are widespread (e.g. air pollution, which affects billions of people worldwide). (ii) They frequently occur at low doses (e.g. endocrine disrupters in numerous foods and products). In specific populations, environmental exposures may be high (e.g. air pollution in low- and middle-income countries or in the case of accidents). (iii) They frequently occur in mixtures (e.g. the hundreds of chemicals in drinking-water). (iv) They occur throughout the lifetime (e.g. exposure may begin in utero and continue in childhood and adult life). (v) They may concern single agents and routes (e.g. dioxins originating from incomplete combustion of waste and ingested through contaminated food), or they may concern mixtures of chemicals from multiple sources and routes (e.g. heavy metals, gaseous pollutants, particulate matter, and dioxins from complex industrial settings such as smelters, steel factories, and chemical plants).

The high prevalence of such exposures and the lifetime duration of exposure result in high population attributable risks, even though the relative risks may be low. Recently, technological developments have been applied to studies on environmental carcinogens, and an exposome approach has enabled extensive assessments of multiple exposures and linked them with biological pathways [1–5].

Exposure to specific environmental carcinogens may differ widely across populations, and the mixture

of environmental carcinogens to which populations are exposed varies in time and space. Multiple major environmental pollutants have been evaluated by the IARC Monographs in terms of carcinogenic hazard to humans (Table 2.9.1).

The characteristics of environmental exposures have implications for risk assessment that are complex and frequently depend on extrapolation from higher doses. The prevention of exposure to environmental pollutants, which derives mainly from uncontrolled urbanization and industrialization, requires both regulatory action and community commitment [6].

This chapter focuses on chemical pollutants; for information on radiation of various types, please see Chapters 2.4 and 2.5.

Air pollution

The Global Burden of Disease Study 2017 considered 84 behavioural, environmental, occupational, and metabolic risk factors with convincing or probable evidence of causation of human diseases [7]. (Estimates and metadata from the Global Burden of Disease Study 2017 are available from the Institute for Health Metrics and Evaluation at http://ghdx.healthdata.org/gbd-2017, http://ghdx.healthdata.org/gbd-results-tool, and http://www.healthdata.org/data-visualization/gbd-compare.)

Air pollution – which includes airborne particulate matter with particles of aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), ambient ozone, and household $PM_{2.5}$ due to the use of solid cooking fuel – was the fifth highest cause of death among the 84 risk factors in the Global Burden of Disease Study 2017, with 4.9 million attributable deaths and 147.4 million disability-adjusted life years (DALYs). For lung cancer, the overall burden attributable to indoor and outdoor $PM_{2.5}$ pollution was estimated to be 350 167 deaths and 7.8 million DALYs, related mostly to outdoor $PM_{2.5}$ pollution (265 267 deaths and 5.9 million DALYs) [7].

Outdoor air pollution

Outdoor air pollution is a complex mixture of pollutants originating mainly from fuel combustion for transportation, power generation, industrial activity, combustion of biomass, and domestic heating and cooking (https://www.who.int/airpollution/ambient/pollutants/en/).

Outdoor air pollution comprises a multitude of chemical and physical constituents that vary globally as a result of differences in emission sources, climate, and meteorology. Among these constituents, several agents or mixtures have been established to be carcinogenic to humans, including benzene, 1,3-butadiene, diesel engine exhaust, silica dust, benzo[*a*]pyrene, chromium, arsenic, and asbestos (Table 2.9.1).

In long-term longitudinal studies of exposure to outdoor air pollution, the most consistent predictor of adverse health effects is the concentration of $PM_{2.5}$. On the basis of results from these studies and on strong experimental and mechanistic evidence, the IARC Monographs classified overall outdoor air pollution as well as particulate matter in outdoor air pollution as carcinogenic to humans (Group 1), causing lung cancer [8]. The IARC Monographs also reviewed the evidence for exposure to air pollution and other cancer types, including bladder cancer, breast cancer, leukaemia and lymphoma, childhood cancers, and all cancers combined, and concluded that the evidence was positive but limited for bladder cancer only. More recently, large studies, including the European Study of Cohorts for Air Pollution Effects (ESCAPE) project, have not identified an association between air pollution and risk of incident bladder cancer; however, there was some additional evidence that long-term exposure to outdoor air pollution may be associated with risk of kidney cancer, breast cancer, brain cancer, and liver cancer [9–13].

WHO provides air quality guidelines and interim targets for the concentration of outdoor $PM_{2.5}$ [14]. In 2017, 92% of the world's population lived in areas that exceeded the WHO air quality guideline of 10 μg/m^3

FUNDAMENTALS

- Environmental carcinogenesis has been extensively studied since the 1980s, but only recently has the evolution of study protocols, integrating population-based observational and mechanistic experimental studies, provided a comprehensive evidence base for causal inference and supported reliable estimation of the burden of cancer attributable to pollution.
- Exposure to outdoor air pollution from multiple sources, including diesel engine exhaust and industrial processes, causes lung cancer, and continuing household use of solid fuels causes lung cancer.
- Contamination of drinking-water by arsenic causes lung cancer, bladder cancer, and skin cancer.
- A variety of other potentially carcinogenic pollutants occur in various communities worldwide, but their impact on cancer causation is still not well known.
- Research on environment and cancer has focused largely on high-income countries, where exposure to environmental carcinogens is in many instances decreasing as a result of regulatory action.
- The impact of regulation can be seen as resulting in the relocation of certain industrial processes to low-income countries, exposing the local population to carcinogenic products or waste. International cooperation is needed to redress this phenomenon.
- The exposome approach aims to assess and prevent health risks due to environmental exposures by integrating information on the external environment (contaminants, lifestyle factors, diet, socioeconomic status, etc.) and the internal environment (biological factors such as genetic and metabolic factors). The exposome approach is particularly relevant in assessing environmental exposures to complex chemical mixtures, which are possibly related to cancer and other health effects.

Table 2.9.1. Environmental pollutants evaluated in terms of carcinogenic hazard to humans, the main associated cancer sites or types, and the level of evidence (IARC Monographs classification)

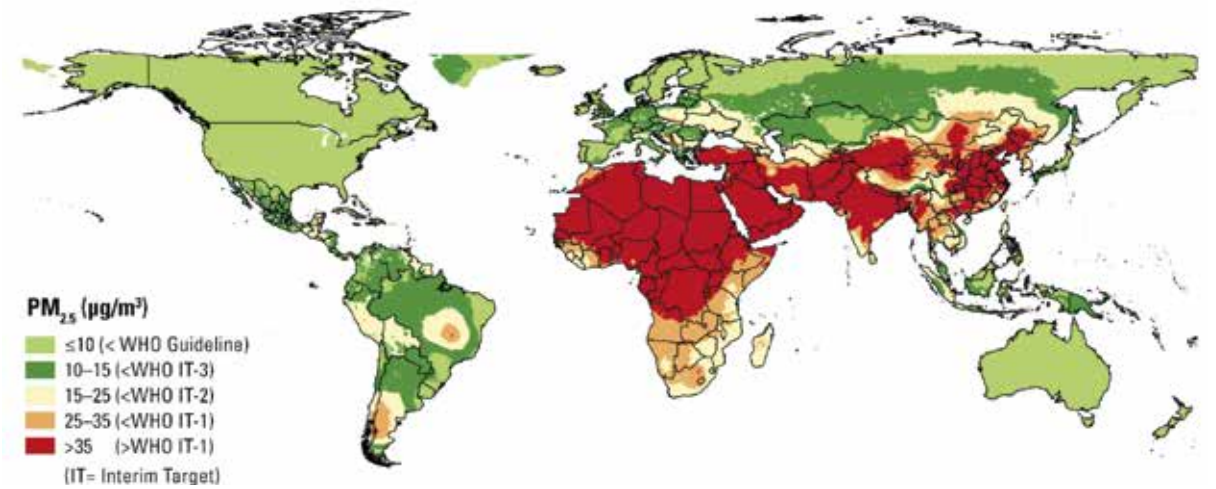
Agent	Cancer site or type	IARC Monographs classification[a]
Outdoor air pollution		
Outdoor air pollution, particulate matter in outdoor air pollution	Lung	Group 1
Outdoor air pollutants, other[b] Diesel engine exhaust, silica dust, benzene	Lung, leukaemia	Group 1
Indoor air pollution		
Indoor emissions from household combustion of coal	Lung	Group 1
Indoor emissions from household combustion of biomass fuel (primarily wood)	Lung	Group 2A
Second-hand tobacco smoke	Lung	Group 1
Indoor air pollutants, other[b] Benzene, 1,3-butadiene, diesel engine exhaust, ethylene oxide, formaldehyde, polychlorinated biphenyls	Lung, leukaemias, lymphoma, nasopharynx, and others	Group 1
Asbestos and other fibres		
Asbestos	Lung, mesothelioma, larynx, ovary	Group 1
Erionite, fluoro-edenite	Mesothelioma	Group 1
Drinking-water contaminants		
Arsenic	Lung, skin, bladder	Group 1
Disinfection by-products	Bladder	Group 2B and Group 3
Nitrates	Stomach	Group 2A
Contaminants of soil and food, including pesticides		
Dioxin (2,3,7,8-tetrachlorodibenzo-*para*-dioxin)	All neoplasms	Group 1
Polychlorinated biphenyls	Skin, melanoma	Group 1
Lindane	Lymphomas	Group 1
Several other pesticides	Mostly leukaemia and lymphoma	Group 2A
Metals in water and soil		
Cadmium, lead, chromium(VI)	Lung	Group 1
Endocrine disrupters		
Food, cosmetics, and other products[c]	Breast, testis	Specific Group 1 carcinogens (e.g. 2,3,7,8-tetrachlorodibenzo-*para*-dioxin) are endocrine disrupters
Ionizing and ultraviolet radiation		
Radon-222 and its decay products (indoor air)	Lung	Group 1
Solar radiation	Skin, malignant melanoma	Group 1
Tanning devices that emit ultraviolet radiation	Cutaneous malignant melanoma, ocular melanoma	Group 1
Non-ionizing radiation		
Extremely low frequency magnetic fields	Childhood leukaemia	Group 2B
Radiofrequency electromagnetic fields	Brain	Group 2B

[a] Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, not classifiable as to its carcinogenicity to humans.

[b] Identified primarily in the occupational environment but also present in the general environment.

[c] Not evaluated by the IARC Monographs.

Fig. 2.9.1. Global map comparing concentrations of outdoor fine particulate matter (with particles of aerodynamic diameter less than 2.5 µm [$PM_{2.5}$]) in 2017 with the WHO air quality guideline and Interim Target levels.



for outdoor $PM_{2.5}$; 82% lived in areas that exceeded Interim Target 3 (15 µg/m³), 67% lived in areas that exceeded Interim Target 2 (25 µg/m³), and 54% lived in areas that exceeded Interim Target 1 (35 µg/m³) (Fig. 2.9.1).

Among the world's most populous countries, wide disparities exist in the changes in air quality from 1990 to 2017. The largest improvements in $PM_{2.5}$ levels occurred in only a few countries (Brazil, Japan, the Russian Federation, the USA, and countries in the European Union), whereas large percentages of the populations of Bangladesh, China, India, Nigeria, and Pakistan continue to live in areas with $PM_{2.5}$ levels that still exceed the less stringent WHO Interim Target 1 (35 µg/m³).

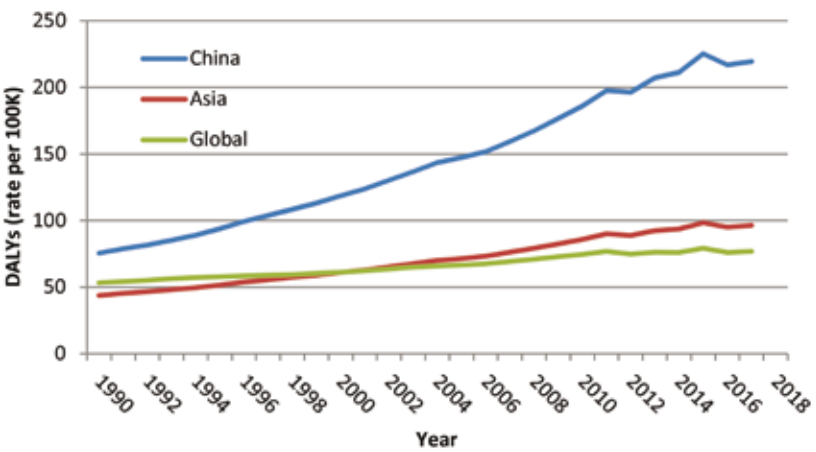
Outdoor $PM_{2.5}$ was the eighth highest cause of death among the 84 risk factors in the Global Burden of Disease Study 2017, responsible for an overall burden of 2.9 million deaths and 83.0 million DALYs. Large proportions of the global burden of disease due to outdoor $PM_{2.5}$ occurred in China (851 660 deaths and 19.8 million DALYs) and India (673 129 deaths and 21.3 million DALYs) [7].

More recent assessments of the disease burden of outdoor $PM_{2.5}$, incorporating new evidence from studies in countries with high levels of pollution, produced much higher estimates ranging up to 8.9 million deaths worldwide, including those from lung cancer [15].

Ambient $PM_{2.5}$ is the second leading cause of lung cancer deaths (265 267 deaths and 5.9 million DALYs globally), after smoking (see Chapter 2.1). The global burden of lung cancer deaths due to outdoor $PM_{2.5}$ increased from 53 DALYs per 100 000 people in 1990 to 77 DALYs per 100 000 people in 2017; this increase was more rapid in Asia and particularly in China, where the burden increased from 75 DALYs per 100 000 people in 1990 to 220 DALYs per 100 000 people in 2017 (Fig. 2.9.2).

It should be noted that the burden of disease estimates for air pollution and lung cancer and other causes of death have considerable uncertainty. This is because they are estimated by extrapolating the results of studies in high-income countries with low $PM_{2.5}$ concentrations to the high levels of exposure measured in China and other low- and middle-income countries, using an integrated exposure–response function for $PM_{2.5}$. This approach may underestimate the actual burden of lung cancer and

Fig. 2.9.2. Disability-adjusted life years (DALYs, rate per 100 000 people) due to lung cancer attributable to outdoor fine particulate matter (with particles of aerodynamic diameter less than 2.5 µm [$PM_{2.5}$]) in China, in Asia, and globally from 1990 to 2017, for both sexes and all ages.



other causes of death in low- and middle-income countries. Numerous exposome studies have examined personal measurements of air pollution using sensors or have used other advanced models for exposure assessment in relation to different –omics data, such as DNA methylation, and provide new evidence on biological pathways that associate air pollution with disease [16].

New research on noncommunicable diseases has examined the influence of urban environments in a wider perspective than examining only air pollution. Features of the built environment and green spaces have been associated with improvements in various health outcomes, including psychological well-being, birth outcomes, cardiovascular diseases, cancer, and overall mortality. Results from a large cohort study of women in the USA indicated that surrounding greenness (vegetation) at the place of residence is associated with reduced cancer mortality [17]; this effect was mediated only to a small extent by physical activity. In a study in Spain, residential proximity to green spaces was found to be related to a reduced risk of breast cancer; physical activity did not seem to mediate these results [18].

Indoor air pollution

At a global level, by far the most important contributor to indoor pollution is household air pollution caused by the incomplete combustion of solid fuels for cooking and heating [19].

Indoor emissions from the household combustion of coal have been classified as carcinogenic to humans (Group 1), and indoor emissions from the household combustion of biomass fuel are currently classified as probably carcinogenic to humans (Group 2A) (Table 2.9.1).

Trials that are currently under way have shown benefits from the use of an advanced combustion cookstove that reduces indoor air pollutants and thus the associated health effects, including lung cancer [20].

Globally, the proportion of households that rely on solid fuels for cooking decreased from about 57% in 2005 to 47% in 2017. Although this proportion is decreasing in many countries, the number of people who are potentially exposed to household air pollution may remain the same or even increase as populations continue to grow. In 2017, the numbers and proportions of people exposed to household air pollution from the combustion of solid fuels for cooking were as follows: in India, 846 million people (60% of the population); in China, 452 million people (32% of the population); in Bangladesh, 124 million people (79% of the population), and in the Democratic Republic of the Congo, 78 million people (96% of the population) (Fig. 2.9.3).

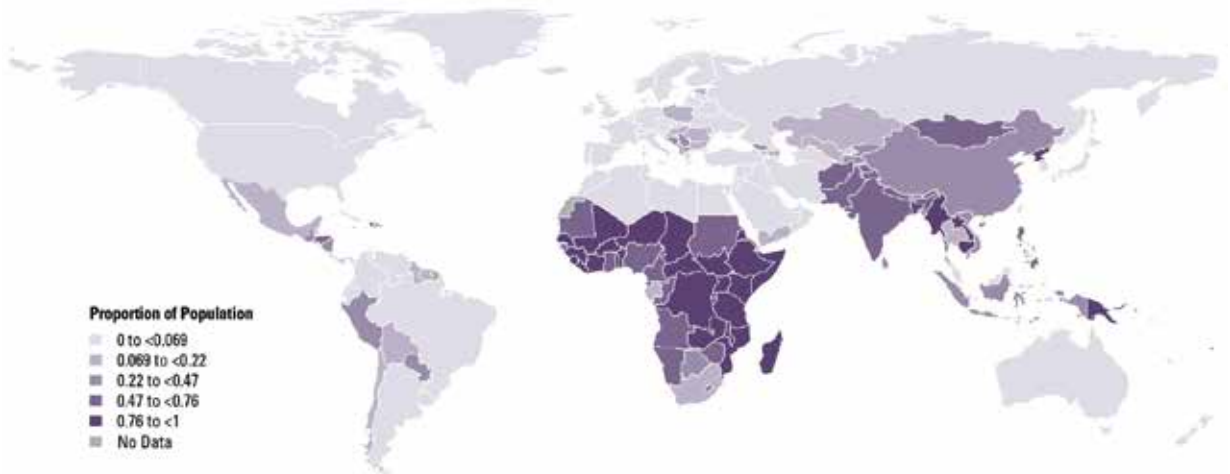
Although the global situation has improved recently, in 2017 household air pollution from the combustion of solid fuels still contributed to 1.6 million deaths (almost 3% of all deaths globally) and 59.5 million DALYs. Of those deaths, almost one half (46%) occurred in China and India, and about one quarter (24%) occurred in sub-Saharan Africa – the parts of the world in which use of solid fuel is most prevalent.

Other important contributors to indoor air pollution, from non-combustion sources, are radon and construction and building materials (glues, formaldehyde, lead in paint or pipes, and asbestos). Second-hand tobacco smoke also contributes to indoor air pollution, and although progress in combating tobacco smoking has resulted in global declines, the most recent estimates from the Global Burden of Disease Study 2017 showed that the burden of lung cancer attributable to second-hand tobacco smoke was still increasing: from 77 635 deaths and 1.8 million DALYs in 2007 to 99 579 deaths and 2.2 million DALYs in 2017 [7]. Most of the above-mentioned contributors to indoor air pollution have been classified by the IARC Monographs as carcinogenic to humans (Table 2.9.1).

Asbestos and other fibres

The majority of mesothelioma cases worldwide are due to occupational

Fig. 2.9.3. Global map comparing the proportion of the population exposed to household air pollution from the combustion of solid fuels for cooking in 2017.



exposure to asbestos. In addition, an etiological role of environmental exposure is well assessed with respect to occurrence of asbestos in the home or the presence of asbestos industrial facilities in the vicinity [21]. Although a few cases of mesothelioma have been reported in individuals who had indoor asbestos exposure, the available evidence on risk for inhabitants of asbestos-roofed houses is inadequate to assess risk of cancer.

The available estimates of the proportion of mesothelioma cases caused by environmental asbestos exposure range from 4% to 20% [22]. Naturally occurring asbestos or asbestiform fibres in soils have been reported in different geographical areas. Erionite has been shown to cause mesothelioma in studies in Turkey, and these findings have recently been confirmed in a study in Mexico [23]. The most recent findings concern fluoro-edenite, an amphibolic fibre. Fluoro-edenite is found in Sicily, Italy, in a volcanic area near Mount Etna. It was classified by the IARC Monographs as carcinogenic to humans (Group 1) [24].

The evidence that asbestos is carcinogenic to humans is overwhelming, and bans on the production and use of asbestos have been adopted by many countries, including former asbestos producers such as Brazil and Canada. However, the majority of the world's population lives in countries where the use of asbestos is still legal [25]. An asbestos ban alone, in the absence of thorough environmental remediation, does not ensure the prevention of asbestos-related disease. Therefore, the long-lasting legacy of the carcinogenicity of asbestos is likely to affect countries where environmental health preventive interventions are less stringent.

Water contaminants

Drinking-water, or water used for agricultural or recreational activities, can be polluted by naturally occurring carcinogenic contaminants or by anthropogenic pollutants. The strongest evidence on exposure to water contaminants and risk of cancer is for arsenic in drinking-water. Numerous studies have associated exposure to water disinfection by-products with risk of bladder cancer. The epidemiological evidence is limited or inconsistent for other water contaminants, including nitrates, perfluorinated alkylated substances, metals, and radionuclides. The United States Environmental Protection Agency provides a list of drinking-water contaminants, which identifies various carcinogens (https://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf).

Use of water is also associated with risk of cancer through the transmission of infectious agents, for example squamous cell carcinoma of the bladder in relation to infection by *Schistosoma haematobium* (see Chapter 2.2).

Arsenic in drinking-water

Evidence linking arsenic in drinking-water with risk of lung cancer, skin cancer, and bladder cancer comes mainly from populations in areas with naturally occurring very high arsenic content, including Argentina, Bangladesh, northern Chile, West Bengal in India, and Taiwan, China [26]. The average exposure to arsenic varies, and in areas of high arsenic content the concentrations are typically above 100 µg/L.

Blackfoot disease is a severe form of peripheral vascular disease that is linked to arsenic exposure from drinking-water and is endemic in areas of Taiwan, China, where well water with a high concentration of arsenic has been used for many years. Ecological, case–control, and cohort studies have been conducted in those areas, and excess risks of bladder cancer, lung cancer, skin cancer, and other cancer types have been consistently found in both sexes, with an exposure–response relationship by years of consumption and by concentration of arsenic in well water. In an area of high arsenic exposure in southwestern Taiwan, China, a progressive decrease in bladder cancer mortality was observed after the installation of a tap-water supply system [27].

Exposure to low levels of arsenic is widespread. Evidence on risk of bladder cancer at low to moderate levels of exposure to arsenic comes mostly from studies in Europe and the USA, and the findings are less consistent. The excess incidence of bladder cancer in the New England region of the USA has been attributed, in part, to the high arsenic content of well water [28].

Water disinfection by-products

Chlorination by-products in drinking-water have been consistently associated with risk of bladder cancer [29,30]. Chlorination of drinking-water is used for disinfection. During chlorination, chlorine reacts with organic matter in water to produce a mixture of by-products, including trihalomethanes, haloacetic acids, and hundreds of other compounds. Several of these compounds are mutagenic to bacteria, and some are carcinogenic to animals.

A pooled analysis of case–control studies identified a 50% higher risk of bladder cancer among individuals with long-term exposure to trihalomethanes in tap water at concentrations of about 50 mg/L [31]; such levels are currently observed in many high- and middle-income countries. Exposure to chlorination by-products in water through inhalation and dermal absorption contributes to the total exposure to trihalomethanes more than exposure through ingestion does, and one study identified increased risks of bladder cancer for exposure in showers and baths and for swimming in pools [29]. Recent studies of the water exposome examined metabolomics, transcriptomics, and proteomics in subjects exposed to disinfection by-products and identified novel biological pathways and genomic responses indicative of increased risk of cancer [32,33].

Nitrates, perfluorinated alkylated substances, and other water contaminants

Nitrate is a widespread contaminant in drinking-water. Nitrate levels above the WHO guideline concentration of

50 mg/L as nitrate are observed in several countries, mainly in groundwater sources from agricultural areas where use of nitrogen-containing fertilizers is common. The evaluation of ingested nitrate and nitrite is complex, because there is an active endogenous nitrogen cycle in humans that under certain conditions generates *N*-nitroso compounds, a class of genotoxic compounds of which many are carcinogenic to animals.

Exposure to nitrates in drinking-water has been examined in case–control and cohort studies in relation to several cancer types, including stomach cancer, oesophageal cancer, brain cancer, lymphomas, bladder cancer, colorectal cancer, and breast cancer. Several studies have identified positive associations with estimates of nitrate uptake from water, particularly for stomach cancer, but the evidence, overall, is not consistent. The IARC Monographs concluded that there is inadequate evidence in humans for the carcinogenicity of nitrate in drinking-water but that ingested nitrate or nitrite under conditions that result in endogenous nitrosation is probably carcinogenic to humans (Group 2A) [34]. A subsequent study suggested a positive association between waterborne ingested nitrates and risk of colorectal cancer [35].

Perfluorinated alkylated substances are chemicals that are widely used as surfactants and are classified as persistent organic pollutants. Evidence on perfluorinated alkylated substances in water and risk of cancer is available for perfluorooctanoic acid, after widespread exposure of residents in the Mid-Ohio Valley, USA, through drinking-water contaminated by chemical plant emissions. In this population, increased risks were found for kidney cancer and testicular cancer [36]. The IARC Monographs classified perfluorooctanoic acid as possibly carcinogenic to humans (Group 2B) after evaluating the carcinogenicity of perfluorooctanoic acid in animals and humans [37].

Few ecological or case–control studies have examined other water contaminants, such as metals (cadmium, nickel, and lead), radionuclides, and tetrachloroethylene, in relation to risk of bladder cancer. The evaluation of new contaminants, such as pharmaceuticals and microplastics, and of mixtures of agents is limited.

Soil

Contamination of the soil may be a risk factor for cancer, because carcinogenic agents present in the soil, either naturally or as a result of human activities, may be inhaled (as in the case of asbestos or other mineral fibres, as previously discussed), accidentally ingested (especially by children playing in direct contact with the ground), or absorbed through the food chain, as a consequence of their release from soil into both groundwater and surface water.

According to a report by the European Joint Research Centre [38], there are estimated to be 342 000 sites in European Union countries with soil contamination, and only 15% of those sites have been subject to remediation interventions. Industrial activities, including industrial waste disposal and treatment, are responsible for about two thirds of the overall contamination. The main contaminants are heavy metals, mineral oils, and aromatic hydrocarbons.

The United States Environmental Protection Agency has developed tools for risk assessment in industrially contaminated sites (https://www.epa.gov/risk/superfund-risk-assessment).

A comprehensive public health assessment encompassing health outcome data, including cancer occurrence in affected communities, is provided by the United States Agency for Toxic Substances and Disease Registry in the *Public Health Assessment Guidance Manual* (www.atsdr.cdc.gov/hac/PHAManual/toc.html). The Agency for Toxic Substances and Disease Registry investigates the occurrence of a wide range of chemical agents in a large number of affected communities, and conducts health assessments considering the available information on contamination, routes of exposure, and mortality and morbidity data. The Superfund Research Program, coordinated by the United States National Institute for Environmental Health Sciences [39], has provided clues to understanding the health impact of hazardous waste dumping sites, including mechanisms through which environmental chemicals may contribute to cancer.

Estimates of cancer risk for populations living near contaminated sites are available in a few countries. An example is in Italy, where an epidemiological surveillance project of 44 sites designated as national priority contaminated sites has specifically considered 23 sites served by cancer registries (Fig. 2.9.4). For each contaminated site, the incidence of all cancers combined and of 35 cancer sites was analysed for the period 1995–2005. In both sexes, an excess was observed for overall cancer incidence (9% in men and 7% in women) as well as for specific cancer sites [40]. An excess of mesothelioma has been subsequently demonstrated, with an ascertained role of environmental, non-occupational exposure to asbestos at three sites and to fluoro-edenite at one site [41,24].

Both in the USA and in Europe, a large proportion of contaminated sites, including those designated as national priority contaminated sites, are characterized by the presence of hazardous waste, which has been dumped, burned, or otherwise improperly managed (Fig. 2.9.5). Hazardous waste may be defined, in general terms, as non-household waste that includes hazardous chemicals (see “Hazardous waste and cancer”).

Food

Contaminants can enter the food chain at various stages: during primary production, transformation, and distribution. Therefore, control is required at each of these stages. In this context, a priority is prevention of the occurrence of endocrine disrupters in food.

Fig. 2.9.4. Air pollution at the industrial area of Priolo, in eastern Sicily, Italy, which has been designated a contaminated site of national priority for remediation.

Endocrine disrupters interfere with the production, release, metabolic action, and elimination of hormones and may act at low doses, with no detectable threshold [42,43]. Endocrine disrupters that are present in the environment and are involved in cancer causation include dioxins, furans, polychlorinated biphenyls, various solvents, heavy metals, pesticides, cosmetics, plastics, and numerous chemicals in consumer products.

Human exposure to persistent organic pollutants and heavy metals occurs mainly from foods of animal origin, because of bioaccumulation and biomagnification. Despite the numerous positive effects of breastfeeding, which should be promoted, maternal milk can be a carrier of a wide range of toxic chemicals, including polychlorinated biphenyls, 4,4′-dichlorodiphenyltrichloroethane (DDT) and its metabolites, dioxins, and dibenzofurans.

Plants can also absorb and accumulate carcinogenic chemicals, such as arsenic, from contaminated soils (for more details, see [44]). The contribution of pesticides to cancer risk deserves special attention (see “Pesticides and cancer”).

Public health interventions enforcing prohibition of consumption of food produced at contaminated sites have been shown to be effective in reducing absorption of toxic chemicals. An example is a study of a community in northern Italy living near a plant that produced polychlorinated biphenyls, which had contaminated the soil, the surface water, and the food chain; after public health measures were implemented, serum concentrations of polychlorinated biphenyls decreased significantly [45].

In the absence of preventive interventions and appropriate communication strategies, vulnerable populations may experience hazardous exposures (see Chapter 6.8). For example, Arctic Indigenous populations, whose traditional diet is based on consumption of the meat of marine mammals, are thus exposed to polybrominated diphenyl ethers, which may disrupt thyroid homeostasis [46].

The main cancer sites for which an etiological role of environmental endocrine disrupters has been suggested are the thyroid, together with the breast, testis, and prostate.

Cancer and environment in children

Cancer is a major cause of death in children, and the incidence of childhood cancers is increasing worldwide in both high- and low-income regions [47]. However, the causes of childhood neoplasms are largely unknown; only about 5% of tumours are of hereditary origin, and ionizing radiation is the only ascertained environmental carcinogen (see Chapter 2.5).

For many agents, such as benzene, arsenic, and dioxins, the evidence of carcinogenicity is well established in adults but only limited in children. Nevertheless, many cancers in children, like in adults, are thought to be activated by somatic mutations. In adults, this is associated with ageing and long-term exposure to carcinogens; in children, the rarity of cancers and the difficulties in evaluating what children might have been exposed to early in life make it difficult to establish a causal role of the environment (https://www.cancer.gov/types/childhood-cancers).

Compared with adults, children are more vulnerable to environmental agents, because of their unique activity patterns, behaviour, and physiology, as well as the immaturity of their organs; in addition, many children – especially those living in low-income regions of the world – are involved in hazardous work, such as that involving contact with pesticides, and are exposed to emerging threats such as toxic components of electronic waste (e-waste) [48,49].

Cancer types in children are different from those in adults; in children, the most common cancer types are leukaemia, lymphoma, and tumours of the central nervous system. This pattern should be further explored, with investigation of specific mutation profiles that are possibly related to environmental carcinogens. Several large-scale studies, for example the International Childhood Cancer Cohort Consortium, are currently addressing the issues of carcinogenic risk in children associated with exposure to chemical contaminants and electromagnetic fields.

Conclusions

Environmental exposure to carcinogens is a well-defined and preventable contributor to the global cancer burden. The most important environmental cancer risk is from

Hazardous waste and cancer

The potential adverse health effects associated with waste management practices have been extensively investigated [1], although firm conclusions have not been reached with respect to cancer risk in terms of causal link or burden of disease. However, the specific issue of hazardous waste has been the subject of a large body of studies, and the findings of those studies are summarized here.

A systematic review of the scientific literature on the health impact of exposure to hazardous waste for populations living near dumping sites was conducted for studies published in 1999–2015 [2]. The reliability of the studies was assessed by evaluating exposure and outcome assessment in terms of possible bias, random error, and confounding. The evaluation of the evidence of an association between exposure to hazardous waste and each health outcome was assessed on the basis of the reliability of the studies, the magnitude and accuracy of the estimated association, and concordance between the findings of studies. The evidence of an association between exposure to hazardous waste and each health outcome was rated as sufficient, limited, or inadequate (partly derived from the IARC Monographs approach), essentially indicating a decreasing gradient of confidence in a causal link (for more details, see [2]).

Limited evidence of an association was detected for cancer of the liver, breast, testis, and bladder, and for non-Hodgkin lymphoma. Among the chemical agents reported in the studies that showed excesses of bladder cancer were heavy metals, β-hexachlorocyclohexane, benzyl chloride, organic sulfur compounds, chlorobenzenes, sodium sulfide/sulfhydrates, and dioxins. The studies that showed excesses of non-Hodgkin lymphoma reported, among others, the presence of vinyl chloride, β-hexachlorocyclohexane, heavy metals, and benzene.

Both for breast cancer and for testicular cancer, the hypothesis of an etiological role of endocrine disrupters was discussed. In this context, it should be noted that an excess of one or more hormone-sensitive cancer types was recently reported in a study of contaminated sites in Italy characterized by the presence of endocrine disrupters [3].

Hazardous waste includes electronic waste (e-waste), the occurrence of which is increasing rapidly. If hazardous waste is inappropriately managed, it has the potential to cause adverse health effects in populations living in areas where the waste was dumped, burned, or not suitably processed. Despite a growing awareness of these issues, illegal trafficking of hazardous waste still occurs, especially towards low- and middle-income countries where environmental regulation is still absent or is poorly enforced [1].

References

1. WHO (2016). Waste and human health: evidence and needs. WHO Meeting Report, 5–6 November 2015, Bonn, Germany. Copenhagen, Denmark: World Health Organization Regional Office for Europe. Available from: http://www.euro.who.int/__data/assets/pdf_file/0003/317226/Waste-human-health-Evidence-needs-mtg-report.pdf?ua=1.
2. Fazzo L, Minichilli F, Santoro M, Ceccarini A, Della Seta M, Bianchi F, *et al.* (2017). Hazardous waste and health impact: a systematic review of the scientific literature. Environ Health. 16(1):107. https://doi.org/10.1186/s12940-017-0311-8 PMID:29020961
3. Benedetti M, Zona A, Beccaloni E, Carere M, Comba P (2017). Incidence of breast, prostate, testicular, and thyroid cancer in Italian contaminated sites with presence of substances with endocrine disrupting properties. Int J Environ Res Public Health. 14(4):E355. https://doi.org/10.3390/ijerph14040355 PMID:28353667

breathing polluted air that contains known human carcinogens. Contamination of water and of the food chain as a result of both naturally occurring carcinogens and anthropogenic pollutants has been less extensively investigated, but such contamination appears to significantly affect high-risk populations, such as those living near industrially contaminated sites. Compared with adults, children are more vulnerable to environmental agents. The situation with respect to exposure to environmental carcinogens is currently improving in high-income countries and worsening in low- and middle-income countries, because of different standards of environmental protection and mechanisms of economic globalization.

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Pesticides and cancer

Laura E. Beane Freeman and Manolis Kogevinas

Pesticides encompass a large and diverse number of chemicals designed to kill pests, including weeds, insects, rodents, algae, and moulds, for agricultural, residential, and public health purposes. These chemicals make important contributions to the production and protection of agricultural commodities and the control of insect disease vectors. They also present potential hazards to human health.

Unlike many other chemical agents, pesticides are designed for release into the environment, and exposure can occur occupationally, through environmental bystander exposure, and through ingestion of foods containing pesticides or pesticides residues. In 2012, 2.6 million tonnes (5.8 billion pounds) of pesticide active ingredients were applied worldwide (https://www.epa.gov/sites/production/files/2017-01/documents/pesticides-industry-sales-usage-2016_0.pdf).

Despite widespread potential exposure, cancer risks associated with long-term exposure to specific pesticides are generally not well characterized. Only one group of pesticides (inorganic arsenic compounds, which are not currently used), one pesticide contaminant (the dioxin 2,3,7,8-tetrachlorodibenzo-*para*-dioxin), and two insecticides with limited current usage (lindane and pentachlorophenol, which is also used as a biocide) are classified by the IARC Monographs as carcinogenic to humans (Group 1). The fungicide captafol, the insecticides 4,4′-dichlorodiphenyltrichloroethane (DDT), malathion, diazinon, and dieldrin (and aldrin metabolized to dieldrin) [1,2], the fumigant ethylene dibromide, and the herbicide glyphosate are classified as probably carcinogenic to humans (Group 2A), as is occupational exposure in the application of non-arsenical insecticides [3]. Of those, only glyphosate and malathion are extensively used today. Several pesticides are classified as possibly carcinogenic to humans (Group 2B), and even more are categorized as not classifiable as to their carcinogenicity to humans (Group 3), largely due to inadequate evidence in humans, although there are indicators from animal bioassays or mechanistic studies that require further investigation.

Exposure assessment is a major challenge in epidemiological studies of pesticides. Some issues include the seasonal nature of many exposures, which may be either indoor or outdoor, and the large number and types of agents, as well as variability in exposure intensity, duration, and frequency, depending on the application and the purpose. There are multiple routes of exposure, and pesticide products can include both active ingredients and inert ingredients such as adjuvants. In addition, most pesticides in use today have short half-lives, which are measured in days or even hours. Finally, the general population may also be exposed, but exposure assessment in the general population poses its own set of challenges.

Because of these and other challenges, few studies are currently available that can evaluate associations between exposure to specific pesticides and risk of cancer. One study that has accomplished this is the Agricultural Health Study in the USA (https://aghealth.nih.gov/). Another study that has more recently been evaluating pesticides and cancer risk is the AGRICAN study in France [4]. These unique studies provide detailed exposure and outcome information, but they examine specific work environments in only two agricultural regions.

Work practices – including the amount and types of pesticides used – and application methods vary around the world. Therefore, there is a need for additional large, diversified epidemiological cohort studies applying modern research approaches. It is important for future research to also assess the effects of environmental exposures, because of the widespread use of these chemicals. Future studies should evaluate specific chemicals and mixtures, and consider potential mechanisms of action to support the biological plausibility of the epidemiological observations. Exposome approaches may open up new possibilities for research and advanced risk assessment, bridging toxicology and epidemiology.

References

1. Loomis D, Guyton K, Grosse Y, El Ghissasi F, Bouvard V, Benbrahim-Tallaa L, et al.; International Agency for Research on Cancer Monograph Working Group (2015). Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid. Lancet Oncol. 16(8):891–2. https://doi.org/10.1016/S1470-2045(15)00081-9 PMID:26111929

2. Guyton KZ, Loomis D, Grosse Y, El Ghissassi F, Benbrahim-Tallaa L, Guha N, et al.; International Agency for Research on Cancer Monograph Working Group (2015). Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. Lancet Oncol. 16(5):490–1. https://doi.org/10.1016/S1470-2045(15)70134-8 PMID:25801782

3. IARC (1991). Occupational exposures in insecticide application, and some pesticides. IARC Monogr Eval Carcinog Risks Hum. 53:5–586. Available from: http://publications.iarc.fr/71 PMID:1688189

4. Levêque-Morlais N, Tual S, Clin B, Adjemian A, Baldi I, Lebailly P (2015). The AGRIculture and CANcer (AGRICAN) cohort study: enrollment and causes of death for the 2005-2009 period. Int Arch Occup Environ Health. 88(1):61–73. https://doi.org/10.1007/s00420-014-0933-x PMID:24599726

References

1. Wild CP (2005). Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev. 14(8):1847–50. https://doi.org/10.1158/1055-9965.EPI-05-0456 PMID:16103423

2. Vineis P, Chadeau-Hyam M, Gmuender H, Gulliver J, Herceg Z, Kleinjans J, et al.; EXPOsOMICS Consortium (2017). The exposome in practice: design of the EXPOsOMICS project. Int J Hyg Environ Health. 220(2 Pt A):142–51. https://doi.org/10.1016/j.ijheh.2016.08.001 PMID:27576363

3. Herceg Z, Ghantous A, Wild CP, Sklias A, Casati L, Duthie SJ, et al. (2018). Roadmap for investigating epigenome deregulation and environmental origins of cancer. Int J Cancer. 142(5):874–82. https://doi.org/10.1002/ijc.31014 PMID:28836271

4. Sarigiannis D, Karakitsios SP (2018). Addressing complexity of health impact assessment in industrially contaminated sites via the exposome paradigm. Epidemiol Prev. 42(5–6S1):37–48. https://doi.org/10.19191/EP18.5-6.S1.P037.086 PMID:30322234

5. Vineis P, Fecht D (2018). Environment, cancer and inequalities – the urgent need for prevention. Eur J Cancer. 103:317–26. https://doi.org/10.1016/j.ejca.2018.04.018 PMID:29903684

6. WHO (2017). Declaration of the Sixth Ministerial Conference on Environment and Health, Ostrava, Czech Republic, 13–15 June 2017. Available from: http://www.euro.who.int/en/media-centre/events/events/2017/06/sixth-ministerial-conference-on-environment-and-health/documentation/declaration-of-the-sixth-ministerial-conference-on-environment-and-health.

7. GBD 2017 Risk Factor Collaborators (2018). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 392(10159):1923–94. https://doi.org/10.1016/S0140-6736(18)32225-6 PMID:30496105

8. IARC (2016). Outdoor air pollution. IARC Monogr Eval Carcinog Risks Hum. 109:1–448. Available from: http://publications.iarc.fr/538.

9. Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, et al. (2013). Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). Lancet Oncol. 14(9):813–22. https://doi.org/10.1016/S1470-2045(13)70279-1 PMID:23849838

10. Andersen ZJ, Stafoggia M, Weinmayr G, Pedersen M, Galassi C, Jørgensen JT, et al. (2017). Long-term exposure to ambient air pollution and incidence of postmenopausal breast cancer in 15 European cohorts within the ESCAPE project. Environ Health Perspect. 125(10):107005. https://doi.org/10.1289/EHP1742 PMID:29033383

11. Andersen ZJ, Pedersen M, Weinmayr G, Stafoggia M, Galassi C, Jørgensen JT, et al. (2018). Long-term exposure to ambient air pollution and incidence of brain tumor: the European Study of Cohorts for Air Pollution Effects (ESCAPE). Neuro Oncol. 20(3):420–32. https://doi.org/10.1093/neuonc/nox163 PMID:29016987

12. Pedersen M, Andersen ZJ, Stafoggia M, Weinmayr G, Galassi C, Sørensen M, et al. (2017). Ambient air pollution and primary liver cancer incidence in four European cohorts within the ESCAPE project. Environ Res. 154:226–33. https://doi.org/10.1016/j.envres.2017.01.006 PMID:28107740

13. Turner MC, Krewski D, Diver WR, Pope CA 3rd, Burnett RT, Jerrett M, et al. (2017). Ambient air pollution and cancer mortality in the Cancer Prevention Study II. Environ Health Perspect. 125(8):087013. https://doi.org/10.1289/EHP1249 PMID:28886601

14. WHO (2006). Air quality guidelines. Global update 2005. Particulate matter, ozone, nitrogen dioxide and sulfur dioxide. Copenhagen, Denmark: World Health Organization Regional Office for Europe. Available from: http://www.euro.who.int/__data/assets/pdf_file/0005/78638/E90038.pdf.

15. Burnett R, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope III CA, et al. (2018). Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. Proc Natl Acad Sci U S A. 115(38):9592–97. https://doi.org/10.1073/pnas.1803222115 PMID:30181279

16. Mostafavi N, Vermeulen R, Ghantous A, Hoek G, Probst-Hensch N, Herceg Z, et al. (2018). Acute changes in DNA methylation in relation to 24 h personal air pollution exposure measurements: a panel study in four European countries. Environ Int. 120:11–21. https://doi.org/10.1016/j.envint.2018.07.026 PMID:30055357

17. James P, Hart JE, Banay RF, Laden F (2016). Exposure to greenness and mortality in a nationwide prospective cohort study of women. Environ Health Perspect. 124(9):1344–52. https://doi.org/10.1289/ehp.1510363 PMID:27074702

18. O'Callaghan-Gordo C, Kogevinas M, Cirach M, Castaño-Vinyals G, Aragonés N, Delfrade J, et al. (2018). Residential proximity to green spaces and breast cancer risk: the multicase-control study in Spain (MCC-Spain). Int J Hyg Environ Health. 221(8):1097–106. https://doi.org/10.1016/j.ijheh.2018.07.014 PMID:30076044

19. WHO (2016). Burning opportunity: clean household energy for health, sustainable development, and wellbeing of women and children. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/airpollution/publications/burning-opportunities/en/.

20. Quansah R, Semple S, Ochieng CA, Juvekar S, Armah FA, Luginaah I, et al. (2017). Effectiveness of interventions to reduce household air pollution and/or improve health in homes using solid fuel in low-and-middle income countries: a systematic review and meta-analysis. Environ Int. 103:73–90. https://doi.org/10.1016/j.envint.2017.03.010 PMID:28341576

21. Ferrante D, Mirabelli D, Tunesi S, Terracini B, Magnani C (2016). Authors's response: Pleural mesothelioma and occupational and non-occupational asbestos exposure: a case-control study with quantitative risk assessment. Occup Environ Med. 73(10):713–4. https://doi.org/10.1136/oemed-2016-103851 PMID:27298458

22. Fazzo L, Minelli G, De Santis M, Bruno C, Zona A, Conti S, et al. (2018). Epidemiological surveillance of mesothelioma mortality in Italy. Cancer Epidemiol. 55:184–91. https://doi.org/10.1016/j.canep.2018.06.010 PMID:29990795

23. Ortega-Guerrero MA, Carrasco-Núñez G, Barragán-Campos H, Ortega MR (2015). High incidence of lung cancer and malignant mesothelioma linked to erionite fibre exposure in a rural community in Central Mexico. Occup Environ Med. 72(3):216–8. https://doi.org/10.1136/oemed-2013-101957 PMID:25231672

24. IARC (2017). Fluoro-edenite. Some nanomaterials and some fibres. IARC Monogr Eval Carcinog Risks Hum. 111:215–42. Available from: http://publications.iarc.fr/552.

25. Marsili D, Terracini B, Santana VS, Ramos-Bonilla JP, Pasetto R, Mazzeo A, et al. (2016). Prevention of asbestos-related disease in countries currently using asbestos. Int J Environ Res Public Health. 13(5):E494. https://doi.org/10.3390/ijerph13050494 PMID:27187433

26. IARC (2004). Some drinking-water disinfectants and contaminants, including arsenic. IARC Monogr Eval Carcinog Risks Hum. 84:1–477. Available from: http://publications.iarc.fr/102 PMID:15645577

27. Su CC, Lu JL, Tsai KY, Lian IeB (2011). Reduction in arsenic intake from water has different impacts on lung cancer and bladder cancer in an arseniasis endemic area in Taiwan. Cancer Causes Control. 22(1): 101–8. https://doi.org/10.1007/s10552-010-9679-2 PMID:21052815

28. Baris D, Waddell R, Beane Freeman LE, Schwenn M, Colt JS, Ayotte JD, et al. (2016). Elevated bladder cancer in northern New England: the role of drinking water and arsenic. J Natl Cancer Inst. 108(9):djw099. https://doi.org/10.1093/jnci/djw099 PMID:27140955

29. Villanueva CM, Cantor KP, Grimalt JO, Malats N, Silverman D, Tardon A, et al. (2007). Bladder cancer and exposure to water disinfection by-products through ingestion, bathing, showering, and swimming in pools. Am J Epidemiol. 165(2):148–56. https://doi.org/10.1093/aje/kwj364 PMID:17079692

30. Beane Freeman LE, Cantor KP, Baris D, Nuckols JR, Johnson A, Colt JS, et al. (2017). Bladder cancer and water disinfection by-product exposures through multiple routes: a population-based case-control study (New England, USA). Environ Health Perspect. 125(6):067010. https://doi.org/10.1289/EHP89 PMID:28636529

31. Costet N, Villanueva CM, Jaakkola JJ, Kogevinas M, Cantor KP, King WD, et al. (2011). Water disinfection by-products and bladder cancer: is there a European specificity? A pooled and meta-analysis of European case-control studies. Occup Environ Med. 68(5):379–85. https://doi.org/10.1136/oem.2010.062703 PMID:21389011

32. van Veldhoven K, Keski-Rahkonen P, Barupal DK, Villanueva CM, Font-Ribera L, Scalbert A, et al. (2018). Effects of exposure to water disinfection by-products in a swimming pool: a metabolome-wide association study. Environ Int. 111:60–70. https://doi.org/10.1016/j.envint.2017.11.017 PMID:29179034

33. Espín-Pérez A, Font-Ribera L, van Veldhoven K, Krauskopf J, Portengen L, Chadeau-Hyam M, et al. (2018). Blood transcriptional and microRNA responses to short-term exposure to disinfection by-products in a swimming pool. Environ Int. 110:42–50. https://doi.org/10.1016/j.envint.2017.10.003 PMID:29122314

34. IARC (2010). Ingested nitrate and nitrite, and cyanobacterial peptide toxins. IARC Monogr Eval Carcinog Risks Hum. 94:1–448. Available from: http://publications.iarc.fr/112 PMID:21141240

35. Espejo-Herrera N, Gràcia-Lavedan E, Boldo E, Aragonés N, Pérez-Gómez B, Pollán M, et al. (2016). Colorectal cancer risk and nitrate exposure through drinking water and diet. Int J Cancer. 139(2):334–46. https://doi.org/10.1002/ijc.30083 PMID:26954527

36. Barry V, Winquist A, Steenland K (2013). Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect. 121(11–12):1313–8. https://doi.org/10.1289/ehp.1306615 PMID:24007715

37. IARC (2017). Perfluorooctanoic acid. Some chemicals used as solvents and in polymer manufacture. IARC Monogr Eval Carcinog Risks Hum. 110:37–110. Available from: http://publications.iarc.fr/547.

38. van Liedekerke M, Prokop G, Rabl-Berger S, Kibblewhite M, Louwagie G (2014). Progress in the management of contaminated sites in Europe. Report EUR 26376. Luxembourg: Publications Office of the European Union. https://doi.org/10.2788/4658

39. Landrigan PJ, Wright RO, Cordero JF, Eaton DL, Goldstein BD, Hennig B, et al. (2015). The NIEHS Superfund Research Program: 25 years of translational research for public health. Environ Health Perspect. 123(10):909–18. https://doi.org/10.1289/ehp.1409247 PMID:25978799

40. Comba P, Ricci P, Iavarone I, Pirastu R, Buzzoni C, Fusco M, et al.; ISS-AIRTUM Working Group for the study of cancer incidence in contaminated sites (2014). Cancer incidence in Italian contaminated sites. Ann Ist Super Sanita. 50(2):186–91. https://doi.org/10.4415/ANN_14_02_13 PMID:24968919

41. Binazzi A, Marinaccio A, Corfiati M, Bruno C, Fazzo L, Pasetto R, et al. (2017). Mesothelioma incidence and asbestos exposure in Italian national priority contaminated sites. Scand J Work Environ Health. 43(6):550–9. https://doi.org/10.5271/sjweh.3676 PMID:28985440

42. Bergman A, Heindel JJ, Jobling S, Kidd KA, Zoeller RT, editors (2013). State of the science of endocrine disrupting chemicals 2012. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/ceh/publications/endocrine/.

43. Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR Jr, Lee DH, et al. (2012). Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr Rev. 33(3):378–455. https://doi.org/10.1210/er.2011-1050 PMID:22419778

44. Mancini FR, Busani L, Tait S, La Rocca C (2016). The relevance of the food production chain with regard to the population exposure to chemical substances and its role in contaminated sites. Ann Ist Super Sanita. 52(4):505–10. https://doi.org/10.4415/ANN_16_04_08 PMID:27999220

45. Raffetti E, Speziani F, Donato F, Leonardi L, Orizio G, Scarcella C, et al. (2017). Temporal trends of polychlorinated biphenyls serum levels in subjects living in a highly polluted area from 2003 to 2015: a follow-up study. Int J Hyg Environ Health. 220(2 Pt B):461–7. https://doi.org/10.1016/j.ijheh.2017.01.002 PMID:28108193

46. Byrne SC, Miller P, Seguinot-Medina S, Waghiyi V, Buck CL, von Hippel FA, et al. (2018). Associations between serum polybrominated diphenyl ethers and thyroid hormones in a cross sectional study of a remote Alaska Native population. Sci Rep. 8(1):2198. https://doi.org/10.1038/s41598-018-20443-9 PMID:29396447

47. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al.; IICC-3 contributors (2017). International incidence of childhood cancer, 2001-10: a population-based registry study. Lancet Oncol. 18(6):719–31. https://doi.org/10.1016/S1470-2045(17)30186-9 PMID:28410997

48. WHO (2017). Inheriting a sustainable world? Atlas on children's health and the environment. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/ceh/publications/inheriting-a-sustainable-world/en/.

49. Laborde A, Tomasina F, Bianchi F, Bruné MN, Buka I, Comba P, et al. (2015). Children's health in Latin America: the influence of environmental exposures. Environ Health Perspect. 123(3):201–9. https://doi.org/10.1289/ehp.1408292 PMID:25499717

2.10 Occupation
The need for continuing vigilance

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SUMMARY

- To date, 38 occupational agents and 12 occupational exposure circumstances have been classified as carcinogenic to humans, and 41 occupational agents and 6 occupational exposure circumstances have been classified as probably carcinogenic to humans.
- Workplace exposure to several well-recognized carcinogens, such as asbestos, polycyclic aromatic hydrocarbons, heavy metals, diesel engine exhaust, and silica, is still widespread.
- The proportion of cancer cases attributable to occupational carcinogens may be substantial.
- Prevention of occupational cancer is feasible, and during recent decades there have been many successful regulations and programmes to eliminate or reduce exposure to carcinogens in the workplace, particularly in high-income countries.
- Little information is available on occupational cancer risk in low-income countries, but it can be reasonably expected to become a large problem in the future.

Until the recognition in the 1950s of the cancer-causing effects of cigarette smoking, almost the only known causes of human cancer were occupational circumstances [1]. In most such instances of increased risk, the relevant information concerned a particular occupation or industry, with little or no information that enabled risk to be attributed to particular chemicals.

Since then, many more causes of cancer have been identified, both occupational and non-occupational. However, even today occupational carcinogens make up a large fraction of all known human carcinogens. Although the discovery of occupational carcinogens provides a means for preventing occupational cancer, the potential benefit of such discoveries goes beyond the factory walls, because most occupational carcinogens are also found in the general environment and in consumer products, sometimes at concentrations as high as those encountered in the workplace.

Specifying occupational carcinogens

This chapter includes tables listing established and probable occupational carcinogens, as well as the occupations and industries in which exposure to them occurs and their target organs. Although it may seem simple, drawing up an unambiguous list of occupational carcinogens is challenging [2,3].

The first source of ambiguity is the definition of an occupational carcinogen. As mentioned above, exposures to most occupational carcinogens also occur in the general environment (see Chapter 2.9) and/or in the course of using consumer products, and, reciprocally, most environmental exposures and those associated with using certain consumer products, including medications, foods, and others, also occur in some occupational context. For instance, whereas exposures to tobacco smoke, solar radiation, and immunosuppressive medications are generally not identified as occupational exposures, there are people whose occupation results in them being in contact with these agents to a degree that would not otherwise occur. Also, whereas asbestos, benzene, diesel engine exhaust, and radon gas are considered to be occupational carcinogens, exposure to these agents is also experienced by the general population, and indeed many more people are probably exposed to these substances in the course of day-to-day life than are exposed at work.

Given the definitional ambiguity, the following operational convention is adopted here: a carcinogen is considered to be “occupational” if there is significant human exposure to the agent in the workplace, in terms of either prevalence or level of exposure, and/or if the main epidemiological studies that led to the identification of an elevated risk of cancer were undertaken among workers. This operational definition requires judgement in its implementation.

Fig. 2.10.1. If there is a requirement to continue using and distributing a chemical known to be carcinogenic to humans, specifically in an occupational context, a range of preventive measures may be implemented, in this case illustrated by warning signs concerning benzene in the USA.

FUNDAMENTALS

- It has long been recognized that a large fraction of known human carcinogens are agents that are found in the workplace.
- Recognized carcinogens include chemical, physical, and biological agents of various families of agents. Important occupational carcinogens are polycyclic aromatic hydrocarbons, aromatic amines, certain metals involved in smelting and related work, and dusts that involve exposure to asbestos and crystalline silica.
- Some of the most frequent cancer types for which excess risk has been observed from one or more occupational carcinogens are lung cancer, bladder cancer, and skin cancer.
- Among the challenges in discovering occupational carcinogens is the fact that there is typically a long time period between exposure to carcinogens and onset of cancer, and therefore information is required about workers' exposures many years before the onset of cancer.
- Prevention of occupational cancer can be achieved through the use of less-hazardous materials, engineering controls, optimal procedures and training, and the use of personal protective equipment, together with the monitoring of exposure levels. Such measures may be supported by regulation.

Another source of ambiguity derives from the nature of those occupations, circumstances, and industries that have been determined to involve increased risk of cancer, although the responsible agent has not been identified. Examples are work as a painter, as a hairdresser, or in aluminium production. Such determinations have somewhat different implications from the determinations that a particular chemical, or related chemicals, confers an excess risk, as is the case for benzene and nickel compounds.

A determination of carcinogenicity of a specified chemical is a statement about the properties of that chemical that are invariant in time and place; conditional on the level of exposure to the agent, the chemical or chemicals should always be considered to be capable of causing cancer. A determination that a given occupation involves a carcinogenic risk does not have such a universal quality. Cancer risks associated with an occupation or industry may well change if there are differences in technologies or processes between the workers who were studied and other workers in the same occupation but in different times or places.

Occupational agents or exposure circumstances evaluated as carcinogenic or probably carcinogenic

The IARC Monographs provide authoritative information for compiling a list of occupational carcinogens [4]. The objective of the Monographs programme, which has been operating since 1971, is to publish critical reviews of epidemiological, experimental, and mechanistic data on carcinogenicity for chemicals, groups of chemicals, industrial processes, other complex mixtures, physical agents, and biological agents to which humans are known to be exposed, and to evaluate data indicative of carcinogenicity.

Expert Working Groups are convened to evaluate all relevant data. As of 2018, 123 Monographs meetings have been held and more than 1000 agents have been evaluated, including many for which relevant epidemiological data primarily involve occupational exposure. IARC Monographs evaluations are respected worldwide and are widely used.

A review was performed of all Monographs that were based on the 125 meetings held up to November

Fig. 2.10.2. Workers in Kolkata, India, tend a furnace in the course of producing fertilizer and fish feed. "Dirty" workplaces are still the norm in many countries.

2019. Table 2.10.1 lists 50 occupational agents, occupations, and industries that have been classified as carcinogenic to humans (Group 1). The table explicitly distinguishes between 38 chemical or physical agents and 12 occupations and industries that involve an increased risk of cancer but for which the responsible agent has not been specified. The table also indicates which agents have been added to the list of Group 1 agents since 2014.

Some of the carcinogens listed occur naturally (e.g. wood dust, solar radiation), whereas some are anthropogenic (e.g. 1,3-butadiene, vinyl chloride). Some are single chemical compounds (e.g. benzene, trichloroethylene). Others are families of compounds that include some carcinogens, and still others are mixtures of varying chemical composition (e.g. diesel engine exhaust, mineral oils). Most known human carcinogens have been established to induce only one type of cancer or a few different types of cancer; notable exceptions include ionizing radiation and asbestos, which are each associated with multiple target organs.

Among the high-risk occupations and industries shown in the second part of Table 2.10.1, most are industries in which the number of workers is quite small, at least in high-income countries. However, one occupational group – painters – stands out as an occupation that is very prevalent. The excess risk of bladder cancer among painters may be due to aromatic amines in paints, and the excess risk of lung cancer may be due to exposures to asbestos or silica in the construction industry.

Table 2.10.2 lists occupational agents, occupations, and industries that have been classified as probably carcinogenic to humans (Group 2A). The table explicitly distinguishes between 41 chemical or physical agents and 4 occupations and industries that have been found to present a probable risk but for which a causative agent has not been identified, and 2 other at-risk occupational circumstances (food frying and shift work). Most of the agents listed in Table 2.10.2 are carcinogenic in experimental animals, with little or no epidemiological evidence to confirm or contradict the evidence in animals. For a few of the agents, including night shift work, lead compounds, and creosotes, there is a reasonable body of epidemiological evidence. However, the studies in humans and in experimental animals, taken together, provide limited evidence of carcinogenicity to humans by IARC Monographs criteria. The relevant epidemiological evidence is not sufficient, because bias, confounding, or chance cannot be excluded as contributing to the association that is evident, or because different studies provide conflicting results.

The family of polycyclic aromatic hydrocarbons poses a particular challenge. This class of chemicals includes several potent experimental carcinogens, such as benzo[*a*]pyrene. However, humans are always exposed to *mixtures* of polycyclic aromatic hydrocarbons; several sources of such mixtures are indicated in Tables 2.10.1 and 2.10.2, including coal tars, soot, and creosotes. Because of the difficulty of isolating the impact of specific polycyclic aromatic hydrocarbons in exposure assessment, it is difficult to evaluate human cancer risks associated with individual members of this family. Only for benzo[*a*]pyrene has the evidence warranted an evaluation of carcinogenic to humans (Group 1), based on mechanistic data taken together with other available evidence, but there are probably more individual polycyclic aromatic hydrocarbons that are carcinogenic to humans.

Loomis et al. [3] recently undertook a similar effort to list occupational carcinogens. They used slightly different criteria for defining an agent as occupational, and their resulting list is slightly different. Even when the criteria are identical, implementing them requires judgement, and this can legitimately vary between experts.

Table 2.10.1. Occupational exposures, occupations, industries, and occupational circumstances classified as carcinogenic to humans (Group 1) by the IARC Monographs, Volumes 1–125

Agent, occupation, or industry	Cancer site or type	Where exposure occurs (industry, occupation, or use)
Chemical or physical agent		
Acid mists, strong inorganic	Larynx, lung	Pickling operations, steel and petrochemical industries, manufacturing of phosphate fertilizer
4-Aminobiphenyl	Bladder	Rubber
Arsenic and inorganic arsenic compounds	Lung, skin, bladder	Glass, metals, pesticides
Asbestos (all forms)	Larynx, lung, mesothelioma, ovary	Insulation, construction, renovation
Benzene	Leukaemia (acute non-lymphocytic leukaemia, acute myeloid leukaemia)	Starter and intermediate in chemical production, solvent
Benzidine	Bladder	Pigments
Benzo[*a*]pyrene	Uncertain	Coal liquefaction and gasification, coke production, coke ovens, coal-tar distillation, roofing, paving, aluminium production, and others
Beryllium and beryllium compounds	Lung	Aerospace, metals, nuclear industry
Bis(chloromethyl)ether; chloromethyl methyl ether	Lung	Production of bis(chloromethyl)ether; manufacturing of plastics, resins, and polymers
1,3-Butadiene	Leukaemia and/or lymphoma	Plastics, rubber
Cadmium and cadmium compounds	Lung	Pigments, batteries
Chromium(VI) compounds	Lung	Metal plating, pigments
Coal-tar pitch	Lung, skin	Construction, electrodes
1,2-Dichloropropane[a]	Biliary tract	Production of chlorinated chemicals
Diesel engine exhaust	Lung	Transportation, mining
Ethylene oxide	Uncertain	Many, including chemical, sterilizing agent
Formaldehyde	Nasopharynx, leukaemia	Formaldehyde production; plastics, textiles
Ionizing radiation (including radon-222 progeny)	Thyroid, leukaemia, salivary gland, lung, bone, oesophagus, stomach, colon, rectum, skin, breast, kidney, bladder, brain	Radiology, nuclear industry, underground mining
Leather dust	Nasal cavity	Shoe manufacture and repair
Lindane[a]	Non-Hodgkin lymphoma	Pesticide
4,4′-Methylenebis(2-chloro-aniline) (MOCA)	Uncertain	Rubber
Mineral oils, untreated or mildly treated	Skin	Lubricant
2-Naphthylamine	Bladder	Pigments
Nickel compounds	Nasal cavity, lung, paranasal sinus	Metal alloy
Outdoor air pollution[a]	Lung	Outdoor workers
Pentachlorophenol[a]	Non-Hodgkin lymphoma	Pesticide
Polychlorinated biphenyls (PCBs)[a]	Melanoma of skin	Transformer manufacturing, electric power workers
Shale oils	Skin	Lubricant, fuel
Silica dust, crystalline, in the form of quartz or cristobalite	Lung	Construction, mining
Solar radiation	Skin, melanoma	Outdoor work
Soot	Lung, skin	Chimney sweeps, masons, firefighters

Table 2.10.1. Occupational exposures, occupations, industries, and occupational circumstances classified as carcinogenic to humans (Group 1) by the IARC Monographs, Volumes 1–125 (continued)

Agent, occupation, or industry	Cancer site or type	Where exposure occurs (industry, occupation, or use)
Tobacco smoke, second-hand	Lung	Bars, restaurants, offices
ortho-Toluidine	Bladder	Pigments
Trichloroethylene	Kidney	Solvent, dry cleaning
Ultraviolet radiation from welding[a]	Melanoma of eye	Welding
Vinyl chloride	Liver	Plastics
Welding fumes[a]	Lung	Welders, construction workers
Wood dust	Nasal cavity, nasopharynx	Wood sawing, construction, furniture
Occupation or industry, without specification of the responsible agent		
Acheson process[a]	Lung	Production of silicon carbide fibres
Aluminium production	Lung, bladder	–
Auramine production	Bladder	–
Coal gasification	Lung	–
Coal-tar distillation	Skin	–
Coke production	Lung	–
Haematite mining (underground)	Lung	–
Iron and steel founding	Lung	–
Isopropyl alcohol manufacture using strong acids	Nasal cavity	–
Magenta production	Bladder	–
Painter	Bladder, lung, mesothelioma	–
Rubber manufacture	Stomach, bladder, leukaemia	–

[a] Added to the list of Group 1 agents since 2014.

Challenges and trends in establishing and understanding lists of occupational carcinogens

Although the lists of occupational carcinogens and associated exposures shown in Tables 2.10.1 and 2.10.2 are long, they are not complete. There are likely to be many more occupational carcinogens that have not yet been discovered or properly documented. For most occupational circumstances, there is no relevant epidemiological evidence about carcinogenic risk. One of the foremost challenges in occupational epidemiology is to reveal as-yet-unrecognized carcinogens and carcinogenic risks.

There are many obstacles to the discovery and characterization of occupational carcinogens. Because of the long latency between exposure to carcinogens and onset of cancer, it is necessary to be able to ascertain occupational circumstances many years before the onset of cancer. The documentation to enable this to be done is often fragmentary, unreliable, or non-existent. Although large companies may have industrial hygiene data for their workforce, these data are often of dubious representativeness. Small companies rarely have any such data. Companies in low- and middle-income countries are even less likely to have and maintain such data over long periods. Even if long-term exposure data can be obtained, there are significant challenges in the statistical modelling of such time-related information. In many occupational cancer studies, it is difficult or impossible to obtain reliable information on potential confounding variables, such as smoking. It would help if physicians or government agencies such as cancer registries routinely recorded the occupations of patients, but this does not often occur. Although epidemiological and toxicological studies are best suited to the investigation of single agents, the occupational environment is complex and shifting and comprises many agents; this poses significant difficulties in assessing risks. The statistical power of epidemiological studies is often limited by the size of various workforces; this limitation could sometimes be overcome by collaborative pooling of data among investigators.

In the past, epidemiological research on occupational risk factors has focused largely on occupational exposures associated with “dirty” industrial environments.

Table 2.10.2. Occupational exposures, occupations, industries, and occupational circumstances classified as probably carcinogenic to humans (Group 2A) by the IARC Monographs, Volumes 1–125

Agent, occupation, or industry	Cancer site or type	Where exposure occurs (industry, occupation, or use)
Chemical or physical agent		
Acrylamide	–	Plastics
Bitumens (combustion products)	Lung	Roofing
Captafol	–	Fungicide
α-Chlorinated toluenes combined with benzoyl chloride	–	Pigments, chemicals
4-Chloro-*ortho*-toluidine	Bladder	Pigments, textiles
Cobalt metal with tungsten carbide	Lung	Hard-metal production
Creosotes	Skin	Wood preserving, brick making
Diazinona	–	Insecticide
4,4′-Dichlorodiphenyltrichloro-ethane (DDT)[a]	–	Biocide
Dichloromethane (methylene chloride)[a]	–	Organic solvent
Dieldrin, and aldrin metabolized to dieldrin	Breast	Biocide
Diethyl sulfate	–	Production of dyes, pigments, textiles
Dimethylcarbamoyl chloride	–	Production; manufacture of pharmaceuticals; pesticides and dyes
Dimethylformamide[a]	–	Solvent in production of acrylic fibres, plastics, pharmaceuticals, pesticides, adhesives, synthetic leathers, and surface coatings
1,2-Dimethylhydrazine	–	Laboratory use only; DNA methylation
Dimethyl sulfate	–	Used in methylation of phenols, amines, and thiols; plastics, pharmaceuticals, herbicides
Epichlorohydrin	–	Plastics
Ethylene dibromide	–	Fumigant
Glycidol	–	Pharmaceutical industry
Glyphosate[a]	Non-Hodgkin lymphoma	Herbicide, agriculture
Hydrazine[a]	Lung	Production of gases, propellants, pharmaceuticals, pesticides, solvent
Indium phosphide	–	Semiconductors
Lead compounds, inorganic	Lung, stomach	Metals, pigments
Malathion[a]	–	Organophosphate insecticide
2-Mercaptobenzothiazole[a]	–	Sulfur vulcanization of rubber
Methyl methanesulfonate	–	Methylating agent
6-Nitrochrysene[a]	–	Transportation, vehicle mechanic
1-Nitropyrene[a]	–	Transportation, vehicle mechanic
2-Nitrotoluene	–	Production of dyes
Non-arsenical insecticides	–	Agriculture
Polycyclic aromatic hydrocarbons Cyclopenta[*cd*]pyrene Dibenz[*a*,*h*]anthracene Dibenz[*a*,*j*]acridine Dibenzo[*a*,*l*]pyrene	–	Combustion of organic matter, coal liquefaction and gasification, coke production, coke ovens, coal-tar distillation, roofing, paving, aluminium production, foundries, steel mills, firefighters, vehicle mechanics
1,3-Propane sultone[a]	–	Laboratory use, photographic chemicals, pharmaceuticals, insecticides, dyes, chemical industry

Table 2.10.2. Occupational exposures, occupations, industries, and occupational circumstances classified as probably carcinogenic to humans (Group 2A) by the IARC Monographs, Volumes 1–125 (continued)

Agent, occupation, or industry	Cancer site or type	Where exposure occurs (industry, occupation, or use)
Silicon carbide whiskers[a]	–	Mineral, abrasives
Styrene and styrene-7,8-oxide	–	Plastics
Tetrabromobisphenol A[a]	–	Fire retardant
Tetrachloroethylene (perchloroethylene)	–	Solvent
Tetrafluoroethylene[a]	–	Alkylating agent used in production of polymers, non-stick coatings, resistant tubing
1,2,3-Trichloropropane	–	General-purpose solvent
Tris(2,3-dibromopropyl) phosphate	–	Plastics, textiles
Vinyl bromide	–	Plastics, textiles
Vinyl fluoride	–	Production of various polymers, solar panels
Occupation or industry, without specification of the responsible agent		
Art glass, glass containers, and pressed ware (manufacture of)	Lung, stomach	–
Carbon electrode manufacture	Lung	–
Hairdressers or barbers	Bladder, lung	–
Petroleum refining	–	–
Occupational circumstance, without specification of the responsible agent		
Food frying at high temperature	–	–
Night shift work	Breast, prostate, colon, rectum	Health care, transportation, services

[a] Added to the list of Group 2A agents since 2014.

However, in recent decades occupational hygiene in many industries has improved or different technology has been adopted such that the historical risks no longer apply, at least in high-income countries.

Increasing attention is now being paid to non-chemical agents in the work environment. Physical agents such as solar radiation and electromagnetic fields have been investigated, as have behavioural and ergonomic characteristics of particular occupations, such as physical activity and shift work. For almost all of these risk factors, the distinction between occupational and non-occupational exposure is becoming more blurred.

Industries and occupations are constantly evolving. Even if we knew all there was to know about the cancer risks in today's occupational

Fig. 2.10.3. This factory worker in Thailand has a degree of protection from occupational exposures, including gloves to reduce dermal exposure.

environments (which we do not), continuing to monitor cancer risks in occupational settings would remain an important activity, because occupational exposure circumstances change over time and novel exposure circumstances may be introduced; recent examples include video display terminals and nanoparticles.

Estimates of the fraction of cancer that is attributable to occupational exposures

Estimates have been made in various countries, using various methodologies, of the fraction of cancer that may be attributable to occupational exposures, and that could potentially be prevented if those hazards were eliminated. In general, it has been estimated that the fraction of cancer attributable to occupational exposures is between 2% and 8% in high-income countries [5]. The estimates vary considerably among different types of cancer.

The estimates of occupational burden of cancer vary among countries, depending on the industrial profiles of the countries, and will change over time as new occupational carcinogens are discovered or the impact of old ones diminishes. The estimates also vary with the methodology used, including whether the estimates are based only on established carcinogens or on both established and probable carcinogens.

The most detailed and intensive effort to date to estimate occupational burden of cancer was conducted in Great Britain [6]. The study, which took into account cancer latency, workforce turnover, and changing employment trends and life expectancy over time, estimated that 5.3% of all cancers (8.2% in men, 2.3% in women) were attributable to past exposure to occupational carcinogens, corresponding to about 13 600 new cancers per year and about 8000 deaths per year in Great Britain in 2004 (the numbers are expected to increase over time). The main cancer types attributable to occupational carcinogens were mesothelioma, lung cancer, bladder cancer, breast cancer, non-melanoma skin cancer, and sinonasal cancer. Among the main occupational exposures contributing to this burden were asbestos, shift work (night work), mineral oils, solar radiation, silica, diesel engine exhaust, and the following industries: construction, metal working, service industries, mining, and several manufacturing sectors. The total annual economic cost of new cases of work-related cancer in Great Britain in 2010 was estimated to be £12.3 billion, of which 98% was due to "human" costs – a monetary value on the effects of cancer on quality of life, or loss of life for fatal cancers [7].

The International Labour Organization and WHO have estimated that 5–7% of global deaths are attributable to work-related illnesses and occupational injuries, corresponding to 2.3 million occupation-related deaths per year, of which the majority, 2.0 million, are due to occupational diseases [8,9]. Overall, cancer makes up the largest component (~32%), corresponding to 660 000 deaths, and asbestos is the exposure that contributes the largest proportion.

The WHO Global Burden of Disease Study 2017 estimated that in 2017, about 334 000 cancer deaths were due to occupational exposures, and the major contributors were asbestos, silica, and diesel engine exhaust [9].

Studies on occupational cancer burden are influencing the prioritization and development of strategies for risk reduction, galvanizing campaigns to raise awareness of issues related to occupational cancer [10], and encouraging the introduction or reduction of occupational limit values. In Europe, a socioeconomic health and environmental impact assessment has already led to binding occupational exposure limits being set for all 28 European Union Member States. Such studies have also drawn attention to the inequalities of occupational cancer burden between different sectors of society [11].

Fig. 2.10.4. Hazmat suits (hazardous materials suits) are an example of personal protective equipment, an option to be used to control workplace exposures to occupational carcinogens.

Prevention

The designation of an agent as carcinogenic is an important public health statement, as well as a scientific one.

Such a designation, together with findings from occupational research, has implications for engineering and/or industrial hygiene measures to reduce or eliminate occupational exposure to the agent.

Approaches to preventing workplace exposures to occupational carcinogens and reduction of occupational cancer include eliminating the production or use of carcinogens and controlling exposure to below a minimal risk exposure level, for example an occupational exposure limit (Table 2.10.3).

Even though older, "dirty" industries are declining in importance as a source of employment in high-income countries, it remains true – and will for the foreseeable future – that small companies in all countries may continue to operate with older and dirtier technologies and processes without appropriate preventive measures. For high-income countries and rapidly industrializing countries, risk reduction strategies, such as improvement of compliance with current occupational exposure limits (e.g. for silica exposure) and targeting small- and medium-sized industries, have been demonstrated to be effective (see Chapter 6.8) [12]. The problem is more acute in low- and middle-income countries. Some particularly dirty and dangerous industrial work, like removing asbestos from ships that have been decommissioned, is now being performed in low-income countries. Furthermore, the rapid growth of industry in low- and middle-income countries is often unregulated and has inadequate occupational hygiene.

Fig. 2.10.5. In this scrapyard associated with "ship breaking", located north of Chittagong in Bangladesh, workers have no protection from toxic agents they may encounter.

Effective regulation and control measures need to be appropriately adapted to different circumstances. For some agents, reduction of exposure levels is feasible and appropriate; for others, more extreme measures, such as banning use, may be appropriate. Large numbers of workers continue to be exposed to low levels of occupational carcinogens; some of these workers may well develop cancers as a result of these exposures.

Concurrent exposure to multiple carcinogens is of concern, and in some situations a concerted industry-focused strategy may be needed. Protection measures for a single carcinogen may also simultaneously reduce exposure from others (e.g. measures to reduce general dust); measures to protect against carcinogens will also potentially reduce the incidence of non-malignant occupational disease, such as respiratory ill health.

Monitoring of the workplace can rely on various types of approaches, from industrial hygiene to biomonitoring. Technical advances in these areas should be encouraged.

Table 2.10.3. Measures to control workplace exposures to occupational carcinogens

Control method	Examples of good practice
Elimination	Remove the hazard from the workplace, for example change a process so that the chemicals, materials, or equipment are no longer required.
Substitution	Replace a hazardous material or piece of equipment with a less-hazardous one.
Engineering controls	Redesign the equipment or process so that the hazard is controlled at its source, for example through a physical barrier.
Worker education	Provide information and training on all workplace carcinogens and the use of appropriate control methods. Use information media (e.g. posters, leaflets, data sheets) imaginatively and strategically.
Administrative controls	Design and operate effective and reliable processes and activities to minimize exposure. Provide safe storage, handling, and transportation, and disposal facilities.
Personal protective equipment	Use suitable personal protective equipment, for example gloves, coveralls, respirators, hard hats, safety glasses, high-visibility clothing, and safety footwear.

All stakeholders, including regulators, employers, and employees, should be encouraged to work together on prevention and to develop effective policies and procedures. Unfortunately, precise and reliable data on the magnitude of risks associated with different agents, and on the nature of dose–response relationships, are not always available, or are not available in a form that facilitates intervention. In addition, reliable reporting systems for occupational disease are scarce, particularly for cancers with long latency. Increased efforts are needed to push for more education on occupationally related ill health, for example in medical training and more generally.

Conclusions

Prevention of cancer depends on the identification and management of cancer-causing circumstances. The workplace remains an important locus for research to identify carcinogens and for mitigating or eliminating the impact of carcinogens.

References

1. Siemiatycki J, Richardson L, Boffetta P (2006). Occupation. In: Schottenfeld D, Fraumeni JF Jr, editors. Cancer epidemiology and prevention. 3rd ed. New York (NY), USA: Oxford University Press; pp. 322–54. https://doi.org/10.1093/acprof:oso/9780195149616.003.0018
2. Siemiatycki J, Richardson L, Straif K, Latreille B, Lakhani R, Campbell S, et al. (2004). Listing occupational carcinogens. Environ Health Perspect. 112(15): 1447–59. https://doi.org/10.1289/ehp.7047 PMID:15531427
3. Loomis D, Guha N, Hall AL, Straif K (2018). Identifying occupational carcinogens: an update from the IARC Monographs. Occup Environ Med. 75(8):593–603. https://doi.org/10.1136/oemed-2017-104944 PMID:29769352
4. IARC (2019). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volumes 1–123. Lyon, France: International Agency for Research on Cancer. Available from: http://publications.iarc.fr/.
5. Purdue MP, Hutchings SJ, Rushton L, Silverman DT (2015). The proportion of cancer attributable to occupational exposures. Ann Epidemiol. 25(3):188–92. https://doi.org/10.1016/j.annepidem.2014.11.009 PMID:25487971
6. Rushton L, Bagga S, Bevan R, Brown TP, Cherrie JW, Holmes P, et al. (2010). Occupation and cancer in Britain. Br J Cancer. 102(9):1428–37. https://doi.org/10.1038/sj.bjc.6605637 PMID:20424618
7. Zand M, Rushbrook C, Spencer I, Donald K, Barnes A (2016). Costs to Britain of work-related cancer. Health and Safety Executive, Research Report RR1074. Available from: http://www.hse.gov.uk/research/rrhtm/rr1074.htm.
8. Takala J (2015). Eliminating occupational cancer. Ind Health. 53(4):307–9. https://doi.org/10.2486/indhealth.53-307 PMID:26377441
9. GBD 2017 Risk Factor Collaborators (2018). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 392(10159):1923–94. https://doi.org/10.1016/S0140-6736(18)32225-6 PMID:30496105
10. IOSH (2016). Institution of Occupational Safety and Health "No Time to Lose" campaign: working together to beat occupational cancer. https://www.notimetolose.org.uk/
11. Cherrie JW, Hutchings S, Gorman Ng M, Mistry R, Corden C, Lamb J, et al. (2017). Prioritising action on occupational carcinogens in Europe: a socioeconomic and health impact assessment. Br J Cancer. 117(2):274–81. https://doi.org/10.1038/bjc.2017.161 PMID:28609433
12. Hutchings S, Cherrie JW, Van Tongeren M, Rushton L (2012). Intervening to reduce the future burden of occupational cancer in Britain: what could work? Cancer Prev Res (Phila). 5(10):1213–22. https://doi.org/10.1158/1940-6207.CAPR-12-0070 PMID:22961776

2.11 Pharmaceutical drugs
A current focus on hormones

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SUMMARY

- Evaluating any possible cancer effects of pharmaceutical drugs is problematic, even if a drug is used by many people, given the long surveillance period required for any cancer risks or benefits to emerge.
- Hormonal contraceptives are often used for prolonged periods; the very long-term cancer effects of combined oral contraceptives can now be investigated, because the women who were the first users of these products, in the 1960s, are now entering later life.
- Evidence is starting to emerge about the cancer risks associated with contemporary hormonal contraceptives, including new routes of delivery, new progestogens, and progestogen-only contraceptives.
- The relationship between menopausal hormone therapy and the risk of cancer of the ovary and colorectum has been examined.
- Fertility drugs are being used by increasing numbers of women; studies examining the risk of cancer of the breast, ovary, and endometrium have many methodological challenges, particularly because subfertile women have an inherently increased cancer risk independent of any fertility treatments.

Both the health benefits (often immediate) and the risks of adverse outcomes (often associated with dose and duration of treatment, and experienced at a later time) of using pharmaceutical drugs need to be fully considered by health professionals and patients [1]. Evaluating any possible cancer effects of pharmaceutical drugs is problematic, even if a drug is used by many people, given the long surveillance period required for any cancer risks or benefits to emerge.

Over decades, causation of cancer by pharmaceutical drugs has been discovered in a variety of circumstances. This chapter focuses on research during the past 5 years, and the central issue has been hormonal agents.

Hormonal contraceptives

Hormonal contraceptives are used, often for prolonged periods, to prevent pregnancy, not as a treatment for a disease. Hormonal contraceptives are commonly used – every day, at least 100 million women worldwide are using hormonal contraception [2]. The IARC Monographs programme has evaluated the carcinogenic hazards associated with combined estrogen–progestogen contraceptives [3] and progestogen-only contraceptives [4] and concluded that there was sufficient evidence for combined hormonal contraceptives to be classified as carcinogenic to humans (Group 1), whereas progestogen-only contraceptives were classified as possibly carcinogenic to humans (Group 2B) (Table 2.11.1).

Most of the evidence about hormonal contraceptives relates to combined estrogen–progestogen products, and in particular oral contraceptives (Fig. 2.11.1). Current or recent users of combined oral contraceptives have an increased risk of breast cancer and cervical cancer and, in regions at low risk of hepatitis B virus infection, an increased risk of liver cancer. Users of combined oral contraceptives have a reduced risk of ovarian cancer; this protective effect increases with duration of use and persists for many years after stopping use. Combined oral contraceptives may also be associated with a reduced risk of colorectal cancer, although no consistent relationship has been demonstrated with duration or recency of use.

In 2015, an individual participant meta-analysis of 27 276 women with endometrial cancer (see Chapter 5.11) found that use of oral contraceptives for 10–15 years halves the risk of endometrial cancer, and that a significant protective effect remains more than 30 years after stopping use [5]. These effects varied by histological type: ever use of oral contraceptives was strongly associated with a reduced risk of type I and type II endometrial cancer but was not associated with a reduced risk of uterine sarcoma, which is a much rarer type. During the 50-year period from 1965 to 2014, an estimated 400 000 cases of endometrial cancer in women younger than 75 years were avoided in

Fig. 2.11.1. Most of the evidence about the cancer risks and benefits of hormonal contraception relates to combined estrogen–progestogen products, and mainly oral products, such as the contraceptive pills shown here.

high-income countries as a result of use of oral contraceptives.

Long-term cancer effects

The very long-term cancer risks or benefits of combined oral contraceptives can now be investigated, because the women who were the first users of these products, in the 1960s, are now entering the later stages of their lives.

The most recent findings from the Nurses' Health Study in the USA, after 36 years and 3.6 million person-years of follow-up, were that overall ever use of oral contraceptives was not associated with risk of death from cancer of the breast, cervix, uterus/endometrium, or large bowel and rectum [6]. A reduced risk of death from ovarian cancer was of borderline statistical significance (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.74–1.00). However, use of oral contraceptives for 5 years or more was associated with an increased risk of death from breast cancer (P_{trend} < 0.0001) and a decreased risk of death from ovarian cancer (P_{trend} = 0.002). The increased risk of death from breast cancer diminished with time since last use, with no increased risk 10 years or more after stopping use. For risk of death from ovarian cancer, no trends were found by time since last use.

The Royal College of General Practitioners' Oral Contraception Study in the United Kingdom followed up an initial cohort of 46 022 women for up to 44 years and included more than 1.2 million person-years of observation. It found that an increased risk of incident breast cancer and cervical cancer seen in current and recent users of oral contraception was lost within approximately 5 years of stopping use, with no evidence of an increased risk of either cancer type in ever users later in life [7]. When risks were stratified by time since last use, ever users had a reduced risk of endometrial cancer 25–35 years after stopping use (incidence rate ratio, 0.58; 99% CI, 0.38–0.88). The risk of ovarian cancer (incidence rate ratio, 0.50; 99% CI, 0.29–0.84) and colorectal cancer (incidence rate ratio, 0.67; 99% CI, 0.49–0.91) was reduced 35 years or more since last use. If it is assumed that the incidence rate ratios represent a causal relationship, approximately one third of endometrial cancers and ovarian cancers and one fifth of colorectal cancers among ever users in this study might have been prevented by the use of oral contraceptives. Importantly, the study found no evidence of new cancer risks appearing later in life among ever users, providing strong evidence that most women do not expose themselves to long-term cancer harm if they use oral contraceptives.

FUNDAMENTALS

- Over decades, a range of pharmaceutical drugs has been recognized as causing particular cancers among the people using them. Cytotoxic drugs, either alone or in combination, may cause second cancers, and their use must take into account these and other adverse effects.
- Some drugs, for example diethylstilbestrol and phenacetin, have been withdrawn from widespread use as a result of cancer causation.
- The IARC Monographs programme concluded that there was sufficient evidence for combined hormonal contraceptives to be classified as carcinogenic to humans (Group 1), whereas progestogen-only contraceptives were classified as possibly carcinogenic to humans (Group 2B).
- Most of the evidence about hormonal contraceptives relates to combined estrogen–progestogen products, and in particular oral contraceptives.
- Current or recent users of combined oral contraceptives have an increased risk of breast cancer, cervical cancer, and (in regions at low risk of hepatitis B virus infection) liver cancer.
- Users of combined oral contraceptives have a reduced risk of ovarian cancer; this protective effect increases with duration of use and persists for many years after stopping use. The risk of colorectal cancer may be reduced, although no consistent relationship has been found with duration or recency of use.
- The IARC Monographs programme concluded that estrogen-only menopausal hormone therapy is associated with cancer of the endometrium, ovary, and breast, and that combined estrogen–progestogen hormone therapy is associated with cancer of the breast and endometrium and is unlikely to increase the risk of colorectal cancer or alter the risk of ovarian cancer.

Table 2.11.1. Summary of hormonal contraceptives, hormone therapy, and fertility drugs and cancer risks

Drug	IARC Monographs evaluation	Cancer site	Increased or decreased risk?
Combined estrogen–progestogen oral contraceptives	Carcinogenic to humans (Group 1)	Breast	Increased in current or recent users; evidence emerging of similar risk patterns associated with contemporary products[a]
		Cervix	Increased in current or recent users
		Liver[b]	Increased in current or recent users
		Ovary	Decreased in current or recent users; decreased in ever users; persistent reduced risk many years after stopping use; evidence emerging of similar risk patterns associated with contemporary products[a]
		Endometrium	Decreased in ever users; persistent reduced risk many years after stopping use
		Colorectum	May be decreased in ever users; no consistent relationship shown for duration or recency of use
Progestogen-only contraceptives	Possibly carcinogenic to humans (Group 2B)	Breast	Evidence emerging of increased risk associated with current or recent use of contemporary oral products[a] and the levonorgestrel-releasing intrauterine system
		Ovary	Mixed evidence, with one study finding no reduced risk associated with contemporary products[a]; others found a reduced risk associated with the levonorgestrel-releasing intrauterine system but did not examine risk in exclusive users
Estrogen-only hormone therapy	Carcinogenic to humans (Group 1)	Endometrium	Increased
		Ovary	Increased
		Breast	Increased
Combined estrogen–progestogen hormone therapy	Carcinogenic to humans (Group 1)	Breast	Increased
		Endometrium	Increased (risk of endometrial cancer reduced proportionally by number of days per month that progestogens are added to regimen)
		Ovary	Increased (based on prospective studies) and associated with recency of use
		Colorectum	Possible reduced risk, but current evidence insufficient
Fertility drugs (can include clomiphene citrate[c], gonadotropins, gonadotropin-releasing hormone agonists and antagonists, and human chorionic gonadotropin)	Not assessed	Breast	No association, but possible concerns raised about clomiphene citrate. Lack of good-quality evidence
		Ovary	No evidence of an association; possible increased risk of borderline tumours. Lack of good-quality evidence
		Endometrium	Lack of good-quality evidence

[a] Hormonal contraceptives available on the market during 1995–2014.

[b] In regions at low risk of hepatitis B virus infection.

[c] IARC Monographs evaluation: not classifiable as to its carcinogenicity to humans (Group 3).

The National Institutes of Health-AARP Diet and Health Study of 196 536 mostly postmenopausal women at recruitment reported reductions in the risk of incident ovarian cancer (HR, 0.74; 95% CI, 0.65–0.84), endometrial cancer (HR, 0.78; 95% CI, 0.70–0.86), and any cancer (HR, 0.97; 95% CI, 0.95–0.99) among users of oral contraceptives [8]. For longer durations of use, the risk reductions were stronger for both ovarian cancer and endometrial cancer. The effects of time since last use (recency) were not examined. An increased risk of breast cancer was of borderline statistical significance (HR, 1.04; 95% CI, 1.00–1.09) and was not associated with duration of use.

A study that combined data from 310 290 women who were participants in three large cohorts in the USA (the National Institutes of Health-AARP Diet and Health Study, the California Teachers Study, and the Women's Health Initiative) found that the reduction in the risk of epithelial ovarian cancer per 5 years of oral contraceptive use did not wane with age (50–64 years: HR, 0.88; 95% CI, 0.80–0.98; 65–74 years: HR, 0.82; 95% CI, 0.74–0.91; ≥ 75 years: HR, 0.85; 95% CI, 0.71–1.02; $P_{interaction}$ = 0.79) [9].

In all of these studies [6–9], the combined oral contraceptives assessed usually contained a higher dose of estrogen combined with an older progestogen compared with the products that are currently available. Evidence is starting to emerge about the cancer risks associated with contemporary hormonal contraceptives, including new routes of delivery, new progestogens, and progestogen-only contraceptives.

Contemporary hormonal contraceptives

A study of 1 797 932 women living in Denmark and aged 15–49 years in 1995–2012 examined the risk of breast cancer associated with currently available hormonal contraceptives [10]. During 19.6 million person-years of follow-up, 11 517 incident breast cancers occurred. The relative risk of breast cancer among current or recent users of combined oral contraceptives was 1.19 (95% CI, 1.13–1.26). The strength of the association increased with duration of use. The relative risk estimate was similar to that previously reported [11] but, importantly, was based on contraceptive products available since 1995, whereas the earlier estimate was based on products prescribed in the 1980s or earlier. There were no major differences between the risk associated with combined oral contraceptives containing different progestogens.

The same study also examined progestogen-only contraceptives and found that both the levonorgestrel-only pill and the levonorgestrel-releasing intrauterine system (LNG-IUS) (Fig. 2.11.2) were associated with an increased risk of breast cancer. The absolute increase in the risk of breast cancer in current and recent users was small: 13 (95% CI, 10–16) per 100 000 person-years, or 1 extra breast cancer for every 7690 women using hormonal contraception for 1 year.

The results of the study in Denmark concurred with those of a study of women with menorrhagia aged 30–49 years, which investigated the cancer risks of the LNG-IUS using national registries in Finland [12]. The study in Finland found a higher-than-expected incidence of breast cancer (standardized incidence ratio, 1.19; 95% CI, 1.13–1.25) among users of the LNG-IUS. The users had an increased risk of both ductal and lobular breast cancer, and the risk estimates were highest in women who had purchased the contraceptive at least twice [13]. These results contradict those of the Norwegian Women and Cancer Study, which did not find an increased risk of breast cancer in ever or current users of the LNG-IUS, although few participants in that study were younger than 46 years and the mean time since stopping use was 7.5 years [14].

Another recent study of more than 1.8 million women living in Denmark and aged 15–49 years in 1995–2014 investigated use of contemporary combined hormonal contraceptives and risk of ovarian cancer [15]. Both current or recent use (relative risk [RR], 0.58; 95% CI, 0.49–0.68) and former use (RR, 0.77; 95% CI, 0.66–0.91) of hormonal contraceptives was associated with a reduced risk of ovarian cancer; this effect was directly associated with duration of use and persisted for several years after stopping use. There was little evidence of major differences in risk estimates by the progestogen content of combined oral contraceptives or by tumour type. There was no evidence of a protective effect for ovarian cancer associated with use of progestogen-only contraceptives, although the evidence was limited because few women were exclusive users of progestogen-only products.

Both the Finnish study [12,13] and the Norwegian study [14] found a decreased risk of ovarian cancer and endometrial cancer among ever users of the LNG-IUS. Although the studies adjusted for

Fig. 2.11.2. Evidence is starting to emerge about the cancer risks associated with contemporary hormonal contraceptives, including new routes of delivery, new progestogens, and progestogen-only contraceptives such as the levonorgestrel-releasing intrauterine system, shown here.

some possible confounding factors, neither was able to calculate risks among exclusive users of this progestogen-only product. Therefore, it is possible that the findings were due to a persisting protective effect from previous use of combined oral contraceptives. Such limitations highlight the need for more studies of the possible cancer effects of progestogen-only contraceptives.

Menopausal hormone therapy

Hormone therapy to manage menopausal symptoms such as vasomotor hot flushes, night sweats, and vaginal atrophy includes estrogen-only therapy (which is prescribed mainly to women who have had a hysterectomy) and combined estrogen–progestogen preparations.

The IARC Monographs programme has evaluated these drugs [3] and concluded that estrogen-only hormone therapy is associated with cancer of the endometrium, ovary, and breast, and that combined estrogen–progestogen hormone therapy is associated with cancer of the breast and endometrium (the risk of endometrial cancer is reduced proportionally by the number of days per month that progestogens are added to the regimen). The IARC Monographs also concluded that combined hormone therapy is unlikely to increase the risk of colorectal cancer or alter the risk of ovarian cancer.

Since the IARC Monographs evaluation, the Collaborative Group on Epidemiological Studies of Ovarian Cancer [16] analysed data from 52 observational studies involving 21 488 women with ovarian cancer; more than half of the cancers (12 110) occurred in prospective studies. In the prospective studies, ever users of hormone therapy had an increased risk of ovarian cancer (RR, 1.20; 95% CI, 1.15–1.26) compared with never users, and the risk was strongly associated with recency of use. Current use or recent use (within the past 5 years) was associated with an increased risk of ovarian cancer (RR, 1.37; 95% CI, 1.27–1.48).

The risk was highest among women last recorded as current users (RR, 1.41; 95% CI, 1.32–1.50). Even relatively short duration of use (< 5 years of current use) was associated with an increased risk (RR, 1.43; 95% CI, 1.31–1.56). The risk appeared to decline with time since stopping use of hormone therapy, although there was the suggestion of a small increased risk remaining in past users who had used hormone therapy for at least 5 years and who had stopped use 5 years or more ago.

The risk of ovarian cancer was increased in both users of estrogen-only therapy and users of combined estrogen–progestogen therapy. Risk estimates were similar regardless of the age when hormone therapy started. There were differences in results by tumour type, with increased risks found only for serous or endometrioid tumours (see Chapter 5.12). The Collaborative Group estimated that use of hormone therapy for 5 years from about age 50 years results in 1 additional ovarian cancer per 1000 users and 1 additional ovarian cancer death per 1700 users.

Critics of the findings of the Collaborative Group have highlighted the absence of a relationship with duration of use, the potential for diagnostic bias, the smaller risk estimates from retrospective studies, and inadequate adjustment for some important confounders; therefore, causality could not be established [17]. Nevertheless, the work of the Collaborative Group is the most comprehensive so far and forms the basis for many current clinical guidelines for the prescribing of menopausal hormone therapy.

Two recent large observational studies have both linked national registries to investigate use of hormone therapy and risk of colorectal cancer [18,19].

A cohort of 1 006 219 women living in Denmark and aged 50–79 years was followed up from 1995 to 2009; 8377 incident colon cancers and 4742 rectal cancers occurred [18]. Current users of any systemic hormones (all types of hormone therapy) had a decreased risk of colon cancer (RR, 0.84; 95% CI, 0.78–0.90) and of rectal cancer (RR, 0.87; 95% CI, 0.79–0.95) compared with never users. A stronger reduction in the risk of colon cancer was found in long-term current users with 10 years or more of use (RR, 0.72; 95% CI, 0.61–0.85). Use of tibolone, vaginal estrogen, and transdermal combined preparations was not associated with colorectal cancer. There was little evidence for differences in risk for different progestogen doses or progestogen types. Risk estimates were generally lower among current users of transdermal estrogen-only therapy compared with oral estrogen. The benefits of hormone therapy appeared to be stronger for advanced stage 4 colorectal cancer.

Over the 4-year period from 2004 to 2008, 3799 colorectal cancers occurred in a cohort of 466 822 women aged 55–79 years who were born in Norway and were living in Norway in 2004 [19]. Current, but not past, use of hormone therapy was associated with a reduced risk of colorectal cancer (RR, 0.88; 95% CI, 0.80–0.98). The short follow-up period of the study meant that the influence of duration of use could not be examined.

Risk estimates were similar for estrogen-only therapy and combined estrogen–progestogen therapy and for colon cancer and rectal cancer. Similarly to the findings of the Danish study, use of hormone therapy was associated with a reduction in the risk of regionally advanced tumours (by 19%) and of metastatic colorectal cancer (by 21%) but not of localized tumours. Although the association was not statistically significant, in current users the risk of colorectal cancer tended to decrease with higher doses of oral estrogen, but not of progestogen.

Both of the recent studies accounted for several confounders but were unable to adjust for previous use of oral contraceptives and for

some colorectal cancer risk factors, including body mass index, physical activity, and smoking (see Chapter 5.5). Therefore, the evidence about menopausal hormone therapy and a possible reduced risk of colorectal cancer remains inconclusive.

The Collaborative Group on Hormonal Factors in Breast Cancer recently published an individual participant meta-analysis of the worldwide epidemiological evidence on the type and timing of menopausal hormone therapy and risk of breast cancer in 143 887 women with breast cancer and 424 972 controls [20]. All types of menopausal hormone therapy, except vaginal estrogens, were associated with an increased risk of breast cancer, which increased with duration of use. Risks were larger for combined estrogen–progestogen therapy than for estrogen-only therapy, especially with daily rather than intermittent progestogen. After cessation of use, an increased risk of breast cancer remained for more than 10 years, which was dependent on duration of prior use. Risks were similar regardless of whether women were aged 40–44, 45–49, 50–54, or 55–59 years when starting menopausal hormone therapy. It was estimated that approximately 1 million of the 20 million breast cancers diagnosed in high-income countries since 1990 would have been caused by use of menopausal hormone therapy [20].

Fertility drugs

Treatment for subfertility typically involves the use of ovary-stimulating agents, including selective estrogen-receptor modulators such as clomiphene citrate, gonadotropins, gonadotropin-releasing hormone agonists and antagonists, and human chorionic gonadotropin [21]. Use of these drugs is becoming increasingly common. During 2011, more than 1.5 million assisted reproductive technology cycles [22] were estimated to have been initiated worldwide, in addition to an unknown number of ovulation induction cycles. Concerns have been raised about the long-term effects of fertility drugs on the risk of cancers of the breast, ovary, and endometrium [23].

A systematic review and meta-analysis of 20 cohort studies including 207 914 women who had hormonal treatments for infertility concluded overall that there was no association with risk of breast cancer (summary RR, 1.05; 95% CI, 0.96–1.14) [24]. However, there was significant heterogeneity among the studies (I^2 = 58.5%; P = 0.001). Subgroup analysis found an increased risk of breast cancer in three studies of women who were treated before 1980 and therefore did not have in vitro fertilization (summary RR, 1.26; 95% CI, 1.06–1.50). This finding raised concerns about the association of clomiphene citrate treatment with breast cancer risk, although it was noted that during the time period before in vitro fertilization, use of this agent was not limited to anovulatory women.

A systematic review of 14 cohort studies and 11 case–control studies (including a total of 182 972 women) was conducted to evaluate the risk of ovarian cancer in women treated with ovary-stimulating drugs [25]. Because of the heterogeneity among the studies, meta-analysis was not performed. The review concluded that there was no convincing evidence of an increased risk of invasive ovarian cancer and that there may be an increased risk of borderline ovarian tumours with use of fertility drugs.

The association between use of ovary-stimulating drugs and risk of endometrial cancer has been examined in a systematic review of 19 studies (16 retrospective cohort studies and 3 case–control studies) including 1 937 880 women [21]. Clomiphene citrate appeared to be associated with an increased risk of endometrial cancer when used at high doses or when used for more than seven cycles, but the effect of clomiphene citrate could not be separated from the underlying clinical reasons for such usage patterns. Accordingly, the review reported that because of very low-quality evidence, robust conclusions could not be reached.

These systematic reviews [21, 24,25] highlight several methodological limitations of research to date. Many studies have a relatively short follow-up period, are limited by risk estimates based on small event numbers, lack adjustment for confounders, could be prone to detection or surveillance bias, and do not provide details of the fertility drugs used (including regimens, doses, and number of cycles). The choice of comparator varies between studies; the comparator can be the general population, subfertile women, or both groups. It is also important to note that women who take fertility drugs are a heterogeneous group, and for many of them the underlying reasons for subfertility are risk factors for cancers of the breast, ovary, or endometrium independent of any fertility treatments. Such limitations mean that it is challenging to interpret the findings of studies of the association between use of fertility drugs and risk of cancer.

Based on the evidence to date, the Practice Committee of the American Society for Reproductive Medicine has concluded that there does not appear to be a meaningful increase in the risk of breast cancer, invasive ovarian cancer, or endometrial cancer associated with the use of fertility drugs, and that although there may be an increased risk of borderline ovarian tumours, any absolute risk is small [23]. Given the growing numbers of women using fertility drugs, good-quality evidence about their possible cancer effects is required.

References

1. Friis S, Kesminiene A, Espina C, Auvinen A, Straif K, Schüz J (2015). European Code against Cancer 4th Edition: medical exposures, including hormone therapy, and cancer. Cancer Epidemiol. 39(Suppl 1):S107–19. https://doi.org/10.1016/j.canep.2015.08.003 PMID:26390952

2. United Nations, Department of Economic and Social Affairs, Population Division (2015). Trends in contraceptive use worldwide 2015 (ST/ESA/SER.A/349). New York (NY), USA: United Nations. Available from: http://www.un.org/en/development/desa/population/publications/pdf/family/trendsContraceptiveUse2015Report.pdf.

3. IARC (2012). Pharmaceuticals. IARC Monogr Eval Carcinog Risks Hum. 100A: 1–437. Available from: http://publications.iarc.fr/118 PMID:23189749

4. IARC (1999). Hormonal contraception and post-menopausal hormonal therapy. IARC Monogr Eval Carcinog Risks Hum. 72: 1–660. Available from: http://publications.iarc.fr/90.

5. Collaborative Group on Epidemiological Studies on Endometrial Cancer (2015). Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 16(9):1061–70. https://doi.org/10.1016/S1470-2045(15)00212-0 PMID:26254030

6. Charlton BM, Rich-Edwards JW, Colditz GA, Missmer SA, Rosner BA, Hankinson SE, et al. (2014). Oral contraceptive use and mortality after 36 years of follow-up in the Nurses' Health Study: prospective cohort study. BMJ. 349:g6356. https://doi.org/10.1136/bmj.g6356 PMID:25361731

7. Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC (2017). Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. Am J Obstet Gynecol. 216(6):580.e1–9. https://doi.org/10.1016/j.ajog.2017.02.002 PMID:28188769

8. Michels KA, Brinton LA, Pfeiffer RM, Trabert B (2018). Oral contraceptive use and risks of cancer in the NIH-AARP Diet and Health Study. Am J Epidemiol. 187(8):1630–41. https://doi.org/10.1093/aje/kwx388 PMID:29394309

9. McGuire V, Hartge P, Liao LM, Sinha R, Bernstein L, Canchola AJ, et al. (2016). Parity and oral contraceptive use in relation to ovarian cancer risk in older women. Cancer Epidemiol Biomarkers Prev. 25(7):1059–63. https://doi.org/10.1158/1055-9965.EPI-16-0011 PMID:27197274

10. Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø (2017). Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med. 377(23):2228–39. https://doi.org/10.1056/NEJMoa1700732 PMID:29211679

11. Collaborative Group on Hormonal Factors in Breast Cancer (1996). Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet. 347(9017):1713–27. https://doi.org/10.1016/S0140-6736(96)90806-5 PMID:8656904

12. Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J, Pukkala E (2014). Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. Obstet Gynecol. 124(2 Pt 1):292–9. https://doi.org/10.1097/AOG.0000000000000356 PMID:25004338

13. Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J, Joensuu H, et al. (2016). Levonorgestrel-releasing intrauterine system and the risk of breast cancer: a nationwide cohort study. Acta Oncol. 55(2):188–92. https://doi.org/10.3109/0284186X.2015.1062538 PMID:26243443

14. Jareid M, Thalabard J-C, Aarflot M, Bøvelstad HM, Lund E, Braaten T (2018). Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer. Results from the NOWAC Study. Gynecol Oncol. 149(1):127–32. https://doi.org/10.1016/j.ygyno.2018.02.006 PMID:29482839

15. Iversen L, Fielding S, Lidegaard Ø, Mørch LS, Skovlund CW, Hannaford PC (2018). Association between contemporary hormonal contraception and ovarian cancer in women of reproductive age in Denmark: prospective, nationwide cohort study. BMJ. 362:k3609. https://doi.org/10.1136/bmj.k3609 PMID:30257920

16. Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, Peto R; Collaborative Group on Epidemiological Studies of Ovarian Cancer (2015). Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet. 385(9980):1835–42. https://doi.org/10.1016/S0140-6736(14)61687-1 PMID:25684585

17. Gompel A, Burger H (2015). A Commentary on a recent update of the ovarian cancer risk attributable to menopausal hormone therapy. Climacteric. 18(3):376–8. https://doi.org/10.3109/13697137.2015.1023615 PMID:25812672

18. Mørch LS, Lidegaard Ø, Keiding N, Løkkegaard E, Kjær SK (2016). The influence of hormone therapies on colon and rectal cancer. Eur J Epidemiol. 31(5):481–9. https://doi.org/10.1007/s10654-016-0116-z PMID:26758900

19. Botteri E, Støer NC, Sakshaug S, Graff-Iversen S, Vangen S, Hofvind S, et al. (2017). Menopausal hormone therapy and colorectal cancer: a linkage between nationwide registries in Norway. BMJ Open. 7(11):e017639. https://doi.org/10.1136/bmjopen-2017-017639 PMID:29146641

20. Collaborative Group on Hormonal Factors in Breast Cancer (2019). Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 394:1159–68. https://doi.org/10.1016/S0140-6736(19)31709-X

21. Skalkidou A, Sergentanis TN, Gialamas SP, Georgakis MK, Psaltopoulou T, Trivella M, et al. (2017). Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility. Cochrane Database Syst Rev. 3:CD010931. https://doi.org/10.1002/14651858.CD010931.pub2 PMID:28349511

22. Adamson GD, de Mouzon J, Chambers GM, Zegers-Hochschild F, Mansour R, Ishihara O, et al. (2018). International Committee for Monitoring Assisted Reproductive Technology: world report on assisted reproductive technology, 2011. Fertil Steril. 110(6):1067–80. https://doi.org/10.1016/j.fertnstert.2018.06.039 PMID:30396551

23. Pfeifer S, Butts S, Dumesic D, Fossum G, Gracia C, La Barbera A, et al.; Practice Committee of the American Society for Reproductive Medicine (2016). Fertility drugs and cancer: a guideline. Fertil Steril. 106(7):1617–26. https://doi.org/10.1016/j.fertnstert.2016.08.035 PMID:27573989

24. Gennari A, Costa M, Puntoni M, Paleari L, De Censi A, Sormani MP, et al. (2015). Breast cancer incidence after hormonal treatments for infertility: systematic review and meta-analysis of population-based studies. Breast Cancer Res Treat. 150(2):405–13. https://doi.org/10.1007/s10549-015-3328-0 PMID:25744295

25. Rizzuto I, Behrens RF, Smith LA (2013). Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility. Cochrane Database Syst Rev. 8(8):CD008215. https://doi.org/10.1002/14651858.CD008215.pub2 PMID:23943232

World Cancer Research Fund International/ American Institute for Cancer Research

Martin J. Wiseman

The global network of World Cancer Research Fund (WCRF) International comprises registered charities in the United Kingdom and the Netherlands as well as the American Institute for Cancer Research (AICR) in the USA. AICR was established in 1982 after the review by the United States National Academy of Sciences in that year, which drew attention to the increasing epidemiological evidence of links between food and nutrition and several cancer types, as well as the growing understanding of the influence of nutritional factors on the process of carcinogenesis. However, even then, scientific research into the link between diet and cancer was in its infancy. The WCRF International network was the first organization to focus exclusively on the links between cancer and nutrition, and more recently physical activity. The WCRF International network has a vision to live in a world where no one develops a preventable cancer, and over the past decades WCRF International has funded millions of dollars in cancer prevention research and awareness-raising programmes. Through its Expert Reports and now the Continuous Update Project, WCRF International has set the standard for the synthesis and analysis of published research on the links between diet, body weight, and physical activity and cancer, and in translating the findings into recommendations for cancer prevention for use by health professionals, individuals, and governments worldwide.

The first WCRF/AICR Expert Report, *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*, was published in 1997. This synthesis of mostly epidemiological research on nutrition and cancer laid the foundations for the following decades of scientific interest in this area.

An initially sceptical scientific community has been persuaded not only by the now large number of studies of increasingly high quality but also by a series of state-of-the-art reviews conducted by WCRF and AICR. In particular, the second WCRF/AICR Expert Report, published in 2007, explored the epidemiology of the links between food, nutrition (in particular adiposity), and physical activity and cancers as well as the potential mechanistic underpinning of those links; that created a step change in the perception of the importance of these exposures for the global distribution, and burden, of cancer, second only to that of smoking. The importance of the 2007 Expert Report lay in the rigorous systematic methods used to review the evidence, as well as the care taken in developing criteria to evaluate the evidence.

The WCRF/AICR recommendations developed by the independent expert panel based on the systematic evidence reviews now constitute the most authoritative statement of the opportunity to prevent cancer through food, nutrition, and physical activity, highlighting the importance of maintaining a healthy body weight through appropriate levels of physical activity and a balanced diet, predominantly based on plant foods, with no more than modest amounts of meat and dairy, and limiting the amounts of processed meat, salt, and alcohol, as well as of high-energy foods with high levels of fat, sugar, and salt (so-called fast foods).

The same rigorous approach to the evidence underpinned the next phase of development, the WCRF/AICR Continuous Update Project, in which the database of information extracted for the articles identified by systematic review is maintained on a continuous basis. The past decade of research was summarized in 2018 in the third WCRF/AICR Expert Report. The revised recommendations were not strikingly different from those in the previous reports, but there was a shift in emphasis away from individual foods and nutrients and towards an overall package, with healthy patterns of food and beverage consumption and physical activity, and with an

additional emphasis on the importance of body weight.

The 2018 Expert Report also identified some areas where more work would help to derive better recommendations. First, there remains a dearth of high-quality studies to inform nutritional guidance to people living with and beyond cancer. Second, the report identified that, although cancer appears clinically mostly after the age of 50 years, events that occur early in life (marked by, for example, birth weight or adult attained height) seem to be important in determining cancer susceptibility in later life. Finally, new research on nutritional influences in developing areas such as the colonic microbiome, and in immune surveillance, is likely to provide important insights in the future.

The WCRF/AICR series of Expert Reports and the Continuous Update Project are recognized as the most authoritative summary statement of the links between diet, nutrition, and physical activity and the risk and progression of cancer.

3 Biological processes in cancer development

Knowledge of how normal cells become cancerous – the process of malignant transformation – may underpin cancer prevention. Changes evident in premalignant tissues or at the earliest stage of tumour development are key to improve screening and to monitor people with an increased risk of cancer because of their genetic makeup, and also have implications for cancer treatment. Two scenarios are covered: cancer that develops after exposure to carcinogens, including hazardous chemicals, radiation, or infectious organisms, and cancer that is categorized as sporadic, for which no such exposure is evident. Cancer development after exposure includes the induction of carcinogen-related mutations; critical mutations may also occur spontaneously. DNA repair may be protective, epigenetic events may be as important as mutations, and chronic inflammation plays a key role. Malignant transformation is marked by metabolic, immunological, and hormonal changes. Knowledge of such biological processes has contributed to reducing cancer incidence and mortality.

3.1 Sporadic cancer
Tumorigenesis in the absence of an established or avoidable cause

David Schottenfeld

Paul Brennan (reviewer)
George Davey Smith (reviewer)

SUMMARY

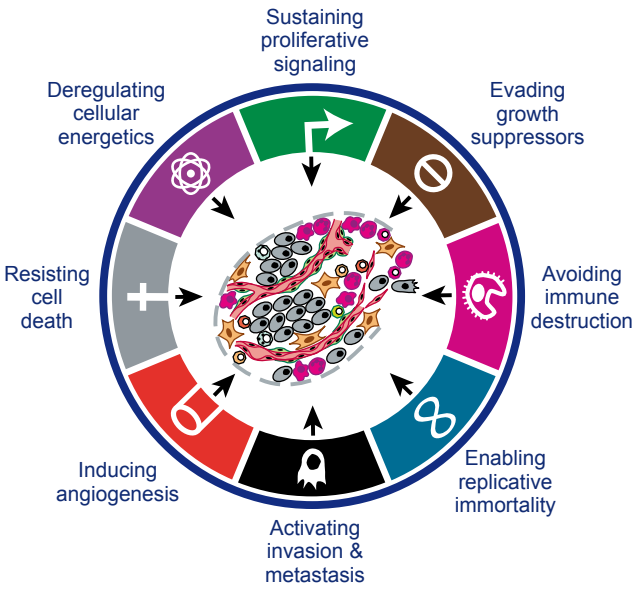
- Multiple factors are recognized as contributing to the development of sporadic cancers.
- Telomeric DNA shortens progressively as cell lineages pass through repeated division cycles and ultimately senescence. The immortalization of cancer cells may occur through activating expression of the telomerase polymerase.
- Stem cell quiescence may be viewed as an evolutionarily conserved mechanism that modulates stochastic events of cell replication and the acquisition of tumorigenic mutations.
- Cancer stem cells are a selective clonal subset of tumour cells that have avoided various cell regulatory mechanisms, including terminal differentiation, and yet have retained the self-renewal properties and proliferative potential of adult stem cells.
- Epigenetic events are intimately associated with fetal organ development, pathological events associated with ageing, biochemical effects of micronutrients, and the tumorigenic effects of cytokine mediators of chronic inflammation. The proposed tumorigenic event is a polyclonal epigenetic disruption of stem/progenitor cells mediated by aberrant regulation of tumour progenitor genes.

Sporadic cancers occur ostensibly in the absence of a demonstrable cause or history of familial susceptibility. At the germline or somatic cellular level, the biology of the cancer cell is viewed as a complex genetic disorder.

The publications of Hanahan and Weinberg have provided a logical framework for comprehending the multistep process of human tumour pathogenesis [1]. The hallmarks of the neoplastic phenotype include sustaining proliferative signalling, evading growth suppression, avoiding immune destruction, enabling replicative immortality, resisting apoptosis, deregulating cellular energetics, inducing angiogenesis, and activating invasion and metastasis (Fig. 3.1.1).

More recently, additional emphasis has been placed on the interaction of tumour cells and the mesenchymal cells forming the tumour-associated stroma or tumour microenvironment. The above-mentioned essential functional capabilities of cancer cells to survive,

Fig. 3.1.1. The hallmarks of cancer.



proliferate, and disseminate are enabled by genomic instability and inflammatory responses mediated by the immune cells recruited by the stroma of malignant cells.

Ageing, telomeres, and cancer susceptibility

Ageing

Ageing is a complex biological phenomenon that is exhibited by all living organisms and is accompanied by a gradual decline in physiological functions. The convergence of biological mechanisms in ageing and neoplasia is explored by relating the effects of telomere dysfunction on cellular senescence and genomic instability.

Increasing age is a major predictor of adult-onset cancer incidence. A logarithmic pattern of overall cancer incidence and age (i.e. the incidence of cancer increases approximately exponentially as a function of age) has suggested a multistep biological mechanism in human carcinogenesis [2,3]. In industrialized countries, the overall cancer incidence rates more than doubled with each increase of 10 years in attained age. In an analysis of adults in the USA in 2012–2014 [4], the probability (as a percentage) of developing invasive cancer at attained ages 50–59 years was 6%, as contrasted with 26% in women and 32% in men at ages 70 years and older.

Cellular senescence

Cellular senescence refers to irreversible arrest of cell proliferation. Although senescent cells are not dividing, they remain metabolically active, secreting factors that may stimulate or inhibit the growth of tumours. In vitro, senescent cells display an enlarged and flattened morphology, have elevated β-galactosidase activity, and express markers consistent with activation of tumour suppressor pathways, cell-cycle arrest, and DNA damage response signalling [5].

In the context of tumour suppression, factors secreted by senescent cells attract components of the innate and adaptive immune system that serve to remove damaged and stressed senescent cells. In addition to arrested growth and failure to re-enter the cell cycle, senescent cells show widespread changes in chromatin organization. Senescent cells may also secrete pro-inflammatory cytokines, chemokines, and growth factors that are demonstrated to enhance cell proliferation and transformation [6]. Pro-angiogenic factors secreted from senescent cells promote tissue vascularization and increase invasiveness of premalignant cells by driving epithelial-to-mesenchymal transitions (Fig. 3.1.2). DNA double-strand breaks or telomere dysfunction caused by oxidative stress may induce a senescent response.

Telomeres

Human telomeres, which are specialized structures at the ends of chromosomes, consist of tandem repetitive arrays of the hexameric sequence TTAGGG. Functional telomeres are required to protect chromosome ends, provide chromosome stability, and ensure, upon cell division, the fidelity of segregation of genetic material into daughter cells. Telomeric dysfunction has consequences for ageing and carcinogenesis [7,8].

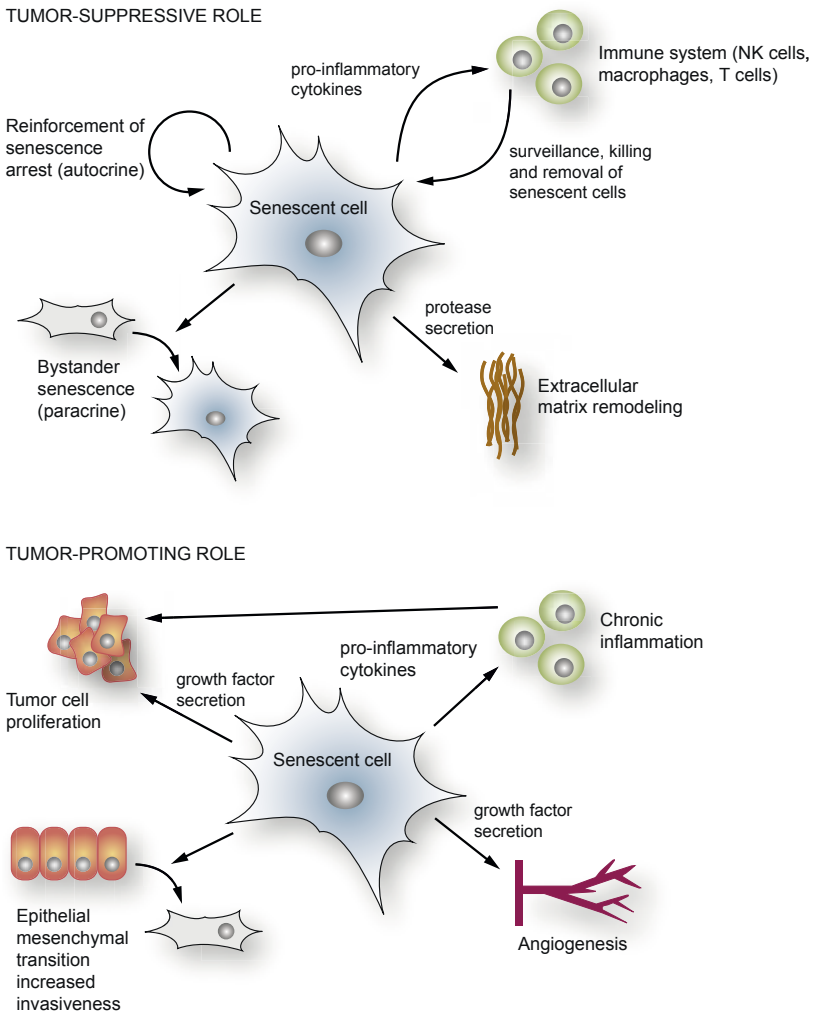
The mechanisms that govern exposure of cells to metabolic stress or crisis involve the cell genome, and more specifically the telomeres. The ends of the telomeric DNA are not copied completely during each cycle of DNA replication, because of an intrinsic limitation in the DNA polymerases responsible for DNA replication. In addition, the ends of telomeric DNA are susceptible to the action of exonucleases, which contribute to erosion of telomeric DNA length [9]. As a consequence, the telomeres shorten progressively as cell lineages pass through repeated division cycles and ultimately senescence.

The immortalization of cancer cells may occur through activating expression of the telomerase polymerase, a ribonucleoprotein enzyme, which restores and maintains telomeric DNA length [10]. The enzyme telomerase consists of a subunit that has reverse transcriptase activity, an RNA element that is the template on which DNA is synthesized, and the protein dyskerin, which has the ability to bind to and stabilize the RNA element [11]. Upregulated telomerase expression is a characteristic of pluripotent stem cells. Telomerase activity is detectable in most human tumours as a result of induction of expression by a complex array of trans-activating oncoproteins.

FUNDAMENTALS

- At the germline or somatic cellular level, the biology of the cancer cell and its nurturing microenvironment is viewed as a complex genetic disorder.
- The convergence of biological mechanisms in ageing and neoplasia reflects the effects of telomere dysfunction on cellular senescence and genomic instability.
- Adult stem cells are observed in close association with differentiated cells of various organs and tissues, and exhibit properties of self-renewal and asymmetric division.
- Epigenetic events are stochastic, discrete, and heritable, may confer the propensity for aberrant growth, and are influenced by environmental oncogenic agents.
- The terminology “sporadic cancer” reflects a currently dynamic but incomplete knowledge of the etiology and pathogenesis of a biologically and morphologically heterogeneous class of diseases.

Fig. 3.1.2. Senescent cells secrete multiple factors that can have effects on the tissue microenvironment.



Somatic stem cells and human carcinogenesis

Stem cells

Adult stem cells are observed in close association with differentiated cells of a given tissue. They are usually located within specialized tissue microenvironments or stem cell "niches" composed of stromal cells and paracrine signalling factors [12].

Stem cells exhibit properties of self-renewal and asymmetric division. Self-renewal signifies that in mitotic activity of stem cells there is resistance to genetic and epigenetic mechanisms that trigger senescence or a permanent state of cell-cycle arrest. Asymmetric division results when a stem cell divides into one daughter cell that replicates a stem cell, while the other daughter cell proceeds along some differentiating pathway (Fig. 3.1.3). The homeostatic balance between self-renewal and differentiation is essential for physiological maintenance of the architecture and functioning of adult organs and tissues [13].

Although adult somatic stem cells have the potential to proliferate actively, they are relatively dormant in their microenvironment. Stem cell quiescence may be viewed as an evolutionarily conserved mechanism that modulates stochastic events of cell replication and the acquisition of tumorigenic mutations.

Cancer stem cells and progenitor cells

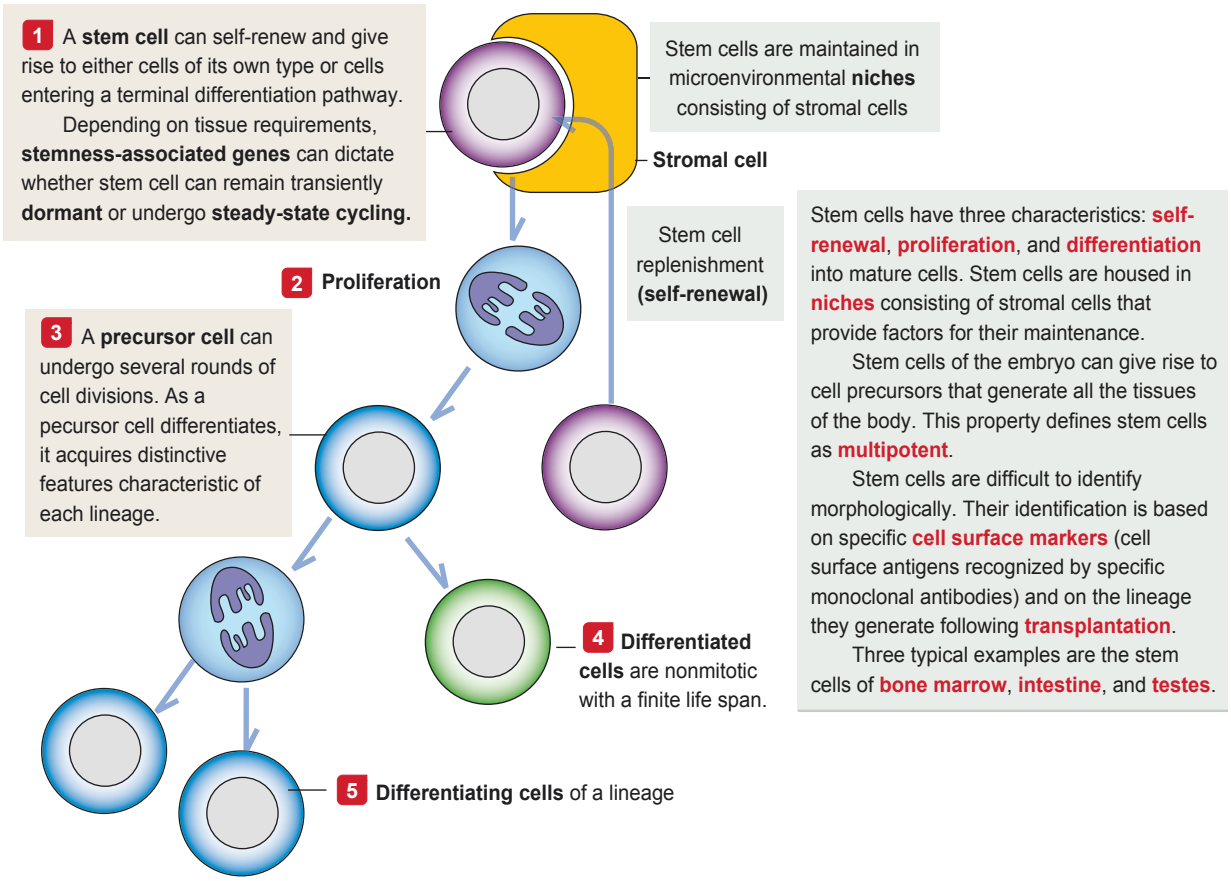
Cancer stem cells are a selective clonal subset of tumour cells that have avoided various cell regulatory mechanisms, including terminal differentiation, and yet have retained the self-renewal properties and proliferative potential of adult stem cells. Most tumours are maintained by a subpopulation of clonal stem cells.

As defined by the American Association for Cancer Research [14], a cancer stem cell is "a cell within a tumor that possesses the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor". By maintaining at least some of the properties of their tissue of origin, cancer stem cells give rise to tumours that phenotypically share in their morphological features and patterns of expression of tissue-specific genes. Progenitor cells are progeny of tissue-specific stem cells with limited potential for self-renewal.

Two models of carcinogenesis have been proposed. A stochastic model proposes that neoplasia evolves potentially in any somatic cell through a sequence of mutational and epigenetic events that are amplified by selective clonal growth. In contrast to the stochastic model, the cancer stem cell model hypothesizes that the cellular origin of cancer resides in tissue-specific stem cells or progenitor cells that possess or acquire the property of self-renewal [15]. The development of biomarkers to identify cancer stem cells has facilitated the isolation and characterization of cells from human tumours. The neoplastic evolution from normal tissue cells is signalled by the loss of homeostatic mechanisms that regulate mitotic activity and differentiation.

A contemporary view would tend to combine biological features advanced by both experimental models. Cancer stem cells are regulated by and interact with the tumour microenvironment. Cells recruited to the microenvironment include growth factors, cytokine

Fig. 3.1.3. Properties of stem cells.



networks, and immunomodulatory T cells and macrophages. The notion of interaction between a stem cell (the "seed") and the tumour microenvironment (the "soil") has relevance to understanding tumour metastasis and resistance to anticancer therapy.

Epigenetic mechanisms in tumour development

Epigenetic events are composed of potentially heritable alterations in gene expression that do not entail a structural change in DNA sequencing. Epigenetic events are associated with patterns of DNA methylation and histone modification that serve to modulate the expression of proto-oncogenes and tumour suppressor genes [16].

The methylation of DNA refers to the covalent addition of a methyl group to the 5-carbon position of cytosine in a CpG dinucleotide. Methylated cytosine residues have a tendency to deaminate spontaneously, causing C → T transitions. Histone proteins are subject to diverse post-translational modifications, such as acetylation, methylation, phosphorylation, and ubiquitination [17].

Epigenetic mechanisms are essential for normal functioning and development of human cells and tissues, as well as for maintenance of gene expression patterns. Epigenetic events are intimately associated with fetal organ development, pathological events associated with ageing, biochemical effects of micronutrients, and the tumorigenic effects of cytokine mediators of chronic inflammation.

Epigenetic events are stochastic, discrete, and heritable, may confer the propensity for aberrant growth, and are influenced by environmental factors, namely physical and chemical carcinogens and oncogenic infectious agents. Abnormal epigenetic programmes may silence large groups of genes, causing genomic instability. Epigenetic post-translational modifications of core histone patterns and DNA methylation may influence or accompany the ageing process.

Feinberg et al. [18] proposed an epigenetic progenitor cell or epigenetic mediator model as a strategic step in human carcinogenesis. The proposed tumorigenic event is a polyclonal epigenetic disruption of stem/progenitor cells mediated by aberrant regulation of tumour progenitor genes. The authors' proposed terminology of "epigenetic mediators" underscores functions that affect the emergence and

maintenance of cancer stem cells, and the facilitation of cancer initiation and progression (see Chapter 3.8).

Population attributable risks of sporadic cancers

The terminology "sporadic cancers" reflects a currently dynamic but incomplete knowledge of the etiology and pathogenesis of a biologically and morphologically heterogeneous class of diseases. The subtext of the terminology, namely the absence of a demonstrable cause, underscores the view of assigning "bad luck" in the affected populace. Tomasetti and Vogelstein have hypothesized that the patterns of cancer incidence in various cells and tissues are highly correlated with the estimated lifetime number of stem cell divisions [19,20]. Each somatic stem cell division entails a risk of random mutations. The variable number of divisions appears to be a major determinant of differences in cancer risks in different organs. The authors reviewed the risks of 17 types of cancers in 69 countries. The median correlation coefficient between the lifetime risk of cancer in each tissue and the reported lifetime number of stem cell divisions within that tissue was $r = 0.80$ (95% confidence interval, 0.67–0.84). The linearity of the positive correlations was observed consistently among the countries studied.

The estimated proportion of total variation in cancer incidence explained by the number of stem cell divisions may be estimated by r^2 or 0.64 (95% confidence interval, 0.45–0.71). The authors concluded that approximately two thirds of global cancer incidence may be attributed to random replication errors, with a confidence boundary as low as 45% and as high as 71%. Would this be a measure of the global burden of "sporadic cancers"?

A counterpoint epidemiological perspective on the stem cell hypothesis in human carcinogenesis will now be summarized. The attributable fraction in the population at risk (population attributable fraction) is generally interpreted as the proportion of cases, or excess number of cases, that – based on current knowledge – could be eliminated if the exposed people were to experience the same risks as the unexposed people [21]. The population attributable fraction reflects the magnitude of the relative risk of the association of the exposure and the disease outcome, and the prevalence of the exposure in the population. This assumes that the estimation of population attributable fraction is unbiased, that the exposure is causal, and that elimination of the risk factor has no effect on the distribution of other risk factors. It is important to establish that the measure of the prevalence of the exposure in the population matches as closely as possible the population source for deriving the measure of relative risk.

Is there a consensus on the population cancer burden that may be attributable to lifestyle behavioural and environmental risk factors that would be interactive with stem cell replication activity? In the 1981 publication by Doll and Peto on the avoidable risks of cancer in the USA, the authors concluded that 75–80% of cancer deaths in the 1970s could have been avoided [22]. A review by Parkin et al. estimated that for the United Kingdom in 2010, 14 lifestyle and environmental risk factors (tobacco smoke, ethanol consumption, obesity and overweight, physical inactivity, dietary factors including consumption of red meat and processed meat, cancer-causing infectious agents, occupational exposures, ionizing and solar radiation, and exogenous hormones) were associated with 45% of cancer cases in men and 40% in women [23]. Colditz and Wei, in their review of biological agents, lifestyle behavioural patterns, and physical environmental factors, concluded that 50–60% of cancer deaths and more than 60% of cancer cases in the USA were potentially avoidable [24]. The World Cancer Research Fund/American Institute for Cancer Research report in 2015 estimated that 20–22% of all incident cancers in the United Kingdom and the USA were due to the combined risk factors of diet, physical inactivity, and overweight or obesity [25]. Specific aspects of dietary factors included high consumption of red meat and processed meat and low consumption of folate (see Chapter 2.6).

Fig. 3.1.4. In the absence of a demonstrable cause, the view of assigning "bad luck" to cancer development arose from the proposal that the patterns of cancer incidence in various cells and tissues are highly correlated with the estimated lifetime number of stem cell divisions within those cells or tissues. Each somatic stem cell division entails a risk of random mutations.

Tomasetti and Vogelstein have described a biological mechanism of tissue-specific stem cell replication patterns that are positively correlated with, and universally applicable in comprehending the diversity of, organ-specific cancer incidence patterns. The unifying nature of their hypothesis must be viewed in the context of diverse and contrasting global trends and patterns of types and "causes" of cancers that are closely linked with economic development and cultural lifestyle practices. The terminology "sporadic cancer" does not adequately address the complexity of interactions already established in epidemiological and experimental studies that describe the burden of cancers that may be attributable to avoidable or remediable risk factors.

References

1. Hanahan D, Weinberg RA (2011). Hallmarks of cancer: the next generation. Cell. 144(5):646–74. https://doi.org/10.1016/j.cell.2011.02.013 PMID:21376230
2. Armitage P, Doll R (1954). The age distribution of cancer and a multi-stage theory of carcinogenesis. Br J Cancer. 8(1):1–12. https://doi.org/10.1038/bjc.1954.1 PMID:13172380
3. Hiller J, Vallejo C, Betthauser L, Keesling J (2017). Characteristic patterns of cancer incidence: epidemiological data, biological theories, and multistage models. Prog Biophys Mol Biol. 124:41–8. https://doi.org/10.1016/j.pbiomolbio.2016.11.002 PMID:27836510
4. Siegel RL, Miller KD, Jemal A (2018). Cancer statistics, 2018. CA Cancer J Clin. 68(1):7–30. https://doi.org/10.3322/caac.21442 PMID:29313949
5. Ershler WB, Longo DL (1997). The biology of aging: the current research agenda. Cancer. 80(7):1284–93. https://doi.org/10.1002/(SICI)1097-0142(19971001)80:7<1284::AID-CNCR14>3.0.CO;2-3 PMID:9317181
6. Bolden JE, Lowe SW (2015). Cellular senescence. In: Mendelsohn J, Gray JW, Howley PM, Israel MA, Thompson CB, editors. The molecular basis of cancer. Philadelphia (PA), USA: Elsevier; pp. 229–38.
7. Aubert G, Lansdorp PM (2008). Telomeres and aging. Physiol Rev. 88(2):557–79. https://doi.org/10.1152/physrev.00026.2007 PMID:18391173
8. Finkel T, Serrano M, Blasco MA (2007). The common biology of cancer and ageing. Nature. 448(7155):767–74. https://doi.org/10.1038/nature05985 PMID:17700693
9. Blasco MA (2005). Telomeres and human disease: ageing, cancer and beyond. Nat Rev Genet. 6(8):611–22. https://doi.org/10.1038/nrg1656 PMID:16136653
10. Haycock PC, Burgess S, Nounu A, Zheng J, Okoli GN, Bowden J, et al.; Telomeres Mendelian Randomization Collaboration (2017). Association between telomere length and risk of cancer and non-neoplastic diseases: a Mendelian randomization study. JAMA Oncol. 3(5):636–51. https://doi.org/10.1001/jamaoncol.2017.2316 PMID:28241208
11. Donate LE, Blasco MA (2011). Telomeres in cancer and ageing. Philos Trans R Soc Lond B Biol Sci. 366(1561):76–84. https://doi.org/10.1098/rstb.2010.0291 PMID:21115533
12. Rossi DJ, Jamieson CHM, Weissman IL (2008). Stems cells and the pathways to aging and cancer. Cell. 132(4):681–96. https://doi.org/10.1016/j.cell.2008.01.036 PMID:18295583
13. Beachy PA, Karhadkar SS, Berman DM (2004). Tissue repair and stem cell renewal in carcinogenesis. Nature. 432(7015):324–31. https://doi.org/10.1038/nature03100 PMID:15549094
14. Clarke MF, Dick JE, Dirks PB, Eaves CJ, Jamieson CHM, Jones DL, et al. (2006). Cancer stem cells – perspectives on current status and future directions: AACR Workshop on cancer stem cells. Cancer Res. 66(19):9339–44. https://doi.org/10.1158/0008-5472.CAN-06-3126 PMID:16990346
15. Sugihara E, Saya H (2013). Complexity of cancer stem cells. Int J Cancer. 132(6):1249–59. https://doi.org/10.1002/ijc.27961 PMID:23180591
16. Herceg Z, Ghantous A, Wild CP, Sklias A, Casati L, Duthie SJ, et al. (2018). Roadmap for investigating epigenome deregulation and environmental origins of cancer. Int J Cancer. 142(5):874–82. https://doi.org/10.1002/ijc.31014 PMID:28836271
17. Sharma S, Kelly TK, Jones PA (2010). Epigenetics in cancer. Carcinogenesis. 31(1):27–36. https://doi.org/10.1093/carcin/bgp220 PMID:19752007
18. Feinberg AP, Koldobskiy MA, Göndör A (2016). Epigenetic modulators, modifiers and mediators in cancer aetiology and progression. Nat Rev Genet. 17(5):284–99. https://doi.org/10.1038/nrg.2016.13 PMID:26972587
19. Tomasetti C, Vogelstein B (2015). Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science. 347(6217):78–81. https://doi.org/10.1126/science.1260825 PMID:25554788
20. Tomasetti C, Li L, Vogelstein B (2017). Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. Science. 355(6331):1330–4. https://doi.org/10.1126/science.aaf9011 PMID:28336671
21. Poole C (2015). A history of the population attributable fraction and related measures. Ann Epidemiol. 25(3):147–54. https://doi.org/10.1016/j.annepidem.2014.11.015 PMID:25721747
22. Doll R, Peto R (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst. 66(6):1191–308. https://doi.org/10.1093/jnci/66.6.1192 PMID:7017215
23. Parkin DM, Boyd L, Walker LC (2011). The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 105(Suppl 2):S77–81. https://doi.org/10.1038/bjc.2011.489 PMID:22158327
24. Colditz GA, Wei EK (2012). Preventability of cancer: the relative contributions of biologic and social and physical environmental determinants of cancer mortality. Annu Rev Public Health. 33(1):137–56. https://doi.org/10.1146/annurev-publhealth-031811-124627 PMID:22224878
25. WCRF/AICR (2015). Cancer preventability estimates for diet, nutrition, body fatness, and physical activity. Available from: http://www.wcrf.org/int/cancer-facts-figures/preventability-estimates/cancer-preventability-estimates-diet-nutrition.

3.2 Genomics
Susceptibility and somatic patterns

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SUMMARY

- Next-generation sequencing has accelerated the pace of discovery of new genes in which one or more mutations can confer an increased risk of cancer. More than 120 such genes have been identified, of which more than 50% are also somatically altered in cancers.
- Genome-wide association studies have accelerated the pace of discovery of common genetic susceptibility variants. More than 85% of the loci identified in cancer genome-wide association studies have been discovered in individuals of European ancestry, with approximately 10% in Asian ancestry and less than 5% in African ancestry; this reflects the scope of studies undertaken to date.
- Although the pace of discoveries from genome-wide association studies has accelerated with large collaborative networks, the investigation of each individual susceptibility locus has not advanced at a comparable speed.
- Landscape analyses of events across entire cancer genomes have revealed a wide range of types of somatic genetic events (from single base mutations to the shattering of entire chromosomes), many involving driver genes, and even more mutations that appear to be passengers.
- The density of single-nucleotide mutations across a genome differs by nearly 4 orders of magnitude (> 10 000-fold) between cancer types with strong environmental factors and tumours with little such evidence, such as paediatric cancers.

The advent of the age of genomic analyses has dramatically accelerated the pace of discovery and characterization of susceptibility to cancer and of the hallmarks of the genomic changes that cancer cells undergo, both as consequential events and as a result of the genomic changes in the cancer cells (see Chapter 3.1). The development of a cancer represents a new, distinct cell population characterized by a range of genetic events, some of which drive the cancer. The germline genome (i.e. the genome that a person has at birth) confers susceptibility to or protection against contributions to the cancer and its clinical course. The next generation of studies will integrate these two genomes, providing more precise insights into how the environment, including lifestyle factors, contributes to cancer etiology and the outcomes associated with a cancer. This chapter discusses major trends in elucidating how the germline genome informs the understanding of the cancer genome.

Principles of germline genetic susceptibility to cancer

The concept of familial cancer was appreciated before the discovery of genes. In 1866, the astute French physician Broca described a cluster of breast cancers in his wife's family, heralding the idea of familial risk for breast cancer. Although the heritable contribution of cancer has been investigated for a century and a half through family and twin studies, it is the advent of genetic technologies, including the rise of next-generation sequencing in the past 15 years, that has accelerated the pace of discovery of mutations in cancer predisposition genes and, more recently, cancer susceptibility alleles.

The annotation of the human genome revealed a wide spectrum of genetic variation, from the most frequent variant – the single base change – to large structural changes in copy number. Early studies in families identified damaging mutations in *BRCA1*, the first hereditary breast and ovarian cancer gene discovered [1]. The search for familial cancer genes has identified more than 120 genes in which rare mutations can confer an increased risk of cancer [2]; most of these mutations are also seen in tumours, serving as somatic drivers of the cancer. From a public health perspective, these account for less than 10% of cancers.

More recently, the focus has been on the identification of many common variants, each of which provides a

small contribution to cancer risk [3,4]. The search has been to scan across the most common variant, the single-nucleotide polymorphism (SNP), defined as a substitution of one base, with at most minimal impact on the biology of the gene or the genomic region. The frequency of the alternative base pair, known as the minor allele frequency, varies greatly by population genetics history. Often, the effect of common SNP variants is on the regulation of a gene and not the gene or protein function itself. The combined effects of selection and background drift in allele frequencies are etched in the patterns of genetic variation; this includes both the correlation between nearby variants, known as linkage disequilibrium, and the actual frequencies of common variants, measured by the minor allele frequency. In turn, these differences have become attractive for investigating differences in incidence for distinct cancer types, by either population or exposure.

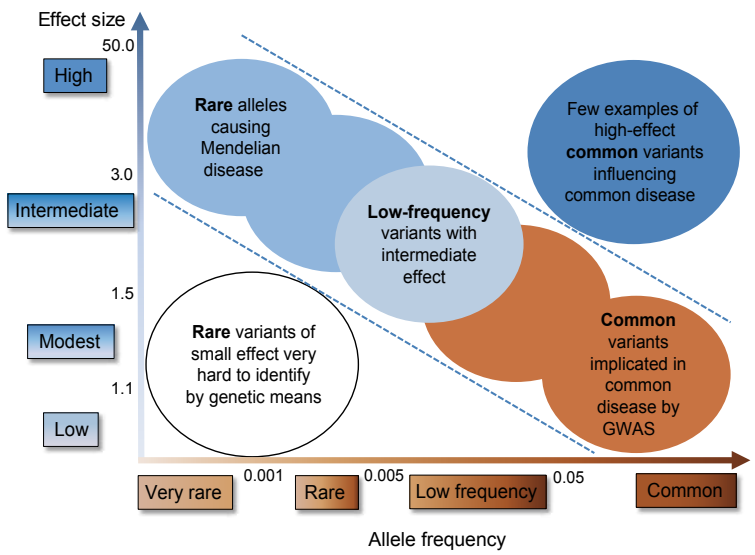
Cancer susceptibility alleles can be discovered by different approaches, including linkage, association, and now next-generation sequencing analyses. Not all alleles have comparable estimated effects. Linkage analyses in family studies are used to discover highly penetrant mutations, such as those in *BRCA1* or *TP53*, which are rare but have a strong predictive value for cancer over time. Common susceptibility alleles, which confer a smaller cancer risk, are discovered by association studies, which compare the frequency of sets of alleles between affected and unaffected individuals [5]. The estimated effect sizes are smaller for common variants and are neither necessary nor sufficient for cancer susceptibility. For each cancer type and subtype, it has emerged that there is a distinct underlying genetic architecture, comprising common variants with small effects, rare variants with strong effects, and the still-to-be-defined less common variants with moderate effects (Fig. 3.2.1) [6,7]. Moreover, the set of common variants can be combined to generate a polygenic model for cancer susceptibility [8].

The search for regions of the genome that confer susceptibility to cancer

Cancer predisposition genes

For decades, cancer geneticists have investigated families or special populations in which multiple

Fig. 3.2.1. Distribution of susceptibility alleles by frequency and strength of genetic effect, illustrating the distribution of susceptibility alleles as well as the feasibility of identifying variants through genome-wide association studies (GWAS) and sequence analysis.



FUNDAMENTALS

- Investigations of the contribution of the germline genome have successfully identified many new susceptibility variants, most of which are unique to a cancer type; these variants vary substantially in both effect size and distribution in distinct populations.
- The discovery of germline variants that contribute to cancer susceptibility has provided new mechanistic clues to cancer etiology, including changes in the regulation of key genes and pathways. The relationship between germline susceptibility alleles and somatic alterations may uncover new pathways and targets for therapeutic and preventive measures.
- Understanding the underlying genetic architecture of common and rare cancer types provides a foundation for developing effective approaches towards precision prevention in oncology.
- One of the hallmarks of cancer is an altered genome, which features mutations that drive abnormal growth and can lead to cancer-related deaths. The disruption of normal functions by cancer mutations can also generate many passenger mutations.
- Globally, major differences in the patterns of mutations for distinct types and subtypes of cancer correlate with distinct exposure and population diversity, providing etiological clues that could be used to develop new prevention, detection, and treatment strategies.

members developed the same type or types of cancer. Most of the early studies were based on collections of families with similar cancers, and these, in turn, provided an opportunity to identify rare mutations that confer a high risk of cancer in other family members. The concept of penetrance – i.e. the likelihood that other family members carrying the same variant will develop cancer – has been intensely studied in families, yielding estimates in a small subset of genes that genetic counsellors and health-care providers use to guide patients and family members to consider early detection or prevention strategies [9]. Many of these genes are now tested in clinical settings, but the number of variants identified has exceeded the threshold for adequate interpretation [10]. Consequently, many variants are known as variants of unknown significance, and further work is required before classification can be determined – as either a pathogenic mutation or a benign mutation [10]. These two categories are key for clinicians to recommend next steps when encountering these variants in families or genetic testing venues (see Chapter 6.5).

The advent of next-generation sequencing has accelerated the pace of discovery of new genes in which one or more mutations can confer an increased risk of cancer. More than 120 such genes have already been identified, and the expectation is that more will be discovered [2]. However, not all genetic variants in a cancer predisposition gene confer risk; this underscores the importance of careful annotation of variants in particular genes, with the data ideally shared publicly. Large consortium efforts are under way to publicly annotate and classify iconic and rare cancer predisposition genes, such as *BRCA1* and *BRCA2*, based on the accumulation of data from many resources [11].

Until recently, the field was dominated by reports of families with high cancer burdens, not always due to a particular cancer type. In 1969, Li and Fraumeni reported multiple cancers in families who were later determined to harbour loss-of-function mutations in *TP53* [12]. Somatic mutations in *TP53* are common in many adult cancers and constitute the most common set of drivers [13]. For the set of more than 120 known cancer predisposition genes, it is estimated that more than 50% are also somatically altered in cancers, serving as key drivers of carcinogenesis [2]. Population and clinic-based sequencing (targeted to cancer genes, exomes, and whole genomes) has shown that the prevalence of cancer gene mutations could be higher than anticipated, suggesting that not all mutations alone confer cancer risk [14,15]. Even highly penetrant mutations are complex and are modified by environmental factors and other genetic factors, which are not yet well explained. In some settings, the presence of pathogenic mutations is much higher than expected [16].

Common susceptibility alleles in cancer

The advent of genome-wide association studies (GWAS) has substantially accelerated the pace of discovery of common genetic susceptibility variants for a wide range of human diseases and traits (Box 3.2.1). The previous decades of candidate gene studies yielded very few results that have withstood the rigours of multiple testing. After a draft human genome sequence and its annotation were available, advances in microarray technologies, together with new analytical tools and standards, enabled researchers to interrogate hundreds of thousands of SNPs in parallel. The resultant success of GWAS has been based on an agnostic approach to the discovery of markers, based primarily on statistical grounds [4]. Rarely does a GWAS initially find the causal or functional variant [17]. This is because SNP microarrays have been designed to provide varying degrees of coverage of the blocks of haplotypes across the genome with optimal genetic surrogate markers, which usually do not include the functional variant or variants.

In GWAS, many statistical tests are conducted, raising the spectre of false positives. The community has embraced a threshold of genome-wide significance for reporting GWAS results, defined as a trend association test with $P \leq 5 \times 10^{-8}$ after adjustment as per the GWAS study design [18]. Follow-up studies

Box 3.2.1. Current status of genome-wide association studies.

1. **Discovery of new regions in the genome associated with diseases or traits**
   - New candidate genes and regions
2. **Clues for mechanistic insights into the contribution of common genetic variation to cancer biology**
   - Etiology
   - Gene–environment/lifestyle interactions
   - Outcomes and pharmacogenomics
3. **Challenge of genetic markers for risk prediction for individual or public health decisions**
   - Common variants represent a fraction of the genetic contribution to risk
   - Polygenic risk models

or large meta-analyses are required to establish a conclusive finding. Independent replication guards against the pursuit of false positives; this is particularly important because mapping and laboratory investigation are expensive with respect to time and resources. The actual functional marker does not have to be tested; instead, a surrogate in linkage disequilibrium can be replicated in subsequent studies (Fig. 3.2.2). Occasionally, a common genetic marker may point towards a less common variant with a stronger effect, known as a synthetic association [19]. Because GWAS genotyping has been performed with different commercial and custom SNP microarrays, techniques for imputation of data have been developed to combine data sets. Imputation programs successfully infer untested and highly correlated SNPs based on reference data sets, such as the International HapMap Project, the 1000 Genomes Project, or newly generated next-generation sequencing of populations [20].

Discoveries from cancer GWAS

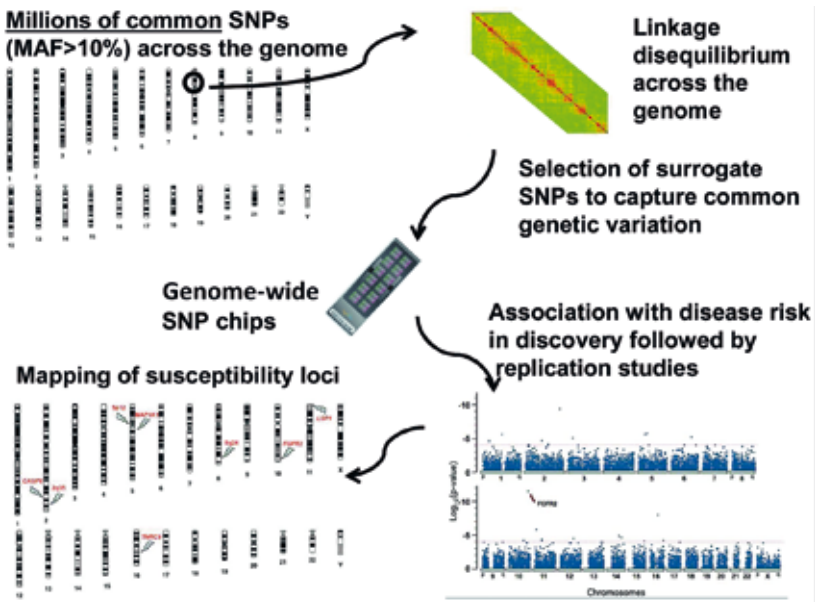
Cancer GWAS are scalable with respect to discovery. Large international collaborative efforts have yielded the discovery of more than 1000 independent loci (specific regions harbouring one or more functional variants) in at least 30 different cancer types. The larger consortia for breast cancer and prostate cancer, two of the most common cancer types, have established more than 180 distinct regions in each of these cancer types, and each region harbours an allele with a small effect [21,22].

Cancer GWAS have discovered common susceptibility alleles. To date, nearly all markers discovered by cancer GWAS have a minor allele frequency greater than 10%, with a handful in the 5–10% range. The per-allele estimated effect sizes are small, with estimated odds ratios of 1.1–1.3; in paediatric cancers, estimates of 1.6–1.8 are not unusual – this may be related to their rapid development but could also be due to the homogeneity of the tumours studied [23]. In testicular cancer, a disease that has a very high heritability but is relatively rare, the per-allele effect estimate is greater than 2.5 for *KITLG* on chromosome 12 [24].

More than 85% of the loci identified in cancer GWAS have been discovered in individuals of European ancestry, with approximately 10% in Asian ancestry and less than 5% in African ancestry [4]. This is not surprising, because most studies to date have been conducted in cases and controls of European ancestry. Because the population genetics of different continental ancestry can yield different allele frequencies, which are key for discovery, a small fraction appear to be specific to distinct populations. However, with further fine-mapping, it is likely that most signals from GWAS will yield one or more SNPs in distinct populations.

With rare exceptions, the etiological markers are not associated with clinical outcomes, including metastatic disease or survival. Several of the markers for neuroblastoma appear to discriminate between aggressive and milder disease [25]. Of the more than 180 independent loci identified for prostate cancer, not one accurately discriminates between aggressive and non-aggressive prostate cancer [22].

Fig. 3.2.2. Genetic analysis of a genome-wide association study. Multiple steps are conducted, including the choice of single-nucleotide polymorphisms (SNPs) across the genome (usually included on a commercial SNP microarray) based on linkage disequilibrium in a region, enabling the selection of a surrogate to test for the region. Association analysis is conducted in a case–control setting, examining all SNPs in a Manhattan plot, followed by replication analyses that pinpoint markers on chromosomes, which are fine-mapped and investigated in the laboratory. MAF, minor allele frequency.



Investigation of cancer GWAS susceptibility alleles

Although the pace of discoveries from GWAS has accelerated with large collaborative networks, the investigation of each individual susceptibility locus has not advanced at a comparable speed; therefore, the ability to gain new mechanistic insights has lagged behind [17]. This is because it is necessary to conduct a series of studies to determine the variants that are actually responsible for the functional effect identified in the large population-based

GWAS, based on correlated markers. Moreover, most variants map to non-coding sequences, and in the more than 40 susceptibility alleles that have been well investigated, the vast majority confer effect by altering the regulation of expression or function of one or more genes nearby [26]. Only a handful of variants appear to map to actual coding changes, resulting in non-synonymous base changes, which lead to an alteration of an amino acid. In this regard, one of the major themes of cancer GWAS is the appreciation of the accumulation of many small regulatory changes in cancer etiology, unlike the strong effects of highly penetrant mutations, which often co-occur in known oncogenes or tumour suppressor genes.

Risk stratification based on many GWAS susceptibility alleles holds great promise for improving screening and prevention strategies, especially for common cancer types with substantial absolute risks, such as breast cancer and prostate cancer. Recent studies have demonstrated the value of combining data sets of the common GWAS variants in a polygenic risk score [8]. The proof of principle has been established with goodness-of-fit tests in breast cancer, showing that the polygenic risk score can be calibrated and predicts risk accurately in the tails of the highest and lowest risk distribution. It is likely that the polygenic risk score, combined with classic epidemiological risk factors, will drive major advances in early detection and prevention strategies during the next decade.

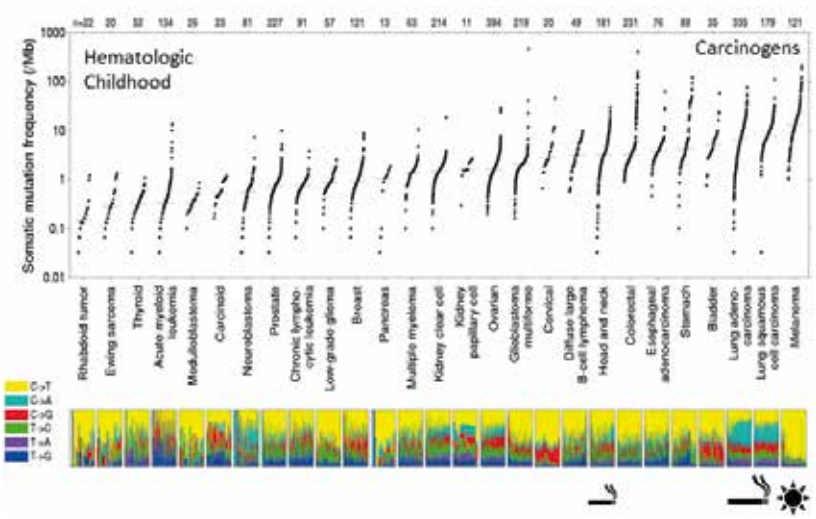
The landscape of mutational changes in cancer genomes

The application of next-generation sequencing technology to the analysis of somatic mutations in cancer genomes has transformed the understanding of cancer, beginning with the identification of key drivers of tumorigenesis. Large international consortia, such as the International Cancer Genome Consortium (ICGC) and the Cancer Genome Atlas (TCGA), have laid the foundation for understanding the scope and complexity of cancer genomes and have already identified many driver mutations (defined as mutations that initiate or perpetuate carcinogenesis). Building on the success of these consortia, investigators worldwide are continuing to search for distinct characteristics in rare and common cancer types that can shed light on the etiology of cancer, lead to the discovery of new targets, and provide a deeper understanding of clinical successes and failures with known anticancer agents based on genetic mutations [13]. Accordingly, substantial efforts have been focused on the principle of precision oncology, i.e. the matching of drugs tailored to individuals based on specific tumour mutations [27]. The use of genomics to guide therapy has emerged as a major effort in oncology, whether it is defining specific targets for new drugs or identifying the predictors of success with immunotherapy, such as human leukocyte antigen (HLA) alleles or neo-antigens.

Landscape analyses of events across entire cancer genomes have revealed several key points: a wide range of types of genetic events (from single base mutations to the shattering of entire chromosomes), many involving driver genes, and even more mutations that appear to be passengers, arising as a consequence of the sloppy proliferative process of cancer genomes [13,28]. Moreover, characterization of cancer genomes has revealed that the origins of cancer are complex. Although the hallmark processes of driver genes frequently become dysregulated through somatic alterations in the genome, many different events can occur. Accordingly, the list of recurrently mutated cancer genes is relatively short, but there are many rarely mutated genes (Fig. 3.2.3) [28].

There is substantial heterogeneity of cancer mutations across the globe, reflecting distinct geographical exposures and differences in underlying population ancestry. The

Fig. 3.2.3. Mutation rates across cancer types. The frequency of point mutations can vary by 4 orders of magnitude; the lowest frequencies are found in haematological and paediatric tumours and the highest in tumours induced by carcinogens such as tobacco smoke and ultraviolet radiation. The patterns and signatures of the distribution of base changes are highly variable and can reflect distinct environmental or genetic mechanisms (e.g. homologous recombination deficiency of the APOBEC family of cytidine deaminases).



identification of a more comprehensive set of cancer genes has set in motion the process of mapping them against different cancer types and subtypes. Distinct environmental exposures (e.g. chemical exposures, dietary and lifestyle factors, and infections) as well as different population genetic backgrounds can partially explain the geographical and biological differences. Mapping genomic features against different environmental exposures should lead to new discoveries and eventually generate new approaches to early detection or prevention.

A multitude of international articles on landscape analyses have detailed the mutational events across a wide range of cancer types and have begun to reveal important patterns that overlap between different types of cancer (but not all cancer types); these are known as pan-cancer analyses [13]. Major efforts are under way to catalogue and understand the underlying biology for the hundreds of cancer genes that have been identified, but to date, most studies have reported on protein-coding regions (~2% of the genome) (Table 3.2.1). There is an extensive "dark matter" space outside the protein-coding regions that has emerged from landscape analyses but cannot be easily interpreted. Widely available data sharing within the research community, albeit within controlled circumstances, is critical to better understand what has already been generated, because new algorithms and perspectives regularly uncover novel biological processes underlying carcinogenesis, especially with respect to cancers across the globe [29].

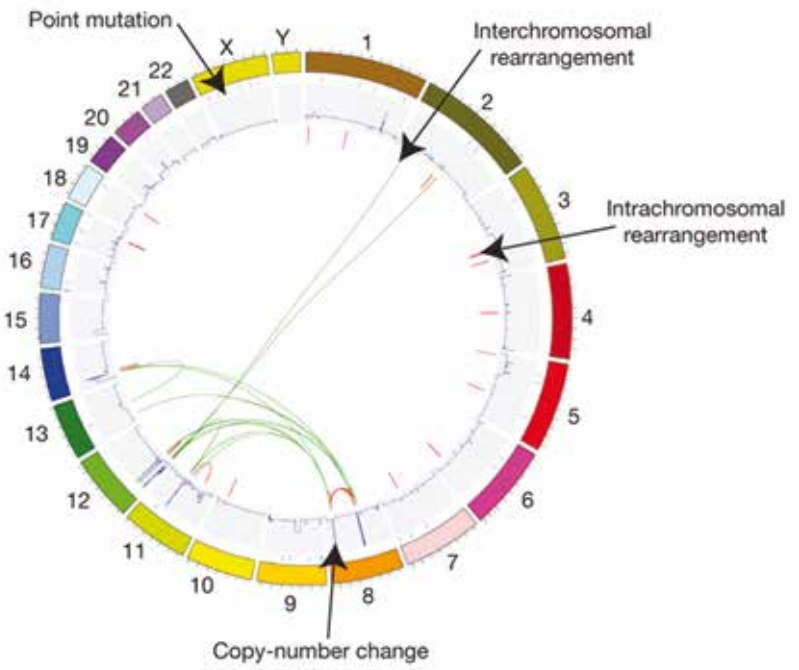
By definition, somatic alterations arise as a postzygotic event. When cancer develops, it is because of a disruption of one or more key cellular functions that confer a selective advantage for tumour growth [30] (Fig. 3.2.4). Some mutations inactivate genes that protect the cell from abnormal growth, known as tumour suppressor genes, whereas other mutations activate genes that accelerate abnormal growth, known as oncogenes. More recently, studies have shown that mutations can also disrupt pathways of expression or epigenetic regulators of gene pathways or that, in some cases, sets of genes can contribute to cancer [29].

Because cancer is a disease that alters the genome, mutational events can range in size from a single nucleotide to an entire chromosome [30]. Although gains and losses of entire chromosomes occur in many cancers, it is daunting to separate the driver gene events from those that result from alterations in genome structure. Previously, a handful of driver fusion genes had been identified in elegant molecular genetics studies. An example is the Philadelphia translocation in chronic myeloid leukaemia cells, in which the *ABL1* gene on chromosome 9 is juxtaposed onto the *BCR* gene on chromosome 22 to yield a tyrosine kinase signal that is perpetually "on". Fusion genes have been identified in a wide range of cancer types. For instance, a substantial fraction of papillary thyroid cancer is driven by fusion genes involving the RAS pathway [31]. Concatenation of somatically altered regions (either within a chromosome or between chromosomes) can occur in most cancer types

Table 3.2.1. Large resources for cancer genomics data

Resource	Website	Description
International Cancer Genome Consortium (ICGC)	https://dcc.icgc.org/	The ICGC Data Portal provides access to cancer genome data and project data from ICGC members.
The Cancer Genome Atlas (TCGA)	https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga	The TCGA Data Portal provides a platform for researchers to search, download, and analyse cancer genome data sets generated by institutions in the USA contributing to TCGA.
Genomic Data Commons (GDC), National Cancer Institute, USA	https://portal.gdc.cancer.gov	The GDC Data Portal includes data from TCGA and other cancer genome sequencing projects supported by the National Cancer Institute, as well as analytical pipelines.
Catalogue of Somatic Mutations in Cancer (COSMIC)	https://cancer.sanger.ac.uk/cosmic	COSMIC stores and displays curated somatic mutation data and other information related to human cancer.
Pan-Cancer Analytical Framework	https://www.cell.com/pb-assets/consortium/pancanceratlas/pancani3/index.html	The Pan-Cancer Atlas resource includes many linked articles detailing analyses across cancer types using TCGA and ICGC, known as pan-cancer analyses.
Broad Institute Integrative Genomics Viewer (IGV)	https://broadinstitute.org/igv/	IGV is a visualization tool for interactive exploration of large, integrated genomic data sets.
University of California Santa Cruz (UCSC) Cancer Genomics Browser	https://genome-cancer.ucsc.edu	The UCSC Cancer Genomics Browser is a suite of web-based tools to visualize, integrate, and analyse cancer genomics and associated clinical data.

Fig. 3.2.4. Figurative depiction of somatic mutations present in a cancer cell in the small cell lung cancer cell line NCI-H2171. Individual chromosomes are depicted on the outer circle. Concentric circles show point mutations, copy number events, and rearrangements. Arrows indicate distinct types of somatic mutational events.



but to varying degrees of density. Distinct types of structural variants can occur. Chromosomal shattering, known as chromothripsis, can result in thousands of rearrangements that occur in a single crisis due to imperfect DNA repair mechanisms (see Chapter 3.4). Similarly, hypermutation of a region can result in kataegis, often due to the APOBEC family of genes. Major shifts in the balance between regulators of genes – i.e. epigenetic mechanisms – have emerged as an important driver in some cancer types, either with overactive methylation (which usually silences a genetic fragment) or with low levels of methylation (known as hypomethylation).

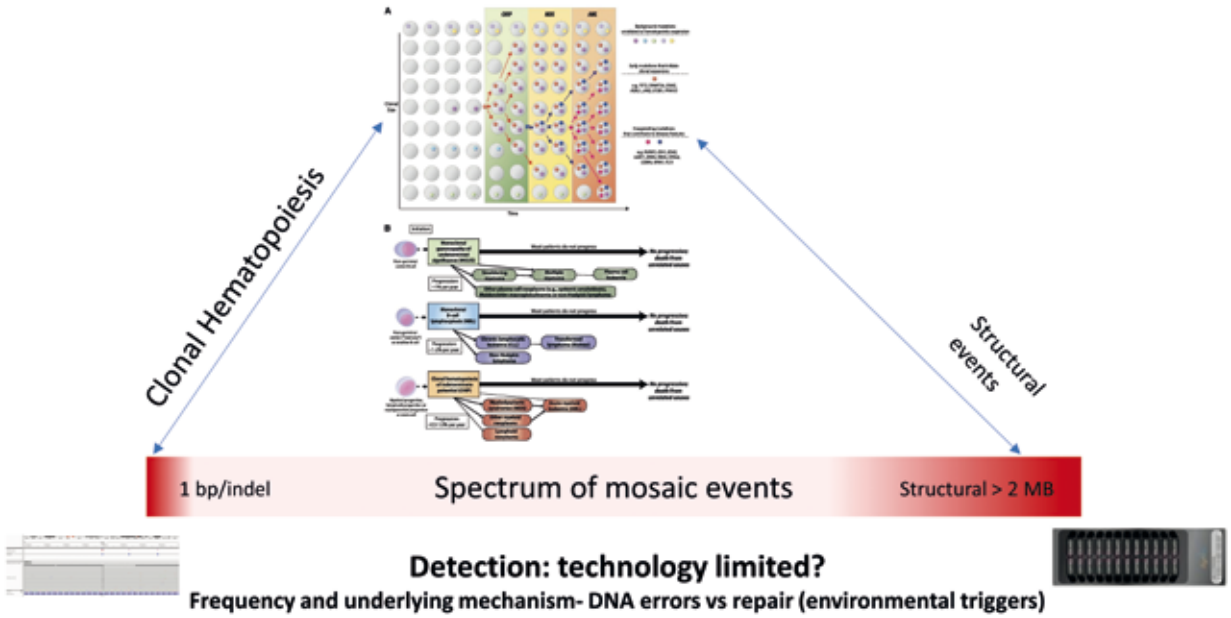
Mutational rates vary greatly by type of cancer. So far, the density of single-nucleotide mutations across a genome differs by nearly 4 orders of magnitude (> 10 000-fold) between cancer types with strong environmental factors (e.g. tobacco use and lung adenocarcinoma or exposure to ultraviolet radiation and melanoma) and paediatric cancers (e.g. Ewing sarcoma and retinoblastoma) [28]. The patterns of specific mutations can leave mutational signatures – or footprints – based on the specific types of mutations and their adjacent base pair context [32]. Some of the signatures have been correlated with tobacco use (see Chapter 2.1), exposure to potent mutagens such as aflatoxins or aristolochic acid (see Chapter 2.8), or host defence systems (e.g. *APOBEC3* genes, which protect against small pathogens) [33,34]. New efforts are under way to search for mutational signatures that could point to novel risk factors for specific cancer types by looking for epidemiological factors associated with specific signatures. The Mutographs project (which results from a Cancer Research UK Grand Challenge grant and is analysing five cancer types: colorectal cancer, kidney cancer, pancreatic cancer, and both oesophageal squamous cell carcinoma and oesophageal adenocarcinoma) and the Sherlock-*lung* study (of lung adenocarcinoma in never-smokers) are conducting landscape genomic analyses in common cancer types with distinct geographical patterns and linking the epidemiological factors with signatures of carcinogenesis to understand geographical differences in cancer incidence and subtypes. It is plausible to identify signatures that point towards an environmental or lifestyle risk factor that could be avoided or controlled. Similarly, signatures could be used to determine driver events that could be targeted with specific therapeutic strategies, including immunotherapy.

The pattern of distribution of mutations in the DNA binding region of *TP53*, an iconic tumour suppressor gene, has led to new insights into its role in responding to cellular stress and approximating genomic stability. The distribution of *TP53* mutations varies widely by cancer types, including by age and by geographical distribution, which suggests key opportunities to investigate the role of environmental triggers in carcinogenesis [35].

Future use of genomics in cancer research

In the process of characterizing cancer genomes as well as cancer susceptibility alleles, it has become apparent that as cells divide, they accumulate somatic mutations. Recent analyses of normal tissues have shown that mutations can accumulate in healthy individuals with age, particularly in response to strong environmental mutagens (e.g. ultraviolet radiation and the skin, nutritional elements and the oesophagus, and inhalants like tobacco smoke and the lung) [36,37]. Surprisingly, even if the mutations are known cancer drivers (e.g. in *TP53* and *NOTCH1*), cancer may not have developed yet; this clearly signals that additional local tumour microenvironmental and immune interactions contribute to malignant transformation [38]. The assessment of genomic changes in precancerous states has

Fig. 3.2.5. Mosaicism and ageing. Distribution and types of postzygotic somatic events leading to clonal mosaicism, from single point events to large chromosomal events, always in a subset of cells. Mosaic events can vary by tissue of origin and can be driven by new mutations that achieve selective advantage balanced by effective or ineffective surveillance repair mechanisms.



tremendous potential for early detection and prevention.

Genetic mosaicism (defined as the presence of a subpopulation of cells with an alternative genotype) has been well established across the spectrum of mutational events, generally accumulating with age (Fig. 3.2.5) [39]. Whether large structural events increase with age or single base pair mutations emerge, current research is focused on how detection of these events could be a biomarker for cancer and other complex adult diseases (e.g. cardiovascular disease, diabetic diseases, or neurodegenerative diseases) [40,41]. For haematological cancers, it is possible to detect a subset of mutations well before the diagnosis of cancer. This is known as clonal haematopoiesis, and it has been shown to be an important risk factor for subsequent leukaemia [42].

The technology of next-generation sequencing holds the promise of detecting either free circulating tumour DNA or tumour cells. Early studies suggest that it is possible to detect circulating DNA in advanced cases, but major questions remain about the sensitivity and timing of such diagnostic tools, especially because genetic mosaicism could be more common than previously appreciated. Large studies will be required to define the utility of a liquid biopsy in cancer diagnosis and care.

References

1. Zuppan P, Hall JM, Lee MK, Ponglikitmongkol M, King MC (1991). Possible linkage of the estrogen receptor gene to breast cancer in a family with late-onset disease. Am J Hum Genet. 48(6):1065–8. PMID:2035527

2. Rahman N (2014). Realizing the promise of cancer predisposition genes. Nature. 505(7483):302–8. https://doi.org/10.1038/nature12981 PMID:24429628

3. Chung CC, Chanock SJ (2011). Current status of genome-wide association studies in cancer. Hum Genet. 130(1):59–78. https://doi.org/10.1007/s00439-011-1030-9 PMID:21678065

4. Park SL, Cheng I, Haiman CA (2018). Genome-wide association studies of cancer in diverse populations. Cancer Epidemiol Biomarkers Prev. 27(4):405–17. https://doi.org/10.1158/1055-9965.EPI-17-0169 PMID:28637795

5. Risch NJ (2000). Searching for genetic determinants in the new millennium. Nature. 405(6788):847–56. https://doi.org/10.1038/35015718 PMID:10866211

6. Park JH, Gail MH, Weinberg CR, Carroll RJ, Chung CC, Wang Z, et al. (2011). Distribution of allele frequencies and effect sizes and their interrelationships for common genetic susceptibility variants. Proc Natl Acad Sci U S A. 108(44):18026–31. https://doi.org/10.1073/pnas.1114759108 PMID:22003128

7. Zhang Y, Qi G, Park JH, Chatterjee N (2018). Estimation of complex effect-size distributions using summary-level statistics from genome-wide association studies across 32 complex traits. Nat Genet. 50(9):1318–26. https://doi.org/10.1038/s41588-018-0193-x PMID:30104760

8. Mavaddat N, Michailidou K, Dennis J, Lush M, Fachal L, Lee A, et al.; ABCTB Investigators; kConFab/AOCS Investigators; NBCS Collaborators (2019). Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. Am J Hum Genet. 104(1):21–34. https://doi.org/10.1016/j.ajhg.2018.11.002 PMID:30554720

9. Rehm HL, Berg JS, Brooks LD, Bustamante CD, Evans JP, Landrum MJ, et al.; ClinGen (2015). ClinGen – the Clinical Genome Resource. N Engl J Med. 372(23):2235–42. https://doi.org/10.1056/NEJMsr1406261 PMID:26014595

10. Tavtigian SV, Greenblatt MS, Goldgar DE, Boffetta P; IARC Unclassified Genetic Variants Working Group (2008). Assessing pathogenicity: overview of results from the IARC Unclassified Genetic Variants Working Group. Hum Mutat. 29(11):1261–4. https://doi.org/10.1002/humu.20903 PMID:18951436

11. Cline MS, Liao RG, Parsons MT, Paten B, Alquaddoomi F, Antoniou A, et al.; BRCA Challenge Authors (2018). BRCA Challenge: BRCA Exchange as a global resource for variants in *BRCA1* and *BRCA2*. PLoS Genet. 14(12):e1007752. https://doi.org/10.1371/journal.pgen.1007752 PMID:30586411

12. Li FP, Fraumeni JF Jr (1969). Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med. 71(4):747–52. https://doi.org/10.7326/0003-4819-71-4-747 PMID:5360287

13. Bailey MH, Tokheim C, Porta-Pardo E, Sengupta S, Bertrand D, Weerasinghe A, et al.; MC3 Working Group; Cancer Genome Atlas Research Network (2018). Comprehensive characterization of cancer driver genes and mutations. Cell. 174(4):1034–5. https://doi.org/10.1016/j.cell.2018.07.034 PMID:30096302

14. Carlo MI, Mukherjee S, Mandelker D, Vijai J, Kemel Y, Zhang L, et al. (2018). Prevalence of germline mutations in cancer susceptibility genes in patients with advanced renal cell carcinoma. JAMA Oncol. 4(9):1228–35. https://doi.org/10.1001/jamaoncol.2018.1986 PMID:29978187

15. Mandelker D, Zhang L, Kemel Y, Stadler ZK, Joseph V, Zehir A, et al. (2017). Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. JAMA. 318(9):825–35. https://doi.org/10.1001/jama.2017.11137 PMID:28873162

16. de Andrade KC, Frone MN, Wegman-Ostrosky T, Khincha PP, Kim J, Amadou A, et al. (2019). Variable population prevalence estimates of germline *TP53* variants: a gnomAD-based analysis. Hum Mutat. 40(1):97–105. https://doi.org/10.1002/humu.23673 PMID:30352134

17. Freedman ML, Monteiro AN, Gayther SA, Coetzee GA, Risch A, Plass C, et al. (2011). Principles for the post-GWAS functional characterization of cancer risk loci. Nat Genet. 43(6):513–8. https://doi.org/10.1038/ng.840 PMID:21614091

18. Chanock SJ, Manolio T, Boehnke M, Boerwinkle E, Hunter DJ, Thomas G, et al.; NCI-NHGRI Working Group on Replication in Association Studies (2007). Replicating genotype-phenotype associations. Nature. 447(7145):655–60. https://doi.org/10.1038/447655a PMID:17554299

19. Goldstein DB (2011). The importance of synthetic associations will only be resolved empirically. PLoS Biol. 9(1):e1001008. https://doi.org/10.1371/journal.pbio.1001008 PMID:21267066

20. Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, et al.; 1000 Genomes Project Consortium (2015). A global reference for human genetic variation. Nature. 526(7571):68–74. https://doi.org/10.1038/nature15393 PMID:26432245

21. Michailidou K, Lindström S, Dennis J, Beesley J, Hui S, Kar S, et al.; NBCS Collaborators; ABCTB Investigators; ConFab/AOCS Investigators (2017). Association analysis identifies 65 new breast cancer risk loci. Nature. 551(7678):92–4. https://doi.org/10.1038/nature24284 PMID:29059683

22. Schumacher FR, Al Olama AA, Berndt SI, Benlloch S, Ahmed M, Saunders EJ, et al.; Profile Study; Australian Prostate Cancer BioResource (APCB); IMPACT Study; Canary PASS Investigators; Breast and Prostate Cancer Cohort Consortium (BPC3); PRACTICAL (Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome) Consortium; Cancer of the Prostate in Sweden (CAPS); Prostate Cancer Genome-wide Association Study of Uncommon Susceptibility Loci (PEGASUS); Genetic Associations and Mechanisms in Oncology (GAME-ON)/Elucidating Loci Involved in Prostate Cancer Susceptibility (ELLIPSE) Consortium (2018). Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. Nat Genet. 50(7):928–36. https://doi.org/10.1038/s41588-018-0142-8 PMID:29892016

23. Machiela MJ, Grünewald TGP, Surdez D, Reynaud S, Mirabeau O, Karlins E, et al. (2018). Genome-wide association study identifies multiple new loci associated with Ewing sarcoma susceptibility. Nat Commun. 9(1):3184. https://doi.org/10.1038/s41467-018-05537-2 PMID:30093639

24. Kanetsky PA, Mitra N, Vardhanabhuti S, Li M, Vaughn DJ, Letrero R, et al. (2009). Common variation in *KITLG* and at 5q31.3 predisposes to testicular germ cell cancer. Nat Genet. 41(7):811–5. https://doi.org/10.1038/ng.393 PMID:19483682

25. Capasso M, Devoto M, Hou C, Asgharzadeh S, Glessner JT, Attiyeh EF, et al. (2009). Common variations in *BARD1* influence susceptibility to high-risk neuroblastoma. Nat Genet. 41(6):718–23. https://doi.org/10.1038/ng.374 PMID:19412175

26. Bigot P, Colli LM, Machiela MJ, Jessop L, Myers TA, Carrouget J, et al. (2016). Functional characterization of the 12p12.1 renal cancer-susceptibility locus implicates *BHLHE41*. Nat Commun. 7(1):12098. https://doi.org/10.1038/ncomms12098 PMID:27384883

27. Collins FS, Varmus H (2015). A new initiative on precision medicine. N Engl J Med. 372(9):793–5. https://doi.org/10.1056/NEJMp1500523 PMID:25635347

28. Lawrence MS, Stojanov P, Polak P, Kryukov GV, Cibulskis K, Sivachenko A, et al. (2013). Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature. 499(7457):214–8. https://doi.org/10.1038/nature12213 PMID:23770567

29. Hoadley KA, Yau C, Hinoue T, Wolf DM, Lazar AJ, Drill E, et al. (2018). Cell-of-origin patterns dominate the molecular classification of 10,000 tumors from 33 types of cancer. Cell. 173(2):291–304.e6. https://doi.org/10.1016/j.cell.2018.03.022 PMID:29625048

30. Stratton MR, Campbell PJ, Futreal PA (2009). The cancer genome. Nature. 458(7239):719–24. https://doi.org/10.1038/nature07943 PMID:19360079

31. Agrawal N, Akbani R, Aksoy BA, Ally A, Arachchi H, Asa SL, et al.; Cancer Genome Atlas Research Network (2014). Integrated genomic characterization of papillary thyroid carcinoma. Cell. 159(3):676–90. https://doi.org/10.1016/j.cell.2014.09.050 PMID:25417114

32. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al.; Australian Pancreatic Cancer Genome Initiative; ICGC Breast Cancer Consortium; ICGC MMML-Seq Consortium; ICGC PedBrain (2013). Signatures of mutational processes in human cancer. Nature. 500(7463):415–21. https://doi.org/10.1038/nature12477 PMID:23945592

33. Alexandrov LB, Ju YS, Haase K, Van Loo P, Martincorena I, Nik-Zainal S, et al. (2016). Mutational signatures associated with tobacco smoking in human cancer. Science. 354(6312):618–22. https://doi.org/10.1126/science.aag0299 PMID:27811275

34. Turesky RJ, Yun BH, Brennan P, Mates D, Jinga V, Harnden P, et al. (2016). Aristolochic acid exposure in Romania and implications for renal cell carcinoma. Br J Cancer. 114(1):76–80. https://doi.org/10.1038/bjc.2015.402 PMID:26657656

35. Ding L, Bailey MH, Porta-Pardo E, Thorsson V, Colaprico A, Bertrand D, et al. (2018). Perspective on oncogenic processes at the end of the beginning of cancer genomics. Cell. 173(2):305–320.e10. https://doi.org/10.1016/j.cell.2018.03.033 PMID:29625049

36. Martincorena I, Campbell PJ (2015). Somatic mutation in cancer and normal cells. Science. 349(6255):1483–9. https://doi.org/10.1126/science.aab4082 PMID:26404825

37. Martincorena I, Fowler JC, Wabik A, Lawson ARJ, Abascal F, Hall MWJ, et al. (2018). Somatic mutant clones colonize the human esophagus with age. Science. 362(6417):911–7. https://doi.org/10.1126/science.aau3879 PMID:30337457

38. Chanock SJ (2018). The paradox of mutations and cancer. Science. 362(6417):893–4. https://doi.org/10.1126/science.aav5697 PMID:30467157

39. Machiela MJ, Chanock SJ (2017). The ageing genome, clonal mosaicism and chronic disease. Curr Opin Genet Dev. 42:8–13. https://doi.org/10.1016/j.gde.2016.12.002 PMID:28068559

40. Jacobs KB, Yeager M, Zhou W, Wacholder S, Wang Z, Rodriguez-Santiago B, et al. (2012). Detectable clonal mosaicism and its relationship to aging and cancer. Nat Genet. 44(6):651–8. https://doi.org/10.1038/ng.2270 PMID:22561519

41. Forsberg LA, Gisselsson D, Dumanski JP (2017). Mosaicism in health and disease – clones picking up speed. Nat Rev Genet. 18(2):128–42. https://doi.org/10.1038/nrg.2016.145 PMID:27941868

42. Abelson S, Collord G, Ng SWK, Weissbrod O, Mendelson Cohen N, Niemeyer E, et al. (2018). Prediction of acute myeloid leukaemia risk in healthy individuals. Nature. 559(7714):400–4. https://doi.org/10.1038/s41586-018-0317-6 PMID:29988082

3.3 Gene–environment interactions
The preventive implications are still not clear

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Ghislaine Scelo (reviewer)

SUMMARY

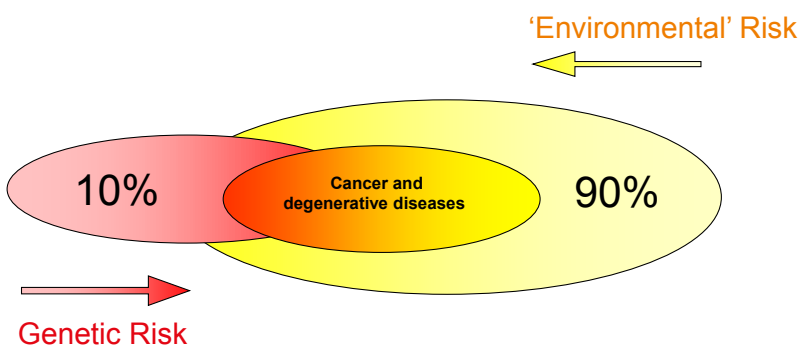
- Genetic susceptibility is related to changes in gene structure or function that predispose to disease, including cancer.
- Generally, about 5–10% of all cancers are estimated to be due to highly penetrant inherited mutations. The remaining cancers are due to environmental agents, exposure to endogenous carcinogens, or the interaction between weak genetic susceptibility and external or endogenous agents.
- Some gene–environment interactions are due to low-penetrance gene variants as indicated by single-nucleotide polymorphisms.
- Phenotypes described in relation to the key characteristics of carcinogens can be modulated by single-nucleotide polymorphisms.
- An example of gene–environment interactions is the carcinogenicity of alcohol, specifically in relation to *ADH* and *ALDH* gene variants. The strength of association between *ALDH* variants and aerodigestive cancers is such that *ALDH* has been successfully used in Mendelian randomization studies.
- The assessment of causality is not straightforward, and few gene–environment interactions in cancer have been replicated in a convincing way.
- Approaches to achieving optimal prevention are still debated and include a stratified or precision prevention approach that focuses on high-risk populations.

What is genetic susceptibility?

Genetic susceptibility is related to changes in gene structure or function that predispose to disease, including cancer. Here, only structural changes are considered; susceptibility due to epigenetic modifications is not addressed (see Chapter 3.8). Gene–environment interactions occur when different genotypes, as indicated by gene variants, respond to environmental variation in different ways. Generally, about 5–10% of all cancers are estimated to be due to highly penetrant inherited mutations. The remaining cancers are due to environmental agents, exposure to endogenous carcinogens, or the interaction between weak genetic susceptibility and external or endogenous agents (Fig. 3.3.1).

Structural changes, in the form of base substitutions in the sequence of DNA, can have higher or lower penetrance, and hence have a higher or lower strength of association with disease. Rare variants, indicated by minor allele frequency lower than 1%, are called mutations and tend to have high penetrance. Common variants, as described by single-nucleotide polymorphisms (SNPs), have low penetrance (i.e. their association with cancer is weaker). Examples of rare variants are inherited mutations in the *BRCA1* gene predisposing to breast cancer or in the *RB1* gene

Fig. 3.3.1. The risk of cancer and degenerative diseases is determined by a complex interplay of genetic and environmental factors. The contribution of genetic factors to the risk varies, but several lines of evidence show that non-genetic ("environmental") factors have high attributable risks, often in the range of 80–90%.



predisposing to retinoblastoma (see Chapter 3.2). In this chapter, low-penetrance variants as indicated by SNPs are considered.

SNPs can occur in all genes involved in the modulation of the effects of environmental agents. For historical reasons, the most studied SNPs are in genes involved in carcinogen metabolism and in DNA repair. However, expression of all key characteristics of carcinogens [1] (see Chapter 3.11) can be modulated by SNPs. For each of the key characteristics of carcinogens, which in some instances loosely correspond to the hallmarks of cancer, there are examples of genes whose SNPs may modulate the mechanism of action (Table 3.3.1).

In the early phases of gene–environment interaction studies, genotyping was not available, and evidence came from a phenotypic characterization of susceptibility. People were known to react differently to drugs, including with respect to adverse effects, because of more or less rapid metabolism, usually related to enzymes of the cytochrome P450 (CYP) system, often identified as members of the CYP family. Some phenotypes were also discovered that predisposed individuals to the action of carcinogens. Examples are N-acetyltransferase 2 (NAT2) and its modulation of the risk of bladder cancer in subjects exposed to aromatic amines, and the modulation of outcomes from exposure to polycyclic aromatic hydrocarbons due to CYP1A1 variants [2].

The literature grew exponentially when gene variants related to metabolic phenotypes were discovered and polymerase chain reaction (PCR) techniques enabled systematic searches to be done for such candidate variants in populations. Given the large amount of evidence, this chapter refers to reviews and presents some examples of gene–environment interactions. An early review was published by IARC in 1999 [2], but much more evidence is currently available. To synthesize the evidence, a set of criteria – known as the Venice criteria because they were proposed by the Human Genome Epidemiology (HuGE) Network at a meeting in Venice – is used [3]. The criteria assess the quality of the evidence based on three general categories: amount of evidence, degree of replication, and protection from bias.

Table 3.3.1. Key characteristics of carcinogens and examples of genes with low-penetrance variants (single-nucleotide polymorphisms) that may modulate the mechanism of action

Key characteristic	Examples of genes
1. Is electrophilic or can be metabolically activated to electrophiles	Phase I (CYP) or phase II (*NAT2*, *GSTM1*) metabolizing genes
2. Is genotoxic	DNA repair genes (e.g. *XRCC1*)
3. Alters DNA repair or causes genomic instability	DNA repair genes
4. Induces epigenetic alterations	Genes involved in DNA methylation or histone acetylation
5. Induces oxidative stress	*OGG1*
6. Induces chronic inflammation	Interleukin-1 gene family
7. Is immunosuppressive	Several genes involved in immunosuppression
8. Modulates receptor-mediated effects	*AHRR*
9. Causes immortalization	Genes involved in senescence (e.g. pRB and p53 cell-cycle control pathways)
10. Alters cell proliferation, cell death, or nutrient supply	*NOTCH1*

FUNDAMENTALS

- Many gene variants that interact with environmental agents have been identified. However, the assessment of causal evidence is often uncertain, because of the very large sample sizes required to investigate interactions.
- For each of the key characteristics of carcinogens, genes with inherited variants can be found, but the real impact of these variants in modulating the effect of environmental exposures is largely unknown.
- The gene–environment interactions investigated most frequently have included environmental factors categorized as energy balance (e.g. indicated by body mass index, diet), exogenous hormonal factors (e.g. oral contraceptives), endogenous hormonal factors (e.g. indicated by menopausal status), particular chemical exposures (e.g. consumption of grilled meats), and lifestyle factors (e.g. smoking, alcohol consumption).
- The magnitudes of the interactions reported were usually modest, with risks increased or decreased by 20–50%.
- There are very few examples of actionable gene–environment interactions prompting specific prevention strategies, partly because a large number of people at a small risk may give rise to more cases of disease than the small number who are at a high risk.

ADH and *ALDH*, aerodigestive cancers, and Mendelian randomization

One example that has been studied extensively and belongs to the highest categories according to the Venice criteria is the different ability that individuals have to metabolize ethanol to acetaldehyde. Alcohol consumption has been associated with the risk of cancer at different organ sites (see Chapter 2.3), and acetaldehyde is believed to be the active agent.

Individuals have different susceptibilities to the acute effects of ethanol (notably, some people of Asian descent are particularly susceptible), and this has been related to common variants as indicated by SNPs of the alcohol dehydrogenase (*ADH*) and aldehyde dehydrogenase (*ALDH*) genes. Such variants are also associated with greater susceptibility to the carcinogenic effects of ethanol, for example for laryngeal cancer and oesophageal cancer.

In one study, six *ADH* gene variants were investigated in more than 3800 people with aerodigestive cancer and 5200 controls [4]. The gene variants rs1229984 (*ADH1B*) and rs1573496 (*ADH7*) were significantly protective against aerodigestive cancers. These effects became more apparent with increasing alcohol consumption. The gene effects were independent of each other, implying that multiple *ADH* genes may be involved in the etiology of upper aerodigestive cancers.

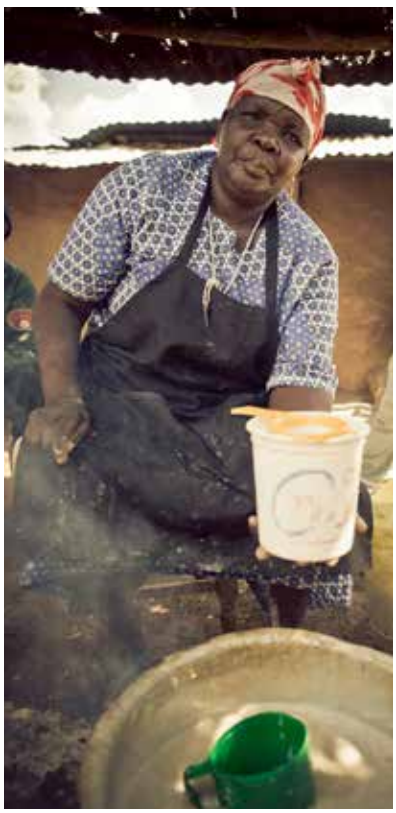
ADH gene variants have been included in studies on alcoholism based on a Mendelian randomization design (e.g. [5]). In turn, *ALDH* variants have been successfully investigated in relation to aerodigestive cancers with Mendelian randomization. In brief, gene variants are transmitted randomly from parents to their offspring, because of random assortment in meiosis. Therefore, they are expected not to be affected by confounding in epidemiological studies and are used as instrumental variables to assess causality between environmental exposures and cancer. Here, this is illustrated by examining, as an example, the association between the *ALDH2* polymorphisms and oesophageal cancer.

Fig. 3.3.2. Smoke from tobacco cigarettes is a major source of human exposure to polycyclic aromatic hydrocarbons. Through gene–environment interaction studies, some phenotypes were discovered that predisposed individuals to the action of carcinogens, including the modulation of outcomes from exposure to polycyclic aromatic hydrocarbons due to CYP1A1 variants.

The *ALDH2*2* allele produces an inactive protein, which is unable to metabolize acetaldehyde. An individual's genotype at this locus may influence their risk of developing oesophageal cancer via two mechanisms: by influencing alcohol intake, and by influencing acetaldehyde levels. In a meta-analysis of studies investigating the *ALDH2* genotype and oesophageal cancer, the risk was reduced among **2*2* homozygotes (odds ratio, 0.36; 95% confidence interval, 0.16–0.80) and increased among heterozygotes (odds ratio, 3.19; 95% confidence interval, 1.86–5.47) relative to **1*1* homozygotes. This provides evidence that acetaldehyde plays a carcinogenic role in oesophageal cancer [6].

Mendelian randomization can also be used to clarify dose–response relationships. For example, the relationship between alcohol consumption (using a variant in the *ADH1B* gene as an instrumental variable) and risk of cardiovascular disease was investigated. Alcohol consumption was found to increase risk of cardiovascular disease, with no evidence of a cardioprotective effect at moderate consumption levels [7].

Fig. 3.3.3. People in Turbo, a small town in Kenya, brew a traditional alcoholic beverage called *changaa*. Individuals have different susceptibilities to the acute effects of ethanol, and this has been related to common variants as indicated by SNPs of the *ADH* and *ALDH* genes.



A review of the literature

Many gene variants that interact with environmental agents have been identified. However, the assessment of causal evidence is often uncertain, because of the very large sample sizes required to investigate interactions. For each of the key characteristics of carcinogens, genes with inherited variants can be found (Table 3.3.1), but the real impact of these variants in modulating the effect of environmental exposures is largely unknown.

Simonds et al. [8] performed a systematic review of published literature from two databases of genetic association studies: the HuGE literature finder and the Cancer Genome-Wide Association and Meta Analyses Database (Cancer GAMAdb). Of 3019 articles identified in the searches, only 272 articles met the inclusion criteria. In both searches, the majority of the publications examined gene–environment interactions in cancers of the colon, rectum, colorectum, breast, or lung. The interactions examined most frequently included environmental factors categorized as energy balance (e.g. indicated by body mass index, diet), exogenous hormonal factors (e.g. oral contraceptives), endogenous hormonal factors (e.g. indicated by menopausal status), particular chemical exposures (e.g. consumption of grilled meats), and lifestyle factors (e.g. smoking, alcohol consumption) (Fig. 3.3.4).

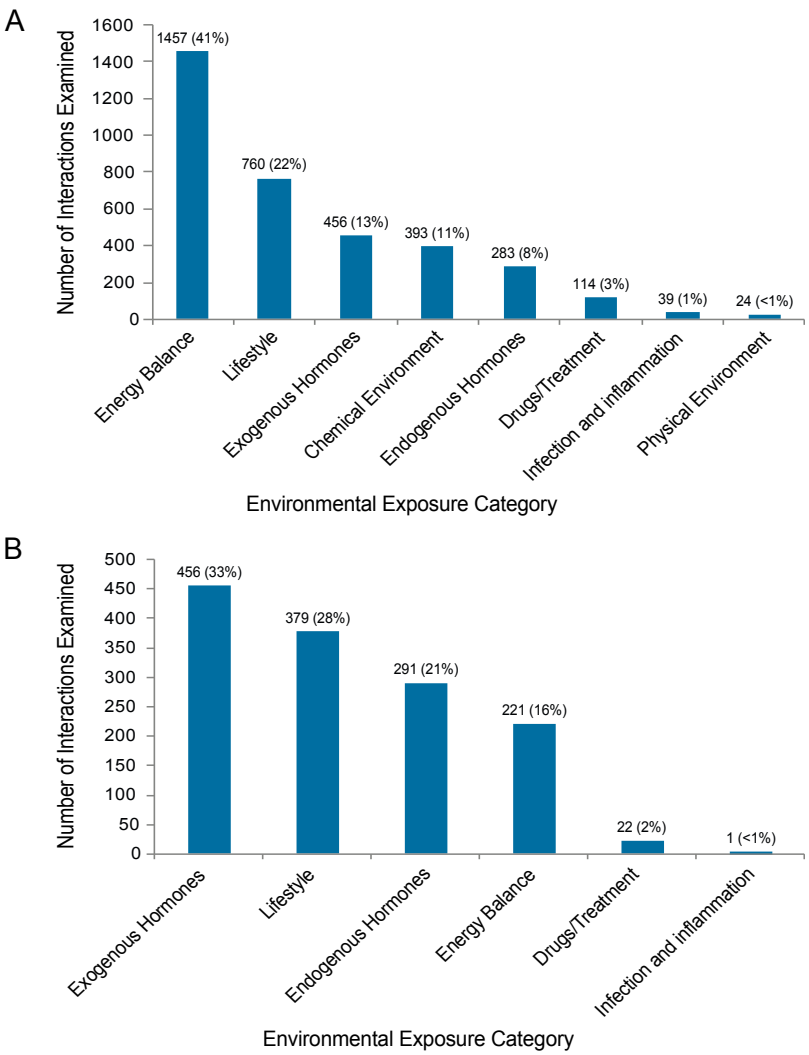
Interestingly, the majority of the interactions examined used loci from candidate gene studies, and none of the studies were genome-wide interaction studies (i.e. studies based on genome-wide association studies [GWAS]). The magnitudes of the interactions reported were modest, as is usually the case in the literature on gene–environment interactions in cancer: the risks increased or decreased by 20–50% in carriers of the minor allele compared with wild-type individuals for the same exposure [9] (some examples are given below). More recently, GWAS gene–environment interaction studies have been published by the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO). An example is a study on the gene–environment interaction for use of aspirin and non-steroidal anti-inflammatory drugs and risk of colorectal cancer [10].

For colon cancer, several studies have evaluated the role of gene–diet interactions. Results from candidate gene studies were inconsistent, with little replication across studies. In recent years, GWAS have identified several colorectal cancer susceptibility loci, but limited evidence was provided that these loci may modify the risk associated with dietary habits. Larger sample sizes are probably needed to elucidate modest or weak interaction in GWAS of gene–diet interaction [11]. Potential chemoprevention of colorectal cancer mediated by aspirin and related drugs is not necessarily an exception, because in this case (in spite of very low *P* values), the relative risks are about 0.66–0.69 for gene variants [10,12].

Functional interpretation

The underlying biological mechanism contributing to disease risk is known for only a small proportion of

Fig. 3.3.4. Distribution of the number of gene–environment interactions examined by environmental exposure category in (A) primary and (B) supplemental literature searches. A total of 3526 interactions were examined in the primary search, and 1370 interactions were examined in the supplemental search from relevant publications.



the loci identified through GWAS (see Chapter 3.2). More research is needed to functionally characterize risk loci. This includes: using functional annotations for discovery and validation; studying molecular phenotypes, including epigenetics or gene expression, to improve gene–environment interaction discovery; and leveraging in vitro and in vivo models for these studies [13]. Large public databases, such as the Encyclopedia of DNA Elements (ENCODE), the Epigenomics Roadmap, and Genotype-Tissue Expression (GTEx), enable functional annotation and interpretation of many genomic regions; this can be used to prioritize candidate gene–environment interaction markers [14].

Can genetic susceptibility be used to select high-risk populations?

The concept of precision medicine has recently attracted significant attention [15]. As is stated on the website of the United States National Institutes of Health [16], "Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. While significant advances in precision medicine have been made for selected cancers, the practice is not currently applied to most diseases. Many efforts are under way to help make precision medicine the norm rather than the exception." Prevention is mentioned side by side with treatment, and the potential impact of environment and lifestyle is also cited.

According to Collins and Varmus [17], "The concept of precision medicine – prevention and treatment strategies that take individual variability into account – is not new; blood typing, for instance, has been used to guide blood transfusions for more than a century." The concept of taking inter-individual variation into account – which seems key to the definition of precision prevention – is indeed an old one: focusing on more susceptible subgroups has been discussed for decades, in particular in relation to screening or surveillance for chronic diseases.

Also for primary prevention, focusing on individuals who are at higher risk (e.g. because of their genetic background) has been repeatedly proposed. A typical example is screening for phenylketonuria at birth, where the detection of a particular set of mutations enables the identification of individuals who will benefit enormously from simple preventive actions, such as avoiding phenylalanine in the diet. In this example, the screening test has high sensitivity and specificity and the preventive action is highly effective; hence, precision prevention is highly attractive for phenylketonuria.

Sick individuals and sick populations

The strategic problems of the population science of primary prevention were already addressed in 2001 by Rose in an article titled "Sick individuals and sick populations" [18]. Rose compared the advantages and disadvantages of an approach to prevention that is focused on high-risk individuals or subgroups – which today would be termed stratified or personalized or precision prevention – and of the population-based approach.

The first advantage of the "high-risk" strategy is that it produces interventions that are appropriate for the particular individuals who are advised to follow them, and therefore the motivation to do so is enhanced. Also, the "high-risk" approach generally offers a more cost-effective use of limited resources, and it has a more favourable ratio of the benefits to the risks. (If an intervention has some adverse effects, then the ratio of the benefits to the risks will be more favourable if the benefits are greater.) However, the "high-risk" strategy has drawbacks. The first disadvantage is related to the difficulties and costs of screening individuals to identify those who are most susceptible, even with the more refined measures of susceptibility that result from the improved molecular understanding of cancer. The second disadvantage is that it is a temporary solution and not a definitive – or what Rose called "radical" – solution: with a population-based approach the risk factor can in principle be eradicated, whereas with the "high-risk" strategy it is not. The main problem that Rose identified with this approach, which is also the case for the concept of precision prevention, is that "a large number of people at a small risk may give rise to more cases of disease than the small number who are at a high risk" [18].

Hence, the preference is for population-based approaches, which have multiple advantages. They are definitive, because they attempt to remove the underlying causes of disease, and they may lead to large dividends, because they target the

Fig. 3.3.5. Blood from the heel of a newborn baby is applied to a card for a phenylketonuria test. If a particular set of mutations is detected, precision prevention can be implemented by avoiding phenylalanine in the diet.

whole population instead of a relatively small fraction of it. Rose used data from the Framingham Heart Study to calculate that a lowering of the blood pressure distribution of the population as a whole by 10 millimetres of mercury would correspond to a reduction of about 30% in the total attributable mortality [18]. Today, the evidence indicates that elimination of certain risk factors such as smoking, and hence a reduction of exposure to the main carcinogenic agents in tobacco smoke, might prevent 40–50% of cancers, a goal that is not achievable by selecting only high-risk populations [19]. However, the population-based approach to prevention does have some drawbacks. In particular, it offers only a small benefit to each individual, because most of the treated individuals will not develop the disease anyway. This leads to the so-called prevention paradox: "a preventive measure which brings much benefit to the population offers little to each participating individual" [18].

Conclusions

In general, the literature on gene–environment interactions in cancer contains few convincing and replicated examples that can be transferred into practice. First, risks are not all or nothing. One can identify people who are more susceptible or less susceptible to prostate cancer or breast cancer, but the risk still remains in the residual portion of the population. Second, an intervention may be potentially targetable to a subgroup in a population but may not be easily applicable in such a selective manner. Therefore, for pragmatic reasons of service delivery, to achieve effectiveness in a national programme one may have to trade off the precision against the practicalities of the intervention and aim at everyone. The practicalities of implementation are where the theoretical strategies of prevention often fail, even among susceptible subgroups, as exemplified by strategies to encourage smokers to quit [15].

References

1. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect. 124(6):713–21. https://doi.org/10.1289/ehp.1509912 PMID:26600562
2. Vineis P, Malats N, Lang M, d'Errico A, Caporaso N, Cuzick J, et al., editors (1999). Metabolic polymorphisms and susceptibility to cancer. Lyon, France: International Agency for Research on Cancer (IARC Scientific Publications, No. 148).
3. Ioannidis JP, Gwinn M, Little J, Higgins JP, Bernstein JL, Boffetta P, et al.; Human Genome Epidemiology Network and the Network of Investigator Networks (2006). A road map for efficient and reliable human genome epidemiology. Nat Genet. 38(1):3–5. https://doi.org/10.1038/ng0106-3 PMID:16468121
4. Hashibe M, McKay JD, Curado MP, Oliveira JC, Koifman S, Koifman R, et al. (2008). Multiple *ADH* genes are associated with upper aerodigestive cancers. Nat Genet. 40(6):707–9. https://doi.org/10.1038/ng.151 PMID:18500343
5. Wium-Andersen MK, Ørsted DD, Tolstrup JS, Nordestgaard BG (2015). Increased alcohol consumption as a cause of alcoholism, without similar evidence for depression: a Mendelian randomization study. Int J Epidemiol. 44(2):526–39. https://doi.org/10.1093/ije/dyu220 PMID:25433705
6. Lewis SJ, Smith GD (2005). Alcohol, ALDH2, and esophageal cancer: a meta-analysis which illustrates the potentials and limitations of a Mendelian randomization approach. Cancer Epidemiol Biomarkers Prev. 14(8):1967–71. https://doi.org/10.1158/1055-9965.EPI-05-0196 PMID:16103445
7. Holmes MV, Dale CE, Zuccolo L, Silverwood RJ, Guo Y, Ye Z, et al.; InterAct Consortium (2014). Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. BMJ. 349:g4164. https://doi.org/10.1136/bmj.g4164 PMID:25011450
8. Simonds NI, Ghazarian AA, Pimentel CB, Schully SD, Ellison GL, Gillanders EM, et al. (2016). Review of the gene-environment interaction literature in cancer: what do we know? Genet Epidemiol. 40(5):356–65. https://doi.org/10.1002/gepi.21967 PMID:27061572
9. Hutter CM, Mechanic LE, Chatterjee N, Kraft P, Gillanders EM; NCI Gene-Environment Think Tank (2013). Gene-environment interactions in cancer epidemiology: a National Cancer Institute Think Tank report. Genet Epidemiol. 37(7):643–57. https://doi.org/10.1002/gepi.21756 PMID:24123198
10. Nan H, Hutter CM, Lin Y, Jacobs EJ, Ulrich CM, White E, et al.; CCFR; GECCO (2015). Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants. JAMA. 313(11):1133–42. https://doi.org/10.1001/jama.2015.1815 PMID:25781442
11. Kantor ED, Giovannucci EL (2015). Gene-diet interactions and their impact on colorectal cancer risk. Curr Nutr Rep. 4(1):13–21. https://doi.org/10.1007/s13668-014-0114-2 PMID:25844273
12. Wender RC (2015). Aspirin and NSAID chemoprevention, gene-environment interactions, and risk of colorectal cancer. JAMA. 313(11):1111–2. https://doi.org/10.1001/jama.2015.1032 PMID:25781439
13. Ritchie MD, Davis JR, Aschard H, Battle A, Conti D, Du M, et al. (2017). Incorporation of biological knowledge into the study of gene-environment interactions. Am J Epidemiol. 186(7):771–7. https://doi.org/10.1093/aje/kwx229 PMID:28978191
14. McAllister K, Mechanic LE, Amos C, Aschard H, Blair IA, Chatterjee N, et al. (2017). Current challenges and new opportunities for gene-environment interaction studies of complex diseases. Am J Epidemiol. 186(7):753–61. https://doi.org/10.1093/aje/kwx227 PMID:28978193
15. Vineis P, Wild CP (2017). The science of precision prevention of cancer. Lancet Oncol. 18(8):997–8. https://doi.org/10.1016/S1470-2045(17)30331-5 PMID:28759370
16. United States National Institutes of Health (2017). The future of health begins with *All of Us*. https://allofus.nih.gov/about/about-all-us-research-program
17. Collins FS, Varmus H (2015). A new initiative on precision medicine. N Engl J Med. 372(9):793–5. https://doi.org/10.1056/NEJMp1500523 PMID:25635347
18. Rose G (2001). Sick individuals and sick populations. Int J Epidemiol. 30(3):427–32, discussion 433–4. https://doi.org/10.1093/ije/30.3.427 PMID:11416056
19. Vineis P, Wild CP (2014). Global cancer patterns: causes and prevention. Lancet. 383(9916):549–57. https://doi.org/10.1016/S0140-6736(13)62224-2 PMID:24351322

3.4 DNA repair and genetic instability
Endogenous and exogenous sources of damage and hereditary syndromes

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SUMMARY

- Environmental exposures and reactive species generated during normal cellular processes can damage DNA, which can lead to genetic instability. DNA damage repair and signalling pathways operate to maintain genome integrity.
- Some highly cancer-prone inherited human diseases are associated with DNA repair deficiencies. This indicates that cancer can be a disease of mutation resulting from DNA damage.
- Mutational analysis of individual cancer genes and sequencing of cancer genomes provides direct evidence that DNA insults leave mutational fingerprints on tumour DNA.
- Environmental factors, heredity, and random DNA damage all contribute to the burden of cancer mutations. The relative contributions of these factors are currently under investigation.
- Knowing how DNA lesions are generated, processed, and repaired will continue to provide insights and opportunities for cancer prevention and treatment.

Genetic information must be preserved for cellular homeostasis, organismal development, and cancer suppression. Multiple, redundant DNA damage repair and signalling pathways combine to avoid errors during DNA replication and to remove DNA lesions from endogenous or exogenous sources. This chapter highlights the role of DNA repair in preventing mutation and cancer development and suggests how this knowledge can be exploited for cancer prevention and therapy.

DNA damage and repair pathways

In the 1920s, well before the structure of DNA was elucidated, work in *Drosophila melanogaster* revealed that exposure to exogenous agents, such as ionizing radiation and chemicals, may cause mutations. Only much later was it recognized that spontaneous hydrolysis and reactive species generated endogenously during normal metabolism are also potentially mutagenic and that this reflects their ability to damage DNA. The human genome sustains approximately 70 000 lesions per day [1]. The majority are single-strand DNA breaks, which arise from oxidation or base loss via glycosyl bond hydrolysis. Single-strand breaks may be converted into double-strand breaks, a particularly hazardous form of damage that can cause cell death or chromosomal rearrangements. Furthermore, the addition, deletion, and incorporation of erroneous bases during DNA replication contribute to spontaneous mutation (Fig. 3.4.1).

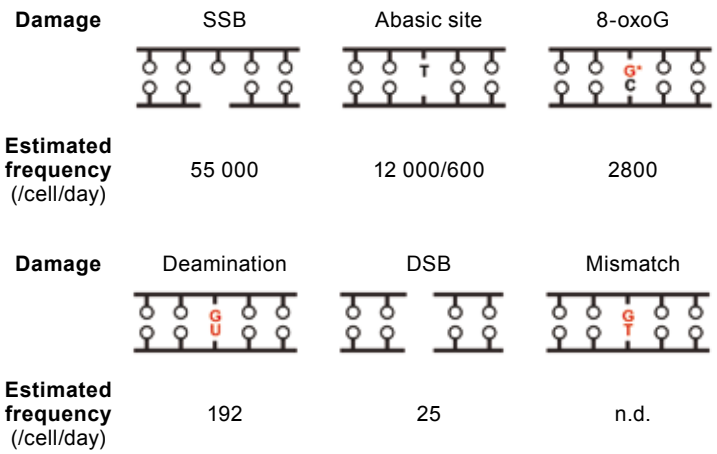
Exogenous agents such as ionizing radiation and chemicals damage DNA in a variety of ways. Ionizing radiation and endogenous oxidizing metabolites induce similar DNA lesions, although to different extents. Ultraviolet radiation, which is non-ionizing, causes dimerization of adjacent DNA pyrimidines. Simple alkylating agents and polycyclic aromatic hydrocarbons generate addition products (adducts) with DNA bases. In some cases, second reactions generate DNA interstrand and intrastrand cross-links.

The relative contributions of intrinsic and extrinsic factors to human mutagenesis remain unclear. Exogenous carcinogens were long considered to be the main source of mutation, but large-scale sequencing of cancer genomes suggests a significant contribution from endogenous DNA damage factors [2].

Several DNA repair pathways provide protection against both endogenous and exogenous DNA damage. These operate either through direct reversal of DNA damage or by excision of DNA lesions.

Fig. 3.4.2 is a schematic representation of the main DNA repair pathways. Nucleotide excision repair removes bulky DNA lesions by two distinct subpathways: global genome nucleotide excision repair, which operates throughout the genome, and transcription-coupled nucleotide excision repair, which targets transcribed DNA regions [3,4].

Fig. 3.4.1. Types of endogenous DNA damage and estimated frequency (per cell per day) in human cells. The frequencies shown for an abasic site refer to depurination and depyrimidination events, respectively. 8-oxoG, 8-hydroxyguanine; DSB, double-strand break, SSB, single-strand break.



Base excision repair removes more subtly damaged DNA bases by either short-patch or long-patch base excision repair [5,6]. Homologous recombination and non-homologous end joining repair double-strand breaks [7]. Mismatch repair corrects DNA replication errors [8].

Homologous recombination, non-homologous end joining, and mismatch repair contribute to replication fidelity and to the recovery from replication fork stalling or collapse. In the case of lesions that are complete blocks for DNA replication, such as interstrand and intrastrand cross-links, repair is achieved by subpathways that contain components of both homologous recombination and nucleotide excision repair [9]. Direct reversal of damage is provided by O^6-methylguanine-DNA methyltransferase, which transfers a methyl group from a promutagenic DNA base to itself, and by AlkB human homologues, which perform dealkylation repair of N1-methyladenine and N3-methylcytosine [5].

DNA repair is part of a wider DNA damage response in which DNA damage triggers signalling to a checkpoint response that arrests cell-cycle progression, inhibits transcription and translation, and initiates DNA repair. If DNA damage is very extensive, activation of death pathways occurs. In the context of cancer avoidance, both the DNA damage response and DNA repair play major roles in the maintenance of genome stability and in cancer avoidance [10].

DNA repair disorders and cancer

The formal proof of the underlying role of DNA damage repair in cancer development is the presence of germline mutations in specific DNA repair or DNA damage response genes in cancer-prone hereditary syndromes (Table 3.4.1).

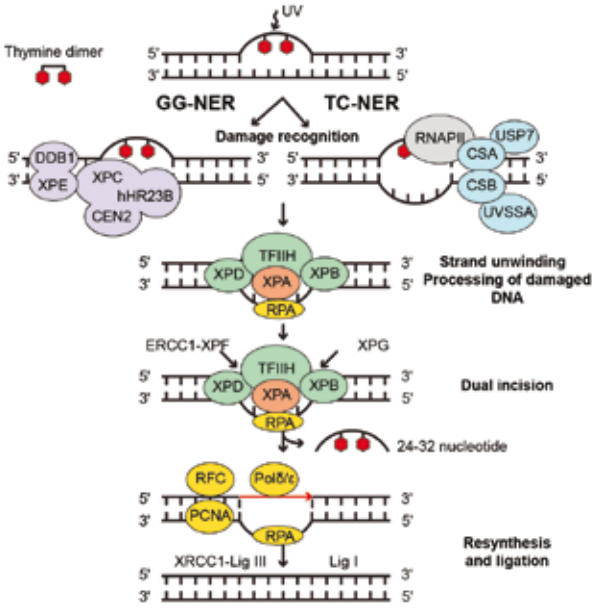
The autosomal recessive disease xeroderma pigmentosum was the first example that linked defective DNA repair to cancer development. Defects in the global genome nucleotide excision repair subpathway in individuals with xeroderma pigmentosum increase sun sensitivity and skin cancer risk more than 1000-fold [11]. Defects in transcription-coupled nucleotide excision repair are associated with several pathologies, including ultraviolet-sensitive syndrome and severe premature ageing conditions such as Cockayne syndrome and trichothiodystrophy. However, these syndromes do not exhibit increased cancer predisposition.

FUNDAMENTALS

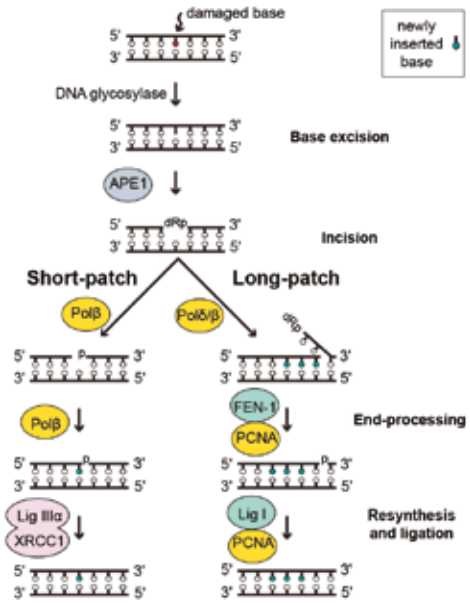
- Many chemical carcinogens cause tumours as a result of being metabolized to reactive intermediates, which may become covalently bound to DNA and give rise to mutation. Carcinogen adducts may be eliminated from DNA in vivo via a range of enzyme-mediated DNA repair processes.
- Human skin cancers that are attributable to exposure to ultraviolet radiation occur at a markedly increased rate in individuals with the autosomal recessive disease xeroderma pigmentosum, a condition arising from defects in a particular DNA repair pathway. This was the first example to indicate the role of DNA repair in preventing cancer development.
- The enzymes that mediate DNA repair, and their genes, have been characterized and are specific for particular categories of DNA damage.
- DNA damage may also occur spontaneously as a result of various biological processes, including the production of reactive oxygen species.
- Failure of effective DNA repair, as exemplified by a range of heritable syndromes, may contribute to increased mutation rates and related chromosomal structural changes, leading to tumour development.
- Malignant cells have a high mutation rate and manifest chromosomal instability, which facilitates the development of drug-resistant cell populations and leads to the failure, in the longer term, of some cancer therapies.

Fig. 3.4.2. The main DNA repair pathways. (A) Nucleotide excision repair with its two subpathways, global genome nucleotide excision repair (GG-NER) and transcription-coupled nucleotide excision repair (TC-NER). (B) Base excision repair takes place by short-patch or long-patch repair. (C) Pathways of double-strand break (DSB) repair: homologous recombination (HR) and non-homologous end joining (NHEJ). (D) Mismatch repair.

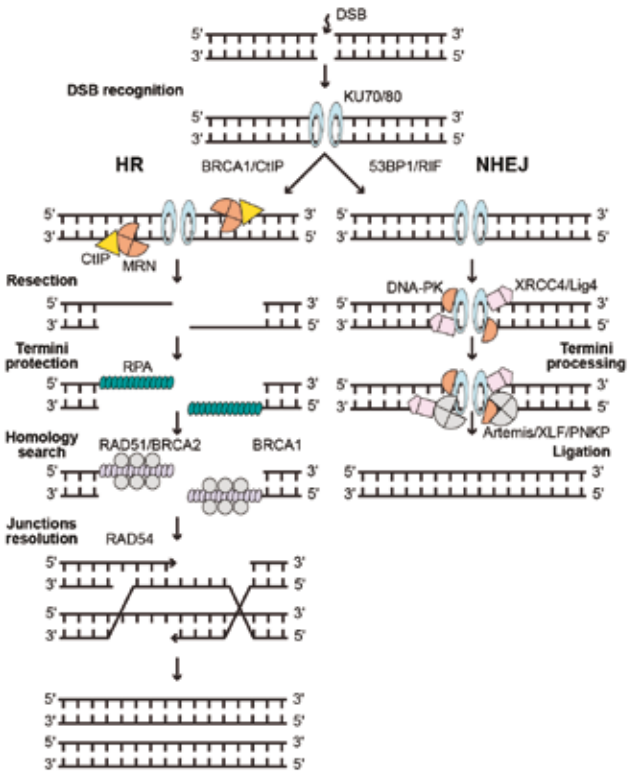
A Nucleotide excision repair



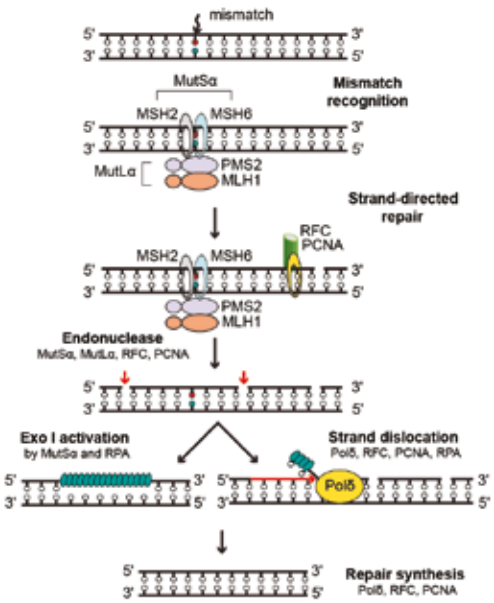
B Base excision repair



C Double-strand break repair



D Mismatch repair



Defects in mismatch repair are associated with both familial and sporadic colon cancer (see Chapter 5.5). Colorectal cancer in autosomal dominant Lynch syndrome (also called hereditary non-polyposis colorectal cancer [HNPCC]) is caused by a germline mutation in a mismatch repair gene (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) [12]. Defective mismatch repair destabilizes repetitive DNA sequences that are prone to replication errors. Frameshift mutations and microsatellite instability are the hallmarks of HNPCC. A milder type of colon cancer predisposition in some cases of familial adenomatous polyposis is associated with mutations in the *MUTYH* gene (see "The 8-hydroxyguanine mutational signature: from mechanistic studies in bacteria to human cancer"). MUTYH, a base excision repair DNA glycosylase, participates in the removal of DNA 8-hydroxyguanine, a pre-mutagenic lesion. Homozygosity for mutations in *NTHL1*, which encodes a DNA glycosylase involved in the base excision repair of oxidized pyrimidines, also causes adenomatous polyposis

Table 3.4.1. Inherited mutations in DNA repair and DNA damage response genes and cancer risk

Syndrome	Genes	Pathway	Tumours	Neurological abnormalities	Immunological defects
Xeroderma pigmentosum	7 genes (*XPA* to *XPG*)	NER	Skin cancer	No/Yes	No/Yes
MUTYH-associated polyposis (MAP)	*MUTYH*, *NTHL1*	BER	Colorectal cancer and gastric cancer	No	No
Lynch syndrome (hereditary non-polyposis colorectal cancer [HNPCC])	*MSH2*, *MSH6*, *MLH1*, *PMS2*	MMR	Colorectal cancer; carcinoma of the stomach, endometrium, biliary and pancreatic system, urinary tract	No	No
Werner syndrome	*WRN*	HR, RFR	Soft tissue sarcomas, osteosarcomas, meningiomas, malignant melanomas, thyroid carcinomas	No	No
Bloom syndrome	*BLM*	HR, RFR	Lymphoma, leukaemia, carcinoma	No	Yes
Rothmund–Thomson syndrome	*RECQL4*	HR, RFR	Osteosarcoma, skin cancer	No	No/Yes
Ataxia–telangiectasia	*ATM*	DDR	Leukaemia, lymphomas, breast cancer	Yes	Yes
Ataxia–telangiectasia-like disorder 1	*MRE11*	DDR	Leukaemia, lymphomas, breast cancer	Yes	Yes
Nijmegen breakage syndrome	*NBS1*	DDR	Lymphoid malignancies and cancer at multiple sites	Yes	Yes
Nijmegen breakage syndrome-like	*RAD50*	DDR	Lymphoid malignancies and cancer at multiple sites	Yes	Yes
Li–Fraumeni syndrome	*TP53*	DDR	Multiple primary sites (brain, breast, ovary, prostate, osteosarcoma)	No	No
Seckel syndrome type 1	*ATR*, *ATRIP*	DDR, RFR	Acute myeloid leukaemia	Yes	Yes
Fanconi anaemia	19 genes (*FANCA* to *FANCT*)	ICLR, RFR	Acute myeloid leukaemia, squamous cell carcinoma	Yes/No	Yes
Hereditary breast and ovarian cancer	*BRCA2*, *BRCA1*	ICLR, RFR	Breast cancer and ovarian cancer	No	No
Severe combined immunodeficiency with radiosensitivity (RS-SCID)	*Artemis*	NHEJ	Lymphoma	No	Yes
DNA ligase IV syndrome	*LIG4*	NHEJ	Lymphoma	Yes	Yes

BER, base excision repair; DDR, DNA damage response; HR, homologous recombination; ICLR, interstrand cross-link repair; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end joining; RFR, replication fork repair.

Fig. 3.4.3. Extreme measures taken to protect French children diagnosed with xeroderma pigmentosum from sunlight. This autosomal recessive disease provided the first evidence that linked defective DNA repair to cancer development.

and colorectal cancer [13]. Germline mutations in DNA polymerase δ or ε have also been shown to be responsible for some types of early-onset colon cancer and endometrial cancer characterized by a massive mutational burden [14]. Defective repair of interstrand and intrastrand cross-links and of double-strand breaks characterizes Fanconi anaemia. Patients with mutations in genes of the Fanconi anaemia pathway have growth retardation, infertility, bone marrow failure, and a susceptibility to leukaemia and various solid tumours [9]. Inherited mutations significantly influence risk of breast cancer and ovarian cancer. Most familial breast and ovarian cancers can be ascribed to highly penetrant germline mutations in the *BRCA1* or *BRCA2* homologous recombination genes [15].

The ATM protein is a major regulator of the DNA damage response. The importance of the DNA damage response in cancer prevention is emphasized by the clinical profile of individuals with ataxia–telangiectasia who carry homozygous *ATM* mutations. In addition to hypersensitivity to ionizing radiation, patients with ataxia–telangiectasia exhibit chromosomal instability and cancer predisposition, particularly to lymphoid tumours [16]. Individuals heterozygous for dominant missense *ATM* mutations have a higher risk of breast cancer, colorectal cancer, and stomach cancer. Somatic *ATM* mutations or deletions are also commonly found in lymphoid malignancies and a variety of solid tumours. Inherited mutations affecting the MRE11–NBS1–RAD50 complex cause disorders that present similar clinical and cellular features to those seen in patients with ataxia–telangiectasia, although the features do not fully overlap. These disorders include Nijmegen breakage syndrome and ataxia–telangiectasia-like disorder. Patients with Nijmegen breakage syndrome are highly cancer-prone; in ataxia–telangiectasia-like disorder, the cancer predisposition is somewhat milder [17].

In addition to cancer, defective DNA repair is often associated with pleiotropic phenotypes including immunodeficiency, neurodegeneration, and developmental abnormalities. This is not surprising, because several DNA repair proteins contribute to immune development and a tight control of genome stability is required for the function of the nervous system and the development of the whole organism [18,19].

The link between DNA damage repair, mutagenesis, and carcinogenesis

In vitro and in vivo models

Work in Ames's laboratory confirmed the functional link between carcinogenicity and mutagenicity [20] and led to the incorporation of mutagenicity tests into regulatory and industrial decision-making. Knowledge of the importance of DNA repair in counteracting mutagenesis informed the design of DNA repair-defective *Salmonella* tester strains with increased sensitivity to chemical mutagenesis. Assays based on cultured mammalian cells were developed in parallel. The bacterial reversion (Ames) assay together with the mammalian chromosomal aberration, gene mutation, and micronucleus tests comprise the standard battery of assays of in vitro genotoxicity. These are currently an essential component of the safety assessment of chemicals.

In vitro bacterial or mammalian cell systems have also been used to determine the relative biological importance of DNA lesions by transfecting into host cells plasmid or viral vectors either globally modified by a DNA-damaging agent or engineered to contain a single DNA lesion [21]. Mutational analysis of chromosomal reporter genes (*lacI*, *HPRT*) also enabled the identification of specific mutational spectra generated by exposures to DNA-damaging agents. The use of cells defective in a specific DNA repair enzyme or expressing a specialized DNA polymerase has defined the roles of specific enzymes as protectors from damage or inducers of damage. These basic studies of mutagenesis have been instrumental for the decoding of cancer mutational signatures and associated clinical developments (see below).

Animal models provide an alternative means to explore the contribution of DNA repair to genome stability and tumour suppression. Nucleotide excision repair-defective

animal models have been largely used to understand the molecular mechanisms underlying the association between DNA repair defect and cancer risk. However, remarkable differences in these animal models in clinical phenotype and/or DNA repair abilities weaken their use as models of human disease [3]. Cancer in patients with HNPCC is due to heterozygous germline mutations, predominantly in *MSH2* or *MLH1*, and the subsequent somatic inactivation of the remaining wild-type allele in the colonic epithelium. HNPCC mouse models in which inactivation of mismatch repair genes is targeted to the intestinal epithelium exhibit a high frequency of intestinal adenocarcinomas within the first year of life. It is currently unclear why HNPCC mouse models develop tumours in the small intestine rather than the colorectal cancers that are associated with Lynch syndrome in humans.

The effects of mutational inactivation of enzymes in the base excision repair pathway are more complex. Mice with targeted disruptions of DNA glycosylases often exhibit moderately increased mutation frequencies without overt disease. The limited effect of inactivation of single DNA glycosylases is probably due to redundancy in repair pathways. As a consequence, the phenotypes are enhanced in double-knockout mice, affecting back-up functions. Therefore, a cancer-prone phenotype is observed only in double-knockout mice deficient in NTHL1 and NEIL1, two enzymes that repair oxidized pyrimidines and ring-opened purines, with some overlapping substrate specificities. Similarly, only double inactivation of two DNA glycosylases involved in the removal of 8-hydroxyguanine from the genome, i.e. OGG1 and MUTYH, leads to a cancer-prone phenotype and a shortened lifespan (see "The 8-hydroxyguanine mutational signature: from mechanistic studies in bacteria to human cancer"). However, in humans, single germline mutations in the *MUTYH* or *NTHL1* genes are responsible for the increased risk of colorectal cancer.

Mutational signatures in human cancer

Sequencing of human cancer genomes revealed a great variation in the mutational load among cancer types: the number of mutations per tumour ranged from 500 in acute myeloid leukaemia to 100 000 in melanoma [22,23]. More than 40 years ago, it was hypothesized that human cancers express a mutator phenotype, because of the anticipated impact of mutations in DNA polymerases and/or repair genes, and as a result of the progressive accumulation of large numbers of mutations during tumour progression [24]. This hypothesis has been controversial for many years, and recently an argument was advanced that the number of stem cell divisions alone is sufficient to generate the large number of mutations found in human tumours, and that increased mutation rates are not required [25]. The relative contributions of environmental factors, heredity, and chance (random mutations during DNA replication) are currently a matter of debate (see Chapter 3.1).

Although the origin of mutations in tumours remains to be firmly established, the spectra of mutations in many tumours provide some clues. Mutational analysis of individual cancer genes, in particular *TP53*, provided the first evidence that carcinogenic insults leave mutational fingerprints on tumour DNA [26]. A compilation of mutant DNA sequences from specific tumour types has identified mutational signatures. These define both the type and the sequence context of mutations [23] and provide a record of the multiple mutagenic processes that have been operative over the lifetime of an individual.

Some mutational signatures reflect environmental exposures [27,28]. For example, the distinctive dipyrimidine mutations known to be associated with ultraviolet radiation-induced DNA lesions comprise the predominant mutational class in cutaneous tumours (see Chapter 2.4). The C → A transversion mutations that are characteristic of DNA adducts formed by benzo[*a*]pyrene, the major carcinogen in tobacco smoke, comprise the main signature in smoking-associated cancers of the lung and larynx. This signature is absent in tumours from never-smokers [29].

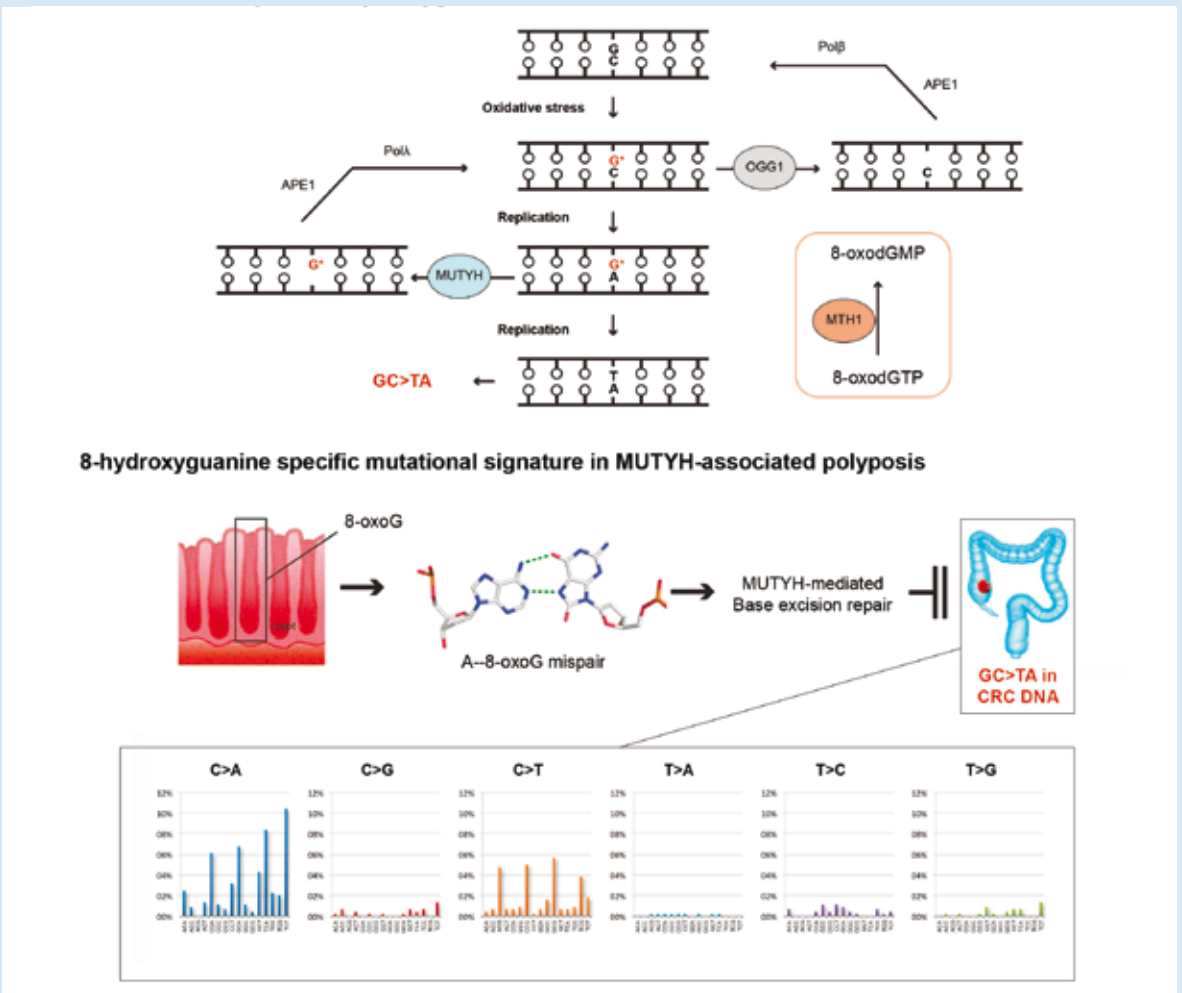
Examples of mutational signatures associated with exposure to genotoxic natural products include those of aflatoxin B_1 and aristolochic acid (see Chapter 2.8). Various experimental systems indicate that aflatoxin B_1 induces a mutational spectrum dominated by G → T transversions. This signature has been found in hepatocellular carcinomas from regions with possible exposure to this mycotoxin. Some hepatocellular carcinomas harbour the *TP53* R249S G → T transversion, which occurs in about half of the hepatocellular carcinomas of aflatoxin B_1-exposed people with hepatitis B virus infection. The variable prevalence of this mutation is probably due to different levels of aflatoxin B_1 exposure [30]. The mutational signature of aristolochic acid, characterized by A → T transversions, was initially associated with upper tract urothelial carcinomas [31] and, more recently, was widely implicated in liver cancer (see "The aristolochic acid mutational signature in many tumours: a warning"). The DNA lesions responsible for these mutations are all substrates for nucleotide excision repair, and mutational strand bias is consistent with incomplete repair by this pathway.

A similar example of overloading of DNA repair is provided by analysis of the genomic landscape of recurrent glioma in patients treated with the chemotherapeutic alkylating temozolomide. In this case, loss of expression of the repair enzyme O^6-methylguanine-DNA methyltransferase, which reverses potentially mutagenic DNA methylation damage induced by temozolomide, is associated with a characteristic G → A mutational signature [32].

The 8-hydroxyguanine mutational signature: from mechanistic studies in bacteria to human cancer

Endogenously or exogenously generated reactive oxygen species induce pre-mutagenic DNA lesions. 8-Hydroxyguanine (8-oxoG) – one of many oxidized DNA bases – has been extensively studied because of its miscoding properties. The frequent insertion of dAMP opposite 8-oxoG by replicative DNA polymerases causes G:C → T:A transversions. A three-tier error-avoidance repair system, discovered in *Escherichia coli* [1] and conserved in eukaryotes, prevents these mutations by the combined action of the base excision repair glycosylases OGG1 and MUTYH. Removal of 8-oxoG from 8-oxoG:C pairs by OGG1 and subsequent base excision repair restores the normal G:C base pairing. When

Fig. B3.4.1. Top panel: The three-tier system for removal of 8-hydroxyguanine (8-oxoG). Oxidative stress can introduce oxidized lesions in DNA. 8-oxoG can be removed by OGG1, and subsequent base excision repair restores the normal G:C base pairing. In the case of unrepaired 8-oxoG, adenine (A) is misincorporated opposite the 8-oxoG (G*) as a consequence of inaccurate replication. A removal by MUTYH is followed by resynthesis via long-patch base excision repair by a much less error-prone DNA polymerase (Polλ). This results in a C:8-oxoG pair, again a substrate for OGG1. Insert: Oxidative damage can also produce an oxidized pool of dNTPs. MTH1 hydrolyses 8-oxo-dGTP to 8-oxo-dGMP, effectively preventing its incorporation into DNA. Bottom panel: The mutational signature in *MUTYH*-associated polyposis tumours identifies the location at which mutations arise because of unrepaired 8-oxoG:A mispairs by a defective MutY DNA glycosylase. In the bar graphs, the triplets where the mutation is located (including the 5′ and 3′ bases) are shown on the horizontal axes and the mutation type probability is shown on the vertical axes. CRC, colorectal cancer.



adenine is incorporated opposite 8-oxoG during replication, its removal by MUTYH is followed by resynthesis by a less error-prone polymerase (Polλ). This generates OGG1 substrate C:8-oxoG base pairs. A third level of protection is provided by the MTH1 hydrolase, which degrades 8-oxodGTP to the monophosphate to prevent incorporation of pro-mutagenic 8-oxodGMP into DNA. Inactivation of any of these genes confers a mutator phenotype.

Although no human disease has been associated with defective OGG1 or MTH1 activities, germline biallelic *MUTYH* mutations underlie *MUTYH*-associated polyposis (MAP), a recessively heritable colorectal polyposis syndrome with a predisposition to colorectal cancer. Colorectal cancer in patients with MAP bears distinctive somatic G:C → T:A transversions in the *APC* gene [2]. Thus, whole-exome DNA sequencing of colorectal cancer from patients with MAP offered the unique opportunity to identify a mutational fingerprint of persistent 8-oxoG:A mismatches. A distinct mutational signature of G:C → T:A transversions (signature 36) was identified in MAP colorectal cancer. This mutational signature is reflected in the specific pattern of oncogenes and tumour suppressor genes involved in colorectal carcinogenesis and associated with inactive MUTYH. It is remarkable that the MAP-specific signature 36 has never been identified in sporadic colorectal cancer. However, it was noted that signature 36 [3] closely resembles signature 18 [4], which is particularly prevalent in neuroblastoma and at lower levels in pancreatic cancer, breast cancer, and gastric cancer. Therefore, it is possible that oxidative DNA damage also contributes to cancer etiology in these organ sites.

References

1. Michaels ML, Miller JH (1992). The GO system protects organisms from the mutagenic effect of the spontaneous lesion 8-hydroxyguanine (7,8-dihydro-8-oxoguanine). J Bacteriol. 174(20):6321–5. https://doi.org/10.1128/jb.174.20.6321-6325.1992 PMID:1328155
2. Sieber OM, Lipton L, Crabtree M, Heinimann K, Fidalgo P, Phillips RKS, et al. (2003). Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in *MYH*. N Engl J Med. 348(9):791–9. https://doi.org/10.1056/NEJMoa025283 PMID:12606733
3. Viel A, Bruselles A, Meccia E, Fornasarig M, Quaia M, Canzonieri V, et al. (2017). A specific mutational signature associated with DNA 8-oxoguanine persistence in MUTYH-defective colorectal cancer. EBioMedicine. 20:39–49. https://doi.org/10.1016/j.ebiom.2017.04.022 PMID:28551381
4. Alexandrov LB, Kim J, Haradhvala NJ, Huang MN, Ng AWT, Wu Y, et al.; PCAWG Mutational Signatures Working Group and the ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Network (2020). The repertoire of mutational signatures in human cancer. Nature. https://doi.org/10.1101/322859 (forthcoming)

Disruption of DNA repair pathways acting on endogenous lesions also leaves a molecular mark on the genome and results in specific mutational signatures. The mutational signature associated with inactive mismatch repair in both HNPCC and sporadic gastrointestinal cancers involves the expected increase in base substitution mutations as well as insertions or deletions at repetitive sequences. Similarly, the homologous recombination pathway was altered in nearly 40% of cancers, for example in *BRCA1/2*-mutated ovarian cancers and triple-negative breast cancers [33]. Because of the central role of DNA repair and DNA damage response genes in cell survival after DNA damage, mutations in these genes, which have been observed in several tumour types, provide a predictive marker of likely therapeutic response and clinical outcome.

In some tumours, the majority of genomic rearrangements appear to be acquired at an early stage of tumour evolution in a single catastrophic event known as chromothripsis [34]. These signatures might originate from sporadic bursts of massive endogenous or oncogenic stress [2], leading to a temporary saturation of the DNA repair capacity or to activation of an error-prone DNA repair pathway or pathways.

Several different mutational signatures can be linked to modification of DNA bases occurring spontaneously. Specific signatures have been ascribed to deamination of a canonical cytosine or 5-methylcytosine in DNA. In the deamination of a canonical cytosine, overactivity of members of the AID/APOBEC family of cytidine deaminases has been implicated [23]. As an example of endogenous DNA oxidation, tumours in which repair by the MUTYH DNA glycosylase was genetically impaired bear a signature associated with unrepaired DNA 8-hydroxyguanine (see "The 8-hydroxyguanine mutational signature: from mechanistic studies in bacteria to human cancer").

Therapeutic approaches that target DNA repair

Current cancer therapy is based largely on DNA damage and saturation of DNA repair in highly proliferative tumour cells. These treatments frequently result in side-effects, such as secondary tumours and drug resistance. Precision therapies targeted to cancer-specific DNA repair defects, either by synthetic lethality or by immunotherapy, aim to reduce collateral damage to normal cells.

Synthetic lethal interaction

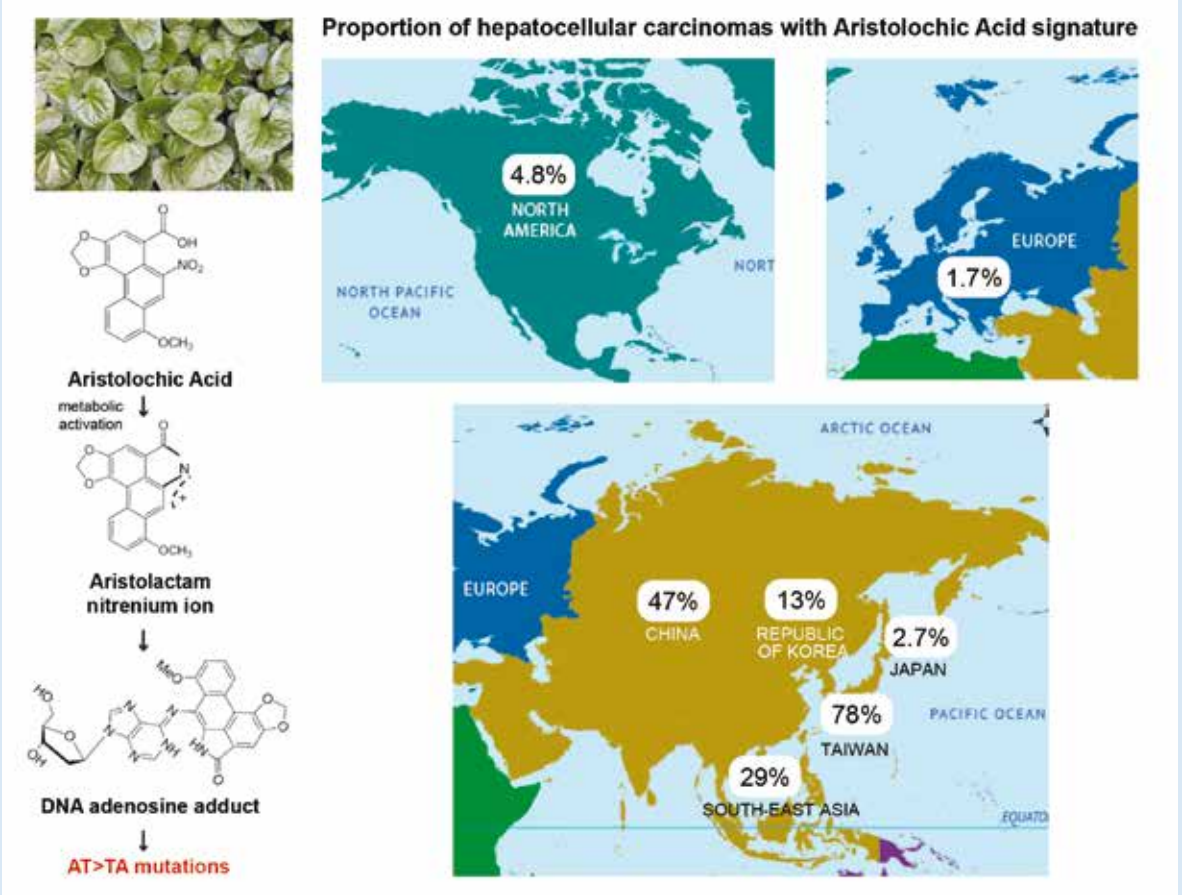
In 2005, a description was published of the synthetic lethal interaction between mutations in the homologous recombination genes *BRCA1* and *BRCA2* and inhibitors of poly-(ADP-ribose) polymerase 1 (PARP1). PARP1 acts as a sensor of DNA single-strand breaks and prevents

The aristolochic acid mutational signature in many tumours: a warning

Aristolochic acids (AAs) are a family of carcinogenic, mutagenic, and nephrotoxic compounds that are present in plants of the genera *Aristolochia* and *Asarum* (wild ginger), which are commonly used in Chinese herbal medicines (see Chapter 2.8). The main components of the plant extract, AAI and AAII, have been shown to form DNA adducts after metabolic activation, preferentially targeting purines. In vivo the most persistent of these adducts in target tissue is 7-(deoxyadenosin-N^6-yl)-aristolactam I (dA–AAI), which leads to A:T → T:A transversions in vitro. AAI-induced tumours in rodents show this same transversion mutation in codon 61 of the *H-ras* oncogene, suggesting that dA–AAI may be the critical lesion in the carcinogenic process in rodents.

These mechanistic key steps, i.e. typical DNA adducts and mutation type, have been identified and are consistent with events occurring in patients with upper tract urothelial carcinomas associated with AA poisoning and Balkan endemic nephropathy. More recently, two groups [1,2] independently determined the mutational signature of AA-exposed upper tract urothelial carcinomas from Taiwan, China. Both groups observed a very high mutation rate in exposed tumours and identified the typical AA mutational signature (A:T → T:A transversions) occurring preferentially at splice sites. This signature was then found in a variety of tumour types, such as renal cell carcinoma, intrahepatic bile duct carcinoma, and hepatocellular

Fig. B3.4.2. Left panel: Mechanisms of mutagenesis of aristolochic acid (AA). AA is derived from plants of the genus *Aristolochia*. AAI is shown. The metabolic activation to aristolactam nitrenium ions is followed by DNA binding preferentially to adenosine and production of specific A:T → T:A transversion mutations. Right panel: Proportion of hepatocellular carcinomas with the AA signature in various geographical regions. The percentage for South-East Asia comprises data from several countries, including Viet Nam.



carcinoma. In particular, the analysis of the role of AA in hepatocellular carcinomas [3] revealed that countries in Asia, especially Taiwan, China, are highly affected, and almost half of the hepatocellular carcinomas from China showed the AA signature, consistent with exposure through herbal medicines. Because exposure to AA seems to be widespread, additional measures should be taken to avoid exposure to these harmful compounds. Moreover, the hepatocellular carcinomas from Taiwan, China, that present heavy burdens of AA signature mutations may be good candidates for immune checkpoint inhibitors.

References

1. Hoang ML, Chen CH, Sidorenko VS, He J, Dickman KG, Yun BH, et al. (2013). Mutational signature of aristolochic acid exposure as revealed by whole-exome sequencing. Sci Transl Med. 5(197):197ra102. https://doi.org/10.1126/scitranslmed.3006200 PMID:23926200
2. Poon SL, Pang ST, McPherson JR, Yu W, Huang KK, Guan P, et al. (2013). Genome-wide mutational signatures of aristolochic acid and its application as a screening tool. Sci Transl Med. 5(197):197ra101. https://doi.org/10.1126/scitranslmed.3006086 PMID:23926199
3. Ng AWT, Poon SL, Huang MN, Lim JQ, Boot A, Yu W, et al. (2017). Aristolochic acids and their derivatives are widely implicated in liver cancers in Taiwan and throughout Asia. Sci Transl Med. 9(412):eaan6446. https://doi.org/10.1126/scitranslmed.aan6446 PMID:29046434

their conversion into double-strand breaks, which are selectively lethal in homologous recombination-defective cells [35]. Clinical trials clearly showed that PARP inhibitors, such as olaparib, are effective therapy for *BRCA1/2*-mutated cancers. Although tumour resistance developed in the overwhelming majority of patients, PARP inhibitor combination regimens provide promising alternative therapeutic approaches [36].

Immunotherapy response and DNA repair deficiencies

Hypermutated tumours express numerous mutant peptides that are not expressed in normal cells (neo-antigens). This renders the tumour cells more immunogenic and prone to recognition by cytotoxic T cells. The burden of neo-antigens is particularly high in mismatch repair-deficient tumours with a tendency to frameshift mutation. Consistent with this phenotype, mismatch repair-defective colorectal cancers respond well to the anti-programmed cell death 1 (PD-1) immune checkpoint inhibitor pembrolizumab [37]. Responsiveness is independent of the tumour histology and is driven only by the mutator phenotype as defined by microsatellite instability [38]. Indeed, the clinical benefit of anti-PD-1 immune checkpoint inhibitors is correlated with tumour somatic mutation frequency. The efficacy of this approach is not confined to mismatch repair-defective tumours. Any tumour with a high somatic mutation burden (these include mutagen-induced cancers such as cutaneous cancers and smoking-related non-small cell lung tumours) is likely to respond to immunotherapy, and this approach offers considerable promise in the treatment of a significant subgroup of human cancers.

References

1. Lindahl T, Barnes DE (2000). Repair of endogenous DNA damage. Cold Spring Harb Symp Quant Biol. 65(0):127–33. https://doi.org/10.1101/sqb.2000.65.127 PMID:12760027
2. Tubbs A, Nussenzweig A (2017). Endogenous DNA damage as a source of genomic instability in cancer. Cell. 168(4):644–56. https://doi.org/10.1016/j.cell.2017.01.002 PMID:28187286
3. Marteijn JA, Lans H, Vermeulen W, Hoeijmakers JHJ (2014). Understanding nucleotide excision repair and its roles in cancer and ageing. Nat Rev Mol Cell Biol. 15(7):465–81. https://doi.org/10.1038/nrm3822 PMID:24954209
4. Hanawalt PC, Spivak G (2008). Transcription-coupled DNA repair: two decades of progress and surprises. Nat Rev Mol Cell Biol. 9(12):958–70. https://doi.org/10.1038/nrm2549 PMID:19023283
5. Lindahl T (2013). My journey to DNA repair. Genomics Proteomics Bioinformatics. 11(1):2–7. https://doi.org/10.1016/j.gpb.2012.12.001 PMID:23453014
6. Dogliotti E, Fortini P, Pascucci B, Parlanti E (2001). The mechanism of switching among multiple BER pathways. Prog Nucleic Acid Res Mol Biol. 68:3–27. https://doi.org/10.1016/S0079-6603(01)68086-3 PMID:11554307
7. Kakarougkas A, Jeggo PA (2014). DNA DSB repair pathway choice: an orchestrated handover mechanism. Br J Radiol. 87(1035):20130685. https://doi.org/10.1259/bjr.20130685 PMID:24363387
8. Modrich P (2016). Mechanisms in *E. coli* and human mismatch repair (Nobel lecture). Angew Chem Int Ed Engl. 55(30):8490–501. https://doi.org/10.1002/anie.201601412 PMID:27198632
9. Ceccaldi R, Sarangi P, D'Andrea AD (2016). The Fanconi anaemia pathway: new players and new functions. Nat Rev Mol Cell Biol. 17(6):337–49. https://doi.org/10.1038/nrm.2016.48 PMID:27145721
10. Ciccia A, Elledge SJ (2010). The DNA damage response: making it safe to play with knives. Mol Cell. 40(2):179–204. https://doi.org/10.1016/j.molcel.2010.09.019 PMID:20965415
11. Cleaver JE (1968). Defective repair replication of DNA in xeroderma pigmentosum. Nature. 218(5142):652–6. https://doi.org/10.1038/218652a0 PMID:5655953
12. Lynch HT, Snyder CL, Shaw TG, Heinen CD, Hitchins MP (2015). Milestones of Lynch syndrome: 1895-2015. Nat Rev Cancer. 15(3):181–94. https://doi.org/10.1038/nrc3878 PMID:25673086

13. Weren RD, Ligtenberg MJ, Kets CM, de Voer RM, Verwiel ET, Spruijt L, et al. (2015). A germline homozygous mutation in the base-excision repair gene *NTHL1* causes adenomatous polyposis and colorectal cancer. Nat Genet. 47(6):668–71. https://doi.org/10.1038/ng.3287 PMID:25938944

14. Palles C, Cazier JB, Howarth KM, Domingo E, Jones AM, Broderick P, et al.; CORGI Consortium; WGS500 Consortium (2013). Germline mutations affecting the proofreading domains of *POLE* and *POLD1* predispose to colorectal adenomas and carcinomas. Nat Genet. 45(2):136–44. https://doi.org/10.1038/ng.2503 PMID:23263490

15. Nielsen FC, van Overeem Hansen T, Sørensen CS (2016). Hereditary breast and ovarian cancer: new genes in confined pathways. Nat Rev Cancer. 16(9):599–612. https://doi.org/10.1038/nrc.2016.72 PMID:27515922

16. Shiloh Y, Lederman HM (2017). Ataxia-telangiectasia (A-T): an emerging dimension of premature ageing. Ageing Res Rev. 33:76–88. https://doi.org/10.1016/j.arr.2016.05.002 PMID:27181190

17. Stracker TH, Roig I, Knobel PA, Marjanović M (2013). The ATM signaling network in development and disease. Front Genet. 4:37. https://doi.org/10.3389/fgene.2013.00037 PMID:23532176

18. Gennery AR, Cant AJ, Jeggo PA (2000). Immunodeficiency associated with DNA repair defects. Clin Exp Immunol. 121(1):1–7. https://doi.org/10.1046/j.1365-2249.2000.01257.x PMID:10886231

19. McKinnon PJ (2013). Maintaining genome stability in the nervous system. Nat Neurosci. 16(11):1523–9. https://doi.org/10.1038/nn.3537 PMID:24165679

20. McCann J, Choi E, Yamasaki E, Ames BN (1975). Detection of carcinogens as mutagens in the *Salmonella*/microsome test: assay of 300 chemicals. Proc Natl Acad Sci U S A. 72(12):5135–9. https://doi.org/10.1073/pnas.72.12.5135 PMID:1061098

21. Delaney JC, Essigmann JM (2008). Biological properties of single chemical-DNA adducts: a twenty year perspective. Chem Res Toxicol. 21(1):232–52. https://doi.org/10.1021/tx700292a PMID:18072751

22. Cancer Genome Atlas Network (2012). Comprehensive molecular characterization of human colon and rectal cancer. Nature. 487(7407):330–7. https://doi.org/10.1038/nature11252 PMID:22810696

23. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al.; Australian Pancreatic Cancer Genome Initiative; ICGC Breast Cancer Consortium; ICGC MMML-Seq Consortium; ICGC PedBrain (2013). Signatures of mutational processes in human cancer. Nature. 500(7463):415–21. https://doi.org/10.1038/nature12477 PMID:23945592

24. Loeb LA, Springgate CF, Battula N (1974). Errors in DNA replication as a basis of malignant changes. Cancer Res. 34(9):2311–21. PMID:4136142

25. Tomasetti C, Vogelstein B (2015). Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science. 347(6217):78–81. https://doi.org/10.1126/science.1260825 PMID:25554788

26. Olivier M, Hollstein M, Hainaut P (2010). TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2(1):a001008. https://doi.org/10.1101/cshperspect.a001008 PMID:20182602

27. Helleday T, Eshtad S, Nik-Zainal S (2014). Mechanisms underlying mutational signatures in human cancers. Nat Rev Genet. 15(9):585–98. https://doi.org/10.1038/nrg3729 PMID:24981601

28. Hollstein M, Alexandrov LB, Wild CP, Ardin M, Zavadil J (2017). Base changes in tumour DNA have the power to reveal the causes and evolution of cancer. Oncogene. 36(2):158–67. https://doi.org/10.1038/onc.2016.192 PMID:27270430

29. Alexandrov LB, Ju YS, Haase K, Van Loo P, Martincorena I, Nik-Zainal S, et al. (2016). Mutational signatures associated with tobacco smoking in human cancer. Science. 354(6312):618–22. https://doi.org/10.1126/science.aag0299 PMID:27811275

30. Huang MN, Yu W, Teoh WW, Ardin M, Jusakul A, Ng AWT, et al. (2017). Genome-scale mutational signatures of aflatoxin in cells, mice, and human tumors. Genome Res. 27(9):1475–86. https://doi.org/10.1101/gr.220038.116 PMID:28739859

31. Grollman AP (2013). Aristolochic acid nephropathy: harbinger of a global iatrogenic disease. Environ Mol Mutagen. 54(1):1–7. https://doi.org/10.1002/em.21756 PMID:23238808

32. Johnson BE, Mazor T, Hong C, Barnes M, Aihara K, McLean CY, et al. (2014). Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. Science. 343(6167):189–93. https://doi.org/10.1126/science.1239947 PMID:24336570

33. Knijnenburg TA, Wang L, Zimmermann MT, Chambwe N, Gao GF, Cherniack AD, et al.; Cancer Genome Atlas Research Network (2018). Genomic and molecular landscape of DNA damage repair deficiency across The Cancer Genome Atlas. Cell Rep. 23(1):239–254.e6. https://doi.org/10.1016/j.celrep.2018.03.076 PMID:29617664

34. Zhang CZ, Leibowitz ML, Pellman D (2013). Chromothripsis and beyond: rapid genome evolution from complex chromosomal rearrangements. Genes Dev. 27(23):2513–30. https://doi.org/10.1101/gad.229559.113 PMID:24298051

35. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. (2005). Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 434(7035):913–7. https://doi.org/10.1038/nature03443 PMID:15829966

36. Brown JS, O'Carrigan B, Jackson SP, Yap TA (2017). Targeting DNA repair in cancer: beyond PARP inhibitors. Cancer Discov. 7(1):20–37. https://doi.org/10.1158/2159-8290.CD-16-0860 PMID:28003236

37. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. (2015). PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 372(26):2509–20. https://doi.org/10.1056/NEJMoa1500596 PMID:26028255

38. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. (2017). Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 357(6349):409–13. https://doi.org/10.1126/science.aan6733 PMID:28596308

3.5 Inflammation
Playing a pivotal role in cancer pathogenesis

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SUMMARY

- Factors linking chronic inflammation and cancer are of great interest, and increasing evidence suggests that constitutive activation of pro-inflammatory transcription factors can mediate carcinogenesis.
- An inflammatory condition often precedes the development of cancer, and pro-inflammatory transcription factors such as NF-κB and STAT3 are constitutively active in various cancer types.
- Chemotherapeutic agents and gamma irradiation can activate NF-κB and/or STAT3, which can lead to chemoresistance and radioresistance.
- Suppression of NF-κB and STAT3 may inhibit the proliferation and invasion of cancer cells, and most chemopreventive agents mediate their effects through inhibition of the NF-κB and STAT3 activation pathways.
- Modulation of these pro-inflammatory pathways may provide opportunities for both prevention and treatment of chronic diseases, including cancer.

Virchow (in the 19th century) and others (in the early 20th century) proposed an association between inflammation and cancer [1–4]. Worldwide, about 15% of all cancer cases are estimated to be linked to inflammation [5]. Inflammation by itself may not lead to cancer; additional mutations and epigenetic events that occur in the genome of cells as a result of environmental exposures or changes in immunity are also important contributors to oncogenesis [6].

Through the immune response to acute inflammation, activated cells, including macrophages, monocytes, lymphocytes, neutrophils, and leukocytes, are attracted to the injured site and reduce the inflammation (see Chapter 3.9). However, in cases of severe inflammation, these cells contribute to excessive production of pro-inflammatory molecules, such as the cytokine tumour necrosis factor α (TNF-α), interleukin-1β (IL-1β) and IL-6, the chemokine receptor CXCR4 and its ligand CXCL12, cyclooxygenase 2 (COX-2), prostaglandins, nitric oxide, and leukotrienes, which dysregulate signal transduction pathways, thereby contributing to the development of cancer [6].

Inflammation is a tightly regulated process that can be very effectively turned on or off under normal physiological conditions [7]. Acute inflammation is mainly a self-limiting process and can be treated therapeutically; however, prolonged chronic inflammation is mostly detrimental [6]. Factors linking chronic inflammation and cancer are of great interest, and several lines of evidence suggest that constitutive activation of pro-inflammatory transcription factors plays a critical role in the sustained cell proliferation observed in cancers [5]. The majority of cancers are a consequence of chronic inflammation, infection, dysfunctional cell death mechanisms, and dysregulation of cell-cycle molecules. Chronic inflammation is associated with the production of pro-inflammatory cytokines and chemokines, which constitutively activate pro-survival transcription factors that may act as key regulators of carcinogenesis [6].

There are some exceptions; for example, chronic inflammation of the joint or muscle may not lead to the development of cancer. Nonetheless, tumour-associated persistent infection and inflammation are associated with 15–20% of cancer deaths worldwide (see Chapter 2.2), and obesity-associated inflammation is likely to contribute further to cancer-related deaths (see Chapter 2.7) [8]. Tumour-caused inflammation, such as necrotic death of cancer cells, insufficient blood supply, and viral infections in the tumour bed, contributes to malignant progression of organ-specific cancers such as liver cancer (see Chapter 5.6) and colon cancer (see Chapter 5.5) [9]. In addition, in patients who are undergoing chemotherapy or radiotherapy, induced tumour necrosis is often associated with an increase in tumour-associated inflammation, leading to the development of resistance to therapy and/or the induction of anti-tumour immunity. Therefore, inflammation is

an important factor driving tumour growth in most solid and haematopoietic malignancies [10].

The molecular mechanisms that connect chronic inflammation to cancer development have become a major area of research. This chapter focuses on the role of the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Other notable transcription factors that are implicated in inflammation and tumorigenesis are also discussed, i.e. the signal transducer and activator of transcription (STAT) family as well as the mitogen-activated protein kinase (MAPK) family. Finally, opportunities for the prevention and treatment of inflammation-driven cancers are described.

NF-κB signalling in inflammation and cancer

The first evidence for the link between chronic inflammation and cancer involved a proposed relationship between NF-κB and cancer development. This hypothesis gained prominence from the similarities in structure between the v-Rel protein and the NF-κB c-Rel protein [11]. Cancer development in the presence of chronic inflammation involves the constant presence of activated oncogenes and major transcription factors, such as NF-κB and STAT3.

The NF-κB family, which was discovered in 1986 by Baltimore and Sen [12], plays a pivotal role in wide-ranging processes, including immunity, inflammation, apoptosis, learning, and memory [13]. These proteins have a key role in innate and adaptive immune functions that can regulate proliferation and survival and stimulate angiogenesis, invasion, and migration, thereby leading to metastasis [14].

Structural components and organization of the NF-κB pathway

The mammalian NF-κB family of transcription factors is composed of RelA (p65), c-Rel, RelB, NF-κB1 (p50), and NF-κB2 (p52). They all contain a conserved Rel homology domain of about 300 amino acids that plays a critical role in their functions, such as dimerization and DNA binding via the N-terminal part of the Rel homology domain, and heterodimerization interaction with inhibitory κBs (IκBs) involving the C-terminal part of the Rel homology domain, both of which are intracellular inhibitors of NF-κB [12]. NF-κB family members can also form diverse homodimers or heterodimers, and the subunits RelA, c-Rel, and RelB contain a C-terminal transcriptional activation domain (absent in p50 and p52), which enables them to dimerize and physically bind via promoter/enhancer molecules to specific DNA sequences in κB sites: 5′-GGGRNYYYCC-3′, where R is a purine, Y is a pyrimidine, and N is any nucleotide [15].

In resting cells, most NF-κB subunit complexes are primarily cytoplasmic and exist as homodimers or heterodimers bound to IκBs and present in an inactive form. This is because their binding to IκB proteins prevents DNA binding and, as a consequence, prevents nuclear accumulation [6]. The IκB family of proteins is composed of the typical IκBs (IκBα, IκBβ, and IκBε), the atypical IκBs (Bcl-3 and IκBζ), and the precursor IκBs (p100 and p105). They have been characterized, and contain in their C terminus up to seven 33-amino acid consensus ankyrin repeats, which regulate protein–protein interaction and bind to Rel proteins, thereby masking their nuclear localization signal. The IκB kinase (IKK) complex is composed of two catalytic kinases (IKKα and IKKβ) and one non-catalytic subunit, called IKKγ or NF-κB essential modulator (NEMO). Upon activation, IKK can phosphorylate IκB and abrogate the suppressive effect of IκBs on NF-κB dimers [6]. This effectively releases NF-κB for subsequent phosphorylation and acetylation, and promotes nuclear translocation (Fig. 3.5.1).

NF-κB signalling pathways

Activation of NF-κB is fairly rapid, and it can be activated by exposure to diverse stimuli. There are

FUNDAMENTALS

- Historically, inflammation was described in Latin by four major signs: *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain).
- In 1858, the German physician Virchow postulated that micro-inflammation that results from irritation may lead to the development of cancer.
- Inflammation is typically designated by adding the suffix "–itis". Such conditions, for example colitis and pancreatitis, often predispose to cancer.
- Alcohol consumption, smoking, chronic infections, obesity, exposure to environmental pollutants, radiation exposure, a high energy intake, and other factors have been recognized as risk factors for most chronic diseases, including cancer. All of these risk factors may be linked to cancer through the process of chronic inflammation.
- Inflammation may be caused by a range of diseases due to infectious organisms that are recognized to cause cancer. These include hepatitis from hepatitis B virus and hepatitis C virus, gastritis from *Helicobacter pylori*, and cervicitis from human papillomavirus.
- The major defence response initiated by the human body upon injury or infection is the activation of the immune system via active recruitment of diverse cells such as macrophages, monocytes, lymphocytes, neutrophils, and leukocytes.

The STAT signalling pathway

Several published studies have indicated the pivotal role of the signal transducer and activator of transcription (STAT) family as pro-inflammatory transcription factors that are found to be constitutively activated in several cancer types. STAT3 was first discovered as an acute-phase response protein, thereby indicating its causal link to inflammation [1]. The STAT family of transcription factors was discovered in 1994 during the evaluation of the molecular pathways involved in interferon-triggered gene regulation [2]. A total of seven STAT proteins (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) have been identified to date in mammalian cells [3].

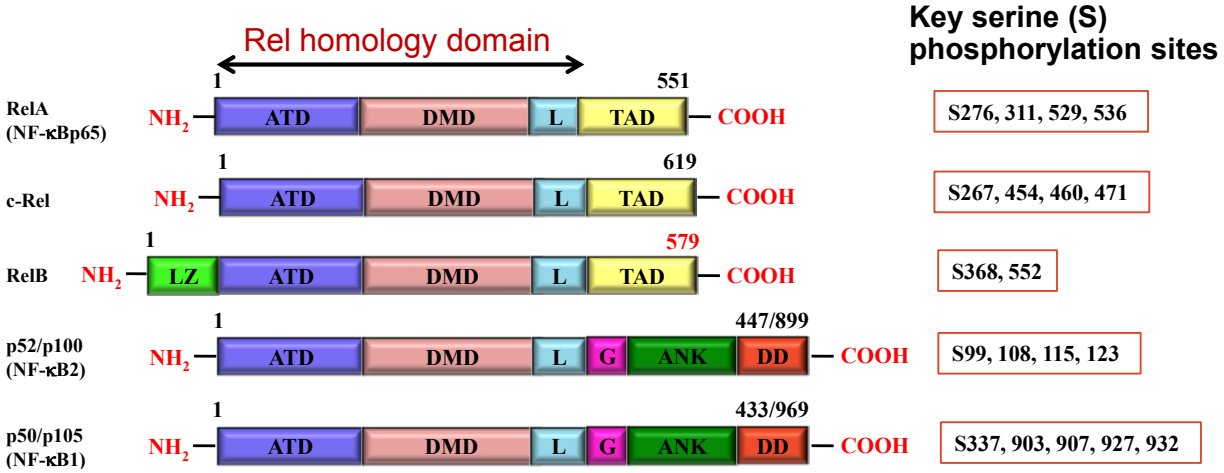
Among the STAT family of proteins, STAT3 is the most active. STAT3 plays a critical role in the regulation of intracellular signalling, the synthesis of pro-inflammatory cytokines and chemokines, and the oncogenic signalling pathway. Binding of a ligand, for example IL-6, to its specific receptor subunit can induce dimerization of glycoprotein 130 and activation of non-receptor tyrosine kinases called Janus kinases (JAKs). This, in turn, can phosphorylate STAT3 at tyrosine 705, and activated STAT dimers can translocate to the nucleus, bind to specific elements, and regulate gene transcription.

In addition, it has been reported that STAT3 may directly interact with the NF-κB family member RelA, thereby increasing the production of pro-inflammatory molecules such as IL-6, TNF, and growth factors, which in turn act in and can sustain a chronic inflammatory microenvironment in tumours. STAT3 can also be acetylated at lysine K685 by lysine acetyltransferase p300/CBP, which may upregulate STAT3 dimerization, increase DNA binding and transcriptional activation, and mediate cancer progression [3].

References

1. Wegenka UM, Buschmann J, Lütticken C, Heinrich PC, Horn F (1993). Acute-phase response factor, a nuclear factor binding to acute-phase response elements, is rapidly activated by interleukin-6 at the posttranslational level. Mol Cell Biol. 13(1):276–88. https://doi.org/10.1128/MCB.13.1.276 PMID:7678052
2. Darnell JE Jr, Kerr IM, Stark GR (1994). Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. Science. 264(5164):1415–21. https://doi.org/10.1126/science.8197455 PMID:8197455
3. Zhong Z, Wen Z, Darnell JE Jr (1994). Stat3: a STAT family member activated by tyrosine phosphorylation in response to epidermal growth factor and interleukin-6. Science. 264(5155):95–8. https://doi.org/10.1126/science.8140422 PMID:8140422

Fig. 3.5.1. The structure of the mammalian NF-κB family of transcription factors. ANK, ankyrin repeats; ATD, amino terminal domain; DD, death domain; DMD, dimerization domain; G, glycine-rich region; L, 10-amino acid polypeptide linker to nuclear localization signal; LZ, leucine zipper; TAD, transcriptional activation domain.



two major types of NF-κB signalling pathways [6]. The classical pathway (also known as the canonical pathway) leads to the generation of the active RelA–NF-κB1 (p50/p105) complex. This pathway can be activated by upstream transforming growth factor β-activated kinase (TAK) upon induction by pro-inflammatory cytokines such as TNF-α, IL-1β, and lipopolysaccharide. The alternative pathway (also known as the non-canonical pathway) leads to the formation of the RelB–NF-κB2 (p52/p100) complex. Activation of this pathway is mediated through the catalytic activity of NF-κB-inducing kinase (NIK), and

can be initiated by lymphotoxin, receptor activator of NF-κB ligand (RANKL), CD40 ligand, and B cell-activating factor of the TNF family (BAFF) [6,16] (Fig. 3.5.2).

Upon activation of the classical pathway, NF-κB can transcribe various genes encoding the pro-inflammatory enzyme COX-2, inducible nitric oxide synthase, cytokines such as TNF-α, IL-1, and IL-6, chemokines, growth factors, matrix metalloproteinases, cell-cycle proteins, anti-apoptotic proteins such as Bcl-2, Bcl-xL, and FLIP, vascular endothelial growth factor, adhesion molecules such as ICAM-1 and VCAM-1, and inhibitors of NF-κB signalling, including IκBs and A20.

Recent studies have also indicated that NF-κB can be positively or negatively regulated by microRNAs (such as miR-21, miR-146, miR-155, miR-181b, and miR-301a) that target messenger RNAs regulating NF-κB subunits, IκBs, and IKKs; in turn, NF-κB can regulate microRNA expression [6]. Therefore, NF-κB may have a key role in the inflammatory responses in normal cells coordinating both acute inflammation and chronic inflammation, and any dysregulation of this signalling pathway can lead to diverse malignancies.

Role of NF-κB in the tumour microenvironment

Tumorigenesis is often associated with the presence of tumour-associated macrophages, mast cells, neutrophils, dendritic cells, myeloid-derived suppressor cells, T cells, B cells, natural killer cells, natural killer T cells, endothelial cells, and cancer-associated fibroblasts. NF-κB signalling can regulate recruitment of these cells and thereby modulate inflammation, tumour progression, and metastasis [17] (Fig. 3.5.3).

Epigenetic modifications in NF-κB

Chronic inflammation, which is often driven by inflammatory response mediated through NF-κB activation, is associated with epigenetic modifications such as lysine acetylation and methylation and arginine methylation [18]. The major modification is lysine acetylation, which has been reported to be an important regulator of expression of pro-inflammatory genes. Acetylation of distinct lysine residues of RelA at K218, K221, and K310 by lysine acetyltransferase p300/CBP can regulate NF-κB transcriptional activation, DNA binding affinity, IκBα assembly, and subcellular localization [19]. However,

Fig. 3.5.2. The canonical (or classical) and non-canonical (or alternative) NF-κB signalling pathways. BAFF, B cell-activating factor of the TNF family; CD40L, CD40 ligand; IκB, inhibitor of NF-κB; IKK, inhibitory κB (IκB) kinase; IL-1β, interleukin-1β; LPS, lipopolysaccharide; LT-β, lymphotoxin β; NEMO, NF-κB essential modulator; NIK, NF-κB-inducing kinase; RANKL, receptor activator of NF-κB ligand; TAK, transforming growth factor β-activated kinase; TNF-α, tumour necrosis factor α.

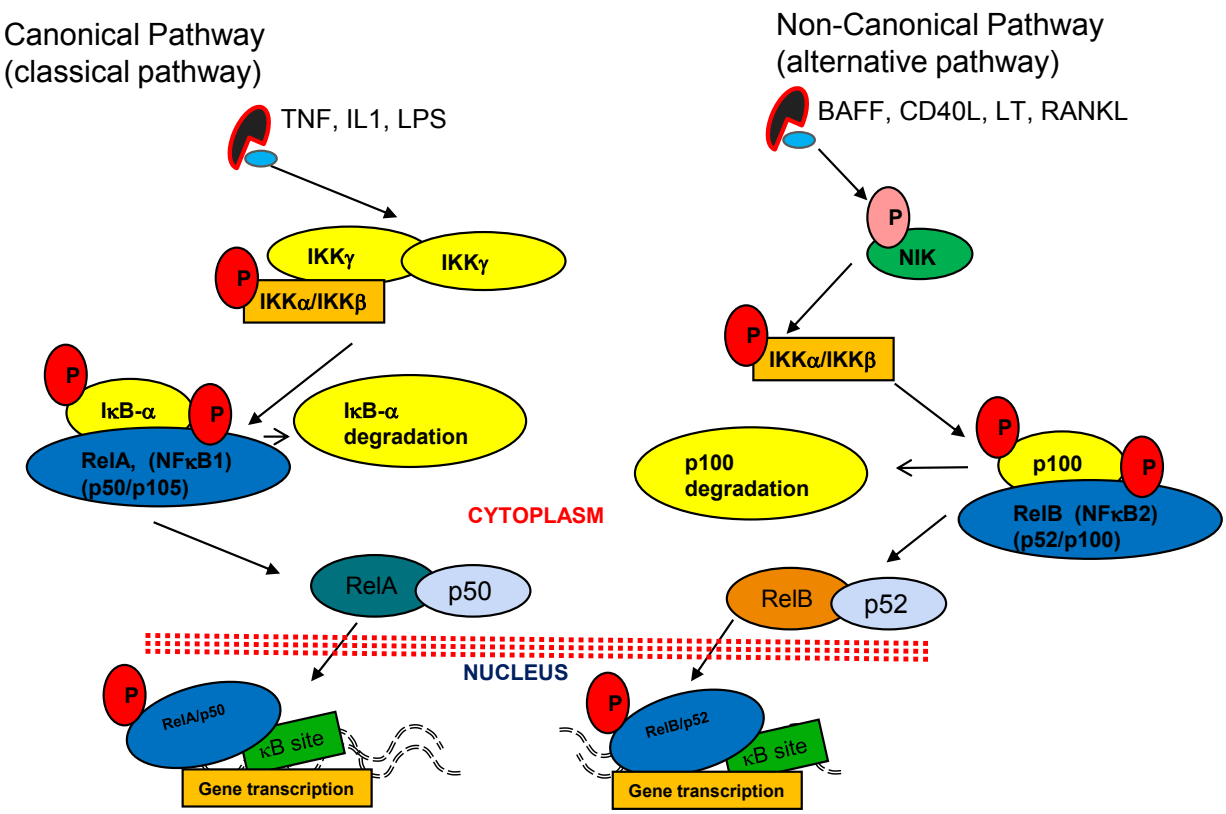
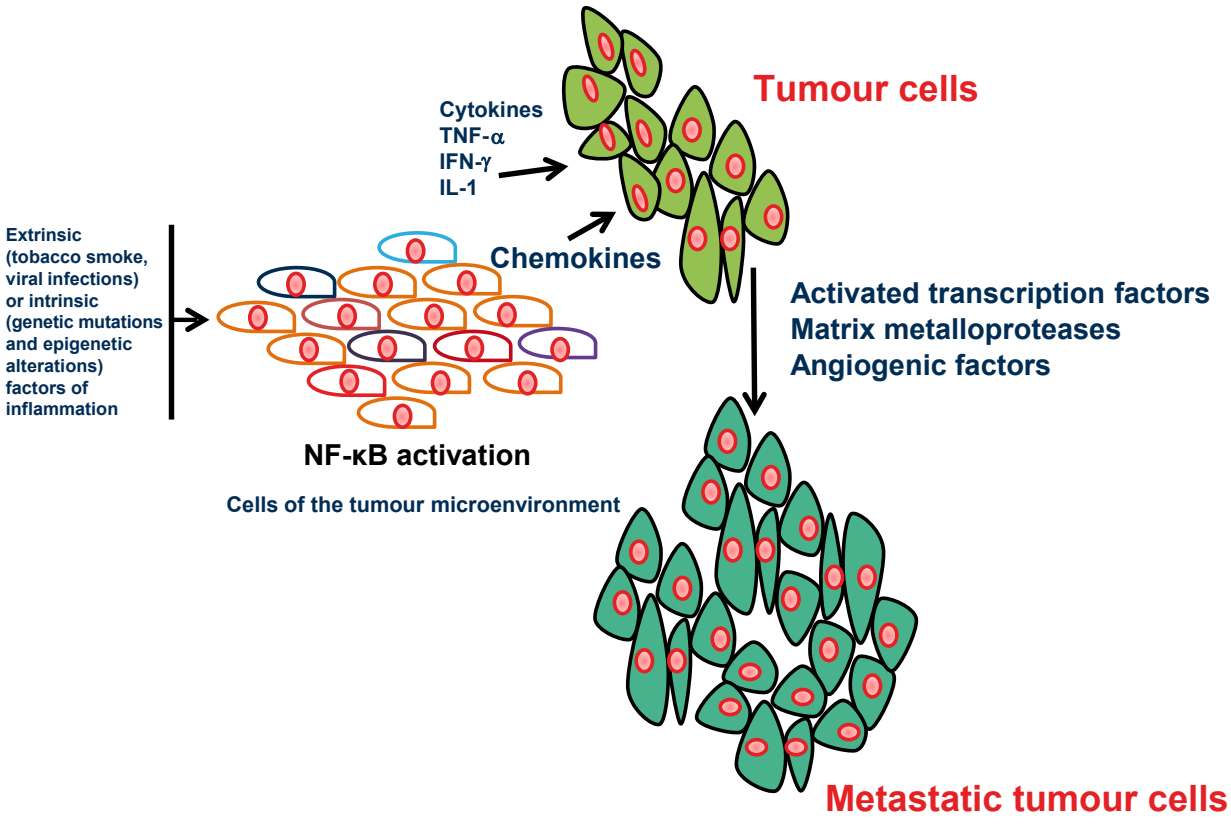


Fig. 3.5.3. The role of NF-κB in the tumour microenvironment. Different types of cells in the tumour microenvironment, including tumour-associated macrophages, mast cells, neutrophils, dendritic cells, myeloid-derived suppressor cells, T cells, B cells, natural killer cells, natural killer T cells, endothelial cells, and cancer-associated fibroblasts, can augment NF-κB activation, modulate inflammation, and lead to sustained tumorigenesis and metastasis. IFN-γ, interferon γ; IL-1, interleukin-1; TNF-α, tumour necrosis factor α.



acetylation of RelA at K122 and K123 by p300/CBP was found to reduce DNA binding and increase IκB binding to RelA, thereby indicating negative regulation of inflammation. Another NF-κB family member, p50 (NF-κB1), can be acetylated at K431, K440, and K441, which may also upregulate transcriptional activation, thereby indicating positive regulation of inflammation [18,19]. Acetylation of histone H3 is often found in cytokine-mediated inflammation and NF-κB activation, and thus histone-modifying enzymes can have critical functions in tumour progression.

Opportunities for prevention and treatment

Early detection or screening for pre-symptomatic cancers or cancer precursors as a potential strategy to prevent the development of cancer can work, because of the long time frame required for the cancer to progress from a benign state to a malignant phenotype.

Preventable risk factors for cancer initiation and progression

Primary prevention is aimed at preventing the development of cancer in the first place by reducing the exposures of individuals to risk factors, through strategies such as smoking cessation; abstaining from chronic alcohol consumption; vaccination against oncogenic viruses; reducing or eliminating environmental, occupational, or behavioural exposures to carcinogens; the use of novel screening methods; and the possibility of delaying ageing, thereby preventing or delaying the development of cancer.

Infection with the Gram-negative bacterium *Helicobacter pylori* is a major risk factor for gastritis, gastric ulcers, and stomach cancer (see Chapter 5.4). A significant decline in the incidence of stomach cancer has been observed as a result of improved sanitation, refrigeration, and food preservation as well as the use of antibiotics to effectively eradicate *H. pylori* infection [20].

Lifestyle factors such as obesity, unhealthy diet, and physical inactivity have also been identified as potential risk factors for cancer (see Chapter 2.6). All of these risk factors are linked to cancer through the process of chronic inflammation. In addition, consumption of fruits, legumes, and green leafy vegetables has been found to considerably reduce the risk of cancer development, potentially through an antioxidant activity. Skin cancer can be

The MAPK signalling pathway

Mitogen-activated protein kinases (MAPKs) are a family of serine/threonine-specific protein kinases. MAPKs regulate cellular processes such as cell proliferation, differentiation, cell survival, and apoptosis in response to a variety of external stimuli, including mitogens, heat shock, osmotic stress, and inflammatory cytokines, and MAPKs are often found to be dysregulated in cancer cells. The mammalian MAPKs comprise extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinases (JNKs), and p38 MAPK [1].

In the MAPK signalling pathway, MAPK kinase kinase (MAPKKK) phosphorylates and activates MAPK kinase (MAPKK), which in turn can phosphorylate and activate various MAPKs during the inflammatory response. Dysregulated p38 MAPK signalling is highly active in different cancer types, favouring tumour growth. p38 MAPKs are central to inflammatory processes and to the production of pro-inflammatory molecules that contribute to colitis-associated colorectal cancer pathogenesis. p38α can also mediate inflammation in inflammatory bowel disease and is substantially phosphorylated and active in the inflamed intestinal mucosa of patients with inflammatory bowel disease [2].

References

1. Dhillon AS, Hagan S, Rath O, Kolch W (2007). MAP kinase signalling pathways in cancer. Oncogene. 26(22):3279–90. https://doi.org/10.1038/sj.onc.1210421 PMID:17496922
2. Docena G, Rovedatti L, Kruidenier L, Fanning A, Leakey NA, Knowles CH, et al. (2010). Down-regulation of p38 mitogen-activated protein kinase activation and proinflammatory cytokine production by mitogen-activated protein kinase inhibitors in inflammatory bowel disease. Clin Exp Immunol. 162(1):108–15. https://doi.org/10.1111/j.1365-2249.2010.04203.x PMID:20731675

prevented by reducing exposure to ultraviolet radiation from sunlight or artificial sources (see Chapter 2.4).

The role of inflammation as a crucial mediator of colorectal cancer is also well established, and the use of non-steroidal anti-inflammatory drugs such as aspirin and ibuprofen has been found to significantly reduce the risk of colorectal cancer in some patient populations (see Chapter 6.4) [21]. In addition, reduced consumption of red meat and processed meat has been associated with a decreased risk of colorectal cancer [22].

Fig. 3.5.4. Potential cancer risk factors include obesity, unhealthy diet, and physical inactivity. Such factors may mediate cancer risk by provoking inflammatory change in relevant tissues.

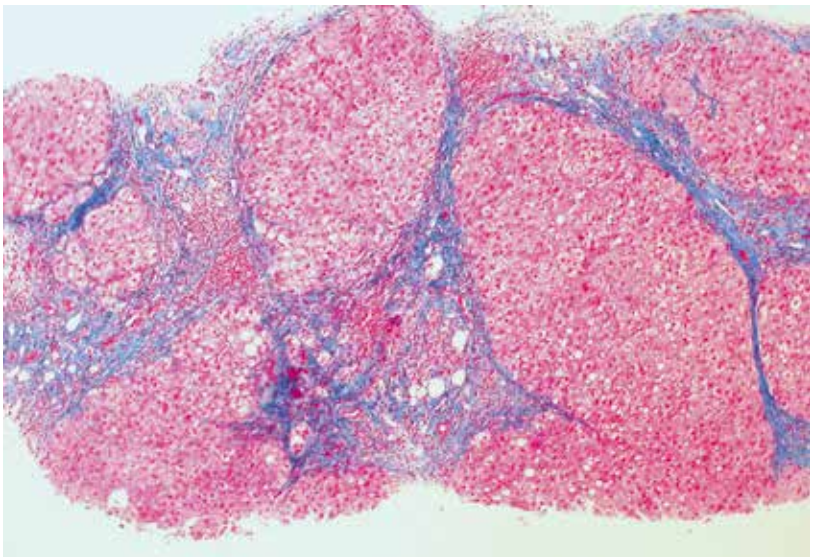
Microbial pathogens can also drive tumorigenesis in 15–20% of cancer cases. The gut microbiota has been shown to alter cancer susceptibility and progression by modulating inflammation and by producing metabolites that may be involved in either oncogenesis or tumour suppression (see Chapter 3.10). For example, in the colon *Clostridium scindens* bacteria can produce toxic secondary bile acids in response to dietary fat. Furthermore, diets high in fats induce blooms of *Bilophila wadsworthia*, a sulfite-reducing bacterium that has been found to be associated with increased risk of inflammatory bowel disease and malignancies. However, there are examples of whole foods and dietary components, such as soy-based products, cruciferous vegetables containing sulforaphane and isothiocyanates, and berries containing ellagic acid, that can inhibit COX-2 production and subsequent development of cancer. The diet may also dictate whether the gut microbiota can produce active metabolites that may aggravate or ameliorate tumour development and progression [23].

Avoiding chronic alcohol consumption has been found to lower the risk of liver cancer by reducing inflammation and cirrhosis of the liver (see Chapter 2.3). The success of cancer prevention strategies will require comprehensive planning and the incorporation of diverse approaches, including public policy, education, and research, to identify acceptable and effective ways to modify people's behaviour over long periods of time.

Ageing is also closely associated with the development of chronic inflammation, which forms the basis for the development of various age-related disorders (see Chapter 3.1). Epidemiological data clearly indicate that elevated levels of IL-6 and C-reactive protein in the blood may lead to multiple cellular changes. Compared with younger people, those aged 64–102 years were found to have higher levels of inflammatory biomarkers, including IL-6, TNF-α, IL-8, and C-reactive protein [24], which may contribute to tumour development by forming a pro-tumorigenic inflammatory environment and by recruiting various immune cells that can promote tumour progression by both autocrine and paracrine mechanisms.

Chronic inflammation is a low-grade sustained process driven by

Fig. 3.5.5. Histological section from a cirrhotic liver. Avoiding chronic alcohol consumption has been found to lower the risk of liver cancer by reducing inflammation and cirrhosis of the liver.



continuous activation of various transcription factors, such as NF-κB and STAT3, leading to oncogenesis. The bacterial population in the gut microbiota has been found to have an important function in the development of inflammatory bowel disease and in increased risk of chronic diseases such as diabetes, obesity, and cancer. Long-term administration of non-steroidal anti-inflammatory drugs has been shown to reduce the risk of development of various inflammation-driven ailments. Therefore, a better understanding of the diverse molecular players involved in the inflammatory cascade may aid in the development of novel anti-cancer treatment strategies [25].

Compounds from natural products as inhibitors of NF-κB- and STAT3-mediated inflammation-driven cancers

Targeting NF-κB and STAT3 has become an attractive strategy, and various pharmacological inhibitors can modulate NF-κB and STAT3 activation in tumour models. Some important natural compounds have been shown to inhibit inflammatory mediators involved in cancer progression; examples are curcumin, ursolic acid, oleanolic acid, garcinol, zerumbone, resveratrol, thymoquinone, diosgenin, celastrol, butein, sulforaphane, and epigallocatechin gallate [26].

The link between inflammation and cancer is well established, and strategies to prevent chronic cancer inflammation include (i) reducing the recruitment of inflammatory response elements to the tumour site and (ii) blocking pro-tumorigenic inflammatory elements or redirecting inflammation with properties that are anti-tumour, immunostimulatory, or both.

References

1. Virchow R (1858). Reizung und Reizbarkeit. Arch Pathol Anat Physiol Klin Med. 14(1–2):1–63. https://doi.org/10.1007/BF01877355
2. Yamagiwa K, Ichikawa K (1916). Experimental study on the pathogenesis of epithelial tumors (the first report) [in Japanese]. Tokyo Igakukai Zasshi. 30:1–43.
3. Yamagiwa K, Ichikawa K (1918). Experimental study of the pathogenesis of carcinoma. J Cancer Res. 3(1):1–29.
4. Fujiki H (2014). Gist of Dr. Katsusaburo Yamagiwa's papers entitled "Experimental study on the pathogenesis of epithelial tumors" (I to VI reports). Cancer Sci. 105(2):143–9. https://doi.org/10.1111/cas.12333 PMID:24313817
5. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A (2009). Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. 30(7):1073–81. https://doi.org/10.1093/carcin/bgp127 PMID:19468060
6. Taniguchi K, Karin M (2018). NF-κB, inflammation, immunity and cancer: coming of age. Nat Rev Immunol. 18(5):309–24. https://doi.org/10.1038/nri.2017.142 PMID:29379212
7. Medzhitov R (2010). Inflammation 2010: new adventures of an old flame. Cell. 140(6):771–6. https://doi.org/10.1016/j.cell.2010.03.006 PMID:20303867
8. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S (2016). Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 4(9):e609–16. https://doi.org/10.1016/S2214-109X(16)30143-7 PMID:27470177
9. Grivennikov SI, Greten FR, Karin M (2010). Immunity, inflammation, and cancer. Cell. 140(6):883–99. https://doi.org/10.1016/j.cell.2010.01.025 PMID:20303878
10. Shalapour S, Karin M (2015). Immunity, inflammation, and cancer: an eternal fight between good and evil. J Clin Invest. 125(9):3347–55. https://doi.org/10.1172/JCI80007 PMID:26325032
11. Gilmore TD, Starczynowski DT, Kalaitzidis D (2004). RELevant gene amplification in B-cell lymphomas? Blood. 103(8):3243–4, author reply 3244–5. https://doi.org/10.1182/blood-2003-11-4019 PMID:15070712
12. Sen R, Baltimore D (2006). Multiple nuclear factors interact with the immunoglobulin enhancer sequences. *Cell* 1986. 46: 705–716. J Immunol. 177(11):7485–96. PMID:17114415
13. Perkins ND (2007). Integrating cell-signalling pathways with NF-κB and IKK function. Nat Rev Mol Cell Biol. 8(1):49–62. https://doi.org/10.1038/nrm2083 PMID:17183360
14. Puar YR, Shanmugam MK, Fan L, Arfuso F, Sethi G, Tergaonkar V (2018). Evidence for the involvement of the master transcription factor NF-κB in cancer initiation and progression. Biomedicines. 6(3):E82. https://doi.org/10.3390/biomedicines6030082 PMID:30060453
15. Oeckinghaus A, Ghosh S (2009). The NF-κB family of transcription factors and its regulation. Cold Spring Harb Perspect Biol. 1(4):a000034. https://doi.org/10.1101/cshperspect.a000034 PMID:20066092
16. Sethi G, Tergaonkar V (2009). Potential pharmacological control of the NF-κB pathway. Trends Pharmacol Sci. 30(6):313–21. https://doi.org/10.1016/j.tips.2009.03.004 PMID:19446347
17. Sethi G, Shanmugam MK, Ramachandran L, Kumar AP, Tergaonkar V (2012). Multifaceted link between cancer and inflammation. Biosci Rep. 32(1):1–15. https://doi.org/10.1042/BSR20100136 PMID:21981137
18. Kaypee S, Sudarshan D, Shanmugam MK, Mukherjee D, Sethi G, Kundu TK (2016). Aberrant lysine acetylation in tumorigenesis: implications in the development of therapeutics. Pharmacol Ther. 162:98–119. https://doi.org/10.1016/j.pharmthera.2016.01.011 PMID:26808162
19. Shanmugam MK, Sethi G (2012). Role of epigenetics in inflammation-associated diseases. In: Kundu TK, editor. Epigenetics: development and disease. London, UK: Springer Dordrecht; pp. 627–58.
20. Crew KD, Neugut AI (2006). Epidemiology of gastric cancer. World J Gastroenterol. 12(3):354–62. https://doi.org/10.3748/wjg.v12.i3.354 PMID:16489633
21. Todoric J, Antonucci L, Karin M (2016). Targeting inflammation in cancer prevention and therapy. Cancer Prev Res (Phila). 9(12):895–905. https://doi.org/10.1158/1940-6207.CAPR-16-0209 PMID:27913448
22. O'Keefe SJ (2016). Diet, microorganisms and their metabolites, and colon cancer. Nat Rev Gastroenterol Hepatol. 13(12):691–706. https://doi.org/10.1038/nrgastro.2016.165 PMID:27848961
23. Bhatt AP, Redinbo MR, Bultman SJ (2017). The role of the microbiome in cancer development and therapy. CA Cancer J Clin. 67(4):326–44. https://doi.org/10.3322/caac.21398 PMID:28481406
24. Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, et al. (2012). Gut microbiota composition correlates with diet and health in the elderly. Nature. 488(7410):178–84. https://doi.org/10.1038/nature11319 PMID:22797518
25. Zinger A, Cho WC, Ben-Yehuda A (2017). Cancer and aging – the inflammatory connection. Aging Dis. 8(5):611–27. https://doi.org/10.14336/AD.2016.1230 PMID:28966805
26. Shanmugam MK, Lee JH, Chai EZ, Kanchi MM, Kar S, Arfuso F, et al. (2016). Cancer prevention and therapy through the modulation of transcription factors by bioactive natural compounds. Semin Cancer Biol. 40–41:35–47. https://doi.org/10.1016/j.semcancer.2016.03.005 PMID:27038646

3.6 Reproductive and hormonal factors
Important contributors to several cancer sites

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SUMMARY

- Reproductive and hormonal factors appear to have particular associations for different subtypes of cancers in women, including those defined by either histology or hormone receptor status.
- Use of oral contraceptives is related to substantial reductions in the risk of endometrial cancer and ovarian cancer, and the reduction in risk persists for extended durations after discontinuation of use. Use of oral contraceptives appears to be related to an increased risk of cervical cancer, consistent with growing evidence for a possible role of hormonal factors in cervical carcinogenesis.
- Obese women are at increased risk of postmenopausal breast cancer and endometrial cancer, presumably through hormonal mechanisms; further support for this derives from findings that obesity can affect risks associated with use of menopausal hormone therapy.
- Studies are beginning to emphasize the role of reproductive and hormonal factors in the etiology of some cancer types in men, although further studies are needed to clarify risk relationships.
- Recent advances in measuring endogenous hormones support that estrogens are important in the etiology of female breast cancer, endometrial cancer, and male breast cancer, and possibly advanced prostate cancer.

It is now well recognized that reproductive and hormonal factors play a major role in the etiology of many cancer types in women. This is particularly true for breast cancer, endometrial cancer, and ovarian cancer, in which such factors are likely to explain large proportions of disease occurrence. A few cancer types in men may also be influenced by hormonal factors, although the relationships are less well defined.

Female breast cancer

The role of parity in the etiology of breast cancer is well established. Parous women have approximately half the risk of nulliparous women, and multiparous women have even lower risk. Women with early age at first birth also have a reduced risk, and risk rises steadily with later ages at first birth. Women with a first birth at age 30 years or older are generally at higher risk than nulliparous women, presumably because of promotional effects of pregnancy on previously initiated cells in older mothers. These relationships are generally strongest for hormone receptor-positive tumours, and less conclusive effects have been found for other breast cancer subtypes [1]. Pregnancy has an effect on breast cancer risk only if it is a full-term pregnancy; there is little evidence for relationships with short-term pregnancies, including miscarriages and abortions.

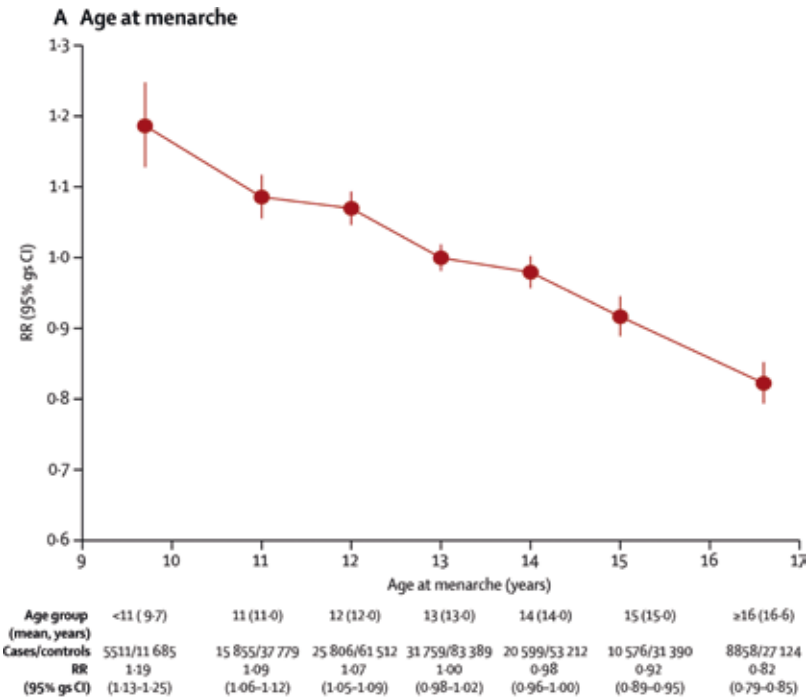
The reduced risk associated with parity may be further enhanced if a woman breastfeeds. However, the protection appears to be dependent on longer periods of breastfeeding; therefore, in most high-income countries, in which numbers of births are limited and each child is breastfed for a relatively short period, there is little evidence of a relationship of risk with breastfeeding. The most conclusive findings on the protective effects of breastfeeding derive from studies of women who have given birth to multiple children and have breastfed them for long periods (e.g. 2 years or more per child), leading to long durations of cumulative breastfeeding.

In contrast to the other established reproductive risk factors, use of oral contraceptives is not generally associated with risk of breast cancer, although there may be some increased risk in younger women as well as in those who have either used oral contraceptives recently or used them before a first birth (see Chapter 2.11).

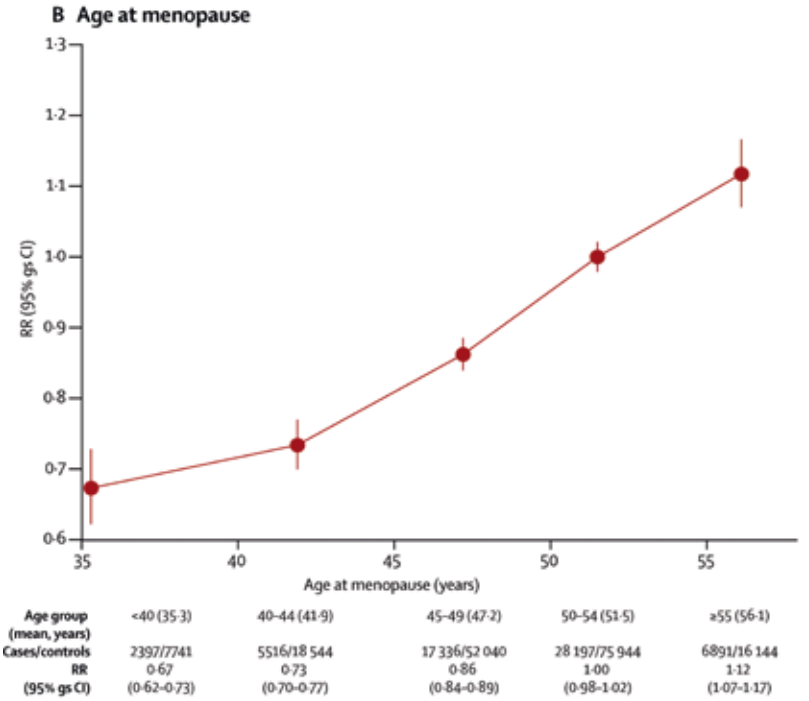
Menstrual factors are also predictive of risk. Early age at menarche and late age at natural menopause are associated with the highest risks, presumably reflecting in part an influence of ovulatory activity (Fig. 3.6.1) [2]. These relationships appear to be consistent across risk subgroups, including those defined

by use of exogenous hormones. Women who have an early surgical menopause involving removal of both ovaries have a lower risk; those who undergo this operation before age 40 years have approximately half the risk of those who have a natural menopause after age 55 years.

Fig. 3.6.1. Relative risk of breast cancer by (A) age at menarche and (B) age at menopause, based on multiple studies. Calculated stratifying by study, age, year of birth, parity, age at first birth, smoking, alcohol consumption, height, and current body mass index. CI, confidence interval; gs, group-specific; RR, relative risk.



Age group (mean, years)	<11 (9·7)	11 (11·0)	12 (12·0)	13 (13·0)	14 (14·0)	15 (15·0)	≥16 (16·6)
Cases/controls	5511/11 685	15 855/37 779	25 806/61 512	31 759/83 389	20 599/53 212	10 576/31 390	8858/27 124
RR (95% gs CI)	1·19 (1·13–1·25)	1·09 (1·06–1·12)	1·07 (1·05–1·09)	1·00 (0·98–1·02)	0·98 (0·96–1·00)	0·92 (0·89–0·95)	0·82 (0·79–0·85)



Age group (mean, years)	<40 (35·3)	40–44 (41·9)	45–49 (47·2)	50–54 (51·5)	≥55 (56·1)
Cases/controls	2397/7741	5516/18 544	17 336/52 040	28 197/75 944	6891/16 144
RR (95% gs CI)	0·67 (0·62–0·73)	0·73 (0·70–0·77)	0·86 (0·84–0·89)	1·00 (0·98–1·02)	1·12 (1·07–1·17)

FUNDAMENTALS

- Parity is strongly and negatively related to the risk of breast cancer, endometrial cancer, ovarian cancer, and cervical cancer, supporting the notion that hormonal factors are important contributors for these cancer sites. Breast cancer risk is further affected by the woman's age when her first child is born.
- Use of oral contraceptives is related to long-term reduced risks of endometrial cancer and ovarian cancer, but does not have a generalized effect on breast cancer risk. Although use of menopausal hormone therapy has been recognized for some time as being related to increased risks of breast cancer and endometrial cancer, it has been more difficult to resolve how changing prescribing patterns (including the addition of progestins to estrogen therapy) affect risk.
- A variety of menstrual factors, including age at menarche, age at menopause, and type of menopause, appear to be related to risk of breast cancer, endometrial cancer, and ovarian cancer.
- Additional support for the importance of hormonal factors derives from findings that obese women are at increased risk of postmenopausal breast cancer and endometrial cancer, and that obesity can affect the influence of exogenous hormones.
- Until recently, investigations that have attempted to assess the influence of endogenous hormones on various cancer sites have been hindered by the limitations of assays for measuring hormones.

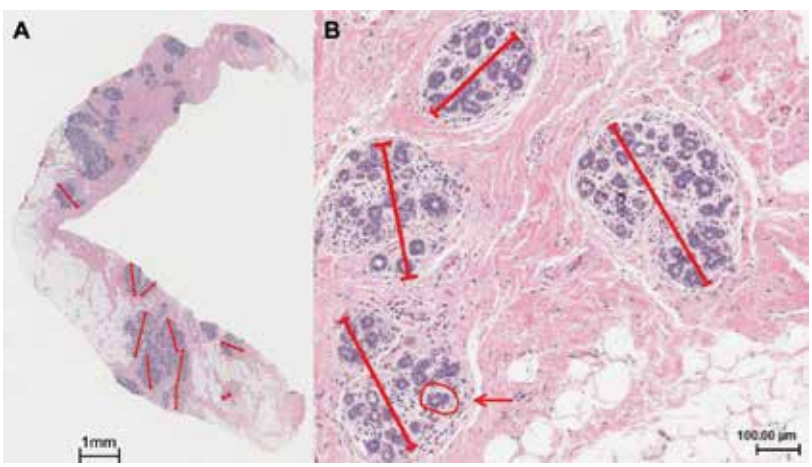
Reproductive and menstrual factors are major risk factors and can be used to estimate individual risks via the Breast Cancer Risk Assessment Tool (http://www.cancer.gov/bcrisktool/) and other risk prediction models. Despite the well-recognized role of reproductive and menstrual factors in breast cancer etiology, studies have been unable to relate these factors to specific underlying biological mechanisms. It is generally assumed that changes in endogenous hormonal profiles are involved, but additional research is needed to clarify the effects. It is also unclear how hormonally induced changes in breast tissue are involved. Recent attention has focused on the effects of parity on involution of lobules, the structures from which the majority of breast cancers are thought to arise (Fig. 3.6.2) [3].

The relationship of obesity with breast cancer risk is complex (see Chapter 2.7). Obesity is inversely related to risk of premenopausal-onset breast cancer and is directly associated with risk of postmenopausal breast cancer. Obesity-associated anovulation has been hypothesized as responsible for the decreased risk, and conversion of androgens to estrogens in adipose tissue appears to influence the increased risk.

Menopausal hormone use has been associated with increased breast cancer risk in postmenopausal women, and the highest risks have been observed in thin women. The type of hormones used is also a major predictor of risk; higher risks are observed for use of estrogen plus progestin than for use of unopposed estrogen therapy. This has been hypothesized as being due to mitotic influences of progestins on breast tissues.

Endogenous hormones are important predictors of breast cancer risk, although it has been difficult for studies to fully define relationships with either breast cancer risk or patterns of risk factors (see Chapter 5.9). This probably reflects difficulties in measuring hormones or the complexity of patterns of many interrelated markers, including not only estrogens but also androgens, progesterone, prolactin, and insulin-like growth factors. In addition, the importance of large inter-individual differences in metabolism, which may have etiological implications, is being increasing recognized. Pooling efforts have provided evidence that estrogens and androgens are directly related to both hormone receptor-positive and hormone receptor-negative breast cancers [4], and additional analyses that use more precise hormone measurement techniques may provide further clarity about relationships. Mass spectrometry–liquid chromatography assays that enable measurements of 15 individual estrogen metabolites have shown an important etiological role for parent estrogens and individual estrogens, as well as for certain hydroxylation pathways (Fig. 3.6.3) [5]. Additional research is needed to assess the influence of other endogenous hormones, such as androgens and progestogens, on risk, both overall and according to the hormone receptor status of the tumours.

Fig. 3.6.2. Assessment of terminal ductal lobular unit (TDLU) involution in the Susan G. Komen Tissue Bank. Three quantitative measures (TDLU count, TDLU span, and number of acini per TDLU) associated with reduced levels of TDLU involution were assessed. (A) Digital haematoxylin–eosin section with multiple TDLUs (TDLU count). For up to 10 TDLUs per section, the longest TDLU span was measured and the counts of acini per TDLU were categorized. (B) Representative TDLUs for which the longest TDLU span was measured. A representative acinus is circled in red and indicated with an arrow.

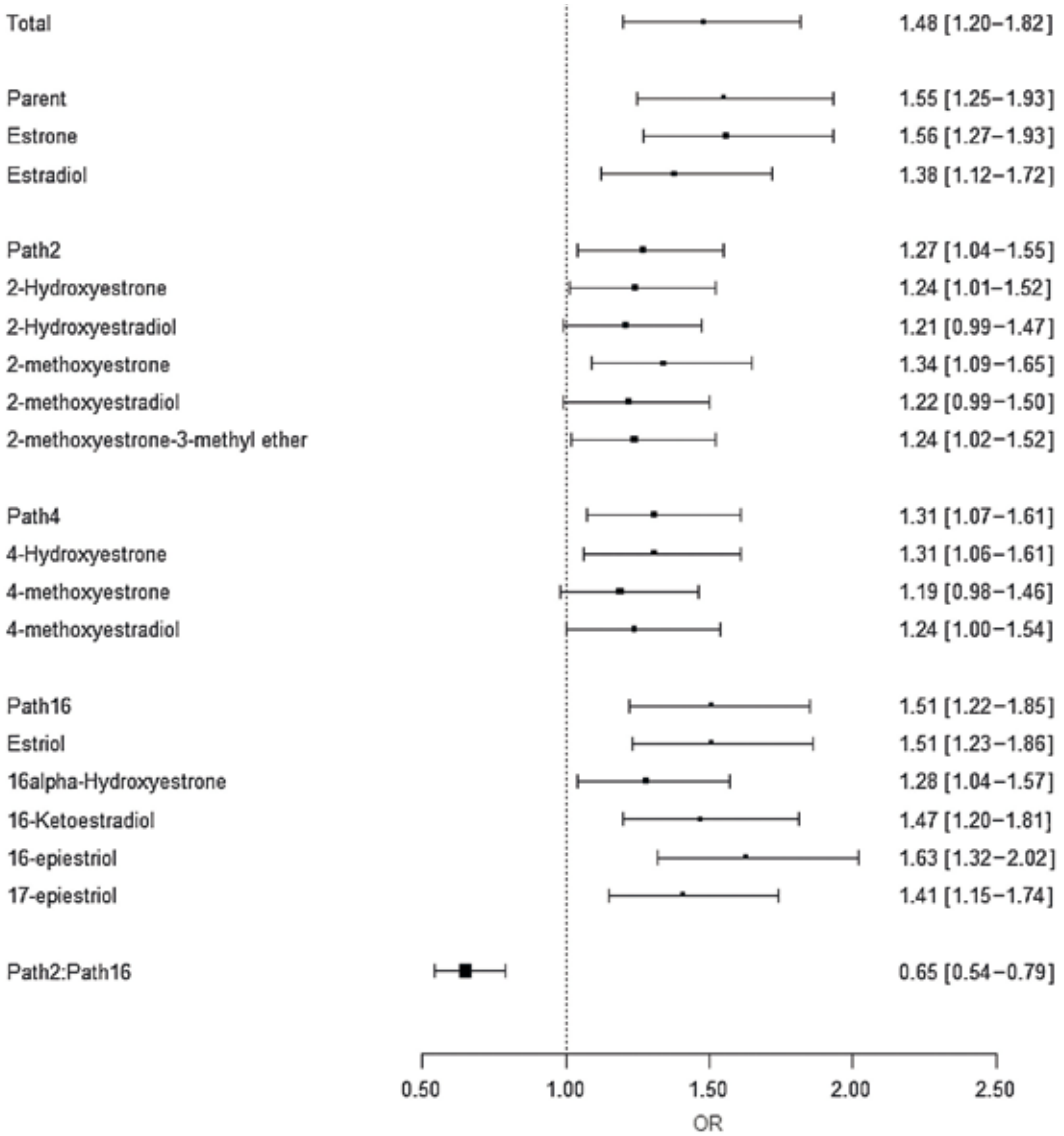


Endometrial cancer

Endometrial tissue is extremely hormonally responsive, and endometrial cancer is believed to arise as a result of estrogen stimulation that is unopposed by progestins. One of the strongest risk factors for postmenopausal-onset endometrial cancer is obesity (see Chapter 5.11), presumably reflecting the conversion of androstenedione to estrone in adipose tissue. Particularly high risks have also been noted for use of unopposed estrogen therapy, which has been associated with 2–10-fold increases in risk, depending on the duration of use and the woman's body size (higher relative risks are observed in thin women). Use of tamoxifen has also been strongly related to an increased risk of endometrial cancer.

In contrast to breast cancer, for which especially elevated risks are associated with use of estrogen plus progestin menopausal hormone therapy (combination therapy), endometrial cancer shows a favourable risk profile for such users. Data from the Women's Health Initiative clinical trial support that relative risks are substantially lower for users of combination therapy

Fig. 3.6.3. Odds ratios (ORs) and 95% confidence intervals comparing the risk of breast cancer in individuals with a higher analyte or pathway concentration (90th percentile) with that in individuals with a lower concentration (10th percentile).



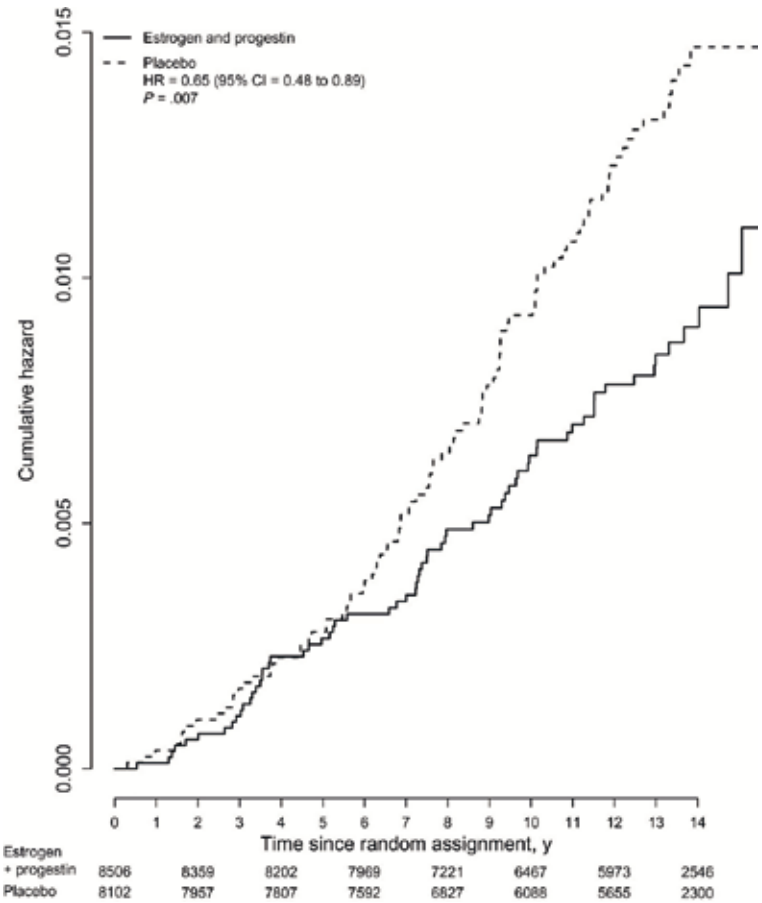
than for non-users of hormones (Fig. 3.6.4) [6].

These risks also appear to be modified by body mass, although in contrast to the situation for use of unopposed estrogen therapy, the greatest reductions in relative risks are seen in heavier women. Because of these complexities, more meaningful insights can be derived by a focus on absolute risks. The lowest risks are seen in thin women (either non-hormone users or users of continuous estrogen plus progestin therapy), and the highest risks are observed in obese non-hormone users (who are at higher risk than obese users of continuous estrogen plus progestin therapy), although the confidence intervals on these risks are often broad and overlapping (Fig. 3.6.5) [7]. The effects of combination therapy may also be influenced by how it is prescribed (estrogens given sequentially vs continuously), but studies are only beginning to investigate this issue.

Although use of sequential oral contraceptives (estrogen-only pills followed by progestin pills for a limited number of days) has been related to elevated risks of endometrial cancer in premenopausal women, for the more commonly used combined oral contraceptives (a combination of estrogen and progestin), use has been related to substantial reductions in risk. Long-term users have the lowest risk, and the reduction in risk persists for some time after discontinuation of use [8]. Although the progesterone content of the pills used may affect risk, studies have not been able to confirm this hypothesis.

Nulliparous women have high risks of developing endometrial

Fig. 3.6.4. Kaplan–Meier estimates of cumulative hazards of endometrial cancer in the Women's Health Initiative randomized trial of continuous combined estrogen plus progestin with the intention-to-treat principle. CI, confidence interval; HR, hazard ratio; y, years.



cancer, and multiparous women have the lowest risks, but no effect on risk has been demonstrated according to age at first birth. Instead, age at last birth or interval since last birth may be important contributors to risk, although studies are still attempting to understand these relationships. Early age at menarche and late age at menopause are even stronger risk factors for endometrial cancer than for breast cancer, presumably because these parameters indicate an enhanced opportunity for circulating estrogens to influence risk. Like for breast cancer, recent efforts have been made to develop individualized risk prediction models based on identified risk factors for endometrial cancer.

Although it is recognized that hormonal factors have a strong role in the etiology of endometrial cancer, relatively few studies have assessed the role of endogenous hormones in the etiology of endometrial cancer, and it has often been difficult to disentangle effects of endogenous hormones from those associated with obesity. A recent study showed that parent estrogens and individual estrogen metabolites all appear to exert uterotropic activity [9], but further studies are needed to clarify the effects on endometrial cancer risk of additional hormones, including androgens. In such studies, it will be important to distinguish patterns of risk according to specific tumour subtypes (e.g. type 1 or endometrioid vs the rarer type 2 endometrial tumours, including serous cancers). The tumour subtypes have been shown to be etiologically heterogeneous, and stronger relationships of hormonal risk factors (such as obesity and parity) are seen for type 1 tumours than for type 2 tumours.

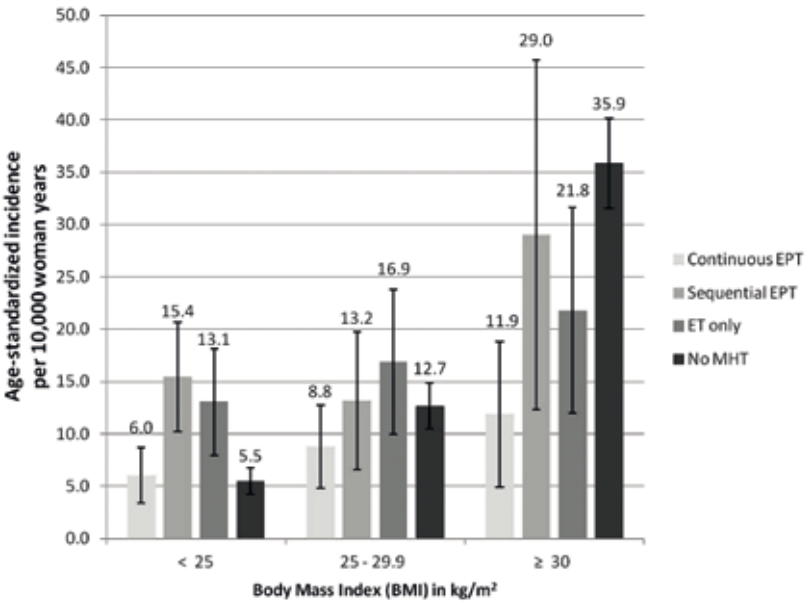
Ovarian cancer

Nulliparity is a well-recognized risk factor for ovarian cancer, as is infertility. Although there has been extensive controversy about the potential effects of fertility drugs, the latest studies suggest that the indications for use are more important than the drugs themselves (see Chapter 2.11). Endometriosis is a well-established predictor of certain types of ovarian cancer, including clear cell and endometrioid cancers (Table 3.6.1) [10]. Unlike for breast cancer and endometrial cancer, body size is not strongly related to risk of ovarian cancer, although it may have some modest effect for certain tumour subtypes.

Some studies have suggested elevated risks with early age at menarche and late age at menopause, but the results are not entirely consistent. Substantially reduced risks have been observed in women who have had a simple hysterectomy or tubal ligation. Although this finding may reflect detection of abnormalities and removal of ovaries during either of these procedures, more recent attention has focused on the effects of partial devascularization or partial removal of tubes, given increasing evidence of the tubal origin of many serous cancers.

Use of oral contraceptives is related to substantial reductions in the risk of ovarian cancer, particularly when long-term use is involved. However, use of menopausal hormones has been linked with increases in risk (Fig. 3.6.6) [11]. This has been most clearly demonstrated for unopposed estrogen therapy, but there is growing evidence that combined estrogen plus progestin therapy may also be linked with elevated risk [12].

Fig. 3.6.5. Age-standardized incidence of endometrial cancer by use of menopausal hormone therapy and body mass index, from the United States National Institutes of Health-AARP (NIH-AARP) Diet and Health Study. Error bars indicate 95% confidence interval on the age-standardized incidence rate. EPT, estrogen plus progestin therapy; ET, unopposed estrogen therapy; MHT, menopausal hormone therapy.



Although many of the identified risk factors for ovarian cancer are consistent with a protective effect of reduced ovulation, this does not appear to entirely explain all of the identified risk factors (see Chapter 5.12). Recent attention has focused on the possible role of hormonal and immunological factors (including inflammation) and their interplay.

Conflicting results have emerged about the respective roles of estrogens, androgens, follicle-stimulating hormone, sex hormone-binding globulin, and insulin-like growth factor [13]. Further investigation appears to be warranted, particularly with respect to specific ovarian cancer subtypes, especially serous versus non-serous tumours, for which there is growing evidence of etiological heterogeneity [14].

Cervical cancer

Infection with human papillomavirus (HPV) is recognized as a necessary cause of cervical cancer, but other co-factors are important (see Chapter 5.10). Although the relationship of reproductive factors with cervical cancer risk is controversial, one project that involved combining data from 25 epidemiological studies demonstrated that risk of invasive cervical cancer increased with the number of full-term pregnancies within each stratum of age at first full-term pregnancy, and vice versa (Fig. 3.6.7) [15].

The same investigation found an increased risk of cervical cancer related to current and long-term use of oral contraceptives. The relationship of risk with use of menopausal hormone therapy remains less clear. There is some evidence that endogenous sex steroids, particularly testosterone and estradiol, may play an etiological role [16], but it remains unclear how hormonal factors might interact with HPV. Studies are also needed to separately examine relationships for squamous cell cancers versus adenocarcinomas, given suggestions that adenocarcinomas may be more affected by hormonal risk

Table 3.6.1. Associations between history of endometriosis and the histological subtypes of ovarian cancer

Histological subtype	Stratified and adjusted OR[a] (95% CI)	*P* value
Invasive	1.46 (1.31–1.63)	< 0.0001
Clear cell	3.05 (2.43–3.84)	< 0.0001
Endometrioid	2.04 (1.67–2.48)	< 0.0001
Mucinous	1.02 (0.69–1.50)	0.93
High-grade serous	1.13 (0.97–1.32)	0.13
Low-grade serous	2.11 (1.39–3.20)	< 0.0001
Borderline	1.12 (0.93–1.35)	0.24
Mucinous	1.12 (0.84–1.48)	0.45
Serous	1.20 (0.95–1.52)	0.12

CI, confidence interval; OR, odds ratio

[a] Stratified by age (5-year categories) and ethnic origin (non-Hispanic White, Hispanic White, Black, Asian, other), and adjusted for duration of oral contraceptive use (never, < 2 years, 2–4.99 years, 5–9.99 years, ≥ 10 years) and parity (0, 1, 2, 3, ≥ 4). Pooled analysis of 13 ovarian cancer case–control studies: 1 in Australia, 3 in Europe, and 9 in the USA.

Fig. 3.6.6. Relative risk of ovarian cancer by duration of use in current and past users of hormone therapy. * Risk relative to never-users of hormone therapy, stratified by age at diagnosis, study, and body mass index, and adjusted for age at menopause, hysterectomy, oral contraceptive use, and parity. CI, confidence interval.

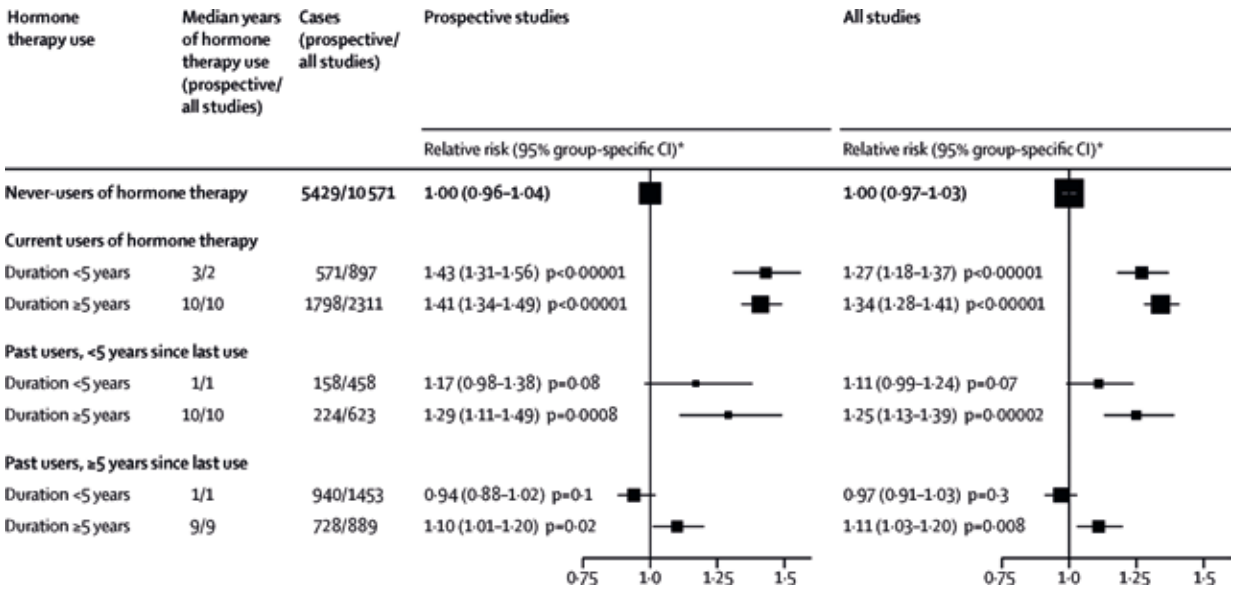
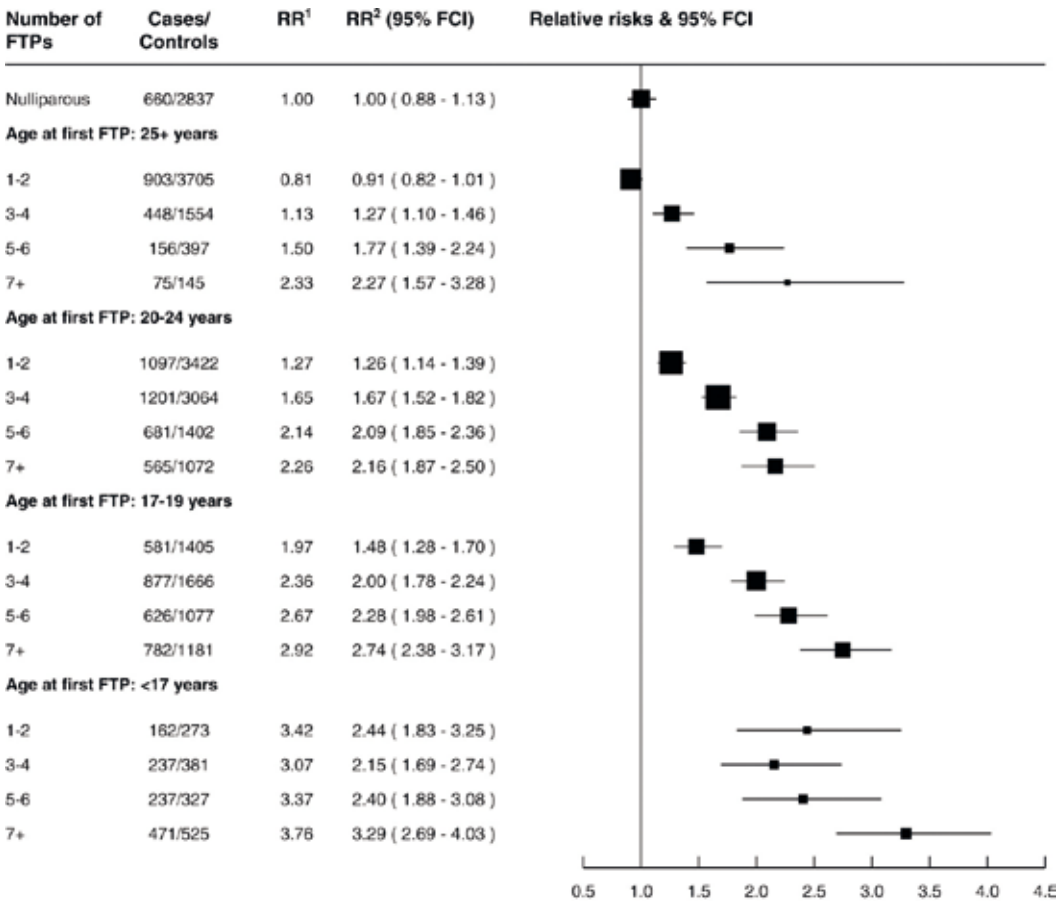


Fig. 3.6.7. Relative risks (RRs) of invasive cervical carcinoma and corresponding 95% floating confidence intervals (FCIs) by number of full-term pregnancies (FTPs) stratified by age at first FTP. [1] Conditioned on age and study or study centre. [2] As in [1], and conditioned on age at first sexual intercourse and lifetime number of sexual partners.



factors such as obesity and use of exogenous hormones.

Testicular cancer

Hormonal factors play a role in the etiology of testicular cancer, as evidenced by the rise in incidence starting at adolescence and a variety of risk factors, including height, subfertility, and possibly exposure to endocrine disrupters (see Chapter 5.14). Several risk factors also support an influence of exposures received in utero, including cryptorchidism, hypospadias, inguinal hernia, low birth weight, short gestational age, and being a twin, some of which may reflect the influence of endogenous hormones [17]. Recent studies have attempted to assess the role of endogenous hormones in the etiology of testicular cancer, but further studies are needed to fully understand the relationships.

Male breast cancer

The incidence of breast cancer in men is only about 1% that in women, complicating the evaluation of etiological factors. However, the few available studies appear to implicate several hormonally related risk factors, with suggestions of increased risks related to obesity, Klinefelter syndrome, and gynaecomastia (Table 3.6.2) [18]. Data are also beginning to emerge that implicate the importance of endogenous hormones (particularly estrogens) in the etiology of male breast cancer [19].

Prostate cancer

Prostate cancers respond well to anti-androgen therapies, and both surgical and medical castration results in substantial reductions in the risk of metastatic disease. Although it has been assumed that androgens play a role in the etiology of prostate cancer, studies to date have provided conflicting evidence of a role for any hormones as risk factors. One large pooling project showed no association between risk of prostate cancer and circulating concentrations of testosterone, calculated free testosterone, and conversion products; the major conversion product is dihydrotestosterone, to which testosterone is converted in the prostate by 5α-reductase (Fig. 3.6.8) [20]. The only evidence of association observed was an inverse relationship with sex hormone-binding globulin.

Use of finasteride reduces risk of prostate cancer by blocking the conversion of testosterone to dihydrotestosterone; use has also been associated with increases in estradiol levels. The Prostate Cancer Prevention Trial has shown substantial reductions in prostate cancer incidence associated with exposure to finasteride (https://www.cancer.gov/types/prostate/research/prostate-cancer-prevention-trial-qa). This has raised questions about whether estrogen levels may play a role in prostate cancer etiology (see Chapter 5.13). The fact that trial participants who developed prostate cancer while taking finasteride experienced higher-grade tumours has prompted interest in examining subgroup relationships. The most recent study that assessed such relationships observed a strong inverse association between the ratio of estradiol to testosterone and aggressive prostate cancer (Table 3.6.3) [21]. However, given the conflicting data from other studies on the role of both estrogens and androgens in the etiology of prostate cancer [22],

Table 3.6.2. Relationship of anthropometric and hormonal risk factors with risk of male breast cancer: results from the Male Breast Cancer Pooling Project

Factors	Odds ratio[a] (95% confidence interval)		
	Meta-analysis	Case–control studies	Cohort studies
Adult body mass index (kg/m^2)			
Lowest tertile, ≤ 24.6	1.00 (referent)	1.00 (referent)	1.00 (referent)
Middle tertile, 24.7–27.4	1.15 (1.00–1.33)	1.22 (1.02–1.46)	1.04 (0.81–1.32)
Highest tertile, > 27.4	1.30 (1.12–1.51)	1.39 (1.16–1.67)	1.16 (0.91–1.49)
Klinefelter syndrome			
No	1.00 (referent)	1.00 (referent)	1.00 (referent)
Yes	24.73 (8.94–68.38)	22.30 (1.98–251.70)	25.28 (8.24–77.54)
Gynaecomastia			
No	1.00 (referent)	1.00 (referent)	1.00 (referent)
Yes	9.78 (7.52–12.71)	14.57 (10.13–20.96)	6.34 (4.34–9.27)

[a] Estimated via unconditional logistic regression, with adjustment for study and age.

additional studies are needed to clarify the relationship of hormones to prostate cancer risk, both overall and according to tumour subtypes.

Other cancer types

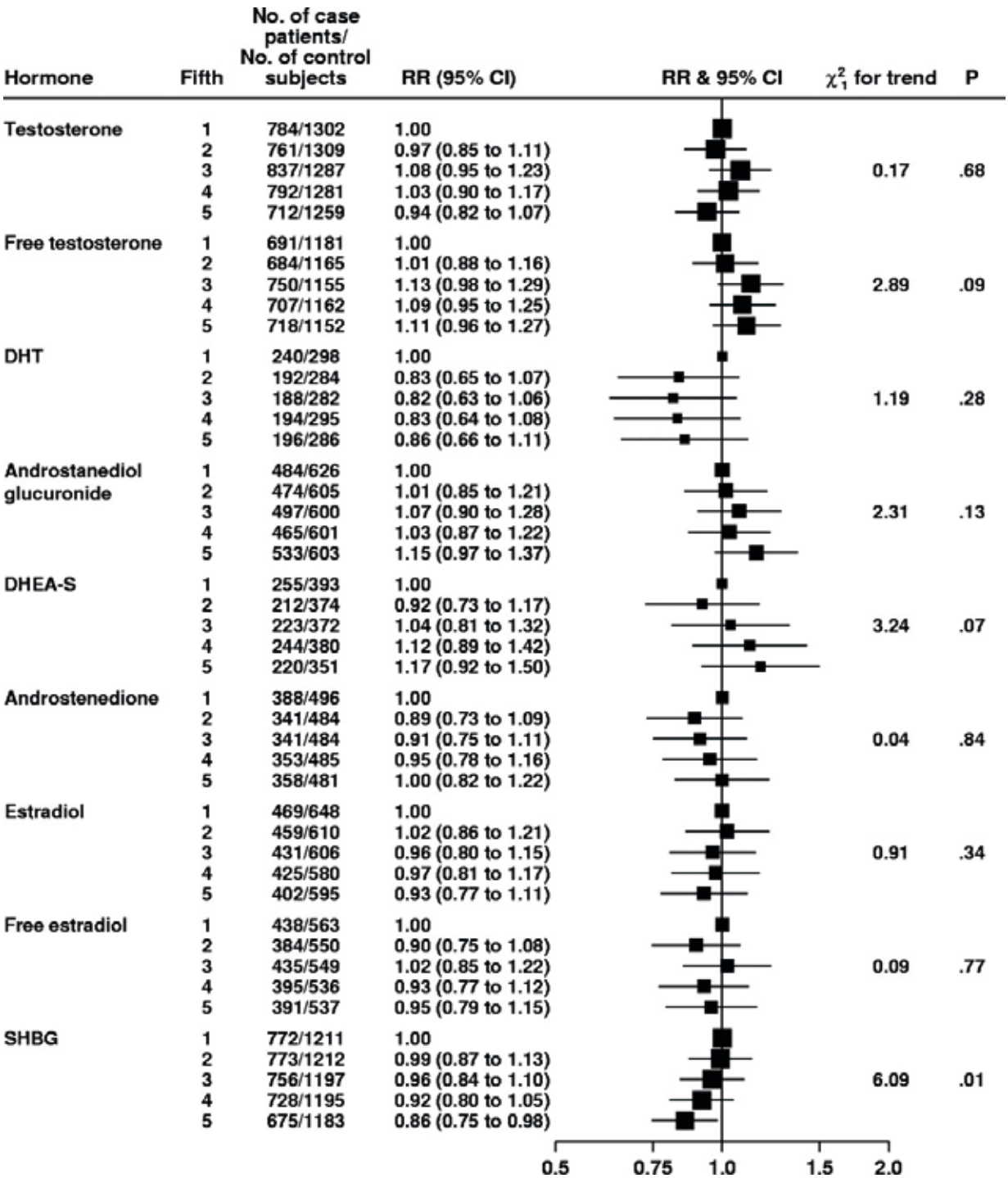
Although some studies have suggested possible influences of various reproductive and hormonal factors on other cancer types, there are many inconsistent findings. Findings with respect to some of the better studied cancer types, including cancers of the colorectum [23], liver [24], and lung [25], are particularly difficult to decipher. Studies have also attempted to assess whether reproductive and hormonal factors are associated with the risk of cancers of the stomach, thyroid, and central nervous system as well as melanomas, again without conclusive results.

Table 3.6.3. Associations between circulating sex steroid hormone concentrations and aggressive prostate cancer

Estrogen and estrogen metabolism measures	Odds ratio[a] (95% confidence interval)				P_{trend}
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
All estrogens and estrogen metabolites	1.00	1.27 (0.72–2.23)	1.28 (0.72–2.27)	0.84 (0.46–1.54)	0.65
2-Hydroxylation pathway	1.00	1.53 (0.87–2.70)	1.27 (0.71–2.28)	0.94 (0.51–1.72)	0.69
2-Hydroxylation pathway catechols	1.00	1.35 (0.75–2.41)	1.63 (0.92–2.87)	0.87 (0.47–1.62)	0.95
2-Hydroxyestrone	1.00	1.48 (0.82–2.65)	1.49 (0.84–2.64)	0.91 (0.49–1.68)	0.89
2-Hydroxyestradiol	1.00	1.23 (0.70–2.16)	0.94 (0.52–1.68)	0.92 (0.52–1.65)	0.79
2-Hydroxylation pathway methylated catechols	1.00	0.54 (0.30–0.98)	0.71 (0.41–1.24)	0.59 (0.33–1.06)	0.14
2-Methoxyestrone	1.00	0.47 (0.26–0.85)	0.65 (0.37–1.13)	**0.53 (0.29–0.94)**	0.06
2-Methoxyestradiol	1.00	1.07 (0.61–1.88)	0.96 (0.54–1.70)	0.80 (0.44–1.45)	0.38
2-Hydroxyestrone-3-methyl ether	1.00	0.75 (0.42–1.33)	0.65 (0.36–1.15)	0.82 (0.47–1.44)	0.34
4-Hydroxylation pathway	1.00	0.82 (0.46–1.45)	1.13 (0.65–1.97)	0.63 (0.34–1.14)	0.33
4-Hydroxyestrone	1.00	1.85 (1.05–3.28)	1.20 (0.66–2.17)	1.07 (0.58–1.97)	0.89
4-Hydroxylation pathway methylated catechols	1.00	0.63 (0.32–1.27)	0.60 (0.30–1.20)	0.54 (0.27–1.10)	0.09
4-Methoxyestrone	1.00	0.48 (0.24–0.97)	0.67 (0.34–1.30)	**0.45 (0.22–0.92)**	0.08
4-Methoxyestradiol	1.00	0.58 (0.29–1.17)	0.70 (0.36–1.37)	0.52 (0.25–1.06)	0.12
16-Hydroxylation pathway	1.00	1.02 (0.58–1.81)	1.04 (0.59–1.83)	0.76 (0.42–1.38)	0.43
16α-Hydroxyestrone	1.00	1.54 (0.86–1.77)	1.73 (0.97–3.07)	0.84 (0.44–1.58)	0.87
Estriol	1.00	1.00 (0.57–1.75)	0.77 (0.43–1.38)	0.82 (0.46–1.49)	0.33
17-Epiestriol	1.00	0.73 (0.41–1.30)	0.85 (0.48–1.50)	0.83 (0.47–1.47)	0.72
16-Ketoestradiol	1.00	1.23 (0.69–2.19)	1.41 (0.80–2.48)	0.87 (0.47–1.60)	0.80
16-Epiestriol	1.00	0.75 (0.42–1.34)	0.75 (0.42–1.34)	0.72 (0.41–1.28)	0.30
Estrogen metabolic pathway ratios					
2-Hydroxylation pathway:parent estrogens	1.00	1.54 (0.86–2.76)	0.85 (0.45–1.60)	1.69 (0.95–3.02)	0.24
4-Hydroxylation pathway:parent estrogens	1.00	1.11 (0.62–2.01)	1.40 (0.79–2.47)	1.14 (0.63–2.05)	0.51
16-Hydroxylation pathway:parent estrogens	1.00	1.32 (0.74–2.35)	0.98 (0.55–1.77)	0.99 (0.55–1.78)	0.71
2-Hydroxylation pathway:16-hydroxylation pathway	1.00	1.31 (0.71–2.42)	1.73 (0.96–3.12)	1.53 (0.84–2.79)	0.10
2-Hydroxyestrone:16-hydroxyestrone	1.00	1.24 (0.65–2.37)	**1.87 (1.01–3.44)**	**2.44 (1.34–4.45)**	**0.001**
2-Hydroxylation pathway:4-hydroxylation pathway	1.00	1.41 (0.78–2.52)	1.09 (0.61–1.98)	1.29 (0.72–2.31)	0.62
4-Hydroxylation pathway:16-hydroxylation pathway	1.00	1.14 (0.63–2.03)	1.18 (0.66–2.10)	1.27 (0.71–2.27)	0.42
2-Hydroxylation pathway methylated catechols:catechols	1.00	1.12 (0.65–1.94)	0.56 (0.31–1.02)	0.73 (0.41–1.30)	0.08
4-Hydroxylation pathway methylated catechols:catechols	1.00	0.60 (0.30–1.22)	1.01 (0.52–1.94)	**0.37 (0.17–0.80)**	0.08

[a] Adjusted for age at blood draw, body mass index, and sex hormone-binding globulin. Boldface indicates findings that are statistically significant.

Fig. 3.6.8. Association between risk of prostate cancer and increasing fifths of hormone concentrations, from a collaborative analysis of 18 prospective studies. The position of each square indicates the magnitude of the relative risk (RR), and the area of the square is proportional to the amount of statistical information available. The length of the horizontal line through the square indicates the 95% confidence interval (CI). The chi-square 1 degree of freedom statistic for linear trend (χ^2_1 for trend) is calculated by replacing the categorical variables with a continuous variable scored as 0, 0.25, 0.5, 0.75, and 1. The *P* value was two-sided for statistical significance of χ^2_1 for trend. DHEA-S, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; SHBG, sex hormone-binding globulin.



References

1. Anderson KN, Schwab RB, Martinez ME (2014). Reproductive risk factors and breast cancer subtypes: a review of the literature. Breast Cancer Res Treat. 144(1):1–10. https://doi.org/10.1007/s10549-014-2852-7 PMID:24477977
2. Collaborative Group on Hormonal Factors in Breast Cancer (2012). Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 13(11):1141–51. https://doi.org/10.1016/S1470-2045(12)70425-4 PMID:23084519
3. Figueroa JD, Pfeiffer RM, Patel DA, Linville L, Brinton LA, Gierach GL, et al. (2014). Terminal duct lobular unit involution of the normal breast: implications for breast cancer etiology. J Natl Cancer Inst. 106(10):dju286. https://doi.org/10.1093/jnci/dju286 PMID:25274491
4. James RE, Lukanova A, Dossus L, Becker S, Rinaldi S, Tjønneland A, et al. (2011). Postmenopausal serum sex steroids and risk of hormone receptor-positive and -negative breast cancer: a nested case-control study. Cancer Prev Res (Phila). 4(10):1626–35. https://doi.org/10.1158/1940-6207.CAPR-11-0090 PMID:21813404
5. Sampson JN, Falk RT, Schairer C, Moore SC, Fuhrman BJ, Dallal CM, et al. (2017). Association of estrogen metabolism with breast cancer risk in different cohorts of postmenopausal women. Cancer Res. 77(4):918–25. https://doi.org/10.1158/0008-5472.CAN-16-1717 PMID:28011624
6. Chlebowski RT, Anderson GL, Sarto GE, Haque R, Runowicz CD, Aragaki AK, et al. (2015). Continuous combined estrogen plus progestin and endometrial cancer: the Women's Health Initiative randomized trial. J Natl Cancer Inst. 108(3):djv350. https://doi.org/10.1093/jnci/djv350 PMID:26668177
7. Trabert B, Wentzensen N, Yang HP, Sherman ME, Hollenbeck AR, Park Y, et al. (2013). Is estrogen plus progestin menopausal hormone therapy safe with respect to endometrial cancer risk? Int J Cancer. 132(2):417–26. https://doi.org/10.1002/ijc.27623 PMID:22553145
8. Collaborative Group on Epidemiological Studies on Endometrial Cancer (2015). Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 16(9):1061–70. https://doi.org/10.1016/S1470-2045(15)00212-0 PMID:26254030
9. Brinton LA, Trabert B, Anderson GL, Falk RT, Felix AS, Fuhrman BJ, et al. (2016). Serum estrogens and estrogen metabolites and endometrial cancer risk among postmenopausal women. Cancer Epidemiol Biomarkers Prev. 25(7):1081–9. https://doi.org/10.1158/1055-9965.EPI-16-0225 PMID:27197275
10. Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, et al.; Ovarian Cancer Association Consortium (2012). Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol. 13(4):385–94. https://doi.org/10.1016/S1470-2045(11)70404-1 PMID:22361336
11. Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, Peto R; Collaborative Group on Epidemiological Studies of Ovarian Cancer (2015). Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet. 385(9980):1835–42. https://doi.org/10.1016/S0140-6736(14)61687-1 PMID:25684585
12. Trabert B, Wentzensen N, Yang HP, Sherman ME, Hollenbeck A, Danforth KN, et al. (2012). Ovarian cancer and menopausal hormone therapy in the NIH-AARP Diet and Health Study. Br J Cancer. 107(7):1181–7. https://doi.org/10.1038/bjc.2012.397 PMID:22929888
13. Brown SB, Hankinson SE (2015). Endogenous estrogens and the risk of breast, endometrial, and ovarian cancers. Steroids. 99(Pt A):8–10. https://doi.org/10.1016/j.steroids.2014.12.013 PMID:25555473
14. Wentzensen N, Poole EM, Trabert B, White E, Arslan AA, Patel AV, et al. (2016). Ovarian cancer risk factors by histologic subtype: an analysis from the Ovarian Cancer Cohort Consortium. J Clin Oncol. 34(24):2888–98. https://doi.org/10.1200/JCO.2016.66.8178 PMID:27325851
15. International Collaboration of Epidemiological Studies of Cervical Cancer (2006). Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. Int J Cancer. 119(5):1108–24. https://doi.org/10.1002/ijc.21953 PMID:16570271
16. Rinaldi S, Plummer M, Biessy C, Castellsagué X, Overvad K, Krüger Kjær S, et al. (2011). Endogenous sex steroids and risk of cervical carcinoma: results from the EPIC study. Cancer Epidemiol Biomarkers Prev. 20(12):2532–40. https://doi.org/10.1158/1055-9965.EPI-11-0753 PMID:21994406
17. McGlynn KA, Trabert B (2012). Adolescent and adult risk factors for testicular cancer. Nat Rev Urol. 9(6):339–49. https://doi.org/10.1038/nrurol.2012.61 PMID:22508459
18. Brinton LA, Cook MB, McCormack V, Johnson KC, Olsson H, Casagrande JT, et al.; European Rare Cancer Study Group (2014). Anthropometric and hormonal risk factors for male breast cancer: Male Breast Cancer Pooling Project results. J Natl Cancer Inst. 106(3):djt465. https://doi.org/10.1093/jnci/djt465 PMID:24552677
19. Brinton LA, Key TJ, Kolonel LN, Michels KB, Sesso HD, Ursin G, et al. (2015). Prediagnostic sex steroid hormones in relation to male breast cancer risk. J Clin Oncol. 33(18):2041–50. https://doi.org/10.1200/JCO.2014.59.1602 PMID:25964249
20. Roddam AW, Allen NE, Appleby P, Key TJ; Endogenous Hormones and Prostate Cancer Collaborative Group (2008). Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst. 100(3):170–83. https://doi.org/10.1093/jnci/djm323 PMID:18230794
21. Black A, Pinsky PF, Grubb RL 3rd, Falk RT, Hsing AW, Chu L, et al. (2014). Sex steroid hormone metabolism in relation to risk of aggressive prostate cancer. Cancer Epidemiol Biomarkers Prev. 23(11):2374–82. https://doi.org/10.1158/1055-9965.EPI-14-0700 PMID:25178985
22. Boyle P, Koechlin A, Bota M, d'Onofrio A, Zaridze DG, Perrin P, et al. (2016). Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis. BJU Int. 118(5):731–41. https://doi.org/10.1111/bju.13417 PMID:26779889
23. Rennert G (2017). Reproductive factors, hormones and colorectal cancer-still unresolved. Br J Cancer. 116(1):1–3. https://doi.org/10.1038/bjc.2016.388 PMID:27898659
24. Zhong GC, Liu Y, Chen N, Hao FB, Wang K, Cheng JH, et al. (2016). Reproductive factors, menopausal hormone therapies and primary liver cancer risk: a systematic review and dose-response meta-analysis of observational studies. Hum Reprod Update. 23(1):126–38. https://doi.org/10.1093/humupd/dmw037 PMID:27655589
25. Siegfried JM, Stabile LP (2014). Estrogenic steroid hormones in lung cancer. Semin Oncol. 41(1):5–16. https://doi.org/10.1053/j.seminoncol.2013.12.009 PMID:24565577

3.7 Metabolic change and metabolomics
Emerging approaches and new insights

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SUMMARY

- Metabolomics has been applied to blood, tissue, and other biospecimens in cancer research. Comparison of metabolic profiles in tumour samples and in normal tissues leads to the identification of metabolic pathways that are more specific for tumours.
- The metabolites that are most commonly reported as cancer discriminants in case–control studies include various amino acids, nucleotides, polyamines, sugars, organic acids from the tricarboxylic acid cycle, and bile acids.
- In the past 5 years, 15 prospective metabolomics studies on cancers of the colorectum, liver, pancreas, prostate, and breast have been published, with the number of case–control pairs varying from 100 to more than 1000.
- Prospective studies that show associations of blood metabolites several years before diagnosis with risk of cancer suggest new pathophysiological mechanisms that lead to cancer.
- Metabolomics is emerging an essential tool, complementary to genomics, transcriptomics, and proteomics, to identify novel biomarkers for cancer and to better understand cancer etiology.

Metabolism refers to the sum of a large number of chemical reactions that occur in biological tissues. These reactions involve several thousands of metabolites, organized in hundreds of metabolic pathways. More than 18 000 metabolites have been detected in human tissues or biofluids, and about 80 000 have been predicted but still await precise characterization [1]. The totality of these metabolites constitutes the metabolome.

Compared with the genome, the epigenome, the proteome, and the transcriptome, the metabolome is the most downstream expression or "readout" of the phenotype. A single determination of the metabolome defines metabolic phenotypes that characterize an individual at a given time in their life. Metabolic phenotypes vary between individuals and within individuals (e.g. repeated samples over time) according to diverse factors, such as genotype, age, body mass index, disease status, physical exercise, diet, and other environmental factors. Metabolic phenotypes can be measured in biofluids or tissues, including, for example, tumour tissues, and they provide valuable information on the mechanisms that link metabolism and diseases.

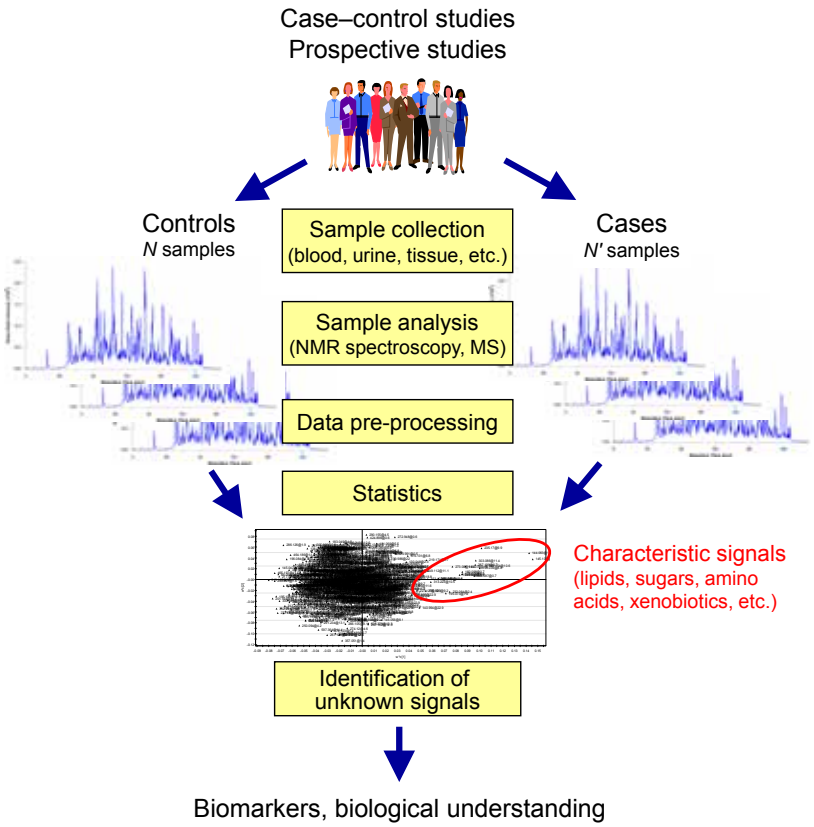
Metabolomics as a powerful tool to characterize metabolic phenotypes

Metabolomics has been defined as the quantitative measurement of the multivariate metabolic responses of a cell, tissue, or organism to pathophysiological stimuli or genetic modification [2]. Metabolomics was initially proposed as an approach to compare metabolic profiles in various biological samples – for example, in samples from individuals with specific diseases compared with those from healthy subjects (Fig. 3.7.1).

Typically, samples are analysed using nuclear magnetic resonance (NMR) spectroscopy or mass spectrometry (MS), two universal analytical techniques that are able to measure a multiplicity of organic compounds in complex matrices such as blood, urine, or tissues. NMR spectroscopy is a robust method that is well adapted to the analysis of large series of samples. However, MS is a much more sensitive technique that enables the measurement of hundreds to thousands of metabolites in a single sample. For this reason, it is now widely used in metabolomics studies.

These techniques can be applied to various biospecimens, such as blood, urine, tissue, saliva, faecal samples, or hair. Although many metabolites are shared between these matrices, they also differ in some aspects, such as ease of collection, chemical composition, stability during storage, and intra-individual reproducibility in a particular individual over time. The selection of a matrix or matrices will depend on the particular study and its objectives.

Fig. 3.7.1. Metabolomics workflow. MS, mass spectrometry; NMR, nuclear magnetic resonance.



FUNDAMENTALS

- Metabolic profiles are defined by the nature and concentrations of low-molecular-weight compounds, which are naturally present in human biospecimens such as blood, urine, or tissues. These compounds are products of the metabolism and are described as metabolites. Metabolic profiles characterize the human phenotypes.
- Metabolomics compares metabolic profiles in various individuals. When applied to people at risk of developing cancer and to healthy subjects, it provides new data on metabolic pathways that contribute to cancer etiology.
- Recent applications of metabolomics to cancer epidemiology have shown that various metabolic pathways are influenced by cancers, and some of them are causally linked to cancer development.
- Characterization of these metabolic changes is applied to the identification of new biomarkers for early detection of cancer and new risk factors for cancer.

After data acquisition, metabolite levels are statistically compared in various groups of individuals to identify metabolites that vary in their concentrations in any given condition. Data are interpreted on the basis of current knowledge of factors that can influence concentrations of these metabolites and the corresponding metabolic pathways. Novel hypotheses on mechanisms that lead to diseases can be generated, and new biomarkers for diagnosis, prognosis, or disease susceptibility can be discovered.

Two different MS-based metabolomics approaches are commonly used: the targeted and untargeted approaches. In targeted metabolomics, a limited number of metabolites (typically 50–200), defined a priori, are measured by MS against calibration curves for each metabolite measured. These metabolites generally belong to specific chemical classes, such as amino acids, bile acids, fatty acids, and lipids. In untargeted metabolomics, thousands of metabolites can be detected by MS, and the only limit to the number of metabolites measured is the sensitivity of the analytical instrument. The large volume of information collected makes this approach ideal for biomarker discovery studies [3].

However, untargeted metabolomics also has some limitations. The first is that despite the large number of metabolites that can be measured in a single analytical run, no single method is able to comprehensively measure the metabolome. Combinations of methods are often recommended to maximize analytical coverage.

In addition, targeted MS assays may be needed to measure compounds that are present at low concentrations. The large number of compounds measured makes calibration with chemical standards impossible, and therefore measurements for any given metabolite are expressed in study-based relative, rather than absolute, concentrations. This means that specific procedures are required to monitor the stability of the response of the mass spectrometer over the analysis of large series of samples (typically a few hundred to a few thousand) and to check the quality of the data.

A second important limitation of untargeted metabolomics is related to the identification of the metabolites detected. There are about 8000 known metabolites in blood, and about 1000 of those can be identified in untargeted metabolomics experiments. Many more signals are detected but are still unknown, because of the lack of reference mass spectra in metabolite databases and of commercial standards needed for their identification.

Applications of metabolomics to understanding cancer development

Currently, applications of metabolomics to cancer research are quite diverse. Tumour samples have been compared with normal tissues to identify metabolites that vary in their concentrations in the two types of tissues. Metabolic alterations in tumour samples were investigated in 11 studies for 7 cancer types, and a meta-analysis was performed of the results from each individual study [4]. Some metabolites were differentially abundant in tumour samples and normal tissues for multiple cancer types; these included taurine, acylcarnitine, kynurenine, and lactate, reflecting common alterations in pathways notably related to sugar metabolism, glutathione metabolism, and fatty acid biosynthesis. Similarly, the comparison of metabolic profiles of 60 primary cancer cell lines from 9 tumour types showed that several pathways were commonly affected in the different cell lines, and that glycine was highly correlated with rate of proliferation [5], leading to the recognition of the oncogenic role of glycine decarboxylase.

Metabolomics and fluxomics have been applied to tumour cell cultures to identify metabolic alterations and adaptations, which are now recognized as a hallmark of cancer [6]. As an example, the systematic overexpression of individual enzymes in the 12 steps linking extracellular glucose to excreted lactate combined with flux analysis led to the identification of 4 steps in the pathway that enhance glycolysis in the tumour cell and underlie the Warburg effect [7].

Metabolomics is also used to compare metabolic profiles of cells treated with various enzyme inhibitors or drugs. Koningic acid was identified as a highly specific inhibitor of glyceraldehyde 3-phosphate dehydrogenase, a rate-controlling enzyme in the glycolytic pathway, with limited perturbations of other metabolic pathways [8].

Initial applications of metabolomics to cancer epidemiology were case–control studies of small sample size aimed at the identification of biomarkers for diagnosis, prognosis, and response to therapy [9,10]. Results of 106 case–control studies were systematically analysed, showing that the cancer discriminants most commonly reported in blood or urine samples were various amino acids, nucleotides, polyamines, sugars, organic acids from the tricarboxylic acid cycle, bile acids, and closely related metabolites in their respective metabolic pathways [10]. Many of these metabolites are affected by different types of cancer, whereas others appear to be more specific for a particular cancer type; for example, bilirubin and bile acids are associated with hepatocellular carcinoma.

Most of these metabolites are common, universally occurring metabolites, which can also be influenced by various confounding factors, such as other diseases, age, or body mass index (see Chapter 2.7). Therefore, there is little likelihood that any of these metabolites can be used on their own as a biomarker for diagnosis, but they may have applications in the context of panels made up of several metabolites, proteins, and/or clinical biomarkers. A combination of three serum metabolites differentiated with high accuracy between individuals with low-grade bladder cancer and healthy controls, with a receiver operating characteristic (ROC) area under the curve (AUC) value of 0.99, and between individuals with high-grade bladder cancer and those with low-grade bladder cancer (ROC AUC, 0.96) [11].

Less-common biomarkers, which are often present at low concentrations in blood or urine, may be more specific for a particular cancer type and better predictors of cancer or of specific stages of the cancer. Several such markers were identified in untargeted metabolomics studies using high-resolution MS.

A conjugated steroid, 27-nor-5β-cholestane-3,7,12,24,25 pentol glucuronide, was significantly upregulated in the serum of women with epithelial ovarian cancer in both early-stage and late-stage patients when compared with healthy women or women with benign ovarian tumours [12]. Compared with α-fetoprotein, phenylalanyl-tryptophan and glycocholate were better able to differentiate individuals with hepatocellular carcinoma from those with cirrhosis, with ROC AUC values greater than 0.89 [13]. These two metabolites also had higher diagnostic performance than α-fetoprotein for early-stage hepatocellular carcinoma.

In a similar metabolomics study, several hydroxylated long-chain fatty acids with anti-inflammatory properties were identified and found to be downregulated in serum samples from colorectal cancer cases in three independent groups of patients in Japan and the USA [14]. Two of these fatty acids were good predictors of colorectal cancer cases, with ROC AUC values ranging from 0.85 to 0.93. A later study in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort confirmed the low concentrations of these two fatty acids in pre-diagnostic samples of subjects who developed colorectal cancer [15]. The differences in the levels of the fatty acids between cases and controls were seen 3–7 years before diagnosis, suggesting possible clinical applications as early biomarkers of disease.

Applications of metabolomics to prospective epidemiological studies are relatively recent. The earliest application of metabolomics within a prospective study involved 189 individuals who developed type 2

diabetes and 189 matched controls from the Framingham Offspring Study [16]. Among 61 metabolites measured at baseline by MS, 5 metabolites (leucine, isoleucine, valine, tyrosine, and phenylalanine) were associated with risk of type 2 diabetes [16]. Subsequently, more studies were performed on risk of type 2 diabetes, and a recent meta-analysis of results from eight original publications showed consistent associations of levels of these five amino acids with the risk of developing type 2 diabetes [17].

In the past 5 years, 15 prospective metabolomics studies on cancers of the colorectum, liver, pancreas, prostate, and breast have been published, with the number of case–control pairs varying from 100 to more than 1000. All of the studies used blood samples that were analysed by NMR spectroscopy or MS.

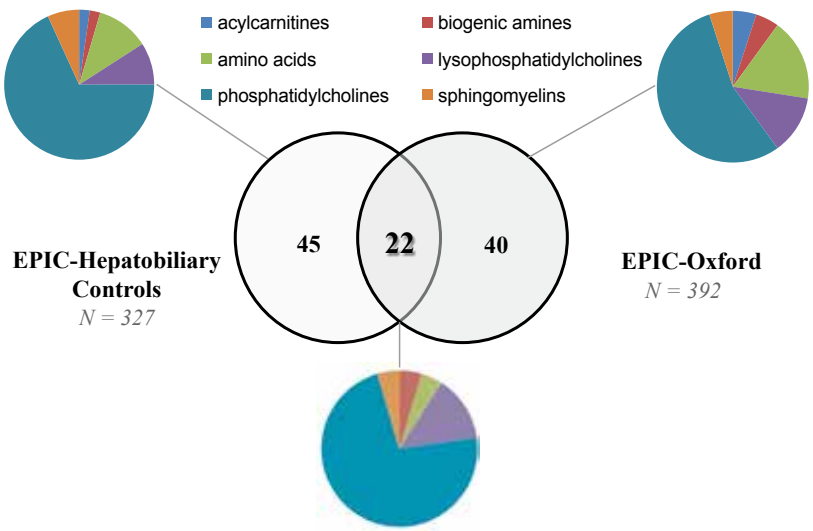
In a case–control study on colorectal cancer nested in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort, 676 metabolites, including 447 metabolites of known identity, were measured [18]. The bile acid glycochenodeoxycholate was associated with risk of colorectal cancer in women. In a case–control study nested in the EPIC cohort, several metabolites related to amino acid, lipid, and carbohydrate metabolism were associated with risk of hepatocellular carcinoma [19,20]. In a prospective study involving subjects from four cohorts in the USA (453 cases and 898 matched controls), 83 metabolites were measured; three branched-chain amino acids – leucine, isoleucine, and valine – were associated with risk of pancreatic cancer, and these associations were independent of diabetes development [21]. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study and the EPIC study, several metabolites related to energy and lipid metabolism were associated with risk of prostate cancer [22,23].

These prospective studies, which show associations of blood metabolites several years before diagnosis with risk of cancer, suggest new pathophysiological mechanisms that lead to cancer. Such studies face two main challenges. First, few of these results have yet been replicated in independent cohorts [3,12]. They will need to be confirmed in future studies, as has been done for type 2 diabetes. Second, complementary approaches will be needed to interpret these new data. The combination of metabolomics with other –omics will help to establish the causal implications of specific metabolites or metabolic pathways in carcinogenesis, as illustrated by a Mendelian randomization analysis on branched-chain amino acids and type 2 diabetes [24]. This analysis showed that genetic variants associated with levels of branched-chain amino acids were significantly associated with risk of type 2 diabetes. This finding confirms results from earlier rat feeding studies that showed a contribution of branched-chain amino acids to the development of insulin resistance [25].

Metabolomics and biomarkers of exposure to cancer risk factors

Anthropometric, lifestyle, and environmental factors all influence blood metabolic profiles (Fig. 3.7.2). Their effects have been described in an increasing number of intervention studies and observational studies, which aid in the interpretation of results from prospective studies on cancer. Metabolites that are simultaneously associated with a specific risk factor for cancer and with cancer risk are possible

Fig. 3.7.2. Metabolites associated with body mass index in two independent subcohorts of healthy subjects from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. A total of 22 metabolites replicate in both subcohorts (EPIC-Oxford and EPIC-Hepatobiliary controls). Arrows indicate the direction of the associations: positive association (↗), negative association (↘), and inconsistent direction (?). PCs, phosphatidylcholines; SM, sphingomyelin.



1 biogenic amine: Kynurenine(↗);
1 amino acid: Glutamate(↗);
1 sphingomyelin: SM C18:0(↗);
3 lysoPCs: C18:1(↘), C18:2(↘), C28:0(?);
8 diacyl PCs: C32:2(↗), C34:4(↗), C38:3(↗), C38:4(↗), C40:6(↗), C42:0(↘), C42:1(↘), C42:2(↘);
8 acyl-alkyl PCs: C38:2(↘), C40:5(↘), C42:3(↘), C42:4(↘), C42:5(↘), C44:4(↘), C44:5(↘), C44:6(↘)

mediators of the risk. In a nested case–control study that included 621 postmenopausal breast cancer cases and 621 matched controls, 4 metabolites (16α-hydroxydehydroepiandrosterone-3-sulfate, 3-methylglutarylcarnitine, allo-isoleucine, and 2-methylbutyrylcarnitine) were associated with both body mass index and risk of invasive breast cancer. These four metabolites may point towards metabolic pathways that contribute to breast carcinogenesis and explain the positive association of body mass index with risk of postmenopausal breast cancer [26].

This example and those given in the previous section illustrate how metabolomics aids in understanding mechanisms that link exposures to risk factors for cancer. In all of these examples, the focus was put on endogenous metabolites, as indicators of changes in host metabolism. Beyond endogenous metabolites, a large array of exogenous compounds, directly derived from the diet, pollutants, and drugs and mainly absorbed through the gut mucosa, are found in blood or urine, often at low concentrations. The use of sensitive MS techniques enables the detection in blood or urine of hundreds of these compounds, which together constitute the internal exposome [27,28]. Many of these compounds are direct indicators of exposure to environmental factors. They have been measured in population studies as proxy biomarkers of exposures to environmental factors. Detailed information on these biomarkers is curated in the Exposome-Explorer database [29].

Metabolomics approaches have the potential to play an important role in the discovery of new biomarkers of exposure in intervention studies or cross-sectional studies [30,31]. A classic early example is the identification of proline betaine as a biomarker for intake of citrus fruit [32]. Since then, many other dietary biomarkers have been identified. These biomarkers of exposure can be simultaneously measured in exposome-wide association studies (EWAS) using untargeted or targeted metabolomics approaches to study their association with cancer risk. In a case–control study on breast cancer nested in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort, of 113 metabolites related to dietary exposures, 19 metabolites were associated with risk of estrogen receptor-positive breast cancer, enabling the generation of novel hypotheses on the role of diet in breast cancer risk [33].

Metabolomics data, once collected in a prospective study, can be further mined to selectively examine associations of specific markers of dietary exposures with cancer risk [28]. Among 657 metabolites measured in serum samples, trigonelline, a biomarker of coffee intake, was found to be inversely associated with risk of colorectal cancer, suggesting a protective role of coffee intake against colorectal cancer [34].

Conclusions

The potential of metabolomics for elucidating mechanisms of carcinogenesis and for identifying novel risk factors for cancer is established. Techniques for metabolomics have improved considerably over the past few years, and there is now little doubt that metabolomics is emerging as an essential tool, complementary to the well-established genomics, transcriptomics, and proteomics approaches, to identify novel biomarkers for cancer and to better understand cancer etiology.

References

1. Wishart DS, Feunang YD, Marcu A, Guo AC, Liang K, Vázquez-Fresno R, et al. (2018). HMDB 4.0: the Human Metabolome Database for 2018. Nucleic Acids Res. 46(D1):D608–17. https://doi.org/10.1093/nar/gkx1089 PMID:29140435
2. Nicholson JK, Wilson ID (2003). Opinion: understanding 'global' systems biology: metabonomics and the continuum of metabolism. Nat Rev Drug Discov. 2(8):668–76. https://doi.org/10.1038/nrd1157 PMID:12904817
3. Scalbert A, Ferrari P (2020). Biomarker discovery. In: Adamski J, editor. Metabolomics for biomedical research. Elsevier. (forthcoming)
4. Reznik E, Luna A, Aksoy BA, Liu EM, La K, Ostrovnaya I, et al. (2018). A landscape of metabolic variation across tumor types. Cell Syst. 6(3):301–313.e3. https://doi.org/10.1016/j.cels.2017.12.014 PMID:29396322
5. Jain M, Nilsson R, Sharma S, Madhusudhan N, Kitami T, Souza AL, et al. (2012). Metabolite profiling identifies a key role for glycine in rapid cancer cell proliferation. Science. 336(6084):1040–4. https://doi.org/10.1126/science.1218595 PMID:22628656
6. Hanahan D, Weinberg RA (2011). Hallmarks of cancer: the next generation. Cell. 144(5):646–74. https://doi.org/10.1016/j.cell.2011.02.013 PMID:21376230
7. Tanner LB, Goglia AG, Wei MH, Sehgal T, Parsons LR, Park JO, et al. (2018). Four key steps control glycolytic flux in mammalian cells. Cell Syst. 7(1):49–62.e8. https://doi.org/10.1016/j.cels.2018.06.003 PMID:29960885
8. Liberti MV, Dai Z, Wardell SE, Baccile JA, Liu X, Gao X, et al. (2017). A predictive model for selective targeting of the Warburg effect through GAPDH inhibition with a natural product. Cell Metab. 26(4):648–659.e8. https://doi.org/10.1016/j.cmet.2017.08.017 PMID:28918937
9. Spratlin JL, Serkova NJ, Eckhardt SG (2009). Clinical applications of metabolomics in oncology: a review. Clin Cancer Res. 15(2):431–40. https://doi.org/10.1158/1078-0432.CCR-08-1059 PMID:19147747
10. Liesenfeld DB, Habermann N, Owen RW, Scalbert A, Ulrich CM (2013). Review of mass spectrometry-based metabolomics in cancer research. Cancer Epidemiol Biomarkers Prev. 22(12):2182–201. https://doi.org/10.1158/1055-9965.EPI-13-0584 PMID:24096148

11. Tan G, Wang H, Yuan J, Qin W, Dong X, Wu H, et al. (2017). Three serum metabolite signatures for diagnosing low-grade and high-grade bladder cancer. Sci Rep. 7(1):46176. https://doi.org/10.1038/srep46176 PMID:28382976

12. Chen J, Zhang X, Cao R, Lu X, Zhao S, Fekete A, et al. (2011). Serum 27-nor-5β-cholestane-3,7,12,24,25 pentol glucuronide discovered by metabolomics as potential diagnostic biomarker for epithelium ovarian cancer. J Proteome Res. 10(5): 2625–32. https://doi.org/10.1021/pr200173q PMID:21456628

13. Luo P, Yin P, Hua R, Tan Y, Li Z, Qiu G, et al. (2018). A large-scale, multicenter serum metabolite biomarker identification study for the early detection of hepatocellular carcinoma. Hepatology. 67(2): 662–75. https://doi.org/10.1002/hep.29561 PMID:28960374

14. Ritchie SA, Ahiahonu PWK, Jayasinghe D, Heath D, Liu J, Lu Y, et al. (2010). Reduced levels of hydroxylated, polyunsaturated ultra long-chain fatty acids in the serum of colorectal cancer patients: implications for early screening and detection. BMC Med. 8(1):13. https://doi.org/10.1186/1741-7015-8-13 PMID:20156336

15. Perttula K, Edmands WMB, Grigoryan H, Cai X, Iavarone AT, Gunter MJ, et al. (2016). Evaluating ultra-long-chain fatty acids as biomarkers of colorectal cancer risk. Cancer Epidemiol Biomarkers Prev. 25(8):1216–23. https://doi.org/10.1158/1055-9965.EPI-16-0204 PMID:27257090

16. Wang TJ, Larson MG, Vasan RS, Cheng S, Rhee EP, McCabe E, et al. (2011). Metabolite profiles and the risk of developing diabetes. Nat Med. 17(4):448–53. https://doi.org/10.1038/nm.2307 PMID:21423183

17. Guasch-Ferré M, Hruby A, Toledo E, Clish CB, Martínez-González MA, Salas-Salvadó J, et al. (2016). Metabolomics in prediabetes and diabetes: a systematic review and meta-analysis. Diabetes Care. 39(5):833–46. https://doi.org/10.2337/dc15-2251 PMID:27208380

18. Cross AJ, Moore SC, Boca S, Huang W-Y, Xiong X, Stolzenberg-Solomon R, et al. (2014). A prospective study of serum metabolites and colorectal cancer risk. Cancer. 120(19):3049–57. https://doi.org/10.1002/cncr.28799 PMID:24894841

19. Fages A, Duarte-Salles T, Stepien M, Ferrari P, Fedirko V, Pontoizeau C, et al. (2015). Metabolomic profiles of hepatocellular carcinoma in a European prospective cohort. BMC Med. 13(1):242. https://doi.org/10.1186/s12916-015-0462-9 PMID:26399231

20. Stepien M, Duarte-Salles T, Fedirko V, Floegel A, Barupal DK, Rinaldi S, et al. (2016). Alteration of amino acid and biogenic amine metabolism in hepatobiliary cancers: findings from a prospective cohort study. Int J Cancer. 138(2):348–60. https://doi.org/10.1002/ijc.29718 PMID:26238458

21. Mayers JR, Wu C, Clish CB, Kraft P, Torrence ME, Fiske BP, et al. (2014). Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development. Nat Med. 20(10):1193–8. https://doi.org/10.1038/nm.3686 PMID:25261994

22. Mondul AM, Moore SC, Weinstein SJ, Karoly ED, Sampson JN, Albanes D (2015). Metabolomic analysis of prostate cancer risk in a prospective cohort: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. Int J Cancer. 137(9):2124–32. https://doi.org/10.1002/ijc.29576 PMID:25904191

23. Schmidt JA, Fensom GK, Rinaldi S, Scalbert A, Appleby PN, Achaintre D, et al. (2017). Pre-diagnostic metabolite concentrations and prostate cancer risk in 1077 cases and 1077 matched controls in the European Prospective Investigation into Cancer and Nutrition. BMC Med. 15(1):122. https://doi.org/10.1186/s12916-017-0885-6 PMID:28676103

24. Lotta LA, Scott RA, Sharp SJ, Burgess S, Luan J, Tillin T, et al. (2016). Genetic predisposition to an impaired metabolism of the branched-chain amino acids and risk of type 2 diabetes: a Mendelian randomisation analysis. PLoS Med. 13(11):e1002179. https://doi.org/10.1371/journal.pmed.1002179 PMID:27898682

25. Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, Lien LF, et al. (2009). A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab. 9(4):311–26. https://doi.org/10.1016/j.cmet.2009.02.002 PMID:19356713

26. Moore SC, Playdon MC, Sampson JN, Hoover RN, Trabert B, Matthews CE, et al. (2018). A metabolomics analysis of body mass index and postmenopausal breast cancer risk. J Natl Cancer Inst. 110(6):588–97. https://doi.org/10.1093/jnci/djx244 PMID:29325144

27. Rappaport SM, Barupal DK, Wishart D, Vineis P, Scalbert A (2014). The blood exposome and its role in discovering causes of disease. Environ Health Perspect. 122(8):769–74. https://doi.org/10.1289/ehp.1308015 PMID:24659601

28. Scalbert A, Huybrechts I, Gunter MJ (2019). The food exposome. In: Dagnino S, Macherone A, editors. Unravelling the exposome: a practical view. Cham, Switzerland: Springer; pp. 217–45.

29. Neveu V, Moussy A, Rouaix H, Wedekind R, Pon A, Knox C, et al. (2017). Exposome-Explorer: a manually-curated database on biomarkers of exposure to dietary and environmental factors. Nucleic Acids Res. 45(D1):D979–84. https://doi.org/10.1093/nar/gkw980 PMID:27924041

30. Scalbert A, Rothwell JA, Keski-Rahkonen P, Neveu V (2017). The food metabolome and dietary biomarkers. In: Schoeller DA, Westerterp-Plantenga M, editors. Advances in the assessment of dietary intake. Boca Raton (FL), USA: CRC Press; pp. 259–82. https://doi.org/10.1201/9781315152288-16

31. Vlaanderen JJ, Janssen NA, Hoek G, Keski-Rahkonen P, Barupal DK, Cassee FR, et al. (2017). The impact of ambient air pollution on the human blood metabolome. Environ Res. 156:341–8. https://doi.org/10.1016/j.envres.2017.03.042 PMID:28391173

32. Heinzmann SS, Brown IJ, Chan Q, Bictash M, Dumas M-E, Kochhar S, et al. (2010). Metabolic profiling strategy for discovery of nutritional biomarkers: proline betaine as a marker of citrus consumption. Am J Clin Nutr. 92(2):436–43. https://doi.org/10.3945/ajcn.2010.29672 PMID:20573794

33. Playdon MC, Ziegler RG, Sampson JN, Stolzenberg-Solomon R, Thompson HJ, Irwin ML, et al. (2017). Nutritional metabolomics and breast cancer risk in a prospective study. Am J Clin Nutr. 106(2):637–49. https://doi.org/10.3945/ajcn.116.150912 PMID:28659298

34. Guertin KA, Loftfield E, Boca SM, Sampson JN, Moore SC, Xiao Q, et al. (2015). Serum biomarkers of habitual coffee consumption may provide insight into the mechanism underlying the association between coffee consumption and colorectal cancer. Am J Clin Nutr. 101(5):1000–11. https://doi.org/10.3945/ajcn.114.096099 PMID:25762808

3.8 Epigenetics
Potential in diagnostics, therapy, and prevention

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SUMMARY

- DNA methylation, histone modifications, and non-coding RNAs, the three main epigenetic mechanisms, are all known to be critical for high-fidelity propagation of gene activity states in a cell type-specific manner.
- Many cancer risk factors, including ageing, inflammation, tobacco smoking, alcohol consumption, fungal toxins, biological agents, and diet as well as air and water pollution and certain endocrine disrupters, are associated with epigenome dysregulation.
- Epigenetic changes, especially DNA methylation, are useful as biomarkers for cancer. Methylation changes can be detected in a large number of cells in normal-appearing tissues, and such change has been correlated with risk of cancer development for major cancer types in humans.
- Epigenetic change can be reversed by drugs, and the relevant agents have expanded from those affecting DNA methylation and histone acetylation to now include histone methylation modifications.
- Epigenetic changes in normal cells and cancer cells can be used as diagnostic targets.
- Suppressing the induction of epigenetic changes and reversing induced epigenetic changes have potential for cancer prevention.

In recent years, epigenetics has been consolidated as a mainstream field of cancer research, fundamental to the understanding of the etiology and biology of cancer. The importance of epigenetic dysregulation in cancer initiation and progression has been highlighted at multiple levels, and many conceptual breakthroughs in the field have revolutionized the traditional concepts of cancer development. In addition, the emergence of powerful technologies that enable the detection of epigenetic changes in high-throughput and genome-wide settings has dramatically accelerated cancer research and opened up new perspectives. This has resulted in a broader appreciation of the importance of epigenetics in the etiology of human cancer.

In the past, the term “epigenetics” was used to describe all biological phenomena that do not follow normal genetic principles. Nowadays, epigenetics refers to the study of all changes in gene expression that are transmitted across cell generations and that do not involve changes in the DNA sequence (i.e. mutations). In this chapter, three main epigenetic mechanisms are described: DNA methylation, histone modifications, and non-coding RNAs. All of these mechanisms are known to be critical for high-fidelity propagation of gene activity states in a cell type-specific manner. In addition, some investigators include nucleosome positioning and formation of higher-order chromatin structure as epigenetic mechanisms.

Consistent with the importance of epigenetic mechanisms in critical cellular processes, dysregulation of epigenetic mechanisms has been linked to various noncommunicable diseases in humans, most notably cancer [1,2]. Almost all critical processes in cancer cells – such as self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion and metastasis, limitless replicative potential, sustained angiogenesis, and evasion of apoptosis – can be caused not only by genetic changes but also by epigenetic alterations (Fig. 3.8.1) [3].

It has been proposed that the epigenome may function as an interface between environmental factors and the genome; however, the epigenetic mechanisms by which risk factors induce dysregulation of the epigenome and the functional impact of this dysregulation in specific human cancers remain poorly understood [4]. The challenges posed by numerous efforts to sequence human cancers are to identify the epigenome changes and consequently dysregulated genes and pathways that precede and promote tumour development, and to distinguish functionally important events

("drivers") from events that are merely "passengers". Accordingly, epigenetics may have potential in the prevention, early detection, and treatment of cancer.

Epigenetic mechanisms

The three main epigenetic mechanisms described here – DNA methylation, histone modifications, and non-coding RNAs – have been studied primarily in the context of regulation of gene expression. In addition to this well-established context, they are now recognized as important for other chromatin-based processes, such as DNA repair, DNA replication, and formation of higher-order chromatin structure [5].

DNA methylation

Of the three main epigenetic mechanisms, the best studied is DNA methylation. The methylation of DNA refers to the covalent addition of a methyl group to the 5-carbon position of cytosine in a CpG dinucleotide. DNA methylation, via the function of maintenance DNA methyltransferase (mainly DNMT1), has long been considered a highly stable epigenetic modification. However, recent studies showed that the ten–eleven translocation (TET) family of proteins are involved in active DNA demethylation, and that DNA methylation can be dynamically regulated at specific stages of life, such as during early embryogenesis. The TET proteins hydrolyse methyl cytosines, either fully methylated or hemi-methylated, and produce 5-hydroxymethylcytosine and its further metabolites, which will eventually be removed by base excision repair [6].

Histone modifications

The second main epigenetic mechanism encompasses various modifications of histone proteins. Typically, two copies each of the histones H2A, H2B, H3, and H4 compose an octamer, which is wrapped by an approximately 147-base-pair stretch of DNA to form a nucleosome. Histone modifications include acetylation, methylation, phosphorylation, and ubiquitination at specific residues of histone proteins, mostly in the N-terminal "tails" of histone proteins. Histone modifications regulate multiple cellular processes, including gene transcription, DNA repair, and DNA replication [7].

Histone acetylation is regulated by histone acetyltransferases and histone deacetylases (HDACs), and HDACs consist of 11 different molecules in classes I, IIa, IIb, and IV and sirtuins in class III. Histone methylation at specific amino acid residues is regulated by histone methyltransferases, such as EZH2, MLL, SETD2, and DOT1L, and by histone demethylases, such as KDM1A (LSD1) and KDM4A (JMJD2A). Multiple histone modification enzymes are mutated or dysregulated in human neoplasms [7]. Therefore, the importance of histone modifications in cancer and other diseases is now recognized.

Non-coding RNAs

Non-coding RNAs consist of small RNAs – microRNAs, Piwi-interacting RNAs (piRNAs), and small nucleolar RNAs (snoRNAs) – and long non-coding RNAs, and many investigators consider them as the third class of epigenetic mechanisms [8]. MicroRNAs can regulate expression levels of messenger RNA, and piRNAs are important to suppress the transcription of retrotransposons. Long non-coding RNAs, defined as endogenous cellular RNAs longer than 200 base pairs, tend to be expressed at lower levels compared with the majority of protein-coding genes. Interest in long non-coding RNAs has been stimulated by the recent finding that almost the entire mammalian genome is transcribed, although only a small fraction (~2%) of the genome is established to encode proteins [9]. A variety of human malignancies were found to exhibit aberrant expression of long non-coding RNAs, some of which were demonstrated to be involved in cancer onset and progression [10].

Experimental evidence suggests that there is intimate and mutually reinforcing cross-talk between these three epigenetic mechanisms in setting up and maintaining the genome-wide expression programme in a tissue-specific and lineage-specific manner.

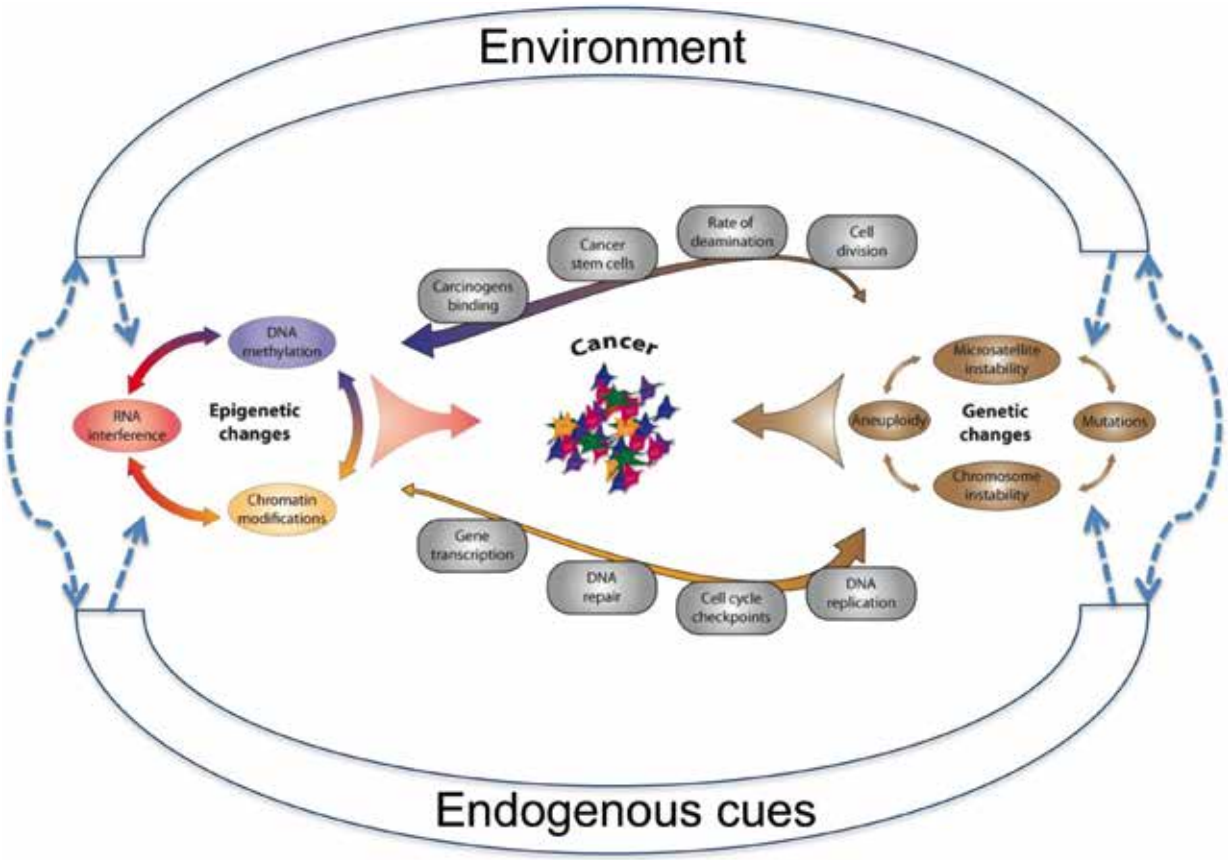
FUNDAMENTALS

- Epigenetics refers to all mitotically heritable changes in gene expression and associated phenotypic traits that are not coded in the DNA sequence itself. These changes are mediated by DNA methylation, histone modifications, and non-coding RNAs.
- Epigenetic changes can be induced by environmental and nutritional factors, and they are involved in a variety of human cancer types and in other chronic disorders.
- Growing evidence suggests that epigenetic changes may be risk factor-specific ("signatures"), which may prove instrumental in the discovery of novel biomarkers of cancer.
- Recent advances in epigenetics and epigenomics present an exciting opportunity to incorporate epigenetic data into carcinogen identification and safety assessment.
- Epigenetic changes in cancer cells are now targets for cancer therapy, and correction of epigenetic changes can form the basis for a cancer prevention strategy.

Epigenomic changes in cancer

Consistent with the critical role of epigenetic mechanisms in the control of cellular processes, a plethora of studies have revealed that the epigenome is markedly dysregulated in almost all malignancies [1,2] (Fig. 3.8.1).

Fig. 3.8.1. Interplay between genetics and epigenetics in cancer development. Epigenetic mechanisms regulate key cellular processes (such as gene transcription, DNA repair, and differentiation) and play critical roles in cellular responses to environmental exposures and endogenous stimuli. Dysregulation of epigenetic mechanisms may promote the development of abnormal phenotypes and cancer. There is cross-talk between epigenetic and genetic changes in the process of cancer development and progression. Given that epigenetic and genetic changes coexist in all cancers, it is important to identify the functionally important changes ("drivers") that are pertinent to carcinogenesis, and to distinguish them from events that are not functionally important ("passengers").



DNA methylation

Traditionally, two forms of aberrant DNA methylation have been described in human cancer: the overall loss of 5-methylcytosine (global hypomethylation) and gene promoter-associated (CpG island-specific) hypermethylation [11]. Genome-wide hypomethylation can induce chromosomal instability and hypomethylation of cancer/testis antigen genes. The impact of genome-wide or gene-specific hypomethylation on the activation of cellular proto-oncogenes is still debated, but hypermethylation of gene promoters is well established to be associated with gene inactivation. When hypermethylated, gene promoters become unable to bind the factors that are responsible for gene expression [12], and the gene is not transcribed. A large number of studies have indicated that the silencing of tumour suppressor genes and other cancer-related genes may occur through hypermethylation of their promoters.

Histone modifications

Recent genetic and molecular studies have directly implicated histone modifications and histone-modifying and histone-remodelling enzymes in human cancer. Consistent with the critical role of histone modifications in the establishment and maintenance of gene expression programmes that underpin key cellular processes and cell identity, dysregulation of histone modification patterns has a global impact on regulation of gene expression across the genome. This notion is supported by recent studies showing that recurrent mutations in the genes encoding histone modifiers and remodellers were associated with widespread transcriptome and epigenome changes in many cancer types [13,14]. It has also been observed that cancer cells exhibit dysregulated occupancy of the histone modifications H3K27ac (at enhancers) and H3K27me (at promoters), revealing distinct mechanisms underlying transcriptional dysregulation in cancer [15].

Current and future studies aimed at characterizing the functional impact of dysregulation of chromatin modifiers should provide valuable mechanistic insights into tumorigenesis and reveal potential molecular targets for biomarker discovery and therapeutic intervention. A growing emphasis in drug discovery on small molecules targeting HDACs, histone acetyltransferases, or histone methyltransferases ("epigenetic drugs") may result in novel strategies for efficient treatment and overcoming resistance to therapies.

Non-coding RNAs

Many recent studies also provided evidence that the dysregulation of non-coding RNAs is involved in the development of human neoplasia [1,2]. Although epigenetic changes have been implicated in different stages of tumour development and progression, the challenge is to identify functionally important epigenetic changes, which may be referred to as "epigenetic drivers" ("epidrivers") in the same way that this term is used for mutations, and hence differentiate them from "passenger" events, which are evident but not functionally important.

One of the most remarkable and groundbreaking findings of the international high-resolution cancer genome sequencing efforts, spearheaded by the Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC), is the high frequency of mutational and non-mutational (expression) changes in the genes encoding proteins that directly regulate the epigenome in malignancies [14,16–18]. About half of all newly identified genes that are found to be recurrently mutated in cancer encode proteins that are part of epigenetic machineries involved in DNA methylation and chromatin modifications [17,19]. Furthermore, it is now evident that frequent dysregulation of these epigenetic players may be mediated not only through mutational events but also through epigenetic events; this suggests a potential mechanism for epigenetic changes that are rampant in almost all human malignancies [14,18]. These findings should prove pivotal in facilitating functional studies, aimed at a better mechanistic understanding of tumour development (see Chapter 3.2) and of the plasticity of cancer cells that underlies tumour resilience and therapy failure.

Environmental influences on epigenomes

A profound dysregulation of the epigenome is a universal feature across almost all cancer types, and increasing evidence points to an important role of epigenetic mechanisms in mediating gene–environment interactions and their effect throughout the tumorigenesis process (see Chapter 3.3) [4]. Remarkable progress in the field of epigenetics, in conjunction with the emergence of powerful epigenomic technologies and computational tools, has led to the establishment of the impact of different endogenous and external risk factors on the epigenome. A wide range of established and suspected cancer risk factors (including ageing, inflammation, tobacco smoking, alcohol consumption, fungal toxins, biological agents, and diet) as well as some less widely studied exposures and lifestyle factors (such as air and water pollution and certain endocrine disrupters) have been shown to be associated with epigenome dysregulation (Fig. 3.8.2).

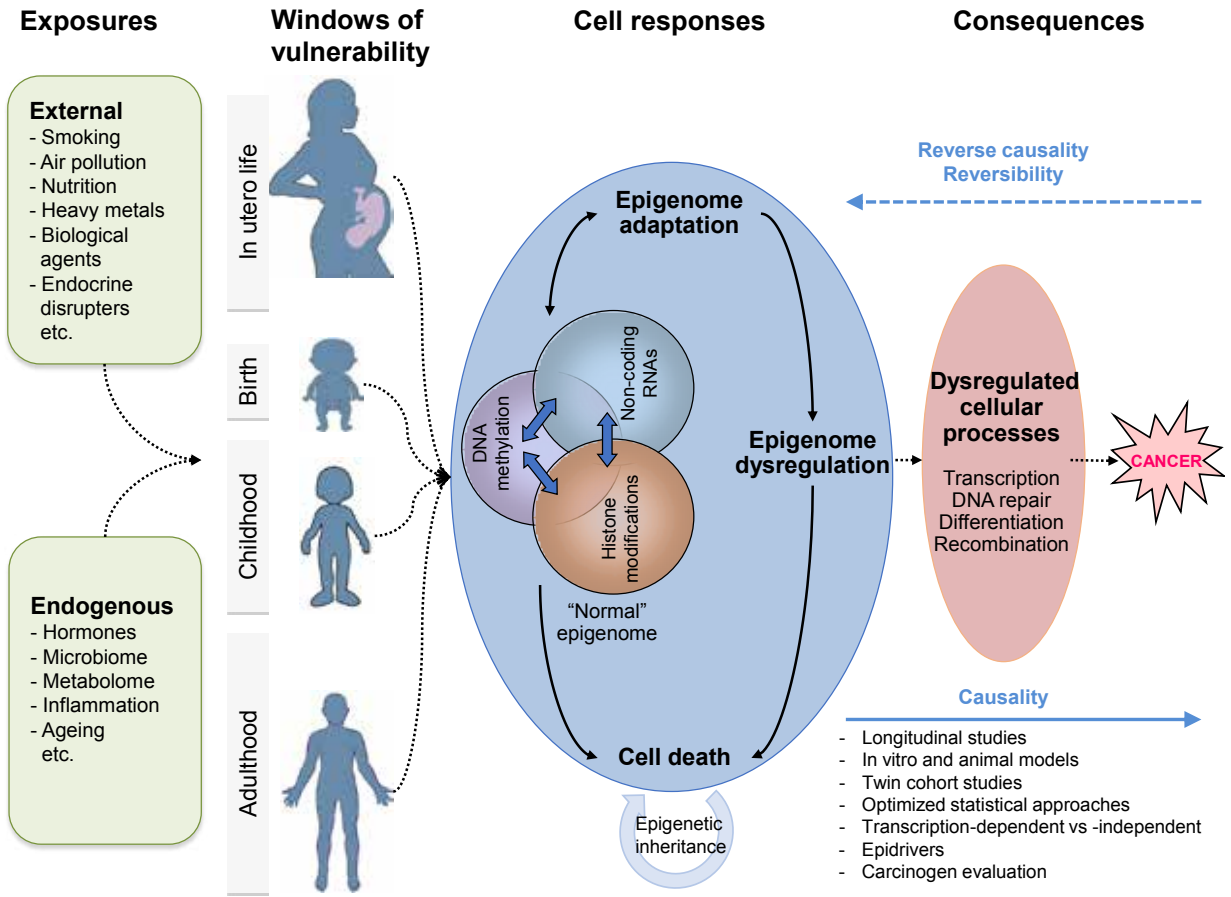
In addition to the type of environmental exposure, the timing of exposure may also play a critical role in influencing cancer risk. In utero and early life may represent particularly vulnerable periods in humans, because of the profound reconfiguration of the epigenome during embryonic development. Epigenetic changes can be stably propagated over many cell generations, and therefore epigenome dysregulation brought about by early-life exposures may have lifelong health outcomes. Accumulating evidence suggests that in utero exposure to different agents, including tobacco smoke (see Chapter 2.1) [20], aflatoxin B_1 (see Chapter 2.8) [21], and inorganic arsenic and heavy metals (see Chapter 2.9) [22], may leave epigenetic signatures in the fetus that may be detected in neonatal samples. These observations not only suggest potential mechanisms of cancer development involving epigenome dysregulation but also underscore that early life may represent a critical period for intervention and cancer prevention.

Although the importance of the environment in the development of a wide variety of cancer types is well supported by both epidemiological and laboratory-based studies, the mechanisms by which environmental exposures dysregulate the epigenome remain poorly characterized [4,23]. The recent establishment of reference epigenomes for normal cell types and cancer-specific epigenomes provided by several major international projects should facilitate the identification of environmental factors that are associated with epigenomic alterations. Ultimately, intervention studies in animals or humans are important to establish causal associations between environmental exposures and epigenetic alterations.

Epigenetic changes as biomarkers

Epigenetic changes, especially DNA methylation, are useful as cancer biomarkers in multiple ways (Fig. 3.8.3). The accumulation levels of aberrant DNA methylation in normal tissues can be correlated with future cancer risk, and can be used for cancer risk diagnosis (see Chapter 6.7) [24,25]. Initially, the accumulation of DNA methylation changes in normal-appearing tissues of cancer patients was shown for multiple cancer types. Unlike mutations, methylation changes can be detected in a large number of cells in normal-appearing tissues, and can be readily measured [26]. The accumulation can be associated with past exposure to carcinogenic stimuli, and the genes that are methylated can be specific to the exposure [27].

Fig. 3.8.2. Epigenetic mechanisms and cancer: an interface between the environment and the genome. Exposures arising from external sources (such as environmental chemicals, air pollution, infectious agents, diet, tobacco smoking, alcohol consumption, and endocrine disrupters) and internal processes (such as metabolism, hormones, inflammation, gut microflora, and ageing) may induce stable and potentially reversible changes in the epigenome. The patterns ("signatures") and persistence of these alterations depend on multiple factors, including the type of epigenetic changes (some genomic regions remain methylated for longer periods than others), the duration and dosage of the exposure (longer and more intense exposures could minimize the reversibility of DNA methylation), the tissue type, and the developmental stage (in utero life or puberty may be particularly sensitive periods for some exposures). Thus, epigenetic mechanisms may represent "sensors" of exposure and "mediators" of the outcomes, including cancer development. Epigenomic alterations should prove instrumental in the discovery of new biomarkers for risk stratification and early detection, and attractive targets for novel therapies and preventive strategies.

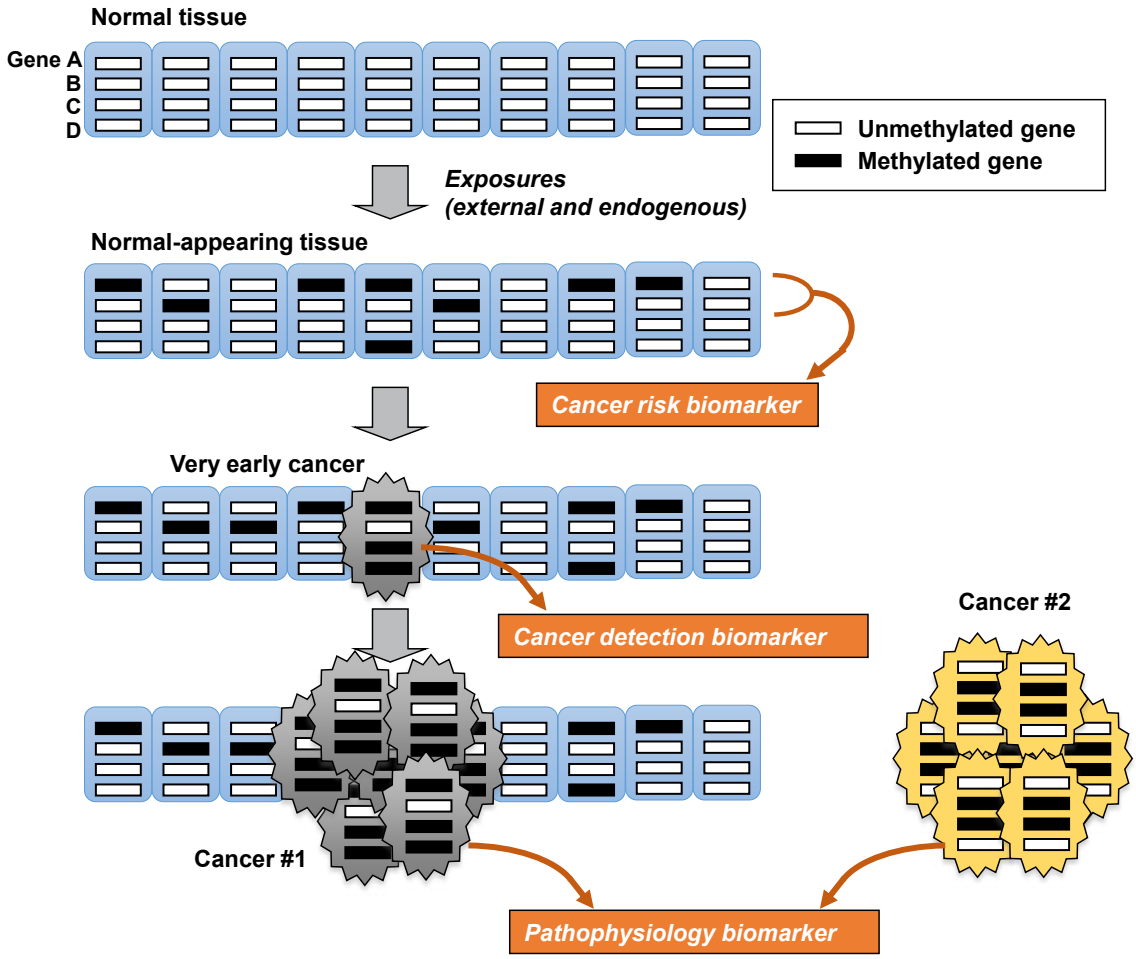


The accumulation levels of aberrant DNA methylation can be correlated with risk of cancer development for gastric cancer, liver cancer, cervical cancer, and other cancer types [24,25]. The usefulness in cancer risk diagnosis has been shown by a prospective clinical study for gastric cancer and cervical cancer [28,29]. Similar approaches appear to be promising for multiple cancer types in which aberrant DNA methylation is deeply involved.

Cancer cell-specific DNA methylation can be used as a biomarker to detect cancer. Because DNA methylation can be sensitively detected by technologies based on polymerase chain reaction (PCR) amplification of methylated DNA molecules, the detection of cancer cell-derived DNA has been attempted for decades. As a result, there are many cancer detection systems using materials that are likely to contain cancer cells or cancer cell-derived DNA, such as stool, urine, sputum, and cervical smear, and some of them are already commercially available [30]. In contrast, the attempts at using serum or plasma DNA have had mixed results [31,32]. In addition, distinct DNA methylation patterns according to cancer types have been established, and the specific patterns were used to predict the origin of cancers, with a very promising result [33].

Even in a specific cancer type, methylation of specific genes or methylation profiles can be associated with the pathophysiology of cancers, and may be useful to determine patient prognosis and responsiveness to a particular therapy [32]. In sharp distinction to patterns of gene expression, DNA methylation

Fig. 3.8.3. DNA methylation as a biomarker. Normal tissues without exposure have minimal levels of aberrant methylation. Exposure to environmental factors, such as *Helicobacter pylori* infection and tobacco smoke, is known to induce aberrant DNA methylation of specific genes in normal-appearing tissue. Further accumulation of aberrant DNA methylation and genetic alterations will lead to the development of cancer, and each cancer has individual epigenetic profiles that can be associated with pathophysiology, such as aggressiveness, response to therapy, and prognosis. Measurement of methylation in normal-appearing tissues can be used as a biomarker of cancer risk. Cancer cell-specific DNA methylation can be used as a biomarker for cancer detection. Methylation of specific genes that are associated with pathophysiology can be used as a biomarker of pathophysiology.



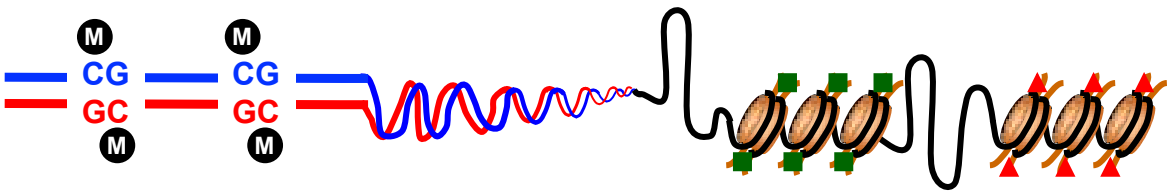
can indicate that a particular gene cannot be expressed even if its expression is induced in the future. For example, if the promoter region of O^6-methylguanine-DNA methyltransferase (*MGMT*) is determined to be methylated at biopsy of a brain tumour, this gene will never be expressed even after future chemotherapy involving an alkylating agent. In the absence of *MGMT* expression, such chemotherapy has been shown to be effective [34].

DNA methylation of multiple genes – the CpG island methylator phenotype – is associated with patient prognosis in several cancer types, including colorectal and gastric malignancies as well as neuroblastomas. Specifically, the CpG island methylator phenotype in neuroblastoma provides prognostic information that is more precise than that from the amplification of the *MYCN* oncogene, one of the clearest prognostic indicators in clinical oncology [35].

Epigenetic therapy

One of the most important aspects of epigenetic change, which distinguishes such change from mutation, is the fact that it can be reversed by drugs [1,19,36]. During the past decade, this field has rapidly expanded from agents affecting DNA methylation and histone acetylation to now include histone methylation modifications (Fig. 3.8.4). DNA methylation can be reversed by DNA demethylating agents. Two such drugs, azacitidine and decitabine, have been approved by the United States Food and Drug Administration and other regulatory agencies for treating myelodysplastic syndrome and acute myeloid

Fig. 3.8.4. Epigenetic targets for drugs. DNA methylation and histone modifications are written, erased, and read by specific proteins. Many of the writers, erasers, and readers are now used as drug targets. Among these, DNA methyltransferase (DNMT) inhibitors and histone deacetylase (HDAC) inhibitors (targets shaded in blue) are already approved by the United States Food and Drug Administration. Only major drug targets are shown here; novel targets are still being identified. BRDs, bromodomains; HATs, histone acetyltransferases; TETs, ten–eleven translocation proteins; MBDs, methyl-CpG-binding domains.



	DNA methylation	Histone modifications				
		Acetylation	H3K4me	H3K9me	H3K27me	H3K79me
Writer	DNMT1	HATs		G9a	EZH2	DOT1L
Eraser	TETs	HDACs	LSD1			
Reader	MBDs	BRDs				

leukaemia, and are now being explored for treating solid tumours. In addition to these two drugs, multiple new DNA demethylating agents, such as SGI-110 and CC-486, are being developed. All these drugs are incorporated into DNA and covalently bind to DNMT1, which ultimately leads to its degradation. As a result, cell replication in the absence of maintenance methylation leads to DNA demethylation. DNA demethylation leads to the activation of aberrantly silenced tumour suppressor genes and an increased immune response. To achieve this mode of action, low-dose and long-term administration are seen to be important [19].

Histone deacetylation can be reversed by HDAC inhibitors [1,19, 36]. Three such drugs have been approved for treating cutaneous lymphoma, and one for treating multiple myeloma, and many new HDAC inhibitors are being developed. Individual HDAC inhibitors have different specificities to the individual molecules of HDAC1–HDAC11 in classes I, IIa, IIb, and IV. All the HDAC inhibitors induce expression of many genes, and thus have pleiotropic effects on cancer cell phenotypes. In addition, some HDAC inhibitors induce acetylation of non-histone proteins, including p53, signal transducer and activator of transcription 1/3 (STAT1/3), and heat shock protein 90 (Hsp90).

In contrast to HDAC inhibitors, overactivity of oncogenes and other genes due to the formation of extensively histone-acetylated enhancers (super-enhancers) can be targeted by inhibitors of proteins that bind to acetylated histones, namely bromodomain and extraterminal domain (BET) proteins [37]. Multiple BET inhibitors are being developed against haematological malignancies and brain tumours.

Mutations of histone methyltransferases and histone demethylases have also provided novel therapeutic targets [1,19,36]. Especially the H3K27 methyltransferase EZH2 is mutationally activated in some tumour types, such as lymphomas, and is overexpressed in many tumour types. Multiple EZH2 inhibitors are being developed. In addition, inhibitors of the H3K79 methyltransferase DOT1L and the H3K9 methyltransferase G9a are considered as drug targets, and their specific inhibitors have been developed. Some histone demethylases are also targets for therapy. Currently, the most successful target is LSD1, which demethylates di- and monomethylated H3K4. Inhibition of LSD1 induces differentiation of leukaemia cells and apoptosis of brain tumour cells by activating enhancers and promoters of related genes.

Epigenetic cancer prevention

Suppressing the induction of epigenetic changes and reversing induced epigenetic changes are also useful for cancer prevention [38]. As a proof of concept, in experimental animals, tumours such as those of the colon, prostate, and stomach have been suppressed by repression of DNA methyltransferases by gene engineering and DNA demethylating agents [39–41]. However, it must be recognized that DNA methylation is physiologically essential to repress transposons and some genes, and nonspecific demethylation is expected to lead to long-term adverse effects.

Therefore, to enable epigenetic cancer prevention by reversing epigenetic changes in the human population, the specificity of preventive agents for genes with aberrant epigenetic modifications must be improved. Instead, suppressing the induction of epigenetic changes appears to be more practical. Also, it is now possible to identify individuals at extremely high risk of some cancers by assessing accumulated levels of aberrant DNA methylation in normal-appearing tissues, as previously discussed. These individuals represent a population that is likely to benefit from effective chemoprevention by balancing the benefit and the potential adverse effects (see Chapter 6.4). Because epigenetic cancer prevention has great potential, multiple relevant studies are required in a timely manner.

References

1. Dawson MA (2017). The cancer epigenome: concepts, challenges, and therapeutic opportunities. Science. 355(6330): 1147–52. https://doi.org/10.1126/science.aam7304 PMID:28302822
2. Feinberg AP, Koldobskiy MA, Göndör A (2016). Epigenetic modulators, modifiers and mediators in cancer aetiology and progression. Nat Rev Genet. 17(5):284–99. https://doi.org/10.1038/nrg.2016.13 PMID:26972587
3. Herceg Z, Lambert MP, van Veldhoven K, Demetriou C, Vineis P, Smith MT, et al. (2013). Towards incorporating epigenetic mechanisms into carcinogen identification and evaluation. Carcinogenesis. 34(9):1955–67. https://doi.org/10.1093/carcin/bgt212 PMID:23749751
4. Herceg Z, Ghantous A, Wild CP, Sklias A, Casati L, Duthie SJ, et al. (2018). Roadmap for investigating epigenome deregulation and environmental origins of cancer. Int J Cancer. 142(5):874–82. https://doi.org/10.1002/ijc.31014 PMID:28836271
5. Dabin J, Fortuny A, Polo SE (2016). Epigenome maintenance in response to DNA damage. Mol Cell. 62(5):712–27. https://doi.org/10.1016/j.molcel.2016.04.006 PMID:27259203
6. Schübeler D (2015). Function and information content of DNA methylation. Nature. 517(7534):321–6. https://doi.org/10.1038/nature14192 PMID:25592537
7. Greer EL, Shi Y (2012). Histone methylation: a dynamic mark in health, disease and inheritance. Nat Rev Genet. 13(5): 343–57. https://doi.org/10.1038/nrg3173 PMID:22473383
8. Kopp F, Mendell JT (2018). Functional classification and experimental dissection of long noncoding RNAs. Cell. 172(3):393–407. https://doi.org/10.1016/j.cell.2018.01.011 PMID:29373828
9. Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, et al. (2015). The landscape of long noncoding RNAs in the human transcriptome. Nat Genet. 47(3): 199–208. https://doi.org/10.1038/ng.3192 PMID:25599403
10. Lin C, Yang L (2018). Long noncoding RNA in cancer: wiring signaling circuitry. Trends Cell Biol. 28(4):287–301. https://doi.org/10.1016/j.tcb.2017.11.008 PMID:29274663
11. Sinčić N, Herceg Z (2011). DNA methylation and cancer: ghosts and angels above the genes. Curr Opin Oncol. 23(1):69–76. https://doi.org/10.1097/CCO.0b013e3283412eb4 PMID:21119515
12. Vaissière T, Sawan C, Herceg Z (2008). Epigenetic interplay between histone modifications and DNA methylation in gene silencing. Mutat Res. 659(1–2):40–8. https://doi.org/10.1016/j.mrrev.2008.02.004 PMID:18407786
13. Plass C, Pfister SM, Lindroth AM, Bogatyrova O, Claus R, Lichter P (2013). Mutations in regulators of the epigenome and their connections to global chromatin patterns in cancer. Nat Rev Genet. 14(11): 765–80. https://doi.org/10.1038/nrg3554 PMID:24105274
14. Timp W, Feinberg AP (2013). Cancer as a dysregulated epigenome allowing cellular growth advantage at the expense of the host. Nat Rev Cancer. 13(7): 497–510. https://doi.org/10.1038/nrc3486 PMID:23760024
15. Hnisz D, Abraham BJ, Lee TI, Lau A, Saint-André V, Sigova AA, et al. (2013). Super-enhancers in the control of cell identity and disease. Cell. 155(4):934–47. https://doi.org/10.1016/j.cell.2013.09.053 PMID:24119843
16. Gonzalez-Perez A, Jene-Sanz A, Lopez-Bigas N (2013). The mutational landscape of chromatin regulatory factors across 4,623 tumor samples. Genome Biol. 14(9):r106. https://doi.org/10.1186/gb-2013-14-9-r106 PMID:24063517
17. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW (2013). Cancer genome landscapes. Science. 339(6127):1546–58. https://doi.org/10.1126/science.1235122 PMID:23539594
18. Plass C, Pfister SM, Lindroth AM, Bogatyrova O, Claus R, Lichter P (2013). Mutations in regulators of the epigenome and their connections to global chromatin patterns in cancer. Nat Rev Genet. 14(11):765–80. https://doi.org/10.1038/nrg3554 PMID:24105274
19. Jones PA, Issa JP, Baylin S (2016). Targeting the cancer epigenome for therapy. Nat Rev Genet. 17(10):630–41. https://doi.org/10.1038/nrg.2016.93 PMID:27629931
20. Joubert BR, Felix JF, Yousefi P, Bakulski KM, Just AC, Breton C, et al. (2016). DNA methylation in newborns and maternal smoking in pregnancy: genome-wide consortium meta-analysis. Am J Hum Genet. 98(4):680–96. https://doi.org/10.1016/j.ajhg.2016.02.019 PMID:27040690
21. Hernandez-Vargas H, Castelino J, Silver MJ, Dominguez-Salas P, Cros M-P, Durand G, et al. (2015). Exposure to aflatoxin B_1 in utero is associated with DNA methylation in white blood cells of infants in The Gambia. Int J Epidemiol. 44(4):1238–48. https://doi.org/10.1093/ije/dyv027 PMID:25855716
22. Green BB, Karagas MR, Punshon T, Jackson BP, Robbins DJ, Houseman EA, et al. (2016). Epigenome-wide assessment of DNA methylation in the placenta and arsenic exposure in the New Hampshire Birth Cohort Study (USA). Environ Health Perspect. 124(8):1253–60. https://doi.org/10.1289/ehp.1510437 PMID:26771251
23. Hattori N, Ushijima T (2016). Epigenetic impact of infection on carcinogenesis: mechanisms and applications. Genome Med. 8(1):10. https://doi.org/10.1186/s13073-016-0267-2 PMID:26823082
24. Ushijima T, Hattori N (2012). Molecular pathways: involvement of *Helicobacter pylori*-triggered inflammation in the formation of an epigenetic field defect, and its usefulness as cancer risk and exposure markers. Clin Cancer Res. 18(4):923–9. https://doi.org/10.1158/1078-0432.CCR-11-2011 PMID:22205689

25. Ushijima T (2007). Epigenetic field for cancerization. J Biochem Mol Biol. 40(2): 142–50. PMID:17394762

26. Ushijima T, Asada K (2010). Aberrant DNA methylation in contrast with mutations. Cancer Sci. 101(2):300–5. https://doi.org/10.1111/j.1349-7006.2009.01434.x PMID:19958364

27. Takeshima H, Ushijima T (2010). Methylation destiny: Moira takes account of histones and RNA polymerase II. Epigenetics. 5(2):89–95. https://doi.org/10.4161/epi.5.2.10774 PMID:20160507

28. Asada K, Nakajima T, Shimazu T, Yamamichi N, Maekita T, Yokoi C, et al. (2015). Demonstration of the usefulness of epigenetic cancer risk prediction by a multicentre prospective cohort study. Gut. 64(3):388–96. https://doi.org/10.1136/gutjnl-2014-307094 PMID:25379950

29. Maeda M, Moro H, Ushijima T (2017). Mechanisms for the induction of gastric cancer by *Helicobacter pylori* infection: aberrant DNA methylation pathway. Gastric Cancer. 20(Suppl 1):8–15. https://doi.org/10.1007/s10120-016-0650-0 PMID:27718135

30. Leygo C, Williams M, Jin HC, Chan MWY, Chu WK, Grusch M, et al. (2017). DNA methylation as a noninvasive epigenetic biomarker for the detection of cancer. Dis Markers. 2017:3726595. https://doi.org/10.1155/2017/3726595 PMID:29038612

31. Worm Ørntoft MB (2018). Review of blood-based colorectal cancer screening: how far are circulating cell-free DNA methylation markers from clinical implementation? Clin Colorectal Cancer. 17(2):e415–33. https://doi.org/10.1016/j.clcc.2018.02.012 PMID:29678513

32. Koch A, Joosten SC, Feng Z, de Ruijter TC, Draht MX, Melotte V, et al. (2018). Analysis of DNA methylation in cancer: location revisited. Nat Rev Clin Oncol. 15(7):459–66. https://doi.org/10.1038/s41571-018-0004-4 PMID:29666440

33. Moran S, Martínez-Cardús A, Sayols S, Musulén E, Balañá C, Estival-Gonzalez A, et al. (2016). Epigenetic profiling to classify cancer of unknown primary: a multicentre, retrospective analysis. Lancet Oncol. 17(10):1386–95. https://doi.org/10.1016/S1470-2045(16)30297-2 PMID:27575023

34. Jacinto FV, Esteller M (2007). Mutator pathways unleashed by epigenetic silencing in human cancer. Mutagenesis. 22(4):247–53. https://doi.org/10.1093/mutage/gem009 PMID:17412712

35. Abe M, Ohira M, Kaneda A, Yagi Y, Yamamoto S, Kitano Y, et al. (2005). CpG island methylator phenotype is a strong determinant of poor prognosis in neuroblastomas. Cancer Res. 65(3):828–34. PMID:15705880

36. Pfister SX, Ashworth A (2017). Marked for death: targeting epigenetic changes in cancer. Nat Rev Drug Discov. 16(4):241–63. https://doi.org/10.1038/nrd.2016.256 PMID:28280262

37. Stathis A, Bertoni F (2018). BET proteins as targets for anticancer treatment. Cancer Discov. 8(1):24–36. https://doi.org/10.1158/2159-8290.CD-17-0605 PMID:29263030

38. Feinberg AP (2018). The key role of epigenetics in human disease prevention and mitigation. N Engl J Med. 378(14):1323–34. https://doi.org/10.1056/NEJMra1402513 PMID:29617578

39. McCabe MT, Low JA, Daignault S, Imperiale MJ, Wojno KJ, Day ML (2006). Inhibition of DNA methyltransferase activity prevents tumorigenesis in a mouse model of prostate cancer. Cancer Res. 66(1):385–92. https://doi.org/10.1158/0008-5472.CAN-05-2020 PMID:16397253

40. Yoo CB, Chuang JC, Byun HM, Egger G, Yang AS, Dubeau L, et al. (2008). Long-term epigenetic therapy with oral zebularine has minimal side effects and prevents intestinal tumors in mice. Cancer Prev Res (Phila). 1(4):233–40. https://doi.org/10.1158/1940-6207.CAPR-07-0008 PMID:19138966

41. Niwa T, Toyoda T, Tsukamoto T, Mori A, Tatematsu M, Ushijima T (2013). Prevention of *Helicobacter pylori*-induced gastric cancers in gerbils by a DNA demethylating agent. Cancer Prev Res (Phila). 6(4):263–70. https://doi.org/10.1158/1940-6207.CAPR-12-0369 PMID:23559452

3.9 Immune function
From the tumour microenvironment to therapeutic targeting

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Graham Pawelec (reviewer)

SUMMARY

- Immune cells and mediators of innate and adaptive immunity are essential components of the tumour microenvironment.
- Innate and adaptive immunity in the tumour microenvironment are double-edged swords.
- Appropriately activated adaptive immune responses mediate resistance to carcinogenesis and progression.
- In contrast, cancer-related inflammation orchestrated by innate immunity, such as macrophages and the complement system, facilitates tumour progression via several mechanisms, including suppression of adaptive immune responses.
- Progress has been made in defining the beneficial anti-cancer immunity cycle, its cellular and molecular brakes (checkpoints), and its relevance to prognosis and treatment of human cancers.
- A revised view of the role of the tumour microenvironment in cancer progression, and the dissection of molecular mechanisms, has opened up a new frontier in oncology, represented by tumour immunology and immunotherapy.

The ecological niche in which cell transformation and tumour progression occur is an essential component of malignancy [1,2]. Innate and adaptive immunity play key roles in the tumour microenvironment (TME) by interacting with cancer cells as well as with stroma and the vascular bed.

Immunity in all its diversity and plasticity acts as a double-edged sword during carcinogenesis, invasion, and metastasis. Appropriately activated T cells and innate immune effectors (natural killer [NK] cells) mediate early elimination of transformed cells and limit progression [3]. In contrast, inflammatory cells and myeloid cells – in particular, macrophages – act as "corrupted policemen", promoting carcinogenesis and tumour progression at different levels, including suppression of effective adaptive immune responses [4,5].

This chapter concisely summarizes key aspects of the yin–yang relationship between immunity and cancer, emphasizing clinical implications. Inflammation and innate immunity are discussed first, in a schematic way, followed by a description of lymphoid cell-mediated immune responses that have impacts on prevention, diagnosis, and treatment.

Inflammation, innate immunity, and cancer

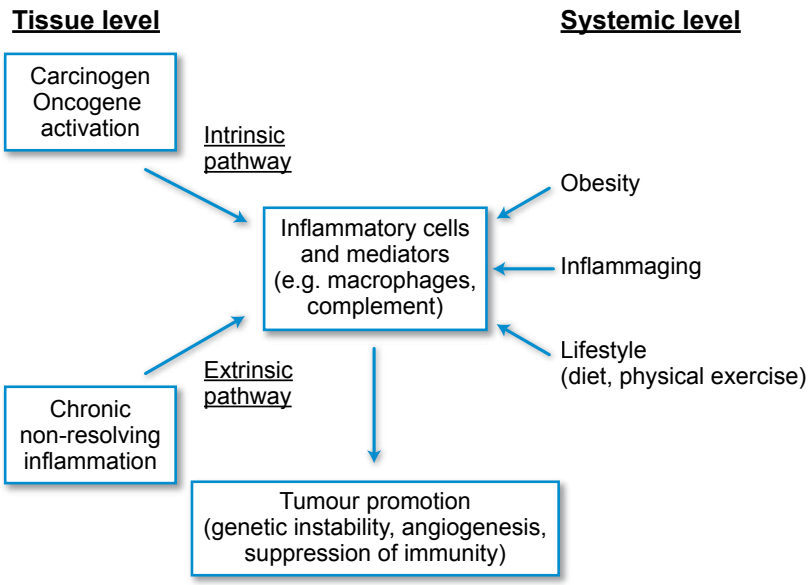
A connection between inflammation and cancer (Fig. 3.9.1) has long been perceived [1,4,6] (see also Chapter 3.5). Inflammatory cells including macrophages, neutrophils, mast cells, and eosinophils are present in the TME. Tumour-associated macrophages (TAMs) are prototypic inflammatory cells, playing a key role in the orchestration of the TME.

Mononuclear phagocytes are extremely plastic. In the context of interferon-driven type 1 immune responses, macrophages acquire tumoricidal activity. Type 1 immunity signatures are generally associated with better prognosis in human tumours [7]. Moreover, type 1 immunity resulting in M1 polarization of macrophages mediates the initial (elimination) phase in the natural history of carcinogenesis [8].

During neoplastic progression, macrophage function is skewed in a pro-tumour direction (M2 or M2-like) [7]. Signals responsible for the pro-tumour function of TAMs are known to originate from tumour cells (e.g. interleukin-10 [IL-10], transforming growth factor β [TGF-β]); T helper type 2 (Th2) cells, eosinophils, or basophils (IL-4 or IL-13, resulting in M2 activation); B cells (antibodies, immune complexes); and stromal cells (IL-1).

There is evidence suggesting that the relative importance of different pathways for regulating the function of TAMs varies in different tissues [9]. Single-cell analysis has added a new dimension to the dissection of myeloid cell diversity in cancer [10]. Clusters of more than 10 differentiation/activation states have been identified. The microanatomical

Fig. 3.9.1. Pathways connecting inflammation and cancer at the tissue level and at the systemic level.



FUNDAMENTALS

- Immune cells are a key component of the tumour microenvironment.
- Components of innate immunity drive tumour-promoting inflammation.
- Macrophages promote tumour progression and immunosuppression.
- T cells eliminate and edit cancer cells.
- Checkpoints and other pathways of suppression restrain the anti-tumour activity of T cells, natural killer cells, and macrophages.
- Immune components have strong prognostic significance.
- Immunology and immunotherapy represent a new frontier in the fight against cancer.

signals responsible for the diversity of cancer-associated myeloid cells remain to be defined.

Phagocytosis is the eponymous function of mononuclear phagocytes. CD47 on normal and tumour cells delivers a "don't eat me" signal via signal regulatory protein 1α (SIRP1α) on macrophages [11]. CD47 is amplified downstream of the oncogene *MYC* [5]. CD47, which is one of the negative regulators (checkpoints) of myeloid cells, can serve as a therapeutic target [12]. Recent evidence suggests that blocking CD47 may unleash antibody-dependent cellular cytotoxicity and phagocytosis mediated by TAMs [13]. TAMs and other myeloid cells – for example, operationally defined myeloid-derived suppressor cells (MDSCs) [14] – have now been shown to have impacts on diverse aspects of cancer progression, including tumour cell proliferation and invasion, construction of a metastatic niche, angiogenesis, and immunosuppression. Immunosuppression, a key function of myeloid cells, is discussed below.

Components of the humoral arm of innate immunity have recently been recognized as important elements in the TME [15,16]. The complement system can also act as a double-edged sword by mediating complement-dependent cytotoxicity in the presence of antibodies or, alternatively, by recruiting tumour-promoting myeloid cells. The long pentraxin PTX3 was shown to act as an extrinsic oncosuppressor, which is epigenetically silenced in selected human tumours [15]. PTX3 silencing unleashes complement-driven recruitment and functional orientation (M2-like) of TAMs, which is responsible for tumour promotion and increased genetic instability.

Cytokines are a key component of tumour-promoting inflammation. In particular, IL-1 has been shown to drive myeloid cell infiltration, generation of MDSCs, and angiogenesis [8]. Recent evidence is consistent with IL-1 being an important driver of progression in human tumours [17,18]. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) was originally designed to assess the impact of an anti-IL-1β antibody (canakinumab) on atherosclerosis-related cardiovascular pathology. In more than 10 000 patients, blocking of IL-1β was associated with reductions of more than 50% in the incidence of and mortality from lung cancer [17]. These and other results provide a strong proof-of-principle rationale for targeting tumour-promoting inflammation in human tumours.

Anti-tumour immunity and immunosuppression

T-cell-orchestrated type 1 immune responses mediate host resistance during the early phases of carcinogenesis (Fig. 3.9.2). Moreover, in human tumours, the presence of T cells and type 1 immunity or interferon signatures is associated with better prognosis [7,19]. Genomics has provided a more in-depth view of immune cell recognition of tumour-specific antigens, arising from mutations, or tumour-associated antigens, resulting from overexpression of normal cell genes. Evidence in mouse and human tumours has indicated that mutations and genetic instability represent the fundamental molecular basis for T-cell-dependent anti-tumour

immunity [3,7,9,20]. The intersection of genomics and the dissection of immunity is paving the way to personalized immunotherapy approaches.

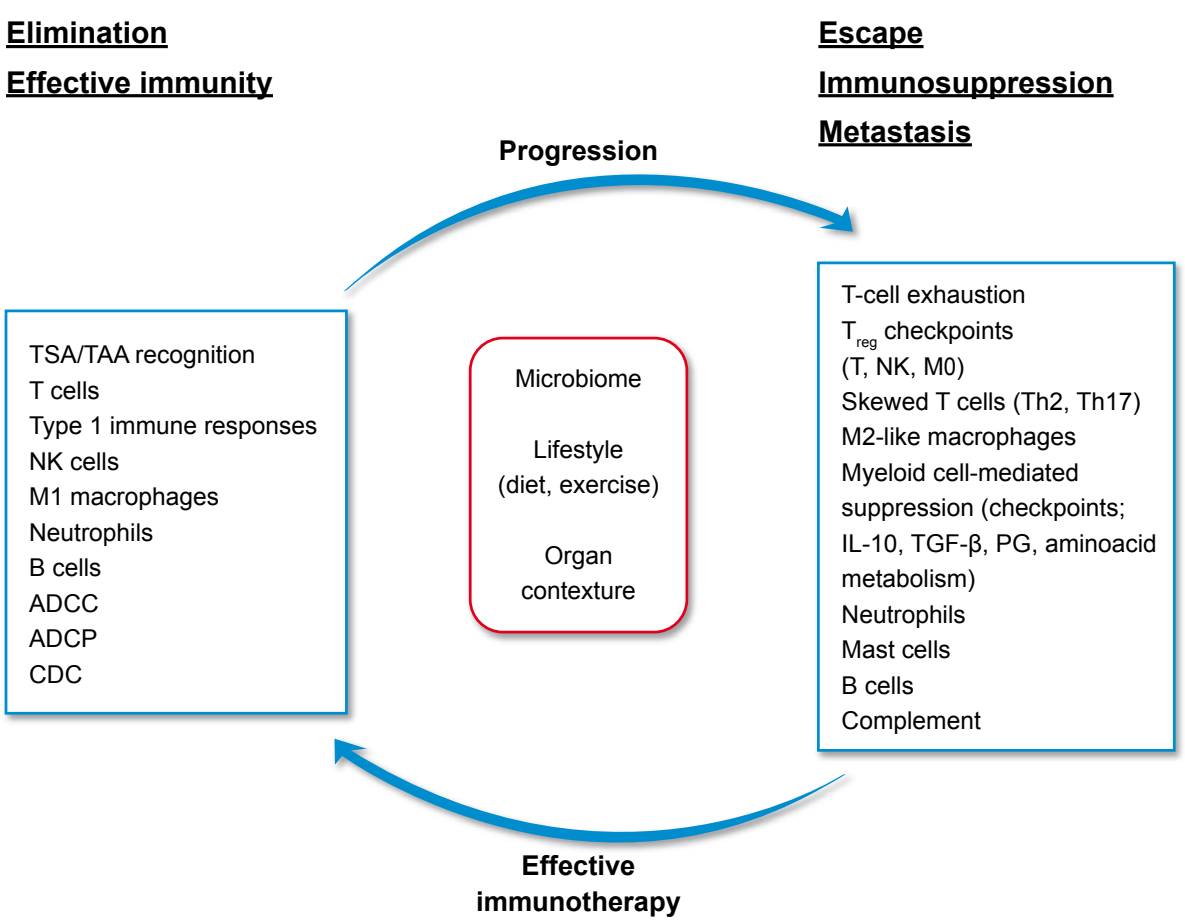
Failure of effective immunity is associated with progression and the appearance of clinical cancer. In the Darwinian TME, tumour cell-centred and host cell-centred mechanisms of immune evasion drive progression, invasion, and metastasis (Fig. 3.9.2). Mechanisms of physical exclusion (e.g. extracellular matrix deposition [21]), and selection of less immunogenic variants, can hamper effective recognition.

T-cell exhaustion is an effector T-cell-intrinsic mechanism for failure to mount an effective immune response. Single-cell genomic analysis has provided new vistas on the T-cell receptor repertoire and functional properties of tumour-infiltrating lymphocytes. Regulatory T cells (T_{reg} cells) have long been associated with immunosuppression in cancer. Single-cell analysis has led to the identification of molecules expressed by infiltrating T_{reg} cells [22]. For instance, the IL-1 decoy receptor IL-1R2 was found to be expressed at very high levels in infiltrating T_{reg} cells.

Whereas a Th1-orchestrated cytotoxic T-cell-mediated response has a protective function, Th2-polarized T cells and Th17 cells trigger tumour-promoting cascades. IL-4 and IL-13 produced by Th2 cells or by eosinophils elicit alternative M2 polarization of macrophages, which results in tumour promotion. Evidence suggests that this pathway plays a dominant role in carcinoma of the breast and in pancreatic ductal adenocarcinoma. Th17 cells activate a neutrophil-dependent pathway of immunity to extracellular pathogens, and neutrophils can contribute to myeloid cell-mediated tumour promotion [23].

Whereas a skewed, inappropriate response and exhaustion are important determinants of the failure of immunity to restrain cancer, active immunosuppression has emerged as a dominant mechanism of progression. Checkpoints are physiological mechanisms to restrain uncontrolled T-cell activation and tissue damage. Targeting of the programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1)

Fig. 3.9.2. The immunity–immunosuppression circle. ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; IL-10, interleukin-10; NK, natural killer; PG, prostaglandin; TAA, tumour-associated antigens; TGF-β, transforming growth factor β; Th2, T helper type 2; TSA, tumour-specific antigens.



axis and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) has had an unprecedented impact on cancer treatment. A host of molecular brakes acting on T cells as well as other cell types have been identified [3], and these represent candidate therapeutic targets.

Immunosuppression in the TME is orchestrated by tumour cells and/or by stromal cells, in particular myelomonocytic cells. Tumour cells produce immunosuppressive cytokines (IL-10, TGF-β) and express triggers of checkpoint blockade, such as PD-L1. PD-L1 gene amplification was found to occur in Hodgkin lymphoma, in which PD-L1 is also prominently expressed by TAMs. In general, the relative contribution of tumour cells versus myeloid cells to PD-L1 expression in the TME varies considerably in different human cancer types [15].

Myelomonocytic cells at different stages of differentiation or activation have the capacity to strongly suppress T-cell-mediated responses. MDSCs are operationally defined as a mixed population of relatively immature myeloid cells with potent suppressive activity [24]. Depending on the system examined among MDSCs, suppression was mediated by neutrophils or, more frequently, monocytes. Monocytic MDSCs differentiate into TAMs in the TME [24].

TAMs were found to exert immunosuppressive activity via diverse mechanisms. These include immunosuppressive cytokines (IL-10, TGF-β), triggers of checkpoint blockade (e.g. PD-L1), amino acid metabolism (arginase, tryptophan metabolites), and prostaglandins. Prostaglandins are particularly significant in view of the protective effect of aspirin on several human tumour types.

B cells and antibodies are part of the anti-tumour response. However, evidence suggests that B cells can contribute to tumour progression in certain epithelial tumours, such as prostate cancer. B-cell-mediated tumour promotion has been shown to involve different mechanisms, such as production of immunosuppressive cytokines (IL-10) and/or production of antibodies and formation of immune complexes that skew TAMs in an M2-like direction [6].

Adaptive T-cell-orchestrated immunity and its subversion are central in the control of carcinogenesis and progression. Recent results have shed new light on the long-overlooked role of innate lymphoid cells. NK cells are a population of innate lymphoid cells that has not been credited with playing a major role in resistance against solid tumour carcinogenesis. Evidence suggests that NK cells mediate resistance against haematopoietic neoplasms and restrain haematogenous dissemination of cancer cells. The differentiation and activity of NK cells are also controlled by negative regulators. Recently, novel NK cell checkpoints (e.g. IL-1R8) were identified, and unleashed NK cells were found to mediate resistance to carcinogenesis and metastasis at NK-cell-rich anatomical sites, such as the liver and the lung [25]. Elucidation of the molecular mechanisms that regulate the function of NK cells and innate lymphoid cells may pave the way to therapeutic strategies that are complementary to the current checkpoint blockade.

Prognosis versus prediction

As expected given the complexity and diversity of the roles of innate and adaptive immunity, infiltration of different components of the immune system has different, at times divergent, prognostic significance. Infiltration of TAMs is generally associated with worse prognosis [5], which is a reflection of their pro-tumour function. However, infiltration of TAMs is associated with better prognosis in colorectal cancer. The positive prognostic significance of TAMs in colorectal cancer reflects the association with response to chemotherapy. If these results are confirmed and extended, they raise the possibility of using TAMs to guide eligibility to chemotherapy.

In many human tumours, in particular colorectal cancer, T-cell infiltration is a positive prognostic indicator, independent of other parameters. The so-called Immunoscore to assess T-cell infiltration was validated in a large cooperative study. A recent study involving more than 3500 patients worldwide confirmed the value of the Immunoscore in colorectal cancer as an independent prognostic factor [19]. That study proposed moving from a tumour–node–metastasis (TNM) classification to a TNM-I classification of colorectal cancer, where "I" stands for immunity.

The results obtained in the past few years prove that assessment of the quantity and diversity of immune cell infiltration has prognostic significance. Genomic analysis of the TME has confirmed these observations and has provided tools for TME-based classification of cancer, as illustrated by colorectal cancer [19]. Conventional immunohistology as well as gene expression profiling are faced with the challenge of moving from prognosis to prediction, particularly in the context of immunotherapy.

Implications for immunotherapy

Immunotherapy in the form of PD-1/PD-L1 and CTLA-4 checkpoint blockade inhibitors and chimeric antigen receptor T cells is now part of the anticancer armamentarium. A recent review discussed the mechanisms, resistance to, and stumbling blocks of this approach [20]. In spite of the unprecedented broad impact of checkpoint blockade inhibitors, only approximately 20% of treated patients benefit from current checkpoint blockade. As discussed above, new vistas on fundamental mechanisms, including novel checkpoints, targeting of tumour-promoting myeloid cells [12], and harnessing NK cell potential, hold promise to help predict which patients will be responsive, thus sparing toxicity and contributing to the financial sustainability and to the improvement of therapeutic results.

Conclusions

Immunity is an essential component of the TME and a key determinant of metastasis [1,2,7]. Inflammatory cells, in particular TAMs, pave the way to tissue invasion and intravasation and provide a nurturing microenvironment for metastasis, serving as a component of the cancer cell niche at distant sites. NK cells are innate lymphoid cells that have long been considered to play a role in resistance against haematogenous dissemination of cancer cells, in particular to the lungs. Tumour progression and escape are associated with immunosuppressive pathways in innate and adaptive anti-tumour responses, which include, among others, suppressive myeloid cells, activation of checkpoint blockade, and induction and recruitment of T_{reg} cells.

Quantification of the immune and inflammatory landscape of the TME has provided novel prognostic indicators of cancer progression, as shown by quantification of tumour-infiltrating T cells and TAMs. Genomic technologies have added a new dimension to the characterization of the TME and to the classification of cancers. Finally, the elucidation of the mode of action of conventional cytoreductive strategies, the impact of checkpoint blockade inhibitors, the introduction of therapeutic antibodies, and, very recently, adoptive cell therapy for haematological malignancies [8,26,27] have proven the principle that the immune system can be harnessed to cope with advanced disseminated neoplastic diseases.

Full exploitation of the diagnostic and therapeutic potential of innate and adaptive immunity will require: an integrated in-depth analysis of its components in primary tumours versus spreading, metastatic tumours; the dissection of the diversity of metastatic niches; and the identification and development of new molecular and cellular tools. Moreover, the integration of –omics approaches with the elucidation of immunological complexity holds promise for the development of personalized immunotherapy, and for addressing the fundamental issue of the sustainability of these innovative approaches for health-care systems.

References

1. Balkwill F, Mantovani A (2001). Inflammation and cancer: back to Virchow? Lancet. 357(9255):539–45. https://doi.org/10.1016/S0140-6736(00)04046-0 PMID:11229684
2. Hanahan D, Weinberg RA (2011). Hallmarks of cancer: the next generation. Cell. 144(5):646–74. https://doi.org/10.1016/j.cell.2011.02.013 PMID:21376230
3. Chen DS, Mellman I (2017). Elements of cancer immunity and the cancer-immune set point. Nature. 541(7637):321–30. https://doi.org/10.1038/nature21349 PMID:28102259
4. Mantovani A, Allavena P, Sica A, Balkwill F (2008). Cancer-related inflammation. Nature. 454(7203):436–44. https://doi.org/10.1038/nature07205 PMID:18650914
5. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P (2017). Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol. 14(7):399–416. https://doi.org/10.1038/nrclinonc.2016.217 PMID:28117416
6. Coussens LM, Zitvogel L, Palucka AK (2013). Neutralizing tumor-promoting chronic inflammation: a magic bullet? Science. 339(6117):286–91. https://doi.org/10.1126/science.1232227 PMID:23329041
7. Fridman WH, Zitvogel L, Sautès-Fridman C, Kroemer G (2017). The immune contexture in cancer prognosis and treatment. Nat Rev Clin Oncol. 14(12):717–34. https://doi.org/10.1038/nrclinonc.2017.101 PMID:28741618
8. Gubin MM, Artyomov MN, Mardis ER, Schreiber RD (2015). Tumor neoantigens: building a framework for personalized cancer immunotherapy. J Clin Invest. 125(9):3413–21. https://doi.org/10.1172/JCI80008 PMID:26258412
9. Schumacher TN, Schreiber RD (2015). Neoantigens in cancer immunotherapy. Science. 348(6230):69–74. https://doi.org/10.1126/science.aaa4971 PMID:25838375
10. Azizi E, Carr AJ, Plitas G, Cornish AE, Konopacki C, Prabhakaran S, et al. (2018). Single-cell map of diverse immune phenotypes in the breast tumor microenvironment. Cell. 174(5):1293–1308.e36. https://doi.org/10.1016/j.cell.2018.05.060 PMID:29961579
11. Tseng D, Volkmer JP, Willingham SB, Contreras-Trujillo H, Fathman JW, Fernhoff NB, et al. (2013). Anti-CD47 antibody-mediated phagocytosis of cancer by macrophages primes an effective antitumor T-cell response. Proc Natl Acad Sci U S A. 110(27):11103–8. https://doi.org/10.1073/pnas.1305569110 PMID:23690610
12. Mantovani A, Longo DL (2018). Macrophage checkpoint blockade in cancer – back to the Future. N Engl J Med. 379(18):1777–9. https://doi.org/10.1056/NEJMe1811699 PMID:30380398
13. Advani R, Flinn I, Popplewell L, Forero A, Bartlett NL, Ghosh N, et al. (2018). CD47 blockade by Hu5F9-G4 and rituximab in non-Hodgkin's lymphoma. N Engl J Med. 379(18):1711–21. https://doi.org/10.1056/NEJMoa1807315 PMID:30380386
14. Bronte V, Brandau S, Chen SH, Colombo MP, Frey AB, Greten TF, et al. (2016). Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. Nat Commun. 7(1):12150. https://doi.org/10.1038/ncomms12150 PMID:27381735
15. Bonavita E, Gentile S, Rubino M, Maina V, Papait R, Kunderfranco P, et al. (2015). PTX3 is an extrinsic oncosuppressor regulating complement-dependent inflammation in cancer. Cell. 160(4):700–14. https://doi.org/10.1016/j.cell.2015.01.004 PMID:25679762
16. Reis ES, Mastellos DC, Ricklin D, Mantovani A, Lambris JD (2018). Complement in cancer: untangling an intricate relationship. Nat Rev Immunol. 18(1):5–18. https://doi.org/10.1038/nri.2017.97 PMID:28920587
17. Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ; CANTOS Trial Group (2017). Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet. 390(10105):1833–42. https://doi.org/10.1016/S0140-6736(17)32247-X PMID:28855077
18. Wu TC, Xu K, Martinek J, Young RR, Banchereau R, George J, et al. (2018). IL1 receptor antagonist controls transcriptional signature of inflammation in patients with metastatic breast cancer. Cancer Res. 78(18):5243–58. https://doi.org/10.1158/0008-5472.CAN-18-0413 PMID:30012670
19. Pagès F, Mlecnik B, Marliot F, Bindea G, Ou FS, Bifulco C, et al. (2018). International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. Lancet. 391(10135):2128–39. https://doi.org/10.1016/S0140-6736(18)30789-X PMID:29754777
20. Wei SC, Duffy CR, Allison JP (2018). Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov. 8(9):1069–86. https://doi.org/10.1158/2159-8290.CD-18-0367 PMID:30115704
21. Pearce OMT, Delaine-Smith RM, Maniati E, Nichols S, Wang J, Böhm S, et al. (2018). Deconstruction of a metastatic tumor microenvironment reveals a common matrix response in human cancers. Cancer Discov. 8(3):304–19. https://doi.org/10.1158/2159-8290.CD-17-0284 PMID:29196464
22. De Simone M, Arrigoni A, Rossetti G, Gruarin P, Ranzani V, Politano C, et al. (2016). Transcriptional landscape of human tissue lymphocytes unveils uniqueness of tumor-infiltrating T regulatory cells. Immunity. 45(5):1135–47. https://doi.org/10.1016/j.immuni.2016.10.021 PMID:27851914
23. Coffelt SB, Kersten K, Doornebal CW, Weiden J, Vrijland K, Hau CS, et al. (2015). IL-17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis. Nature. 522(7556):345–8. https://doi.org/10.1038/nature14282 PMID:25822788
24. Bronte V (2018). The mesenchymal and myeloid regulation of immunity: power is nothing without control. Semin Immunol. 35:1–2. https://doi.org/10.1016/j.smim.2018.03.001 PMID:29566937
25. Molgora M, Bonavita E, Ponzetta A, Riva F, Barbagallo M, Jaillon S, et al. (2017). IL-1R8 is a checkpoint in NK cells regulating anti-tumour and anti-viral activity. Nature. 551(7678):110–4. https://doi.org/10.1038/nature24293 PMID:29072292
26. Sadelain M, Rivière I, Riddell S (2017). Therapeutic T cell engineering. Nature. 545(7655):423–31. https://doi.org/10.1038/nature22395 PMID:28541315
27. Anderson KG, Stromnes IM, Greenberg PD (2017). Obstacles posed by the tumor microenvironment to T cell activity: a case for synergistic therapies. Cancer Cell. 31(3):311–25. https://doi.org/10.1016/j.ccell.2017.02.008 PMID:28292435

3.10 The microbiome
Its influence on tumorigenesis and therapy

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Mazda Jenab (reviewer)
Herbert Tilg (reviewer)

SUMMARY

- Changes in the human microbiota – particularly in the large intestine, but also in other locations – have been associated with multiple tumour types in retrospective case–control studies. However, it often remains unclear whether these alterations are consequential, or relevant to cancer etiology. Currently, evidence is strongest for an enrichment of pathogenic species in the gut microbiota associated with cancers of the digestive tract.
- To date, bacterial mechanisms that promote carcinogenesis are still incompletely elucidated. However, a few bacterial genotoxins and carcinogens are well described, as well as mechanisms by which bacteria reprogramme host signalling towards neoplastic transformation, promote inflammation, or protect against immunosurveillance.
- Recent research has uncovered profound effects of the gut microbiota on cancer therapies. Strikingly, response to immunotherapy depends partially on an intact gut microbiota with immunostimulatory function. Whereas antibiotics compromise immunotherapy response, microbiome reconstitution (e.g. by probiotics) improves outcomes in animal models.
- Microbiota-targeted cancer prevention strategies appear promising, but they have yet to be evaluated in prospective studies.

The understanding of the complex relationship between the human microbiota and its host organism has expanded rapidly in recent years, fuelled by high-throughput metagenomic sequencing technologies, advanced bioinformatics analysis methodology, and the development of experimental model systems [1]. Research focusing primarily on the gut microbiome has led to a growing appreciation of its key role in maintaining health, and of dysbiotic gut microbiome states being associated with many common human disorders, including cancer [1].

The microbiota, in particular in the gut, is shaped by, and in turn modulates, many environmental and host factors by chemical transformation of endogenous (host) and exogenous (diet, medication) metabolites as well as host–microbiota signalling. Recently, we have begun to understand the contribution of these processes to individual-specific cancer risks and therapy outcomes (Fig. 3.10.2) [1–7].

Central to this host–microbiota cross-talk is the host immune system (see Chapter 3.9) [3,7]. Host cells sense commensal and pathogenic bacteria through pattern recognition receptors. These bind to microbe-associated molecular patterns, which are conserved components of bacterial cell walls [3]. Under homeostatic conditions, mucus and epithelial cells shield host tissues from unrestricted exposure to microbe-associated molecular patterns. However, many dysbiotic microbiome states, both in the intestine and in the oral cavity, are characterized by microbes degrading and penetrating the mucus. This compromised barrier eventually permits bacterial translocation and allows increased levels of microbe-associated molecular patterns to reach the circulation. The inflammatory responses that ensue both locally and systemically are a central factor in many pathologies and contribute to neoplastic transformations in many organs [3,8].

Cancers associated with a single microbial pathogen

Helicobacter pylori is the best-understood model bacterium with a causal role in infection-related cancer, and the only one that has been classified as carcinogenic to humans (Group 1) by the IARC Monographs (see Chapter 2.2). As a persistent colonizer of gastric mucosa, *H. pylori* can develop pathogenic traits, and its presence is a major risk factor for gastric cancer. Consistent with its causal role, eradication of *H. pylori* was found to significantly reduce the incidence of gastric cancer, both in animals and in humans [9].

Fig. 3.10.1. A street in Busan, a large city in the Republic of Korea. The presence of *Helicobacter pylori* bacteria, a major risk factor for gastric cancer, is particularly relevant to parts of China, Japan, and the Republic of Korea.

Research on *Helicobacter* has unveiled many of the key molecular mechanisms by which bacteria persistently colonize host tissues and create a pro-oncogenic milieu. Many of these might be generalizable to other cancer-associated pathogens (Fig. 3.10.3) [10]. Key features of *H. pylori* virulence include bacterial surface proteins facilitating attachment to epithelial cells, enzymes capable of modifying the host environment to facilitate colonization (e.g. urease permitting survival in a low-pH environment), and manipulation of host signalling. Reprogramming of cellular signalling can be achieved via diffusible toxins and/or export of effector proteins into host cells through a bacterial secretion system. This can locally alter mucus and acid secretion of the host, which further facilitates colonization; it can also entail stimulation of host pathways that drive proliferation and cell survival or compromise tumour suppression and DNA damage response (see Chapter 3.4). Manipulation of other host pathways can alter host cell morphology and polarity. Finally, despite its ability to sustain a chronic inflammatory response, *Helicobacter* largely evades the immune system to persist in the host (Fig. 3.10.3) [9,10].

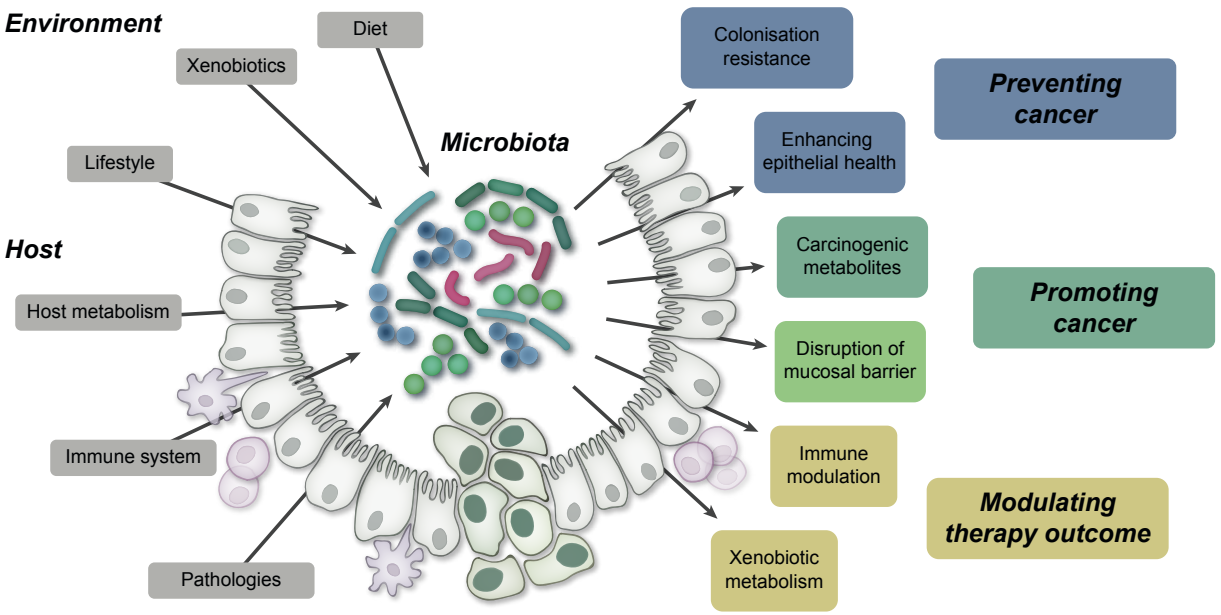
Another well-studied example of a single bacterial pathogen that may promote tumorigenesis during chronic infection is *Salmonella enterica* serovar Typhi. Epidemiological studies have associated persistent *Salmonella* colonization of the gall bladder with strongly increased risk of biliary cancer. This is further supported by research on mouse models of long-term *Salmonella* infection [10,11].

In these etiologies, a single infectious agent is sufficient to promote neoplastic transformation. Based on culture-independent metagenomic sequencing of the more diverse microbial communities that inhabit the mouth and the gut, polymicrobial signatures have been statistically associated with several other tumour types, in particular with those that are anatomically close to the gastrointestinal tract. However, because of the complexity of cancer-associated alterations in these communities, the timing of microbial tumour colonization, causalities, and molecular mechanisms remain to be elucidated in most cases. Although some

FUNDAMENTALS

- Epithelial and mucosal surfaces of the human body are colonized by complex microbial communities consisting of bacteria, archaea, eukaryotes (mostly unicellular in this context), and viruses; collectively, they are referred to as the microbiota.
- The microbiota is characterized by large taxonomic diversity and inter-individual heterogeneity, and also possesses enormous metabolic capabilities, which far exceed the enzymatic repertoire of the host.
- Collectively, the microbiota and its genes and metabolites, which shape the environmental milieu, are referred to as the microbiome.
- The microbiota has co-evolved with its host to fulfil many important physiological functions in co-metabolism with the rest of the organism; these include the digestion of dietary compounds and the synthesis of micronutrients, as well as the breakdown of endogenous (host) and xenobiotic compounds, including drugs.
- Culture-independent metagenomic sequencing (and other –omics technologies) has enabled microbiome characterization in situ. Based on this technology, microbiome-wide association studies have linked many common human diseases, including cancers, with changes in microbiota composition; disease-associated microbiome states are sometimes referred to as dysbiosis.
- Experimental studies based on in vitro systems and animal models complement microbiome-wide association studies as they have started to unravel causal relationships and molecular mechanisms underlying microbe–host interactions in health and disease, including in the etiology of several cancers.

Fig. 3.10.2. Environment- and host-dependent effects of the microbiota on carcinogenesis, cancer prevention, and therapy. The composition of the microbiota is shaped by many environmental factors, such as diet and xenobiotics (pharmaceuticals), as well as host factors, which include lifestyle, metabolism, the immune system, and pathophysiological conditions (e.g. cancer) that alter mucosal milieus. The microbiota itself modulates many of these effects, which contributes to individual-specific cancer risk and therapy outcomes. Examples of such modulations are (i) gut microbial fermentation of dietary fibre into butyrate (and other short-chain fatty acids), which promotes epithelial health and prevents neoplastic transformation; (ii) gut microbial metabolism of primary bile acids into carcinogenic secondary bile acids; (iii) disruption of mucosal barriers by microbial mucus degradation and pro-inflammatory metabolites, which promotes cancer development; (iv) gut microbial drug metabolism and reversal of host detoxification processes; and (v) microbial immunostimulation. Both (iv) and (v) can affect the outcome of cancer therapy. Current knowledge of cancer-preventing or cancer-promoting mechanisms is based on preclinical and observational studies. However, because large-scale cohort studies in multiple countries are now collecting faecal samples, it will soon become possible to evaluate gut microbial risk factors for several cancer types prospectively. Similarly, prospective follow-up studies of cancer patients will enable better definition of prognostic microbial biomarkers for general survival or treatment success. (For more details, see [2–5,20].)



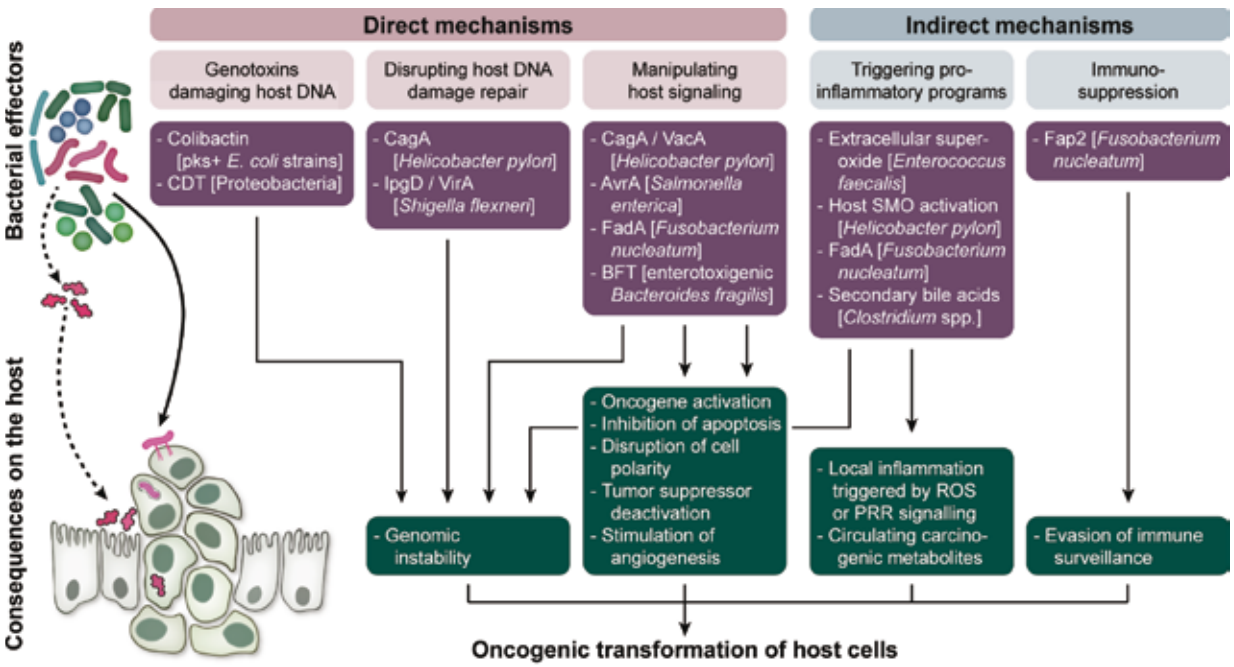
bacterial pathogens and their pro-oncogenic mechanisms have been characterized in animal models, the evidence from clinical studies is still limited. To date, the role of the gut microbiota in gastrointestinal tumour development has been most conclusively defined.

Cancers of the gastrointestinal tract associated with altered gut microbiota composition

Many independent studies have linked colorectal cancer at the time of diagnosis to alterations in gut (faecal and mucosal) microbiota composition. Metagenomic meta-analyses confirmed a broad agreement of tumour-enriched bacterial taxa between studies. These include the genera *Fusobacterium*, *Parvimonas*, *Porphyromonas*, and *Escherichia* [4,12–15]. Preclinical studies have complemented these microbiome-wide association studies by elucidating the molecular mechanisms through which gut microbes may directly or indirectly promote colorectal carcinogenesis (Fig. 3.10.3). Mouse models have revealed several virulence factors and metabolites from *Fusobacterium nucleatum* and strains of *Bacteroides fragilis* or *Escherichia coli* that can trigger pro-oncogenic signalling and cellular transformation programmes (Fig. 3.10.3) [2,4,13]. In addition, colorectal cancer appears to be linked to a shift in the metabolic products of bacterial digestion of dietary and host metabolites (contained in meat, fat, fibre, or digestive juices) from those that promote epithelial health (e.g. short-chain fatty acids, vitamins, and antioxidants) towards those that contribute to carcinogenesis and inflammation (including secondary bile acids and protein degradation products) (see Chapter 5.5) [4,5,14–16].

Because the liver is connected to the intestine through the portal vein, it is exposed to gut bacterial metabolites translocating through the epithelium into the circulation. Especially when the intestinal barrier is compromised, microbial metabolites and microbe-associated molecular patterns reach the liver in higher concentrations. There, upon binding to pattern recognition receptors at multiple liver cell types, they can elicit persistent inflammatory programmes. This process was found to be a hallmark of many chronic liver diseases that are

Fig. 3.10.3. Molecular mechanisms by which bacteria promote carcinogenesis. Although most mechanisms remain to be characterized in detail, they can be broadly grouped into direct and indirect mechanisms. Bacteria can directly contribute to genomic instability of host cells via diffusible genotoxins such as colibactin or cytolethal distending toxin (CDT). Another means of directly promoting genomic instability is to interfere with host DNA damage repair (in some cases via manipulation of p53 activity). Bacterial pathogens have further evolved a range of mechanisms that divert host signalling processes to promote cell survival and proliferation. As a consequence, various pro-oncogenic cellular programmes are triggered, for instance via activation of oncogenes and deactivation of tumour suppressors, or via disruption of cell–cell junctions, cell polarity, and epithelial barrier integrity (through interference with β-catenin/WNT signalling). Bacterial manipulation of the mitogen-activated protein kinase (MAPK), the signal transducer and activator of transcription 3 (STAT3) protein, and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathways can result in pro-inflammatory signalling (see also Chapter 3.5). Systemic inflammation can also be promoted indirectly via signalling of host pattern recognition receptors (PRRs) binding to microbe-associated molecular patterns, which include bacterial cell-wall antigens such as lipopolysaccharide. Bacteria are also capable of producing pro-inflammatory metabolites, such as secondary bile acids, which can act systemically when reaching the circulation. Indirect ways of triggering local inflammation include the production of reactive oxygen species (ROS), such as extracellular superoxide, or the induction of the host spermine oxidase (SMO), an enzyme that is involved in generating hydrogen peroxide from polyamine breakdown. Finally, some bacteria can also elicit immunosuppressive responses, thereby indirectly contributing to tumour survival through evasion of immune surveillance. AvrA, avirulence A; BFT, *Bacteroides fragilis* toxin; CagA, cytotoxin-associated gene A; FadA, *Fusobacterium* adhesin A; IpgD, inositol phosphate phosphatase; VacA, vacuolating cytotoxin A. (For a more detailed presentation of these mechanisms, see [2,10].)

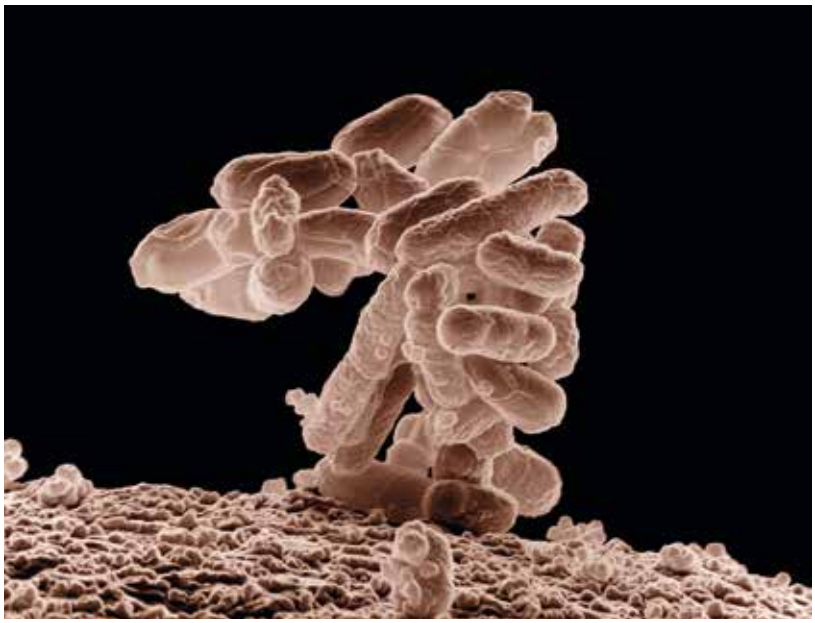


precursors to hepatocellular carcinoma (see Chapter 5.6) [8]. Another process by which intestinal bacteria promote hepatocellular carcinoma involves bile acids. Primary bile acids are secreted from the liver into the gut, where they can be converted into secondary bile acids, such as deoxycholic acid, by intestinal *Clostridium* spp. After re-uptake, deoxycholic acid circulates back to the liver, where it exerts its carcinogenic effects. In sum, several clinical studies have revealed profound changes in the gut microbiota associated with chronic liver diseases, and preclinical findings support a causal role of an altered microbiome in liver inflammation and malignancy [8].

There is also emerging evidence for a bacterial contribution to pancreatic cancer development [13]. In mouse models, germ-free conditions or administration of antibiotics were shown to slow down progression of pancreatic ductal adenocarcinoma. Moreover, the microbiota colonizing the pancreas was found to play an important role in regulating the inflammatory tone in the pancreatic tumour microenvironment in mice via pattern recognition receptor signalling [17]. However, larger clinical studies are needed to validate individual microbial taxa enriched in pancreatic tissue [18] or in the mouth and the gut of patients with pancreatic ductal adenocarcinoma.

Although microbiome-wide association studies of medium scale (with $n \approx 300$ each) have investigated the oral microbiota in case–control studies for oesophageal cancer and head and neck cancers, bacteria–tumour associations were relatively weak in these patient populations. In addition, it is currently unclear whether microbial markers

Fig. 3.10.4. Low-temperature electron micrograph of a cluster of *Escherichia coli* bacteria, ×10 000. *E. coli* strains can produce the carcinogenic colibactin toxin.



would have diagnostic or prognostic value for these tumour types [19,20].

Cancers in organs outside the gastrointestinal tract

Breast cancer

Among tumour types outside the digestive tract, breast cancer has been most extensively examined for potential associations with microbiota at various body sites [7,21]. As in the liver, tumorigenesis in the breast may potentially be influenced by the gut microbiota through pro-inflammatory metabolites (microbe-associated molecular patterns). Another potential connection occurs via estrogen metabolism. Intestinal bacteria may affect estrogen exposure, a major risk factor for breast cancer (see Chapter 2.11), via activation (or reactivation) of estrogens (excreted in conjugated form from the liver into the intestine) or dietary xeno-estrogens [21].

Clinical studies have found estrogen-dependent and estrogen-independent microbiome associations with breast cancer, but a mechanistic understanding of hormonal co-metabolism between the host and its gut microbiome has yet to be elucidated, and its clinical significance remains to be established [21]. Other studies have examined microbiota residing in breast tissue of women with and without breast cancer. Whereas structural alterations were not detected in association with breast cancer, some studies found rare taxa to differ in abundance in tumour tissue. However, among the published microbiome-wide association studies there is little agreement on the precise breast cancer-associated bacterial taxa [21].

Lung cancer

An involvement of the respiratory tract microbiota in lung cancer development is conceivable, based on epidemiological studies showing bacterial lung infections (including pneumonia) to be associated with lung cancer risk [13]. However, only few studies of relatively small scale have directly investigated this question; hence, the evidence on the role of the airway microbiota in lung cancer is currently still inconclusive.

Role of the gut microbiome in cancer therapy

The gut microbiota is increasingly appreciated as a versatile “microbial pharmacist within us” [22], because evidence is accumulating that it can also affect the pharmacokinetics, efficacy, and toxicity of various anticancer therapies (Fig. 3.10.5) [6,22].

Chemotherapy

As one of the first examples, irinotecan was reported to be metabolized by intestinal bacteria. This chemotherapeutic drug, used to treat colorectal cancer, is detoxified (glucuronidated) in the liver to SN-38-G. After SN-38-G is excreted into the intestine, it can be reactivated by bacterial β-glucuronidases, and this causes intestinal toxicity, such as severe diarrhoea [6].

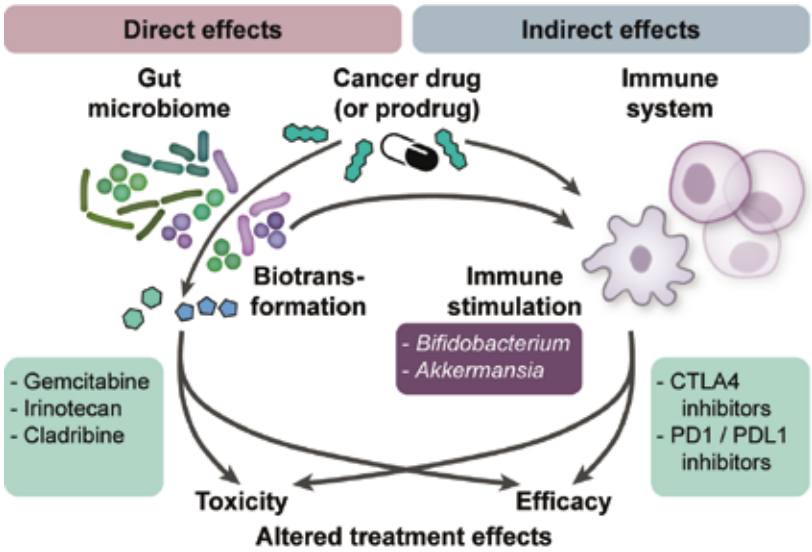
Another example is the chemotherapeutic drug gemcitabine, which can be rendered inactive by bacterial enzymes, as has been demonstrated in mouse models. Bacteria capable of this biotransformation were found in tissue samples from patients with pancreatic ductal adenocarcinoma, suggesting that this bacterial resistance mechanism is clinically relevant [6,16,23,24].

There is also recent evidence that the gut microbiota modulates the anti-tumour efficacy of platin-based and cyclophosphamide chemotherapies. The efficacy of cisplatin and oxaliplatin is greatly decreased in mice under germ-free conditions or when their gut microbiome has been perturbed with broad-spectrum antibiotics. The immunogenic cell death that these drugs induce is dependent on inflammatory responses (partially mediated by signalling through pattern recognition receptors), which in mouse models were enhanced by the administration of specific bacterial species [6,7].

Immunotherapy

Clinical and preclinical studies have indicated that the composition of

Fig. 3.10.5. Effects that the gut microbiota can have on cancer treatment. The gut microbiota can influence cancer therapy either directly, via biotransformation of drugs, or indirectly, via immune modulation. The indirect effects have recently been found to play a critical role in response to cancer immunotherapy. Examples of intestinal bacterial genera with immunostimulatory effects are highlighted in dark magenta, and cancer treatments that are known to be affected by bacteria are highlighted in cyan. (For more details, see the text and [6,7,20,21].)



the gut microbiota is an important cause of heterogeneous patient response to cancer immunotherapy, among several other factors that determine the cancer immune phenotype [6,24,25].

These studies have shown that the composition and diversity of a patient's gut microbiota (assessed before the start of treatment) are predictive of the response to immunotherapy with checkpoint inhibitors – primarily targeting the programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) interaction, but also cytotoxic T lymphocyte-associated protein 4 (CTLA-4) [6,24,26–28]. In patients with melanoma, renal cell carcinoma, or non-small cell lung cancer, the diversity of the gut microbiota was predictive of a favourable prognosis and response to immunotherapy [26–28]. These data are consistent with clinical observations that treatment with antibiotics can compromise the efficacy of immunotherapy, presumably due to a dramatic loss of microbiota diversity [24,26].

Collectively, these studies established that the gut microbiota has a systemic effect on the outcome of treatments targeting various cancers types, including some that are distal to the gastrointestinal tract (e.g. melanoma and non-small cell lung cancer). The molecular mechanisms through which the gut microbiota achieves immune activation are still poorly defined. Consequently, elucidation of the cross-talk between the microbiota and innate as well as adaptive immunity has become a major research focus [3,29].

Clinical studies published to date have been limited in size (n < 100 in most cases) and only partially agree on the gut commensal markers for response to immunotherapy. However, by examining how the response phenotype from human patients can be transferred to animals, these studies have provided strong data supporting a causal role of gut microbes. When the faecal microbiome from patients who responded to immunotherapy was transplanted into mice, the recipients showed slower tumour progression and improved efficacy of anti-PD-1 treatment. Similar effects were observed in mouse tumour models upon administration of defined bacterial marker species predictive of PD-1 response [6,24,26–28,30].

Allogeneic haematopoietic stem cell transplantation

Allogeneic haematopoietic stem cell transplantation can be seen as a form of immunotherapy that is primarily used to treat various haematological malignancies (and also immune disorders). Although potentially curative, it is associated with a range of serious, life-threatening complications, which include graft-versus-host disease and systemic infections. Therefore, several preclinical and clinical studies have examined whether the gut microbiome influences relapse or mortality after allogeneic haematopoietic stem cell transplantation. They found that general microbial diversity and the abundance of specific microbial taxa (from within the classes of Clostridiales, Bacteroidia, and Actinobacteria) were prognostic markers of allograft maintenance and survival [31,32].

Probiotics/prebiotics and dietary interventions for improved cancer therapies?

The accumulating evidence that gut microbes affect cancer therapy has reinforced interest in microbiome modulations that aim to improve response rates. Along these lines, preclinical studies have found beneficial effects of probiotics (oral administration of defined live bacterial strains) on progression-free survival in mice when administered alone or in combination with immunotherapy [7,24,26,30]. However, current regulations impede the rapid clinical translation of these findings; strict regulation of probiotics as combination therapies with immunotherapeutic treatment modalities necessitates extensive clinical trials [24].

An attractive alternative may be to instead focus on prebiotics (dietary compounds that stimulate

the growth of certain gut microbial clades) or diets that are rationally designed to modulate the gut microbiome. These could promote microbiota diversity and the expansion of gut commensal taxa that are predictive of therapy response and progression-free survival relative to those that are associated with non-response or severe complications [7,24,27,31].

Microbiome-based approaches to cancer prevention

The current understanding of microbial processes with a causal effect on carcinogenesis is still very incomplete, and this limits primary cancer prevention approaches targeting the microbiota. Nevertheless, a few directions are emerging, and in particular approaches that closely integrate with nutrition appear promising (see Chapter 2.6). Reconsidering dietary recommendations in view of the emerging knowledge of their direct effects on, and their modulation by, gut microbial metabolism may be warranted. For instance, increasing dietary fibre content (beyond current recommendations) may help to prevent malignancies in a microbiota-dependent manner via stimulation of butyrate production (Fig. 3.10.2) [5]. The recently discovered impact of the gut microbiome on cancer immunosurveillance suggests that early interventions aiming to rectify gut microbiota dysbiosis and to promote microbiota diversity may also help to prevent cancer. These questions are anticipated to also be addressed in prospective cohort studies or directly in prospective intervention studies aiming to modulate the microbiome. However, these intervention studies will have to be sufficiently powered to overcome the large inter-individual heterogeneity in microbiota composition and response [7].

Eradication of *H. pylori* has proven to be an effective strategy for the prevention of gastric cancer [9]. However, studies of more complex microbial communities have had difficulties to precisely pinpoint cancer-associated bacterial strains and metabolic processes and to establish their carcinogenic effects. At least for some tumour types, for example colorectal cancer, research towards this goal has nonetheless progressed rapidly in the past 5 years. Growing appreciation of diverse microbial processes with potential roles in cancer etiology (Fig. 3.10.3) also drives the continuing search for specific microbiome modulation strategies. These could either aim to suppress pathogenic species with narrow-spectrum antibiotics that minimize collateral damage to commensal microbes, or directly target pathogenic or carcinogenic processes with small-molecule inhibitors (e.g. Fusobacterial adhesion proteins, required for their virulence, or the Clostridial 7α-dehydroxylation pathway, which results in carcinogenic secondary bile acids; see Fig. 3.10.3) [5,7].

Secondary cancer prevention strategies based on the microbiome are closer to actual implementation. Several studies have suggested that microbiota alterations in colorectal cancer are characteristic enough to hold promise for non-invasive cancer screening (potentially also in combination with existing non-invasive tests) [4,13–16]. However, no microbial biomarkers for accurate detection of precancerous colonic lesions (advanced adenomas) have been discovered yet [13]. Early microbiome-wide association studies for several other cancer types – although they are of small scale and lack independent confirmation – fuel the hope for microbiome-based early detection of cancer. Continuing efforts for liver cancer (primary cancer and metastases) and pancreatic cancer are particularly promising [13,33], but all these microbiome-based secondary prevention approaches will also have to be evaluated in large prospective trials.

References

1. Lynch SV, Pedersen O (2016). The human intestinal microbiome in health and disease. N Engl J Med. 375(24):2369–79. https://doi.org/10.1056/NEJMra1600266 PMID:27974040
2. Garrett WS (2015). Cancer and the microbiota. Science. 348(6230):80–6. https://doi.org/10.1126/science.aaa4972 PMID:25838377
3. Belkaid Y, Hand TW (2014). Role of the microbiota in immunity and inflammation. Cell. 157(1):121–41. https://doi.org/10.1016/j.cell.2014.03.011 PMID:24679531
4. Tilg H, Adolph TE, Gerner RR, Moschen AR (2018). The intestinal microbiota in colorectal cancer. Cancer Cell. 33(6):954–64. https://doi.org/10.1016/j.ccell.2018.03.004 PMID:29657127
5. O'Keefe SJ (2016). Diet, microorganisms and their metabolites, and colon cancer. Nat Rev Gastroenterol Hepatol. 13(12):691–706. https://doi.org/10.1038/nrgastro.2016.165 PMID:27848961
6. Roy S, Trinchieri G (2017). Microbiota: a key orchestrator of cancer therapy. Nat Rev Cancer. 17(5):271–85. https://doi.org/10.1038/nrc.2017.13 PMID:28303904
7. Zitvogel L, Galluzzi L, Viaud S, Vétizou M, Daillère R, Merad M, et al. (2015). Cancer and the gut microbiota: an unexpected link. Sci Transl Med. 7(271):271ps1. https://doi.org/10.1126/scitranslmed.3010473 PMID:25609166
8. Yu LX, Schwabe RF (2017). The gut microbiome and liver cancer: mechanisms and clinical translation. Nat Rev Gastroenterol Hepatol. 14(9):527–39. https://doi.org/10.1038/nrgastro.2017.72 PMID:28676707

9. Wroblewski LE, Peek RM Jr, Wilson KT (2010). *Helicobacter pylori* and gastric cancer: factors that modulate disease risk. Clin Microbiol Rev. 23(4):713–39. https://doi.org/10.1128/CMR.00011-10 PMID:20930071

10. Gagnaire A, Nadel B, Raoult D, Neefjes J, Gorvel JP (2017). Collateral damage: insights into bacterial mechanisms that predispose host cells to cancer. Nat Rev Microbiol. 15(2):109–28. https://doi.org/10.1038/nrmicro.2016.171 PMID:28045107

11. Gunn JS, Marshall JM, Baker S, Dongol S, Charles RC, Ryan ET (2014). *Salmonella* chronic carriage: epidemiology, diagnosis, and gallbladder persistence. Trends Microbiol. 22(11):648–55. https://doi.org/10.1016/j.tim.2014.06.007 PMID:25065707

12. Sze MA, Schloss PD (2018). Leveraging existing 16S rRNA gene surveys to identify reproducible biomarkers in individuals with colorectal tumors. MBio. 9(3):e00630-18. https://doi.org/10.1128/mBio.00630-18 PMID:29871916

13. Vogtmann E, Goedert JJ (2016). Epidemiologic studies of the human microbiome and cancer. Br J Cancer. 114(3):237–42. https://doi.org/10.1038/bjc.2015.465 PMID:26730578

14. Thomas AM, Manghi P, Asnicar F, Pasolli E, Armanini F, Zolfo M, et al. (2019). Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation. Nat Med. 25(4):667–78. https://doi.org/10.1038/s41591-019-0405-7 PMID:30936548

15. Wirbel J, Pyl PT, Kartal E, Zych K, Kashani A, Milanese A, et al. (2019). Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. Nat Med. 25(4):679–89. https://10.1038/s41591-019-0406-6 PMID:30936547

16. Zeller G, Tap J, Voigt AY, Sunagawa S, Kultima JR, Costea PI, et al. (2014). Potential of fecal microbiota for early-stage detection of colorectal cancer. Mol Syst Biol. 10(11):766. https://doi.org/10.15252/msb.20145645 PMID:25432777

17. Pushalkar S, Hundeyin M, Daley D, Zambirinis CP, Kurz E, Mishra A, et al. (2018). The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression. Cancer Discov. 8(4):403–16. https://doi.org/10.1158/2159-8290.CD-17-1134 PMID:29567829

18. Geller LT, Barzily-Rokni M, Danino T, Jonas OH, Shental N, Nejman D, et al. (2017). Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. Science. 357(6356):1156–60. https://doi.org/10.1126/science.aah5043 PMID:28912244

19. Hayes RB, Ahn J, Fan X, Peters BA, Ma Y, Yang L, et al. (2018). Association of oral microbiome with risk for incident head and neck squamous cell cancer. JAMA Oncol. 4(3):358–65. https://doi.org/10.1001/jamaoncol.2017.4777 PMID:29327043

20. Peters BA, Wu J, Pei Z, Yang L, Purdue MP, Freedman ND, et al. (2017). Oral microbiome composition reflects prospective risk for esophageal cancers. Cancer Res. 77(23):6777–87. https://doi.org/10.1158/0008-5472.CAN-17-1296 PMID:29196415

21. Fernández MF, Reina-Pérez I, Astorga JM, Rodríguez-Carrillo A, Plaza-Díaz J, Fontana L (2018). Breast cancer and its relationship with the microbiota. Int J Environ Res Public Health. 15(8):1747. https://doi.org/10.3390/ijerph15081747 PMID:30110974

22. Spanogiannopoulos P, Bess EN, Carmody RN, Turnbaugh PJ (2016). The microbial pharmacists within us: a metagenomic view of xenobiotic metabolism. Nat Rev Microbiol. 14(5):273–87. https://doi.org/10.1038/nrmicro.2016.17 PMID:26972811

23. Lehouritis P, Cummins J, Stanton M, Murphy CT, McCarthy FO, Reid G, et al. (2015). Local bacteria affect the efficacy of chemotherapeutic drugs. Sci Rep. 5(1):14554. https://doi.org/10.1038/srep14554 PMID:26416623

24. Zitvogel L, Ma Y, Raoult D, Kroemer G, Gajewski TF (2018). The microbiome in cancer immunotherapy: diagnostic tools and therapeutic strategies. Science. 359(6382):1366–70. https://doi.org/10.1126/science.aar6918 PMID:29567708

25. Chen DS, Mellman I (2017). Elements of cancer immunity and the cancer-immune set point. Nature. 541(7637):321–30. https://doi.org/10.1038/nature21349 PMID:28102259

26. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, et al. (2018). Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 359(6371):91–7. https://doi.org/10.1126/science.aan3706 PMID:29097494

27. Matson V, Fessler J, Bao R, Chongsuwat T, Zha Y, Alegre ML, et al. (2018). The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science. 359(6371):104–8. https://doi.org/10.1126/science.aao3290 PMID:29302014

28. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. (2018). Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 359(6371):97–103. https://doi.org/10.1126/science.aan4236 PMID:29097493

29. Schirmer M, Smeekens SP, Vlamakis H, Jaeger M, Oosting M, Franzosa EA, et al. (2016). Linking the human gut microbiome to inflammatory cytokine production capacity. Cell. 167(4):1125–36.e8. https://doi.org/10.1016/j.cell.2016.10.020 PMID:27814509

30. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, et al. (2015). Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science. 350(6264):1084–9. https://doi.org/10.1126/science.aac4255 PMID:26541606

31. Shono Y, van den Brink MRM (2018). Gut microbiota injury in allogeneic haematopoietic stem cell transplantation. Nat Rev Cancer. 18(5):283–95. https://doi.org/10.1038/nrc.2018.10 PMID:29449660

32. Peled JU, Devlin SM, Staffas A, Lumish M, Khanin R, Littmann ER, et al. (2017). Intestinal microbiota and relapse after hematopoietic-cell transplantation. J Clin Oncol. 35(15):1650–9. https://doi.org/10.1200/JCO.2016.70.3348 PMID:28296584

33. Ren Z, Li A, Jiang J, Zhou L, Yu Z, Lu H, et al. (2018). Gut microbiome analysis as a tool towards targeted non-invasive biomarkers for early hepatocellular carcinoma. Gut. 68(6):1014–23. http://dx.doi.org/10.1136/gutjnl-2017-315084 PMID:30045880

3.11 Identifying carcinogens from 10 key characteristics

A new approach based on mechanisms

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SUMMARY

- The key characteristics of human carcinogens were recently introduced as the basis for a uniform approach to evaluating mechanistic evidence to support cancer hazard identification.
- The key characteristics reflect the chemical and biological properties of established human carcinogens, including "is genotoxic", "is immunosuppressive", and "modulates receptor-mediated effects". The key characteristics are distinct from the hallmarks of cancer, which relate to the properties of cancer cells.
- The key characteristics approach avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence. Therefore, data on the key characteristics can provide independent evidence of carcinogenicity when data from studies in humans are lacking, and can help in establishing biological plausibility.
- The key characteristics approach is being increasingly applied by agencies throughout the world, and key characteristics for other toxicological hazards are being developed.
- The key characteristics approach can inform the design of high-throughput testing systems and human biomarker studies with greater relevance to cancer hazard identification – the first step in cancer prevention.

The IARC Monographs programme identifies the causes of human cancer, based on the systematic assembly, review, and integration of evidence of cancer in humans, cancer in experimental animals, and carcinogen mechanisms. Of the approximately 120 agents classified by the IARC Monographs as carcinogenic to humans (Group 1), most have *sufficient evidence of carcinogenicity* in humans, based on epidemiological studies. However, epidemiological studies of cancer in exposed humans are often limited in number, and may have deficiencies in terms of sample size, confounding, and exposure characterization. Furthermore, for chemicals that have recently been introduced on the market, epidemiological studies may not exist or may not be relevant, because of the long latency period for cancer development. The number of lifetime rodent cancer bioassays being performed is declining, and only a fraction of the approximately 75 000 chemicals that are listed in the Toxic Substances Control Act Chemical Substance Inventory of the United States Environmental Protection Agency (EPA) have been formally evaluated by the United States National Toxicology Program (NTP) [1] or other national testing programmes (e.g. the Japan Bioassay Research Center of the Japan Organization of Occupational Health and Safety). In contrast, data on carcinogen mechanisms from human biomarker studies, in vivo animal tests, and in vitro cell culture models are increasing in both volume and diversity [2–5].

When the evidence from human epidemiological studies is *less than sufficient*, strong mechanistic data can play a pivotal role in the overall carcinogen hazard classification [6]. For instance, even though the evidence from rodent cancer bioassays provided *sufficient evidence of carcinogenicity* in experimental animals, D-limonene was categorized as not classifiable as to its carcinogenicity to humans (Group 3) on the basis of mechanistic and other relevant data, because the probable mechanism of carcinogenicity in experimental animals was unlikely to operate in humans. Other agents have been classified as probably carcinogenic to humans (Group 2A) or even as carcinogenic to humans (Group 1) based on strong evidence for recognized carcinogen mechanisms, such as genotoxicity (for ethylene oxide), inhibiting DNA repair (for etoposide), or binding to the aryl hydrocarbon receptor and subsequent downstream effects (for 2,3,7,8-tetrachlorodibenzo-*para*-dioxin).

A recent review of all the agents classified as carcinogenic to humans (Group 1) in IARC Monographs Volumes 1–99 revealed several issues relevant to improving the evaluation of mechanistic data for carcinogen hazard identification [7]. First, many human carcinogens show a number of characteristics that are shared among carcinogenic agents. Second, different human carcinogens may exhibit a different spectrum of these key characteristics and operate through distinct mechanisms. Third, for many carcinogens evaluated before Volume 100 of the IARC Monographs, few data were available on some mechanisms of recognized importance in carcinogenesis, such as epigenetic alterations (see Chapter 3.8) [8]. Fourth, the evaluation of mechanistic and other relevant data has been further challenged by the lack of a systematic and transparent method of searching for and assembling mechanistic data for cancer hazard identification. Specifically, there was no widely accepted method to systematically search for relevant mechanisms, and this resulted in a lack of uniformity in the mechanistic topics addressed across assessments. Finally, there was no procedure to efficiently organize, analyse, and interpret the voluminous data from mechanistic studies.

To address these challenges, the key characteristics of human carcinogens were recently introduced as the basis for a uniform approach to searching for, organizing, and evaluating mechanistic evidence to support cancer hazard identification [7]. The key characteristics comprise the properties of known human carcinogens. These characteristics are distinct from the hallmarks of cancer, which relate to the properties of cancer cells (see Chapter 3.1) [9,10]; instead, they reflect the chemical and biological properties of cancer-causing agents (see Table 3.11.1). Established human carcinogens commonly exhibit one or more of these characteristics. Therefore, data on these characteristics can provide independent evidence of carcinogenicity when data from studies in humans are lacking. Data on key characteristics can also help in interpreting the relevance and importance of findings of cancer in experimental animals and in humans.

This chapter describes the key characteristics and discusses their application in IARC Monographs evaluations that have taken advantage of the systematic consideration of mechanistic evidence. The strengths and the weaknesses of this approach are discussed, as are opportunities for further progress

Table 3.11.1. Key characteristics of carcinogens

1. Is electrophilic or can be metabolically activated to electrophiles
2. Is genotoxic
3. Alters DNA repair or causes genomic instability
4. Induces epigenetic alterations
5. Induces oxidative stress
6. Induces chronic inflammation
7. Is immunosuppressive
8. Modulates receptor-mediated effects
9. Causes immortalization
10. Alters cell proliferation, cell death, or nutrient supply

FUNDAMENTALS

- The biological mechanisms by which certain chemicals, some types of radiation, and some infectious agents cause cancer in humans have been intensively investigated.
- For chemical carcinogens, no single sequence of biological events is evident for all such agents.
- Studies in experimental animals have established that some classes of organic compounds include multiple carcinogens, and such agents are metabolized in mammalian tissue, causing mutations as a result of binding of these agents to DNA. These carcinogens are described as genotoxic.
- The distribution of cancer in humans has implicated a variety of inorganic and/or naturally occurring compounds, including asbestos, as well as immunosuppressive drugs, which are not characterized as genotoxic.
- For decades, mechanisms of carcinogenesis involved a primary reference to genotoxicity, with binding to critical protein receptors being common to many non-genotoxic carcinogens.
- The recent description of certain key characteristics, one or more of which is exhibited by all established human carcinogens, is an innovative approach to identifying carcinogens.

and refinement. The last section of the chapter further discusses how the paradigm could be expanded to other end-points and how future toxicological and molecular epidemiological studies could be developed to generate more useful information for the process of carcinogen evaluation.

Descriptions of the key characteristics of carcinogens

The number of ways in which agents contribute to carcinogenesis can be extensive. However, these mechanisms can be grouped into a limited number of categories (genotoxicity, immunosuppression, etc.). Guyton et al. described 15 types of "key events" associated with human carcinogens that collectively represented many carcinogen mechanisms [1]. As part of its review of the agents classified in Group 1, IARC convened two meetings in 2012 to review mechanisms of established human carcinogens. At the first of the meetings, 24 mechanistic end-points were identified. However, these were considered too impractical as a guide for categorizing the evidence on carcinogen mechanisms. Therefore, at the second meeting, these end-points were merged into 10 categories. The 10 key characteristics listed in Table 3.11.1 represent the majority of the chemical and biological properties of human carcinogens, as described below and in more detail elsewhere [7].

Characteristic 1: Is electrophilic or can be metabolically activated to electrophiles

Electrophiles are electron-seeking molecules that form addition products, commonly referred to as adducts, with cellular macromolecules including DNA, RNA, lipids, and proteins (see Chapter 3.3). Some chemical carcinogens (e.g. sulfur mustard) are direct-acting electrophiles, whereas others (e.g. aflatoxins, benzene) require chemical conversion within the body [11] or metabolic activation [12]. The ability to form adducts with nucleic acids and proteins is a common property of these inherently electrophilic and/or metabolically activated human carcinogens [13].

Characteristic 2: Is genotoxic

A genotoxic agent induces damage to a cell's genetic material (see Chapter 3.2). Examples of DNA damage include DNA strand breaks (breaks in the phosphodiester bonds), protein–DNA cross-links, and oxidative damage to DNA. Genotoxic agents may also induce damage at the chromosomal level, including chromosomal aberrations, micronuclei, sister chromatid exchanges, and aneuploidy. A mutation, which is a change in the DNA sequence, usually arises as the cell attempts to repair the DNA damage [14]. A large proportion of the agents classified by IARC in Group 1 are genotoxic.

Characteristic 3: Alters DNA repair or causes genomic instability

Carcinogens may act not only by producing DNA damage directly but also by altering the processes that control normal DNA replication or repair of DNA damage (see Chapter 3.4). Examples include the inhibition of DNA repair by cadmium [15] and formaldehyde [16]. In cells exposed to ionizing radiation, genetic instability is a relatively late-occurring event that appears several cell generations after irradiation and results in a reduced ability to replicate the genotype faithfully [17].

Characteristic 4: Induces epigenetic alterations

The term "epigenetic" refers to stable changes in gene expression and chromatin organization that are not caused by changes in the DNA sequence itself and can be inherited over cell divisions [8]. Epigenetic phenomena – including changes in the DNA methylome, in chromatin compaction states, and in histone modification – are important aspects of normal developmental processes that can be usurped during the carcinogenic process, with impacts on gene expression and DNA repair dynamics [8]. A wide range of carcinogens have been shown to dysregulate the epigenome [18].

Characteristic 5: Induces oxidative stress

Many carcinogens are capable of influencing redox balance within target cells. If an imbalance occurs, favouring the formation of reactive oxygen species at the expense of their detoxification, this is referred to as oxidative stress. This may be accompanied by the production of reactive nitrogen species, or nitrative stress. Oxidative stress can lead to the generation of mutations in DNA, and more than 100 different types of oxidative damage to DNA have been identified [19]. The induction of oxidative stress and subsequent injury is a characteristic of a diverse group of carcinogens, including radiation, asbestos, chemicals, and carcinogenic infectious agents.

Characteristic 6: Induces chronic inflammation

Chronic inflammation from persistent infections, such as that caused by *Helicobacter pylori*, has been associated with several forms of cancer (see Chapter 3.5) [20]. Various other carcinogens also induce chronic inflammation, including fibres (e.g. silica, asbestos) and chemicals (e.g. polychlorinated biphenyls) [7].

Characteristic 7: Is immunosuppressive

Immunosuppression is a reduction in the capacity of the immune system to respond effectively to foreign antigens, including antigens on tumour cells. Persistent immunosuppression presents a risk of cancer (see Chapter 3.9), especially excess risk of lymphoma. Several carcinogens act entirely or largely by immunosuppression, often in concert with oncogenic infectious agents. The Group 1 agents that act by immunosuppression include HIV-1 and the immunosuppressive

drug ciclosporin (also known as cyclosporine) [21].

Characteristic 8: Modulates receptor-mediated effects

All actions of hormonally active agents are mediated by their ability to interact with a receptor, with the hormone acting as an endogenous ligand (see Chapter 2.11). For a chemical to interfere with hormone signalling and produce adverse effects, it must ultimately interfere with hormone receptor activation – either directly or indirectly. Numerous carcinogens act as ligands to receptor proteins, including hormone replacement therapy and 2,3,7,8-tetrachlorodibenzo-*para*-dioxin. Many exogenous agents act directly as agonists or antagonists by competing for binding with the endogenous ligand (e.g. a hormone, such as testosterone). However, there are also receptors for which few or no endogenous ligands have been identified, such as the aryl hydrocarbon receptor [22,23]; in these cases, the carcinogenic chemical is the activating ligand. Carcinogens may also act indirectly on receptor-mediated effects by altering the bioavailability of endogenous ligands by affecting the biosynthesis, bioactivation, and/or degradation of the ligand. These direct and indirect effects all modulate receptor-based regulation of gene transcription, and ultimately cell growth and proliferation.

Characteristic 9: Causes immortalization

Several human DNA and RNA viruses are carcinogenic to humans. Although oncogenic viruses belong to different families, their strategies in human cancer development show many similarities and involve viral-encoded oncoproteins targeting the key cellular proteins that regulate cell growth [24]. These targets may include important tumour suppressor genes and/or oncogenes. The result of these viral effects is to immortalize the cells of the target tissue such that they divide continuously (see Chapter 3.1).

Characteristic 10: Alters cell proliferation, cell death, or nutrient supply

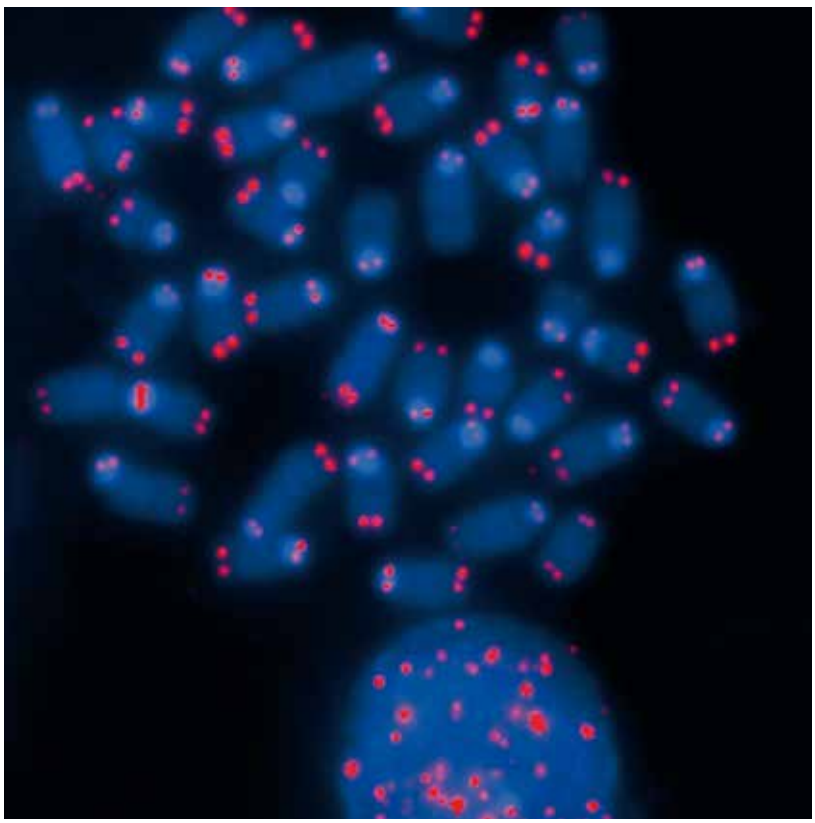
A component common to many types of cancer is the evasion of programmed cell death, via apoptosis, or of other terminal programming, including autophagy, in at least a proportion of the cell population [25]. In contrast to apoptosis and autophagy, necrotic cell death releases pro-inflammatory signals into the surrounding tissue, which can enhance cancer cell proliferation and promote cancer metastasis [26,27]. Many agents affect necrosis, apoptosis, and/or autophagy, and they can have profoundly divergent effects on cancer induction in different tissues.

In addition to cell death caused directly by the toxicity of an agent, cells within a tumour may die as a result of an impaired nutrient supply. The number of neoplastic cells can increase exponentially, quickly outstripping the supply capabilities of the existing tissue vasculature. Neo-angiogenesis, in which new blood vessels grow into a tumour, is key to providing a supply of nutrients. Thus, agents that promote or inhibit angiogenesis, such as arsenic, will promote or delay tumour growth [28,29].

Using the key characteristics to identify carcinogens

Recently, Guyton et al. [30] reviewed the feasibility and the limitations of applying the 10 key characteristics of carcinogens to comprehensively search for, screen, and evaluate mechanistic evidence in cancer hazard identification. The methods and

Fig. 3.11.1. Typically, various classes of oncogenic viruses mediate immortalization of target cells, such that cell proliferation continues indefinitely, rather than being constrained by shortening of telomeres [7]. Telomeres are unique DNA sequences located at the ends of chromosomes, as visualized by red fluorescence in this micrograph.



results of mechanistic data evaluations were compiled from eight recent IARC Monographs meetings in which expert Working Groups classified 34 diverse chemicals and complex exposures into Group 1, Group 2A, Group 2B (possibly carcinogenic to humans), or Group 3. For these evaluations, the key characteristics served as the basis for targeted literature searches to identify published mechanistic studies, and the Health Assessment Workplace Collaborative (https://HAWCproject.org) was used to record the literature search terms, sources, articles retrieved, exclusion criteria, and categorization of included articles.

As illustrated by the resulting literature flow diagram for pentachlorophenol (Fig. 3.11.2), a broad literature encompassing multiple key characteristics was identified for most of the 16 carcinogens classified in Group 1 or Group 2A at those eight IARC Monographs meetings. Mechanistic data were used as part of the overall evaluation to classify two agents in Group 2A: tetrabromobisphenol A and tetrachloroazobenzene, both of which modulate receptor-mediated effects in combination with other key characteristics. Fewer studies were available for the 17 agents classified in Group 2B or Group 3, and only one agent classified in Group 2B (1-bromopropane) had strong evidence of more than one key characteristic. Thus, this objective approach to identify and evaluate mechanistic studies revealed strong evidence for multiple key characteristics for most agents classified in Group 1 or Group 2A, but it also identified opportunities for improvement. Specifically, further development and mapping of toxicological and biomarker endpoints and pathways relevant to the key characteristics could advance the systematic search for and evaluation of mechanistic data in carcinogen hazard identification.

Notwithstanding the opportunities for further development, the utility of the key characteristics approach is underscored by the fact that it is being increasingly applied by agencies throughout the world, including at the EPA and the NTP Report on Carcinogens in the USA. In parallel, key characteristics for other toxicological hazards are being developed, in line with the recommendations of the report *Using 21st Century Science to Improve Risk-Related Evaluations* [31], which recognized that the key characteristics approach "avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence". Thus, the key characteristics approach can aid in preventing bias and misinterpretation, even when disproportionate resources have been focused on investigating a favoured mechanism [6]. In contrast, focusing on hypothesized modes of action or adverse outcome pathways can result in exclusion of data, leading to analyses that favour a particular

Fig. 3.11.2. Literature flow diagram for pentachlorophenol (classified in Group 1 by the IARC Monographs in Volume 117) illustrates the results of the search, screening, and organization of the published scientific literature, according to the key characteristics and other topics relevant to the evaluation of mechanistic data.

viewpoint. As a related challenge, hypotheses are inherently limited by the current understanding of the disease process and may be shown to be incorrect or incomplete as biological knowledge develops [1]. This limitation was recognized by Hill [32], who noted that "what is biologically plausible depends upon the biological knowledge of the day".

The experience of applying the key characteristics approach for 34 sequentially evaluated chemicals and complex exposures in the IARC Monographs has clearly revealed the variable extent of the mechanistic information available, even for carcinogens with widespread human exposures [30]. Moreover, for most agents, few studies of biomarker end-points relevant to the key characteristics in exposed humans were available. Especially when mechanistic data are sparse, high-throughput testing systems such as the EPA's Toxicity Forecaster (ToxCast) and the NTP's Toxicology in the 21st Century (Tox21) can aid as an additional or supportive source of mechanistic data [30]. However, the experience of applying an approach based on key characteristics to the mechanistic data stream, as further elaborated by Chiu et al. [33], demonstrated the usefulness of high-throughput testing systems for the key characteristic "modulates receptor-mediated effects" while also revealing significant gaps in their coverage for most other key characteristics. These and other challenges have hampered carcinogenicity prediction, which remains imprecise [1,34]. Together, these limitations underscore the need for a testing battery with greater relevance to cancer hazard identification – perhaps a Carcinogenicity Forecaster (CarciCast). In parallel, the report *Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment* [2] has encouraged human biomarker studies to improve hazard prediction; end-points related to the key characteristics could be applied in such studies to better forecast carcinogenic activity in humans [3]. In summary, the application of the key characteristics to cancer hazard identification is a robust new approach that complements other efforts to advance identification of the causes of human cancer – the first step in cancer prevention.

References

1. Guyton KZ, Kyle AD, Aubrecht J, Cogliano VJ, Eastmond DA, Jackson M, et al. (2009). Improving prediction of chemical carcinogenicity by considering multiple mechanisms and applying toxicogenomic approaches. Mutat Res. 681(2–3):230–40. https://doi.org/10.1016/j.mrrev.2008.10.001 PMID:19010444
2. National Research Council (US) Committee on Applications of Toxicogenomic Technologies to Predictive Toxicology (2007). Applications of toxicogenomic technologies to predictive toxicology and risk assessment. Washington (DC), USA: National Academies Press.
3. Fielden MR, Ward LD, Minocherhomji S, Nioi P, Lebrec H, Jacobson-Kram D (2018). Modernizing human cancer risk assessment of therapeutics. Trends Pharmacol Sci. 39(3):232–47. https://doi.org/10.1016/j.tips.2017.11.005 PMID:29242029
4. Tice RR, Austin CP, Kavlock RJ, Bucher JR (2013). Improving the human hazard characterization of chemicals: a Tox21 update. Environ Health Perspect. 121(7):756–65. https://doi.org/10.1289/ehp.1205784 PMID:23603828
5. Collins FS, Gray GM, Bucher JR (2008). Toxicology. Transforming environmental health protection. Science. 319(5865):906–7. https://doi.org/10.1126/science.1154619 PMID:18276874
6. IARC (2019). Preamble to the *IARC Monographs*, amended January 2019. Available from: https://monographs.iarc.fr/preamble-to-the-iarc-monographs/.
7. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect. 124(6):713–21. https://doi.org/10.1289/ehp.1509912 PMID:26600562
8. Herceg Z, Lambert M-P, van Veldhoven K, Demetriou C, Vineis P, Smith MT, et al. (2013). Towards incorporating epigenetic mechanisms into carcinogen identification and evaluation. Carcinogenesis. 34(9):1955–67. https://doi.org/10.1093/carcin/bgt212 PMID:23749751
9. Hanahan D, Weinberg RA (2011). Hallmarks of cancer: the next generation. Cell. 144(5):646–74. https://doi.org/10.1016/j.cell.2011.02.013 PMID:21376230
10. Hanahan D, Weinberg RA (2000). The hallmarks of cancer. Cell. 100(1):57–70. https://doi.org/10.1016/S0092-8674(00)81683-9 PMID:10647931
11. Salnikow K, Zhitkovich A (2008). Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: nickel, arsenic, and chromium. Chem Res Toxicol. 21(1):28–44. https://doi.org/10.1021/tx700198a PMID:17970581
12. Miller JA (1970). Carcinogenesis by chemicals: an overview – G. H. A. Clowes Memorial Lecture. Cancer Res. 30(3):559–76. PMID:4915745
13. Ehrenberg L (1984). Covalent binding of genotoxic agents to proteins and nucleic acids. In: Berlin A, Draper M, Hemminki K, Vainio H, editors. Monitoring human exposure to carcinogenic and mutagenic agents. Lyon, France: International Agency for Research on Cancer (IARC Scientific Publications, No. 59); pp.107–14. PMID:6545273
14. Shaughnessy DT, DeMarini DM (2009). Types and consequences of DNA damage. In: Knasmüller S, DeMarini DM, Johnson I, Gerhäuser C, editors. Chemoprevention of cancer and DNA damage by dietary factors. Weinheim, Germany: Wiley-VCH; pp. 21–33.
15. Candéias S, Pons B, Viau M, Caillat S, Sauvaigo S (2010). Direct inhibition of excision/synthesis DNA repair activities by cadmium: analysis on dedicated biochips. Mutat Res. 694(1–2):53–9. https://doi.org/10.1016/j.mrfmmm.2010.10.001 PMID:20969882
16. Luch A, Frey FCC, Meier R, Fei J, Naegeli H (2014). Low-dose formaldehyde delays DNA damage recognition and DNA excision repair in human cells. PLoS One. 9(4):e94149. https://doi.org/10.1371/journal.pone.0094149 PMID:24722772

17. Kadhim M, Salomaa S, Wright E, Hildebrandt G, Belyakov OV, Prise KM, et al. (2013). Non-targeted effects of ionising radiation – implications for low dose risk. Mutat Res. 752(2):84–98. https://doi.org/10.1016/j.mrrev.2012.12.001 PMID:23262375

18. Pogribny IP, Rusyn I (2013). Environmental toxicants, epigenetics, and cancer. Adv Exp Med Biol. 754:215–32. https://doi.org/10.1007/978-1-4419-9967-2_11 PMID:22956504

19. Klaunig JE, Wang Z, Pu X, Zhou S (2011). Oxidative stress and oxidative damage in chemical carcinogenesis. Toxicol Appl Pharmacol. 254(2):86–99. https://doi.org/10.1016/j.taap.2009.11.028 PMID:21296097

20. Grivennikov SI, Greten FR, Karin M (2010). Immunity, inflammation, and cancer. Cell. 140(6):883–99. https://doi.org/10.1016/j.cell.2010.01.025 PMID:20303878

21. Rafferty P, Egenolf D, Brosnan K, Makropoulos D, Jordan J, Meshaw K, et al. (2012). Immunotoxicologic effects of cyclosporine on tumor progression in models of squamous cell carcinoma and B-cell lymphoma in C3H mice. J Immunotoxicol. 9(1):43–55. https://doi.org/10.3109/1547691X.2011.614646 PMID:22299716

22. Ma Q (2011). Influence of light on aryl hydrocarbon receptor signaling and consequences in drug metabolism, physiology and disease. Expert Opin Drug Metab Toxicol. 7(10):1267–93. https://doi.org/10.1517/17425255.2011.614947 PMID:21883026

23. Baek SH, Kim KI (2014). Emerging roles of orphan nuclear receptors in cancer. Annu Rev Physiol. 76(1):177–95. https://doi.org/10.1146/annurev-physiol-030212-183758 PMID:24215441

24. Saha A, Kaul R, Murakami M, Robertson ES (2010). Tumor viruses and cancer biology: modulating signaling pathways for therapeutic intervention. Cancer Biol Ther. 10(10):961–78. https://doi.org/10.4161/cbt.10.10.13923 PMID:21084867

25. Ryter SW, Mizumura K, Choi AMK (2014). The impact of autophagy on cell death modalities. Int J Cell Biol. 2014:502676. https://doi.org/10.1155/2014/502676 PMID:24639873

26. Pollard JW (2008). Macrophages define the invasive microenvironment in breast cancer. J Leukoc Biol. 84(3):623–30. https://doi.org/10.1189/jlb.1107762 PMID:18467655

27. Coussens LM, Zitvogel L, Palucka AK (2013). Neutralizing tumor-promoting chronic inflammation: a magic bullet? Science. 339(6117):286–91. https://doi.org/10.1126/science.1232227 PMID:23329041

28. Yang MH, Zang Y-S, Huang H, Chen K, Li B, Sun G-Y, et al. (2014). Arsenic trioxide exerts anti-lung cancer activity by inhibiting angiogenesis. Curr Cancer Drug Targets. 14(6):557–66. https://doi.org/10.2174/1568009614666140725090000 PMID:25088040

29. Wang F, Liu S, Xi S, Yan L, Wang H, Song Y, et al. (2013). Arsenic induces the expressions of angiogenesis-related factors through PI3K and MAPK pathways in SV-HUC-1 human uroepithelial cells. Toxicol Lett. 222(3):303–11. https://doi.org/10.1016/j.toxlet.2013.08.008 PMID:23968725

30. Guyton KZ, Rusyn I, Chiu WA, Corpet DE, van den Berg M, Ross MK, et al. (2018). Application of the key characteristics of carcinogens in cancer hazard identification. Carcinogenesis. 39(4):614–22. https://doi.org/10.1093/carcin/bgy031 PMID:29562322

31. National Academies of Sciences, Engineering, and Medicine (2017). Using 21st century science to improve risk-related evaluations. Washington (DC), USA: National Academies Press. Available from: https://doi.org/10.17226/24635.

32. Hill AB (1965). The environment and disease: association or causation? Proc R Soc Med. 58:295–300. PMID:14283879

33. Chiu WA, Guyton KZ, Martin MT, Reif DM, Rusyn I (2018). Use of high-throughput in vitro toxicity screening data in cancer hazard evaluations by IARC Monograph Working Groups. ALTEX. 35(1):51–64. https://doi.org/10.14573/altex.1703231 PMID:28738424

34. Rusyn I, Sedykh A, Low Y, Guyton KZ, Tropsha A (2012). Predictive modeling of chemical hazard by integrating numerical descriptors of chemical structures and short-term toxicity assay data. Toxicol Sci. 127(1):1–9. https://doi.org/10.1093/toxsci/kfs095 PMID:22387746

The IARC Handbooks of Cancer Prevention

Béatrice Lauby-Secretan

The IARC Handbooks of Cancer Prevention series was launched in 1995 to complement the IARC Monographs series. The purpose of the IARC Handbooks is to evaluate scientific evidence on agents and interventions that may reduce the incidence of or mortality from cancer.

The Handbooks assist national and international authorities in assessing the benefits and risks of a particular intervention and in devising programmes of health promotion and cancer prevention. There is a major demand worldwide for such evaluations in order to improve public health. IARC is ideally placed to respond to this demand, because of its expertise, experience, reputation, and independence.

The principles, procedures, and scientific criteria that guide the IARC Handbooks evaluations closely mirror those of the IARC Monographs: interdisciplinary Working Groups of experts review the published studies and evaluate the weight of evidence on the effectiveness of primary and secondary interventions to prevent cancer. The full evaluations are then published in a volume of the Handbooks series, and a summary is published as a Special Report in a leading scientific journal, currently *The New England Journal of Medicine*.

The Handbooks were originally developed for the evaluation of chemopreventive agents (now referred to as preventive therapy; see Chapter 6.4); the scope was later enlarged to cover evaluation of other types of preventive interventions, including primary prevention and cancer screening. So far, the Handbooks have covered cancer-preventive agents, including non-steroidal anti-inflammatory drugs (such as aspirin), vitamin A, carotenoids, and retinoids, preventive actions (e.g. use of sunscreens, absence of excess body fatness, physical activity, and consumption of fruit and vegetables), screening (for breast cancer, cervical cancer, and colorectal cancer), and the efficacy of tobacco control measures (reversal of risk after quitting smoking, smoke-free policies, and tax and price policies).

After a 5-year hiatus due to restructuring and financial restrictions, the Handbooks series was relaunched in 2014. The first in the new series, Volume 15, was a reassessment of breast cancer screening (updating Volume 7, published in 2002). Volume 16 dealt with a preventive action, absence of excess body fatness (updating Volume 6, published in 2002), and Volume 17 was a first-time evaluation of colorectal cancer screening.

At the time of the relaunch, the original Working Procedures were revised in accordance with developments in the Monographs programme, incorporating many of the elements from the update to the Monographs Preamble in 2006. The Handbooks programme undertook a formal update by convening an Advisory Group at IARC in February 2019. The Working Procedures are now referred to as the Preambles.

Planned future Handbooks include evaluations of screening for cervical cancer (updating Volume 10, published in 2005) and oral cavity cancer (first-time evaluation).

The IARC Handbooks of Cancer Prevention have had a broad impact on guidelines, public recommendations, and implementation of health strategies, including the following:

- Numerous national health agencies (including those of Australia, Canada, New Zealand, the United Kingdom, and the USA), the European Committees, and offices of the World Health Organization have used the IARC Handbooks as a basis for developing their public health strategies and guidelines.
- Both Handbooks on breast cancer screening (Volume 7 and Volume 15) have triggered national measures to implement programmes or update guidelines.
- After the publication of the Handbooks on tobacco control (Volumes 11–14), IARC was invited to report to the Conference of the Parties to the World Health Organization Framework Convention on Tobacco Control.

4 Inequalities that affect cancer prevention

This is the first time that a section primarily concerned with inequalities and cancer is being included in a *World Cancer Report*. Inequalities that affect cancer prevention include those determined by educational attainment and by limitations on circumstances; examples are nutrition and housing, which are determined by financial income. Such inequalities may perturb the efficacy of almost all initiatives that are aimed at reducing the burden of cancer. The relevant factors may be specific to particular countries or regions. Recently, there have been improvements in the methods for investigating associations between inequalities and cancer as well as the ways in which adverse outcomes may be minimized. Typically, data are available on variations within a particular country, and the chapters in this section describe such data for certain countries.

4.1 Inequalities between and within countries

Impact on cancer prevention

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SUMMARY

- On average, the incidence rates for all cancers combined, in both sexes, increase with increasing levels of national socioeconomic development: the highest-income countries have much higher rates than the lowest-income countries. In contrast, for the mortality rates for all cancers combined, no clear gradient is observed with average levels of national socioeconomic development.
- Within countries, the socioeconomic gradient for cancer incidence may vary in magnitude and direction across different cancer sites, but cancer mortality is often higher, and cancer survival lower, in groups with low socioeconomic position and other disadvantaged groups (e.g. ethnic and racial minorities and Indigenous populations), for cancer overall and for the large majority of cancer types.
- Individuals with higher socioeconomic position tend to benefit more from cancer prevention interventions and to have earlier detection and diagnosis and better treatment, because they have better access to health-care services, greater health literacy, and fewer financial barriers to health care compared with individuals with lower socioeconomic position.
- Preventive policies, such as elimination of occupational exposure to carcinogens, tobacco control measures, vaccination against cancer-causing infectious agents, and screening for early stages of cancer, are potentially powerful ways to reduce not only the average incidence of and mortality from cancer but also socioeconomic inequalities in cancer occurrence.
- The low budget allocated to cancer prevention contrasts with the large investments made in the development of advanced technological devices and precision medicine, which may, in some cases, increase social inequalities in cancer.

Inequalities in cancer are the systematic differences in cancer occurrence (i.e. in cancer incidence, mortality, and survival) that exist between and within countries. Cancer inequalities are driven by the interplay of many factors, which largely reflect the cultures and environments in which people are born, live, and work, as well as the uneven distribution of resources and services between and within countries. Inequalities in cancer between countries may be due to a combination of contextual factors – such as culture, geography, politics, policies, societal structure, and economic structure – and individual factors.

Inequalities between social groups are observed in every country, whether it is a high-, middle-, or low-income country. Such social inequalities may arise from the various dimensions that make up the structure of society, including socioeconomic position, race and ethnicity, area of residence, sex, and sexual orientation, among others. Despite these complexities, cancer disproportionately affects the most disadvantaged individuals and groups.

Of all the potentially relevant dimensions of social inequalities within countries, this chapter focuses mainly on the socioeconomic dimension. Socioeconomic factors shape the environments in which individuals live as well as the distribution of resources and services, and could therefore be considered the “causes of the causes” of diseases such as cancer [1].

Social factors may have a very different impact on different cancer types and on different steps along the cancer continuum, from the time of an individual’s exposure to a carcinogenic agent to early diagnosis, treatment, and survival [2–7]. Some cancer types are related to social conditions during childhood, whereas others are more closely related to circumstances during adult life. Multiple pathways are involved, resulting in differential exposures to proximal risk factors, such as tobacco smoking, alcohol consumption, unhealthy diet, and

occupational exposures, and in differences in access to health-care services. Therefore, different profiles of cancer types are often observed in groups of individuals and in countries with different socioeconomic conditions.

The large observed variations in cancer occurrence, even between otherwise similar populations, together with the fact that changes in temporal trends may sometimes occur relatively quickly, indicate that these cancer differences could, in principle, be substantially reduced. This chapter provides an overview of inequalities in cancer between and within countries and then discusses possible interventions to reduce these inequalities as well as research priorities, with a particular focus on prevention.

Measuring inequalities in cancer

At the individual level, socioeconomic position reflects a complex set of social and economic factors, often imperfectly correlated with one another. Socioeconomic position is usually measured by the level of educational attainment, the household income, and the occupational classification, and sometimes by the socioeconomic circumstances of the area or the location of the home residence. The choice between these indicators may depend on the availability of data or on the objective of the study, because these indicators may suggest different aspects and mechanisms for the role of social determinants.

Several measures of association can be used to estimate the strength of the relationship between socioeconomic conditions and disease, including cancer, or the extent of inequality. Examples of absolute measures of socioeconomic inequalities in cancer are rate differences and the slope index of inequality. Examples of relative measures are rate ratios, odds ratios, and the relative index of inequality. Because absolute and relative measures may lead to different conclusions, or even opposite trends, both types of measures should be monitored when describing trends in socioeconomic inequalities in cancer and when assessing interventions aimed at reducing socioeconomic inequalities in cancer [8].

At the area or country level, socioeconomic conditions can be measured with macroeconomic indicators, such as national income (e.g. as indicated by gross domestic product) and years of schooling, or with composite measures that include different combinations of indicators, such as the Human Development Index (HDI), which is a composite indicator of health (based on life expectancy at birth), education (based on years of schooling), and standard of living (based on gross national income per capita), or by proxy measures, such as levels of urbanicity or rurality (see Chapter 1.3).

Another option is to use indicators of the extent of socioeconomic inequality within an area or country, such as the Gini index of income inequality or the prevalence of poverty or multiple deprivation. Such aggregate measures are often used in descriptive studies when individual-level data are not available. However, caution should be exercised when linking aggregate-level indicators to health outcomes and attempting to draw conclusions about individual-level relationships. For more details about how to measure inequalities in cancer, see [9].

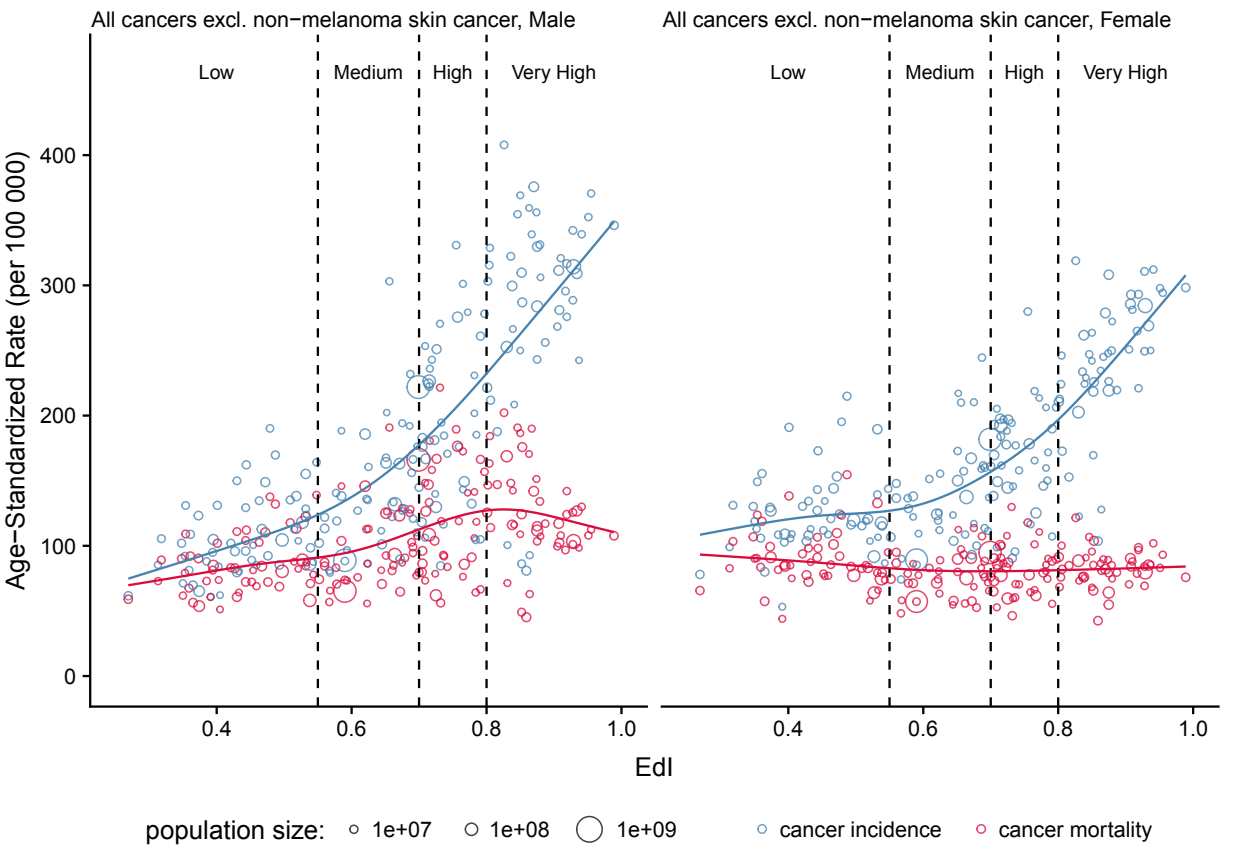
Evidence of cancer inequalities between countries

Large variations in cancer occurrence are observed between countries (see Chapter 1.2), although a distinction must be made between cancer incidence and cancer mortality. On average, the incidence rates for all cancers combined, in both sexes, increase with increasing levels of national socioeconomic development: the highest-income countries have much higher rates than the lowest-income countries (Fig. 4.1.1). In 2018, the estimated total number of new cancer cases worldwide was 18.1 million, of which 44% occurred in countries with very high HDI, and 36%, 15%, and 4% occurred in countries with high, medium, and low HDI, respectively [10]. In contrast, for the mortality rates for all cancers combined, no clear gradient is observed with average levels of national socioeconomic development.

FUNDAMENTALS

- Major differences in cancer occurrence exist between countries and, within countries, between groups with different socioeconomic position.
- Cancer inequalities are driven by the interplay of many factors, which largely reflect the cultures and environments in which people are born, live, and work, as well as the uneven distribution of resources and services between and within countries.
- Exposures to certain cancer risk factors, such as tobacco smoking, alcohol consumption, unhealthy diet, occupational exposures, and cancer-causing infections, are highest predominantly among individuals with low socioeconomic position and among the most disadvantaged groups.
- The availability of and access to high-quality health-care services are often lower in lower-income countries and among groups with low socioeconomic position and other disadvantaged groups.
- Coordinated efforts could lead to efficient interventions, particularly those focusing on prevention, and ultimately to a reduction of social inequalities in cancer.

Fig. 4.1.1. Age-standardized (world population) incidence and mortality rates of all cancer types, by average level of socioeconomic development in 2012. Socioeconomic development is measured by the education and income index (EDI), which is similar to the Human Development Index (HDI) but excludes life expectancy. (HDI was not appropriate for this analysis because life expectancy could be directly affected by cancer mortality.) EDI is calculated by taking the geometric mean of normalized indices of gross national income per capita and of national education level (average and expected years of schooling). EDI is a dimensionless variable between 0 and 1 (the higher a country's score, the higher the level of development). Four categories of socioeconomic development are shown: low (EDI ≤ 0.55), medium (0.55 < EDI ≤ 0.7), high (0.7 < EDI ≤ 0.8), and very high (EDI > 0.8).



Furthermore, the profile of cancer types varies markedly between high- and low-income countries: low-income countries have a higher rate of infection-related cancers [11,12], such as stomach cancer, liver cancer, and cervical cancer (see Chapter 2.2), whereas high-income countries have higher rates of cancer types such as breast cancer, prostate cancer, colorectal cancer, thyroid cancer, and melanoma.

Although there is considerable heterogeneity in cancer patterns between countries and there are several exceptions, depending on the country or area and the cancer type, some general considerations apply. Countries that are undergoing a transition towards higher levels of socioeconomic development have, on average, higher standards of living, improved hygienic conditions, higher life expectancy, and lower rates of infection-related cancers. However, these improvements are often accompanied by changing environments, which may result in increased exposure to other cancer risk factors, particularly among low-income groups, and which may lead to national increases in cancer incidence. In several low- and middle-income countries, particularly those that are undergoing rapid socioeconomic transitions, the decreases in rates of infection-related cancers are counterbalanced by increases in rates of cancer types for which higher rates are currently observed in high-income countries.

In populations in which cancer screening is widely available, "screening pressure" and increased detection of clinically irrelevant cancers in individuals with higher access to the health-care system may contribute, at least partly, to overdiagnosis and overtreatment of certain cancers, such as prostate cancer, breast cancer, and thyroid cancer (see Chapter 6.6). Overdiagnosis may have contributed to the rise in incidence rates observed in several high- and middle-income countries without substantially affecting mortality rates [13]. In high-income countries, access to screening and early detection programmes and to effective treatments

has contributed to keeping mortality rates relatively low, even when incidence rates have increased to very high levels.

The discrepancy between incidence and mortality is generally less pronounced in low- and middle-income countries than in high-income countries, probably because of lower survival rates in low- and middle-income countries as a result of later diagnosis and poorer access to treatment. It is not clear whether it will be possible to provide an adequate response to the growing cancer epidemic in low- and middle-income countries, given the organizational constraints and the limited resources available.

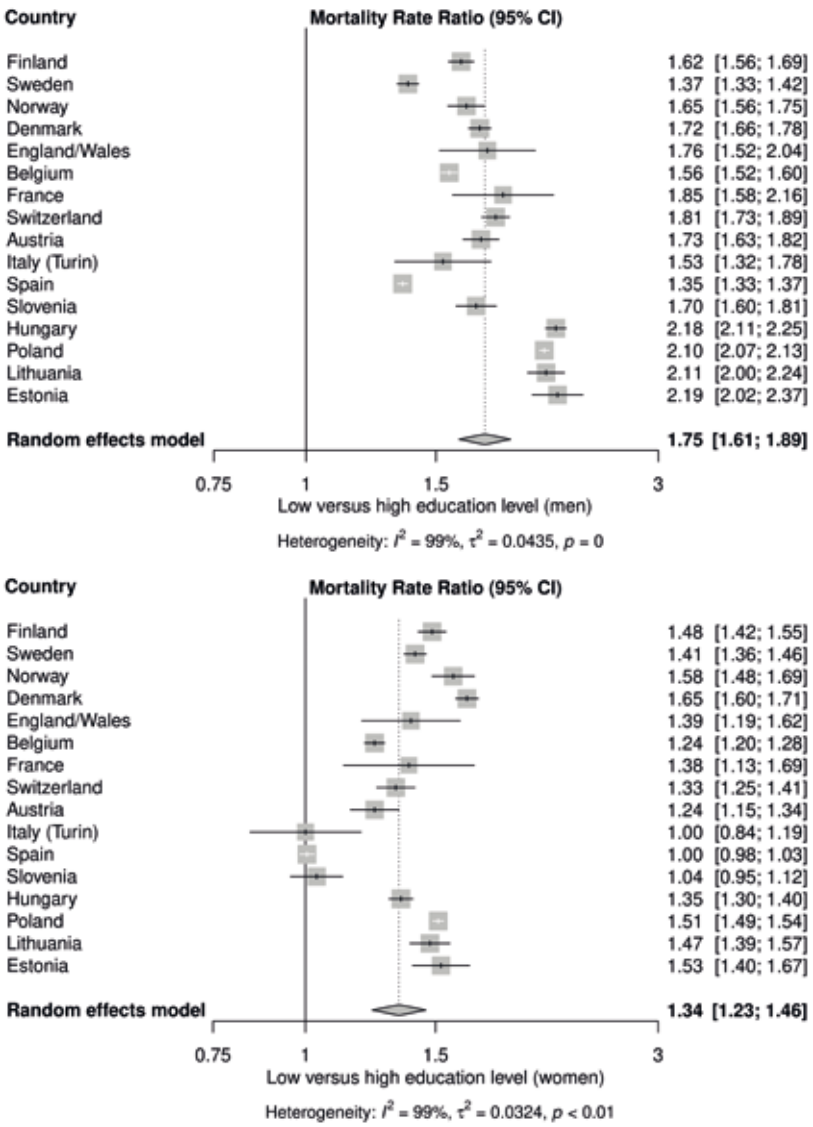
Evidence of cancer inequalities within countries

Within countries, the socioeconomic gradient for cancer incidence may vary in magnitude and direction across different cancer sites, but cancer mortality is often higher, and cancer survival lower, in groups with low socioeconomic position and other disadvantaged groups (e.g. ethnic and racial minorities and Indigenous populations), for cancer overall and for the large majority of cancer types [7,12,14–17] (Fig. 4.1.2). There is a clear gradient of higher overall cancer mortality and lower cancer survival from high to low socioeconomic position [7], which shows that cancer inequalities affect (almost) the entire population and are not limited to low-income sectors of society. Therefore, policies and interventions to reduce cancer inequalities can be beneficial for entire populations, although the potential benefits are largest for disadvantaged groups.

Relatively large socioeconomic inequalities, with much higher cancer incidence and mortality in groups with lower socioeconomic position, have been consistently reported, most markedly for smoking-related cancers (see Chapter 2.1), such as lung cancer, oral cancer, pharyngeal cancer, laryngeal cancer, and oesophageal cancer, and also for infection-related cancers, such as stomach cancer, liver cancer, and cervical cancer [14,18–20].

Data on trends in cancer mortality are available mainly in high-income countries and generally show more favourable trends among people with higher socioeconomic position. Among men and women with higher educational attainment, cancer mortality has generally declined, whereas among men and women with lower educational attainment, cancer mortality has declined at a slower rate, has remained stable, or has even, in some cases, increased. These differential trends can probably be explained by the fact that individuals with higher socioeconomic position tend to benefit more from cancer prevention interventions and to have earlier detection and diagnosis and better treatment, because they have better access to

Fig. 4.1.2. Relative social inequalities in cancer mortality by education level in 17 European countries, by country, for the most recent data available for each country (from 2004 to 2013). The charts show rate ratios and corresponding 95% confidence intervals of mortality from all cancers combined for men (above) and women (below) with a low versus high education level, and a pooled rate ratio estimate obtained from a random effects meta-analysis.



health-care services, greater health literacy, and fewer financial barriers to health care compared with individuals with lower socioeconomic position. The higher severity of comorbidities in individuals with low socioeconomic position is also an important factor that could reduce cancer survival.

When data are available in low- and middle-income countries, they often show similarly strong socioeconomic gradients in cancer as observed in high-income countries, but they also reveal much poorer cancer outcomes than in high-income countries [21,22], with very high cancer mortality and low cancer survival even for preventable or curable cancers, including cervical cancer and childhood cancers. This is generally due to the absence, or at best the limited availability, of resources and infrastructures at all phases of cancer control, from prevention to effective and timely treatment to palliative care. Recently, there have been improvements in survival for most cancer types in many low- and middle-income countries, although with a large variability between cancer types and between countries [23]. The stage at diagnosis, the quality of treatment, and the quality of health-care services are important contributors to the observed inequalities in cancer survival, particularly in disadvantaged populations.

Factors underlying cancer inequalities, and interventions to reduce inequalities

Several factors, usually related and intertwined, underlie the complicated patterns and socioeconomic gradients in different cancer outcomes observed between and within countries. Exposures to certain cancer risk factors, such as tobacco smoking, alcohol consumption, unhealthy diet, occupational exposures, and cancer-causing infections, are highest predominantly among individuals with low socioeconomic position and among the most disadvantaged groups [24–26]. The reasons for this are complex and include cultural, economic, and psychosocial factors, as well as the availability, affordability, and marketing of the products that cause cancer (e.g. tobacco and alcohol) or prevent cancer (e.g. healthy foods and sun-protective clothing).

High-quality health-care services are key to control the burden of disease. Such services may reduce cancer incidence and mortality at all phases of cancer control, from prevention to early detection, diagnosis, and treatment. However, accessing the health-care system is often difficult for disadvantaged groups, and the availability of health-care services is often lower in lower-income countries [27]. Universal health coverage, a current priority of WHO, is key to improve access to essential components of cancer control for all individuals, without exposing them to financial hardships.

Preventive policies are potentially powerful ways to reduce not only the average incidence of and mortality from cancer but also socioeconomic inequalities in cancer occurrence. National and international laws may also have a powerful role, particularly when used in coordination with other initiatives (see Chapter 6.8). Examples of legislative measures are the banning of asbestos in workplaces and comprehensive international tobacco control policies, such as the WHO Framework Convention on Tobacco Control, in which countries make commitments to regulate tobacco use. Taxation is a particularly efficient tool to reduce consumption of tobacco, alcohol, and unhealthy foods.

However, any intervention or legislation that aims to reduce the overall burden of a disease in a population may result in either an increase or a decrease in social inequalities in cancer, depending on how it is designed, on the specific context, and on many other factors. Therefore, there is a need to enhance the use of evidence for the development, implementation, and regulation of interventions, to ensure that these would reduce or, at least, would not exacerbate social inequalities in cancer.

Interventions and policies are likely to be more effective when they are based on approaches that combine a population strategy with a vulnerable-population strategy – an approach called proportionate universalism. In the case of cervical cancer, there is enormous potential to eliminate the disease, and thus reduce inequalities, through a combination of human papillomavirus (HPV) vaccination and screening with HPV testing.

Fig. 4.1.3. In almost all countries, graphic evidence of disparity within particular communities may be illustrated. This photograph shows the physical divide that separates Bloubosrand, a middle-class suburb northwest of Johannesburg, South Africa, from Kya Sands, an informal settlement consisting of improvised housing made of plywood and corrugated metal.

The increasing use of technology in medical practice may be very useful, but in some cases it may also increase social inequalities in cancer. This is because access to innovative technology, and the resulting benefits – like for any other expensive intervention – are likely to be enjoyed predominantly by high-income individuals and countries. In this context, it is relevant to highlight an important phenomenon: there is increasing evidence that individuals and populations with high socioeconomic position may receive unnecessary care and that the harms related to the use of technological advances and expensive interventions may outweigh the benefits. An example is the case of thyroid cancer (see Chapter 5.18); the increased medical surveillance of the thyroid gland and the use of advanced diagnostic techniques have led to massive overdiagnosis and overtreatment, affecting mainly high-income countries and individuals with greater access to health-care services [28].

Fig. 4.1.4. Access to state-of-the-art medical technology, such as this scanner, is restricted to high-income countries and is often available in a disproportionate manner. Individuals with greater access to health-care services are most at risk of overdiagnosis and overtreatment.

Research priorities

Research priorities have recently been identified to inform approaches to tackle cancer inequalities [29]. As a first step, the importance has been recognized of (i) improving the collection of high-quality monitoring data on the magnitude of social inequalities in cancer, (ii) increasing the scientific evidence base on the multidimensional aspects related to social inequalities, particularly in low- and middle-income countries, where data are currently limited, and (iii) improving the understanding of the impact of social factors on all steps of the cancer continuum.

In all countries where data are available, there are striking differences in cancer occurrence between socioeconomic groups. Nevertheless, information on social characteristics is often not collected in population-based studies, including those based on cancer registry data. Improved efforts are needed to generate knowledge and monitor social inequalities in cancer, by implementing and improving the quality of cancer registries, by carrying out surveys to monitor risk factors and access to health care, and by collecting other data in the context of surveillance, whether national, regional, or global. In addition, etiological studies within a life-course framework, exploring opportunities to prevent the disease at all stages of life, should be implemented to provide a more detailed analysis of inequalities in cancer.

Furthermore, although social determinants affect all steps of the cancer continuum, including prevention, diagnosis, treatment, and end-of-life care, it is prevention that has the greatest potential to reduce cancer disparities in all settings. This is particularly true in low- and middle-income countries, where health-care services are lacking or are available almost exclusively for the highest-income individuals. However, despite this great potential, investments in cancer prevention are disproportionately lower compared with other areas, such as basic science and treatment. The low budget allocated to cancer prevention also contrasts with the large investments made in the development of advanced technological devices and precision medicine, which may, in some cases, increase social inequalities in cancer.

There is a strong need to expand both the research focus on and investments in prevention, particularly because of the low interest in investment in this area by the private sector. Of particular importance would be to ensure that all interventions and cancer control initiatives, from prevention to treatment measures, are explicitly designed and evaluated not only for their overall effects but also, ideally, to decrease or eliminate social inequalities or, at least, not exacerbate them. This would represent an attainable, desirable, and ethical objective.

Conclusions

Inequalities in cancer are consistently observed between and within countries. Although social inequalities affect the entire population, it is often the most disadvantaged individuals and groups who suffer the most. This has an impact across societies, causing human and economic costs in the health system, which are borne by society but which could be, in large part, avoided. Coordinated, multisectoral efforts and efficient interventions could ultimately lead to a reduction of social inequalities in cancer.

References

1. CSDH (2008). Closing the gap in a generation: health equity through action on the social determinants of health. Final Report of the Commission on Social Determinants of Health. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/social_determinants/thecommission/finalreport/en/.

2. Gallo V, Mackenbach JP, Ezzati M, Menvielle G, Kunst AE, Rohrmann S, et al. (2012). Social inequalities and mortality in Europe – results from a large multi-national cohort. PLoS One. 7(7):e39013. https://doi.org/10.1371/journal.pone.0039013 PMID:22848347

3. Menvielle G, Boshuizen H, Kunst AE, Vineis P, Dalton SO, Bergmann MM, et al. (2010). Occupational exposures contribute to educational inequalities in lung cancer incidence among men: evidence from the EPIC prospective cohort study. Int J Cancer. 126(8):1928–35. https://doi.org/10.1002/ijc.24924 PMID:19810107

4. Merletti F, Galassi C, Spadea T (2011). The socioeconomic determinants of cancer. Environ Health. 10(Suppl 1):S7. https://doi.org/10.1186/1476-069X-10-S1-S7 PMID:21489217

5. Franceschi S, Plummer M, Clifford G, de Sanjosé S, Bosch X, Herrero R, et al.; International Agency for Research on Cancer Multicentric Cervical Cancer Study Groups; International Agency for Research on Cancer Human Papillomavirus Prevalence Surveys Study Group (2009). Differences in the risk of cervical cancer and human papillomavirus infection by education level. Br J Cancer. 101(5):865–70. https://doi.org/10.1038/sj.bjc.6605224 PMID:19654578

6. Dahlgren G, Whitehead M (2006). European strategies for tackling social inequities in health: levelling up (part 2). Copenhagen, Denmark: World Health Organization Regional Office for Europe. Available from: http://www.who.int/iris/handle/10665/107791.

7. Menvielle G, Kunst AE, Stirbu I, Strand BH, Borrell C, Regidor E, et al. (2008). Educational differences in cancer mortality among women and men: a gender pattern that differs across Europe. Br J Cancer. 98(5):1012–9. https://doi.org/10.1038/sj.bjc.6604274 PMID:18283307

8. Mackenbach JP (2015). Should we aim to reduce relative or absolute inequalities in mortality? Eur J Public Health. 25(2):185. https://doi.org/10.1093/eurpub/cku217 PMID:25818489

9. Conway DI, McMahon AD, Brown D, Leyland AH (2019). Measuring socioeconomic status and inequalities. In: Vaccarella S, Lortet-Tieulent J, Saracci R, Conway DI, Straif K, Wild CP, editors. Reducing social inequalities in cancer: evidence and priorities for research (IARC Scientific Publications, No. 168). Lyon, France: International Agency for Research on Cancer. Available from: http://publications.iarc.fr/580.

10. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today.

11. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S (2016). Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 4(9):e609–16. https://doi.org/10.1016/S2214-109X(16)30143-7 PMID:27470177

12. Bray F, Jemal A, Grey N, Ferlay J, Forman D (2012). Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. Lancet Oncol. 13(8):790–801. https://doi.org/10.1016/S1470-2045(12)70211-5 PMID:22658655

13. Sullivan R, Aggarwal A (2019). Technology and cancer systems: creating better policy to enhance equality. In: Vaccarella S, Lortet-Tieulent J, Saracci R, Conway DI, Straif K, Wild CP, editors. Reducing social inequalities in cancer: evidence and priorities for research (IARC Scientific Publications, No. 168). Lyon, France: International Agency for Research on Cancer. Available from: http://publications.iarc.fr/580.

14. Dalton SO, Steding-Jessen M, Engholm G, Schüz J, Olsen JH (2008). Social inequality and incidence of and survival from lung cancer in a population-based study in Denmark, 1994-2003. Eur J Cancer. 44(14):1989–95. https://doi.org/10.1016/j.ejca.2008.06.023 PMID:18693111

15. AIHW (2013). Cancer in Aboriginal and Torres Strait Islander peoples of Australia: an overview. Canberra, Australia: Australian Institute of Health and Welfare. Available from: https://www.aihw.gov.au/reports/cancer/cancer-in-indigenous-australians-overview/contents/table-of-contents.

16. Blakely T, Shaw C, Atkinson J, Cunningham R, Sarfati D (2011). Social inequalities or inequities in cancer incidence? Repeated census-cancer cohort studies, New Zealand 1981-1986 to 2001-2004. Cancer Causes Control. 22(9):1307–18. https://doi.org/10.1007/s10552-011-9804-x PMID:21717195

17. Bryere J, Dejardin O, Launay L, Colonna M, Grosclaude P, Launoy G; French Network of Cancer Registries (FRANCIM) (2018). Socioeconomic status and site-specific cancer incidence, a Bayesian approach in a French Cancer Registries Network study. Eur J Cancer Prev. 27(4):391–8. https://doi.org/10.1097/CEJ.0000000000000326 PMID:27879493

18. Mouw T, Koster A, Wright ME, Blank MM, Moore SC, Hollenbeck A, et al. (2008). Education and risk of cancer in a large cohort of men and women in the United States. PLoS One. 3(11):e3639. https://doi.org/10.1371/journal.pone.0003639 PMID:18982064

19. Spadea T, Zengarini N, Kunst A, Zanetti R, Rosso S, Costa G (2010). Cancer risk in relationship to different indicators of adult socioeconomic position in Turin, Italy. Cancer Causes Control. 21(7):1117–30. https://doi.org/10.1007/s10552-010-9539-0 PMID:20349125

20. Sharpe KH, McMahon AD, Raab GM, Brewster DH, Conway DI (2014). Association between socioeconomic factors and cancer risk: a population cohort study in Scotland (1991-2006). PLoS One. 9(2):e89513. https://doi.org/10.1371/journal.pone.0089513 PMID:24586838

21. de Vries E, Arroyave I, Pardo C, Wiesner C, Murillo R, Forman D, et al. (2015). Trends in inequalities in premature cancer mortality by educational level in Colombia, 1998-2007. J Epidemiol Community Health. 69(5):408–15. https://doi.org/10.1136/jech-2014-204650 PMID:25492898

22. Dikshit R, Gupta PC, Ramasundarahettige C, Gajalakshmi V, Aleksandrowicz L, Badwe R, et al.; Million Death Study Collaborators (2012). Cancer mortality in India: a nationally representative survey. Lancet. 379(9828):1807–16. https://doi.org/10.1016/S0140-6736(12)60358-4 PMID:22460346

23. Swaminathan R (2019). Cancer survival in countries in transition, with a focus on selected Asian countries. In: Vaccarella S, Lortet-Tieulent J, Saracci R, Conway DI, Straif K, Wild CP, editors. Reducing social inequalities in cancer: evidence and priorities for research (IARC Scientific Publications, No. 168). Lyon, France: International Agency for Research on Cancer. Available from: http://publications.iarc.fr/580.

24. Allen L, Williams J, Townsend N, Mikkelsen B, Roberts N, Foster C, et al. (2017). Socioeconomic status and non-communicable disease behavioural risk factors in low-income and lower-middle-income countries: a systematic review. Lancet Glob Health. 5(3):e277–89. https://doi.org/10.1016/S2214-109X(17)30058-X PMID:28193397

25. Casetta B, Videla AJ, Bardach A, Morello P, Soto N, Lee K, et al. (2017). Association between cigarette smoking prevalence and income level: a systematic review and meta-analysis. Nicotine Tob Res. 19(12):1401–7. https://doi.org/10.1093/ntr/ntw266 PMID:27679607

26. Grittner U, Kuntsche S, Gmel G, Bloomfield K (2013). Alcohol consumption and social inequality at the individual and country levels – results from an international study. Eur J Public Health. 23(2):332–9. https://doi.org/10.1093/eurpub/cks044 PMID:22562712

27. Atun R, Jaffray DA, Barton MB, Bray F, Baumann M, Vikram B, et al. (2015). Expanding global access to radiotherapy. Lancet Oncol. 16(10):1153–86. https://doi.org/10.1016/S1470-2045(15)00222-3 PMID:26419354

28. Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L (2016). Worldwide thyroid-cancer epidemic? The increasing impact of overdiagnosis. N Engl J Med. 375(7):614–7. https://doi.org/10.1056/NEJMp1604412 PMID:27532827

29. Vaccarella S, Lortet-Tieulent J, Saracci R, Fidler MM, Conway DI, Vilahur N, et al. (2018). Reducing social inequalities in cancer: setting priorities for research. CA Cancer J Clin. 68(5):324–6. https://doi.org/10.3322/caac.21463 PMID:30152865

4.2 Socioeconomic factors and cancer prevention in Africa

Cervical cancer as an example

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SUMMARY

- In sub-Saharan Africa, cervical cancer is the second most common cancer in women, after breast cancer, but more women die from cervical cancer than from breast cancer.
- Although cervical cancer is preventable, services for prevention, early detection, and treatment are rare in low-income countries.
- It was found that for women in developing countries the cervical cancer incidence rates were 2-fold higher and the cervical cancer mortality rates were 3-fold higher than those for women in developed countries.
- The poverty rate (a deprivation level measuring the proportion of the population living in extreme poverty) was a strong predictor of cross-national variations in cervical cancer incidence and mortality.

Of the 56.9 million deaths recorded globally in 2016, 40.5 million (71%) were due to noncommunicable diseases. The four main causes of death due to noncommunicable diseases were cardiovascular diseases, cancer, diabetes, and chronic respiratory diseases (see Chapter 6.9). In 2016, more than three quarters of deaths due to noncommunicable diseases (31.5 million) occurred in low- and middle-income countries, and cancer accounted for 9.0 million deaths (22% of all deaths due to noncommunicable diseases) [1]. Approximately one third of cancer cases in sub-Saharan Africa were estimated to be attributable to infections, presenting unique opportunities for prevention and treatment [2].

Inequity in health care exists between countries, within countries, and across continents. The lowest-income countries provide the worst quality of care and spend the smallest amount of national resources on health care. Access to high-quality care is a key factor in predicting good outcomes in all forms of health care; it requires an "ecosystem" of interrelated support, which includes arable land, adequate nutrition, safe drinking-water, sanitation, and transportation infrastructure as a few examples of necessary interventions [3]. In addition, expenditure on health care, health-care professionals, and health infrastructure is key to functional and strong health-care systems [4].

Cancer is a leading cause of premature death and morbidity globally and is rapidly becoming a significant health problem in low- and middle-income countries, particularly in Africa, where there is an epidemiological shift from communicable to noncommunicable diseases (see Chapter 1.3) [5].

This chapter explores the range of effects of socioeconomic factors on cancer care and outcomes in Africa, with cervical cancer as an example.

Overall cancer burden in Africa and globally

The overall cancer burden in Africa in 2012 was estimated at 847 000 new cancer cases and 591 000 cancer deaths [5]. In women, the most common cancer type was breast cancer (133 900 cases), followed by cervical cancer (99 000 cases). In men, prostate cancer was the most common (59 500 cases), followed by liver cancer (38 700 cases) and Kaposi sarcoma (23 800 cases) [5].

CONCORD-3 updated the worldwide surveillance of cancer survival trends to include patients diagnosed up to 2014 [6]. Data were analysed for 322 population-based cancer registries in 71 countries; for Africa, this included 8 registries in 6 countries. The 322 registries covered a combined population of almost 1 billion people in about 2014. Overall, the proportion of the population covered by cancer registries in Africa was 3.5% (Table 4.2.1) [6].

There are vast differences in cervical cancer mortality rates between women in Africa and women in high-income countries (Table 4.2.2) [7]. Singh et al. [7] computed age-adjusted cervical cancer incidence and mortality rates for women in 184 countries using the GLOBOCAN 2008 database. The authors' analysis indicated that overall, for women in developing countries the incidence rates were 2-fold higher and the

Table 4.2.1. Population covered by cancer registries in Africa (number of people and percentage of the national population) and number of patients diagnosed during 2000–2014, by country

Cancer registry	Population covered	Percentage of population covered	Total number of patients
Algeria	2 447 075	6.3%	15 602
Mali (Bamako)	764 245	9.0%	60
Mauritius	1 268 567	100.0%	3 959
Morocco (Casablanca)	2 178 083	12.7%	4 683
Nigeria (Ibadan)	2 797 220	1.6%	8 274
South Africa (Eastern Cape)	1 078 572	2.0%	7 619
Total	10 533 762	3.5%	40 197

Table 4.2.2. Age-adjusted cervical cancer mortality rates per 100 000 (world standard population), in 2008

Country	Number of deaths	Age-adjusted mortality rate
Countries with the highest mortality rates		
Guinea	1217	41.7
Zambia	1276	38.6
Malawi	1621	38.3
Uganda	2464	34.9
Zimbabwe	1286	33.4
Lesotho	178	22.7
Angola	1008	21.9
Countries with the lowest mortality rates		
Australia	241	1.4
Iceland	4	0.8

FUNDAMENTALS

- Cancer is becoming a significant health problem in many low- and middle-income countries, where both incidence and mortality rates are higher than those in some high-income countries, but where the health agenda has been dominated by maternal mortality, communicable diseases, and nutritional diseases.
- The Human Development Index (HDI) and the poverty rate explain more than 50% of the global variance in cervical cancer mortality.
- Cervical cancer is known to be a preventable disease.
- Modern technology has the potential to enable greater precision and sensitivity in the application of screening and early detection for many cancer types, but it is not accessible in low-income countries.
- There are still differences in the occurrence of cancer across different groups, resulting in deepening health inequalities.
- An inadequately trained health-care workforce, inadequate expenditure on health systems and infrastructure, out-of-pocket expenses, and lack of preventive health care are major obstacles to health-care delivery and development in low-income countries.

mortality rates were 3-fold higher than those for women in developed countries. Cervical cancer rates varied widely across countries; rates in many countries in sub-Saharan Africa were 10–20-fold higher than those in some countries in North Africa, the Middle East, and Europe.

Furthermore, Singh et al. modelled the impact of the Human Development Index (HDI), the Gender Inequality Index (a composite index that reflects women's relative social disadvantage in three dimensions: reproductive health, empowerment, and labour market participation), and socioeconomic factors (poverty rate [a deprivation level measuring the proportion of the population living in extreme poverty], health expenditure per capita, urbanization rate, and literacy rate). All were found to be significantly related to cervical cancer incidence and mortality. HDI and the poverty rate each explained more than 52% of the global variance in cervical cancer mortality [7].

The evidence of the impact of socioeconomic factors and cancer prevention in Africa and in low- and middle-income countries in other world regions is found in the different incidence and mortality rates of various cancer types. An estimated 18.1 million new cancer cases and 9.6 million cancer deaths occurred worldwide in 2018 [8]. The average risk of developing cancer before age 75 years was 20%, and the average

risk of dying from cancer before age 75 years was 10%. In men, prostate cancer was the most frequently diagnosed cancer in 12 regions of the world. In both sexes, lung cancer was the most frequent cause of death from cancer in 14 regions of the world. In women, breast cancer was the most frequently diagnosed cancer in all regions of the world, and cervical cancer ranked fourth for both incidence and mortality [8].

Of the 18.1 million new cancer cases in 2018, 5.8% occurred in Africa, 21.0% in the Americas, 23.4% in Europe, 1.4% in Oceania, and 48.4% in Asia. Of the 9.6 million cancer deaths, 7.3% occurred in Africa, 14.4% in the Americas, 20.3% in Europe, 0.7% in Oceania, and 57.3% in Asia [9]. Although the proportion of the global cancer burden is lower for Africa than for other regions of the world, cancer is also low on the health agenda in Africa because of multiple competing health priorities and other needs.

Costs of cancer care

In 2009, the global cost of treating 12.9 million patients diagnosed with cancer was estimated to be US$ 285.8 billion [10]. The indirect costs associated with premature death and lost productivity from the growing cancer burden were estimated to be US$ 1.16 trillion per year [10].

World Health Statistics 2015 presented data on the total expenditure on health as a percentage of gross domestic product (GDP) in the six WHO regions (Fig. 4.2.1) [11]. In most regions, there was very little change in the percentage expenditure between 2000 and 2012. The percentage expenditure was highest in the Americas. For per capita total expenditure on health (Fig. 4.2.2) [11], the values were lowest in Africa and South-East Asia and highest in the Americas and Europe.

The lack of access to screening and early detection and the high costs of treatment are often cited as the causes for a high incidence of a disease that is largely preventable, such as cervical cancer. The high incidence of cervical cancer in Africa is also related to the high rates of HIV infection, particularly in eastern and southern Africa, where HIV infection is epidemic and cervical cancer is classified as an AIDS-defining illness [12].

Out-of-pocket expenditure on health care is a major barrier to accessing health care in low- and middle-income countries, and a significant illness in a family can be catastrophic. Xu et al. [13] used a cross-country analysis design and data from household surveys in 59 countries to explore variables related to catastrophic health expenditure. Expenditure was defined as catastrophic if a household's financial contributions to the health system exceeded 40% of income remaining after subsistence needs had been met. The analysis showed that certain groups were particularly vulnerable, such as older people, people with disabilities, unemployed people, people with low incomes, and people with reduced or no access to health insurance. Wyszewianski [14] made the point that catastrophic health expenditure is common in many countries and can lead to impoverishment that has long been ignored by the health system. There is a significant amount of data showing that low-income households have a limited capacity to cope with health-care expenditure compared with higher-income households.

Fig. 4.2.1. Total expenditure on health as a percentage of gross domestic product (GDP) in 2000 and 2012, by WHO region.

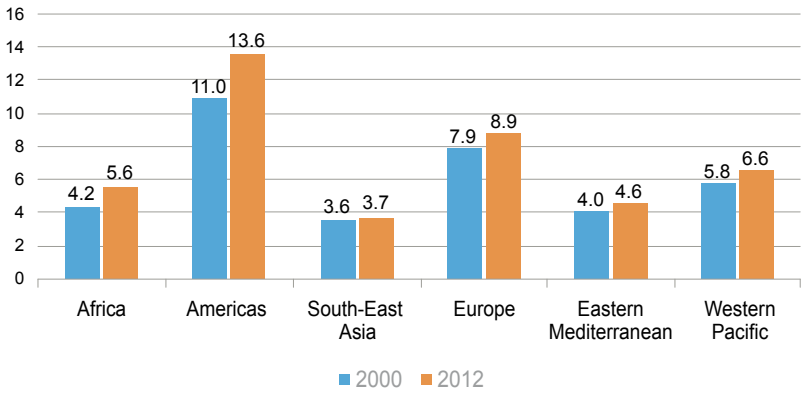
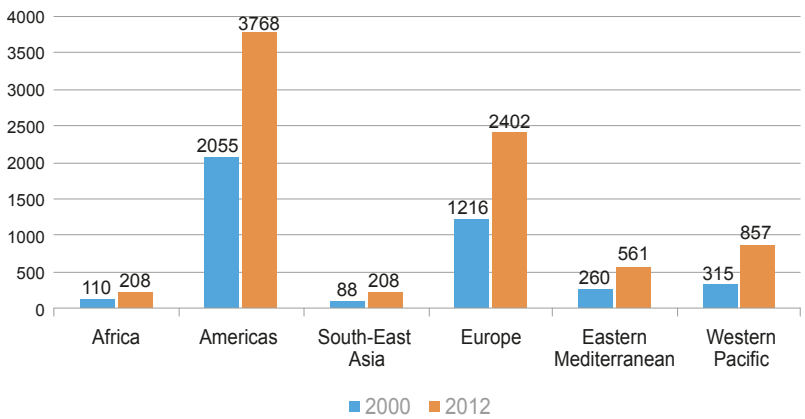


Fig. 4.2.2. Per capita total expenditure on health (purchasing power parity at international dollar rate) in 2000 and 2012, by WHO region.



The American Public Health Association reported that before the introduction of the Patient Protection and Affordable Care Act of 2010 in the USA, about 20% of the population younger than 65 years was medically uninsured, and that after the introduction of the act, about 13% (or one eighth) of people younger than 65 years remained uninsured [15]. The USA spends more on health care than any other high-income country (18% of the GDP), but in terms of life expectancy it ranks 26th out of the 36 member countries of the Organisation for Economic Co-operation and Development. Furthermore, in the USA only about 3% of spending on health is allocated to preventive health care.

Barriers to prevention and treatment of cancer in Africa

Almost all of the 54 countries in sub-Saharan Africa have low HDI values and high values of the Human Poverty Index [16]. Of the total population of sub-Saharan Africa, which was estimated to be more than 1 billion in 2018, only 7.2% were covered by medically certified causes of death and 8.3% by population-based registries.

Moreover, access to anti-cancer therapies is very limited in almost all African countries. A WHO study in 2001 found that only 22% of African countries had access to anti-cancer drugs, compared with 91% in Europe. An analysis by the International Atomic Energy Agency found that in 2010 only 23 of the 52 African countries included in the analysis had facilities for teletherapy (external radiation therapy), which were concentrated in the northern and southern regions of the continent [17]. Brachytherapy resources were available in only 20 of the 52 countries. A total of 160 radiation facilities were recorded in the continent, housing 277 radiotherapy machines (88 cobalt-60 units and 189 linear accelerators) [17].

Barton et al. [18] performed a detailed analysis of the gap between existing radiation facilities in low- and middle-income countries and the needs of the population. They concluded that the African continent had only 18% of the radiation equipment needed for full coverage of the population. Medenwald et al. [19] extracted data from a wide variety of sources and found an inverse linear relationship between the number of radiotherapy machines in the population and the mortality-to-incidence ratio for prostate cancer, breast cancer, and lung cancer. They concluded that the population density of radiotherapy machines is related to cancer mortality independently of other public health parameters. They also found a linear relationship between GDP per capita and the population density of radiotherapy machines, until a GDP per capita of US$ 60 000 [19].

Fig. 4.2.3. Women signing up for free breast cancer and cervical cancer screening in Senegal. Breast cancer and cervical cancer are the two most common cancer types among women in Africa.

Health-care workforce

The African continent has 168 medical schools, located in 41 countries. However, facilities for training in cancer prevention, diagnosis, and management are found mainly in North Africa (Algeria, Egypt, and Morocco) and South Africa, with limited facilities in Libya, Nigeria, and Zimbabwe [20]. Overall, sub-Saharan Africa has a very low physician-to-population ratio of about 18 per 100 000, compared with the ratios of India (60 per 100 000), Brazil (170 per 100 000), and France (370 per 100 000) [20].

Adding to the complexity of the challenges facing sub-Saharan Africa (including environmental disasters, competing health needs, endemic civil strife, war, and lack of safe drinking-water and sanitation, to name just a few) has been the HIV/AIDS epidemic. Sub-Saharan Africa accounts for about 70% of people living with HIV worldwide [21]. HIV infection increases the risk of developing certain types of cancer, and Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer have been classified as AIDS-defining diseases since 1993 [12]. Women living with HIV have an increased risk of being infected with human papillomavirus (HPV) and are therefore considered to be at a higher risk for anogenital cancers.

Socioeconomic determinants of health

The political determinants of health inequity and socioeconomic factors deserve careful analysis. The *Lancet*-University of Oslo Commission on Global Governance

for Health noted that the lowest-income population groups have the heaviest burden of disease; this can be attributed not only to poverty but also to socioeconomic inequality [22]. The commission identified five dysfunctions of the global governance system that allow adverse effects of global political determinants of health inequity to persist: (i) insufficient participation in decision-making by civil society, health experts, and marginalized groups; (ii) weak accountability mechanisms; (iii) lack of response to changing societal needs, enabling entrenchment of power disparities, with adverse effects on health (called "institutional stickiness" by the authors); (iv) inadequate policy space for health; and (v) lack of international institutions to protect and promote health [22].

The Commission on Social Determinants of Health, led by Michael Marmot, stated in its report: "The poor health of the poor, the social gradient in health within countries, and the marked health inequities between countries are caused by the unequal distribution of power, income, goods, and services, globally and nationally, the consequent unfairness in the immediate, visible circumstances of people's lives ... and their chances of leading a flourishing life. This unequal distribution of health-damaging experiences is not in any sense a 'natural' phenomenon but is the result of a toxic combination of poor social policies and programmes, unfair economic arrangements, and bad politics..." [23].

Bray et al. [16] used four tiers of HDI (low, medium, high, and very high HDI) to evaluate cancer-specific patterns in 2008 and trends over the period 1988–2002. They found that in the regions with the highest HDI in 2008, breast cancer, lung cancer, colorectal cancer, and prostate cancer accounted for more than half of the cancer burden. In regions with low HDI, other cancer types were more common: stomach cancer, liver cancer, oesophageal cancer, and cervical cancer. Together, these cancers accounted for 62% of the cancer burden in regions with low HDI. In both settings, lung cancer was the most common cancer diagnosed.

Fig. 4.2.4. Two girls aged 10–14 years are vaccinated against human papillomavirus (HPV) by an outreach nursing team from Binga District Hospital in Matabeleland North Province in Zimbabwe.

Priorities for prevention, research, policy, and development

Men and women with cancer in low- and middle-income countries, particularly in Africa, face multiple challenges because of poor health-care infrastructure. Access to diagnosis, treatment, and timely intervention are lacking, resulting in high case mortality rates, lack of trust in the health-care system, stigmatization, and high rates of premature death.

In a systematic review of nine eligible studies of late presentation of women with breast cancer conducted in Egypt, Ghana, Kenya, Libya, and Nigeria, more than 50% of women presented with advanced disease. The most important drivers for late presentation were: negative interpretation of symptoms; fear; lack of belief, trust, or confidence in orthodox medicine; poor social relations and networks; and lack of access to health care [24].

Challenges associated with cancer care in Africa

Analyses of the causes of ill health are essential to prioritize public policy and to determine the research agenda and the allocation of resources, particularly based on the population-level risk. Attaining the highest standard of health care requires access to safe drinking-water, adequate sanitation, education, health-care education, nutrition, and good employment, among many other factors. Cancer care is relatively expensive, and without effective means of prevention and early detection, aligned with appropriate interventions, the incidence of and mortality from cancer will continue to rise.

References

1. WHO (2018). NCD mortality and morbidity. Global Health Observatory (GHO) data. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/gho/ncd/mortality_morbidity/en/.
2. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S (2016). Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 4(9):e609–16. https://doi.org/10.1016/S2214-109X(16)30143-7 PMID:27470177
3. Wagstaff A (2002). Poverty and health sector inequalities. Bull World Health Organ. 80(2):97–105. PMID:11953787
4. WHO (2018). Global health workforce statistics. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/hrh/statistics/hwfstats/.
5. Parkin DM, Bray F, Ferlay J, Jemal A (2014). Cancer in Africa 2012. Cancer Epidemiol Biomarkers Prev. 23(6):953–66. https://doi.org/10.1158/1055-9965.EPI-14-0281 PMID:24700176
6. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al.; CONCORD Working Group (2018). Global surveillance of trends in cancer survival 2000–2014 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 391(10125):1023–75. https://doi.org/10.1016/S0140-6736(17)33326-3 PMID:29395269
7. Singh GK, Azuine RE, Siahpush M (2012). Global inequalities in cervical cancer incidence and mortality are linked to deprivation, low socioeconomic status, and human development. Int J MCH AIDS. 1(1):17–30. https://doi.org/10.21106/ijma.12 PMID:27621956
8. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. (2019). Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 144(8):1941–53. https://doi.org/10.1002/ijc.31937 PMID:30350310
9. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593
10. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, et al.; Global Burden of Disease Cancer Collaboration (2015). The global burden of cancer 2013. JAMA Oncol. 1(4):505–27. https://doi.org/10.1001/jamaoncol.2015.0735 PMID:26181261
11. WHO (2015). World health statistics 2015. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/gho/publications/world_health_statistics/2015/en/.
12. CDC (1992). 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep. 41(RR-17):1–19. PMID:1361652
13. Xu K, Evans DB, Kawabata K, Zeramdini R, Klavus J, Murray CJL (2003). Household catastrophic health expenditure: a multicountry analysis. Lancet. 362(9378):111–7. https://doi.org/10.1016/S0140-6736(03)13861-5 PMID:12867110
14. Wyszewianski L (1986). Families with catastrophic health care expenditures. Health Serv Res. 21(5):617–34. PMID:3102403
15. APHA (2018). Health reform. American Public Health Association. Available from: https://www.apha.org/topics-and-issues/health-reform.
16. Bray F, Jemal A, Grey N, Ferlay J, Forman D (2012). Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. Lancet Oncol. 13(8):790–801. https://doi.org/10.1016/S1470-2045(12)70211-5 PMID:22658655
17. Abdel-Wahab M, Bourque JM, Pynda Y, Iżewska J, Van der Merwe D, Zubizarreta E, et al. (2013). Status of radiotherapy resources in Africa: an International Atomic Energy Agency analysis. Lancet Oncol. 14(4):e168–75. https://doi.org/10.1016/S1470-2045(12)70532-6 PMID:23561748
18. Barton MB, Frommer M, Shafiq J (2006). Role of radiotherapy in cancer control in low-income and middle-income countries. Lancet Oncol. 7(7):584–95. https://doi.org/10.1016/S1470-2045(06)70759-8 PMID:16814210
19. Medenwald D, Vordermark D, Dietzel CT (2018). Number of radiotherapy treatment machines in the population and cancer mortality: an ecological study. Clin Epidemiol. 10:1249–73. https://doi.org/10.2147/CLEP.S156764 PMID:30288122
20. Mullan F, Frehywot S, Omaswa F, Buch E, Chen C, Greysen SR, et al. (2011). Medical schools in sub-Saharan Africa. Lancet. 377(9771):1113–21. https://doi.org/10.1016/S0140-6736(10)61961-7 PMID:21074256
21. UNAIDS (2018). Geneva, Switzerland: Joint United Nations Programme on HIV and AIDS. Available from: https://www.unaids.org.
22. Ottersen OP, Dasgupta J, Blouin C, Buss P, Chongsuvivatwong V, Frenk J (2014). The political origins of health inequity: prospects for change. Lancet. 383(9917):630–67. https://doi.org/10.1016/S0140-6736(13)62407-1 PMID:24524782
23. CSDH (2008). Closing the gap in a generation: health equity through action on the social determinants of health. Final Report of the Commission on Social Determinants of Health. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/social_determinants/thecommission/finalreport/en/.
24. Donkor A, Lathlean J, Wiafe S, Vanderpuye V, Fenlon D, Yarney J, et al. (2015). Factors contributing to late presentation of breast cancer in Africa: a systematic literature review. Arch Med. 8:2.

4.3 Cancer in urban and rural communities in China

Patterns reflect social dynamics

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SUMMARY

- In China, cancer incidence is lower in rural areas than in urban areas, whereas cancer mortality is higher in rural areas, indicating lower survival in rural areas.
- Incidence rates of colorectal cancer, breast cancer, prostate cancer, and bladder cancer are higher in urban areas than in rural areas, whereas incidence rates of oesophageal cancer, stomach cancer, liver cancer, and cervical cancer are higher in rural areas than in urban areas.
- Differences in lifestyles and dietary patterns between urban and rural communities are becoming more pronounced along with rapid economic development, urbanization, and the ageing of the population. These could partly explain the urban–rural difference in the spectrum of cancer types.
- There is an urgent need to implement cancer prevention and control strategies that are customized for different regions of the country.

As the world's most populous country, China accounts for more than 23% of new cancer cases and about 30% of cancer deaths worldwide [1]. Moreover, about half of the new cases of liver cancer, oesophageal cancer, and stomach cancer and more than one third of the new cases of lung cancer worldwide occur in China [1].

In recent decades the cancer burden in China has been increasing, posing a serious threat to public health and imposing a heavy economic burden. In 2014, there were more than 3.8 million new cancer cases (2.3 million in urban areas and 1.5 million in rural areas) and 2.3 million cancer deaths (1.3 million in urban areas and 1.0 million in rural areas) in China [2]. The crude incidence rate was 278.07 per 100 000, and the age-standardized incidence rate (by world standard population) was 186.53 per 100 000. The crude mortality rate was 167.89 per 100 000, and the age-standardized mortality rate (by world standard population) was 106.09 per 100 000 [2].

The most common cancer types in the whole population were cancers of the lung, stomach, colorectum, liver, breast, oesophagus, thyroid, cervix, brain and central nervous system, and pancreas. Together, these accounted for about 77% of all new cancer cases. Cancers of the lung, liver, stomach, oesophagus, colorectum, pancreas, and breast, collectively, accounted for about 70% of all cancer deaths [2]. The direct economic burden attributable

Fig. 4.3.1. The Shanghai skyline. Differences in lifestyles and dietary patterns between urban and rural communities in China are becoming more pronounced along with rapid economic development, urbanization, and the ageing of the population.

Fig. 4.3.2. Woman preparing rice in rural China.

FUNDAMENTALS

- As the world's most populous country, China accounts for more than 23% of new cancer cases, about half of the new cases of liver cancer, oesophageal cancer, and stomach cancer, and about 30% of cancer deaths worldwide.
- Along with rapid economic development, urbanization, and the ageing of the population, the cancer burden and the spectrum of cancer types show considerable variation between urban and rural areas.
- China is urbanizing rapidly; the percentage of the population living in urban areas increased from 18% in 1978 to 56% in 2015 – an increase of 311.1% in about 40 years – and is expected to reach 71% by 2030.
- Obesity and physical inactivity, which are the leading risk factors for both colorectal cancer and breast cancer, are more prevalent in urban areas than in rural areas, contributing to the rural–urban disparity in the incidence of these two cancer types.
- Although differences in cancer incidence between urban and rural areas still exist in China, the gap has been narrowing every year.

to cancer in 2015 was estimated to be ¥221.4 billion, which was 5.4% of the total health expenditure and 17.7% of the government health expenditure [3].

Cancer burden in urban and rural communities

Along with rapid economic development, urbanization, and the ageing of the population, the cancer burden and the spectrum of cancer types show considerable variation between urban and rural areas [4,5].

In 2014, the age-standardized incidence rate (by world standard population) for all cancers combined was higher in urban areas (191.6 per 100 000) than in rural areas (179.2 per 100 000), whereas the age-standardized mortality rate (by world standard population) for all cancers combined was higher in rural areas (110.3 per 100 000) than in urban areas (102.5 per 100 000) [2], indicating that cancer survival was lower in rural areas than in urban areas. Differences were also seen between urban and rural areas in the spectrum of the major cancer types [6].

These differences in cancer patterns could be related mainly to comprehensive determinants, such as demographic and socioeconomic determinants (e.g. age, sex, education level), as well as to lifestyle factors and inequalities in health-related issues (e.g. allocation of health-care resources, health outcomes).

Quality of life and provision of health-care services have improved greatly in China with the rapid socioeconomic development during the past decades. However, urban–rural inequalities in health care are still striking [7,8]. According to the National Bureau of Statistics of China, in 2015 the average per capita disposable income of urban residents was ¥31 790, almost 3 times that of rural residents (¥10 772) [9]. The average life expectancy for male and female urban residents was estimated to be 7.09 years and 6.64 years longer, respectively, than that of their rural counterparts [10].

Mainly as a result of the one-child policy and increases in life expectancy, China has a lower birth rate and a lower death rate, especially in urban areas [11]. This has led to a rapid ageing of the population, especially in urban areas, thus increasing the pool of older adults, who are more susceptible to cancer [2,11].

In rural areas, there was inadequate allocation of basic educational resources, and teachers were less highly trained than in urban areas [12]. The education level of rural residents was also generally

lower than that of their urban counterparts [13]. In addition, utilization of health-care services of all types was lower in rural areas than in urban areas [14], as a result of the unbalanced development between urban and rural areas in the provision of health-care services.

These differences in socioeconomic status between urban and rural areas could lead to differences in lifestyles and dietary patterns. For example, the prevalence of smoking (see Chapter 2.1) and alcohol consumption (see Chapter 2.3) was still higher in rural residents, whereas in urban residents the level of physical activity was relatively low (see Chapter 2.7), as a result of increasingly sedentary occupations [15]. Surveys also showed that the intake of animal products is significantly higher in urban residents than in rural residents; this may contribute to differences in energy intake [15]. Problems associated with rapid urbanization, including large-scale migration, ageing of the population, and pollution in both urban and rural areas (see Chapter 2.9), have also emerged [10].

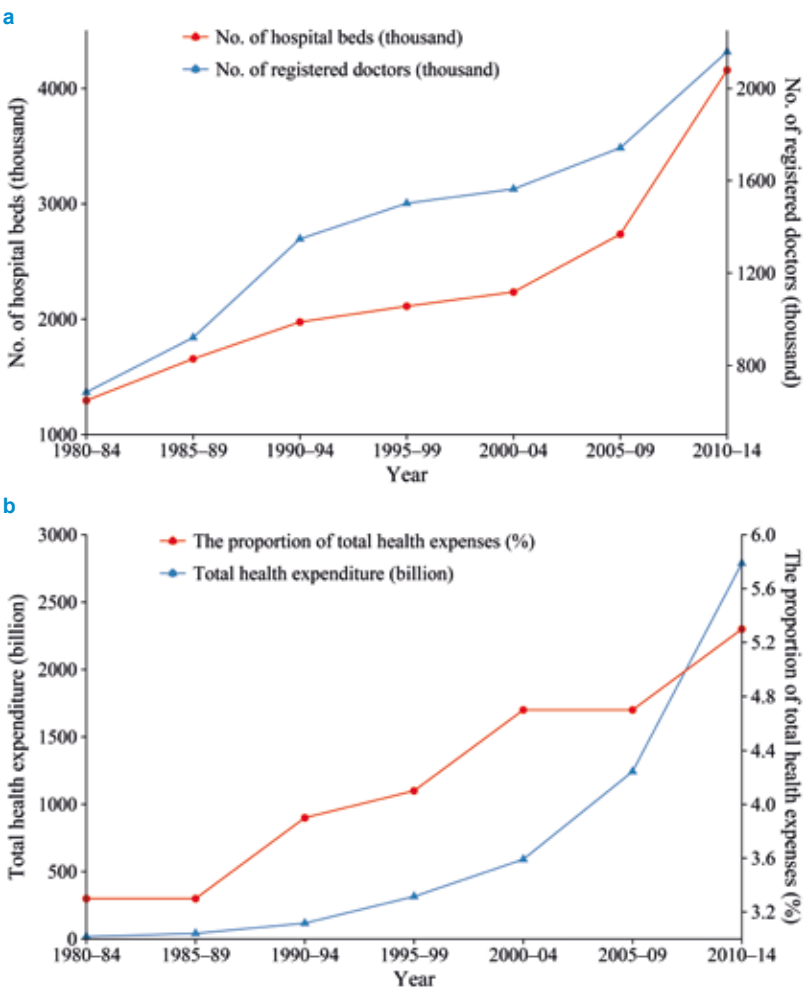
Age-standardized incidence rates of colorectal cancer, breast cancer, prostate cancer, kidney cancer, and bladder cancer were higher in urban areas than in rural areas, and were higher in areas with high gross domestic product (GDP) per capita and high urbanization [16,17]. Obesity and physical inactivity, which are the leading attributable risk factors for both colorectal cancer and breast cancer, are more prevalent in urban areas than in rural areas, not only in China but also worldwide; differences in the prevalence of obesity and physical inactivity are partly responsible for the rural–urban disparity in the incidence of these two cancer types [18–20]. Changes in reproductive factors, such as increasing exposure to xeno-estrogens and oral contraceptives, may also lead to a higher incidence of breast cancer in urban areas [21]. For colorectal cancer and breast cancer, cancer survival was lower in rural areas than in urban areas, as a result of differences in health-care services, socioeconomic inequalities, and lack of awareness about cancer prevention and early detection, as well as the unbalanced allocation of health-care resources, with lower government health expenditure per capita and less advanced health-care facilities in rural areas [6,10].

Age-standardized incidence rates of oesophageal cancer, stomach cancer, liver cancer, and cervical cancer were higher in rural areas than in urban areas, and were higher in areas with low GDP per capita and low urbanization. Strong risk factors for cancer, including smoking, alcohol consumption, and low intake of fruits and vegetables (see Chapter 2.6), are more prevalent in rural areas than in urban areas [2,16,17]. Higher rates of *Helicobacter pylori* and hepatitis B virus infection also contribute to the high incidence of stomach cancer and liver cancer, especially in rural areas (see Chapter 2.2) [22,23]. The lower quality of medical treatment and limited health-care resources led to lower survival in rural areas [24].

Cancer patterns and trends in urban and rural areas

In recent decades, the overall cancer incidence in China has been relatively stable, with a total annual

Fig. 4.3.3. Rapid increases in (a) the numbers of hospital beds and of registered doctors and (b) health expenditures in China, during the period 1980–2014.

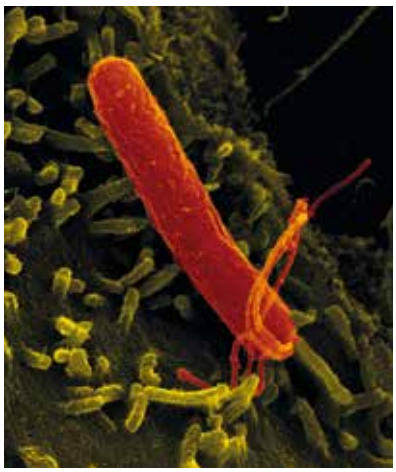


change of 4% in the crude incidence rate, whereas cancer mortality has decreased [4,5].

From 2003–2005 to 2012–2015, age-standardized 5-year relative survival increased significantly for all cancers combined, from 30.9% to 40.5%; age-standardized 5-year relative survival also increased for most cancer types, including cancers of the oesophagus, stomach, larynx, bone, cervix, uterus, bladder, and thyroid [6]. This reflected the overall improvement in the quality of cancer care in China, which could be shown partly by an annual increase in health-care resources, including the numbers of hospital beds and of registered doctors, as well as increases in health expenditures (Fig. 4.3.3) [25].

During the past 40 years, the lung cancer mortality rate in China has increased 4-fold. Consequently, lung cancer has replaced stomach cancer as the leading cause of cancer death [4,5], accounting for 27.3% of all cancer deaths in China. Although the prevalence of tobacco smoking is slowly decreasing in China, the development of lung cancer may take decades. Therefore, the new cases of lung cancer may be the result of a high prevalence of smoking in the past. The effects of current anti-smoking campaigns on the prevalence of cigarette smoking will emerge in the future [26].

Fig. 4.3.4. Colourized scanning electron micrograph of *Helicobacter pylori* and human gastric epithelium cells.



During the past 20 years, there has been a rapid upward trend in the incidence of breast cancer and colorectal cancer, especially in urban areas [4,5]. From the 1970s to the 1990s, liver cancer, stomach cancer, and oesophageal cancer were the most common cancers in both urban and rural areas [4,5].

Oesophageal cancer, stomach cancer, and liver cancer are still the major cancer types in rural residents [5]. Declining trends in age-standardized incidence rates and mortality rates were observed for these three cancer types in both sexes in 2000–2013. These declines are a result of socioeconomic development and a series of cancer prevention and control programmes, such as comprehensive intervention and control strategies implemented in high-risk rural areas since the 1990s and early detection programmes initiated in rural areas and aimed at specific high-risk cancer types [27–30]. Control of infections, including hepatitis B virus and hepatitis C virus for liver cancer and *H. pylori* for stomach cancer, may also contribute to these temporal patterns [22,23]. Studies have shown that the food policy reforms in China dramatically decreased exposure to aflatoxin and reduced overall liver cancer risk in Qidong, a city in Jiangsu Province, even before universal hepatitis B virus vaccination of newborns was implemented [31,32].

Although differences in cancer incidence between urban and rural areas still exist in China, the gap has been narrowing every year. Cancer incidence in rural areas is predicted to surpass that in urban areas in the future [33,34]. As a result of rapid urbanization, a large-scale migration from rural to urban areas is occurring [10]. Although migrants move to cities seeking a better life, most of them can only find jobs in areas like construction, manufacture, or mining, because of their comparatively lower education level. Most of these jobs are associated with air pollution, radiation, and other cancer risk factors, such as exposure to asbestos, which could lead to the development of cancer [35]. According to the *Hukou* policy in China, when a migrant is diagnosed with cancer, the case will be registered in the rural cancer registry where the person was born [36]. Another explanation for the high cancer burden in rural areas could be the lack of awareness among rural residents about health care and cancer prevention [6]. As a result, the willingness to participate in cancer screening programmes and the subsequent follow-up is lower in rural areas than in urban areas, even if the screening is provided free of charge.

Conclusions

Global experience in alleviating the cancer burden has demonstrated the importance of comprehensive strategies such as tobacco control campaigns, vaccination, targeted cancer screening programmes, and appropriate and efficient diagnostic and treatment technology. In China, although some cancer prevention and control programmes have yielded significant benefits, challenges still remain because of the heavy cancer burden, the complicated cancer patterns, and the unbalanced allocation of health-care resources and primary health care between urban and rural areas.

The distinct differences in cancer patterns between urban and rural communities emphasize an urgent need to implement cancer prevention and control strategies that are customized for different regions of the country. For example, the hazards associated with smoking were previously more severe in urban areas, because of the limited availability and affordability of cigarettes in rural areas. However, this difference is diminishing and the situation is even likely to be reversed, because rural residents start smoking at a younger age and with a somewhat higher prevalence than urban residents [37].

It is also important to further improve the primary health-care system in rural areas, including a more comprehensive design and implementation of the health insurance system, which can effectively serve low-income residents of rural areas. Moreover, it is of great importance to improve basic living and sanitary conditions, strengthen public awareness of cancer prevention, and develop programmes for the early detection and treatment of major cancer types that focus on rural residents.

For urban residents, the points of focus are (i) to promote healthy lifestyles and dietary habits, (ii) to control smoking, alcohol consumption, and obesity, and (iii) to improve mental and psychological health. The effective implementation of targeted early diagnosis and treatment programmes is also crucial in urban areas.

In addition, international cooperation should be enhanced, to learn from useful experiences and approaches and to avoid common pitfalls and unnecessary expenditures.

References

1. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today.
2. Chen W, Sun K, Zheng R, Zeng H, Zhang S, Xia C, et al. (2018). Cancer incidence and mortality in China, 2014. Chin J Cancer Res. 30(1):1–12. https://doi.org/10.21147/j.issn.1000-9604.2018.01.01 PMID:29545714
3. Cai Y, Xue M, Chen W, Hu M, Miao Z, Lan L, et al. (2017). Expenditure of hospital care on cancer in China, from 2011 to 2015. Chin J Cancer Res. 29(3):253–62. https://doi.org/10.21147/j.issn.1000-9604.2017.03.11 PMID:28729776
4. Chen Z (2008). Report on Third National Retrospective Sampling Survey on Causes of Death in China. Beijing, China: Chinese Union Medical University Press.
5. Chen W, Zheng R, Zhang S, Zeng H, Xia C, Zuo T, et al. (2017). Cancer incidence and mortality in China, 2013. Cancer Lett. 401:63–71. https://doi.org/10.1016/j.canlet.2017.04.024 PMID:28476483
6. Zeng H, Chen W, Zheng R, Zhang S, Ji JS, Zou X, et al. (2018). Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries. Lancet Glob Health. 6(5):e555–67. https://doi.org/10.1016/S2214-109X(18)30127-X PMID:29653628
7. Chen Y, Yin Z, Xie Q (2014). Suggestions to ameliorate the inequity in urban/rural allocation of healthcare resources in China. Int J Equity Health. 13(1):34. https://doi.org/10.1186/1475-9276-13-34 PMID:24884614
8. Shi L (1993). Health care in China: a rural-urban comparison after the socioeconomic reforms. Bull World Health Organ. 71(6):723–36. PMID:8313490
9. National Bureau of Statistics of China (2016). Statistical Communiqué of the People's Republic of China on the 2015 National Economic and Social Development. Available from: http://www.stats.gov.cn/english/PressRelease/201602/t20160229_1324019.html.
10. Yang J, Siri JG, Remais JV, Cheng Q, Zhang H, Chan KKY, et al. (2018). The Tsinghua-Lancet Commission on Healthy Cities in China: unlocking the power of cities for a healthy China. Lancet. 391(10135):2140–84. https://doi.org/10.1016/S0140-6736(18)30486-0 PMID:29678340
11. Song Y (2014). Losing an only child: the one-child policy and elderly care in China. Reprod Health Matters. 22(43):113–24. https://doi.org/10.1016/S0968-8080(14)43755-8 PMID:24908462
12. Zhang JY, Chen T (2009). Empirical analysis on the allocation of the urban and rural educational resource in China. Zhongguo Nong-Jihua. (6):115–9.
13. National Bureau of Statistics of China (2010). Tabulation on the 2010 Population Census of the People's Republic of China. Available from: http://www.stats.gov.cn/tjsj/pcsj/rkpc/6rp/indexch.htm.
14. Haggerty JL, Roberge D, Lévesque JF, Gauthier J, Loignon C (2014). An exploration of rural-urban differences in health-care-seeking trajectories: implications for measures of accessibility. Health Place. 28:92–8. https://doi.org/10.1016/j.healthplace.2014.03.005 PMID:24793139
15. Zeng Q, Zeng Y (2018). Eating out and getting fat? A comparative study between urban and rural China. Appetite. 120:409–15. https://doi.org/10.1016/j.appet.2017.09.027 PMID:28964905
16. Yang Z, Zheng R, Zhang S, Zeng H, Xia C, Li H, et al. (2017). Comparison of cancer incidence and mortality in three GDP per capita levels in China, 2013. Chin J Cancer Res. 29(5):385–94. https://doi.org/10.21147/j.issn.1000-9604.2017.05.02 PMID:29142457
17. Chen W, Zheng R, Zhang S, Zeng H, Zuo T, Xia C, et al. (2017). Cancer incidence and mortality in China in 2013: an analysis based on urbanization level. Chin J Cancer Res. 29(1):1–10. https://doi.org/10.21147/j.issn.1000-9604.2017.01.01 PMID:28373748
18. Fang C, Liang Y (2017). Social disparities in body mass index (BMI) trajectories among Chinese adults in 1991-2011. Int J Equity Health. 16(1):146. https://doi.org/10.1186/s12939-017-0636-5 PMID:28814339
19. Attard SM, Howard AG, Herring AH, Zhang B, Du S, Aiello AE, et al. (2015). Differential associations of urbanicity and income with physical activity in adults in urbanizing China: findings from the population-based China Health and Nutrition Survey 1991-2009. Int J Behav Nutr Phys Act. 12(1):152. https://doi.org/10.1186/s12966-015-0321-2 PMID:26653097
20. Islami F, Chen W, Yu XQ, Lortet-Tieulent J, Zheng R, Flanders WD, et al. (2017). Cancer deaths and cases attributable to lifestyle factors and infections in China, 2013. Ann Oncol. 28(10):2567–74. https://doi.org/10.1093/annonc/mdx342 PMID:28961829
21. Fan L, Strasser-Weippl K, Li JJ, St Louis J, Finkelstein DM, Yu KD, et al. (2014). Breast cancer in China. Lancet Oncol. 15(7):e279–89. https://doi.org/10.1016/S1470-2045(13)70567-9 PMID:24872111
22. Nagy P, Johansson S, Molloy-Bland M (2016). Systematic review of time trends in the prevalence of *Helicobacter pylori* infection in China and the USA. Gut Pathog. 8(1):8. https://doi.org/10.1186/s13099-016-0091-7 PMID:26981156
23. Cui Y, Jia J (2013). Update on epidemiology of hepatitis B and C in China. J Gastroenterol Hepatol. 28(Suppl 1):7–10. https://doi.org/10.1111/jgh.12220 PMID:23855289

24. Miao J, Wu X (2016). Urbanization, socioeconomic status and health disparity in China. Health Place. 42:87–95. https://doi.org/10.1016/j.healthplace.2016.09.008 PMID:27750075

25. National Bureau of Statistics of China (2015). China Statistical Yearbook. Beijing, China: China Statistics Press. Available from: http://www.stats.gov.cn/tjsj/ndsj/2015/indexeh.htm.

26. WHO (2018). WHO global report on trends in prevalence of tobacco smoking 2000–2025. 2nd ed. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/tobacco/publications/surveillance/trends-tobacco-smoking-second-edition/en/.

27. Chen TJ, Lian SY, Liu ZC, Lu JB, Sun XB, Wei WQ (2010). Retrospection and prospection on esophageal cancer scene in Linzhou City, Henan Province. China Cancer Chinese Journal. 19(1):24–8.

28. Qiao YL, Dawsey SM, Kamangar F, Fan JH, Abnet CC, Sun XD, et al. (2009). Total and cancer mortality after supplementation with vitamins and minerals: follow-up of the Linxian General Population Nutrition Intervention Trial. J Natl Cancer Inst. 101(7):507–18. https://doi.org/10.1093/jnci/djp037 PMID:19318634

29. Chen JG, Parkin DM, Chen QG, Lu JH, Shen QJ, Zhang BC, et al. (2003). Screening for liver cancer: results of a randomised controlled trial in Qidong, China. J Med Screen. 10(4):204–9. https://doi.org/10.1258/096914103771773320 PMID:14738659

30. Zhao P, Dai M, Chen W, Li N (2010). Cancer trends in China. Jpn J Clin Oncol. 40(4):281–5. https://doi.org/10.1093/jjco/hyp187 PMID:20085904

31. Chen JG, Egner PA, Ng D, Jacobson LP, Muñoz A, Zhu YR, et al. (2013). Reduced aflatoxin exposure presages decline in liver cancer mortality in an endemic region of China. Cancer Prev Res (Phila). 6(10):1038–45. https://doi.org/10.1158/1940-6207.CAPR-13-0168 PMID:23963804

32. Sun Z, Chen T, Thorgeirsson SS, Zhan Q, Chen J, Park JH, et al. (2013). Dramatic reduction of liver cancer incidence in young adults: 28 year follow-up of etiological interventions in an endemic area of China. Carcinogenesis. 34(8):1800–5. https://doi.org/10.1093/carcin/bgt007 PMID:23322152

33. Chen W (2016). Discussion on the clinical characteristics and trends of cancers in China according to cancer registry data. Zhonghua Jiankang Guanlixue Zazhi. 10(4):249–52.

34. Zheng RS, Gu XY, Li XT, Zhang SW, Zeng HM, Sun KX, et al. (2018). Analysis on the trend of cancer incidence and age change in cancer registry areas of China, 2000 to 2014. [in Chinese] Zhonghua Yu Fang Yi Xue Za Zhi. 52(6):593–600. PMID:29886680

35. Mou J, Griffiths SM, Fong H, Dawes MG (2013). Health of China's rural-urban migrants and their families: a review of literature from 2000 to 2012. Br Med Bull. 106(1):19–43. https://doi.org/10.1093/bmb/ldt016 PMID:23690451

36. Qian Y, Ge D, Zhang L, Sun L, Li J, Zhou C (2018). Does *Hukou* origin affect establishment of health records in migrant inflow communities? A nation-wide empirical study in China. BMC Health Serv Res. 18(1):704. https://doi.org/10.1186/s12913-018-3519-6 PMID:30200941

37. Chen Z, Peto R, Zhou M, Iona A, Smith M, Yang L, et al.; China Kadoorie Biobank (CKB) collaborative group (2015). Contrasting male and female trends in tobacco-attributed mortality in China: evidence from successive nationwide prospective cohort studies. Lancet. 386(10002):1447–56. https://doi.org/10.1016/S0140-6736(15)00340-2 PMID:26466050

4.4 Socioeconomic factors and cancer prevention in India

Diverse interventions are needed

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SUMMARY

- Cancer incidence rates differ markedly within India. In the north-eastern state of Mizoram, 1 in 5 men and women will develop cancer during their lifetimes, compared with 1 in 22 men and 1 in 18 women in the Barshi region.
- There are currently 164 million users of smokeless tobacco, 69 million smokers, and 42 million smokers and chewers in India. More than 90% of patients with oral cancer have low or lower-middle socioeconomic status.
- Among people with lower socioeconomic status, non-awareness of the harms of tobacco use in any form and of chewing products that contain areca nut is common, as is inadequate comprehension of the associated health risks.
- Urbanization appears to be associated with an increasing incidence of breast cancer. Similarly, the incidence of colorectal cancer is increasing in the most developed states in India and in urban populations.
- Given the focus of primary prevention on health literacy, awareness, and behaviour change, addressing the socioeconomic determinants that influence these factors is critical to advance cancer prevention in India.
- As the reduction of socioeconomic inequalities in population groups in India is addressed, highly focused and tailored public health interventions are needed to target different socioeconomic groups to reduce the disparities in cancer prevention.

During the past two decades, India has had one of the world's best performing and most stable economies, which has grown by more than 7% annually in most years, despite a global economic slowdown. This economic development has given rise to vast socioeconomic changes, with improvements in life expectancy and education and reductions in rates of poverty, hunger, and malnutrition. Between 1990 and 2017, the value of the Human Development Index (HDI) for India increased from 0.427 to 0.640, an increase of about 50%, and the country's gross national income per capita increased by 267% [1].

However, in a large country like India, consideration of aggregate economic indicators may hide inequalities of socioeconomic progress and of HDI. For instance, four of the five most developed states are in southern India, and all nine states with HDI values less than the national average are in northern and eastern India. Unfortunately, the progress in economic development is associated with an increasing prevalence of overweight and obesity, an increasing adoption of sedentary lifestyles and lower levels of physical activity (see Chapter 2.7), and an increasing risk of noncommunicable diseases, including cancer [2].

Socioeconomic factors such as education level, income, occupation, and standard of living determine the social standing of an individual or a population in terms of low, middle, and high socioeconomic status. Compared with people with high socioeconomic status, those with low socioeconomic status are resource-constrained. The vast differences in socioeconomic factors within a country can lead to significant disparities in access to cancer prevention and control services.

Cancer disparities refer to differences in cancer occurrence, the availability of and access to cancer health services, cancer survival, cancer deaths, quality of life, and the adverse economic impact of cancer in populations. There is convincing evidence that the striking socioeconomic differences among various regions and states in India are a major responsible factor for the cancer disparities observed in the country [3]. Cancer control initiatives can reduce disparities across the country only if such initiatives go hand in hand with policies and programmes directed towards the rapid elimination of poverty and illiteracy, an increase in purchasing power to improve the affordability and accessibility of healthy foods, and the alleviation of social inequalities.

Cancer prevention aims to reduce the burden of cancer (i) by decreasing the frequency of new cases of cancer, by avoiding or reducing exposure to cancer risk factors, and (ii) by detecting and treating precancerous lesions through screening programmes linked with diagnosis and treatment. Socioeconomic factors play a major role in determining the exposure of an individual and a population to cancer risk factors. Socioeconomic factors also affect the behaviour patterns of the population, in adopting lifestyles conducive to cancer prevention, including a healthy diet and adequate physical activity, among others, and in accessing cancer prevention services, such as vaccination, screening, and treatment of cancer precursor lesions (see Chapter 6.1).

The inherent differences in socioeconomic development and cultural practices across India are reflected in the major differences observed in cancer incidence and patterns, as documented by data provided by the 29 population-based cancer registries under the National Cancer Registry Programme of the Indian government [4]. Given the focus of primary prevention on health literacy, awareness, and behaviour change, addressing the socioeconomic determinants that influence these factors is critical to advance cancer prevention in India [5].

Cancer burden and patterns in India

For the age-standardized incidence rate of all cancers observed during 2012–2014, there was an almost 7-fold difference between the lowest and highest reported rates in men (40.9 per 100 000 in the Barshi expanded rural registry vs 270.7 per 100 000 in Aizawl district in Mizoram state) and an almost 5-fold difference in women (52.0 per 100 000 in the Barshi expanded rural registry vs 249.0 per 100 000 in Papumpare district in the state of Arunachal Pradesh) [4]. These rates indicate that in the north-eastern state of Mizoram, 1 in 5 men and women will develop cancer during their lifetimes, compared with 1 in 22 men and 1 in 18 women in the Barshi region.

The estimated cancer burden in India in 2018 is given in Box 4.4.1 [6]. Six cancer types – breast cancer, oral cancer, cervical cancer, lung cancer, stomach cancer, and colorectal cancer – together account for almost half of the new cancer cases occurring in India. Whereas tobacco-related cancers account for 34–69% of all cancers in men, they constitute 10–27% of all cancers in women in most regions in India.

Increasing trends (e.g. breast cancer, colorectal cancer) or decreasing trends (e.g. cervical cancer) in the incidence of the major cancer types over time (since the documentation of incidence began in different cancer registries) are evident with the socioeconomic changes that are occurring in different regions and states in India [4,7]. Recently, an increasing trend in the incidence of oral cancer has been observed among men in the fourth to seventh decades of life [4], possibly as a result of the increasing consumption of unregulated flavoured

FUNDAMENTALS

- During the past two decades, India has had one of the world's best performing and most stable economies, which has grown by more than 7% annually in most years. This economic development has given rise to vast socioeconomic changes, with an increasing risk of noncommunicable diseases, including cancer, and significant disparities in access to cancer prevention and control services.
- Cancer patterns in India are dominated by a high burden of tobacco-related head and neck cancers, particularly oral cancer, in men and of cervical cancer in women; both of these cancer types are associated with lower socioeconomic status.
- The burden of cancer types associated with overweight and obesity, lower levels of physical activity, and sedentary lifestyles, such as breast cancer and colorectal cancer, is increasing, and these cancer types are associated with higher socioeconomic status.

Box 4.4.1. Cancer burden and patterns in India in 2018.

- There are an estimated 1.16 million new cancer cases, 784 800 cancer deaths, and 2.26 million 5-year prevalent cases in India's population of 1.35 billion.
- The six most common cancer types are breast cancer (162 500 cases), oral cancer (120 000 cases), cervical cancer (97 000 cases), lung cancer (68 000 cases), stomach cancer (57 000 cases), and colorectal cancer (57 000); together, these account for 49% of all new cancer cases.
- Of the 570 000 new cancer cases in men, oral cancer (92 000), lung cancer (49 000), stomach cancer (39 000), colorectal cancer (37 000), and oesophageal cancer (34 000) account for 45% of cases.
- Of the 587 000 new cancer cases in women, breast cancer (162 500), cervical cancer (97 000), ovarian cancer (36 000), oral cancer (28 000), and colorectal cancer (20 000) account for 60% of cases.
- 1 in 10 Indians will develop cancer during their lifetimes, and 1 in 15 Indians will die of cancer.

chewing products that contain areca nut, such as paan masala [8].

There is a clear increasing trend in the incidence rates of breast cancer across the country, with an annual percentage increase that ranges from 1.4% to 2.8% and is more pronounced in urban areas than in rural areas (Fig. 4.4.1). Incidence rates are also increasing for cancer types associated with overweight and obesity and lower levels of physical activity, such as colorectal cancer (annual percentage change, 1.0–3.9%), uterine cancer (annual percentage change, 2.7–5.5%), ovarian cancer (annual percentage change, 0.8–2.4%), and prostate cancer (annual percentage change, 1.2–4.1%).

There is a clear decreasing trend in the incidence rates of cervical cancer in most regions in India (annual percentage change, −2.0% to −3.5%), with age-standardized incidence rates as low as 6 per 100 000 in women in Kerala [4] (Fig. 4.4.2). However, rates of cervical cancer are still high in less educated women with low socioeconomic status [7].

The underlying socioeconomic factors and changes that influence risk factors, exposure patterns, patterns of health beliefs, health-seeking behaviours, and the availability of and access to health-care services are largely responsible for the observed cancer patterns in India.

Fig. 4.4.1. Trends in age-standardized incidence rates (per 100 000 women) of breast cancer in selected populations in India, 1983–2015.

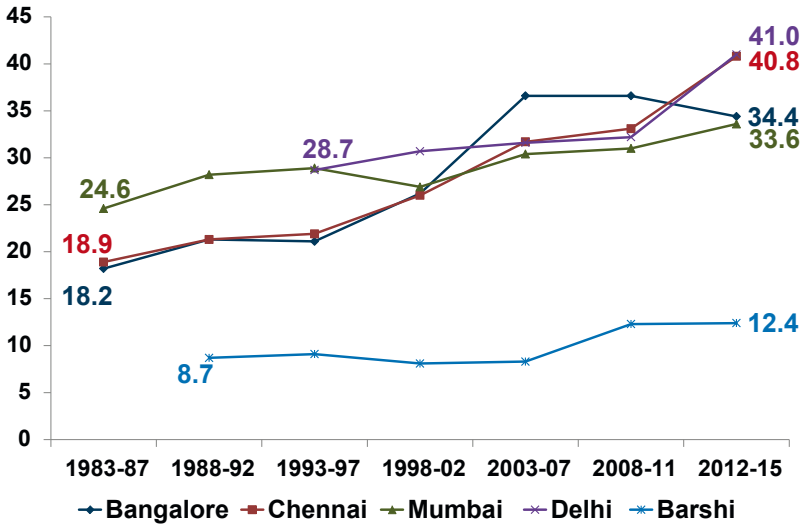
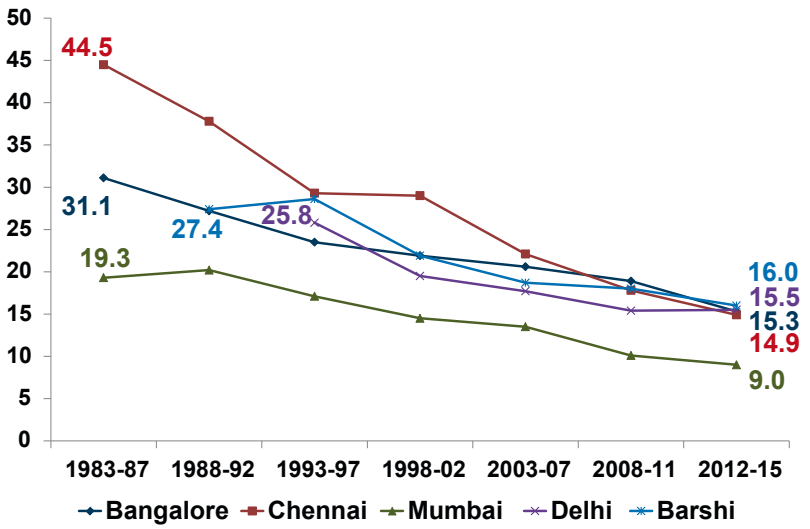


Fig. 4.4.2. Trends in age-standardized incidence rates (per 100 000 women) of cervical cancer in selected populations in India, 1983–2015.



Socioeconomic factors and cancer prevention

Prevention of lung cancer, oral cancer, and other tobacco-related cancers

Socioeconomic determinants of tobacco use patterns have a major impact on the prevention of cancer types associated with tobacco use, such as lung cancer, oral cancer, and other head and neck cancers (see Chapter 2.1). There are currently 164 million users of smokeless tobacco, 69 million smokers, and 42 million smokers and chewers in India, and tobacco-related cancers constitute a major burden in the country.

Recent studies indicate that between 2000 and 2012, the prevalence of any form of tobacco use decreased in the richest households (from 43.8% to 36.8%) and remained stable in the poorest households (from 61.5% to 62.7%) [9]. Despite the implementation of preventive interventions, in India there is a distinct and unique pattern of tobacco use; the use of smokeless tobacco and areca nut products has increased in all socioeconomic groups, with a greater increase in households with higher income and higher education levels, and the volume of smokeless tobacco and areca nut products used is increasing [10]. The reported prevalence of tobacco use in tribal populations exceeded 80%.

Because inadequate attention has been paid to curtailing the use of smokeless tobacco and areca

Fig. 4.4.3. A woman in India rolling bidis.

nut products, the anti-tobacco policies need to be reviewed to address inequalities in their use. Although 11 states in India have banned all forms of smokeless tobacco, various tobacco chewing products are still clandestinely sold.

Oral cancer is the major tobacco-related cancer type in India, and low socioeconomic status is associated with a high risk of oral cancer and precancerous lesions such as leukoplakia, erythroplakia, and oral submucous fibrosis (see Chapter 5.2) [11–13]. Alcohol consumption is an independent risk factor and substantially increases the risk of oral cancer when combined with tobacco use. In India, substantial differences exist in the sociodemographic correlates of alcohol consumption and types of alcoholic beverages.

Socioeconomic disadvantages appear to have a cumulative effect over the life course and are associated with a high risk of oral cancer. Early-life socioeconomic disadvantages have a lasting effect on oral cancer risk in adulthood [12]. More than 90% of patients with oral cancer have low or lower-middle socioeconomic status; use of various forms of tobacco and chewing of flavoured products that contain areca nut, such as paan masala, are more common among people with lower socioeconomic status [14].

In India, tobacco use occurs as smoking of cigarettes and bidis (made of shredded tobacco leaves wrapped in dried temburni leaf), as use of smokeless tobacco in the form of chewing paan (a mixture of lime, pieces of areca nut, cured tobacco, and spices wrapped in betel leaf) and many other forms, such as tobacco-containing paan masala, gutka (tobacco with crushed areca nut, wax, catechu, slaked lime, and sweet flavourings), khaini, mishri (burned tobacco), zarda (boiled tobacco), mawa (tobacco, lime, and areca nut), or as dual use (both smoking and chewing).

The prevalence of tobacco use in any form exceeds 60% in adult men (age 15 years and older) in the north-eastern states in India and in the less developed states, such as Bihar, Jharkhand, Chhattisgarh, and Madhya Pradesh, and exceeds 45% in West Bengal, Uttar Pradesh, Rajasthan, Uttarakhand, Odisha, and Gujarat [14]. The prevalence of tobacco use (mostly as chewing) in adult women exceeds 40% in the north-eastern states and in Bihar, Chhattisgarh, and Odisha [15].

Paan masala is packed in attractive, user-friendly packets and containers. Increasing disposable incomes, convenient packaging, aggressive advertising campaigns by manufacturers, and the large-scale switching by consumers from

Fig. 4.4.4. A man in West Bengal, India, holding gutka in his hand.

tobacco products to paan masala are currently encouraging the growth of the paan masala market. The Indian paan masala market was valued at about US$ 5 billion in 2017 and is expected to increase to US$ 8 billion by 2023.

In 2016, after a Supreme Court order, the central government issued a complete ban across India on the production, promotion, and sale of food products containing tobacco and nicotine as ingredients, including gutka, paan masala, zarda, and tobacco-based flavoured mouth fresheners. However, several states have yet to follow suit, and illegal sales continue (see Chapter 6.8).

Among people with lower socioeconomic status, non-awareness of the harms of tobacco use in any form and of chewing products that contain areca nut is common, as is inadequate comprehension of the associated health risks. The use of hookah (water pipes) and e-cigarettes is increasing among young people, and this is creating a new problem. There is an urgent need to create comprehensive awareness about the health hazards of all forms of tobacco and areca nut use among every subsection of society and to regulate the availability, affordability, and accessibility of tobacco and areca nut products, to prevent all tobacco-related cancers.

In a randomized trial of oral cancer screening with oral visual inspection in Kerala, which demonstrated a significant reduction in oral cancer mortality in users of tobacco or alcohol or both, participation was significantly higher among people with higher socioeconomic status than among those with lower socioeconomic status [16,17].

Breast cancer control

In India, the incidence of breast cancer is consistently increasing and the incidence of cervical cancer is decreasing with time, as shown by data from several population-based cancer registries [4]. The diverging incidence trends for breast cancer and cervical cancer in India may be partly explained by

Fig. 4.4.5. Mobile oral cancer screening in India.

improvements in the socioeconomic status of women, as indicated by higher education levels, increasing household incomes, later ages at marriage and at first birth, lower parity, and increasing adoption of sedentary lifestyles, dietary patterns typical of industrialized countries, and lower levels of physical activity in successive generations of women (see Chapter 5.9).

The most developed states report the highest breast cancer rates in the country [4]. In India, high socioeconomic status is associated with a higher prevalence of overweight and obesity and with a shift towards sedentary lifestyles and dietary patterns typical of industrialized countries, which are established risk factors for breast cancer; households with high socioeconomic status spend less on cereals, millets, and vegetables and more on beverages, processed foods, dairy products, meat, eggs, and fish [18].

The most effective intervention for breast cancer control is early detection and prompt treatment. Breast awareness and participation in screening are conducive to early detection and completion of treatment. In a cross-sectional study of breast cancer screening practices in Kerala, women with higher socioeconomic status were found to be more likely to participate in screening compared with other women [19]. In a recent study in Mumbai, women with higher socioeconomic status were found to have higher breast awareness than women with lower socioeconomic status [20].

Two large randomized trials of screening by clinical breast examination in India have shown that clinical breast examination screening is followed by early diagnosis of breast cancer [21,22]. Findings from a randomized trial in Kerala indicated that women who had a higher education level and a higher household income, were employed in non-manual occupations, and were living in better housing were more likely to have breast awareness and to practice breast self-examination but less likely to participate in clinical breast examination screening, which was offered in the trial by the public health services [23]. A possible explanation for these paradoxical findings is that women with higher socioeconomic status have less faith in public health services, can afford private health care, and seek mammography screening elsewhere. Similar findings were reported in a breast cancer screening trial in Mumbai [22].

Cervical cancer prevention

India accounts for about one fifth of the global burden of cervical cancer, despite decreasing incidence rates in several regions of the country (see Chapter 5.10). Thus, elimination of cervical cancer in India will have a major impact on global elimination of the disease as a public health problem. Cervical cancer disproportionately affects women with lower socioeconomic status, who are at a considerable disadvantage in the availability of and access to public health services for prevention and early detection, and therefore this is an equity issue. Low socioeconomic status is a major risk factor for cervical cancer [24].

It is well established that persistent infection with one of the high-risk human papillomavirus (HPV) types is the necessary cause of cervical cancer. HPV types 16 and 18 are detected in about 80% of all cervical cancers in India [25]. Low socioeconomic status is associated with a high prevalence of HPV infection in India [26,27]. Cervical cancer is an eminently preventable disease, by HPV vaccination and screening. The decreasing incidence rates of cervical cancer provide an exciting opportunity to rapidly decrease risk and eliminate cervical cancer by implementing an integrated HPV vaccination and screening programme.

A large randomized trial in India has shown a 50% reduction in cervical cancer mortality after a single round of HPV screening; in another trial, a 35% reduction in cervical cancer mortality was seen after a single round of screening by visual inspection of the cervix with acetic acid [28,29]. An HPV vaccination study that is under way in India to assess the effectiveness of fewer than three doses of HPV vaccine has demonstrated that two doses of quadrivalent vaccine offer an equivalent immune response and similar protection against persistent HPV16 and 18 infections as three doses and has shown that even a single dose is immunogenic and provides lasting protection against HPV16 and 18 infections, similar to the three-dose and two-dose vaccine schedules [30,31]. Currently, Punjab is implementing two doses of HPV vaccination in an incremental fashion, and Sikkim has implemented a statewide HPV vaccination programme targeting girls aged 11–12 years, with high vaccination coverage and an excellent safety profile. Delhi state is implementing opportunistic HPV vaccination supported by the state government.

Despite the decreasing incidence of cervical cancer, there is a 6-fold difference in age-standardized rates, ranging from 5 per 100 000 women to 30 per 100 000 women, reflecting the underlying differences in socioeconomic factors and HPV prevalence, among other risk factors [4]. Incidence rates are about 6 per 100 000 women in Kerala, which has achieved 100% literacy and has the highest HDI value (0.784) of any state in the country [4]. Because cervical cancer disproportionately affects women with low socioeconomic status, the lack of effective interventions such as HPV vaccination and screening in public health services will widen the disparities and increase the inequities in the cervical cancer burden in India.

Prevention of other cancer types related to lifestyle factors

Given the association between diet, overweight, obesity, and physical activity and cancer types such as colorectal cancer, ovarian cancer, endometrial cancer, and prostate cancer, among others, and the emerging trends in the prevalence of these lifestyle factors accompanying socioeconomic changes, the incidence of these cancer types is increasing in various regions in India [4]. Colorectal cancer, for which incidence rates in India were previously low, is already the sixth most common cancer (Box 4.4.1), and increasing trends are evident in the most developed states in India and in urban populations [4,6]. To curtail the future burden of these lifestyle-related cancer types, including breast cancer, it is critical to reverse the emerging trends in risk factors and to preserve the lifestyles that kept the incidence of these cancer types low.

Conclusions

Because cancer is not one disease but a group of many diseases that differ in their etiology and biology, it is not surprising that socioeconomic determinants of cancer risk are variable for different cancer types, reflecting the underlying complex relationships. There is a positive association of low socioeconomic status with the incidence of tobacco-related cancer types. However, improvements in education, increasing disposable incomes, and higher overall socioeconomic status are associated with an increasing risk of breast cancer and colorectal cancer, among other lifestyle-related cancer types.

The limited available data indicate disparities in participation in cancer screening by socioeconomic status. Good participation by people with low socioeconomic status in the cervical cancer screening studies and the high participation of girls in all socioeconomic groups in HPV vaccination programmes in Punjab and Sikkim indicate the importance of appropriate educational initiatives.

As the reduction of socioeconomic inequalities in population groups in India is addressed, highly focused and tailored public health interventions are needed to target different socioeconomic groups to reduce the disparities in cancer prevention.

References

1. UNDP (2018). Human development indices and indicators, 2018 statistical update. New York (NY), USA: United Nations Development Programme. Available from: http://hdr.undp.org/sites/default/files/2018_human_development_statistical_update.pdf.
2. Dandona L, Dandona R, Kumar GA, Shukla DK, Paul VK, Balakrishnan K, et al.; India State-Level Disease Burden Initiative Collaborators (2017). Nations within a nation: variations in epidemiological transition across the states of India, 1990-2016 in the Global Burden of Disease Study. Lancet. 390(10111):2437–60. https://doi.org/10.1016/S0140-6736(17)32804-0 PMID:29150201
3. Goss PE, Strasser-Weippl K, Lee-Bychkovsky BL, Fan L, Li J, Chavarri-Guerra Y, et al. (2014). Challenges to effective cancer control in China, India, and Russia. Lancet Oncol. 15(5):489–538. https://doi.org/10.1016/S1470-2045(14)70029-4 PMID:24731404
4. National Cancer Registry Programme (2016). Three-year report of population-based cancer registries: 2012–2014. Bengaluru, India: Indian Council of Medical Research.
5. Mathur MR, Singh A, Dhillon PK, Dey S, Sullivan R, Jain KK, et al. (2014). Strategies for cancer prevention in India – catching the 'low hanging fruits'. J Cancer Policy. 2(4):105–6. https://doi.org/10.1016/j.jcpo.2014.07.001
6. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today.
7. Gandhi AK, Kumar P, Bhandari M, Devnani B, Rath GK (2017). Burden of preventable cancers in India: time to strike the cancer epidemic. J Egypt Natl Canc Inst. 29(1):11–8. https://doi.org/10.1016/j.jnci.2016.08.002 PMID:27591115
8. Shridhar K, Rajaraman P, Koyande S, Parikh PM, Chaturvedi P, Dhillon PK, et al. (2016). Trends in mouth cancer incidence in Mumbai, India (1995-2009): an age-period-cohort analysis. Cancer Epidemiol. 42:66–71. https://doi.org/10.1016/j.canep.2016.03.007 PMID:27043865
9. Bhan N, Karan A, Srivastava S, Selvaraj S, Subramanian SV, Millett C (2016). Have socioeconomic inequalities in tobacco use in India increased over time? Trends from the National Sample Surveys (2000–2012). Nicotine Tob Res. 18(8):1711–8. https://doi.org/10.1093/ntr/ntw092 PMID:27048274
10. Misra PJ, Mini GK, Thankappan KR (2014). Risk factor profile for non-communicable diseases among *Mishing* tribes in Assam, India: results from a WHO STEPs survey. Indian J Med Res. 140(3):370–8. PMID:25366204
11. Hashibe M, Jacob BJ, Thomas G, Ramadas K, Mathew B, Sankaranarayanan R, et al. (2003). Socioeconomic status, lifestyle factors and oral premalignant lesions. Oral Oncol. 39(7):664–71. https://doi.org/10.1016/S1368-8375(03)00074-5 PMID:12907205
12. Rao SVK (2014). Epidemiology of oral cancer in India – a life course study [thesis]. Adelaide, Australia: The University of Adelaide. Available from: https://digital.library.adelaide.edu.au/dspace/bitstream/2440/91305/3/02whole.pdf.
13. Gupta B, Ariyawardana A, Johnson NW (2013). Oral cancer in India continues in epidemic proportions: evidence base and policy initiatives. Int Dent J. 63(1):12–25. https://doi.org/10.1111/j.1875-595x.2012.00131.x PMID:23410017
14. Sharma S, Satyanarayana L, Asthana S, Shivalingesh KK, Goutham BS, Ramachandra S (2018). Oral cancer statistics in India on the basis of first report of 29 population-based cancer registries. J Oral Maxillofac Pathol. 22(1):18–26. PMID:29731552
15. Singh A, Ladusingh L (2014). Prevalence and determinants of tobacco use in India: evidence from recent Global Adult Tobacco Survey data. PLoS One. 9(12):e114073. https://doi.org/10.1371/journal.pone.0114073 PMID:25474196
16. Sankaranarayanan R, Ramadas K, Thara S, Muwonge R, Thomas G, Anju G, et al. (2013). Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India. Oral Oncol. 49(4):314–21. https://doi.org/10.1016/j.oraloncology.2012.11.004 PMID:23265945
17. Ramadas K, Arrossi S, Thara S, Thomas G, Jissa V, Fayette JM, et al. (2008). Which socio-demographic factors are associated with participation in oral cancer screening in the developing world? Results from a population-based screening project in India. Cancer Detect Prev. 32(2):109–15. https://doi.org/10.1016/j.cdp.2008.02.008 PMID:18632218
18. Varadharajan KS, Thomas T, Kurpad AV (2013). Poverty and the state of nutrition in India. Asia Pac J Clin Nutr. 22(3):326–39. https://doi.org/10.6133%2fapjcn.2013.22.3.19 PMID:23945402
19. Sreedevi A, Quereshi MA, Kurian B, Kamalamma L (2014). Screening for breast cancer in a low middle income country: predictors in a rural area of Kerala, India. Asian Pac J Cancer Prev. 15(5):1919–24. https://doi.org/10.7314/APJCP.2014.15.5.1919 PMID:24716912
20. Gadgil A, Sauvaget C, Roy N, Grosse Frie K, Chakraborty A, Lucas E, et al. (2015). Breast cancer awareness among middle class urban women – a community-based study from Mumbai, India. Asian Pac J Cancer Prev. 16(15):6249–54. https://doi.org/10.7314/APJCP.2015.16.15.6249 PMID:26434824
21. Sankaranarayanan R, Ramadas K, Thara S, Muwonge R, Prabhakar J, Augustine P, et al. (2011). Clinical breast examination: preliminary results from a cluster randomized controlled trial in India. J Natl Cancer Inst. 103(19):1476–80. https://doi.org/10.1093/jnci/djr304 PMID:21862730
22. Mittra I, Mishra GA, Singh S, Aranke S, Notani P, Badwe R, et al. (2010). A cluster randomized, controlled trial of breast and cervix cancer screening in Mumbai, India: methodology and interim results after three rounds of screening. Int J Cancer. 126(4):976–84. https://doi.org/10.1002/ijc.24840 PMID:19697326
23. Grosse Frie K, Ramadas K, Anju GA, Mathew BS, Muwonge R, Sauvaget CS, et al. (2013). Determinants of participation in a breast cancer screening trial in Trivandrum district, India. Asian Pac J Cancer Prev. 14(12):7301–7. https://doi.org/10.7314/APJCP.2013.14.12.7301 PMID:24460292
24. Thulaseedharan JV, Malila N, Hakama M, Esmy PO, Cheriyan M, Swaminathan R, et al. (2012). Socio demographic and reproductive risk factors for cervical cancer – a large prospective cohort study from rural India. Asian Pac J Cancer Prev. 13(6):2991–5. https://doi.org/10.7314/APJCP.2012.13.6.2991 PMID:22938495
25. Deodhar K, Gheit T, Vaccarella S, Romao CC, Tenet V, Nene BM, et al. (2012). Prevalence of human papillomavirus types in cervical lesions from women in rural Western India. J Med Virol. 84(7):1054–60. https://doi.org/10.1002/jmv.23310 PMID:22585722
26. Franceschi S, Rajkumar R, Snijders PJ, Arslan A, Mahé C, Plummer M, et al. (2005). Papillomavirus infection in rural women in southern India. Br J Cancer. 92(3):601–6. https://doi.org/10.1038/sj.bjc.6602348 PMID:15668709

27. Gupta S, Sodhani P, Sharma A, Sharma JK, Halder K, Charchra KL, et al. (2009). Prevalence of high-risk human papillomavirus type 16/18 infection among women with normal cytology: risk factor analysis and implications for screening and prophylaxis. Cytopathology. 20(4):249–55. https://doi.org/10.1111/j.1365-2303.2008.00611.x PMID:19018810

28. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, et al. (2009). HPV screening for cervical cancer in rural India. N Engl J Med. 360(14):1385–94. https://doi.org/10.1056/NEJMoa0808516 PMID:19339719

29. Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S, et al. (2007). Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. Lancet. 370(9585):398–406. https://doi.org/10.1016/S0140-6736(07)61195-7 PMID:17679017

30. Bhatla N, Nene BM, Joshi S, Esmy PO, Poli URR, Joshi G, et al.; Indian HPV vaccine study group (2018). Are two doses of human papillomavirus vaccine sufficient for girls aged 15-18 years? Results from a cohort study in India. Papillomavirus Res. 5:163–71. https://doi.org/10.1016/j.pvr.2018.03.008 PMID:29578097

31. Sankaranarayanan R, Joshi S, Muwonge R, Esmy PO, Basu P, Prabhu P, et al.; Indian HPV vaccine study group (2018). Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study. Vaccine. 36(32 Pt A):4783–91. https://doi.org/10.1016/j.vaccine.2018.02.087 PMID:29551226

4.5 Variations in implementation of cancer screening in European countries

Striving for best practice

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SUMMARY

- Basic differences are evident between screening practices followed in European Union countries, including the target age ranges for screening, the interval between screening tests, and the screening procedures used.
- For breast cancer screening, there is a nearly 2-fold difference in the coverage by invitations and a more than 5-fold difference in the attendance reported.
- For cervical cancer screening, both the number of tests that are offered over a woman's lifetime and the actual number of screens received differ tremendously, leading to high health inequalities across the European Union.
- Research shows that achieving relatively high participation rates in cancer screening will reduce health inequalities. In patients with breast cancer, screen detection is an independent favourable prognostic factor.
- There appears to be a lack of quantified country-specific knowledge on the expected benefits and harms of the screening policies.
- Much effort is needed to ensure the implementation of high-quality organized screening programmes with fair attendance rates, provision of informed choice, and fair designs, specifically with respect to benefits and harms, and taking equity into account.

Cancer is the second leading cause of death in Europe [1]. Together, colorectal cancer, breast cancer, and cervical cancer are responsible for 20% of cancer mortality and for approximately 250 000 deaths in the European Union (EU) per year [2–5]. Each year more than 1 million people in the EU are diagnosed with one of these three cancer types. The burden of disease is unevenly distributed across countries in the EU, and it is estimated that by 2050 the burden will grow by up to 50% as a result of population growth and ageing [4–6].

Substantial progress has been made in the early detection and treatment of breast cancer, cervical cancer, and colorectal cancer; in many countries, mortality has decreased by 1–2% per year since the early 1990s [4,7]. However, great inequity persists in mortality trends [8]. In addition, there is considerable debate about whether this decline in mortality can be attributed to screening or to improvements in treatment. Some have estimated that if all countries in the EU could reduce mortality rates to those in the best-performing country, each year there would be more than 4000 fewer deaths from cervical cancer and 17 000 fewer deaths from breast cancer [8].

Screening programmes

Breast cancer, cervical cancer, and colorectal cancer are currently the only three cancer types for which the European Council recommends screening [9]. Currently, all EU countries have some form of screening for breast cancer and cervical cancer, and most countries have started to implement screening for colorectal cancer (see Chapter 6.6).

It has been estimated that 125 million people in the EU could have been screened in 2007 if the screening tests had been available to and utilized by all EU citizens in the target age ranges. However, in 2007 approximately 55 million screening tests were actually performed in the EU [10]. Therefore, successfully improving screening coverage would potentially have an impact on the lives of millions of people, but would also put further pressure on the available clinical and economic resources. The 55 million screening tests alone are estimated to cost more than €500 million per year [11]. In the light of the current economic crisis, it is especially important to ensure that this money is well spent and that people benefit optimally and equally well, if possible.

In December 2003 the European Council recommended mammography screening for breast cancer, Pap smear (cytology) screening

for cervical cancer, and faecal occult blood test (FOBT) screening for colorectal cancer. The latest revision of the EU code reconfirms the appropriateness of population-based screening programmes for these three cancer types, and not yet for other cancer types [12]. In most EU countries, organized or opportunistic screening is available for these cancer types.

The total target population in the EU is massive: almost 68 million women in the EU are eligible for breast cancer screening (age range, 50–69 years), and more than 100 million women can participate in Pap smear screening (age range, 30–59 years). Although the potential target population for colorectal cancer screening is even larger (more than 150 million people; age range, 50–74 years), approximately 25% of this population had not yet been targeted by a screening programme. The number of screening tests that are actually performed in the EU is much lower. In addition, the existing screening programmes for breast cancer, cervical cancer, and colorectal cancer vary in terms of their application, both within countries and across countries throughout Europe (Tables 4.5.1, 4.5.2, and 4.5.3).

Breast cancer

There is wide agreement within the EU on different aspects of the policy for breast cancer screening, such as the screening test based on mammography, the minimum target age range of 50–69 years, and the screening interval of 2 years (Table 4.5.1) [10,13–16].

However, there are substantial differences within the EU in the extent to which target populations are actually exposed to screening [13]. Among the EU countries, there is a nearly 2-fold difference in the coverage by invitations and a more than 5-fold difference in the attendance reported.

Cervical cancer

Cervical cancer screening usually starts at age 20–30 years and stops at age 60–70 years. Some countries recommend starting screening before age 20 years (Table 4.5.2) [10,13,17,18].

For the screening interval, nine countries recommend an interval of 5 years, and six countries recommend an interval of 1 year; most countries recommend a screening interval of 3 years. As a result, the number of tests that women in the EU have over their lifetimes ranges from 6 to more than 40. The proportion of the target population covered by the screening test ranges from 10% to approximately 80%, and for several countries this proportion is unknown.

FUNDAMENTALS

- Currently, based on the recommendations of the European Council, all European Union countries have some form of screening for breast cancer and cervical cancer, and most countries have started to implement screening for colorectal cancer.
- It would not be appropriate to implement a single, uniform screening programme per cancer type for all countries; however, in many instances, there is no plausible reason for the huge variations in the three cancer screening programmes across the European Union.
- Successfully improving screening coverage would potentially have an impact on the lives of millions of people, but would also put further pressure on the available clinical and economic resources.
- Organized population-based screening programmes could be very effective in reducing health inequalities.
- Although nearly all countries make some degree of national recommendations for screening policy, the decision-making and implementation are often delegated to lower-level health authorities.

Fig. 4.5.1. A woman undergoing breast cancer screening in Moscow, Russian Federation.

Table 4.5.1. Breast cancer screening practices in countries in the European Union

Country	Starting age (years)	Stopping age (years)	Interval (years)	Attendance (%)[a]	Primary test
Austria	45	69	2	57	Mammography/US
Belgium	50	69	2	33[b]	Mammography
Bulgaria	50	69	–	ND	Mammography
Croatia	50	69	2	45	Mammography
Cyprus	50	69	2	17[c]	Mammography/CBE
Czechia	45	69[d]	2	70	Mammography
Denmark	50	69	2	72	Mammography
Estonia	50	64	2	46	Mammography
Finland	50	69	2	76	Mammography
France	50	74	2	53	Mammography/CBE
Germany	50	69	2	53	Mammography
Greece	40 > 50	49	2 1	1 –	Mammography/CBE Mammography/CBE
Hungary	45	64	2	56	Mammography
Ireland	50	69	2	74	Mammography
Italy Piedmont and Emilia-Romagna	50 45[f] 50	69 49[f] 74	2 1 2	ND[e] ND ND	Mammography Mammography Mammography
Latvia	50	69	2	34	Mammography
Lithuania	50	69	2	45	Mammography
Luxembourg	50	69	2	60	Mammography
Malta	50	69	3	36	Mammography
Netherlands	50	75	2	80	Mammography
Poland	50	69	2	44	Mammography
Portugal Algarve Azores Other regions	 50 45 45	 69 74 69	 2 2 2	60 56 ND ND	Mammography Mammography Mammography Mammography
Romania	50	69	–	0.2[g]	Mammography
Slovakia	–	–	–	ND	Mammography/US
Slovenia	50	69	2	19	Mammography
Spain Some regions	50[h] 45	64[h] 69	2 2	67 ND	Mammography Mammography
Sweden	40	74	1.5–2	70	Mammography
United Kingdom	50	70	3	84[i]	Mammography

CBE clinical breast examination; ND, no data available; US, ultrasound.

[a] The attendance (%) represents the proportion of the target population that has been screened.

[b] In Belgium, large regional differences are seen in attendance: Flemish Region, 50%; Brussels, 10%; Wallonia, 8%.

[c] In Cyprus, large regional differences are seen in attendance: Nicosia, 42%; other regions, 0%.

[d] In Czechia, the invitations are sent only to women up to age 70 years.

[e] For Italy, no data about national attendance were found. Regional attendance was: North, 61%; Centre, 56%; South and Islands, 40%.

[f] In Italy, the target age range is 45–74 years only in Piedmont and Emilia-Romagna. In other regions, the target age range is 50–69 years.

[g] In Romania, large regional differences are seen in attendance: Cluj, 49%; other regions, 0%.

[h] In Spain, the standard target age range is 50–64 years, but in some regions the target age range is 45–69 years.

[i] In the United Kingdom, regional differences are seen in attendance: England, 86%; Northern Ireland, 80%; Scotland, 73%; Wales, 74%.

Table 4.5.2. Cervical cancer screening practices in countries in the European Union

Country	Starting age (years)	Stopping age (years)	Interval (years)	Coverage (%)[a]	Triage test
Austria	≥ 18		1	ND	Cytology
Belgium	25	64	3	37[b]	Cytology/HPV
Bulgaria	30	59	3	47	
Croatia	25	64	3	105	Cytology/HPV
Cyprus	24	65	3	67	Cytology
Czechia	≥ 15		1	53	Cytology/HPV
Denmark	23 60	59 65	3 5	74 (total)	Cytology/HPV
Estonia	30	59	5	77	Cytology/HPV
Finland	30[c]	64[c]	5	98	Cytology/HPV[c]
France	25	64	3	8[d]	Cytology/HPV
Germany	≥ 20		1	53	Cytology/HPV
Greece	≥ Age of sexual onset		1	69	Cytology
Hungary	25	65	3	15	Cytology
Ireland	25 45	44 60	3 5	70	Cytology
Italy	25	64	3	67[e]	Cytology/HPV
Latvia	25	69	3	94	Cytology
Lithuania	25	59	3	78	Cytology/HPV
Luxembourg	≥ 18		1	55	Cytology/HPV
Malta[f]	25	35	3	49	Cytology/HPV
Netherlands	30	64	5	95	Cytology/HPV
Poland Co-test	25 30	29 59	3 3	98	Cytology/HPV
Portugal Azores Lisbon/Madeira	25 25 –	59 64 –	3 3 –	19[g] ND –	Cytology/HPV Cytology/HPV No programme
Romania	25	64	5	65	Cytology
Slovakia	23 25	24 64	1 3	48 (total)	Cytology
Slovenia	20 22	21 64	1 3	71	Cytology/HPV
Spain	25	64	3	73	Cytology/HPV
Sweden	23 51	50 60	3 5	81	Cytology/HPV
United Kingdom	25 50	49 64	3 5	101[h]	Cytology/HPV

HPV, human papillomavirus; ND, no data available.

[a] The coverage exceeds 100% in some cases. Using a single index year to estimate coverage for screening with intervals of 3–5 years entails some imprecision because of variability between years, and may lead to estimates exceeding 100%.

[b] In Belgium, large regional differences can be seen in attendance: Flemish Region, 65%.

[c] In Finland, some municipalities target women younger than 30 years and older than 60 years. The screening test can be either cytology or HPV.

[d] In France, an attendance of 89% was found in the 13 departments.

[e] In Italy, large regional differences can be seen in attendance: North, 65%; Centre, 83%; South, 60%.

[f] In Malta, the screening programme is being piloted.

[g] Azores excluded from attendance. In Portugal, large regional differences can be seen in attendance: North, 34%; Centre, 100%; Alentejo, 57%; Algarve, 13%.

[h] In the United Kingdom, regional differences can be seen in attendance: England, 104%; Northern Ireland, 91%; Scotland, 93%; Wales, 104%.

Fig. 4.5.2. A biomedical scientist in England making an assessment in relation to cellular characteristics in the context of cervical cancer screening.

Cytology is the most commonly recommended primary screening test in Europe, with human papillomavirus (HPV)-based follow-up for women with minor cytological abnormalities (atypical squamous cells of undetermined significance [ASCUS] and low-grade squamous intraepithelial lesion [LSIL] cytology). However, there is no consensus on the use of cytology or HPV testing as a triage test for a given cytological diagnosis. Currently, the Netherlands and some regions of Italy are the only parts of Europe where HPV-based screening is offered [5,10].

Colorectal cancer

For colorectal cancer, the most widely used FOBT is guaiac FOBT (gFOBT), which is based on a biochemical test that detects haemoglobin in the stool (Table 4.5.3) [10,13,19–21]. For a gFOBT, dietary restrictions are required before testing, to reduce the number of false positives. For a faecal immunochemical test (FIT), which is based on human haemoglobin antibodies, a special diet is not required before testing.

Assessment of the colorectal cancer screening strategies currently adopted by the 28 EU countries reveals remarkable differences. For example, in France, the target population is invited to gFOBT screening; in Italy, FIT screening is used, except in some areas in the north of the country, where sigmoidoscopy is offered once in a lifetime at age 58–60 years. The target age groups also differ substantially: in some countries, screening is confined to people aged 60–69 years, whereas in others it covers a much larger range of at-risk individuals (aged 50–74 years).

Attendance rates for screening programmes based on FOBT range from 8% to 71% in different EU countries. Because colorectal cancer screening is currently still being implemented in many countries, clear guidance on reducing inequities is crucial now.

Variation in programmes

The underlying risk of cancer varies across the EU – and, in the case of colorectal cancer, between the sexes. The countries also vary in terms of capacity and organizational resources. Therefore, it would not be appropriate to implement a single, uniform screening programme per cancer type for all countries. However, in many instances, there is no plausible reason for the huge variations in the three cancer screening programmes.

These substantial differences may result in inappropriate interventions, excessive screening, and overtreatment, or in delayed provision of appropriate treatment. The differences certainly result in a higher disease burden, a lower quality of life, health inequities, and increased costs for health and care systems. For example, there are countries where cervical cancer screening is performed in a non-organized manner and where, even though very large numbers of tests are performed, no appropriate benefit has been seen in terms of reduced incidence of and mortality from cervical cancer [22,23]. Major modifiable barriers to effective screening programmes are responsible for the observed differences [24], and there appears to be a lack of quantified country-specific knowledge on the expected benefits and harms of the policies.

In 2014, an international comparison was made of screening policy-making in Europe and globally [25], with a focus on comparing these processes with, for example, those used in the United Kingdom. The authors found some important differences: (i) Although all of the countries considered except Spain made some degree of national recommendations for screening policy, the decision-making and implementation were often delegated to lower-level health authorities. (ii) Although in the United Kingdom proposals for new screening programmes from stakeholder organizations would generally be reviewed, considerations for deciding which topics to work on varied across the countries to a very large extent. (iii) Required measures of effectiveness varied across countries, ranging from high-quality evidence from randomized controlled trials (in the United Kingdom) to Grading of Recommendations Assessment, Development and Evaluation (GRADE) working groups (in Sweden) to including international consensus (in France); the United

Fig. 4.5.3. Elements of a community-based campaign to encourage colorectal cancer screening, from the Institut Paoli-Calmettes in Marseille, France.

Kingdom explicitly required consideration of the public pressure for widening the inclusion criteria. (iv) Differences were found in the methods for appraising the quality of evidence and in the methodologies for synthesizing the evidence. (v) Differences were found in the decision-making process itself (ranging from voting to decision support systems).

Health inequalities research related to screening

Two studies in Italy showed that the introduction of an organized breast cancer screening programme can have an impact in reducing health inequalities. In both study areas, in the period before the introduction of screening, overall survival was significantly lower in women with a lower education level than in those with a higher education level, in both the younger and older age groups. After the screening programme was fully implemented, the differences in survival decreased in both age groups and then disappeared completely among women in the age group invited to screening. These findings suggest that an organized population-based mammography screening programme could be effective in reducing differences in survival in the target population [26,27]. A study in the Netherlands among patients with breast cancer showed that screen detection was a significant independent prognostic variable, after adjustment for all well-known predictive variables, including tumour size, lymph node status, and other stage characteristics [28].

A cross-sectional study in 22 European countries using individual-level data from the WHO World Health Survey showed substantial socioeconomic inequalities in countries with opportunistic screening for cervical cancer (comparing highest with lowest education level, relative index of inequality [RII], 1.28; 95% confidence interval [CI],

Table 4.5.3. Colorectal cancer screening practices in countries in the European Union, and in European Council countries outside of the European Union

Country	Starting age (years)	Stopping age (years)	Interval (years)	Attendance (%)	Primary test
European Union countries					
Austria[a]	40	80	1	61	gFOBT
	> 50		10	2	TC
Burgenland	40	80	1	ND	FIT
	> 50		10	ND	TC
Belgium				28	
Wallonia–Brussels	50	74	2	6–7	FIT or gFOBT
	50	74	10	ND	TC
Flemish Region	56	74	2	47–49	FIT
	56	74	10	ND	TC
Bulgaria	40	60	1	ND	FOBT
Croatia	50	74	2	15	gFOBT
Cyprus	50	69	2	ND	FIT
Czechia	50	54	1	21–26	FIT
	≥ 55		2	(total FIT)	FIT
	≥ 55		10	1–2	TC
Denmark	50	74	2	ND	FIT
Estonia[b]	60	69	2	ND	FIT
Finland	60	69	2	14–17	gFOBT
France	50	74	2	25–28	gFOBT
Calvados				22–27	FIT
Germany	50	54	1	19	gFOBT/FIT
	≥ 55		2	ND	gFOBT/FIT
	≥ 55		10	3–4	TC
Greece	50	70	2	8	FOBT/gFOBT
	50	70	5	ND	TC
Hungary	50	70	2	1	FIT
Ireland	60[c]	69[c]	2	12	FIT
Italy	50	69	2	29[d]	FIT
Piedmont	58	60	Once in a lifetime	ND	FS[e]
	59	69	2	ND	FIT
Latvia	50	74	1	11	gFOBT
Lithuania	50	74	2	47–58	FIT
Luxembourg	55	74	2	ND	FIT/TC
Malta	55	66	2	45	FIT
Netherlands	55	75	2	27–28	FIT
Poland	55	64	≥ 10	2	TC
Portugal	50	70	2	1	FIT/gFOBT
Romania	–		–	ND	–
Slovakia	> 50			ND	TC
Slovenia	50	74	2	43–52	FIT
Spain	50	69	2	8–9	FIT
Sweden	60	69	2	11–13	gFOBT
United Kingdom	60	74	2	56[f]	gFOBT
England	60	74	2	50–60	gFOBT
				ND	FS
Scotland	50	74	2	61–65	gFOBT

Table 4.5.3. Colorectal cancer screening practices in countries in the European Union, and in European Council countries outside of the European Union (continued)

Country	Starting age (years)	Stopping age (years)	Interval (years)	Attendance (%)	Primary test
Non-European Union countries					
Bosnia and Herzegovina	> 50		–	ND	FOBT
Georgia	50	69	2	53	gFOBT
Iceland	55 50	75 59	2 –	84 ND	FOBT TC
Monaco	50	80	2	60	FIT
Montenegro	50	74	–	33	FIT
Norway	55	64	2 –	ND 65	FIT FOBT + FS
Russian Federation Saint Petersburg Kazan/Tatarstan	48	75	–	 ND ND	 FIT FOBT + DRE
San Marino	50	79	2	65	FIT
Serbia	50	74	2	58	FIT
Switzerland	50 50 50	80 80 69	2/10 – –	22 ND ND	FOBT or TC FOBT and/or TC FIT or TC
Turkey	50	69	–	30	FOBT
Ukraine	–	–	–	ND	ND

DRE, digital rectal examination; FIT, faecal immunochemical test; FOBT, faecal occult blood test; FS, sigmoidoscopy; gFOBT, guaiac faecal occult blood test; ND, no data available; TC, colonoscopy.

[a] In Austria, a population-based screening programme has been implemented only in the state of Burgenland. In the rest of the country, screening is opportunistic.

[b] In Estonia, the population-based pilot programme started in 2016 among a cohort aged 60 years, with an intended target group of age 60–69 years.

[c] Ireland is planning to extend the target age range to 55–74 years.

[d] In Italy, large regional differences can be seen in attendance: North, 48–52%; Centre, 21–24%; South, 8%; Piedmont (FS + FIT), 17–20%.

[e] In Piedmont, Italy, FIT is offered to individuals aged 59–69 years if they are unwilling to undergo FS. For both FIT and FS together, the attendance is 17–20%.

[f] In the United Kingdom, regional differences can be seen in gFOBT attendance: England, 50–60%; Northern Ireland, 54%; Scotland, 61–65%; Wales, 52–56%.

1.12–1.48) and for breast cancer (RII, 3.11; 95% CI, 1.78–5.42) [29], as well as in countries with regional programmes. In countries with organized programmes (limited to Denmark, Finland, the Netherlands, Sweden, and the United Kingdom for cervical cancer, and those countries plus Luxembourg for breast cancer), such inequalities were not found for cervical cancer (RII, 1.13; 95% CI, 0.92–1.40) or for breast cancer (RII, 1.03; 95% CI, 0.88–1.20). An early study in the Netherlands had found the same positive and unfavourable association in women not screened for breast cancer or cervical cancer, and the disappearance of this effect in screened women.

European data on colorectal cancer screening are even more limited, but in the first 2.6 million invitations in England, there was a clear gradient in screening participation rates across quintiles of deprivation, ranging from 35% in the most deprived quintile to 61% in the least deprived quintile (with an average rate of 54%) [30]. Multivariate analyses confirmed an independent effect of deprivation, with stronger effects in women, in older people, and in the most ethnically diverse areas. It is possible that the lower participation rates in colorectal cancer screening, compared with breast cancer and cervical cancer screening, may lead to substantial inequalities.

The possible reasons for socioeconomic differences in participation in cancer screening are not well known. In the United Kingdom Flexible Sigmoidoscopy Screening Trial, at the Scottish centre, 6383 people responded to a questionnaire about psychosocial and cognitive factors and interest in screening [31]. The results showed the predicted gradient in interest with socioeconomic status, but also showed that the groups with lower socioeconomic status felt at high risk of cancer and were more worried about

cancer. Therefore, the lesser interest did not derive from complacency or lack of concern about cancer. In contrast, in the groups with higher socioeconomic status, perceived benefits were higher and perceived barriers, fear, and fatalism were lower. The authors described these findings as being consistent with evidence that groups with lower socioeconomic status are less hopeful that behaviour change will yield health gains [32] and more fatalistic about the future [33].

It is likely that immigrant subgroups in many European countries experience the same inequalities, although evidence is sparse. In southern Italy, attendance rates for breast cancer and cervical cancer screening were about 40% for immigrants [34], and in Norway, registry data showed that in immigrants, rates of non-adherence to the cervical cancer screening programme were 1.7 times those in the autochthonous population [35].

Reducing health inequalities

Research shows that achieving relatively high participation rates in cancer screening will reduce health inequalities. In patients with breast cancer, it has been shown that screen detection is an independent favourable prognostic factor. Therefore, much effort is still needed in the EU to ensure the implementation of high-quality organized screening programmes with fair attendance rates, provision of informed choice, and fair designs, specifically with respect to benefits and harms. Equity should be taken into account in all the decision-making and implementation processes.

References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 380(9859):2095–128. https://doi.org/10.1016/S0140-6736(12)61728-0 PMID:23245604
2. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today.
3. Mackenbach JP, editor (2011). Successen van preventie 1970–2010. Rotterdam, Netherlands: Erasmus Publishing.
4. LEBA (2011). Landelijke Evaluatie Bevolkingsonderzoek Baarmoederhalskanker. LEBA rapportage tot en met 2011. Available from: https://www.rivm.nl/landelijke-evaluatie-van-bevolkingsonderzoek-baarmoederhalskanker-leba.
5. Gezondheidsraad (2011). Screening op baarmoederhalskanker. The Hague, Netherlands: Health Council of the Netherlands. Available from: https://www.gezondheidsraad.nl/documenten/adviezen/2011/05/24/screening-op-baarmoederhalskanker.
6. Modig K, Drefahl S, Andersson T, Ahlbom A (2012). The aging population in Sweden: can declining incidence rates in MI, stroke and cancer counterbalance the future demographic challenges? Eur J Epidemiol. 27(2):139–45. https://doi.org/10.1007/s10654-012-9653-2 PMID:22350145
7. Bosetti C, Bertuccio P, Malvezzi M, Levi F, Chatenoud L, Negri E, et al. (2013). Cancer mortality in Europe, 2005-2009, and an overview of trends since 1980. Ann Oncol. 24(10):2657–71. https://doi.org/10.1093/annonc/mdt301 PMID:23921790
8. Mackenbach J, McKee M, editors (2013). Successes and failures of health policy in Europe: four decades of diverging trends and converging challenges. Buckingham, UK: Open University Press. Available from: http://www.euro.who.int/en/publications/abstracts/successes-and-failures-of-health-policy-in-europe.-four-decades-of-divergent-trends-and-converging-challenges-2013.
9. European Council (2003). Council recommendation of 2 December 2003 on cancer screening (2003/878/EC). Off J Eur Union. L 327/34–38. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:327:0034:0038:EN:PDF
10. von Karsa L, Anttila A, Ronco G, Ponti A, Malila N, Arbyn M, et al. (2008). Cancer screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening. First report. Luxembourg: European Communities. Available from: https://ec.europa.eu/health/ph_determinants/genetics/documents/cancer_screening.pdf.
11. EU-topia (2018). EU-topia: towards improved cancer screening in all of Europe. Available from: http://eu-topia.org/about-eu-topia/background/.
12. Vale DB, Anttila A, Ponti A, Senore C, Sankaranaryanan R, Ronco G, et al. (2019). Invitation strategies and coverage in the population-based cancer screening programmes in the European Union. Eur J Cancer Prev. 28(2):131–40. https://doi.org/10.1097/CEJ.0000000000000426 PMID:29570103
13. Ponti A, Anttila A, Ronco G, Senore C, Basu P, Segnan N, et al. (2017). Against Cancer. Cancer screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening. Brussels, Belgium: European Commission. Available from: https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf.
14. Altobelli E, Rapacchietta L, Angeletti PM, Barbante L, Profeta FV, Fagnano R (2017). Breast cancer screening programmes across the WHO European Region: differences among countries based on national income level. Int J Environ Res Public Health. 14(4):452. https://doi.org/10.3390/ijerph14040452 PMID:28441745
15. Simou E, Tsimitselis D, Tsopanlioti M, Anastasakis I, Papatheodorou D, Kourlaba G, et al. (2011). Early evaluation of an organised mammography screening program in Greece 2004-2009. Cancer Epidemiol. 35(4):375–80. https://doi.org/10.1016/j.canep.2011.02.013 PMID:21474412

16. Ventura L, Giorgi D, Giordano L, Frigerio A, Mantellini P, Zappa M; Italian breast cancer screening survey group (2015). Mammographic breast cancer screening in Italy: 2011-2012 survey. Epidemiol Prev. 39(3 Suppl 1):21–9. PMID:26405773

17. Elfström KM, Arnheim-Dahlström L, von Karsa L, Dillner J (2015). Cervical cancer screening in Europe: quality assurance and organisation of programmes. Eur J Cancer. 51(8):950–68. https://doi.org/10.1016/j.ejca.2015.03.008 PMID:25817010

18. Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, et al. (2019). Human papillomavirus and related diseases in the world: summary report. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Available from: http://hpvcentre.net/statistics/reports/XWX.pdf.

19. Altobelli E, Lattanzi A, Paduano R, Varassi G, di Orio F (2014). Colorectal cancer prevention in Europe: burden of disease and status of screening programs. Prev Med. 62:132–41. https://doi.org/10.1016/j.ypmed.2014.02.010 PMID:24530610

20. Navarro M, Nicolas A, Ferrandez A, Lanas A (2017). Colorectal cancer population screening programs worldwide in 2016: an update. World J Gastroenterol. 23(20):3632–42. https://doi.org/10.3748/wjg.v23.i20.3632 PMID:28611516

21. Altobelli E, D'Aloisio F, Angeletti PM (2016). Colorectal cancer screening in countries of European Council outside of the EU-28. World J Gastroenterol. 22(20):4946–57. https://doi.org/10.3748/wjg.v22.i20.4946 PMID:27239121

22. Anttila A, Ronco G; Working Group on the Registration and Monitoring of Cervical Cancer Screening Programmes in the European Union; within the European Network for Information on Cancer (EUNICE) (2009). Description of the national situation of cervical cancer screening in the member states of the European Union. Eur J Cancer. 45(15):2685–708. https://doi.org/10.1016/j.ejca.2009.07.017 PMID:19744852

23. Arbyn M, Rebolj M, De Kok IM, Fender M, Becker N, O'Reilly M, et al. (2009). The challenges of organising cervical screening programmes in the 15 old member states of the European Union. Eur J Cancer. 45(15):2671–8. https://doi.org/10.1016/j.ejca.2009.07.016 PMID:19695867

24. Priaulx J, de Koning HJ, de Kok IMCM, Széles G, McKee M (2018). Identifying the barriers to effective breast, cervical and colorectal cancer screening in thirty one European countries using the Barriers to Effective Screening Tool (BEST). Health Policy. 122(11):1190–7. https://doi.org/10.1016/j.healthpol.2018.08.004 PMID:30177278

25. Seedat F, Cooper J, Cameron L, Stranges S, Kandala NB, Burton H, et al. (2014). International comparisons of screening policy-making: a systematic review. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/444227/FINAL_REPORT_International_Screening.pdf.

26. Puliti D, Miccinesi G, Manneschi G, Buzzoni C, Crocetti E, Paci E, et al. (2012). Does an organised screening programme reduce the inequalities in breast cancer survival? Ann Oncol. 23(2):319–23. https://doi.org/10.1093/annonc/mdr121 PMID:21515663

27. Pacelli B, Carretta E, Spadea T, Caranci N, Di Felice E, Stivanello E, et al. (2014). Does breast cancer screening level health inequalities out? A population-based study in an Italian region. Eur J Public Health. 24(2):280–5. https://doi.org/10.1093/eurpub/ckt119 PMID:24008553

28. Mook S, Van 't Veer LJ, Rutgers EJ, Ravdin PM, van de Velde AO, van Leeuwen FE, et al. (2011). Independent prognostic value of screen detection in invasive breast cancer. J Natl Cancer Inst. 103(7):585–97. https://doi.org/10.1093/jnci/djr043 PMID:21350218

29. Palència L, Espelt A, Rodríguez-Sanz M, Puigpinós R, Pons-Vigués M, Pasarín MI, et al. (2010). Socio-economic inequalities in breast and cervical cancer screening practices in Europe: influence of the type of screening program. Int J Epidemiol. 39(3):757–65. https://doi.org/10.1093/ije/dyq003 PMID:20176587

30. von Wagner C, Baio G, Raine R, Snowball J, Morris S, Atkin W, et al. (2011). Inequalities in participation in an organized national colorectal cancer screening programme: results from the first 2.6 million invitations in England. Int J Epidemiol. 40(3):712–8. https://doi.org/10.1093/ije/dyr008 PMID:21330344

31. Wardle J, McCaffery K, Nadel M, Atkin W (2004). Socioeconomic differences in cancer screening participation: comparing cognitive and psychosocial explanations. Soc Sci Med. 59(2):249–61. https://doi.org/10.1016/j.socscimed.2003.10.030 PMID:15110417

32. Clark DO, Patrick DL, Grembowski D, Durham ML (1995). Socioeconomic status and exercise self-efficacy in late life. J Behav Med. 18(4):355–76. https://doi.org/10.1007/BF01857660 PMID:7500327

33. Wardle J, Steptoe A (2003). Socioeconomic differences in attitudes and beliefs about healthy lifestyles. J Epidemiol Community Health. 57(6):440–3. https://doi.org/10.1136/jech.57.6.440 PMID:12775791

34. Bianco A, Larosa E, Pileggi C, Nobile CGA, Pavia M (2017). Cervical and breast cancer screening participation and utilisation of maternal health services: a cross-sectional study among immigrant women in Southern Italy. BMJ Open. 7(10):e016306. https://doi.org/10.1136/bmjopen-2017-016306 PMID:29038177

35. Leinonen MK, Campbell S, Ursin G, Tropé A, Nygård M (2017). Barriers to cervical cancer screening faced by immigrants: a registry-based study of 1.4 million women in Norway. Eur J Public Health. 27(5):873–9. https://doi.org/10.1093/eurpub/ckx093 PMID:28957477

4.6 Disparities in cancer prevention services in the USA

A long-standing, persistent cause of inequity

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SUMMARY

- In the USA, overall cancer mortality has declined among men and women in all racial and ethnic groups, but disparities in cancer mortality persist between non-Hispanic Whites and racial and ethnic minority groups for many cancer types.
- Persistent disparities in health, health services, and health outcomes are associated with race and ethnicity, sexual and gender minority status, lower education level, lower income, lack of health insurance, lower health literacy, lower access to health services, low-quality health services, distance from health services, rural residence, and racial segregation.
- Low-quality care also may be influenced by implicit racial and class bias, which reflects automatic and unconscious negative attitudes towards low-income and minority groups and has been shown to negatively influence patient communication, clinical care, and cancer outcomes.
- Disparities in access to cancer prevention and early detection and in cancer incidence and mortality can be reduced by a combination of national policies and local initiatives that remove barriers to care.

Health disparities are not simply differences between groups, but rather differences that are avoidable, unfair, unjust, and result from "systemic and potentially remediable differences in one or more aspects of health across socially, demographically, or geographically defined populations or population subgroups" [1]. Broadly defined, health disparities may be evident in any group of people who systematically experience social and/or economic obstacles to health and health care.

In the USA, social, economic, and geographical inequalities have long been associated with persistent inequity in health outcomes. Disparities in cancer outcomes in the USA are largely attributable to the lack of a national system of universal health care, and to an opportunistic model of access to cancer prevention and early detection, which poorly serves both advantaged and disadvantaged groups. This health-care model results in unequal access to health care, because of differences in health insurance coverage, quality of care, and health literacy (i.e. a person's ability to obtain, process, and understand basic health education), as well as the lack of a usual source of care and barriers to accessing care when it is needed.

These disparities are predominantly linked to race and ethnicity, to socioeconomic status (which accounts for most of the inequality in outcomes between racial and ethnic groups), and to geographical differences in availability of and access to high-quality care in rural versus suburban and urban areas, and in urban areas that have high poverty rates. However, these predominant, more apparent categories do not cover the full spectrum of disparities, which may also be experienced according to age, disability, obesity, mental health, sexual identity, and other characteristics linked to systematic discrimination. In 2016, the United States National Institute on Minority Health and Health Disparities announced the formal designation of sexual and gender minorities – an all-encompassing umbrella term to ensure inclusion of all sexual orientations and gender identities, including those who may not self-identify as lesbian, gay, bisexual, or transgender – as a specific health disparity population for National Institutes of Health research (https://www.edi.nih.gov/sites/default/files/EDI_Public_files/sgm-strategic-plan.pdf).

Morris et al. [2] conceptualized that cancer outcomes could be best understood as a function of three underlying mechanistic domains: patient factors, utilization of care, and provider factors (Fig. 4.6.1). Patient factors also include behaviours that increase risk of cancer or comorbid conditions, each of which may differentially have its roots in social inequality, and each of which may also contribute to inequity in outcomes. Low-quality care, regardless

of health insurance coverage, also may be influenced by structural inequality and by implicit racial and class bias, which reflects automatic and unconscious negative attitudes towards low-income and minority groups and has been shown to negatively influence patient communication and clinical care [3].

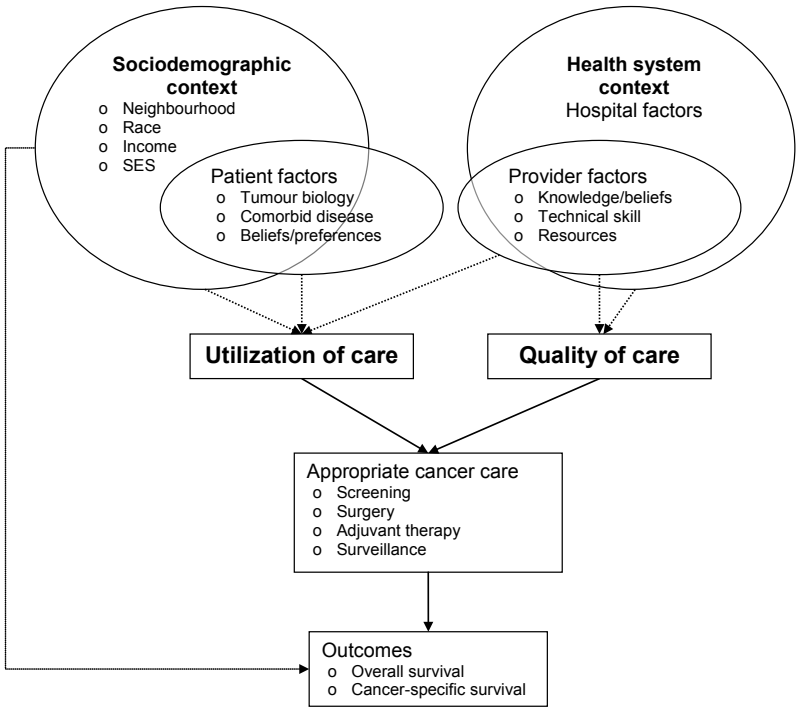
From 2009 to 2013, the trends in overall cancer incidence in the USA for all cancers combined in men and women in each racial and ethnic group were similar in direction to those in the overall population [4]. Also, from 2010 to 2014, overall cancer death rates declined in men and women in all racial and ethnic groups [4]. These trends were attributed mostly to reductions in tobacco use, the contribution of screening to early detection of invasive cancer and precursor lesions, and improvements in therapy. However, Black men and women still had the highest cancer mortality rates among all racial and ethnic groups, and 5-year relative survival rates varied considerably by race and ethnicity; the adjusted relative risk of cancer death was 33% higher in non-Hispanic Blacks and 51% higher in non-Hispanic American Indians/Alaska Natives than in non-Hispanic Whites [4].

This chapter focuses on both the descriptive epidemiology of cancer disparities in the USA and the structural and systemic factors that contribute to their persistence.

Racial and ethnic disparities

The United States Census Bureau defines race as an individual's self-identification as Asian, Black, Native Hawaiian or another Pacific Islander, American Indian, Alaska Native, and White. Hispanic origin is considered an ethnicity, and a person of any race may also identify themselves as Hispanic or Latino. Health disparities research consistently shows racial inequalities across most health outcomes. Socioeconomic status contributes

Fig. 4.6.1. A conceptual model of mechanisms underlying disparities in cancer care and outcomes. SES, socioeconomic status.



FUNDAMENTALS

- At the core of cancer disparities in the USA is an opportunistic model of access to cancer prevention and early detection versus a national system of universal health care, which is deeply rooted in societal beliefs about access to health care as a basic human right.
- Enduring disparities in cancer incidence and mortality are attributable mostly to persistent, systemic racial, ethnic, and class bias, geographical location, and inequality in education, income, geography, and access to high-quality health services.
- Factors associated with disparities in access to high-quality care and in cancer outcomes are interrelated and interdependent, have historical and systemic antecedents, and reflect a combination of patient factors, provider factors, the availability and quality of health care, and for some cancer types, differences in tumour biology.
- Increasing access to health insurance has been shown to be an effective, low-intensity intervention to reduce cancer disparities in disadvantaged groups; however, interventions that only improve insurance coverage without ensuring direct pathways to high-quality care will not reduce disparities.
- Patient navigation has been shown to improve disease outcomes by overcoming institutional barriers attributable to the difficulty of manoeuvring through complex and often unresponsive health-care institutions.
- Recent evidence has shown that the most effective interventions to reduce disparities in cancer outcomes occur when key institutions and leaders in local settings commit to the implementation of multicomponent interventions that target specific barriers to care.

to racial inequalities, but generally residual disparities by race and ethnicity remain after adjustment for socioeconomic status [5].

In 2003, the Institute of Medicine published a landmark report on racial and ethnic disparities in health care in the USA [6]. The report's conclusions were direct and unhesitant. In the USA, racial and ethnic minorities receive less and lower-quality health care, for reasons that go beyond lower socioeconomic status and being uninsured or underinsured. These disparities are attributable to structural racism, which has its roots in historical and enduring inequities that continue to be enabled by health systems, their administrations, and healthcare professionals. This direct and indirect discrimination also leads to patient-level attributes that further contribute to disparities, such as refusing recommended services because of mistrust, prior adverse experiences, and so on [6].

Racial and ethnic disparities in recent cancer screening are shown in Table 4.6.1. In general, reported cancer screening rates are similar between Blacks and Whites but lower in Hispanics and Asians [7]. However, these data overestimate recent cancer screening rates, because of recall bias and social desirability, which has been shown to be highest in Blacks and lowest in Hispanics [8].

Socioeconomic disparities

Income

In 2017, the United States federal government's poverty level was an annual income of US$ 12 140 for a single individual or US$ 25 100 for a family of four. In the USA, recent cancer screening is strongly associated with a usual source of care,

Table 4.6.1. Prevalence (%) of recent cancer screening examinations among adults in the USA by race and ethnicity, health insurance coverage, and education level, from the 2015 National Health Interview Survey

Screening examination	Race and ethnicity[a]								Health insurance[b]				Education level							
	White		Black		Hispanic		Asian		Yes		No		Some high school or less		High school diploma or GED		Some college/ associate degree		College graduate	
	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE
Colorectal cancer (adults aged ≥ 50 years)																				
Endoscopy[c]	63.3	0.7	59.3	1.4	47.6	1.5	44.8	2.6	56.8	0.9	24.0	2.2	45.3	1.4	56.4	1.0	61.6	0.9	68.9	1.0
Stool-based test[d]	6.9	0.3	8.0	0.9	7.3	0.8	9.2	1.4	6.2	0.4	4.0	1.1	6.3	0.7	7.1	0.6	7.2	0.6	7.7	0.5
Stool-based test or endoscopy[e]	65.4	0.7	61.8	1.4	49.9	1.5	49.4	2.7	59.6	0.9	25.1	2.2	47.4	1.4	58.6	1.0	64.3	0.9	71.3	1.0
Breast cancer (women aged ≥ 40 years)																				
Mammogram within the preceding year	50.3	0.8	55.4	1.8	45.7	1.5	47.1	2.6	52.5	0.9	20.9	2.3	38.9	1.8	45.0	1.5	51.2	1.3	57.9	1.1
Mammogram within the preceding 2 years	64.8	0.8	68.8	1.6	60.8	1.6	59.4	2.5	67.8	0.8	30.7	2.4	50.8	1.9	58.0	1.4	65.9	1.2	73.2	1.0
Cervical cancer (women aged 21–64 years)																				
Pap test[f]	83.3	0.7	84.8	1.1	77.5	1.2	73.3	2.0	84.4	0.5	60.8	1.7	70.1	1.8	75.4	1.4	84.0	0.9	88.8	0.6

GED, General Educational Development test; SE, standard error.

[a] Estimates for Whites, Blacks, and Asians are among non-Hispanics.

[b] Health insurance status was analysed among adults aged ≤ 64 years.

[c] Endoscopy included sigmoidoscopy within the preceding 5 years or colonoscopy within the preceding 10 years.

[d] Stool-based tests included faecal occult blood test (FOBT) or faecal immunochemical test (FIT) using a home test kit performed within the preceding year. The 2015 data include FIT; data for prior years do not.

[e] Stool-based test within the preceding year or sigmoidoscopy within the preceding 5 years or colonoscopy within the preceding 10 years.

[f] Women with intact uteri who had a Pap test within the preceding 3 years. Estimates by education level are among women aged 25–64 years.

a personal health-care provider, a recommendation from a health-care professional, and a recent health maintenance visit, each of which is strongly associated with having health insurance. Low-income groups have higher rates of being uninsured.

Access to health insurance has improved as a result of the Patient Protection and Affordable Care Act of 2010 [9,10], which expanded eligibility for Medicaid coverage to those with incomes at or below 138% of the federal poverty level and provided tax subsidies to low-income populations with incomes too high to qualify for Medicaid. However, in 2018 25% of those with incomes of 100% to less than 200% of the poverty level still reported lacking health insurance [10].

Lower socioeconomic status is associated with lower rates of cancer screening. Compared with people who have incomes above 400% of the federal poverty level, women with incomes of less than 139% of the federal poverty level are less likely to have had a recent mammogram (58.7% vs 78.8%) or Pap test (75.2% vs 89.7%), and among both men and women, those with incomes of less than 139% of the federal poverty level are less likely to have recently been screened for colorectal cancer (46.9% vs 70.0%) [11].

Education level

In the USA, data on individual and family incomes are difficult to obtain in research studies on health-care utilization. Given the strong correlation between educational attainment, unemployment, occupation, and income, education level has been used as a surrogate measure for an individual's socioeconomic status. Education level also is strongly associated with health literacy [12]. An assessment of the health literacy of adults in the USA found that 49% of adults who did not complete high school had a below basic level of health literacy, compared with 15% of adults with a high school diploma and 3% of adults with a bachelor's degree [12].

Low educational attainment, low health literacy, and limited English proficiency have been shown to be negatively correlated with rates of recent cancer screening [13]. Similar to the associations between income and recent cancer screening, there is a significant linear relationship between educational attainment and being adherent with all cancer screening recommendations (Table 4.6.1) [7].

Health insurance coverage

Some of the largest gaps that are observed in cancer prevention, early detection, and cancer outcomes are those between insured and uninsured populations. Preliminary data from the 2018 National Health Interview Survey showed that among adults aged 18–64 years, 12.5% had no health insurance, 20.0% had public insurance (including Medicaid), and 69.2% had private insurance [10].

Under the Patient Protection and Affordable Care Act, individuals with private insurance may receive preventive services recommended by the United States Preventive Services Task Force at no cost to the patient, and this also applies to public insurance in the 37 states that expanded access to Medicaid to low-income individuals. The expansion of Medicaid eligibility has been associated with higher rates of screening for cervical cancer and colorectal cancer for low-income adults [14]. Adults with health insurance report significantly higher rates of cancer screening compared with adults who report that they are uninsured (Table 4.6.1) [7]. However, health insurance coverage alone does not guarantee access to high-quality care.

Geographical disparities

Geographical disparities in cancer outcomes have been documented since the mid-20th century. More recently, greater attention has been focused on improving the measurement of health disparities by examining data from smaller, more homogeneous geographical units of analysis, and developing geospatial epidemiological methods to explore the interplay between population characteristics, health resources, social and environmental barriers, and the influence of spatial patterning on social inequality and disparities [15].

Modern approaches to medical geography recognize that there are independent and interdependent factors associated with context (place) and composition (people) that contribute to health disparities [16]. For example, a review of research on the association between segregation and Black–White cancer disparities showed a common association between racial segregation and higher rates of late-stage diagnosis of breast cancer and lung cancer after adjustment for socioeconomic status and health insurance coverage [17].

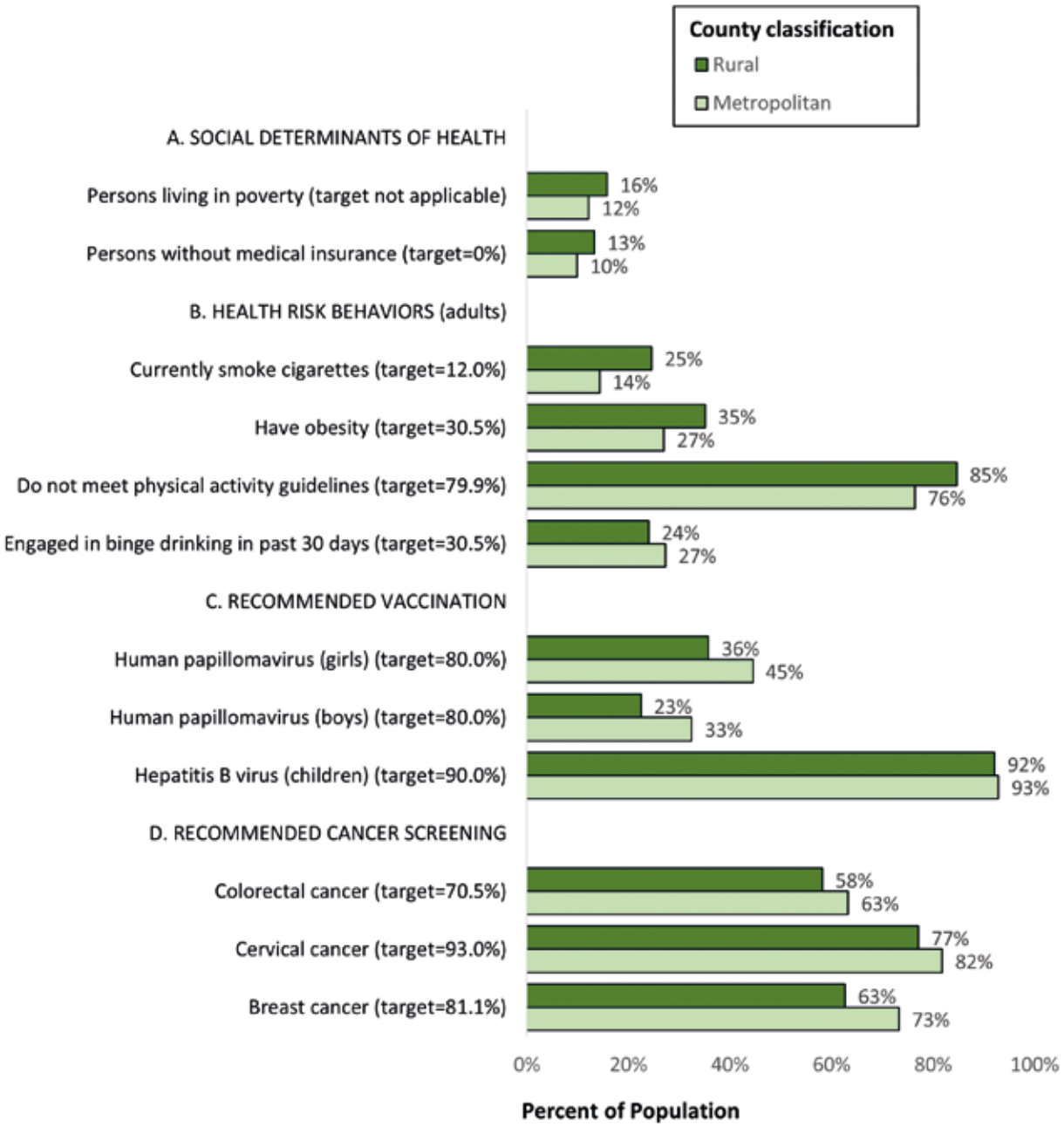
Rural–urban disparities

In the USA, about 46 million people (~14% of the population) live in rural areas. According to the Pew Research Center (https://www.pewsocialtrends.org/2018/05/22/what-unites-and-divides-urban-suburban-and-rural-communities/), rural counties are predominantly White (79%); compared with cities, rural areas have a higher proportion of adults with a high school education or less (51% vs 38%) and a substantially higher proportion of counties in which the poverty rate exceeds 20% (31% vs 19%), and nearly twice as many rural residents (63% vs 36%) report that access to health care is a problem. Compared with people who live in metropolitan areas, rural residents have higher rates of being uninsured, have higher rates of smoking, obesity, and physical inactivity, and have lower rates of human papillomavirus (HPV) vaccination and cancer screening (Fig. 4.6.2) [18].

Disparities by state and region

States and regions of the USA vary in the proportions of men and women who have incomes below the poverty level, have health insurance, have convenient access to health services, have been vaccinated against HPV infection, and

Fig. 4.6.2. Healthy People 2020 objectives related to cancer, including social determinants of health, health risk behaviours, recommended vaccination against cancer-causing viruses, and recommended cancer screening, by rural versus urban residence.



have access to cancer screening and to specialty care if they are diagnosed with cancer [19]. States also vary in the prevalence of obesity and physical activity, in the proportion of adults who use tobacco and who have access to cessation treatment coverage, and in spending on tobacco control and the implementation of tobacco control policies, such as Tobacco 21 (banning the sale of tobacco products to people younger than 21 years) and excise taxes [20].

Taken together, these factors contribute to considerable variation in cancer incidence and mortality rates across states and in trends over time, as is evident in the variability in the decline in the breast cancer mortality rates in states. In the USA, from 1988–1990 to 2013–2015, the breast cancer mortality rate declined by 39% overall, but by only 20–29% in 10 states (Fig. 4.6.3) [21]. Similar variability is evident for colorectal cancer mortality: from 1980–1982 to 2013–2015, the rate

declined by 49% overall, but by only 12–31% in eight states, of which six also had the smallest reductions in breast cancer mortality [21].

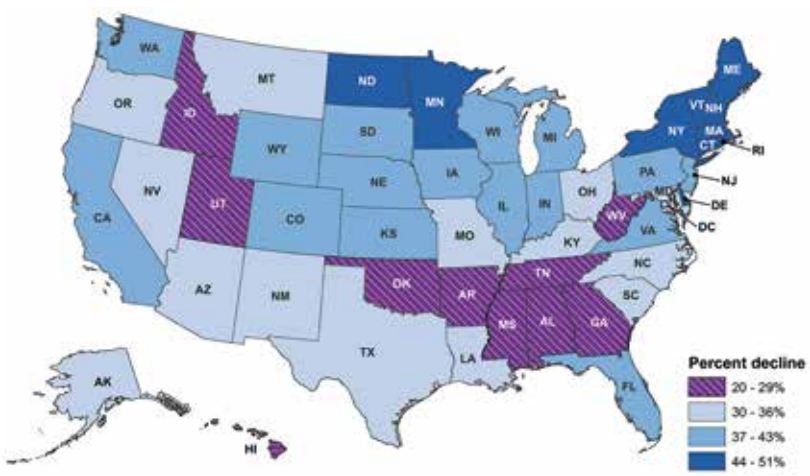
Siegel et al. [22] examined colorectal cancer mortality rates in the USA to assess trends over time from 1970 to 2011 and to identify clusters of significantly higher mortality rates, designated as hotspots. The regions with the highest colorectal cancer mortality rates shifted over the 40-year period from 1970 to 2009 (Fig. 4.6.4). Before 1990, the rates were high in the mid-central and north-eastern parts of the USA and low in the south of the country. By 2000–2009, there was a more homogeneous pattern of similar rates across most of the country, with the exception of three distinct hotspots: the Lower Mississippi Delta, west central Appalachia, and eastern Virginia/North Carolina. In these three hotspots, the mortality rates in 2009–2011 were respectively 40%, 18%, and 9% higher than those in non-hotspot counties.

Interventions to reduce disparities

By the late 1980s, the accumulation of evidence of broad disparities in cancer care and outcomes led the American Cancer Society, the National Cancer Institute, and the Centers for Disease Control to collaborate on a fact-finding mission in which Dr Harold Freeman of Harlem Hospital Center convened seven fact-finding hearings across the USA to gather testimony from low-income people affected by cancer and from clinicians who served low-income populations [23,24]. In its 1989 Report to the Nation, the American Cancer Society described the disproportionate pain, suffering, institutional indifference, and obstacles faced by low-income cancer patients and their families and issued 10 broad recommendations to reduce inequities in cancer prevention, early detection, and treatment, and to reform healthcare services [23].

There are now annual reports on cancer disparities, and in the decades since 1989, there have been investments in research, implementation of interventions such as patient navigation (Fig. 4.6.5; see also “Patient navigation”), special programmes to increase access to screening, and policy changes, such as legislation to increase access to health insurance. Although these interventions have been beneficial, they are unable to overcome the core underpinnings of systemic inequality and the lack of universal access to health care in the USA.

Fig. 4.6.3. Decline in breast cancer mortality rates from 1988–1990 to 2013–2015, by state.



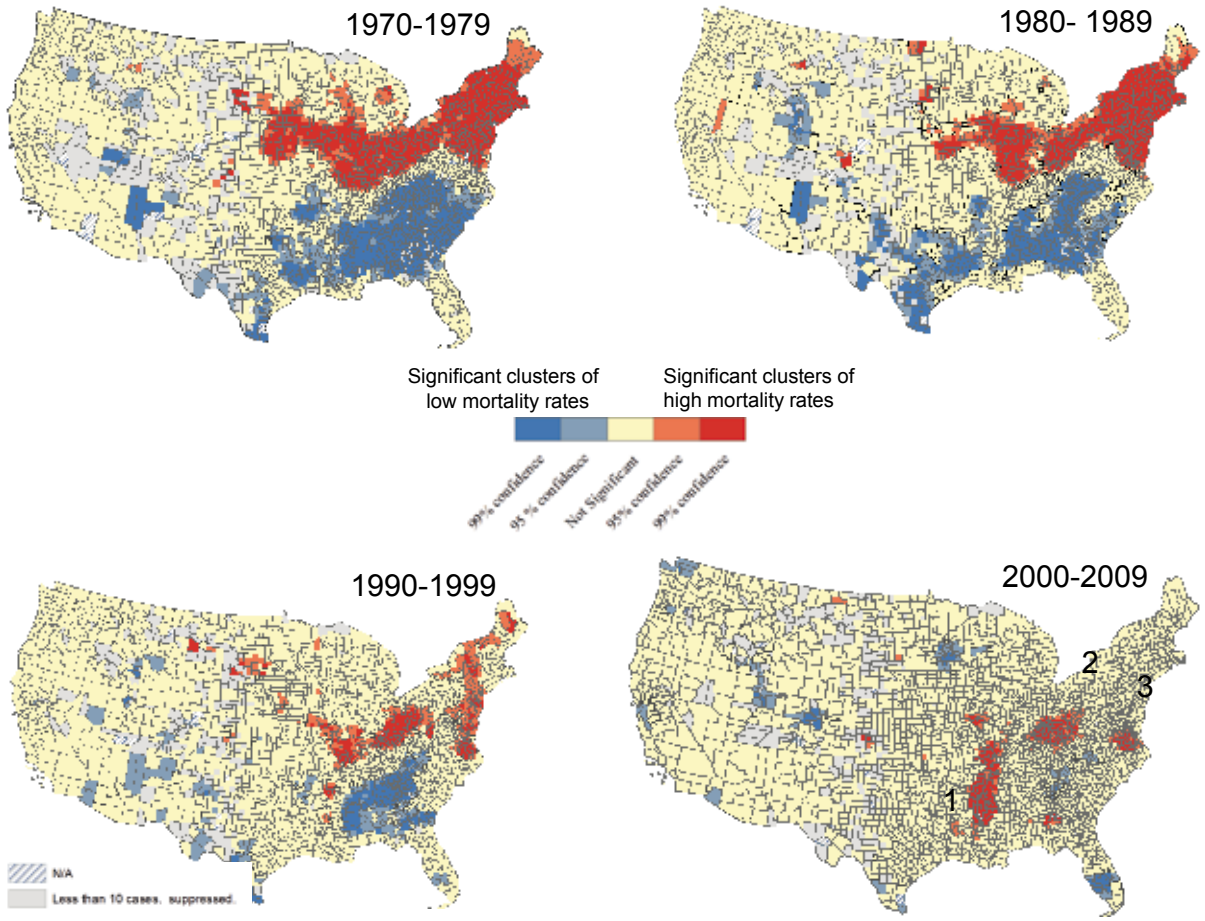
National Breast and Cervical Cancer Early Detection Program

In 1990, the United States Congress passed the Breast and Cervical Cancer Mortality Prevention Act, which directed the Centers for Disease Control and Prevention to establish a programme to provide breast cancer and cervical cancer screening services to low-income women in all states, the District of Columbia, United States territories, and tribes or tribal organizations (https://www.cdc.gov/cancer/nbccedp/index.htm). Uninsured and underinsured women who have incomes at or below 250% of the federal poverty level and who meet the recommended age requirements (~1 in 10 women) are eligible for the programme. However, the federal government only appropriates enough funding to cover services for a small fraction of eligible women (6.5% for Pap testing and 10.5% for mammography) [25]. Since 1991, the National Breast and Cervical Cancer Early Detection Program has served more than 5.4 million women [25]. A similar programme exists to increase colorectal cancer screening rates (the Colorectal Cancer Control Program; https://www.cdc.gov/cancer/crccp/index.htm), but it covers even fewer eligible people.

Patient Protection and Affordable Care Act of 2010

The Patient Protection and Affordable Care Act of 2010 has improved the quality of health insurance, eliminated patient costs for recommended preventive services, and increased the availability of affordable health care to millions of Americans [9]. The insurance coverage provisions went into effect in 2014. The original legislation intended that states would expand Medicaid eligibility to all individuals with incomes at or below 138% of the federal poverty level. However, in 2012, the United States Supreme Court ruled that states could reject Medicaid expansion, and as of 2018, 17 states have not expanded their public insurance programmes, leaving 4.2 million non-elderly adults uninsured.

Fig. 4.6.4. Hotspot analysis of county-level colorectal cancer mortality rates during the four decades from 1970 to 2009. Three hotspots are indicated for 2000–2009: (1) the Lower Mississippi Delta, (2) west central Appalachia, and (3) eastern Virginia/North Carolina.



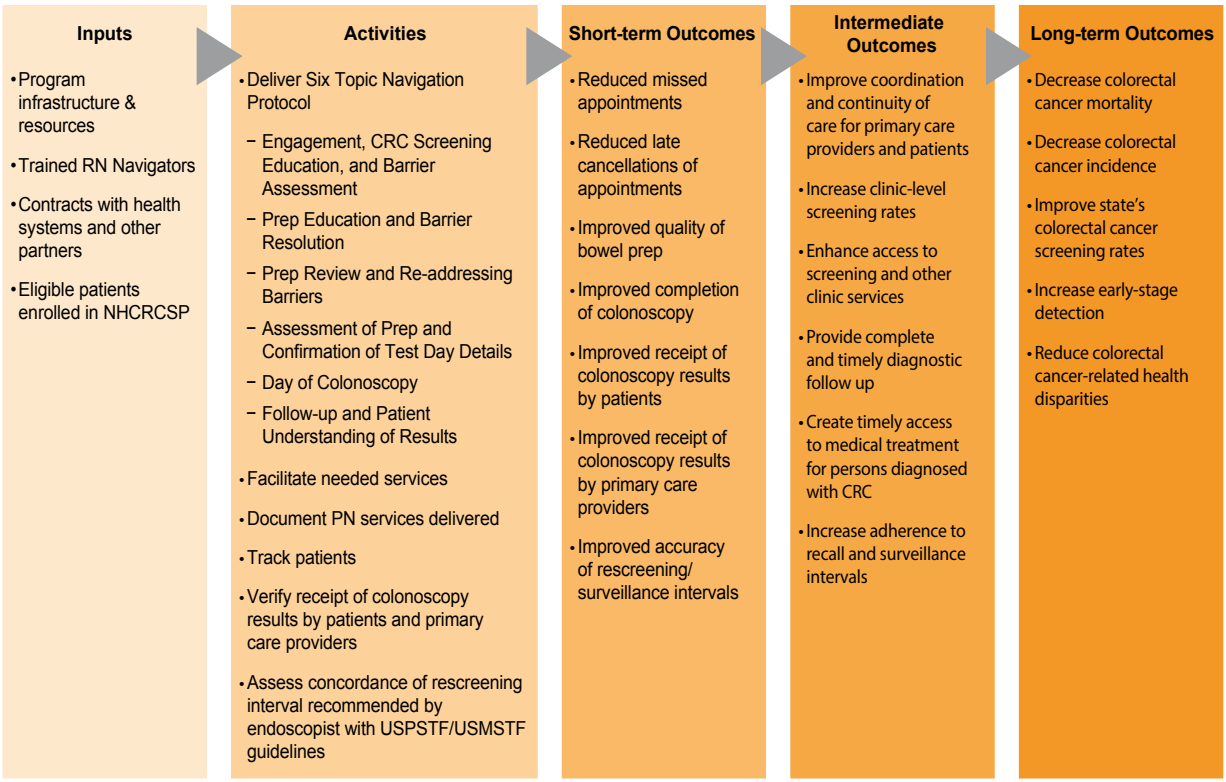
Although insurance coverage increased substantially, the short period since the beginning of coverage in 2014 and the lags in data availability limit the ability to measure the impact of new coverage on use of cancer preventive services and outcomes. However, a review of 14 studies concluded that the Patient Protection and Affordable Care Act had improved access to cancer screening, and especially colorectal cancer screening, among adults who had faced the highest cost barriers before its passage [26].

Conclusions

Despite progress in cancer control in most population demographics in the USA, smaller gains in the groups for which disparities have persisted are just another inequity added to the others. A growing emphasis on genetics and personalized medicine overshadows the persistent failure to ensure that disadvantaged groups have equal access to long-standing, conventional, evidence-based cancer prevention, early detection, and state-of-the-art treatment services.

National policies can contribute to reducing disparities, but there is an increasing realization that major, enduring change can occur only when community leaders commit to removing barriers in access to high-quality care. A statewide effort in Delaware to eliminate disparities in colorectal cancer outcomes led to a 42% reduction in the colorectal cancer mortality rate in Blacks, resulting in an annual mortality rate in Blacks that was nearly the same as that in Whites [27]. In San Francisco, California (www.sfcancer.org), and in Chicago, Illinois (www.chicagobreastcancer.org; see also "The enduring disparity in breast cancer mortality between Black and White women in the USA"), there is a city-wide commitment to reduce cancer disparities by engaging local health systems, local government, community leaders, and the population. The knowledge needed to eliminate cancer disparities exists; what must also exist is the national and local commitment to do so.

Fig. 4.6.5. The patient navigation (PN) model of the New Hampshire Colorectal Cancer Screening Program (NHCRCSP), showing inputs, activities, and outcomes. CRC, colorectal cancer; RN, registered nurse; USMSTF, United States Multi-Society Task Force on Colorectal Cancer; USPSTF, United States Preventive Services Task Force.



Patient navigation

The first patient navigation programmes in the USA were developed by Dr Harold Freeman and established at Harlem Hospital Center in New York City to reduce disparities in breast cancer care for low-income Black and Hispanic women [1]. Patient navigation was initially designed to ensure timely follow-up of abnormal screening findings and eliminate delays in diagnosis and initiation of treatment. The substantial investment in research funding to further develop this concept has extended navigation programmes to improve rates of cancer screening; to ensure timely progress through follow-up of abnormal screening findings, diagnostic evaluation, and initiation of treatment; and to build trust between patients and families and the health-care system.

Patient navigation has been shown to overcome common barriers attributable to poverty, low education level and health literacy, lack of English fluency, poor clinical communication, lack of knowledge and confidence required to manoeuvre in a complex health system, lack of insurance and need to access financial aid, and lack of transportation [2]. A skilled navigator can recognize and address barriers that may exist at the system level, with the clinician, or with the patients themselves, and thus prevent delays in the receipt of care.

Although the benefits of patient navigation are well documented, there are still some areas where the benefit of navigation has yet to be determined, such as accrual to clinical trials, cost–effectiveness, and the expansion of the range of cancer types included in navigation programmes. Therefore, a range of remaining and new questions are being addressed.

- Which patients need navigation services? At the National Academies of Sciences, Engineering, and Medicine workshop on Establishing Effective Patient Navigation Programs in Oncology [2], there was agreement that all patients would probably benefit from some degree of navigation; however, because of the limited resources available to support navigation, it was suggested that programmes should target those patients at greatest risk for delays in care, and expand to cancer types that are not so commonly studied, for example types other than breast cancer.

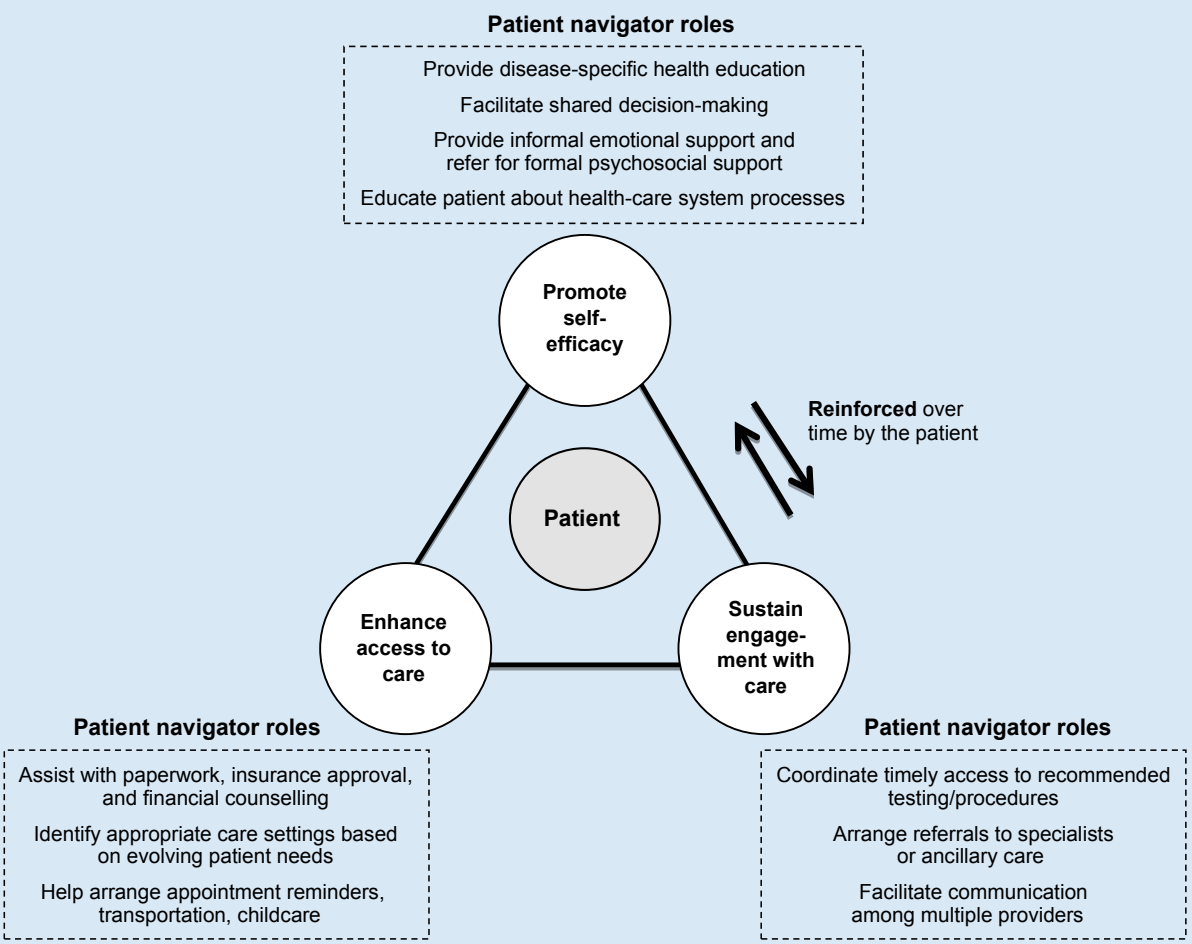
- What background is needed to be a navigator? Experience has shown that the answer to this question lies in the principal needs of the patients being served. Navigators include nurses, social workers, and non-clinical community workers with the same racial or ethnic and religious backgrounds as the populations they serve.
- How can support for patient navigation programmes be acquired? Currently, patient navigation is not covered by health insurance, so patient navigation programmes commonly depend on grants, institutional resources, and volunteer efforts. The National Colorectal Cancer Roundtable has developed a toolkit to support the efforts of navigation programmes to make the financial case for institutional support for navigation services [3].

The American Cancer Society supports the National Navigation Roundtable (https://navigationroundtable.org), a coalition of leading oncology, public health, social work, and advocacy organizations to address evidence-based practices, training and certification criteria, and policy issues to enhance and promote the effectiveness of patient navigation programmes across all areas of the cancer control continuum and in all populations at risk for or diagnosed with cancer.

References

1. Vargas RB, Ryan GW, Jackson CA, Rodriguez R, Freeman HP (2008). Characteristics of the original patient navigation programs to reduce disparities in the diagnosis and treatment of breast cancer. Cancer. 113(2):426–33. https://doi.org/10.1002/cncr.23547 PMID:18470906
2. National Academies of Sciences, Engineering, and Medicine (2018). Establishing effective patient navigation programs in oncology: proceedings of a workshop. Washington (DC), USA: National Academies Press. https://doi.org/10.17226/25073
3. National Colorectal Cancer Roundtable (2019). Paying for colorectal cancer screening patient navigation toolkit: strategies for payment and sustainability. Available from: http://nccrt.org/intervention/navigation.

Fig. B4.6.1. Patient navigator model.



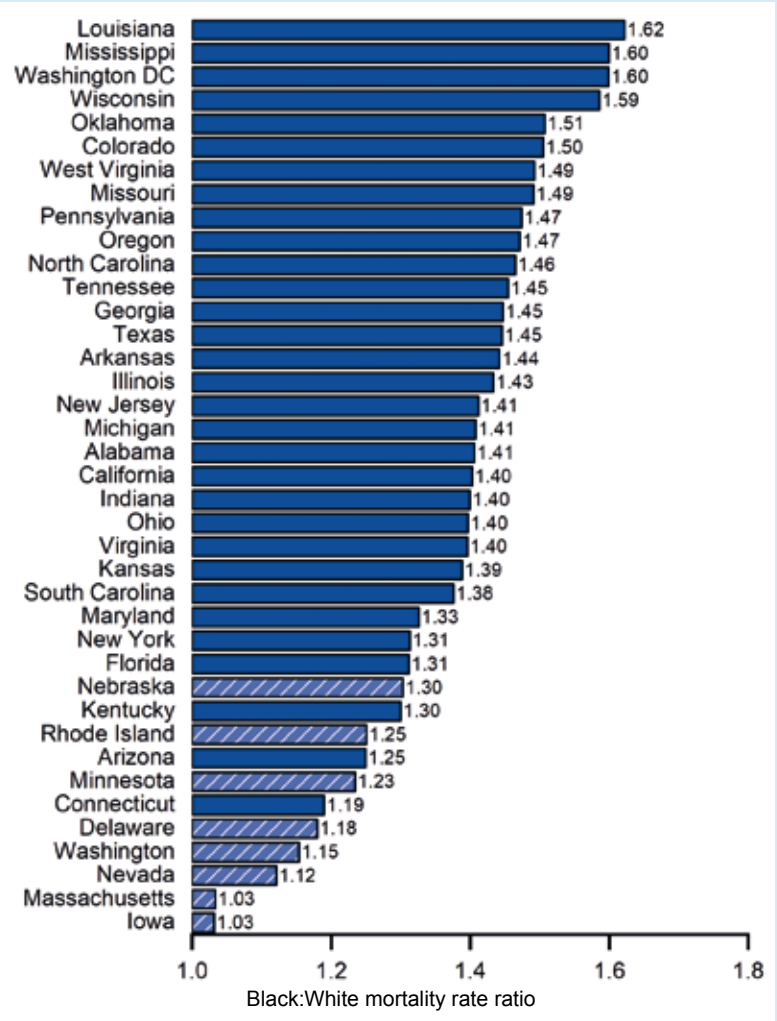
The enduring disparity in breast cancer mortality between Black and White women in the USA

In the USA, there has persistently been a significantly higher breast cancer mortality rate in Black women than in White women [1]. Past efforts to understand this disparity focused on differences in socioeconomic status or inherent differences in tumour biology; today, the disparity in breast cancer mortality is better understood as complex and multifactorial. Daly and Olopade [2] described racial disparities in cancer mortality as a "perfect storm" (in which a combination of circumstances aggravates the situation) resulting from the collision of tumour biology, genomics, and health-care delivery patterns.

Differences in tumour biology are well documented, including higher percentages of hormone receptor-negative tumours in Black women, intratumour genetic heterogeneity, and a higher rate of triple-negative disease in Black women (approximately double the rate in White women).

Health services research in various communities in the USA has revealed disparities in standards of breast cancer-related care. Among younger women diagnosed with breast cancer, Black women are less likely to report a discussion about *BRCA* testing and less likely to undergo *BRCA* testing compared with White women, and among carriers of *BRCA* mutations, Black women are significantly less likely to undergo risk-reducing surgery compared with White women. Black women are less likely to have undergone recent mammography screening, are less likely to have access to high-quality mammography screening, and are more likely to experience a longer duration from abnormal mammography results to diagnosis, and from diagnosis to treatment. Compared with White women, Black women are more likely to be undertreated for breast cancer, are less likely to receive therapy that adheres to practice guidelines, and are more likely to discontinue hormone therapy early. The higher rate of being uninsured and underinsured is associated with these health services disparities, as is well-documented poor communication with health-care providers, especially among African immigrants. Differences in breast cancer mortality have also been associated with higher rates of obesity, diabetes, and hypertension in Black women, although variation between states is attributable mainly to differences in access to high-quality health care. Differences in these disparities across states probably account for much of the range in breast cancer mortality rate ratios between Black women and White women (Fig. B4.6.2) [1].

Fig. B4.6.2. Mortality rate ratios comparing breast cancer mortality rates in Black women versus White women in the USA, by state, in 2012–2016. Lighter shaded bars indicate that mortality rates in Black women and in White women were not statistically different.



The racial disparity in breast cancer mortality rates in the USA will only be overcome through local, multilevel interventions, such as those initiated by the Metropolitan Chicago Breast Cancer Task Force, which established a partnership between community organizations, medical providers, and government leaders to improve the quality of mammography and follow-up of abnormal findings in Black women living in low-income, segregated neighbourhoods [3]. For the period 1999–2013, Chicago was the only United States city among 10 studied in which the breast cancer mortality rate in Black women decreased more (by 13.9%) than the rate in White women (which decreased by 7.7%) [3].

References

1. DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A (2017). Breast cancer statistics, 2017, racial disparity in mortality by state. CA Cancer J Clin. 67(6):439–48. https://doi.org/10.3322/caac.21412 PMID:28972651
2. Daly B, Olopade OI (2015). A perfect storm: how tumor biology, genomics, and health care delivery patterns collide to create a racial survival disparity in breast cancer and proposed interventions for change. CA Cancer J Clin. 65(3):221–38. https://doi.org/10.3322/caac.21271 PMID:25960198
3. Sighoko D, Murphy AM, Irizarry B, Rauscher G, Ferrans C, Ansell D (2017). Changes in the racial disparity in breast cancer mortality in the ten US cities with the largest African American populations from 1999 to 2013: the reduction in breast cancer mortality disparity in Chicago. Cancer Causes Control. 28(6):563–8. https://doi.org/10.1007/s10552-017-0878-y PMID:28275936

References

1. Whitehead M (1992). The concepts and principles of equity and health. Int J Health Serv. 22(3):429–45. https://doi.org/10.2190/986L-LHQ6-2VTE-YRRN PMID:1644507

2. Morris AM, Rhoads KF, Stain SC, Birkmeyer JD (2010). Understanding racial disparities in cancer treatment and outcomes. J Am Coll Surg. 211(1):105–13. https://doi.org/10.1016/j.jamcollsurg.2010.02.051 PMID:20610256

3. Paradies Y, Truong M, Priest N (2014). A systematic review of the extent and measurement of healthcare provider racism. J Gen Intern Med. 29(2):364–87. https://doi.org/10.1007/s11606-013-2583-1 PMID:24002624

4. Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson B, et al. (2017). Annual report to the nation on the status of cancer, 1975-2014, featuring survival. J Natl Cancer Inst. 109(9):djx030. https://doi.org/10.1093/jnci/djx030 PMID:28376154

5. Nuru-Jeter AM, Michaels EK, Thomas MD, Reeves AN, Thorpe RJ Jr, LaVeist TA (2018). Relative roles of race versus socioeconomic position in studies of health inequalities: a matter of interpretation. Annu Rev Public Health. 39(1):169–88. https://doi.org/10.1146/annurev-publhealth-040617-014230 PMID:29328880

6. Institute of Medicine of the National Academies (2003). Unequal treatment: confronting racial and ethnic disparities in health care. Washington (DC), USA: National Academies Press. https://doi.org/10.17226/12875

7. Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, et al. (2017). Cancer screening in the United States, 2017: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 67(2):100–21. https://doi.org/10.3322/caac.21392 PMID:28170086

8. Cronin KA, Miglioretti DL, Krapcho M, Yu B, Geller BM, Carney PA, et al. (2009). Bias associated with self-report of prior screening mammography. Cancer Epidemiol Biomarkers Prev. 18(6):1699–705. https://doi.org/10.1158/1055-9965.EPI-09-0020 PMID:19505902

9. Compilation of Patient Protection and Affordable Care Act, in Title X (2010). Senate and House of Representatives of the United States of America: Washington (DC), USA. Available from: https://www.hhs.gov/sites/default/files/ppacacon.pdf.

10. Martinez ME, Zammitti EP, Cohen RA (2018). Health insurance coverage: early release of estimates from the National Health Interview Survey, January–June 2018. National Health Interview Survey Early Release Program. Atlanta (GA), USA: National Center for Health Statistics. Available from: https://www.cdc.gov/nchs/data/nhis/earlyrelease/insur201811.pdf.

11. White A, Thompson TD, White MC, Sabatino SA, de Moor J, Doria-Rose PV, et al. (2017). Cancer screening test use – United States, 2015. MMWR Morb Mortal Wkly Rep. 66(8):201–6. https://doi.org/10.15585/mmwr.mm6608a1 PMID:28253225

12. Kutner M, Greenberg ER, Jin Y, Paulsen C (2006). The health literacy of America's adults: results from the 2003 National Assessment of Adult Literacy. Washington (DC), USA: National Center for Education Statistics. Available from: https://nces.ed.gov/pubs2006/2006483.pdf.

13. Oldach BR, Katz ML (2014). Health literacy and cancer screening: a systematic review. Patient Educ Couns. 94(2):149–57. https://doi.org/10.1016/j.pec.2013.10.001 PMID:24207115

14. Hendryx M, Luo J (2018). Increased cancer screening for low-income adults under the Affordable Care Act Medicaid expansion. Med Care. 56(11):944–9. https://doi.org/10.1097/MLR.0000000000000984 PMID:30199428

15. Schootman M, Gomez SL, Henry KA, Paskett ED, Ellison GL, Oh A, et al. (2017). Geospatial approaches to cancer control and population sciences. Cancer Epidemiol Biomarkers Prev. 26(4):472–5. https://doi.org/10.1158/1055-9965.EPI-17-0104 PMID:28325736

16. Smyth F (2008). Medical geography: understanding health inequalities. Prog Hum Geogr. 32(1):119–27. https://doi.org/10.1177/0309132507080628

17. Landrine H, Corral I, Lee JGL, Efird JT, Hall MB, Bess JJ (2017). Residential segregation and racial cancer disparities: a systematic review. J Racial Ethn Health Disparities. 4(6):1195–205. https://doi.org/10.1007/s40615-016-0326-9 PMID:28039602

18. Henley SJ, Jemal A (2018). Rural cancer control: bridging the chasm in geographic health inequity. Cancer Epidemiol Biomarkers Prev. 27(11):1248–51. https://doi.org/10.1158/1055-9965.EPI-18-0807 PMID:30385497

19. American Cancer Society (2017). Colorectal cancer facts & figures, 2017–2019. Atlanta (GA), USA: American Cancer Society. Available from: https://www.cancer.org/research/cancer-facts-statistics/colorectal-cancer-facts-figures.html.

20. American Cancer Society (2017). Cancer prevention & early detection facts and figures, 2017–2018. Atlanta (GA), USA: American Cancer Society. Available from: https://www.cancer.org/research/cancer-facts-statistics/cancer-prevention-early-detection.html.

21. Siegel RL, Jemal A, Wender RC, Gansler T, Ma J, Brawley OW (2018). An assessment of progress in cancer control. CA Cancer J Clin. 68(5):329–39. https://doi.org/10.3322/caac.21460 PMID:30191964

22. Siegel RL, Sahar L, Robbins A, Jemal A (2015). Where can colorectal cancer screening interventions have the most impact? Cancer Epidemiol Biomarkers Prev. 24(8):1151–6. https://doi.org/10.1158/1055-9965.EPI-15-0082 PMID:26156973

23. American Cancer Society (1989). A summary of the American Cancer Society Report to the Nation: cancer in the poor. CA Cancer J Clin. 39(5):263–5. https://doi.org/10.3322/canjclin.39.5.263 PMID:2513098

24. Freeman HP (1989). Cancer in the socioeconomically disadvantaged. CA Cancer J Clin. 39(5):266–88. https://doi.org/10.3322/canjclin.39.5.266 PMID:2513099

25. Centers for Disease Control and Prevention (2016). National Breast and Cervical Cancer Early Detection Program (NBCCEDP). Available from: https://www.cdc.gov/cancer/nbccedp/about.htm.

26. Sabik LM, Adunlin G (2017). The ACA and cancer screening and diagnosis. Cancer J. 23(3):151–62. https://doi.org/10.1097/PPO.0000000000000261 PMID:28537960

27. Grubbs SS, Polite BN, Carney J Jr, Bowser W, Rogers J, Katurakes N, et al. (2013). Eliminating racial disparities in colorectal cancer in the real world: it took a village. J Clin Oncol. 31(16):1928–30. https://doi.org/10.1200/JCO.2012.47.8412 PMID:23589553

4.7 Cancer in Indigenous populations
Focusing on inequalities that are sometimes invisible

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SUMMARY

- Cancer data relating to Indigenous people tend to be absent or of poor quality, making many Indigenous peoples statistically invisible.
- Indigenous peoples tend to have higher rates of cancers related to tobacco exposure, alcohol consumption, poor diet, and high body mass index.
- These are all expected relationships given the higher exposure of Indigenous peoples to these risk factors; however, these patterns of exposure are in turn related to societal and systemic determinants that can be traced to colonialism and racism.
- Rates of chronic oncogenic infections, particularly those that are related to poverty and overcrowding, tend to be higher in Indigenous populations; examples are *Helicobacter pylori*, and hepatitis B virus in regions where vaccination is not occurring.
- Toxic contamination of the environment has been linked to high cancer rates in some Indigenous populations, such as those living near nuclear test sites in the Pacific.
- Comprehensive, sustained efforts are needed to improve cancer outcomes for Indigenous peoples, centred around Indigenous leadership and participation.

In 2018, WHO Director-General Dr Tedros Adhanom Ghebreyesus wrote, in an article on improving the health of Indigenous people globally, "Health equity for the current generation cannot wait, and we cannot fail future generations of Indigenous people" [1].

Indigenous peoples live in all regions of the world. There are estimated to be 370 million Indigenous people worldwide, living in more than 90 countries and representing 90% of the world's cultural diversity [2]. The United Nations, acknowledging that some countries use different terms – such as First Peoples, First Nations, Nations, Tribal, Aboriginal, Native, and ethnic groups – and that self-identification is a fundamental principle, recognizes Indigenous peoples as "inheritors and practitioners of unique cultures and ways of relating to people and the environment. They have retained social, cultural, economic, and political characteristics that are distinct from those of the dominant societies in which they live" [3]. (For more details, see "Who are Indigenous peoples?".)

Indigenous paradigms commonly embrace a holistic worldview that understand lands, waterways, seas, the people, and all living things as vitally connected. Indigenous models emphasize the importance of keeping social and economic activity in balance with the natural environment, thereby ensuring sustainability for generations to come.

Colonization disrupts systems of kinship between peoples and with the natural world, intrudes on

Who are Indigenous peoples?

The United Nations Permanent Forum on Indigenous Issues uses the following criteria to identify Indigenous peoples:

- self-identification as Indigenous peoples at the individual level, and accepted by the community as their member;
- historical continuity with pre-colonial and/or pre-settler societies;
- strong link to territories and surrounding natural resources;
- distinct social, economic, or political systems;
- distinct language, culture, and beliefs;
- form non-dominant groups of society;
- resolve to maintain and reproduce their ancestral environments and systems as distinctive peoples and communities.

Reference

1. United Nations Permanent Forum on Indigenous Issues (2018). Who are Indigenous peoples? Available from: https://www.un.org/esa/socdev/unpfii/documents/5session_factsheet1.pdf.

traditional social and legal structures, and imposes new cultural values, languages, and economic and political systems that serve to advantage the colonizing populations [4].

Through historical and current colonialism, the health of Indigenous peoples is adversely affected by destruction of their lands, resources, and cultures, typically resulting in marginalization, loss of autonomy, lower income levels, worse living conditions, greater food insecurity, and poorer access to health, education, and other services [2,5]. These factors are exacerbated by health systems and other systems that generally do not reflect the worldview or practices of Indigenous peoples. Indigenous people may experience discrimination and racism in their everyday lives and in their encounters with the health system (Fig. 4.7.1) [2,6].

There is a lack of data relating to Indigenous peoples in almost every country in which they live; this greatly limits the extent to which inequalities in health and in upstream determinants of health can be defined, measured, and addressed [2,7]. The United Nations estimates that about 80% of Indigenous peoples live in Africa, Asia, and Latin America, but very little detailed information is available about the health status of these peoples. For Indigenous and minority peoples in high-income countries like Australia, Canada, and the USA, there is not necessarily better reporting or measurement of health outcomes. For example, in Canada, authors have described "the absence of relevant, consistent, and inclusive Indigenous identifiers in core population health data sources" [8].

Despite this lack of data, it is clear from the existing literature that Indigenous peoples frequently face the double burden of high rates of infectious diseases and a rapidly increasing burden of non-communicable diseases, including cancer, as well as poor access to health services [2]. For example, in Asia, where there are massively diverse Indigenous populations, these groups tend to have the worst health of identifiable ethnic groups; the United Nations report on the state of Indigenous peoples concluded that "discrimination against Indigenous peoples, based on language, race, culture, and identity, is rampant across the Asian states" [2].

Where data are available, Indigenous peoples tend to have high rates of preventable cancers, related to tobacco exposure, alcohol consumption, poor diet, and infections [2,9,10].

The relationships between overarching historical and contemporary forces shape the social determinants of health, in turn influencing both factors that enhance health and prevent cancer and those that affect access to effective health care (Fig. 4.7.1). These interacting elements all affect cancer outcomes, both positively and negatively, in Indigenous peoples globally.

Preventing cancer in Indigenous peoples

Tobacco exposure

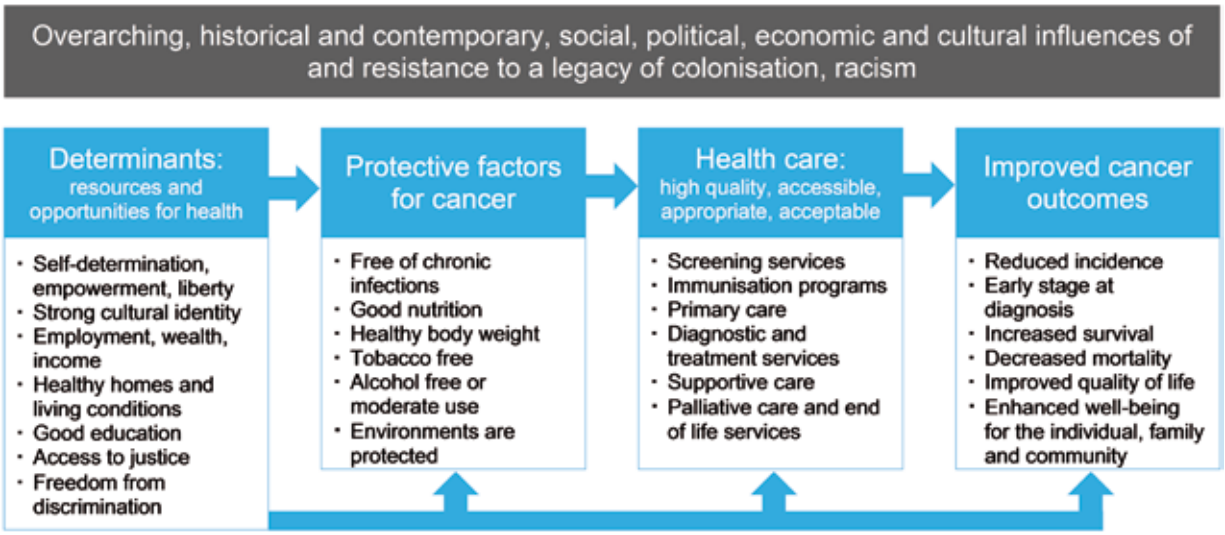
In several regions of the world, Indigenous populations have high rates of exposure to tobacco [10–15]. In Australia, Canada, and New Zealand, the prevalence of smoking is declining in all populations, but despite that, Indigenous peoples still have smoking rates that are 2–3 times those of non-Indigenous peoples [11,12,14]. This pattern is also seen in the USA and in some regions of Latin America, although the differences between Indigenous and non-Indigenous populations vary [10,13].

As a result, rates of tobacco-related cancers, particularly lung cancer, tend to be higher in Indigenous peoples [9,16]. For example, in New Zealand, the risk of lung cancer in Māori is 3–4 times that in non-Māori [16]. However, it is also worth noting that tobacco holds a sacred place in the culture of some Indigenous populations and is used in traditional rituals and ceremonies, although it is not necessarily smoked or inhaled.

FUNDAMENTALS

- There are estimated to be 370 million Indigenous people worldwide, living in more than 90 countries.
- Indigenous peoples are the first peoples of a country or region. They have traditions and social, cultural, economic, and political characteristics that are distinct from those of the new arrivals who later became dominant through invasion, occupation, settlement, or other means.
- Indigenous peoples have a special relationship to their ancestral lands, seas, and waterways, and holistic understandings of health that are fundamentally important for their cultural and physical survival and well-being.
- Colonization has taken different forms, involving varying degrees of violence, dispossession, dislocation, cultural oppression, and discrimination. Each has had impacts on the social determinants of health and on disparities in conditions of daily life experienced by Indigenous peoples.
- Colonization and systemic racism drive health inequities by the establishment of, and perpetuation of, forces and systems, social norms, social policies, and political systems that serve to advantage the colonizing populations.
- The cancer burden and, more generally, the health of Indigenous peoples are significantly affected by the broader social, political, and economic environments as well as by the legacy of colonization and racism.
- Indigenous peoples must be involved in the design, implementation, monitoring, and quality improvement processes of all policies related to health (including the determinants of health) and to the elimination of inequities in health care.

Fig. 4.7.1. Drivers of equitable cancer outcomes among Indigenous peoples.



In the USA, some tobacco companies historically appealed to these cultural connections to encourage the use of tobacco among Native Americans [17]. In Australia, tobacco was used by early colonists as payment for labour or as government-funded rations – along with flour, tea, and sugar – to encourage Indigenous people to remain in White settlements. The underlying sentiment of that time was one of colonization, which has had serious long-term effects on the health of Indigenous Australians [18].

Alcohol consumption

Alcohol consumption is related to several cancer types, including breast cancer, liver cancer, colorectal cancer, oral cancer, and stomach cancer (see Chapter 2.3). Patterns of alcohol consumption vary markedly around the world, including in Indigenous populations. In some regions, marginalized people in general, and Indigenous peoples in particular, tend to have higher or more hazardous alcohol consumption; examples are the Scheduled Tribes in some regions of India and Indigenous peoples in Australia and Canada [12,14,19,20]. In New Zealand and the USA, Indigenous people and non-Indigenous people are similarly likely to consume alcohol, but Indigenous people are more likely to have a consumption pattern that is hazardous to their health [13,21].

Fig. 4.7.2. A woman from the Tupi–Guarani tribe in Brazil smoking tobacco in a pipe.

Diet, physical activity, and body mass index

Commonly, traditional diets of Indigenous people were high in fruits and vegetables. As Indigenous people have lost access to their traditional foods and land, and societies have become more urbanized, food insecurity has been cited as a major contributor to the health inequalities faced by Indigenous people. For example, in New Zealand, 29% of Māori reported food insecurity compared with 14% of New Zealand Europeans [22]. In Africa and Asia, Indigenous people are more likely to be poorly nourished compared with non-Indigenous people [2].

Fig. 4.7.3. A Mayan woman selling fruits and vegetables at a market in San Cristóbal, Mexico.

Patterns of physical activity are highly variable, and few countries measure the physical activity of their Indigenous populations. In those countries that do report this, the picture is a mixed one, with some countries reporting similar or mixed levels of physical activity between Indigenous and non-Indigenous peoples [14,21], and some countries suggesting that Indigenous peoples may be more likely to be sedentary [12,13].

Consistent with patterns globally, rates of overweight and obesity are tending to increase in Indigenous populations; however, the increases are tending to occur more rapidly and more severely in Indigenous populations in many countries, including Canada, the USA, Australia, New Zealand, and countries in several regions of Latin America [10,12–14,23]. A recent study in New Zealand showed that although tobacco-related cancers remained the main driver of inequalities in cancer incidence between Māori and non-Māori, rates of obesity-related cancers, including breast cancer and endometrial cancer, were increasing the most rapidly [16].

Chronic infections

Infection with human papillomavirus (HPV) is common in many countries, and generally does not seem to occur with substantially greater frequency in Indigenous populations, although the specific patterns vary between countries [10,24–26]. Despite this, rates of cervical cancer are often higher in Indigenous people, probably reflecting poorer access to screening and other health services [9,10,27,28].

In contrast, rates of oncogenic infections that are strongly related to poverty and overcrowding tend to be substantially higher in Indigenous people. An example is *Helicobacter pylori*, an important cause of stomach cancer (see Chapter 5.4). Infection with *H. pylori* is strongly related to overcrowding, particularly in childhood. Rates of *H. pylori* infection in Indigenous people are 2–3 times those in non-Indigenous people in both Australia and New Zealand, and very high prevalence rates of *H. pylori* infection have been found in Indigenous populations in Canada, the USA, the circumpolar region, and Latin America [29–32]. Similarly, rates of chronic hepatitis B virus infection, which increases the risk of primary liver cancer, remain higher in Indigenous people in Australia and New Zealand, and in the Inuit of Canada, although infection rates are generally declining as a result of successful vaccination programmes [33–36]. In general, rates of infections including HIV, zoonotic infections, and tuberculosis tend to be high in Indigenous populations in Africa and Asia [2].

In parts of Africa and Asia, Indigenous peoples have higher rates of HIV infection than other groups because of a range of factors, which are compounded by the fact that many of the Indigenous peoples live in remote and hard-to-reach places, making access to health care extremely difficult. HIV infection is associated with several cancer types, including Kaposi sarcoma and B-cell lymphomas. Although very few data exist on these populations, it is likely that the rates of these associated cancer types are also high in these Indigenous populations [2].

Environmental degradation

Loss and degradation of land and resources are critical determinants of health for Indigenous populations around the globe. These factors result in disempowerment, political marginalization, and loss of autonomy, which have impacts on all aspects of health and well-being. In addition to these broad considerations, there are many examples of environmental damage that potentially has a direct impact on cancer risk in Indigenous peoples.

Environmental contamination has been associated with concerns about increased risk of cancer in some Indigenous groups in the western USA, through contamination of water and soil with cadmium, arsenic, uranium, and other heavy metals [37]. Similarly, oil drilling in the Amazon basin of Ecuador caused continuous contamination, which may have resulted in higher cancer incidence in local Indigenous populations [38]. However, the starkest

Fig. 4.7.4. Two members of the Nunukul Yuggera Aboriginal Dance Company perform at the opening ceremony of the inaugural World Indigenous Cancer Conference, held in Australia in 2016.

example of environmental contamination was seen after the nuclear testing in the Pacific. Testing by the USA on Bikini Atoll in the Marshall Islands in 1954 was "the most serious episode of radioactive contamination in the history of nuclear weapons testing" [39]. It resulted in a continuing excess of thyroid cancer and other cancer types in the local Indigenous population, as well as massive pollution of the marine ecosystem. Nuclear testing by France in the Moruroa and Fangataufa atolls has also resulted in continuing high rates of thyroid cancer in the Indigenous populations of French Polynesia [40].

Cancer screening

Effective cancer screening can reduce both the incidence and the impact of cancer (see Chapter 6.6), but services may not meet the needs of Indigenous peoples. In Australia, Whop et al. found that 3-year participation in cervical cancer screening was 26 percentage points lower for Indigenous women than for non-Indigenous women (41.8% vs 68.3%) [27]. In New Zealand, participation rates in screening for breast cancer, colorectal cancer, and cervical cancer have improved for Māori over time but still remain lower than rates for non-Māori [16]. In Canada and the USA, there are smaller differences in rates for breast cancer and cervical cancer screening between Indigenous and non-Indigenous women, and in general screening rates are improving [13,14]. In low- and middle-income countries throughout Africa, Asia, and the Pacific region, screening services are frequently poorly coordinated, of low quality, or completely absent for many Indigenous people.

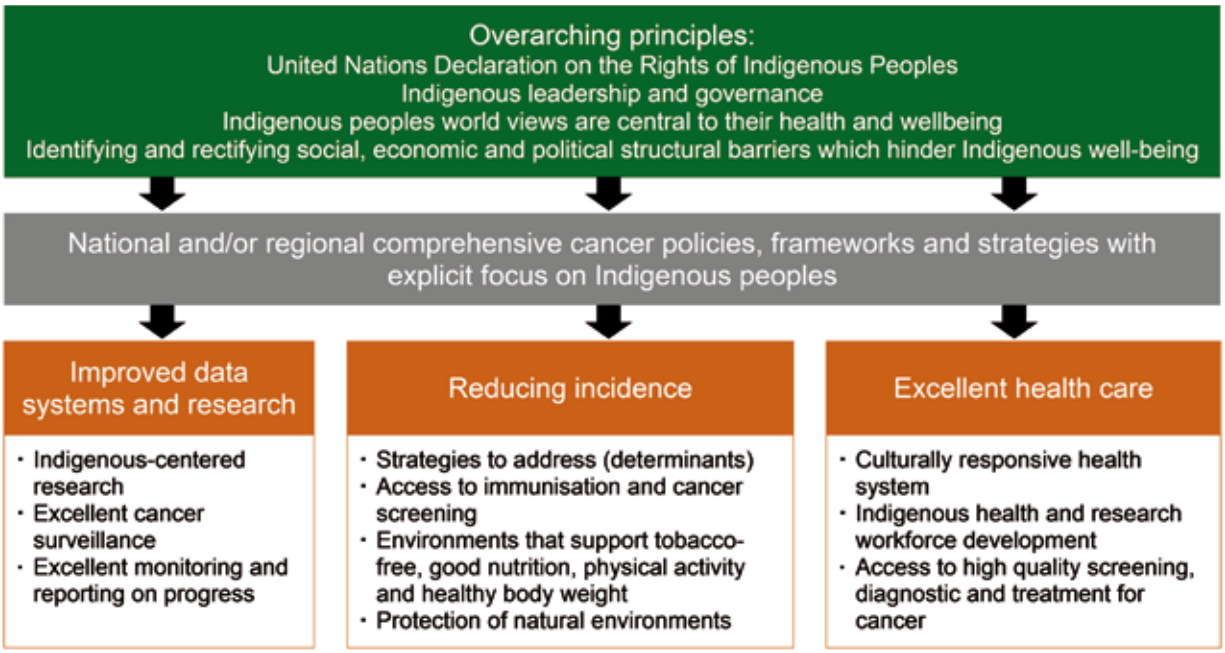
How cancer outcomes in Indigenous peoples may be improved

Indigenous people are among the most marginalized peoples globally. They often face political and social isolation, prejudice, and poverty. These influence their health and quality of life, and are reflected in issues across the cancer continuum. The current state of Indigenous health is the direct result of past policies related to colonization [2,4,5,41]. Data relating to Indigenous people are scarce. Indigenous people are more likely to be exposed to risk factors for many cancer types, and for many Indigenous groups there are substantial barriers to accessing cancer services and other health services.

Indigenous peoples have rich, holistic, complex, and heterogeneous worldviews, which are central to their health and well-being. Article 24 of the United Nations Declaration on the Rights of Indigenous Peoples clearly articulates that Indigenous peoples have the right to the highest attainable standard of health. Signatories are obliged to take action to improve the health of Indigenous peoples within their countries. This means actively identifying and addressing social, economic, and political structural barriers, which hinder the attainment of equitable health for Indigenous peoples.

Improving cancer outcomes for Indigenous peoples requires that achieving equity is a central priority and that all action must have Indigenous leadership, participation, and decision-making at its core [2,5]. It must include improvement of data related to Indigenous peoples, including Indigenous identifiers, which will enable Indigenous peoples to identify and prioritize their health needs [7,42]. There is an urgent need for comprehensive, sustained efforts to improve cancer outcomes for Indigenous peoples, grounded in the principles of Indigenous autonomy and empowerment (Fig. 4.7.5).

Fig. 4.7.5. Framework for intervention to improve cancer outcomes among Indigenous peoples.



References

1. Ghebreyesus TA (2018). Improving the health of Indigenous people globally. Lancet Oncol. 19(6):e277. https://doi.org/10.1016/S1470-2045(18)30375-9 PMID:29893252
2. United Nations Department of Economic and Social Affairs (2015). State of the world's Indigenous peoples, 2nd volume: Indigenous peoples' access to health services. United Nations Publications. Available from: https://www.un.org/esa/socdev/unpfii/documents/2016/Docs-updates/SOWIP_Health.pdf.
3. United Nations (2018). Indigenous peoples at the UN. https://www.un.org/development/desa/indigenouspeoples/about-us.html
4. Reid P, Robson B (2007). Understanding health inequities. In: Robson B, Harris R, editors. Haoura: Māori standards of health IV: a study of the years 2000–2005. Wellington, New Zealand: Te Rōpū Rangahau Hauora a Eru Pōmare; pp. 3–10.
5. King M, Smith A, Gracey M (2009). Indigenous health part 2: the underlying causes of the health gap. Lancet. 374(9683):76–85. https://doi.org/10.1016/S0140-6736(09)60827-8 PMID:19577696
6. Harris R, Tobias M, Jeffreys M, Waldegrave K, Karlsen S, Nazroo J (2006). Effects of self-reported racial discrimination and deprivation on Māori health and inequalities in New Zealand: cross-sectional study. Lancet. 367(9527):2005–9. https://doi.org/10.1016/S0140-6736(06)68890-9 PMID:16782491
7. Sarfati D, Garvey G, Robson B, Moore S, Cunningham R, Withrow D, et al. (2018). Measuring cancer in indigenous populations. Ann Epidemiol. 28(5):335–42. https://doi.org/10.1016/j.annepidem.2018.02.005 PMID:29503062
8. Smylie J, Firestone M (2015). Back to the basics: identifying and addressing underlying challenges in achieving high quality and relevant health statistics for indigenous populations in Canada. Stat J IAOS. 31(1):67–87. http://doi.org/10.3233/SJI-150864 PMID:26793283
9. Moore SP, Antoni S, Colquhoun A, Healy B, Ellison-Loschmann L, Potter JD, et al. (2015). Cancer incidence in indigenous people in Australia, New Zealand, Canada, and the USA: a comparative population-based study. Lancet Oncol. 16(15):1483–92. https://doi.org/10.1016/S1470-2045(15)00232-6 PMID:26476758
10. Moore SP, Forman D, Piñeros M, Fernández SM, de Oliveira Santos M, Bray F (2014). Cancer in indigenous people in Latin America and the Caribbean: a review. Cancer Med. 3(1):70–80. https://doi.org/10.1002/cam4.134 PMID:24403278
11. Ball J, Stanley J, Wilson N, Blakely T, Edwards R (2016). Smoking prevalence in New Zealand from 1996-2015: a critical review of national data sources to inform progress toward the Smokefree 2025 goal. N Z Med J. 129(1439):11–22. PMID:27507718
12. AIHW (2016). Australia's Health 2016. 4.8: Health behaviours and biomedical risks of Indigenous Australians. Canberra, Australia: Australian Institute of Health and Welfare.
13. Cobb N, Espey D, King J (2014). Health behaviors and risk factors among American Indians and Alaska Natives, 2000-2010. Am J Public Health. 104(Suppl 3):S481–9. https://doi.org/10.2105/AJPH.2014.301879 PMID:24754662
14. Withrow DR, Amartey A, Marrett LD (2014). Cancer risk factors and screening in the off-reserve First Nations, Métis and non-Aboriginal populations of Ontario. Chronic Dis Inj Can. 34(2–3):103–12. PMID:24991773

15. Janakiram C, Joseph J, Vasudevan S, Taha F, Deepan Kumar C, Venkitachalam R, et al. (2016). Prevalence and dependency of tobacco use in an Indigenous population of Kerala, India. J Oral Hyg Health. 4(1):198. https://doi.org/10.4172/2332-0702.1000198

16. Teng AM, Atkinson J, Disney G, Wilson N, Sarfati D, McLeod M, et al. (2016). Ethnic inequalities in cancer incidence and mortality: census-linked cohort studies with 87 million years of person-time follow-up. BMC Cancer. 16(1):755. https://doi.org/10.1186/s12885-016-2781-4 PMID:27669745

17. Maron DF (2018). The fight to keep tobacco sacred. Scientific American. 29 March 2018. https://www.scientificamerican.com/article/the-fight-to-keep-tobacco-sacred/

18. Gracey M, King M (2009). Indigenous health part 1: determinants and disease patterns. Lancet. 374(9683):65–75. https://doi.org/10.1016/S0140-6736(09)60914-4 PMID:19577695

19. Kumar RK, Tiwari R (2016). A cross sectional study of alcohol consumption among tribal and non-tribal adults of Narayanganj block in Mandla district of Madhya Pradesh, India. Int J Community Med Public Health. 3(4):791–5. https://doi.org/10.18203/2394-6040.ijcmph20160737

20. Mohindra KS, Narayana D, Anushreedha SS, Haddad S (2011). Alcohol use and its consequences in South India: views from a marginalised tribal population. Drug Alcohol Depend. 117(1):70–3. https://doi.org/10.1016/j.drugalcdep.2010.12.021 PMID:21282019

21. Ministry of Health (2016). Annual update of key results 2015/16: New Zealand Health Survey. Wellington, New Zealand: Ministry of Health. Available from: https://www.health.govt.nz/publication/annual-update-key-results-2015-16-new-zealand-health-survey.

22. Carter KN, Lanumata T, Kruse K, Gorton D (2010). What are the determinants of food insecurity in New Zealand and does this differ for males and females? Aust N Z J Public Health. 34(6):602–8. https://doi.org/10.1111/j.1753-6405.2010.00615.x PMID:21134063

23. Ministry of Health (2011). A focus on Māori nutrition: findings from the 2008/09 New Zealand Adult Nutrition Survey. Wellington, New Zealand: Ministry of Health. Available from: https://www.health.govt.nz/publication/focus-nutrition-key-findings-2008-09-nz-adult-nutrition-survey.

24. Garland SM, Brotherton JML, Condon JR, McIntyre PB, Stevens MP, Smith DW, et al.; WHINURS study group (2011). Human papillomavirus prevalence among indigenous and non-indigenous Australian women prior to a national HPV vaccination program. BMC Med. 9(1):104–104. https://doi.org/10.1186/1741-7015-9-104 PMID:21910918

25. Schmidt-Grimminger DC, Bell MC, Muller CJ, Maher DM, Chauhan SC, Buchwald DS (2011). HPV infection among rural American Indian women and urban White women in South Dakota: an HPV prevalence study. BMC Infect Dis. 11(1):252. https://doi.org/10.1186/1471-2334-11-252 PMID:21943050

26. Zehbe I, Moeller H, Severini A, Weaver B, Escott N, Bell C, et al. (2011). Feasibility of self-sampling and human papillomavirus testing for cervical cancer screening in First Nation women from Northwest Ontario, Canada: a pilot study. BMJ Open. 1(1):e000030. https://doi.org/10.1136/bmjopen-2010-000030 PMID:22021733

27. Whop LJ, Garvey G, Baade P, Cunningham J, Lokuge K, Brotherton JML, et al. (2016). The first comprehensive report on Indigenous Australian women's inequalities in cervical screening: a retrospective registry cohort study in Queensland, Australia (2000-2011). Cancer. 122(10):1560–9. https://doi.org/10.1002/cncr.29954 PMID:27149550

28. McLeod M, Harris R, Purdie G, Cormack D, Robson B, Sykes P, et al. (2010). Improving survival disparities in cervical cancer between Māori and non-Māori women in New Zealand: a national retrospective cohort study. Aust N Z J Public Health. 34(2):193–9. https://doi.org/10.1111/j.1753-6405.2010.00506.x PMID:23331365

29. Goodman KJ, Jacobson K, Veldhuyzen van Zanten S (2008). *Helicobacter pylori* infection in Canadian and related Arctic Aboriginal populations. Can J Gastroenterol. 22(3):289–95. https://doi.org/10.1155/2008/258610 PMID:18354758

30. McDonald AM, Sarfati D, Baker MG, Blakely T (2015). Trends in *Helicobacter pylori* infection among Māori, Pacific, and European birth cohorts in New Zealand. Helicobacter. 20(2):139–45. https://doi.org/10.1111/hel.12186 PMID:25403622

31. Robinson L-GE, Black FL, Lee FK, Sousa AO, Owens M, Danielsson D, et al. (2002). *Helicobacter pylori* prevalence among indigenous peoples of South America. J Infect Dis. 186(8):1131–7. https://doi.org/10.1086/343803 PMID:12355364

32. Windsor HM, Abioye-Kuteyi EA, Leber JM, Morrow SD, Bulsara MK, Marshall BJ (2005). Prevalence of *Helicobacter pylori* in Indigenous Western Australians: comparison between urban and remote rural populations. Med J Aust. 182(5):210–3. PMID:15748129

33. Addidle M (2011). Impact of universal hepatitis B vaccination on antenatal hepatitis B prevalence in the Midlands region of the North Island, New Zealand. N Z Med J. 124(1332):40–4. PMID:21747422

34. Graham S, Guy RJ, Cowie B, Wand HC, Donovan B, Akre SP, et al. (2013). Chronic hepatitis B prevalence among Aboriginal and Torres Strait Islander Australians since universal vaccination: a systematic review and meta-analysis. BMC Infect Dis. 13(1):403–403. https://doi.org/10.1186/1471-2334-13-403 PMID:24004727

35. Kim WR (2009). Epidemiology of hepatitis B in the United States. Hepatology. 49(5 Suppl):S28–34. https://doi.org/10.1002/hep.22975 PMID:19399791

36. Minuk GY, Uhanova J (2003). Viral hepatitis in the Canadian Inuit and First Nations populations. Can J Gastroenterol. 17(12):707–12. https://doi.org/10.1155/2003/350175 PMID:14679425

37. Lewis J, Hoover J, MacKenzie D (2017). Mining and environmental health disparities in Native American communities. Curr Environ Health Rep. 4(2):130–41. https://doi.org/10.1007/s40572-017-0140-5 PMID:28447316

38. Hurtig A-K, San Sebastián M (2002). Geographical differences in cancer incidence in the Amazon basin of Ecuador in relation to residence near oil fields. Int J Epidemiol. 31(5):1021–7. https://doi.org/10.1093/ije/31.5.1021 PMID:12435778

39. Prăvălie R (2014). Nuclear weapons tests and environmental consequences: a global perspective. Ambio. 43(6):729–44. https://doi.org/10.1007/s13280-014-0491-1 PMID:24563393

40. Simon SL, Bouville A, Land CE (2006). Fallout from nuclear weapons tests and cancer risks. Am Sci. 94(1):48–57. https://doi.org/10.1511/2006.57.982

41. Truth and Reconciliation Commission of Canada (2015). Calls to action. Winnipeg, Canada: Truth and Reconciliation Commission of Canada. Available from: https://nctr.ca/assets/reports/Calls_to_Action_English2.pdf.

42. Coleman C, Elias B, Lee V, Smylie J, Waldon J, Schanche Hodge F, et al. (2016). International Group for Indigenous Health Measurement: recommendations for best practice for estimation of Indigenous mortality. Stat J IAOS. 32(4):729–38. https://doi.org/10.3233/SJI-161023

Towards the World Code Against Cancer

Carolina Espina and Joachim Schüz

Prevention offers the greatest public health potential and the most cost-effective long-term cancer control. However, with today's multiple media streams, the general public is often overwhelmed by an abundance of confusing, ambiguous, or apparently contradictory messages on disease prevention. It has been estimated that at least 40% of cancer cases could be prevented through actions targeted towards risk prevention at the individual or population level. What can we recommend to people to reduce their risk of cancer?

The European Code Against Cancer (ECAC) is an integrated multirisk instrument for cancer prevention that informs the general public about how to avoid or reduce exposures to established causes of cancers, to adopt behaviours to reduce cancer risk, and to participate in vaccination programmes and organized screening programmes according to the respective national guidelines, by following 12 recommendations [1]. The ECAC carries the authority of the leading expert scientists, who worked under the coordination of IARC to develop a rigorous evidence-based methodology to synthesize the scientific evidence, leading to the update of the ECAC (4th edition) in 2014. Several working groups of cancer experts and, importantly, experts in the communication of health messages worked together to revise the previous recommendations. As a result, the ECAC stands out among other initiatives for its clarity and accessibility as a short set of recommendations for the general public.

The messages of the ECAC are aimed at individuals and have been enthusiastically promoted by the European cancer associations. The ECAC also acts as a guide to aid in the development of national health policies in cancer prevention and provides an important basis for health promotion. However, for the ECAC to achieve its full impact, wider dissemination among both the general public and policymakers is needed, as well as periodic updates. The ECAC emphasizes that its 12 recommendations need to be aligned with population-level preventive actions, either supported by policies aimed at minimizing exposures that are beyond the control of individuals or by empowering individuals to enable them to comply with the recommendations.

The experience of developing and promoting the ECAC has generated interest in developing such a set of recommendations for other regions of the world. Under the overall umbrella of a World Code Against Cancer using the same IARC methodology, regional Codes Against Cancer would be developed. They would focus on regions sufficiently large but also distinct enough to merit the development of versions adapted to differences in risk factors and cancer patterns, as well as economic, social, and cultural conditions [2].

The main goal of developing regional Codes Against Cancer would be to raise awareness about risk factors and the available prevention measures by effectively communicating the current state of the science and, as a consequence, empowering individuals and communities. Other world regions differ from the European context in terms of sociocultural norms, risk factor patterns, cancer burden, and the state of development of health systems. These differences underscore the importance of an in-depth appraisal of the recommendations on primary and secondary prevention of cancer in other regions of the world.

The adapted Codes Against Cancer will offer exceptional public health tools to support governments in the implementation of cancer control strategies adapted to the local needs, priorities, and resources. Consideration of such an adapted model illustrates why a simple translation of the ECAC would not be sufficient to promote cancer prevention globally. In addition, support from authoritative regional leaders in cancer prevention and in cancer control enables regional ownership of the recommendations, and may help to secure the highest acceptance and uptake, both by the general public and by those working in the health system. Broad involvement of the scientific community and of civil society networks to ensure the most suitable dissemination and advocacy is key for the successful implementation of the recommendations.

References

1. Schüz J, Espina C, Villain P, Herrero R, Leon ME, Minozzi S, et al.; Working Groups of Scientific Experts (2015). European Code against Cancer 4th Edition: 12 ways to reduce your cancer risk. Cancer Epidemiol. 39(Suppl 1):S1–10. https://doi.org/10.1016/j.canep.2015.05.009 PMID:26164654

2. Espina C, Herrero R, Sankaranarayanan R, Krug E, Wild CP, Schüz J (2018). Toward the World Code Against Cancer. J Glob Oncol. (4):1–8. https://doi.org/10.1200/JGO.17.00145 PMID:30241265

EUROPEAN CODE AGAINST CANCER

12 ways to reduce your cancer risk

1. Do not smoke. Do not use any form of tobacco.
2. Make your home smoke free. Support smoke-free policies in your workplace.
3. Take action to be a healthy body weight.
4. Be physically active in everyday life. Limit the time you spend sitting.
5. Have a healthy diet:
   - Eat plenty of whole grains, pulses, vegetables and fruits.
   - Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks.
   - Avoid processed meat; limit red meat and foods high in salt.
6. If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention.
7. Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds.
8. In the workplace, protect yourself against cancer-causing substances by following health and safety instructions.
9. Find out if you are exposed to radiation from naturally high radon levels in your home. Take action to reduce high radon levels.
10. For women:
    - Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby.
    - Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT.
11. Ensure your children take part in vaccination programmes for:
    - Hepatitis B (for newborns)
    - Human papillomavirus (HPV) (for girls).
12. Take part in organized cancer screening programmes for:
    - Bowel cancer (men and women)
    - Breast cancer (women)
    - Cervical cancer (women).

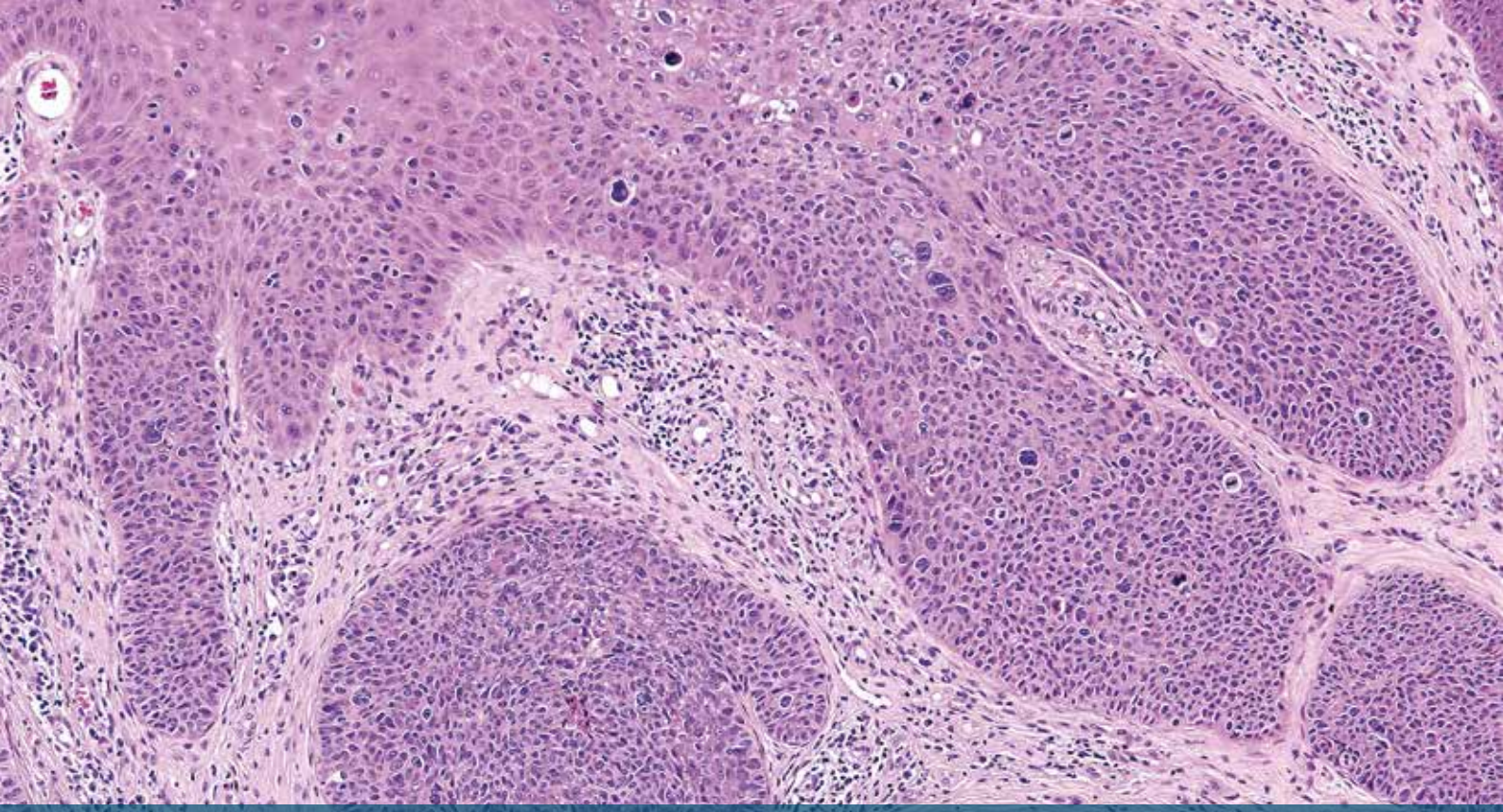
The European Code Against Cancer focuses on actions that individual citizens can take to help prevent cancer. Successful cancer prevention requires these individual actions to be supported by governmental policies and actions.

Find out more about the European Code Against Cancer at: http://cancer-code-europe.iarc.fr

This project is co-financed by the European Union and coordinated by the specialized cancer agency of the World Health Organization, the International Agency for Research on Cancer.

International Agency for Research on Cancer

World Health Organization



5 Preventing particular tumour types

Cancer is not a single disease but a multiplicity of variously related diseases. This understanding is as applicable and relevant to cancer prevention as it is to the clinical management of cancer. Broad knowledge about cancer causation, development, detection, and avenues to prevention must be qualified according to the tumour type or subtype being considered. Descriptions of causation and prevention cannot be given uniformly for all cancer types. For example, exogenous causes of prostate cancer are not evident; for now, prevention of prostate cancer must focus on sporadic disease and detection of precancerous lesions. Screening procedures can be meaningfully explored only with respect to particular cancer sites. For many cancer types, there are no recognized population-based screening procedures. However, success with respect to any research aspect of tumour development or a preventive measure for one tumour type often indicates a possible way to approach the same challenge for at least one other tumour type and perhaps many other tumour types.

A guide to the epidemiology data in Section 5: Preventing particular tumour types

Typically, epidemiology is dealt with at the beginning of each chapter. Unless otherwise stated, all of the incidence and mortality data are from the GLOBOCAN 2018 database. Further information about the epidemiology data is provided here.

Incidence

Cancer incidence is defined as the number of new cancer cases arising in a specified population over a given period of time (typically 1 year). It can be expressed as an absolute number of cases within the entire population per year or as a rate per 100 000 persons per year. The incidence rate provides an approximation of the average risk of developing a cancer. Incidence information is collected routinely by cancer registries.

Mortality

Cancer mortality is defined as the number of deaths due to cancer occurring in a specified population over a given period of time (typically 1 year). It can be expressed as an absolute number of deaths within the entire population per year or as a rate per 100 000 persons per year. The mortality rate provides an approximation of the average risk of death from a cancer. Mortality data are provided by national statistical offices.

Data source

The incidence and mortality data are based on national incidence and mortality estimates from the GLOBOCAN 2018 database [1]. This provides estimates of incidence and mortality for 36 site-specific cancer types and for all cancer sites combined for 185 countries or territories of the world in 2018, by sex and age group. The underlying principle in the estimation process is a reliance on the best available data on cancer incidence and/or mortality within a country to build up the global picture. The results are more accurate or less accurate for different countries, depending on the extent and accuracy of locally available data.

Data visualization tools

The Cancer Today subsection of the Global Cancer Observatory [2] provides data visualization tools to explore the current scale and profile of cancer worldwide using incidence, mortality, and prevalence estimates from the GLOBOCAN 2018 database.

Age standardization

All incidence and mortality rates provided in the chapters are age-standardized. An age-standardized rate (ASR) is a summary measure of the rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations (or the same population at different time points); age has a powerful influence on the risk of cancer, and populations differ with respect to their age distribution. Here, the ASR uses the World Standard Population (of Segi [3], as modified by Doll et al. [4]). The calculated incidence or mortality rate is then called the age-standardized incidence or mortality rate (World) and is conventionally expressed per 100 000 person-years.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593

2. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today.

3. Segi M (1960). Cancer mortality for selected sites in 24 countries (1950–57). Department of Public Health, Tohoku University of Medicine, Sendai, Japan.

4. Doll R, Payne P, Waterhouse JAH, editors (1966). Cancer incidence in five continents. Volume I. Geneva, Switzerland: International Union Against Cancer.

5.1 Lung cancer
Continues to be the leading cause of cancer death

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SUMMARY

- Lung cancer continues to be the most common cancer type and the leading cause of cancer death worldwide.
- Relative to the hazards of smoking tobacco cigarettes, the hazards presented by e-cigarettes and by cannabis smoking are largely unknown.
- The role of lung diseases, including chronic obstructive pulmonary disease and emphysema, in lung cancer is now clearer.
- Several lung cancer susceptibility loci have been identified in the past decade, and more continue to be discovered through large-scale collaborations.
- Comprehensive molecular profiling of adenocarcinoma, squamous cell carcinoma, and small cell carcinoma has been carried out. Some molecular changes provide druggable targets.
- Lung cancer in never-smokers is a specific disease entity.
- Lung cancer screening by low-dose computed tomography in high-risk populations represents an opportunity for mortality reduction, but its efficiency will be improved by individual risk prediction.

There are four main histological types of lung cancer: adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma, each with different morphological features, molecular characterization, and etiology; the most common types are adenocarcinoma and squamous cell carcinoma [1].

Epidemiology

Lung cancer continues to be the leading cause of cancer death worldwide, accounting for about 18% of all cancer deaths [2]. The highest incidence rates of lung cancer are observed in parts of North America, in East Asia, and in parts of central and eastern Europe (Fig. 5.1.1) [2]. Incidence rates in men have declined during the past four decades in most countries, whereas incidence rates in women continue to rise, with a few exceptions (Fig. 5.1.2) [3]. Because lung cancer survival is low globally, in general the trends in mortality rates over time correspond to the trends in incidence rates.

Etiology

Carcinogens

The major cause of lung cancer is tobacco smoking (see Chapter 2.1), which is responsible for 80–85% of lung cancer cases worldwide; tobacco smoke contains more than 7000 chemicals and at least 69 carcinogens, including polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, and benzene [4,5].

Tobacco smoking is known to have a stronger effect on squamous cell carcinoma and small cell lung carcinoma (SCLC) than on adenocarcinoma [6]. In addition, the effect of smoking on risk of squamous cell carcinoma and SCLC increases with increased smoking duration and decreases rapidly after smoking cessation. The effect of smoking on risk of adenocarcinoma decreases less rapidly after smoking cessation; this partly explains the increasing percentage of adenocarcinoma in countries that are in a late stage of the tobacco epidemic. Another contributor to the increase in lung adenocarcinoma in smokers is the introduction of filtered and low-tar or low-nicotine cigarettes [7].

Apart from tobacco smoking, about 29 agents have been recognized to cause lung cancer, with varying degrees of risk and prevalences of exposure. These include asbestos, silica, several heavy metals, and radon (see Chapter 2.10). In addition, indoor air pollution from household combustion of solid fuel and cooking fumes in poorly ventilated homes was established as a lung carcinogen, predominantly on the basis of studies in female never-smokers in Asia (see Chapter 4.3). More recently, outdoor air pollution, particulate matter in outdoor air pollution, and one specific pollutant – diesel engine exhaust – have each been classified by the IARC Monographs as carcinogenic

to humans (Group 1), on the basis of consistency in large pooled analyses and prospective cohort studies (see Chapter 2.9). These agents can have increasing importance as causes of lung cancer, especially in never-smokers. The established lung cancer carcinogens are included in the list of IARC Monographs classifications [8] (see also "Known causes of human cancer by organ site").

The prevalence of tobacco smoking has declined in most high-income countries during the past few decades [9]. Recently, alternative smoking products have become popular. In addition, the use of cannabis has been legalized in some countries. Therefore, recent research efforts related to putative lung cancer risk factors have focused on electronic nicotine delivery systems (also called e-cigarettes) and cannabis smoking.

To date, studies on e-cigarettes have been based predominantly on cell culture or animal studies, which have demonstrated that e-cigarettes have pulmonary toxicity, although to a much smaller extent than tobacco smoking [10]. Therefore, e-cigarettes are considered by some to be an effective tool for harm reduction. However, because very limited data are available in humans, much effort will be required to fully monitor the effect of e-cigarettes on lung cancer risk and nicotine addiction, given the increasing popularity of e-cigarettes as an alternative to tobacco cigarettes, particularly among young people [10,11].

Cannabis has been legalized in Canada, in 28 states of the USA for medicinal use, and in several European countries. Cannabis smoke has some of the same carcinogenic constituents as tobacco smoke, such as selected polycyclic aromatic hydrocarbons [12]. Therefore, several studies have been conducted to evaluate its potential association with risk of lung cancer [13,14]. However, most studies are limited by either potential underreporting or sparse data among heavy cannabis users, and therefore the possibility of an association in heavy users cannot be excluded [14].

Previous lung disease

In addition to the known lung carcinogens, previous lung diseases were shown to be associated with risk of lung cancer. In particular, it is well established that chronic obstructive pulmonary disease is associated with risk of lung cancer [15]; this association can be explained at least partly by shared etiology, such as tobacco smoking and chronic inflammation [16]. The International Lung Cancer Consortium conducted a series of pooled analyses based on 17 studies with a total of 24 607 lung cancer cases and 81 829 controls. Although a history of chronic obstructive pulmonary disease was shown to be associated with lung cancer risk, only emphysema was associated with risk of lung cancer in never-smokers, and this association persisted even when considering a history of emphysema 5–10 years before the diagnosis of lung cancer [17]. A similar association was found for pneumonia, based on a pooled analysis of 12 studies [17].

Genetic susceptibility

Although tobacco smoking is the main risk factor for lung cancer, only about 15% of smokers eventually develop lung cancer [18]. A genetic component of lung cancer etiology is recognized on the basis of familial studies, and the analyses either accounted for smoking or focused on never-smokers [18]. The familial relative risk of lung cancer is consistently estimated to be about 2-fold across several large cancer registries [19], and the heritability of lung cancer has been estimated as 18% [20]. Having a first-degree relative with lung cancer increases the risk of lung cancer by 1.25–1.5-fold in never-smokers [21].

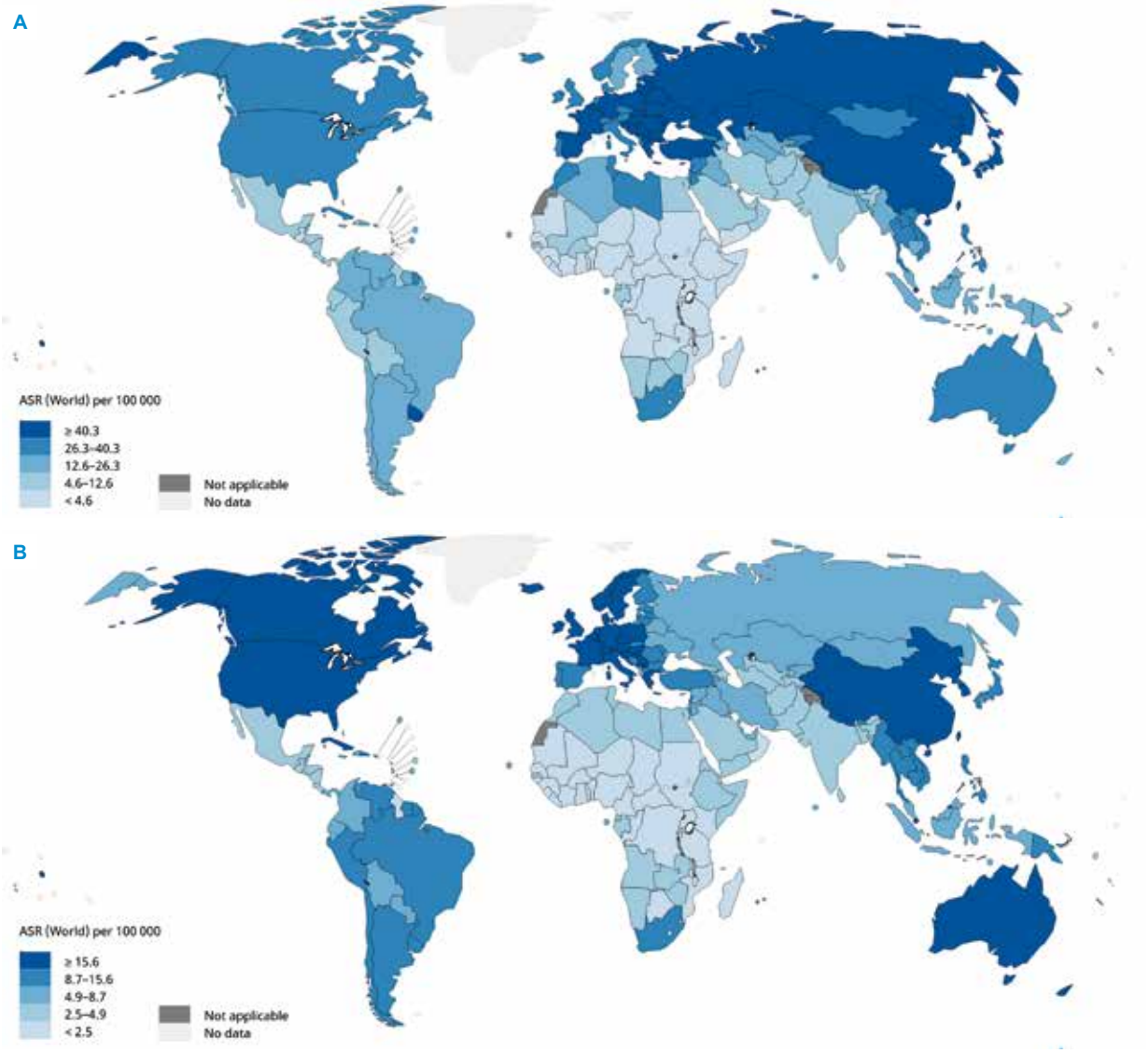
High-penetrance genetic syndromes, such as Li–Fraumeni syndrome and hereditary retinoblastoma, are associated with increased risk of lung cancer [18]. In addition, high-penetrance germline mutations in *EGFR* and *HER2* in predominantly never-smokers have recently been described [22,23]. However, these high-penetrance mutations only account for perhaps 1% of lung cancer cases.

In the past decade, genome-wide association studies (GWAS) (see Chapter 3.2) have identified several lung cancer susceptibility loci, including *CHRNA3/5*, *TERT-CLPTM1L*, the HLA/MHC region, *RAD52*, *BRCA2*, and *CHEK2*, with extensive validations [24,25]. A list of major lung cancer susceptibility loci for European descendants was reported in the most recent and largest GWAS analysis to date [25]. The loci identified so far accounted for about 12% of the familial relative risk of lung cancer.

FUNDAMENTALS

- There are four main histological types of lung cancer: adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma, each with different morphological features, molecular characterization, and etiology; the most common types are adenocarcinoma and squamous cell carcinoma.
- The major cause of lung cancer is tobacco smoking. Other causes of lung cancer include asbestos, silica, several heavy metals, radon, and indoor and outdoor air pollution.
- Risk of lung cancer is also affected by an individual's genetic susceptibility.
- Lung cancer survival remains dismal, with 5-year survival rates of 10–20%, because most patients are diagnosed at late stages of the disease.

Fig. 5.1.1. Global distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000 person-years for lung cancer (A) in men and (B) in women, 2018.

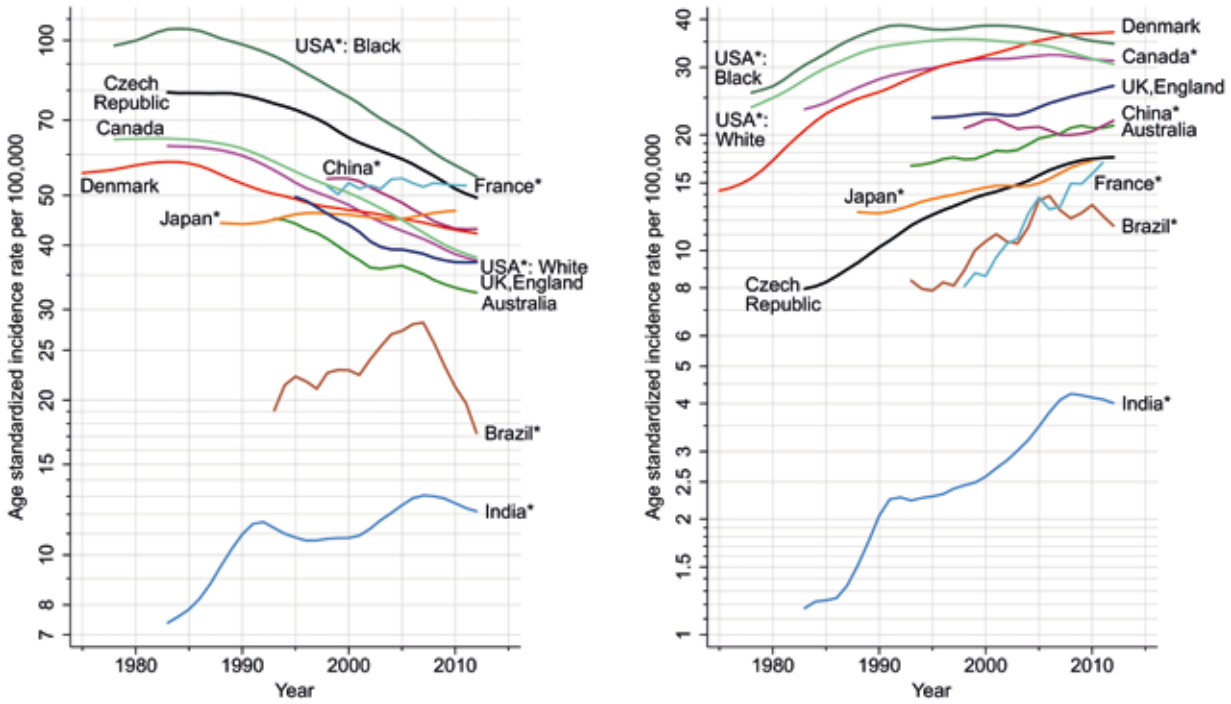


Several large-scale GWAS analyses conducted in Asian populations have identified multiple Asian-specific lung cancer susceptibility loci, such as *ROS1*, along with several loci in common with those found in European descendants, such as *TERT-CLPTM1L*. A detailed list of lung cancer susceptibility loci in both European and Asian populations is included in a recent review [26]. Data on the African American population are currently limited to a single study, which confirmed the association of the *CHRNA5* and *TERT-CLPTM1* loci with lung cancer [27].

Somatic characteristics of histological types

Comprehensive genomic characterizations were conducted by the Cancer Genome Atlas Research Network for lung adenocarcinoma and squamous cell carcinoma [28,29]. Both tumour types showed a very high average tumour mutation burden of about 8–9 somatic mutations per megabase. In adenocarcinoma, mutations in *KRAS* were mutually exclusive with those in *EGFR*. *EGFR* mutations were the main mutations in adenocarcinoma in never-smokers (Fig. 5.1.3B), and *KRAS* mutations were the predominant mutations in adenocarcinomas arising in patients in Europe and North America, of which about 85% were ever-smokers (Fig. 1.5.3A). *TP53* mutations occurred in 46% of adenocarcinomas [29] and in almost all squamous cell carcinomas, along with a variety of activating mutations, although none at very high frequencies [28]. Biallelic inactivation of *TP53* and *RB1* appears to be a universal feature of SCLC [30]. All three of these types of lung tumours have marked genomic complexity,

Fig. 5.1.2. Age-standardized (World) incidence rates per 100 000 person-years by calendar year in selected countries for lung cancer (left) in men and (right) in women, circa 1978–2012.



including rearrangements and copy number variations.

The mutation spectra shown in Fig. 5.1.3 are markedly different by histological type, suggesting that they may arise via very different molecular pathways. In addition, spatial and temporal intratumour heterogeneity in the processes of genomic instability is an active new area of research, with potential value as a prognostic predictor. The morphological and molecular features of the main histological subtypes are described below.

Adenocarcinoma

Adenocarcinomas have more morphological heterogeneity than other types of lung cancer; a uniform terminology was recently proposed and has been widely accepted [31,32]. The new subtypes, along with their major morphological features and the presence of frequent gene mutations, are summarized in Table 5.1.1 and illustrated in Fig. 5.1.4. However, most adenocarcinomas are composed of more than one subtype, and the tumours are classified by the most common subtype present [31].

The adenocarcinoma in situ subtype is characterized by lepidic (scale-like) growth along existing alveolar walls without underlying tissue invasion. The papillary subtype has fibrovascular cores, which distinguish it from the micropapillary subtype. The acinar subtype is frequent and has gland formation as its hallmark feature. These three subtypes have frequent *EGFR* mutations. The solid with mucin subtype is poorly differentiated and is associated with *KRAS* mutations or translocations in *ALK*, *ROS*, *RET*, and *NTRK*. The recently recognized micropapillary subtype lacks fibrovascular cores and may contain *ALK* or *HER2* mutations. Mucinous carcinomas, although not an official subtype, are relatively rare and have frequent *KRAS* mutations.

Squamous cell carcinoma

Squamous cell carcinoma has three subtypes: keratinizing, non-keratinizing, and basaloid. The morphological difference between the keratinizing subtype and the non-keratinizing subtype, which is less well differentiated, is the presence or absence of visible keratin on histological examination. No other molecular features have been described that separate these two common subtypes. The basaloid subtype has cells that are morphologically similar to those found in the basal layer of the large airways and that have a specific mRNA expression profile [33]. The mutation spectrum for squamous cell carcinoma is shown in Fig. 5.1.3C.

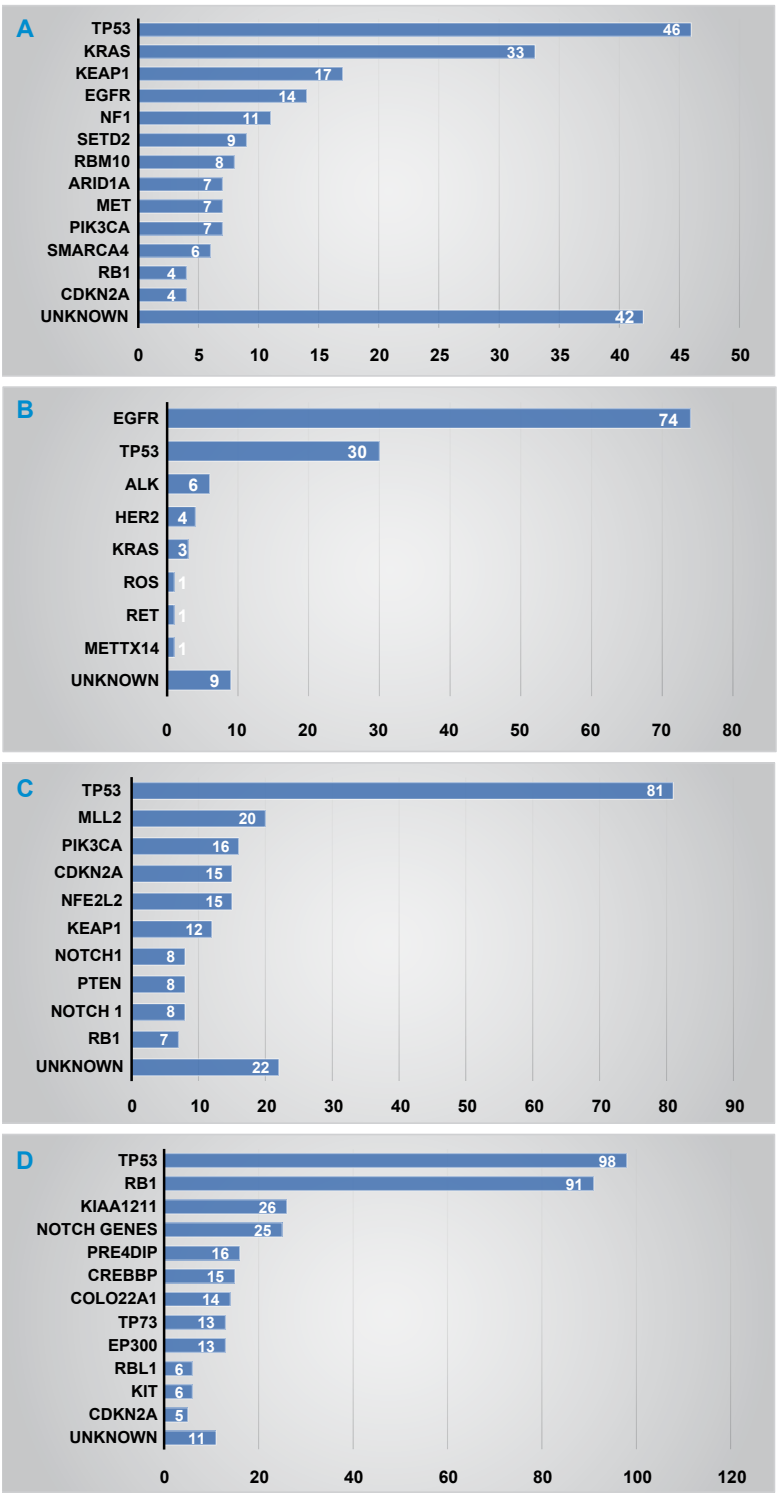
Small cell lung carcinoma

SCLCs are aggressive carcinomas that originate from neuroendocrine cells in the bronchial epithelium. Only two SCLC subtypes are recognized: pure SCLCs and combined SCLCs. Combined SCLCs have a non-SCLC (NSCLC) component that consists of at least 10% of the tumour [34].

Epigenetics of lung cancer

The epigenetic landscape of lung cancer commences early during pathogenesis and consists of two major components: methylation and

Fig. 5.1.3. Mutation spectra by histological type of lung cancer, showing the percentage of samples with a mutation detected by automated analysis. "Unknown" refers to potentially druggable mutations and excludes tumour recessive genes including *TP53*. (A) Mutation pattern of adenocarcinomas arising in patients in Europe and North America, of which about 85% were ever-smokers. (B) Mutation pattern of adenocarcinomas in Asian never-smokers. (C) Mutation pattern of squamous cell carcinomas. (D) Mutation pattern of small cell lung carcinomas.



histone modifications (see Chapter 3.8) [35].

Global hypomethylation is a common feature of cancer. Smoking-related hypomethylation measured in pre-diagnostic blood samples was shown to be associated with increased risk of lung cancer, and the most consistently replicated change was in the *AHRR* gene [36]. DNA hypermethylation, mainly in the promoter region, is a major mechanism for the silencing of tumour suppressor genes, although it may also occur in the body of the gene, where it may result in gene activation. Several hundred genes are methylated in lung cancers, and the best studied and most frequently methylated genes are listed in Table 5.1.2. Methylation results in inactivation of one allele, and the other allele is usually deleted.

In addition to methylation, many covalent modifications can occur on the N-terminal tail that protrudes from each of the four histone proteins. Histone modifications target many key tumour suppressor genes. The major histone changes that characterize NSCLC are listed in Table 5.1.2.

Although most epigenetic studies of lung cancer focus on NSCLC, the epigenetics of SCLC has both similarities and differences with NSCLC. In particular, *EZH2*, a master regulator of transcription that affects DNA methylation via upregulation of DNA methyltransferases, is upregulated in many cancer types, including SCLC, where it plays a major role in tumour progression and is associated with poor prognosis. These findings have led to widespread efforts to therapeutically target *EZH2*. The genetic and epigenetic somatic alterations of lung cancer have recently been reviewed [37].

Lung cancer in never-smokers

Lung cancer in never-smokers is a specific disease entity, because there are significant differences in etiology and clinical characteristics between lung cancer in never-smokers

Fig. 5.1.4. Morphological features of adenocarcinoma subtypes: (A) adenocarcinoma in situ, (B) acinar, (C) solid with mucin, (D) papillary, (E) micropapillary, and (F) mucinous.

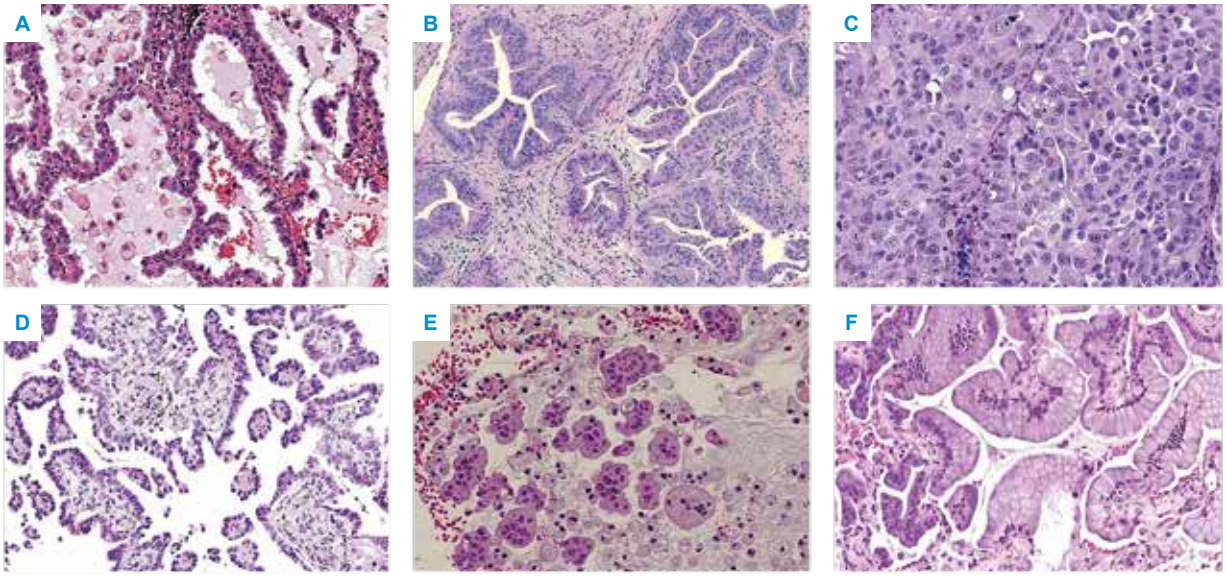


Table 5.1.1. Lung adenocarcinoma subtypes, growth patterns, and frequent gene mutations

Subtype[a]	Major growth features	Frequent gene mutations[b]
Adenocarcinoma in situ	Lepidic growth	*EGFR*
Acinar	Gland-forming, occasional cribriform pattern	*EGFR*
Solid with mucin	Predominantly solid with focal mucin production	*KRAS*, *ALK*
Papillary	Papillary invasive, with fibrovascular cores	*EGFR*
Micropapillary	Small papillary-like structures without fibrovascular cores	*ALK*, *HER2*
Mucinous	Predominantly lepidic with abundant intracellular and occasionally extracellular mucin	*KRAS*

[a] Most adenocarcinomas consist of mixtures of more than one subtype. The major component should be identified and its percentage estimated. The other subtypes present should also be identified.

[b] Certain mutations are more common in certain subtypes, but there is considerable heterogeneity. Very little information is available for *BRAF* and *ROS1* mutations and their associations with adenocarcinoma subtypes.

versus ever-smokers. For example, adenocarcinomas are more prevalent in never-smoker patients with lung cancer [38]. In addition, lung cancers in never-smokers have different somatic characteristics (Fig. 5.1.3). Most notably, never-smoker patients with lung cancer have a lower prevalence of *KRAS* mutations and a higher prevalence of *EGFR* mutations and show longer survival after treatment with *EGFR* inhibitors than do ever-smokers. Overall, there are extensive differences between smokers and never-smokers with regard to the tumour mutation landscape, burden, and affected genes; *TP53* is the most extensively documented gene [39]. Other features that distinguish lung cancer in never-smokers and ever-smokers, such as methylation patterns, have also been reported [39].

Prevention and mortality reduction

Currently, the best hopes for reducing lung cancer mortality are preventing smoking through effective tobacco control and promoting successful smoking cessation in current smokers. However, in populations where the prevalence of smoking is low, an increasing proportion of lung cancer occurs in never-smokers and former smokers.

Screening

The National Lung Screening Trial in the USA reported that the low-dose computed tomography (LDCT) screening reduced the lung cancer mortality by 20% in former and current smokers who were eligible to be screened, based on age (age 55 years to 74 or 80 years) and history of tobacco smoking (at least

Table 5.1.2. Frequent abnormalities of genes involved in the epigenetic regulation of lung cancers

Frequently methylated genes	Mutations or dysregulation of epigenetic regulators	
SHOX2	Histone acetyltransferase	EP300
TCF21	Histone acetyltransferase	CREBBP
APC	Histone deacetylase	HDAC4
EPBH1K3	Histone deacetylase	HDAC9
PYCARD	Lysine methyltransferase	KMT2A–D
FHIT	Lysine methyltransferase	PRDM9
TSLC1	Lysine methyltransferase	SETD2
RAR	Lysine methyltransferase	NSD1
CDH1	Lysine methyltransferase	EZH2
RASSF1A	Lysine demethylase	KDM5A–C
CDKN2A	DNA methyltransferase	DNMT1, 3A, and 3B
DAPK	H3K9 methyltransferase	SETDB9
CDH13	H3K36 demethylase	KDM2A
PTEN	SWI/SNF complex	SMARCA4
RUNX3	SWI/SNF complex	ARID1A

30 pack-years of smoking, or have smoked within the past 15 years). This presented an appealing complementary strategy for reducing lung cancer mortality through detection of early-stage lung cancer, which is still potentially curable by surgical resection [40].

As a result, many public health agencies and medical institutions are now considering implementing LDCT lung cancer screening at the population level, and the United States Preventive Services Task Force has issued the Grade B recommendation for LDCT screening. Since 2015, several major health insurance programmes in the USA, including Medicare, have started to approve LDCT screening for insurance coverage.

Fig. 5.1.5. A man undergoing lung cancer screening at the University of Connecticut Health Center, USA.

Currently, in the USA most of the screening recommendations provided by health agencies are derived from the National Lung Screening Trial eligibility criteria based on age and history of tobacco smoking, and a recent National Comprehensive Cancer Network Category 2 recommendation also included family history and non-tobacco risk factors to improve the screening criteria [41]. However, studies have shown that applying individual risk probability-based screening criteria could prevent more lung cancer deaths and reduce the number needed to screen to prevent one lung cancer death [42]. Although substantial efforts have been made to establish lung cancer risk prediction models based on personal health and exposure history [43], lung cancer researchers are now working towards integrating individual molecular profiles to improve risk prediction.

Biomarkers

The development of biomarkers for early detection of lung cancer is an

active research area, which encompasses a wide range of biomarker research, including markers and metabolites that could be found in the various biological fluids, particularly circulating blood, urine, or sputum. The main types of circulating biomarkers are protein-based markers, metabolites, autoantibodies from humoral immune response, epigenetic markers, and circulating tumour DNA.

Although most of the biomarkers have failed to be replicated in independent studies, several promising biomarkers have been established across multiple prospective cohort studies. For example, plasma level of pro-surfactant protein B was shown to be an independent predictor of lung cancer risk based on a pan-Canadian screening programme and the Carotene and Retinol Efficacy Trial, after adjusting for demographic factors and lung cancer risk factors [44]. It has become clear that a panel of multiple biomarkers, rather than any single marker, would be needed to improve risk prediction [45]. A succinct review of various reported biomarker panels was recently published [46].

In terms of epigenetic markers, in addition to methylation and histone modification as mentioned above, microRNAs and long non-coding RNAs are also potential epigenomic biomarkers. In particular, several previous studies have shown a promising predictive performance of multi-microRNA panels [47], although the sample sizes tend to be limited and external validation in independent studies is still required.

In addition to blood-based biomarkers, another type of biomarker for early detection of lung cancer focuses on the gene expression profile of the airway epithelium, based on the theory of field of injury and field cancerization [48,49]. Finally, given the known association between chronic obstructive pulmonary disease and risk of lung cancer, previous studies have evaluated the added predictive performance of lung function [50,51].

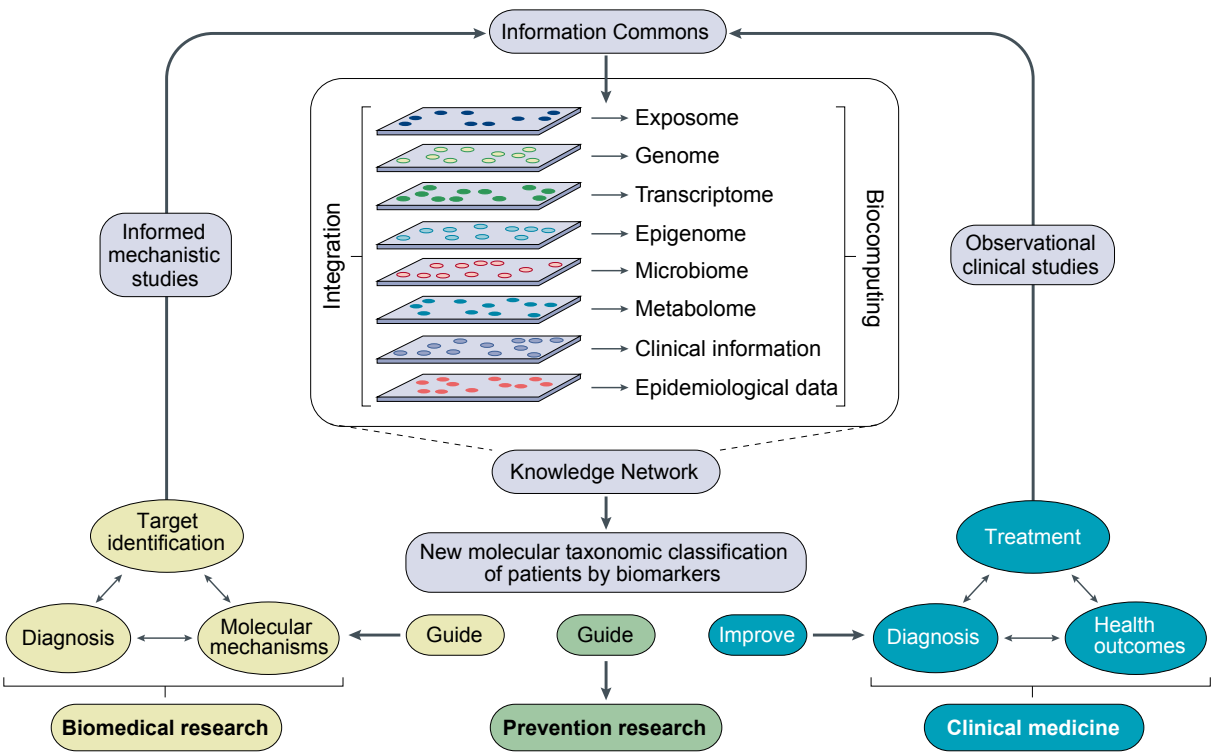
Biomarker research for early detection of lung cancer can help to better identify individuals who are at high risk of lung cancer and should be recommended for LDCT screening. To yield an optimal predictive performance for early detection of lung cancer, one can consider multiple layers of data, including epidemiological and clinical information and an individual's molecular profiles; this aligns with the concept of precision medicine (Fig. 5.1.6) [52].

It is anticipated that biomarkers may also help to differentiate malignant nodules from benign ones. The challenge is to establish a panel that would be applicable in the clinical setting and remain cost-effective for the health-care system.

Nodule malignancy

For individuals who undergo LDCT screening, about 15–20% of chest scans detect non-calcified pulmonary nodules. However, the National Lung Screening Trial reported that only 1 in 20 nodules detected by LDCT screening are actually lung cancers [40]. To address this issue, several clinical probability models

Fig. 5.1.6. A concept schema of biomarker integration for precision medicine.



were proposed to improve the assessment of nodules, and use of the Lung CT Screening Reporting and Data System (Lung-RADS) classification of the American College of Radiology was shown to substantially decrease the false-positive rate, with a moderate reduction in sensitivity [53]. However, currently there is still a wide range of clinical protocols for how patients with pulmonary nodules detected on LDCT screening are managed, and the diagnostic evaluation of suspicious abnormalities can range from watchful waiting and monitoring to needle biopsy and pulmonary resection.

In response to the need to differentiate between benign and malignant nodules, radiomics has emerged as a field of study. Radiomics is the analysis of high-dimensional imaging data, focusing on the extraction of quantitative variables from radiographic features for subsequent agnostic data mining [54]. This field has shown promise to better differentiate nodules with malignant potential. However, there is no standardized process of feature extraction, the analytical methods vary greatly across studies, and proper validation is still required for robust reproducibility. Therefore, it is currently considered premature to implement radiomics as part of the routine diagnostic process.

Prognosis and targeted treatment

Lung cancer survival remains dismal, with 5-year survival rates of only 10–20% in most parts of the world [55,56]. The stage at diagnosis is a major determinant of lung cancer prognosis; 5-year survival rates range from 50–70% for diagnosis at stage I to 1–5% for diagnosis at stage IV, because surgical resection at an early stage is still the most effective treatment [55]. However, fewer than 20% of patients are diagnosed at stage I, and most are diagnosed at stage IIIB or IV [55]; hence, early detection is important.

The clinical outcome varies by histological type. SCLC is the most aggressive type, and combined SCLC may have a worse prognosis, perhaps because the NSCLC component is resistant to cytotoxic therapies. Adenocarcinoma in situ usually has an excellent prognosis if it is completely resected, even if small foci of invasion are present (microinvasive carcinomas).

Despite the growing number of mutations that continue to be identified, only a few somatic mutations can be used for targeted therapy, such as *EGFR* mutation, *ROS1* fusion, and *ALK* translocation; more recently, immunotherapy agents have been developed that target programmed cell death 1 (PD-1) protein. A range of other targeted and immunotherapy trials are currently in progress, with the hope of improving treatment response based on the principle of precision medicine. A complete review has been provided by the International Association for the Study of Lung Cancer [57].

In summary, lung cancer comprises very different types and subtypes, which affect the strategies for prevention, early detection, diagnosis, and clinical management.

References

1. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al.; WHO Panel (2015). The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol. 10(9):1243–60. https://doi.org/10.1097/JTO.0000000000000630 PMID:26291008

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593

3. Ferlay J, Colombet M, Bray F (2018). Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr.

4. Parkin DM, Boyd L, Walker LC (2011). 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 105(Suppl 2):S77–81. https://doi.org/10.1038/bjc.2011.489 PMID:22158327

5. U.S. Department of Health and Human Services (2014). The health consequences of smoking – 50 years of progress: a report of the Surgeon General. Atlanta (GA), USA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. Available from: https://www.ncbi.nlm.nih.gov/books/NBK179276/.

6. Freedman ND, Abnet CC, Caporaso NE, Fraumeni JF Jr, Murphy G, Hartge P, et al. (2016). Impact of changing US cigarette smoking patterns on incident cancer: risks of 20 smoking-related cancers among the women and men of the NIH-AARP cohort. Int J Epidemiol. 45(3):846–56. https://doi.org/10.1093/ije/dyv175 PMID:26411408

7. Song MA, Benowitz NL, Berman M, Brasky TM, Cummings KM, Hatsukami DK, et al. (2017). Cigarette filter ventilation and its relationship to increasing rates of lung adenocarcinoma. J Natl Cancer Inst. 109(12):djx075. https://doi.org/10.1093/jnci/djx075 PMID:28525914

8. IARC (2019). List of classifications by cancer sites with *sufficient* or *limited evidence* in humans, Volumes 1 to 124. Lyon, France: International Agency for Research on Cancer. Available from: https://monographs.iarc.fr/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf.

9. GBD 2015 Tobacco Collaborators (2017). Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the Global Burden of Disease Study 2015. Lancet. 389(10082):1885–906. https://doi.org/10.1016/S0140-6736(17)30819-X PMID:28390697

10. Shields PG, Berman M, Brasky TM, Freudenheim JL, Mathe E, McElroy JP, et al. (2017). A review of pulmonary toxicity of electronic cigarettes in the context of smoking: a focus on inflammation. Cancer Epidemiol Biomarkers Prev. 26(8):1175–91. https://doi.org/10.1158/1055-9965.EPI-17-0358 PMID:28642230

11. Dautzenberg B, Garelik D (2017). Patients with lung cancer: are electronic cigarettes harmful or useful? Lung Cancer. 105:42–8. https://doi.org/10.1016/j.lungcan.2016.05.011 PMID:27241679

12. Moir D, Rickert WS, Levasseur G, Larose Y, Maertens R, White P, et al. (2008). A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. Chem Res Toxicol. 21(2):494–502. https://doi.org/10.1021/tx700275p PMID:18062674

13. Callaghan RC, Allebeck P, Sidorchuk A (2013). Marijuana use and risk of lung cancer: a 40-year cohort study. Cancer Causes Control. 24(10):1811–20. https://doi.org/10.1007/s10552-013-0259-0 PMID:23846283

14. Zhang LR, Morgenstern H, Greenland S, Chang SC, Lazarus P, Teare MD, et al. (2015). Cannabis smoking and lung cancer risk: pooled analysis in the International Lung Cancer Consortium. Int J Cancer. 136(4):894–903. https://doi.org/10.1002/ijc.29036 PMID:24947688

15. Skillrud DM, Offord KP, Miller RD (1986). Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective, matched, controlled study. Ann Intern Med. 105(4):503–7. https://doi.org/10.7326/0003-4819-105-4-503 PMID:3752756

16. Punturieri A, Szabo E, Croxton TL, Shapiro SD, Dubinett SM (2009). Lung cancer and chronic obstructive pulmonary disease: needs and opportunities for integrated research. J Natl Cancer Inst. 101(8):554–9. https://doi.org/10.1093/jnci/djp023 PMID:19351920

17. Brenner DR, Boffetta P, Duell EJ, Bickeböller H, Rosenberger A, Muscat JE, et al.; International Lung Cancer Consortium (2012). Previous lung diseases and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium. Am J Epidemiol. 176(7):573–85. https://doi.org/10.1093/aje/kws151 PMID:22986146

18. Thun MJ, Henley SJ, Travis WD (2018). Lung cancer. In: Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, editors. Cancer epidemiology and prevention. 4th ed. New York (NY), USA: Oxford University Press; pp. 519–52.

19. Penney KL, Michailidou K, Carere DA, Zhang C, Pierce B, Lindstrom S, et al. (2018). Genetic epidemiology of cancer. In: Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, editors. Cancer epidemiology and prevention. 4th ed. New York (NY), USA: Oxford University Press; pp. 53–76.

20. Mucci LA, Hjelmborg JB, Harris JR, Czene K, Havelick DJ, Scheike T, et al.; Nordic Twin Study of Cancer (NorTwinCan) Collaboration (2016). Familial risk and heritability of cancer among twins in Nordic countries. JAMA. 315(1):68–76. https://doi.org/10.1001/jama.2015.17703 PMID:26746459

21. Coté ML, Liu M, Bonassi S, Neri M, Schwartz AG, Christiani DC, et al. (2012). Increased risk of lung cancer in individuals with a family history of the disease: a pooled analysis from the International Lung Cancer Consortium. Eur J Cancer. 48(13):1957–68. https://doi.org/10.1016/j.ejca.2012.01.038 PMID:22436981

22. Gazdar A, Robinson L, Oliver D, Xing C, Travis WD, Soh J, et al. (2014). Hereditary lung cancer syndrome targets never smokers with germline *EGFR* gene T790M mutations. J Thorac Oncol. 9(4):456–63. https://doi.org/10.1097/JTO.0000000000000130 PMID:24736066

23. Yamamoto H, Higasa K, Sakaguchi M, Shien K, Soh J, Ichimura K, et al. (2014). Novel germline mutation in the transmembrane domain of *HER2* in familial lung adenocarcinomas. J Natl Cancer Inst. 106(1):djt338. https://doi.org/10.1093/jnci/djt338 PMID:24317180

24. Hung RJ, McKay JD, Gaborieau V, Boffetta P, Hashibe M, Zaridze D, et al. (2008). A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature. 452(7187):633–7. https://doi.org/10.1038/nature06885 PMID:18385738

25. McKay JD, Hung RJ, Han Y, Zong X, Carreras-Torres R, Christiani DC, et al.; SpiroMeta Consortium (2017). Large-scale association analysis identifies new lung cancer susceptibility loci and heterogeneity in genetic susceptibility across histological subtypes. Nat Genet. 49(7):1126–32. https://doi.org/10.1038/ng.3892 PMID:28604730

26. Bossé Y, Amos CI (2018). A decade of GWAS results in lung cancer. Cancer Epidemiol Biomarkers Prev. 27(4):363–79. https://doi.org/10.1158/1055-9965.EPI-16-0794 PMID:28615365

27. Zanetti KA, Wang Z, Aldrich M, Amos CI, Blot WJ, Bowman ED, et al. (2016). Genome-wide association study confirms lung cancer susceptibility loci on chromosomes 5p15 and 15q25 in an African-American population. Lung Cancer. 98: 33–42. https://doi.org/10.1016/j.lungcan.2016.05.008 PMID:27393504

28. Cancer Genome Atlas Research Network (2012). Comprehensive genomic characterization of squamous cell lung cancers. Nature. 489(7417):519–25. https://doi.org/10.1038/nature11404 PMID:22960745

29. Cancer Genome Atlas Research Network (2014). Comprehensive molecular profiling of lung adenocarcinoma. Nature. 511(7511):543–50. https://doi.org/10.1038/nature13385 PMID:25079552

30. Gazdar AF, Bunn PA, Minna JD (2017). Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer. 17(12):725–37. https://doi.org/10.1038/nrc.2017.87 PMID:29077690

31. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger K, Yatabe Y, et al. (2011). International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol. 6(2):244–285. https://doi.org/10.1097/JTO.0b013e318206a221 PMID:21252716

32. Austin JH, Garg K, Aberle D, Yankelevitz D, Kuriyama K, Lee HJ, et al. (2013). Radiologic implications of the 2011 classification of adenocarcinoma of the lung. Radiology. 266(1):62–71. https://doi.org/10.1148/radiol.12120240 PMID:23070271

33. Brambilla C, Laffaire J, Lantuejoul S, Moro-Sibilot D, Mignotte H, Arbib F, et al. (2014). Lung squamous cell carcinomas with basaloid histology represent a specific molecular entity. Clin Cancer Res. 20(22):5777–86. https://doi.org/10.1158/1078-0432.CCR-14-0459 PMID:25189482

34. Gazdar AF (2018). Morphologic and other forms of heterogeneity in small cell lung cancer: what can we learn from them? J Thorac Oncol. 13(2):148–50. https://doi.org/10.1016/j.jtho.2017.11.004 PMID:29425612

35. Langevin SM, Kelsey KT (2017). Clinical epigenetics of lung cancer. In: Laurence J, Van Beusekom M, editors. Translating epigenetics to the clinic. London, UK: Elsevier; pp. 97–133. https://doi.org/10.1016/B978-0-12-800802-7.00005-8

36. Bojesen SE, Timpson N, Relton C, Davey Smith G, Nordestgaard BG (2017). *AHRR* (cg05575921) hypomethylation marks smoking behaviour, morbidity and mortality. Thorax. 72(7):646–53. https://doi.org/10.1136/thoraxjnl-2016-208789 PMID:28100713

37. Swanton C, Govindan R (2016). Clinical implications of genomic discoveries in lung cancer. N Engl J Med. 374(19):1864–73. https://doi.org/10.1056/NEJMra1504688 PMID:27168435

38. Sun S, Schiller JH, Gazdar AF (2007). Lung cancer in never smokers – a different disease. Nat Rev Cancer. 7(10): 778–90. https://doi.org/10.1038/nrc2190 PMID:17882278

39. Govindan R, Ding L, Griffith M, Subramanian J, Dees ND, Kanchi KL, et al. (2012). Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell. 150(6):1121–34. https://doi.org/10.1016/j.cell.2012.08.024 PMID:22980976

40. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al.; National Lung Screening Trial Research Team (2011). Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 365(5):395–409. https://doi.org/10.1056/NEJMoa1102873 PMID:21714641

41. Wood DE, Kazerooni EA, Baum SL, Eapen GA, Ettinger DS, Hou L, et al. (2018). Lung cancer screening, version 3.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 16(4):412–41. https://doi.org/10.6004/jnccn.2018.0020 PMID:29632061

42. Katki HA, Kovalchik SA, Berg CD, Cheung LC, Chaturvedi AK (2016). Development and validation of risk models to select ever-smokers for CT lung cancer screening. JAMA. 315(21):2300–11. https://doi.org/10.1001/jama.2016.6255 PMID:27179989

43. Tammemagi MC, Lam S (2014). Screening for lung cancer using low dose computed tomography. BMJ. 348:g2253. https://doi.org/10.1136/bmj.g2253 PMID:24865600

44. Sin DD, Tammemagi CM, Lam S, Barnett MJ, Duan X, Tam A, et al. (2013). Pro-surfactant protein B as a biomarker for lung cancer prediction. J Clin Oncol. 31(36):4536–43. https://doi.org/10.1200/JCO.2013.50.6105 PMID:24248694

45. Guida F, Sun N, Bantis LE, Muller DC, Li P, Taguchi A, et al.; Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL) Consortium for Early Detection of Lung Cancer (2018). Assessment of lung cancer risk on the basis of a biomarker panel of circulating proteins. JAMA Oncol. 4(10):e182078. https://doi.org/10.1001/jamaoncol.2018.2078 PMID:30003238

46. Hanash SM, Ostrin EJ, Fahrmann JF (2018). Blood based biomarkers beyond genomics for lung cancer screening. Transl Lung Cancer Res. 7(3):327–35. https://doi.org/10.21037/tlcr.2018.05.13 PMID:30050770

47. Moretti F, D'Antona P, Finardi E, Barbetta M, Dominioni L, Poli A, et al. (2017). Systematic review and critique of circulating miRNAs as biomarkers of stage I-II non-small cell lung cancer. Oncotarget. 8(55):94980–96. https://doi.org/10.18632/oncotarget.21739 PMID:29212284

48. Perez-Rogers JF, Gerrein J, Anderlind C, Liu G, Zhang S, Alekseyev Y, et al.; AEGIS Study Team (2017). Shared gene expression alterations in nasal and bronchial epithelium for lung cancer detection. J Natl Cancer Inst. 109(7):djw327. https://doi.org/10.1093/jnci/djw327 PMID:28376173

49. Billatos E, Vick JL, Lenburg ME, Spira AE (2018). The airway transcriptome as a biomarker for early lung cancer detection. Clin Cancer Res. 24(13):2984–92. https://doi.org/10.1158/1078-0432.CCR-16-3187 PMID:29463557

50. Tammemagi MC, Lam SC, McWilliams AM, Sin DD (2011). Incremental value of pulmonary function and sputum DNA image cytometry in lung cancer risk prediction. Cancer Prev Res (Phila). 4(4): 552–61. https://doi.org/10.1158/1940-6207.CAPR-10-0183 PMID:21411501

51. Muller DC, Johansson M, Brennan P (2017). Lung cancer risk prediction model incorporating lung function: development and validation in the UK Biobank Prospective Cohort Study. J Clin Oncol. 35(8):861–9. https://doi.org/10.1200/JCO.2016.69.2467 PMID:28095156

52. Vargas AJ, Harris CC (2016). Biomarker development in the precision medicine era: lung cancer as a case study. Nat Rev Cancer. 16(8):525–37. https://doi.org/10.1038/nrc.2016.56 PMID:27388699

53. Oudkerk M, Devaraj A, Vliegenthart R, Henzler T, Prosch H, Heussel CP, et al. (2017). European position statement on lung cancer screening. Lancet Oncol. 18(12):e754–66. https://doi.org/10.1016/S1470-2045(17)30861-6 PMID:29208441

54. Parmar C, Grossmann P, Bussink J, Lambin P, Aerts HJWL (2015). Machine learning methods for quantitative radiomic biomarkers. Sci Rep. 5(1):13087. https://doi.org/10.1038/srep13087 PMID:26278466

55. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, et al., editors (2018). SEER cancer statistics review, 1975–2015. Bethesda (MD), USA: National Cancer Institute. Available from: https://seer.cancer.gov/csr/1975_2015/.

56. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al.; CONCORD Working Group (2015). Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet. 385(9972):977–1010. https://doi.org/10.1016/S0140-6736(14)62038-9 PMID:25467588

57. Soo RA, Stone ECA, Cummings KM, Jett JR, Field JK, Groen HJM, et al. (2017). Scientific advances in thoracic oncology 2016. J Thorac Oncol. 12(8):1183–209. https://doi.org/10.1016/j.jtho.2017.05.019 PMID:28579481

5.2 Head and neck cancers
New etiological insights

Laia Alemany Vilches

Devasena Anantharaman (reviewer)
Paul Brennan (reviewer)
C. René Leemans (reviewer)

SUMMARY

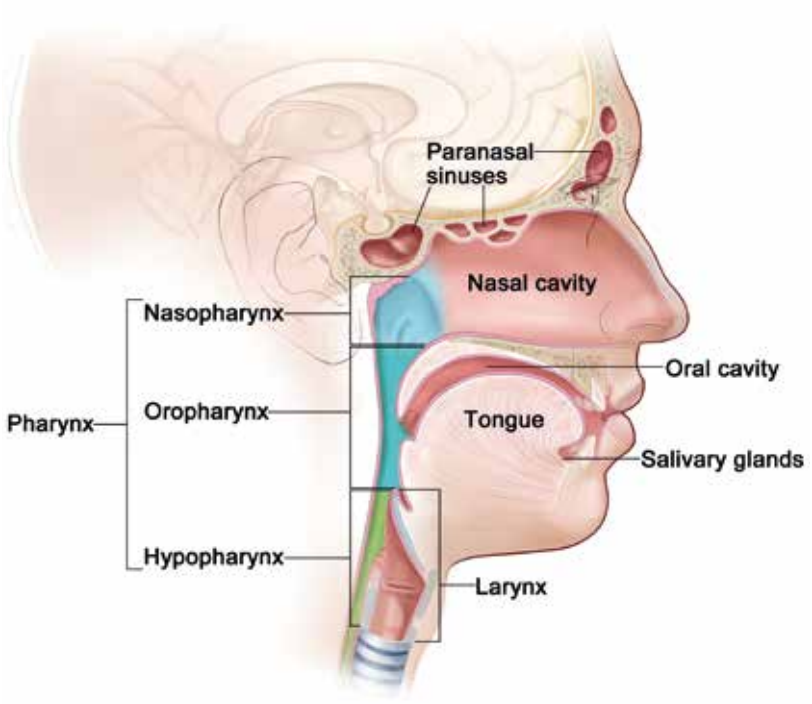
- Worldwide, head and neck cancer is the seventh most common cancer overall (the fifth most common in men and the 12th most common in women), accounting for an estimated 888 000 new cases in 2018.
- In the past 15 years, strong evidence has accumulated that infection with certain human papillomaviruses (HPVs) is etiologically involved in a subset of head and neck cancers, particularly oropharyngeal cancer.
- HPV-related oropharyngeal cancers differ from those that are non-HPV-related, in terms of epidemiological, clinical, and molecular characteristics. HPV-related cases of oropharyngeal cancer have better survival than non-HPV-related cases.
- The main carcinogenic process in HPV-related head and neck cancers is through the action of viral oncoproteins: E6 affects p53 and E7 affects retinoblastoma, disrupting these pathways.
- HPV vaccination is a potential tool for prophylaxis of HPV-related head and neck cancers. There are promising new potential screening and monitoring biomarkers, such as HPV16 E6 serology.

Head and neck cancers originate from squamous cells located in the mucosal epithelium inside the head and neck. They can also begin in the salivary glands, but cancers of the salivary glands are relatively uncommon [1].

Head and neck cancers are further classified by the anatomical area in which they arise (Fig. 5.2.1): (i) oral cavity: lips, front two thirds of the tongue, hard palate, mucosa inside the cheeks, gums, and floor of the mouth; (ii) pharynx: nasopharynx (upper part), oropharynx (middle part, including the soft palate, uvula, the base of the tongue, the tonsils, tonsillar pillars, and oropharyngeal wall), and hypopharynx (lower part); (iii) larynx: located below the pharynx, including the supraglottic and infraglottic areas, with the vocal cords in the middle; (iv) nasal cavity and paranasal sinuses; and (v) salivary glands.

Within these major anatomical areas, the head and neck can be further subdivided into at least 14 subsites, according to the International

Fig. 5.2.1. Major anatomical areas within the head and neck.



Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). These numerous locations give rise to tumours that exhibit heterogeneous pathology.

Epidemiology

Worldwide, head and neck cancer is the seventh most common cancer overall (the fifth most common in men and the 12th most common in women), accounting for an estimated 888 000 new cases in 2018 [2]. The male-to-female incidence ratio is 3:1, and about 70% of new cases occur in low- and middle-income countries. In 2018, there were an estimated 453 000 deaths from head and neck cancer globally. About 75% of those deaths occurred in low- and middle-income countries.

Oral cavity cancer

Almost 50% of head and neck cancers arise in the oral cavity. In 2018, there were an estimated 355 000 new cases and 177 000 deaths worldwide for oral cavity cancer [2]. Of the cancers of anatomical areas in the head and neck, cancer of the oral cavity has the highest age-standardized incidence rate globally for both sexes combined: 4 per 100 000 (Fig. 5.2.2). The highest age-standardized incidence rates (per 100 000) are observed in Papua New Guinea (20.4), Pakistan (12.2), Bangladesh (9.5), India (9.1), Sri Lanka (7.6), and Hungary (7.5). The burden in South and Central Asia (160 000) is more than one third of the global burden of oral cavity cancer. In 2018, India was the country with the highest burden, with 120 000 new cases.

Trends in incidence rates of oral cavity cancer were evaluated for 23 countries across four continents in 1983–2002. In men, incidence rates increased significantly in Denmark, the Netherlands, the United Kingdom, Brazil, and India. In women, the burden is much lower, and incidence rates of oral cavity cancer increased significantly only in European countries [3]. The male-to-female incidence ratio is 2:1 (Fig. 5.2.3).

Pharyngeal cancer

Cancers of the pharynx (nasopharynx, oropharynx, and hypopharynx) together accounted for an estimated 302 000 new cancer cases worldwide in 2018, of which about 40% were nasopharyngeal cancer, about 30% were oropharyngeal cancer, and about 30% were hypopharyngeal cancer [2].

Globally, age-standardized incidence rates for both sexes combined are 1.5 per 100 000 for nasopharyngeal cancer and 2.0 per 100 000 for other pharyngeal cancers (Fig. 5.2.2). The burden of nasopharyngeal cancer falls predominantly on low- and middle-income countries (93% of the worldwide burden), such as countries in East Asia, where almost 50% of the global cases of nasopharyngeal cancer occur. For other pharyngeal cancers, the difference is smaller: 60% of the cases occur in low- and middle-income countries. The male-to-female incidence ratio is 3:1 for nasopharyngeal cancer and 5:1 for other pharyngeal cancers (Fig. 5.2.3). In 2018, there were an estimated 73 000 deaths from nasopharyngeal cancer and 86 000 deaths from other pharyngeal cancers.

In 1970–2007, the age-standardized incidence rates of nasopharyngeal cancer decreased significantly in South and East Asia, North America, and the Nordic countries. The declines in the age-standardized mortality rates in 1970–2013 were even more remarkable and extensive. Decreasing trends in incidence are probably due to tobacco control, changes in dietary patterns, and economic development. Declines in mortality rates are the results of advances in diagnostic and radiotherapy techniques, as well as decreased incidence rates [4]. In 1983–2002, incidence rates of oropharyngeal cancer increased significantly, predominantly in high-income countries and at younger ages [3].

FUNDAMENTALS

- Most head and neck cancers are squamous cell carcinomas of the upper aerodigestive tract: predominantly cancers of the oral cavity, pharynx, and larynx. Other tumours that occur in this anatomical area, such as brain cancer, thyroid cancer, and some melanomas, are not usually included in this category.
- The male-to-female incidence ratio for head and neck cancers is 3:1. These tumours are typically caused by tobacco smoking, alone or in combination with alcohol consumption. In some countries, such as India, oral cavity cancer is mainly caused by betel quid chewing.
- Infection with human papillomaviruses was initially recognized as causing cancers of the oropharynx and the base of the tongue.
- Nasopharyngeal cancers are common in parts of South-East Asia and North Africa; their etiology worldwide involves Epstein–Barr virus, wood dust, formaldehyde, and genetic factors.
- Early-stage tumours of the upper aerodigestive tract can be cured; for late-stage disease, prognosis is poor.

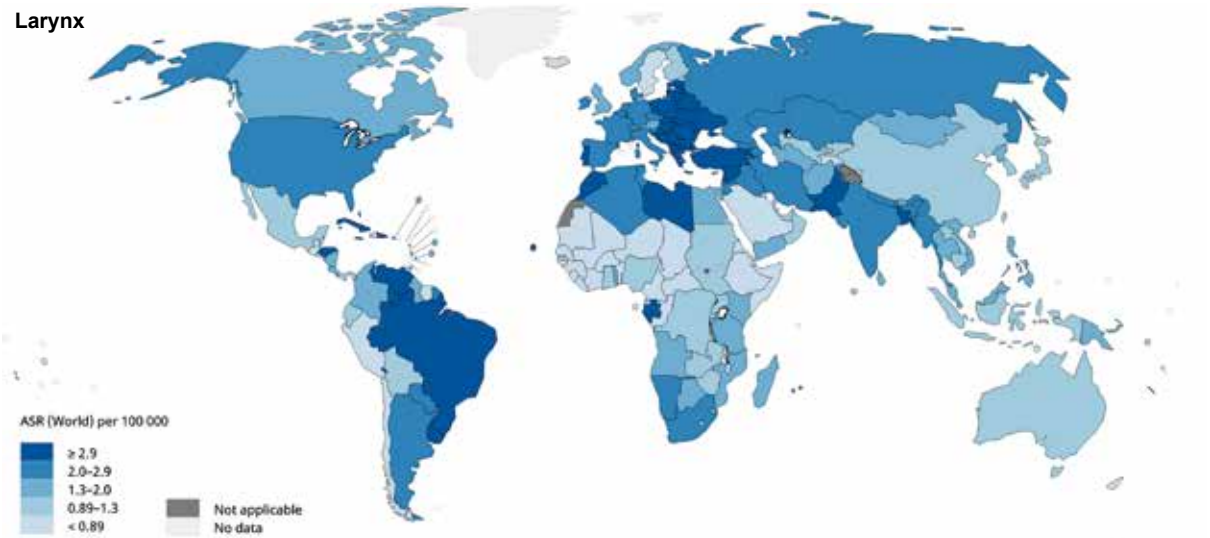
Laryngeal cancer

Laryngeal cancer is the 16th most common cancer in men and is rare in women; the male-to-female incidence ratio is 7:1 (Fig. 5.2.3). In 2018, there were an estimated 177 000 new cases of laryngeal cancer worldwide [2]. About 66% of the new cases occurred in low- and middle-income

Fig. 5.2.2. Global distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000 person-years for head and neck cancers in both sexes, 2018: (A) lip and oral cavity, (B) larynx, (C) nasopharynx, (D) oropharynx, and (E) hypopharynx.

A Lip and oral cavity

B Larynx



C Nasopharynx

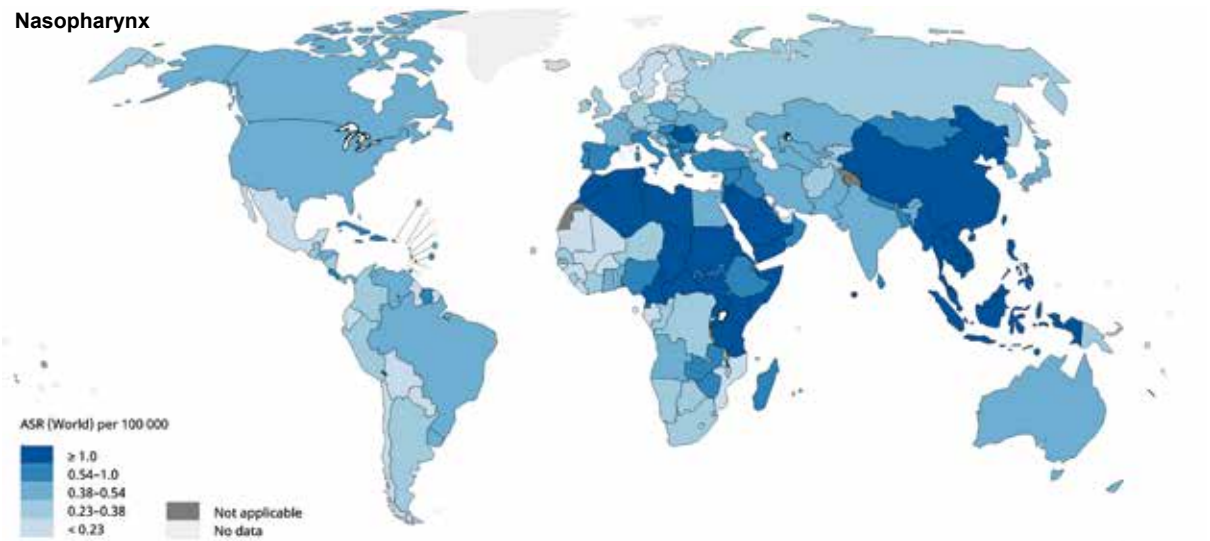
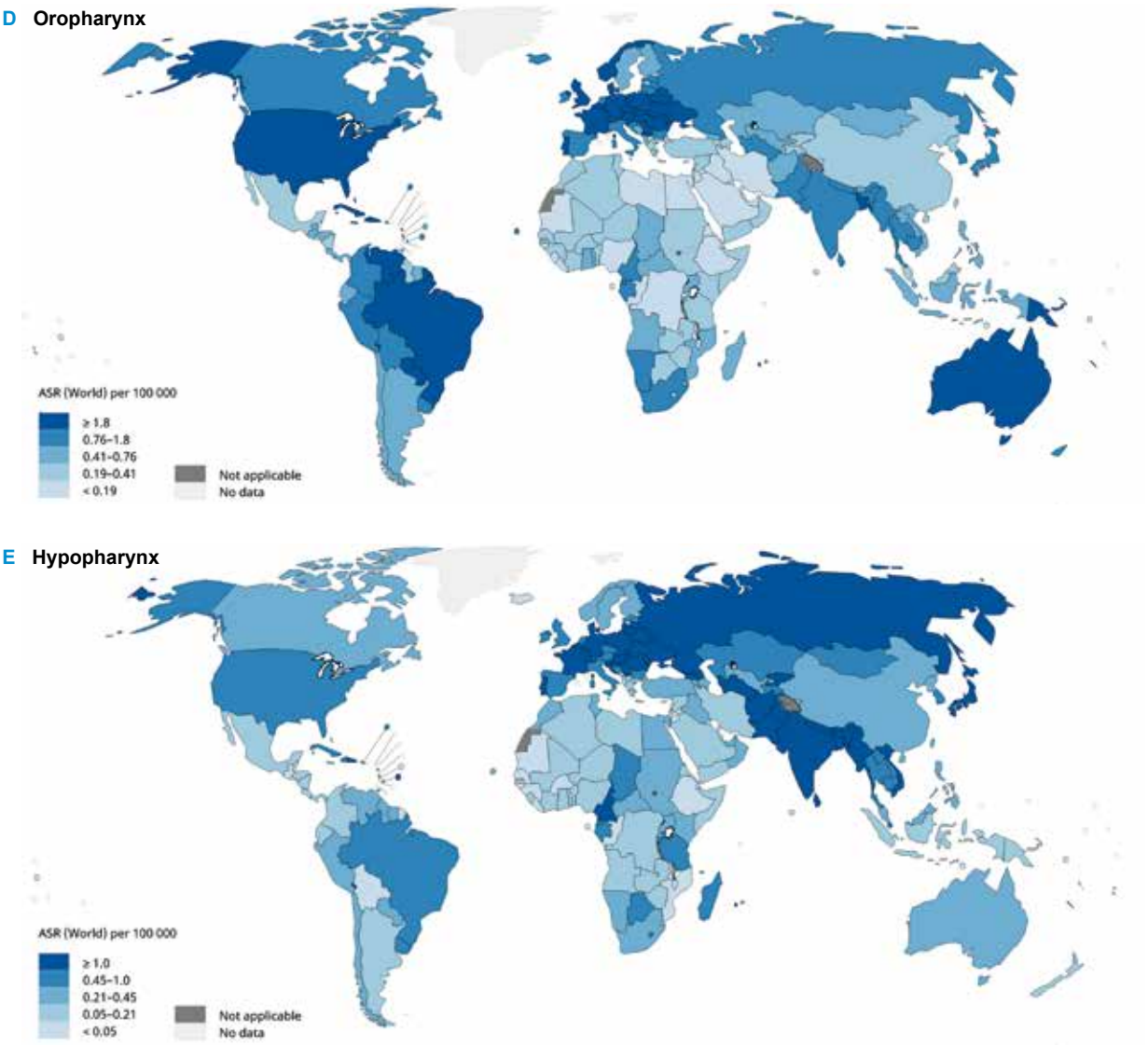


Fig. 5.2.2. Global distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000 person-years for head and neck cancers in both sexes, 2018: (A) lip and oral cavity, (B) larynx, (C) nasopharynx, (D) oropharynx, and (E) hypopharynx.



countries, and about half of the cases occurred in Asia.

Age-standardized incidence rates tend to be higher in the Caribbean and in some countries in eastern Europe (Fig. 5.2.2). In 2018, laryngeal cancer accounted for an estimated 95 000 deaths worldwide. In some countries, such as in most of Europe, a declining trend in incidence and mortality was observed over the past few decades, after favourable changes in tobacco use and, mostly for Mediterranean countries, alcohol consumption [5].

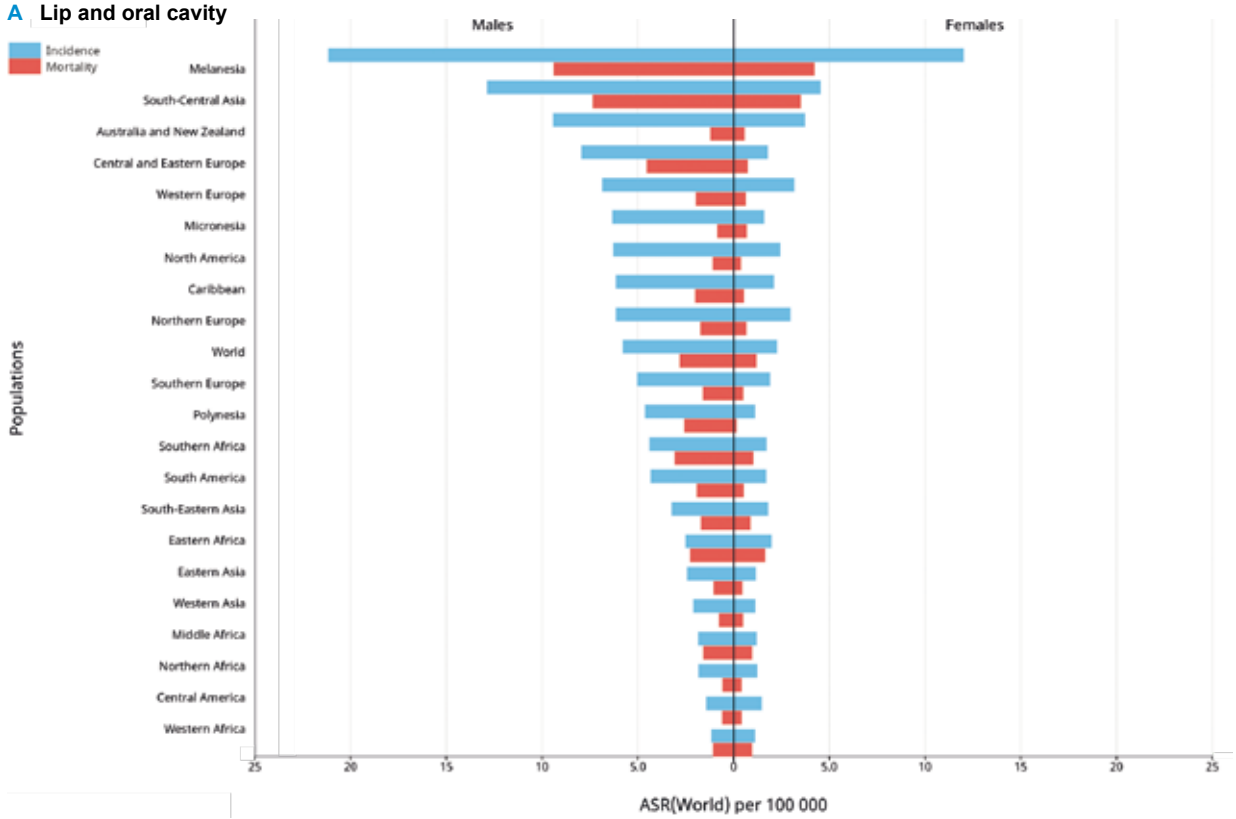
Etiology

Human papillomaviruses

In the past 15 years, strong evidence has accumulated that infection with certain human papillomaviruses (HPVs) is etiologically involved in a subset of head and neck cancers, particularly oropharyngeal cancer [6]. Although almost all squamous cell carcinomas of the cervix are considered to be HPV-driven [7], quantitative assessment of the etiological involvement of HPVs in head and neck cancer is challenging because of their multifactorial etiology, which is largely attributed to tobacco use and alcohol consumption [6,8].

The mere presence of HPV DNA is not sufficient to prove viral causation, because it may reflect only a transient infection unrelated to the carcinogenic process (see Chapter 2.2) [9,10]. Most early studies and meta-analyses assessing the quantitative contribution of HPVs in head and neck cancer used the presence and detection of HPV DNA in the tumour as the sole criterion. To accurately classify a tumour as HPV-driven, it is crucial to

Fig. 5.2.3. Estimated age-standardized (World) incidence and mortality rates (ASR) per 100 000 person-years for head and neck cancers, by sex and region, 2018: (A) lip and oral cavity, (B) larynx, (C) nasopharynx, (D) oropharynx, and (E) hypopharynx.



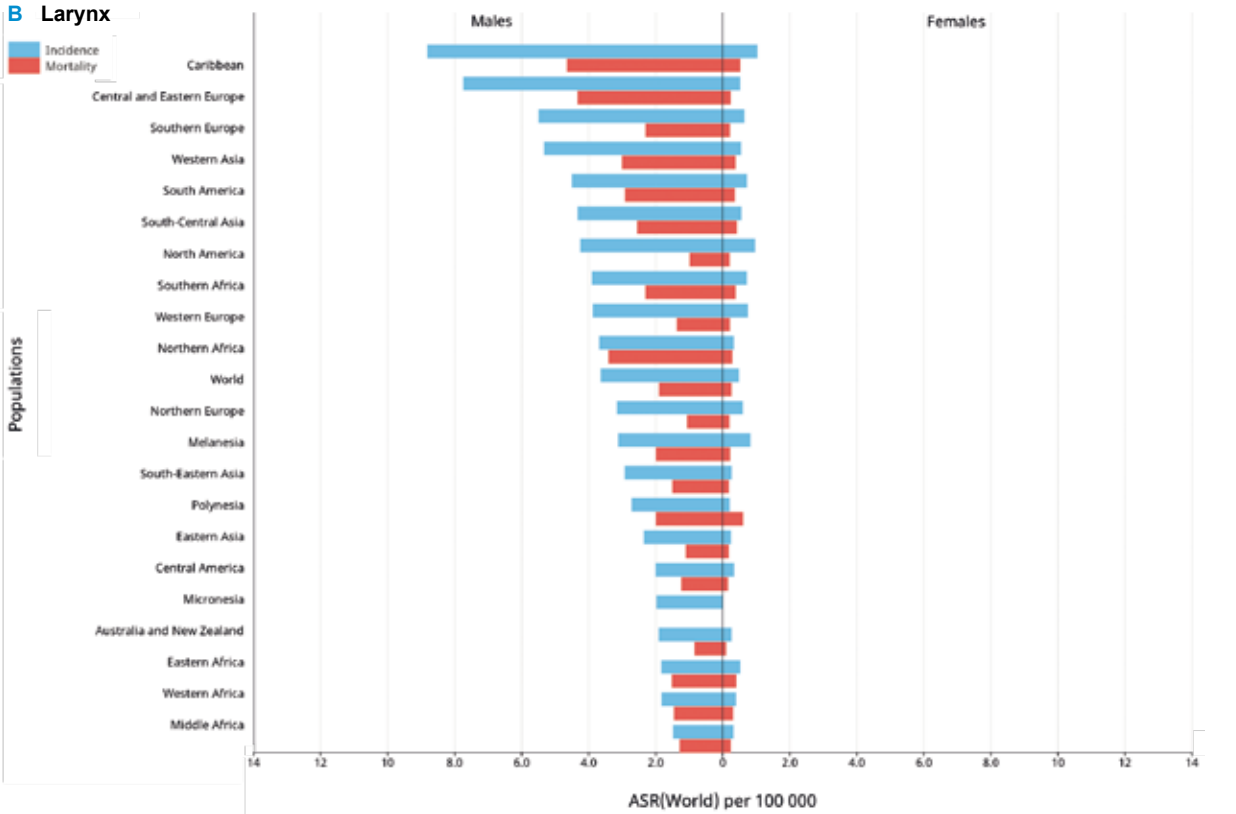
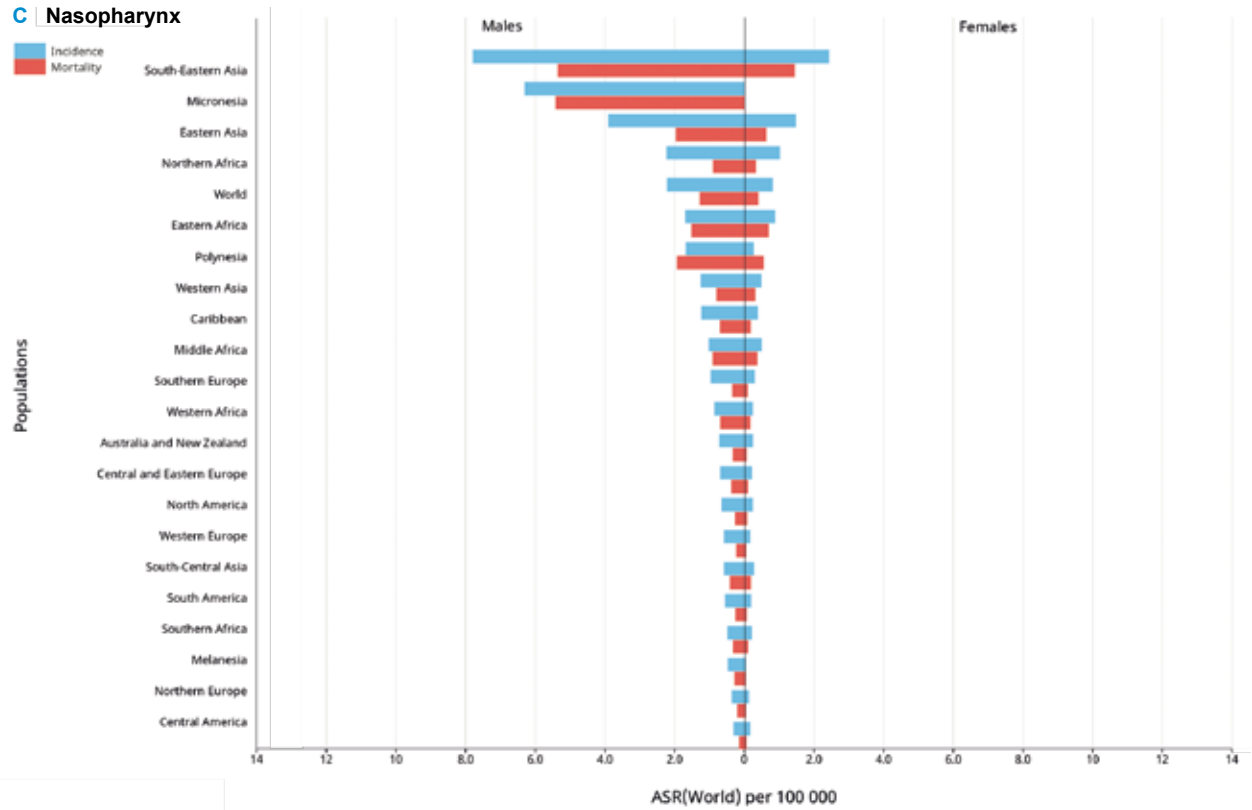


Fig. 5.2.3. Estimated age-standardized (World) incidence and mortality rates (ASR) per 100 000 person-years for head and neck cancers, by sex and region, 2018: (A) lip and oral cavity, (B) larynx, (C) nasopharynx, (D) oropharynx, and (E) hypopharynx.



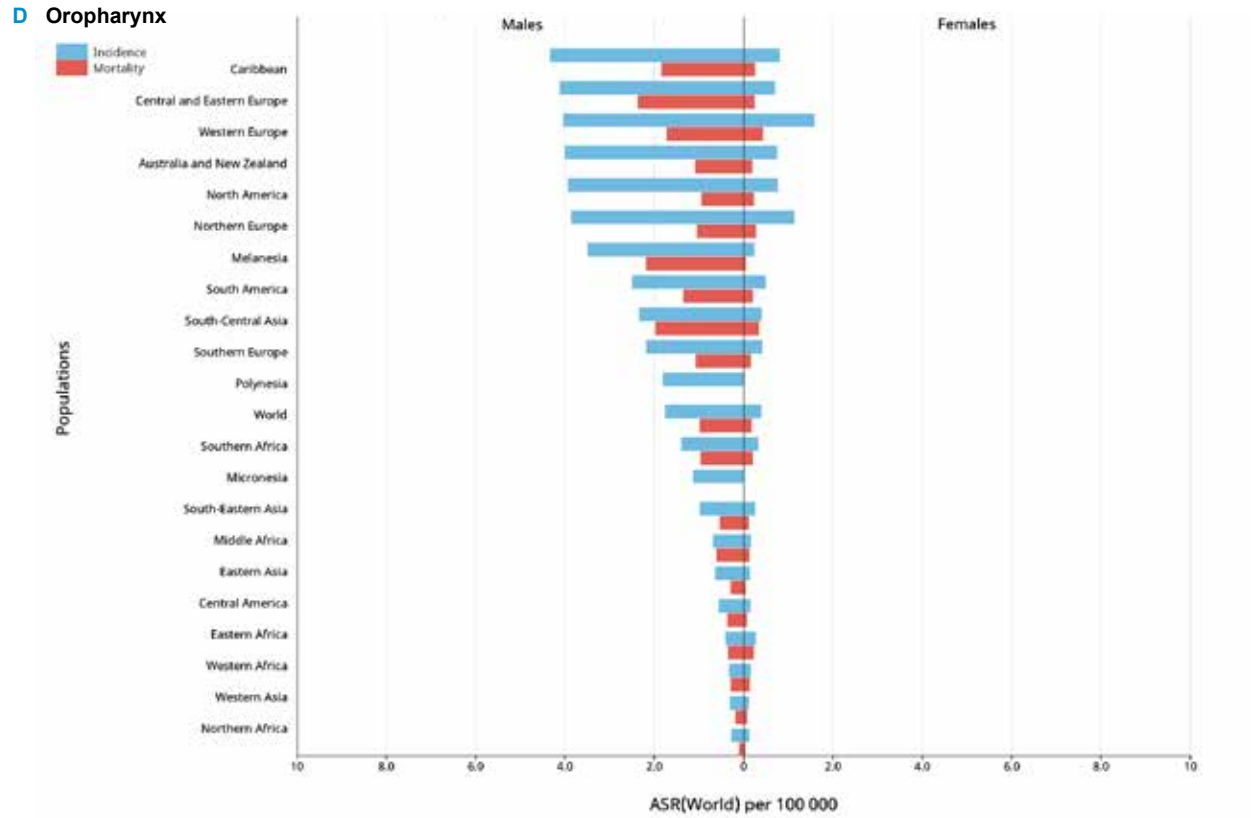
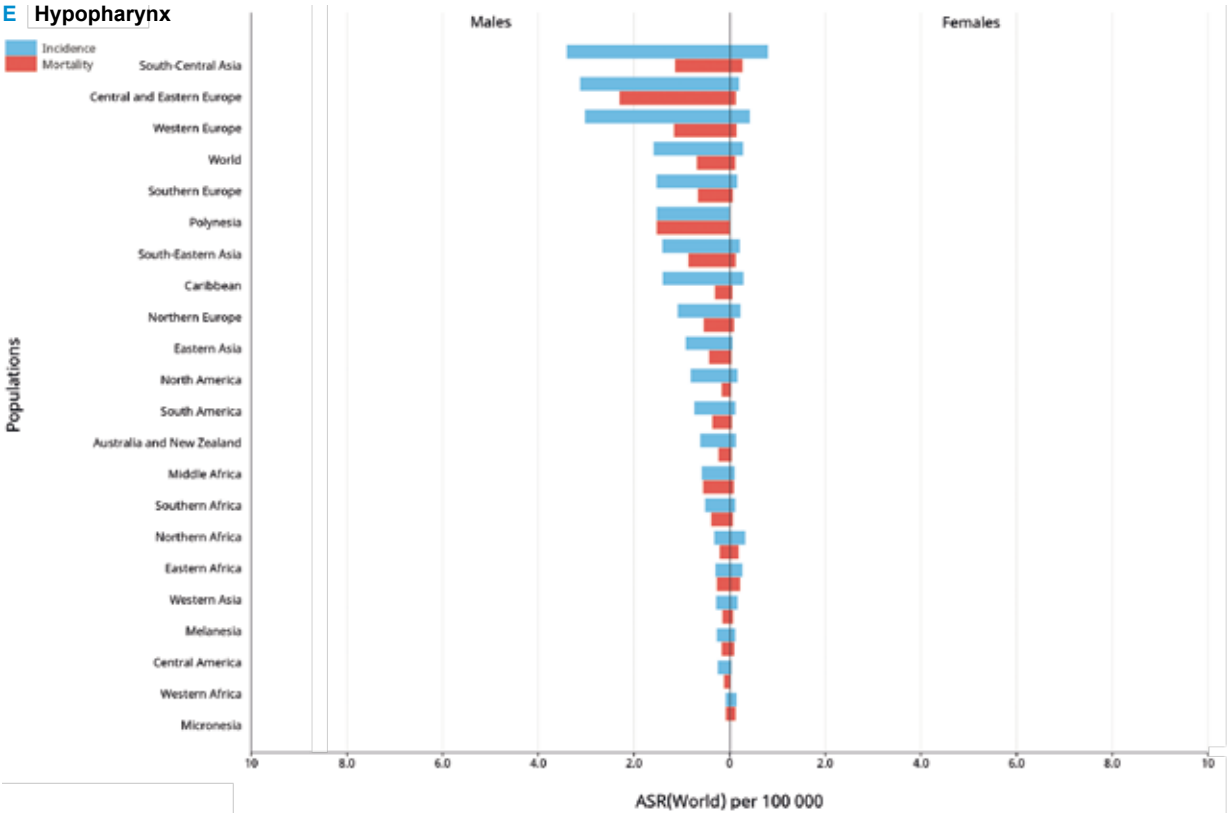


Fig. 5.2.3. Estimated age-standardized (World) incidence and mortality rates (ASR) per 100 000 person-years for head and neck cancers, by sex and region, 2018: (A) lip and oral cavity, (B) larynx, (C) nasopharynx, (D) oropharynx, and (E) hypopharynx.



include other markers related to HPV-induced carcinogenesis, such as $p16^{INK4a}$ and messenger RNA (mRNA) of the viral oncoproteins E6 and E7. A recent systematic review reported on the attributable fractions in head and neck cancers, on the basis of HPV DNA and viral E6/E7 mRNA and the numbers of new cases from the *Cancer Incidence in Five Continents* database (Table 5.2.1) [11].

HPV-related cases of head and neck cancer arise more often in the oropharynx (for which 30.8% of cases are HPV-related), and particularly in the tonsils. Recent estimates showed that previous figures based on HPV DNA for HPV-related oral cavity cancer and laryngeal cancer were overestimated. Currently, the attributable fractions are estimated as 2.2% for oral cavity cancer and 2.4% for laryngeal cancer [11]; these figures have been confirmed with recent comprehensive studies [10].

Globally, approximately 38 000 cases of head and neck cancer are

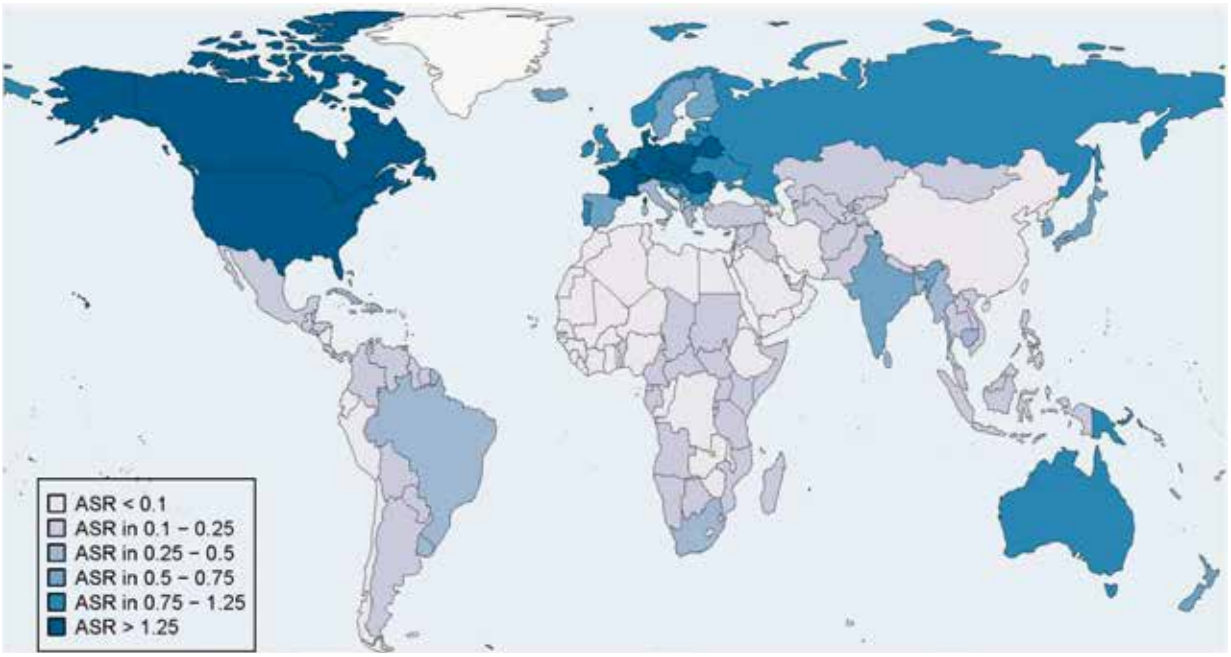
Table 5.2.1. Numbers of new cases of head and neck cancer attributable to human papillomavirus (HPV) infection and corresponding attributable fractions by cancer site, worldwide, 2012[a]

Number or fraction	Cancer site (ICD-10 code)			
	Oral cavity (C02–06)	Oropharynx (C01, C09–10)	Other pharynx (C12–14)	Larynx (C32)
Number of incident cases	200 000	96 000	78 000	160 000
Attributable fraction (%)	2.2	30.8	0	2.4
Number attributable to HPV	4 400	29 000	0	3 800
Number attributable to HPV by sex				
Male	2 900	24 000	0	3 300
Female	1 500	5 500	0	460

ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision.

[a] Numbers are rounded to two significant digits.

Fig. 5.2.4. Global distribution of age-standardized (World) incidence rates (ASR) per 100 000 of head and neck cancer cases (oropharynx, oral cavity, and larynx) attributable to human papillomavirus (HPV) in both sexes, 2012.



HPV-related (Fig. 5.2.4). The burden of HPV-related oropharyngeal cancer is higher in high-income regions such as North America and northern Europe, where HPV-related cancers make up about 70–80% of cases [10–12].

In several countries, particularly in high-income regions, there has been an increasing trend in oropharyngeal cancer, attributed to an increase in HPV-related cases [8,12]. This increasing trend could be explained partly by changes in the prevalence of risk factors, with decreases in tobacco use and changes in sexual behaviour resulting in an increase in the likelihood of oral HPV infection.

There is a greater predominance of HPV16 in head and neck cancers compared with other HPV-related cancers. Globally, 84.9% of HPV-related head and neck cancers are attributable to HPV16/18; for HPV6/11/16/18/31/33/45/52/58, the proportion is 89.7% (Table 5.2.2) [11].

Tobacco use and alcohol consumption

Tobacco use and alcohol consumption are the most important causes of tumours in locations such as the oral cavity, larynx, and hypopharynx and are responsible for a different fraction of oropharyngeal cancers across regions, with a higher attributable fraction in regions with a lower rate of HPV-related cancers. The risk of cancer is higher in heavy smokers, as identified by a high product of smoking rate in packs per day and duration of smoking in years ("pack-years"), and is higher for longer duration of smoking and in smokers of black tobacco (see Chapter 2.1).

Use of chewing tobacco, other smokeless tobacco products, and other substances, such as through betel quid and areca nut chewing, is associated with risk of oral cavity cancer, particularly in India and China, and specifically affects the floor of the mouth and the pharynx.

The interaction between tobacco use and alcohol consumption is greater than additive. For alcohol consumption (see Chapter 2.3), the risk is related to the duration of heavy drinking more than to the quantity consumed per day. The types of interactions between HPV infection and tobacco use and alcohol consumption are still poorly understood. Studies have produced diverse results [8].

Other risk factors

Other risk factors include poor oral hygiene, smoking marijuana, drinking hot beverages such as maté, and some occupational exposures, such as metal smelting and textile production. These etiological agents cause a field cancerization background that produces a high probability of developing second primary cancers at different sites in the head and neck. This is not the case for HPV-related cancers of the head and neck, for which the incidence of second primary cancers is lower than that for non-HPV-related cancers. HPV-related cancers result from a persistent localized epithelial infection, which – if not resolved – may evolve by a transformation process.

Epstein–Barr virus (EBV) is classified by the IARC Monographs as carcinogenic to humans (Group 1) for nasopharyngeal cancers, considering that almost all tumours harbour the EBV genome and express certain

EBV gene products [13]. Other risk factors for nasopharyngeal cancers include genetic susceptibility (the familial relative risk of nasopharyngeal cancer is estimated to be greater than 4–fold) [14]; consumption of preserved foods, particularly Chinese-type salted fish, probably because of their high content of nitrosamines [15]; and, less consistently, other exposures such as tobacco use or, perhaps, alcohol consumption [16,17].

Table 5.2.2. Numbers of cases of head and neck cancer attributable to human papillomavirus (HPV) infection by region and sex, and relative contributions by specific HPV types, worldwide, 2012[a]

Number or proportion	Male	Female
Number attributable to HPV		
Africa	600	230
Asia	9 810	2 200
Americas	7 980	2 180
Europe	11 000	2 800
Oceania	320	90
Less-developed countries	8 600	2 100
More-developed countries	22 000	5 500
Number of cases and proportion among HPV-related cases		
HPV16/18	32 000; 84.9%	
HPV6/11/16/18/31/33/45/52/58	34 000; 89.7%	

[a] Numbers are rounded to two significant digits.

Genetics

HPV-related head and neck cancers are a distinct entity, compared with those that are non-HPV-related, in terms of epidemiological, clinical, and molecular characteristics. The epidemiology has been described above.

Clinically, HPV-related cases of oropharyngeal cancer have better survival than non-HPV-related cases [18]. In HPV-related cancers, $p16^{INK4a}$ is overexpressed through disruption by E7 of the retinoblastoma pathway. The eighth edition of the American Joint Committee on Cancer and Union for International Cancer Control tumour–node–metastasis (TNM) classification presented a different staging system for $p16^{INK4a}$-positive tumours, resulting in a lower stage of these tumours compared with the previous edition [19].

With respect to molecular differences, the main carcinogenic process in HPV-related head and neck cancers is through the action of the viral oncoproteins. E6 binds to and degrades p53, preventing apoptosis, whereas E7 binds to and degrades retinoblastoma, promoting cell proliferation [20]. The genes that are most affected in non-HPV-related head and neck cancers, *TP53* and cyclin-dependent kinase inhibitor 2A (*CDKN2A*), are unaffected in HPV-related tumours. In addition to the actions of the viral oncoproteins, the most common genetic changes in HPV-related tumours are in the phosphoinositide 3-kinase (PI3K) pathway, particularly involving activating mutations and amplifications of the *PIK3CA* oncogene [21]. For some additional alterations, the crucial role as driver events is not yet clear: the losses of chromosomal loci 14q32 and 9q, which contain the tumour necrosis factor receptor-associated factor 3 (*TRAF3*) and ataxia telangiectasia mutated (*ATM*) genes, respectively [22]. Finally, APOBEC has a specific mutational profile in HPV-related tumours, with high cytosine deaminase activity [22].

The driver genes and pathways most affected in non-HPV-related tumours have been reported in the published genomic data, involving 279 cases of head and neck cancer and available data for more than 500 cases from the Cancer Genome Atlas [21]. These data have recently been summarized in a review on genomics in head and neck cancers [23]. The main driver genes implicated in the carcinogenesis of non-HPV-related tumours are summarized in Table 5.2.3.

Genomic profiling is not regularly used at clinics for the management of patients with head and neck cancer. However, such classifications will be more relevant in the future, with increasing information on genetics and potential druggable targets and differential management of patients.

The management of HPV-related oropharyngeal cancers is not modified by the HPV diagnosis, but this information is used for prognostic purposes [24]. In these cancers, an accurate diagnosis of HPV as the main carcinogen of a particular tumour is crucial, because of the new proposals on de-intensification of treatments for HPV-related cancers, which are undergoing evaluation.

The reference standard in assigning HPV causality is detection of E6/E7 mRNA (E6*I mRNA by reverse transcriptase polymerase chain reaction); however, this is a rather complicated technique for routine clinical laboratories [9]. Other alternatives considered are in situ hybridization, which is specific but lacks sensitivity; $p16^{INK4a}$, which has high sensitivity but moderate specificity; and double testing of HPV DNA and $p16^{INK4a}$, which is emerging as the most suitable and reliable strategy for HPV-driven oropharyngeal cancers [24]. In addition, HPV16 E6 serology has recently been proposed as a potential biomarker for diagnosis of HPV-driven oropharyngeal cancers, with good sensitivity and specificity reported, and also as a potential biomarker for prevention and follow-up.

In addition to being useful for HPV diagnosis in HPV-related cancers, genomic profiling reveals interesting patterns. A recent systematic review of the available literature reported the following potential genomic progression models and genomic profiles (Fig. 5.2.5) [23].

HPV-related head and neck cancers

HPV infection in oral squamous epithelium leads mainly to productive

Table 5.2.3. Genes with frequent and highly significant somatic genetic changes in human papillomavirus (HPV)-negative head and neck cancers

Cellular process	Gene	Protein	Type of gene	Mutation frequency (%)	Frequency of copy number alterations (%)
Cell cycle	*TP53*	p53	Tumour suppressor	72	1.4
	CDKN2	$p16^{INK4a}$	Tumour suppressor	22	32
	CCND1	Cyclin D1	Oncogene	0.6	25
Growth signals	*EGFR*	Epidermal growth factor receptor	Oncogene	4	11
Survival	*PIK3CA*	Catalytic p110α subunit of class 1 PI3Ks	Oncogene	18	21
	PTEN	PTEN	Tumour suppressor	3	4
WNT signalling	*FAT1*	Protocadherin FAT1	Tumour suppressor	23	8
	AJUBA	LIM domain-containing protein AJUBA	Tumour suppressor	7[a]	1
	NOTCH1	NOTCH1	Tumour suppressor	18	4
Epigenetic regulation	*KMT2D*	Histone-lysine *N*-methyltransferase KMT2D	Tumour suppressor	16	0.4
	NSD1	Histone-lysine *N*-methyltransferase NSD1	Tumour suppressor	12[a]	0.8

[a] Putative passenger mutation that requires further functional studies.

infections, whereas the viral transformation process more commonly arises from the epithelium of the tonsillar crypts. The tonsillar epithelium may be a non-permissive productive medium in which HPV infection progresses at a higher frequency directly to a transformation process, without a clear pre-neoplastic lesion.

Two genomic profiles can be described for HPV-related cancers on the basis of expression profiling: (i) immune response and mesenchymal cell differentiation, indicated by enrichment of 16q losses; and (ii) keratinocyte differentiation and oxidative reduction process, indicated by enrichment of 3q copy number alterations (CNA) and *PIK3CA* mutations [25]. There is no evidence that these two groups behave differently in terms of survival.

Non-HPV-related head and neck cancers

Although a high proportion of cases present with tumours de novo, there are precancerous lesions that are visible, such as leukoplakia and erythroplakia lesions, and many invisible pre-malignant lesions are also identified microscopically as dysplastic mucosal epithelium.

Two potential genomic profiles can be identified for non-HPV-related cancers: (i) a profile presumably related to ageing, with CNA-silent tumours, wild-type *TP53*, and *HRAS* and *CASP8* mutations; and (ii) a tobacco-related profile, in which deregulation of the cell cycle by abrogation of the retinoblastoma and p53 pathways seems to occur at the very beginning of the carcinogenic process. The first profile seems to have better prognosis than the second. Within the second group, at least three subgroups can be identified on the basis of expression profiling: classical, basal, and mesenchymal. The classical subgroup is characterized by mutations of the nuclear factor erythroid 2-related factor 2 (*NFE2L2*) pathway. More subgroups may exist, and further research is required, also on the clinical implications [26–28].

Finally, it is noteworthy that immune checkpoint inhibitors have recently emerged as novel potential therapeutic options [29,30].

Prevention and monitoring biomarkers

Early-stage tumours of the upper aerodigestive tract can be cured; for late-stage disease, prognosis is poor. For non-HPV-related cancers, prevention strategies could include oral cancer screening through visual oral examination, which has been demonstrated to result in a lower mortality rate in a randomized controlled trial setting.

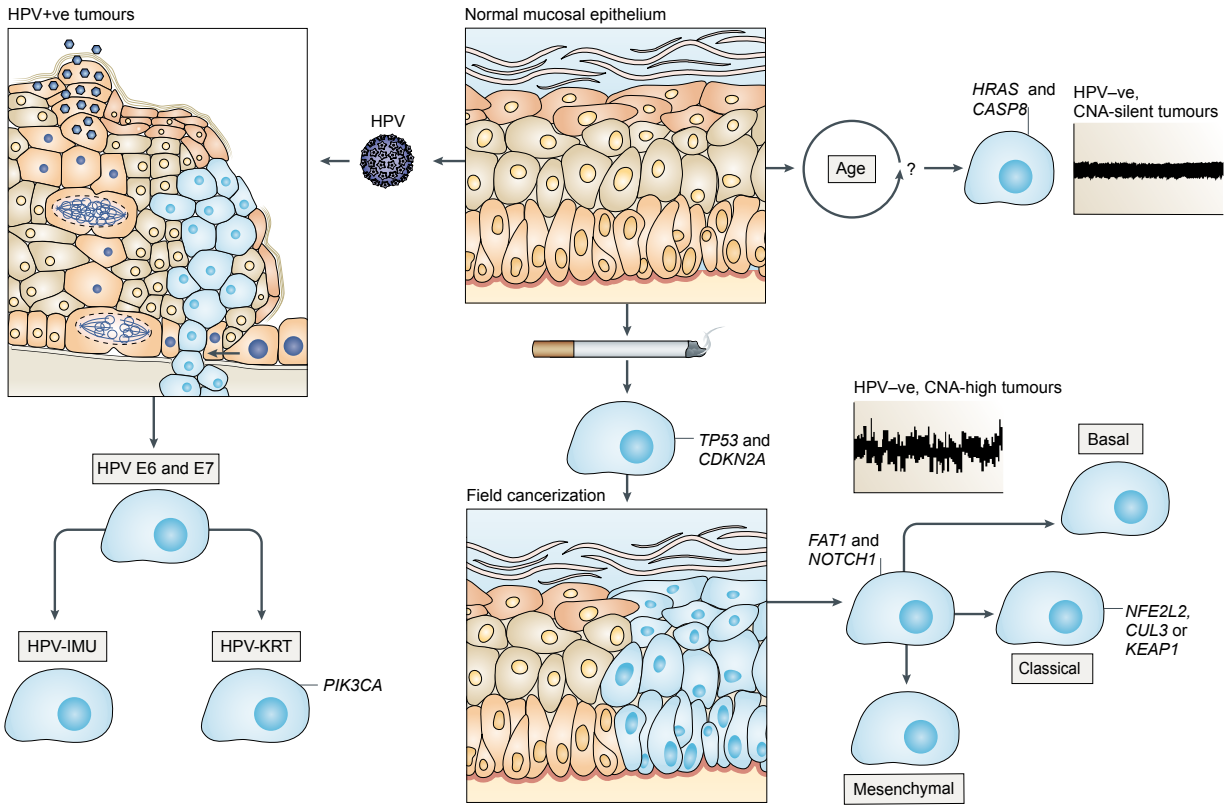
Options for prevention of head and neck cancer depend on the type of etiological factor involved in various situations and the type of prevention.

Primary prevention

The aim of primary prevention is to intervene before health effects occur. Globally, the burden of cancers attributable to tobacco use has been reduced in some world regions as a result of intensive campaigns to prevent and reduce tobacco use. Reduced alcohol consumption may also be a consideration.

An increasing proportion of cases, such as those of oropharyngeal

Fig. 5.2.5. Genomic carcinogenesis models of head and neck squamous cell carcinoma. CNA, copy number alterations; HPV, human papillomavirus; IMU, immune response and mesenchymal cell differentiation; KRT, keratinocyte differentiation and oxidative reduction process.



cancer, are caused by other agents, such as HPV. Therefore, HPV vaccination is a potential tool for primary prevention (see Chapter 6.3). Only one study has reported on the efficacy of the bivalent HPV vaccine as prophylaxis against oral infection [31]. In the context of this vaccine clinical trial in women aged 18–25 years, the estimated efficacy of the vaccine in reducing oral HPV infection was 93.3% (95% confidence interval, 63–100%) [31].

Two recently published studies have assessed the effectiveness of the quadrivalent HPV vaccine in reducing oral HPV infection [32,33]. The first study included 3040 people aged 18–30 years who participated in the National Health and Nutrition Examination Survey (NHANES) in the USA in 2009–2014 [32]. Vaccinated individuals had a significantly lower prevalence of oral HPV6/11/16/18 infections compared with non-vaccinated individuals (1.99% vs 3.52%; $P = 0.04$). The second study analysed data from 2627 people aged 18–33 years who participated in NHANES in 2011–2014 [33]. The prevalence of oral HPV6/11/16/18 infections was significantly lower in vaccinated individuals than in non-vaccinated individuals (0.11% vs 1.61%; $P = 0.008$), corresponding to an estimated reduction in prevalence of 88.2% (95% confidence interval, 5.7–98.5%) after adjustment for age, sex, and race.

Screening

Because a considerable proportion of cases are diagnosed at locally advanced stages, screening (secondary prevention) for early detection of disease is of great importance.

Early detection strategies based on cytology, such as for cervical cancer, have not been proven to be successful for head and neck cancer. However, repeated visual oral examination has been demonstrated to have long-term effects in reducing oral cancer incidence and mortality in a randomized trial in India; this result supports the introduction of visual oral screening, particularly targeting users of smoking or chewing tobacco, alcohol drinkers, or both in high-incidence countries [34].

Serological detection of antibodies against HPV (anti-HPV16 E6) has recently been postulated as a potential biomarker for HPV-related oropharyngeal cancer. In cohort studies, seroconversion has been detected up to 10 years before the diagnosis of oropharyngeal cancer [35]. This observation is very relevant given that it is not yet known what the pre-neoplastic lesion of oropharyngeal cancer is. However, there are still many gaps in knowledge that must be filled,

such as determining the best clinical triage algorithm for identifying potential lesions once an HPV-positive case has been detected, among other considerations.

Monitoring biomarkers

The prognostic value of monitoring anti-HPV antibody titres throughout a patient's treatment in the survival-free period of disease is not well characterized. So far, only three studies have provided information on this topic. Two of the studies observed an association of increased levels of antibodies in blood with increased risk of recurrence, and the third study did not observe differences [36–38]. In relation to the persistence of viral HPV DNA in oral rinses after treatment, one study reported that persistence could be linked with the incidence of recurrence [39].

In 2015, a study explored tumour-specific DNA as a biomarker detected in saliva or plasma for head and neck cancer by searching for somatic mutations or HPV genes (collectively referred to as tumour DNA) in 93 cases [40]. The fraction of patients with detectable tumour DNA was 100% for early-stage disease and 95% for late-stage disease. Saliva was observed to be preferentially enriched for tumour DNA from the oral cavity, whereas plasma was preferentially enriched for tumour DNA from the other sites. Tumour DNA in saliva was found after surgery in three patients before clinical diagnosis of recurrence, but in none of the five patients without recurrence. These findings, if confirmed, have direct implications in the follow-up and clinical management of patients.

References

1. NCI (2018). Head and neck cancer. United States National Cancer Institute, National Institutes of Health. Available from: https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593
3. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. (2013). Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol. 31(36):4550–9. https://doi.org/10.1200/JCO.2013.50.3870 PMID:24248688
4. Tang LL, Chen WQ, Xue WQ, He YQ, Zheng RS, Zeng YX, et al. (2016). Global trends in incidence and mortality of nasopharyngeal carcinoma. Cancer Lett. 374(1):22–30. https://doi.org/10.1016/j.canlet.2016.01.040 PMID:26828135
5. Chatenoud L, Garavello W, Pagan E, Bertuccio P, Gallus S, La Vecchia C, et al. (2016). Laryngeal cancer mortality trends in European countries. Int J Cancer. 138(4):833–42. https://doi.org/10.1002/ijc.29833 PMID:26335030
6. IARC (2007). Human papillomaviruses. IARC Monogr Eval Carcinog Risks Hum. 90:1–636. Available from: http://publications.iarc.fr/108 PMID:18354839
7. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 189(1):12–9. https://doi.org/10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F PMID:10451482
8. Gillison ML, Alemany L, Snijders PJ, Chaturvedi A, Steinberg BM, Schwartz S, et al. (2012). Human papillomavirus and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. Vaccine. 30(Suppl 5):F34–54. https://doi.org/10.1016/j.vaccine.2012.05.070 PMID:23199965
9. Holzinger D, Schmitt M, Dyckhoff G, Benner A, Pawlita M, Bosch FX (2012). Viral RNA patterns and high viral load reliably define oropharynx carcinomas with active HPV16 involvement. Cancer Res. 72(19):4993–5003. https://doi.org/10.1158/0008-5472.CAN-11-3934 PMID:22991302
10. Castellsagué X, Alemany L, Quer M, Halec G, Quirós B, Tous S, et al.; ICO International HPV in Head and Neck Cancer Study Group (2016). HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients. J Natl Cancer Inst. 108(6):djv403. https://doi.org/10.1093/jnci/djv403 PMID:26823521
11. de Martel C, Plummer M, Vignat J, Franceschi S (2017). Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 141(4):664–70. https://doi.org/10.1002/ijc.30716 PMID:28369882
12. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. (2011). Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 29(32):4294–301. https://doi.org/10.1200/JCO.2011.36.4596 PMID:21969503
13. IARC (2012). Biological agents. IARC Monogr Eval Carcinog Risks Hum. 100B:1–441. Available from: http://publications.iarc.fr/119 PMID:23189750
14. Liu Z, Chang ET, Liu Q, Cai Y, Zhang Z, Chen G, et al. (2017). Quantification of familial risk of nasopharyngeal carcinoma in a high-incidence area. Cancer. 123(14):2716–25. https://doi.org/10.1002/cncr.30643 PMID:28241094
15. IARC (2012). Personal habits and indoor combustions. IARC Monogr Eval Carcinog Risks Hum. 100E:1–575. Available from: http://publications.iarc.fr/122 PMID:23193840
16. Chua MLK, Wee JTS, Hui EP, Chan ATC (2016). Nasopharyngeal carcinoma. Lancet. 387(10022):1012–24. https://doi.org/10.1016/S0140-6736(15)00055-0 PMID:26321262
17. Tsao SW, Yip YL, Tsang CM, Pang PS, Lau VMY, Zhang G, et al. (2014). Etiological factors of nasopharyngeal carcinoma. Oral Oncol. 50(5):330–8. https://doi.org/10.1016/j.oraloncology.2014.02.006 PMID:24630258
18. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. (2010). Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 363(1):24–35. https://doi.org/10.1056/NEJMoa0912217 PMID:20530316
19. Brierly JD, Gospodarowicz MK, Wittekind C, editors (2017). TNM classification of malignant tumours. 8th ed. Oxford, UK: Wiley Blackwell.
20. Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, et al. (2012). The biology and life-cycle of human papillomaviruses. Vaccine. 30(Suppl 5):F55–70. https://doi.org/10.1016/j.vaccine.2012.06.083 PMID:23199966

21. The Cancer Genome Atlas Network (2015). Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 517(7536):576–82. https://doi.org/10.1038/nature14129 PMID:25631445

22. Hayes DN, Van Waes C, Seiwert TY (2015). Genetic landscape of human papillomavirus-associated head and neck cancer and comparison to tobacco-related tumors. J Clin Oncol. 33(29):3227–34. https://doi.org/10.1200/JCO.2015.62.1086 PMID:26351353

23. Leemans CR, Snijders PJF, Brakenhoff RH (2018). The molecular landscape of head and neck cancer. Nat Rev Cancer. 18(5):269–82. https://doi.org/10.1038/nrc.2018.11 PMID:29497144

24. Prigge ES, Arbyn M, von Knebel Doeberitz M, Reuschenbach M (2017). Diagnostic accuracy of $p16^{INK4a}$ immunohistochemistry in oropharyngeal squamous cell carcinomas: a systematic review and meta-analysis. Int J Cancer. 140(5):1186–98. https://doi.org/10.1002/ijc.30516 PMID:27859245

25. Zhang Y, Koneva LA, Virani S, Arthur AE, Virani A, Hall PB, et al. (2016). Subtypes of HPV-positive head and neck cancers are associated with HPV characteristics, copy number alterations, *PIK3CA* mutation, and pathway signatures. Clin Cancer Res. 22(18):4735–45. https://doi.org/10.1158/1078-0432.CCR-16-0323 PMID:27091409

26. Chung CH, Parker JS, Karaca G, Wu J, Funkhouser WK, Moore D, et al. (2004). Molecular classification of head and neck squamous cell carcinomas using patterns of gene expression. Cancer Cell. 5(5):489–500. https://doi.org/10.1016/S1535-6108(04)00112-6 PMID:15144956

27. Walter V, Yin X, Wilkerson MD, Cabanski CR, Zhao N, Du Y, et al. (2013). Molecular subtypes in head and neck cancer exhibit distinct patterns of chromosomal gain and loss of canonical cancer genes. PLoS One. 8(2):e56823. https://doi.org/10.1371/journal.pone.0056823 PMID:23451093

28. Keck MK, Zuo Z, Khattri A, Stricker TP, Brown CD, Imanguli M, et al. (2015). Integrative analysis of head and neck cancer identifies two biologically distinct HPV and three non-HPV subtypes. Clin Cancer Res. 21(4):870–81. https://doi.org/10.1158/1078-0432.CCR-14-2481 PMID:25492084

29. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al. (2016). Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 375(19):1856–67. https://doi.org/10.1056/NEJMoa1602252 PMID:27718784

30. Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, et al. (2016). Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol. 17(7):956–65. https://doi.org/10.1016/S1470-2045(16)30066-3 PMID:27247226

31. Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, et al.; CVT Vaccine Group (2013). Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. PLoS One. 8(7):e68329. https://doi.org/10.1371/journal.pone.0068329 PMID:23873171

32. Hirth JM, Chang M, Resto VA, Guo F, Berenson AB; HPV Study Group (2017). Prevalence of oral human papillomavirus by vaccination status among young adults (18–30 years old). Vaccine. 35(27):3446–51. https://doi.org/10.1016/j.vaccine.2017.05.025 PMID:28526331

33. Chaturvedi AK, Graubard BI, Broutian T, Pickard RKL, Tong ZY, Xiao W, et al. (2018). Effect of prophylactic human papillomavirus (HPV) vaccination on oral HPV infections among young adults in the United States. J Clin Oncol. 36(3):262–7. https://doi.org/10.1200/JCO.2017.75.0141 PMID:29182497

34. Sankaranarayanan R, Ramadas K, Thara S, Muwonge R, Thomas G, Anju G, et al. (2013). Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India. Oral Oncol. 49(4):314–21. https://doi.org/10.1016/j.oraloncology.2012.11.004 PMID:23265945

35. Kreimer AR, Johansson M, Waterboer T, Kaaks R, Chang-Claude J, Drogen D, et al. (2013). Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer. J Clin Oncol. 31(21):2708–15. https://doi.org/10.1200/JCO.2012.47.2738 PMID:23775966

36. Koslabova E, Hamsikova E, Salakova M, Klozar J, Foltynova E, Salkova E, et al. (2013). Markers of HPV infection and survival in patients with head and neck tumors. Int J Cancer. 133(8):1832–9. https://doi.org/10.1002/ijc.28194 PMID:23564321

37. Fakhry C, Qualliotine JR, Zhang Z, Agrawal N, Gaykalova DA, Bishop JA, et al. (2016). Serum antibodies to HPV16 early proteins warrant investigation as potential biomarkers for risk stratification and recurrence of HPV-associated oropharyngeal cancer. Cancer Prev Res (Phila). 9(2):135–41. https://doi.org/10.1158/1940-6207.CAPR-15-0299 PMID:26701665

38. Lang Kuhs KA, Kreimer AR, Trivedi S, Holzinger D, Pawlita M, Pfeiffer RM, et al. (2017). Human papillomavirus 16 E6 antibodies are sensitive for human papillomavirus-driven oropharyngeal cancer and are associated with recurrence. Cancer. 123(22):4382–90. https://doi.org/10.1002/cncr.30966 PMID:28950407

39. Rettig EM, Wentz A, Posner MR, Gross ND, Haddad RI, Gillison ML, et al. (2015). Prognostic implication of persistent human papillomavirus type 16 DNA detection in oral rinses for human papillomavirus-related oropharyngeal carcinoma. JAMA Oncol. 1(7):907–15. https://doi.org/10.1001/jamaoncol.2015.2524 PMID:26226294

40. Wang Y, Springer S, Mulvey CL, Silliman N, Schaefer J, Sausen M, et al. (2015). Detection of somatic mutations and HPV in the saliva and plasma of patients with head and neck squamous cell carcinomas. Sci Transl Med. 7(293):293ra104. https://doi.org/10.1126/scitranslmed.aaa8507 PMID:26109104

5.3 Oesophageal cancer
A tale of two malignancies

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SUMMARY

- Oesophageal cancer is the sixth most common cause of cancer death worldwide, and it is an important global health challenge.
- Oesophageal squamous cell carcinoma and oesophageal adenocarcinoma are very different diseases that occur in the same organ; they have distinct biological characteristics, geographical distributions, risk factors, and time trends.
- The eastern coast of Africa is a recognized area of high risk for oesophageal squamous cell carcinoma. Unique to this high-risk corridor is that up to 20% of cases occur in people younger than 40 years.
- Genome-wide association studies of both types of oesophageal cancer have identified a modest number of germline polymorphisms associated with risk of these tumours, but genetic predisposition has not been definitively characterized. High rates of *TP53* mutations occur in both tumour types in most, but not all, populations.
- Tobacco use and alcohol consumption are the known and primary causes of oesophageal squamous cell carcinoma, particularly in low-incidence countries. Other risk factors may be more important in high-incidence regions of Asia and Africa, including poor diet, indoor air pollution, consumption of hot beverages, poor oral health, use of non-piped water, and opium use.
- Evaluations of preventive strategies are under way for both types of oesophageal cancer, including efforts to reduce exposure to known carcinogens, chemoprevention trials, and development of effective early detection and treatment protocols for populations at high risk.

Oesophageal cancer is the eighth most common cancer and the sixth most common cause of cancer death worldwide, and it is an important global health challenge [1]. The two histological types of oesophageal cancer differ in the populations that are affected and have completely distinct biological characteristics, geographical distributions, risk factors, and time trends [2,3].

Five-year survival rates for oesophageal cancer are about 20% in Europe and the USA and less than 5% in low- and middle-income countries [1], mainly because of the late occurrence of symptoms and the consequent usually advanced stage at diagnosis. Therefore, identifying and reducing exposure to modifiable risk factors (primary prevention) and development and implementation of practical and accurate methods for early detection and treatment (secondary prevention) are the most important strategies to reduce the burden of this fatal cancer [1].

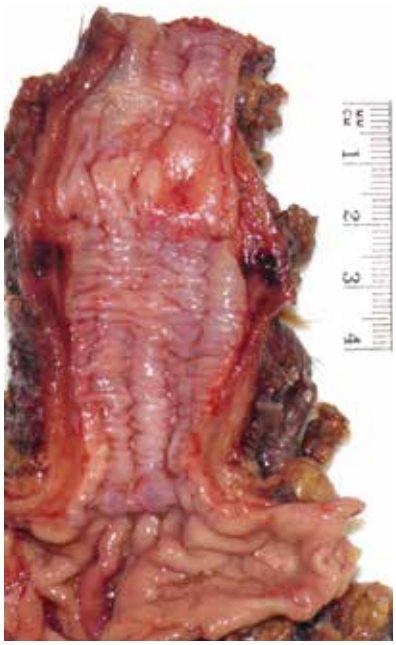
Molecular characteristics

Oesophageal cancer has two main histological types: oesophageal squamous cell carcinoma (Fig. 5.3.1) and oesophageal adenocarcinoma. There are molecular similarities between squamous cell carcinoma of the oesophagus and squamous cancers of other organs, and between oesophageal adenocarcinoma and stomach adenocarcinoma, but there are significant molecular differences at both the genomic and epigenomic levels between oesophageal squamous cell carcinoma and oesophageal adenocarcinoma [4]. These two cancer types have different sets of driver genes, mutational signatures, and prognostic biomarkers, which are almost mutually exclusive [4]. Recently, several mutations and mutational signatures have been correlated with the overall survival of patients with oesophageal cancer; in the future, these may serve as prognostic biomarkers [4].

Epidemiology

In 2012, there were an estimated 398 000 new cases of oesophageal squamous cell carcinoma and 52 000 new cases of oesophageal adenocarcinoma worldwide, corresponding to global incidence rates

Fig. 5.3.1. Oesophageal squamous cell carcinoma. Macroscopic appearance of a mid-oesophageal mass.



of 5.2 per 100 000 for oesophageal squamous cell carcinoma and 0.7 per 100 000 for oesophageal adenocarcinoma [2]. Oesophageal squamous cell carcinoma makes up about 87% of all cases of oesophageal cancer globally; more than half of the cases occur in China, and 25% occur in India, South-East Asia, and Central Asia [2]. For oesophageal adenocarcinoma, about 44% of the global burden occurs in North America and western Europe [2].

The global distribution of age-standardized incidence rates for oesophageal cancer is shown in Fig. 5.3.2. The incidence of oesophageal squamous cell carcinoma is remarkably uneven geographically, with a 21-fold difference between the countries with the lowest and the highest incidence rates. The incidence of oesophageal squamous cell carcinoma is very high within sharply defined regions in the north-eastern Islamic Republic of Iran, Central Asia, north-central China, East Africa, southern Africa, and southern South America [1,2]. Unique to the African high-risk corridor is that large numbers (up to 20%) of cases occur in people younger than 40 years [5]. Worldwide, the male-to-female incidence ratio is 2.7:1 for oesophageal squamous cell carcinoma and 4.4:1 for oesophageal adenocarcinoma [2].

Genetics and genomics

A moderate familial susceptibility to oesophageal cancer has been reported for both oesophageal squamous cell carcinoma and oesophageal adenocarcinoma; this is thought to be at least partially due to the inheritance of susceptibility alleles [3].

Genome-wide association studies for oesophageal squamous cell carcinoma [6] and oesophageal adenocarcinoma [7] have identified a modest number of germline polymorphisms associated with risk of these tumours, but neither disease has been studied in large enough numbers to comprehensively define genetic predisposition overall or in different ethnic groups. Several rare, high-penetrance genetic defects, such as tylosis and Fanconi anaemia, have been linked to high risk of oesophageal squamous cell carcinoma, but they explain only a small fraction of cases.

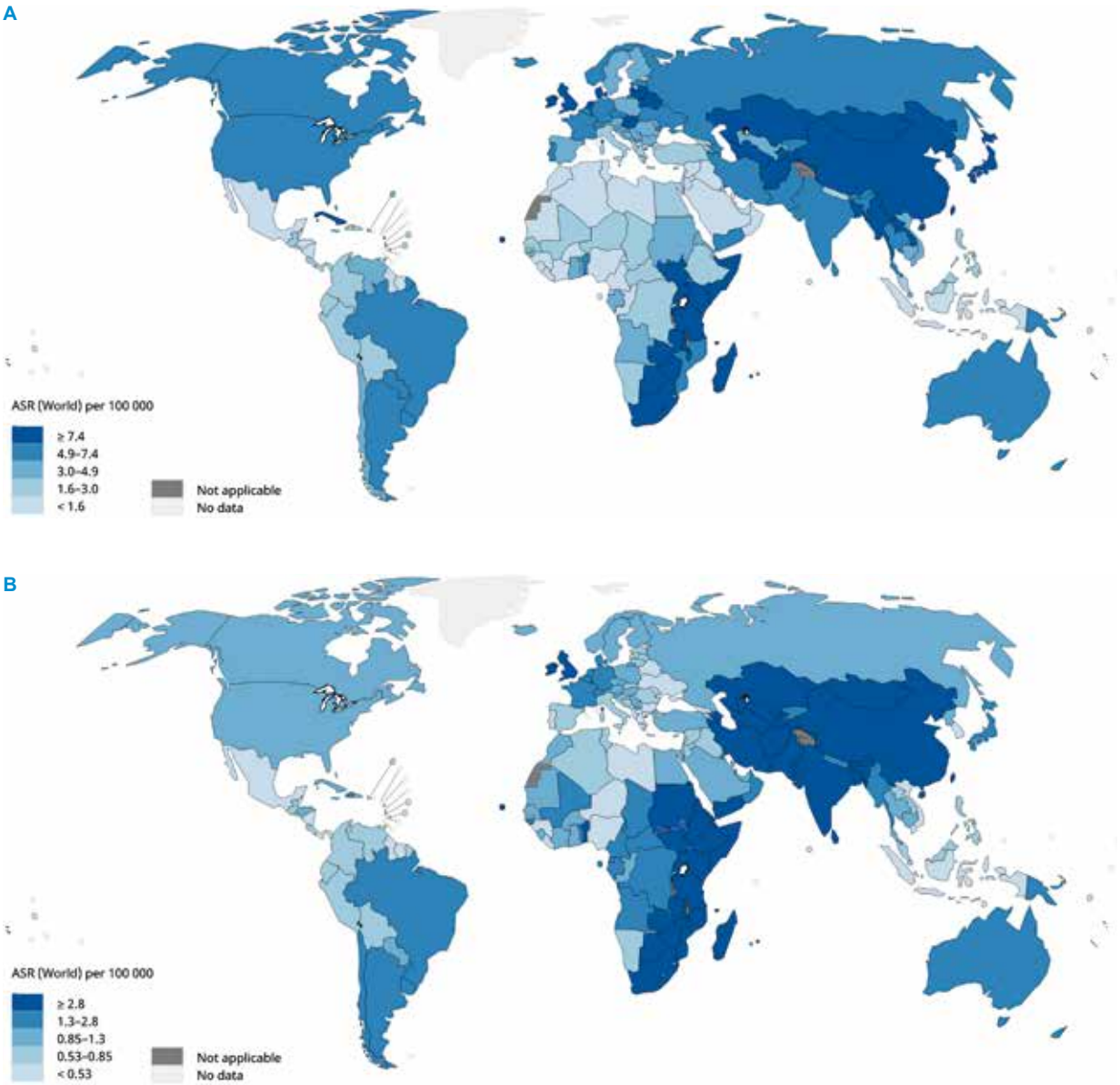
Whole-genome and whole-exome sequencing of paired tumour and normal tissues from Chinese patients with oesophageal squamous cell carcinoma has revealed eight genes with frequent somatic mutations, including six known tumour-associated genes (*TP53*, *RB1*, *CDKN2A*, *PIK3CA*, *NOTCH1*, and *NFE2L2*) and two novel genes (*ADAM29* and *FAM135B*) [3]. Whole-exome sequencing of paired tumour and normal tissues from patients with oesophageal adenocarcinoma found mutations in 28 genes, of which five (*TP53*, *CDKN2A*, *SMAD4*, *ARID1A*, and *PIK3CA*) are relevant to the pathogenesis of adenocarcinoma [3]. A minority (15–29%) of oesophageal adenocarcinomas show overexpression or amplification of human epidermal growth factor receptor 2 (HER2; also known as ERBB2) [8], suggesting a potential role for therapy with trastuzumab (an anti-HER2 monoclonal antibody) in these tumours [9]. Studies are under way to find mutational signatures associated with both tumour types.

Oesophageal squamous cell carcinoma tumours in people from Golestan Province, Islamic Republic of Iran, have the highest rate of *TP53* mutations ever reported in any cancer [10]. The heterogeneous

FUNDAMENTALS

- Oesophageal cancer has two main histological types: oesophageal squamous cell carcinoma and oesophageal adenocarcinoma.
- Oesophageal squamous cell carcinoma makes up about 87% of all cases of oesophageal cancer worldwide. The incidence is very uneven geographically, with large proportions of cases occurring in a few populations at high risk.
- Oesophageal adenocarcinoma makes up the majority of oesophageal cancer cases in North America, western Europe, Australia, and New Zealand.
- Although incidence rates of oesophageal squamous cell carcinoma are declining, incidence rates of oesophageal adenocarcinoma are increasing in many regions.
- Oesophageal cancer has very poor survival, with mortality rates (7.7 per 100 000) that are close to the incidence rates (9.0 per 100 000).
- The low survival rates for oesophageal cancer are due to the advanced stage at diagnosis, but practical, cost-effective population-based screening has not yet been developed.

Fig. 5.3.2. Global distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000 person-years for oesophageal cancer (A) in men and (B) in women, 2018.



mutation pattern is highly suggestive of a causative role for multiple environmental carcinogens, including polycyclic aromatic hydrocarbons (PAHs) [10]. In contrast, a substantial fraction of oesophageal squamous cell carcinoma tumours in East Africa do not appear to have *TP53* mutations, and a novel mutational signature suggests that another, as-yet-unknown carcinogen could be important in this high-incidence area [11].

Etiology

Risk factors for oesophageal squamous cell carcinoma and oesophageal adenocarcinoma are listed in Table 5.3.1.

Oesophageal squamous cell carcinoma

Oesophageal squamous cell carcinoma is well known for its marked etiological heterogeneity [1,12]. In the USA, Europe, Australia, and New Zealand, almost 90% of cases of oesophageal squamous cell carcinoma are attributable to tobacco use and heavy alcohol consumption, and the incidence rate in men is 3–4 times that in women [1,3,12]. However, in the oesophageal squamous cell carcinoma hotspots in Asia, Africa, and South America, where the incidence rates in men and women can be nearly equal, multiple additional risk factors have been implicated, including a poor

diet deficient in vitamins (especially riboflavin), indoor air pollution, consumption of hot beverages, poor oral health, use of non-piped water, and opium use [1,12–14], with different profiles of attributable risks in different hotspot regions.

Low socioeconomic status is also a consistent risk factor for oesophageal squamous cell carcinoma, even after comprehensive adjustment for tobacco use, alcohol consumption, age, and many other potential risk factors (see Chapter 4.3) [15]. In addition, as suggested by the novel mutational signature seen in the genomic study of tumours in East Africa mentioned above [11], there may also be as-yet-unknown risk factors that may be important for the carcinogenesis of oesophageal squamous cell carcinoma in the high-risk regions of the world. Recent epidemiological studies have shown no evidence for a role of human papillomavirus (HPV) in the etiology of oesophageal squamous cell carcinoma [1,12], and tumour sequencing has not revealed any viral sequences incorporated into the host DNA [11,12].

In most populations at high risk, many of the above-mentioned risk factors occur together. It is not known how they interact to increase risk, but a recent prospective analysis estimated the combined effects of multiple risk factors. Low socioeconomic status, opium smoking, drinking hot tea, low intake of fruits and vegetables, excessive tooth loss, drinking non-piped water, and exposure to indoor air pollution had a combined population attributable risk of 76% for oesophageal squamous cell carcinoma [16].

Polycyclic aromatic hydrocarbons and nitrosamines

One of the main suspected carcinogens for oesophageal squamous cell carcinoma is PAHs. PAHs are important carcinogens in tobacco smoke (see Chapter 2.1) as well as in the combustion products of other organic materials, such as opium, automobile and industrial fuels, coal, and wood; exposure to PAHs from both sources could contribute to high incidence rates in certain regions [17]. In populations at high risk, exposure to PAHs from indoor air pollution caused by heating and cooking with open coal or wood fires in poorly ventilated rooms may be a major factor for both the high rates of oesophageal squamous cell carcinoma and the nearly equal rates in men and women [12,18].

Table 5.3.1. Risk factors for squamous cell carcinoma and adenocarcinoma of the oesophagus[a]

Risk factor	Oesophageal squamous cell carcinoma	Oesophageal adenocarcinoma
Sex	Male > female	Male > female
Race	Black > White	White > Black
Genetic susceptibility	++	+
Gastro-oesophageal reflux disease	No data	++++
Obesity	Limited data	++++
Tobacco use	++++	++
Alcohol consumption	++++	No association
Very hot beverages	+++	No data
Diet low in fruits and vegetables	+++	+
Low socioeconomic status	+++	Limited data
Helicobacter pylori infection	No association	Protective
Poor oral health	++	Limited data
Opium use	++	No data
Indoor air pollution	+	No data
Non-piped water	+	No data

[a] +, positive association (the number of + signs is based on the amount of evidence).

Fig. 5.3.3. A woman in Jamkhed, India, cooks indoors in smoky conditions. Exposure to polycyclic aromatic hydrocarbons from combustion is a suspected carcinogen for oesophageal squamous cell carcinoma.

Opium use

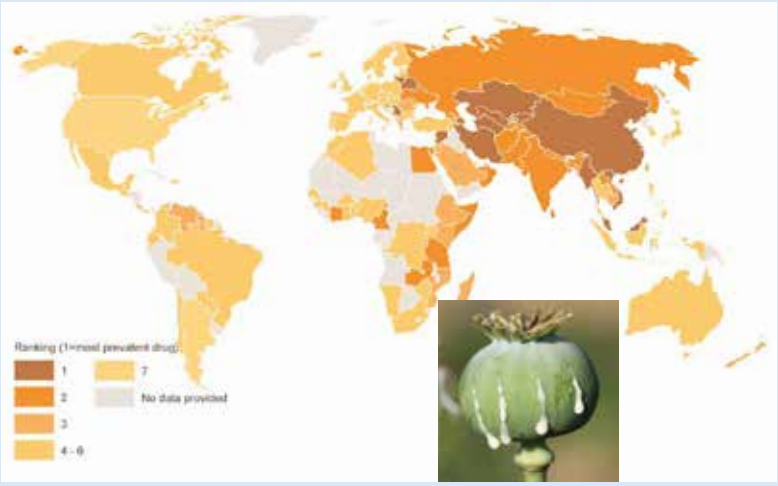
The cultivation of opium and the consumption of raw opium take place mainly in West and Central Asia. These regions have a relatively high incidence of oesophageal cancer. In these areas, opium has traditionally been used for recreational purposes – in lieu of alcohol, which is strictly forbidden in Islam – and as a medication to relieve pain from chronic conditions.

The first evidence that opium use may increase the risk of oesophageal squamous cell carcinoma came from ecological and case–control studies of urinary metabolites in north-eastern Islamic Republic of Iran in the early 1970s [1]. A more recent case–control study of 300 cases of oesophageal squamous cell carcinoma and 571 neighbourhood controls found an odds ratio of 2.00 (95% confidence interval, 1.39–2.88) for ever use of opium and showed dose–response trends for intensity, duration, and cumulative use [2]. Since the 1970s, opium use has also been shown to increase the risk of other malignancies, including cancers of the stomach, larynx, lung, and bladder [1].

The Golestan Cohort Study is the only long-term prospective study that has detailed information on opium use from large numbers of participants. Of the cohort participants, 17% reported opium use, which is largely without negative social stigma. Over a median of 11 years of follow-up, 317 cases of oesophageal squamous cell carcinoma were diagnosed. Compared with participants who had never smoked opium, those in the highest tertile of cumulative opium smoking had a hazard ratio of 1.85 (95% confidence interval, 1.18–2.90) for developing oesophageal squamous cell carcinoma, and there was a significant dose–response trend [3]. In another analysis of total mortality in the Golestan Cohort Study, 40% of deaths among opium users and 10% of all deaths were attributable to opium use.

There are at least two mechanisms by which opium could cause oesophageal squamous cell carcinoma [1]. Opium smoke and opium dross – the material left in the pipe after opium is smoked, which is sometimes eaten – contain carcinogenic pyrolysis products, including polycyclic aromatic hydrocarbons, heterocyclic amines, and *N*-nitrosamines. Some opium constituents can prolong exposure of the oesophagus to ingested carcinogens: papaverine reduces oesophageal peristalsis, and morphine inhibits relaxation of the lower oesophageal sphincter.

Figure B5.3.1. Opium use in the Central Asia oesophageal cancer belt. Global map showing ranking of opiates in order of prevalence among most commonly used drugs, in 2004. Inset: "tears" of the opium poppy.



References

1. Kamangar F, Shakeri R, Malekzadeh R, Islami F (2014). Opium use: an emerging risk factor for cancer? Lancet Oncol. 15(2): e69–77. https://doi.org/10.1016/S1470-2045(13)70550-3 PMID:24480557
2. Nasrollahzadeh D, Kamangar F, Aghcheli K, Sotoudeh M, Islami F, Abnet CC, et al. (2008). Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. Br J Cancer. 98(11):1857–63. https://doi.org/10.1038/sj.bjc.6604369 PMID:18475303
3. Sheikh M, Poustchi H, Pourshams A, Etemadi A, Islami F, Khoshnia M, et al. (2019). Individual and combined effects of environmental risk factors for esophageal cancer based on results from the Golestan Cohort Study. Gastroenterology. 156(5):1416–27. https://doi.org/10.1053/j.gastro.2018.12.024 PMID:30611753

A case–control study in the Islamic Republic of Iran, which measured exposure to PAHs in endoscopically normal oesophageal tissues from cases of oesophageal squamous cell carcinoma and controls, reported odds ratios of more than 25 for the most exposed quintile compared with the least exposed quintile [19]. This finding strongly implicates PAHs in the carcinogenesis of oesophageal squamous cell carcinoma, but confirmation in prospective studies is required.

Nitrosamines are probably another important carcinogen for oesophageal squamous cell carcinoma. They are an important carcinogen in

tobacco smoke, and they are thought to be the main factor contributing to the increased risk of oesophageal squamous cell carcinoma associated with poor oral health and the consumption of non-piped water [12,13]. Further studies to identify sources of and routes of exposure to PAHs and nitrosamines are needed to confirm their role in the etiology of oesophageal squamous cell carcinoma and to translate the knowledge of these associations into strategies for primary prevention in regions with high incidence of oesophageal squamous cell carcinoma.

Low selenium status

Another risk factor for oesophageal squamous cell carcinoma that deserves special attention is low selenium status. The selenium content of soil is variable worldwide, and soil selenium levels are reflected in local plants and animals as well as in people, assuming that they eat local foods.

In both China and Africa, there are suggestive similarities in the distribution of low selenium availability (low soil selenium levels in China and low dietary intake of selenium in Africa) and the high-risk areas for oesophageal squamous cell carcinoma [1]. In addition, cohort studies in both China and the Netherlands have shown significant inverse associations between low serum or toenail selenium levels and risk of oesophageal squamous cell carcinoma [12], and two intervention trials in China have reported results suggesting that selenium supplementation may be able to prevent oesophageal squamous cell carcinoma in populations with low selenium status when it is given early in the course of the disease (see Chapter 6.4) [12].

Low selenium status is not an important risk factor for oesophageal squamous cell carcinoma in all high-risk populations, and specifically it is not a risk factor in the Islamic Republic of Iran, but it is the only suspected risk factor in China and Africa that is *not* commonly present in the low-risk populations of these regions as well. Furthermore, low selenium status is also known to combine with other exposures (especially viral infections) to cause novel diseases that require both exposures, as in Keshan disease [20], so it may also be important for the oesophageal carcinogenicity of other exposures. Further studies are needed to confirm the association of low selenium status and oesophageal squamous cell carcinoma in Africa, and to explore how low selenium status and other risk factors interact to increase risk of oesophageal squamous cell carcinoma.

Oesophageal adenocarcinoma

The main etiological factors for oesophageal adenocarcinoma are similar across the world and include gastro-oesophageal reflux disease, obesity (especially visceral obesity), tobacco use, and genetic risk factors [3,21]. People who have never been infected with *Helicobacter pylori* also appear to be at elevated risk of oesophageal adenocarcinoma. Several recent studies have suggested that sex hormones, physical activity, certain medications, and diet may also play a role in altering the risk of oesophageal adenocarcinoma [21].

The markedly higher risk in men compared with women (up to 6-fold) and in Whites compared with Blacks (up to 8-fold) cannot be explained by any of the confirmed risk factors, although visceral obesity, which is more common in men and is more strongly associated with oesophageal adenocarcinoma, may contribute to the sex difference. Age–period–cohort analyses suggest that a change in exposures in about 1950 may have started the subsequent rapid increase in oesophageal adenocarcinoma rates in high-income countries [22].

Early detection

Detection of oesophageal cancer at an earlier, potentially curable stage of disease is critical to improve patient survival. Oesophageal squamous dysplasia and Barrett oesophagus are the established precursor lesions for oesophageal squamous cell carcinoma and oesophageal adenocarcinoma, respectively, but most of these tumours are diagnosed in patients without a prior diagnosis of these precursor lesions [1,3]. Endoscopic screening for precursor lesions and endoscopic resection or ablation of the dysplastic lesions have been shown to reduce the risk of developing oesophageal squamous cell carcinoma and dying from the disease [23]. A large trial is now under way.

Screening for Barrett oesophagus has been used in clinics on an individual basis in high-income countries, but no randomized controlled trials have shown a significant benefit [3]. Population-based endoscopic screening will require well-trained health workers with diverse skills as well as considerable infrastructure; these are not widely available, especially in low- and middle-income countries, where most cases of oesophageal squamous cell carcinoma occur.

Non-endoscopic screening of oesophageal cells obtained with balloon or sponge samplers and molecular biomarker identification of precursor lesion cells are now being evaluated for early detection of Barrett oesophagus and oesophageal adenocarcinoma in Europe [24] and for early detection of squamous dysplasia and oesophageal squamous cell carcinoma in the Islamic Republic of Iran [25], with promising preliminary results. However, further randomized controlled trials or well-conducted, accurate studies are required before these procedures can be recommended for implementation outside of research studies.

Sampling of blood or other body fluids (referred to as liquid biopsies) to measure tumour-derived material is also being evaluated for its potential in early detection (see Chapter 6.7), including interrogation of circulating cell-free tumour DNA, circulating tumour cells, exosomes, and microRNAs [26]. For example, one recent study investigated the

Drinking hot beverages

Many observational studies have found an association between drinking hot beverages and the development of oesophageal squamous cell carcinoma [1]. The IARC Monographs classified drinking very hot beverages at above 65 °C as probably carcinogenic to humans (Group 2A), especially for oesophageal squamous cell carcinoma. However, nearly all of the relevant studies were questionnaire-based studies that analysed only subjective estimates of beverage temperatures.

The first large study to measure actual beverage temperatures was the Golestan Cohort Study of 50 000 adults in Golestan Province, in north-eastern Islamic Republic of Iran. In this study, a fresh cup of tea was prepared for each participant, and the temperature was measured. When the temperature was 75 °C, the participant was asked to sip the tea and say whether that was the temperature at which they usually drank tea. If not, the tea was allowed to cool further and the question was asked again at 5 °C intervals until the relevant temperature was reached.

At baseline, the cohort drank a mean tea volume of 1179 mL/day, at a mean temperature of 62.4 °C. After a median follow-up of 10 years, 328 cases of oesophageal cancer (96% of them oesophageal squamous cell carcinoma) were diagnosed. Compared with drinking less than 700 mL/day of tea at less than 60 °C, drinking 700 mL/day or more of tea at 60 °C or above was associated with a 75% higher risk of oesophageal cancer; drinking any amount of tea at less than 60 °C was not associated with risk [2].

In a cross-sectional study of 188 villagers in rural United Republic of Tanzania, in the African corridor of high risk of oesophageal squamous cell carcinoma, 62% of the participants drank milky tea (or chai), which is common in East Africa and is made by boiling black tea leaves and equal amounts of cow's milk and water, and 37% drank black tea. The same protocol as in the Golestan Cohort Study was used. Participants started drinking tea at a mean temperature of 70.6 °C, and those who consumed milky tea drank their tea an average of 1.9 °C hotter than those who drank black tea [3].

Thermal injury may increase risk of oesophageal cancer by inducing inflammatory processes. Formation of carcinogenic *N*-nitroso compounds may be relevant. Thermal injury may impair the barrier function of the oesophageal mucosa, thereby increasing exposure to intraluminal carcinogens such as *N*-nitroso compounds and polycyclic aromatic hydrocarbons.

Figure B5.3.2. Measurement of the temperature of tea, in the Golestan Cohort Study. Inset: close-up of the measuring device.

References

1. Islami F, Boffetta P, Ren JS, Pedoeim L, Khatib D, Kamangar F (2009). High-temperature beverages and foods and esophageal cancer risk – a systematic review. Int J Cancer. 125(3):491–524. https://doi.org/10.1002/ijc.24445 PMID:19415743
2. Islami F, Poustchi H, Pourshams A, Khoshnia M, Gharavi A, Kamangar F, et al. (2020). A prospective study of tea drinking temperature and risk of esophageal squamous cell carcinoma. 146(1):18–25. https://doi.org/10.1002/ijc.32220 PMID:30891750
3. Munishi MO, Hanisch R, Mapunda O, Ndyetabura T, Ndaro A, Schüz J, et al. (2015). Africa's oesophageal cancer corridor: do hot beverages contribute? Cancer Causes Control. 26(10):1477–86. https://doi.org/10.1007/s10552-015-0646-9 PMID:26245249

use of next-generation sequencing of a multigene panel to detect mutations in cell-free DNA in plasma samples to identify biomarkers of oesophageal cancer that could be clinically useful for early detection of this malignancy in a population at high risk [27]. These evaluations of body fluids are only beginning, and many studies will be needed to identify markers and to develop protocols that have clinical utility.

Prevention

Reduced exposure to carcinogens

The translation of epidemiological studies into preventive strategies –

such as prevention of tobacco use, smoking cessation, moderation of alcohol consumption, weight loss, and modification of diet – is promising but is difficult to accomplish [3]. However, it should be possible to reduce exposure to several risk factors for oesophageal squamous cell carcinoma by relatively straightforward interventions. Finland was able to eliminate the low selenium status of its population by inexpensive supplementation of chemical fertilizers [28]. Indoor air pollution from coal or wood fires can be reduced by improving room ventilation, replacing open fires with stoves, and adding chimneys to stoves. Exposure to nitrosamines can probably be reduced by campaigns to encourage tooth brushing and by increasing the availability of treated water.

A comprehensive way to reduce many of these harmful exposures, and hence rates of oesophageal squamous cell carcinoma, may be to improve living standards and the socioeconomic status of the population. This appears to be what has happened in north-eastern Islamic Republic of Iran over the past several decades. In 1968–1971, the age-standardized incidence of oesophageal cancer in what is now Golestan Province was estimated to be 80 per 100 000 in both sexes [29]. A retrospective study of cases in the same area in 1996–2000 reported rates of 44 per 100 000 in men and 36 per 100 000 in women [29], and the prospective Golestan Population-Based Cancer Registry reported rates in 2004–2008 of 24 per 100 000 in men and 19 per 100 000 in women [30].

During the 40 years between 1968 and 2008, living standards improved significantly, with better housing, use of natural gas instead of biomass for cooking and heating (resulting in the elimination of indoor air pollution from biomass smoke), and use of piped water instead of non-piped cistern water (preventing exposure to high concentrations of nitrosamines) [29]. In 1970, fewer than 5% of people in the rural areas had refrigerators; this proportion has now increased to more than 98%, enabling better food storage and decreased consumption of salted and smoked foods. In addition, electricity, telephone communication, and transportation networks are now available to 98% of the population in the urban areas and 92% in the rural areas [29]. These dramatic changes in living standards in Golestan are probably the main reasons for the sharp decrease in incidence rates of oesophageal squamous cell carcinoma [29].

Cancer management in groups at high risk

In high-risk regions in the Islamic Republic of Iran and China, the availability of free endoscopy services for early diagnosis and of therapeutic capabilities including endoscopic therapy, surgery, radiotherapy, and chemotherapy have resulted in much better care for patients with oesophageal squamous cell carcinoma, including improved survival and better quality of life after treatment. In more resource-limited settings, oesophageal stents can provide significant palliation [31].

Chemoprevention

Several clinical cohort studies have shown that use of proton-pump inhibitors can significantly reduce the risk of progression from Barrett oesophagus to high-grade dysplasia or oesophageal adenocarcinoma [32]. However, emerging data suggest that a comprehensive assessment of the health effects of proton-pump inhibitors is critical to assess the overall effects of these agents.

Aspirin and other non-steroidal anti-inflammatory drugs have also been shown in observational studies to be associated with reduced risk, by up to 50%, of oesophageal squamous cell carcinoma and oesophageal adenocarcinoma [33]. A meta-analysis of 13 studies showed a reduction of 28% overall in the risk of oesophageal adenocarcinoma among users of statins, compared with non-users, and a reduction of 41% in the risk of oesophageal adenocarcinoma in patients with Barrett oesophagus who took statins [3]. Given the additional preventive benefits of use of aspirin and statins for other cancer types and for cardiovascular disease, these drugs may be good candidates for chemoprevention in groups at high risk.

Several large trials examining the effects of proton-pump inhibitors, aspirin, and statins for prevention of oesophageal cancer are in progress [3]. Recent results from a randomized trial of protein-pump inhibitors and aspirin in Barrett oesophagus patients without high-grade dysplasia showed a significant reduction in a combined end-point of death, oesophageal adenocarcinoma, or high-grade dysplasia in patients taking high-dose proton-pump inhibitors, compared with those taking low-dose proton-pump inhibitors, and there was some evidence that adding aspirin improved the beneficial effect of the high-dose proton-pump inhibitors regimen [34].

References

1. Murphy G, McCormack V, Abedi-Ardekani B, Arnold M, Camargo MC, Dar NA, et al. (2017). International cancer seminars: a focus on esophageal squamous cell carcinoma. Ann Oncol. 28(9):2086–93. https://doi.org/10.1093/annonc/mdx279 PMID:28911061

2. Arnold M, Soerjomataram I, Ferlay J, Forman D (2015). Global incidence of oesophageal cancer by histological subtype in 2012. Gut. 64(3):381–7. https://doi.org/10.1136/gutjnl-2014-308124 PMID:25320104

3. Rustgi AK, El-Serag HB (2014). Esophageal carcinoma. N Engl J Med. 371(26):2499–509. https://doi.org/10.1056/NEJMra1314530 PMID:25539106

4. Lin DC, Dinh HQ, Xie JJ, Mayakonda A, Silva TC, Jiang YY, et al. (2018). Identification of distinct mutational patterns and new driver genes in oesophageal squamous cell carcinomas and adenocarcinomas. Gut. 67(10):1769–79. https://doi.org/10.1136/gutjnl-2017-314607 PMID:28860350

5. Parker RK, Dawsey SM, Abnet CC, White RE (2010). Frequent occurrence of esophageal cancer in young people in western Kenya. Dis Esophagus. 23(2):128–35. https://doi.org/10.1111/j.1442-2050.2009.00977.x PMID:19473205

6. Wu C, Wang Z, Song X, Feng XS, Abnet CC, He J, et al. (2014). Joint analysis of three genome-wide association studies of esophageal squamous cell carcinoma in Chinese populations. Nat Genet. 46(9):1001–6. https://doi.org/10.1038/ng.3064 PMID:25129146

7. Levine DM, Ek WE, Zhang R, Liu X, Onstad L, Sather C, et al. (2013). A genome-wide association study identifies new susceptibility loci for esophageal adenocarcinoma and Barrett's esophagus. Nat Genet. 45(12):1487–93. https://doi.org/10.1038/ng.2796 PMID:24121790

8. Plum PS, Gebauer F, Krämer M, Alakus H, Berlth F, Chon SH, et al. (2019). HER2/neu (ERBB2) expression and gene amplification correlates with better survival in esophageal adenocarcinoma. BMC Cancer. 19(1):38. https://doi.org/10.1186/s12885-018-5242-4 PMID:30621632

9. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al.; ToGA Trial Investigators (2010). Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 376(9742):687–97. https://doi.org/10.1016/S0140-6736(10)61121-X PMID:20728210

10. Abedi-Ardekani B, Kamangar F, Sotoudeh M, Villar S, Islami F, Aghcheli K, et al. (2011). Extremely high *Tp53* mutation load in esophageal squamous cell carcinoma in Golestan Province, Iran. PLoS One. 6(12):e29488. https://doi.org/10.1371/journal.pone.0029488 PMID:22216294

11. Liu W, Snell JM, Jeck WR, Hoadley KA, Wilkerson MD, Parker JS, et al. (2016). Subtyping sub-Saharan esophageal squamous cell carcinoma by comprehensive molecular analysis. JCI Insight. 1(16):e88755. https://doi.org/10.1172/jci.insight.88755 PMID:27734031

12. Abnet CC, Arnold M, Wei WQ (2018). Epidemiology of esophageal squamous cell carcinoma. Gastroenterology. 154(2):360–73. https://doi.org/10.1053/j.gastro.2017.08.023 PMID:28823862

13. Golozar A, Etemadi A, Kamangar F, Fazeltabar Malekshah A, Islami F, Nasrollahzadeh D, et al. (2016). Food preparation methods, drinking water source, and esophageal squamous cell carcinoma in the high-risk area of Golestan, Northeast Iran. Eur J Cancer Prev. 25(2):123–9. https://doi.org/10.1097/CEJ.0000000000000156 PMID:25851181

14. Islami F, Poustchi H, Pourshams A, Khoshnia M, Gharavi A, Kamangar F, et al. (2020). A prospective study of tea drinking temperature and risk of esophageal squamous cell carcinoma. Int J Cancer. 146(1):18–25. https://doi.org/10.1002/ijc.32220 PMID:30891750

15. Islami F, Kamangar F, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, Abedi-Ardekani B, et al. (2009). Socio-economic status and oesophageal cancer: results from a population-based case-control study in a high-risk area. Int J Epidemiol. 38(4):978–88. https://doi.org/10.1093/ije/dyp195 PMID:19416955

16. Sheikh M, Poustchi H, Pourshams A, Etemadi A, Islami F, Khoshnia M, et al. (2019). Individual and combined effects of environmental risk factors for esophageal cancer based on results from the Golestan Cohort Study. Gastroenterology. 156(5):1416–27. https://doi.org/10.1053/j.gastro.2018.12.024 PMID:30611753

17. Etemadi A, Poustchi H, Chang CM, Blount BC, Calafat AM, Wang L, et al. (2019). Urinary biomarkers of carcinogenic exposure among cigarette, waterpipe, and smokeless tobacco users and never users of tobacco in the Golestan Cohort Study. Cancer Epidemiol Biomarkers Prev. 28(2):337–47. https://doi.org/10.1158/1055-9965.EPI-18-0743 PMID:30622099

18. Kayamba V, Heimburger DC, Morgan DR, Atadzhanov M, Kelly P (2017). Exposure to biomass smoke as a risk factor for oesophageal and gastric cancer in low-income populations: a systematic review. Malawi Med J. 29(2):212–7. https://doi.org/10.4314/mmj.v29i2.25 PMID:28955435

19. Abedi-Ardekani B, Kamangar F, Hewitt SM, Hainaut P, Sotoudeh M, Abnet CC, et al. (2010). Polycyclic aromatic hydrocarbon exposure in oesophageal tissue and risk of oesophageal squamous cell carcinoma in north-eastern Iran. Gut. 59(9):1178–83. https://doi.org/10.1136/gut.2010.210609 PMID:20584779

20. Beck MA, Levander OA, Handy J (2003). Selenium deficiency and viral infection. J Nutr. 133(5 Suppl 1):1463S–7S. https://doi.org/10.1093/jn/133.5.1463S PMID:12730444

21. Coleman HG, Xie SH, Lagergren J (2018). The epidemiology of esophageal adenocarcinoma. Gastroenterology. 154(2):390–405. https://doi.org/10.1053/j.gastro.2017.07.046 PMID:28780073

22. Edgren G, Adami HO, Weiderpass E, Nyrén O (2013). A global assessment of the oesophageal adenocarcinoma epidemic. Gut. 62(10):1406–14. https://doi.org/10.1136/gutjnl-2012-302412 PMID:22917659

23. Wei WQ, Chen ZF, He YT, Feng H, Hou J, Lin DM, et al. (2015). Long-term follow-up of a community assignment, one-time endoscopic screening study of esophageal cancer in China. J Clin Oncol. 33(17):1951–7. https://doi.org/10.1200/JCO.2014.58.0423 PMID:25940715

24. Ross-Innes CS, Debiram-Beecham I, O'Donovan M, Walker E, Varghese S, Lao-Sirieix P, et al.; BEST2 Study Group (2015). Evaluation of a minimally invasive cell sampling device coupled with assessment of trefoil factor 3 expression for diagnosing Barrett's esophagus: a multicenter case-control study. PLoS Med. 12(1):e1001780. https://doi.org/10.1371/journal.pmed.1001780 PMID:25634542

25. Roshandel G, Merat S, Sotoudeh M, Khoshnia M, Poustchi H, Lao-Sirieix P, et al. (2014). Pilot study of cytological testing for oesophageal squamous cell dysplasia in a high-risk area in Northern Iran. Br J Cancer. 111(12):2235–41. https://doi.org/10.1038/bjc.2014.506 PMID:25247319

26. Perakis S, Speicher MR (2017). Emerging concepts in liquid biopsies. BMC Med. 15(1):75. https://doi.org/10.1186/s12916-017-0840-6 PMID:28381299

27. Lan YT, Chen MH, Fang WL, Hsieh CC, Lin CH, Jhang FY, et al. (2017). Clinical relevance of cell-free DNA in gastrointestinal tract malignancy. Oncotarget. 8(2):3009–17. https://doi.org/10.18632/oncotarget.13821 PMID:27936467

28. Alfthan G, Eurola M, Ekholm P, Venäläinen ER, Root T, Korkalainen K, et al.; Selenium Working Group (2015). Effects of nationwide addition of selenium to fertilizers on foods, and animal and human health in Finland: from deficiency to optimal selenium status of the population. J Trace Elem Med Biol. 31:142–7. https://doi.org/10.1016/j.jtemb.2014.04.009 PMID:24908353

29. Semnani S, Sadjadi A, Fahimi S, Nouraie M, Naeimi M, Kabir J, et al. (2006). Declining incidence of esophageal cancer in the Turkmen Plain, eastern part of the Caspian Littoral of Iran: a retrospective cancer surveillance. Cancer Detect Prev. 30(1):14–9. https://doi.org/10.1016/j.cdp.2005.11.002 PMID:16495018

30. Roshandel G, Sadjadi A, Aarabi M, Keshtkar A, Sedaghat SM, Nouraie SM, et al. (2012). Cancer incidence in Golestan Province: report of an ongoing population-based cancer registry in Iran between 2004 and 2008. Arch Iran Med. 15(4):196–200. PMID:22424034

31. White RE, Parker RK, Fitzwater JW, Kasepoi Z, Topazian M (2009). Stents as sole therapy for oesophageal cancer: a prospective analysis of outcomes after placement. Lancet Oncol. 10(3):240–6. https://doi.org/10.1016/S1470-2045(09)70004-X PMID:19230771

32. Singh S, Garg SK, Singh PP, Iyer PG, El-Serag HB (2014). Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. Gut. 63(8):1229–37. https://doi.org/10.1136/gutjnl-2013-305997 PMID:24221456

33. Qiao Y, Yang T, Gan Y, Li W, Wang C, Gong Y, et al. (2018). Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies. BMC Cancer. 18(1):288. https://doi.org/10.1186/s12885-018-4156-5 PMID:29534696

34. Jankowski JAZ, de Caestecker J, Love SB, Reilly G, Watson P, Sanders S, et al.; AspECT Trial Team (2018). Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. Lancet. 392(10145):400–8. https://doi.org/10.1016/S0140-6736(18)31388-6 PMID:30057104

5.4 Stomach cancer
Still one of the main cancer types worldwide

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SUMMARY

- Two systematic reviews and meta-analyses have been performed of the worldwide prevalence of *Helicobacter pylori* infection, the main (necessary but not sufficient) risk factor for gastric cancer. The global prevalence in adults is close to 50%, with large differences between continents and a trend towards a decrease over the years.
- A recent emergence of gastric cancer possibly not related to *H. pylori* in younger patients should be explored.
- The Stomach Cancer Pooling Project, by using individual data, confirmed the role of additional risk factors such as tobacco smoking and alcohol consumption but at a lower magnitude than previously established.
- Among emerging risk factors, a modified composition of the gastric microbiota may contribute to gastric carcinogenesis by increasing inflammation and producing carcinogenic compounds.
- The molecular profiles of gastric cancer were recently identified, and two molecular classifications are based on sequencing; these will provide a roadmap for trials of targeted therapies.
- New treatments are being proposed, especially those using immune checkpoint inhibitors in resectable gastric cancer. New cellular markers are putative biomarkers for diagnosis and therapeutic targets.

In the 19th century, stomach cancer was one of the major causes of cancer-related death. The situation changed in the 20th century in high-income countries after an improvement in the socioeconomic status of the populations and the introduction of antibiotics. However, stomach cancer is still an important cause of death in many countries.

The breakthrough in understanding the causation of stomach cancer was the discovery that a bacterium – *Helicobacter pylori* – was the main causal agent of this disease. The role of *H. pylori* was determined by Warren and Marshall in 1982, and they subsequently described its role in the development of peptic ulcer disease. For this discovery, Warren and Marshall were awarded the Nobel Prize in Physiology or Medicine 2005. The IARC Monographs classified infection with *H. pylori* as carcinogenic to humans (Group 1) in 1994, on the basis of epidemiological evidence [1], and this classification was confirmed in 2009 [2].

Stomach cancers, often referred to as gastric cancers, are mostly gastric adenocarcinomas. They are classified according to stage (early or advanced), anatomical location (in the proximal or distal part of the stomach), and histological subtype. The 2010 WHO classification of gastric cancer specifies five main histological subtypes: tubular, papillary, mucinous, poorly cohesive (including signet ring cell carcinoma), and mixed. Tubular, papillary, and mucinous adenocarcinomas correspond to the intestinal type described by Laurén in 1965, and poorly cohesive carcinomas correspond to the diffuse type of Laurén (Table 5.4.1).

Although both the intestinal and diffuse types of gastric cancer are related mainly to *H. pylori* infection, the intestinal type is often related to environmental factors, diet, and lifestyle, and the diffuse type

Fig. 5.4.1. Scanning electron micrograph of *Helicobacter pylori* bacterium.

is more often associated with genetic abnormalities. The molecular profiles of gastric cancer were recently identified and classified by the Cancer Genome Atlas (TCGA) Research Network and the Asian Cancer Research Group (ACRG).

Epidemiology

The incidence of gastric cancer is still high, and it is the third most common cause of cancer death worldwide, responsible for an estimated 783 000 deaths in 2018 [3]. However, there is considerable geographical heterogeneity. The countries with the highest incidence rates are in East Asia, and incidence rates in men are much higher than those in women.

Infection with *H. pylori* is a necessary but not sufficient cause; this explains why the incidence of gastric cancer does not mirror the prevalence of *H. pylori* infection. It is now well known that the important risk factors are the host's genetic makeup, the characteristics of *H. pylori* strains, and environmental factors, notably diet.

People in East Asia harbour aggressive strains of *H. pylori*, have a diet that is high in salt, and may have genetic elements that favour the development of gastric cancer, whereas people in Africa harbour less aggressive strains of *H. pylori* and generally have a diet that includes more vitamins and less salt. Recently, a dietary inflammatory index was calculated for participants in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. The results showed that the inflammatory potential of the diet was associated with the risk of gastric cancer, but no differences were seen between the intestinal and diffuse types [4]. In addition, in African populations, parasitic infections that drive the immune response appear to be beneficial (i.e. Th2 response rather than Th1 response), leading to less inflammation [5]. Because gastric cancer typically occurs later in life, the shorter life expectancy of populations in many African countries also contributes to the low rate of gastric cancer in these populations.

Two systematic reviews and meta-analyses of the worldwide prevalence of *H. pylori* infection were published in 2017 and 2018. Hooi et al. covered the period 1970–2016 and 62 countries (531 880 subjects) [6], whereas Zamani et al. analysed the period 2000–2017 and 73 countries (410 879 subjects) (Fig. 5.4.2) [7]. Both studies showed the same global prevalence of *H. pylori* infection in adults (48.5% and 48.6%, respectively). The prevalence was highest in Africa, followed by Latin America and Asia, and the prevalence was lowest in Australia, North America, and western Europe. However, large differences were observed between countries on the same continent and between areas within large countries. There was a trend towards a decrease in prevalence in 2009–2016 compared with 2000–2009 [7].

Several relevant studies have been performed in East Asia. In the Republic of Korea, the prevalence of *H. pylori* infection, determined in 4920 asymptomatic subjects by serology, was 51.0%. The prevalence decreased progressively from 1998 to 2005, 2011, and 2015–2016. Interestingly, the prevalence was lower in urban areas than in rural areas [8]. In south-western China, a cross-sectional study carried out in 2014 on 10 912 subjects using the urea breath test found a 34.4% prevalence of *H. pylori* infection, and an association was noted with low albumin levels and hyperglycaemia [9]. In Viet Nam, the observed

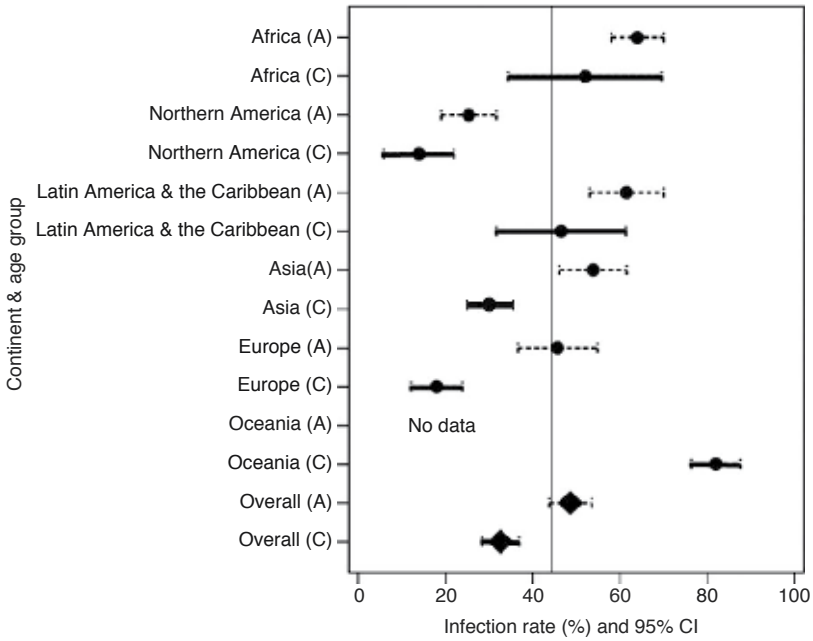
FUNDAMENTALS

- Stomach cancer is the third most common cause of cancer death worldwide.
- Stomach cancers, often referred to as gastric cancers, are mostly gastric adenocarcinomas. They are classified according to stage (early or advanced), anatomical location (in the proximal or distal part of the stomach), and histological subtype.
- The principal cause of gastric cancer is infection with the bacterium *Helicobacter pylori*, which is particularly prevalent in Africa, Latin America, and Asia. Infection with *H. pylori* is a necessary but not sufficient cause.
- Decreases in the incidence of stomach cancer over the decades before the role of *H. pylori* was known have been correlated with environmental factors such as type of diet, i.e. decreased consumption of salt-preserved food, avoidance of a diet that is high in salt, and availability of fresh fruits and vegetables throughout the year.
- Patients with stomach cancer are often diagnosed with advanced disease, and survival is poor.

Table 5.4.1. Histological subtypes of gastric adenocarcinoma according to the Laurén classification and the WHO classification

Classification	Histological subtype of gastric adenocarcinoma					
Laurén (1965)	Intestinal			Diffuse	Mixed	Indeterminate
WHO (2010)	Tubular	Papillary	Mucinous	Poorly cohesive	Mixed	Uncommon variants

Fig. 5.4.2. Prevalence of *Helicobacter pylori* infection for adults (A) and children (C) across six continents. The reference line represents the overall global prevalence (44.3%).



prevalence was similar (38.1%), but it varied according to ethnicity [10].

Mortality from gastric cancer was also studied in China (see Chapter 4.3). When mortality rates were standardized by the age scale of the population in 2010, a 17.8% decrease was observed between 2006 and 2013, which is in line with the global decrease in the prevalence of *H. pylori* infection during that period. The age-standardized mortality rate was higher in rural areas than in urban areas. However, a surprising finding was an increasing trend in mortality rates in young age groups (0–29 years) between 2006 and 2013 [11]. In Mongolia, which has high gastric cancer incidence and mortality rates, the prevalence of *H. pylori* infection was 80.0%. Dyspepsia is common in this population, and the salty diet was considered to worsen the atrophy observed.

In Japan, insurance coverage for *H. pylori* eradication began in 2000 for peptic ulcer disease and in 2013 for gastritis, leading to eradication in about 650 000 patients per year from 2001 to 2012, and double that number annually since 2013. The prevalence of *H. pylori* infection in Japan was estimated to be 27% in 2016 [12], and the spontaneous decrease has been boosted by the eradication policy. The incidence of gastric cancer is also decreasing more rapidly since this policy was implemented [13]. *H. pylori* eradication reduces the cumulative incidence of gastric cancer in a healthy asymptomatic population, and the effect on the prevention of gastric cancer is observed in all age groups [14].

In the USA, a study of 11 million patients investigated the prevalence of *H. pylori* infection in people of five ethnic groups who had upper gastrointestinal symptoms. The relative risk of gastric diseases associated with *H. pylori* infection was highest in Blacks and Asian Pacific Islanders, and the prevalence of *H. pylori* infection was highest in Native Americans and Alaska Natives [15].

A study assessed incidence trends in 1995–2013 in the USA. There were 137 447 non-cardia gastric cancers in 4.4 billion person-years of observation. An overall decline in incidence rates was seen, but a slight increase was observed in non-Hispanic Whites younger than 50 years (Fig. 5.4.3). This increase was more marked in women than in men; the incidence in women born in 1983 was double that in those born 30 years earlier. These data were collected from registries where there was no information on *H. pylori* infection status, but given the socioeconomic status of these cases and the predominant localization of the tumours to the corpus of the stomach, *H. pylori* infection is unlikely to have played a role. One hypothesis is that gastric cancer in these patients is the consequence of autoimmunity related to dysbiosis of the gastric microbiome [16].

In an evaluation of trends in gastric cancer incidence, an increased risk was also noted in recent birth cohorts in several countries in South America and Europe, for both men and women [17]. This change, which is most likely to be related to lifestyle and environmental risk factors, needs to be explored further. In a systematic review of the prevalence of *H. pylori* infection in Europe, the prevalence was lowest in northern Europe and highest in eastern and southern Europe. Two countries still had a high prevalence (84%): Poland and Portugal. Studies on the impact of lifestyle indicated the usual risk factors for gastric cancer [18].

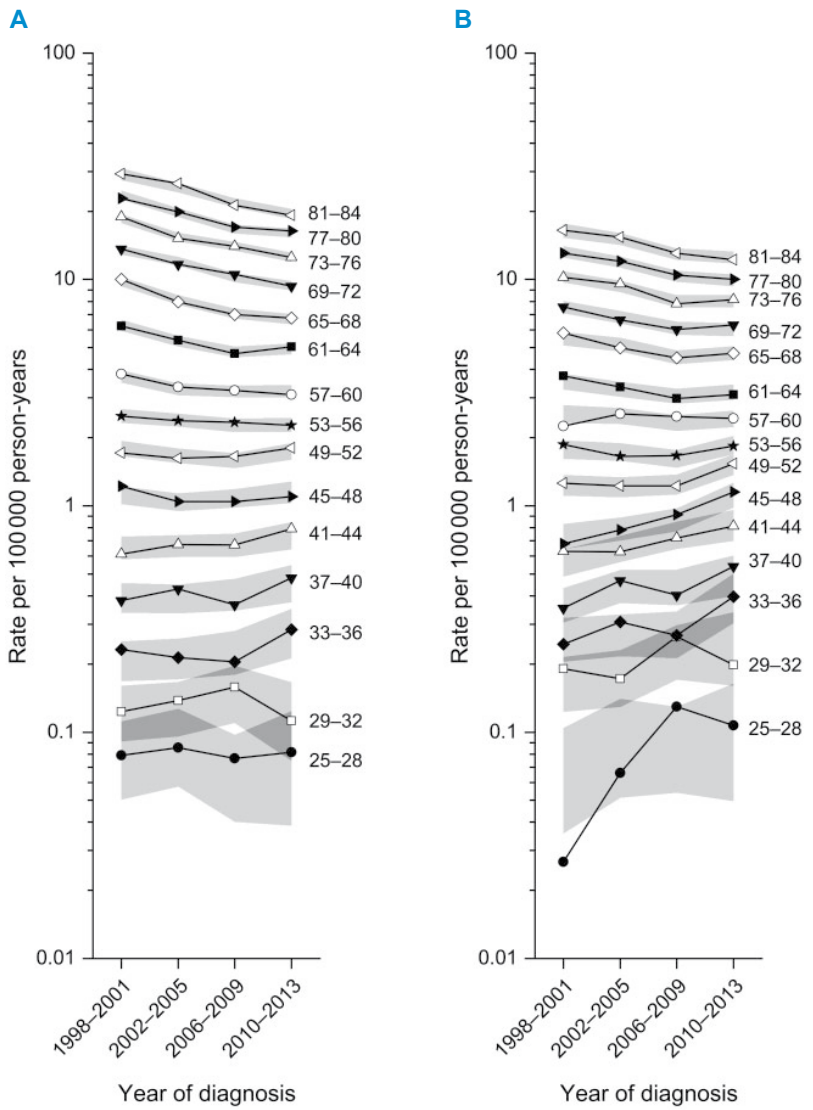
Genetics and genomics

Genetic susceptibility

Hereditary gastric cancer makes up about 1–3% of cases of gastric cancer. It includes mainly hereditary diffuse gastric cancer, gastric adenocarcinoma and proximal polyposis of the stomach, and familial intestinal gastric cancer [18].

About 30–40% of cases of hereditary diffuse gastric cancer are linked to a dominant germline pathogenic mutation in *CDH1*, which encodes E-cadherin. In whole-exome sequencing studies, germline mutations in the tumour suppressor genes *CTNNA1*, *STK11*, and *SDHB* and the DNA repair-related genes *PALB2*, *BRCA2*, and *ATM* were identified

Fig. 5.4.3. Age-specific incidence trends of non-cardia gastric cancer among non-Hispanic White men (A) and women (B). The symbols represent the observed incidence rates in 15 4-year age groups over four 4-year time periods. The shaded areas denote 95% confidence intervals from the age–period–cohort models. The modelled 95% confidence intervals provide a good fit to the observed data for every age group except women aged 25–28 years.



in hereditary diffuse gastric cancer without *CDH1* mutation [19].

Hereditary gastric cancer also develops in patients with Lynch syndrome (mutations in the mismatch repair genes *MSH2*, *MSH6*, *PMS2*, or *MLH1*) and, more rarely, in patients with Li–Fraumeni syndrome (*TP53* germline mutation), Peutz–Jeghers syndrome (*STK11* mutation), and familial adenomatous polyposis (*APC* mutation) [20].

Genomics

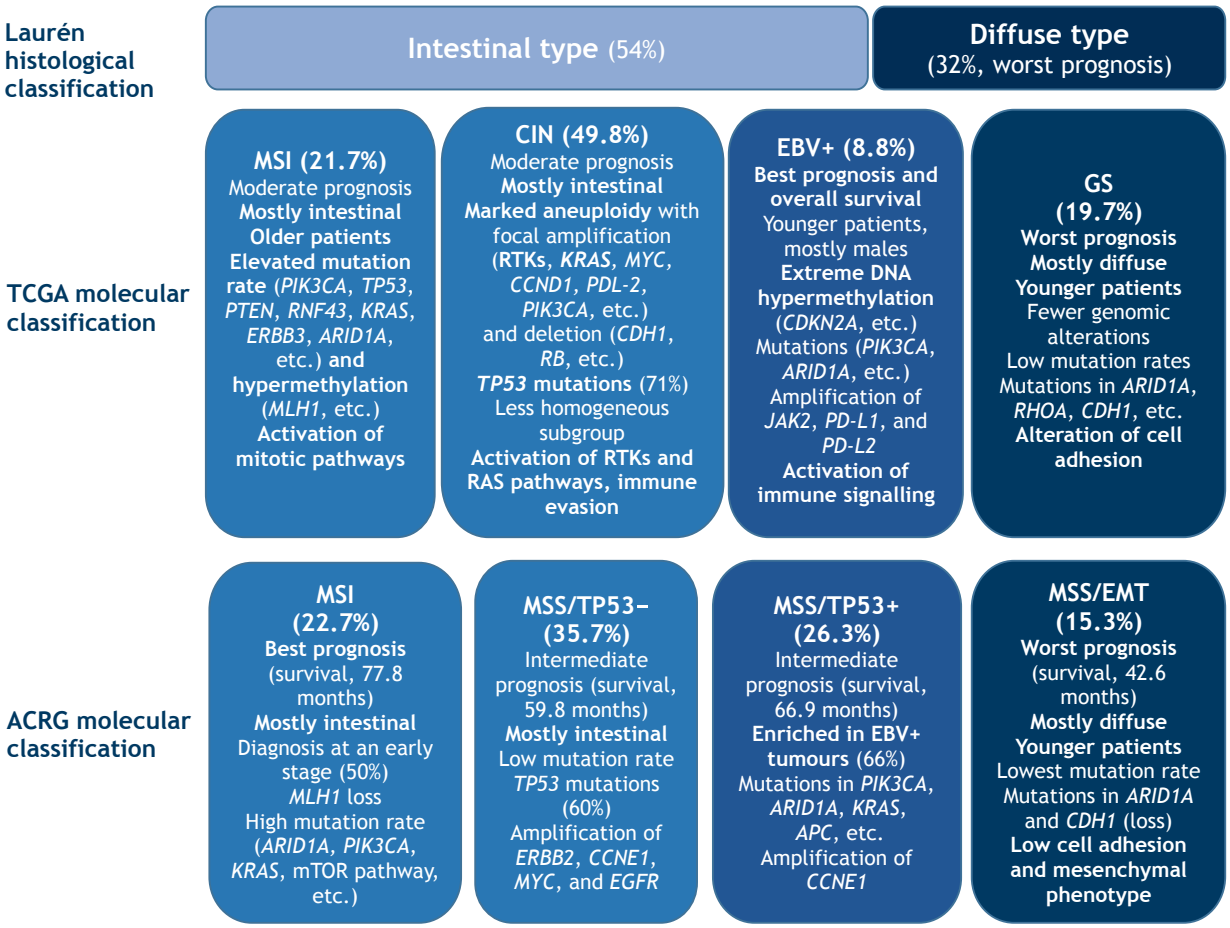
In 2014, by integrating whole-genome sequencing, genomic data, and proteomic data, TCGA [21] and ACRG [22] each defined four molecular subtypes of gastric cancer, to provide a roadmap for patient stratification and trials of targeted therapies.

TCGA distinguished the following four molecular subtypes of gastric cancer (Fig. 5.4.4): (i) tumours positive for Epstein–Barr virus (EBV) (8.8%), which display recurrent *PIK3CA* mutations, extreme DNA hypermethylation, and amplification of *JAK2*, *PD-L1*, and *PD-L2*; (ii) tumours with microsatellite instability (MSI) (21.7%), which have elevated mutation rates in oncogenes such as human epidermal growth factor receptor 2 (*HER2*), epidermal growth factor receptor 1 (*EGFR1*), and *HER3* (also known as *ERBB3*); (iii) genomically stable tumours (19.7%), which are enriched for the diffuse type and mutations of *CDH1*, *RHOA*, and genes associated with the cytoskeleton and cell junctions; and (iv) tumours with chromosomal instability (49.8%), which are of the intestinal type and show marked aneuploidy, *TP53* mutations, and focal amplification of RAS and receptor tyrosine kinases. The EBV-positive subtype was associated with the most favourable prognosis, followed by the MSI and chromosomal instability subtypes.

ACRG reported a similar classification of gastric cancer and distinguished the following four molecular subtypes (Fig. 5.4.4): (i) MSI hypermutated tumours, which are of the intestinal type and are mostly localized to the antrum, and microsatellite stable (MSS) tumours, subdivided into (ii) those that exhibit features of epithelial–mesenchymal transition (MSS/EMT), which occur at a younger age and are mostly of the diffuse type; (iii) those that lose p53 activity (MSS/TP53−) and show amplification of *HER2* (*ERBB2*); and (iv) those with wild-type *TP53* (MSS/TP53+), which are associated with EBV. The MSS/EMT and MSS/TP53− gastric cancers had the poorest survival [23].

A recent meta-analysis confirmed the prognostic value of histological subtyping of gastric cancer, showing that the diffuse subtype is associated with younger patients and poorer prognosis than the intestinal type [24]. According to the TCGA and ACRG molecular classifications, the genomically stable and MSS/EMT subtypes, which are composed mostly of tumours of the diffuse type, have the worst prognosis and overall survival (Fig. 5.4.4) [25,26,27].

Fig. 5.4.4. The main subtypes of gastric adenocarcinoma defined according to the Laurén histological classification and the Cancer Genome Atlas (TCGA) Research Network and Asian Cancer Research Group (ACRG) molecular classifications. The global distribution frequencies of gastric cancer subtypes are indicated as percentages. TCGA subtypes: MSI, microsatellite instability; CIN, chromosomal instability; EBV+, positive for Epstein–Barr virus; GS, genomically stable. ACRG subtypes: MSI, microsatellite instability; MSS/TP53−, microsatellite stable with inactive *TP53*; MSS/TP53+, microsatellite stable with active *TP53*; MSS/EMT, microsatellite stable with features of epithelial–mesenchymal transition. For each subtype, the clinical characteristics and the main genetic and molecular alterations are listed. mTOR, mammalian target of rapamycin; RTKs, receptor tyrosine kinases.



Recent studies using integrated bioinformatics analyses have led to the proposal of a panel of genes that are associated with the pathogenesis of gastric cancer, the value of adjuvant therapy, and the prognosis of resectable gastric cancer [28,29]. There is a need for further validation in prospective studies and for standardization of tools that can be used in clinical practice to screen gene expression in tumours.

Etiology

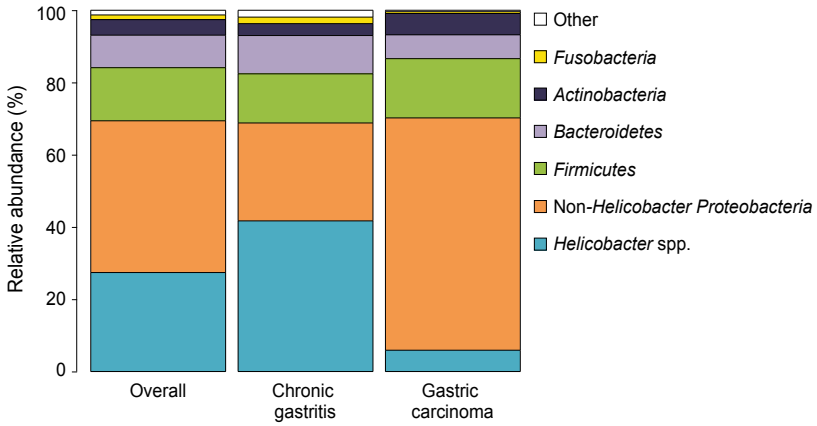
It is now agreed that *H. pylori* infection is responsible for about 90% of gastric adenocarcinomas – via the Correa cascade of multistep gastric carcinogenesis for the intestinal type and by other mechanisms for the diffuse type – and that about 10% of gastric cancers are the consequence of EBV infection. However, since the development of new molecular methods to study the microbiota (see Chapter 3.10), it has been shown that *H. pylori* is not the only bacterium that is found in the stomach, and the question of the newly recognized role of the microbiota in gastric carcinogenesis has emerged.

Recent studies, mainly in Asia, have identified the microbiota from gastric biopsies by 16S ribosomal DNA sequencing and compared the microbiota of patients with gastritis, precancerous lesions, and gastric cancer. A study in Singapore and Malaysia compared cases of gastric cancer and controls with functional dyspepsia (n = 32) and found that patients with gastric cancer had higher relative abundances of bacterial species that are commonly found in the oral cavity [30]. A study in Taiwan, China, compared patients with gastritis, intestinal metaplasia, and gastric cancer (n = 27) and found a gastric cancer-specific bacterial signature consisting of *Clostridium*

(mainly *C. colicanis*), *Fusobacterium* (*F. nucleatum*), and *Lactobacillus* (*L. gasseri* and *L. reuteri*) [31]. A study in Xi'an, China, observed significant microbial dysbiosis in cases of intestinal metaplasia and gastric cancer compared with cases of superficial gastritis only (n = 81) and highlighted a group of five species of oral bacteria that are associated with gastric cancer [32]. In contrast, a study in Portugal of patients with chronic gastritis and with gastric carcinoma (n = 135) found an enrichment of intestinal bacteria rather than oral bacteria, and these results were confirmed in validation cohorts in China and Mexico (Fig. 5.4.5) [33]. A study in Nicaragua determined the presence of viable bacteria by metatranscriptomic analysis of stomach biopsy specimens from patients undergoing endoscopy (n = 25) and found that the gastric microbiota did not change in relation to the level of atrophy in the tissue but that there was a significant positive correlation between expression of *Deinococcus*, *Sulfurospirillum*, and *Campylobacter* and *H. pylori* genes, especially those involved in pH regulation and nickel transport [34].

The main limitation of these studies is that they are cross-sectional and cannot reveal whether the gastric microbiota described corresponds to bacteria that are resident or only transitory. However, because high pH is an important determinant of bacterial colonization, it is logical to imagine that these bacteria can colonize the stomach in the case of atrophy and intestinal metaplasia, which leads to decreased acid production and is the outcome of long-term *H. pylori* infection. Once established, these bacteria could contribute to carcinogenesis by increasing inflammation, producing *N*-nitroso compounds or acetaldehyde, and also modifying the physiology of the stomach.

Fig. 5.4.5. The influence of *Helicobacter pylori* in the microbiota composition of chronic gastritis and gastric carcinoma. Relative abundance of the different bacterial phyla overall (i.e. in all patients), in patients with chronic gastritis only, and in patients with gastric carcinoma. NS, not significant.



Taxa	Chronic gastritis (%)	Gastric carcinoma (%)	*P* value
Proteobacteria	68.8	70.2	NS
Helicobacter spp.	41.7	5.9	< 0.001
Non-*Helicobacter Proteobacteria*	27.1	64.3	< 0.001
Firmicutes	13.6	16.4	0.040
Bacteroidetes	10.6	6.6	0.003
Actinobacteria	3.3	5.9	< 0.001
Fusobacteria	1.8	0.5	< 0.001

More studies are needed on patient cohorts, on humanized animal models, and on different populations; also, elements of the microbiota other than bacteria should be included, such as fungi, archaea, and viruses [35]. A more in-depth knowledge of the gastric microbiota in relation to gastric cancer should help researchers to develop strategies for reducing the burden of this disease.

Biological characteristics and early detection

Biomarkers

Many biomarkers for gastric cancer diagnosis have been described, including CA72-4, CA12-5, SLE, BCA-225, hCG, and the ratio between the levels of pepsinogen I and II; the most frequently used biomarkers in clinical practice are CEA and CA19-9 [36]. Cellular heterogeneity must be considered in research on biomarkers for early detection, prognosis, and targeted therapy. Cancer stem cells are a rare subpopulation of gastric cancer cells at the origin of tumour initiation and progression [37]. Several cell surface markers of gastric cancer stem cells have been identified using mouse models of patient-derived tumour xenografts, gastric organoid culture, and transgenic mouse models. These markers include CD44, CD133, Lgr5, CD24, CD166, and ALDH, all of which are putative biomarkers for diagnosis and therapeutic targets [25].

The pathogenesis of gastric cancer also involves epigenetic mechanisms (see Chapter 3.8). Infection with *H. pylori* and EBV and the subsequent chronic inflammation all participate in aberrant DNA methylation and more generally in this epigenetic dysregulation. The detection of *CDH1* promoter methylation in blood samples has been proposed as a diagnostic tool [38]. Other non-invasive biomarkers have been proposed for gastric cancer diagnosis and follow-up, including long non-coding RNAs and small non-coding RNAs such as microRNAs,

Table 5.4.2. Current topics of molecular markers associated with diagnosis, prognosis, and prediction of therapeutic response of gastric cancer

Marker	Alteration	Clinical purpose	Detection method
Metastasis-related genes			
Growth factors			
HER2, FGFR, PI3K/Akt/mTOR (*PIK3CA*), MET, VEGF (VEGFR2, VEGFD)	Overexpression	Diagnostic, prognostic, therapeutic	Tissue
Cell-cycle regulation			
TP53	Mutation	Diagnostic	Tissue
Adhesion molecule			
E-cadherin (*CDH1*)	Mutation, epigenetic alteration	Diagnostic, prognostic	Tissue, blood
Immune checkpoint			
PD-L1	Mutation	Prognostic, therapeutic	Tissue
Comprehensive gene analysis			
CEACEM6, *APOC1*, *YF13H12*, *CDH17*, *REG4*, *OLFM4*, *HOXA10*, *DSC2*, *TSPAN8*, *TM9SF3*, *FUS*, *COLIA1*, *COLIA2*, *APOE*	Upregulation	Diagnostic, prognostic, therapeutic	Tissue
ATP4B, *S100A9*, *CYP20A1*, *ARPC3*, *DDX5*, *CLDN18*	Downregulation	Diagnostic, prognostic, therapeutic	Tissue
Microsatellite instability	High level	Prognostic, therapeutic	Tissue
Epigenetic alterations			
CDH1, *CHFR*, *DAPK*, *GSTP1*, *p15*, *p16*, *RARβ*, *RASSF1A*, *RUNX3*, *TFPI2*	Hypermethylation	Diagnostic	Tissue
Genetic polymorphism			
IL-1β, *IL-1RN*, *CD44*	Single-nucleotide polymorphism	Prognostic	Tissue
TP53, *SYNE1*, *CSMD3*, *LRP1B*, *CDH1*, *PIK3CA*, *ARID1A*, *PKHD*, *KRAS*, *JAK2*, *CD274*, *PDCD1LG2*	Copy number variations, mutations	Diagnostic, prognostic, therapeutic	Tissue
Circulating tumour cells			
CD44, N-cadherin, vimentin	Overexpression	Diagnostic, therapeutic	Blood
pan-CK, E-cadherin	Decreased expression	EMT process	Blood
HER2	Overexpression	Therapeutic	Blood
Circulating cell-free DNA			
APC promotor 1, RASSF1A	Hypermethylation	Diagnostic	Blood, plasma
ERBB2	Copy number variations	Therapeutic	Plasma
MicroRNAs			
miR-21, miR-23a, miR-27a, miR-106b-25, miR-130b, miR-199a, miR-215, miR-222-221, miR-370	Upregulation	Diagnostic, prognostic, therapeutic	Blood, plasma
miR-29a, miR-101, miR-125a, miR-129, miR-148b, miR-181c, miR-212, miR-218, miR-335, miR-375, miR-449, miR-486, miR-512	Upregulation	Diagnostic, prognostic, therapeutic	Blood, plasma
Cell-free microRNAs			
miR-331 and miR-21	Upregulation	Diagnostic, prognostic	Blood
miR-20b, miR-125a, miR-137, miR-141, miR-146a, miR-196a, miR-206, miR-218, miR-486-5p	Upregulation	Prognostic	Blood, plasma
miR-10b-5p, miR-132-3p, miR-185-5p, miR-195-5p, miR-20a-3p, miR-296-5p	Upregulation	Prognostic	Plasma
Long non-coding RNAs			
ncRuPAR	Downregulation	Diagnostic, prognostic	Tissue
AI364715, GACAT1, GACAT2	Downregulation	Prognostic	Tissue
PVT1	Upregulation	Prognostic	Tissue

Table 5.4.2. Current topics of molecular markers associated with diagnosis, prognosis, and prediction of therapeutic response of gastric cancer (continued)

Marker	Alteration	Clinical purpose	Detection method
Exosomes			
miR-19b, miR-106a	Upregulation	Diagnostic, prognostic	Plasma
miR-21, miR-1225-5p	Upregulation	Diagnostic, therapeutic	Peritoneal lavage fluid
Stomach-specific biomarkers			
ADAM23, GDNF, MINT25, MLF1, PRDM5, RORA	Hypermethylation	Diagnostic	Gastric wash
BARHL2	Hypermethylation	Diagnostic, therapeutic	Gastric wash, gastric juice
PVT1	Upregulation	Diagnostic, prognostic	Gastric juice
miR-421, miR-21, miR-106a, miR-129	Upregulation	Diagnostic	Gastric juice
CagA	Upregulation	Diagnostic	Tissue
VacA	Upregulation	Diagnostic	Tissue
Gastrokine 1	Inactivation	Prognostic	Tissue

CagA, cytotoxin-associated gene A; EMT, epithelial–mesenchymal transition; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; MSI, microsatellite instability; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; PD-L1, programmed death-ligand 1; VacA, vacuolating toxin A; VEGF, vascular endothelial growth factor; VEGFD, vascular endothelial growth factor D; VEGFR2, vascular endothelial growth factor receptor 2.

which are abnormally expressed in tumour tissue and can be detected by sensitive molecular methods in body fluids including serum, plasma, gastric juice, and urine of patients. Additional studies are required to improve their diagnostic and prognostic accuracy (Table 5.4.2) [36].

Targeted therapies

Trastuzumab therapy for patients with HER2-positive tumours was the first example of molecular targeted therapy for gastric cancer. The Trastuzumab for Gastric Cancer international randomized clinical trial demonstrated that treatment with trastuzumab (a monoclonal antibody targeting HER2) plus chemotherapy significantly improved survival of patients with HER2-positive advanced disease [39]. HER2 amplification is routinely detected in resected tumours by standard immunohistochemistry. In an international randomized multicentre trial, ramucirumab, which targets vascular endothelial growth factor receptor 2 (VEGFR2), has also shown efficacy as anti-angiogenic therapy for previously treated advanced gastric cancer [40].

The MSI and mismatch repair status has an impact on responsiveness to chemotherapy and on prognosis in resectable gastric cancer. In two clinical trials, patients with either MSI-high or mismatch repair-deficient tumours (6.6%) had better overall survival than patients with neither MSI-high nor mismatch repair-deficient tumours when treated with surgery alone [41,42]. Inhibition of anti-tumour immune cell activity, mediated by programmed death-ligand 1 (PD-L1) or PD-L2, is particularly upregulated in EBV-positive tumours [21]. The successful outcomes of multicentre trials of the immune checkpoint inhibitor pembrolizumab support the use of tumour PD-L1 and MSI status as a guide to therapy and prognosis in resectable gastric cancer [43,44].

Prevention

Reduced exposure to carcinogens

The consumption of processed meat has been associated with gastric cancer in several case–control and cohort studies in many countries worldwide. For gastric cancer specifically, the IARC Monographs found the evidence to be limited for processed meat and inadequate for red meat (see Chapter 2.6) [45].

Carcinogens from red meat include heterocyclic aromatic amines and polycyclic aromatic hydrocarbons produced by cooking meat at high temperatures. *N*-nitroso compounds and polycyclic aromatic hydrocarbons are found in processed meat after curing and smoking. Red meat and processed meat also contain salt; high dietary salt intake, low intake of fresh fruits and vegetables, and tobacco smoking are behavioural factors that increase the risk of gastric cancer [2].

Fig. 5.4.6. The consumption of processed meat has been associated with increased risk of gastric cancer.

The Stomach Cancer Pooling Project, a consortium that included 23 epidemiological studies with 10 290 cases and 26 145 controls from Europe, North America, and Asia, evaluated the risk factors for gastric cancer using individual data rather than conventional meta-analysis. Tobacco smoking was confirmed as an important risk factor. The risk was higher for cardia tumours than for non-cardia tumours, both with and without *H. pylori* infection. In addition, the risk increased with the intensity and duration of smoking and decreased after smoking cessation [46]. Alcohol consumption was also a risk factor for both cardia and non-cardia gastric cancer and for both the intestinal and diffuse histological subtypes, but at a lower magnitude than that found in conventional meta-analysis [47].

Screening and improved methods of detection and diagnosis

In countries with low or medium incidence of gastric carcinoma, and in subjects at increased risk on the basis of family history, *H. pylori* infection history, ethnic background, or immigration from a geographical location where risk of gastric cancer is high, endoscopic surveillance with multiple biopsies for a topographical mapping of the entire stomach and staging of gastric histology according to the Operative Link on Gastritis Assessment (OLGA) and the Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) systems is recommended [48,49]. *CDH1* testing is recommended for patients with a family history of hereditary diffuse gastric cancer and those with precursor lesions for signet ring cell carcinoma [50]. Guidelines were also developed for follow-up of individuals at risk [51].

The development of new endoscopy imaging technologies will help health professionals to diagnose intestinal metaplasia and early gastric cancer [52]. Another strategy, in addition to upper digestive endoscopy, for the diagnosis and surveillance of gastric pre-neoplastic lesions is the use of both serum pepsinogen levels and *H. pylori* serology [53]. A low serum pepsinogen I level or a low pepsinogen I/II ratio is associated with gastric atrophy and is the best available marker, despite its limited sensitivity for predicting risk of gastric cancer. A recent meta-analysis of 27 studies including 8654 patients from different geographical regions confirmed the potential use of serum pepsinogen I and II levels in combination with gastrin-17 and anti-*H. pylori* antibodies for the non-invasive diagnosis and screening of atrophic gastritis of the corpus and the antrum [54].

Fig. 5.4.7. A patient undergoing endoscopy.

References

1. IARC (1994). Schistosomes, liver flukes and *Helicobacter pylori*. IARC Monogr Eval Carcinog Risks Hum. 61:1–241. Available from: http://publications.iarc.fr/79 PMID:7715068
2. IARC (2012). Biological agents. IARC Monogr Eval Carcinog Risks Hum. 100B:1–441. Available from: http://publications.iarc.fr/119 PMID:23189750
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593
4. Agudo A, Cayssials V, Bonet C, Tjønneland A, Overvad K, Boutron-Ruault M-C, et al. (2018). Inflammatory potential of the diet and risk of gastric cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Am J Clin Nutr. 107(4):607–16. https://doi.org/10.1093/ajcn/nqy002 PMID:29635497

5. Whary MT, Sundina N, Bravo LE, Correa P, Quinones F, Caro F, et al. (2005). Intestinal helminthiasis in Colombian children promotes a Th2 response to *Helicobacter pylori*: possible implications for gastric carcinogenesis. Cancer Epidemiol Biomarkers Prev. 14(6):1464–9. https://doi.org/10.1158/1055-9965.EPI-05-0095 PMID:15941957

6. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, et al. (2017). Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. Gastroenterology. 153(2):420–9. https://doi.org/10.1053/j.gastro.2017.04.022 PMID:28456631

7. Zamani M, Ebrahimtabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J, et al. (2018). Systematic review with meta-analysis: the worldwide prevalence of *Helicobacter pylori* infection. Aliment Pharmacol Ther. 47(7):868–76. https://doi.org/10.1111/apt.14561 PMID:29430669

8. Lee JH, Choi KD, Jung H-Y, Baik GH, Park JK, Kim SS, et al.; Korean College of *Helicobacter* and Upper Gastrointestinal Research (2018). Seroprevalence of *Helicobacter pylori* in Korea: a multicenter, nationwide study conducted in 2015 and 2016. Helicobacter. 23(2):e12463. https://doi.org/10.1111/hel.12463 PMID:29345022

9. Liu J, Wang Y, Zhao Q, Luo R, Xiao M, Zhang M, et al. (2017). Prevalence and risk factors for *Helicobacter pylori* infection in southwest China: a study of health examination participants based on ^{13}C-urea breath test. Turk J Med Sci. 47(5):1456–62. https://doi.org/10.3906/sag-1605-149 PMID:29151317

10. Binh TT, Tuan VP, Dung HDQ, Tung PH, Tri TD, Thuan NPM, et al. (2018). Molecular epidemiology of *Helicobacter pylori* infection in a minor ethnic group of Vietnam: a multiethnic, population-based study. Int J Mol Sci. 19(3):E708. https://doi.org/10.3390/ijms19030708 PMID:29494554

11. Yin J, Song JN, Bai ZG, Cai J, Zhang J, Zheng Z, et al. (2017). Gastric cancer mortality trends in China (2006–2013) reveal increasing mortality in young subjects. Anticancer Res. 37(8):4671–9. https://doi.org/10.21873/anticanres.11871 PMID:28739770

12. Hiroi S, Sugano K, Tanaka S, Kawakami K (2017). Impact of health insurance coverage for *Helicobacter pylori* gastritis on the trends in eradication therapy in Japan: retrospective observational study and simulation study based on real-world data. BMJ Open. 7(7):e015855. https://doi.org/10.1136/bmjopen-2017-015855 PMID:28760790

13. Tsuda M, Asaka M, Kato M, Matsushima R, Fujimori K, Akino K, et al. (2017). Effect on *Helicobacter pylori* eradication therapy against gastric cancer in Japan. Helicobacter. 22(5):e12415. https://doi.org/10.1111/hel.12415 PMID:28771894

14. Bae SE, Choi KD, Choe J, Kim SO, Na HK, Choi JY, et al. (2018). The effect of eradication of *Helicobacter pylori* on gastric cancer prevention in healthy asymptomatic populations. Helicobacter. 23(2):e12464. https://doi.org/10.1111/hel.12464 PMID:29345408

15. Huerta-Franco MR, Banderas JW, Allsworth JE (2018). Ethnic/racial differences in gastrointestinal symptoms and diagnosis associated with the risk of *Helicobacter pylori* infection in the US. Clin Exp Gastroenterol. 11:39–49. https://doi.org/10.2147/CEG.S144967 PMID:29403299

16. Anderson WF, Rabkin CS, Turner N, Fraumeni JF Jr, Rosenberg PS, Camargo MC (2018). The changing face of noncardia gastric cancer incidence among US non-Hispanic whites. J Natl Cancer Inst. 110(6):608–15. https://doi.org/10.1093/jnci/djx262 PMID:29361173

17. Luo G, Zhang Y, Guo P, Wang L, Huang Y, Li K (2017). Global patterns and trends in stomach cancer incidence: age, period and birth cohort analysis. Int J Cancer. 141(7):1333–44. https://doi.org/10.1002/ijc.30835 PMID:28614909

18. Venneman K, Huybrechts I, Gunter MJ, Vandendaele L, Herrero R, Van Herck K (2018). The epidemiology of *Helicobacter pylori* infection in Europe and the impact of lifestyle on its natural evolution toward stomach cancer after infection: a systematic review. Helicobacter. 23(3):e12483. https://doi.org/10.1111/hel.12483 PMID:29635869

19. Fewings E, Larionov A, Redman J, Goldgraben MA, Scarth J, Richardson S, et al. (2018). Germline pathogenic variants in *PALB2* and other cancer-predisposing genes in families with hereditary diffuse gastric cancer without *CDH1* mutation: a whole-exome sequencing study. Lancet Gastroenterol Hepatol. 3(7):489–98. https://doi.org/10.1016/S2468-1253(18)30079-7 PMID:29706558

20. Oliveira C, Pinheiro H, Figueiredo J, Seruca R, Carneiro F (2015). Familial gastric cancer: genetic susceptibility, pathology, and implications for management. Lancet Oncol. 16(2):e60–70. https://doi.org/10.1016/S1470-2045(14)71016-2 PMID:25638682

21. The Cancer Genome Atlas Research Network (2014). Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 513(7517):202–9. https://doi.org/10.1038/nature13480 PMID:25079317

22. Wang K, Yuen ST, Xu J, Lee SP, Yan HHN, Shi ST, et al. (2014). Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. Nat Genet. 46(6):573–82. https://doi.org/10.1038/ng.2983 PMID:24816253

23. Cristescu R, Lee J, Nebozhyn M, Kim K-M, Ting JC, Wong SS, et al. (2015). Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med. 21(5):449–56. https://doi.org/10.1038/nm.3850 PMID:25894828

24. Petrelli F, Berenato R, Turati L, Mennitto A, Steccanella F, Caporale M, et al. (2017). Prognostic value of diffuse versus intestinal histotype in patients with gastric cancer: a systematic review and meta-analysis. J Gastrointest Oncol. 8(1):148–63. https://doi.org/10.21037/jgo.2017.01.10 PMID:28280619

25. Carrasco-Garcia E, García-Puga M, Arevalo S, Matheu A (2018). Towards precision medicine: linking genetic and cellular heterogeneity in gastric cancer. Ther Adv Med Oncol. 10:1758835918794628. https://doi.org/10.1177/1758835918794628 PMID:30181784

26. Sohn BH, Hwang J-E, Jang H-J, Lee H-S, Oh SC, Shim J-J, et al. (2017). Clinical significance of four molecular subtypes of gastric cancer identified by The Cancer Genome Atlas project. Clin Cancer Res. 23(15):4441–9. https://doi.org/10.1158/1078-0432.CCR-16-2211 PMID:28747339

27. Cisło M, Filip AA, Arnold Offerhaus GJ, Ciseł B, Rawicz-Pruszyński K, Skierucha M, et al. (2018). Distinct molecular subtypes of gastric cancer: from Laurén to molecular pathology. Oncotarget. 9(27):19427–42. https://doi.org/10.18632/oncotarget.24827 PMID:29721214

28. Li X, Wu WKK, Xing R, Wong SH, Liu Y, Fang X, et al. (2016). Distinct subtypes of gastric cancer defined by molecular characterization include novel mutational signatures with prognostic capability. Cancer Res. 76(7):1724–32. https://doi.org/10.1158/0008-5472.CAN-15-2443 PMID:26857262

29. Liu X, Meltzer SJ (2017). Gastric cancer in the era of precision medicine. Cell Mol Gastroenterol Hepatol. 3(3):348–58. https://doi.org/10.1016/j.jcmgh.2017.02.003 PMID:28462377

30. Castaño-Rodríguez N, Goh K-L, Fock KM, Mitchell HM, Kaakoush NO (2017). Dysbiosis of the microbiome in gastric carcinogenesis. Sci Rep. 7(1):15957. https://doi.org/10.1038/s41598-017-16289-2 PMID:29162924

31. Hsieh YY, Tung S-Y, Pan H-Y, Yen C-W, Xu H-W, Lin Y-J, et al. (2018). Increased abundance of *Clostridium* and *Fusobacterium* in gastric microbiota of patients with gastric cancer in Taiwan. Sci Rep. 8(1):158. https://doi.org/10.1038/s41598-017-18596-0 PMID:29317709

32. Coker OO, Dai Z, Nie Y, Zhao G, Cao L, Nakatsu G, et al. (2018). Mucosal microbiome dysbiosis in gastric carcinogenesis. Gut. 67(6):1024–32. https://doi.org/10.1136/gutjnl-2017-314281 PMID:28765474

33. Ferreira RM, Pereira-Marques J, Pinto-Ribeiro I, Costa JL, Carneiro F, Machado JC, et al. (2018). Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota. Gut. 67(2):226–36. https://doi.org/10.1136/gutjnl-2017-314205 PMID:29102920

34. Thorell K, Bengtsson-Palme J, Liu OH-F, Palacios Gonzales RV, Nookaew I, Rabeneck L, et al. (2017). *In vivo* analysis of the viable microbiota and *Helicobacter pylori* transcriptome in gastric infection and early stages of carcinogenesis. Infect Immun. 85(10):e00031–17. https://doi.org/10.1128/IAI.00031-17 PMID:28694295

35. Noto JM, Peek RM Jr (2017). The gastric microbiome, its interaction with *Helicobacter pylori*, and its potential role in the progression to stomach cancer. PLoS Pathog. 13(10):e1006573. https://doi.org/10.1371/journal.ppat.1006573 PMID:28982167

36. Matsuoka T, Yashiro M (2018). Biomarkers of gastric cancer: current topics and future perspective. World J Gastroenterol. 24(26):2818–32. https://doi.org/10.3748/wjg.v24.i26.2818 PMID:30018477

37. Nguyen PH, Giraud J, Chambonnier L, Dubus P, Wittkop L, Belleannée G, et al. (2017). Characterization of biomarkers of tumorigenic and chemoresistant cancer stem cells in human gastric carcinoma. Clin Cancer Res. 23(6):1586–97. https://doi.org/10.1158/1078-0432.CCR-15-2157 PMID:27620279

38. Wen J, Zheng T, Hu K, Zhu C, Guo L, Ye G (2017). Promoter methylation of tumor-related genes as a potential biomarker using blood samples for gastric cancer detection. Oncotarget. 8(44):77783–93. https://doi.org/10.18632/oncotarget.20782 PMID:29100425

39. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al.; ToGA Trial Investigators (2010). Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 376(9742):687–97. https://doi.org/10.1016/S0140-6736(10)61121-X PMID:20728210

40. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al.; REGARD Trial Investigators (2014). Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 383(9911):31–9. https://doi.org/10.1016/S0140-6736(13)61719-5 PMID:24094768

41. Choi Y, Kim H, Yang H, Kim WH, Kim YW, Kook M-C, et al. (2017). Clinical impact of microsatellite instability in patients with stage II and III gastric cancer: results from the CLASSIC trial. J Clin Oncol. 35(15_suppl):4022. https://doi.org/10.1200/JCO.2017.35.15_suppl.4022

42. Smyth EC, Wotherspoon A, Peckitt C, Gonzalez D, Hulkki-Wilson S, Eltahir Z, et al. (2017). Mismatch repair deficiency, microsatellite instability, and survival: an exploratory analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial. JAMA Oncol. 3(9):1197–203. https://doi.org/10.1001/jamaoncol.2016.6762 PMID:28241187

43. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. (2015). PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 372(26):2509–20. https://doi.org/10.1056/NEJMoa1500596 PMID:26028255

44. Muro K, Chung HC, Shankaran V, Geva R, Catenacci D, Gupta S, et al. (2016). Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. Lancet Oncol. 17(6):717–26. https://doi.org/10.1016/S1470-2045(16)00175-3 PMID:27157491

45. Bouvard V, Loomis D, Guyton KZ, Grosse Y, Ghissassi FE, Benbrahim-Tallaa L, et al.; International Agency for Research on Cancer Monograph Working Group (2015). Carcinogenicity of consumption of red and processed meat. Lancet Oncol. 16(16):1599–600. https://doi.org/10.1016/S1470-2045(15)00444-1 PMID:26514947

46. Praud D, Rota M, Pelucchi C, Bertuccio P, Rosso T, Galeone C, et al. (2018). Cigarette smoking and gastric cancer in the Stomach Cancer Pooling (StoP) Project. Eur J Cancer Prev. 27(2):124–33. https://doi.org/10.1097/CEJ.0000000000000290 PMID:27560662

47. Ferro A, Morais S, Pelucchi C, Aragonés N, Kogevinas M, López-Carrillo L, et al. (2019). Smoking and *Helicobacter pylori* infection: an individual participant pooled analysis (Stomach Cancer Pooling- StoP Project). Eur J Cancer Prev. 28(5):390–6. https://doi.org/10.1097/CEJ.0000000000000471 PMID:30272597

48. Rugge M, Genta RM, Fassan M, Valentini E, Coati I, Guzzinati S, et al. (2018). OLGA gastritis staging for the prediction of gastric cancer risk: a long-term follow-up study of 7436 patients. Am J Gastroenterol. 113(11):1621–8. https://doi.org/10.1038/s41395-018-0353-8 PMID:30333540

49. den Hollander WJ, Holster IL, den Hoed CM, Capelle LG, Tang TJ, Anten M-P, et al. (2019). Surveillance of premalignant gastric lesions: a multicentre prospective cohort study from low incidence regions. Gut. 68(4):585–93. https://doi.org/10.1136/gutjnl-2017-314498 PMID:29875257

50. van der Post RS, Vogelaar IP, Carneiro F, Guilford P, Huntsman D, Hoogerbrugge N, et al. (2015). Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline *CDH1* mutation carriers. J Med Genet. 52(6):361–74. https://doi.org/10.1136/jmedgenet-2015-103094 PMID:25979631

51. Dinis-Ribeiro M, Areia M, de Vries AC, Marcos-Pinto R, Monteiro-Soares M, O'Connor A, et al.; European Society of Gastrointestinal Endoscopy; European Helicobacter Study Group; European Society of Pathology; Sociedade Portuguesa de Endoscopia Digestiva (2012). Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Endoscopy. 44(1):74–94. https://doi.org/10.1055/s-0031-1291491 PMID:22198778

52. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al.; faculty members of Kyoto Global Consensus Conference (2015). Kyoto global consensus report on *Helicobacter pylori* gastritis. Gut. 64(9):1353–67. https://doi.org/10.1136/gutjnl-2015-309252 PMID:26187502

53. Miki K (2011). Gastric cancer screening by combined assay for serum anti-*Helicobacter pylori* IgG antibody and serum pepsinogen levels - "ABC method". Proc Jpn Acad Ser B Phys Biol Sci. 87(7):405–14. https://doi.org/10.2183/pjab.87.405 PMID:21785258

54. Syrjänen K (2016). A panel of serum biomarkers (GastroPanel®) in non-invasive diagnosis of atrophic gastritis. Systematic review and meta-analysis. Anticancer Res. 36(10):5133–44. https://doi.org/10.21873/anticanres.11083 PMID:27798873

5.5 Colorectal cancer
Decreasing disparities and promoting prevention are policy priorities

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SUMMARY

- The estimated age-standardized incidence rates of colorectal cancer in countries with higher Human Development Index are about 5 times those in countries with lower Human Development Index. In Australia and Europe, the rates are 35–42 per 100 000 in men and 24–32 per 100 000 in women, compared with 7 per 100 000 in men and 6 per 100 000 in women in West Africa and 6 per 100 000 in men and 4 per 100 000 in women in South Asia.
- Sporadic colorectal cancers have traditionally been described as developing along two molecular pathways: (i) the conventional adenoma–carcinoma, or chromosomal instability, pathway, and (ii) the serrated pathway.
- The chromosomal instability pathway, which involves Wnt signalling and *KRAS* mutation, accounts for about 70–75% of sporadic colorectal cancers.
- The serrated pathway involves *BRAF* mutation and the accumulation of epigenetic alterations, which cause silencing of regulatory genes, often including *MLH1* (CpG island methylator phenotype and microsatellite instability-high phenotype); this pathway accounts for about 25–30% of sporadic colorectal cancers.
- Dietary patterns characterized by high intakes of fruits and vegetables, whole grains, nuts and legumes, fish and other seafood, and milk and other dairy products are associated with a lower risk of colorectal cancer. Dietary patterns characterized by high intakes of red meat, processed meat, sugar-sweetened beverages, refined grains, desserts, and potatoes are associated with a higher risk of colorectal cancer.
- There is convincing evidence that physical activity decreases the risk of colon cancer.
- Screening, with stool-based tests for occult blood or with endoscopic methods, is associated with a reduction in colorectal cancer incidence and mortality.
- Use of aspirin appeared to reduce colorectal cancer incidence and mortality, after a latency of about 10 years.

Epidemiology

Global burden

Worldwide, colorectal cancer is the third most common cancer in men and the second most common in women, accounting for an estimated 1.85 million new cases and 881 000 deaths in 2018 [1]. The global disease burden in 2016 was estimated as 17.2 million (95% confidence interval, 6.5–17.9 million) disability-adjusted life years, of which 97% came from years of life lost due to premature mortality and 3% came from years of healthy life lost due to disability. Colorectal cancer survivors diagnosed with the disease during the previous 5 years made up about 11% of all 5-year cancer survivors estimated to be alive at the end of 2018 [1].

In general, colorectal cancer incidence rates are now considered to be one of the clearest indicators of disease transition within countries that are undergoing socioeconomic development, which is associated with shifts to lifestyles more typical of industrialized countries, because colorectal cancer rates show a strong positive gradient with Human Development Index (HDI) or Sociodemographic Index (SDI) (see Chapter 1.3) [2].

The estimated age-standardized incidence rates of colorectal cancer in countries with higher HDI (e.g. Australia, New Zealand, and European countries) are about 5 times those in countries with lower HDI (e.g. countries in Africa and South Asia). In Australia and Europe, the rates are 35–42 per 100 000 in men and 24–32 per 100 000 in women, compared with 7 per 100 000 in men and 6 per 100 000 in women in West Africa and 6 per 100 000 in men and 4 per 100 000 in women in South Asia [1].

Colorectal cancer tends to occur more frequently in men than in women, although the male-to-female ratio decreases from 1.6 in countries with high SDI to 1.0 in countries with low SDI [3]. The incidence rates increase with age: of the estimated 1.85 million new cases worldwide in 2018, about 10% were estimated to occur in people younger than 50 years, 59% in people aged 50–74 years, and 31% in people aged 75 years and older [1].

Those countries with the highest incidence rates tend to have relatively low mortality rates, compared with the regions of Africa, Asia, and South America, which have considerably higher mortality-to-incidence ratios [1,4,5]. The observed association of colorectal cancer mortality-to-incidence ratios with health system ranking suggests that health-care organization, including cancer-related screening and care, has a substantial impact on colorectal cancer mortality [6].

Geographical patterns of colorectal cancer incidence and mortality are related to indexes of development. In addition, colorectal cancer mortality is strongly associated with indexes of socioeconomic status, also within high-income countries. Most reports have documented higher colorectal cancer mortality in people with lower socioeconomic status; this is consistent with the observed association of lower colorectal cancer survival with lower socioeconomic status [7,8].

Over the past decades, evolving cancer treatment, as well as the more recent availability of innovative drugs and chemotherapy regimens, has resulted in a trend towards improved stage-specific survival outcomes, in particular for patients with stage II and III colorectal cancer. Improvement in patient management and closer adherence to treatment guidelines – reflected in a higher use of curative surgery, chemotherapy, and radiotherapy – have contributed to the increasing trends in survival [9–11].

Financial and cultural barriers, which delay or limit access to diagnostic assessment or to appropriate high-quality oncological care after diagnosis, have emerged as the most likely determinants of the lower survival in disadvantaged groups. Indeed, a more advanced stage at diagnosis, a lower chance of receiving curative treatment, and a higher risk of having permanent stoma have been observed in patients with low socioeconomic status, as well as in low-income countries [7,8,12,13].

Time trends

Independent analyses of trends in colorectal cancer incidence and mortality rates by SDI quintile revealed three distinct patterns [3,4].

The first pattern, characterized by increases in both incidence rates and mortality rates, was observed in rapidly transitioning countries, i.e. in countries in the low-middle and low SDI quintiles, in which the economic growth was often associated with a shift towards unhealthy dietary habits, together with reductions in levels of physical activity and increases in the prevalence of overweight and obesity. In countries in the low SDI quintile, there was a larger increase in mortality rates than in incidence rates.

The second pattern was characterized by a decrease in mortality rates and an increase in incidence rates. The decrease in mortality rates is probably related to an increased availability of health-care resources, which favour the dissemination of best practices in cancer management. The increase in incidence rates is probably related to the recent introduction of screening and/or to persisting unfavourable lifestyle patterns. This pattern was observed in countries in the high-middle and middle SDI quintiles, as well as in some countries with high HDI and high SDI, reflecting the observed variability in the implementation of screening and in the patterns of risk factors.

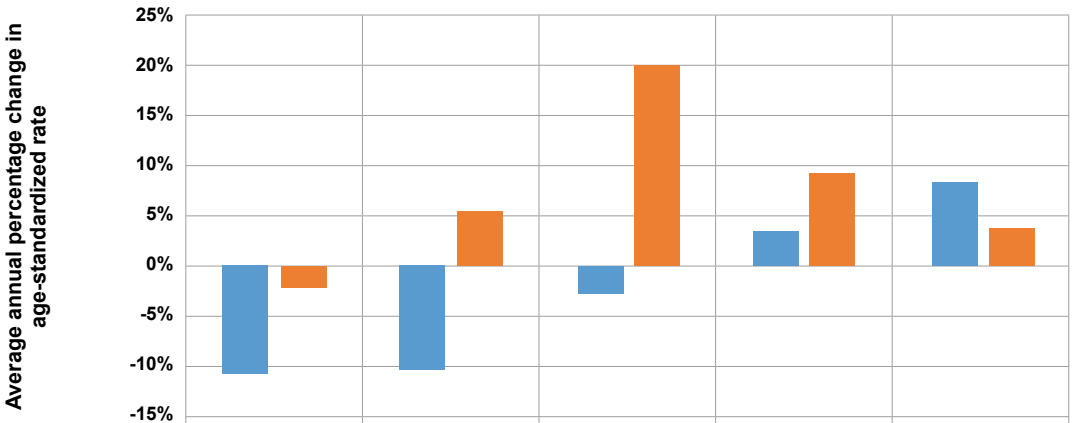
The third pattern, characterized by decreases in both incidence rates and mortality rates, was observed in countries with high HDI and high SDI. This pattern may be explained by the early introduction of screening as well as changes in profiles of risk factors and protective factors, together with the availability of high-quality cancer care.

On the basis of currently estimated incidence and mortality rates, the projected demographic changes in the global population alone will result in increases of about 80% both

FUNDAMENTALS

- Colorectal cancer is a highly preventable disease. A substantial proportion of the colorectal cancer burden is attributable to modifiable lifestyle factors and environmental factors. Effective screening methods are available.
- An improved understanding of the biology and the natural history of colorectal cancer has been associated with a trend towards more favourable outcomes in more recent years.
- As long as the stage at diagnosis remains the main determinant of survival, access to appropriate, high-quality screening can make a crucial contribution to improving colorectal cancer outcomes.
- Public health strategies aimed at reducing the prevalence of obesity, promoting physical activity, and discouraging the consumption of high-energy, obesogenic foods are gradually being implemented in many regions of the world.
- Together with policies that promote prevention, policies aimed at decreasing disparities in timely access to diagnostic assessment and to high-quality oncological care are priorities, to reduce the colorectal cancer burden.

Fig. 5.5.1. Time trends in colorectal cancer incidence and mortality for countries by quintile of the Sociodemographic Index (SDI). Average annual percentage change in age-standardized death rate (ASDR) and age-standardized incidence rate (ASIR) between 2006 and 2016 for both sexes, by SDI quintile.



	High SDI	High-middle SDI	Middle SDI	Low-middle SDI	Low SDI
Change in ASDR 2006–2016 (%)	-11%	-10%	-3%	3%	8%
Change in ASIR 2006–2016 (%)	-2%	5%	20%	9%	4%

SDI quintile

in the annual incidence of colorectal cancer (from 1.2 million new cases in 2008 to 2.2 million in 2030) and in the mortality from colorectal cancer (from 0.6 million deaths in 2008 to 1.1 million in 2030). Most of this additional disease burden will occur in countries with lower HDI, as a result of the demographic transition and the adoption of lifestyles more typical of industrialized countries. Although the number of new cases per year will remain higher in countries with high HDI, by 2035 the number of deaths from colorectal cancer will be greatest in countries with low HDI [14].

Pathogenesis

Colorectal cancer is a heterogeneous disease. The majority of cases are sporadic tumours, which have traditionally been described as developing along two molecular pathways: (i) the conventional adenoma–carcinoma, or chromosomal instability, pathway, and (ii) the serrated pathway. These two pathways account for about 70–75% and 25–30%, respectively, of sporadic colorectal cancers.

Chromosomal instability pathway

The chromosomal instability pathway is thought to be driven by the accumulation of mutational events in oncogenes and tumour suppressor genes during the progression from small adenoma to invasive carcinoma [15]. The earliest genetic event is the activation of Wnt signalling by an inactivating mutation of the adenomatous polyposis coli (*APC*) tumour suppressor gene. Sporadic *APC* mutations are detected in 5% of aberrant crypt foci, in 30–70% of adenomas, and in more than 70% of colorectal cancers. Mutation of the *KRAS* oncogene occurs preferentially in early phases of the adenoma–carcinoma sequence. *KRAS* mutations are detected in about 50% of large polyps and colorectal cancers and result in promotion of adenomatous growth. Mutations of *TP53*, *SMAD4*, *PIK3C*, and *PTEN* are late events in colorectal carcinogenesis [16]. The dwell time of these lesions (i.e. the period of time for a benign polyp to evolve into cancer) is thought to be about 10–15 years, and because of their regular, slow growth, they are likely to be detected at screening [17].

Different mechanisms contribute to chromosomal instability, resulting in karyotypic abnormalities, such as chromosome number alterations, telomere dysfunction or overexpression, or loss of heterozygosity, which has been reported in more than 70% of colorectal cancers at chromosome 18q. The stage of colorectal carcinogenesis at which the chromosomal instability phenotype arises is still uncertain. A role of *APC* mutation in favouring the initiation of chromosomal instability has been proposed, although chromosomal abnormalities have also been observed at very early stages of tumorigenesis [16].

Serrated pathway

Sessile serrated adenoma

The initiating event in the development of sessile serrated adenoma is thought to be activation of the mitogen-activated protein kinase (MAPK) pathway through mutation of the *BRAF* oncogene; this triggers downregulation of apoptosis and enables cell proliferation. In the serrated pathway, *BRAF* mutation is associated

Trends by age, sex, site, and stage

Data from the United States Surveillance, Epidemiology, and End Results (SEER) programme have shown that colorectal cancer incidence and mortality rates have declined in people older than 50 years since the late 1980s. This decline is probably related to the implementation of screening. In contrast, there has been a continuous increase in colorectal cancer incidence rates in adults younger than 50 years, from the 1990s until 2014 [1].

Although an increase in the screening of adults younger than 50 years may have contributed to the observed increase in colorectal cancer incidence in people aged 40–49 years [1], age–period–cohort modelling of the colorectal cancer incidence data indicated only a modest period effect. A trend towards an increase in age-specific risk of colon and rectal cancer was observed in more recent birth cohorts. This supports the hypothesis of a strong birth cohort effect that began in people born in the 1950s [1].

The results of a decision-analytic modelling analysis suggested that starting screening at age 45 years instead of age 50 years may have a favourable balance between benefits and costs for all people at average risk in the USA [2]. This result holds only under the assumption of an increase in the age-specific risks of colorectal cancer for all ages older than 40 years that is proportional to the observed incidence trends for people younger than 40 years, resulting in an increase in the lifetime risk of colorectal cancer. However, colorectal cancer mortality rates have remained stable since the mid-1990s in adults younger than 50 years, with a modest increase only in White people in the most recent years, and the large relative increase in colorectal cancer incidence was based on a small increase in the absolute risk [3]. Also, a similar trend towards an increase in colorectal cancer incidence in younger cohorts has not yet been reported in other high-income countries. Therefore, the net benefit of starting screening at a younger age remains uncertain.

The proportion of colorectal cancers and adenomas located in the proximal colon has an increasing trend with age [4]. The shift to a higher proportion of colorectal cancers located in the proximal colon occurs at a younger age in women than in men [5,6]. This may also suggest a need to design sex-specific screening strategies.

The stage distribution of colorectal cancer at diagnosis has remained stable over the past decades in several high-income countries, with a shift towards a more favourable stage distribution after the introduction of screening [7,8].

References

1. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. (2017). Colorectal cancer incidence patterns in the United States, 1974–2013. J Natl Cancer Inst. 109(8):109. https://doi.org/10.1093/jnci/djw322 PMID:28376186
2. Peterse EFP, Meester RGS, Siegel RL, Chen JC, Dwyer A, Ahnen DJ, et al. (2018). The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline. Cancer. 124(14):2964–73. https://doi.org/10.1002/cncr.31543 PMID:29846933
3. Murphy CC, Lund JL, Sandler RS (2017). Young-onset colorectal cancer: earlier diagnoses or increasing disease burden? Gastroenterology. 152(8):1809–1812.e3. https://doi.org/10.1053/j.gastro.2017.04.030 PMID:28461196
4. Senore C, Bellisario C, Segnan N (2017). Distribution of colorectal polyps: implications for screening. Best Pract Res Clin Gastroenterol. 31(4):481–8. https://doi.org/10.1016/j.bpg.2017.04.008 PMID:28842058
5. Koo JH, Leong RW (2010). Sex differences in epidemiological, clinical and pathological characteristics of colorectal cancer. J Gastroenterol Hepatol. 25(1):33–42. https://doi.org/10.1111/j.1440-1746.2009.05992.x PMID:19874446
6. Massat NJ, Moss SM, Halloran SP, Duffy SW (2013). Screening and primary prevention of colorectal cancer: a review of sex-specific and site-specific differences. J Med Screen. 20(3):125–48. https://doi.org/10.1177/0969141313501292 PMID:24197771
7. Goodyear SJ, Leung E, Menon A, Pedamallu S, Williams N, Wong LS (2008). The effects of population-based faecal occult blood test screening upon emergency colorectal cancer admissions in Coventry and north Warwickshire. Gut. 57(2):218–22. https://doi.org/10.1136/gut.2007.120253 PMID:18048571
8. Zorzi M, Mangone L, Sassatelli R, Baracco S, Budroni M, Castaing M, et al.; IMPATTO COLONRETTO working group (2015). Screening for colorectal cancer in Italy: 2011–2012 survey. Epidemiol Prev. 39(3 Suppl 1):115–25. PMID:26405783

with the accumulation over time of epigenetic alterations, in the form of global methylation of CpG islands (the CpG island methylator phenotype [CIMP]), which cause silencing of regulatory genes. Methylation of the promoter region and suppression of the mismatch repair gene *MLH1*, resulting in a phenotype characterized by high microsatellite instability (MSI-high), are frequently associated with the development of cytological dysplasia [17]. Epigenetic silencing of *p16* is associated with the development of high-grade dysplasia or invasive carcinoma [18].

Although serrated colorectal cancers arising in sessile serrated adenomas with these features have a *BRAF*-mutated/CIMP-high/MSI-high molecular profile, it was suggested that a subset of sessile serrated adenomas, with methylation of the DNA repair gene *MGMT*, may be precursors of *BRAF*-mutated/CIMP-high/microsatellite stable serrated colorectal cancers [18].

Sessile serrated adenomas may have an indolent course in the early phase after *BRAF* mutation, with a rapid progression to invasive colorectal cancer after the development of cytological dysplasia, which is associated with the development of MSI [17]. This hypothesis is supported by the observation of a very low risk of *BRAF*-mutated colorectal cancers in people younger than 60 years, who, however, have a similar prevalence of sessile serrated adenomas to older people [19].

The prevalence of sessile serrated adenomas in people at average risk who undergo colonoscopy or stool-based tests for occult blood – guaiac faecal occult blood test (gFOBT) or faecal immunochemical test (FIT) – has been reported to be 2–7%. Sessile serrated adenomas are located predominantly in the proximal colon; they have a flat or sessile morphology, and they are often covered by a mucus cap. These features interfere with their detection, both by endoscopy (their subtle endoscopic appearance and indistinct borders are associated with a higher miss rate and a higher proportion of incomplete excisions) and by gFOBT or FIT (their morphology and the mucus cap are associated with a lower likelihood to bleed) [17].

Traditional serrated adenoma

Traditional serrated adenomas make up less than 1% of all serrated lesions. Therefore, limited evidence is available about their epidemiology and natural history. Traditional serrated adenomas are located predominantly in the distal colon and have a polypoid morphology and a villous component, similar to advanced conventional adenomas.

Activation of the MAPK pathway is more frequently associated with mutation of the *KRAS* oncogene, although traditional serrated adenomas may also have *BRAF* mutation. Both CIMP-high and CIMP-low phenotypes have been described in different series; the variance is probably related also to differences in the panel of markers used to define CIMP [18]. *MLH1* is rarely methylated in traditional serrated adenomas; this supports the hypothesis that traditional serrated adenomas are precursors of microsatellite stable or MSI-low colorectal cancers. Inactivation of p53 has been associated with the development of high-grade dysplasia and invasive carcinoma [18].

Recent efforts using data on RNA expression and immune response have led to new classifications associated with survival, which are undergoing validation [20]. Also, the detection of tumour mutational signatures on the basis of genome-wide data may yield possible targets for prevention, because specific signatures have been associated with particular exposures [21]. However, tumour–node–metastasis (TNM) stage and markers associated with the chromosomal instability pathway and the serrated pathway remain the guides in clinical decision-making.

KRAS mutations have been associated with reduced survival and with treatment failure in patients with advanced colorectal cancer who undergo targeted treatment with anti-epidermal growth factor receptor (anti-EGFR) antibodies [22].

CIMP-high status and *BRAF* mutation have been associated with poor prognosis [23]. MSI-high colorectal cancers generally have a favourable prognosis; this may relate to an immune response, because these tumours are strongly infiltrated by T lymphocytes, opening up opportunities for immunotherapy [24]. *BRAF* mutation is also associated with poorer survival within the MSI group [25]. MSI has been associated with resistance to 5-fluorouracil chemotherapy [24].

Risk factors

Of 17.2 million disability-adjusted life years due to colorectal cancer, 6.8 million (39.4%) are attributable to lifestyle factors [26]. This fraction appears to be fairly constant across different countries, irrespective of the large differences in colorectal cancer risk. The available evidence supports the association of diet, physical activity, and smoking with risk of colorectal cancer (Table 5.5.1) [27–31].

Dietary and nutrient patterns

The analysis of dietary or nutrient patterns has been developed as a complementary approach to analyses of single foods or nutrients, to adequately account for the interaction between food components and to characterize specific dietary habits in a more comparable way across populations (see Chapter 2.6).

Fig. 5.5.2. In high-income countries, a dietary pattern characterized by, among other things, high intakes of fruits and vegetables, whole grains, and nuts and legumes is associated with a lower risk of colorectal cancer.

Genetic susceptibility

Germline mutations or epimutations of genes involved in colorectal carcinogenesis, which are also involved in sporadic colorectal cancer pathways, are associated with hereditary syndromes. These syndromes can be divided into three broad categories: (i) non-polyposis syndromes, (ii) adenomatous polyposis syndromes, and (iii) non-adenomatous polyposis syndromes. They collectively account only for a small fraction of colorectal cancer risk attributable to genetic factors. These syndromes are characterized by an increased risk of colorectal cancer during the individual's lifetime. The estimated cumulative probability of developing the disease by age 70 years ranges from 90% in familial adenomatous polyposis to almost 0% in some variants of Lynch syndrome [1]. A summary of these syndromes is presented in Table B5.5.1.

Much of the heritable risk is probably explained by co-inheritance of low-penetrance genetic variants. Genome-wide association studies have so far identified about 60 common single-nucleotide polymorphisms that influence individual susceptibility to colorectal cancer [2]. Although the risk associated with variation at each locus is modest, risk genotypes are common in the population. It has been suggested that developing genome-wide polygenic scores may enable the identification of individuals with risk levels comparable to those of people with hereditary syndromes.

Accounting for the interaction between genetic and lifestyle-related factors may present a challenge. However, the development of risk prediction models that incorporate genetic risk scores together with other risk factor information offers the prospect of tailoring colorectal cancer screening to an individual's level of risk, thereby optimizing the use of screening resources. Assessments of the feasibility and cost–effectiveness of this approach in the setting of population-based screening are being planned.

A recent report from a large prospective cohort study showed that a genetic risk score composed of 41 published, genome-wide significant single-nucleotide polymorphisms for colorectal cancer did not meaningfully improve model discrimination of two previously validated risk prediction models for colorectal cancer, and did not substantially influence the predicted probabilities for 95% of participants [3]. These findings suggest that a genetic risk score for colorectal cancer risk prediction may have some additional practical benefit only if it is applied to people who are already predicted to be at high risk, on the basis of existing models, rather than to people at average risk.

Implementing such an approach also requires taking into account the confidentiality and ethical implications of genetic testing, and this consideration influences the acceptability of this approach.

Table B5.5.1. Genetic syndromes associated with increased risk of colorectal cancer

Syndrome	Gene mutations	Inheritance pattern
Non-polyposis syndromes		
Lynch syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*	Autosomal dominant
Familial colorectal cancer (previously known as familial colorectal cancer type X)	Not defined	
Adenomatous polyposis syndromes		
Familial adenomatous polyposis Attenuated familial adenomatous polyposis	*APC*	Autosomal dominant
MUTYH-associated polyposis[a]	*MUTYH*	Autosomal recessive
Non-adenomatous polyposis syndromes		
Peutz–Jeghers syndrome[b]	*SKT11*	Autosomal dominant
Cowden syndrome (*PTEN* hamartoma tumour syndrome)	*PTEN*	Autosomal dominant
Juvenile polyposis syndrome	*SMAD4* and *BMPR1A*	Autosomal dominant
Serrated polyposis syndrome[c]	*GREM1* and *MUTYH*	

[a] The phenotype is highly variable, presenting also with both adenomatous and hyperplastic polyps.

[b] Genetic testing may be negative in up to 50% of the cases that meet the clinical criteria.

[c] Not universal. Associated with increased risk of sporadic mismatch repair-deficient colorectal cancer.

References

1. IARC (2019). Colorectal cancer screening. IARC Handb Cancer Prev. 17:1–300. Available from: http://publications.iarc.fr/573.
2. Schmit SL, Edlund CK, Schumacher FR, Gong J, Harrison TA, Huyghe JR, et al. (2019). Novel common genetic susceptibility loci for colorectal cancer. J Natl Cancer Inst. 111(2):146–57. https://doi.org/10.1093/jnci/djy099 PMID:29917119
3. Smith T, Gunter MJ, Tzoulaki I, Muller DC (2018). The added value of genetic information in colorectal cancer risk prediction models: development and evaluation in the UK Biobank prospective cohort study. Br J Cancer. 119(8):1036–9. https://doi.org/10.1038/s41416-018-0282-8 PMID:30323197

Table 5.5.1. Risk factors and protective factors for colorectal cancer[a]

Evidence grade[b]	Reduced risk	Increment/contrast	Increased risk	Increment/contrast
Strong – convincing	Physical activity[c,d]	Higher versus lower levels	Processed meat	per 50 g/day
			Alcoholic beverages	> about 2 drinks a day
			Body fatness	
			Adult attained height[e]	
Strong – probable	Whole grains	per 90 g/day	Red meat	> 100 g/day
	Foods containing dietary fibre	per 10 g/day		
	Dairy products	per 400 g/day overall (milk: 200 g/day)		
	Calcium supplements	> 200 mg/day		
Limited – suggestive	Foods containing vitamin C		Low intake of starchy vegetables	
	Vitamin D[f]		Low intake of fruits	< 100 g/day
	Fish	per 100 g/day	Foods containing haem iron	
	Multivitamin supplements			
Sufficient evidence			Smoking[g]	Never-smoker/former smoker/current smoker

[a] Risk factors and protective factors for colorectal adenomas are generally consistent with those identified for colorectal cancer. Also, risk factors and protective factors for conventional adenomas and for sessile serrated adenomas generally overlap; the main difference is the higher risk of sessile serrated adenoma in women, as opposed to the higher prevalence of conventional adenomas in men [29].

[b] Evidence grade is based on the classification used in the WCRF/AICR report [27] and, for smoking only, in the IARC Monographs [28].

[c] Protective effect observed for colon cancer only [30].

[d] Measured as: active versus sedentary; vigorous or high versus low; < 10 metabolic equivalent (MET) hours/week, or < 1 hour/week, or < 10 minutes per day, compared with higher levels.

[e] Probably as a marker of factors that influence growth in early life.

[f] Epidemiological studies have consistently shown an inverse association between circulating concentrations of vitamin D and risk of colorectal cancer, although findings from recent Mendelian randomization analyses do not necessarily support a causal relationship [31].

[g] Current smoking was associated with risk of rectal cancer and proximal colorectal cancer, but not of distal colorectal cancer [30].

Fig. 5.5.3. In high-income countries, a dietary pattern characterized by high intakes of red meat, processed meat, sugar-sweetened beverages, refined grains, desserts, and potatoes is associated with a higher risk of colorectal cancer.

Two distinct dietary patterns have been associated with risk of colorectal cancer, and the association is stronger for men than for women. A "healthy" pattern, which is associated with a lower risk of colorectal cancer, is characterized by high intakes of fruits and vegetables, whole grains, nuts and legumes, fish and other seafood, and milk and other dairy products. In contrast, an "unhealthy" pattern, which is associated with a higher risk of colorectal cancer, is characterized by high intakes of red meat, processed meat, sugar-sweetened beverages, refined grains, desserts, and potatoes [32].

In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, higher scores on two nutrient patterns have been associated with a reduction in risk of colorectal

cancer (mainly for lesions located in the proximal colon) [33]. One of the nutrient patterns is characterized by a high variety of vitamins and minerals, and the other is characterized by vitamin B_{12}, calcium, phosphorus, riboflavin, cholesterol, and total proteins.

Adiposity and body fatness

Overweight, obesity, and type 2 diabetes (see Chapter 2.7) are established risk factors for colorectal cancer, and it has been estimated that they may account for more than 10% of cases worldwide [34]. Given the worldwide rising prevalence of obesity and type 2 diabetes, these diseases are likely to have significant impacts on colorectal cancer incidence in the future [35].

Public health strategies aimed at reducing the prevalence of obesity, promoting physical activity, and discouraging the consumption of high-energy, obesogenic foods are gradually being implemented in many regions of the world. Although such strategies could, if successful, lead to a reduction in the colorectal cancer burden, the scale of the obesity epidemic and the high incidence of colorectal cancer may necessitate more direct preventive interventions that target people at higher risk.

Microbiota

There is a growing body of experimental and observational evidence implicating the gut microbiome in the development of colorectal cancer (see Chapter 3.10). However, human studies linking variation in the gut microbiome with colorectal cancer are limited, and more are needed.

A small case–control study with available faecal samples demonstrated differences between colorectal cancer cases and controls in the relative abundance of bacterial taxa, with enrichment of Bacteroidetes and depletion of Firmicutes in cases [36]. In addition, increased carriage of the genera *Fusobacterium*, *Atopobium*, and *Porphyromonas* has been associated with colorectal cancer [36,37]. *Fusobacterium* are prevalent in colon tissue, are maintained in distal metastases, and are thought to be pro-inflammatory [38]. *Atopobium*, a gram-positive anaerobic bacterium, is associated with Crohn disease and was reported to inhibit colonocyte apoptosis in vitro [39]. These studies are consistent with microbiotic imbalance (known as dysbiosis) leading to a pro-inflammatory microenvironment, which is conducive to colorectal tumorigenesis. However, caution is required in the interpretation of case–control and cross-sectional studies, because of the potential of reverse causality [40].

Prevention and screening

Screening

The available evidence suggests that screening, with stool-based tests for occult blood (gFOBT or FIT) or with endoscopic methods, is associated with a reduction in colorectal cancer incidence and mortality (Table 5.5.2) [41,42].

Colorectal cancer incidence and mortality have been observed to decline in countries where the

Table 5.5.2. Evidence supporting colorectal cancer screening methods

Screening method[a]	Evidence for reduction in mortality/incidence	Benefit–harm ratio	Screening interval Target age range
Guaiac faecal occult blood test (gFOBT)	Sufficient evidence for reduction in mortality Evidence suggestive of a lack of effect for reduction in incidence	Sufficient evidence	2 years 50–60 to 75 years
Higher-sensitivity guaiac faecal occult blood test (gFOBT) (with rehydration)	Sufficient evidence for reduction in mortality Limited evidence for reduction in incidence	Sufficient evidence	1 or 2 years 50–60 to 75 years
Faecal immunochemical test for haemoglobin (FIT)	Sufficient evidence for reduction in mortality Limited evidence for reduction in incidence	Sufficient evidence	2 years 50–60 to 75 years
Sigmoidoscopy	Sufficient evidence for reduction in mortality Sufficient evidence for reduction in incidence	Sufficient evidence	Once in lifetime[b]
Colonoscopy	Sufficient evidence for reduction in mortality Sufficient evidence for reduction in incidence	Sufficient evidence	Once in lifetime[c]
Computed tomography (CT) colonography	Limited evidence for reduction in mortality Limited evidence for reduction in incidence	Inadequate evidence	Once in lifetime[d]

[a] Evidence on newer techniques that have emerged recently was deemed insufficient. In particular, only one study was available assessing the accuracy of a multitarget stool DNA test combined with the faecal immunochemical test (FIT); it showed an increased sensitivity for sessile serrated adenoma, compared with FIT alone. Similarly, only one study has been conducted to assess the accuracy of a blood biomarker (methylated septin 9 DNA); it showed a low sensitivity for advanced adenomas.

[b] Screening trial included people 55 years or older, and current population-based programmes offer screening between age 55 years and age 59 years.

[c] Available evidence supporting the colonoscopy screening test refers to people aged 50 years and older and suggests that the impact is lower in elderly people (aged > 75 years).

[d] Evidence about the optimal target age is limited.

implementation of interventions for early detection started in the 1990s already [43]. In addition, preliminary reports show a reduction in colorectal cancer incidence, mortality, and surgery rates after the introduction of population-based screening programmes [42,44,45]. These findings confirm the beneficial impact of screening on the colorectal cancer burden at the population level.

However, screening rates in adults aged 50–75 years remain low, and non-adherence to recommended protocols is an important attributable factor for colorectal cancer mortality, in particular in disadvantaged groups.

Trends in colorectal cancer mortality in the USA have been observed to be associated with socioeconomic status. This association, together with the timing of the implementation of screening in the USA, is consistent with the hypothesis that the gradient in screening uptake with socioeconomic status and the later adoption of screening in disadvantaged groups resulted in widening disparities in colorectal cancer mortality – a disparity that is now in favour of groups with higher socioeconomic status (see Chapter 4.5) [46]. In the USA, use of screening remains consistently lower, independent of ethnicity and education level, in uninsured people and in those without access to primary care, because of economic and organizational barriers (see Chapter 4.6) [47].

Reports from organized gFOBT-based or FIT-based screening programmes still document lower participation in screening in the most disadvantaged groups [48]. However, screening rates are higher and the gap by socioeconomic status is smaller in settings with organized programmes than in settings with opportunistic screening; this suggests that implementing population-based screening can ensure the organizational framework for enhancing participation, while reducing inequities in access [49,50].

Chemoprevention

There is some evidence that aspirin and cyclooxygenase 2 (COX-2) inhibitors may reduce recurrence of adenomas and incidence of advanced adenomas in individuals at an increased risk of colorectal cancer (see Chapter 6.4) [51]. In individuals at average risk, calcium supplementation (> 200 mg/day) was associated with a reduction in risk of colorectal cancer [32], and use of aspirin (daily or alternate-day dose, ≥ 75 mg) appeared to reduce colorectal cancer incidence and mortality, after a latency of about 10 years, with a small reduction in all-cause mortality within 10 years of initiating use [52]. In a recent network meta-analysis, low-dose aspirin appeared to be as effective as gFOBT or sigmoidoscopy in reducing colorectal cancer incidence and mortality, and more effective for cancers located in the proximal colon [53]. The cost–effectiveness of an approach combining screening and chemoprevention still needs to be assessed.

Primary prevention

Preventive interventions aimed at promoting healthier lifestyles may reduce the risk of colorectal cancer, or may maintain the low risk in those countries where industrialized lifestyles are not yet common. Such preventive measures may be implemented at the population level and/or at the individual level.

Regular cancer screening offers the opportunity to convey health education messages, and the overall impact of primary prevention and screening could reduce the incidence of colorectal cancer by up to 60% in screenees who comply with health education recommendations. Studies assessing the impact of lifestyle interventions proposed in the screening setting showed that counselling can be effective in encouraging the adoption of healthier dietary patterns, but not in promoting an increase in physical activity or in prompting smoking cessation [54].

In evaluating trends of colorectal cancer risk, the impact of interventions not specifically designed for colorectal cancer prevention, but targeting multiple chronic diseases sharing the same risk factors, should also be considered.

Fig. 5.5.4. This food from Ethiopia exemplifies a vegetable-based diet. Incidence rates of colorectal cancer continue to be low in many countries, and in such countries industrialized lifestyles are typically not yet common.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593

2. Fidler MM, Bray F, Vaccarella S, Soerjomataram I (2017). Assessing global transitions in human development and colorectal cancer incidence. Int J Cancer. 140(12):2709–15. https://doi.org/10.1002/ijc.30686 PMID:28281292

3. Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, Allen C, et al.; Global Burden of Disease Cancer Collaboration (2018). Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol. 4(11):1553–68. https://doi.org/10.1001/jamaoncol.2018.2706 PMID:29860482

4. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F (2017). Global patterns and trends in colorectal cancer incidence and mortality. Gut. 66(4):683–91. https://doi.org/10.1136/gutjnl-2015-310912 PMID:26818619

5. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al.; CONCORD Working Group (2018). Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 391(10125):1023–75. https://doi.org/10.1016/S0140-6736(17)33326-3 PMID:29395269

6. Sunkara V, Hébert JR (2015). The colorectal cancer mortality-to-incidence ratio as an indicator of global cancer screening and care. Cancer. 121(10):1563–9. https://doi.org/10.1002/cncr.29228 PMID:25572676

7. Aarts MJ, Lemmens VE, Louwman MW, Kunst AE, Coebergh JW (2010). Socioeconomic status and changing inequalities in colorectal cancer? A review of the associations with risk, treatment and outcome. Eur J Cancer. 46(15):2681–95. https://doi.org/10.1016/j.ejca.2010.04.026 PMID:20570136

8. Manser CN, Bauerfeind P (2014). Impact of socioeconomic status on incidence, mortality, and survival of colorectal cancer patients: a systematic review. Gastrointest Endosc. 80(1):42–60.e9. https://doi.org/10.1016/j.gie.2014.03.011 PMID:24950641

9. Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson B, et al. (2017). Annual report to the nation on the status of cancer, 1975–2014, featuring survival. J Natl Cancer Inst. 109(9):109. https://doi.org/10.1093/jnci/djx030 PMID:28376154

10. Guren MG, Kørner H, Pfeffer F, Myklebust TA, Eriksen MT, Edna TH, et al. (2015). Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993–2010. Acta Oncol. 54(10):1714–22. https://doi.org/10.3109/0284186X.2015.1034876 PMID:25924970

11. Brouwer NPM, Bos ACRK, Lemmens VEPP, Tanis PJ, Hugen N, Nagtegaal ID, et al. (2018). An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients. Int J Cancer. 143(11):2758–66. https://doi.org/10.1002/ijc.31785 PMID:30095162

12. Goss PE, Lee BL, Badovinac-Crnjevic T, Strasser-Weippl K, Chavarri-Guerra Y, St Louis J, et al. (2013). Planning cancer control in Latin America and the Caribbean. Lancet Oncol. 14(5):391–436. https://doi.org/10.1016/S1470-2045(13)70048-2 PMID:23628188

13. Kingham TP, Alatise OI, Vanderpuye V, Casper C, Abantanga FA, Kamara TB, et al. (2013). Treatment of cancer in sub-Saharan Africa. Lancet Oncol. 14(4):e158–67. https://doi.org/10.1016/S1470-2045(12)70472-2 PMID:23561747

14. Karsa LV, Lignini TA, Patnick J, Lambert R, Sauvaget C (2010). The dimensions of the CRC problem. Best Pract Res Clin Gastroenterol. 24(4):381–96. https://doi.org/10.1016/j.bpg.2010.06.004 PMID:20833343

15. Fearon ER, Vogelstein B (1990). A genetic model for colorectal tumorigenesis. Cell. 61(5):759–67. https://doi.org/10.1016/0092-8674(90)90186-I PMID:2188735

16. Zoratto F, Rossi L, Verrico M, Papa A, Basso E, Zullo A, et al. (2014). Focus on genetic and epigenetic events of colorectal cancer pathogenesis: implications for molecular diagnosis. Tumour Biol. 35(7):6195–206. https://doi.org/10.1007/s13277-014-1845-9 PMID:25051912

17. Haque T, Greene KG, Crockett SD (2014). Serrated neoplasia of the colon: what do we really know? Curr Gastroenterol Rep. 16(4):380. https://doi.org/10.1007/s11894-014-0380-6 PMID:24595617

18. Bettington M, Walker N, Clouston A, Brown I, Leggett B, Whitehall V (2013). The serrated pathway to colorectal carcinoma: current concepts and challenges. Histopathology. 62(3):367–86. https://doi.org/10.1111/his.12055 PMID:23339363

19. Bettington M, Brown I, Rosty C, Walker N, Liu C, Croese J, et al. (2019). Sessile serrated adenomas in young patients may have limited risk of malignant progression. J Clin Gastroenterol. 53(3):e113–6. https://doi.org/10.1097/MCG.0000000000001014 PMID:29570172

20. Guinney J, Dienstmann R, Wang X, de Reyniès A, Schlicker A, Soneson C, et al. (2015). The consensus molecular subtypes of colorectal cancer. Nat Med. 21(11):1350–6. https://doi.org/10.1038/nm.3967 PMID:26457759

21. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al.; Australian Pancreatic Cancer Genome Initiative; ICGC Breast Cancer Consortium; ICGC MMML-Seq Consortium; ICGC PedBrain (2013). Signatures of mutational processes in human cancer. Nature. 500(7463):415–21. https://doi.org/10.1038/nature12477 PMID:23945592

22. Dahabreh IJ, Terasawa T, Castaldi PJ, Trikalinos TA (2011). Systematic review: anti-epidermal growth factor receptor treatment effect modification by *KRAS* mutations in advanced colorectal cancer. Ann Intern Med. 154(1):37–49. https://doi.org/10.7326/0003-4819-154-1-201101040-00006 PMID:21200037

23. Alwers E, Jia M, Kloor M, Bläker H, Brenner H, Hoffmeister M (2019). Associations between molecular classifications of colorectal cancer and patient survival: a systematic review. Clin Gastroenterol Hepatol. 17(3):402–410.e2. https://doi.org/10.1016/j.cgh.2017.12.038 PMID:29306042

24. Gupta R, Sinha S, Paul RN (2018). The impact of microsatellite stability status in colorectal cancer. Curr Probl Cancer. 42(6):548–59. https://doi.org/10.1016/j.currproblcancer.2018.06.010 PMID:30119911

25. Rosty C, Williamson EJ, Clendenning M, Walters RJ, Walsh MD, Win AK, et al. (2014). Re: Microsatellite instability and *BRAF* mutation testing in colorectal cancer prognostication. J Natl Cancer Inst. 106(8):106. https://doi.org/10.1093/jnci/dju180 PMID:25114271

26. Institute for Health Metrics and Evaluation (2018). Global Burden of Disease (GBD) 2017 data. Available from: http://www.healthdata.org/gbd.

27. WCRF/AICR (2018). Diet, nutrition, physical activity and colorectal cancer. Continuous Update Project Expert Report 2018. World Cancer Research Fund/American Institute for Cancer Research. Available from: https://www.aicr.org/continuous-update-project/reports/colorectal-cancer-2017-report.pdf.

28. IARC (2012). Personal habits and indoor combustions. IARC Monogr Eval Carcinog Risks Hum. 100E:1–575. Available from: http://publications.iarc.fr/122 PMID:23193840

29. Haque TR, Bradshaw PT, Crockett SD (2014). Risk factors for serrated polyps of the colorectum. Dig Dis Sci. 59(12):2874–89. https://doi.org/10.1007/s10620-014-3277-1 PMID:25030942

30. Murphy N, Ward HA, Jenab M, Rothwell JA, Boutron-Ruault MC, Carbonnel F, et al. (2019). Heterogeneity of colorectal cancer risk factors by anatomical subsite in 10 European countries: a multinational cohort study. Clin Gastroenterol Hepatol. 17(7):1323–1331.e6. https://doi.org/10.1016/j.cgh.2018.07.030 PMID:30056182

31. Dimitrakopoulou VI, Tsilidis KK, Haycock PC, Dimou NL, Al-Dabhani K, Martin RM, et al.; GECCO Consortium; PRACTICAL Consortium; GAME-ON Network (CORECT, DRIVE, ELLIPSE, FOCI-OCAC, TRICL-ILCCO) (2017). Circulating vitamin D concentration and risk of seven cancers: Mendelian randomisation study. BMJ. 359:j4761. https://doi.org/10.1136/bmj.j4761 PMID:29089348

32. Tabung FK, Brown LS, Fung TT (2017). Dietary patterns and colorectal cancer risk: a review of 17 years of evidence (2000–2016). Curr Colorectal Cancer Rep. 13(6):440–54. https://doi.org/10.1007/s11888-017-0390-5 PMID:29399003

33. Moskal A, Freisling H, Byrnes G, Assi N, Fahey MT, Jenab M, et al. (2016). Main nutrient patterns and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition study. Br J Cancer. 115(11):1430–40. https://doi.org/10.1038/bjc.2016.334 PMID:27764841

34. Pearson-Stuttard J, Zhou B, Kontis V, Bentham J, Gunter MJ, Ezzati M (2018). Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment. Lancet Diabetes Endocrinol. 6(6):e6–15. https://doi.org/10.1016/S2213-8587(18)30150-5 PMID:29803268

35. Murphy N, Jenab M, Gunter MJ (2018). Adiposity and gastrointestinal cancers: epidemiology, mechanisms and future directions. Nat Rev Gastroenterol Hepatol. 15(11):659–70. https://doi.org/10.1038/s41575-018-0038-1 PMID:29970888

36. Ahn J, Sinha R, Pei Z, Dominianni C, Wu J, Shi J, et al. (2013). Human gut microbiome and risk for colorectal cancer. J Natl Cancer Inst. 105(24):1907–11. https://doi.org/10.1093/jnci/djt300 PMID:24316595

37. Arthur JC, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, et al. (2012). Intestinal inflammation targets cancer-inducing activity of the microbiota. Science. 338(6103):120–3. https://doi.org/10.1126/science.1224820 PMID:22903521

38. Bullman S, Pedamallu CS, Sicinska E, Clancy TE, Zhang X, Cai D, et al. (2017). Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer. Science. 358(6369):1443–8. https://doi.org/10.1126/science.aal5240 PMID:29170280

39. Chen W, Liu F, Ling Z, Tong X, Xiang C (2012). Human intestinal lumen and mucosa-associated microbiota in patients with colorectal cancer. PLoS One. 7(6):e39743. https://doi.org/10.1371/journal.pone.0039743 PMID:22761885

40. Amitay EL, Werner S, Vital M, Pieper DH, Höfler D, Gierse IJ, et al. (2017). *Fusobacterium* and colorectal cancer: causal factor or passenger? Results from a large colorectal cancer screening study. Carcinogenesis. 38(8):781–8. https://doi.org/10.1093/carcin/bgx053 PMID:28582482

41. Armaroli P, Villain P, Suonio E, Almonte M, Anttila A, Atkin WS, et al. (2015). European Code Against Cancer, 4th edition: cancer screening. Cancer Epidemiol. 39(Suppl 1):S139–52. https://doi.org/10.1016/j.canep.2015.10.021 PMID:26596722

42. IARC (2019). Colorectal cancer screening. IARC Handb Cancer Prev. 17:1–300. Available from: http://publications.iarc.fr/573.

43. Yang DX, Gross CP, Soulos PR, Yu JB (2014). Estimating the magnitude of colorectal cancers prevented during the era of screening: 1976 to 2009. Cancer. 120(18):2893–901. https://doi.org/10.1002/cncr.28794 PMID:24894740

44. Fedeli U, Zorzi M, Urso ED, Gennaro N, Dei Tos AP, Saugo M (2015). Impact of fecal immunochemical test-based screening programs on proximal and distal colorectal cancer surgery rates: a natural multiple-baseline experiment. Cancer. 121(22):3982–9. https://doi.org/10.1002/cncr.29623 PMID:26264471

45. McClements PL, Madurasinghe V, Thomson CS, Fraser CG, Carey FA, Steele RJ, et al. (2012). Impact of the UK colorectal cancer screening pilot studies on incidence, stage distribution and mortality trends. Cancer Epidemiol. 36(4):e232–42. https://doi.org/10.1016/j.canep.2012.02.006 PMID:22425027

46. Breen N, Lewis DR, Gibson JT, Yu M, Harper S (2017). Assessing disparities in colorectal cancer mortality by socioeconomic status using new tools: health disparities calculator and socioeconomic quintiles. Cancer Causes Control. 28(2):117–25. https://doi.org/10.1007/s10552-016-0842-2 PMID:28083800

47. White A, Thompson TD, White MC, Sabatino SA, de Moor J, Doria-Rose PV, et al. (2017). Cancer screening test use – United States, 2015. MMWR Morb Mortal Wkly Rep. 66(8):201–6. https://doi.org/10.15585/mmwr.mm6608a1 PMID:28253225

48. de Klerk CM, Gupta S, Dekker E, Essink-Bot ML; Expert Working Group 'Coalition to reduce inequities in colorectal cancer screening' of the World Endoscopy Organization (2018). Socioeconomic and ethnic inequities within organised colorectal cancer screening programmes worldwide. Gut. 67(4):679–87. https://doi.org/10.1136/gutjnl-2016-313311 PMID:28073892

49. Carrozzi G, Sampaolo L, Bolognesi L, Sardonini L, Bertozzi N, Giorgi Rossi P, et al.; Regional and local PASSI coordinators (2015). Cancer screening uptake: association with individual characteristics, geographic distribution, and time trends in Italy. Epidemiol Prev. 39(3 Suppl 1):9–18. PMID:26405772

50. Levin TR, Corley DA, Jensen CD, Schottinger JE, Quinn VP, Zauber AG, et al. (2018). Effects of organized colorectal cancer screening on cancer incidence and mortality in a large community-based population. Gastroenterology. 155(5):1383–1391.e5. https://doi.org/10.1053/j.gastro.2018.07.017 PMID:30031768

51. Lang M, Gasche C (2015). Chemoprevention of colorectal cancer. Dig Dis. 33(1):58–67. https://doi.org/10.1159/000366037 PMID:25531498

52. Chubak J, Whitlock EP, Williams SB, Kamineni A, Burda BU, Buist DS, et al. (2016). Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. Preventive Services Task Force. Ann Intern Med. 164(12):814–25. https://doi.org/10.7326/M15-2117 PMID:27064482

53. Emilsson L, Holme Ø, Bretthauer M, Cook NR, Buring JE, Løberg M, et al. (2017). Systematic review with meta-analysis: the comparative effectiveness of aspirin vs. screening for colorectal cancer prevention. Aliment Pharmacol Ther. 45(2):193–204. https://doi.org/10.1111/apt.13857 PMID:27859394

54. Senore C, Giordano L, Bellisario C, Di Stefano F, Segnan N (2012). Population based cancer screening programmes as a teachable moment for primary prevention interventions. A review of the literature. Front Oncol. 2:45. https://doi.org/10.3389/fonc.2012.00045 PMID:22649789

5.6 Liver cancer
An infectious disease for many communities

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SUMMARY

- From 1990 to 2015, there was a 75% increase in global cases of incident liver cancer, of which 47% could be attributed to changing population age structures, 35% to population growth, and −8% to decreasing age-specific incidence rates.
- Genetic modifications observed in liver cancer development include alterations at *TP53*, *MYC*, *WNT*, *CTNNB1* (β-catenin), and other genes that mediate cell-cycle regulation, telomere stability, epigenetic regulation, and chromatin remodelling.
- The incidence of liver cancer and the prevalence of infection with hepatitis B virus and hepatitis C virus are consistently high in East and South-East Asia and sub-Saharan Africa.
- Ethanol-induced liver injury results in fibrosis and cirrhosis, which predisposes to the development of liver cancer. Alcohol acts synergistically with chronic viral hepatitis and tobacco use in causing hepatocellular carcinoma.
- There is a dose–response relationship between risk of hepatocellular carcinoma and increasing serum level of aflatoxin B_1–albumin adducts, a biomarker that provides a cumulative measure of aflatoxin B_1 exposure over several months.
- Viral hepatitis control is included within the United Nations Sustainable Development Goals. The hepatitis B virus vaccine has high efficacy and cost–effectiveness to prevent hepatocellular carcinoma.

Primary liver cancer is a group of pathologically heterogeneous malignancies [1]. It includes mainly (~80%) hepatocellular carcinoma (HCC), as well as intrahepatic cholangiocarcinoma, mucinous cystic neoplasms, intraductal papillary biliary neoplasms, hepatoblastoma in children, angiosarcoma, and other types, with different underlying etiologies and carcinogenic mechanisms.

Epidemiology

In 2018, liver cancer was the sixth most common cancer and the fourth most common cause of cancer death worldwide [2]. The cumulative incidence of liver cancer from birth to age 75 years was 1.6% for males and 0.6% for females, and the cumulative mortality from liver cancer was 1.5% for males and 0.5% for females. There is substantial geographical variation in liver cancer incidence and mortality globally. Age-standardized rates in Africa and Asia are 2–3 times those in the Americas, Europe, and Oceania.

The Global Burden of Disease Study reported that from 1990 to 2015, there was a 75% increase in global cases of incident liver cancer, of which 47% could be attributed to changing population age structures, 35% to population growth, and −8% to decreasing age-specific incidence rates. Globally, hepatitis B virus (HBV) infection was responsible for 33% of deaths from liver cancer, alcohol consumption for 30%, hepatitis C virus (HCV) infection for 21%, and other causes for 16%, with significant variation in the underlying etiologies among regions and countries [3].

A recent review documented that both the incidence of and mortality from liver cancer have declined significantly in the past two decades after the launch of the first HBV immunization programme in the world in 1984 and the first chronic viral hepatitis therapy programme in the world in 2003 [4].

Most of the burden of disease from HBV infection comes from infections acquired before age 5 years. A significant decrease in the global incidence of liver cancer is expected in the future, because the worldwide prevalence of chronic HBV infection in children younger than 5 years has been reduced dramatically by HBV vaccination programmes.

Genetics and genomics

Hereditary diseases that are associated with an increased risk of HCC include haemochromatosis,

α-1-antitrypsin deficiency, acute intermittent porphyria, and porphyria cutanea tarda. Although the familial tendency of liver cancer may be attributable to common environmental factors shared by family members, such as HBV infection, HCV infection, liver fluke infection, alcohol consumption, and aflatoxin exposure, the familial tendency remains significant after adjustment for these environmental factors, suggesting that common genes shared by family members also play an important role. For example, genetic polymorphisms of the sodium taurocholate co-transporting peptide (NTCP, an HBV receptor), human leukocyte antigen (HLA), interferon lambda (*IFNL*) genes, metabolism enzymes, oncogenes, tumour suppressor genes, and the androgen receptor are associated with risk of HCC [4].

Numerous somatic genetic alterations have been observed in HCC, including mutations, copy number alterations, and intra- and inter-chromosomal rearrangements [5]. Frequent alterations are at genes that play key roles in cancer development (*TP53*, *MYC*, and *CTNNB1* [β-catenin]), cell-cycle regulation (*CCND1*, *CDKN2A*, and *RB1*), telomere stability (*TERT*), epigenetic regulation (*IDH1* and *IDH2*), and chromatin remodelling (*ARID1*, *ARID2*, *MLL*, *BAP*, and *EZH2*). Alterations are frequent in the following 11 pathways: telomerase reverse transcriptase (TERT), WNT/β-catenin, PI3K/AKT/mTOR, TP53/cell cycle, mitogen-activated protein kinase (MAPK), hepatic differentiation, epigenetic regulation, chromatin remodelling, oxidative stress, interleukin 6 (IL-6)/JAK/STAT, and transforming growth factor β (TGF-β). The total mutation burden is moderate, and hypermutated cases, which are expected to respond to immunotherapy, are not common [6,7]. Epigenetic silencing of *CDKN2A*, *HHIP*, *CPS1*, and other tumour suppressor genes has also been reported [8,9].

Etiology

The major etiological factors for liver cancer are HBV infection, HCV infection, alcohol consumption, aflatoxin exposure, liver fluke infection, and obesity (Table 5.6.1). The incidence of liver cancer and the prevalence of HBV and HCV infection are consistently high in East and South-East Asia and sub-Saharan Africa. However, the relative etiological proportion of HBV and HCV in HCC varies in different countries. For example, HBV is more important in China and the Republic of Korea, HCV is more important in Japan, and both HBV and HCV are important in Mongolia.

Alcohol consumption (see Chapter 2.3) is the most prevalent risk factor for HCC in eastern Europe, central Europe, southern Latin America, southern sub-Saharan Africa, Australia, and North America. Aflatoxin exposure (see Chapter 2.8) is ubiquitous in many of the lowest-income populations worldwide, showing a synergistic effect with HBV on HCC. Liver fluke infection, a major risk factor for intrahepatic cholangiocarcinoma, is prevalent only in parts of East Asia, including Thailand, Lao People's Democratic Republic, China, the Republic of Korea, the Russian Federation, and Viet Nam.

Hepatitis virus infection

Both HBV infection and HCV infection have been classified by the IARC Monographs as carcinogenic to humans; they cause HCC and intrahepatic cholangiocarcinoma. The estimated global number of chronic infections in 2015 was 257 million for HBV and 71 million for HCV [4]. In the natural history of HBV infection, about 10–20% of people with HBV infection will become chronic carriers of HBV, depending on the age at infection.

Spontaneous seroclearance of HBV e antigen (HBeAg), HBV DNA, and even HBV surface antigen (HBsAg) may occur sequentially in patients with chronic HBV infection (Fig. 5.6.2). Seroclearance of HBeAg, HBV DNA, and HBsAg may lead to a decreased risk of HCC [10].

HCC occurs mostly in patients with HBeAg-seropositive status or high viral load, infection with HBV genotype C or basal core promoter (BCP) A1762T/G1764A double mutations, and co-infection with HCV or HIV. In the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL) study, for patients with chronic hepatitis B the lifetime (ages 30–75 years) cumulative incidence of HCC was 27% for men and 8%

FUNDAMENTALS

- Liver cancer includes mainly hepatocellular carcinoma, as well as intrahepatic cholangiocarcinoma and hepatoblastoma.
- Major etiological factors for liver cancer include hepatitis B virus infection, hepatitis C virus infection, alcohol consumption, aflatoxin exposure, liver fluke infection, obesity, and several genetic diseases. The global variation in liver cancer incidence rates coincides with the geographical distribution of its major causes.
- Hepatocarcinogenesis is a multistage process with a multifactorial etiology of host–environment interactions.
- Hepatitis B immunization, antiviral therapy for chronic viral hepatitis, reduction in aflatoxin exposure, and elimination of liver fluke infection have been well documented to lower the risk of liver cancer.
- When the relevant options are available and affordable, liver cancer can be detected early, by seromarkers and imaging technology, and can be treated promptly, by surgical resection, transplantation, ablation, embolization, radiotherapy, targeted therapy, chemotherapy, and immunotherapy.

Table 5.6.1. Major etiological factors for liver cancer with their biomarkers and related major genes

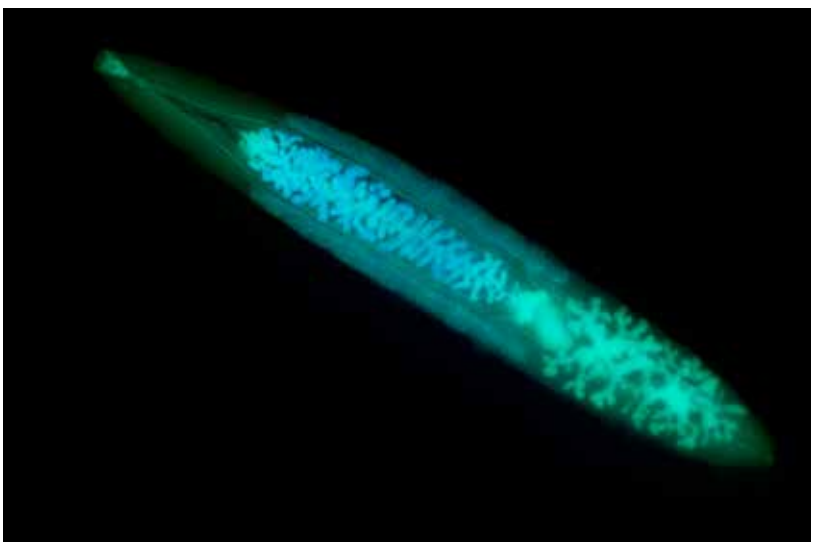
Etiological factor	Cancer type	Biomarkers	Related major genes
Hepatitis B virus infection	Hepatocellular carcinoma	HBsAg/HBeAg serostatus	*NTCP*
	Intrahepatic cholangiocarcinoma	Viral load (HBV DNA)	HLA
		Genotypes/mutant types	
		Serum HBsAg level	
Hepatitis C virus infection	Hepatocellular carcinoma	Anti-HCV	*IFNL3*
	Intrahepatic cholangiocarcinoma	Viral load (HCV RNA)	HLA
		Genotypes/mutant types	
Alcohol consumption	Hepatocellular carcinoma	Frequency	*ADH*
		Quantity	*ALDH*
		Duration/starting age	
Aflatoxin exposure	Hepatocellular carcinoma	Metabolites in urine	*TP53*
		Guanine adducts	GST M1/T1
		Albumin adducts	
Liver fluke infection	Intrahepatic cholangiocarcinoma	Eggs in faeces	–
Obesity	Hepatocellular carcinoma	Body mass index	Adiponectin
		Waist circumference	

Anti-HCV, hepatitis C antibody; HBeAg, HBV e antigen; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

for women. The AA genotype of the S267F (rs2296651) variant on NTCP was found to be associated with HBsAg-seropositive status, and the GA or AA genotype was associated with a low risk of progression to cirrhotic and non-cirrhotic HCC in patients with chronic hepatitis B [11].

HCV infection is infrequently diagnosed during the acute phase, because most people who are infected have no or mild symptoms. Most asymptomatic infections progress to chronic hepatitis, with the patient not being aware of this until end-stage liver diseases, including cirrhosis and HCC, occur. Spontaneous clearance of HCV RNA occurs in about 8–36% of patients with chronic hepatitis C without antiviral treatment. In the REVEAL study, for patients with chronic hepatitis C the lifetime (ages 30–75 years) cumulative incidence of HCC was 24% for men and 17% for women. Co-infection with HBV may increase the lifetime cumulative risk of HCC to 38% for men and 27% for women. Polymorphisms near the *IFNL3* gene (formerly known as *IL28B*) are associated with spontaneous clearance of HCV RNA and reduced risk of HCC [12]. In particular, the TT variant of rs8099917 near *IFNL3* is significantly associated with increased spontaneous clearance of HCV RNA and decreased risk of HCC.

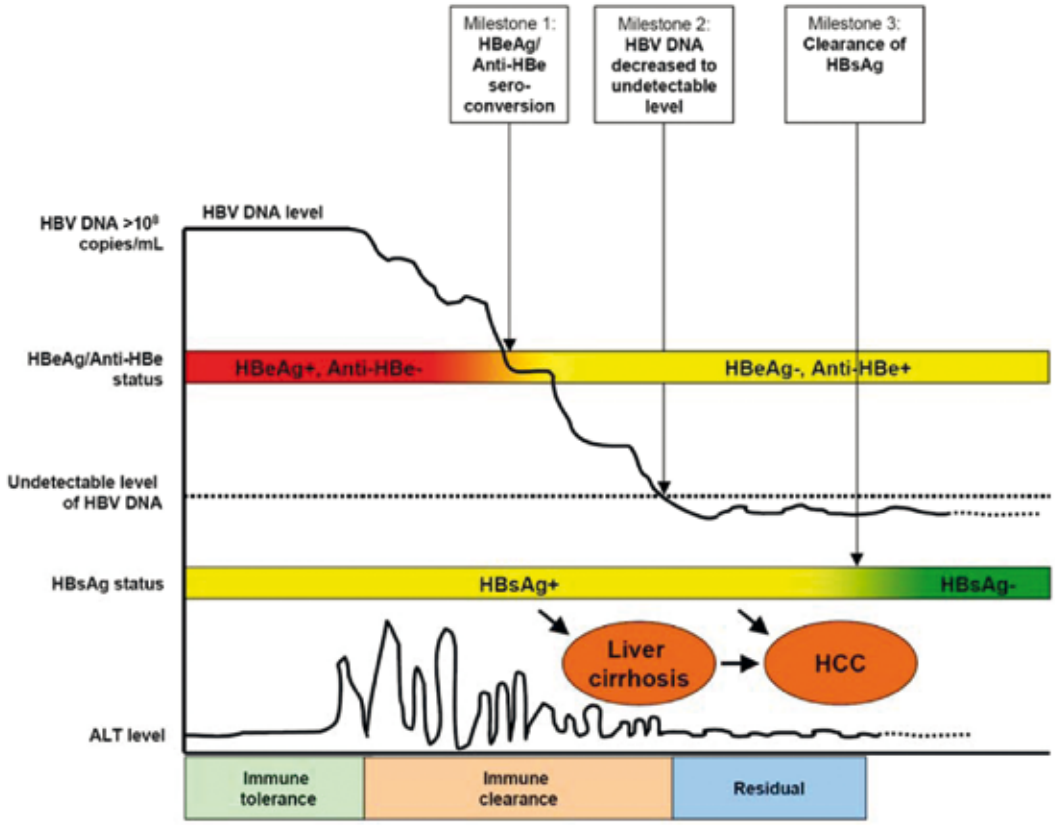
Fig. 5.6.1. Chinese liver fluke. Human liver fluke infection, a major risk factor for intrahepatic cholangiocarcinoma, is prevalent in parts of East Asia.



HLA also plays an important role in the progression of chronic hepatitis C. For example, eight single-nucleotide polymorphisms near *HLA-DQB1* are associated with risk of HCC in patients with HCV genotype 1 infection. *DQB1*03:01* has a protective effect, and *DQB1*06:02* increases the risk of HCC [13].

Hepatocarcinogenesis caused by infection with HBV or HCV is a multistage process with a multifactorial etiology (Fig. 5.6.3). Infection with HBV or HCV also causes intrahepatic cholangiocarcinoma, at a much lower incidence than HCC.

Fig. 5.6.2. In the natural history of chronic hepatitis B, there are milestone transitions of three hepatitis B virus (HBV) seromarkers. The serum HBV DNA level (viral load) remains high during the immune tolerance phase. Both HBV e antigen (HBeAg) seroclearance and anti-HBe seropositivity occur after a period of elevation of serum level of alanine aminotransferase (ALT), a seromarker of liver inflammation, during the immune clearance phase. The serum HBV DNA level (viral load) may remain high or may gradually decline in patients with HBeAg-seronegative status. Seroclearance of HBV surface antigen (HBsAg) may occur after the serum HBV DNA level becomes undetectable during the residual phase. HCC, hepatocellular carcinoma.



Alcohol consumption

Alcohol consumption has been classified by the IARC Monographs as carcinogenic to humans; it causes HCC. Ethanol as a solvent may increase the exposure of hepatocytes to carcinogens such as 4-aminobiphenyl and polycyclic aromatic hydrocarbons in tobacco smoke. Ethanol may also be converted by alcohol dehydrogenase into carcinogenic acetaldehyde.

Ethanol-induced liver injury results in fibrosis and cirrhosis, which predisposes to the development of HCC [1]. Alcohol acts synergistically with chronic viral hepatitis and tobacco use in causing HCC. A synergistic effect on HCC between alcohol consumption and obesity has been reported, showing a substantially increased risk of HCC in obese alcohol drinkers compared with non-obese never-drinkers [14].

Polymorphisms of enzymes involved in alcohol metabolism (see Chapter 3.3), including alcohol dehydrogenase 1B (ADH1B) and aldehyde dehydrogenase 2 (ALDH2), were found to have significant effects on risk of HCC, mediated through alcohol consumption [15]. Genotypes of both enzymes were associated with the frequency and quantity of alcohol consumption, and with the development of subsequent HCC.

Aflatoxin

Aflatoxin has been classified by the IARC Monographs as carcinogenic to humans; it causes HCC. Urinary and serum biomarkers have been developed to estimate exposure to aflatoxins, particularly aflatoxin B_1. Aflatoxin exposure increases the risk of cirrhosis and HCC in patients with chronic hepatitis B [16]. Aflatoxin exposure also increases the risk of HCC in patients with chronic hepatitis C and in habitual alcohol drinkers without chronic viral hepatitis [17].

There is a dose–response relationship between risk of HCC and increasing serum level of aflatoxin B_1–albumin adducts, a biomarker that provides a cumulative measure of aflatoxin B_1 exposure over several months. Glutathione *S*-transferase (GST) M1 and T1 are the enzymes involved in the detoxification of aflatoxins. The increasing risk of HCC with aflatoxin exposure is significant in

Fig. 5.6.3. The progression from self-limited hepatitis B virus (HBV) and hepatitis C virus (HCV) infection through chronic hepatitis and cirrhosis to hepatocellular carcinoma (HCC) is a multistage pathogenic process driven by the interaction among viral, host, and environmental factors. Viral co-factors include viral load and genotype of HBV and HCV. Environmental co-factors for virus-related HCC include alcohol consumption, aflatoxin exposure, cigarette smoking, low intake of carotenes and selenium, and others. Host co-factors include age, sex, family history of HCC, obesity, serum level of alanine aminotransferase (ALT, a seromarker of hepatic inflammation), fibrosis score, serum testosterone level, and genetic polymorphisms of metabolism enzymes, oncogenes, tumour suppressor genes, hormone-related genes, immunity-related genes, inflammation-related genes, and others. F, female; HBeAg, HBV e antigen; M, male.

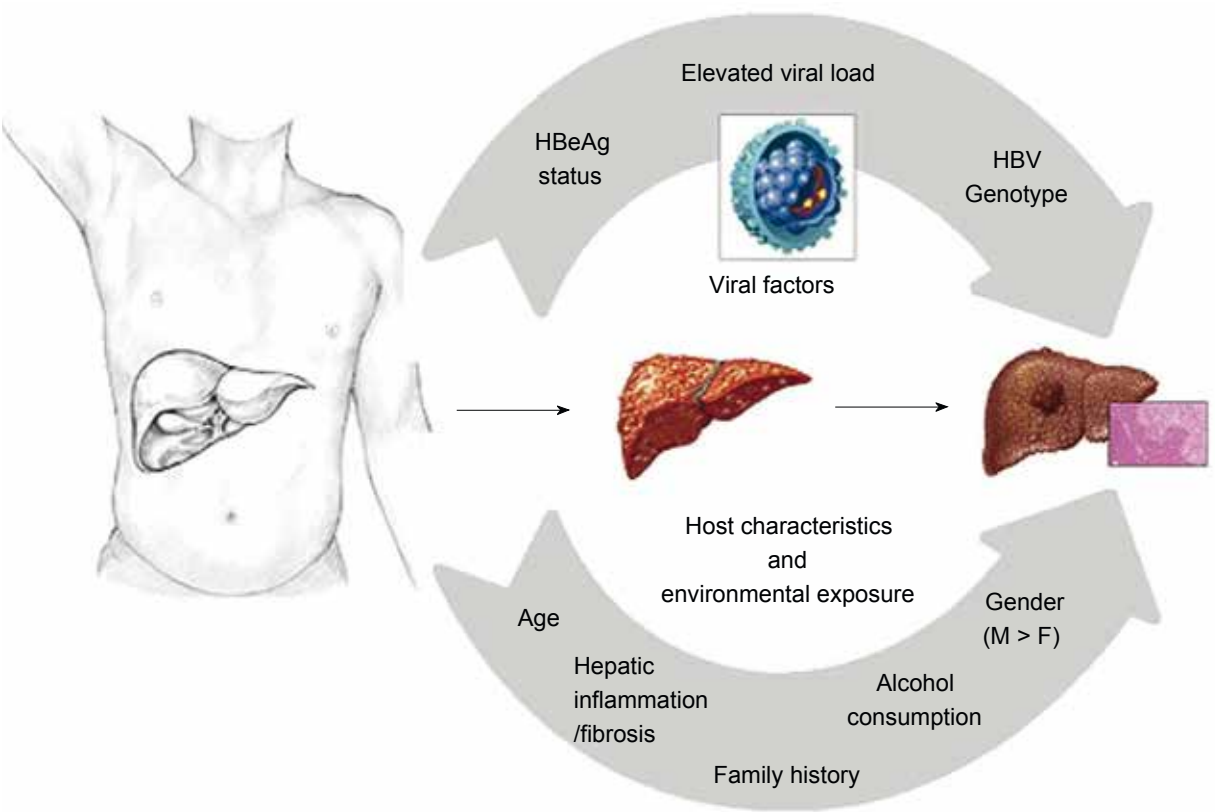
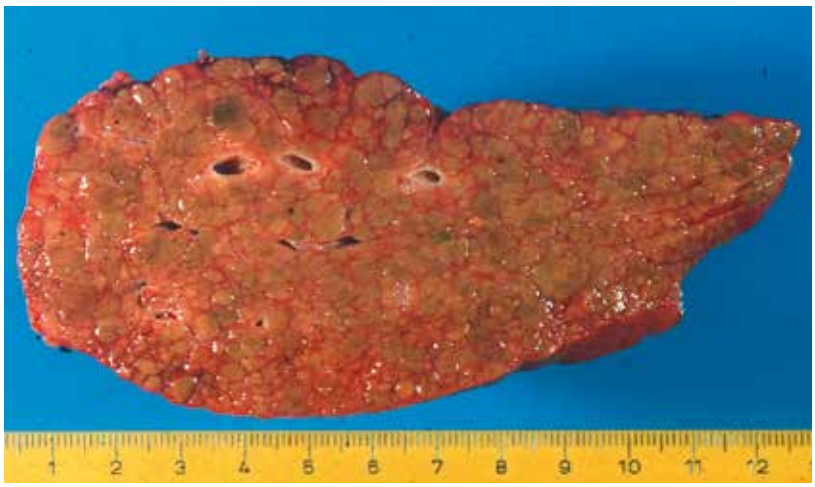


Fig. 5.6.4. A liver with cirrhosis. Cirrhosis induced by alcohol consumption predisposes to the development of hepatocellular carcinoma.



patients with chronic hepatitis B with null genotypes of GST M1 or T1 (i.e. without detoxification capability), but not in those with non-null genotypes.

The *TP53* tumour suppressor gene is critically important for the regulation of the cell cycle and the maintenance of genomic integrity. A specific mutation at codon 249 in exon 7 of *TP53* has been associated with aflatoxin B_1-induced HCC.

Liver flukes

Both *Opisthorchis viverrini* infection and *Clonorchis sinensis* infection have been classified by the IARC Monographs as carcinogenic to humans; they cause intrahepatic cholangiocarcinoma. Globally, the

estimated number of infections with *O. viverrini* is at least 10 million and with *C. sinensis* is at least 35 million [1]. The spread of these flukes is restricted by the distribution of two definitive hosts other than humans – particular species of snails and cyprinid fish – and by the cultural practice of eating raw fish. The transmission cycle requires eggs from fish-eating hosts, which emerge in faeces to contaminate the freshwater inhabited by snails and fish.

Obesity and diabetes

Both obesity (see Chapter 2.7) and diabetes are associated with the development of HCC. Obesity may influence HCC through non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, which progress through fibrosis and cirrhosis to liver cancer [18].

Higher plasma levels of adiponectin are associated with a lower HBsAg seroclearance rate and persistently higher serum levels of HBV DNA [19]. There is a dose–response relationship between increasing adiponectin levels and risk of cirrhosis and HCC in patients with chronic hepatitis B.

Diabetes increases risk of HCC with or without chronic viral hepatitis. Patients with HCV infection have a significantly increased incidence of diabetes, with a multivariate-adjusted hazard ratio of 1.5 in a long-term prospective study [20].

Fine particulate matter

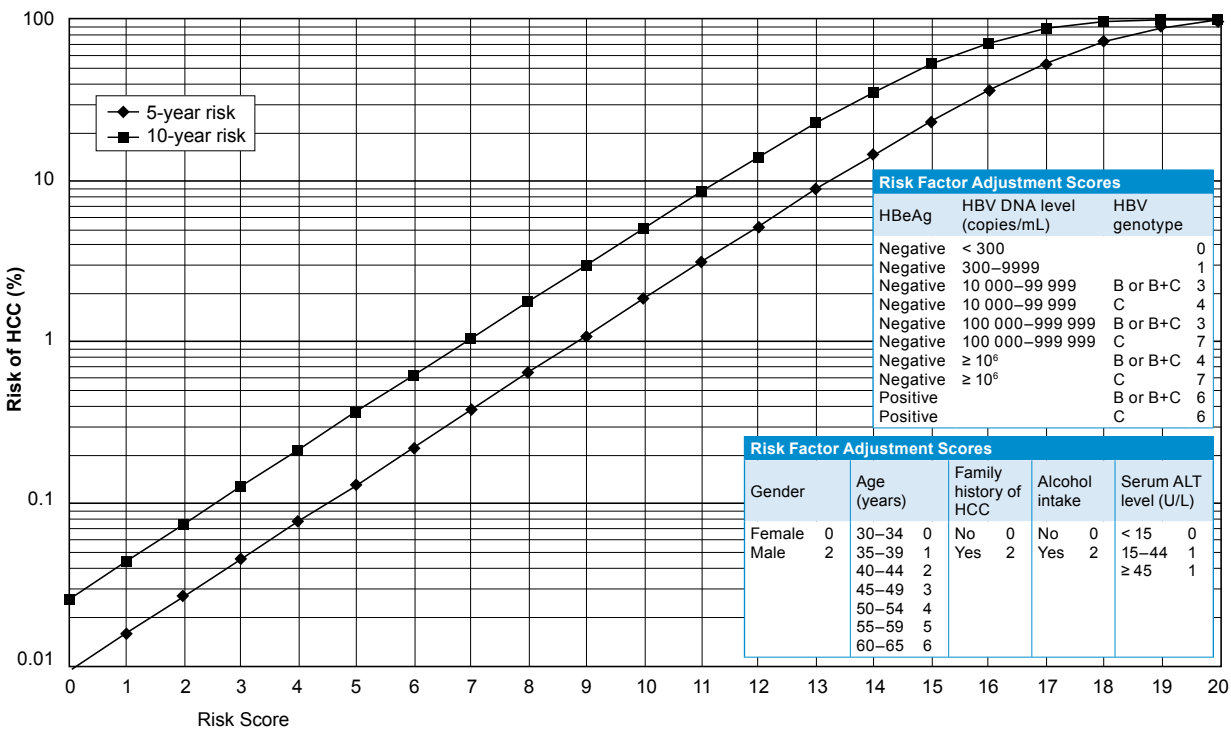
Exposure to fine particulate matter (particulate matter with particles of aerodynamic diameter less than 2.5 μm [$PM_{2.5}$]) is associated with systematic inflammation markers and serum levels of liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase, and gamma-glutamyl transferase. In a recent study, long-term exposure to $PM_{2.5}$ was found to increase the risk of liver cancer mediated by serum ALT level, after adjustment for age, sex, alcohol consumption, cigarette smoking, and HBV and HCV infection [21]. However, this finding needs further scrutiny.

Risk prediction

Because several risk factors interact to cause liver cancer, it is important to integrate them into a risk prediction model to derive one measure of absolute risk, for the appropriate identification of people at high risk who require clinical intervention. Risk prediction is very important for the personalized health care of those who are susceptible to liver cancer.

Easy-to-use nomograms have been developed for predicting long-term risk of HCC in patients with

Fig. 5.6.5. Nomograms from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer of Hepatitis B Virus (REVEAL-HBV) study are some of the earliest risk calculators for predicting risk of cirrhosis or hepatocellular carcinoma (HCC) in patients with chronic hepatitis B. Integer risk scores are assigned to various groups of eight predictors: sex, age, family history of HCC, alcohol intake, serum alanine aminotransferase (ALT) level, HBV e antigen (HBeAg) serostatus, serum HBV DNA level, and HBV genotype. Both 5-year and 10-year risks of HCC by summed risk score are depicted in the nomogram. It is easy to identify the long-term HCC risk by summing the risk scores. These nomograms have high internal validity and discriminatory ability to triage patients with chronic hepatitis B into different risk groups.



Hepatocellular carcinoma risk calculators for patients with chronic viral hepatitis

In the era of precision medicine, it is important to classify patients with viral hepatitis into subgroups that differ in their susceptibility to liver cancer, their prognosis, and their response to clinical management. Preventive or therapeutic interventions can then be concentrated on those who will benefit, thus sparing expense and side-effects for those who will not. In the past decade, risk calculators for predicting long-term risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B and C have been derived and validated internationally [1].

For the derivation and validation of the risk of liver cancer, well-designed prospective cohort studies on a large cohort of patients with viral hepatitis with comprehensive collection of serial biomarkers during long-term follow-up are essential. For example, the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL) study recruited a cohort of 23 820 adult male and female residents of seven townships in 1991–1992. The health examination at study entry and follow-up visit included abdominal ultrasonography and serological tests of (i) hepatitis B biomarkers, including HBV surface antigen (HBsAg), HBV e antigen (HBeAg), genotype, mutant types, and DNA (HBV DNA); (ii) hepatitis C biomarkers, including HCV antibody (anti-HCV), genotype, and RNA (HCV RNA); and (iii) liver function biomarkers, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST). A total of 4155 HBsAg-seropositive and 1313 anti-HCV-seropositive participants were enrolled, and among them 384 new cases of HCC occurred until 30 June 2008. A series of HCC risk calculators were developed and validated for patients with chronic hepatitis B and those with chronic hepatitis C, from the REVEAL study [2,3].

The Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) scoring systems were derived from the community cohort of the REVEAL-HBV study and validated internationally in hospital cohorts. Important risk predictors including age, sex, HBeAg serostatus, and serum levels of ALT, HBV DNA, and HBsAg were incorporated into the REACH-B scores. These scores have high validity for HCC risk prediction. Table B5.6.1

Table B5.6.1. Projected risk of developing hepatocellular carcinoma in patients with chronic hepatitis B, from the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) IIa prediction model

Predictor	Risk score	Cumulative (summed) risk score	Projected risk of developing hepatocellular carcinoma (%)		
			3-year	5-year	10-year
Sex		0	0.002	0.007	0.02
Female	0	1	0.003	0.01	0.03
Male	2	2	0.006	0.02	0.06
Age, 5-year increment	1	3	0.01	0.03	0.09
Serum ALT level (U/L)		4	0.02	0.05	0.15
< 15	0	5	0.03	0.08	0.25
15–44	1	6	0.05	0.13	0.42
≥ 45	2	7	0.08	0.22	0.69
HBeAg/HBV DNA (copies/mL)/HBsAg (IU/mL)		8	0.13	0.37	1.13
Negative/< 10^4/< 100	0	9	0.21	0.61	1.87
Negative/< 10^4/< 100–999	2	10	0.35	1.01	3.08
Negative/< 10^4/≥ 1000	3	11	0.59	1.66	5.04
Negative/10^4–10^6/< 100	2	12	0.97	2.74	8.21
Negative/10^4–10^6/100–999	3	13	1.60	4.49	13.21
Negative/10^4–10^6/≥ 1000	4	14	2.63	7.32	20.91
Negative/≥ 10^6/any	6	15	4.32	11.82	32.18
Positive	7	16	7.04	18.80	47.42
		17	11.39	29.15	65.49

ALT, alanine aminotransferase; HBeAg, HBV e antigen; HBsAg, HBV surface antigen; HBV, hepatitis B virus.

shows the risk scores assigned to different groups of risk predictors, together with the projected risk of developing HCC for potential cumulative risk scores in the REACH-B IIa prediction model [2].

An HCC risk score for anti-HCV-seropositive patients was derived from the REVEAL study and validated in another community-based high-risk cohort [3]. Important risk predictors, including age, serum ALT level, serum AST/ALT ratio, cirrhosis status, serum HCV RNA level, and HCV genotype, were incorporated into the risk score. The risk score has satisfactory to high validity and discriminatory ability for HCC risk prediction. However, it needs to be validated internationally for its application in other countries.

References

1. Chen CJ, Lee M-H, Liu J, Yang H-I (2015). Hepatocellular carcinoma risk scores: ready to use in 2015? Hepat Oncol. 2(1):1–4. https://doi.org/10.2217/hep.14.32 PMID:30190979
2. Yang HI, Tseng TC, Liu J, Lee MH, Liu CJ, Su TH, et al. (2016). Incorporating serum level of hepatitis B surface antigen or omitting level of hepatitis B virus DNA does not affect calculation of risk for hepatocellular carcinoma in patients without cirrhosis. Clin Gastroenterol Hepatol. 14(3):461–468.e2. https://doi.org/10.1016/j.cgh.2015.10.033 PMID:26598229
3. Lee MH, Lu SN, Yuan Y, Yang HI, Jen CL, You SL, et al. (2014). Development and validation of a clinical scoring system for predicting risk of HCC in asymptomatic individuals seropositive for anti-HCV antibodies. PLoS One. 9(5):e94760. https://doi.org/10.1371/journal.pone.0094760 PMID:24801353

chronic viral hepatitis (Fig. 5.6.5). These risk calculators are helpful for the triage of patients with viral hepatitis who need intensive liver surveillance and/or antiviral therapy, and for the evaluation of the efficacy of clinical management of patients with chronic viral hepatitis in South and East Asia. Risk calculators for predicting cirrhosis, the most important predisposing factor for HCC, in patients with chronic hepatitis B have also been derived and validated internally [22].

Prevention

Liver cancer may be prevented through interventions related to its major etiological factors (Table 5.6.2). Viral hepatitis control is included within the United Nations Sustainable Development Goals. The HBV vaccine has high efficacy and cost–effectiveness to prevent HCC. It is the first vaccine to prevent a cancer type in humans (see Chapter 6.3). The HBV vaccine has been incorporated into the national immunization programmes of 187 countries. The worldwide percentage of children younger than 5 years living with chronic HBV infection fell from 4.7% in the pre-vaccine era to 1.3% in 2015. HBV vaccination prevents an estimated 4.5 million HBV infections per year in children [23].

Several antiviral drugs have been approved for viral hepatitis therapy. Lamivudine was first approved in 1998 for the treatment of chronic hepatitis B. It significantly decreases the risk of HCC in treated patients but has the disadvantage of inducing antiviral-resistant YMDD mutants. Newly developed antiviral drugs for chronic hepatitis B have higher genetic barriers, to limit the development of antiviral-resistant strains. A recent cohort study reported a significant decrease in the incidence of HCC in 973 patients with chronic hepatitis B treated with pegylated interferon or any anti-HBV nucleoside/nucleotide analogue. The study found a 77% reduction in HCC incidence in treated patients, compared with 4935 untreated patients, after adjustment for the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) predictive risk score [24]. In a European study of 1951 adult Caucasian patients with chronic hepatitis B treated with entecavir or tenofovir, there was a significant decline in the annual HCC incidence rate in patients with cirrhosis, from 3.22% within the first 5 years of therapy to 1.57% within 5–10 years after enrolment [25].

The standard treatment for chronic hepatitis C was interferon-based therapy until the advent of direct-acting antiviral agents in 2013. HCV genotypes 1 and 4 are less responsive to interferon-based therapy compared with other genotypes. *IFNL3* variants were found to be associated with the efficacy of interferon-based therapy for chronic hepatitis C, and ethnicities in the Asia-Pacific region were shown to have a high frequency of favourable genotypes.

Direct-acting antiviral agents are highly effective for all HCV genotypes, without any ethnic variation. They are convenient oral agents with a low side-effect profile. In a recent study of 62 354 patients with chronic hepatitis C treated with interferon and/or direct-acting antiviral agents, sustained virological response (versus non-sustained virological response) was associated with a significant reduction in risk of HCC in patients treated with direct-acting antiviral agents only (71% reduction), with both direct-acting antiviral agents and interferon (52% reduction), and with interferon only (68% reduction), after adjustment for multiple risk factors [26]. In a study of 4639 patients with chronic hepatitis C treated with pegylated interferon and ribavirin, sustained virological response (versus non-sustained virological response) was associated with a significant decline in HCC incidence in patients with cirrhosis (46% reduction) and in those without cirrhosis (63% reduction) [27].

The global targets for 2030 set by WHO include 90% HBV vaccination coverage, 90% prevention of mother-to-child HBV transmission, 100% blood transfusion safety and injection safety, diagnosis of 90% of

Table 5.6.2. Prevention of liver cancer through interventions related to its major etiological factors

Etiological factor	Cancer type	Intervention
Hepatitis B virus infection	Hepatocellular carcinoma Intrahepatic cholangiocarcinoma	Immunization with HBIg and vaccine Interruption of mother-to-child transmission Early diagnosis of HBV infection Treatment of eligible patients with HBV infection
Hepatitis C virus infection	Hepatocellular carcinoma Intrahepatic cholangiocarcinoma	Injection safety using engineered devices Blood safety by donation screening Harm reduction for people who inject drugs Early diagnosis of HCV infection Treatment of eligible patients with HCV infection
Alcohol consumption	Hepatocellular carcinoma	Increase in alcohol taxes Limitation on days and/or hours of sale Enforcement of laws against privatizing retail sale of alcohol Regulation of density of alcohol outlets Enhancement of prohibiting sales to minors Behavioural intervention
Aflatoxin exposure	Hepatocellular carcinoma	Pre-harvest good agricultural practices to reduce crop stress Post-harvest sorting, storing, and drying Improvement in grain storage Introduction of fungus-resistant strains Avoidance or reduction of consumption of contaminated foods Biocontrol to reduce aflatoxin-producing fungi
Liver fluke infection	Intrahepatic cholangiocarcinoma	Stopping the consumption of raw fish Cooking fish before eating Screening and treatment with single-dose praziquantel Practising hygienic defecation
Obesity	Hepatocellular carcinoma	Diet control Exercise

HBIg, hepatitis B immunoglobulin; HBV, hepatitis B virus; HCV, hepatitis C virus.

HBV and HCV infections, and treatment of 80% of eligible patients [23]. To reach these targets, concerted national and international efforts are urgently needed. The coverage of diagnosis and treatment should be rapidly scaled up through a public health approach to benefit all. Sustainable financing and innovation are also required for the development and delivery of vaccines, diagnostics, and treatments to transform the global hepatitis response.

Several effective interventions are recommended to reduce the prevalence of alcohol consumption, aflatoxin exposure, liver fluke infection, and obesity (Table 5.6.2). [1]. Basic improvements in sorting, drying, and storing the groundnut crop in West Africa resulted in a marked reduction in aflatoxin contamination, in a feasible and cost-effective approach [28]. Reductions in aflatoxin biomarkers over time in China, linked to changes in consumption of aflatoxin-contaminated foods, were also associated with reduced incidence of HCC [29]. Concerted efforts to control liver fluke infection have been implemented in Thailand and have resulted in a large reduction in the prevalence of infection [1].

Table 5.6.3. Methods for early detection, diagnosis, and treatment of liver cancer

Clinical strategy	Methods
Early detection and diagnosis	α-Fetoprotein (low sensitivity for small tumours) Serum M2BPGi level Ultrasonography (< 1 cm) High-resolution computed tomography (CT) scan Contrast magnetic resonance imaging (MRI) scan Angiogram Laparoscopy Biopsy (not required for diagnosis)
Treatment	Surgical resection (partial hepatectomy) Liver transplantation Radiofrequency ablation Radiotherapy Chemoembolization Radioembolization Targeted therapy Immunotherapy

M2BPGi, Mac-2-binding protein glycosylation isomer.

Detection

Methods for screening, diagnosis, and treatment of liver cancer are shown in Table 5.6.3. Both serum α-fetoprotein (AFP) level and abdominal ultrasonography are used for the screening of HCC in high-risk patients: those with chronic viral hepatitis and those with cirrhosis.

Efficacy of viral hepatitis control to reduce risk of liver cancer

Because chronic hepatitis B virus (HBV) infection and chronic hepatitis C virus (HCV) infection are major etiological factors for liver cancer, their effective control may significantly reduce the burden of disease globally. Hepatitis B may be prevented by immunization, and both hepatitis B and hepatitis C may be treated with antiviral drugs. Successful reduction of liver cancer incidence and mortality has been demonstrated through several national programmes of viral hepatitis control.

The first national immunization programme in the world was launched in July 1984 [1]. From July 1984 to June 1986, only babies born to HBV surface antigen (HBsAg)-positive mothers were immunized; after July 1986, all newborns were immunized. Although all newborns received vaccines, only babies born to high-risk mothers with HBV e antigen (HBeAg)-seropositive status or with a high HBsAg titre received hepatitis B immunoglobulin with the first dose of vaccine at birth. From July 1987, previously unimmunized preschool children were also vaccinated, which means that birth cohorts born in 1981–1984 were vaccinated after age 1 year. The immunization rate of eligible infants was more than 90%. The rate of HBsAg-seropositive status at age 6 years decreased significantly, from more than 10% in unimmunized birth cohorts to less than 1% in immunized birth cohorts.

This immunization programme has been well documented to prevent hepatocellular carcinoma (HCC) in immunized birth cohorts, showing a very high efficacy 30 years after the launch of the immunization programme (Table B5.6.2) [1]. Both the incidence of and mortality from HCC in people aged 5–29 years have decreased significantly from birth cohorts born in 1977–1980 to those born in 1997–2000. The age- and sex-adjusted rate ratio for HCC incidence was 0.37 and for HCC mortality was 0.21, for the 1997–2000 birth cohorts compared with the 1977–1980 birth cohorts. From a study of 3.8 million vaccinees, incomplete immunization and maternal serostatus of HBsAg and HBeAg are important predictors of HCC risk for the vaccinees [2].

For patients with chronic viral hepatitis, prompt treatment is the only strategy to prevent liver cancer. The first national programme to treat patients with chronic viral hepatitis in the world was launched in October 2003 [3]. Available treatments for chronic HBV infection include interferon-α, pegylated interferon-α, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. Available treatments for chronic

Table B5.6.2. Significant reductions in hepatocellular carcinoma (HCC) incidence and mortality through national programmes of hepatitis B virus immunization and chronic viral hepatitis therapy

Hepatitis B virus immunization programme				
Birth year	**HCC mortality (ages 5–29 years)**		**HCC incidence (ages 5–29 years)**	
	Rate per 100 000 person-years	**Age- and sex-adjusted rate ratio (95% CI)**	**Rate per 100 000 person-years**	**Age- and sex-adjusted rate ratio (95% CI)**
1977–1980	0.81	1.00 (reference)	1.14	1.00 (reference)
1981–1984	0.56	0.70 (0.59–0.83)	0.77	0.73 (0.63–0.85)
1985–1988	0.30	0.43 (0.33–0.55)	0.37	0.48 (0.38–0.60)
1989–1992	0.17	0.27 (0.19–0.39)	0.23	0.37 (0.27–0.51)
1993–1996	0.12	0.21 (0.13–0.34)	0.22	0.43 (0.30–0.62)
1997–2000	0.12	0.21 (0.12–0.38)	0.17	0.37 (0.21–0.62)
Chronic viral hepatitis therapy programme				
Calendar year	**HCC mortality (ages 30–69 years)**		**HCC incidence (ages 30–69 years)**	
	Rate per 100 000 person-years	**Age- and sex-adjusted rate ratio (95%CI)**	**Rate per 100 000 person-years**	**Age- and sex-adjusted rate ratio (95% CI)**
2000–2003	36.59	1.00 (reference)	54.12	1.00 (reference)
2004–2007	35.77	0.95 (0.93–0.97)	54.79	0.98 (0.96–0.99)
2008–2011	30.21	0.76 (0.75–0.78)	50.77	0.86 (0.85–0.88)
2012–2015	27.44	0.64 (0.62–0.65)	47.55	0.76 (0.74–0.77)

CI, confidence interval; HCC, hepatocellular carcinoma.

HCV infection include ribavirin, pegylated interferon, and direct-acting antiviral agents.

From 2000–2003 to 2012–2015, there was a significant reduction in the incidence of and mortality from liver cancer (Table B5.6.2). The age- and sex-adjusted rate ratio for HCC incidence was 0.76 and for HCC mortality was 0.64, for 2012–2015 compared with 2000–2003, the 4-year period before the launch of the chronic viral hepatitis therapy programme. Further diagnosis and treatment of more eligible patients with viral hepatitis are still needed.

References

1. Chiang CJ, Yang YW, You SL, Lai MS, Chen CJ (2013). Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. JAMA. 310(9):974–6. https://doi.org/10.1001/jama.2013.276701 PMID:24002285
2. Chien YC, Jan CF, Chiang CJ, Kuo HS, You SL, Chen CJ (2014). Incomplete hepatitis B immunization, maternal carrier status, and increased risk of liver diseases: a 20-year cohort study of 3.8 million vaccinees. Hepatology. 60(1):125–32. https://doi.org/10.1002/hep.27048 PMID:24497203
3. Chiang CJ, Yang YW, Chen JD, You SL, Yang HI, Lee MH, et al. (2015). Significant reduction in end-stage liver diseases burden through the national viral hepatitis therapy program in Taiwan. Hepatology. 61(4):1154–62. https://doi.org/10.1002/hep.27630 PMID:25476749

Ultrasonography may detect HCC tumours smaller than 1 cm. AFP level has a screening sensitivity of about 70% for detecting early-stage, small HCC tumours. However, AFP level remains a useful seromarker for short-term prediction of HCC after antiviral treatment in patients with chronic hepatitis C [27]. The serum level of Mac-2-binding protein glycosylation isomer (M2BPGi) is able to accurately distinguish between stages of fibrosis in patients with chronic viral hepatitis. It has been reported to be a seromarker that is as good as AFP level for short-term prediction of HCC in patients with chronic hepatitis B [30].

There are several options for the treatment of liver cancer. The methods of choice depend on the tumour size, lymph node involvement, metastasis, liver function and cirrhosis status, overall health condition, and patient preference. However, detection and treatment options are very limited in low- and middle-income countries, where liver cancer is a major health problem.

References

1. Gelband H, Chen CJ, Chen W, Franceschi S, Hall A, London WT, et al. (2015). Liver cancer. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. Disease control priorities. 3rd ed. Vol. 3, Cancer. Washington (DC), USA: World Bank; pp. 147–164.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593
3. Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, et al.; Global Burden of Disease Liver Cancer Collaboration (2017). The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at global, regional, and national level: results from the Global Burden of Disease Study 2015. JAMA Oncol. 3(12):1683–91. https://doi.org/10.1001/jamaoncol.2017.3055 PMID:28983565
4. Chen CJ (2018). Global elimination of viral hepatitis and hepatocellular carcinoma: opportunities and challenges. Gut. 67(4): 595–8. http://dx.doi.org/10.1136/gutjnl-2017-315407 PMID:29367206
5. Castelli G, Pelosi E, Testa U (2017). Liver cancer: molecular characterization, clonal evolution and cancer stem cells. Cancers (Basel). 9(9):127–74. https://doi.org/10.3390/cancers9090127 PMID:28930164
6. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Biankin AV, et al.; Australian Pancreatic Cancer Genome Initiative; ICGC Breast Cancer Consortium; ICGC MMML-Seq Consortium; ICGC PedBrain (2013). Signatures of mutational processes in human cancer. Nature. 500(7463):415–21. https://doi.org/10.1038/nature12477 PMID:23945592
7. Totoki Y, Tatsuno K, Covington KR, Ueda H, Creighton CJ, Kato M, et al. (2014). Trans-ancestry mutational landscape of hepatocellular carcinoma genomes. Nat Genet. 46(12):1267–73. https://doi.org/10.1038/ng.3126 PMID:25362482
8. Shibata T, Aburatani H (2014). Exploration of liver cancer genomes. Nat Rev Gastroenterol Hepatol. 11(6):340–9. https://doi.org/10.1038/nrgastro.2014.6 PMID:24473361
9. The Cancer Genome Atlas Research Network (2017). Comprehensive and integrative genomic characterization of hepatocellular carcinoma. Cell. 169(7):1327–1341.e23. https://doi.org/10.1016/j.cell.2017.05.046 PMID:28622513
10. Liu J, Yang HI, Lee MH, Lu SN, Jen CL, Batrla-Utermann R, et al.; R.E.V.E.A.L.-HBV Study Group (2014). Spontaneous seroclearance of hepatitis B seromarkers and subsequent risk of hepatocellular carcinoma. Gut. 63(10):1648–57. https://doi.org/10.1136/gutjnl-2013-305785 PMID:24225939
11. Hu HH, Liu J, Lin YL, Luo WS, Chu YJ, Chang CL, et al.; REVEAL-HBV Study Group (2016). The rs2296651 (S267F) variant on NTCP (*SLC10A1*) is inversely associated with chronic hepatitis B and progression to cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis B. Gut. 65(9):1514–21. https://doi.org/10.1136/gutjnl-2015-310686 PMID:26642861
12. Lee MH, Yang HI, Lu SN, Lin YJ, Jen CL, Wong KH, et al. (2015). Polymorphisms near the *IFNL3* gene associated with HCV RNA spontaneous clearance and hepatocellular carcinoma risk. Sci Rep. 5(1):17030. https://doi.org/10.1038/srep17030 PMID:26602024

13. Lee MH, Huang YH, Chen HY, Khor SS, Chang YH, Lin YJ, et al.; REVEAL-HCV Cohort Study Group (2017). Human leukocyte antigen variants and risk of hepatocellular carcinoma modified by hepatitis C virus genotypes: a genome-wide association study. Hepatology. 67(2):651–61. https://doi.org/10.1002/hep.29531 PMID:28921602

14. Loomba R, Yang HI, Su J, Brenner D, Barrett-Connor E, Iloeje U, et al. (2013). Synergism between obesity and alcohol in increasing the risk of hepatocellular carcinoma: a prospective cohort study. Am J Epidemiol. 177(4):333–42. https://doi.org/10.1093/aje/kws252 PMID:23355498

15. Liu J, Yang HI, Lee MH, Jen CL, Hu HH, Lu SN, et al. (2016). Alcohol drinking mediates the association between polymorphisms of *ADH1B* and *ALDH2* and hepatitis B-related hepatocellular carcinoma. Cancer Epidemiol Biomarkers Prev. 25(4):693–9. https://doi.org/10.1158/1055-9965.EPI-15-0961 PMID:26827895

16. Chu YJ, Yang HI, Wu HC, Liu J, Wang LY, Lu SN, et al. (2017). Aflatoxin B_1 exposure increases the risk of cirrhosis and hepatocellular carcinoma in chronic hepatitis B virus carriers. Int J Cancer. 141(4):711–20. https://doi.org/10.1002/ijc.30782 PMID:28509392

17. Chu YJ, Yang HI, Wu HC, Lee MH, Liu J, Wang LY, et al. (2018). Aflatoxin B_1 exposure increases the risk of hepatocellular carcinoma associated with hepatitis C virus infection or alcohol consumption. Eur J Cancer. 94(5):37–46. https://doi.org/10.1016/j.ejca.2018.02.010 PMID:29533866

18. Michelotti GA, Machado MV, Diehl AM (2013). NAFLD, NASH and liver cancer. Nat Rev Gastroenterol Hepatol. 10(11):656–65. https://doi.org/10.1038/nrgastro.2013.183 PMID:24080776

19. Chen CL, Yang W-S, Yang H-I, Chen C-F, You S-L, Wang L-Y, et al. (2014). Plasma adipokines and risk of hepatocellular carcinoma in chronic hepatitis B virus-infected carriers: a prospective study in Taiwan. Cancer Epidemiol Biomarkers Prev. 23(8):1659–71. https://doi.org/10.1158/1055-9965.EPI-14-0161 PMID:24895413

20. Lin YJ, Shaw TG, Yang HI, Lu SN, Jen CL, Wang LY, et al.; R.E.V.E.A.L.-HCV Study Group (2017). Chronic hepatitis C virus infection and the risk for diabetes: a community-based prospective study. Liver Int. 37(2):179–86. https://doi.org/10.1111/liv.13194 PMID:27363856

21. Pan WC, Wu CD, Chen MJ, Huang YT, Chen CJ, Su HJ, et al. (2015). Fine particle pollution, alanine transaminase, and liver cancer: a Taiwanese prospective cohort study (REVEAL-HBV). J Natl Cancer Inst. 108(3):djv341. https://doi.org/10.1093/jnci/djv341 PMID:26561636

22. Lee MH, Yang HI, Liu J, Batrla-Utermann R, Jen CL, Iloeje UH, et al.; R.E.V.E.A.L.-HBV Study Group (2013). Prediction models of long-term cirrhosis and hepatocellular carcinoma risk in chronic hepatitis B patients: risk scores integrating host and virus profiles. Hepatology. 58(2):546–54. https://doi.org/10.1002/hep.26385 PMID:23504622

23. WHO (2017). Global hepatitis report, 2017. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/.

24. Lin D, Yang HI, Nguyen N, Hoang J, Kim Y, Vu V, et al. (2016). Reduction of chronic hepatitis B-related hepatocellular carcinoma with anti-viral therapy, including low risk patients. Aliment Pharmacol Ther. 44(8):846–55. https://doi.org/10.1111/apt.13774 PMID:27549411

25. Papatheodoridis GV, Idilman R, Dalekos GN, Buti M, Chi H, van Boemmel F, et al. (2017). The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology. 66(5):1444–53. https://doi.org/10.1002/hep.29320 PMID:28622419

26. Ioannou GN, Green PK, Berry K (2018). HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol. 68(1):25–32. https://doi.org/10.1016/j.jhep.2017.08.030 PMID:28887168

27. Lee MH, Huang CF, Lai HC, Lin CY, Dai CY, Liu CJ, et al. (2017). Clinical efficacy and post-treatment seromarkers associated with the risk of hepatocellular carcinoma among chronic hepatitis C patients. Sci Rep. 7(1):3718. https://doi.org/10.1038/s41598-017-02313-y PMID:28623331

28. Turner PC, Sylla A, Gong YY, Diallo MS, Sutcliffe AE, Hall AJ, et al. (2005). Reduction in exposure to carcinogenic aflatoxins by postharvest intervention measures in west Africa: a community-based intervention study. Lancet. 365(9475):1950–6. https://doi.org/10.1016/S0140-6736(05)66661-5 PMID:15936422

29. Chen JG, Egner PA, Ng D, Jacobson LP, Muñoz A, Zhu YR, et al. (2013). Reduced aflatoxin exposure presages decline in liver cancer mortality in an endemic region of China. Cancer Prev Res (Phila). 6(10):1038–45. https://doi.org/10.1158/1940-6207.CAPR-13-0168 PMID:23963804

30. Liu J, Hu HH, Lee MH, Jen CL, Batrla-Utermann R, Lu SN, et al. (2017). Serum levels of M2BPGi as short-term predictors of hepatocellular carcinoma in untreated chronic hepatitis B patients. Sci Rep. 7(1):14352. https://doi.org/10.1038/s41598-017-14747-5 PMID:29085039

5.7 Pancreatic cancer

Many risk factors too poorly characterized to enable prevention

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SUMMARY

- Pancreatic cancer is the seventh most common cause of cancer-related mortality worldwide, with an overall 5-year survival rate of 9%. The most common type of pancreatic cancer (> 90%) is infiltrating pancreatic ductal adenocarcinoma.
- Smoking, obesity, and long-standing type 2 diabetes are known risk factors for pancreatic cancer development. New-onset diabetes can be an early sign of pancreatic cancer.
- More than 90% of cases of pancreatic cancer are sporadic (i.e. due to spontaneous rather than inherited mutations), although a family history increases risk, particularly where more than one first-degree family member is involved. The presence of pathogenic germline mutations in patients with sporadic pancreatic cancer, even in the absence of a positive family history, is increasingly recognized.
- Activating mutations in the *KRAS* oncogene and loss-of-function mutations in the tumour suppressor genes *TP53*, *SMAD4*, and *CDKN2A* are prevalent in pancreatic adenocarcinoma. None of these genetic alterations can be targeted with current chemotherapeutics.

Pancreatic cancer is the seventh most common cause of cancer-related mortality worldwide, with an overall 5-year survival rate of 9%. The most common type of pancreatic cancer (> 90%) is infiltrating pancreatic ductal adenocarcinoma.

The epidemiological study of pancreatic ductal adenocarcinoma is complicated by significant geographical and temporal variations in the sensitivity and specificity of clinical diagnosis and in the proportion of cases that are histologically verified. Differences in access to health care, such as differences related to social classes or age groups, can affect the reported incidence and mortality rates.

In 2018 an estimated 459 000 new cases of pancreatic ductal adenocarcinoma were diagnosed worldwide, with age-standardized incidence rates in both sexes of 6.2 per 100 000 in more-developed countries and 1.5 per 100 000 in less-developed countries. In the USA, there were projected to be 55 440 new cases and 44 310 deaths from pancreatic cancer in 2018. The USA has one of the highest pancreatic cancer incidence rates in the world, and it is still rising. Pancreatic cancer is projected to become the second most common cause of cancer death in the USA by 2030 [1].

Despite advances in the understanding of the biology of pancreatic cancer, clinical translation into effective treatment and early detection options has been challenging. In the 15% of patients who present with resectable tumours, the 5-year survival rate of 30% remains much lower than that for many other cancer types; this highlights the unique propensity for pancreatic cancer to metastasize early in the course of the disease. Biomarkers for early detection are lacking for clinical use, and established modifiable risk factors remain inadequately characterized to enable an impactful plan for primary prevention of pancreatic cancer.

Epidemiology

Pancreatic cancer is among the deadliest types of cancer. In 2018, there were an estimated 459 000 new cases of pancreatic cancer worldwide. Incidence rates of pancreatic cancer in 2018 were highest in western Europe (8.3 per 100 000) and North America (7.6 per 100 000). The lowest incidence rates of pancreatic cancer (~1.0 per 100 000) were observed in East Africa and South-Central Asia.

Global differences in pancreatic cancer incidence rates have been attributed largely to exposure to known or suspected risk factors related to lifestyle or the environment, although heritable factors may contribute. The contributions of international differences in diagnostic capacity or registry quality to observed pancreatic cancer incidence rates are not known.

Etiology

Several non-modifiable factors are associated with risk of pancreatic cancer. Increasing age correlates with risk of pancreatic cancer; most patients are diagnosed at ages 60–80 years, and pancreatic cancer is unusual in people younger than 45 years. Pancreatic cancer affects men and women equally. Studies in the USA have shown that pancreatic cancer is more common in the African American population than it is in the White population, but the potential confounding contribution of socioeconomic factors, smoking status, and the presence of type 2 diabetes and obesity has not been calculated (see Chapter 4.6). Higher attained adult height and non-O blood group are also associated with increased risk.

Among the known modifiable risk factors, smoking is the best documented and is thought to be responsible for about 25% of cases of pancreatic cancer (see Chapter 2.1). Smokers have a relative risk of 1.5–1.9 of developing pancreatic cancer [2], with a documented dose–risk relationship and a positive benefit identified with smoking cessation. Use of smokeless tobacco products is also associated with increased risk of pancreatic cancer.

Certain dietary habits, including high intake of saturated fats, fructose, and red meat and low intake of fruits and vegetables, have been associated with higher risk of pancreatic cancer. Very few studies – notably the European Prospective Investigation into Cancer and Nutrition (EPIC) study [3], the Nurses' Health Study [4], and the Health Professionals Follow-Up Study [5] – have comprehensively investigated the effects of individual nutrition components on risk of pancreatic cancer.

Current evidence on diet, nutrition, and physical activity related to reduction of higher risk of pancreatic cancer is available as part of the Continuous Update Project of the World Cancer Research Fund/American Institute for Cancer Research [6]. Heavy alcohol consumption (three or more drinks per day) has been linked to risk of pancreatic cancer (see Chapter 2.3). This association may be related to an increased incidence in this population of chronic pancreatitis, which is known to increase the risk of pancreatic cancer 2-fold. There is no link with moderate alcohol consumption. A low level of physical activity has also been associated with risk of pancreatic cancer [7].

Large case–control and cohort studies have identified obesity and long-standing type 2 diabetes as risk factors for pancreatic cancer [2]. There is a complex relationship between obesity and type 2 diabetes, because they often coexist. Several large studies have consistently shown that obesity is a dose-dependent risk factor for pancreatic cancer, independent of the presence of type 2 diabetes. For example, in a pooled cohort of more than 900 000 people in whom 2454 pancreatic cancers were diagnosed, the incidence of pancreatic cancer was increased by 19% in the group with body mass index 30–35 kg/m^2 (compared with the group with normal weight; body mass index 18.5–25 kg/m^2), independent of the presence of type 2 diabetes [8].

Paradoxically, diabetes has been established as both a risk factor for pancreatic cancer (long-standing type 2 diabetes) and a manifestation of early-stage pancreatic cancer (new-onset type 3c diabetes). Long-standing type 2 diabetes increases the risk of pancreatic cancer development about 2-fold [9]. Diabetes can also be caused by the presence of pancreatic cancer (type 3c diabetes). New-onset diabetes can be an early sign of pancreatic cancer, and it is being explored as a biomarker for early detection (as discussed below).

Obesity and type 2 diabetes are increasingly recognized as systemic, low-grade inflammatory conditions with increased expression of pro-inflammatory cytokines, adipokines, and reactive oxygen species [10]. In mouse models, obesity has been demonstrated to be associated with increased pancreatic inflammation, acceleration of tumour progression, and resistance to chemotherapy [11,12]. Targeting obesity by calorie restriction decreased inflammation and reduced pancreatic cancer incidence and progression [13]. Similarly, type 2 diabetes and hyperinsulinaemia have been shown to lead to chronic inflammation and increased cancer risk and progression in mouse models, and inhibition of inflammatory

FUNDAMENTALS

- Pancreatic ductal adenocarcinoma is an aggressive disease with innate resistance to standard chemotherapy and radiotherapy regimens.
- Most patients with pancreatic cancer present with advanced disease. No reliable screening test is currently available for the early detection of pancreatic cancer.
- In the minority of patients who present with early-stage, localized disease, the 5-year survival rate is 30%, even with surgical resection; this highlights that pancreatic cancer metastasizes early in the course of the disease.
- Most pancreatic cancers harbour oncogenic *KRAS* mutations, which occur early in the tumorigenic process. Secondary events – either genetic changes, such as acquisition of loss-of-function mutations in *TP53*, *SMAD4*, and *CDKN2A*, or tissue damage or inflammation – are required, along with *KRAS* mutations, for formation of pancreatic intraepithelial neoplasia and tumour progression.
- Pancreatic cancer is characterized by an intense desmoplastic stromal reaction, which contributes to the biology of the disease and challenges medical treatment.

signalling pathways reduced tumour growth in an animal model [14].

Oral antidiabetic medications have significant potential to decrease risk of pancreatic cancer. In a meta-analysis, use of metformin was associated with reduced risk of pancreatic cancer in patients with type 2 diabetes [15], and metformin has been shown to inhibit pancreatic tumour growth in mouse models [16].

The inflammatory microenvironment is also thought to be a major mechanism by which chronic pancreatitis leads to the development of pancreatic cancer (see Chapter 3.5). Although the population attributable fraction is less than 3% [2], chronic pancreatitis has been associated with pancreatic cancer in multiple independent epidemiological studies. A recent systematic review of 17 587 cases of pancreatitis confirmed a strong association between chronic pancreatitis and risk of pancreatic cancer [17]. In that study, the risk of pancreatic cancer was associated with the duration of pancreatitis, with the highest risk in pancreatitis cases diagnosed within 1 year. It is possible that the very strong association in this group could be ascribed to pre-existing pancreatic cancer that presented as pancreatitis; however, the high risk of pancreatic cancer in the groups with pancreatitis duration of 2, 5, and 10 years highlights the clear association. Further evidence of the link between pancreatitis and risk of pancreatic cancer is evident in the rare cases of hereditary pancreatitis, caused by mutations in the cationic trypsinogen (*PRSS1*) gene. In people with hereditary pancreatitis, the lifetime risk of pancreatic cancer is about 40%.

Family history and genetic risk factors also play a role in risk of pancreatic cancer. Up to 8–10% of patients with pancreatic cancer carry a pathogenic germline variant in a known cancer risk gene (including *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *STK11*, and *TP53*) [18–20]; these confer a lifetime risk of pancreatic cancer that ranges from 3% to 58%. An additional group of patients with two or more family members with pancreatic cancer have familial pancreatic cancer without an identifiable genetic risk factor; this is associated with a lifetime risk of 3–32%, depending on the number of close relatives affected. Patients with symptomatic pancreatitis who carry a pathogenic germline variant in *PRSS1* or have a documented family history of chronic pancreatitis also have an elevated lifetime risk, of up to 44%. Data on risk of pancreatic cancer associated with inherited syndromes are summarized in Table 5.7.1.

Common single-nucleotide polymorphisms (SNPs) in the population may account for an additional portion of pancreatic cancer cases. Large-scale efforts – including the Pancreatic Disease Research Consortium [21], the Pancreatic Cancer Cohort Consortium, and the Pancreatic Cancer Case-Control Consortium [22] – have identified loci associated with risk of pancreatic cancer. Further studies will be needed to understand the functional consequences of the identified common variants. Risk models could potentially be developed to estimate risk using validated SNPs and the presence of other modifiable and non-modifiable risk factors to identify patients at higher risk [23].

Pathology

Infiltrating pancreatic ductal adenocarcinoma is characterized by glandular neoplastic epithelial cells typically surrounded by an intense desmoplastic stromal reaction (Fig. 5.7.1). Therefore, the bulk of a pancreatic cancer is composed of stromal cells and collagen, with inflammatory cells and blood vessels.

Pancreatic cancers are known to contain a high interstitial pressure, and blood vessels within the tumour are compressed, creating a hypoxic environment with decreased perfusion, as evidenced by the presence of a hypodense mass on cross-sectional imaging (Fig. 5.7.2). The desmoplastic stromal reaction has been proposed to limit effective delivery of therapeutic agents within the tumour. Therapeutic strategies that target the stroma are being developed. Perineural tumour invasion is also

Table 5.7.1. Inherited syndromes associated with risk of pancreatic cancer

Syndrome	Genes mutated	Published risk estimates
Peutz–Jeghers syndrome	*STK11*	Cumulative risk: 32–36% by age 70 years
Familial atypical multiple mole melanoma (FAMMM) syndrome	*CDKN2A*	Cumulative risk: 17% by age 75 years
Familial pancreatic cancer	Unknown	Overall: SIR = 9.0 Three affected first-degree relatives: SIR = 32
Hereditary pancreatitis	*PRSS1*	Cumulative risk: 44% by age 70 years
Hereditary breast and ovarian cancer syndrome	*BRCA1* *BRCA2*	Relative risk: 2.6 Relative risk: 3.5–5.9
Lynch syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*	Cumulative risk: 3–4% by age 70 years
	ATM, *PALB2*	Unknown

SIR, standardized incidence ratio.

Fig. 5.7.1. Histopathology of infiltrating pancreatic ductal adenocarcinoma, highlighting desmoplastic stroma.

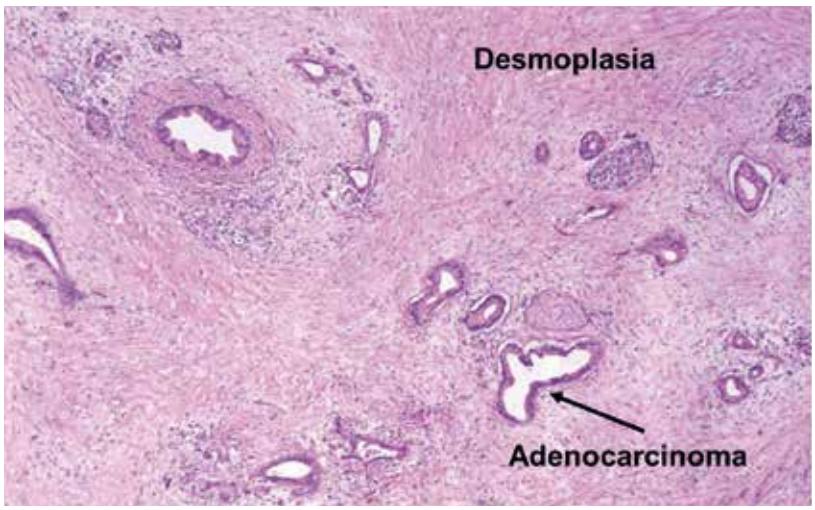
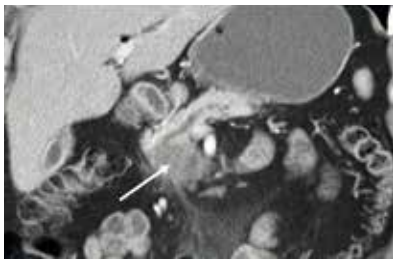


Fig. 5.7.2. A hypodense mass in the pancreas, indicated by a white arrow, shows the characteristic imaging appearance of a pancreatic ductal adenocarcinoma.



common and causes pain in many patients with pancreatic cancer.

Pancreatic adenocarcinoma can develop from any of at least three histologically distinct precursor lesions. Pancreatic intraepithelial neoplasia lesions are microscopic proliferations that can progress to pancreatic cancer. However, they are not detectable with current imaging modalities. Intraductal papillary mucinous neoplasms are relatively common cystic lesions of the pancreatic ducts. They are often identified incidentally on abdominal imaging, and they can have dysplasia and malignant potential. Mucinous cystic neoplasms are recognized by the unique presence of ovarian-type stroma. They occur more commonly in women and have a higher associated risk, with a chance of about 30% of progressing to adenocarcinoma.

Genetics

Extensive studies to characterize the genomic landscape of pancreatic cancer have improved the understanding of intertumour heterogeneity in patients with pancreatic cancer. The most commonly mutated genes in pancreatic adenocarcinoma include the *KRAS* oncogene and the tumour suppressor genes *TP53*, *SMAD4*, and *CDKN2A* [24] (Fig. 5.7.3). Beyond these common mutations, deeper whole-genome analyses have identified potential subtypes of pancreatic cancer [25]. In an analysis of 150 samples of pancreatic ductal adenocarcinoma, including samples with the low cellularity that is characteristic of many tumours, a subset of tumours harboured multiple *KRAS* mutations, with some evidence of biallelic mutations [24]. The contribution of this finding to tumour biology remains to be discerned.

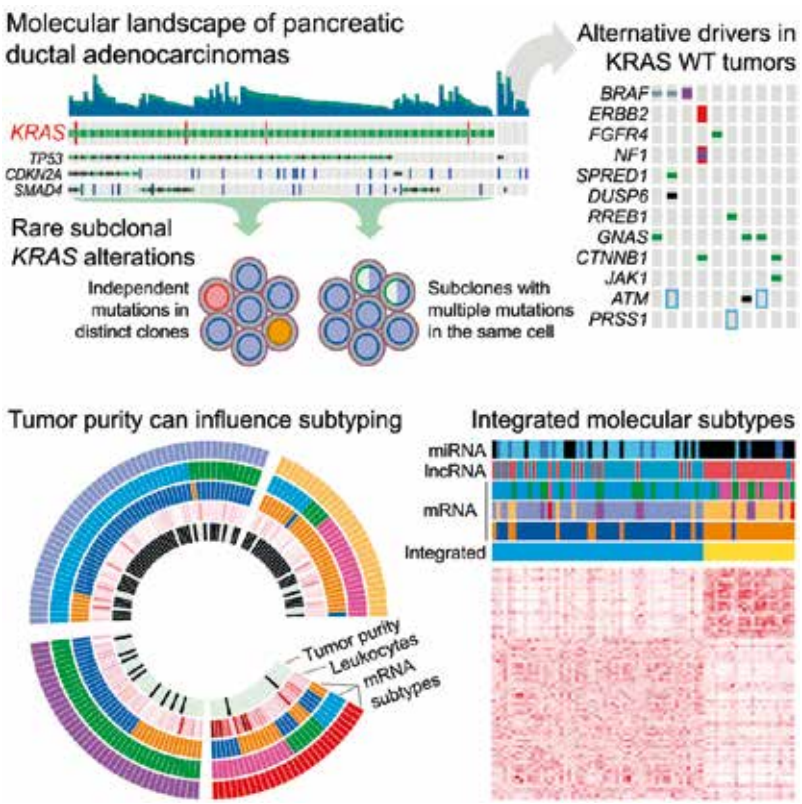
Next-generation sequencing for patients with pancreatic cancer identifies alterations in about 40% of sequenced patients. This information is currently used in clinical research to inform enrolment in a genotype-directed clinical trial. For example, germline or somatic alterations in DNA repair genes such as *BRCA1*, *BRCA2*, *PALB2*, or *ATM* give rise to genomic instability in a subset of pancreatic ductal adenocarcinomas; this could make them more sensitive to platinum-based chemotherapy and/or poly(ADP-ribose) polymerase (PARP) inhibitors. It is not currently recommended in clinical practice.

Biomarkers

Several putative biomarkers that may play a role in early detection of pancreatic cancer have been identified, although most have been studied in small retrospective cohorts using samples collected from late-stage disease, with relatively small numbers of control samples from patients with chronic pancreatitis, diabetes, or non-cancerous biliary obstruction. Some recently identified biomarkers that are being actively studied include single markers [26], multi-analyte panels [27], and immune-based proteomic panels [28]. Specific phylotypes in oral flora have been associated with risk of pancreatic cancer in a large prospective cohort study of the oral microbiome, suggesting that microbiome signatures also hold promise as biomarkers for early detection [29]. Prospective studies in a large-scale high-risk cohort are needed to validate the clinical utility of biomarkers for early detection, separately and in combination.

Recently, detailed work has shed light on the potential role of new-onset diabetes as a biomarker for early pancreatic cancer. In a study in Olmsted County, Minnesota, USA, which had near-complete clinical data capture of the entire population of the county, fasting blood glucose level was associated with time to diagnosis of pancreatic cancer, and the data showed that patients diagnosed with pancreatic cancer were hyperglycaemic for a mean of 30–36 months before diagnosis [30] (Fig. 5.7.4). From this work, a risk prediction model was developed that incorporated change in weight,

Fig. 5.7.3. Overview of the molecular genomic features of pancreatic ductal adenocarcinoma, from the Cancer Genome Atlas Research Network [24]. lncRNA, long noncoding RNA; mRNA, messenger RNA; miRNA, microRNA; WT, wild-type.



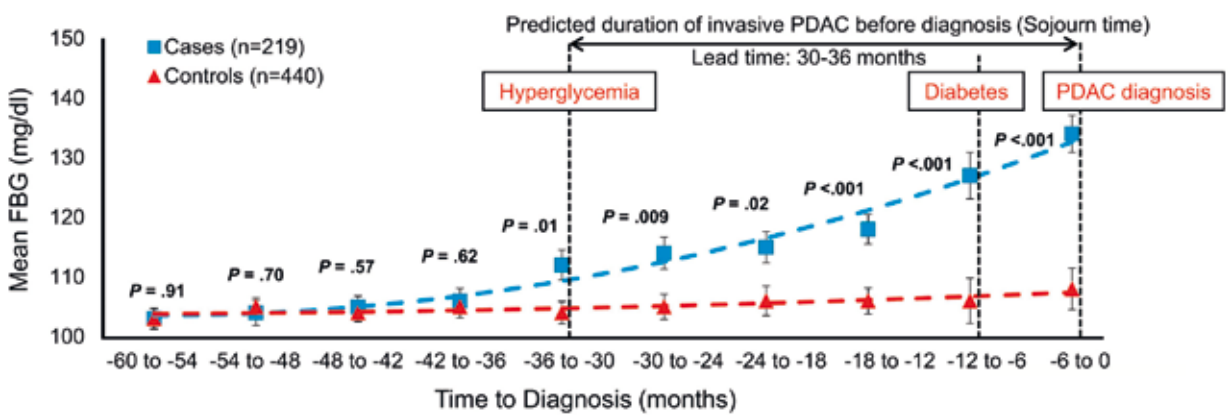
change in blood glucose level, and age at onset of diabetes. The model identified patients who developed pancreatic cancer within 3 years of onset of diabetes with an area under the receiver operating characteristic curve value of 0.87 [31].

Screening and identification of high-risk groups

No reliable screening test is currently available for the early detection of pancreatic cancer in the general population. In individuals with significantly increased risk of pancreatic cancer on the basis of family history and genetic risk factors, imaging of the pancreas is performed for screening. Endoscopic ultrasonography and magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography (MRCP) are used in the clinical setting. However, clear definitions of who should be screened and at what age screening should commence have not been formalized.

The potential benefit of screening of high-risk individuals has been demonstrated in a study in Europe, which noted that *CDKN2A* mutation carriers were more likely to be diagnosed with a resectable pancreatic cancer and had a higher 5-year survival rate [32]. Recent data from the International Cancer of the Pancreas Screening Consortium showed that 9 of 10 screen-detected pancreatic cancers were resectable, suggesting a benefit of screening in individuals at high risk [33]. An effort to engage in larger-scale, collaborative consortia is needed to provide more rigorous evidence of the value of screening of high-risk individuals. Patients with new-onset diabetes and intraductal papillary mucinous neoplasms are also groups with elevated risk in which studies of the benefits of screening are under way.

Fig. 5.7.4. The elevation of fasting blood glucose (FBG) levels beginning 30–36 months before diagnosis of pancreatic ductal adenocarcinoma (PDAC) is an area of interest for early detection strategies.



Prevention

Risk factors such as age, attained adult height, race, and family history cannot be modified, but primary prevention by the alteration of modifiable risk factors has the potential to decrease the overall risk of pancreatic cancer and warrants further study. Potentially modifiable risk factors include smoking, obesity, diabetes, diet, and alcohol consumption. The best strategy for risk reduction is lifestyle modification: smoking cessation, maintaining a healthy weight, a diet high in fruits and vegetables, regular physical activity, and avoiding heavy alcohol consumption.

In the absence of effective screening methods, options for primary prevention of pancreatic cancer are of significant importance, and chemoprevention for pancreatic cancer is a high priority for translational research. A review of epidemiological data performed by a working group in 2015 suggested that aspirin and statins may provide some protective effect, whereas for vitamin D the results have been mixed. Non-aspirin non-steroidal anti-inflammatory drugs do not appear to have an effect on risk [34]. Metformin appears to protect against genomic instability through various mechanisms in vitro, and metformin in combination with aspirin has been shown to inhibit tumour growth in a mouse model of pancreatic cancer [35]. These studies have provided some insights for planning future prospective prevention trials.

References

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM (2014). Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 74(11):2913–21. https://doi.org/10.1158/0008-5472.CAN-14-0155 PMID:24840647
2. Maisonneuve P, Lowenfels AB (2015). Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol. 44(1):186–98. https://doi.org/10.1093/ije/dyu240 PMID:25502106
3. Riboli E, Kaaks R (1997). The EPIC project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol. 26(Suppl 1):S6–14. https://doi.org/10.1093/ije/26.suppl_1.S6 PMID:9126529
4. Belanger CF, Hennekens CH, Rosner B, Speizer FE (1978). The Nurses' Health Study. Am J Nurs. 78(6):1039–40. PMID:248266
5. Rimm EB, Stampfer MJ, Colditz GA, Giovannucci E, Willett WC (1990). Effectiveness of various mailing strategies among nonrespondents in a prospective cohort study. Am J Epidemiol. 131(6):1068–71. https://doi.org/10.1093/oxfordjournals.aje.a115598 PMID:2343859
6. WCRF/AICR (2018). Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and pancreatic cancer risk. World Cancer Research Fund/American Institute for Cancer Research. Available from: https://www.wcrf.org/sites/default/files/Pancreatic-cancer-report.pdf.
7. Behrens G, Jochem C, Schmid D, Keimling M, Ricci C, Leitzmann MF (2015). Physical activity and risk of pancreatic cancer: a systematic review and meta-analysis. Eur J Epidemiol. 30(4):279–98. https://doi.org/10.1007/s10654-015-0014-9 PMID:25773752
8. Jiao L, Berrington de Gonzalez A, Hartge P, Pfeiffer RM, Park Y, Freedman DM, et al. (2010). Body mass index, effect modifiers, and risk of pancreatic cancer: a pooled study of seven prospective cohorts. Cancer Causes Control. 21(8):1305–14. https://doi.org/10.1007/s10552-010-9558-x PMID:20383573
9. Bosetti C, Rosato V, Li D, Silverman D, Petersen GM, Bracci PM, et al. (2014). Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium. Ann Oncol. 25(10):2065–72. https://doi.org/10.1093/annonc/mdu276 PMID:25057164
10. Eibl G, Cruz-Monserrate Z, Korc M, Petrov MS, Goodarzi MO, Fisher WE, et al.; Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (2018). Diabetes mellitus and obesity as risk factors for pancreatic cancer. J Acad Nutr Diet. 118(4):555–67. https://doi.org/10.1016/j.jand.2017.07.005 PMID:28919082
11. Dawson DW, Hertzer K, Moro A, Donald G, Chang H-H, Go VL, et al. (2013). High-fat, high-calorie diet promotes early pancreatic neoplasia in the conditional KrasG12D mouse model. Cancer Prev Res (Phila). 6(10):1064–73. https://doi.org/10.1158/1940-6207.CAPR-13-0065 PMID:23943783
12. Incio J, Liu H, Suboj P, Chin SM, Chen IX, Pinter M, et al. (2016). Obesity-induced inflammation and desmoplasia promote pancreatic cancer progression and resistance to chemotherapy. Cancer Discov. 6(8):852–69. https://doi.org/10.1158/2159-8290.CD-15-1177 PMID:27246539
13. Harvey AE, Lashinger LM, Hays D, Harrison LM, Lewis K, Fischer SM, et al. (2014). Calorie restriction decreases murine and human pancreatic tumor cell growth, nuclear factor-κB activation, and inflammation-related gene expression in an insulin-like growth factor-1-dependent manner. PLoS One. 9(5):e94151. https://doi.org/10.1371/journal.pone.0094151 PMID:24804677
14. Wang L, Bai Y-Y, Yang Y, Hu F, Wang Y, Yu Z, et al. (2016). Diabetes mellitus stimulates pancreatic cancer growth and epithelial-mesenchymal transition-mediated metastasis via a p38 MAPK pathway. Oncotarget. 7(25):38539–50. https://doi.org/10.18632/oncotarget.9533 PMID:27413117
15. Wang Z, Lai ST, Xie L, Zhao JD, Ma NY, Zhu J, et al. (2014). Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Res Clin Pract. 106(1):19–26. https://doi.org/10.1016/j.diabres.2014.04.007 PMID:24837144

16. Kato K, Iwama H, Yamashita T, Kobayashi K, Fujihara S, Fujimori T, et al. (2016). The anti-diabetic drug metformin inhibits pancreatic cancer cell proliferation in vitro and in vivo: study of the microRNAs associated with the antitumor effect of metformin. Oncol Rep. 35(3):1582–92. https://doi.org/10.3892/or.2015.4496 PMID:26708419

17. Tong GX, Geng Q-Q, Chai J, Cheng J, Chen P-L, Liang H, et al. (2014). Association between pancreatitis and subsequent risk of pancreatic cancer: a systematic review of epidemiological studies. Asian Pac J Cancer Prev. 15(12):5029–34. https://doi.org/10.7314/APJCP.2014.15.12.5029 PMID:24998582

18. Yurgelun MB, Chittenden AB, Morales-Oyarvide V, Rubinson DA, Dunne RF, Kozak MM, et al. (2019). Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. Genet Med. 21(1):213–23. https://doi.org/10.1038/s41436-018-0009-5 PMID:29961768

19. Hu C, Hart SN, Polley EC, Gnanaolivu R, Shimelis H, Lee KY, et al. (2018). Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. JAMA. 319(23):2401–9. https://doi.org/10.1001/jama.2018.6228 PMID:29922827

20. Brand R, Borazanci E, Speare V, Dudley B, Karloski E, Peters MLB, et al. (2018). Prospective study of germline genetic testing in incident cases of pancreatic adenocarcinoma. Cancer. 124(17):3520–7. https://doi.org/10.1002/cncr.31628 PMID:30067863

21. Campa D, Matarazzi M, Greenhalf W, Bijlsma M, Saum KU, Pasquali C, et al. (2019). Genetic determinants of telomere length and risk of pancreatic cancer: a PANDoRA study. Int J Cancer. 144(6):1275–83. PMID:30325019

22. Klein AP, Wolpin BM, Risch HA, Stolzenberg-Solomon RZ, Mocci E, Zhang M, et al. (2018). Genome-wide meta-analysis identifies five new susceptibility loci for pancreatic cancer. Nat Commun. 9(1):556. https://doi.org/10.1038/s41467-018-02942-5 PMID:29422604

23. Nakatochi M, Lin Y, Ito H, Hara K, Kinoshita F, Kobayashi Y, et al. (2018). Prediction model for pancreatic cancer risk in the general Japanese population. PLoS One. 13(9):e0203386. https://doi.org/10.1371/journal.pone.0203386 PMID:30192808

24. The Cancer Genome Atlas Research Network (2017). Integrated genomic characterization of pancreatic ductal adenocarcinoma. Cancer Cell. 32(2):185–203.e13. https://doi.org/10.1016/j.ccell.2017.07.007 PMID:28810144

25. Bailey P, Chang DK, Nones K, Johns AL, Patch A-M, Gingras M-C, et al.; Australian Pancreatic Cancer Genome Initiative (2016). Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 531(7592):47–52. https://doi.org/10.1038/nature16965 PMID:26909576

26. Kim J, Bamlet WR, Oberg AL, Chaffee KG, Donahue G, Cao X-J, et al. (2017). Detection of early pancreatic ductal adenocarcinoma with thrombospondin-2 and CA19-9 blood markers. Sci Transl Med. 9(398):eaah5583. https://doi.org/10.1126/scitranslmed.aah5583 PMID:28701476

27. Cohen JD, Javed AA, Thoburn C, Wong F, Tie J, Gibbs P, et al. (2017). Combined circulating tumor DNA and protein biomarker-based liquid biopsy for the earlier detection of pancreatic cancers. Proc Natl Acad Sci U S A. 114(38):10202–7. https://doi.org/10.1073/pnas.1704961114 PMID:28874546

28. Mellby LD, Nyberg AP, Johansen JS, Wingren C, Nordestgaard BG, Bojesen SE, et al. (2018). Serum biomarker signature-based liquid biopsy for diagnosis of early-stage pancreatic cancer. J Clin Oncol. 36(28):2887–94. https://doi.org/10.1200/JCO.2017.77.6658 PMID:30106639

29. Fan X, Alekseyenko AV, Wu J, Peters BA, Jacobs EJ, Gapstur SM, et al. (2018). Human oral microbiome and prospective risk for pancreatic cancer: a population-based nested case-control study. Gut. 67(1):120–7. https://doi.org/10.1136/gutjnl-2016-312580 PMID:27742762

30. Sharma A, Smyrk TC, Levy MJ, Topazian MA, Chari ST (2018). Fasting blood glucose levels provide estimate of duration and progression of pancreatic cancer before diagnosis. Gastroenterology. 155(2):490–500.e2. https://doi.org/10.1053/j.gastro.2018.04.025 PMID:29723506

31. Sharma A, Kandlakunta H, Nagpal SJS, Feng Z, Hoos W, Petersen GM, et al. (2018). Model to determine risk of pancreatic cancer in patients with new-onset diabetes. Gastroenterology. 155(3):730–739.e3. https://doi.org/10.1053/j.gastro.2018.05.023 PMID:29775599

32. Vasen H, Ibrahim I, Ponce CG, Slater EP, Matthäi E, Carrato A, et al. (2016). Benefit of surveillance for pancreatic cancer in high-risk individuals: outcome of long-term prospective follow-up studies from three European expert centers. J Clin Oncol. 34(17):2010–9. https://doi.org/10.1200/JCO.2015.64.0730 PMID:27114589

33. Canto MI, Almario JA, Schulick RD, Yeo CJ, Klein A, Blackford A, et al. (2018). Risk of neoplastic progression in individuals at high risk for pancreatic cancer undergoing long-term surveillance. Gastroenterology. 155(3):740–751.e2. https://doi.org/10.1053/j.gastro.2018.05.035 PMID:29803839

34. Miller MS, Allen P, Brentnall TA, Goggins M, Hruban RH, Petersen GM, et al. (2016). Pancreatic Cancer Chemoprevention Translational Workshop: meeting report. Pancreas. 45(8):1080–91. https://doi.org/10.1097/MPA.0000000000000705 PMID:27518363

35. Yue W, Zheng X, Lin Y, Yang CS, Xu Q, Carpizo D, et al. (2015). Metformin combined with aspirin significantly inhibit pancreatic cancer cell growth *in vitro* and *in vivo* by suppressing anti-apoptotic proteins Mcl-1 and Bcl-2. Oncotarget. 6(25):21208–24. https://doi.org/10.18632/oncotarget.4126 PMID:26056043

5.8 Skin cancer
A focus on primary prevention

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SUMMARY

- The highest incidence rates of skin cancer are observed in the predominantly fair-skinned populations living in areas with very high ambient levels of solar radiation, such as Australia and New Zealand.
- Genes associated with pigmentation or with naevi, together with DNA repair genes and other genes of unknown function, have been confirmed to increase heritable melanoma risk.
- Genes critical for melanoma development, which often have ultraviolet radiation-induced mutation, include genes that control cell proliferation (e.g. *BRAF*), cell cycle and replication (e.g. *TP53*), and metabolic pathways.
- Cutaneous melanomas may arise from a pre-existing benign naevus or occur on chronically sun-damaged skin. Since 2007, the incidence of melanoma has been declining overall in Australia, driven largely by significant reductions in recent birth cohorts, consistent with a successful intervention to reduce sun exposure.
- Sunlight is the principal environmental cause of basal cell carcinoma and squamous cell carcinoma, mediated through direct mutagenic effects on regulatory genes as well as through localized immunosuppression. High mutational burdens have been identified in both tumour types, consistent with extensive ultraviolet radiation-induced damage, but the driver genes differ between the two.

Cancers of the skin are the most common cancer type in humans. The term "skin cancer" covers a range of pathological entities that arise from different cells of the epidermis and dermis. This chapter is restricted to cutaneous melanomas and the keratinocyte cancers (basal cell carcinomas and squamous cell carcinomas).

Melanoma

Pathology

Melanoma, the most aggressive type of skin cancer, arises from melanocytes – pigment-producing cells in the skin. Most melanomas (> 95%) are cutaneous tumours that arise on skin surfaces exposed to the sun, but melanomas also occur on skin of the palms and soles. Melanomas also occur in the eye, in the meninges, and on mucous membranes of the gastrointestinal and genital tracts; these types of melanoma are not discussed here.

Various histological subtypes of cutaneous melanomas are recognized, reflecting patterns of growth and attendant changes in the epidermis and dermis. The most commonly described subtypes are superficial spreading melanomas (with an initial radial growth phase in the epidermis, followed by dermal invasion) and nodular melanomas (with early vertical growth and little or no radial growth). Lentigo maligna melanomas occur on chronically sun-damaged skin, and acral lentiginous melanomas are distinctive tumours that arise on palmar and plantar surfaces.

Histological characteristics of melanomas, notably tumour thickness and presence of ulceration, correlate strongly with mortality. The American Joint Committee on Cancer incorporates these prognostic features into its staging system. Recent analyses of long-term survival have led to changes in melanoma staging criteria, particularly for thinner lesions [1]. The eighth (2017) edition of the American Joint Committee on Cancer staging system recognizes a new threshold for melanoma thickness (0.8 mm), which now separates T1a from T1b melanomas. Also, whereas earlier staging criteria incorporated both ulceration and tumour mitotic rate as prognostic features, in the eighth edition only ulceration has been retained (Table 5.8.1).

The most recent (2018) edition of the WHO classification of skin tumours introduced a pathway-based classification of melanoma, which explains many of the differences in pathology and clinical behaviour

Table 5.8.1. Categorization of primary cutaneous melanoma on the basis of histological characteristics of the primary tumour, according to the eighth (2017) edition of the American Joint Committee on Cancer staging system for melanoma

T category	Thickness (mm)	Ulceration
Tis (melanoma in situ)	Not applicable	Not applicable
T1	≤ 1.0	Unknown or unspecified
T1a	< 0.8	Ulceration absent
T1b	< 0.8	Ulceration present
T1b	0.8–1.0	Ulceration present or absent
T2	> 1.0–2.0	Unknown or unspecified
T2a	> 1.0–2.0	Ulceration absent
T2b	> 1.0–2.0	Ulceration present
T3	> 2.0–4.0	Unknown or unspecified
T3a	> 2.0–4.0	Ulceration absent
T3b	> 2.0–4.0	Ulceration present
T4	> 4.0	Unknown or unspecified
T4a	> 4.0	Ulceration absent
T4b	> 4.0	Ulceration present

between the different types. The primary diagnostic tool remains histopathology, and the histopathological patterns recognized by pathologists have now very clearly been shown to correspond to distinct genetic profiles. The classification of melanoma is divided into nine pathways. The tumours included in three of these pathways are common at sun-exposed sites, and the remainder are tumours that are less common (although important because of their global occurrence) and arise in sun-shielded skin, in mucosae, and in the eye. The melanomas that occur at sun-exposed sites are subdivided according to whether they are associated with a low degree or a high degree of cumulative sun damage [2].

Epidemiology

In 2018, there were estimated to be almost 290 000 new cases of melanoma and about 61 000 deaths from melanoma worldwide [3]. The global range of population incidence of melanoma is the greatest of any cancer type. The incidence in a given region is determined largely by the pigmentation characteristics of individuals in that population and the ambient levels of solar radiation.

The highest incidence is observed in the predominantly fair-skinned populations living in areas with very high ambient levels of solar radiation, such as Australia and New Zealand (~50 per 100 000 person-years). In those populations, melanomas are the most common cancer type in people younger than 40 years, and are among the most common cancer type overall. The incidence of melanoma is also high in low-latitude parts of North America (~30 per 100 000 person-years), and there is an overall inverse gradient of incidence with increasing latitude. At higher latitudes in both North America and Europe, the incidence of melanoma has been rising steadily in recent decades; this trend is probably due to the advent of inexpensive leisure travel and the widespread use of tanning devices (sunlamps and sunbeds).

Melanoma remains an uncommon cancer in Central and South America, Asia, Africa, and the Pacific (< 3 per 100 000 person-years). In recent years, the incidence of melanoma has been falling in Australia, particularly in more recent birth cohorts; this is consistent with the impact of prolonged public health campaigns (as discussed below).

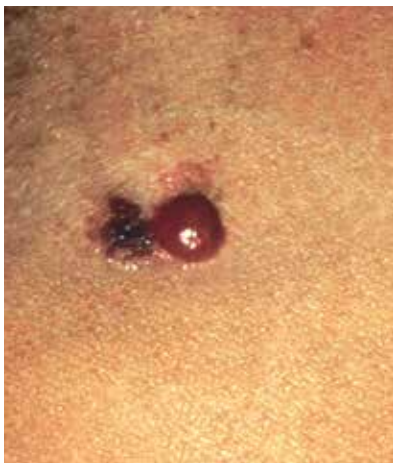
Risk factors

Observational epidemiological studies long ago identified both solar ultraviolet (UV) radiation [4] and host factors [5,6] as causes of melanoma. Recent genomic sequencing studies have confirmed the causal role of UVB radiation for the vast majority of cutaneous melanomas, manifesting as a very high mutational burden in key regulatory genes that bear UVB signature mutations [7] (see Chapter 2.4). In addition to solar UV radiation, there is strong evidence that repeated exposures to artificial sources of UV radiation from tanning devices and phototherapy also increase risk of melanoma.

FUNDAMENTALS

- Melanoma is a potentially aggressive cancer that arises from pigment-producing cells in the skin. The incidence of melanoma has been rising in most populations with predominantly European ancestry.
- Recent studies have documented the extremely high burden of mutations in the melanoma genome induced by ultraviolet radiation. This confirms earlier epidemiological observations that the incidence of melanoma is strongly correlated with ambient levels of solar radiation.
- The constitutional genes that confer susceptibility to melanoma include those associated with pigmentation characteristics as well as telomere length and cell-cycle control.
- Immunotherapies and targeted therapies have recently shown enormous promise in treating metastatic melanoma; this area of research is developing very quickly and will change rapidly in the next few years.
- Basal cell carcinomas and squamous cell carcinomas are the most common cancer types in humans. They are caused by sunlight and are largely preventable through control programmes.

Fig. 5.8.1. Malignant melanoma. At the left is a plaque of early-stage superficial spreading melanoma in the radial growth phase. At the right, contiguous with the plaque, is a pink (amelanotic) nodule of deeply invasive melanoma in the vertical growth phase. Melanomas diagnosed at this stage have a poor prognosis.



Host factors that confer an increased risk of melanoma relate to the function or number of melanocytes. Overall, the strongest phenotypic risk factor for melanoma is the propensity to develop large numbers of melanocytic naevi (moles) on the skin. People with very large numbers of naevi (> 100) have risks of melanoma up to 7 times those in people with very few naevi (< 15) [5]. The pigmentation characteristics consistently associated with increased risks of melanoma include fair skin that burns and does not tan, red or light hair, blue eyes, and the propensity to develop freckles; therefore, melanoma is rare in populations with non-European ancestry [6]. Immunosuppression increases the risk of melanoma 2–3-fold [8].

Constitutional genetics

About 5–10% of patients with cutaneous melanoma have a strong family history of the disease. About half of these patients are found to carry a highly penetrant germline mutation in one of a small number of genes (in descending order of frequency: *CDKN2A*, *CDK4*, *BAP1*, *MITF*, *POT1*, *ACD*, *TERF2IP*, and *TERT*), and the remainder are presumed to carry private mutations [9]. However, for most patients genetic susceptibility is conferred through multiple polymorphisms in low-risk genes that act through many different pathways.

The genes first linked to melanoma were candidates identified through their association with pigmentation characteristics. Of these, the highly polymorphic gene that encodes the melanocortin 1 receptor (*MC1R*) is the most prevalent and the most strongly associated with melanoma. A large and growing number of genes associated either with pigmentation (*ASIP*, *TYR*, and *SLC45A2*) or with naevi (*CDKN2A-MTAP*, *PLA2G6*, and *TERT*) have also been confirmed to increase risk of melanoma. Large meta-analyses of genome-wide association studies have extended the list of confirmed gene variants associated with melanoma to at least 20, including several genes not associated with pigmentation or with naevi [10]. Other variants that have been confirmed are for genes involved in DNA repair (*PARP1* and *ATM*), as well as genes for which the functional relevance remains unclear (*ARNT-SETDB1*, *CASP8*, *FTO*, and *MX2*). To date, no susceptibility loci have been identified for acral melanomas.

Somatic mutations

With the advent of high-throughput genomic sequencing (see Chapter 3.2), in the past few years there has been an explosion in knowledge about the cascade of mutations that lead to melanoma. The first report described the mutational burden in a cell line derived from a metastatic deposit in one patient [11]. Subsequent investigations expanded the catalogue; hundreds of melanomas have now been sequenced [7,12], including growing numbers of acral, desmoplastic, and uveal melanomas [13].

All sequencing studies have reported exceptionally high mutational burdens in cutaneous melanomas (> 10 mutations per megabase, the highest rate observed among all solid tumours); this is largely due to damage from UV radiation. The very high rate of mutations in melanoma presented an analytical challenge when attempting to identify which of the mutations were “drivers” (i.e. those occurring in key genes at critical points in the evolution of melanoma) and which were “passengers”.

Using sophisticated bioinformatics techniques that control for patient-specific and gene-specific parameters, investigators have converged on a core group of genes that are critical for melanoma development. These include genes that control cell proliferation (*BRAF*, *NRAS*, and *NF1*), cell cycle and replication (*CDKN2A*, *TP53*, and *TERT*), and metabolic pathways (*PTEN* and *KIT*). Other genes that have been shown to be important in subsets of cutaneous melanomas include *RAC1*, *MAP2K1*, *PPP6C*, *ARID1*, *IDH1*, and *RB1.*

The mutational spectrum for cutaneous melanomas differs according to anatomical site, as predicted by earlier epidemiological studies. Melanomas that occur at habitually

Fig. 5.8.2. A woman applying sunscreen. Use of sunscreen has a recognized role in reducing the burden of skin cancer in fair-skinned populations.

sun-exposed sites have markedly higher overall mutational loads than those that occur at sun-shielded sites. Thus, mucosal and acral melanomas exhibit strikingly different mutational spectra from other cutaneous melanomas, with much lower mutation frequencies overall and different driver genes implicated [13]. Mutations in *TP53*, *PTEN*, or *RB1* are infrequent in acral melanomas, but a diverse range of triple wild-type mutations are evident, including mutations in *KIT* and *GNAQ*, as well as notably higher occurrence of breakpoints and structural variants.

Pathogenesis

Recent studies have sought to overlay the sequence order in which driver mutations are acquired onto the histologically discernible stages of progression from benign melanocytic tumours to metastatic melanoma [14]. Findings from epidemiological studies about 30 years ago and subsequent genetic studies led to and elaborated the hypothesis that cutaneous melanomas can arise through multiple pathways, depending on the anatomical site of the target cell, the age and constitutional characteristics of the host, and the pattern of sun exposure [15,16]. Many cutaneous melanomas arise from a pre-existing benign naevus (the naevus pathway). Other cutaneous melanomas, particularly those that occur on chronically sun-damaged skin, do not arise from pre-existing naevi but rather arise through a variety of intermediate lesions (e.g. lentigo maligna) or frankly invasive tumours (nodular melanoma), which are associated epidemiologically with high levels of cumulative sun exposure.

For tumours that arise through the naevus pathway, the initial mutation is in *BRAF.* In the absence of any further mutations, the naevus enters a senescence-like state and eventually involutes in middle life. However, a very small fraction of naevi acquire additional mutations in targets such as *TERT* promoter sites (probably due to additional exposure to UV radiation, although other mutagens are also possible), followed by biallelic loss of *CDKN2A*. Combinations of mutational events of this type allow the naevus to escape senescence and acquire proliferative and invasive characteristics, eventually leading to metastasis. At this later stage, as the cancers are becoming invasive, it appears that they acquire additional mutations in *TP53* and *PTEN*, as well as increasing frequencies of copy number alterations and structural rearrangements. Melanomas that arise through the chronic sun exposure pathway exhibit a different sequence of driver mutations, often harbouring mutations in *NRAS* and *NF1*, as well as mutations in *TERT* promoter sites and heterozygous *CDKN2A* mutations [17] (Fig. 5.8.4).

Fig. 5.8.3. Children playing on the beach wearing sun-protective clothing. Sun protection at an early age and avoidance of sunburn are key goals in programmes aimed at reducing the incidence of skin cancer.

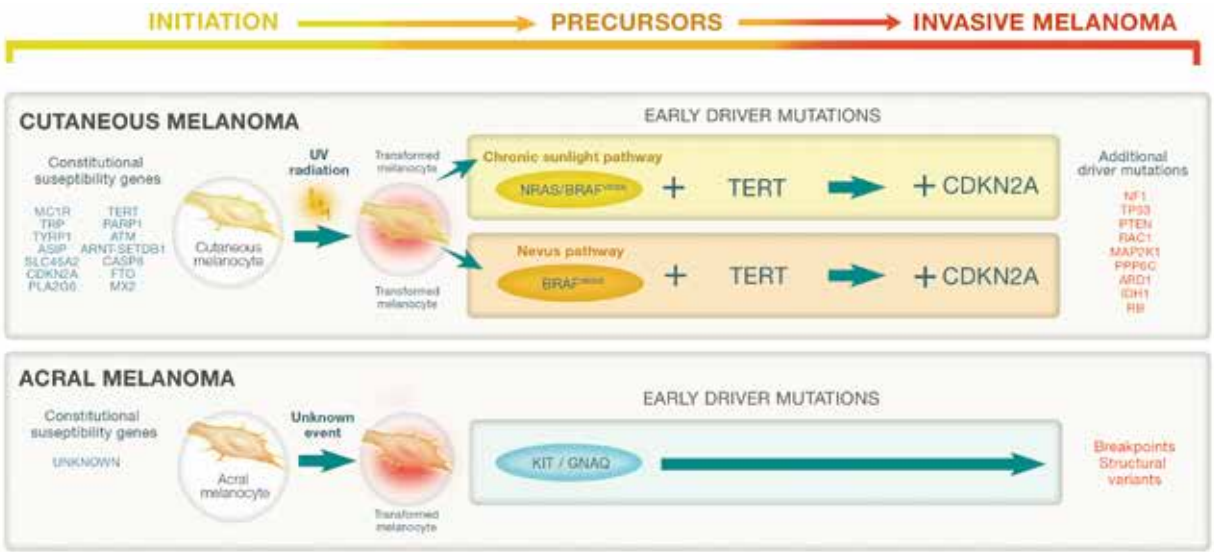
Prevention

Primary prevention

Despite exciting progress in new therapies to treat melanoma, preventive strategies remain of paramount importance to deliver cost-effective melanoma control. The population attributable fraction estimates the proportion of melanoma that would, in theory, be prevented if exposure to sunlight was reduced to historical lows. For populations with predominantly European ancestry, the population attributable fraction for exposure to solar UV radiation has been variously estimated at 65–90%, with most estimates closer to the upper bound, underscoring the potential gains to be had from primary prevention [18]. Encouraging behaviours that minimize hazardous exposure to sunlight remains the mainstay of primary prevention efforts, supported by evidence that regularly applying sunscreen significantly reduces the risk of melanoma [19]. In many jurisdictions, the use of tanning devices is being restricted through regulation.

Primary prevention campaigns have been running in Australia since the 1980s and have focused on reducing sun exposure through rescheduling outdoor activities, seeking shade, using clothing to protect the skin, and applying sunscreen to exposed body sites. There is moderately strong evidence from controlled trials that sun protection including use of sunscreen reduces development of naevi and risk of melanoma [19,20]. Since 2007, the incidence of melanoma has been declining overall in Australia, driven largely by significant reductions in recent birth cohorts, consistent with a successful intervention to reduce sun exposure [21].

Fig. 5.8.4. Schematic pathogenesis of cutaneous melanomas. Cutaneous melanomas arise on a background of susceptibility conferred by a large number of genetic variants. Most cutaneous melanomas appear to be initiated by exposure to ultraviolet B radiation in early life, which causes mutations in *BRAF* in melanocytes. Further progression depends on the site of the target cell and the genetic background of the host, but several key driver genes appear to be important in all pathways.



Early detection and screening

Currently, no national or international authorities (except in Germany) recommend population-based screening for melanoma, based on the assessment that there is insufficient evidence of mortality benefit. In most jurisdictions where melanoma is prevalent, people deemed at high risk are advised to engage in early detection strategies. Several prediction algorithms have been developed to identify those at high risk, incorporating information on demographic, phenotypic, and clinical factors [22] and, in some instances, genetic data as well. The performance of these tools varies and is influenced by setting-specific characteristics including ambient insolation and population diversity, but discrimination indices of 0.65–0.75 are typical, which is indicative of moderate accuracy. In Germany, a biannual skin cancer screening programme was introduced nationwide in 2008 for insured people 35 years and older. As yet, there is no evidence of a sustained change in mortality from melanoma after the introduction of the screening programme [23].

Keratinocyte cancers

Keratinocyte cancers of the skin – basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) – are the most common cancer types in humans. Although mortality rates from these cancer types are very low, they impose a heavy financial burden on health systems in many countries, because of their frequency and the attendant costs of diagnosis and surgery.

Etiology

BCCs are slow-growing tumours that occur most frequently on the face, neck, shoulders, and chest of fair-skinned people who are exposed to high levels of solar radiation. BCCs can be locally invasive

Fig. 5.8.5. Deliberate sun exposure by fair-skinned people to attain a tanned appearance is at odds with cancer prevention.

but rarely metastasize. The cell of origin remains an open question, but emerging consensus points to cells in the hair follicle.

SCCs are epidermal cancers that grow more rapidly and are much more likely to invade and metastasize. SCCs arise on habitually sun-exposed sites, particularly the face, ears, neck, and exposed surfaces of the limbs. Precancerous skin lesions that have similar morphology to SCCs include actinic keratoses (sunspots), intraepidermal or in situ SCCs, and Bowen disease. There is debate about whether these are true precursors of SCC or concomitant actinic lesions, and about whether the term "Bowen disease" encompasses all intraepidermal SCCs [24].

Fig. 5.8.6. The shade structure above this basketball court in San Antonio, Texas, USA, provides sun protection.

Epidemiology

Because BCC and SCC primarily (although not exclusively) affect populations of European ancestry, incidence correlates strongly with ambient insolation. Therefore, these cancer types occur most frequently among the fair-skinned residents of Australia, New Zealand, and low-latitude states of the USA. However, the incidence of BCC and SCC has been rising rapidly in most European countries in recent decades; currently, the incidence in Scandinavian countries is approaching that in the USA [25].

For both BCC and SCC, the incidence increases with age, although BCCs tend to present at earlier ages than SCCs and the age effect is much stronger for SCCs than for BCCs. Consequently, the ratio of BCC to SCC changes rapidly, from about 10:1 at age 40 years to about 3:1 at age 60 years.

Both BCC and SCC are prone to multiplicity. Data from Australia suggest that most people who develop one lesion will develop more within 3 years; a small proportion will develop more than 20 cancers, and this has important consequences for detection and control [26]. People who are immunosuppressed, particularly in connection with organ transplantation, have the highest SCC multiplicity rates [27].

Risk factors

Sunlight is the principal environmental cause of BCC and SCC, mediated through direct mutagenic effects on key regulatory genes as well as through localized immunosuppression. As noted, people who are immunosuppressed, either therapeutically (e.g. after organ transplantation) or as a result of disease (e.g. HIV/AIDS), may have markedly increased incidence of SCC, and to a lesser extent BCC. Other environmental factors that are known to increase the risks of cutaneous SCC include exposure to arsenic, polycyclic aromatic hydrocarbons, and ionizing radiation (particularly for BCC).

Cutaneous infection with human papillomavirus (HPV), specifically the beta types, has been repeatedly implicated as a cause of SCC, although the connection is not completely certain and the precise mechanism remains open to question [28]. A suite of phenotypic characteristics confers increased risks for both BCC and SCC, including fair skin that does not tan, light or red hair, propensity to freckling, and blue eyes.

Genetics

Several very rare but highly penetrant gene loci have been identified in families with clinical syndromes characterized by very high incidence of BCC. Mutation or deletion of the *PTCH1* gene is the cause of Gorlin syndrome, an autosomal dominantly inherited disease characterized by a very high risk of BCC, an increased risk of some other (mainly benign) neoplasms, and some non-neoplastic manifestations. Families with germline mutations in several DNA repair genes (*XPA1*, *XPA2*, *XRCC2*, and *XRCC3*) exhibit several different traits, including extreme sensitivity to UV radiation. Such patients manifest with multiple, early-onset SCCs.

In the general population, host susceptibility is conferred by polymorphisms in many genes, all with small effect. Genome-wide association studies have confirmed a suite of previously identified pigmentation genes as risk loci for BCC and SCC, including *MC1R*, *ASIP*, *TYR*, *SLC45A2*, *OCA2*, *IRF4*, and *BNC2*. At least 31 loci have now been implicated in BCC [29]. Recently, four loci not known to be associated with pigmentation were identified as putative risk loci exclusively for SCC: 2p22.3, *AHR*, *SEC16A*, and *CADM1-BUD13* [30]. The mechanisms enabled by

polymorphism of these loci remain to be elucidated.

Sequencing studies have identified extremely high mutational burdens in both BCC and SCC, consistent with extensive UV radiation-induced damage, but the lists of driver genes differ for BCC and SCC. Mutations in genes in the hedgehog pathway appear to be critical for BCC development, particularly *PTCH1* and *SMO* [31]. *TP53* is also very often mutated in BCC. Recurrent mutations have also been reported in *MYCN*, *PPP6C*, *STK19*, *LATS1*, *ERBB2*, *PIK3CA*, and the *RAS* family.

For SCC, *NOTCH1* appears to be a gatekeeper, although mutations in other key genes such as *TP53*, *CDKN2A*, and *HRAS* (sometimes within the same tumour) suggest that tumours arise through multiple pathways and may be polyclonal in origin. *NOTCH1* plays a key role in cell–cell signalling and serves to regulate the switch between proliferation and differentiation of keratinocytes; hence, it is a highly credible candidate [32]. Notably, many of the driver mutations in SCC, except for *CDKN2A*, are also readily detectable in macroscopically normal photo-exposed skin [33], suggesting that of all the candidates, *CDKN2A* may be the key suppressor of SCC formation.

Fig. 5.8.7. Genetic makeup corresponding to a Celtic complexion – as characterized by blue eyes, red hair, and fair skin – contributes markedly to increased risk of skin cancer.

Prospects

Although mortality from BCC and SCC is very low, these cancer types exact a sizeable toll in terms of morbidity and costs. The recent steady rises in incidence reported across Europe and North America are likely to continue in the absence of systematic primary prevention campaigns. Randomized trials have demonstrated the benefit of daily use of sunscreen for preventing SCC and actinic keratoses, but not BCC. It is possible that the lack of any observed effect for BCC was because the intervention was delivered to adults, and not earlier in life. Encouraging behaviours that minimize hazardous exposure to sunlight remains the mainstay of primary prevention efforts, complemented by regulating against the use of tanning devices and other sources of artificial UV radiation.

References

1. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. (2017). Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 67(6):472–92. https://doi.org/10.3322/caac.21409 PMID:29028110
2. Elder DE, Massi D, Scolyer RA, Willemze R, editors (2018). WHO classification of skin tumours. Lyon, France: International Agency for Research on Cancer (WHO Classification of Tumours series, 4th edition). Available from: http://publications.iarc.fr/560.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593
4. Armstrong BK, Kricker A (1993). How much melanoma is caused by sun exposure? Melanoma Res. 3(6):395–401. https://doi.org/10.1097/00008390-199311000-00002 PMID:8161879
5. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Abeni D, Boyle P, et al. (2005). Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur J Cancer. 41(1):28–44. https://doi.org/10.1016/j.ejca.2004.10.015 PMID:15617989
6. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Zanetti R, Masini C, et al. (2005). Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur J Cancer. 41(14):2040–59. https://doi.org/10.1016/j.ejca.2005.03.034 PMID:16125929

7. Akbani R, Akdemir KC, Aksoy BA, Albert M, Ally A, Amin SB, et al.; Cancer Genome Atlas Network (2015). Genomic classification of cutaneous melanoma. Cell. 161(7):1681–96. https://doi.org/10.1016/j.cell.2015.05.044 PMID:26091043

8. Green AC, Olsen CM (2015). Increased risk of melanoma in organ transplant recipients: systematic review and meta-analysis of cohort studies. Acta Derm Venereol. 95(8):923–7. https://doi.org/10.2340/00015555-2148 PMID:26012553

9. Aoude LG, Wadt KA, Pritchard AL, Hayward NK (2015). Genetics of familial melanoma: 20 years after CDKN2A. Pigment Cell Melanoma Res. 28(2):148–60. https://doi.org/10.1111/pcmr.12333 PMID:25431349

10. Law MH, Bishop DT, Lee JE, Brossard M, Martin NG, Moses EK, et al.; GenoMEL Consortium; Essen-Heidelberg Investigators; SDH Study Group; Q-MEGA and QTWIN Investigators; AMFS Investigators; ATHENS Melanoma Study Group (2015). Genome-wide meta-analysis identifies five new susceptibility loci for cutaneous malignant melanoma. Nat Genet. 47(9):987–95. https://doi.org/10.1038/ng.3373 PMID:26237428

11. Pleasance ED, Cheetham RK, Stephens PJ, McBride DJ, Humphray SJ, Greenman CD, et al. (2010). A comprehensive catalogue of somatic mutations from a human cancer genome. Nature. 463(7278):191–6. https://doi.org/10.1038/nature08658 PMID:20016485

12. Hodis E, Watson IR, Kryukov GV, Arold ST, Imielinski M, Theurillat JP, et al. (2012). A landscape of driver mutations in melanoma. Cell. 150(2):251–63. https://doi.org/10.1016/j.cell.2012.06.024 PMID:22817889

13. Hayward NK, Wilmott JS, Waddell N, Johansson PA, Field MA, Nones K, et al. (2017). Whole-genome landscapes of major melanoma subtypes. Nature. 545(7653):175–80. https://doi.org/10.1038/nature22071 PMID:28467829

14. Shain AH, Yeh I, Kovalyshyn I, Sriharan A, Talevich E, Gagnon A, et al. (2015). The genetic evolution of melanoma from precursor lesions. N Engl J Med. 373(20):1926–36. https://doi.org/10.1056/NEJMoa1502583 PMID:26559571

15. Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC (2003). Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. J Natl Cancer Inst. 95(11):806–12. https://doi.org/10.1093/jnci/95.11.806 PMID:12783935

16. Armstrong BK, Cust AE (2017). Sun exposure and skin cancer, and the puzzle of cutaneous melanoma: a perspective on Fears et al. Mathematical models of age and ultraviolet effects on the incidence of skin cancer among whites in the United States. American Journal of Epidemiology 1977; 105: 420–427. Cancer Epidemiol. 48:147–56. https://doi.org/10.1016/j.canep.2017.04.004 PMID:28478931

17. Shain AH, Bastian BC (2016). From melanocytes to melanomas. Nat Rev Cancer. 16(6):345–58. https://doi.org/10.1038/nrc.2016.37 PMID:27125352

18. Arnold M, de Vries E, Whiteman DC, Jemal A, Bray F, Parkin DM, et al. (2018). Global burden of cutaneous melanoma attributable to ultraviolet radiation in 2012. Int J Cancer. 143(6):1305–14. https://doi.org/10.1002/ijc.31527 PMID:29659012

19. Green AC, Williams GM, Logan V, Strutton GM (2011). Reduced melanoma after regular sunscreen use: randomized trial follow-up. J Clin Oncol. 29(3):257–63. https://doi.org/10.1200/JCO.2010.28.7078 PMID:21135266

20. Milne E, Johnston R, Cross D, Giles-Corti B, English DR (2002). Effect of a school-based sun-protection intervention on the development of melanocytic nevi in children. Am J Epidemiol. 155(8):739–45. https://doi.org/10.1093/aje/155.8.739 PMID:11943692

21. Whiteman DC, Green AC, Olsen CM (2016). The growing burden of invasive melanoma: projections of incidence rates and numbers of new cases in six susceptible populations through 2031. J Invest Dermatol. 136(6):1161–71. https://doi.org/10.1016/j.jid.2016.01.035 PMID:26902923

22. Olsen CM, Neale RE, Green AC, Webb PM, The QSkin Study, The Epigene Study, Whiteman DC (2015). Independent validation of six melanoma risk prediction models. J Invest Dermatol. 135(5):1377–84. https://doi.org/10.1038/jid.2014.533 PMID:25548858

23. Stang A, Jöckel KH (2016). Does skin cancer screening save lives? A detailed analysis of mortality time trends in Schleswig-Holstein and Germany. Cancer. 122(3):432–7. https://doi.org/10.1002/cncr.29755 PMID:26480048

24. Martin AA, Hudgins EM, McMullan FH (2010). All Bowen's disease is squamous cell carcinoma in situ, but all squamous cell carcinoma in situ is not Bowen's disease. J Cutan Pathol. 37(11):1186–7. https://doi.org/10.1111/j.1600-0560.2010.01580.x PMID:20579212

25. Lomas A, Leonardi-Bee J, Bath-Hextall F (2012). A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol. 166(5):1069–80. https://doi.org/10.1111/j.1365-2133.2012.10830.x PMID:22251204

26. Pandeya N, Olsen CM, Whiteman DC (2017). The incidence and multiplicity rates of keratinocyte cancers in Australia. Med J Aust. 207(8):339–43. https://doi.org/10.5694/mja17.00284 PMID:29020905

27. Grulich AE, Vajdic CM (2015). The epidemiology of cancers in human immunodeficiency virus infection and after organ transplantation. Semin Oncol. 42(2):247–57. https://doi.org/10.1053/j.seminoncol.2014.12.029 PMID:25843729

28. Hasche D, Vinzón SE, Rösl F (2018). Cutaneous papillomaviruses and non-melanoma skin cancer: causal agents or innocent bystanders? Front Microbiol. 9:874. https://doi.org/10.3389/fmicb.2018.00874 PMID:29770129

29. Chahal HS, Wu W, Ransohoff KJ, Yang L, Hedlin H, Desai M, et al. (2016). Genome-wide association study identifies 14 novel risk alleles associated with basal cell carcinoma. Nat Commun. 7(1):12510. https://doi.org/10.1038/ncomms12510 PMID:27539887

30. Chahal HS, Lin Y, Ransohoff KJ, Hinds DA, Wu W, Dai HJ, et al. (2016). Genome-wide association study identifies novel susceptibility loci for cutaneous squamous cell carcinoma. Nat Commun. 7(1):12048. https://doi.org/10.1038/ncomms12048 PMID:27424798

31. Jayaraman SS, Rayhan DJ, Hazany S, Kolodney MS (2014). Mutational landscape of basal cell carcinomas by whole-exome sequencing. J Invest Dermatol. 134(1):213–20. https://doi.org/10.1038/jid.2013.276 PMID:23774526

32. South AP, Purdie KJ, Watt SA, Haldenby S, den Breems N, Dimon M, et al. (2014). *NOTCH1* mutations occur early during cutaneous squamous cell carcinogenesis. J Invest Dermatol. 134(10):2630–8. https://doi.org/10.1038/jid.2014.154 PMID:24662767

33. Martincorena I, Roshan A, Gerstung M, Ellis P, Van Loo P, McLaren S, et al. (2015). High burden and pervasive positive selection of somatic mutations in normal human skin. Science. 348(6237):880–6. https://doi.org/10.1126/science.aaa6806 PMID:25999502

5.9 Breast cancer
Multiple, often complex, risk factors

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SUMMARY

- Exposures occurring in utero and until menopause can influence breast cancer risk. Therefore, prevention efforts should be considered throughout a woman's life.
- Some breast cancer risk factors (e.g. mammographic density) are similarly associated with most currently recognized breast cancer subtypes, whereas for others (e.g. parity) the relationships vary significantly by subtype; reliable estimates of these differences have only recently begun to emerge.
- Tumour subtypes should be considered when evaluating etiology and in developing prevention strategies.
- Breast cancer risk conferred by an increasing number of high-penetrance predisposition genes has been better quantified and characterized. Panels of single-nucleotide polymorphisms both modify penetrance of the strong susceptibility genes and confer quantifiable breast cancer risk themselves.
- Large population studies and major international collaborations, particularly those integrating new technologies and basic science discoveries, are providing novel insights into breast cancer etiology and prevention.
- Emerging data indicate that many risk factors directly influence the numbers and/or properties of breast epithelial progenitors.

Breast cancer is a heterogeneous disease, with wide variation in tumour morphology, molecular characteristics, and clinical response. Invasive ductal carcinoma is the most common type of breast cancer, making up about 70% of tumours, and about 15–20% of tumours are invasive lobular carcinomas.

Assessment of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression status of tumours has been used in clinical decision-making for many years. Tumour molecular subtypes have subsequently been identified, for example on the basis of prognostic multigene classifiers, to derive at least the luminal A, luminal B, HER2-enriched, and basal-like classifications.

The importance of distinguishing between ER-positive and ER-negative breast cancer in epidemiological studies of etiology and prevention is now established. Studies linking risk factors with specific molecular subtypes of breast cancer are more recent, and several consistent findings, noted below, have emerged. Most recently, several subtypes of triple-negative (i.e. ER-negative, PR-negative, and HER2-negative) breast cancer have been identified [1], but these have yet to be considered in epidemiological studies.

Epidemiology

Breast cancer is the most commonly diagnosed cancer type and the leading cause of cancer death in women worldwide. In 2018, there were an estimated 2.1 million new cases of breast cancer and 627 000 deaths from breast cancer worldwide [2]. The incidence and mortality rates show marked international variation (Fig. 5.9.1 and Fig. 5.9.2). However, incidence and mortality data remain extremely limited for several world regions, such as Africa.

More than half of breast cancer cases are now diagnosed in low- and middle-income countries [3], where a greater proportion of cases (and sometimes a markedly greater proportion) are diagnosed at later stages, which are linked to poorer survival (see Chapter 1.3) (Fig. 5.9.3). Continuing reductions in the prevalence of infectious diseases and associated increases in life expectancy, along with changes in population reproductive patterns (e.g. later age at first birth) and lifestyle factors (e.g. increasing obesity) portend an ever-increasing burden of breast cancer in low- and middle-income countries [3].

Genetics and genomics

An inherited component to breast cancer susceptibility has long been

recognized. Progress in recent years has included the identification of multiple breast cancer susceptibility genes, improved estimates of their penetrance, the identification of modifier genes, and increases in the yield of genome-wide association studies (GWAS) for breast cancer both overall (i.e. all subtypes of breast cancer combined) and by subtype [4].

High-penetrance gene mutations

The most common high-penetrance susceptibility alleles remain *BRCA1* and *BRCA2*, both of which are critical for repair of DNA double-strand breaks and remodelling of stalled replication forks. Data and specimens from large cohorts of well-characterized germline mutation carriers, such as the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA), have permitted stable estimates of breast cancer risk [5].

Other genes involved in DNA repair (see Chapter 3.4) were identified through mechanistic studies elucidating DNA repair pathways, Fanconi anaemia complementation groups, and interacting genes associated with novel functions of known genes [4,6]. The widespread adoption of next-generation sequencing technologies has led to the identification of germline mutations in individuals and families without classic phenotypic characteristics of a syndrome or syndromes associated with specific gene mutations, suggesting important selection bias in early studies (e.g. *TP53*, *CDH1*) [6,7].

BRCA1 and *BRCA2* have been studied in the greatest detail in large collaborative cohorts (e.g. CIMBA), from which the available data include genotype–phenotype correlations and the identification of modifier single-nucleotide polymorphisms (SNPs) [8], although none are yet used clinically to improve individual risk prediction. Examination of somatic and germline mutational signatures (Fig. 5.9.4) may provide clues to breast cancer etiology based on specific patterns of acquired DNA alteration [9].

Susceptibility loci

Recent GWAS analyses (see Chapter 3.2) have increased in size [10] and have yielded multiple new susceptibility loci both for breast cancer overall and for specific breast cancer subtypes, especially triple-negative breast cancer [11]. A group of SNPs has been included in a personalized risk score that shows increased risk of breast cancer in women with and without a family history of breast cancer [12]. One cluster of SNPs has been shown to improve the performance of the Tyrer–Cuzick breast cancer risk prediction model, with the incorporation of mammographic density as well. These loci are entering clinical use, but most have been subjected to only limited validation [13].

Etiology

Several reproductive and lifestyle factors are confirmed contributors to breast cancer risk. In recent years, the understanding of the impact of these exposures on risk has been improved largely through assessment of these exposures over a woman's lifetime, according to breast tumour subtype, and through detailed assessments in large consortia.

Lifestyle and environmental exposures

A notable aspect of breast cancer etiology is the long-term influence of exposures experienced over the life-course. The best current example is body size (see Chapter 2.7): birth weight is positively associated with breast cancer risk; childhood, adolescent, and premenopausal body size are inversely related to risk; and postmenopausal body size is positively related to risk [14]. On the basis of recent data from 19 prospective cohorts, the inverse association with larger adult body size in premenopausal women is strong and linear [15] and is apparent for both ER-positive and ER-negative disease and across race and ethnicity [15]; furthermore, on the basis of a large Mendelian randomization study [16], the association is probably causal. Multiple studies also have assessed childhood and adolescent body size and have noted similar inverse associations [14]. Mechanistic understanding of these inverse associations may offer future targets for prevention.

A consortium analysis with more than 36 000 breast cancer cases reported that long duration of smoking before a first pregnancy was associated with a significant 18% (95% confidence interval [CI], 12–24%) increase in breast cancer risk; the associations were not confounded

FUNDAMENTALS

- Breast cancer is the most commonly diagnosed cancer type and the leading cause of cancer death in women worldwide.
- Reproductive factors, including late age at menarche, early age at menopause, parity, early age at first birth, and breastfeeding, all decrease risk of breast cancer overall (i.e. all subtypes of breast cancer combined).
- Family history of breast cancer, personal history of proliferative benign breast disease, dense breasts on mammogram, radiation exposure, alcohol consumption, low physical activity, being lean before menopause, postmenopausal obesity, recent use of postmenopausal hormone therapy (particularly estrogen plus progestin), and recent use of oral contraceptives are all associated with increases in overall breast cancer risk.
- Inherited mutations in breast cancer predisposition genes confer increased risk of breast cancer, often preferentially by tumour subtype. Elucidation of the mechanisms of action of these genes provides clues to breast cancer etiology, treatment, and prevention.

Fig. 5.9.1. Global distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000 person-years for breast cancer in women, 2018.

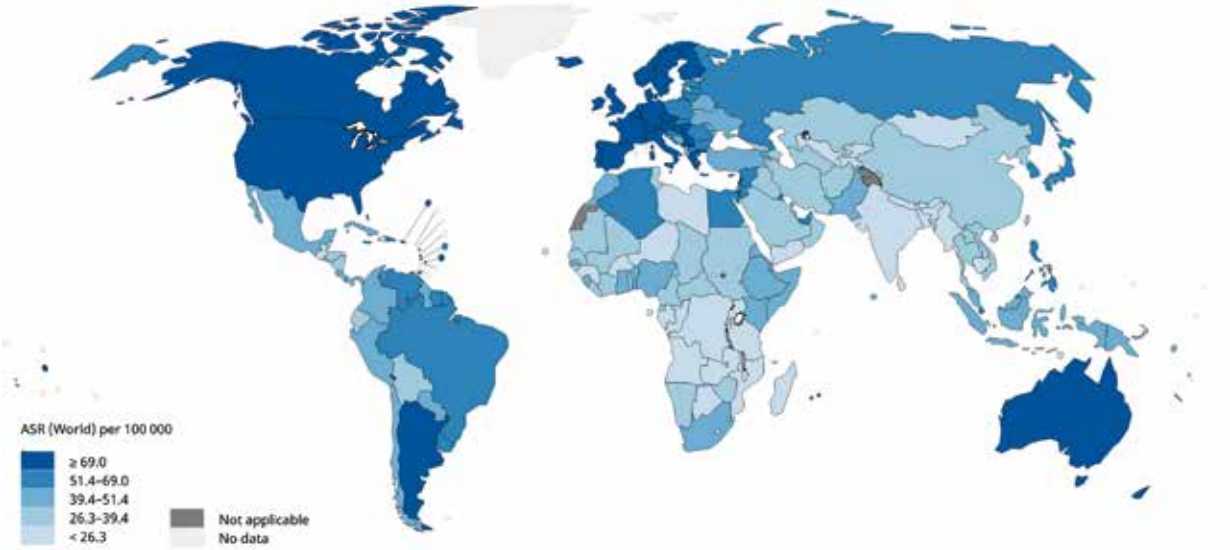
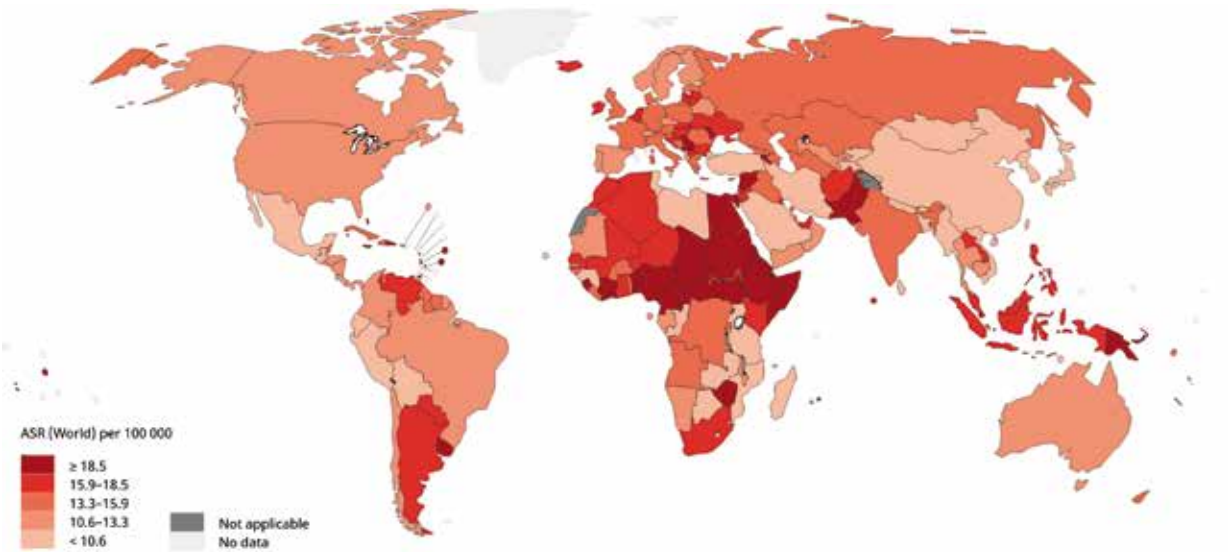


Fig. 5.9.2. Global distribution of estimated age-standardized (World) mortality rates (ASR) per 100 000 person-years for breast cancer in women, 2018.

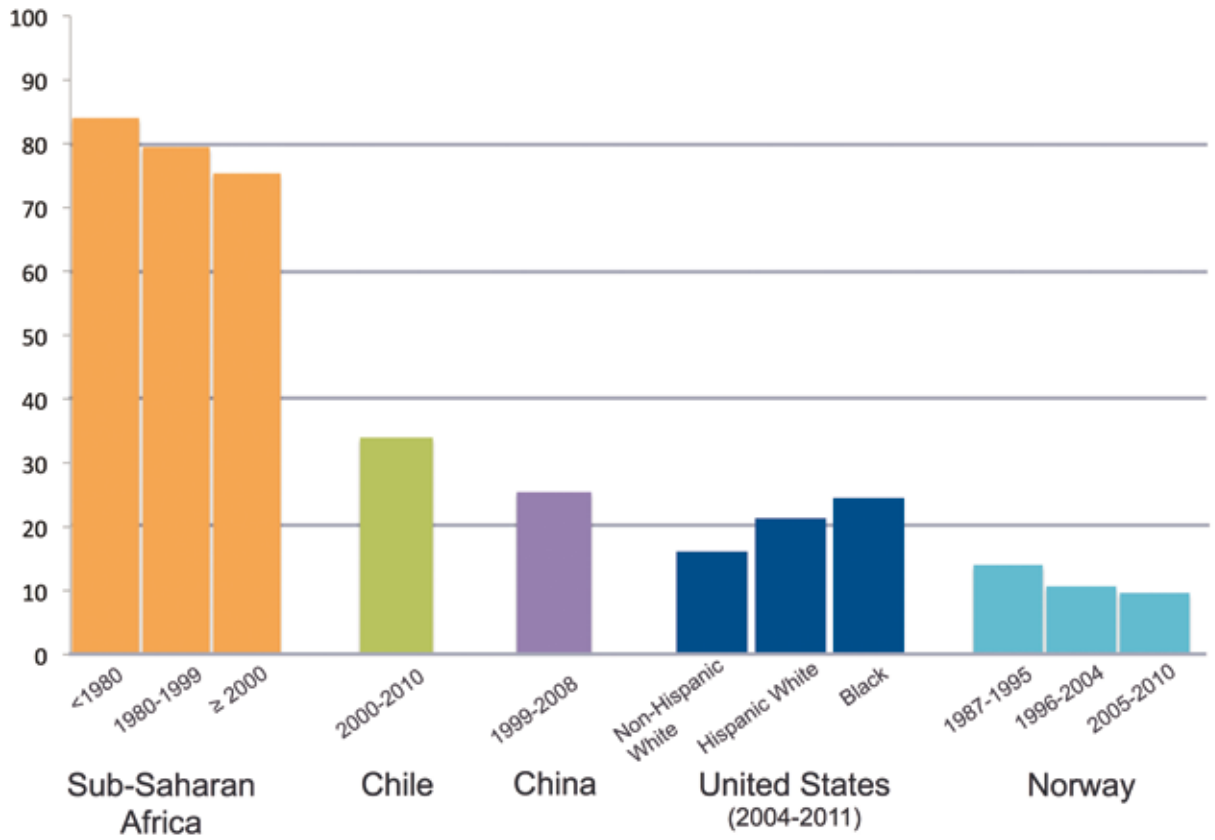


by current alcohol consumption and were observed predominantly for ER-positive tumours [17]. These data support a causal link of smoking with breast cancer risk and re-emphasize the importance of smoking prevention and cessation programmes in adolescents and young adults (see "Tobacco cessation: the WHO perspective").

Studies suggest that carotenoids, or other constituents in carotenoid-rich foods, may decrease breast cancer risk [14], particularly for ER-negative disease; similarly, several studies have observed an inverse association between a Mediterranean diet score and ER-negative breast cancer [18].

The potential role of environmental and occupational exposures in breast carcinogenesis has remained a major interest, although challenges in exposure assessment and study design have limited the conclusions. Increasingly, efforts have focused on evaluating exposure during windows of susceptibility, by assessing links between contaminants and intermediate markers of risk such as breast density, and by increasing transdisciplinary research efforts. Such efforts are providing new insights into the potential for exposures such as endocrine disrupters to influence breast cancer risk [19].

Fig. 5.9.3. Percentage of breast cancer cases diagnosed at a late stage (stages III and IV combined), by country or region and by time period or population group.



Reproductive factors

The inverse association observed between parity and risk of breast cancer overall is consistently seen for ER-positive disease, whereas no association or a positive association has been observed for ER-negative and triple-negative disease [20]. In addition, breastfeeding has been associated with lower risk of hormone receptor-negative (including ER-negative, triple-negative, and basal-like) breast cancer; weaker and less consistent associations have been observed for ER-positive tumour subtypes [21]. These studies have been conducted largely in populations of European ancestry. Recently, across four studies of African American women, parity was observed to significantly increase risk of ER-negative and triple-negative breast cancer, and to modestly lower risk of ER-positive breast cancer. Women who breastfed versus never breastfed had lower risk of ER-negative and triple-negative disease (Fig. 5.9.5) [22]. Importantly from a prevention perspective, breastfeeding appears to reduce risk of these breast cancer subtypes that have poorer prognosis. (For a discussion of reproductive factors such as age at menarche, age at first birth, and age at menopause, see Chapter 3.6.)

Breast tumour subtypes

Studies have increasingly focused on evaluating risk factors by molecular characteristics of breast tumours, to provide causal insight for observed associations and to better inform prevention strategies. The differential associations of postmenopausal obesity and use of hormone therapy with ER-positive but not ER-negative breast cancer are established; differences observed more recently include dietary factors [14,18]. Furthermore, associations of parity and breastfeeding with risk appear to vary by molecular subtype [20,22,23]. Such analyses require both large sample sizes and the availability of tumour tissue; hence, reliable estimates of these differences have only recently begun to emerge.

Population attributable risks

Several recent efforts have evaluated the population attributable risks for breast cancer. In a study that combined data from two large cohorts and assessed a range of well-established breast cancer risk factors in relation to breast cancer in postmenopausal women, the population attributable risk was 70.0% (95% CI, 55.0–80.7%) overall [24]. For modifiable risk factors only, the population attributable risk was 34.6% overall and was higher for

Fig. 5.9.4. Pathway enrichment map for susceptibility loci based on summary association statistics for 65 new breast cancer loci. Each coloured circle (node) represents a pathway (gene set), coloured by enrichment score, where redder nodes indicate lower false discovery rates. Larger nodes indicate pathways with more genes. Green lines connect pathways with overlapping genes (minimum overlap, 0.55). Pathways are grouped by similarity and organized into major themes (large labelled circles).

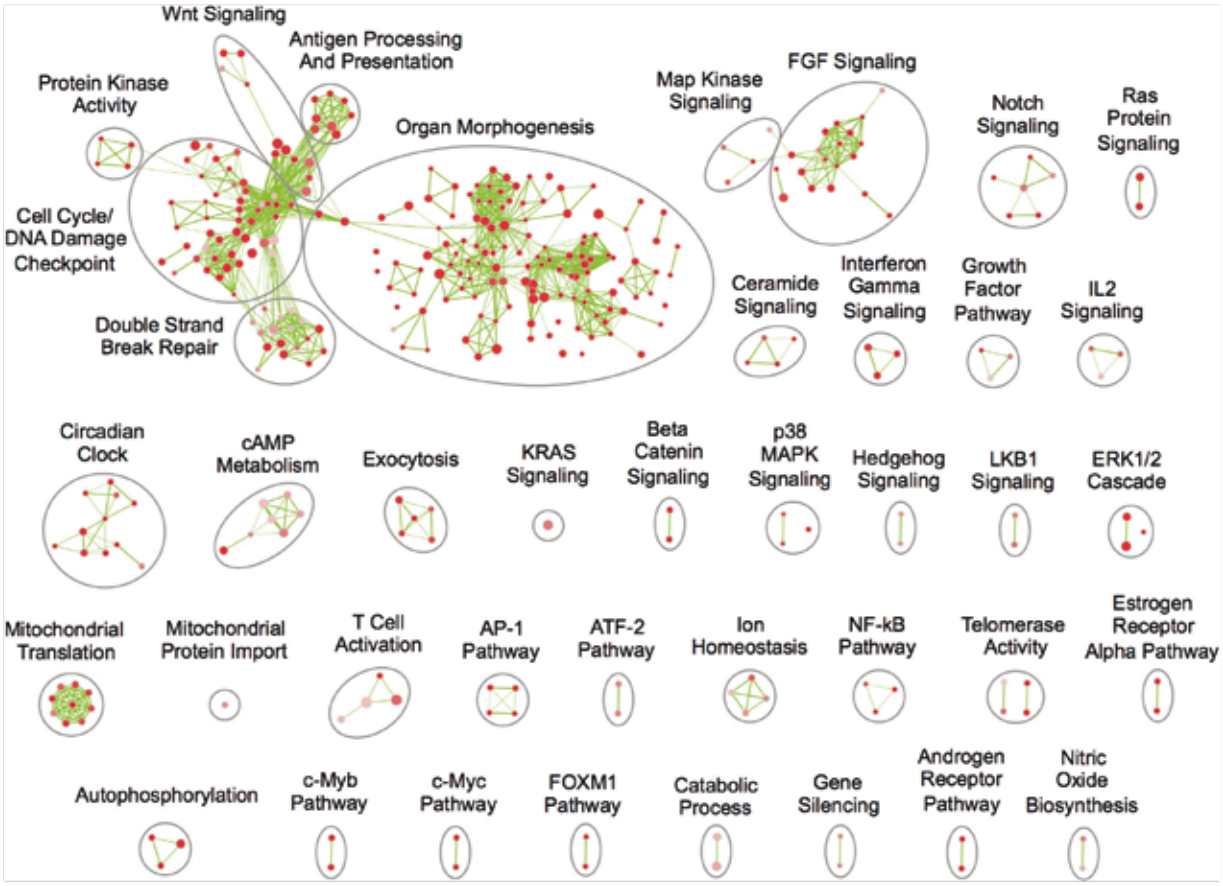
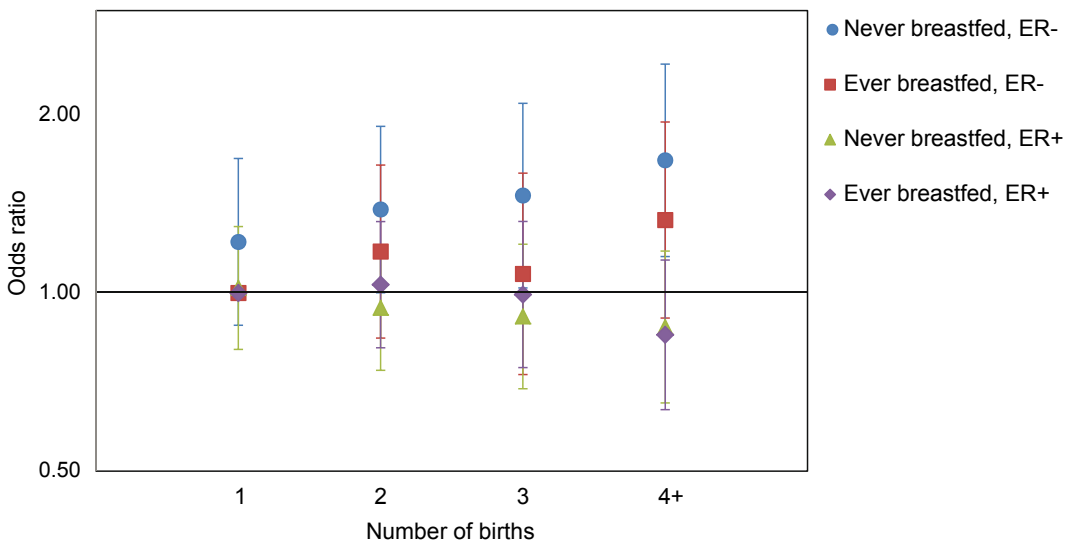


Fig. 5.9.5. Relative risks (with 95% confidence intervals) for number of births in relation to estrogen receptor (ER) status, according to history of breastfeeding, from the African American Breast Cancer Epidemiology and Risk (AMBER) Consortium. The reference for both ER-positive (ER+) and ER-negative (ER-) analyses is women who had only one birth and had breastfed.



Clues to the biology of breast cancer risk

Breast epithelial stem cells and progenitors are the cells of origin of breast carcinomas; therefore, cancer risk factors are expected to affect the numbers and/or properties of these cells [1]. Despite the importance of this issue, the knowledge of cancer risk-associated differences in the normal breast is rather limited. Among the best-understood risk factors are early full-term pregnancy and obesity. A full-term pregnancy in young adulthood (age < 20 years) decreases the risk of estrogen receptor (ER)-positive postmenopausal breast cancer. In contrast, the risk of ER-negative breast tumours is not decreased by pregnancy, and multiple early pregnancies, coupled with lack of breastfeeding, is one of the most significant risk factors for triple-negative breast cancer.

Comprehensive comparative analysis of normal human breast tissues from nulliparous and parous women, including *BRCA1* and *BRCA2* germline mutation carriers, determined that the most significant gene expression and epigenetic changes occur in lineage-negative progenitor-enriched cells and that the numbers of these cells are higher in nulliparous women and even higher in *BRCA1* and *BRCA2* mutation carriers [2]. Transforming growth factor β (TGF-β), WNT, and insulin-like growth factor 1 (IGF-1) signalling were identified as candidate regulators of hormone-responsive progenitors, and p27 was identified as a marker of quiescent cells with proliferative potential.

A follow-up study analysed the frequencies of cells with expression of the proliferative marker Ki-67 and the quiescent marker p27 in normal breast biopsies of women in the Nurses' Health Study. Premenopausal women with high Ki-67-positive and low p27-positive cell frequencies had a 5-fold higher risk of breast cancer compared with women with low Ki-67-positive and low p27-positive cell frequencies. These results suggest that the higher number of cycling cells in the normal mammary epithelium increases the probability of mutations; thus, the fraction of these cells may be a biomarker of breast cancer risk [3].

One potential mechanism by which obesity influences breast cancer risk is via alterations in the local and systemic microenvironments [4]. Obesity is associated with inflammation in white adipose tissue, which is characterized by crown-like structures formed by macrophages surrounding dead or dying adipocytes. Such structures lead to the release of free fatty acids that trigger Toll-like receptor signalling and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-mediated upregulation of pro-inflammatory cytokines (e.g. tumour necrosis factor α [TNF-α] and interleukin-1β [IL-1β]). Besides creating a pro-inflammatory environment, these cytokines and cyclooxygenase 2 (COX-2) also upregulate the expression of aromatase, an enzyme that is key for estrogen biosynthesis, resulting in higher local estrogen levels. The presence of crown-like structures was associated with poor clinical outcome independent of body mass index and in all breast cancer subtypes, suggesting that inflammation is a general inducer of cancer risk. In addition to local effects, obesity also increases circulating levels of leptin and IL-6, which can promote tumour initiation via direct effects on the mammary epithelial cells and by changing the microenvironment.

References

1. Visvader JE, Stingl J (2014). Mammary stem cells and the differentiation hierarchy: current status and perspectives. Genes Dev. 28(11):1143–58. https://doi.org/10.1101/gad.242511.114 PMID:24888586
2. Meier-Abt F, Bentires-Alj M, Rochlitz C (2015). Breast cancer prevention: lessons to be learned from mechanisms of early pregnancy-mediated breast cancer protection. Cancer Res. 75(5):803–7. https://doi.org/10.1158/0008-5472.CAN-14-2717 PMID:25660950
3. Atashgaran V, Wrin J, Barry SC, Dasari P, Ingman WV (2016). Dissecting the biology of menstrual cycle-associated breast cancer risk. Front Oncol. 6:267. https://doi.org/10.3389/fonc.2016.00267 PMID:28083513
4. Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA (2016). Obesity and cancer mechanisms: tumor microenvironment and inflammation. J Clin Oncol. 34(35):4270–6. https://doi.org/10.1200/JCO.2016.67.4283 PMID:27903155

ER-positive tumours (39.7%) than for ER-negative tumours (27.9%) [24].

The Breast Cancer Surveillance Consortium reported that 52.7% and 54.7% of breast cancers in premenopausal and postmenopausal women, respectively, could potentially be attributed to six risk factors: Breast Imaging Reporting and Data System (BI-RADS) breast density, parity, age at first birth, body mass index (BMI), first-degree family history of breast cancer, and personal history of benign breast disease; the greatest contributors to these estimates were BMI and breast density [25].

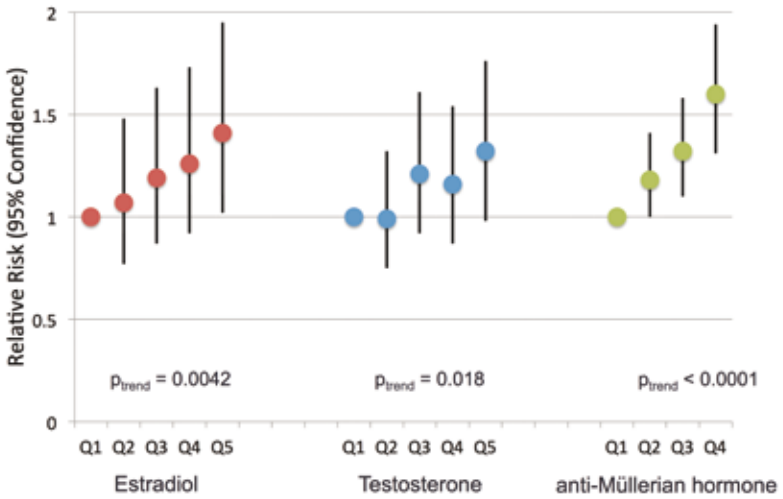
Biological characteristics

Endogenous hormones

Substantial progress has been made to further the understanding of the link between endogenous hormone concentrations, measured in blood or urine, and risk of breast cancer. Postmenopausal levels of estradiol and testosterone are established risk factors, with relative risks of breast cancer of 1.5–3.0 when comparing women in the top versus the bottom 20–25% of hormone levels.

Data in premenopausal women have been sparse, largely because of complexities in measuring estrogen levels during the menstrual cycle. In a recent pooled analysis of

Fig. 5.9.6. Relative risks (with 95% confidence intervals) of premenopausal breast cancer by quantile of circulating hormone concentrations.



prospective studies with 767 cases and 1699 controls, a modest but significant positive association was noted for estradiol and testosterone levels in premenopausal women, with comparable relative risks of 1.41 (P_{trend} = 0.01) for estradiol and 1.32 (P_{trend} = 0.02) for testosterone (Fig. 5.9.6); no association was observed for plasma progesterone levels [26]. A positive association between prolactin levels and risk of breast cancer, primarily in postmenopausal women, also has increasingly been documented [27].

Estrogen metabolites have been hypothesized to independently influence risk via effects on proliferation or by inducing oxidative damage. With an improved assay technology [28]

Mammographic density

Mammographic density represents the relative amounts of dense (epithelial and stromal) tissue versus non-dense (adipose) tissue in the breast as seen on mammogram. Mammographic density varies widely between women. Both qualitative measures (e.g. the four-category Breast Imaging Reporting and Data System [BI-RADS]) and quantitative measures (e.g. quantitative thresholding using the Cumulus software) of mammographic density are strongly predictive of breast cancer risk, with relative risks of 4–6 (when comparing women with high versus low percentage density) that do not vary by tumour estrogen receptor status [1,2].

Recent large genome-wide association studies (GWAS) have pointed to a shared genetic basis between mammographic density and breast cancer [2]. Newer studies also have suggested that assessment of mammographic density can add substantially to current breast cancer risk prediction models, and that change in mammographic density (e.g. > 10% decrease in density) can be used as a surrogate marker for breast cancer to indicate who will most benefit from chemoprevention or other prevention efforts [3].

Increasing efforts have focused on delineating the biological mechanisms underlying mammographic density and its strong association with breast carcinogenesis. Recent findings suggest roles for multiple factors, including those that influence the composition and stiffness of the extracellular matrix, and genes associated with increased cellular proliferation, although further work is needed.

In the past few years, several novel approaches have begun to be evaluated to fully automate assessments of mammographic density (e.g. using Volpara, a program that provides an automated volumetric measure of density) and to assess additional parenchymal textural features (e.g. run-length and structural features) that may better characterize tissue complexity on mammogram. These studies have generally shown similar or stronger associations with breast cancer risk, indicating that, relative to traditional density assessment, some of the new measures are likely to substantially improve upon or add independent new information in risk prediction [1]. Emerging research with a deep learning approach, using either neural networks or autoencoders, for mammogram-based breast cancer risk assessment has also been promising [1]. Although these new approaches have shown great potential, there is currently a lack of evaluations of multiple approaches simultaneously in large and diverse populations to determine the optimal combination of tissue features and the strength of their association with future risk across different tumour subtypes.

References

1. Gastounioti A, Conant EF, Kontos D (2016). Beyond breast density: a review on the advancing role of parenchymal texture analysis in breast cancer risk assessment. Breast Cancer Res. 18(1):91. https://doi.org/10.1186/s13058-016-0755-8 PMID:27645219
2. Sherratt MJ, McConnell JC, Streuli CH (2016). Raised mammographic density: causative mechanisms and biological consequences. Breast Cancer Res. 18(1):45. https://doi.org/10.1186/s13058-016-0701-9 PMID:27142210
3. Shawky MS, Martin H, Hugo HJ, Lloyd T, Britt KL, Redfern A, et al. (2017). Mammographic density: a potential monitoring biomarker for adjuvant and preventative breast cancer endocrine therapies. Oncotarget. 8(3):5578–91. https://doi.org/10.18632/oncotarget.13484 PMID:27894075

used across five studies in postmenopausal women, a relative increase in levels of 2-hydroxylation pathway metabolites versus 16-hydroxylation pathway metabolites was associated with a 34% decrease (95% CI, 16–48%) in breast cancer risk independent of total estrogen levels [29]. Data in premenopausal women are limited but are suggestive of similar associations [28].

Anti-Müllerian hormone is produced by the ovaries, is measurable only before menopause, reflects the size of the ovarian follicular pool, and is strongly correlated with age at menopause [30]. In a large consortium analysis of 10 prospective studies, a significant positive association was observed, with a multivariable relative risk comparing the top versus the bottom quartile categories of 1.60 (95% CI, 1.31–1.94; P_{trend} < 0.001) (Fig. 5.9.6) [30]. The findings were unchanged after accounting for testosterone concentrations, were similar regardless of menopausal status at diagnosis, and were observed primarily for ER-positive tumours. Anti-Müllerian hormone is one of the few hormones assessed in premenopausal women that is now confirmed to predict later risk of breast cancer. Additional facets of this association, as well as the biological mechanisms underlying the association, require further study.

Novel technologies

New analytical technologies such as metabolomics and proteomics (see Chapter 3.7) can be used in population-based studies and are beginning to provide new insights into the biological mechanisms underlying known breast cancer risk factors, as well as offering the potential to identify new biomarkers of risk or early detection. For example, several diet-related metabolites (related to alcohol, vitamin E, and animal fat) were associated with risk of breast cancer, particularly for ER-positive disease, thus suggesting additional factors that may play a mechanistic role underlying these dietary exposures and modulation of risk [31].

Risk stratification

Breast cancer risk prediction models have been developed to estimate the risk of carrying a high-risk germline mutation, the risk of developing breast cancer, or both [32]. Until recently, existing models, such as the Breast Cancer Risk Assessment Tool (also known as the Gail model) and the Rosner–Colditz model, generally included reproductive factors, family history of breast cancer, and a subset of lifestyle factors. Recent work has suggested significant improvements in model performance with the addition of several biological markers, including mammographic breast density, genetic risk scores, and plasma endogenous hormone levels (e.g. [12,33]). Further enhancements are needed, including incorporation of newly confirmed risk factors (e.g. anti-Müllerian hormone), more specific disease definitions, and development and validation in a wider range of study populations. Other priorities are assessment of clinical utility and strategies to successfully implement these models in clinical practice.

The current Women Informed to Screen Depending on Measures of Risk (WISDOM) clinical trial examining risk-stratified mammographic screening, and the work by the group in Manchester, United Kingdom, incorporating risk SNPs and mammographic density into the Tyrer–Cuzick multivariable model, among others, will provide data with which to assess the impact of these approaches.

Social inequalities in risk and burden

Socioeconomic differences

In epidemiological studies, a positive association between socioeconomic status and breast cancer risk is well established. This is due in large part to different distributions by socioeconomic status of breast cancer risk factors such as parity, age at first birth, and use of hormone therapy. Other possible contributors include differences in screening practices across socioeconomic status [34].

Given the increasing proportion of breast cancer cases in low- and middle-income countries, as well as the changing patterns of risk factors in these countries, it is critical to identify feasible strategies to improve prevention and early detection in these settings.

Racial and ethnic variations

Racial differences in breast cancer incidence and mortality exist, and it has become increasingly clear that differences in the distribution of both individual risk factors and societal and contextual factors, as well as tumour biology, all contribute to this variation.

For example, from the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) programme, the 2007–2011 age-adjusted incidence rate (per 100 000) for breast cancer was 128 for non-Hispanic White women and 123 for African American women, but the age-adjusted mortality rate (per 100 000) was 21.7 for non-Hispanic White women and 30.6 for African American women. African American women have a higher prevalence of triple-negative breast cancers [35], for which outcomes are poorer, and this is a likely contributor to the higher SEER mortality rates. However, even among the subset of women diagnosed with similar early-stage disease, mortality rates were higher for African American women, indicating that other factors, such as differences in patterns of care [35], contribute as well. (See also "The enduring disparity in breast cancer mortality between Black and White women in the USA" in Chapter 4.6.)

Prevention

Prevention trials require large study populations and long follow-up periods, which makes them both costly and challenging to conduct. Therefore, preliminary data for prevention trials often come from biomarker modulation studies, or from evaluation of the effects of interventions on contralateral breast cancer events in breast cancer treatment

trials. Colditz and Bohlke recently reviewed the evidence that acting on already established information about modifiable risk factors could substantially reduce breast cancer incidence in high-income countries (Table 5.9.1) [36].

Weight loss

There have not been compelling new data for weight loss, but Breast Cancer Weight Loss (BWEL) is a current randomized trial addressing the ability of a weight-loss intervention to prevent breast cancer recurrence [37]. If BWEL is successful, weight loss would probably be further targeted in a trial for breast cancer risk reduction.

Metformin

Metformin, which is used for treatment of metabolic syndrome and diabetes, has been linked with lower risk of breast cancer in observational studies. In a pre-surgical trial in Italy, metformin taken before surgery decreased levels of Ki-67, a marker of breast tissue proliferation, in women with insulin resistance [38], but in a meta-analysis on metformin and cancer risk, after adjustment for BMI, no significant reduction in breast cancer incidence was observed [38].

Familial or other high-risk groups

Other medical interventions generally target women who have substantial risk of breast cancer. The duration of the effects of selective

Table 5.9.1. Current strategies to prevent breast cancer

Health message	Risk group	Estimated proportion of female population in the USA aged < 50 years affected (%)[a]	Possible reduction in risk (%)[b]	Time until benefit (years)
Premenopausal women				
Alcohol intake: none	Youth (aged 12–17 years), drinking ≥ 1 drink in the past 30 days	13	20–30	10–20
Alcohol intake: none or ≤ 4 servings/day	Young adults (aged 18–24 years) drinking ≥ 4 drinks/week	15	20–30	10–20
	Adults (aged ≥ 18 years) drinking ≥ 4 drinks/week	13	35	10–20
Healthy weight: avoid weight gain	All women	100	50 (after menopause)	10–30
Physical activity: ≥ 30 minutes/day	Women not meeting physical activity guidelines	54	20	10–30
Healthy diet: fruits, vegetables, and whole grains	Youth eating few fruits and vegetables	5–11	20–50	5–20
Breastfeed: 1 year total across all children	Women who have given birth	81	18	5
Prophylactic bilateral oophorectomy	*BRCA1* and *BRCA2* mutation carriers	< 1	50	≥ 2
Tamoxifen	High-risk women aged ≥ 35 years (≥ the risk for an average woman aged 60 years)	3	50	2
Postmenopausal women				
Alcohol intake: none or < 1 serving/day	Women drinking ≥ 4 drinks/week	13	35	5–10
Healthy weight: weight loss	Overweight and obese women	64	50	2–5
Physical activity: ≥ 30 minutes/day	Women not meeting physical activity guidelines	54	20	10–20
Estrogen plus progestin postmenopausal hormone therapy: avoid	Current users	1.7	10	1
	Long-term current users	1	50	2
Tamoxifen and raloxifene[c]	High-risk women (≥ the risk for an average woman aged 60 years)	30	50	2

[a] Estimates are from nationally representative samples of women in the USA.

[b] Risk factors in the table are not necessarily biologically independent of each other.

[c] Exemestane is not listed for prevention, because the United States Food and Drug Administration has not approved this agent for primary breast cancer risk reduction.

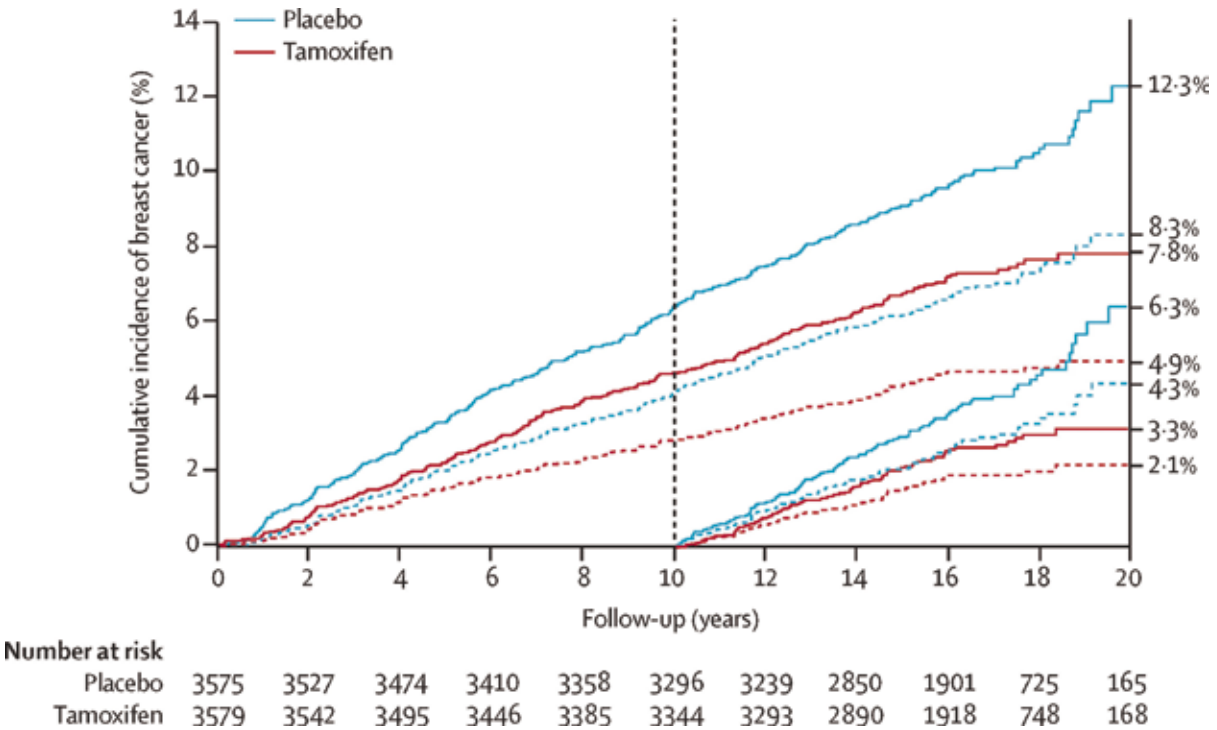
ER modulators, such as tamoxifen and raloxifene, on breast cancer prevention was estimated in a meta-analysis, which demonstrated a measurable reduction in breast cancer incidence that was greatest in the first 5 years of follow-up but also extended into years 5–10 of follow–up [39].

In the follow-up of the International Breast Cancer Intervention Study (IBIS) trial (tamoxifen vs placebo), the hazard ratio for the occurrence of all breast cancers in the tamoxifen group versus the placebo group in the first 10 years of follow-up was 0.72 (95% CI, 0.59–0.88) and after 10 years of follow-up was 0.69 (95% CI, 0.53–0.91) (Fig. 5.9.7) [40]. The effect was observed for both ER-positive breast cancer and ductal carcinoma in situ, but not for triple-negative breast cancer. Aromatase inhibitors, both anastrozole and exemestane, have been shown to reduce breast cancer risk by about half [41]. There is a lack of proven strategies for reducing the risk of HER2-positive and triple-negative breast cancers.

The management of women at high risk based on predisposing mutations in cancer susceptibility genes includes risk-reducing mastectomies and premenopausal oophorectomies, which may reduce risk of ER-positive breast cancer and of ovarian cancer. The timing and advisability may be considered in a framework put forward by Tung et al. (see Chapter 6.5) [42].

Recent data indicating that RANK ligand is an essential molecule in the development of breast cancer in *BRCA1* mutation carriers have led to an international chemoprevention trial evaluating the RANK ligand inhibitor denosumab in *BRCA1* mutation carriers, led by the Austrian Breast and Colorectal Cancer Study Group (ABCSG). The next phase of trials will focus on bringing progress in cancer immunology to prevention.

Fig. 5.9.7. Cumulative incidence of breast cancer over time in the International Breast Cancer Intervention Study I (IBIS-I) trial, according to treatment group (tamoxifen or placebo) and duration of follow-up. Solid lines indicate all breast cancers, and dashed lines indicate invasive estrogen receptor (ER)-positive breast cancers.



References

1. Lehmann BD, Jovanović B, Chen X, Estrada MV, Johnson KN, Shyr Y, et al. (2016). Refinement of triple-negative breast cancer molecular subtypes: implications for neoadjuvant chemotherapy selection. PLoS One. 11(6):e0157368. https://doi.org/10.1371/journal.pone.0157368 PMID:27310713

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593

3. Ginsburg O, Bray F, Coleman MP, Vanderpuye V, Eniu A, Kotha SR, et al. (2017). The global burden of women's cancers: a grand challenge in global health. Lancet. 389(10071):847–60. https://doi.org/10.1016/S0140-6736(16)31392-7 PMID:27814965

4. Nielsen FC, van Overeem Hansen T, Sørensen CS (2016). Hereditary breast and ovarian cancer: new genes in confined pathways. Nat Rev Cancer. 16(9):599–612. https://doi.org/10.1038/nrc.2016.72 PMID:27515922

5. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al.; *BRCA1* and *BRCA2* Cohort Consortium (2017). Risks of breast, ovarian, and contralateral breast cancer for *BRCA1* and *BRCA2* mutation carriers. JAMA. 317(23):2402–16. https://doi.org/10.1001/jama.2017.7112 PMID:28632866

6. Easton DF, Pharoah PDP, Antoniou AC, Tischkowitz M, Tavtigian SV, Nathanson KL, et al. (2015). Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med. 372(23):2243–57. https://doi.org/10.1056/NEJMsr1501341 PMID:26014596

7. Rana HQ, Gelman R, LaDuca H, McFarland R, Dalton E, Thompson J, et al. (2018). Differences in *TP53* mutation carrier phenotypes emerge from panel-based testing. J Natl Cancer Inst. 110(8):863–70. https://doi.org/10.1093/jnci/djy001 PMID:29529297

8. Rebbeck TR, Mitra N, Wan F, Sinilnikova OM, Healey S, McGuffog L, et al.; CIMBA Consortium (2015). Association of type and location of *BRCA1* and *BRCA2* mutations with risk of breast and ovarian cancer. JAMA. 313(13):1347–61. https://doi.org/10.1001/jama.2014.5985 PMID:25849179

9. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al.; Australian Pancreatic Cancer Genome Initiative; ICGC Breast Cancer Consortium; ICGC MMML-Seq Consortium; ICGC PedBrain (2013). Signatures of mutational processes in human cancer. Nature. 500(7463):415–21. https://doi.org/10.1038/nature12477 PMID:23945592

10. Michailidou K, Beesley J, Lindstrom S, Canisius S, Dennis J, Lush MJ, et al.; BOCS; kConFab Investigators; AOCS Group; NBCS; GENICA Network (2015). Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet. 47(4):373–80. https://doi.org/10.1038/ng.3242 PMID:25751625

11. Milne RL, Kuchenbaecker KB, Michailidou K, Beesley J, Kar S, Lindström S, et al.; ABCTB Investigators; EMBRACE; GEMO Study Collaborators; HEBON; kConFab/AOCS Investigators; NBSC Collaborators (2017). Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer. Nat Genet. 49(12):1767–78. https://doi.org/10.1038/ng.3785 PMID:29058716

12. Mavaddat N, Pharoah PD, Michailidou K, Tyrer J, Brook MN, Bolla MK, et al. (2015). Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst. 107(5):djv036. https://doi.org/10.1093/jnci/djv036 PMID:25855707

13. Evans DG, Brentnall A, Byers H, Harkness E, Stavrinos P, Howell A, et al.; FH-Risk Study Group (2017). The impact of a panel of 18 SNPs on breast cancer risk in women attending a UK familial screening clinic: a case-control study. J Med Genet. 54(2):111–3. https://doi.org/10.1136/jmedgenet-2016-104125 PMID:27794048

14. WCRF/AICR (2018). Diet, nutrition, physical activity and cancer: a global perspective. Continuous Update Project Expert Report 2018. World Cancer Research Fund/American Institute for Cancer Research. Available from: https://www.wcrf.org/dietandcancer.

15. Schoemaker MJ, Nichols HB, Wright LB, Brook MN, Jones ME, O'Brien KM, et al.; Premenopausal Breast Cancer Collaborative Group (2018). Association of body mass index and age with subsequent breast cancer risk in premenopausal women. JAMA Oncol. 4(11):e181771. https://doi.org/10.1001/jamaoncol.2018.1771 PMID:29931120

16. Guo Y, Warren Andersen S, Shu XO, Michailidou K, Bolla MK, Wang Q, et al. (2016). Genetically predicted body mass index and breast cancer risk: Mendelian randomization analyses of data from 145,000 women of European descent. PLoS Med. 13(8):e1002105. https://doi.org/10.1371/journal.pmed.1002105 PMID:27551723

17. Gaudet MM, Carter BD, Brinton LA, Falk RT, Gram IT, Luo J, et al. (2017). Pooled analysis of active cigarette smoking and invasive breast cancer risk in 14 cohort studies. Int J Epidemiol. 46(3):881–93. https://doi.org/10.1093/ije/dyw288 PMID:28031315

18. Du M, Liu SH, Mitchell C, Fung TT (2018). Associations between diet quality scores and risk of postmenopausal estrogen receptor-negative breast cancer: a systematic review. J Nutr. 148(1):100–8. https://doi.org/10.1093/jn/nxx015 PMID:29378048

19. Forman MR, Winn DM, Collman GW, Rizzo J, Birnbaum LS (2015). Environmental exposures, breast development and cancer risk: through the looking glass of breast cancer prevention. Reprod Toxicol. 54:6–10. https://doi.org/10.1016/j.reprotox.2014.10.019 PMID:25499721

20. Anderson KN, Schwab RB, Martinez ME (2014). Reproductive risk factors and breast cancer subtypes: a review of the literature. Breast Cancer Res Treat. 144(1):1–10. https://doi.org/10.1007/s10549-014-2852-7 PMID:24477977

21. Islami F, Liu Y, Jemal A, Zhou J, Weiderpass E, Colditz G, et al. (2015). Breastfeeding and breast cancer risk by receptor status – a systematic review and meta-analysis. Ann Oncol. 26(12):2398–407. https://doi.org/10.1093/annonc/mdv379 PMID:26504151

22. Palmer JR, Viscidi E, Troester MA, Hong CC, Schedin P, Bethea TN, et al. (2014). Parity, lactation, and breast cancer subtypes in African American women: results from the AMBER Consortium. J Natl Cancer Inst. 106(10):dju237. https://doi.org/10.1093/jnci/dju237 PMID:25224496

23. Brouckaert O, Rudolph A, Laenen A, Keeman R, Bolla MK, Wang Q, et al.; kConFab (2017). Reproductive profiles and risk of breast cancer subtypes: a multi-center case-only study. Breast Cancer Res. 19(1):119. https://doi.org/10.1186/s13058-017-0909-3 PMID:29116004

24. Tamimi RM, Spiegelman D, Smith-Warner SA, Wang M, Pazaris M, Willett WC, et al. (2016). Population attributable risk of modifiable and nonmodifiable breast cancer risk factors in postmenopausal breast cancer. Am J Epidemiol. 184(12):884–93. https://doi.org/10.1093/aje/kww145 PMID:27923781

25. Engmann NJ, Golmakani MK, Miglioretti DL, Sprague BL, Kerlikowske K; Breast Cancer Surveillance Consortium (2017). Population-attributable risk proportion of clinical risk factors for breast cancer. JAMA Oncol. 3(9):1228–36. https://doi.org/10.1001/jamaoncol.2016.6326 PMID:28152151

26. Key TJ, Appleby PN, Reeves GK, Travis RC, Alberg AJ, Barricarte A, et al.; Endogenous Hormones and Breast Cancer Collaborative Group (2013). Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. Lancet Oncol. 14(10):1009–19. https://doi.org/10.1016/S1470-2045(13)70301-2 PMID:23890780

27. Tworoger SS, Eliassen AH, Zhang X, Qian J, Sluss PM, Rosner BA, et al. (2013). A 20-year prospective study of plasma prolactin as a risk marker of breast cancer development. Cancer Res. 73(15):4810–9. https://doi.org/10.1158/0008-5472.CAN-13-0665 PMID:23783576

28. Ziegler RG, Fuhrman BJ, Moore SC, Matthews CE (2015). Epidemiologic studies of estrogen metabolism and breast cancer. Steroids. 99(Pt A):67–75. https://doi.org/10.1016/j.steroids.2015.02.015 PMID:25725255

29. Sampson JN, Falk RT, Schairer C, Moore SC, Fuhrman BJ, Dallal CM, et al. (2017). Association of estrogen metabolism with breast cancer risk in different cohorts of postmenopausal women. Cancer Res. 77(4):918–25. https://doi.org/10.1158/0008-5472.CAN-16-1717 PMID:28011624

30. Ge W, Clendenen TV, Afanasyeva Y, Koenig KL, Agnoli C, Brinton LA, et al. (2018). Circulating anti-Müllerian hormone and breast cancer risk: a study in ten prospective cohorts. Int J Cancer. 142(11):2215–26. https://doi.org/10.1002/ijc.31249 PMID:29315564

31. Playdon MC, Ziegler RG, Sampson JN, Stolzenberg-Solomon R, Thompson HJ, Irwin ML, et al. (2017). Nutritional metabolomics and breast cancer risk in a prospective study. Am J Clin Nutr. 106(2):637–49. https://doi.org/10.3945/ajcn.116.150912 PMID:28659298

32. Cintolo-Gonzalez JA, Braun D, Blackford AL, Mazzola E, Acar A, Plichta JK, et al. (2017). Breast cancer risk models: a comprehensive overview of existing models, validation, and clinical applications. Breast Cancer Res Treat. 164(2):263–84. https://doi.org/10.1007/s10549-017-4247-z PMID:28444533

33. Zhang X, Rice M, Tworoger SS, Rosner BA, Eliassen AH, Tamimi RM, et al. (2018). Addition of a polygenic risk score, mammographic density, and endogenous hormones to existing breast cancer risk prediction models: a nested case-control study. PLoS Med. 15(9):e1002644. https://doi.org/10.1371/journal.pmed.1002644 PMID:30180161

34. Verdial FC, Etzioni R, Duggan C, Anderson BO (2017). Demographic changes in breast cancer incidence, stage at diagnosis and age associated with population-based mammographic screening. J Surg Oncol. 115(5):517–22. https://doi.org/10.1002/jso.24579 PMID:28194807

35. Daly B, Olopade OI (2015). A perfect storm: how tumor biology, genomics, and health care delivery patterns collide to create a racial survival disparity in breast cancer and proposed interventions for change. CA Cancer J Clin. 65(3):221–38. https://doi.org/10.3322/caac.21271 PMID:25960198

36. Colditz GA, Bohlke K (2014). Priorities for the primary prevention of breast cancer. CA Cancer J Clin. 64(3):186–94. https://doi.org/10.3322/caac.21225 PMID:24647877

37. Demark-Wahnefried W, Schmitz KH, Alfano CM, Bail JR, Goodwin PJ, Thomson CA, et al. (2018). Weight management and physical activity throughout the cancer care continuum. CA Cancer J Clin. 68(1):64–89. https://doi.org/10.3322/caac.21441 PMID:29165798

38. Gandini S, Puntoni M, Heckman-Stoddard BM, Dunn BK, Ford L, DeCensi A, et al. (2014). Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders. Cancer Prev Res (Phila). 7(9):867–85. https://doi.org/10.1158/1940-6207.CAPR-13-0424 PMID:24985407

39. Cuzick J, Sestak I, Bonanni B, Costantino JP, Cummings S, DeCensi A, et al.; SERM Chemoprevention of Breast Cancer Overview Group (2013). Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet. 381(9880):1827–34. https://doi.org/10.1016/S0140-6736(13)60140-3 PMID:23639488

40. Cuzick J, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A, et al.; IBIS-I Investigators (2015). Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol. 16(1):67–75. https://doi.org/10.1016/S1470-2045(14)71171-4 PMID:25497694

41. Cuzick J, Sestak I, Forbes JF, Dowsett M, Knox J, Cawthorn S, et al.; IBIS-II investigators (2014). Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet. 383(9922):1041–8. https://doi.org/10.1016/S0140-6736(13)62292-8 PMID:24333009

42. Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, et al. (2016). Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol. 13(9):581–8. https://doi.org/10.1038/nrclinonc.2016.90 PMID:27296296

5.10 Cervical cancer
Successes in some communities to be extended worldwide

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Maribel Almonte (reviewer)
Karen Canfell (reviewer)
Lynette Denny (reviewer)

SUMMARY

- In 2018, there were an estimated 570 000 new cases of cervical cancer and 311 000 deaths from the disease worldwide.
- WHO has issued a call to action for the elimination of cervical cancer as a public health problem.
- Some changes to the WHO classification of neoplasms of the cervix were introduced in 2014.
- The essential molecular interactions of the different human papillomavirus (HPV) oncoproteins to induce cervical carcinogenesis are now better understood.
- HPV infection causes almost all cervical squamous cell carcinomas. About 5–10% of cervical adenocarcinomas are unrelated to HPV infection.
- Primary HPV testing is a more effective screening modality than cytology. It is now being introduced in many high-income countries, with an increasing focus on effective delivery in low- and middle-income countries.
- There is increased interest in the use of biomarkers in cervical cancer screening to better triage women with high-risk HPV infection.
- Because of the limitations of clinical staging, new staging guidelines were introduced in 2018 that incorporate imaging and pathology results. Lymph node involvement, an important adverse prognostic factor, is now included in the staging.
- Remarkable progress has been made worldwide to scale up HPV vaccination, especially in high-income countries.

Epidemiology

Cervical cancer constitutes 80% of all cancers attributable to human papillomavirus (HPV) infection [1]. The global disparity in cervical cancer incidence and mortality rates is an indicator of the enormous inequities in access to health services.

Cervical cancer is the fourth most common cancer type diagnosed in women and the fourth most common cause of cancer death in women. In 2018, there were an estimated 570 000 new cases of cervical cancer and 311 000 deaths from the disease worldwide [2]. Cervical cancer remains the most common cause of cancer death in many countries in Africa and South-East Asia, where the incidence and mortality rates are about 10 times those in North America, Australia and New Zealand, and West Asia [2] (Fig. 5.10.1 and Fig. 5.10.2).

In regions with a high burden of cervical cancer, the incidence of cervical cancer has been decreasing in some countries, such as Colombia, India, and the Philippines; this is probably because of improving socioeconomic conditions, and possibly because of associated changes in behaviour and lifestyle. However, an increasing trend in incidence has been observed in countries in sub-Saharan Africa, such as Uganda and Zimbabwe, and in some countries in eastern Europe [3].

The elimination of cervical cancer as a public health problem is considered a priority under the WHO 13th General Programme of Work. In some high-income countries, the combined approach of implementation of wide-scale HPV vaccination with adequate population coverage, improved primary screening for high-risk HPV, and treatment of cervical cancer makes the elimination of cervical cancer a possibility in the foreseeable future [4].

Pathology

The most recent (2014) edition of the WHO classification of tumours of the female reproductive organs introduced changes to the classification of neoplasms of the cervix [5] (Box 5.10.1). These include the introduction of a stratified mucin-producing intraepithelial lesion as a variant of adenocarcinoma in situ, restructuring of the nomenclature of adenocarcinomas, and the classification of cervical precursor lesions into a two-tiered system in line with the Bethesda classification for cytology [5] (Table 5.10.1).

Box 5.10.1. Significant changes in the 2014 WHO classification of neoplasms of the cervix.

- Two-tiered subdivision of precursor lesions of squamous cell carcinoma (according to the Bethesda classification for cytology)
- Stratified mucin-producing intraepithelial lesion (SMILE) as a variant of adenocarcinoma in situ (AIS)
- Subdivision of adenocarcinomas
- Relation of the individual carcinoma types to human papillomavirus (HPV)
- Neuroendocrine tumours

The Lower Anogenital Squamous Terminology Standardization Project also recommended the use of a two-tiered classification system for cervical precursor lesions, as well as the use of p16 immunohistochemical staining as a biomarker to differentiate between cervical precancerous lesions and their mimics, and in the stratification of cervical intraepithelial neoplasia grade 2 (CIN2) lesions [6]. Low-grade squamous intraepithelial lesions encompass HPV infection and CIN1, whereas high-grade squamous intraepithelial lesions include CIN2 and CIN3.

Invasive squamous cell carcinomas

Invasive squamous cell carcinoma of the cervix (Fig. 5.10.3) accounts for 80–85% of cervical carcinomas. HPV infection causes almost 100% of cases of cervical squamous cell carcinoma, and in most cases an underestimation of HPV prevalence is due to the limitations of relevant studies [7].

The histological subtypes of cervical squamous cell carcinoma are shown in Table 5.10.2. The term "squamous cell carcinoma, not otherwise specified" was introduced to include most squamous cell carcinomas without any specific differentiation or cornification.

Invasive glandular cell carcinomas

Invasive cervical adenocarcinomas (Fig. 5.10.4) constitute 10–25% of cervical carcinomas. About 5–10% of cervical adenocarcinomas are unrelated to HPV infection.

The histological subtypes of cervical adenocarcinoma are shown in Table 5.10.3. The most frequent histological variant is HPV-related adenocarcinoma of the usual type. Other types include the various subtypes of mucinous adenocarcinomas and clear cell carcinomas, which occur more commonly in younger women. Primary serous adenocarcinomas are uncommon. Immunohistochemistry aids in the diagnosis of mesonephric tumours and mixed adenocarcinoma and neuroendocrine carcinoma [8].

Rare epithelial cervical tumours

Rare epithelial neoplasms of the cervix (Table 5.10.4) include adenosquamous carcinomas (1–2%),

Table 5.10.1. Comparison of classifications of precursor lesions of squamous cell carcinoma of the cervix

1975/1994 WHO classification	2003 WHO classification	2014 WHO classification
Low (mild) dysplasia	CIN grade 1 (CIN1)	Low-grade squamous intraepithelial lesion (LSIL)
Moderate dysplasia Severe dysplasia Carcinoma in situ	CIN grade 2 (CIN2) CIN grade 3 (CIN3)	High-grade squamous intraepithelial lesion (HSIL)

CIN, cervical intraepithelial neoplasia.

FUNDAMENTALS

- Infection with high-risk human papillomavirus (HPV) types causes almost all cases of cervical cancer.
- Cytology-based screening programmes have demonstrated remarkable success in reducing the incidence of and mortality from cervical cancer in high-income countries. The main limitation of cytology is its relatively low sensitivity, especially if comprehensive quality assurance processes are not in place. Because of the complexities and cost involved in setting up cytology-based screening programmes, most low- and middle-income countries have either opportunistic screening or no screening at all.
- Advances in molecular technology have made testing for high-risk HPV widely available, albeit mostly in high-income countries, and the increasing focus is now on demonstrating its broader applicability to low- and middle-income countries. Testing for high-risk HPV types is currently being used for primary screening, to triage women with atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesion cytology results, for co-testing with cytology, and as a test of cure.
- The high negative predictive value of high-risk HPV DNA testing has enabled screening intervals to be safely increased.
- Previously, it was considered that a limitation of high-risk HPV testing was its lower specificity for detection of high-grade squamous intraepithelial lesions. However, this is effectively managed through the use of clinically validated tests, by limiting the age range of testing, and – in some settings and in some countries – by the effect of HPV vaccination, which enables HPV-based screening to be done in women younger than 30 years.
- There is much interest in biomarkers to predict which cervical precancerous lesions are likely to progress in women with high-risk HPV infection and normal, atypical squamous cells of undetermined significance, or low-grade squamous intraepithelial lesion cytology results.

Fig. 5.10.1. Global distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000 person-years for cervical cancer, 2018.

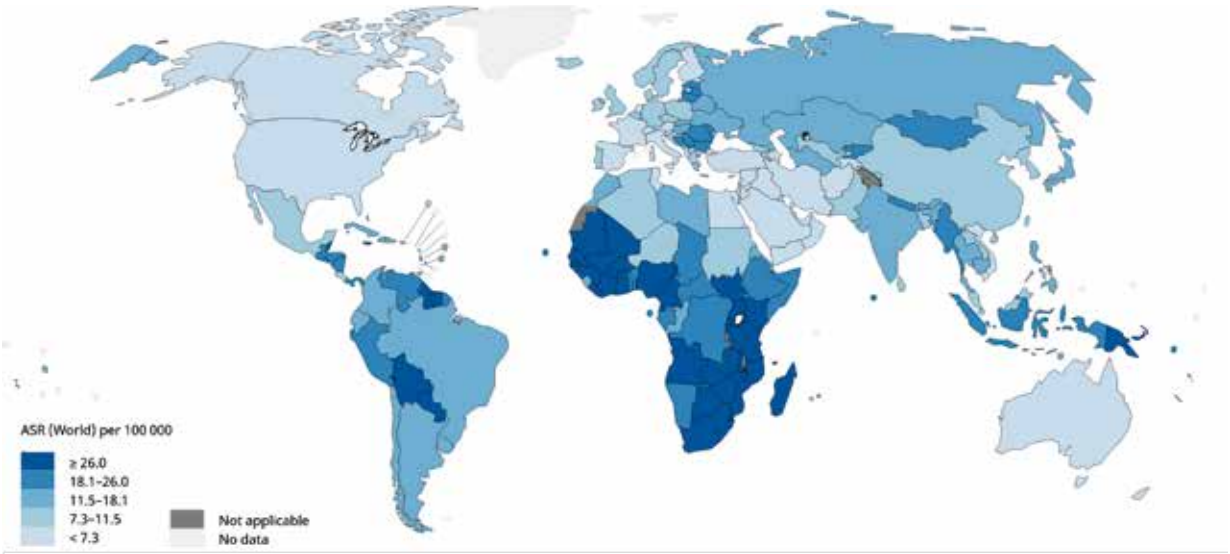
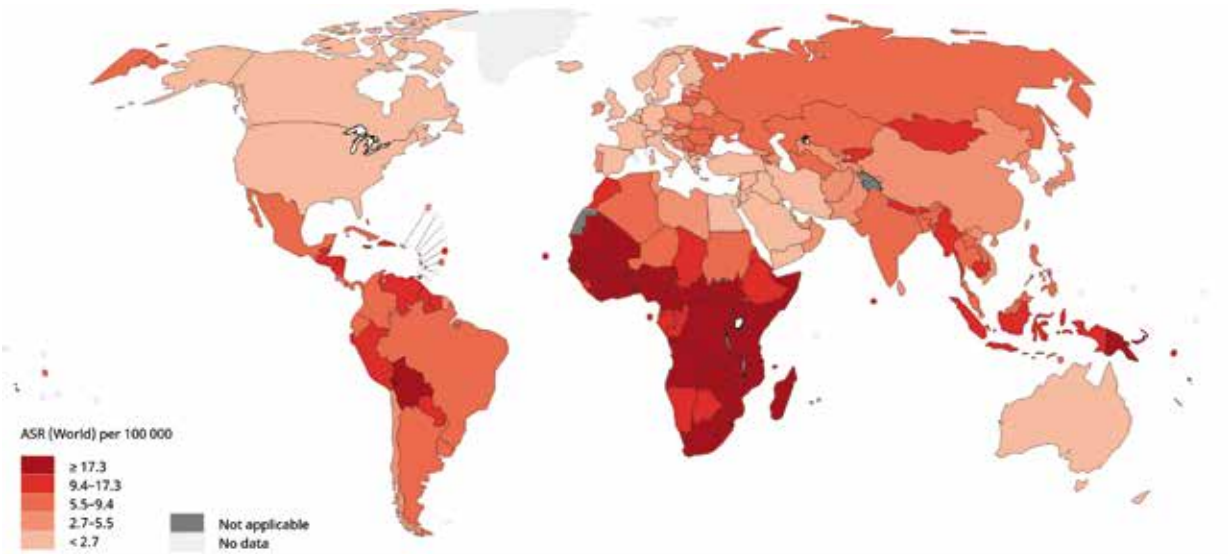


Fig. 5.10.2. Global map of estimated age-standardized (World) mortality rates (ASR) per 100 000 person-years for cervical cancer, 2018.



glassy cell carcinomas, and neuroendocrine tumours.

Rare non-epithelial cervical tumours

Rare non-epithelial neoplasms of the cervix include mesenchymal types and other tumorous changes, such as postoperative spindle cell nodules. The occurrence of a secondary malignancy in the cervix is clinically important but is very rare.

Genetics and genomics

Cervical cancer is a rare outcome in women with HPV infection. The biological underpinnings of this process are not yet clearly understood. There is renewed interest in the role of host genetics in the development of cervical cancer.

In the Han Chinese population, loci at 4q12 and 17q12 were associated with a higher risk of cervical cancer; in the Swedish population, loci within 6p21.3 were associated with increased susceptibility to cervical cancer [9,10].

Persistent HPV infection is due to both viral and host immune system factors. Several factors attributable to HPV contribute to the ability of the infection to evade the host immune system. Host genetic variants influence the ability of the immune system to clear HPV infection.

New data from genome-wide association studies have shown

Fig. 5.10.3. Photomicrograph of invasive cervical squamous cell carcinoma, showing invasive squamous cells (bottom right) budding off from a focus of cervical high-grade squamous intraepithelial lesion (centre). Normal non-dysplastic cervical squamous epithelium is present at the periphery (top right and top left). Haematoxylin and eosin stain, 40× magnification.

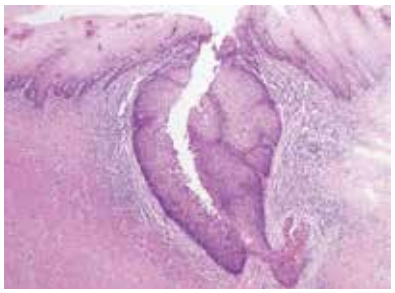


Table 5.10.2. Histological types of squamous cell carcinoma of the cervix (2014 WHO classification)

Histological type	ICD-O code
Squamous cell carcinoma, NOS	8070/3
Keratinizing squamous cell carcinoma	8071/3
Non-keratinizing squamous cell carcinoma	8072/3
Papillary squamous cell carcinoma	8052/3
Basaloid squamous cell carcinoma	8083/3
Warty squamous cell carcinoma	8051/3
Verrucous squamous cell carcinoma	8051/3
Squamotransitional carcinoma	8120/3
Lymphoepithelioma-like carcinoma	8082/3

ICD-O, International Classification of Diseases for Oncology; NOS, not otherwise specified.

that the amino acids carried at positions 13 and 71 in pocket 4 of human leukocyte antigen (HLA)-DRB1 and at position 156 in HLA-B control whether HLA haplotypes increase the risk of cervical neoplasia or protect against cervical cancer [11]. Three HLA haplotypes were identified that are associated with an increased risk of both HPV16- and HPV18-associated cervical cancer, and for the development of both cervical squamous cell carcinoma and adenocarcinoma. The HLA-B*15 haplotype was associated with a lower risk of squamous cell carcinomas and other HPV16-associated cervical cancers, but no association was seen with HPV18-associated cervical cancers [11].

Genetic analysis of 80 tumours of the cervix for 1250 known mutations in 139 genes found the highest mutation rates in the *PIK3CA* (31.3%), *KRAS* (8.8%), and *EGFR* (3.8%) genes. *PIK3CA* mutation rates did not differ significantly between adenocarcinomas and squamous cell carcinomas. *KRAS* mutations were identified only in adenocarcinomas, and a new *EGFR* mutation was detected only in squamous cell carcinomas [12]. *PIK3CA* mutations may be associated with shorter survival.

Etiology

Persistent infection with high-risk HPV is necessary for the development of cervical cancer (see Chapter 2.2). Co-factors associated with disease progression are well established.

HPV DNA encodes for six early genes and two late genes. In the most recent evaluation by the IARC Monographs programme, the following 12 HPV types were classified as carcinogenic to humans: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 [13]. The most common oncogenic

Fig. 5.10.4. Photomicrograph of invasive cervical adenocarcinoma, showing fused glandular structures (top) as well as small nests and cords of invasive glandular cells (bottom centre and bottom left) surrounded by pale pink, inflamed mucus. Haematoxylin and eosin stain, 40× magnification.

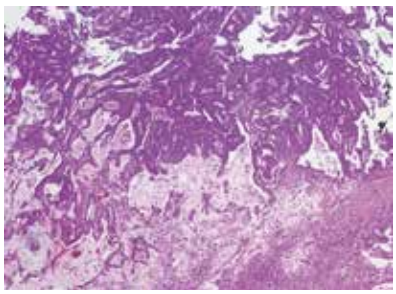


Table 5.10.3. Histological types of adenocarcinoma of the cervix (2014 WHO classification) related to human papillomavirus infection

Histological type	Related HPV	ICD-O code
Endocervical adenocarcinoma, usual type	HR-HPV	8140/3
Mucinous adenocarcinoma, NOS	–	8480/3
Mucinous adenocarcinoma, stomach type	No	8482/3
Mucinous adenocarcinoma, intestinal type	HR-HPV	8144/3
Mucinous adenocarcinoma, signet ring cell type	Partial HR-HPV	8490/3
Villoglandular carcinoma	HPV16, HPV18, HPV45	8263/3
Endometrioid carcinoma	No[a]	8380/3
Clear cell carcinoma	No or HR-HPV[b]	8310/3
Serous carcinoma	No[a]	8441/3
Mesonephric carcinoma	No	9110/3
Mixed adenocarcinoma and neuroendocrine carcinoma	HR-HPV	8574/3

HR-HPV, high-risk human papillomavirus; ICD-O, International Classification of Diseases for Oncology; NOS, not otherwise specified.

[a] If these tumour types contain HPV DNA, they are considered a morphological variant of endocervical adenocarcinoma, usual type.

[b] There is conflicting information in the literature on the HPV reference of the clear cell type.

Table 5.10.4. Other rare epithelial neoplasms of the cervix (2014 WHO classification) related to human papillomavirus infection

Histological type	Related HPV	ICD-O code
Adenosquamous carcinoma	HPV18, HPV16	8560/3
Glassy cell carcinoma	HPV18	8015/3
Adenoid basal carcinoma	HPV16, HPV33	8098/3
Adenoid cystic carcinoma	HPV16	8200/3
Undifferentiated carcinoma	HPV16	8020/3
Neuroendocrine tumours	–	–
"Low-grade" neuroendocrine tumour	HR-HPV	–
Carcinoid tumour	–	8240/3
Atypical carcinoid tumour	–	8249/3
"High-grade" neuroendocrine carcinoma	HR-HPV (HPV18)	–
Small cell neuroendocrine carcinoma	–	8041/3
Large cell neuroendocrine carcinoma	–	8013/3

HR-HPV, high-risk human papillomavirus; ICD-O, International Classification of Diseases for Oncology.

HPV types identified in cervical cancer include HPV16 (53%), HPV18 (15%), HPV45 (9%), HPV31 (6%), and HPV33 (3%) [14].

The integration of the viral episome into the host genome is a necessary step in the development of cervical cancer. The E6 and E7 oncoproteins deactivate the protein products of the *TP53* and retinoblastoma (*RB*) tumour suppressor genes, respectively. Overexpression of the E6 and E7 oncogenes results in the loss of cell-cycle control and leads to uncontrolled cellular proliferation, immortalization, and reduced apoptosis; the result is chromosomal instability and the development of cervical cancer. The essential molecular interactions of the different HPV oncoproteins to induce cervical carcinogenesis are summarized in Fig. 5.10.5.

In most women, the activity of humoral and cellular-mediated immunity helps to clear the HPV infection within 12–24 months. If persistent high-grade squamous intraepithelial lesions are left untreated, the risk of developing cervical cancer is about 30%.

Known co-factors associated with disease progression include infection with HIV and other immunosuppressive conditions, smoking (in squamous cell carcinomas only), multiparity, and long-term use of oral contraceptives [15].

Prognostic markers for invasive cervical cancer

Despite the wide availability of screening in high-income countries and recent advances in radiotherapy techniques, the 5-year overall survival in cervical cancer remains about 60–70% in high-income countries and is much lower in low- and middle-income countries. Research is under way on potential biomarkers that could help to identify the disease in early stages, predict tumour burden, detect recurrences early, and offer prognostic information, thus providing a potential way to improve survival. Many of these biomarkers are not yet in routine clinical use.

HPV integration mutation was shown to be a molecular marker of circulating tumour DNA in HPV-associated tumours. Tumour burden, an adverse prognostic marker, correlated well with serum levels of circulating tumour DNA. Therefore, circulating tumour DNA may provide important prognostic information and may also play a role in detecting minimal residual disease after treatment and subclinical recurrence [16].

Squamous cell carcinoma antigen (SCC-Ag) is a protein-based biomarker with a good correlation between its levels before treatment and tumour burden. It can potentially be used to provide prognostic information, as well as to detect recurrences early. SCC-Ag was also shown to be a useful adjunct to imaging in detecting lymph node metastasis, an important adverse prognostic factor [17]. There is an association between SCC-Ag levels and disease recurrence and mortality in women with newly diagnosed cervical cancer [18].

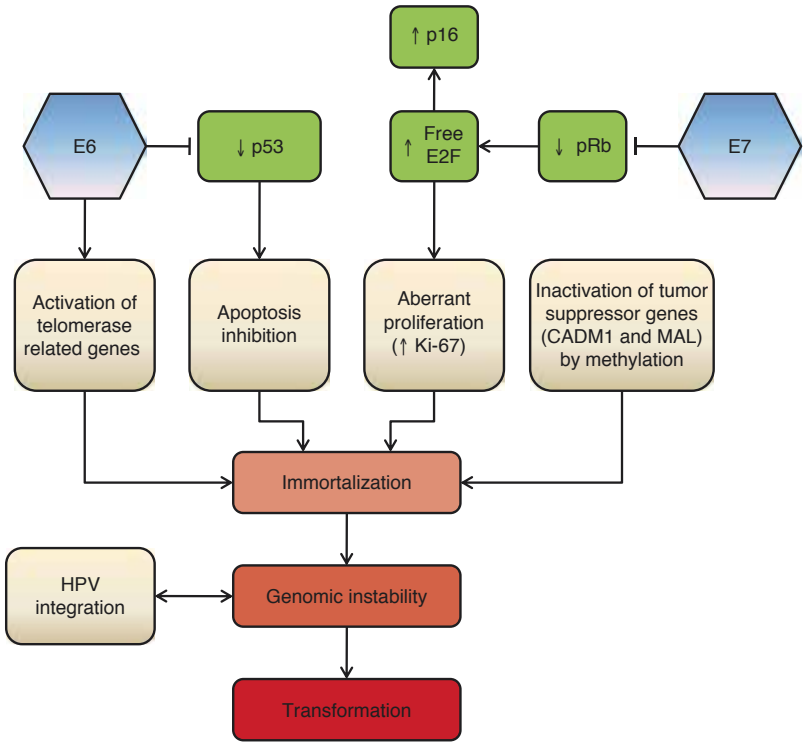
Normal epithelium and carcinomas of the uterine cervix produce serum cytokeratin 19 fragments (CYFRA 21.1). CYFRA 21.1 was shown to be a useful biomarker in predicting parametrial invasion, another important adverse prognostic factor. A predictive model using CYFRA 21.1 levels, tumour size, and SCC-Ag levels demonstrated an ability to accurately predict parametrial invasion in patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB cervical cancer [19].

Socioeconomic, racial, and ethnic differences

In large parts of sub-Saharan Africa, as well as in countries in Melanesia, cervical cancer is the leading cause of cancer death in women, whereas in countries with high values of the Human Development Index (HDI), cervical cancer incidence and mortality rates are declining [20].

In some countries with high HDI, racial disparities in disease burden and mortality are common. In the USA, the incidence of and mortality from cervical cancer in African American women was shown to be twice that in White women [21]. These disparities are caused by unequal access to primary prevention (see Chapter 4.6), screening, and treatment services. Compared with other ethnicities, African American girls were less likely to complete

Fig. 5.10.5. The role of promising biomarkers in the molecular mechanisms that lead to a transforming infection. Schematic diagram of molecular and cellular processes that are affected during cervical carcinogenesis after infection with high-risk human papillomavirus (HPV). E6 leads to activation of telomerase-related genes as well as to the ubiquitination of p53. This results in the degradation of p53 and therefore inhibits apoptosis. E7 inactivates pRb and therefore increases the amount of free E2F in the cell, leading to both an increase in p16 and aberrant proliferation (which can be detected by increased levels of Ki-67 expression). In combination with the inactivation of tumour suppressor genes (*CADM1* and *MAL*), these actions lead to the immortalization of the cell. This, in turn, leads to genomic instability, which cannot be counteracted by DNA repair mechanisms because these mechanisms are inactivated by the high-risk HPV oncogenes. Whether viral integration should be considered as an initiator of genomic instability or a result of it is currently unclear. Nevertheless, the mechanisms shown in this flow chart lead to a transforming infection, causing the occurrence of severe dysplasia and ultimately resulting in cervical malignancy.



the three doses of the HPV vaccine required at the time of the study [22]. In the USA, women in minority groups with low socioeconomic status tend to be underinsured, which limits their access to screening and clinical services. When these women are screened, they are more likely to be lost to follow-up and to later present with advanced disease [22]. The geographical location may also play a role in these disparities. Women living in rural areas have the lowest screening rates and the highest incidence rates of cervical cancer, both in countries with low HDI and in countries with high HDI [21].

These disparities across socioeconomic, racial, and ethnic groups have also been documented both in other countries with high HDI and in countries with low HDI (see Chapter 1.3). However, the burden and impact of cervical cancer on communities can be mitigated by implementing national HPV vaccination and screening programmes with effective treatment of high-grade squamous intraepithelial lesions, early detection and treatment of cervical cancer, and improvement of palliative care services for women with advanced disease. These interventions form part of targets and indicators of the WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020 [23].

Prevention

Primary prevention

Remarkable progress has been made worldwide to scale up HPV vaccination, especially in high-income countries (see Chapter 6.3). In the past 5 years, very few low- and middle-income countries have rolled out countrywide HPV vaccination programmes. More countries are preparing to introduce national vaccination programmes with the support of Gavi, the Vaccine Alliance.

For both the bivalent and the quadrivalent HPV vaccine, two doses were shown to be non-inferior to three doses, and WHO now recommends the use of two doses in girls younger than 14 years [24]. There is emerging evidence that one dose of HPV vaccine may be equally efficacious; this will reduce the cost of vaccines and make the delivery of vaccines easier in low- and middle-income countries. The introduction in 2014 of the nonavalent HPV vaccine (against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58) was a significant scientific advance that expanded the number of oncogenic HPV types for which infection is preventable through vaccination. For the nonavalent vaccine, WHO also recommends the use of two doses in girls younger than 14 years.

New HPV vaccines are currently undergoing clinical trials, and they may become available by 2020. However, the insufficient HPV vaccine supply is a major challenge and will remain a constraint in low- and middle-income countries for the foreseeable future.

Secondary prevention

Secondary prevention of cervical cancer with cytology screening has reduced the incidence of cervical cancer in high-income countries.

Large clinical trials have shown that HPV-based screening leads to increased detection of precursor lesions and decreased rates of invasive cervical cancer [25]. WHO and other organizations have recommended primary HPV testing in settings with sufficient resources. The advent of portable point-of-care testing devices will lead to the wide availability of this screening modality and increase its use in low- and middle-income countries.

HPV self-sampling was introduced to overcome known barriers to screening, which include restrictive work schedules as well as cultural and religious beliefs. Therefore, self-sampling has the potential to increase coverage of cervical cancer screening in non-attendees in both high-income and low-income countries. In Argentina, the uptake of screening improved from 20% with cytology-based screening to 86% with the implementation of HPV self-sampling [26]. The diagnostic accuracy of self-collected samples compares favourably with that of clinician-collected specimens.

Improved methods of detection and diagnosis

Biomarkers are also being extensively evaluated for incorporation into cervical cancer screening programmes, to predict which cervical precancerous lesions are likely to progress.

Dual staining with $p16^{INK4a}$ and Ki-67 has shown high sensitivity in detecting high-grade squamous intraepithelial lesions in both cytological and histological specimens [27–29]. Clinically, it can be used to differentiate reactive from dysplastic cervical lesions and to detect high-grade squamous intraepithelial lesions with higher accuracy.

Persistent infection with high-risk HPV results in overexpression of the E6 and E7 viral oncogenes, which leads to cellular proliferation, immortalization, and transformation. The PreTect HPV-Proofer assay and the NucliSENS EasyQ HPV assay are nucleic acid sequence-based amplification tests designed to detect HPV E6/E7 messenger RNA (mRNA) of the five most common oncogenic high-risk HPV types (16, 18, 31, 33, and 45). The APTIMA HPV assay is a target amplification nucleic acid probe test that detects the viral mRNA of 14 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).

In women who have negative cytology and are positive for high-risk HPV, a positive mRNA test result implies an increased risk of progressive lesions compared with a negative mRNA result; mRNA tests showed a higher specificity than DNA tests in detecting high-grade cervical lesions [30]. Clinically, HPV E6/E7 mRNA molecular testing is being incorporated into cervical cancer screening algorithms to triage women who are positive for high-risk HPV and have negative cytology to either immediate colposcopy or close follow-up. Testing for E6/E7 mRNA of high-risk HPV types has also been found to be useful as a test of cure.

Women with HPV16 or HPV18 infection have a much higher risk of developing high-grade squamous intraepithelial lesions compared with women who are positive for other high-risk HPV types and have negative cytology [31]. This finding has been incorporated into cervical cancer screening algorithms to triage women with normal, atypical squamous cells of undetermined significance, and low-grade squamous intraepithelial lesion cytology results to either immediate colposcopy or repeat co-testing after 12 months. This strategy effectively reduces the number of women referred for colposcopy.

Methylation of the cell adhesion molecule 1 (*CADM1*) and T-lymphocyte maturation-associated protein (*MAL*) genes was associated with a high risk of developing CIN3. In cytology samples positive for high-risk HPV, a sensitivity of 70% and a specificity of 78% were demonstrated for the detection of lesions of CIN3 or worse [32,33].

Management of invasive cervical cancer

Microinvasive cervical cancer is typically an incidental histological diagnosis after large loop excision of the transformation zone (type 1 and 2 excision) or cone biopsy (type 3 excision). Macroscopic cervical cancer is often suspected clinically, because most of the women present with a foul-smelling watery and sometimes bloody vaginal discharge, irregular vaginal bleeding, and contact bleeding.

Until recently, FIGO staging of cervical cancer was performed mainly by clinical examination, with a few other procedures that were allowed to change the stage. In 2018, the FIGO Gynecologic Oncology Committee revised this to include imaging and pathology results, where available, to assign the stage. The revised FIGO staging is shown in Table 5.10.5 [34]. FIGO stage IB has now been subdivided into three (instead of two) substages, and lymph node involvement, an important adverse prognostic factor, is now included in FIGO stage IIIC.

Treatment for early-stage disease is surgical. However, concurrent chemoradiotherapy has similar outcomes. In locally advanced disease, concurrent chemoradiotherapy is the treatment of choice. Treatment of women with FIGO stage IVB and recurrent disease is highly individualized. Palliative care remains an important component of management of cervical cancer. Women with advanced disease should have an early referral to a palliative care team. There is a role for fertility-sparing surgery in young women with early-stage disease who desire to become parents. Long-term follow-up is required to detect recurrence.

Table 5.10.5. 2018 International Federation of Gynecology and Obstetrics (FIGO) staging of cancer of the cervix uteri

Stage[a]	Description
I	The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion < 5 mm[b]
IA1	Measured stromal invasion < 3 mm in depth
IA2	Measured stromal invasion ≥ 3 mm and < 5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥ 5 mm (greater than stage IA), lesion limited to the cervix uteri[c]
IB1	Invasive carcinoma with ≥ 5 mm depth of stromal invasion and < 2 cm in greatest dimension
IB2	Invasive carcinoma ≥ 2 cm and < 4 cm in greatest dimension
IB3	Invasive carcinoma ≥ 4 cm in greatest dimension
II	The carcinoma invades beyond the uterus but has not extended into the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two thirds of the vagina, without parametrial involvement
IIA1	Invasive carcinoma < 4 cm in greatest dimension
IIA2	Invasive carcinoma ≥ 4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes[d]
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumour size and extent (with r and p notations)[d]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

[a] When in doubt, the lower staging should be assigned.

[b] Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumour size and extent, in all stages.

[c] The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.

[d] Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be stage IIIC1r, and if confirmed by pathological findings, it would be stage IIIC1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.

References

1. de Martel C, Plummer M, Vignat J, Franceschi S (2017). Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 141(4): 664–70. https://doi.org/10.1002/ijc.30716 PMID:28369882

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593

3. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. (2012). Global burden of human papillomavirus and related diseases. Vaccine. 30(Suppl 5):F12–23. https://doi.org/10.1016/j.vaccine.2012.07.055 PMID:23199955

4. Hall MT, Simms KT, Lew JB, Smith MA, Brotherton JM, Saville M, et al. (2019). The projected timeframe until cervical cancer elimination in Australia: a modelling study. Lancet Public Health. 4(1):e19–27. https://doi.org/10.1016/S2468-2667(18)30183-X PMID:30291040

5. Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors (2014). WHO classification of tumours of the female reproductive organs. Lyon, France: International Agency for Research on Cancer (WHO Classification of Tumours series, 4th edition). Available from: https://publications.iarc.fr/16.

6. Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, et al.; Members of LAST Project Work Groups (2012). The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. J Low Genit Tract Dis. 16(3):205–42. https://doi.org/10.1097/LGT.0b013e31825c31dd PMID:22820980

7. de Sanjosé S, Serrano B, Castellsagué X, Brotons M, Muñoz J, Bruni L, et al. (2012). Human papillomavirus (HPV) and related cancers in the Global Alliance for Vaccines and Immunization (GAVI) countries. A WHO/ICO HPV Information Centre report. Vaccine. 30(Suppl 4):D1–83, vi. https://doi.org/10.1016/S0264-410X(12)01435-1 PMID:23510764

8. Lax SF, Horn LC, Löning T (2016). Categorization of uterine cervix tumors: what's new in the 2014 WHO classification [in German]. Pathologe. 37(6):573–84. https://doi.org/10.1007/s00292-016-0247-8 PMID:27770187

9. Chen D, Juko-Pecirep I, Hammer J, Ivansson E, Enroth S, Gustavsson I, et al. (2013). Genome-wide association study of susceptibility loci for cervical cancer. J Natl Cancer Inst. 105(9):624–33. https://doi.org/10.1093/jnci/djt051 PMID:23482656

10. Shi Y, Li L, Hu Z, Li S, Wang S, Liu J, et al. (2013). A genome-wide association study identifies two new cervical cancer susceptibility loci at 4q12 and 17q12. Nat Genet. 45(8):918–22. https://doi.org/10.1038/ng.2687 PMID:23817570

11. Leo PJ, Madeleine MM, Wang S, Schwartz SM, Newell F, Pettersson-Kymmer U, et al. (2017). Defining the genetic susceptibility to cervical neoplasia – a genome-wide association study. PLoS Genet. 13(8):e1006866. https://doi.org/10.1371/journal.pgen.1006866 PMID:28806749

12. Wright AA, Howitt BE, Myers AP, Dahlberg SE, Palescandolo E, Van Hummelen P, et al. (2013). Oncogenic mutations in cervical cancer: genomic differences between adenocarcinomas and squamous cell carcinomas of the cervix. Cancer. 119(21):3776–83. https://doi.org/10.1002/cncr.28288 PMID:24037752

13. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al.; WHO International Agency for Research on Cancer Monograph Working Group (2009). A review of human carcinogens – Part B: biological agents. Lancet Oncol. 10(4):321–2. https://doi.org/10.1016/S1470-2045(09)70096-8 PMID:19350698

14. Muñoz N (2000). Human papillomavirus and cancer: the epidemiological evidence. J Clin Virol. 19(1–2):1–5. https://doi.org/10.1016/s1386-6532(00)00125-6 PMID:11091143

15. International Collaboration of Epidemiological Studies of Cervical Cancer (2007). Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. Int J Cancer. 120(4):885–91. https://doi.org/10.1002/ijc.22357 PMID:17131323

16. Campitelli M, Jeannot E, Peter M, Lappartient E, Saada S, de la Rochefordière A, et al. (2012). Human papillomavirus mutational insertion: specific marker of circulating tumor DNA in cervical cancer patients. PLoS One. 7(8):e43393. https://doi.org/10.1371/journal.pone.0043393 PMID:22937045

17. Zhou Z, Li W, Zhang F, Hu K (2017). The value of squamous cell carcinoma antigen (SCCa) to determine the lymph nodal metastasis in cervical cancer: a meta-analysis and literature review. PLoS One. 12(12):e0186165. https://doi.org/10.1371/journal.pone.0186165 PMID:29227998

18. Charakorn C, Thadanipon K, Chaijindaratana S, Rattanasiri S, Numthavaj P, Thakkinstian A (2018). The association between serum squamous cell carcinoma antigen and recurrence and survival of patients with cervical squamous cell carcinoma: a systematic review and meta-analysis. Gynecol Oncol. 150(1):190–200. https://doi.org/10.1016/j.ygyno.2018.03.056 PMID:29606483

19. Kong TW, Piao X, Chang SJ, Paek J, Lee Y, Lee EJ, et al. (2016). A predictive model for parametrial invasion in patients with FIGO stage IB cervical cancer: individualized approach for primary treatment. Int J Gynecol Cancer. 26(1):184–91. https://doi.org/10.1097/IGC.0000000000000560 PMID:26512782

20. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015). Global cancer statistics, 2012. CA Cancer J Clin. 65(2):87–108. https://doi.org/10.3322/caac.21262 PMID:25651787

21. Musselwhite LW, Oliveira CM, Kwaramba T, de Paula Pantano N, Smith JS, Fregnani JH, et al. (2016). Racial/ethnic disparities in cervical cancer screening and outcomes. Acta Cytol. 60(6):518–26. https://doi.org/10.1159/000452240 PMID:27825171

22. Chatterjee S, Gupta D, Caputo TA, Holcomb K (2016). Disparities in gynecological malignancies. Front Oncol. 6:36. https://doi.org/10.3389/fonc.2016.00036 PMID:26942126

23. WHO (2013). WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/bitstream/handle/10665/94384/9789241506236_eng.pdf?sequence=1.

24. WHO (2014). Meeting of the Strategic Advisory Group of Experts on immunization, April 2014 – conclusions and recommendations. Wkly Epidemiol Rec. 89(21):221–36. PMID:24864348

25. Ogilvie G, Nakisige C, Huh WK, Mehrotra R, Franco EL, Jeronimo J (2017). Optimizing secondary prevention of cervical cancer: recent advances and future challenges. Int J Gynaecol Obstet. 138(Suppl 1):15–9. https://doi.org/10.1002/ijgo.12187 PMID:28691338

26. Arrossi S, Thouyaret L, Laudi R, Marín O, Ramírez J, Paolino M, et al. (2015). Implementation of HPV-testing for cervical cancer screening in programmatic contexts: the Jujuy demonstration project in Argentina. Int J Cancer. 137(7):1709–18. https://doi.org/10.1002/ijc.29530 PMID:25807897

27. von Knebel Doeberitz M, Reuschenbach M, Schmidt D, Bergeron C (2012). Biomarkers for cervical cancer screening: the role of $p16^{INK4a}$ to highlight transforming HPV infections. Expert Rev Proteomics. 9(2):149–63. https://doi.org/10.1586/epr.12.13 PMID:22462787

28. Petry KU, Schmidt D, Scherbring S, Luyten A, Reinecke-Lüthge A, Bergeron C, et al. (2011). Triaging Pap cytology negative, HPV positive cervical cancer screening results with p16/Ki-67 dual-stained cytology. Gynecol Oncol. 121(3):505–9. https://doi.org/10.1016/j.ygyno.2011.02.033 PMID:21420158

29. Schmidt D, Bergeron C, Denton KJ, Ridder R; European CINtec Cytology Study Group (2011). p16/Ki-67 dual-stain cytology in the triage of ASCUS and LSIL Papanicolaou cytology: results from the European Equivocal or Mildly Abnormal Papanicolaou Cytology Study. Cancer Cytopathol. 119(3):158–66. https://doi.org/10.1002/cncy.20140 PMID:21442767

30. Cattani P, Zannoni GF, Ricci C, D'Onghia S, Trivellizzi IN, Di Franco A, et al. (2009). Clinical performance of human papillomavirus E6 and E7 mRNA testing for high-grade lesions of the cervix. J Clin Microbiol. 47(12):3895–901. https://doi.org/10.1128/JCM.01275-09 PMID:19828739

31. Kitchener HC, Gilham C, Sargent A, Bailey A, Albrow R, Roberts C, et al. (2011). A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: extended follow up in the ARTISTIC trial. Eur J Cancer. 47(6):864–71. https://doi.org/10.1016/j.ejca.2011.01.008 PMID:21334200

32. Overmeer RM, Louwers JA, Meijer CJ, van Kemenade FJ, Hesselink AT, Daalmeijer NF, et al. (2011). Combined CADM1 and MAL promoter methylation analysis to detect (pre-)malignant cervical lesions in high-risk HPV-positive women. Int J Cancer. 129(9):2218–25. https://doi.org/10.1002/ijc.25890 PMID:21190187

33. Hesselink AT, Heideman DA, Steenbergen RD, Coupé VM, Overmeer RM, Rijkaart D, et al. (2011). Combined promoter methylation analysis of CADM1 and MAL: an objective triage tool for high-risk human papillomavirus DNA-positive women. Clin Cancer Res. 17(8):2459–65. https://doi.org/10.1158/1078-0432.CCR-10-2548 PMID:21389098

34. Bhatla N, Berek J, Cuello M, Denny L, Grenman S, Karunaratne K, et al. (2018). New revised FIGO staging of cervical cancer (2018). Abstract S020.2. Presented at the XXII FIGO World Congress of Gynecology and Obstetrics, Rio de Janeiro, Brazil, 14–19 October 2018. Int J Gynecol Obstet. 143(S3):43–157. https://doi.org/10.1002/ijgo.12584

5.11 Endometrial cancer
Prevention through control of obesity

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SUMMARY

- A new classification system that categorizes endometrial cancers on the basis of their molecular characteristics – microsatellite instability, *POLE* mutation, no specific molecular features, or *TP53* mutation – provides improved prognostic information, but the implications for etiology are not yet known.
- Although distinct in terms of their histology and clinical outcomes, high-grade type 2 endometrial cancers are not estrogen-independent, as previously considered, but share many risk factors with the more common type 1 endometrial cancers, including factors associated with estrogen exposure.
- Approximately one third of endometrial cancers can be attributed to overweight and obesity and a smaller proportion to physical inactivity; therefore, effective interventions to reduce the prevalence of obesity and increase physical activity levels are likely to have the greatest impact on incidence rates.
- Progestin-containing intrauterine devices, metformin, and, possibly, non-steroidal anti-inflammatory drugs may reduce incidence of endometrial cancer in high-risk women, but the full range of risks and benefits of these potential chemopreventive agents is not yet clear.

It is now more than 40 years since the publication of the first reports of an association between use of estrogen replacement therapy and risk of endometrial cancer, and 35 years since endometrial cancers were classified as either estrogen-dependent (type 1) or estrogen-independent (type 2).

During the decades after this seminal work, endometrial cancer attracted less research interest than cancer types that are more common and more deadly. However, rising incidence rates and a greater focus on the rarer but more aggressive type 2 endometrial cancers have changed this. In the past 5–10 years, there have been major shifts in the understanding of both the molecular biology and the etiology of endometrial cancer.

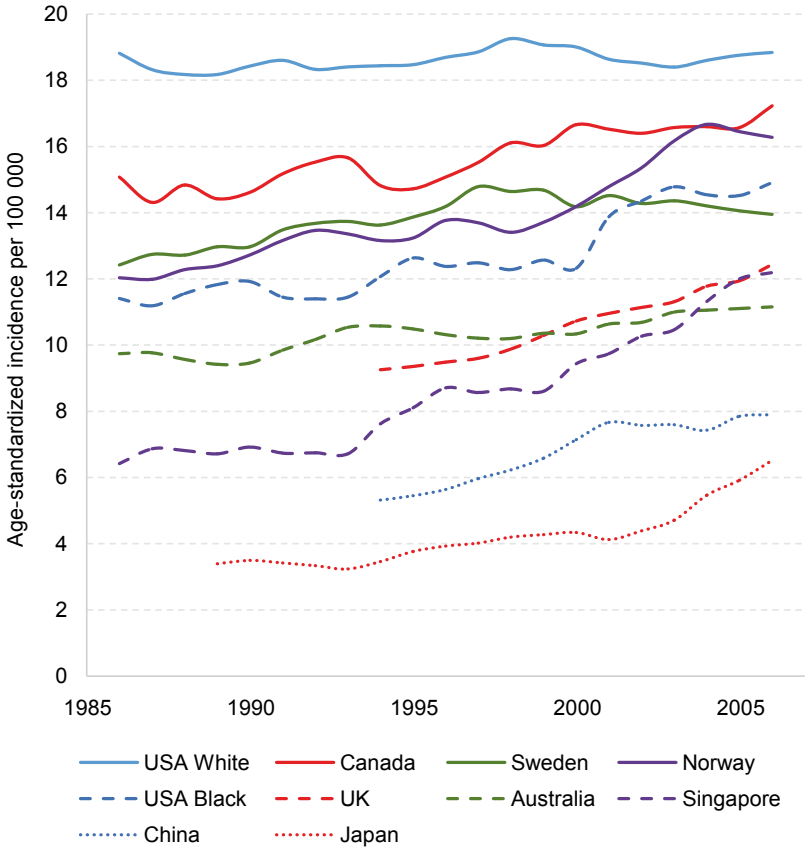
Epidemiology

Globally, uterine cancer is the seventh most common cancer and the 14th most common cause of cancer death in women, with an estimated 382 000 new cases and 90 000 deaths in 2018. Age-standardized incidence rates (per 100 000) vary about 12-fold between countries, from 2 to 24, although in a few countries the reported rates are lower (e.g. 1.5 in Guinea and 1.8 in Mongolia) or higher (e.g. 24.1 in Lithuania and 24.9 in Belarus). The rates are generally lowest in Africa and Asia and highest in Europe and North America [1]. They increase with increasing sociodemographic index (a measure of development based on income, education, and fertility rates); almost three quarters of cases occur in the top two quintiles [2].

Incidence rates of endometrial cancer are increasing, both over time and in successive birth cohorts. Some of the most rapid increases have been seen in countries that have undergone rapid socioeconomic transitions (see Chapter 1.3), such as Japan and Singapore (Fig. 5.11.1) [1]. Interpreting these trends is challenging, because of the multiple external influences on risk and the varying hysterectomy rates, but the increasing prevalence of obesity is likely to be a major contributor (see Chapter 2.7).

Some reports suggest that incidence rates are increasing more rapidly for type 1 cancers; this is consistent with the change being driven by the prevalence of obesity. However, in Denmark increases have been reported in the incidence of type 2 cancers, despite an overall decline in the incidence of endometrial cancer [3]. In the USA, incidence rates of type 2 cancers have also increased more rapidly than those of type 1 cancers, with marked increases in Asian women and particularly in non-Hispanic Black women, who now have the highest rates of these more aggressive endometrial cancers [4].

Fig. 5.11.1. Age-standardized (World) incidence rates per 100 000 person-years by calendar year in selected countries for uterine cancer.



FUNDAMENTALS

- Endometrial cancers, which arise in the lining of the uterus (endometrium), comprise approximately 90% of all uterine cancers.
- Although there is no screening test, endometrial cancers commonly cause abnormal vaginal bleeding or discharge; as a result, a high proportion are diagnosed at an early stage, and 10-year survival rates are about 80%.
- Historically, endometrial cancer is classified into two major types. The more common type 1 cancers, also described as estrogen-dependent, are low-grade endometrioid tumours that arise on a background of endometrial hyperplasia. The less common type 2 cancers, initially labelled estrogen-independent, are typically high-grade serous and clear cell tumours that arise in an atrophic endometrium.
- Type 1 cancers are strongly associated with exposure to estrogen unopposed by a progestogen.
- Well-established risk factors for type 1 cancers include conditions associated with greater endogenous estrogen exposure (obesity, early age at menarche, late age at menopause) or exogenous estrogen exposure (use of menopausal estrogen therapy, use of tamoxifen).
- Factors associated with higher progestogen exposure (pregnancy, use of oral contraceptives) are associated with reduced risk.

Genetics and genomics

Single-gene defects

Endometrial cancer is associated with Lynch syndrome, a hereditary cancer syndrome that is characterized by mutations in the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* or a nearby gene, *EPCAM*, that causes epigenetic silencing of *MSH2*. Women with a germline mutation in one of these genes have a 16–71% increased risk of developing endometrial cancer before age 70 years, and the cancers typically develop at a younger age than in the general population [5]. Women with Cowden syndrome, which is characterized by mutations in the *PTEN* tumour suppressor gene, are also at increased risk of endometrial cancer [5].

Low-risk genetic variants

Having a first-degree relative with endometrial cancer approximately doubles a woman's risk of the disease, but the high-risk genetic mutations described above account for only a small proportion of this risk, suggesting that other, low-risk genes also play a role. Until recently, few such genes had been identified for endometrial cancer, but large-scale genome-wide association studies (see Chapter 3.2) have now identified 16 genetic loci associated with endometrial cancer [6]. These include *HNF1B*, *CYP19A1* (which encodes the aromatase enzyme that converts androgens to estrogens), and the *MYC* multicancer locus.

Somatic changes and molecular subtypes

In addition to the rare germline mismatch repair gene and *PTEN* mutations described above, somatic mutations in these genes and also epigenetic silencing of the *MSH2* promoter through methylation are

common events in endometrial cancer. Other genes that are frequently mutated include *PIK3CA*, *KRAS*, *CTNNB1* (which encodes β-catenin), *ARID1A*, and *TP53*. In 2013, the Cancer Genome Atlas published a comprehensive analysis of the genomic changes in endometrial cancers, in which they identified four subsets of endometrial cancers with differing molecular profiles [7] (Table 5.11.1).

Approximately 25% of endometrial cancers, including a high proportion of high-grade endometrioid tumours, have defective mismatch repair capability, leading to microsatellite instability. In addition, about 10% have a very high overall mutation frequency, including mutations in the exonuclease domain of the *POLE* gene (which encodes DNA polymerase ε). The third and largest group comprises mainly low-grade endometrioid tumours that have no specific molecular features, although *PTEN* mutations are common in this group and in the first two groups. The fourth group, which includes high-grade serous tumours and carcinosarcomas as well as one quarter of high-grade endometrioid cancers, is characterized by high copy number and *TP53* mutation.

The historical classification of endometrial cancer into two types has long been fraught with problems, largely because these groups are defined based on the suspected etiology of the cancer and do not clearly link to its pathological characteristics or prognosis. Also, although the histology and grade of endometrial cancers are used to determine treatment, this classification has poor reproducibility and does not reliably predict risk of recurrence, particularly within the large group of endometrioid cancers, for which outcomes can be very variable. Therefore, the new molecular classification is a major step forward, because it is reproducible and, importantly, differentiates between histologically similar cancers that have very different prognosis [8]. However, it is not yet clear whether it will have any etiological relevance.

Etiology

Table 5.11.2 summarizes factors known or suspected to increase or decrease risk of endometrial cancer.

It has long been recognized that factors associated with increased exposure to estrogen in the absence of a progestogen increase the risk of type 1 endometrial cancer; it is now clear that the major risk factors for type 2 cancers are very similar (Fig. 5.11.2), although the relationship with obesity is somewhat weaker [9]. This suggests that, despite their initial description as estrogen-independent, type 2 cancers are also hormonally driven, although perhaps to a lesser extent than type 1 cancers. There have not yet been any comprehensive studies comparing risk factors for the various molecular subtypes discussed above.

Reproductive factors

In addition to the strong inverse association with increasing parity, recent large-scale analyses have shown that risk also decreases by 13% for every 5-year increase in age at last birth [10] and by 3% for every 3 months that a woman breastfeeds her children [11]. In contrast, a self-reported history of infertility has been associated with a 20% increase in risk [12].

Exogenous hormones

Risk of endometrial cancer is reduced by about 24% for every 5 years of using oral contraceptives; the effects are seen for both type 1 and type 2 cancers, and, notably, the

Table 5.11.1. Molecular subtypes of endometrial cancer

TCGA label	MSI (hypermutated)	*POLE* (ultramutated)	Copy-number low	Copy-number high (serous-like)
ProMisE label	MMR-deficient	*POLE*-EDM	p53 wild-type	p53-aberrant
Leiden/TransPORTEC label	MSI	*POLE*	NSMP	p53
Defining characteristic	Mutation (germline or somatic) or epigenetic modification of *MLH1*, *MSH2*, *MSH6*, or *PMS2*, leading to MMR deficiency and MSI	Mutation in exonuclease domain of *POLE* DNA polymerase	Microsatellite stable, no *POLE* or *TP53* mutation	*TP53* mutation
Common mutations	*PTEN* (~90%) *PIK3CA* (~50%)	*POLE* (100%) *PTEN* (> 90%)	*PTEN* (~75%) *PIK3CA* (~50%)	*TP53* (>90%) *PIK3CA* (~50%) [*PTEN* (~10%)]
Proportion of cancers	~25%	~10%	~40%	~25%
Typical histology	High-grade endometrioid	High-grade endometrioid	Low-grade endometrioid	Serous, carcinosarcoma
Prognosis	Intermediate	Excellent	Intermediate	Poor

EDM, exonuclease domain mutation; MMR, mismatch repair; MSI, microsatellite instability; NSMP, no specific molecular profile; ProMisE, Proactive Molecular Risk Classifier for Endometrial Cancer; TCGA, Cancer Genome Atlas Research Network.

Table 5.11.2. Factors associated with risk of endometrial cancer

Strength of evidence	Factors that increase risk	Factors that decrease risk
Convincing	Family history	Pregnancy
	Use of estrogen replacement therapy	Older age at last birth
	Use of sequential estrogen plus progestin (combination) menopausal hormone therapy (progestin for < 10 days/month)	Use of oral contraceptives
	Use of tamoxifen	
	Body fatness	
	Diabetes	
	Early age at menarche	
	Late age at menopause	
	Infertility	
Probable	Metabolic syndrome	Use of progestin-containing intrauterine devices
	Hypertension	Use of continuous estrogen plus progestin (combination) menopausal hormone therapy (progestin for ≥ 25 days/month)
	Polycystic ovary syndrome	Breastfeeding
	High glycaemic load	Physical activity
	Adult height	Coffee consumption
Possible	Sedentary behaviour	Use of metformin
		Use of aspirin or other non-steroidal anti-inflammatory drugs
		Use of bisphosphonates
Insufficient	Treatment for infertility; endometriosis; use of statins; other aspects of diet	

benefit persists for at least 30 years after last use [13]. Despite reductions in the hormone content of oral contraceptives since their introduction, the effects appear to be similar for formulations used in the 1960s, 1970s, and 1980s [13]. It is too soon to say whether use of newer formulations, including progestin-only oral contraceptives, will reduce risk to the same extent, but early data suggest that progestin-containing intrauterine devices (e.g. the levonorgestrel-releasing intrauterine system) also protect against endometrial cancer [14].

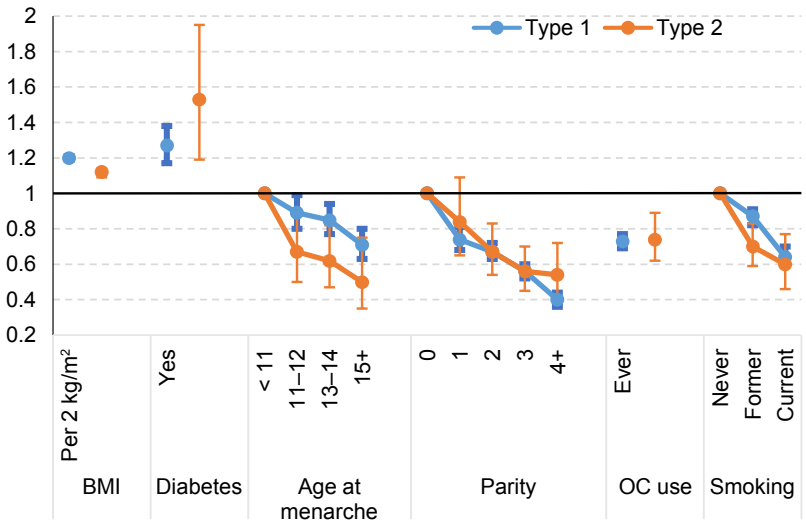
Use of estrogen replacement therapy (unopposed estrogen therapy) and use of sequential estrogen plus progestin (combination) menopausal hormone therapy (progestin for < 10–15 days per month) are associated with an increased risk of endometrial cancer, and this increase in risk may be greater in thin women and normal-weight women, who have lower endogenous estrogen levels. In contrast, use of continuous estrogen plus progestin therapy (progestin for ≥ 25 days per month) has been associated with a reduced risk of endometrial cancer [15]. (See also Chapter 3.6.)

Increasing use of fertility drugs has raised concerns about their potential effects on cancer risk. Although there are suggestions that women who use clomiphene citrate may have an increased risk of endometrial cancer, the current evidence is limited and it is not possible to separate any potential risk associated with use of the medication from that associated with the underlying cause of the infertility [16]. (See also Chapter 2.11.)

Body size and physical activity

In postmenopausal women, the primary source of estrogen is from conversion of androgens to estrogens by aromatase in adipose tissue. Risk

Fig. 5.11.2. A comparison of risk factors for type 1 and type 2 endometrial cancer, showing odds ratios with 95% confidence intervals, from the Epidemiology of Endometrial Cancer Consortium. BMI, body mass index; OC, oral contraceptive.



of endometrial cancer increases by about 50% for every increase of 5 kg/m^2 in body mass index (BMI), with stronger associations seen for type 1 cancers than for type 2 cancers (Fig. 5.11.2). However, the relationship is nonlinear and risk increases more steeply at higher BMI (risks for BMI of 30, 35, and 40 kg/m^2 are approximately 2-, 4-, and 13-fold those for BMI of 20 kg/m^2) [17]. The effect is stronger among premenopausal women and those who have not used menopausal hormone therapy.

Similar patterns are seen for other measures of obesity, including waist circumference, hip circumference, waist-to-hip ratio, and weight gain in adulthood. Greater height has also been associated with greater risk, but it is unlikely that this is a causal relationship; rather, adult height is probably a marker for a range of other genetic factors and non-genetic factors (e.g. nutritional status, hormones) before and around menarche [18].

Independent of its effect on obesity, there is now evidence that physical activity of all types (recreational, occupational, and household) probably reduces risk of endometrial cancer, and a suggestion that more time spent sedentary may increase risk [18].

Diet

Data from prospective studies suggest that a diet with a high glycaemic load probably increases risk of endometrial cancer by approximately 15% per 50 units per day, whereas consumption of coffee (caffeinated and decaffeinated) reduces risk by approximately 7% per cup per day [18]. Although previous reports suggested a possible positive association with intake of red meat and an inverse association with intake of non-starchy vegetables, the current data do not support this, and there is little evidence that other components of diet, including fat, fibre, or soy products, which contain phytoestrogens, play an independent role in the etiology of endometrial cancer [18].

Alcohol consumption and tobacco smoking

Although alcohol intake has been associated with higher estrogen levels and with an increased risk of breast cancer (see Chapter 5.9), there is little evidence to suggest that moderate consumption increases risk of endometrial cancer [18]. Endometrial cancer is one of the few conditions that is less common among smokers, with inverse associations reported for both type 1 and type 2 cancers. This has been attributed to the fact that smokers tend to have lower endogenous estrogen levels than non-smokers [9].

Medical conditions and use of medication

Diabetes and metabolic syndrome

Metabolic syndrome describes a cluster of related metabolic conditions, including abdominal obesity, high blood pressure, impaired fasting glucose or diabetes, high levels of serum triglycerides, and low levels of high-density lipoprotein; the presence of three of these conditions is sufficient for a diagnosis. Of all of these conditions, obesity is most strongly associated with risk of endometrial cancer, but metabolic syndrome, impaired glucose tolerance or diabetes, and hypertension appear to increase risk by an additional 20–40%, independently of any underlying obesity [19].

Endometriosis, polycystic ovary syndrome, and fibroids

The relationship between a history of endometriosis and risk of endometrial cancer is not clear, but there is significant genetic overlap between the two conditions, suggesting that women who are genetically predisposed to developing endometriosis may also be at increased risk of endometrial cancer (see Chapter 3.5) [20]. Other conditions, including polycystic ovary syndrome and fibroids, have been more consistently associated with risk of endometrial cancer, possibly because both conditions are associated with elevated estrogen levels.

Common medications

There has been much interest in the potential chemopreventive effects of non-steroidal anti-inflammatory drugs (NSAIDs) and of medications used to treat diabetes, specifically metformin, and hypercholesterolaemia, namely statins. Regular use – usually defined as at least once per week – of aspirin and, potentially, other NSAIDs has been associated with a reduced risk of endometrial

cancer among obese women; little effect was seen for normal-weight women [21]. It is less clear whether any association is restricted to standard-dose aspirin or whether use of low-dose formulations may also confer a benefit. An effect is plausible because both aspirin and other NSAIDs inhibit cyclooxygenase (COX) activity, leading to a reduction in prostaglandin levels, and COX inhibitors also downregulate aromatase activity in breast cancer cell lines.

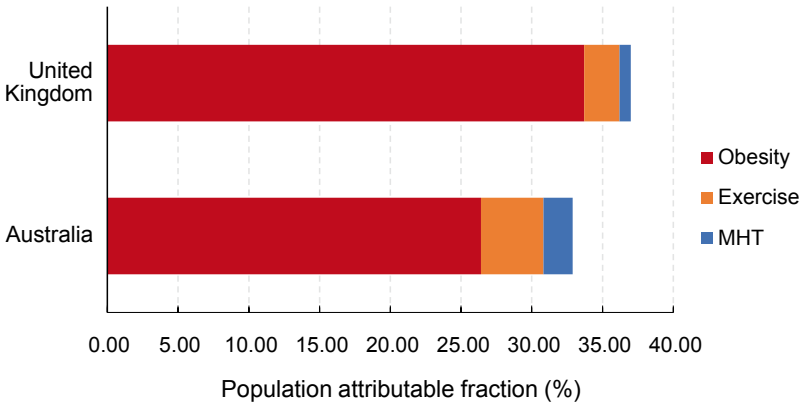
Use of metformin has been reported to reverse endometrial hyperplasia, the precursor of type 1 endometrial cancer, but the current data are very heterogeneous [22]. Although use of statins at baseline was associated with a significantly reduced risk of endometrial cancer during follow-up of the Women's Health Initiative cohorts, there was no association when information about statin use was updated during follow-up [23]. Use of bisphosphonates, which are used to treat osteoporosis, has also been associated with reduced risk of endometrial cancer. The heterogeneous results, the challenges of interpreting observational data on use of medications because they may be subject to confounding by indication, and the lack of trial data mean that further evidence is required before firm conclusions can be drawn about any potential benefits of these medications.

Population attributable risks

Estimates from the United Kingdom, Australia, and globally suggest that between 30% and 40% of endometrial cancers can be attributed to potentially modifiable factors (Fig. 5.11.3). The greatest proportion is attributable to overweight and obesity (26–34%), and smaller proportions are attributable to physical inactivity (4–6%) and use of menopausal hormone therapy (1–3%) [24].

Given that more recent data suggest additional protection from breastfeeding, it is possible that more cancers could be prevented if all parous women breastfed their children for at least 6 months. It has been estimated that use of oral contraceptives prevents approximately 31% of endometrial cancers [24] and that in high-income countries, it prevented approximately 200 000 endometrial cancers in women younger than 75 years in the 10 years from 2005 to 2014 [13].

Fig. 5.11.3. Population attributable fractions for endometrial cancer in the United Kingdom and Australia for overweight and obesity, insufficient physical activity (exercise), and use of menopausal hormone therapy (MHT).



Prevention

The most effective way to prevent endometrial cancer is surgery to remove the uterus (hysterectomy), and this is an option for women at high risk who have completed their family. Greater screening for Lynch syndrome, for example by testing all those diagnosed with colorectal cancer or endometrial cancer and cascade testing of family members, would identify more carriers of high-risk mutations. However, there is currently no screening test for endometrial cancer that could be used in this group (although regular colorectal cancer screening would reduce their risk of colorectal cancer).

Behaviour change

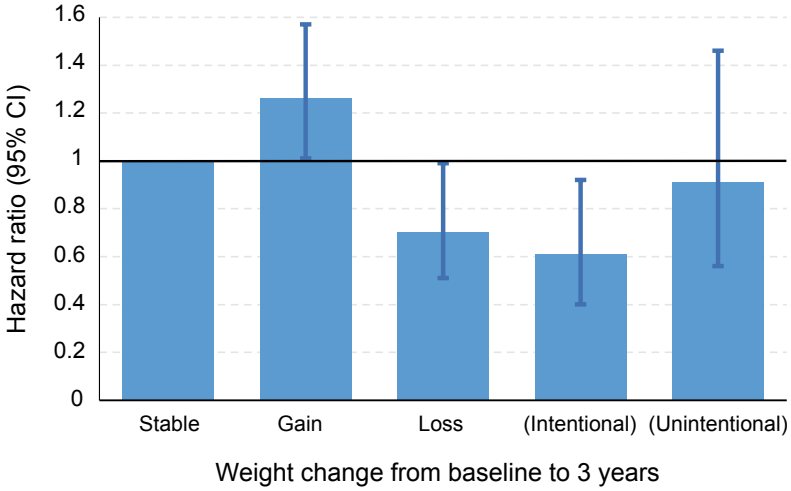
There is increasing evidence that intentional weight loss greatly reduces risk of endometrial cancer (Fig. 5.11.4), and benefits are also seen for those who undergo bariatric surgery [25]. Therefore, interventions that reduce the prevalence of obesity, whether by preventing young women from becoming obese or by encouraging weight loss among women who are already obese, have the greatest potential to reduce risk of endometrial cancer. It is also likely that increasing physical activity levels would have a beneficial effect, both independently and through the effects of exercise on body weight (see Chapter 6.1).

However, preventing the one third of endometrial cancers attributable to obesity would require all women to achieve and maintain a healthy weight – a highly implausible scenario. Under more plausible weight-loss scenarios, the numbers of cases prevented would be much lower. For example, an study in Australia estimated that if the proportion of women who are obese decreased by 10% every year for 10 years and the proportion who are overweight decreased by 5% every year for 10 years, this would prevent 11–18% of endometrial cancers over a 25-year period [26].

Chemoprevention

Use of oral contraceptives cannot be widely recommended for prevention of endometrial cancer, because current users are at increased risk of breast cancer. Progestin-containing intrauterine devices (e.g. the levonorgestrel-releasing intrauterine system), which supply hormones directly to the gynaecological tract, might provide similar gynaecological protection without increasing risk of breast

Fig. 5.11.4. Hazard ratios and 95% confidence intervals for the association between weight change and risk of endometrial cancer in women who gained or lost at least 10 pounds (4.54 kg) over a 3-year period, from the Women's Health Initiative observational study. Weight loss is further separated into intentional and unintentional weight loss.



cancer. An early report suggests that they also increase risk of breast cancer [14], but the current data are restricted to women younger than 55 years so they do not capture the full range of risks and benefits, which, for endometrial cancer, are not likely to be apparent until users reach their 60s and 70s, when endometrial cancer is more common.

Trials are under way to assess whether progestin-containing intrauterine devices, and also metformin, could be used to prevent endometrial cancer in very obese women, who are at greatest risk. If the inverse association between use of aspirin or other NSAIDs and risk of endometrial cancer in obese women is confirmed, this could provide another opportunity for prevention.

References

1. Lortet-Tieulent J, Ferlay J, Bray F, Jemal A (2018). International patterns and trends in endometrial cancer incidence, 1978–2013. J Natl Cancer Inst. 110(4):354–61. https://doi.org/10.1093/jnci/djx214 PMID:29045681
2. Global Burden of Disease Cancer Collaboration (2017). Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol. 3(4):524–48. https://doi.org/10.1001/jamaoncol.2016.5688 PMID:27918777
3. Faber MT, Frederiksen K, Jensen A, Aarslev PB, Kjaer SK (2017). Time trends in the incidence of hysterectomy-corrected overall, type 1 and type 2 endometrial cancer in Denmark 1978–2014. Gynecol Oncol. 146(2):359–67. https://doi.org/10.1016/j.ygyno.2017.05.015 PMID:28545689
4. Cote ML, Ruterbusch JJ, Olson SH, Lu K, Ali-Fehmi R (2015). The growing burden of endometrial cancer: a major racial disparity affecting Black women. Cancer Epidemiol Biomarkers Prev. 24(9):1407–15. https://doi.org/10.1158/1055-9965.EPI-15-0316 PMID:26290568
5. Spurdle AB, Bowman MA, Shamsani J, Kirk J (2017). Endometrial cancer gene panels: clinical diagnostic vs research germline DNA testing. Mod Pathol. 30(8):1048–68. https://doi.org/10.1038/modpathol.2017.20 PMID:28452373
6. O'Mara TA, Glubb DM, Amant F, Annibali D, Ashton K, Attia J, et al. (2018). Identification of nine new susceptibility loci for endometrial cancer. Nat Commun. 9(1):3166. https://doi.org/10.1038/s41467-018-05427-7 PMID:30093612
7. Getz G, Gabriel SB, Cibulskis K, Lander E, Sivachenko A, Sougnez C, et al.; Cancer Genome Atlas Research Network (2013). Integrated genomic characterization of endometrial carcinoma. Nature. 497(7447):67–73. https://doi.org/10.1038/nature12113 PMID:23636398
8. McAlpine J, Leon-Castillo A, Bosse T (2018). The rise of a novel classification system for endometrial carcinoma; integration of molecular subclasses. J Pathol. 244(5):538–49. https://doi.org/10.1002/path.5034 PMID:29344951
9. Setiawan VW, Yang HP, Pike MC, McCann SE, Yu H, Xiang YB, et al.; Australian National Endometrial Cancer Study Group (2013). Type I and II endometrial cancers: have they different risk factors? J Clin Oncol. 31(20):2607–18. https://doi.org/10.1200/JCO.2012.48.2596 PMID:23733771
10. Setiawan VW, Pike MC, Karageorgi S, Deming SL, Anderson K, Bernstein L, et al.; Australian National Endometrial Cancer Study Group (2012). Age at last birth in relation to risk of endometrial cancer: pooled analysis in the Epidemiology of Endometrial Cancer Consortium. Am J Epidemiol. 176(4):269–78. https://doi.org/10.1093/aje/kws129 PMID:22831825
11. Jordan SJ, Na R, Johnatty SE, Wise LA, Adami HO, Brinton LA, et al. (2017). Breastfeeding and endometrial cancer risk: an analysis from the Epidemiology of Endometrial Cancer Consortium. Obstet Gynecol. 129(6):1059–67. https://doi.org/10.1097/AOG.0000000000002057 PMID:28486362
12. Yang HP, Cook LS, Weiderpass E, Adami HO, Anderson KE, Cai H, et al. (2015). Infertility and incident endometrial cancer risk: a pooled analysis from the Epidemiology of Endometrial Cancer Consortium (E2C2). Br J Cancer. 112(5):925–33. https://doi.org/10.1038/bjc.2015.24 PMID:25688738
13. Collaborative Group on Epidemiological Studies on Endometrial Cancer (2015). Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 16(9):1061–70. https://doi.org/10.1016/S1470-2045(15)00212-0 PMID:26254030
14. Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J, Pukkala E (2014). Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. Obstet Gynecol. 124(2 Pt 1):292–9. https://doi.org/10.1097/AOG.0000000000000356 PMID:25004338
15. Brinton LA, Felix AS (2014). Menopausal hormone therapy and risk of endometrial cancer. J Steroid Biochem Mol Biol. 142:83–9. https://doi.org/10.1016/j.jsbmb.2013.05.001 PMID:23680641

16. Skalkidou A, Sergentanis TN, Gialamas SP, Georgakis MK, Psaltopoulou T, Trivella M, et al. (2017). Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility. Cochrane Database Syst Rev. 3:CD010931. https://doi.org/10.1002/14651858.CD010931.pub2 PMID:28349511

17. Aune D, Navarro Rosenblatt DA, Chan DS, Vingeliene S, Abar L, Vieira AR, et al. (2015). Anthropometric factors and endometrial cancer risk: a systematic review and dose-response meta-analysis of prospective studies. Ann Oncol. 26(8):1635–48. https://doi.org/10.1093/annonc/mdv142 PMID:25791635

18. WCRF/AICR (2018). Diet, nutrition, physical activity and endometrial cancer. Continuous Update Project Expert Report 2018. World Cancer Research Fund/American Institute for Cancer Research. Available from: https://www.wcrf.org/sites/default/files/Endometrial-cancer-report.pdf.

19. Trabert B, Wentzensen N, Felix AS, Yang HP, Sherman ME, Brinton LA (2015). Metabolic syndrome and risk of endometrial cancer in the United States: a study in the SEER-Medicare linked database. Cancer Epidemiol Biomarkers Prev. 24(1):261–7. https://doi.org/10.1158/1055-9965.EPI-14-0923 PMID:25587111

20. Painter JN, O'Mara TA, Morris AP, Cheng THT, Gorman M, Martin L, et al. (2018). Genetic overlap between endometriosis and endometrial cancer: evidence from cross-disease genetic correlation and GWAS meta-analyses. Cancer Med. 7(5):1978–87. https://doi.org/10.1002/cam4.1445 PMID:29608257

21. Verdoodt F, Kjaer SK, Friis S (2017). Influence of aspirin and non-aspirin NSAID use on ovarian and endometrial cancer: summary of epidemiologic evidence of cancer risk and prognosis. Maturitas. 100:1–7. https://doi.org/10.1016/j.maturitas.2017.03.001 PMID:28539172

22. Chu D, Wu J, Wang K, Zhao M, Wang C, Li L, et al. (2018). Effect of metformin use on the risk and prognosis of endometrial cancer: a systematic review and meta-analysis. BMC Cancer. 18(1):438. https://doi.org/10.1186/s12885-018-4334-5 PMID:29669520

23. Desai P, Wallace R, Anderson ML, Howard BV, Ray RM, Wu C, et al. (2018). An analysis of the association between statin use and risk of endometrial and ovarian cancers in the Women's Health Initiative. Gynecol Oncol. 148(3):540–6. https://doi.org/10.1016/j.ygyno.2018.01.006 PMID:29422345

24. Whiteman DC, Webb PM, Green AC, Neale RE, Fritschi L, Bain CJ, et al. (2015). Cancers in Australia in 2010 attributable to modifiable factors: summary and conclusions. Aust N Z J Public Health. 39(5):477–84. https://doi.org/10.1111/1753-6405.12471 PMID:26437735

25. Luo J, Chlebowski RT, Hendryx M, Rohan T, Wactawski-Wende J, Thomson CA, et al. (2017). Intentional weight loss and endometrial cancer risk. J Clin Oncol. 35(11):1189–93. https://doi.org/10.1200/JCO.2016.70.5822 PMID:28165909

26. Wilson LF, Baade PD, Green AC, Jordan SJ, Kendall BJ, Neale RE, et al. (2019). The impact of changing the prevalence of overweight/obesity and physical inactivity in Australia: an estimate of the proportion of potentially avoidable cancers 2013–2037. Int J Cancer. 144(9):2088–98. https://doi.org/10.1002/ijc.31943 PMID:30357816

5.12 Ovarian cancer
Complicated etiology and very few preventive options

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SUMMARY

- Accumulating evidence suggests that the majority of "ovarian" carcinomas are of extra-ovarian origin, originating in the fallopian tube from serous tubal intraepithelial carcinomas for tumours with serous histotype, from endometrial cells for endometrioid and clear cell tumours, and from the gastrointestinal mucosa and tubal-peritoneal junction for mucinous tumours.
- To date, there are no effective early detection methods, especially for the aggressive disease subtypes, although preliminary results with markers based on detection of tumour DNA in tissue close to the ovary, for example using Pap or Tao brushes, hold promise.
- Primary prevention of ovarian cancer remains a challenge, given that the disease has relatively few known modifiable risk factors, particularly for the predominant, and lethal, high-grade serous subtype. Bilateral salpingectomy is of increasing interest for prevention, including in women at average risk who are undergoing sterilization or hysterectomy.

Ovarian cancer is frequently aggressive and is generally detected at a late stage. It is the eighth most common cause of cancer death in women worldwide, and the fifth most common cause of cancer death in women in Australia, North America, and western Europe.

In high-income countries, more than 90% of ovarian cancers are carcinomas (i.e. derived from epithelial cells), and the remainder are germ cell tumours and sex cord stromal tumours. The vast majority of ovarian neoplasms are invasive carcinomas; 10–15% are classified as borderline tumours, which present without invasion into the stroma. This chapter focuses on invasive carcinomas.

On the basis of tumour histology and grade, epithelial ovarian carcinomas are classified into histopathological subtypes, or histotypes, with diverse somatic mutation profiles, responses to chemotherapy, and prognosis (Table 5.12.1) and diverse risk factors (Table 5.12.2). These histotypes are considered distinct diseases. The five major subtypes are high-grade serous (~60%), endometrioid (~10%), clear cell (~10%), mucinous (~3%), and low-grade serous (< 5%) ovarian carcinomas. High-grade serous carcinomas are poorly differentiated tumours with high response to chemotherapy but very poor survival. In contrast, endometrioid, low-grade serous, and mucinous carcinomas are generally well-differentiated low-grade tumours with lower response to chemotherapy but favourable prognosis, whereas clear cell tumours are generally high-grade but with intermediate prognosis.

The cell of origin of ovarian carcinomas has been a topic of long-standing controversy. It was long held that ovarian carcinomas develop through neoplastic transformation of the ovarian surface epithelium, favoured by the repeated rupture and repair of the surface epithelium through successive menstrual cycles (the "incessant ovulation" hypothesis) [1]. This theory received support from epidemiological observations that the risk of ovarian cancer is significantly lower in women with a lower cumulative number of lifetime ovulatory cycles as a result of high parity or use of oral contraceptives.

The theory implied that all ovarian carcinomas should have a common cell of origin in the ovarian surface epithelium, which is mesothelial in origin, but provided no direct explanation for the histological diversity of ovarian carcinomas, or for their resemblance to tumours arising in organs that are embryologically derived from the Müllerian ducts, such as the fallopian tubes, endometrium, and vagina. Furthermore, extensive pathological searches generally failed to identify convincing precursor lesions within the ovaries.

There is a growing consensus that ovarian carcinomas derive largely from cells originating in extra-ovarian tissue. This paradigm shift regarding the origins of ovarian cancer

has major implications for strategies for prevention and early detection.

Extensive evidence has accumulated that a large proportion of high-grade serous carcinomas develop from fallopian tube epithelium, a tissue with morphology and genetic and immunohistochemical expression profiles that are similar to those of high-grade serous tumours. Putative precursor lesions for high-grade serous tumours, called serous tubal intraepithelial carcinomas, were first identified at the fimbriated end of fallopian tubes removed prophylactically from high-risk women carrying *BRCA1* or *BRCA2* mutations [2], whereas similar lesions were not found in the ovaries. Subsequent studies identified serous tubal intraepithelial carcinomas in 50–60% of women with sporadic ovarian carcinomas [3] and showed that tumour-specific molecular features such as DNA mutation patterns were mostly shared between serous tubal intraepithelial carcinomas and concurrent high-grade serous carcinomas, implying that serous tubal intraepithelial carcinomas are the origin [4,5].

Although up to 70% of high-grade serous carcinomas potentially arise from fallopian tube fimbria, a subset may also derive from tube-like epithelium found outside the fallopian tube, from small cortical inclusion cysts that are found on the ovarian surface and that are lined with tubal-type epithelium. It is still debated whether the tubal-like epithelium in these cysts derives from implantation of tubal epithelium (i.e. endosalpingiosis) or is formed through metaplasia of the ovarian surface epithelium, or both [6,7].

Invasive low-grade serous tumours are also thought to derive from fallopian tube tissue, developing stepwise from benign hyperplastic lesions referred to as atypical proliferative serous tumours (also known as serous borderline tumours) [8]. In contrast, endometrioid and clear cell carcinomas are both thought to arise from endometrial tissue cells. Results from clinicopathological [9] and epidemiological studies [10,11] have shown associations between both tumour types and endometriosis as well as similarities in molecular genetic profiles of endometrioid and clear cell carcinomas and contiguous endometriotic cysts [12].

The origins of mucinous ovarian carcinomas are perhaps least well understood. These tumours are hypothesized to originate from the gastrointestinal mucosa or transitional-type epithelium at the tubal-peritoneal junction [8].

Epidemiology

Ovarian cancer is a relatively rare cancer, with an estimated 295 414 new cases (3.4% of all incident cancers in women) worldwide in 2018 [13]. However, it is a lethal malignancy, because it is predominantly diagnosed at a late stage. Incidence rates vary by region; the lowest rates (4.7 per 100 000) are observed in the WHO African Region, and the highest rates (9.1 per 100 000) are observed in the WHO European Region (Fig. 5.12.1). Mortality rates also vary across the world (Fig. 5.12.2).

In general, incidence rates have been stable over recent decades, with slight decreases noted in North America and areas of western and northern Europe, and increases observed in parts of eastern Europe (Latvia and Poland) [14] (Fig. 5.12.3). Invasive serous carcinomas are the predominant histotype worldwide. However, there is regional variation in the distribution of ovarian tumours by histotype, with a higher proportion of clear cell carcinomas and a lower proportion of serous carcinomas in countries in Asia, relative to other regions [14].

Genetics and genomics

Germline *BRCA1* and *BRCA2* mutations are observed in up to 15% of patients with invasive ovarian cancers overall, and up to 23% of patients with high-grade serous disease [15,16]. For women with a family history of ovarian cancer in a first-degree relative, the risk of the disease is increased more than 3-fold [15], with an elevated risk of all except the invasive mucinous histotype [17]. A family history of breast cancer is also associated with an increased risk of ovarian cancer; the cumulative risk to age 80 years is 44% for carriers of *BRCA1* mutations and 17% for carriers of *BRCA2* mutations [18]. For the endometriosis-related (endometrioid and clear cell) carcinomas, risk is increased in women with Lynch syndrome (also called hereditary non-polyposis colorectal cancer), which is characterized

FUNDAMENTALS

- Ovarian cancer is the eighth most common cause of cancer death in women worldwide, with the highest incidence rates in Europe and North America. The disease occurs predominantly in postmenopausal women.
- There are multiple major subtypes of ovarian cancer. Risk factor associations, responses to therapy, and survival differ by histopathological subtype.
- The cell type or types that give rise to ovarian cancer remain an area of active investigation, and include cells originating in extra-ovarian tissue. Besides germline genetic variants, the major ovarian cancer subtypes exhibit distinct sets of recurrent somatic mutations.
- Epidemiological evidence implicates pharmacological use of steroids and other risk factors, but opportunities for the primary prevention of ovarian cancer are extremely limited.
- Ovarian cancer is frequently aggressive and is generally detected at a late stage.

Table 5.12.1. Characteristics of the main histotypes of invasive ovarian carcinoma

Characteristic	Histotype				
	High-grade serous	**Low-grade serous**	**Mucinous**	**Endometrioid**	**Clear cell**
Possible tissues of origin	Fallopian tube fimbria; ovarian cortical inclusion cysts	Endosalpingiosis; papillary tubal hyperplasia	Endometriosis or tubal-peritoneal junction	Endometriosis; endometrioid adenofibroma	
Possible cells of origin	Fallopian tube secretory or epithelial cell, or progenitor cell	Fallopian tube secretory or epithelial cell, or progenitor cell	Unknown	Endometrial epithelial cell	
Precursor lesion	Serous tubal intraepithelial carcinoma, p53 signature	Serous borderline tumour/atypical proliferative serous tumour	Mucinous borderline tumour; cystadenoma; Brenner tumour	Endometrioid borderline tumour	
Familial/genetic risk	Germline mutations in *BRCA1*, *BRCA2*, *BRIP1*, *PALB2*, *RAD51C*, *RAD51D*	Not applicable	Not applicable	Lynch syndrome (germline mutations in *MLH1*, *MSH2*, *MSH6*, *PMS2*)	
Frequent somatic mutations	*TP53*, *BRCA1*, *BRCA2*; copy number alterations of *CCNE1*; *PTEN* deletion; loss of *RB1*, *NF1*	*BRAF*, *KRAS*, *NRAS*, *HRAS*, *ERBB2*	*KRAS*	*ARID1A*, *PTEN*, *CTNNB1* (β-catenin), *PIK3CA*, *KRAS*; mismatch repair defects, microsatellite instability	*HNF1β*, *ARID1A*, *PIK3CA*
Proliferation	High	Low	Intermediate	Low	Low
Prognosis	Poor	Favourable	Favourable	Favourable	Intermediate

by germline mutations in genes involved in DNA mismatch repair: *MLH1*, *MSH2*, *MSH6*, and *PMS2*.

Besides germline genetic variants, the major ovarian carcinoma histotypes are associated with distinct sets of recurrent somatic mutations and defects in DNA repair. High-grade serous tumours are ubiquitously characterized by inactivating mutations in the *TP53* gene, often in combination with genomic instability due to *BRCA1* or *BRCA2* defects. Furthermore, a key molecular characteristic of high-grade serous tumours is the presence of widespread copy number alterations [19], including of *CCNE1* (cyclin E1), and this histotype often also shows defects in genes of the retinoblastoma and Notch pathways [20].

Invasive low-grade serous tumours are characterized by (mutually exclusive) sequence mutations in the *KRAS*, *BRAF*, or *ERBB2* oncogenes, and mucinous tumours are characterized by *KRAS* mutations. The endometriosis-associated ovarian cancer (clear cell and endometrioid) histotypes both show loss-of-function mutations in *ARID1A* (rarely observed in other histotypes) and also show associations with activating mutations of *PIK3CA* or loss-of-function alterations in *PTEN*. Endometrioid tumours specifically may also show *KRAS* mutations.

More extensive analyses of ovarian tumour histotypes by whole-genome sequencing also identified structural genomic alterations reflecting specific DNA repair mechanisms, which in combination with mutation patterns form signatures that further segregate tumours into distinct molecular and biological classes, both within and between histotypes [21]. Thus, high-grade serous tumours are distinguished from non-serous tumours by loss of heterozygosity and homologous recombination signatures, and are further split into a subgroup enriched in fold-back inversions and a subgroup characterized by other types of genomic rearrangements. Clear cell tumours are divided into subgroups characterized by deamination of the APOBEC family of cytidine deaminases or age-related mutational signatures. The endometrioid tumours can be divided into three subtypes showing different mutation load and DNA mismatch repair signatures: ultra-mutator, microsatellite instable, and microsatellite stable; the microsatellite stable group has a high proportion of *CTNNB1* (β-catenin) and *KRAS* mutations (Table 5.12.1).

Etiology

Established and putative risk factors

In terms of non-genetic and potentially modifiable risk factors, recent studies increasingly have documented distinct risk factor profiles by tumour histotype. However, the etiology of sporadic invasive ovarian cancer remains poorly understood. Studies in large consortia have shown substantial heterogeneity in the associations between well-established risk factors for ovarian cancer, such as parity and use of oral contraceptives, and disease risk by histotype [11,15,22]. For example, being parous is associated with the largest reductions in risk for clear cell and endometrioid carcinoma (~50–65%) and is more

Fig. 5.12.1. Global distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000 person-years for ovarian cancer, 2018.

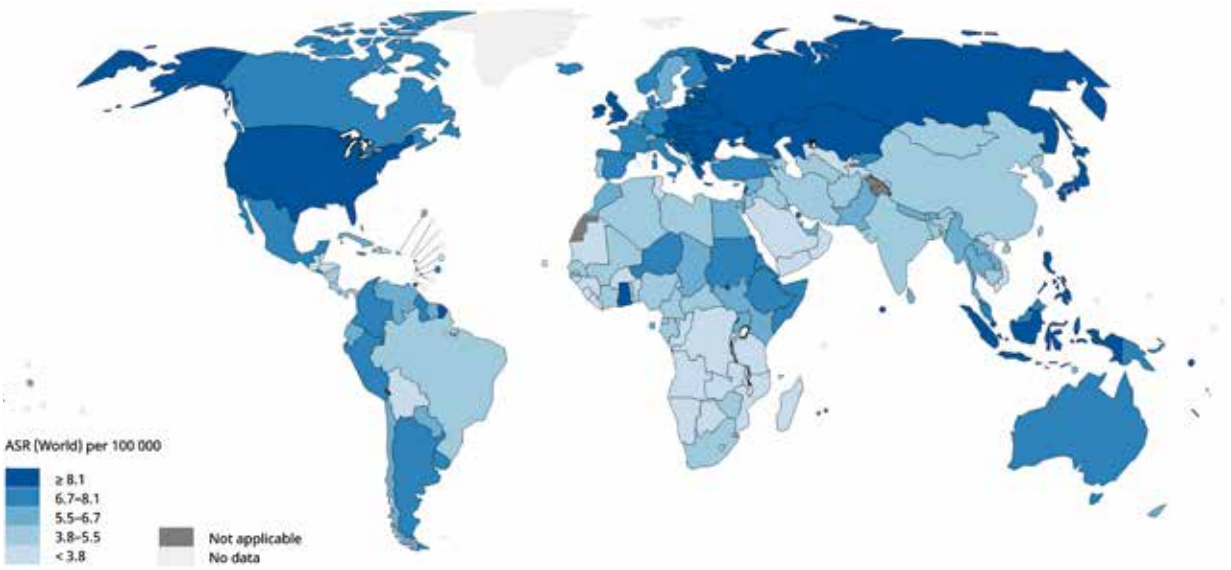
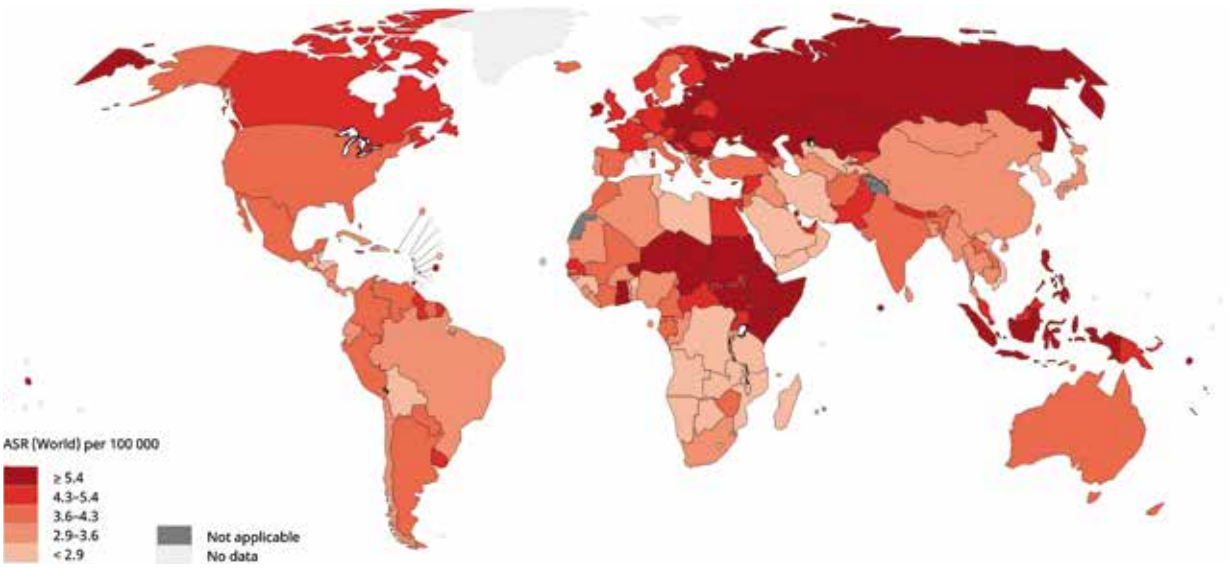


Fig. 5.12.2. Global distribution of estimated age-standardized (World) mortality rates (ASR) per 100 000 person-years for ovarian cancer, 2018.

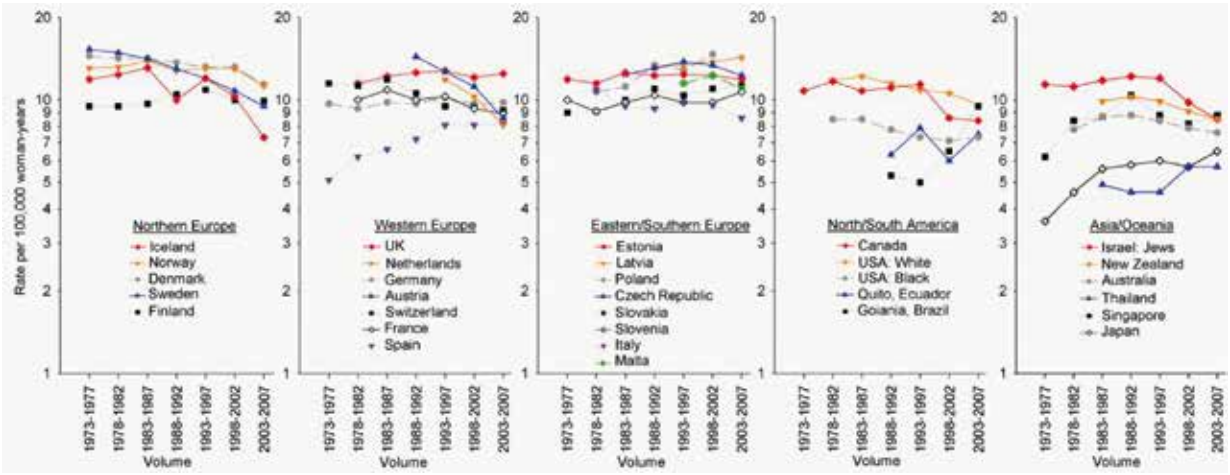


modestly associated with risk of serous disease (~20%) [11]. Longer duration of use of oral contraceptives is inversely associated with risk of serous, endometrioid, and clear cell carcinomas (~15–20% lower risk per 5 years of use) but not of mucinous carcinomas [11,22].

Ever or current/recent use of menopausal hormone therapy is associated with a 40–70% higher risk of serous and endometrioid ovarian carcinomas [11,23]; higher risk is apparent even for short-term use (< 5 years) and for estrogen-only and combined estrogen–progestogen formulations (see Chapter 2.11) [23]. The increase in risk associated with use of menopausal hormone therapy wanes with time since cessation of use; however, this may be dependent on length of use [23]. Findings on use of menopausal hormone therapy are complemented by recent studies on circulating endogenous estrogens and androgens, which have shown higher risks of non-serous ovarian cancer subtypes with higher blood concentrations of both estrogens and androgens [24,25].

Tubal ligation is associated with an approximately 50% reduction in

Fig. 5.12.3. Trends in age-adjusted ovarian cancer incidence rates per 100 000 person-years by region and country from 1973–1977 to 2003–2007, from Volumes IV–X of *Cancer Incidence in Five Continents*.



risk of endometrioid and clear cell ovarian cancer [11,26]; one pooled analysis also indicated a more modest 20% reduction in risk of serous disease and a 32% reduction in risk of mucinous carcinomas [26], whereas a subsequent pooled analysis observed no association in these subtypes [11]. The subtype-specific associations are in line with the hypothesis that tubal ligation reduces disease risk by blocking "retrograde menstruation" or reflux of endometrial tissue through the fallopian tubes, and with the observation that endometriosis, the result of ectopic uterine tissue in the peritoneal cavity, increases the risk of endometrioid, clear cell, and low-grade serous ovarian cancer [10,11].

Relatively few classic lifestyle exposures are associated with risk of ovarian cancer. Higher body mass index is associated with modest increases in the risk of mucinous carcinomas (~8–15% increase in risk per 5 kg/m^2) and endometrioid carcinomas (~8% increase per 5 kg/m^2) [11,27]. The available data do not support strong associations between diet or physical activity and risk of ovarian cancer.

Emerging and possible risk factors

Emerging evidence suggests that inflammation-related exposures, including perineal use of talc-based body power, sexually transmitted infections, and pelvic inflammatory disease, and use of anti-inflammatory analgesics may affect risk of ovarian cancer.

Perineal use of talc-based body powder has been classified by the IARC Monographs as possibly carcinogenic to humans (Group 2B). However, experimental evidence supporting an association is limited, and prospectively collected data on perineal talc exposure are sparse [28]. Prospective consortium-based studies are required to clarify this association.

The sexually transmitted infection *Chlamydia trachomatis* was recently associated with increased risk of ovarian cancer [29], although the results to date on sexually transmitted infections are not consistent. Infection with *C. trachomatis* may increase risk via tubal pathologies induced by pelvic inflammatory disease.

Very frequent use of aspirin (≥ 6 days per week) has been associated with modest reductions in risk of ovarian cancer in both pooled case–control and prospective studies [30,31]. However, the

Fig. 5.12.4. Talcum powder. In relation to ovarian cancer, perineal use of talc-based body powder by women has been classified by the IARC Monographs as possibly carcinogenic to humans, but there is limited evidence of an association and prospective studies to clarify the association are sparse.

Table 5.12.2. Associations between established and putative risk factors for ovarian cancer and risk of invasive epithelial ovarian cancer, by histology[a]

Risk factor	Histology			
	Serous	Endometrioid	Clear cell	Mucinous
Non-modifiable exposures				
Family history of ovarian cancer	↑↑↑↑	↑↑↑↑	↑↑↑↑	–
Age at menarche, per year increase	–	–	↓	–
Age at menopause, per year increase	↑	↑	↑↑	–
Endometriosis	↑↑↑↑[b]	↑↑↑↑	↑↑↑↑	–
Lifestyle and anthropometric exposures				
Parity, per child	↓	↓	↓↓	↓
Use of oral contraceptives, per 5-year duration	↓	↓	↓	–
Use of menopausal hormone therapy, ever or current/recent versus never	↑↑↑	↑↑↑	–	↓
Tubal ligation	↓	↓↓↓	↓↓↓	–
Body mass index, per 5 kg/m^2	–	↑	–	↑
Height, per 5 cm	↑[c]			
Smoking, current versus never	–	↓	↓	↑↑

[a] Relative risks: ↑, > 1.0 to 1.25; ↑↑, 1.25–1.5; ↑↑↑, 1.5–2.0; ↑↑↑↑, > 2.0; ↓, 0.80 to < 1.0; ↓↓, 0.70–0.80; ↓↓↓, 0.50–0.70; ↓↓↓↓, < 0.50.

[b] Low-grade serous carcinomas only.

[c] No significant heterogeneity by histology.

effects of long-term aspirin use (i.e. ≥ 10 years) and use of other analgesics (e.g. acetaminophen) and differential effects by histotype are not well described.

Biological characteristics and early detection

In view of the low absolute incidence rates of ovarian cancer, screening tools must have very high specificity to avoid unnecessary interventions in false-positive cases, while providing good detection sensitivity for early-stage, curable disease. So far, ovarian cancer screening strategies have been based on blood-based biomarkers combined with transvaginal ultrasound imaging.

In randomized trials, multimodal screening by transvaginal ultrasound and CA125 – the best available blood-based biomarker – resulted in a shift towards an earlier disease stage at diagnosis but provided either no reduction in mortality (in the Prostate, Lung, Colorectal and Ovarian Cancer Screening study, in the USA [32]) or only a small (15%) and statistically non-significant reduction when longitudinal changes in CA125 were considered (in the Collaborative Trial of Ovarian Cancer Screening, in the United Kingdom) [33]. Detailed analyses of data from these studies and some smaller trials indicated limited sensitivity of ovarian cancer detection for both CA125 and transvaginal ultrasound [34]. In population cohort studies, analyses of blood samples collected at different lag times before diagnosis under usual care also suggest limited sensitivity of CA125 and other candidate markers (e.g. HE4 and CA72-4) for detection of early-stage disease.

Furthermore, CA125 and transvaginal ultrasound also have only limited specificity, for ovarian cancer in general and more particularly for the more aggressive tumour subtypes. Data from screening trials suggest that transvaginal ultrasound (with or without CA125) may generally be more effective for early detection of more indolent tumours than for the more aggressive high-grade serous carcinomas [35]. A proportion of the less aggressive tumours detected early by transvaginal ultrasound may include disease that would not have been clinically diagnosed if screening had not taken place (i.e. overdiagnosis), or caused symptoms or mortality.

To reduce mortality, screening tools should aim to more specifically detect aggressive tumours at a localized stage. A novel class of promising biomarkers is cell-free tumour DNA or tumour cells from blood or other body fluids and tissue samples (see Chapter 6.7), referred to as liquid biopsies (see “Liquid biopsy: a promising approach for early detection”). However, it remains unknown at present whether liquid biopsy tools, or any other biomarker, will be able to detect serous tubal

Liquid biopsy: a promising approach for early detection

Ovarian cancer is generally diagnosed at advanced stages, for which 5-year survival is about 30%. Diagnosis at an earlier stage yields improved survival, even for aggressive high-grade serous disease; by stage at diagnosis, 5-year survival is 84% for localized disease and 32% for distant disease. However, only about 5% of cases of high-grade serous disease are diagnosed at an early stage [1]. This motivates continued research into effective methods of early detection.

Liquid biopsies of blood samples, or of samples collected closer to the site of a potential malignancy, are of mounting interest, with the promise of high specificity. The first studies using uterine lavage and the Pap test have yielded promising results towards the earlier detection of ovarian cancer.

In a proof-of-concept study, Maritschnegg et al. applied massively parallel sequencing to cell samples obtained by uterine lavage and observed a 60% ovarian cancer detection rate (18 of 30 cases detected) [2]. The predominant mutation detected among cases was in *TP53*; these mutations are ubiquitous in high-grade serous ovarian carcinomas. Among women with benign conditions (e.g. ovarian cyst, fibroma, or secondary infertility), 30% (8 of 27) tested positive for mutations, predominantly in *KRAS* (6 of 8) [2]. *KRAS* mutations are observed in low-grade serous and mucinous ovarian carcinomas but have also been reported in benign and preneoplastic gynaecological conditions. Although the test as applied is limited by a high false-positive rate, the results from this study demonstrate a proof of concept for uterine lavage as a sampling method, and further discovery studies are under way.

An early proof-of-principle study applied massively parallel sequencing to liquid Pap test samples from patients with ovarian cancer and showed a 41% detection rate (9 of 22 cases detected) for known tumour-related mutations in 12 different genes [3].

More recently, a new test (called PapSEEK) was used that incorporates assays for mutations in 18 genes plus an assay for aneuploidy. With this test, analyses of Pap brush samples detected 33% (81 of 245) of patients with ovarian cancer and 34% (30 of 89) of patients with early-stage disease (stages I and II), with a 1.4% false-positive rate in women without cancer (10 of 714; specificity, ~99%) [4]. Intrauterine sampling with a Tao brush increased the detection sensitivity to 45% (23 of 51) of patients with ovarian cancer, with 100% specificity (0 positives among 125 cancer-free controls). Finally, in 83 patients with ovarian cancer for whom plasma was available, circulating tumour DNA was found in 43% of patients, and plasma and Pap brush samples combined yielded an overall detection sensitivity of 63%.

These results show potential for mutation-based detection of gynaecological cancers, with tests tailored to more aggressive, high-grade tumours. If these early results are confirmed, particularly for early-stage cases, early detection via Pap tests would be particularly attractive, given the widespread use of this test in standard care for cervical cancer screening.

References

1. Peres LC, Cushing-Haugen KL, Köbel M, Harris HR, Berchuck A, Rossing MA, et al. (2019). Invasive epithelial ovarian cancer survival by histotype and disease stage. J Natl Cancer Inst. 111(1):60–8. https://doi.org/10.1093/jnci/djy071 PMID:29718305
2. Maritschnegg E, Wang Y, Pecha N, Horvat R, Van Nieuwenhuysen E, Vergote I, et al. (2015). Lavage of the uterine cavity for molecular detection of Müllerian duct carcinomas: a proof-of-concept study. J Clin Oncol. 33(36):4293–300. https://doi.org/10.1200/JCO.2015.61.3083 PMID:26552420
3. Kinde I, Bettegowda C, Wang Y, Wu J, Agrawal N, Shih IeM, et al. (2013). Evaluation of DNA from the Papanicolaou test to detect ovarian and endometrial cancers. Sci Transl Med. 5(167):167ra4. https://doi.org/10.1126/scitranslmed.3004952 PMID:23303603
4. Wang Y, Li L, Douville C, Cohen JD, Yen TT, Kinde I, et al. (2018). Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of endometrial and ovarian cancers. Sci Transl Med. 10(433):10. https://doi.org/10.1126/scitranslmed.aap8793 PMID:29563323

intraepithelial carcinomas or small-volume tumours at a very early (i.e. microscopic) stage, before more widespread dissemination. A parallel challenge is the development of radiological imaging methods with higher sensitivity and specificity for small-volume, aggressive tumours as complementary diagnostic tools.

Prevention

Prevention strategies for ovarian cancer in women at average risk remain elusive, given the limited number of known modifiable risk factors. Increased use of oral contraceptives represents a potential avenue for prevention, with a protective effect that persists for up 20 years after cessation of use [36] and is evident in women at average risk as well as in high-risk populations (i.e. carriers of *BRCA1* or *BRCA2* mutations) (see Chapter 6.5). Although these decreases in the risk of ovarian cancer are compelling, they must be balanced against the increased risks of breast cancer, cervical cancer, and

cardiovascular events. In addition, further data are required on risk associations based on contemporary oral contraceptive formulations.

In terms of other opportunities for chemoprevention (also referred to as preventive therapy; see Chapter 6.4), emerging evidence suggests an inverse association between daily aspirin use and risk of ovarian cancer [30,31]. However, additional studies are required to weigh potential risks and benefits and to delineate target populations.

Use of menopausal hormone therapy and perineal use of talc-based body powder are avoidable exposures. Although associations between body mass index and risk of ovarian cancer are modest, maintaining a healthy body weight has well-documented and widespread health benefits. Furthermore, the recently observed association between *C. trachomatis* infection and risk of ovarian cancer suggests potential novel leads for primary prevention.

In carriers of *BRCA1* or *BRCA2* mutations, prophylactic oophorectomy is recommended at a relatively young age (< 35–40 years for *BRCA1* and < 40–45 years for *BRCA2*) to reduce the risk of both breast cancer and ovarian cancer. Trials investigating salpingectomy with delayed oophorectomy, thus delaying surgical menopause and its sequelae in women who are premenopausal at surgery, are under way in women at high risk [37].

Opportunistic salpingectomy with ovarian conservation (in lieu of tubal ligation) has been suggested as a risk-reducing measure in women at average risk who are undergoing hysterectomy or sterilization. In a large registry-based study, a reduction of up to about 65% in risk was reported for bilateral salpingectomy, compared with 28% for tubal ligation and 94% for hysterectomy with bilateral salpingo-oophorectomy [38]; no data on histotype were available in that study. Although the risk reduction for bilateral salpingectomy is more modest than that for bilateral salpingo-oophorectomy, the procedure may be appropriate for women at average risk of ovarian cancer, and has rates of operative complications as low as those reported for tubal ligation or hysterectomy without salpingectomy [39]. Furthermore, ovarian conservation in women younger than 65 years yields a survival benefit [40] and prevents early surgical menopause in women who are premenopausal at surgery.

Fig. 5.12.5. Women wait for consultation at a health centre in Buhigwe, United Republic of Tanzania. Some of the lowest incidence rates of ovarian cancer are observed in the WHO African Region.

References

1. Fathalla MF (1971). Incessant ovulation – a factor in ovarian neoplasia? Lancet. 2(7716):163. https://doi.org/10.1016/S0140-6736(71)92335-X PMID:4104488
2. Piek JM, van Diest PJ, Zweemer RP, Jansen JW, Poort-Keesom RJJ, Menko FH, et al. (2001). Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer. J Pathol. 195(4):451–6. https://doi.org/10.1002/path.1000 PMID:11745677
3. Gilks CB, Irving J, Köbel M, Lee C, Singh N, Wilkinson N, et al. (2015). Incidental nonuterine high-grade serous carcinomas arise in the fallopian tube in most cases: further evidence for the tubal origin of high-grade serous carcinomas. Am J Surg Pathol. 39(3):357–64. https://doi.org/10.1097/PAS.0000000000000353 PMID:25517954
4. Ducie J, Dao F, Considine M, Olvera N, Shaw PA, Kurman RJ, et al. (2017). Molecular analysis of high-grade serous ovarian carcinoma with and without associated serous tubal intra-epithelial carcinoma. Nat Commun. 8(1):990. https://doi.org/10.1038/s41467-017-01217-9 PMID:29042553
5. Labidi-Galy SI, Papp E, Hallberg D, Niknafs N, Adleff V, Noe M, et al. (2017). High grade serous ovarian carcinomas originate in the fallopian tube. Nat Commun. 8(1):1093. https://doi.org/10.1038/s41467-017-00962-1 PMID:29061967
6. Auersperg N (2015). Article by Natalie Banet and Robert J. Kurman: Two types of ovarian cortical inclusion cysts: proposed origin and possible role in ovarian serous carcinogenesis; *Int. J. Gynecol. Pathol.* 2015;34:3–8. Int J Gynecol Pathol. 34(3):303–4. https://doi.org/10.1097/PGP.0000000000000202 PMID:25844551
7. Park KJ, Patel P, Linkov I, Jotwani A, Kauff N, Pike MC (2018). Observations on the origin of ovarian cortical inclusion cysts in women undergoing risk-reducing salpingo-oophorectomy. Histopathology. 72(5):766–76. https://doi.org/10.1111/his.13444 PMID:29197096
8. Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors (2014). WHO classification of tumours of female reproductive organs. Lyon, France: International Agency for Research on Cancer (WHO classification of tumours series, 4th ed.).
9. Veras E, Mao TL, Ayhan A, Ueda S, Lai H, Hayran M, et al. (2009). Cystic and adenofibromatous clear cell carcinomas of the ovary: distinctive tumors that differ in their pathogenesis and behavior: a clinicopathologic analysis of 122 cases. Am J Surg Pathol. 33(6):844–53. https://doi.org/10.1097/PAS.0b013e31819c4271 PMID:19342944
10. Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, et al.; Ovarian Cancer Association Consortium (2012). Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol. 13(4):385–94. https://doi.org/10.1016/S1470-2045(11)70404-1 PMID:22361336
11. Wentzensen N, Poole EM, Trabert B, White E, Arslan AA, Patel AV, et al. (2016). Ovarian cancer risk factors by histologic subtype: an analysis from the Ovarian Cancer Cohort Consortium. J Clin Oncol. 34(24):2888–98. https://doi.org/10.1200/JCO.2016.66.8178 PMID:27325851
12. Dawson A, Fernandez ML, Anglesio M, Yong PJ, Carey MS (2018). Endometriosis and endometriosis-associated cancers: new insights into the molecular mechanisms of ovarian cancer development. Ecancermedicalscience. 12:803. https://doi.org/10.3332/ecancer.2018.803 PMID:29456620
13. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593
14. Coburn SB, Bray F, Sherman ME, Trabert B (2017). International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. Int J Cancer. 140(11):2451–60. https://doi.org/10.1002/ijc.30676 PMID:28257597
15. Reid BM, Permuth JB, Sellers TA (2017). Epidemiology of ovarian cancer: a review. Cancer Biol Med. 14(1):9–32. https://doi.org/10.20892/j.issn.2095-3941.2016.0084 PMID:28443200
16. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. (2012). *BRCA* mutation frequency and patterns of treatment response in *BRCA* mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 30(21):2654–63. https://doi.org/10.1200/JCO.2011.39.8545 PMID:22711857
17. Zheng G, Yu H, Kanerva A, Försti A, Sundquist K, Hemminki K (2018). Familial risks of ovarian cancer by age at diagnosis, proband type and histology. PLoS One. 13(10):e0205000. https://doi.org/10.1371/journal.pone.0205000 PMID:30281663
18. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips K-A, Mooij TM, Roos-Blom M-J, et al.; *BRCA1* and *BRCA2* Cohort Consortium (2017). Risks of breast, ovarian, and contralateral breast cancer for *BRCA1* and *BRCA2* mutation carriers. JAMA. 317(23):2402–16. https://doi.org/10.1001/jama.2017.7112 PMID:28632866
19. Cancer Genome Atlas Research Network (2011). Integrated genomic analyses of ovarian carcinoma. Nature. 474(7353):609–15. https://doi.org/10.1038/nature10166 PMID:21720365
20. Bowtell DD, Böhm S, Ahmed AA, Aspuria P-J, Bast RC Jr, Beral V, et al. (2015). Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. Nat Rev Cancer. 15(11):668–79. https://doi.org/10.1038/nrc4019 PMID:26493647
21. Wang YK, Bashashati A, Anglesio MS, Cochrane DR, Grewal DS, Ha G, et al. (2017). Genomic consequences of aberrant DNA repair mechanisms stratify ovarian cancer histotypes. Nat Genet. 49(6):856–65. https://doi.org/10.1038/ng.3849 PMID:28436987
22. Beral V, Doll R, Hermon C, Peto R, Reeves G; Collaborative Group on Epidemiological Studies of Ovarian Cancer (2008). Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23 257 women with ovarian cancer and 87 303 controls. Lancet. 371(9609):303–14. https://doi.org/10.1016/S0140-6736(08)60167-1 PMID:18294997
23. Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, Peto R; Collaborative Group on Epidemiological Studies of Ovarian Cancer (2015). Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet. 385(9980):1835–42. https://doi.org/10.1016/S0140-6736(14)61687-1 PMID:25684585
24. Ose J, Poole EM, Schock H, Lehtinen M, Arslan AA, Zeleniuch-Jacquotte A, et al. (2017). Androgens are differentially associated with ovarian cancer subtypes in the Ovarian Cancer Cohort Consortium. Cancer Res. 77(14):3951–60. https://doi.org/10.1158/0008-5472.CAN-16-3322 PMID:28381542
25. Trabert B, Brinton LA, Anderson GL, Pfeiffer RM, Falk RT, Strickler HD, et al. (2016). Circulating estrogens and postmenopausal ovarian cancer risk in the Women's Health Initiative observational study. Cancer Epidemiol Biomarkers Prev. 25(4):648–56. https://doi.org/10.1158/1055-9965.EPI-15-1272-T PMID:26908437
26. Sieh W, Salvador S, McGuire V, Weber RP, Terry KL, Rossing MA, et al.; Australian Cancer Study (Ovarian Cancer); Australian Ovarian Cancer Study Group; Ovarian Cancer Association Consortium (2013). Tubal ligation and risk of ovarian cancer subtypes: a pooled analysis of case-control studies. Int J Epidemiol. 42(2):579–89. https://doi.org/10.1093/ije/dyt042 PMID:23569193

27. Collaborative Group on Epidemiological Studies of Ovarian Cancer (2012). Ovarian cancer and body size: individual participant meta-analysis including 25,157 women with ovarian cancer from 47 epidemiological studies. PLoS Med. 9(4):e1001200. https://doi.org/10.1371/journal.pmed.1001200 PMID:22606070

28. Penninkilampi R, Eslick GD (2018). Perineal talc use and ovarian cancer: a systematic review and meta-analysis. Epidemiology. 29(1):41–9. https://doi.org/10.1097/EDE.0000000000000745 PMID:28863045

29. Trabert B, Waterboer T, Idahl A, Brenner N, Brinton LA, Butt J, et al. (2019). Antibodies against *Chlamydia trachomatis* and ovarian cancer risk in two independent populations. J Natl Cancer Inst. 111(2):129–36. https://doi.org/10.1093/jnci/djy084 PMID:29790947

30. Trabert B, Poole EM, White E, Visvanathan K, Adami HO, Anderson GL, et al.; Ovarian Cancer Cohort Consortium (OC3) (2019). Analgesic use and ovarian cancer risk: an analysis in the Ovarian Cancer Cohort Consortium. J Natl Cancer Inst. 111(2):137–45. https://doi.org/10.1093/jnci/djy100 PMID:29860330

31. Trabert B, Ness RB, Lo-Ciganic WH, Murphy MA, Goode EL, Poole EM, et al.; Australian Ovarian Cancer Study Group, Australian Cancer Study (Ovarian Cancer); Ovarian Cancer Association Consortium (2014). Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. J Natl Cancer Inst. 106(2):djt431. https://doi.org/10.1093/jnci/djt431 PMID:24503200

32. Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al.; PLCO Project Team (2011). Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening randomized controlled trial. JAMA. 305(22):2295–303. https://doi.org/10.1001/jama.2011.766 PMID:21642681

33. Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, et al. (2016). Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 387(10022):945–56. https://doi.org/10.1016/S0140-6736(15)01224-6 PMID:26707054

34. Mathieu KB, Bedi DG, Thrower SL, Qayyum A, Bast RC Jr (2018). Screening for ovarian cancer: imaging challenges and opportunities for improvement. Ultrasound Obstet Gynecol. 51(3):293–303. https://doi.org/10.1002/uog.17557 PMID:28639753

35. Henderson JT, Webber EM, Sawaya GF (2018). Screening for ovarian cancer: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 319(6):595–606. https://doi.org/10.1001/jama.2017.21421 PMID:29450530

36. Havrilesky LJ, Moorman PG, Lowery WJ, Gierisch JM, Coeytaux RR, Urrutia RP, et al. (2013). Oral contraceptive pills as primary prevention for ovarian cancer: a systematic review and meta-analysis. Obstet Gynecol. 122(1):139–47. https://doi.org/10.1097/AOG.0b013e318291c235 PMID:23743450

37. Harmsen MG, Arts-de Jong M, Hoogerbrugge N, Maas AHEM, Prins JB, Bulten J, et al. (2015). Early salpingectomy (TUbectomy) with delayed oophorectomy to improve quality of life as alternative for risk-reducing salpingo-oophorectomy in *BRCA1/2* mutation carriers (TUBA study): a prospective non-randomised multicentre study. BMC Cancer. 15(1):593. https://doi.org/10.1186/s12885-015-1597-y PMID:26286255

38. Falconer H, Yin L, Grönberg H, Altman D (2015). Ovarian cancer risk after salpingectomy: a nationwide population-based study. J Natl Cancer Inst. 107(2):107. https://doi.org/10.1093/jnci/dju410 PMID:25628372

39. McAlpine JN, Hanley GE, Woo MM, Tone AA, Rozenberg N, Swenerton KD, et al.; Ovarian Cancer Research Program of British Columbia (2014). Opportunistic salpingectomy: uptake, risks, and complications of a regional initiative for ovarian cancer prevention. Am J Obstet Gynecol. 210(5):471.e1–11. https://doi.org/10.1016/j.ajog.2014.01.003 PMID:24412119

40. Parker WH, Broder MS, Liu Z, Shoupe D, Farquhar C, Berek JS (2005). Ovarian conservation at the time of hysterectomy for benign disease. Obstet Gynecol. 106(2):219–26. https://doi.org/10.1097/01.AOG.0000167394.38215.56 PMID:16055568

5.13 Prostate cancer
Challenges for prevention, detection, and treatment

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Timothy J. Key (reviewer)
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SUMMARY

- Prostate cancer has one of the largest disparities by race of any major cancer type. Men of African descent (e.g. African American men) have the highest rates of prostate cancer incidence and mortality.
- Prostate cancer has the highest heritability of any major cancer type.
- More than 100 low-penetrance loci have been identified via genome-wide association studies, but the use of this information in predicting prostate cancer risk or outcomes remains limited.
- *BRCA2*, *HOXB13*, and DNA mismatch repair genes are high-penetrance genes that may have clinical utility in predicting prostate cancer risk, outcomes, and treatment options.
- Among studied exposures and lifestyle, nutritional, and dietary factors, only attained adult height and underlying biological factors associated with adult height are likely to be associated with risk of prostate cancer. Factors related to obesity appear to be associated with unfavourable outcomes in men diagnosed with prostate cancer. The evidence for other risk factors is limited. Therefore, interventions to reduce exposures to lifestyle, dietary, or other factors to decrease risk of prostate cancer are currently unavailable.
- Prostate tumour markers have been identified that indicate etiologically and phenotypically distinct groups of tumours, some of which may have different prognosis and response to treatment.
- Chemoprevention for prostate cancer has been limited, despite evidence that some agents (e.g. 5α-reductase inhibitors) may safely reduce the incidence of prostate cancer.

Prostate cancer is a group of histopathologically distinct tumour subtypes. These include glandular neoplasms (acinar adenocarcinoma, intraductal carcinoma, and ductal adenocarcinoma), urothelial carcinoma, squamous carcinoma (adenosquamous carcinoma and squamous cell carcinoma), basal cell carcinoma, and neuroendocrine tumours (adenocarcinoma with neuroendocrine differentiation, small cell neuroendocrine carcinoma, and large cell neuroendocrine carcinoma) [1]. The most common of these tumour subtypes is acinar adenocarcinoma, which accounts for more than 99% of all prostate tumours [2].

There is significant variation across these subtypes by age at diagnosis, race, prostate-specific antigen (PSA) level at diagnosis, and stage [2]. In addition, the WHO classification of tumours in 2016 recommended a grading system that was updated to reflect the five grade groups of Epstein et al. [3], which better reflect disease prognosis and outcomes compared with previous categorizations.

Epidemiology

In 2018, prostate cancer was the second most common non-cutaneous cancer in men worldwide (with an estimated 1.3 million new cases) and the fifth most common cause of cancer death in men (with about 359 000 deaths) [4]. Incidence rates of prostate cancer are highest in North America, Europe, Australia, and New Zealand (Fig. 5.13.1). These elevated rates may reflect a truly higher incidence of disease as well as higher prostate cancer detection rates compared with other areas. Incidence rates in Central and South America appear to be slightly lower, and rates in Asia appear to be the lowest currently reported.

Rates of prostate cancer in Africa, particularly in sub-Saharan Africa, are very poorly captured by population-based tumour registries, and there is limited screening and early detection of prostate cancer in Africa. Therefore, it is not clear that the apparently low rates of prostate cancer in Africa estimated by IARC and others are accurate.

Systematic surveys of the prevalence of prostate cancer in Africa [5] suggest that rates are as high as or higher than those in African

Americans, who have among the highest incidence rates of prostate cancer in the world. These inferences are consistent with findings from autopsy studies that rates of latent (prevalent) prostate cancer are highest in men of African descent, lower in men of European descent, and lowest in men of Asian descent [6]. Therefore, it is likely that prostate cancer incidence in Africa (particularly sub-Saharan Africa) may be substantially higher than is currently reported.

In contrast to prostate cancer incidence, prostate cancer mortality rates are highest in sub-Saharan Africa, somewhat lower in Central and South America and the Caribbean, lower in Europe, and still lower in North America, Australia, and New Zealand (Fig. 5.13.2). The rates are lowest in Asia.

This global variation in prostate cancer mortality rates in part reflects underlying biological differences in risk as well as access to treatment. For example, regions with increased detection of low-grade cancers coupled with advanced treatment options (e.g. the USA) tend to have lower mortality rates compared with regions with low screening rates and the accompanying diagnosis of aggressive tumours coupled with limited treatment options (e.g. sub-Saharan Africa).

Secular trends in prostate cancer incidence rates (Fig. 5.13.3) reflect the patterns of prostate cancer screening, including evaluation of PSA level and digital rectal examination. In North America, Australia, New Zealand, and parts of Central and South America, prostate cancer incidence increased dramatically during the late 1980s and the 1990s as a result of widespread PSA screening. Similar trends were seen in other countries (e.g. in Europe) but occurred about 10 years later, in part because of later adoption of PSA screening compared with North America, Australia, and New Zealand. In many countries, incidence rates of prostate cancer reached a peak about 5 years after the widespread introduction of PSA screening. In Asia, which has lower rates of prostate cancer compared with other parts of the world, the increase in prostate cancer incidence was less profound.

Trends in prostate cancer mortality (Fig. 5.13.4) have been influenced both by patterns of screening-associated detection and by treatment advances in some parts of the world. Since the advent of PSA screening and the availability of new surgical, radiotherapeutic, and chemotherapeutic regimens in the past 20 years, prostate cancer mortality has been slowly declining in most parts of the world. Most recently, it has been reported that mortality rates have levelled off after a period of decline, and the incidence of advanced prostate cancer has increased in the USA since the United States Preventive Services Task Force recommended against PSA screening [7]. As discussed below, screening has a more profound impact on incidence for prostate cancer than for most other cancer types. The relationship of screening with prostate cancer mortality is more complex.

Genetics and genomics

Prostate cancer has the highest reported heritability of any major cancer type [8]. Unlike the situation for other cancer types, the ability to define hereditary prostate cancer syndromes and identify hereditary cancer genes (see Chapter 3.2) has been limited. Family-based linkage studies of hereditary prostate cancer have focused largely on populations of European descent to identify a series of genes responsible for hereditary prostate cancer [9,10]. Although many high-penetrance prostate cancer loci have been reported, very few have been implemented clinically.

Giri et al. reported the recommendations of the first consensus conference to assess the value of genetic testing for risk as well as clinical management of prostate cancer, held in 2017 [11]. This expert group identified that associations of inherited mutations in *BRCA2* had implications for risk assessment and treatment. Among carriers of *BRCA2* mutations, the risk of prostate cancer is increased 2.5–4.7-fold [12]. Also, prostate tumours with *BRCA2* mutations have less favourable clinical characteristics, including higher probability of nodal involvement, metastases, high grade, advanced stage, and lower median survival [13].

Giri et al. also identified *HOXB13* mutations and DNA mismatch repair gene mutations (accounting for Lynch syndrome) as potential candidates for genetic testing [11]. For

FUNDAMENTALS

- Prostate cancer is highly prevalent in middle-aged and older men. The incidence of diagnosed prostate cancer is strongly correlated with the use of screening by prostate-specific antigen (PSA) level.
- Older age, African ancestry or race, and a family history of prostate cancer are the only consistent risk factors for prostate cancer.
- Sociodemographic inequities in prostate cancer screening and treatment are likely to affect prostate cancer outcomes. The specific nature of these inequities remains unclear.
- Screening for prostate cancer by PSA level remains controversial. After recommendations against widespread PSA screening, screening rates declined, followed by an increase in rates of higher-stage tumours at diagnosis. An improved approach is needed that balances early detection of treatable cancers versus overdetection and overtreatment of prostate cancers.

Fig. 5.13.1. Global distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000 person-years for prostate cancer, 2018.

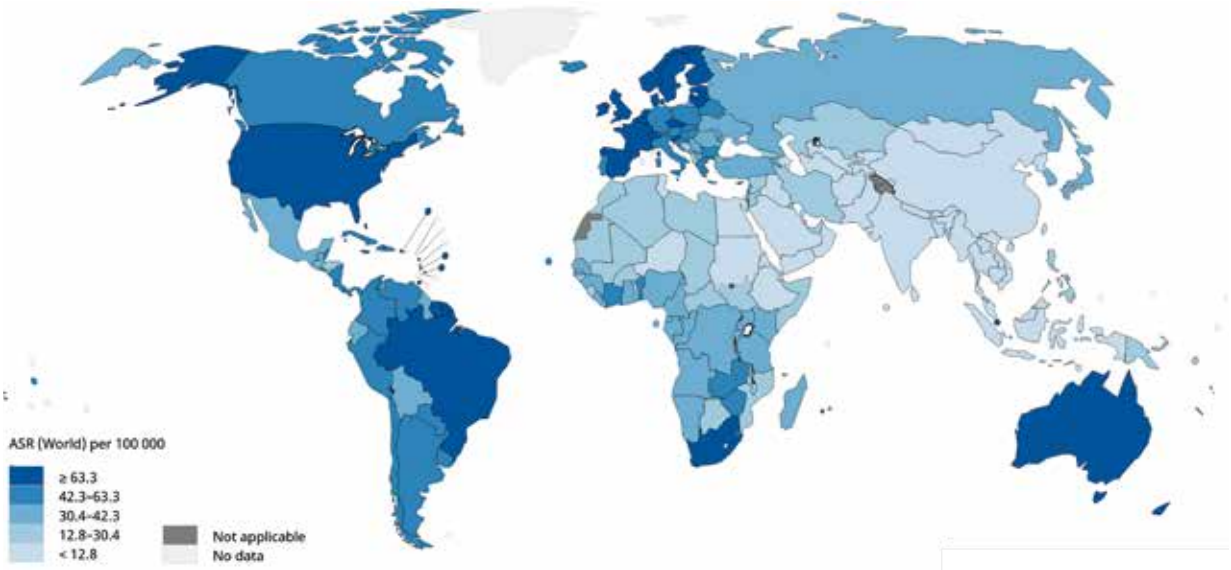
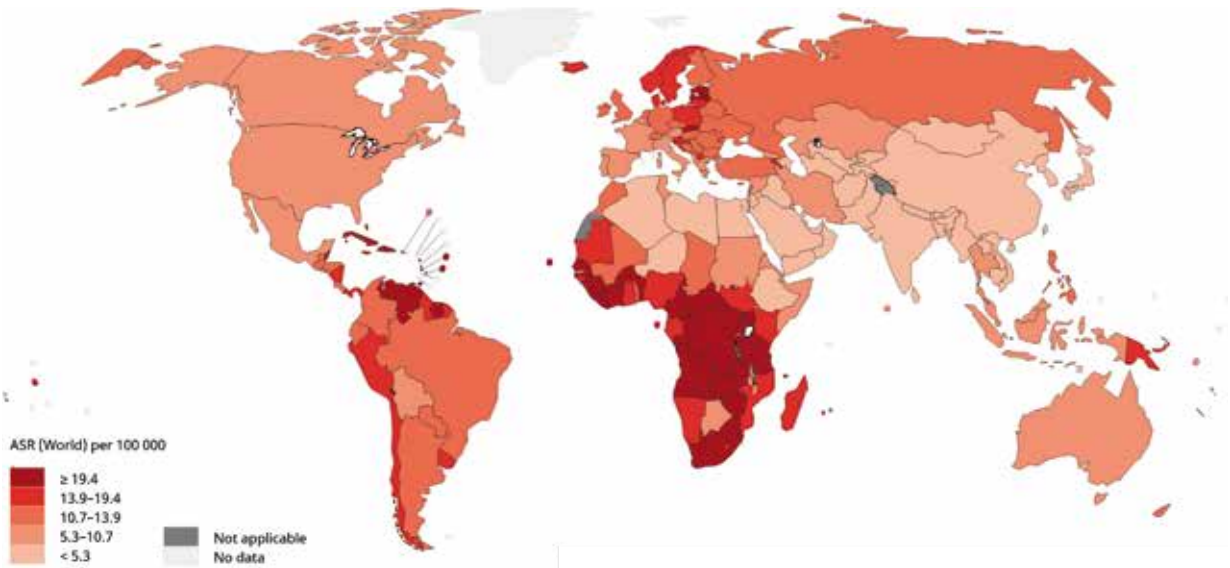


Fig. 5.13.2. Global distribution of age-standardized (World) mortality rates (ASR) per 100 000 person-years for prostate cancer, 2018.

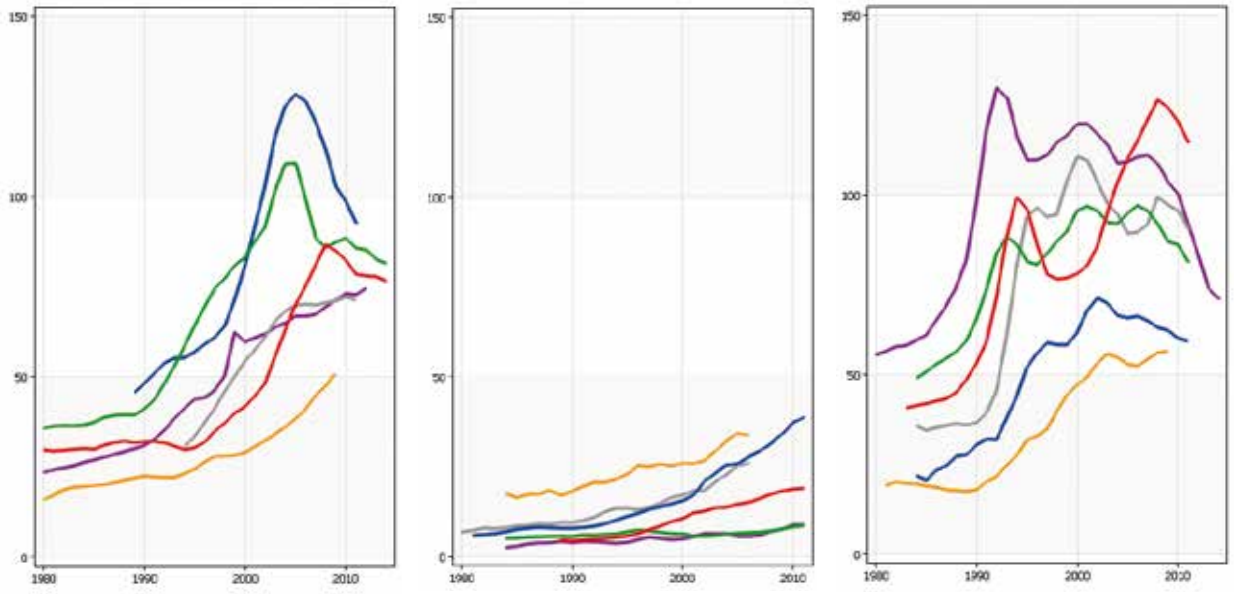


HOXB13 mutations, relative risks were estimated to be greater than 3, and for DNA mismatch repair gene mutations, estimated relative risks were 2.1–3.7 [12].

These associations suggest that mutations at these loci confer sufficiently large effects that they can be considered in prostate cancer risk management and decision-making.

In addition to high-penetrance genes, loci with low to moderate magnitudes of association with prostate cancer have been identified through genome-wide association studies (GWAS) and related approaches. At least 170 common variants associated with prostate cancer have been reported [14]. The NHGRI-EBI Catalog of published GWAS (https://www.ebi.ac.uk/gwas/, accessed 13 October 2018) reported more than 700 GWAS associations for 23 prostate cancer-related traits. The majority of these have reported associations of loci with prostate cancer risk (n = 659) as well as associations with prostate cancer metastasis, aggressiveness, or survival (n = 56). Most associations reported in populations of European or Asian descent have not been replicated in populations of African descent [15]. Few independent GWAS hits have been identified in populations of African descent [16]. Multiple in-

Fig. 5.13.3. Age-standardized (World) incidence rates per 100 000 person-years by calendar year in selected countries for prostate cancer, circa 1978–2012.

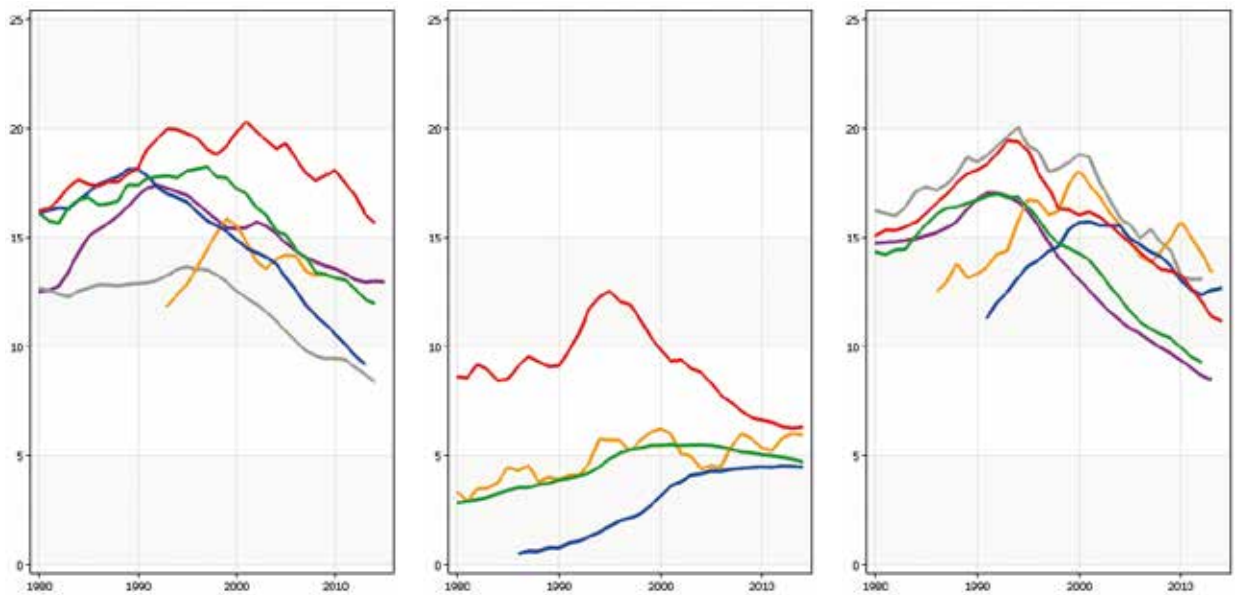


Denmark
Finland
France (regional)
Slovakia
Spain (regional)
UK, England

China (regional)
India (regional)
Japan (regional)
Philippines (regional)
Singapore
Thailand (regional)

Australia
Canada (except Quebec)
Colombia (regional)
Costa Rica
New Zealand
USA (SEER)

Fig. 5.13.4. Age-standardized (World) mortality rates per 100 000 person-years by calendar year in selected countries for prostate cancer, circa 1978–2012.



Denmark
Finland
France
Slovakia
Spain
UK, England and Wales

Israel
Japan
Republic of Korea
Singapore

Australia
Canada
Colombia
Costa Rica
New Zealand
USA

dependent genomic associations at 8q24 have been validated as prostate cancer susceptibility loci in multiple racial groups, including African Americans [17]. Although no gene has been designated to be responsible for this increased risk of prostate cancer, regulation of the downstream gene *MYC* or regulation by long non-coding RNAs has been reported [18].

Etiology

In contrast to the high heritability and large number of genetic associations that influence prostate cancer risk and outcomes, confirmed environmental factors or exposures that influence prostate cancer risk and outcomes are limited [19]. Older age, African ancestry or race, and a family history of prostate cancer are among the few uncontested risk factors for prostate cancer. As summarized by the 2014 Continuous Update Project report on associations between food, nutrition, and physical activity and the risk of prostate cancer, the "convincing" level of evidence was not achieved for any environmental or behavioural risk factors [19].

Attained adult height and underlying biological factors associated with adult height are probably risk factors for prostate cancer. These effects are indirect and involve factors that are correlated with attained adult height. Exogenous exposures, including diet, nutrition, and lifestyle, have not been consistently associated with prostate cancer risk or a protective effect [19]. These include no evidence for prostate cancer risk associated with β-carotene, dietary calcium, vitamin D, dairy products, selenium, vitamin E, lycopene, and other factors that have been widely studied.

The limited convincing evidence for associations of exogenous exposures, physical activity, lifestyle, or dietary exposures with prostate cancer risk or outcomes makes it difficult to identify modifiable factors that may be used in prostate cancer prevention strategies. However, factors related to obesity appear to be associated with unfavourable outcomes in men diagnosed with prostate cancer, because of biological influences or less effective screening or treatment [20].

Biological characteristics and early detection

Molecular signatures found in prostate tumours reflect heterogeneity in tumour etiology [21,22], correlate with a biological propensity to exhibit aggressive phenotypes [23], and/or may direct optimal surveillance and treatment [24]. Decision-making about active treatment with curative intent versus active surveillance depends in part on knowing which prostate tumours are likely to have unfavourable prognosis. Therefore, knowledge of biomarkers that predict the likelihood of aggressive disease may have clinical utility. These biomarkers include the *TMPRSS2-ERG* gene fusion [25], Ki-67 expression [26], and biomarkers involved in androgen metabolism [27]. Multigene genomic classifiers have been identified that assess prostate tumour aggressiveness or prognosis [28].

There are substantial differences in the distribution of prostate tumour biomarkers by race, including *ERG*, *AMACR*, *SPINK1*, *NKX3-1*, *GOLM1*, and androgen receptor. Dysregulation of *AMACR*, *ERG*, *FOXP1*, and *GSTP1* as well as loss-of-function mutations in the tumour suppressor genes *NKX3-1* and *RB1* were found to predict the risk of extraprostatic extension and/or seminal vesicle invasion in a race-dependent manner [29].

Although *TMPRSS2-ERG* translocations do not seem to correlate with clinical outcome in most studies [30], the frequency of these events differs substantially by race [31]. In addition, several predictive or prognostic models have been developed that include molecular biomarkers as well as clinical and other traits (e.g. the Stockholm-3 test, the 4Kscore test, and multiparametric magnetic resonance imaging [mpMRI]). These results suggest that molecular signatures, perhaps in combination with clinical or other traits, may aid in understanding the biological underpinnings of prostate cancer disparities and identify precision surveillance and treatment regimens.

The PAM50 gene expression classifier (which is used to identify the major molecular subtypes of breast cancer) has been used to define three prostate tumour subtypes – luminal A, luminal B, and basal – with significant differences in 10-year biochemical recurrence-free survival, distant metastasis-free survival, prostate cancer-specific

Fig. 5.13.5. A group of African American men. African ancestry or race is one of a few uncontested risk factors for prostate cancer.

survival, and overall survival [32]. Luminal B prostate cancers were significantly associated with post-operative response to androgen deprivation therapy. The biomarkers identified to date may inform screening for prostate cancer (e.g. as an alternative or a supplement to PSA testing), treatment choices, and prognosis.

Socioeconomic differences

Rates of prostate cancer are higher in African American men than in men of other races across the entire spectrum of prostate carcinogenesis, including high-grade prostatic intraepithelial neoplasia, prevalent (autopsy-detected) prostate cancer, screen-detected cancer, incident prostate cancer, and prostate cancer mortality [6,33]. At almost every point along the prostate cancer continuum and for almost every age group, prostate cancer is more common in African American men than in men of other races in the USA. These data suggest that the disparity may have a biological component, because the disparity is evident even before cancer is usually clinically detected. However, the disparity increases in magnitude in clinically detected disease and in mortality, suggesting that factors related to exposure, behaviour, or access to health care are also important in prostate cancer disparities (see Chapter 4.6).

Access to health care, and its social, economic, and behavioural correlates, are associated with prostate cancer outcomes and disparities. For example, the care received by African American or Hispanic men differs in terms of quality from that received by men of other races, and this, in turn, affects outcomes and disparities [34]. Disparities in outcome may persist even within settings where men of different races have equality of care, including in the United States Veterans Administration health-care system, within a clinical trial, or with treatment by standard protocols at a single institution [35]. Other studies report that the disparity by race disappears after equal clinical protocols are applied [36].

Fig. 5.13.6. Access to health care is associated with prostate cancer outcomes and disparities.

Critically, the impact of access to health care on outcomes may vary by the metric used to assess these associations. A systematic review and meta-analysis of differences in prognosis by race reported no disparity in overall survival by race but found evidence for differences in prostate cancer-specific survival and risk of biochemical recurrence [37]. Thus, not all studies have been able to clearly demonstrate that equal treatment leads to equal outcomes. The data available to date do not completely resolve the question of whether racial disparities could be eliminated if treatment were optimized for specific groups on the basis of race and/or socioeconomic status.

Prediction of prostate cancer screening participation, treatment choices, and outcomes may also involve the presence of comorbid conditions, which may influence the clinician to assess whether a patient will be able to benefit from a specific medical intervention, including active surveillance. A variety of indices have been developed that attempt to create a simple metric that captures multivariate comorbidity data [38]. Given that some groups are more likely than others to have co-existent chronic conditions, comorbid conditions may play a role in prostate cancer disparities in treatment and outcomes.

Prevention

Prevention and early detection of prostate cancer have been controversial, and the source of great confusion for both patients and clinicians. PSA screening had been widely used in the USA and other countries since 1992, when professional organizations, including the American Urological Association, recommended annual PSA screening for men aged 50 years and older. Subsequently, a large increase in prostate cancer incidence was observed, particularly for low-stage prostate tumours [39].

This trend continued until the United States Preventive Services Task Force recommended against widespread PSA testing, in 2008 for men older than 75 years and in 2012 for all men. Since that recommendation, rates of prostate tumours, particularly early-stage tumours, have decreased [40]. Subsequently, there has been a trend towards diagnosis

Fig. 5.13.7. A man having blood drawn. Screening has a more profound impact on incidence for prostate cancer than for most other cancer types.

of prostate tumours of unfavourable stage/grade [7].

The public health implications of prostate cancer screening to detect cancers at an early, treatable stage versus a desire to limit overdetection and overtreatment of prostate cancers need to be resolved, particularly for African American men and other men at high risk of developing prostate cancer [41].

Chemoprevention for prostate cancer has been of limited utility to date. In the Prostate Cancer Prevention Trial [42], evidence was reported for reduction in risk of prostate cancer, but a concern was raised by the potential for finasteride to increase the risk of high-grade tumours despite an overall reduction in prostate cancer incidence. The observation of increased high-grade tumours in men using finasteride has proven to be incorrect [43], but use of finasteride as a chemopreventive agent has not been widespread.

Recently, the findings of the earlier Prostate Cancer Prevention Trial were replicated in a large population-based non-randomized study to demonstrate that 5α-reductase inhibitors reduce risk of prostate cancer, without an increase in risk of high-grade disease [44]. These data suggest that hormonally driven chemopreventive regimens may have value in reducing risk of prostate cancer in some men.

Trials of micronutrients have been conducted both in the general population and in men with high-grade prostatic intraepithelial neoplasia [45,46]. These trials ether demonstrated no effect or revealed a reduction in risk of prostate cancer at the cost of greater toxicities in the treatment arm.

References

1. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM (2016). The 2016 WHO classification of tumours of the urinary system and male genital organs - part A: renal, penile, and testicular tumours. Eur Urol. 70(1):93–105. https://doi.org/10.1016/j.eururo.2016.02.029 PMID:26935559

2. Marcus DM, Goodman M, Jani AB, Osunkoya AO, Rossi PJ (2012). A comprehensive review of incidence and survival in patients with rare histological variants of prostate cancer in the United States from 1973 to 2008. Prostate Cancer Prostatic Dis. 15(3):283–8. https://doi.org/10.1038/pcan.2012.4 PMID:22349984

3. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA; Grading Committee (2016). The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol. 40(2):244–52. PMID:26492179

4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593

5. Hsing AW, Yeboah E, Biritwum R, Tettey Y, De Marzo AM, Adjei A, et al. (2014). High prevalence of screen detected prostate cancer in West Africans: implications for racial disparity of prostate cancer. J Urol. 192(3):730–5. https://doi.org/10.1016/j.juro.2014.04.017 PMID:24747091

6. Rebbeck TR, Haas GP (2014). Temporal trends and racial disparities in global prostate cancer prevalence. Can J Urol. 21(5):7496–506. PMID:25347377

7. Eapen RS, Herlemann A, Washington SL 3rd, Cooperberg MR (2017). Impact of the United States Preventive Services Task Force 'D' recommendation on prostate cancer screening and staging. Curr Opin Urol. 27(3):205–9. https://doi.org/10.1097/MOU.0000000000000383 PMID:28221220

8. Mucci LA, Hjelmborg JB, Harris JR, Czene K, Havelick DJ, Scheike T, et al.; Nordic Twin Study of Cancer (NorTwinCan) Collaboration (2016). Familial risk and heritability of cancer among twins in Nordic countries. JAMA. 315(1):68–76. https://doi.org/10.1001/jama.2015.17703 PMID:26746459

9. Berry R, Schaid DJ, Smith JR, French AJ, Schroeder JJ, McDonnell SK, et al. (2000). Linkage analyses at the chromosome 1 loci 1q24-25 (HPC1), 1q42.2-43 (PCAP), and 1p36 (CAPB) in families with hereditary prostate cancer. Am J Hum Genet. 66(2):539–46. https://doi.org/10.1086/302771 PMID:10677314

10. Breyer JP, Avritt TG, McReynolds KM, Dupont WD, Smith JR (2012). Confirmation of the *HOXB13* G84E germline mutation in familial prostate cancer. Cancer Epidemiol Biomarkers Prev. 21(8):1348–53. https://doi.org/10.1158/1055-9965.EPI-12-0495 PMID:22714738

11. Giri VN, Knudsen KE, Kelly WK, Abida W, Andriole GL, Bangma CH, et al. (2018). Role of genetic testing for inherited prostate cancer risk: Philadelphia Prostate Cancer Consensus Conference 2017. J Clin Oncol. 36(4):414–24. https://doi.org/10.1200/JCO.2017.74.1173 PMID:29236593

12. Zhen JT, Syed J, Nguyen KA, Leapman MS, Agarwal N, Brierley K, et al. (2018). Genetic testing for hereditary prostate cancer: current status and limitations. Cancer. 124(15):3105–17. https://doi.org/10.1002/cncr.31316 PMID:29669169

13. Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M, et al. (2013). Germline *BRCA* mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol. 31(14):1748–57. https://doi.org/10.1200/JCO.2012.43.1882 PMID:23569316

14. Benafif S, Kote-Jarai Z, Eeles RA; PRACTICAL Consortium (2018). A review of prostate cancer genome-wide association studies (GWAS). Cancer Epidemiol Biomarkers Prev. 27(8):845–57. https://doi.org/10.1158/1055-9965.EPI-16-1046 PMID:29348298

15. Chang BL, Spangler E, Gallagher S, Haiman CA, Henderson B, Isaacs W, et al. (2011). Validation of genome-wide prostate cancer associations in men of African descent. Cancer Epidemiol Biomarkers Prev. 20(1):23–32. https://doi.org/10.1158/1055-9965.EPI-10-0698 PMID:21071540

16. Haiman CA, Chen GK, Blot WJ, Strom SS, Berndt SI, Kittles RA, et al. (2011). Genome-wide association study of prostate cancer in men of African ancestry identifies a susceptibility locus at 17q21. Nat Genet. 43(6):570–3. https://doi.org/10.1038/ng.839 PMID:21602798

17. Freedman ML, Haiman CA, Patterson N, McDonald GJ, Tandon A, Waliszewska A, et al. (2006). Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men. Proc Natl Acad Sci U S A. 103(38):14068–73. https://doi.org/10.1073/pnas.0605832103 PMID:16945910

18. Ahmadiyeh N, Pomerantz MM, Grisanzio C, Herman P, Jia L, Almendro V, et al. (2010). 8q24 prostate, breast, and colon cancer risk loci show tissue-specific long-range interaction with *MYC*. Proc Natl Acad Sci U S A. 107(21):9742–6. https://doi.org/10.1073/pnas.0910668107 PMID:20453196

19. WCRF Continuous Update Project (2014). World Cancer Research Fund International systematic literature review: the associations between food, nutrition and physical activity and the risk of prostate cancer. Available from: https://www.wcrf.org/sites/default/files/prostate-cancer-slr.pdf.

20. Ma J, Li H, Giovannucci E, Mucci L, Qiu W, Nguyen PL, et al. (2008). Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. Lancet Oncol. 9(11):1039–47. https://doi.org/10.1016/S1470-2045(08)70235-3 PMID:18835745

21. Ahearn TU, Pettersson A, Ebot EM, Gerke T, Graff RE, Morais CL, et al. (2015). A prospective investigation of PTEN loss and ERG expression in lethal prostate cancer. J Natl Cancer Inst. 108(2):djv346. https://doi.org/10.1093/jnci/djv346 PMID:26615022

22. Graff RE, Meisner A, Ahearn TU, Fiorentino M, Loda M, Giovannucci EL, et al. (2016). Pre-diagnostic circulating sex hormone levels and risk of prostate cancer by ERG tumour protein expression. Br J Cancer. 114(8):939–44. https://doi.org/10.1038/bjc.2016.61 PMID:26986253

23. Fine SW, Gopalan A, Leversha MA, Al-Ahmadie HA, Tickoo SK, Zhou Q, et al. (2010). *TMPRSS2-ERG* gene fusion is associated with low Gleason scores and not with high-grade morphological features. Mod Pathol. 23(10):1325–33. https://doi.org/10.1038/modpathol.2010.120 PMID:20562851

24. Netto GJ (2013). Clinical applications of recent molecular advances in urologic malignancies: no longer chasing a "mirage"? Adv Anat Pathol. 20(3):175–203. https://doi.org/10.1097/PAP.0b013e3182863f80 PMID:23574774

25. Demichelis F, Fall K, Perner S, Andrén O, Schmidt F, Setlur SR, et al. (2007). *TMPRSS2:ERG* gene fusion associated with lethal prostate cancer in a watchful waiting cohort. Oncogene. 26(31):4596–9. https://doi.org/10.1038/sj.onc.1210237 PMID:17237811

26. Berney DM, Gopalan A, Kudahetti S, Fisher G, Ambroisine L, Foster CS, et al. (2009). Ki-67 and outcome in clinically localised prostate cancer: analysis of conservatively treated prostate cancer patients from the Trans-Atlantic Prostate Group study. Br J Cancer. 100(6):888–93. https://doi.org/10.1038/sj.bjc.6604951 PMID:19293807

27. Li R, Wheeler T, Dai H, Frolov A, Thompson T, Ayala G (2004). High level of androgen receptor is associated with aggressive clinicopathologic features and decreased biochemical recurrence-free survival in prostate: cancer patients treated with radical prostatectomy. Am J Surg Pathol. 28(7):928–34. https://doi.org/10.1097/00000478-200407000-00013 PMID:15223964

28. Erho N, Buerki C, Triche TJ, Davicioni E, Vergara IA (2012). Transcriptome-wide detection of differentially expressed coding and non-coding transcripts and their clinical significance in prostate cancer. J Oncol. 2012:541353. https://doi.org/10.1155/2012/541353 PMID:22956952

29. Yamoah K, Johnson MH, Choeurng V, Faisal FA, Yousefi K, Haddad Z, et al. (2015). Novel biomarker signature that may predict aggressive disease in African American men with prostate cancer. J Clin Oncol. 33(25):2789–96. https://doi.org/10.1200/JCO.2014.59.8912 PMID:26195723

30. Pettersson A, Graff RE, Bauer SR, Pitt MJ, Lis RT, Stack EC, et al. (2012). The *TMPRSS2:ERG* rearrangement, ERG expression, and prostate cancer outcomes: a cohort study and meta-analysis. Cancer Epidemiol Biomarkers Prev. 21(9):1497–509. https://doi.org/10.1158/1055-9965.EPI-12-0042 PMID:22736790

31. Magi-Galluzzi C, Tsusuki T, Elson P, Simmerman K, LaFargue C, Esgueva R, et al. (2011). *TMPRSS2-ERG* gene fusion prevalence and class are significantly different in prostate cancer of Caucasian, African-American and Japanese patients. Prostate. 71(5):489–97. https://doi.org/10.1002/pros.21265 PMID:20878952

32. Zhao SG, Chang SL, Erho N, Yu M, Lehrer J, Alshalalfa M, et al. (2017). Associations of luminal and basal subtyping of prostate cancer with prognosis and response to androgen deprivation therapy. JAMA Oncol. 3(12):1663–72. https://doi.org/10.1001/jamaoncol.2017.0751 PMID:28494073

33. Cronin KA, Lake AJ, Scott S, Sherman RL, Noone A-M, Howlader N, et al. (2018). Annual report to the nation on the status of cancer, part I: national cancer statistics. Cancer. 124(13):2785–800. https://doi.org/10.1002/cncr.31551 PMID:29786848

34. Jayadevappa R, Chhatre S, Johnson JC, Malkowicz SB (2011). Association between ethnicity and prostate cancer outcomes across hospital and surgeon volume groups. Health Policy. 99(2):97–106. https://doi.org/10.1016/j.healthpol.2010.07.014 PMID:20708815

35. Yamoah K, Deville C, Vapiwala N, Spangler E, Zeigler-Johnson CM, Malkowicz B, et al. (2015). African American men with low-grade prostate cancer have increased disease recurrence after prostatectomy compared with Caucasian men. Urol Oncol. 33(2):70.e15–22. https://doi.org/10.1016/j.urolonc.2014.07.005 PMID:25304288

36. Powell IJ, Banerjee M, Bianco FJ, Wood DP Jr, Dey J, Lai Z, et al. (2004). The effect of race/ethnicity on prostate cancer treatment outcome is conditional: a review of Wayne State University data. J Urol. 171(4):1508–12. https://doi.org/10.1097/01.ju.0000118906.16629.8c PMID:15017209

37. Evans S, Metcalfe C, Ibrahim F, Persad R, Ben-Shlomo Y (2008). Investigating Black-White differences in prostate cancer prognosis: a systematic review and meta-analysis. Int J Cancer. 123(2):430–5. https://doi.org/10.1002/ijc.23500 PMID:18452170

38. Sarfati D (2012). Review of methods used to measure comorbidity in cancer populations: no gold standard exists. J Clin Epidemiol. 65(9):924–33. https://doi.org/10.1016/j.jclinepi.2012.02.017 PMID:22739245

39. Potosky AL, Miller BA, Albertsen PC, Kramer BS (1995). The role of increasing detection in the rising incidence of prostate cancer. JAMA. 273(7):548–52. https://doi.org/10.1001/jama.1995.03520310046028 PMID:7530782

40. Jemal A, Fedewa SA, Ma J, Siegel R, Lin CC, Brawley O, et al. (2015). Prostate cancer incidence and PSA testing patterns in relation to USPSTF screening recommendations. JAMA. 314(19):2054–61. https://doi.org/10.1001/jama.2015.14905 PMID:26575061

41. Loeb S, Bjurlin MA, Nicholson J, Tammela TL, Penson DF, Carter HB, et al. (2014). Overdiagnosis and overtreatment of prostate cancer. Eur Urol. 65(6):1046–55. https://doi.org/10.1016/j.eururo.2013.12.062 PMID:24439788

42. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. (2003). The influence of finasteride on the development of prostate cancer. N Engl J Med. 349(3):215–24. https://doi.org/10.1056/NEJMoa030660 PMID:12824459

43. Redman MW, Tangen CM, Goodman PJ, Lucia MS, Coltman CA Jr, Thompson IM (2008). Finasteride does not increase the risk of high-grade prostate cancer: a bias-adjusted modeling approach. Cancer Prev Res (Phila). 1(3):174–81. https://doi.org/10.1158/1940-6207.CAPR-08-0092 PMID:19138953

44. Wallerstedt A, Strom P, Gronberg H, Nordstrom T, Eklund M (2018). Risk of prostate cancer in men treated with 5α-reductase inhibitors – a large population-based prospective study. J Natl Cancer Inst. 110(11):1216–21. https://doi.org/10.1093/jnci/djy036 PMID:29548030

45. Cui K, Li X, Du Y, Tang X, Arai S, Geng Y, et al. (2017). Chemoprevention of prostate cancer in men with high-grade prostatic intraepithelial neoplasia (HGPIN): a systematic review and adjusted indirect treatment comparison. Oncotarget. 8(22):36674–84. https://doi.org/10.18632/oncotarget.16230 PMID:28415774

46. Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. (2011). Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 306(14):1549–56. https://doi.org/10.1001/jama.2011.1437 PMID:21990298

5.14 Testicular cancer
New inroads into early diagnosis

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SUMMARY

- Testicular cancer comprises mainly germ cell-derived tumours, which according to the most recent (2016) WHO classification are divided into two groups: tumours derived from germ cell neoplasia in situ, which are the most common, and rare tumours unrelated to germ cell neoplasia in situ.
- The incidence of testicular cancer has been rising steeply in many countries that previously had low incidence rates (e.g. Croatia and Finland), whereas in some high-incidence countries (e.g. Denmark) the rates have levelled off.
- Changing incidence trends are consistent with a major role of environmental factors in the pathogenesis of testicular germ cell tumours, acting primarily during early development.
- Testicular cancer is a polygenic syndrome, without major predisposing oncogenic mutations but with a large number of germline susceptibility loci; this renders genetic screening impossible.
- Particular features of germ cell neoplasia in situ, including high expression of pluripotency factors, low levels of DNA methylation, and a specific microRNA profile, can be exploited for early detection of testicular germ cell neoplasia.
- Because testicular cancer occurs predominantly in young men, survivors should be followed up for many years, with attention paid to preservation of reproductive function and prevention of late effects, such as hypogonadism, metabolic syndrome, and secondary cancers.

Testicular cancer is an atypical type of solid tumour. It is the most common cancer type in young men, and its incidence is increasing worldwide. Testicular cancer has strong developmental and environmental links, but also substantial genetic susceptibility.

Although testicular cancer can be derived from several cell types of the testis, germ cell-derived tumours constitute the vast majority of cases. Testicular tumours known as sex cord stromal tumours and Leydig cell tumours are derived from somatic cells present in the testis; these tumours are relatively rare, so they are not discussed in this chapter. Malignancies that are not specific for the testis, such as lymphoma or sarcoma, are not considered here either.

General characteristics and histopathology

Testicular germ cell tumours are most common in adolescents and young men (age 15–45 years). The tumours that occur in this age group are distinct from others through the association with germ cell neoplasia in situ (GCNIS) and testicular dysgenesis syndrome [1]. The pathogenesis of these tumours has a strong developmental component and overlaps with other disorders of the male reproductive system, such as cryptorchidism, other genital malformations, and some forms of male infertility [1].

The histopathology of germ cell tumours is very heterogeneous, because of their plasticity and ability to transdifferentiate. Consequently, there have been frequent changes in classification and disagreements about terminology. The most recent (2016) edition of the WHO classification is the result of a thorough revision and update by a panel of experts, who agreed on a new division and nomenclature to better reflect the biological features and histogenesis of germ cell tumours of the testis [2]. According to this classification (Box 5.14.1), testicular germ cell tumours are divided into two main groups: germ cell tumours derived from GCNIS, and germ cell tumours unrelated to GCNIS.

Germ cell tumours derived from GCNIS

Germ cell tumours derived from GCNIS comprise morphologically homogeneous seminoma and heterogeneous non-seminomatous tumours, which can contain pure or

Box 5.14.1. Main types of germ cell tumours of the testis, according to the 2016 WHO classification.

Germ cell tumours derived from germ cell neoplasia in situ

- Germ cell neoplasia in situ
- Seminoma, pure
- Non-seminomatous germ cell tumours, pure
  - Embryonal carcinoma
  - Yolk sac tumour, postpubertal type
  - Trophoblastic tumours, including choriocarcinoma
  - Teratoma, postpubertal type
- Non-seminomatous germ cell tumours, mixed

Germ cell tumours unrelated to germ cell neoplasia in situ

- Spermatocytic tumour
- Prepubertal (paediatric) tumours
  - Teratoma, prepubertal type
  - Yolk sac tumour, prepubertal type
  - Mixed tumour, prepubertal type

mixed components of embryonal carcinoma, yolk sac tumour, choriocarcinoma, and teratoma. The precursor lesion, GCNIS, consists of gonocyte-like cells that persisted in the immature stage after the fetal/infantile period and then underwent malignant transformation [1]. The pathogenesis of GCNIS is depicted in Fig. 5.14.1.

In individuals with disorders of sexual development, a pre-invasive lesion similar to GCNIS is called gonadoblastoma. Gonadoblastoma and GCNIS can be present in the same patient, and intermediate lesions are not uncommon in patients with testicular dysgenesis syndrome [3].

Germ cell tumours unrelated to GCNIS

Germ cell tumours unrelated to GCNIS include rare spermatocytic tumour of older men (mean age at diagnosis, > 54 years) and childhood testicular tumours (most common in infants and children up to age 4 years). Spermatocytic tumour has been renamed from the previously used term "spermatocytic seminoma", to avoid confusion with seminoma derived from GCNIS [2]. Spermatocytic tumour is thought to grow from expanding spermatogonial clones, which underwent genomic changes that facilitated their survival, such as amplification of chromosome 9 (*DMRT1* locus), activating mutations in *FGFR3*, *HRAS*, and *NRAS*, or whole-chromosome aneuploidy [4]. Childhood germ cell tumours are probably derived from primordial germ cells, but their etiology remains unknown.

Epidemiology

Global burden and incidence trends

Because of the rarity of other types of testicular tumours, germ cell tumours that occur in young men, which are derived from GCNIS, comprise about 95% of cases and hence are responsible for the global burden of testicular cancer. Seminomas are most often diagnosed in men aged 25–45 years, whereas non-seminomatous tumours occur in relatively younger men, mainly in the age group 15–35 years [5].

Testicular cancer is relatively rare compared with other cancer types, with an estimated 71 105 new

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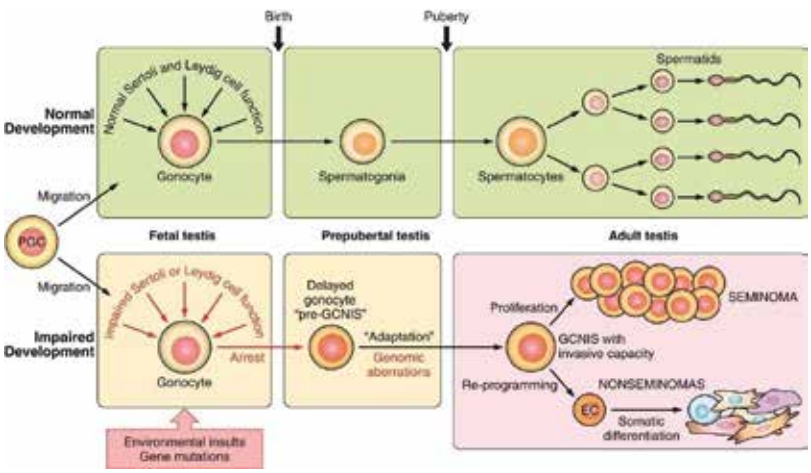
- Testicular germ cell tumours occur predominantly in adolescents and young men (aged 15–45 years), who develop seminoma or non-seminomatous tumours, which are derived from germ cell neoplasia in situ. Testicular tumours in children and older men are relatively rare and have different pathogenesis.
- Incidence rates of testicular cancer vary geographically and ethnically; rates are highest in men of European descent and lowest in men of African and East Asian ancestry.
- Because of phenotypic similarity to fetal germ cells and a strong association with disturbances of early development, testicular germ cell tumours associated with germ cell neoplasia in situ are considered a part of testicular dysgenesis syndrome, together with disorders of sexual development, cryptorchidism, and decreased spermatogenesis with signs of impaired function of Sertoli cells and Leydig cells.
- The majority of cases of testicular cancer cannot be explained by heritability alone and are attributed to still-unknown environmental factors, which act mainly during development.
- Testicular cancer has a generally good prognosis and low mortality, when managed by modern methods that exploit the sensitivity of germ cells to cisplatin-based chemotherapy. Non-seminomas, especially somatically differentiated teratomas, are more resistant to treatment compared with seminomas.

Fig. 5.14.1. Schematic depiction of the pathogenesis of testicular germ cell tumours derived from germ cell neoplasia in situ (GCNIS). These tumours are thought to be caused by a combination of adverse environmental and genetic factors (multifactorial and polygenic), which result in insufficient masculinization of the gonads, mainly because of impaired function of Sertoli cells and Leydig cells. The insufficient stimulation of developing germ cells causes arrest of gonocyte differentiation. The delayed gonocytes (pre-GCNIS cells) begin to proliferate during pubertal hormonal stimulation of the testis. Increased proliferation results in genomic changes that favour malignant transformation of GCNIS cells into an invasive tumour, either a seminoma or a non-seminoma. Normal germ cell development is shown in the top part of the figure, on the green background. EC, embryonal carcinoma; PGC, primordial germ cells.

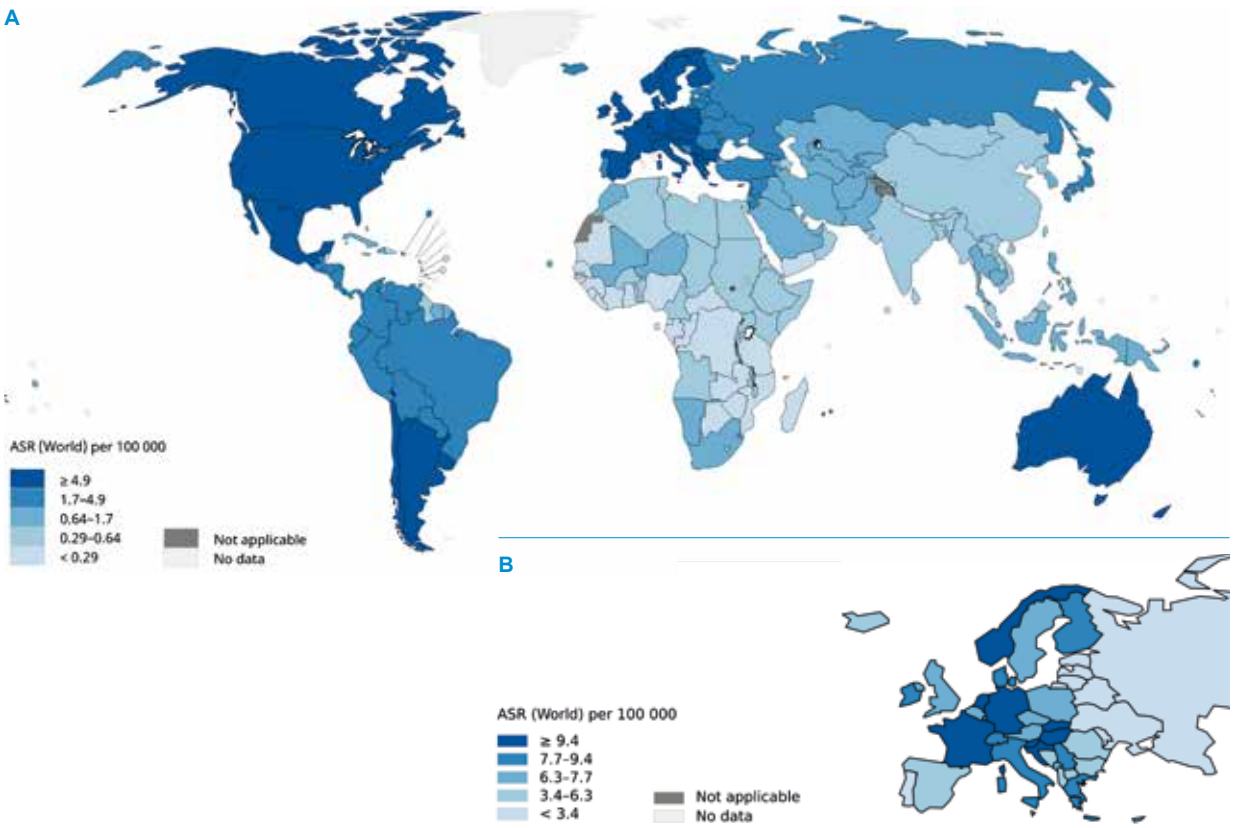


cases worldwide in 2018 (< 1% of the male cancer burden) [6]. However, it is the most common cancer type in young men. Germ cell tumours are most common in men of European descent, whereas the incidence is very low in men of African and East Asian ancestry.

Age-standardized incidence rates range from less than 0.5 per 100 000 in the lowest-incidence areas to more than 10 per 100 000 in high-risk populations (Fig. 5.14.2) [6]. In 2018, the estimated 5-year prevalence of testicular cancer worldwide was 284 073, of which 107 570 prevalent cases (38%) were in Europe [6].

The incidence of testicular germ cell tumours increased markedly around the world in the second half of the 20th century, with substantial geographical differences [7,8]. Recent studies have shown dramatically increasing trends in some European countries that previously had low incidence rates (e.g. Croatia

Fig. 5.14.2. Distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000 person-years for testicular cancer, 2018: (A) globally, (B) in Europe.



and Finland), and in Hispanic populations in the Americas. In contrast, incidence rates in Denmark, which were previously very high, have shown signs of levelling off [8,9] (Fig. 5.14.3).

These changing trends reflect geographical patterns. In 2008–2012, incidence rates in western Europe (9.1 per 100 000 in Germany and 8.8 per 100 000 in Switzerland) and in some countries in south-eastern Europe (8.8 per 100 000 in Slovenia and 8.6 per 100 000 in Slovakia) approached the rates in the high-risk countries in northern Europe [10]. As, for example, in the Nordic countries, incidence rates of testicular cancer can vary widely between neighbouring countries while showing smaller within-country variations compared with other cancer types [9]. In the multiethnic USA, there are large differences between ethnic groups; a recent increase in incidence rates has been noted in Hispanic White men [11]. In most countries in Asia, the incidence is low and is increasing only modestly, whereas in Latin America marked increases have been observed [7,8].

Mortality

In 2018, there were an estimated 9507 deaths from testicular cancer worldwide [6]. Age-standardized mortality rates for testicular cancer are low (≤ 1 per 100 000). This is due in part to the relative ease of

Fig. 5.14.3. Age-standardized (World) incidence rates per 100 000 person-years by calendar year in selected countries for testicular cancer, circa 1955–2010. Asterisks indicate regional registries (other registries are national).

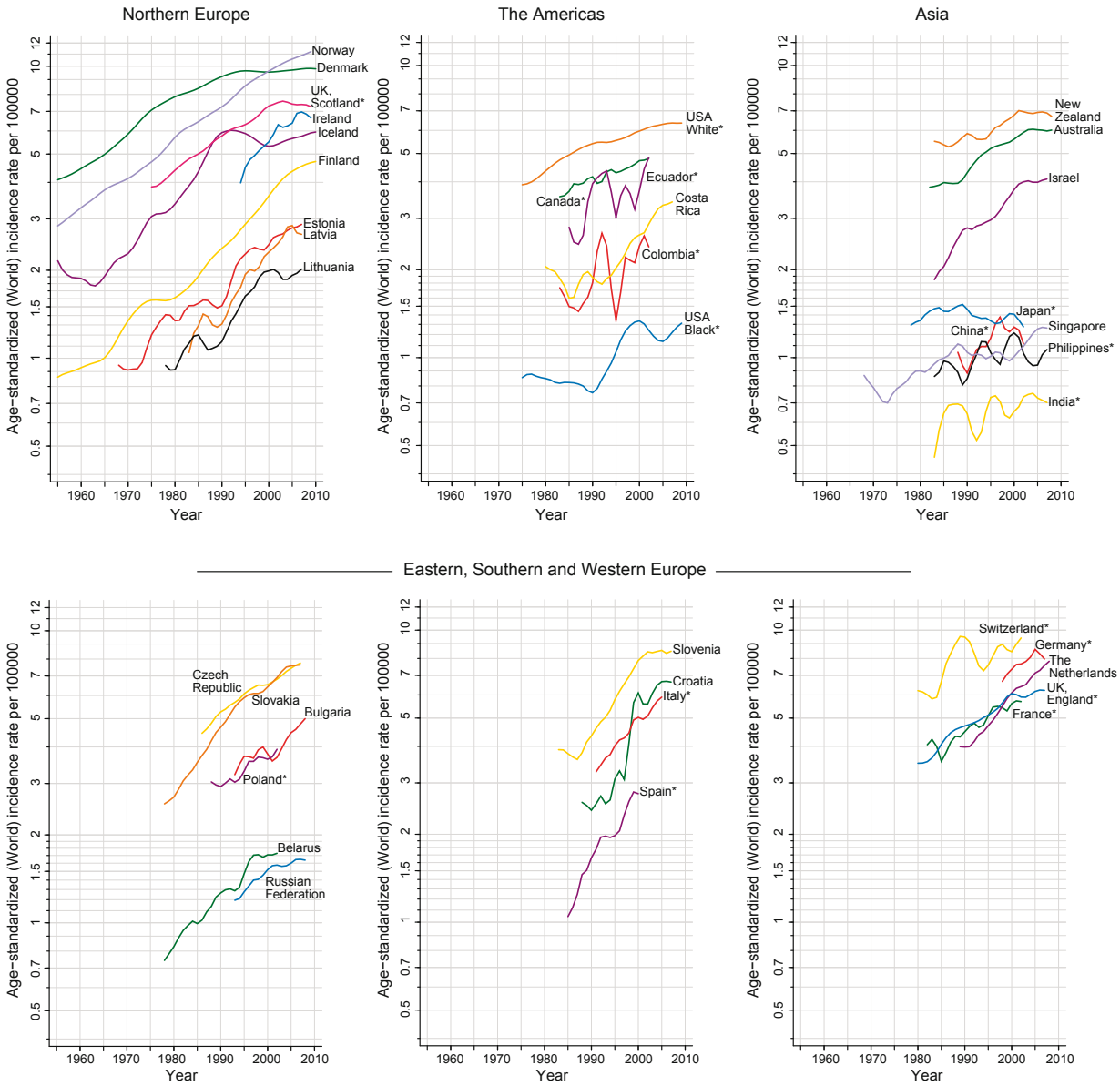
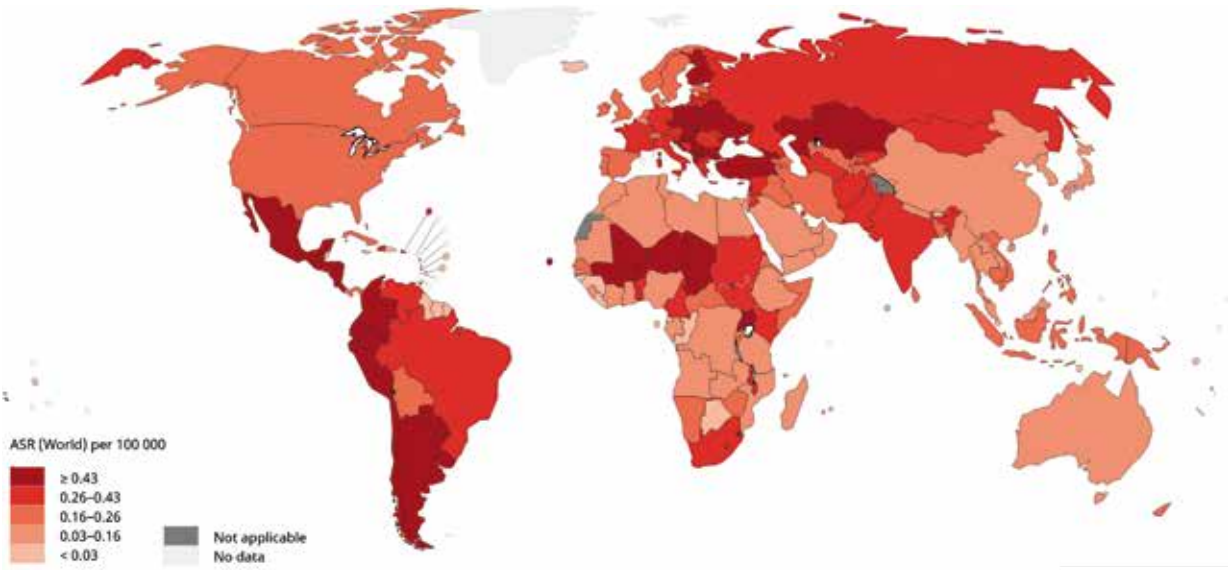


Fig. 5.14.4. Global distribution of estimated age-standardized (World) mortality rates (ASR) per 100 000 person-years for testicular cancer, 2018.



diagnosis and surgical treatment, but predominantly to the very efficient cisplatin-based chemotherapy regimens. For the population of the USA in 2009–2015, the 5-year relative survival was 95.2% overall; for localized testicular cancer it was more than 99%, but for disseminated testicular cancer it was about 73% [12]. Despite the generally good prognosis, studies have revealed that the treatment efficacy of disseminated and refractory testicular cancer, especially for cases that require salvage surgery, is best in high-volume centres with good experience [13].

Although in high-income countries early diagnosis and adequate treatment are available and mortality rates have been declining since the 1970s or 1980s, in low- and middle-income countries access to testicular cancer control is more limited [14]; this is reflected in higher mortality rates in lower-income countries (Fig. 5.14.4) and large global variations in incidence-to-mortality ratios [6,7]. The EUROCARE-5 study reported age-standardized 5-year relative survival for 2005–2007 of 90%, with survival in eastern Europe about 10% lower than that in northern and western Europe [15]. Disparities in mortality have been reported between different world regions, such as between Latin America and North America [7].

Etiology and risk factors

The increasing prevalence of cryptorchidism, other genital malformations, and male infertility synchronous with testicular cancer was the basis for the hypothesis that these conditions could be etiologically linked within testicular dysgenesis syndrome [1]. The causal factors behind the epidemic increase in incidence rates and the rapidly changing trends in testicular cancer remain largely unknown, but they must be related to environment or lifestyle. The primary importance of environmental factors is also supported by studies of migrant populations, in which the risk of testicular cancer changed depending on the geographical location during development (reviewed in [1]).

The etiology is known only in a small percentage of genetically determined cases. Individuals with developmental abnormalities of the gonads and sex differentiation (including testicular dysgenesis syndrome and disorders of sexual development) are at high risk of germ cell neoplasia. The risk in these individuals is variable, but it is greatest in those with mixed gonadal dysgenesis (e.g. 45,X/46,XY karyotype) and with partial androgen insensitivity syndrome [3,16].

Cryptorchidism is the most significant risk factor for sporadic testicular cancer, and about 5% of patients with a history of undescended testis develop a testicular germ cell tumour. Other repeatedly identified risk factors include inguinal hernia, low birth weight, high maternal age, being born first, late age at puberty, and poor spermatogenesis [1].

Epidemiological and clinical studies that identified links to early development are consistent with the biological features of GCNIS, which is characterized by close similarity to fetal gonocytes [17] (see below for details). However, except for the rare cases of disorders of sexual development with obvious genetic defects that lead to germ cell tumours (e.g. mutations in *SRY* or *AR*), identification of specific causal factors that cause delayed maturation of gonocytes has proven difficult. Among multiple hypothetical environmental factors, prenatal maternal lifestyle factors or intrauterine or perinatal exposures to xenobiotics or endocrine disrupters have been suggested.

Early studies investigated estrogenic compounds, including in utero exposure to diethylstilbestrol, followed by anti-androgenic organochlorine compounds, such as 4,4′-dichlorodiphenyltrichloroethane (DDT), and phthalates. Few conclusive results were obtained, except for weak associations with exposure to 4,4′-dichlorodiphenyldichloroethylene (DDE) – a metabolite of DDT that is sometimes used as a biomarker of exposure to DDT – and chlordane [1,18].

Larger, well-controlled studies that are based on novel ideas are needed [19]. Future studies should investigate maternal and developmental exposures to emerging endocrine disrupters and their mixtures, preferably in combination with the evaluation of the genetic predisposition of the studied individuals.

With regard to postpubertal or adult exposures, very few risk factors have been identified. Heavy use of cannabis (defined as use at least weekly or use for at least 10 years), but not occasional use, has been associated with a doubling of the risk of developing a non-seminoma, compared with never use [20]. Among occupational exposures of the relatively young patients with testicular germ cell tumours, no strong associations have been found; furthermore, the few existing studies on maternal or parental exposures have not yielded any consistent results [21].

Genetics

Testicular cancer is among the cancer types with a relatively high heritability. Familial risk is high, especially for brothers of patients with germ cell tumours, who have an estimated 8–10-fold increased risk, whereas the sons of cases have a 4–6-fold increased risk [22]. A greater risk for brothers than for sons is consistent with a strong environmental modulation of the risk during development.

Specific oncogenic driver mutations in a single gene have not been identified in patients with testicular cancer, except for secondary gain-of-function *KIT* mutations, which were detected essentially only in pure seminomas [23], or *KRAS* mutations, which were detected mainly in non-seminomas, as well as a few other secondary passenger mutations [24]. The absence of a major single predisposition gene has recently been confirmed by a large whole-exome sequencing study of 919 patients and 1609 cancer-free controls [25]. This complex polygenic nature of testicular cancer is consistent with a complex and multifactorial pathogenesis, which renders genetic screening for germline mutations impossible in the clinical setting.

Several genome-wide association studies (GWAS) (see Chapter 3.2) performed since 2009 have identified a number of possibly predisposing gene variants. The strongest genetic markers for an increased risk of testicular germ cell tumours are located within or near the following loci: *KITLG*, *SPRY4*, *DMRT1*, *PRDM14*, *DAZL*, and *HPGDS* (reviewed in [26]). Other informative markers have been revealed by recent meta-analytic GWAS that combined data from very large cohorts, increasing the number of predisposing loci to 49 and the combined heritability to more than one third of the studied cases [27,28]. The multicentre meta-analyses currently being carried out by international consortia will probably identify additional susceptibility genes. Most of the predisposing genetic markers identified so far implicate predominantly pathways involved in germ cell development, sex differentiation, and gonadal development, as well as centrosome cycle, DNA repair, and telomere function [26].

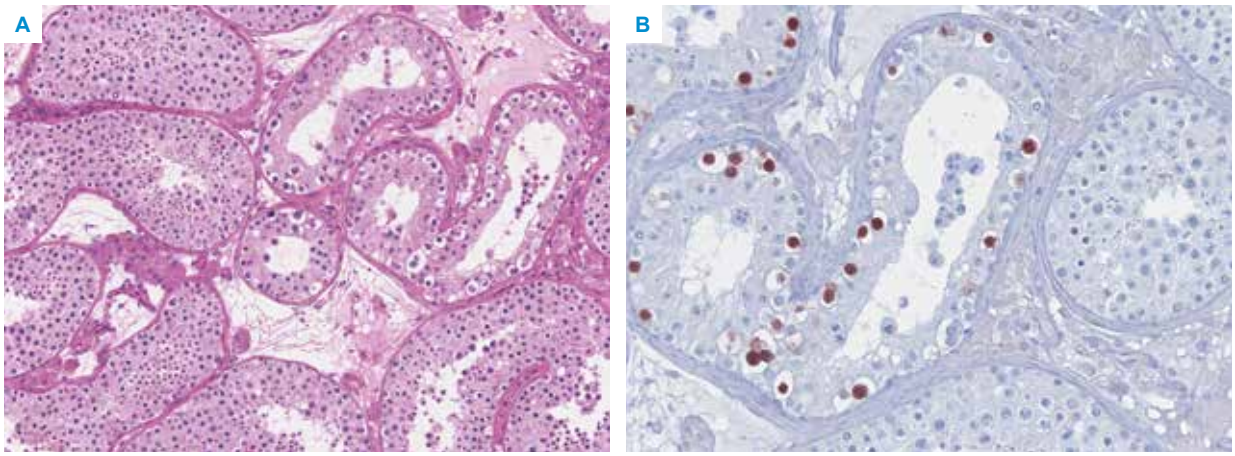
Some of the predisposing variants have different prevalence between racial groups, thus shedding some light on the reasons for the large ethnic differences in the incidence of testicular cancer. One illustrative example is the *KITLG* locus (single-nucleotide polymorphism rs995030), which is carried by most people of European descent but only a minority of people of African descent.

Fig. 5.14.5. A cannabis plant. The only consistently reported postpubertal risk factor for testicular cancer (mainly non-seminoma) is heavy use of cannabis.

Biological characteristics important for diagnosis

The biological features of tumours derived from GCNIS differ markedly from those of the normal germ cells found in the adult testis; this provides insights into their pathogenesis and

Fig. 5.14.6. The precursor lesion of the most prevalent testicular germ cell tumours in young men, germ cell neoplasia in situ (GCNIS), in a testicular biopsy. (A) Haematoxylin and eosin staining showing the difference between tubules with GCNIS (upper right corner) and preserved tubules with ongoing spermatogenesis. (B) A close-up of a tubule with nuclei of GCNIS cells stained positive for OCT4, a pluripotency marker that is not present in normal adult germ cells and helps to detect GCNIS.



facilitates detection and diagnosis. GCNIS and seminoma cells resemble fetal gonocytes and have a similar gene expression profile, characterized by high expression of embryonic pluripotency factors, such as *POU5F1* (OCT4), NANOG, *TFAP2C* (AP2-gamma), and LIN28 [17] (reviewed in [5]). This unusual profile is partly explained by very low levels of DNA methylation of the genome of GCNIS and seminoma, in contrast to non-seminomas, which have high DNA methylation profiles, similar to those of somatic cells [5,23,29–31]. In addition, GCNIS cells are characterized by permissive histone modifications, which render their chromatin accessible to transcription factors; this could potentially explain their plasticity in response to environmental stimuli [1,30,31].

An important recent development in the biology of testicular cancer is the discovery of specific microRNAs (miRNAs) secreted by malignant germ cells, including GCNIS cells, both in adult men and in children (reviewed in [32,33]). The miRNA profile of malignant germ cells is characterized by particularly high levels of the miR-371-3 cluster, as well as miR-302 and miR-367 [32–34]. The presence of additional clusters, miR-519 and miR-375, has been reported in embryonal carcinomas and teratomas, respectively [23]. The miRNA-based tests outperformed the classical serum markers in a large clinical study [34].

Prevention of invasive cancer by early detection of GCNIS

Preventive measures are currently very limited, because of the uncertainty about the causation of testicular cancer in the vast majority of cases. The most effective prevention strategy for invasive cancer is early diagnosis at the pre-invasive stage. This is currently possible only in patients in high-risk groups, including individuals with disorders of sexual development, cryptorchidism, infertility, or other signs of testicular dysgenesis.

Unequivocal diagnosis of GCNIS requires testicular biopsy (usually bilateral) and immunohistochemical staining for at least one specific marker (e.g. PLAP or OCT4) [5] (Fig. 5.14.6). In about 5–6% of cases of seemingly unilateral testicular germ cell tumours, GCNIS is present in the contralateral testis. Therefore, a biopsy of the remaining testis is advised at the time of orchidectomy for the primary tumour, at least in men at high risk, who are defined as presenting with more than one of the following risk factors: history of cryptorchidism, poor semen quality, young age, testicular atrophy, and microlithiasis.

Efforts are under way to develop a less invasive method than testicular biopsy for detection of GCNIS or incipient microinvasive tumour. Such a method would preferably require only a blood or semen sample. An immunocytological detection method has been established, using an automated double-staining assay for alkaline phosphatase and AP2-gamma or OCT4 in the ejaculate, but further improvement of sensitivity is needed for routine use of this approach in the clinic [35]. Novel serum assays exploiting miRNAs have a very good specificity and sensitivity for overt tumours [32–34], but it remains unclear whether these tests will be sensitive enough to detect GCNIS or early microinvasive tumours.

Fertility preservation and prevention of late effects

Because testicular cancer occurs predominantly in young men and modern management means that the prognosis is good, most survivors live for many decades after treatment. Therefore, the emphasis has shifted from saving life to preserving quality of life. Even after being declared cancer-free, survivors

should be followed up for many years, taking into account not only the possibility of a late recurrence of the malignancy but also health issues related to the lack of one or both testes, such as subfertility, hypogonadism, sexual dysfunction, metabolic syndrome, and osteoporosis later in life, which result in decreased life expectancy [36].

Many patients with testicular cancer have poor spermatogenesis and decreased fertility even before the overt tumour has developed, and in most men the situation worsens markedly after orchidectomy or cytotoxic chemotherapy [1,37]. Andrological follow-up is important, with close monitoring of testosterone levels, because Leydig cell dysfunction is common and the ensuing hypogonadism is a major risk factor for metabolic syndrome [37].

In addition, patients treated with radiotherapy or chemotherapy have an increased risk of secondary cancers, cardiovascular disease, peripheral neuropathy, ototoxicity, and hepatotoxicity [38]. Also important are quality-of-life issues related to prolonged anxiety and stress. There is a growing consensus that individualized treatment is needed to diminish immediate and late side-effects, and attention should be paid to issues related to reproductive health and quality of life.

References

1. Skakkebaek NE, Rajpert-De Meyts E, Buck Louis GM, Toppari J, Andersson AM, Eisenberg ML, et al. (2016). Male reproductive disorders and fertility trends: influences of environment and genetic susceptibility. Physiol Rev. 96(1):55–97. https://doi.org/10.1152/physrev.00017.2015 PMID:26582516
2. Ulbright TM, Amin MB, Balzer B, Berney DM, Epstein JI, Guo C, et al. (2016). Germ cell tumours. In: Moch H, Humphrey PA, Ulbright TM, Reuter VE, editors. WHO classification of tumours of the urinary system and male genital organs. Lyon, France: International Agency for Research on Cancer (WHO Classification of Tumours series, 4th edition); pp. 189–226.
3. Jørgensen A, Lindhardt Johansen M, Juul A, Skakkebaek NE, Main KM, Rajpert-De Meyts E (2015). Pathogenesis of germ cell neoplasia in testicular dysgenesis and disorders of sex development. Semin Cell Dev Biol. 45:124–37. https://doi.org/10.1016/j.semcdb.2015.09.013 PMID:26410164
4. Giannoulatou E, Maher GJ, Ding Z, Gillis AJM, Dorssers LCJ, Hoischen A, et al. (2017). Whole-genome sequencing of spermatocytic tumors provides insights into the mutational processes operating in the male germline. PLoS One. 12(5):e0178169. https://doi.org/10.1371/journal.pone.0178169 PMID:28542371
5. Rajpert-De Meyts E, McGlynn KA, Okamoto K, Jewett MAS, Bokemeyer C (2016). Testicular germ cell tumours. Lancet. 387(10029):1762–74. https://doi.org/10.1016/S0140-6736(15)00991-5 PMID:26651223
6. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593
7. Znaor A, Lortet-Tieulent J, Jemal A, Bray F (2014). International variations and trends in testicular cancer incidence and mortality. Eur Urol. 65(6):1095–106. https://doi.org/10.1016/j.eururo.2013.11.004 PMID:24268506
8. Trabert B, Chen J, Devesa SS, Bray F, McGlynn KA (2015). International patterns and trends in testicular cancer incidence, overall and by histologic subtype, 1973-2007. Andrology. 3(1):4–12. https://doi.org/10.1111/andr.293 PMID:25331326
9. Patama T, Engholm G, Larønningen S, Ólafsdóttir E, Khan S, Storm H, et al. (2018). Small-area based map animations of cancer incidence in the Nordic countries, 1971–2015. Nordic Cancer Union. Available from: https://astra.cancer.fi/cancermaps/Nordic_18/.
10. Bray F, Colombet M, Mery L, Piñeros M, Znaor A, Zanetti R, et al., editors (2017). Cancer incidence in five continents, Vol. XI (electronic version). Lyon, France: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr.
11. Ghazarian AA, Trabert B, Devesa SS, McGlynn KA (2015). Recent trends in the incidence of testicular germ cell tumors in the United States. Andrology. 3(1):13–8. https://doi.org/10.1111/andr.288 PMID:25331158
12. National Cancer Institute Surveillance, Epidemiology, and End Results Program (2018). Cancer stat facts: testicular cancer. Available from: https://seer.cancer.gov/statfacts/html/testis.html.
13. Tandstad T, Kollmannsberger CK, Roth BJ, Jeldres C, Gillessen S, Fizazi K, et al. (2017). Practice makes perfect: the rest of the story in testicular cancer as a model curable neoplasm. J Clin Oncol. 35(31):3525–8. https://doi.org/10.1200/JCO.2017.73.4723 PMID:28854068
14. Cherny NI, Sullivan R, Torode J, Saar M, Eniu A (2017). ESMO International Consortium study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in countries outside of Europe. Ann Oncol. 28(11):2633–47. https://doi.org/10.1093/annonc/mdx521 PMID:28950323
15. Trama A, Foschi R, Larrañaga N, Sant M, Fuentes-Raspall R, Serraino D, et al.; EUROCARE-5 Working Group (2015). Survival of male genital cancers (prostate, testis and penis) in Europe 1999-2007: results from the EUROCARE-5 study. Eur J Cancer. 51(15):2206–16. https://doi.org/10.1016/j.ejca.2015.07.027 PMID:26421823
16. Cools M, Wolffenbuttel KP, Hersmus R, Mendonca BB, Kaprová J, Drop SLS, et al. (2017). Malignant testicular germ cell tumors in postpubertal individuals with androgen insensitivity: prevalence, pathology and relevance of single nucleotide polymorphism-based susceptibility profiling. Hum Reprod. 32(12):2561–73. https://doi.org/10.1093/humrep/dex300 PMID:29121256

17. Sonne SB, Almstrup K, Dalgaard M, Juncker AS, Edsgard D, Ruban L, et al. (2009). Analysis of gene expression profiles of microdissected cell populations indicates that testicular carcinoma in situ is an arrested gonocyte. Cancer Res. 69(12):5241–50. https://doi.org/10.1158/0008-5472.CAN-08-4554 PMID:19491264

18. Bonde JP, Flachs EM, Rimborg S, Glazer CH, Giwercman A, Ramlau-Hansen CH, et al. (2016). The epidemiologic evidence linking prenatal and postnatal exposure to endocrine disrupting chemicals with male reproductive disorders: a systematic review and meta-analysis. Hum Reprod Update. 23(1):104–25. https://doi.org/10.1093/humupd/dmw036 PMID:27655588

19. Stang A, Trabert B, Rusner C, Poole C, Almstrup K, Rajpert-De Meyts E, et al. (2015). A survey of etiologic hypotheses among testicular cancer researchers. Andrology. 3(1):19–26. https://doi.org/10.1111/andr.306 PMID:25538016

20. Gurney J, Shaw C, Stanley J, Signal V, Sarfati D (2015). Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis. BMC Cancer. 15(1):897. https://doi.org/10.1186/s12885-015-1905-6 PMID:26560314

21. Ylönen O, Jyrkkiö S, Pukkala E, Syvänen K, Boström PJ (2018). Time trends and occupational variation in the incidence of testicular cancer in the Nordic countries. BJU Int. 122(3):384–93. https://doi.org/10.1111/bju.14148 PMID:29460991

22. Hemminki K, Chen B (2006). Familial risks in testicular cancer as aetiological clues. Int J Androl. 29(1):205–10. https://doi.org/10.1111/j.1365-2605.2005.00599.x PMID:16466541

23. Shen H, Shih J, Hollern DP, Wang L, Bowlby R, Tickoo SK, et al.; Cancer Genome Atlas Research Network (2018). Integrated molecular characterization of testicular germ cell tumors. Cell Rep. 23(11):3392–406. https://doi.org/10.1016/j.celrep.2018.05.039 PMID:29898407

24. Taylor-Weiner A, Zack T, O'Donnell E, Guerriero JL, Bernard B, Reddy A, et al. (2016). Genomic evolution and chemoresistance in germ-cell tumours. Nature. 540(7631):114–8. https://doi.org/10.1038/nature20596 PMID:27905446

25. Litchfield K, Loveday C, Levy M, Dudakia D, Rapley E, Nsengimana J, et al. (2018). Large-scale sequencing of testicular germ cell tumour (TGCT) cases excludes major TGCT predisposition gene. Eur Urol. 73(6):828–31. https://doi.org/10.1016/j.eururo.2018.01.021 PMID:29433971

26. Litchfield K, Levy M, Huddart RA, Shipley J, Turnbull C (2016). The genomic landscape of testicular germ cell tumours: from susceptibility to treatment. Nat Rev Urol. 13(7):409–19. https://doi.org/10.1038/nrurol.2016.107 PMID:27296647

27. Litchfield K, Levy M, Orlando G, Loveday C, Law PJ, Migliorini G, et al.; UK Testicular Cancer Collaboration; PRACTICAL Consortium (2017). Identification of 19 new risk loci and potential regulatory mechanisms influencing susceptibility to testicular germ cell tumor. Nat Genet. 49(7):1133–40. https://doi.org/10.1038/ng.3896 PMID:28604728

28. Wang Z, McGlynn KA, Rajpert-De Meyts E, Bishop DT, Chung CC, Dalgaard MD, et al.; Testicular Cancer Consortium (2017). Meta-analysis of five genome-wide association studies identifies multiple new loci associated with testicular germ cell tumor. Nat Genet. 49(7):1141–7. https://doi.org/10.1038/ng.3879 PMID:28604732

29. Rijlaarsdam MA, Tax DM, Gillis AJ, Dorssers LC, Koestler DC, de Ridder J, et al. (2015). Genome wide DNA methylation profiles provide clues to the origin and pathogenesis of germ cell tumors. PLoS One. 10(4):e0122146. https://doi.org/10.1371/journal.pone.0122146 PMID:25859847

30. Lawaetz AC, Almstrup K (2015). Involvement of epigenetic modifiers in the pathogenesis of testicular dysgenesis and germ cell cancer. Biomol Concepts. 6(3):219–27. https://doi.org/10.1515/bmc-2015-0006 PMID:26103631

31. Lobo J, Gillis AJM, Jerónimo C, Henrique R, Looijenga LHJ (2019). Human germ cell tumors are developmental cancers: impact of epigenetics on pathobiology and clinic. Int J Mol Sci. 20(2):E258. https://doi.org/10.3390/ijms20020258 PMID:30634670

32. Murray MJ, Huddart RA, Coleman N (2016). The present and future of serum diagnostic tests for testicular germ cell tumours. Nat Rev Urol. 13(12):715–25. https://doi.org/10.1038/nrurol.2016.170 PMID:27754472

33. Nappi L, Nichols C (2019). MicroRNAs as biomarkers for germ cell tumors. Urol Clin North Am. 46(3):449–57. https://doi.org/10.1016/j.ucl.2019.04.011 PMID:31277739

34. Dieckmann KP, Radtke A, Geczi L, Matthies C, Anheuser P, Eckardt U, et al. (2019). Serum levels of microRNA-371a-3p (M371 test) as a new biomarker of testicular germ cell tumors: results of a prospective multicentric study. J Clin Oncol. 37(16):1412–23. https://doi.org/10.1200/JCO.18.01480 PMID:30875280

35. Almstrup K, Lippert M, Mogensen HO, Nielsen JE, Hansen JD, Daugaard G, et al. (2011). Screening of subfertile men for testicular carcinoma in situ by an automated image analysis-based cytological test of the ejaculate. Int J Androl. 34(4 Pt 2):e21–30, discussion e30–1. https://doi.org/10.1111/j.1365-2605.2011.01192.x PMID:21696398

36. Capocaccia R, Gatta G, Dal Maso L (2015). Life expectancy of colon, breast, and testicular cancer patients: an analysis of US-SEER population-based data. Ann Oncol. 26(6):1263–8. https://doi.org/10.1093/annonc/mdv131 PMID:25735314

37. Bandak M, Jørgensen N, Juul A, Lauritsen J, Oturai PS, Mortensen J, et al. (2017). Leydig cell dysfunction, systemic inflammation and metabolic syndrome in long-term testicular cancer survivors. Eur J Cancer. 84:9–17. https://doi.org/10.1016/j.ejca.2017.07.006 PMID:28772110

38. Chovanec M, Abu Zaid M, Hanna N, El-Kouri N, Einhorn LH, Albany C (2017). Long-term toxicity of cisplatin in germ-cell tumor survivors. Ann Oncol. 28(11):2670–9. https://doi.org/10.1093/annonc/mdx360 PMID:29045502

5.15 Bladder cancer
A genotoxic causal agent recognized

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SUMMARY

- More than 90% of bladder cancers are urothelial carcinomas, which are usually staged as either muscle-invasive tumours, which have a poorer prognosis, or non-muscle-invasive tumours, which have a better prognosis but frequently recur.
- In addition to causes including inhaled tobacco smoke and certain occupational exposures, aristolochic acid is now recognized as causing bladder cancer, possibly in association with renal failure.
- Aristolactam–DNA adducts and a specific mutational signature (A:T → T:A transversion), initially discovered in the *TP53* gene, may serve as biomarkers of exposure to aristolochic acid.
- With the increasing use of large-scale genome-wide profiling studies, the conventional two-pathway model of bladder cancer pathogenesis is being superseded by a molecular description of disease pathogenesis and clinical behaviour. This approach should provide more adequate information for personalized clinical and therapeutic management.

Bladder cancer causes an estimated 199 900 deaths per year worldwide [1]. Like tumours of the renal pelvis and ureter, tumours of the bladder are derived from transitional epithelia. Together, these tumour types account for 10–15% of all primary malignancies in adults. These urothelial carcinomas are multicentric in nature and often occur – and recur – at multiple sites in the lower urinary tract in an affected patient. The wall of the bladder is the most common site of involvement.

Molecular subtypes

Significant differences in patient characteristics, incidence, and survival exist, and research is continuing on gene–environment interactions with risk of bladder cancer [2].

Urothelial carcinoma is the most common type of bladder cancer, but distinct histomorphological phenotypes have been reported (10–25%) that are associated with more aggressive disease and poor response to existing therapies [3]. These cancers are usually staged as either non-muscle-invasive tumours (~75%) or muscle-invasive tumours (~25%).

The Cancer Genome Atlas (TCGA) project identified genetic drivers for muscle-invasive bladder cancer as well as clusters associated with distinct prognostic factors and therapeutic responses [4]. The TCGA Research Network reported the major genetic determinants of muscle-invasive bladder cancer and showed that bladder cancer can be further subclassified at the molecular level according to gene expression and mutation patterns, including aggressive histological variants with poor response to existing therapies. Muscle-invasive bladder cancers are heterogeneous and can be grouped into the basal and luminal intrinsic subtypes [5].

Five expression subtypes have been identified that may stratify response to different treatments. The luminal-papillary subtype is characterized by *FGFR3* mutations, fusions with *TACC3*, and/or amplification. The luminal-infiltrated subtype is characterized by high expression of epithelial–mesenchymal transition and myofibroblast markers, with medium expression of *PD-L1* and *CTL4* immune markers. The luminal subtype has high expression of luminal markers, as well as *KRT20* and *SNX31*. The basal-squamous subtype is characterized by a higher incidence in women, squamous differentiation, basal keratin expression, and high expression of *PD-L1* and *CTLA4* immune markers. The neuronal subtype is characterized by expression of both neuroendocrine and neuronal genes, as well as a high cell-cycle signature, reflective of a proliferative state [6].

The identification of multiple distinct molecular subtypes of non-muscle-invasive and muscle-invasive bladder cancer suggests multiple pathways within each of the major pathways. Development of histopathologically recognizable urothelial alterations is preceded by clonal expansion of altered cells

within the urothelium. Low-grade papillary tumours may arise via simple hyperplasia and minimal dysplasia, and these are characterized at the molecular level by loss of heterozygosity of chromosome 9 and activating mutations of *FGFR3*, *PIK3CA*, and *STAG2*. These non-invasive tumours frequently recur but are genetically stable [7]. Invasive carcinoma is thought to arise via flat dysplasia and carcinoma in situ, which commonly show *TP53* mutations in addition to chromosome 9 deletions but no *FGFR3* mutations. Invasive tumours are genetically unstable and accumulate many genomic alterations, such as *RB1* loss and *ERBB2* or *PTEN* mutations [6].

Epidemiology

Bladder cancer is a highly prevalent disease and is associated with substantial morbidity, mortality, and cost. Tobacco smoking and occupational exposures to carcinogens remain the factors with the highest attributable risk. In 2018, there were an estimated 549 000 new cases of bladder cancer and 199 900 deaths from bladder cancer globally; bladder cancer was the 12th most common cancer type and the 12th most common cause of cancer death worldwide [1].

Classical epidemiological studies have confirmed a markedly increased incidence of bladder cancer in workers exposed to various aromatic amines used in the dyeing, chemical, and rubber industries. Besides these occupational exposures, inhaled tobacco smoke is the most prominent environmental carcinogen known to cause bladder cancer (see Chapter 2.1). Additional agents include arsenic exposure from contaminated water in endemic areas for blackfoot disease (a type of peripheral vasculitis) in southwestern Taiwan, China. Moreover, a high incidence of bladder cancer of the squamous type has been found in patients with chronic parasitic infestation due to *Schistosoma haematobium* [8].

Exposure to arsenic through contaminated groundwater sources (see Chapter 2.9) and also through food (such as rice and seafood) is a public health problem in many countries. It is estimated that more than 200 million people in 70 countries are chronically exposed to arsenic at levels at or above the WHO threshold of 10 µg/L, leading to cardiovascular, pulmonary, and skin diseases and also different types of cancer, including bladder cancer and urinary tract cancer [9].

Arsenic is classified by the IARC Monographs as carcinogenic to humans (Group 1). Mechanisms of arsenic carcinogenesis are complex and are not fully understood. According to cancer studies conducted mainly in endemic areas of arsenic contamination (Argentina, Bangladesh, northern Chile, and Taiwan, China), the mechanisms involve oxidative stress and DNA damage, epigenetic DNA modification, and genomic instability [10].

Aristolochic acid, a constituent of all *Aristolochia* plants, is a powerful nephrotoxin and human carcinogen, which is associated with chronic kidney disease and upper urinary tract urothelial carcinoma as well as bladder cancer. The term "aristolochic acid nephropathy" actually includes any form of toxic interstitial nephropathy that is caused either by the ingestion of plants containing aristolochic acid as part of traditional phytotherapies (formerly known as "Chinese herbs nephropathy") or by the environmental contamination of food (known as "Balkan endemic nephropathy") [11]. (See also Chapter 2.8.)

In addition to its nephrotoxic effects, possibly leading to end-stage renal disease, exposure to aristolochic acid has frequently been associated with the development of urothelial malignancies. Aristolochic acid (and plants containing it) was classified by the IARC Monographs as carcinogenic to humans (Group 1) in 2008, after an earlier evaluation in 2002 [12]. This finding is consistent with aristolochic acids being listed as "known to be human carcinogens" by the United States National Toxicology Program in 2014 [13].

Since the identification of aristolochic acid nephropathy in the early 1990s in Belgium, an increasing number of cases of aristolochic acid intoxication have been reported around the world [14]. The incidence

FUNDAMENTALS

- Bladder cancer is the 12th most common cancer type worldwide, and urothelial carcinoma is the most common tumour type. Most patients are diagnosed with non-invasive and low-grade tumours.
- Tobacco smoking is the most important cause of bladder cancer. Arsenic and some occupational exposures also cause bladder cancer.
- Aristolochic acid, a constituent of all *Aristolochia* plants, is a powerful nephrotoxin and human carcinogen and causes, among other diseases, bladder cancer and renal cell carcinoma.
- Cystoscopy enables a definitive diagnosis of bladder cancer. Prognosis and management of bladder cancer depend on histopathology.
- Some evidence supports a genetic predisposition to bladder cancer, and genome-wide association studies have found sequence variants that can increase the risk of bladder cancer and of chemoresistance.
- Immunotherapy with checkpoint inhibitors has revolutionized the treatment paradigm of bladder cancer; since 2016, five agents have been approved to treat platinum-refractory bladder cancer.

of upper urinary tract urothelial carcinoma is particularly high in Asian countries, including specifically in Taiwan, China, because traditional medicines are very popular and the complexity of the pharmacopoeia presents a high risk of aristolochic acid intoxication, as a result of some confusion between closely related species [15]. In the Balkan countries, the causative factor was identified as the environmental phytotoxin aristolochic acid contained in *Aristolochia clematitis*, a common plant growing in the wheat fields, which was ingested in home-baked bread [16] (Fig. 5.15.1).

The nephrotoxic effect of aristolochic acid is irreversible. Given that chronic kidney disease and carcinogenic complications may develop very slowly after the initial exposure, aristolochic acid nephropathy and associated upper urinary tract urothelial carcinoma and bladder cancer may become a major public health issue in the next few years [17].

Genetics and genomics

Genetic susceptibility

Some evidence supports a genetic predisposition to bladder cancer. Potential inheritable forms of bladder cancer, such as those that occur in Lynch syndrome, are an active area of research. Lynch syndrome is an inherited condition that increases the risk of cancers, including urothelial carcinoma. Screening of patients known to have Lynch syndrome is important, to evaluate for the development of primary tumours. Inherited mutations in DNA repair genes confer a greater risk of urothelial carcinoma. Additional research is needed to evaluate the optimal frequency and type of screening for individual patients [18].

Genome-wide association studies (GWAS) (see Chapter 3.2) have found sequence variants that can increase the risk of bladder cancer. Most of the significant variants associated with risk of bladder cancer are located in DNA repair genes. Polymorphisms for *GSTM1-null*, *NAT2-slow*, *APOBEC*-rs1014971, *SLC14A1*-rs10775480, *CCNE1*-rs8102137, *PSCA*-rs2294008, *UGT1A*-rs1189203, and *TP63*-rs35592567 confer increased risk [19].

Mutational signature of aristolochic acid

After metabolic activation, aristolochic acid reacts with DNA to form aristolactam–DNA adducts. These lesions concentrate in the renal cortex, serving as a sensitive and specific biomarker of exposure, even more than 10 years after exposure to aristolochic acid. They are also found in the urothelium, where they give rise to a unique mutational signature in the *TP53* gene and generally (Fig. 5.15.2).

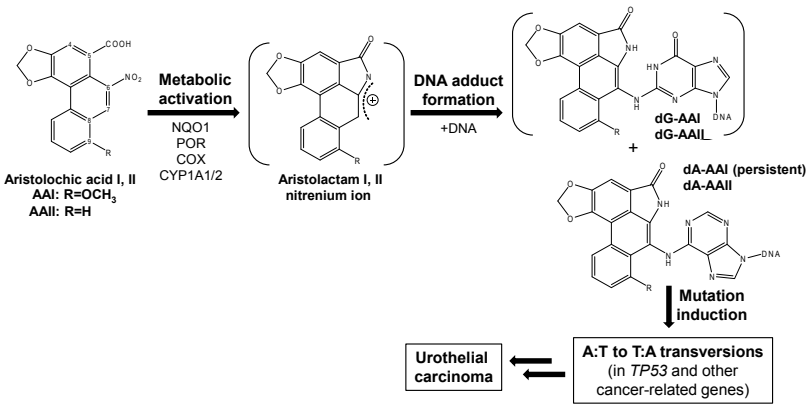
This A:T → T:A transversion – also called COSMIC signature 22 – has frequently been detected in cases of upper urinary tract urothelial carcinoma described in the Balkans and in Taiwan, China [20], whereas this mutation rarely occurs in tumours that are not related to exposure to aristolochic acid [15,21]. In Taiwan, China, such mutations were also detected at activating positions in the *FGFR3* and *HRAS* oncogenes. Extensive analyses of mutation spectra from bladder cancer cases in Singapore and Taiwan, China, suggested a strong involvement of aristolochic acid in bladder cancer development in Asian countries, indicating an important public health issue [22].

Mutational signatures of tobacco smoking

The mechanisms of tobacco carcinogenesis are very complex and may vary between tumour sites. Comparative studies of cancer genome sequences from smokers and non-smokers found that smokers had

Fig. 5.15.1. (Left) *Aristolochia clematitis* blossoming in grasslands in Serbia, and (right) the corresponding fruits and seeds collected during the harvest of the wheat crop from fields in the same area. *A. clematitis* is recognized as the causal agent of Balkan endemic nephropathy and is associated with upper urinary tract urothelial carcinoma and bladder cancer.

Fig. 5.15.2. Metabolic activation and DNA adduct formation by aristolochic acid (AA). R = OCH_3 in AAI, and R = H in AAII. COX, cyclooxygenase; CYP, cytochrome P450; dA-AAI, 7-(deoxyadenosin-N^6-yl)aristolactam I; dA-AAII, 7-(deoxyadenosin-N^6-yl)aristolactam II; dG-AAI, 7-(deoxyguanosin-N^2-yl)aristolactam I; dG-AAII, 7-(deoxyguanosin-N^2-yl) aristolactam II; NQO1, NAD(P)H:quinone oxidoreductase; POR, NADPH:cytochrome P450 oxidoreductase.



higher numbers of base substitutions compared with non-smokers [23]. In tumours of tissues directly exposed to tobacco smoke (the lung and the larynx), COSMIC signature 4 was prominent. This signature is similar to that produced by benzo[*a*]pyrene in cells in vitro and suggests a misreplication of DNA damage (adducts) formed by carcinogens present in tobacco smoke. Other signatures, such as signature 2 (which features GC → AT mutations) and signature 13 (which features GC → CG mutations), are considered to reflect an over-reactivity of the APOBEC family of cytidine deaminases in DNA editing [24]. A multiplatform analysis of more than 400 patients with muscle-invasive bladder cancer confirmed a high mutational load driven by APOBEC-mediated mutagenesis. The detection of this signature corresponded to a 5-year survival rate of 75% [6].

Signature 5 is found in all tumour types related to smoking and has a predominance of AT → GC and GC → AT mutations. In smokers, the frequency of mutations attributable to signature 5 has been found to increase with age at diagnosis; this has been suggested to reflect an acceleration of endogenous mutagenic processes (a "clocklike" process) in some susceptible tissues, in particular in tissues directly exposed to tobacco smoke [23,25].

DNA methylation in urothelial carcinoma

Potential epigenetic signatures, mainly for DNA methylation alterations but also for mutations in chromatin regulators, have been linked to specific carcinogens (see Chapter 3.11). Their validation as potential biomarkers in urine or tissue samples is still required [26].

Etiology

Risk factors

In Asia, *Aristolochia* species are considered an integral part of the herbology used in traditional Chinese medicine, Japanese Kampō medicine, and Ayurvedic medicine. *Aristolochia* is part of the same therapeutic family as the *Akebia*, *Asarum*, *Cocculus*, and *Stephania* plants. These plants are referred to by common names such as Mu Tong, Mokutsu, and Fang Ji, and they are used in a multitude of herbal mixtures for therapeutic use. *Stephania tetrandra* (known as Han Fang Ji) is sometimes mistakenly substituted with *Aristolochia fangchi* (known as Guang Fang Ji), because they are morphologically similar (Fig. 5.15.3).

Originally, aristolochic acid nephropathy was reported in Belgium in more than 100 individuals who had ingested weight-loss capsules containing powdered root extracts of *Aristolochia fangchi*. The causal link with the intake of capsules containing aristolochic acid was demonstrated by the detection of aristolactam–DNA adducts in renal tissue samples. It is estimated that exposure to aristolochic acid affects 100 000 people in the Balkans (where the total number of patients with kidney disease is about 25 000), 8 million people in Taiwan, China, and more than 100 million people in China [16].

In the initial cohorts for iatrogenic aristolochic acid nephropathy, the majority of patients were described as exhibiting a rapid and progressive evolution towards chronic kidney disease or end-stage renal disease [14]. In environmental aristolochic acid nephropathy, the progression rate is much slower, reaching end-stage renal disease after 15–20 years [27].

Activities such as mining, combustion of fossil fuels, and the use of arsenic-based pesticides are known to potentiate the environmental accumulation of arsenic. This presents a major threat to human health because exposure of individuals through inhalation, ingestion, and skin contact can result in numerous adverse health effects [9]. Consumption of drinking-water from contaminated groundwater sources and ingestion of contaminated food (fish and grains) are the major routes of human exposure. Biological factors (sex, race, and age) and lifestyle factors (nutrition and smoking status) may influence the efficacy of the pathways implicated in arsenic metabolism and cytotoxic outcome, resulting in inter-individual variations in susceptibility to arsenic toxicity [9,10].

Evaluation and diagnosis

Patients suspected of having bladder cancer are usually evaluated by white-light cystoscopy, with adjunct

Fig. 5.15.3. (Left) Leaves of the *Stephania tetrandra* S. Moore plant (known as Han Fang Ji in traditional Chinese medicine). (Middle) Leaves of the *Aristolochia elegans* plant; the shape is similar to that of *Stephania tetrandra* leaves. (Right) Transverse sections of the roots of *Aristolochia fangchi* (known as Guang Fang Ji in traditional Chinese medicine) and weightloss capsules containing the powdered root, ingested by a Belgian patient who developed end-stage renal disease. *A. fangchi* is recognized as the causal agent of aristolochic acid-induced severe to end-stage renal failure and multifocal urothelial carcinoma in Belgium.

cytology performed to detect malignant cells. To date, no urinary-based tumour markers have demonstrated sufficient sensitivity and specificity to replace cystoscopy in the detection of bladder cancer.

Cystoscopic detection may be enhanced by optical imaging technologies such as fluorescence cystoscopy or narrow-band imaging. These technologies improve the differentiation of tumorous lesions from normal tissue by taking advantage of the increased metabolic activity (blue light) and vessel architecture (narrow-band) that occur in cancer cells, and they have higher specificity for bladder cancer than traditional cystoscopy does. Especially the detection rate of carcinoma in situ could be significantly increased by the use of these methods.

Microscopic imaging techniques like confocal laser endomicroscopy and optical coherence tomography permit a real-time high-resolution assessment of the bladder mucosa at a cellular and subcellular level with spatial resolutions similar to those of histology, but these techniques are not yet approved for routine use in the diagnosis of bladder cancer [28]. Prognosis and management of bladder cancer depend on histopathology, the only reliable determining factor of tumour biology (Fig. 5.15.4) [29].

The possibility of using circulating tumour cells as a means, among other things, to detect bladder cancer has been discussed [30]. Methylation markers in urine have been described for detection of bladder cancer, but the diagnostic accuracy is highly variable among reports [31].

Prevention

Reduced exposure to carcinogens

With respect to urothelial malignancies associated with aristolochic acid (Fig. 5.15.5), primary prevention through regulation and education is possible. However, the general population considers traditional herbal remedies to be harmless because they are of natural origin. Moreover, most patients who use these natural products fail to inform their physicians of their use. Therefore, these natural products, like all drugs, should be submitted to rigorous pharmacological and toxicological studies to determine their safety and efficacy.

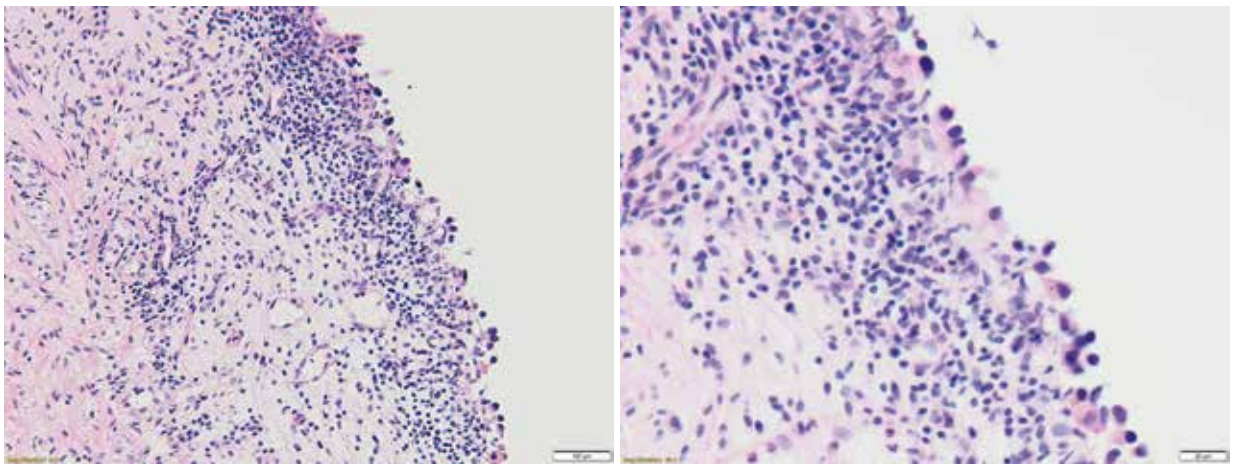
In addition to opportunities for primary prevention, detection of exposure to aristolochic acid by the use of molecular epidemiology studies (biomarkers and endogenous mutagenic processes) would provide opportunities for secondary prevention in populations at risk, in the form of intensified screening.

Recurrent prevention campaigns can provide information about cancers related to tobacco smoking. In contrast, measures to fight environmental arsenic contamination are difficult to implement. Specific equipment to remove arsenic from contaminated water is of poor efficiency (activated carbon-based filters) or expensive (reverse osmosis). Other approaches have been proposed on the basis of animal studies: metal chelators (partially successful), vitamins (vitamin C, vitamin B_{12}, and folic acid) and trace elements for their antioxidant properties, glutathione as an antioxidant and an inhibitor of reactive oxygen species, and plant-derived polyphenols with antioxidant properties [10]. To date, only a few of these have been tested in a clinical setting. Because the proportions of possible responders vary among subgroups of the population, some biomarker-based screening programmes are likely to be developed for individuals with high health risk and arsenic exposure.

Screening

No major organization recommends screening asymptomatic adults for bladder cancer, and current evidence is insufficient to assess the

Fig. 5.15.4. Histological aspect of bladder carcinoma in situ observed adjacent to high-grade papillary urothelial carcinoma in a Belgian patient who underwent a kidney transplant for end-stage aristolochic acid nephropathy. Urothelial carcinoma in situ is characterized by flat, disordered proliferation of urothelial cells with marked cytological abnormalities. Haematoxylin and eosin staining; magnification 100× (left) and 400× (right).



balance of benefits and harms of screening. However, non-randomized trials have demonstrated the ability to detect bladder cancer in selected populations, such as those exposed to aristolochic acid [32,33].

Improved methods of detection and diagnosis

Several urine biomarkers exist, but until now these have had a limited role for the detection of bladder cancer. Emerging studies have been published proposing panels of protein biomarkers for the detection of bladder cancer, and the diagnostic performance of multiplex urinary protein profiling could be improved when it is combined with clinical information about the patient, such as age, race, and smoking status [34].

New research paths

Epidemiological studies have shown differences between the sexes in the incidence and progression of bladder cancer, suggesting an association with steroid hormone pathways; therefore, the role of sex steroids is an emerging research area in the development and progression of bladder cancer [35]. A member of the family of UDP-glucuronosyltransferases (UGTs), UGT1A, is an enzyme that is vital for the detoxification of major carcinogens, such as aromatic amines. UGT1A is involved in tumour progression, and decreased levels of UGT1A are associated with recurrence and progression of bladder cancer. UGT1A is differentially regulated by estrogens, and androgen-mediated signals promote bladder carcinogenesis by downregulating the expression of UGTs [36,37].

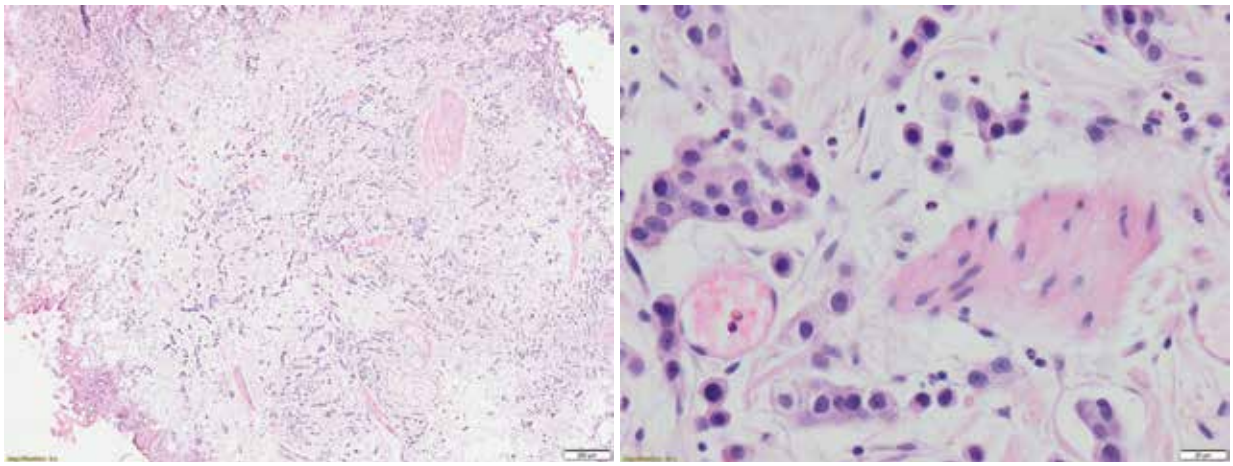
Improved therapeutic strategies

For nearly 30 years, the first-line standard of care treatment for patients with locally advanced or metastatic bladder cancer has been cisplatin-containing combination chemotherapy. The median survival is now approximatively 15 months, compared with the estimated survival of 6 months for patients with metastatic disease before the development of modern chemotherapy. The 5-year survival rate with contemporary regimens remains poor, at 15%. About 21% of patients are treated with cisplatin-based chemotherapy, and cisplatin ineligibility is common because of renal dysfunction, an Eastern Cooperative Oncology Group (ECOG) performance status of 2, or both. Hearing loss, grade 2 neuropathy, and heart failure may also confer cisplatin ineligibility.

Immunotherapy with programmed cell death 1 (PD-1) and programmed death-ligand 1 (PD-L1) checkpoint inhibitors has revolutionized the treatment paradigm of bladder cancer. Since 2016, five agents have been approved to treat platinum-refractory bladder cancer. The approved PD-1 and PD-L1 inhibitor agents have similar efficacy and safety profiles. There is a lack of consensus on the utility of testing for PD-L1 as a predictive biomarker, because patients with no expression also derive some clinical benefit. Tumour mutation burden is another putative predictive biomarker, but further validation is needed [38]. The improved tolerability of immunotherapy over chemotherapy and radiation directly correlates with its targeted mechanism of action. The current landscape is rapidly evolving, and novel immunotherapy combination trials are under way to further improve outcomes and define the ideal patients [39].

With the increasing use of large-scale genome-wide profiling studies, the conventional two-pathway model of bladder cancer pathogenesis is being superseded by a molecular description of disease pathogenesis and clinical behaviour. This approach should provide more adequate information for personalized clinical and therapeutic management.

Fig. 5.15.5. Nested variant of bladder carcinoma infiltrating the muscle wall in another Belgian kidney transplant recipient. Haematoxylin and eosin staining; magnification 100× (left) and 400× (right).



References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593
2. Cumberbatch MGK, Jubber I, Black PC, Esperto F, Figueroa JD, Kamat AM, et al. (2018). Epidemiology of bladder cancer: a systematic review and contemporary update of risk factors in 2018. Eur Urol. 74(6):784–95. https://doi.org/10.1016/j.eururo.2018.09.001 PMID:30268659
3. Willis D, Kamat AM (2015). Nonurothelial bladder cancer and rare variant histologies. Hematol Oncol Clin North Am. 29(2):237–52, viii. https://doi.org/10.1016/j.hoc.2014.10.011 PMID:25836932
4. Cancer Genome Atlas Research Network (2014). Comprehensive molecular characterization of urothelial bladder carcinoma. Nature. 507(7492):315–22. https://doi.org/10.1038/nature12965 PMID:24476821
5. Choi W, Czerniak B, Ochoa A, Su X, Siefker-Radtke A, Dinney C, et al. (2014). Intrinsic basal and luminal subtypes of muscle-invasive bladder cancer. Nat Rev Urol. 11(7):400–10. https://doi.org/10.1038/nrurol.2014.129 PMID:24960601
6. Robertson AG, Kim J, Al-Ahmadie H, Bellmunt J, Guo G, Cherniack AD, et al.; TCGA Research Network (2017). Comprehensive molecular characterization of muscle-invasive bladder cancer. Cell. 171(3):540–556.e25. https://doi.org/10.1016/j.cell.2017.09.007 PMID:28988769
7. Hurst CD, Platt FM, Taylor CF, Knowles MA (2012). Novel tumor subgroups of urothelial carcinoma of the bladder defined by integrated genomic analysis. Clin Cancer Res. 18(21):5865–77. https://doi.org/10.1158/1078-0432.CCR-12-1807 PMID:22932667
8. Miyazaki J, Nishiyama H (2017). Epidemiology of urothelial carcinoma. Int J Urol. 24(10):730–4. https://doi.org/10.1111/iju.13376 PMID:28543959
9. Minatel BC, Sage AP, Anderson C, Hubaux R, Marshall EA, Lam WL, et al. (2018). Environmental arsenic exposure: from genetic susceptibility to pathogenesis. Environ Int. 112:183–97. https://doi.org/10.1016/j.envint.2017.12.017 PMID:29275244
10. Rao CV, Pal S, Mohammed A, Farooqui M, Doescher MP, Asch AS, et al. (2017). Biological effects and epidemiological consequences of arsenic exposure, and reagents that can ameliorate arsenic damage *in vivo*. Oncotarget. 8(34):57605–21. https://doi.org/10.18632/oncotarget.17745 PMID:28915699
11. Jadot I, Declèves A-E, Nortier J, Caron N (2017). An integrated view of aristolochic acid nephropathy: update of the literature. Int J Mol Sci. 18(2):1–23. https://doi.org/10.3390/ijms18020297 PMID:28146082
12. IARC (2002). Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. IARC Monogr Eval Carcinog Risks Hum. 82:1–556. Available from: http://publications.iarc.fr/100 PMID:12687954
13. National Toxicology Program (2014). Aristolochic acids. Report on carcinogens. Research Triangle Park (NC), USA: Department of Health and Human Services; pp. 1–5. Available from: https://ntp.niehs.nih.gov/ntp/roc/content/profiles/aristolochicacids.pdf.
14. Gökmen MR, Cosyns JP, Arlt VM, Stiborová M, Phillips DH, Schmeiser HH, et al. (2013). The epidemiology, diagnosis, and management of aristolochic acid nephropathy: a narrative review. Ann Intern Med. 158(6):469–77. https://doi.org/10.7326/0003-4819-158-6-201303190-00006 PMID:23552405
15. Chen CH, Dickman KG, Moriya M, Zavadil J, Sidorenko VS, Edwards KL, et al. (2012). Aristolochic acid-associated urothelial cancer in Taiwan. Proc Natl Acad Sci U S A. 109(21):8241–6. https://doi.org/10.1073/pnas.1119920109 PMID:22493262
16. Bunel V, Souard F, Antoine M-F, Stévigny C, Nortier JL (2018). Nephrotoxicity of natural products: aristolochic acid and fungal toxins. In: McQueen CA, editor. Comprehensive toxicology. Volume 14. 3rd ed. Oxford, UK: Elsevier Ltd; pp. 340–79. https://doi.org/10.1016/B978-0-12-801238-3.64093-X
17. Grollman AP (2013). Aristolochic acid nephropathy: harbinger of a global iatrogenic disease. Environ Mol Mutagen. 54(1):1–7. https://doi.org/10.1002/em.21756 PMID:23238808

18. Phelan A, Lopez-Beltran A, Montironi R, Zhang S, Raspollini MR, Cheng M, et al. (2018). Inherited forms of bladder cancer: a review of Lynch syndrome and other inherited conditions. Future Oncol. 14(3):277–90. https://doi.org/10.2217/fon-2017-0346 PMID:29345160

19. de Maturana EL, Rava M, Anumudu C, Sáez O, Alonso D, Malats N (2018). Bladder cancer genetic susceptibility. A systematic review. Bladder Cancer. 4(2):215–26. https://doi.org/10.3233/BLC-170159 PMID:29732392

20. Stiborová M, Arlt VM, Schmeiser HH (2017). DNA adducts formed by aristolochic acid are unique biomarkers of exposure and explain the initiation phase of upper urothelial cancer. Int J Mol Sci. 18(10):2144. https://doi.org/10.3390/ijms18102144 PMID:29036902

21. Jelaković B, Karanović S, Vuković-Lela I, Miller F, Edwards KL, Nikolić J, et al. (2012). Aristolactam-DNA adducts are a biomarker of environmental exposure to aristolochic acid. Kidney Int. 81(6):559–67. https://doi.org/10.1038/ki.2011.371 PMID:22071594

22. Poon SL, Huang MN, Choo Y, McPherson JR, Yu W, Heng HL, et al. (2015). Mutation signatures implicate aristolochic acid in bladder cancer development. Genome Med. 7(1):38. https://doi.org/10.1186/s13073-015-0161-3 PMID:26015808

23. Alexandrov LB, Ju YS, Haase K, Van Loo P, Martincorena I, Nik-Zainal S, et al. (2016). Mutational signatures associated with tobacco smoking in human cancer. Science. 354(6312):618–22. https://doi.org/10.1126/science.aag0299 PMID:27811275

24. Phillips DH (2018). Mutational spectra and mutational signatures: insights into cancer aetiology and mechanisms of DNA damage and repair. DNA Repair (Amst). 71:6–11. https://doi.org/10.1016/j.dnarep.2018.08.003 PMID:30236628

25. Fantini D, Seiler R, Meeks JJ (2019). Molecular footprints of muscle-invasive bladder cancer in smoking and nonsmoking patients. Urol Oncol. 37(11):818–25. https://doi.org/10.1016/j.urolonc.2018.09.017 PMID:30446446

26. Schulz WA, Goering W (2016). DNA methylation in urothelial carcinoma. Epigenomics. 8(10):1415–28. https://doi.org/10.2217/epi-2016-0064 PMID:27624974

27. Jelaković B, Dika Ž, Arlt VM, Stiborova M, Pavlović NM, Nikolić J, et al. (2019). Balkan endemic nephropathy and the causative role of aristolochic acid. Semin Nephrol. 39(3):284–96. https://doi.org/10.1016/j.semnephrol.2019.02.007 PMID:31054628

28. Schubert T, Rausch S, Fahmy O, Gakis G, Stenzl A (2017). Optical improvements in the diagnosis of bladder cancer: implications for clinical practice. Ther Adv Urol. 9(11):251–60. https://doi.org/10.1177/1756287217720401 PMID:29662543

29. Soukup V, Čapoun O, Cohen D, Hernández V, Babjuk M, Burger M, et al. (2017). Prognostic performance and reproducibility of the 1973 and 2004/2016 World Health Organization grading classification systems in non-muscle-invasive bladder cancer: a European Association of Urology Non-Muscle Invasive Bladder Cancer Guidelines Panel systematic review. Eur Urol. 72(5):801–13. https://doi.org/10.1016/j.eururo.2017.04.015 PMID:28457661

30. Busetto GM, Ferro M, Del Giudice F, Antonini G, Chung BI, Sperduti I, et al. (2017). The prognostic role of circulating tumor cells (CTC) in high-risk non-muscle-invasive bladder cancer. Clin Genitourin Cancer. 15(4):e661–6. https://doi.org/10.1016/j.clgc.2017.01.011 PMID:28188046

31. Bosschieter J, Lutz C, Segerink LI, Vis AN, Zwarthoff ECA, A van Moorselaar RJ, et al. (2018). The diagnostic accuracy of methylation markers in urine for the detection of bladder cancer: a systematic review. Epigenomics. 10(5):673–87. https://doi.org/10.2217/epi-2017-0156 PMID:29692199

32. Zlotta AR, Roumeguere T, Kuk C, Alkhateeb S, Rorive S, Lemy A, et al. (2011). Select screening in a specific high-risk population of patients suggests a stage migration toward detection of non-muscle-invasive bladder cancer. Eur Urol. 59(6):1026–31. https://doi.org/10.1016/j.eururo.2011.03.027 PMID:21458152

33. Starke N, Singla N, Haddad A, Lotan Y (2016). Long-term outcomes in a high-risk bladder cancer screening cohort. BJU Int. 117(4):611–7. https://doi.org/10.1111/bju.13154 PMID:25891519

34. Szarvas T, Nyirády P, Ogawa O, Furuya H, Rosser CJ, Kobayashi T (2018). Urinary protein markers for the detection and prognostication of urothelial carcinoma. Methods Mol Biol. 1655:251–273. https://doi.org/10.1007/978-1-4939-7234-0_19 PMID:28889391

35. Godoy G, Gakis G, Smith CL, Fahmy O (2016). Effects of androgen and estrogen receptor signaling pathways on bladder cancer initiation and progression. Bladder Cancer. 2(2):127–37. https://doi.org/10.3233/BLC-160052 PMID:27376135

36. Izumi K, Taguri M, Miyamoto H, Hara Y, Kishida T, Chiba K, et al. (2014). Androgen deprivation therapy prevents bladder cancer recurrence. Oncotarget. 5(24):12665–74. https://doi.org/10.18632/oncotarget.2851 PMID:25557268

37. Izumi K, Li Y, Ishiguro H, Zheng Y, Yao JL, Netto GJ, et al. (2014). Expression of UDP-glucuronosyltransferase 1A in bladder cancer: association with prognosis and regulation by estrogen. Mol Carcinog. 53(4):314–24. https://doi.org/10.1002/mc.21978 PMID:23143693

38. Stenehjem DD, Tran D, Nkrumah MA, Gupta S (2018). PD1/PDL1 inhibitors for the treatment of advanced urothelial bladder cancer. Onco Targets Ther. 11:5973–89. https://doi.org/10.2147/OTT.S135157 PMID:30275703

39. Bellmunt J, Powles T, Vogelzang NJ (2017). A review on the evolution of PD-1/PD-L1 immunotherapy for bladder cancer: the future is now. Cancer Treat Rev. 54:58–67. https://doi.org/10.1016/j.ctrv.2017.01.007 PMID:28214651

5.16 Kidney cancer
Multiple risk factors but currently limited preventive strategies

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SUMMARY

- In 2018, there were an estimated 403 000 new cases of kidney cancer worldwide, accounting for 2.4% of all new cancer cases. The predominant tumour type is renal cell carcinoma. Age-standardized incidence rates in men are highest in Belarus, Estonia, Czechia, Latvia, and Lithuania and lowest in India, Thailand, and some countries in Africa.
- Eight genetic syndromes have been reported to increase the risk of renal cell carcinoma. The most common is von Hippel–Lindau syndrome.
- Genetic variants in 13 regions of the genome have been identified as risk factors for renal cell carcinoma through large-scale genome-wide association studies. The implicated pathways include the VHL-HIF pathway.
- The increase in risk of renal cell carcinoma is about 30% in smokers compared with never-smokers. Excess body weight, hypertension, chronic kidney disease, diabetes, and occupational exposure to trichloroethylene are each associated with an increased risk of kidney cancer.
- Opportunities for early detection are limited, and renal cell carcinoma is diagnosed at an advanced stage in 25–30% of patients.

"Kidney cancer" is a broad term referring to a histologically heterogeneous group of tumours that arise in the renal parenchyma and the renal pelvis. Renal cell carcinoma, which denotes cancer originating from the epithelial cells of the renal parenchyma, accounts for more than 90% of all cases of kidney cancer [1].

The most common histological classification of renal cell carcinoma is clear cell renal cell carcinoma (~80%), which is the most commonly diagnosed type of kidney cancer in adults. Other histological subtypes of kidney cancer include papillary (10–15%), chromophobe (~5%), and collecting duct (< 2%) renal cell carcinomas. Oncocytomas are a benign histological subtype. A substantial proportion of renal cell carcinomas can be cured by surgical resection as the main treatment.

Kidney cancer that occurs in children (Wilms tumour, also known as nephroblastoma) is a different entity, which is beyond the scope of this chapter. Tumours that arise in the renal pelvis and the ureter (urothelial carcinomas) are far less common than renal cell carcinomas and have different epidemiological features, which are similar to those of bladder cancer (see Chapter 5.15).

In this chapter, descriptive statistics are reported for the broad classification of kidney cancer; in discussions of features such as risk factors and prognosis, the focus is on the most common subtype (i.e. renal cell carcinoma), with some statements pertaining to other, less common subtypes of kidney cancer.

Epidemiology

Incidence patterns

In 2018, there were an estimated 403 000 new cases of kidney cancer worldwide, accounting for 2.4% of all new cancer cases [2].

Geography and ethnicity

There are large geographical variations in incidence rates of kidney cancer. Age-standardized incidence rates in men vary from more than 20 per 100 000 in five European countries (Belarus, Estonia, Czechia, Latvia, and Lithuania) to less than 2 per 100 000 in low-risk countries such as India, Thailand, and some countries in Africa (Fig. 5.16.1) [2].

In the USA, age-standardized incidence rates of kidney cancer are higher in Blacks (15.6 per 100 000 in males and 8.6 per 100 000 in females) than in Whites (14.0 per 100 000 in males and 7.6 per 100 000 in females) [3]. Incidence rates in Hispanic Whites are similar to those in non-Hispanic Whites. Rates in American Indians and Alaska Natives are intermediate (10.9 per 100 000 in males and 6.6

per 100 000 in females), and rates in Asians and Pacific Islanders are lower (6.4 per 100 000 in males and 2.9 per 100 000 in females) [3].

In Europe, large regional variations have been described within some countries, notably in Germany (higher incidence rates in the eastern regions of the country) and in Italy (higher incidence rates in the northern part of the country) [4].

Age and sex

Incidence rates of kidney cancer increase steadily with age, with a peak of incidence at about age 75 years [3,5]. Worldwide, more than half of all cases are diagnosed in people younger than 65 years [2].

The incidence of kidney cancer in men is about twice that in women, across geographical regions and categories of race and ethnicity [6]. The stability of the male-to-female incidence ratio over time, across countries, and by age groups substantiates that biological differences between men and women – rather than differences in lifestyle factors, such as tobacco smoking – are likely to account for much of this disparity in incidence.

Temporal trends

Incidence rates of kidney cancer have been increasing worldwide since the 1970s [5]. In the USA, incidence rates in males have increased steadily, from 8.0 per 100 000 in 1975 to 13.4 per 100 000 in 2008–2012. In most countries, the average annual percentage increase is about 2–3%. Only Austria and Poland have reported significant decreases in rates, since the early 2000s. Because the effects of both birth cohort and calendar period contribute to the increases in incidence rates, the observed temporal trends are likely to be due to a combination of changes in lifestyle and in exposures to risk factors, as well as changes in tumour detection and in diagnostic practices over time [7].

Mortality patterns

International variations in kidney cancer mortality rates follow the same pattern as for incidence rates. Age-standardized mortality rates are highest in Belarus (11 per 100 000 in males) and the Baltic countries [2]. Globally, mortality rates of kidney cancer have been stable since the 1990s [5]. In recent years, mortality rates have decreased in most countries, with the notable exception of Brazil, Croatia, Greece, Ireland, Portugal, and Slovenia, where rates have increased.

In general, mortality rates appear to be decreasing faster in women than in men. In the USA, the decline in mortality rates is more pronounced in Blacks than in Whites, and mortality rates in Blacks have remained slightly lower than those in Whites since the 1970s [5,8]. Competing mortality may play a role, but ethnic differences in the biology and aggressiveness of kidney cancer could also explain this variation [9].

Genetics and genomics

Genetic syndromes

Approximately 3–5% of renal cell carcinomas occur in a familial context [10]. Only a subset of the familial kidney cancer cases can be explained by known genetic syndromes [10].

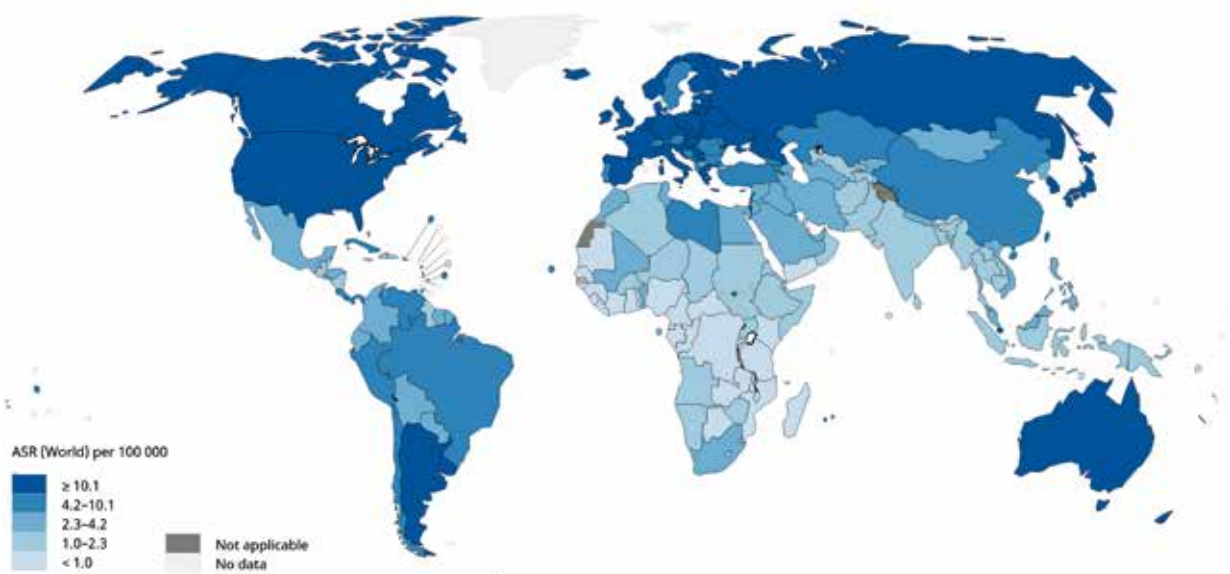
The most common syndrome known to be associated with renal cell carcinoma is von Hippel–Lindau (VHL) syndrome. It affects an estimated 1 per 36 000 live births in the United Kingdom and is suggested to account for approximately 1% of patients with renal cell carcinoma [11]. VHL syndrome is caused by mutations in the *VHL* tumour suppressor gene, which is located on the short arm of chromosome 3. VHL syndrome also increases the risk of a range of other tumours: haemangioblastomas of the brain, spine, and retina; pheochromocytomas of the adrenal gland; and neuroendocrine tumours of the pancreas. The risk of renal cell carcinoma depends on the type of mutation in the *VHL* gene.

Currently, there are seven other syndromes that have been reported to increase the risk of renal cell carcinoma: familial clear cell renal carcinoma with chromosome 3 translocation, hereditary papillary renal carcinoma syndrome, Birt–Hogg–Dubé syndrome, hereditary leiomyomatosis and renal carcinoma syndrome, *PTEN* hamartoma syndrome, succinate dehydrogenase complex-associated renal carcinoma, and *BAP1* mutant syndrome [10]. These syndromes have been described in less detail than VHL syndrome with respect to their association with risk of kidney cancer,

FUNDAMENTALS

- "Kidney cancer" refers to a histologically heterogeneous group of tumours. There are large geographical variations in incidence rates, which are poorly explained, as well as increasing incidence rates in certain populations.
- Incidence rates of kidney cancer have been increasing worldwide since the 1970s.
- The vast majority of cases are sporadic, and known risk factors, such as tobacco smoking, obesity, and hypertension, confer only modest risk increases. This makes it difficult to identify high-risk groups and to develop screening procedures.
- Enhanced early detection efforts that do not result in overdiagnosis are needed, because these would reduce mortality from kidney cancer. For localized, early-stage, low-grade tumours, the prognosis is very good after surgical intervention.
- Kidney cancer is often diagnosed at an advanced stage; for such tumours, prognosis is poor.

Fig. 5.16.1. Global distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000 person-years for kidney cancer in men, 2018.



and their prevalence in the population is mostly unknown.

Genetic polymorphisms

Genetic variants in 13 regions of the genome have been identified as risk factors for renal cell carcinoma through large-scale genome-wide association studies (GWAS) [12]. The implicated pathways include the VHL-HIF pathway – with variants discovered in two regions: the *EPAS1* gene, which encodes hypoxia-inducible factor 2 alpha (HIF-2α), and the 11q13.3 region, which impairs binding of HIF-2α and results in an allelic imbalance of cyclin D1 – as well as mediation of cholesterol transfer, obesity-related pathways, and pathways related to chromatin remodelling. Much remains to be discovered; the risk loci identified so far for renal cell carcinoma are estimated to account for only 10% of the familial risk, leaving about 90% of the heritability unexplained.

Two rare genetic variants may also be implicated in the risk of renal cell carcinoma, with no evidence of familial syndromes. The I157T missense variant in the cell-cycle control gene *CHEK2* increases the risk by about 50% [13]. Although the I157T variant is very rare in most countries, it is present in up to 7% of eastern European populations. Finally, a variant in *MITF* has also been reported to increase the risk of developing cutaneous melanoma, renal cell carcinoma, or both by about 5-fold [14].

Tumour molecular phenotypes

Kidney cancers – even the most common subtype (i.e. renal cell carcinomas) – are histologically heterogeneous clinical entities. A concerted effort is being made to explore the molecular underpinnings of these tumours (i.e. molecular phenotyping) to more accurately define the nature of these cancers. Most of the research has focused on clear cell renal cell carcinomas. Sporadic and familial clear cell renal cell carcinomas are biologically similar; they almost always show a loss of the short arm of chromosome 3, which carries *VHL* and other tumour suppressor genes. It was recently reported that some genomic structural events, typically through chromothripsis, can occur during childhood or adolescence – decades before the development of the renal cell carcinoma tumour [15].

For clear cell renal cell carcinomas, in addition to *VHL*, somatic mutations are recurrent in chromatin remodelling or chromatin modifier genes, including *PBRM1*, *ARID1A*, *SETD2*, *BAP1*, *KDM5C*, and *KDM6A* [16,17]. Several of these genes are located on the X chromosome, and this may play a role in the difference in risk between men and women.

An unusual tumour genomic pattern was reported in cases of clear cell renal cell carcinoma in Romania, marking the mutational signature of exposure to aristolochic acid [17] (see also Chapter 2.8). Although the exposure has been confirmed [18], the causal link between the exposure and the occurrence of the tumour remains to be investigated.

Moving beyond genomics, there are several reports of the presence and clinical significance of other molecular alterations at the RNA and protein levels in renal cell carcinoma (see Chapter 3.8). For example, higher expression levels of survivin, topoisomerase II alpha, and IMP3 have all been reported in clear cell renal cell carcinoma and, more importantly, linked to poor prognosis after curative surgery [19,20]. These biomarkers and others offer opportunities to better manage post-operative follow-up for patients with clear cell renal cell carcinoma.

Non-clear cell renal cell carcinomas have different genomic profiles [21]. For example, papillary renal cell carcinomas are typically characterized by alterations of the MET pathway, and chromophobe renal cell carcinomas are characterized by metabolic pathway alterations with mitochondrial dysfunctions.

Etiology

Tobacco smoking

The effect size of tobacco smoking on the risk of renal cell carcinoma is modest; the increase in risk is 36% in current smokers, 16% in former smokers, and 31% in all smokers, compared with never-smokers [22]. Epidemiological evidence for a causal role of tobacco smoking includes a dose–response relationship between risk and the quantity of tobacco smoked per day, as well as decreased risks with a larger number of years after smoking cessation. In high-income countries, an estimated 6% of deaths from kidney cancer are due to tobacco smoking [23].

Anthropometric measures

The association between excess body weight and risk of renal cell carcinoma has been reported extensively in large prospective cohorts [24]. In several studies the association was shown to be linear, with an increase in risk of about 25% for each increase of 5 kg/m^2 in body mass index (BMI). No data are available on the benefit of weight loss and/or long-term maintenance of a lower BMI in association with risk of kidney cancer. High BMI is estimated to be responsible for 26% of incident cases of renal cell carcinoma worldwide [25].

Height has also been consistently associated with risk of kidney cancer, independently of weight, with an increase in risk of about 30% for each increase of 10 cm in height [26]. The mechanisms involved could include levels of growth hormones, genetic background, and childhood exposures, rather than a direct link with renal cell carcinoma.

Hypertension

In the USA, a history of hypertension has been estimated to double the risk of kidney cancer in Whites, and to triple the risk in Blacks [27]. Prospective cohort studies have consistently reported dose–response associations between blood pressure at baseline and risk of kidney cancer, even when the risk analysis is restricted to more than 5 years after blood pressure measurement in an attempt to minimize reverse causation [28]. In a study with repeated measurements of blood pressure over time, the risk of renal cell cancer decreased with decreasing blood pressure [28].

Fig. 5.16.2. A patient's blood pressure is monitored. Prospective cohort studies have reported associations between blood pressure at baseline and risk of kidney cancer.

Alcohol consumption

Moderate consumption of alcohol reduces the risk of developing renal cell carcinoma, and this protective effect may be stronger in women than in men. The identification of alcohol consumption as a factor associated with lower risk of renal cell carcinoma resulted from early observations in case–control studies and progressed to much more robust and consistent evidence from large prospective cohorts, pooling projects, and meta-analyses [29]. Investigators have begun to explore the possibility that the association between alcohol intake and risk of renal cell carcinoma may be modulated by variation in underlying genetics such as the genes coding for enzymes that metabolize alcohol [30].

Chronic kidney disease

Chronic kidney disease increases the risk of kidney cancer by 2–3-fold [31]. Evidence suggests that in the USA the increase in risk is more pronounced in Blacks than in Whites; this may contribute to the higher observed incidence rates in Blacks, given that chronic kidney disease is also more prevalent in Blacks than in Whites [31,32].

Diabetes

The association between diabetes and risk of kidney cancer has been assessed in several prospective cohort studies, but independence from comorbidities of diabetes, such as obesity, hypertension, and chronic kidney disease, is still unclear [33]. A history of diabetes was found to be associated with a 40% excess risk of kidney cancer [33].

Trichloroethylene

The IARC Monographs classified occupational exposure to trichloroethylene as carcinogenic to humans

(Group 1), on the basis of a body of sufficient evidence that this chemical causes kidney cancer [34]. The most recent meta-analysis estimated that occupational exposure to trichloroethylene confers a 30–40% excess risk of kidney cancer (see Chapter 2.10) [35].

Biology and early detection

Kidney cancer is characterized by the absence of early warning signs and by non-specific symptoms. Patients who are diagnosed with localized renal cell carcinoma (stages I and II) are commonly cured after nephron-sparing nephrectomy as the sole treatment, with limited long-term side-effects. For tumours that invade local tissues (stage III) or have distant metastasis (stage IV), prognosis is poor, with 5-year survival rates of about 50% and 10%, respectively [36].

The majority of curable early-stage tumours are detected incidentally through the wide use of ultrasonography examinations for a range of medical conditions and symptoms. Because renal cell carcinoma usually remains clinically occult for most of its course, it is often diagnosed at an advanced stage, and 25–30% of patients have metastases at diagnosis [37].

Because most kidney tumours develop outside the context of diagnosed genetic cancer syndromes, there is currently no recommended screening practice for primary renal cell carcinoma in people who are not known to carry genetic mutations associated with increased risk of the disease. Given that renal masses can be detected with ultrasonography techniques, which are non-invasive and harmless, the question of whether general screening for early detection of kidney cancer in the population is warranted has arisen from patient associations as well as clinicians. However, there has been no systematic evaluation of the conditions for implementing a screening programme (see Chapter 6.6).

In the absence of clear high-risk groups at the population level and of non-invasive biomarkers for renal cell carcinoma that could be measured in blood or urine, secondary prevention for kidney cancer is still a long way off. Research efforts are under way to identify such biomarkers. Plasma levels of KIM-1 were recently reported to predict the risk of being diagnosed with renal cell carcinoma in the subsequent 5 years [38]. However, the predictive ability would need to be improved for use in a screening setting.

Fig. 5.16.3. Although trichloroethylene has largely been replaced by tetrachloroethylene as the main solvent used in dry cleaning, trichloroethylene is still used as a spot remover. A meta-analysis estimated that occupational exposure to trichloroethylene confers a 30–40% excess risk of kidney cancer.

Opportunities for prevention

Projections from Cancer Research UK indicate that over the next 20 years kidney cancer will be one of the cancer types with the most rapidly rising incidence [39]. These estimates are based on increasing trends over the past decade and may be inflated as a result of overdiagnosis during this period. However, the increasing trends cannot be explained solely by increased detection of asymptomatic tumours: the rise in incidence predates widespread use of sensitive abdominal imaging, and the incidence of late-stage tumours has also increased [36].

Opportunities for primary prevention are limited, because the factors that are responsible for the geographical variations and time trends have not been identified. For example, kidney cancer incidence rates have not benefited from the general reduction in tobacco use.

As discussed earlier, the factors that are known to be associated with renal cell carcinoma confer modest risk increases (relative risks of about 1.2–2.5), resulting in population attributable risks of less than 50% [40]. This poses challenges for identifying high-risk populations that could benefit from enhanced screening protocols. Nevertheless, the discovery of genetic polymorphisms associated with development of renal cell carcinoma and the identification of refined molecular subtypes of the disease provide a clear opportunity to explore gene–environment interactions coupled with molecular subtyping, which could reveal more individualized risk estimates that would support the screening of certain populations. This approach is particularly intriguing given the future possibility of developing lower-cost and scalable screening tests based on circulating biomarkers. However, care must be taken to avoid the risk of overdiagnosis that has occurred with other cancer types (e.g. prostate cancer).

A systematic evaluation is warranted of the conditions for implementing a screening programme. Kidney cancers are asymptomatic and are usually detected incidentally through routine imaging. Therefore, most patients are treated for a suspicious renal mass and are only diagnosed with a cancer or a benign tumour after invasive surgery. The discovery of circulating biomarkers that could stratify renal masses into likely benign or likely malignant would be extremely valuable to overcome the issues of overdiagnosis and overtreatment.

References

1. Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, et al. (2017). Renal cell carcinoma. Nat Rev Dis Primers. 3(1):17009. https://doi.org/10.1038/nrdp.2017.9 PMID:28276433

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593

3. Bray F, Colombet M, Mery L, Piñeros M, Znaor A, Zanetti R, et al., editors (2017). Cancer incidence in five continents, Vol. XI (electronic version). Lyon, France: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr.

4. Li P, Znaor A, Holcatova I, Fabianova E, Mates D, Wozniak MB, et al. (2015). Regional geographic variations in kidney cancer incidence rates in European countries. Eur Urol. 67(6):1134–41. https://doi.org/10.1016/j.eururo.2014.11.001 PMID:25465966

5. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F (2015). International variations and trends in renal cell carcinoma incidence and mortality. Eur Urol. 67(3):519–30. https://doi.org/10.1016/j.eururo.2014.10.002 PMID:25449206

6. Scelo G, Li P, Chanudet E, Muller DC (2018). Variability of sex disparities in cancer incidence over 30 years: the striking case of kidney cancer. Eur Urol Focus. 4(4):586–90. https://doi.org/10.1016/j.euf.2017.01.006 PMID:28753845

7. Znaor A, Laversanne M, Bray F (2017). Less overdiagnosis of kidney cancer? an age-period-cohort analysis of incidence trends in 16 populations worldwide. Int J Cancer. 141(5):925–32. https://doi.org/10.1002/ijc.30799 PMID:28543047

8. Lipworth L, Tarone RE, McLaughlin JK (2011). Renal cell cancer among African Americans: an epidemiologic review. BMC Cancer. 11(1):133. https://doi.org/10.1186/1471-2407-11-133 PMID:21486465

9. Lipworth L, McLaughlin JK, Tarone RE, Blot WJ (2011). Renal cancer paradox: higher incidence but not higher mortality among African-Americans. Eur J Cancer Prev. 20(4):331–3. https://doi.org/10.1097/CEJ.0b013e328345f9b3 PMID:21633203

10. Haas NB, Nathanson KL (2014). Hereditary kidney cancer syndromes. Adv Chronic Kidney Dis. 21(1):81–90. https://doi.org/10.1053/j.ackd.2013.10.001 PMID:24359990

11. Maher ER, Neumann HP, Richard S (2011). von Hippel-Lindau disease: a clinical and scientific review. Eur J Hum Genet. 19(6):617–23. https://doi.org/10.1038/ejhg.2010.175 PMID:21386872

12. Scelo G, Purdue MP, Brown KM, Johansson M, Wang Z, Eckel-Passow JE, et al. (2017). Genome-wide association study identifies multiple risk loci for renal cell carcinoma. Nat Commun. 8(1):15724. https://doi.org/10.1038/ncomms15724 PMID:28598434

13. Brennan P, McKay J, Moore L, Zaridze D, Mukeria A, Szeszenia-Dabrowska N, et al. (2007). Uncommon *CHEK2* mis-sense variant and reduced risk of tobacco-related cancers: case control study. Hum Mol Genet. 16(15):1794–801. https://doi.org/10.1093/hmg/ddm127 PMID:17517688

14. Bertolotto C, Lesueur F, Giuliano S, Strub T, de Lichy M, Bille K, et al.; French Familial Melanoma Study Group (2011). A SUMOylation-defective *MITF* germline mutation predisposes to melanoma and renal carcinoma. Nature. 480(7375):94–8. https://doi.org/10.1038/nature10539 PMID:22012259

15. Mitchell TJ, Turajlic S, Rowan A, Nicol D, Farmery JHR, O'Brien T, et al.; TRACERx Renal Consortium (2018). Timing the landmark events in the evolution of clear cell renal cell cancer: TRACERx Renal. Cell. 173(3):611–623.e17. https://doi.org/10.1016/j.cell.2018.02.020 PMID:29656891

16. Cancer Genome Atlas Research Network (2013). Comprehensive molecular characterization of clear cell renal cell carcinoma. Nature. 499(7456):43–9. https://doi.org/10.1038/nature12222 PMID:23792563

17. Scelo G, Riazalhosseini Y, Greger L, Letourneau L, Gonzàlez-Porta M, Wozniak MB, et al. (2014). Variation in genomic landscape of clear cell renal cell carcinoma across Europe. Nat Commun. 5(1):5135. https://doi.org/10.1038/ncomms6135 PMID:25351205

18. Turesky RJ, Yun BH, Brennan P, Mates D, Jinga V, Harnden P, et al. (2016). Aristolochic acid exposure in Romania and implications for renal cell carcinoma. Br J Cancer. 114(1):76–80. https://doi.org/10.1038/bjc.2015.402 PMID:26657656

19. Parker AS, Eckel-Passow JE, Serie D, Hilton T, Parasramka M, Joseph RW, et al. (2014). Higher expression of topoisomerase II alpha is an independent marker of increased risk of cancer-specific death in patients with clear cell renal cell carcinoma. Eur Urol. 66(5):929–35. https://doi.org/10.1016/j.eururo.2013.12.017 PMID:24388441

20. Pu Z, Wang Q, Xie H, Wang G, Hao H (2017). Clinicalpathological and prognostic significance of survivin expression in renal cell carcinoma: a meta-analysis. Oncotarget. 8(12):19825–33. https://doi.org/10.18632/oncotarget.15082 PMID:28178644

21. Albiges L, Flippot R, Rioux-Leclercq N, Choueiri TK (2018). Non-clear cell renal cell carcinomas: from shadow to light. J Clin Oncol. [Epub ahead of print] https://doi.org/10.1200/JCO.2018.79.2531 PMID:30372389

22. Cumberbatch MG, Rota M, Catto JW, La Vecchia C (2016). The role of tobacco smoke in bladder and kidney carcinogenesis: a comparison of exposures and meta-analysis of incidence and mortality risks. Eur Urol. 70(3):458–66. https://doi.org/10.1016/j.eururo.2015.06.042 PMID:26149669

23. Dy GW, Gore JL, Forouzanfar MH, Naghavi M, Fitzmaurice C (2017). Global burden of urologic cancers, 1990–2013. Eur Urol. 71(3):437–46. https://doi.org/10.1016/j.eururo.2016.10.008 PMID:28029399

24. Wang F, Xu Y (2014). Body mass index and risk of renal cell cancer: a dose-response meta-analysis of published cohort studies. Int J Cancer. 135(7):1673–86. https://doi.org/10.1002/ijc.28813 PMID:24615287

25. Arnold M, Pandeya N, Byrnes G, Renehan PAG, Stevens GA, Ezzati PM, et al. (2015). Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol. 16(1):36–46. https://doi.org/10.1016/S1470-2045(14)71123-4 PMID:25467404

26. Wirén S, Häggström C, Ulmer H, Manjer J, Bjørge T, Nagel G, et al. (2014). Pooled cohort study on height and risk of cancer and cancer death. Cancer Causes Control. 25(2):151–9. https://doi.org/10.1007/s10552-013-0317-7 PMID:24173535

27. Colt JS, Schwartz K, Graubard BI, Davis F, Ruterbusch J, DiGaetano R, et al. (2011). Hypertension and risk of renal cell carcinoma among white and black Americans. Epidemiology. 22(6):797–804. https://doi.org/10.1097/EDE.0b013e3182300720 PMID:21881515

28. Chow WH, Gridley G, Fraumeni JF Jr, Järvholm B (2000). Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med. 343(18):1305–11. https://doi.org/10.1056/NEJM200011023431804 PMID:11058675

29. Bellocco R, Pasquali E, Rota M, Bagnardi V, Tramacere I, Scotti L, et al. (2012). Alcohol drinking and risk of renal cell carcinoma: results of a meta-analysis. Ann Oncol. 23(9):2235–44. https://doi.org/10.1093/annonc/mds022 PMID:22398178

30. Antwi SO, Eckel-Passow JE, Diehl ND, Serie DJ, Custer KM, Wu KJ, et al. (2018). Alcohol consumption, variability in alcohol dehydrogenase genes and risk of renal cell carcinoma. Int J Cancer. 142(4):747–56. https://doi.org/10.1002/ijc.31103 PMID:29023769

31. Hofmann JN, Corley DA, Zhao WK, Colt JS, Shuch B, Chow W-H, et al. (2015). Chronic kidney disease and risk of renal cell carcinoma: differences by race. Epidemiology. 26(1):59–67. https://doi.org/10.1097/EDE.0000000000000205 PMID:25393631

32. Lipworth L, Mumma MT, Cavanaugh KL, Edwards TL, Ikizler TA, Tarone RE, et al. (2012). Incidence and predictors of end stage renal disease among low-income blacks and whites. PLoS One. 7(10):e48407. https://doi.org/10.1371/journal.pone.0048407 PMID:23110237

33. Harding JL, Shaw JE, Peeters A, Cartensen B, Magliano DJ (2015). Cancer risk among people with type 1 and type 2 diabetes: disentangling true associations, detection bias, and reverse causation. Diabetes Care. 38(2):264–70. https://doi.org/10.2337/dc14-1996 PMID:25488912

34. IARC (2013). Trichloroethylene, tetrachloroethylene, and some other chlorinated agents. IARC Monogr Eval Carcinog Risks Hum. 106:1–514. Available from: http://publications.iarc.fr/130 PMID:26214861

35. Karami S, Lan Q, Rothman N, Stewart PA, Lee K-M, Vermeulen R, et al. (2012). Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis. Occup Environ Med. 69(12):858–67. https://doi.org/10.1136/oemed-2012-100932 PMID:23000822

36. Chow WH, Dong LM, Devesa SS (2010). Epidemiology and risk factors for kidney cancer. Nat Rev Urol. 7(5):245–57. https://doi.org/10.1038/nrurol.2010.46 PMID:20448658

37. Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C (2008). Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer Treat Rev. 34(3):193–205. https://doi.org/10.1016/j.ctrv.2007.12.001 PMID:18313224

38. Scelo G, Muller DC, Riboli E, Johansson M, Cross AJ, Vineis P, et al. (2018). KIM-1 as a blood-based marker for early detection of kidney cancer: a prospective nested case-control study. Clin Cancer Res. 24(22):5594–601. https://doi.org/10.1158/1078-0432.CCR-18-1496 PMID:30037816

39. Smittenaar CR, Petersen KA, Stewart K, Moitt N (2016). Cancer incidence and mortality projections in the UK until 2035. Br J Cancer. 115(9):1147–55. https://doi.org/10.1038/bjc.2016.304 PMID:27727232

40. Scelo G, Larose TL (2018). Epidemiology and risk factors for kidney cancer. J Clin Oncol. [Epub ahead of print] https://doi.org/10.1200/JCO.2018.79.1905 PMID:30372394

5.17 Brain cancer
Increasing attention on the immune response

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SUMMARY

- The revised WHO classification of malignant tumours of the central nervous system includes molecular data, along with histology, in defining tumour types.
- The topic of mobile phones and brain tumours remains controversial despite decades of research and results from numerous observational studies. Some studies have reported a higher relative risk for heavy use of mobile phones, but incidence rates of malignant tumours have not increased over the past three decades.
- Various genetic susceptibility loci have been identified for gliomas, and two distinct susceptibility loci have been associated with meningiomas. Some susceptibility loci appear to be specific to tumour grade, and risk variants may also vary by sex.
- Inherited variants or mutations and acquired somatic mutations in or near telomerase genes are associated with increased risk of glioma. This suggests that longer telomere length may be a key contributor to gliomagenesis.
- There is increasing evidence that the immune response plays an important role in the etiology of malignant glioma. Allergies and a history of infection with varicella zoster virus are each inversely associated with risk of glioma, and several markers of immune status are strongly associated with risk.

In 2018, cancer of the brain and central nervous system was the 17th most common cancer type, with an estimated 297 000 new cases worldwide. The study of the etiology of brain tumours is particularly challenging because of the relatively low incidence rates of brain and central nervous system cancers and the high heterogeneity of these tumours. As a result, most research in this field has been based on case–control studies, which have methodological limitations, or cohort studies, which are often limited by small numbers of cases.

Because it is difficult to study brain tumours within individual institutions, international brain cancer consortia have been established to increase sample sizes, improve the classification of tumours, pool data for genetic and molecular analyses, and increase collaboration across different disciplines. These collaborative efforts have been highly successful, resulting in advances in the molecular classification of malignant brain tumours and the identification of new genetic susceptibility regions, and a consensus is being approached on the role of allergies [1] and other risk factors [2] in brain tumours. The collaborations have also highlighted the need for additional research on the causes of non-malignant brain tumours and childhood brain tumours [2].

About 68% of all brain and central nervous system tumours are non-malignant; about half of these tumours are meningiomas, followed by pituitary tumours and nerve sheath tumours [3]. Meningiomas, even when they are non-malignant, can have a devastating impact on health by altering normal brain function. Epidemiological studies that examine genetic and environmental determinants of brain tumours no longer combine meningiomas with other types of brain tumours, given that they are etiologically (as well as clinically) distinct tumours. Among the malignant tumours, heterogeneity is also substantial; almost half of these are glioblastomas, followed by other gliomas [3]. Most epidemiological studies examine gliomas together, given that they originate from the same cell types (i.e. glial cells), although often glioblastomas – the most aggressive brain tumours – are examined separately.

This chapter focuses on research advances in the field of epidemiology in the past 5 years. It highlights findings from pooling studies (consortium efforts) or cohort studies that have confirmed earlier findings, as well as new and promising results from studies examining the role of the immune response in etiology.

There is increasing evidence that the immune response plays an important role in glioma development, and research that is under way in this area should provide new opportunities for the identification of markers for early detection or prognosis prediction. In addition, obtaining a better understanding of underlying immune-related mechanisms may provide new opportunities for the development of immunotherapies to prolong survival.

Revised WHO classification

In 2016, the WHO classification of malignant tumours of the central nervous system was revised to include molecular data, along with histology, in defining tumour types [4]. The updated classification, which includes molecular markers (Fig. 5.17.1), demonstrates the heterogeneity of different malignant brain tumours and the difficulty of classifying these tumours using histology alone.

The importance of the revised classification has been demonstrated in large tumour data sets with clinical and demographic characteristics. Tumours with certain molecular markers have been shown to have distinct clinical behaviour. In a data set that included both high-grade and low-grade gliomas, tumours were classified into five groups on the basis of mutations in the *TERT* promoter, mutations in *IDH*, and co-deletion of chromosome arms 1p and 19q (1p/19q co-deletion); the molecular groups were strongly associated with age at diagnosis, survival, grade, and specific germline variants [5]. Similarly, in a data set of lower-grade gliomas from the Cancer Genome Atlas, three groups of tumours, classified on the basis of the presence or absence of mutations in *IDH* and 1p/19q co-deletions, were strongly linked to clinical characteristics, including histology, age at diagnosis, and survival (Fig. 5.17.2) [6].

Future widespread use of the revised WHO classification in clinical and epidemiological studies may provide new insights into etiological factors, because the differences in patterns of acquired mutations across different groups suggest that these tumours have distinct pathogenesis.

Etiology

True etiological factors for brain tumours have been difficult to identify, because findings for many suspected risk factors have been inconsistent or null. Many potential risk factors have been studied, but most remain classified as "probably not risk factors". These include head injuries, occupational exposures, residential power-frequency electromagnetic fields, dental X-rays, tobacco smoke, and alcohol consumption [2]. In two large prospective cohort studies, no associations were observed between meat intake, or carcinogens derived from meat, and risk of glioma [7,8]. Although obesity has not been consistently associated with risk of glioma, there is a consensus that obesity is associated with risk of meningioma [9].

Mobile phones

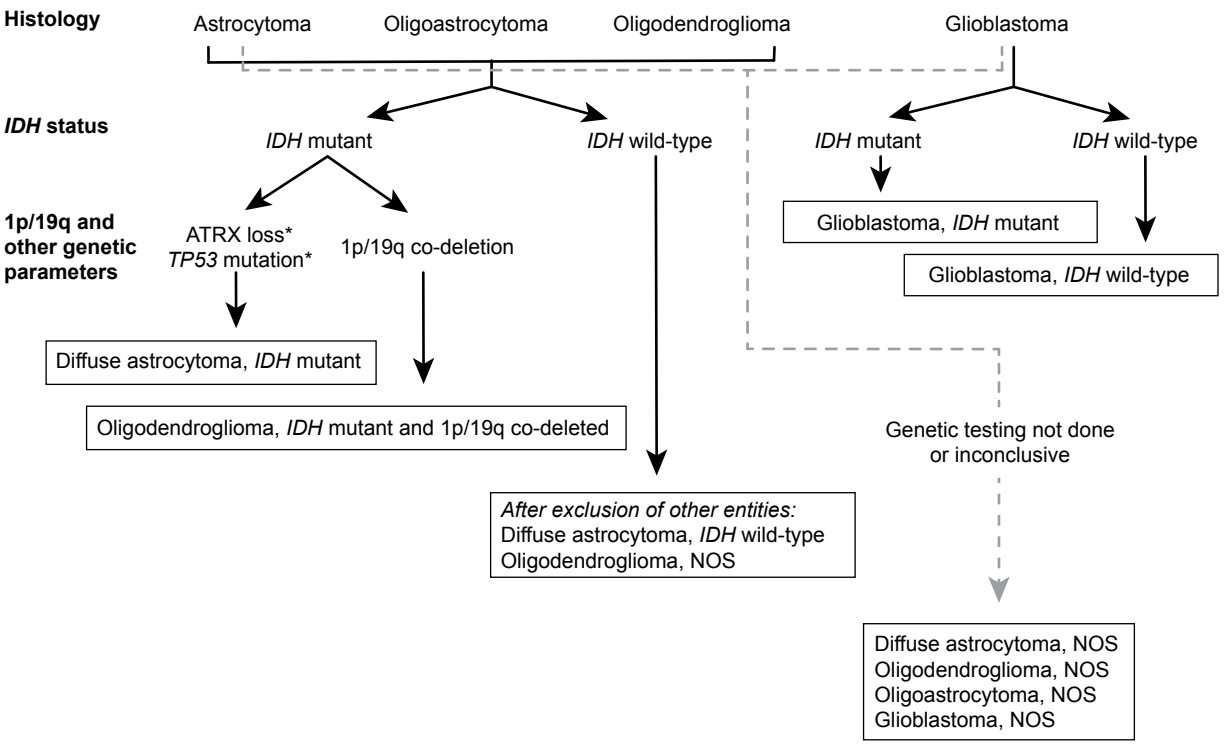
In 2011, an IARC Monographs Working Group tasked with reviewing the evidence on radiofrequency electromagnetic fields, including exposure from mobile phones, concluded that there was limited evidence that these exposures cause cancer in humans and experimental animals, and classified radiofrequency electromagnetic fields as possibly carcinogenic to humans (Group 2B) [10].

In the past 5 years, various commentaries, original studies, and meta-analyses have been published on this subject, which continues to receive substantial news coverage. However, causality remains questionable (see Chapter 2.5). Observational study designs have limitations, some of which are particularly problematic when studying mobile phones and brain cancer. Limitations that contribute to the complexity of determining causality include: difficulties in accurately measuring mobile phone

FUNDAMENTALS

- Brain and other primary central nervous system tumours comprise a group of very heterogeneous tumours, both malignant and non-malignant, which exhibit a wide range of clinical signs and symptoms with varying prognosis.
- Incidence rates of subtypes of brain tumours vary substantially by age; children develop different types of brain tumours than adults. For example, embryonal tumours and pilocytic astrocytomas are rarely observed in adults, whereas adult subtypes, such as glioblastomas, are rare in children.
- Malignant brain cancers, primarily gliomas, are more common in men than in women, whereas non-malignant tumours are more common in women. Incidence rates of malignant brain and other central nervous system tumours are higher in Whites than in Blacks, but incidence rates of non-malignant tumours are higher in Blacks than in Whites. Geographical variations in incidence rates exist but could be attributable to differences in diagnostic, classification, and reporting practices.
- Genetic factors, including certain familial syndromes such as neurofibromatosis and inherited genetic susceptibilities, increase the risk of brain tumours.
- Exposure to ionizing radiation, whether from atomic bombs or therapeutic irradiation, has been firmly established as a cause of brain tumours.
- No excess risk of brain and other central nervous system tumours has been attributed to use of tobacco products.

Fig. 5.17.1. A simplified algorithm for classification of the diffuse gliomas on the basis of histological and genetic features. A caveat to this diagram is that the diagnostic "flow" does not necessarily always proceed from histology first to molecular genetic features next, because molecular signatures can sometimes outweigh histological characteristics in achieving an integrated diagnosis. A similar algorithm can be followed for anaplastic-level diffuse gliomas. NOS, not otherwise specified. * Characteristic but not required for diagnosis.



use, with reference to both dose and duration; the potential for recall bias, especially with respect to use of the phone on a particular side of the head (i.e. laterality); the relative recency of widespread use of mobile phones, which is problematic for examining the possible impact of long latency periods; and the heterogeneity of brain cancer subtypes. The results of experimental studies, whether in vitro, in vivo, or animal studies, are similarly inconsistent [11].

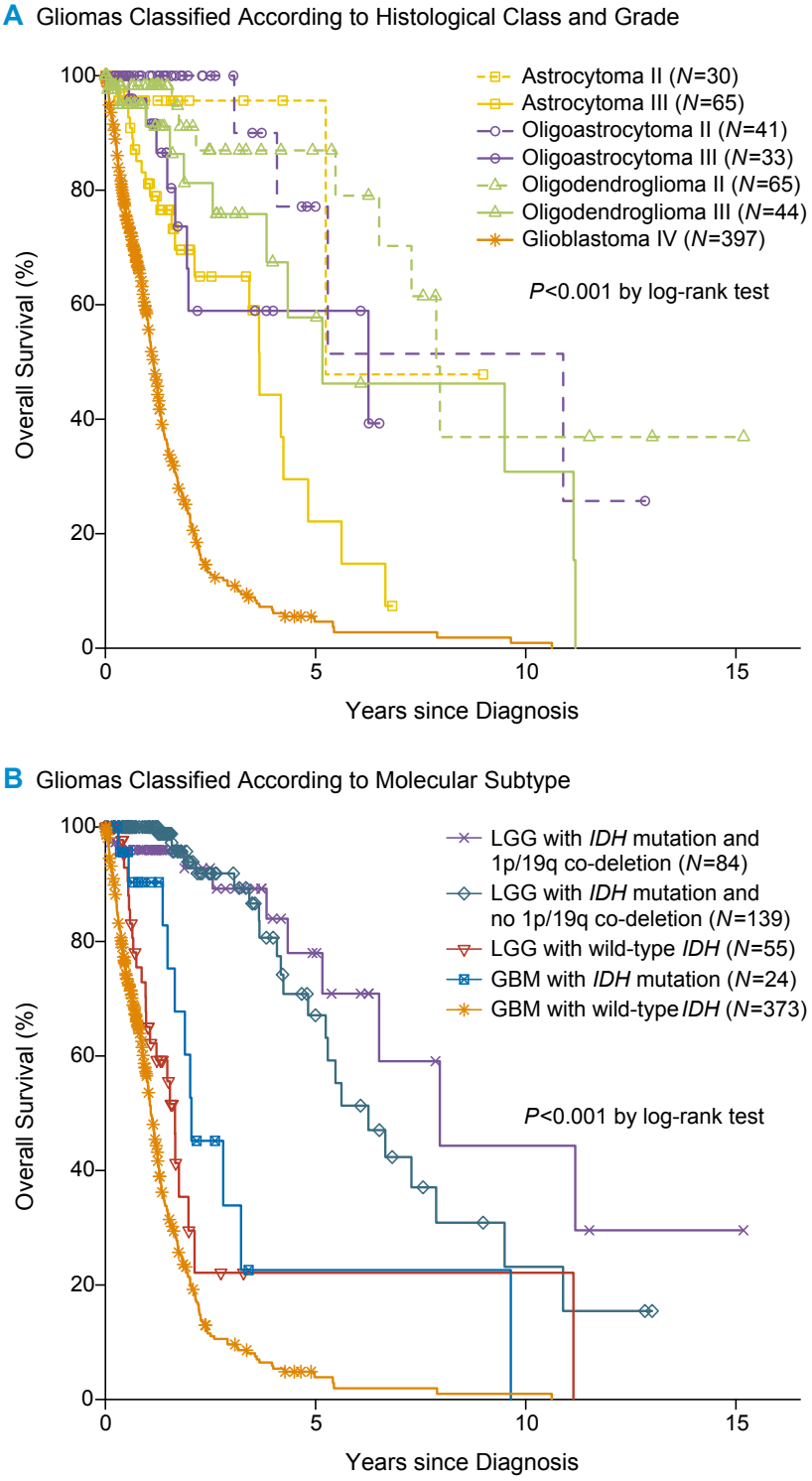
Time trends in the incidence rates of brain cancer in countries where mobile phones have been in widespread use for 25 years or more, including the USA, the Nordic countries, the United Kingdom, and Australia [12], do not support the strong positive relative risks reported in some case–control studies, even after accounting for a 10-year latency period. In the most recent (2018) report on cancer incidence in the USA, age-standardized, delay-adjusted incidence rates of malignant brain and other central nervous system cancers continued to decline in males (annual percentage change, −0.2%) and in females (annual percentage change, −0.7%) in the most recent 5-year period (2010–2014), even with adjustment for delays in reporting to cancer registries [13]. Similarly, stable or decreasing incidence rates of malignant brain tumours (glioma and glioblastoma) were reported across all age groups in 2000–2014 in a summary of the most recent and comprehensive data on rates of malignant and non-malignant brain tumours for 99.9% of the population of the USA (Fig. 5.17.4) [3].

It has been more than 25 years since mobile phones were introduced, and they have been used by billions of people. These facts, combined with the consistent lack of increase in incidence rates in countries with high use of mobile phones, call causality into question. Nevertheless, this topic will continue to be highly controversial, because experts continue to disagree on the interpretation of data that arise from different study designs. Results from prospective cohort studies that collect self-reported data on the use of mobile phones may shed light on the associations, but a long waiting period is expected before these studies provide results [14].

Genetic susceptibility

Genome-wide association studies (GWAS) have identified several genetic variants associated with risk of different brain tumour subtypes. Single-nucleotide polymorphisms (SNPs) in seven genes (*TERT*, *TP53*, *CCDC26*, *EGFR*, *CDKN2B/CDKN2A*, *RTEL1*, and *PHLDB1*) have been consistently linked to risk

Fig. 5.17.2. (A) Kaplan–Meier estimates of overall survival in patients with lower-grade gliomas that are classified according to traditional histological type and grade. Glioblastoma samples (from previously published Cancer Genome Atlas data) are also included for comparison. (B) Overall survival in patients with lower-grade gliomas that are classified according to *IDH* mutation and 1p/19q co-deletion status. Glioblastoma samples classified according to *IDH* mutation status are also included. GBM, glioblastoma; LGG, lower-grade glioma.



of glioma in several large GWAS. Recently, a large meta-analysis identified 13 new susceptibility loci for glioma [15]. Although some susceptibility loci are common to all glioma subtypes (e.g. *TP53*), others appear to be specific to glioblastoma (e.g. *EGFR*) or non-glioblastoma glioma (e.g. *PHLDB1*) [15] or to molecular subgroups of glioma [5,16].

Two genetic variants located near the telomerase genes *TERC* and *TERT* are associated both with increased risk of high-grade glioma and with longer telomere length [17]. The presence of frequent mutations in telomerase genes in gliomas points to an important role for telomere length in glioma development [18].

New research suggests that glioma risk variants are sex-specific [19]. These findings may provide insights into mechanisms that may explain why incidence rates of glioma are higher in men than in women. For meningiomas, two susceptibility loci (10p12.31 and 11p15.5) have been identified [20]; these are distinct from those identified for gliomas.

It has been estimated that 25% of the variation in the risk of developing all forms of glioma is associated with common genetic susceptibility variants [21]. This estimate is derived from a genome-wide complex trait analysis that enables risk to be evaluated on the basis of the contribution of all SNPs simultaneously in GWAS (in contrast to an analysis of the effects of single SNPs). The evidence to date strongly supports a polygenic basis of genetic susceptibility to glioma, and improved molecular classification of glioma subtypes may result in the identification of additional susceptibility loci.

Allergies, infections, and the immune response

There is little or no evidence that common cancer risk factors, including tobacco smoke, obesity, and diet, play a role in the etiology of glioma. This suggests that the environmental factors that influence carcinogenesis in glial cells are unique.

Fig. 5.17.3. A man using a mobile phone. Observational studies have not yet established definitively whether use of mobile phones causes brain cancer.

Allergies

It is becoming increasingly apparent that the immune response plays a central role in the etiology of glioma. Numerous studies have reported inverse associations between allergies, including asthma and eczema, and risk of glioma [22]. Results from the Glioma International Case-Control Study, which was conducted in 2010–2013 and included 4533 cases and 4171 controls, were consistent with those of previous studies, confirming inverse associations for allergies [1]. This large study reported statistically significant reductions in risk of glioma of 30% for any respiratory allergy, 23% for history of asthma, and 30% for history of eczema [1]. These associations were consistent in men and women and across most sites.

In addition, several prospective cohort studies with measurements of pre-diagnostic plasma levels of immunoglobulin E, which reflect allergy status, have observed inverse associations with risk of glioma [23–25]. These findings provide support for a causal relationship, because cohort studies are not prone to recall bias or reverse causation.

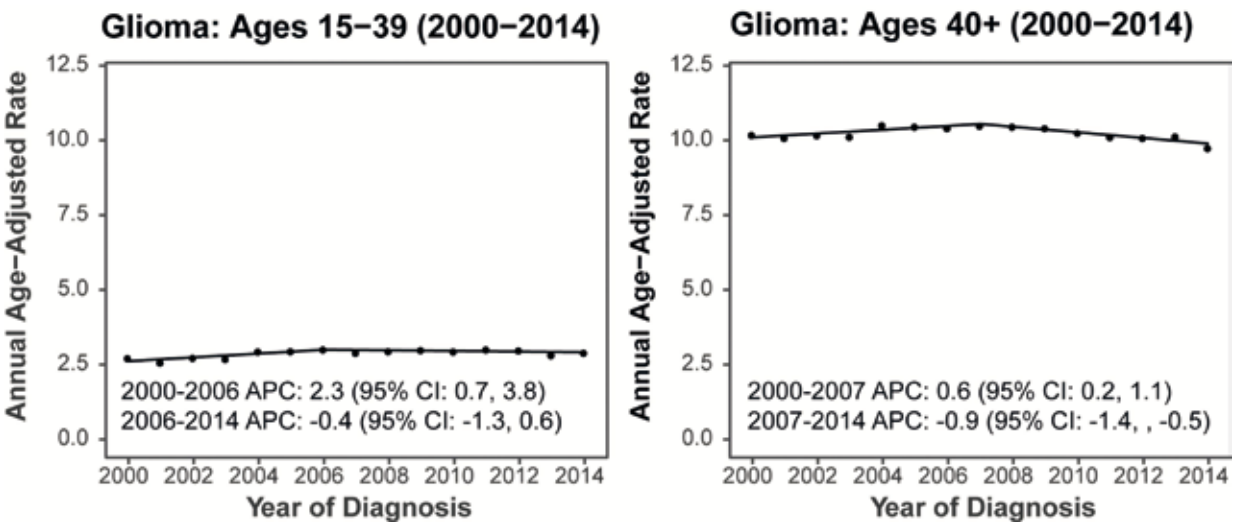
Improved immunosurveillance and protection against environmental toxins in people with allergies have been proposed as mechanisms for how allergies may confer protection against glioma [1]. However, the exact mechanisms for these associations are not known, and further research is required.

Varicella zoster virus

Unlike studies of polyomaviruses (e.g. simian virus 40), which were suspected to increase the risk of brain tumours but were not subsequently confirmed as risk factors, studies of varicella zoster virus (a herpesvirus that causes chickenpox and shingles) have reported inverse associations between a history of infection with the virus and risk of glioma. Fewer studies have examined this association than have investigated those for allergies, but the inverse trend is similarly consistent.

The original study observed inverse associations with risk of glioma for self-reported history of chickenpox or shingles and for

Fig. 5.17.4. Annual age-adjusted incidence rates of primary brain and other central nervous system gliomas in the USA, and incidence trends by age group for diagnosis years 2000–2014. APC, annual percentage change; CI, confidence interval.



elevated levels of immunoglobulin G antibodies to varicella zoster virus [26]. These findings have been reproduced in several studies [27–29]. In the Glioma International Case-Control Study, a history of infection with varicella zoster virus was associated with a 21% reduction in risk of glioma, and the association was slightly stronger for high-grade gliomas [28].

A cohort study with measurements of pre-diagnostic plasma levels of immunoglobulin G antibodies to varicella zoster virus reported an inverse association with risk of glioma [27]. This result provides data suggesting that the association observed in case–control studies may not be due solely to reverse causation. Although the biological mechanism is not known, the immune response clearly plays a central role in this association.

Immunomethylomics

The difficulty of measuring immune cells in archived blood samples – and thus in population studies – using traditional methods (i.e. flow cytometry) has hindered progress in studying altered immune states in glioma etiology. Recently, researchers have identified DNA methylation markers (differentially methylated regions) for specific immune cell types using peripheral blood DNA, and this has opened up the field of immunomethylomics [30].

The identification of differentially methylated regions for immune cell types, including neutrophils, lymphocytes, T cells, and regulatory T cells, has provided new opportunities to study immune cells in relation to risk of glioma and survival [30,31]. Lower levels of regulatory T cells and lower levels of T cells were associated with a higher risk of glioma in a case–control setting [31], and an elevated neutrophil-to-lymphocyte ratio, a marker of immunosuppression, was associated with poor survival in patients with glioma [30].

Although case–control studies are unable to examine pre-diagnostic immune status, cohort studies examining other end-points have suggested that these immune perturbations may exist years before diagnosis [32]. Future studies using archived blood samples from prospective cohorts will undoubtedly provide critical data in this field, which will offer new opportunities for early detection and for the development of therapeutics based on an improved understanding of mechanisms.

Prospects

The development of high-dimensional technologies has opened up new doors to understanding brain cancer risk and survival. Large genomic studies have provided important insights into key pathways that play a role in development of brain cancer and have reinforced the importance of examining tumour subtypes, because they are likely to have different etiologies. Furthermore, improved classification of brain tumours using molecular markers can be used to better predict prognosis and provide targeted therapies.

Epigenomic studies using high-dimensional arrays, as well as other –omics analyses, will probably improve the understanding of the complex biological processes that lead to the development of brain tumours. Given the lack of established associations for modifiable risk factors for brain tumours (with the exception of exposure to ionizing radiation), no recommendations can be provided for primary or secondary prevention.

References

1. Amirian ES, Zhou R, Wrensch MR, Olson SH, Scheurer ME, Il'yasova D, et al. (2016). Approaching a scientific consensus on the association between allergies and glioma risk: a report from the Glioma International Case-Control Study. Cancer Epidemiol Biomarkers Prev. 25(2):282–90. https://doi.org/10.1158/1055-9965.EPI-15-0847 PMID:26908595
2. Bondy ML, Scheurer ME, Malmer B, Barnholtz-Sloan JS, Davis FG, Il'yasova D, et al.; Brain Tumor Epidemiology Consortium (2008). Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium. Cancer. 113(7 Suppl):1953–68. https://doi.org/10.1002/cncr.23741 PMID:18798534
3. Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, et al. (2017). CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. Neuro Oncol. 19(Suppl 5):v1–v88. https://doi.org/10.1093/neuonc/nox158 PMID:29117289
4. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. (2016). The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 131(6):803–20. https://doi.org/10.1007/s00401-016-1545-1 PMID:27157931
5. Eckel-Passow JE, Lachance DH, Molinaro AM, Walsh KM, Decker PA, Sicotte H, et al. (2015). Glioma groups based on 1p/19q, *IDH*, and *TERT* promoter mutations in tumors. N Engl J Med. 372(26):2499–508. https://doi.org/10.1056/NEJMoa1407279 PMID:26061753
6. Brat DJ, Verhaak RG, Aldape KD, Yung WK, Salama SR, Cooper LA, et al.; Cancer Genome Atlas Research Network (2015). Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med. 372(26):2481–98. https://doi.org/10.1056/NEJMoa1402121 PMID:26061751

7. Michaud DS, Holick CN, Batchelor TT, Giovannucci E, Hunter DJ (2009). Prospective study of meat intake and dietary nitrates, nitrites, and nitrosamines and risk of adult glioma. Am J Clin Nutr. 90(3):570–7. https://doi.org/10.3945/ajcn.2008.27199 PMID:19587083

8. Dubrow R, Darefsky AS, Park Y, Mayne ST, Moore SC, Kilfoy B, et al. (2010). Dietary components related to *N*-nitroso compound formation: a prospective study of adult glioma. Cancer Epidemiol Biomarkers Prev. 19(7):1709–22. https://doi.org/10.1158/1055-9965.EPI-10-0225 PMID:20570910

9. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group (2016). Body fatness and cancer – viewpoint of the IARC Working Group. N Engl J Med. 375(8):794–8. https://doi.org/10.1056/NEJMsr1606602 PMID:27557308

10. Baan R, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, et al.; WHO International Agency for Research on Cancer Monograph Working Group (2011). Carcinogenicity of radiofrequency electromagnetic fields. Lancet Oncol. 12(7):624–6. https://doi.org/10.1016/S1470-2045(11)70147-4 PMID:21845765

11. Repacholi MH, Lerchl A, Röösli M, Sienkiewicz Z, Auvinen A, Breckenkamp J, et al. (2012). Systematic review of wireless phone use and brain cancer and other head tumors. Bioelectromagnetics. 33(3):187–206. https://doi.org/10.1002/bem.20716 PMID:22021071

12. Chapman S, Azizi L, Luo Q, Sitas F (2016). Has the incidence of brain cancer risen in Australia since the introduction of mobile phones 29 years ago? Cancer Epidemiol. 42:199–205. https://doi.org/10.1016/j.canep.2016.04.010 PMID:27156022

13. Cronin KA, Lake AJ, Scott S, Sherman RL, Noone AM, Howlader N, et al. (2018). Annual report to the nation on the status of cancer, part I: national cancer statistics. Cancer. 124(13):2785–800. https://doi.org/10.1002/cncr.31551 PMID:29786848

14. Toledano MB, Smith RB, Chang I, Douglass M, Elliott P (2017). Cohort profile: UK COSMOS – a UK cohort for study of environment and health. Int J Epidemiol. 46(3):775–87. https://doi.org/10.1093/ije/dyv203 PMID:26534947

15. Melin BS, Barnholtz-Sloan JS, Wrensch MR, Johansen C, Il'yasova D, Kinnersley B, et al.; GliomaScan Consortium (2017). Genome-wide association study of glioma subtypes identifies specific differences in genetic susceptibility to glioblastoma and non-glioblastoma tumors. Nat Genet. 49(5):789–94. https://doi.org/10.1038/ng.3823 PMID:28346443

16. Labreche K, Kinnersley B, Berzero G, Di Stefano AL, Rahimian A, Detrait I, et al. (2018). Diffuse gliomas classified by 1p/19q co-deletion, *TERT* promoter and IDH mutation status are associated with specific genetic risk loci. Acta Neuropathol. 135(5):743–55. https://doi.org/10.1007/s00401-018-1825-z PMID:29460007

17. Walsh KM, Codd V, Smirnov IV, Rice T, Decker PA, Hansen HM, et al.; ENGAGE Consortium Telomere Group (2014). Variants near *TERT* and *TERC* influencing telomere length are associated with high-grade glioma risk. Nat Genet. 46(7):731–5. https://doi.org/10.1038/ng.3004 PMID:24908248

18. Walsh KM, Wiencke JK, Lachance DH, Wiemels JL, Molinaro AM, Eckel-Passow JE, et al. (2015). Telomere maintenance and the etiology of adult glioma. Neuro Oncol. 17(11):1445–52. https://doi.org/10.1093/neuonc/nov082 PMID:26014050

19. Ostrom QT, Kinnersley B, Wrensch MR, Eckel-Passow JE, Armstrong G, Rice T, et al.; GliomaScan Consortium (2018). Sex-specific glioma genome-wide association study identifies new risk locus at 3p21.31 in females, and finds sex-differences in risk at 8q24.21. Sci Rep. 8(1):7352. https://doi.org/10.1038/s41598-018-24580-z PMID:29743610

20. Claus EB, Cornish AJ, Broderick P, Schildkraut JM, Dobbins SE, Holroyd A, et al. (2018). Genome-wide association analysis identifies a meningioma risk locus at 11p15.5. Neuro Oncol. 20(11):1485–93. https://doi.org/10.1093/neuonc/noy077 PMID:29762745

21. Kinnersley B, Mitchell JS, Gousias K, Schramm J, Idbaih A, Labussière M, et al. (2015). Quantifying the heritability of glioma using genome-wide complex trait analysis. Sci Rep. 5(1):17267. https://doi.org/10.1038/srep17267 PMID:26625949

22. Linos E, Raine T, Alonso A, Michaud D (2007). Atopy and risk of brain tumors: a meta-analysis. J Natl Cancer Inst. 99(20):1544–50. https://doi.org/10.1093/jnci/djm170 PMID:17925535

23. Davis FG, Al-Alem U (2011). Allergies and adult gliomas: cohort results strengthen evidence for a causal association. J Natl Cancer Inst. 103(21):1562–3. https://doi.org/10.1093/jnci/djr397 PMID:22010179

24. Schwartzbaum J, Ding B, Johannesen TB, Osnes LT, Karavodin L, Ahlbom A, et al. (2012). Association between prediagnostic IgE levels and risk of glioma. J Natl Cancer Inst. 104(16):1251–9. https://doi.org/10.1093/jnci/djs315 PMID:22855780

25. Schlehofer B, Siegmund B, Linseisen J, Schüz J, Rohrmann S, Becker S, et al. (2011). Primary brain tumours and specific serum immunoglobulin E: a case-control study nested in the European Prospective Investigation into Cancer and Nutrition cohort. Allergy. 66(11):1434–41. https://doi.org/10.1111/j.1398-9995.2011.02670.x PMID:21726235

26. Wrensch M, Weinberg A, Wiencke J, Masters H, Miike R, Barger G, et al. (1997). Does prior infection with varicella-zoster virus influence risk of adult glioma? Am J Epidemiol. 145(7):594–7. https://doi.org/10.1093/oxfordjournals.aje.a009155 PMID:9098175

27. Sjöström S, Hjalmars U, Juto P, Wadell G, Hallmans G, Tjönneland A, et al. (2011). Human immunoglobulin G levels of viruses and associated glioma risk. Cancer Causes Control. 22(9):1259–66. https://doi.org/10.1007/s10552-011-9799-3 PMID:21717196

28. Amirian ES, Scheurer ME, Zhou R, Wrensch MR, Armstrong GN, Lachance D, et al. (2016). History of chickenpox in glioma risk: a report from the Glioma International Case-Control Study (GICC). Cancer Med. 5(6):1352–8. https://doi.org/10.1002/cam4.682 PMID:26972449

29. Wrensch M, Weinberg A, Wiencke J, Miike R, Sison J, Wiemels J, et al. (2005). History of chickenpox and shingles and prevalence of antibodies to varicella-zoster virus and three other herpesviruses among adults with glioma and controls. Am J Epidemiol. 161(10):929–38. https://doi.org/10.1093/aje/kwi119 PMID:15870157

30. Wiencke JK, Koestler DC, Salas LA, Wiemels JL, Roy RP, Hansen HM, et al. (2017). Immunomethylomic approach to explore the blood neutrophil lymphocyte ratio (NLR) in glioma survival. Clin Epigenetics. 9(1):10. https://doi.org/10.1186/s13148-017-0316-8 PMID:28184256

31. Wiencke JK, Accomando WP, Zheng S, Patoka J, Dou X, Phillips JJ, et al. (2012). Epigenetic biomarkers of T-cells in human glioma. Epigenetics. 7(12):1391–402. https://doi.org/10.4161/epi.22675 PMID:23108258

32. Barth SD, Schulze JJ, Kühn T, Raschke E, Hüsing A, Johnson T, et al. (2015). Treg-mediated immune tolerance and the risk of solid cancers: findings from EPIC-Heidelberg. J Natl Cancer Inst. 107(11):djv224. https://doi.org/10.1093/jnci/djv224 PMID:26298011

5.18 Thyroid cancer
The challenge of overdiagnosis

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SUMMARY

- Thyroid cancer consists of cancers of several different histologies, which differ in terms of cellular origin, incidence, and lethality. The most common subtypes are papillary and follicular thyroid cancers.
- In the past three decades, the incidence of thyroid cancer (particularly of papillary thyroid cancer) in adults has increased markedly, but thyroid cancer mortality rates have not increased proportionally; this suggests that overdiagnosis of thyroid cancer is occurring.
- Although there are specific etiologies that lead to the development of thyroid cancer, as well as disparities in incidence by sex and socioeconomic status, most of the variation in incidence trends is due to healthcare system factors.
- Various risk factors associated with the development of thyroid cancer have been investigated. Robust evidence of causal associations exists only for radiation exposure during childhood. Emerging data indicate an association with overweight and obesity.
- There are also genetic factors that increase the risk of developing thyroid cancer, including tumour predisposition syndromes, multiple endocrine neoplasia type 2, or familial medullary thyroid cancer.
- Population-based screening for thyroid cancer is not recommended, because the harms outweigh the benefits.

Thyroid cancer consists of cancers of several different histologies, which differ in terms of cellular origin, incidence, and lethality [1]. The most common subtypes are well-differentiated carcinomas (i.e. papillary and follicular cancers), which arise from the follicular cells within the thyroid gland. Papillary and follicular thyroid cancers tend to have a more benign course and a lower mortality rate compared with other subtypes, and together they comprise more than 90% of thyroid cancers; their proportion varies by iodine sufficiency. Papillary thyroid cancer spreads through the lymphatics, whereas follicular thyroid cancer spreads haematogenously and has a greater predilection for distant metastases.

Medullary thyroid cancer, which arises from parafollicular calcitonin-secreting C cells, has an intermediate severity and mortality rate. Medullary thyroid cancers comprise fewer than 5% of thyroid cancers and can occur sporadically or as part of the multiple endocrine neoplasia (MEN) syndromes. The rarest and most uniformly lethal subtype is anaplastic thyroid cancer, a very uncommon, poorly differentiated cancer, which originates mainly from follicular cells [1].

Thyroid cancer is much more common in adults than in children. In adults, survival rates for papillary thyroid cancer are higher than 90%, although there are more aggressive subtypes of papillary thyroid carcinoma, such as diffuse sclerosing, tall cell, solid, trabecular, and oncocytic variants. In children younger than 10 years with a history of exposure to radiation, the solid variant is more common. Diffuse sclerosing papillary thyroid cancer is also more common in children and in adults younger than 30 years, and these tumours generally do not show a distinct nodule. Follicular thyroid cancer is much less common and most often occurs in adults.

Epidemiology

In the past three decades, the incidence of thyroid cancer in adults has doubled, tripled, or more in several high-income countries [2]. Dramatic increases in incidence have also been seen in middle-income countries, such as Brazil, China, and Turkey (Fig. 5.18.1) [3].

Studies from a few of the countries with detailed registries show that almost the entire increase in incidence has been due to increased diagnosis of papillary thyroid cancer [4,5]. The size of the cancers that are now being detected is

also notable: most of the increase in incidence has come from the detection of papillary thyroid cancers less than or equal to 2 cm in diameter. Given that cancers of this size are usually difficult to detect through physical examination (palpation), the increased incidence of these small cancers is most likely to be due to increased use of sensitive imaging technologies. The implicated technologies include ultrasonography and cross-sectional imaging that includes the neck, which is driven largely by practice patterns of health-care providers [6].

Recent studies have shown that a large fraction of thyroid cancer diagnoses in high-income countries are likely to be due to the diagnosis of lesions of no clinical significance [7]. In women, this fraction could be as high as 70–80% in Australia, France, Italy, and the USA and 90% in the Republic of Korea. In men, the estimated fraction is 70% in France, Italy, and the Republic of Korea and 45% in Australia and the USA.

During the same period, thyroid cancer mortality rates have not increased proportionally. This pattern of dramatically increasing incidence of thyroid cancer worldwide, particularly of small papillary thyroid cancers, with largely stable mortality rates suggests that the main cause is the diagnosis of lesions that pose no significant risk to the person [8]. For overdiagnosis to occur, three factors must be present: (i) subclinical disease that is detectable by the screening test, (ii) a mechanism by which the tumours can be identified, and (iii) health-care activities that lead to the detection [9]. The necessary components for overdiagnosis of thyroid cancer are all present, as explained below.

Thyroid cancer is a disease that is readily detected subclinically. Papillary thyroid cancer is commonly found at autopsy in people who died of other causes. Depending on the method of examination of the thyroid, about 4% (partial examination) to 11% (whole examination) of thyroid glands can be shown to contain differentiated thyroid cancer, and this rate has been stable over time [10]. The high prevalence at autopsy explains the increasing identification of these smaller tumours.

The mechanism is increasingly sensitive imaging studies. Asymptomatic thyroid nodules are very common and are easily seen on medical imaging studies: up to 16% of computed tomography (CT) scans and magnetic resonance imaging (MRI) scans that include the thyroid gland show thyroid nodules, and with ultrasonography about two thirds of people will be found to have at least one nodule [11,12].

Factors affecting rates of disease burden

The observed variation in thyroid cancer incidence rates by country is driven by rates of well-differentiated thyroid cancer, in particular papillary thyroid cancer. Although there are specific etiologies that lead to the development of thyroid cancer, most of the variation in incidence trends is due to health-care system factors.

Sex

Worldwide, women are about 3 times as likely as men to be diagnosed with thyroid cancer. The reason for this disparity is unclear. The difference may relate to the influence of menarche and pregnancies and corresponding female hormonal variations, because the highest female-to-male ratio of thyroid cancer diagnosis occurs during the reproductive period. Although hormonal factors may play a role, the biological mechanism of this association remains elusive (see Chapter 3.6).

An argument against a biological explanation for the higher incidence rate of thyroid cancer in women is that multiple autopsy studies have shown nearly equivalent detected rates of thyroid cancer in men and women [4]. A more plausible explanation is the consideration that women have higher health-care use during their reproductive period and therefore are more prone to undergo thyroid imaging because of referral bias, which results in higher detection rates [13,14]. Reasons for the striking disparity in thyroid cancer incidence rates between men and women worldwide require further elucidation.

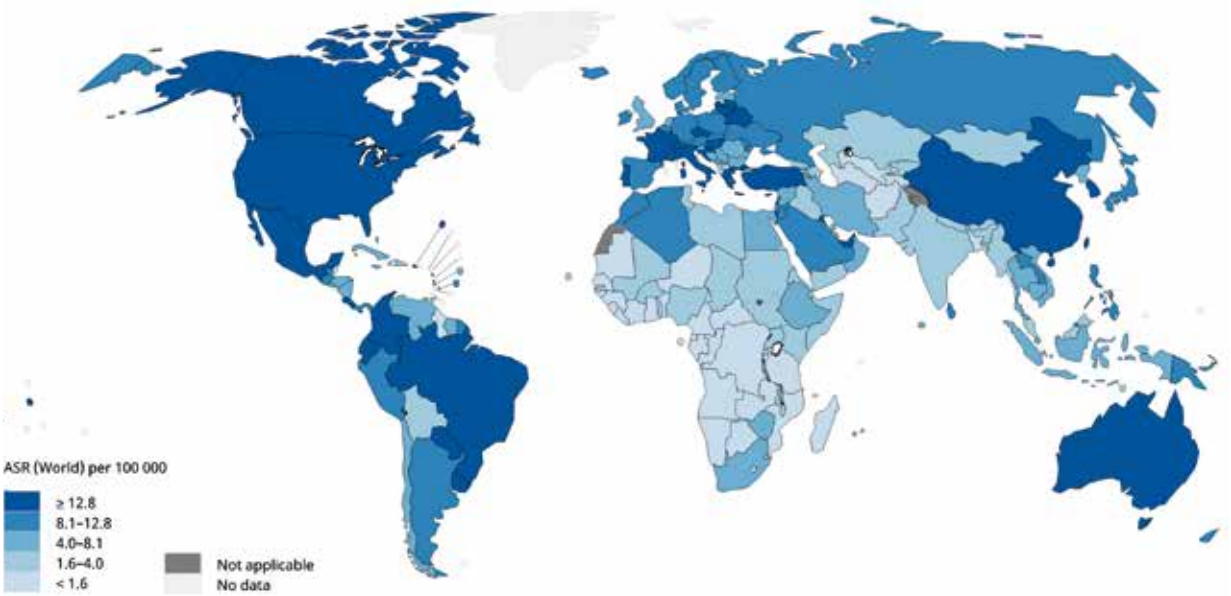
Health-care system model

Studies have shown that the incidence of thyroid cancer is often higher in countries where the

FUNDAMENTALS

- The most common subtypes of thyroid cancer are papillary thyroid cancer, which spreads through the lymphatics, and follicular thyroid cancer, which spreads haematogenously. Papillary thyroid cancer is the subtype with the lowest mortality rate.
- Less common subtypes of thyroid cancer include medullary thyroid cancer, which has an intermediate severity and mortality rate, and anaplastic thyroid cancer, which is the rarest and most uniformly lethal subtype.
- The incidence of thyroid cancer in women is 3 times that in men at all ages, but there are no differences by sex in mortality from thyroid cancer.
- Incidence rates of thyroid cancer have increased around the world. The main cause is probably the detection of subclinical disease that if left undetected would have been unlikely to cause harm to the person.
- Detection of subclinical disease is largely attributable to health-care system factors and practice patterns of health-care providers.

Fig. 5.18.1. Global distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000 person-years for thyroid cancer in women, 2018.



health-care funding model includes fee-for-service options [15]. In studies of countries that have more than one model of funding, patients treated at private hospitals that used a fee-for-service payment model were found to be more likely to have thyroid cancer detected on unrelated imaging compared with patients treated at public hospitals; this suggests that patients with private insurance were more likely to have thyroid cancer detected by imaging than by palpation [16,17]. This disparity may be explained by different factors, including physician incentivization and the availability of advanced imaging technology [18]. The larger the numbers of imaging tests ordered and the more health-care providers intervene for increasingly smaller findings, the more thyroid cancers are detected [19–21].

Socioeconomic status

Recent detailed population-based studies suggest that people with higher socioeconomic status and those living in cities are more frequently diagnosed with thyroid cancer, but that this does not correspond with exposure to environmental pollutants [22]. People with lower socioeconomic status have lower rates of detection of thyroid cancer, more advanced stage at presentation, and higher mortality from thyroid cancer [23]. In the USA, the discrepancy in mortality rates indicates that in some cases, patients with lower socioeconomic status may be undertreated relative to those with higher socioeconomic status, although survival is not always affected (see Chapter 4.6) [24].

Etiology

The vast majority of thyroid cancers are sporadic. However, there are specific risk factors. For medullary thyroid cancer in particular, hereditary syndromes contribute significantly to the disease burden.

Risk factors

Various risk factors associated with the development of thyroid cancer have been investigated. Robust evidence of causal associations exists only for radiation exposure during childhood.

Radiation

Exposure to radiation is the strongest known risk factor for papillary thyroid cancer (see Chapter 2.5). Age at exposure is significantly related to risk. Among survivors of the Hiroshima atomic bomb, those who were younger than 19 years at the time of the bombing had an increased risk relative to the background risk, and that increased risk persisted for at least five decades. Those who were younger than 5 years at the time of exposure had the highest risk, and those who were older than 19 years at the time of exposure did not have an increased risk relative to the background risk [25].

Iodine deficiency can interact with the effects of radiation if the radiation is received from radioactive iodine. This affected the severity of the effects of the Chernobyl accident, because iodine deficiency was common in the populations of the affected areas. People who were exposed thus absorbed more radioactive iodine, and this increased the radiation dose received [26].

After the Chernobyl accident, early analyses suggested that exposure to radiation led to more aggressive thyroid cancer. Compared with non-exposed children, many exposed children had disease that appeared to be more aggressive,

Fig. 5.18.2. The ruined reactor at the Chernobyl nuclear power plant in Ukraine. Exposure to radiation is the strongest known risk factor for papillary thyroid cancer.

with more extensive local invasion, lymph node involvement, and distant metastases. However, subsequent analysis suggested that this observation was related to several variables, including increased absorption of radioactive iodine by iodine-deficient children and the initial lack of a monitoring programme for children, who were the ones at risk of developing thyroid cancer. When the clinical presentation and survival of exposed and non-exposed children of the same age were compared, the suspected difference in clinical aggressiveness was not observed [27].

Exposure to medical radiation has increased in children, and this may also contribute to the development of thyroid cancer [28].

Other factors

In geographical areas where the population has a low dietary intake of stable iodine, there is a higher incidence of goitre, follicular thyroid cancer, and possibly anaplastic thyroid cancer. Iodine excess has been proposed as a cause of increased risk of papillary thyroid cancer, but no plausible mechanism has been identified [29].

In observational studies, overweight, obesity, and type 2 diabetes have all been found to be weakly associated with increased incidence of papillary thyroid cancer. These factors have been postulated to be associated with greater use of health care overall; as described above, this is a known mechanism by which rates of thyroid cancer detection may be higher in one region than in another. For all of these factors, additional research is required to identify the mechanisms that would lead to the development of thyroid cancer [30].

In recent years, it has been suggested that environmental and dietary exposure to nitrites may contribute to the development of papillary thyroid cancer [31,32].

Hereditability

Several inherited conditions with known genetic causes are associated with increased risk of thyroid cancer of different cellular origins [33]. Medullary thyroid cancer can occur as a result of a germline activating mutation in the *RET* oncogene. In children, medullary thyroid cancer is most commonly associated with the MEN type 2 (MEN2) syndrome. Increased risks of differentiated thyroid cancer are seen in people with *PTEN* hamartoma tumour syndrome (Cowden syndrome), *DICER1* pleuropulmonary blastoma syndrome, Carney complex type 1, and familial adenomatous polyposis syndrome.

Familial differentiated thyroid cancer has also been noted, but no chromosomal abnormalities have yet been identified. For a patient to qualify as having familial non-medullary thyroid cancer, there need to be three first-degree relatives with the disease.

Fig. 5.18.3. A child undergoing a computed tomography (CT) scan. Exposure of children to medical radiation may contribute to the development of thyroid cancer and should therefore be minimized.

Genetics and genomics

Differentiated thyroid cancers

Abnormalities of the mitogen-activated protein kinase (MAPK) pathway lead to both papillary and follicular thyroid carcinoma [30].

In adults, papillary thyroid cancers commonly show point mutations in *BRAF* and tend to have relatively large numbers of genetic mutations overall. In children, rearrangements of the *RET* oncogene, leading to activation of this area that is usually silent, are more common than the *BRAF* mutations. In 2014, the Cancer Genome Atlas Research Network showed a low frequency of somatic alterations (relative to other carcinomas for which strong environmental risk factors exist) and extended the set of known papillary thyroid cancer driver alterations to include *EIF1AX*, *PPM1D*, and *CHEK2* and diverse gene fusions [34].

Papillary thyroid cancers in children tend to show more fusion events, rather than the pattern in adults of multiple point mutations. These genetic patterns may be why thyroid cancers in children tend to be more iodine-avid and highly responsive to treatment, whereas those in adults can have wider patterns of spread and loss of differentiation. Staging for thyroid cancer reflects this: the American Joint Committee on Cancer staging system defines all differentiated thyroid cancers in children as stage I or II, regardless of metastases [35].

Follicular thyroid cancers specifically are associated with point mutations in other genes in the MAPK pathway, such as *RAS*, or with rearrangements of *PPAR*γ.

Medullary thyroid cancer

The *RET* proto-oncogene, located on chromosome 10q11.2, encodes a single-pass transmembrane protein of the receptor tyrosine kinase family. RET is expressed in cells derived from the neural crest, such as parafollicular calcitonin-secreting C cells, from which medullary thyroid cancer arises. Most patients with hereditary variants (MEN2A, MEN2B, and familial medullary thyroid cancer) have germline *RET* mutations, and about 50% of sporadic cases have somatic *RET* mutations. The somatic *RET* codon M918T mutation in sporadic medullary thyroid cancer has also been shown to portend a more aggressive clinical course and poorer prognosis.

The genetics of medullary thyroid cancer are important for risk stratification and treatment decision-making. Recent guidelines designated risk categories of *RET* mutations as follows: “highest risk” includes patients with MEN2B and the *RET* codon M918T mutation, “high risk” includes patients with *RET* codon C634 mutations and the *RET* codon A883F mutation, and “moderate risk” includes patients with *RET* codon mutations other than M918T, C634, and A883F [36].

Anaplastic thyroid cancer

Anaplastic thyroid cancers are typically aneuploid and have a complex karyotype with multiple chromosomal abnormalities. Loss of heterozygosity at multiple chromosomal regions is common. A progressive accumulation of chromosomal abnormalities is often seen when comparing differentiated carcinomas with anaplastic carcinomas, thereby supporting the multistep de-differentiation process [37,38]. The more common somatic mutations are in the *TP53* and β-catenin (*CTNNB1*) genes. These mutations are rare in differentiated thyroid cancers. Other mutations, in *BRAF* and *RAS*, are common in both differentiated and anaplastic thyroid cancers and are probably early events in thyroid carcinogenesis that predispose to tumour de-differentiation. Currently, DNA or RNA analysis does not have a role in the staging and management of patients with anaplastic thyroid cancer [39,40].

Prevention

The identification and treatment of iodine deficiency is central to the prevention of thyroid cancer. In population-based studies, follicular thyroid cancer is more common in iodine-deficient areas in low- and middle-income countries, whereas papillary thyroid cancer is the predominant subtype in countries with iodine sufficiency. Follicular thyroid cancers are more aggressive; they spread haematogenously, with a predilection for lung metastases, and have lower survival rates than papillary thyroid cancers [41].

Fig. 5.18.4. Production of iodized salt on the outskirts of Vientiane, Lao People’s Democratic Republic. The identification and treatment of iodine deficiency is central to the prevention of thyroid cancer.

Avoiding unnecessary radiation of the thyroid during childhood and adolescence decreases the risk of papillary thyroid cancer. Even low-dose radiation of children from diagnostic X-rays, for example CT and fluoroscopy, should be minimized. Exposure to radiation increases the risk of thyroid cancer for decades after the exposure. After nuclear accidents, provision of iodine thyroid blocking (i.e. saturating the thyroid gland with stable iodine) up to 24 hours before and up to 2 hours after the exposure may be preventive, particularly for individuals living in iodine-deficient areas [33].

Population-based screening for thyroid cancer is not recommended by major task force bodies, because the harms outweigh the benefits [42]. For the very small proportion of the population with specific identified risks of thyroid cancer, such as associated tumour predisposition syndromes as described above, or with MEN2 or familial medullary thyroid cancer, personalized screening with the appropriate testing method is appropriate.

References

1. Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors (2017). WHO classification of tumours of endocrine organs. Lyon, France: International Agency for Research on Cancer (WHO Classification of Tumours series, 4th edition). Available from: http://publications.iarc.fr/554.
2. La Vecchia C, Malvezzi M, Bosetti C, Garavello W, Bertuccio P, Levi F, et al. (2015). Thyroid cancer mortality and incidence: a global overview. Int J Cancer. 136(9):2187–95. https://doi.org/10.1002/ijc.29251 PMID:25284703
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593
4. Davies L, Welch HG (2014). Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg. 140(4):317–22. https://doi.org/10.1001/jamaoto.2014.1 PMID:24557566
5. Ahn HS, Kim HJ, Welch HG (2014). Korea's thyroid-cancer "epidemic" – screening and overdiagnosis. N Engl J Med. 371(19):1765–7. https://doi.org/10.1056/NEJMp1409841 PMID:25372084
6. Davies L, Morris LGT, Haymart M, Chen AY, Goldenberg D, Morris J, et al.; AACE Endocrine Surgery Scientific Committee (2015). American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: the increasing incidence of thyroid cancer. Endocr Pract. 21(6):686–96. https://doi.org/10.4158/EP14466.DSCR PMID:26135963
7. Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L (2016). Worldwide thyroid-cancer epidemic? The increasing impact of overdiagnosis. N Engl J Med. 375(7):614–7. https://doi.org/10.1056/NEJMp1604412 PMID:27532827
8. Davies L, Welch HG (2006). Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA. 295(18):2164–7. https://doi.org/10.1001/jama.295.18.2164 PMID:16684987
9. Welch HG, Black WC (2010). Overdiagnosis in cancer. J Natl Cancer Inst. 102(9):605–13. https://doi.org/10.1093/jnci/djq099 PMID:20413742
10. Furuya-Kanamori L, Bell KJL, Clark J, Glasziou P, Doi SAR (2016). Prevalence of differentiated thyroid cancer in autopsy studies over six decades: a meta-analysis. J Clin Oncol. 34(30):3672–9. https://doi.org/10.1200/JCO.2016.67.7419 PMID:27601555
11. Yoon DY, Chang SK, Choi CS, Yun EJ, Seo YL, Nam ES, et al. (2008). The prevalence and significance of incidental thyroid nodules identified on computed tomography. J Comput Assist Tomogr. 32(5):810–5. https://doi.org/10.1097/RCT.0b013e318157fd38 PMID:18830117
12. Ezzat S, Sarti DA, Cain DR, Braunstein GD (1994). Thyroid incidentalomas. Prevalence by palpation and ultrasonography. Arch Intern Med. 154(16):1838–40. https://doi.org/10.1001/archinte.1994.00420160075010 PMID:8053752
13. Germano A, Schmitt W, Almeida P, Mateus-Marques R, Leite V (2018). Ultrasound requested by general practitioners or for symptoms unrelated to the thyroid gland may explain higher prevalence of thyroid nodules in females. Clin Imaging. 50:289–93. https://doi.org/10.1016/j.clinimag.2018.05.003 PMID:29738997
14. Singh Ospina N, Brito JP, Maraka S, Espinosa de Ycaza AE, Rodriguez-Gutierrez R, Gionfriddo MR, et al. (2016). Diagnostic accuracy of ultrasound-guided fine needle aspiration biopsy for thyroid malignancy: systematic review and meta-analysis. Endocrine. 53(3):651–61. https://doi.org/10.1007/s12020-016-0921-x PMID:27071659
15. Lee TJ, Kim S, Cho HJ, Lee JH (2012). The incidence of thyroid cancer is affected by the characteristics of a healthcare system. J Korean Med Sci. 27(12):1491–8. https://doi.org/10.3346/jkms.2012.27.12.1491 PMID:23255848
16. Zagzag J, Kenigsberg A, Patel KN, Heller KS, Ogilvie JB (2017). Thyroid cancer is more likely to be detected incidentally on imaging in private hospital patients. J Surg Res. 215:239–44. https://doi.org/10.1016/j.jss.2017.03.059 PMID:28688654
17. Altekruse S, Das A, Cho H, Petkov V, Yu M (2015). Do US thyroid cancer incidence rates increase with socioeconomic status among people with health insurance? An observational study using SEER population-based data. BMJ Open. 5(12):e009843. https://doi.org/10.1136/bmjopen-2015-009843 PMID:26644126
18. Loehrer AP, Murthy SS, Song Z, Lubitz CC, James BC (2017). Association of insurance expansion with surgical management of thyroid cancer. JAMA Surg. 152(8):734–40. https://doi.org/10.1001/jamasurg.2017.0461 PMID:28384780
19. Smith-Bindman R, Miglioretti DL, Johnson E, Lee C, Feigelson HS, Flynn M, et al. (2012). Use of diagnostic imaging studies and associated radiation exposure for patients enrolled in large integrated health care systems, 1996-2010. JAMA. 307(22):2400–9. https://doi.org/10.1001/jama.2012.5960 PMID:22692172
20. Udelsman R, Zhang Y (2014). The epidemic of thyroid cancer in the United States: the role of endocrinologists and ultrasounds. Thyroid. 24(3):472–9. https://doi.org/10.1089/thy.2013.0257 PMID:23937391
21. Zevallos JP, Hartman CM, Kramer JR, Sturgis EM, Chiao EY (2015). Increased thyroid cancer incidence corresponds to increased use of thyroid ultrasound and fine-needle aspiration: a study of the Veterans Affairs health care system. Cancer. 121(5):741–6. https://doi.org/10.1002/cncr.29122 PMID:25376872

22. Fei X, Lou Z, Christakos G, Liu Q, Ren Y, Wu J (2018). Contribution of industrial density and socioeconomic status to the spatial distribution of thyroid cancer risk in Hangzhou, China. Sci Total Environ. 613–614:679–86. https://doi.org/10.1016/j.scitotenv.2017.08.270 PMID:28938210

23. Swegal WC, Singer M, Peterson E, Feigelson HS, Kono SA, Snyder S, et al. (2016). Socioeconomic factors affect outcomes in well-differentiated thyroid cancer. Otolaryngol Head Neck Surg. 154(3):440–5. https://doi.org/10.1177/0194599815620778 PMID:26671905

24. Harari A, Li N, Yeh MW (2014). Racial and socioeconomic disparities in presentation and outcomes of well-differentiated thyroid cancer. J Clin Endocrinol Metab. 99(1):133–41. https://doi.org/10.1210/jc.2013-2781 PMID:24243631

25. Furukawa K, Preston D, Funamoto S, Yonehara S, Ito M, Tokuoka S, et al. (2013). Long-term trend of thyroid cancer risk among Japanese atomic-bomb survivors: 60 years after exposure. Int J Cancer. 132(5):1222–6. https://doi.org/10.1002/ijc.27749 PMID:22847218

26. Iglesias ML, Schmidt A, Ghuzlan AA, Lacroix L, Vathaire F, Chevillard S, et al. (2017). Radiation exposure and thyroid cancer: a review. Arch Endocrinol Metab. 61(2):180–7. https://doi.org/10.1590/2359-3997000000257 PMID:28225863

27. Reiners C, Biko J, Haenscheid H, Hebestreit H, Kirinjuk S, Baranowski O, et al. (2013). Twenty-five years after Chernobyl: outcome of radioiodine treatment in children and adolescents with very high-risk radiation-induced differentiated thyroid carcinoma. J Clin Endocrinol Metab. 98(7):3039–48. https://doi.org/10.1210/jc.2013-1059 PMID:23616148

28. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. (2013). Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ. 346: f2360. https://doi.org/10.1136/bmj.f2360 PMID:23694687

29. Zimmermann MB, Galetti V (2015). Iodine intake as a risk factor for thyroid cancer: a comprehensive review of animal and human studies. Thyroid Res. 8(1):8. https://doi.org/10.1186/s13044-015-0020-8 PMID:26146517

30. Dunlap QD (2019). Differentiated thyroid cancer incidence. In: Randolph GW, editor. Surgery of the thyroid and parathyroid glands. 3rd ed. Philadelphia (PA), USA: Elsevier.

31. Vigneri R, Malandrino P, Gianì F, Russo M, Vigneri P (2017). Heavy metals in the volcanic environment and thyroid cancer. Mol Cell Endocrinol. 457:73–80. https://doi.org/10.1016/j.mce.2016.10.027 PMID:27794445

32. Poulsen R, Cedergreen N, Hayes T, Hansen M (2018). Nitrate: an environmental endocrine disruptor? A review of evidence and research needs. Environ Sci Technol. 52(7):3869–87. https://doi.org/10.1021/acs.est.7b06419 PMID:29494771

33. IARC Expert Group on Thyroid Health Monitoring after Nuclear Accidents (2018). Thyroid health monitoring after nuclear accidents. Lyon, France: International Agency for Research on Cancer (IARC Technical Publications, No. 46). Available from: http://publications.iarc.fr/571.

34. Agrawal N, Akbani R, Aksoy BA, Ally A, Arachchi H, Asa SL, et al.; Cancer Genome Atlas Research Network (2014). Integrated genomic characterization of papillary thyroid carcinoma. Cell. 159(3):676–90. https://doi.org/10.1016/j.cell.2014.09.050 PMID:25417114

35. Amin MB, Greene FL, Compton CC, Gershenwald JE, Brookland RK, Meyer L, et al. (2017). The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 67(2): 93–99. https://doi.org/10.3322/caac.21388 PMID:28094848

36. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al.; American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma (2015). Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 25(6):567–610. https://doi.org/10.1089/thy.2014.0335 PMID:25810047

37. Wreesmann VB, Ghossein RA, Patel SG, Harris CP, Schnaser EA, Shaha AR, et al. (2002). Genome-wide appraisal of thyroid cancer progression. Am J Pathol. 161(5):1549–56. https://doi.org/10.1016/S0002-9440(10)64433-1 PMID:12414503

38. Rodrigues RF, Roque L, Rosa-Santos J, Cid O, Soares J (2004). Chromosomal imbalances associated with anaplastic transformation of follicular thyroid carcinomas. Br J Cancer. 90(2):492–6. https://doi.org/10.1038/sj.bjc.6601530 PMID:14735198

39. Smallridge RC, Ain KB, Asa SL, Bible KC, Brierley JD, Burman KD, et al.; American Thyroid Association Anaplastic Thyroid Cancer Guidelines Taskforce (2012). American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid. 22(11):1104–39. https://doi.org/10.1089/thy.2012.0302 PMID:23130564

40. Haddad RI, Lydiatt WM, Ball DW, Busaidy NL, Byrd D, Callender G, et al. (2015). Anaplastic thyroid carcinoma, version 2.2015. J Natl Compr Canc Netw. 13(9):1140–50. https://doi.org/10.6004/jnccn.2015.0139 PMID:26358798

41. Woodruff SL, Arowolo OA, Akute OO, Afolabi AO, Nwariaku F (2010). Global variation in the pattern of differentiated thyroid cancer. Am J Surg. 200(4):462–6. https://doi.org/10.1016/j.amjsurg.2010.03.009 PMID:20887838

42. Lin JS, Bowles EJA, Williams SB, Morrison CC (2017). Screening for thyroid cancer: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 317(18):1888–903. https://doi.org/10.1001/jama.2017.0562 PMID:28492904

5.19 Non-Hodgkin lymphoma
Complex etiology, including the role of immune function

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SUMMARY

- Non-Hodgkin lymphoma comprises more than 50 different neoplasms that arise from immature or mature B cells, T cells, or natural killer cells.
- The incidence varies globally. The age-standardized rate for both sexes combined is 9.3 per 100 000 in more-developed regions, compared with 4.2 per 100 000 in less-developed regions.
- Accurate diagnosis is imperative for disease management and treatment. Classification of lymphoid malignancies underpins diagnosis and is based on a combination of morphological, phenotypic, genetic/molecular, and clinical features.
- The etiology of non-Hodgkin lymphoma is complex, with multiple known or suspected risk factors. Evidence suggests that some risk factors are common to multiple subtypes of non-Hodgkin lymphoma, but others are subtype-specific.
- Established causes of non-Hodgkin lymphoma include chronic infections (e.g. hepatitis C virus), autoimmune diseases (e.g. Sjögren syndrome), immune alterations (e.g. immunosuppression), exposure to lindane, and family history of non-Hodgkin lymphoma or haematological malignancy.
- To date, more than 120 genetic susceptibility loci have been identified for lymphoid malignancies, including variants in the human leukocyte antigen (HLA) region.

Non-Hodgkin lymphoma (NHL) comprises more than 50 different neoplasms that arise from lymphocytes and can manifest in the lymph nodes, lymphatic organs, and extranodal lymphatic tissue. The classification of these tumours has changed over time with advances in molecular technology and the implementation of the WHO classification system. NHLs are classified broadly by lineage as either B-cell neoplasms or natural killer (NK)/T-cell neoplasms (Table 5.19.1).

In the WHO classification system, plasma cell tumours (e.g. multiple myeloma) and lymphoid leukaemias (discussed in Chapter 5.20) are considered B-cell lymphoid malignancies. Lymphoid malignancies are then further subtyped within major WHO categories on the basis of a combination of morphological, phenotypic, genetic/molecular, and clinical features [1]. These subtype classifications are used in determining disease management and treatment.

Epidemiology

NHL is the 13th most common cancer type worldwide, with an estimated 509 600 new cases (2.8% of all new cancer cases) and 248 700 deaths (2.6% of all cancer deaths) in 2018 [2]. The incidence varies globally (Fig. 5.19.1).

The age-standardized incidence rate for both sexes combined is 9.3 per 100 000 in more-developed regions, compared with 4.2 per 100 000 in less-developed regions (Fig. 5.19.2). Increased detection (especially of more indolent lymphomas), solid organ transplantation, and immunosuppression are some factors that are hypothesized to contribute to this difference, but environmental, viral, or genetic factors may also play a role.

Despite differences in incidence, age-adjusted mortality rates are similar in more-developed regions (2.7 per 100 000) and less-developed regions (2.3 per 100 000). This may reflect better access to treatment and a higher proportion of indolent lymphomas in more-developed regions. Less-developed regions have a greater proportion of poor-prognosis NK/T-cell lymphomas (13.4%) and high-grade B-cell lymphomas (59.6%) compared with more-developed regions (9.3% and 39.2%, respectively) [3].

The incidence trends and patterns of NHL subtypes vary worldwide. In the USA, the incidence rates of most NHL types are high but appear to be relatively stable or declining [4]. Although incidence rates in Asia are lower than those in the USA, the incidence rates of many lymphoma subtypes are rising in Japan [5] and other Asian countries, possibly

Table 5.19.1. Subtypes of non-Hodgkin lymphoma based on the 2016 WHO classification

B-cell neoplasms	NK/T-cell neoplasms
Precursor acute lymphoblastic leukaemia/lymphoma, B-cell	Precursor acute lymphoblastic leukaemia/lymphoma, T-cell
Prolymphocytic leukaemia, B-cell	Prolymphocytic leukaemia, T-cell
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	T-cell large granular lymphocytic leukaemia
Hairy cell leukaemia	Aggressive NK-cell leukaemia
Mantle cell lymphoma	Adult T-cell leukaemia/lymphoma
Marginal zone lymphoma	Systemic EBV-positive T-cell lymphoma of childhood
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	Extranodal NK/T-cell lymphoma, nasal type
Nodal marginal zone lymphoma	Peripheral T-cell lymphoma
Splenic marginal zone lymphoma	Angioimmunoblastic T-cell lymphoma
Follicular lymphoma	Hepatosplenic T-cell lymphoma
Paediatric-type follicular lymphoma	Enteropathy-associated T-cell lymphoma
Primary cutaneous follicle centre lymphoma	Anaplastic large cell lymphoma, ALK-positive
Diffuse large B-cell lymphoma	Anaplastic large cell lymphoma, ALK-negative
Diffuse large B-cell lymphoma, NOS	Subcutaneous panniculitis-like T-cell lymphoma
Germinal centre B-cell subtype	Primary cutaneous gamma delta T-cell lymphoma
Activated B-cell subtype	Monomorphic epitheliotropic intestinal T-cell lymphoma
T-cell/histiocyte-rich large B-cell lymphoma	Hydroa vacciniforme-like lymphoproliferative disorder
Primary DLBCL of the central nervous system	Peripheral T-cell lymphoma, NOS
Primary cutaneous DLBCL, leg type	Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
EBV-positive DLBCL, NOS	Primary cutaneous anaplastic large cell lymphoma
DLBCL associated with chronic inflammation	Mycosis fungoides
Primary mediastinal (thymic) large B-cell lymphoma	Sézary syndrome
Intravascular large B-cell lymphoma	
ALK-positive large B-cell lymphoma	
Plasmablastic lymphoma	
Primary effusion lymphoma	
HHV8-positive DLBCL, NOS	
Burkitt lymphoma	
Burkitt-like lymphoma with 11q aberration	
Lymphoplasmacytic lymphoma	
Waldenström macroglobulinaemia	
Multiple myeloma, plasma cell myeloma	
Plasmacytoma	
Heavy chain diseases, mu/gamma/alpha	
High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements	
High-grade B-cell lymphoma, NOS	

DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; HHV8, human herpesvirus type 8; NK, natural killer; NOS, not otherwise specified.

FUNDAMENTALS

- Lymphomas are clonal tumours of lymphocytes and can manifest in the lymph nodes, lymphatic organs, and extranodal lymphatic tissue.
- Many lymphomas are characterized by recurrent chromosomal translocations, such as the t(11;14) translocation in mantle cell lymphoma.
- These chromosomal translocations may be generated during the extensive genetic remodelling that occurs during normal lymphocyte maturation as part of the adaptive immune system.
- Non-Hodgkin lymphomas are classified broadly by lineage as either B-cell neoplasms or natural killer/T-cell neoplasms. About 85–90% of lymphomas are derived from B lymphocytes, and natural killer/T-cell lymphomas are much less common.
- In the WHO classification system, non-Hodgkin lymphomas are further categorized into specific types. The incidence of non-Hodgkin lymphoma and the distribution of types vary worldwide.
- Chronic antigen stimulation, immunosuppression, immune dysfunction, and hereditary/genetic factors are thought to contribute to the risk of non-Hodgkin lymphoma.

as the result of changes in lifestyle or environmental exposures.

Unlike most NHL types, the incidence rate of Epstein–Barr virus (EBV)-related nasal NK/T-cell lymphoma is higher in Asian countries compared with rates in Whites in the USA [5,6]. For Asians living in the USA, the incidence appears to be intermediate [6], suggesting that both environmental and host factors may contribute to risk.

In the USA, the incidence of most B-cell lymphomas is higher in non-Hispanic Whites than in other racial or ethnic groups; however, NK/T-cell lymphomas, such as mycosis fungoides, peripheral T-cell lymphoma

Fig. 5.19.1. Global distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000 person-years for non-Hodgkin lymphoma in both sexes, 2018.

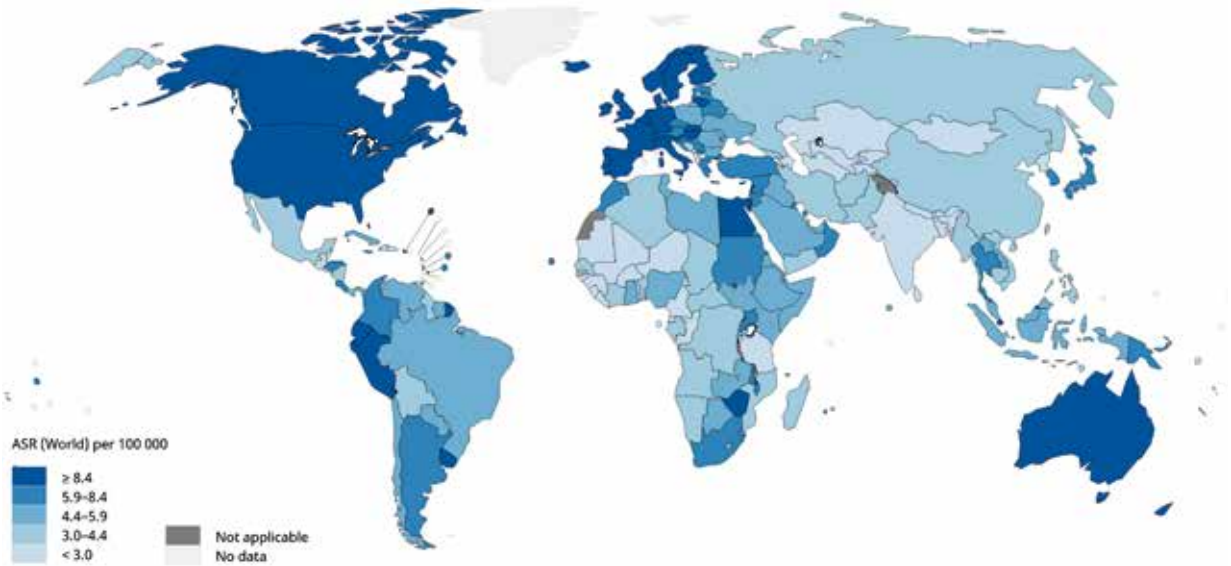
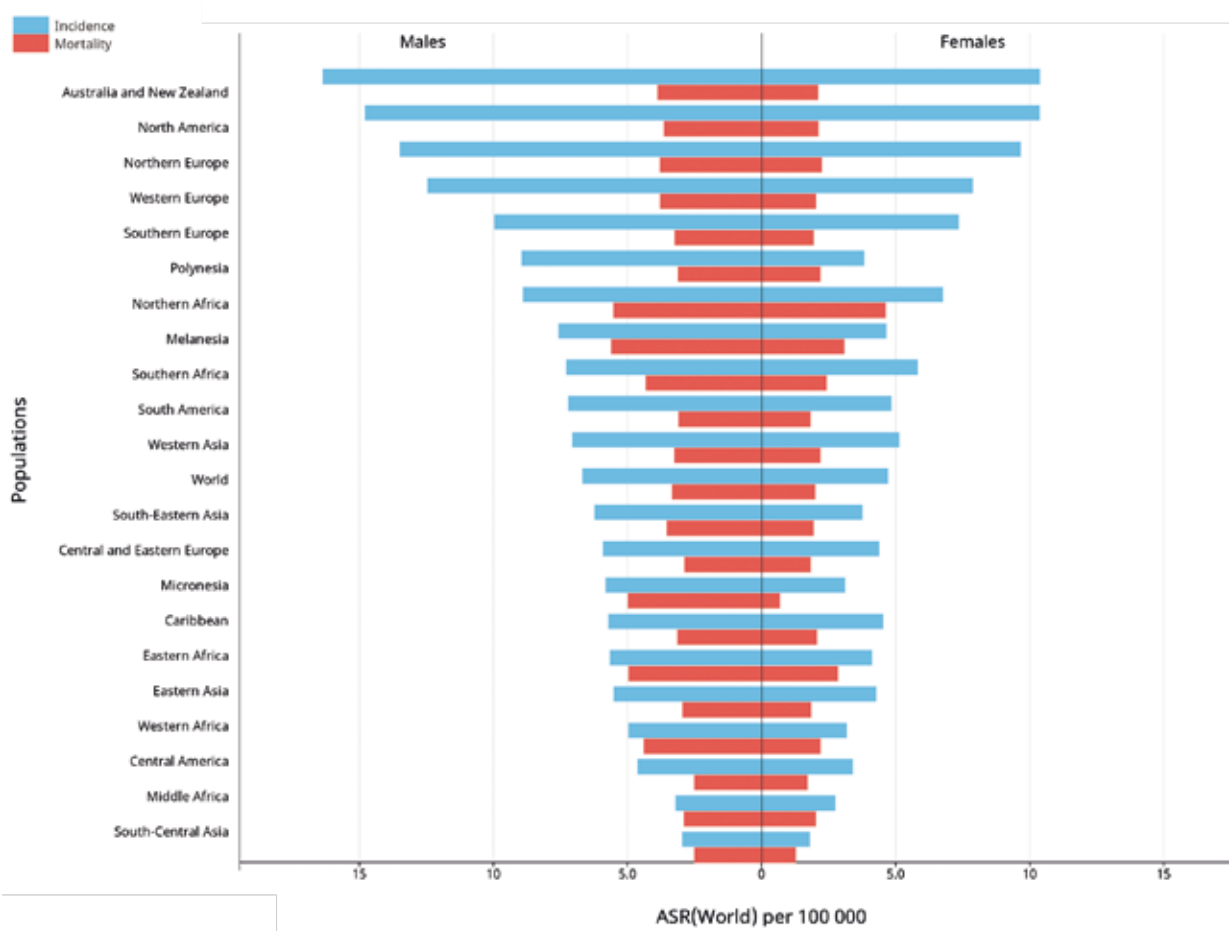


Fig. 5.19.2. Estimated age-standardized (World) incidence and mortality rates (ASR) per 100 000 person-years for non-Hodgkin lymphoma, by sex and region, 2018.



(PTCL), and adult T-cell leukaemia/lymphoma, are more common in non-Hispanic Blacks [4,7]. The percentage of PTCL cases is also higher in southern Africa [3]; this suggests a possible genetic component.

Overall, incidence rates of NHL are higher in males than in females (Fig. 5.19.2), but this difference varies substantially by subtype; the greatest excess risk is seen for mantle cell lymphoma, Burkitt lymphoma, and hairy cell leukaemia [4]. Little difference between the sexes is observed for marginal zone lymphoma (MZL); this may reflect the higher prevalence of autoimmune diseases in women and the strong association between autoimmune disease and risk of MZL [8].

Genetics and genomics

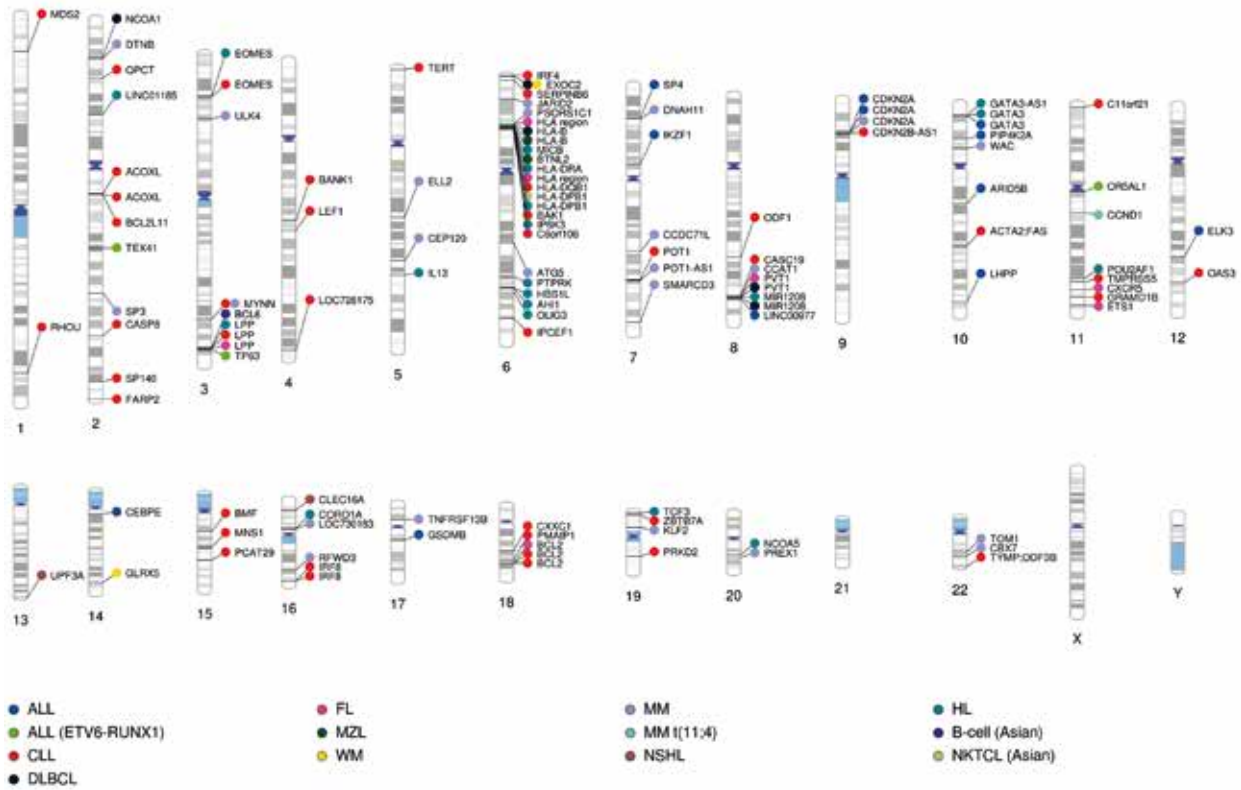
Genome-wide association studies have identified more than 120 germline genetic loci associated with the risk of different lymphoid malignancies (Fig. 5.19.3). The majority of discovered loci confer only a small increase in susceptibility and appear to be subtype-specific. However, a few loci overlap among subtypes, and some chromosomal regions are important for multiple subtypes even if the variants are subtype-specific.

Genetic variants in the human leukocyte antigen (HLA) region, a gene encoding the major histocompatibility complex proteins responsible for immune function, are associated with multiple lymphoma subtypes, including follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), and MZL in European populations and extranodal NK/T-cell lymphoma in Asian populations. Variants in HLA class I are associated with DLBCL [9], variants in HLA class II are associated with NK/T-cell lymphoma [10], and variants in both HLA class I and class II are associated with follicular lymphoma and MZL [11,12].

Susceptibility loci (see Chapter 3.2) have been discovered for both DLBCL and follicular lymphoma at chromosome 8q24 near *MYC* [9,11], a region known to be associated with multiple different cancer types. Genetic variation near *LPP* at chromosome 3q27.3–3q28, a region also associated with immune-related diseases, is associated with both follicular lymphoma in subjects of European descent [11] and DLBCL in the Chinese population [13].

Many B-cell lymphomas are characterized by chromosomal translocations, often involving the immunoglobulin heavy chain locus, although copy number alterations and mutations may also be present. These somatic alterations may

Fig. 5.19.3. Established genetic loci for specific lymphoid malignancies. To date, most loci have been discovered in populations of European ancestry. Two loci have been identified in populations of East Asian ancestry: one locus for B-cell lymphoma, particularly diffuse large B-cell lymphoma (DLBCL), and one locus for natural killer/T-cell lymphoma (NKTCL). ALL, acute lymphoblastic leukaemia; CLL, chronic lymphocytic leukaemia; FL, follicular lymphoma; HL, Hodgkin lymphoma; MM, multiple myeloma; MZL, marginal zone lymphoma; NSHL, nodular sclerosing Hodgkin lymphoma; WM, Waldenström macroglobulinaemia.



be the result of a deviation in the normal lymphocyte maturation process as part of the adaptive immune system, which generates broad antibody diversity and specificity through V(D)J gene recombination (which involves DNA double-strand breaks), germinal centre reaction, clonal expansion, somatic hypermutation of immunoglobulin G genes, class-switch recombination, selection, and differentiation/apoptosis.

Etiology and biological characteristics

Lymphomas arise from clonal tumours of B cells, T cells, or NK cells (Fig. 5.19.4) that have arrested during different stages of differentiation. Emerging evidence indicates that the etiology of NHL is complex, with subtype-specific patterns of risk [14].

Known or suspected risk factors include immune alterations (e.g. immunosuppression), viral infections (e.g. hepatitis C virus [HCV] and human T-cell lymphotropic virus type 1 [HTLV-1]), autoimmune diseases (e.g. Sjögren syndrome), environmental or occupational exposures (e.g. benzene and pentachlorophenol), and lifestyle factors. Some risk factors are shared across multiple subtypes and may be generally associated with risk of NHL, but others are likely to be specific to individual subtypes.

Diffuse large B-cell lymphoma

DLBCL is an aggressive B-cell lymphoma that accounts for 25–45% of NHL cases. It is the most common adult lymphoma worldwide. DLBCL can originate in lymph nodes or extranodal sites, such as the gastrointestinal tract, the testis, and the central nervous system. It is a heterogeneous group of lymphomas on the basis of histology, immunophenotype, and clinical presentation, and some DLBCLs, such as primary mediastinal large B-cell lymphoma, are classified separately by WHO [1].

DLBCL tumours can be categorized according to cell of origin as germinal centre B-cell subtype, activated B-cell subtype, or other. About 1–12% of DLBCL tumours are high-grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangements; these double-hit or triple-hit lymphomas, which are now classified separately [1], have a worse prognosis. More recently, next-generation sequencing technologies have been used to further classify DLBCLs on the basis of specific mutations and chromosomal rearrangements into four or five additional categories with potential prognostic significance [15,16]. Recurrent mutations in *MYD88* and *CD79B*, frequently found in primary central nervous system lymphoma, may lead to activation of the nuclear factor kappa-light-chain-enhancer of activated B (NF-κB) signalling pathway [17].

The etiology of DLBCL is complex, with multiple known or suspected risk factors and differences among sites of origin. Chronic infections (e.g. HCV) and autoimmune diseases, particularly B-cell activating diseases (e.g. Sjögren syndrome) are associated with an increased risk of DLBCL, implicating chronic immune stimulation in the pathogenesis of DLBCL. Solid organ transplantation is a risk factor, possibly as a result of chronic immune activation in response to the donor organ, immunosuppression therapy, or both, resulting in immune dysfunction [18]. HIV infection is also a risk factor for DLBCL, particularly primary central nervous system lymphoma, possibly due to immunosuppression. Family history of NHL is associated with an increased risk, implicating genetic factors. Other suggestive risk factors include higher body mass index, lower socioeconomic status, working as a farmer or field crop worker, and occupation as a hairdresser [19].

Fig. 5.19.4. Lymphocyte development and cell lineages. Lymphoid malignancies arise from immature or mature B cells, T cells, or natural killer cells. MHC, major histocompatibility complex.

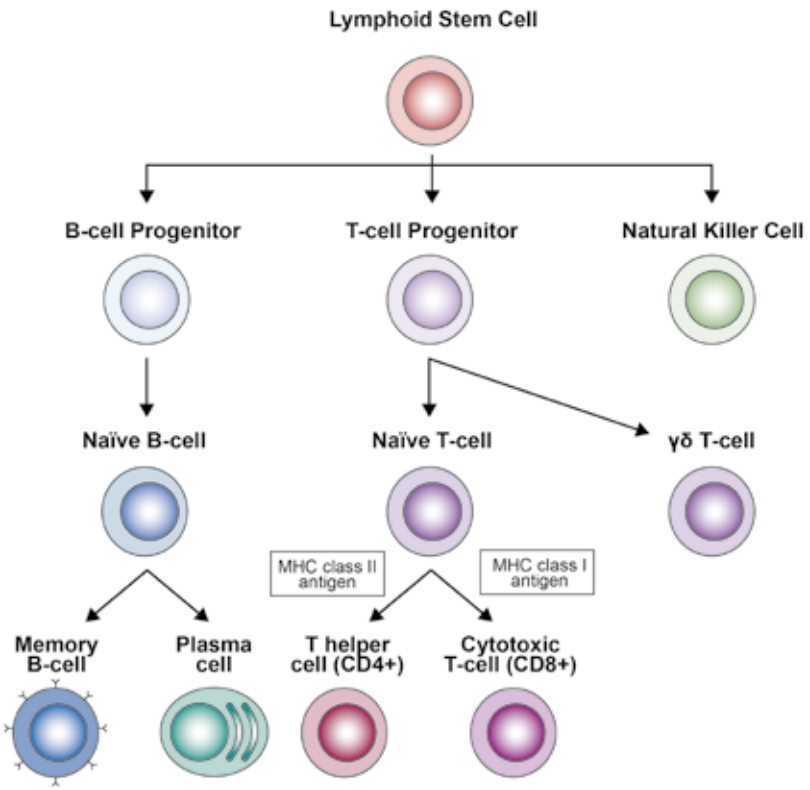


Fig. 5.19.5. A crop duster spraying a cornfield.

Follicular lymphoma

Follicular lymphoma is a slow-growing B-cell malignancy that accounts for 12–20% of NHL cases. It is the second most common adult lymphoma in Europe and the USA. The 5-year survival rates tend to be higher than 80%, with 2–3% of cases transforming to DLBCL per year.

Follicular lymphoma arises from the transformation of germinal centre B cells with varying proportions of centroblasts and centrocytes, which determine the pathological grade of the lymphoma. Grades 1 and 2 are considered low-grade disease, whereas grade 3B is more aggressive. About 80–90% of follicular lymphomas display a t(14;18) translocation, in which the *BCL2* gene is joined to an immunoglobulin heavy (*IGH*) gene, and a subset of cases have *BCL6* translocations. Pesticide exposure has been associated with t(14;18) translocations [20], suggesting a possible etiological link.

Evidence from epidemiological studies points to several risk factors for follicular lymphoma, including family history of NHL [21]. Unlike DLBCL, solid organ transplantation does not appear to increase risk [18], and autoimmune diseases appear to play a smaller role [21]. Allergy and hay fever appear to be protective against follicular lymphoma, possibly because of an increased response against cancer-specific or cancer-related antigens and early eradication of tumour cells. Exposure to the chlorinated insecticide lindane, which is classified as carcinogenic to humans on the basis of epidemiological studies showing an increased risk of NHL, may be a stronger risk factor for follicular lymphoma [22]. Exposures to trichloroethylene and other chlorinated solvents are suspected risk factors [23,24].

Marginal zone lymphoma

MZL is a slow-growing B-cell malignancy that accounts for 7–11% of NHL cases. MZL arises from the marginal zone or edge of lymphoid tissue. There are three distinct types of MZL: extranodal, nodal, and splenic. Extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma) is the most common type of MZL, accounting for about two thirds of MZL cases. It occurs outside the lymph nodes at a variety of anatomical sites, including the stomach, salivary glands, thyroid, and lung. Several chromosomal translocations, some of which involve genes encoding NF-κB regulators, have been reported for MALT lymphoma.

Nodal MZL, which accounts for 10–25% of MZL cases, occurs in the lymph nodes and has a heterogeneous morphology and cytology. Transformation to DLBCL occurs in about 15% of patients with nodal MZL. Splenic MZL occurs in the spleen, blood, and bone marrow; deletion of 7q and *NOTCH2* mutations are characteristic of the malignancy.

Chronic infection, autoimmune disorders, inflammation, and antigen stimulation are thought to be strong contributors to the etiology of MZL. Infection with *Helicobacter pylori* is observed in most cases of gastric MALT lymphoma, and eradication of *H. pylori* with antibiotic treatment leads to regression of MALT lymphoma in 75–80% of cases. *H. pylori* infection is thought to trigger inflammation and immunological responses, leading to the positive selection of malignant B cells. HCV infection is associated with an increased risk of MZL, particularly splenic MZL and nodal MZL. Chronic antigen stimulation leading to B-cell stimulation is thought to underlie the association, and interferon-based antiviral treatment leads to disease regression in more than 70% of cases [25]. B-cell activating autoimmune conditions, such as Sjögren syndrome and systemic lupus erythematosus, are strongly associated with an increased risk of MZL [8].

Mantle cell lymphoma

Mantle cell lymphoma is a rare, aggressive B-cell lymphoma that makes up about 3–6% of NHL cases. It occurs more often in men than in women, and more often in Whites than in Blacks or Asians [4]. It often involves the bone marrow, spleen, peripheral blood, and gastrointestinal tract. Mantle cell lymphoma is characterized by the chromosomal translocation t(11;14) and overexpression of cyclin D1, which is observed in most cases. Overexpression of the transcription factor *SOX11* is often present, but absence of *SOX11* expression is associated with a more favourable prognosis. Overall, mantle cell lymphoma has a poor

prognosis, with 5-year survival rates of less than 50%.

The etiology of mantle cell lymphoma is not well understood. Unlike many other NHL subtypes, solid organ transplantation and most autoimmune diseases do not appear to be associated with risk of mantle cell lymphoma. Hay fever and allergy appear to be protective against mantle cell lymphoma, and having a first-degree relative with a haematological malignancy is associated with an increased risk [26]. Living on a farm may also be associated with increased risk.

Burkitt lymphoma

Burkitt lymphoma is an aggressive, rapidly growing B-cell NHL involving the jaw, central nervous system, colorectum, kidney, or other organs. The hallmark of Burkitt lymphoma is the presence of translocations involving *MYC* and an immunoglobulin gene (e.g. *IGH*). Although they are histologically indistinguishable, there are three etiological subtypes of Burkitt lymphoma: endemic, immunodeficiency-associated, and sporadic.

Endemic Burkitt lymphoma occurs primarily in equatorial Africa and Papua New Guinea, where *Plasmodium falciparum* malaria is holoendemic. It is the most common childhood cancer in those countries, and nearly 100% of tumours are positive for EBV. Although recent malaria infections are hypothesized to contribute to endemic Burkitt lymphoma, the mechanism and interaction with EBV are not well understood.

Immunodeficiency-associated Burkitt lymphoma occurs primarily in individuals with HIV infection and less commonly after organ transplantation. Sporadic Burkitt lymphoma makes up about 30% of lymphoid malignancies in children and about 1–5% in adults in developed countries and often occurs in the abdomen. In contrast to endemic Burkitt lymphoma, EBV is identified in only 30–60% of immunodeficiency-related Burkitt lymphoma tumours and only 15–30% of sporadic Burkitt lymphoma tumours.

Fig. 5.19.6. A girl aged 9 years sits with her mother and baby sister before undergoing treatment for Burkitt lymphoma at Bugando Medical Centre in Mwanza, United Republic of Tanzania.

The risk factors for sporadic Burkitt lymphoma are not well understood. In developed countries, the incidence of Burkitt lymphoma peaks in childhood and then again in late adulthood, and the incidence rate in males is substantially higher than that in females. For younger cases, a history of allergy is associated with a reduced risk of Burkitt lymphoma, suggesting that immunological hypersensitivity may be important [27]. For older cases, HCV infection may be a risk factor.

Peripheral T-cell lymphoma

PTCL is the most common T-cell lymphoma and accounts for 4–7% of NHL cases in Europe and the USA. It is a heterogeneous group of lymphomas with diverse morphological and clinical features. Predominantly nodal PTCLs include anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, and PTCL not otherwise specified. A subset of PTCLs, including angioimmunoblastic T-cell lymphoma and some PTCLs not otherwise specified, have features of follicular helper T cells. Up to 75% of these lymphomas have mutations in *TET2*, and about 60% have mutations in *RHOA*. Anaplastic large cell lymphomas are characterized by the chromosomal translocation t(2;5)(p23;q35) involving *ALK*.

Except for a history of coeliac disease, which is associated primarily with enteropathy-associated T-cell lymphoma, there are few established risk factors for PTCL. HIV infection has been linked to an increased risk of PTCL [28], implicating immune dysregulation in the pathogenesis. Although this is rare, textured breast implants appear to increase the risk of anaplastic large cell lymphoma [29], possibly through chronic immune stimulation. Recent evidence suggests that psoriasis and eczema may be associated with increased risk of PTCL, whereas allergy may be protective [30]. Family history of any haematological malignancy is associated with an increased risk.

Socioeconomic differences

The diagnosis and classification of lymphomas remain challenging in low- and middle-income countries, where immunohistochemistry and other technologies needed

to make an accurate diagnosis are often unavailable. Less-developed countries tend to have a higher percentage of unclassifiable cases and more misclassified cases compared with more-developed countries [3]. As accurate and more refined classification becomes more critical to disease management and treatment, these disparities could result in greater mortality differences in the future. Although NHL is more common in men, some geographical areas have a substantially lower percentage of cases in women [3], suggesting that sex disparities in medical care may exist in some regions.

Prevention

Much progress has been made in identifying risk factors associated with specific NHL types. There is convincing evidence that some infections (e.g. HCV), autoimmune diseases (e.g. Sjögren syndrome), and immunosuppression increase the risk of NHL. Prevention or early treatment of these infections and diseases can decrease the incidence of some subtypes of NHL. Reduced exposure to lindane and other suspected lymphomagens (such as benzene) may also be beneficial. Further research on the etiology of specific NHL subtypes and the identification of early biomarkers may offer insights into pathways of prevention.

References

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. (2016). The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 127(20):2375–90. https://doi.org/10.1182/blood-2016-01-643569 PMID:26980727
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593
3. Perry AM, Diebold J, Nathwani BN, MacLennan KA, Müller-Hermelink HK, Bast M, et al. (2016). Non-Hodgkin lymphoma in the developing world: review of 4539 cases from the International Non-Hodgkin Lymphoma Classification Project. Haematologica. 101(10):1244–50. https://doi.org/10.3324/haematol.2016.148809 PMID:27354024
4. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR (2016). 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin. 66(6):443–59. https://doi.org/10.3322/caac.21357 PMID:27618563
5. Chihara D, Ito H, Matsuda T, Shibata A, Katsumi A, Nakamura S, et al. (2014). Differences in incidence and trends of haematological malignancies in Japan and the United States. Br J Haematol. 164(4):536–45. https://doi.org/10.1111/bjh.12659 PMID:24245986
6. Bassig BA, Au WY, Mang O, Ngan R, Morton LM, Ip DKM, et al. (2016). Subtype-specific incidence rates of lymphoid malignancies in Hong Kong compared to the United States, 2001–2010. Cancer Epidemiol. 42:15–23. https://doi.org/10.1016/j.canep.2016.02.007 PMID:26991956
7. Adams SV, Newcomb PA, Shustov AR (2016). Racial patterns of peripheral T-cell lymphoma incidence and survival in the United States. J Clin Oncol. 34(9):963–71. https://doi.org/10.1200/JCO.2015.63.5540 PMID:26962200
8. Bracci PM, Benavente Y, Turner JJ, Paltiel O, Slager SL, Vajdic CM, et al. (2014). Medical history, lifestyle, family history, and occupational risk factors for marginal zone lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014(48):52–65. https://doi.org/10.1093/jncimonographs/lgu011 PMID:25174026
9. Cerhan JR, Berndt SI, Vijai J, Ghesquières H, McKay J, Wang SS, et al. (2014). Genome-wide association study identifies multiple susceptibility loci for diffuse large B cell lymphoma. Nat Genet. 46(11):1233–8. https://doi.org/10.1038/ng.3105 PMID:25261932
10. Li Z, Xia Y, Feng LN, Chen J-R, Li H-M, Cui J, et al. (2016). Genetic risk of extranodal natural killer T-cell lymphoma: a genome-wide association study. Lancet Oncol. 17(9):1240–7. https://doi.org/10.1016/S1470-2045(16)30148-6 PMID:27470079
11. Skibola CF, Berndt SI, Vijai J, Conde L, Wang Z, Yeager M, et al. (2014). Genome-wide association study identifies five susceptibility loci for follicular lymphoma outside the HLA region. Am J Hum Genet. 95(4):462–71. https://doi.org/10.1016/j.ajhg.2014.09.004 PMID:25279986
12. Vijai J, Wang Z, Berndt SI, Skibola CF, Slager SL, de Sanjose S, et al. (2015). A genome-wide association study of marginal zone lymphoma shows association to the HLA region. Nat Commun. 6(1):5751. https://doi.org/10.1038/ncomms6751 PMID:25569183
13. Tan DE, Foo JN, Bei JX, Chang J, Peng R, Zheng X, et al. (2013). Genome-wide association study of B cell non-Hodgkin lymphoma identifies 3q27 as a susceptibility locus in the Chinese population. Nat Genet. 45(7):804–7. https://doi.org/10.1038/ng.2666 PMID:23749188
14. Morton LM, Slager SL, Cerhan JR, Wang SS, Vajdic CM, Skibola CF, et al. (2014). Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014(48):130–44. https://doi.org/10.1093/jncimonographs/lgu013 PMID:25174034
15. Schmitz R, Wright GW, Huang DW, Johnson CA, Phelan JD, Wang JQ, et al. (2018). Genetics and pathogenesis of diffuse large B-cell lymphoma. N Engl J Med. 378(15):1396–407. https://doi.org/10.1056/NEJMoa1801445 PMID:29641966
16. Chapuy B, Stewart C, Dunford AJ, Kim J, Kamburov A, Redd RA, et al. (2018). Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. Nat Med. 24(5):679–90. https://doi.org/10.1038/s41591-018-0016-8 PMID:29713087
17. Phelan JD, Young RM, Webster DE, Roulland S, Wright GW, Kasbekar M, et al. (2018). A multiprotein supercomplex controlling oncogenic signalling in lymphoma. Nature. 560(7718):387–91. https://doi.org/10.1038/s41586-018-0290-0 PMID:29925955
18. Clarke CA, Morton LM, Lynch C, Pfeiffer RM, Hall EC, Gibson TM, et al. (2013). Risk of lymphoma subtypes after solid organ transplantation in the United States. Br J Cancer. 109(1):280–8. https://doi.org/10.1038/bjc.2013.294 PMID:23756857

19. Cerhan JR, Kricker A, Paltiel O, Flowers CR, Wang SS, Monnereau A, et al. (2014). Medical history, lifestyle, family history, and occupational risk factors for diffuse large B-cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014(48):15–25. https://doi.org/10.1093/jncimonographs/lgu010 PMID:25174023

20. Chiu BC, Dave BJ, Blair A, Gapstur SM, Zahm SH, Weisenburger DD (2006). Agricultural pesticide use and risk of t(14;18)-defined subtypes of non-Hodgkin lymphoma. Blood. 108(4):1363–9. https://doi.org/10.1182/blood-2005-12-008755 PMID:16621961

21. Linet MS, Vajdic CM, Morton LM, de Roos AJ, Skibola CF, Boffetta P, et al. (2014). Medical history, lifestyle, family history, and occupational risk factors for follicular lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014(48):26–40. https://doi.org/10.1093/jncimonographs/lgu006 PMID:25174024

22. Alavanja MC, Hofmann JN, Lynch CF, Hines CJ, Barry KH, Barker J, et al. (2014). Non-Hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the Agricultural Health Study. PLoS One. 9(10):e109332. https://doi.org/10.1371/journal.pone.0109332 PMID:25337994

23. Cocco P, Vermeulen R, Flore V, Nonne T, Campagna M, Purdue M, et al. (2013). Occupational exposure to trichloroethylene and risk of non-Hodgkin lymphoma and its major subtypes: a pooled InterLymph analysis. Occup Environ Med. 70(11):795–802. https://doi.org/10.1136/oemed-2013-101551 PMID:23881218

24. Callahan CL, Stewart PA, Friesen MC, Locke S, De Roos AJ, Cerhan JR, et al. (2018). Case-control investigation of occupational exposure to chlorinated solvents and non-Hodgkin's lymphoma. Occup Environ Med. 75(6):415–20. https://doi.org/10.1136/oemed-2017-104890 PMID:29588333

25. Arcaini L, Besson C, Frigeni M, Fontaine H, Goldaniga M, Casato M, et al. (2016). Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. Blood. 128(21):2527–32. https://doi.org/10.1182/blood-2016-05-714667 PMID:27605512

26. Smedby KE, Sampson JN, Turner JJ, Slager SL, Maynadié M, Roman E, et al. (2014). Medical history, lifestyle, family history, and occupational risk factors for mantle cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014(48):76–86. https://doi.org/10.1093/jncimonographs/lgu007 PMID:25174028

27. Mbulaiteye SM, Morton LM, Sampson JN, Chang ET, Costas L, de Sanjosé S, et al. (2014). Medical history, lifestyle, family history, and occupational risk factors for sporadic Burkitt lymphoma/leukemia: the Interlymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014(48):106–14. https://doi.org/10.1093/jncimonographs/lgu003 PMID:25174031

28. Gibson TM, Morton LM, Shiels MS, Clarke CA, Engels EA (2014). Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. AIDS. 28(15):2313–8. https://doi.org/10.1097/QAD.0000000000000428 PMID:25111081

29. Leberfinger AN, Behar BJ, Williams NC, Rakszawski KL, Potochny JD, Mackay DR, et al. (2017). Breast implant-associated anaplastic large cell lymphoma: a systematic review. JAMA Surg. 152(12):1161–8. https://doi.org/10.1001/jamasurg.2017.4026 PMID:29049466

30. Wang SS, Flowers CR, Kadin ME, Chang ET, Hughes AM, Ansell SM, et al. (2014). Medical history, lifestyle, family history, and occupational risk factors for peripheral T-cell lymphomas: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014(48):66–75. https://doi.org/10.1093/jncimonographs/lgu012 PMID:25174027

5.20 Leukaemias
Understanding pathogenesis through similarities and differences

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SUMMARY

- Globally, there is a lack of population-based descriptive data for many leukaemia subtypes, of which there are more than 30. This information is required to inform etiological hypotheses, plan health-care services, and monitor the impact of therapeutic change.
- Different subtypes of leukaemia dominate at different ages. For example, B-cell acute lymphoblastic leukaemia is most common in children younger than 15 years, and chronic lymphocytic leukaemia, myeloproliferative neoplasms, and acute myeloid leukaemia are far more common at older ages.
- For reasons that are unknown, almost every leukaemia subtype has a male predominance.
- In high-income countries, survival rates vary widely from one subtype to another. The 5-year relative survival is more than 80% for chronic lymphocytic leukaemia and chronic myeloid leukaemia but less than 20% for other subtypes, such as acute myeloid leukaemia.
- Increased understanding of pathogenesis has resulted in marked improvements in survival for some leukaemia subtypes, including chronic myeloid leukaemia.

The leukaemias (literally "white blood") comprise a heterogeneous group of more than 30 lymphoid and myeloid malignancies with diverse etiologies, treatment pathways, and outcomes [1]. They are classified by cell of origin (Fig. 5.20.1).

Leukaemias were first recognized as a distinct entity in the 1850s [2]. The taxonomy of leukaemias has changed markedly over time, as biological understanding of the similarities and differences between the various haematological malignancies – leukaemias, lymphomas, and myelomas – and their relationship to the normal bone marrow and immune system has increased. However, contemporary population-based information about the occurrence and outcome for many leukaemia subtypes is sparse, and for some of the rarer entities is mostly non-existent.

This absence of data largely reflects the paradigm-changing nature of the WHO classification implemented in 2001 (the basis for the International Classification of Diseases for Oncology, third edition [ICD-O-3]), which, for the first time, incorporated genetic data with information on immunology, morphology, and clinical parameters [3]. This resulted not only in significant refinements to previously defined categories but also in the addition of several new entities, including the myelodysplastic syndromes and myeloproliferative neoplasms, which form part of the myeloid leukaemia spectrum. Critically, most of the neoplasms listed in the ICD-O-3 categories of myelodysplastic syndromes and myeloproliferative neoplasms still appear with a code beginning with "D" (neoplasms of unknown or uncertain behaviour) in the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10).

Such radical changes in classification, together with the breadth of investigations required to implement the classification system (histology, cytology, immunophenotyping, cytogenetics, flow cytometry, and clinical data), continue to pose significant challenges for population-based cancer registries; many struggle to capture all diagnoses, and often continue to report using the traditional leukaemia grouping [4,5].

In 2018, there were an estimated 437 000 new cases of leukaemia worldwide, and leukaemia was the 15th most common cancer type, accounting for 2.4% of all new cancer cases [6]. However, because many countries still do not have high-quality and representative cancer registration systems, examining global variation and trends over time is challenging for any cancer type; for leukaemias, the situation is exacerbated by the diagnostic challenges associated with identifying the various leukaemia subtypes, coupled with the inconsistent implementation of the WHO classification [1,7,8]. Furthermore, even in countries with good cancer registration systems,

there is a lack of consistency in the policies applied to progressions and transformations (e.g. from myelodysplastic syndromes to acute myeloid leukaemia [AML]); for example, the United States Surveillance, Epidemiology, and End Results (SEER) programme has different rules to the European Network of Cancer Registries [9,10].

In low-income countries, where mortality and morbidity from infections and nutritional conditions are often high, diagnosing leukaemia presents additional challenges. The symptoms of many types of leukaemia are broadly similar to those of infectious and/or parasitic illnesses, and the diagnostic expertise and/or technologies required to enable leukaemia to be distinguished from background infections are often lacking.

Descriptive epidemiology

Good-quality population-based descriptive data are required not only to inform etiological hypotheses and plan health-care services but also to monitor the impact of therapeutic change in the general population. This need is particularly pertinent in fast-moving areas like haemato-oncology, where treatment protocols are subject to rapid change, and "gold standard" randomized controlled trials, which tend to be conducted almost exclusively in higher-income countries, are frequently restricted to specific patient subgroups, often comprising younger people with fewer comorbidities. Furthermore, in some countries, particularly low-income countries and/or those where universal health coverage is lacking, the likelihood of both treatment and trial entry often varies with socioeconomic status, sex, and ethnicity.

In recent years, there has been an increasing recognition that scientific progress is being impeded by the lack of reliable population-based incidence and survival data on the various leukaemia subtypes [11]. This has led to improvements in national cancer registration procedures as well as the development of several specialist registries [12,13]. One such source is the United Kingdom Haematological Malignancy Research Network (HMRN; https://www.hmrn.org), which since 2004 has collated detailed information on all newly diagnosed haematological malignancies arising in a population of about 4 million [14]. The HMRN data for the 12 years from September 2004 to August 2016 (n = 29 329) for the major subtypes (Fig. 5.20.2) illustrate where the leukaemias sit within the broad WHO ICD-O-3 cell-of-origin haematological malignancy spectrum.

The leukaemias account for about 40% of all haematological malignancies. They comprise all myeloid subtypes and several lymphoid subtypes. The main leukaemia subtypes are shown in Fig. 5.20.3. Mature B-cell chronic lymphocytic leukaemia (CLL) is the largest category, followed by the myeloproliferative neoplasms, the AMLs, and the myelodysplastic syndromes.

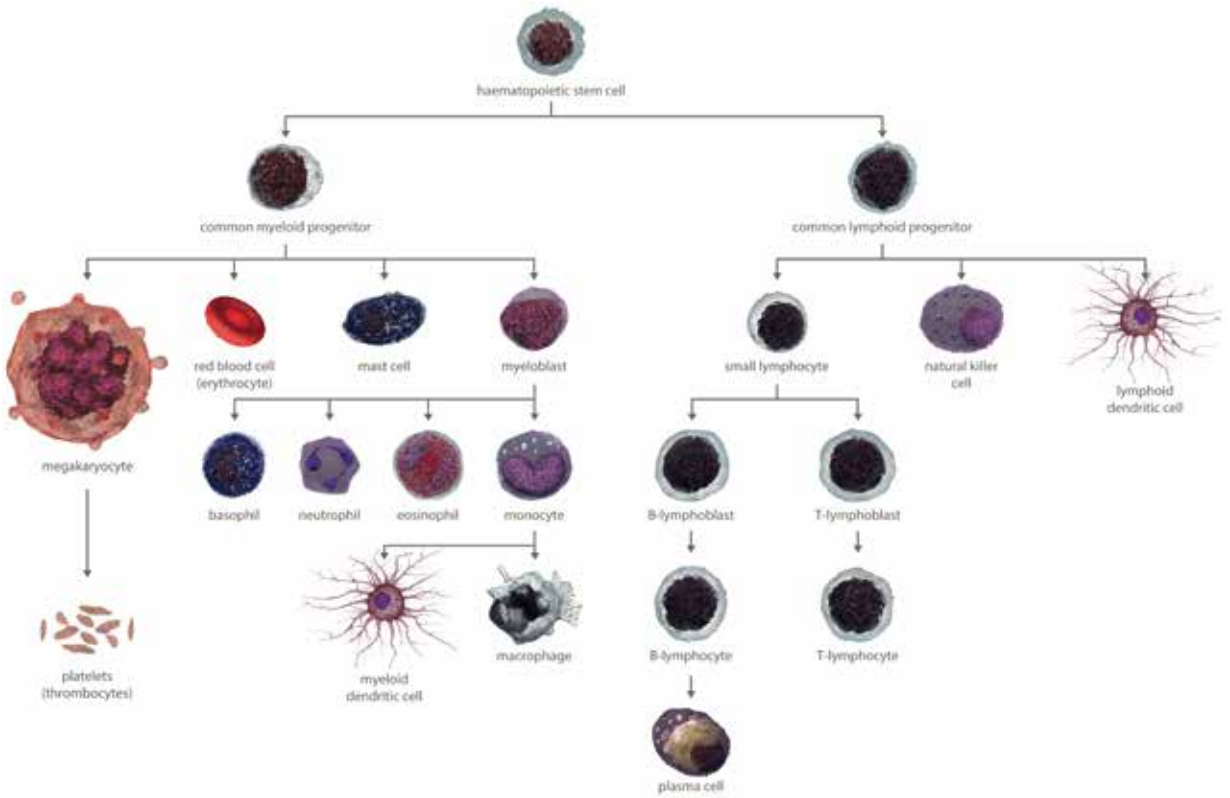
Historically, when CLL cells were found in lymph nodes rather than in peripheral blood, the disease was termed small lymphocytic lymphoma. The different names reflected differences in disease spread rather than in origin. For research purposes, CLL is increasingly grouped with other mature B-cell malignancies, both lymphomas and myelomas, and/or with the non-Hodgkin lymphomas, both T-cell and B-cell; the same is true for hairy cell leukaemia, which also has a mature B-cell origin [15,16]. However, most population-based registries still include CLL and hairy cell leukaemia in their "all leukaemia" category [4,11].

For information and completeness, data on monoclonal B-cell lymphocytosis, which has an ICD-O-3 behaviour code of 1 (and is not listed in ICD-10), are also included in Fig. 5.20.3. Monoclonal B-cell lymphocytosis is defined by a monoclonal B-cell count of less than 5×10^9/L in peripheral blood [1]. Because about 75% of cases have a CLL phenotype, monoclonal

FUNDAMENTALS

- Originating in blood-forming tissues, usually the bone marrow, the leukaemias comprise a heterogeneous group of lymphoid and myeloid malignancies. This simple topographic categorization – cancer in the blood – reflects the pattern of spread rather than the origin.
- The 2001 WHO classification of haematological malignancies, which groups cancers according to their cell of origin, was adopted into worldwide clinical practice but did not have an immediate effect on population-based epidemiological research. Increasing recognition that the lack of data on clinically meaningful groups was impeding scientific progress has led to recent improvements in national cancer registration procedures as well as the development of specialist registries.
- Although the majority of leukaemia subtypes do not appear to have major environmental determinants, a few well-established risk factors continue to produce strong associations, for example cytotoxic chemotherapy and/or radiotherapy and acute myeloid leukaemia/myelodysplastic syndromes.
- Knowledge relating to genetic determinants has increased markedly over the past 5 years. The number of predisposition syndromes recognized to be associated with certain leukaemia subtypes is increasing, and a chapter on myeloid neoplasms with germline predisposition is included in the most recent WHO classification.
- The leukaemias have led the field of cancer genomics. Since the advent of the first targeted cancer therapy (tyrosine kinase inhibitors), advances in molecular biology and therapy have continued to transform the landscape for several – but by no means all – leukaemia subtypes.

Fig. 5.20.1. Overview of haematopoiesis. Leukaemias are classified by cell of origin.



B-cell lymphocytosis is increasingly being studied with a view to increasing the understanding of pathogenesis of CLL (defined by a monoclonal B-cell count of ≥ 5 × 10^9/L with CLL morphology and phenotype).

The overall incidence of leukaemia, like that of many other types of cancer, increases with increasing age, and the incidence rate is higher in men than in women. However, in contrast to many other cancer types, leukaemias can occur at any age, and different subtypes dominate at different ages. The heterogeneity of the various leukaemia subtypes (excluding monoclonal B-cell lymphocytosis) is illustrated in Fig. 5.20.4, which distributes the data by age at diagnosis and sex.

Acute lymphoblastic leukaemias (ALL), notably B-cell ALL, which accounts for less than 4% of the total, predominate in children younger than 15 years, an age group in which some leukaemia subtypes are often rare or non-existent. In contrast, at older ages, CLL, the myeloproliferative neoplasms, and the AMLs are far more common (Fig. 5.20.4). Variations with sex are also marked; the overall male predominance is evident across the full age spectrum and the main diagnostic subtypes.

Additional differences are evident within subtypes [17], as illustrated in Fig. 5.20.5, which presents sex rate ratios for myelodysplastic syndromes and AML. Myelodysplastic syndrome with deletion of chromosome 5q has a strong female predominance, in contrast to the other subtypes of myelodysplastic syndrome. AML with myelodysplasia-related changes has a strong male predominance, whereas AML with *MLL* rearrangement is more common in females.

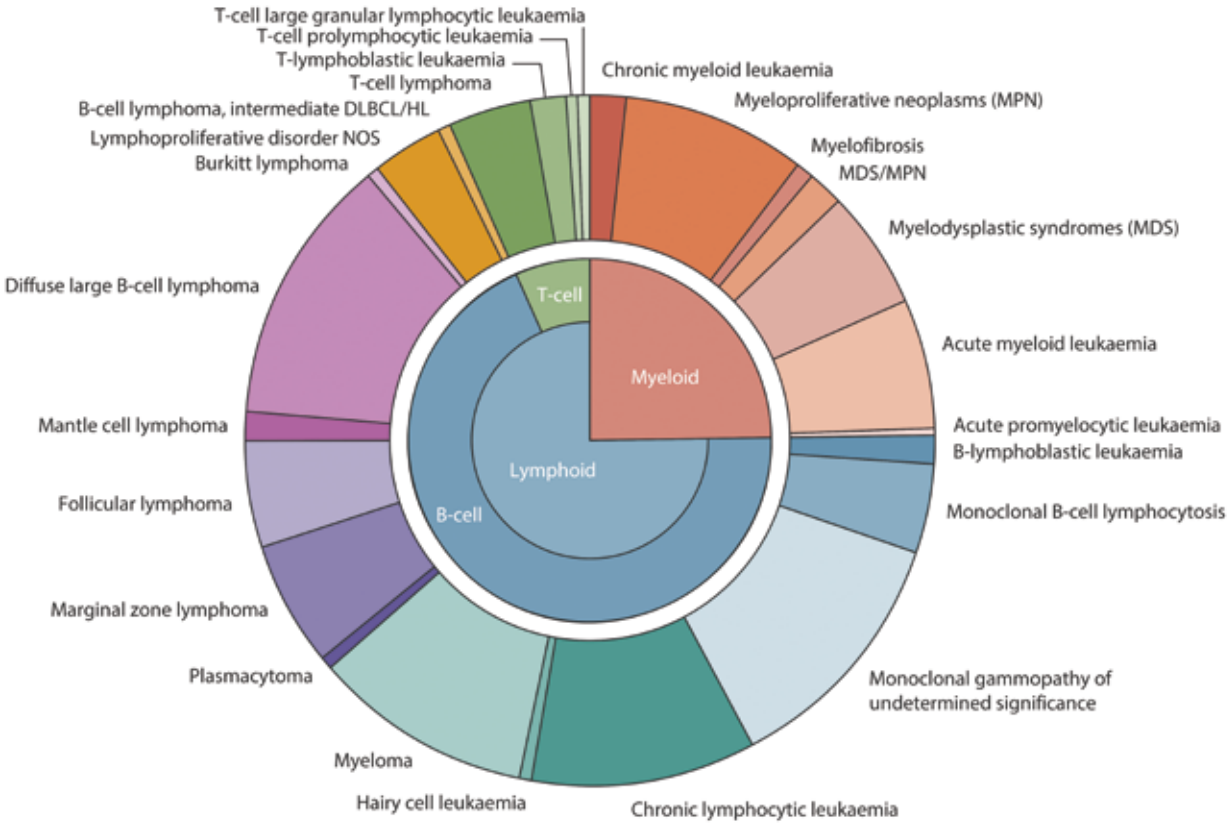
Risk factors

Like all diseases, the leukaemias have both genetic and environmental determinants to their etiology, and the relative contribution of each varies from one subtype to another.

With respect to environmental exposures, relatively little has changed in the past 5 years; well-established risk factors continue to produce strong associations but explain only a small proportion of the total burden of disease. Examples of such associations include those with cytotoxic chemotherapy, benzene, ionizing radiation, and viral infections such as human T-cell lymphotropic virus type 1 (HTLV-1), which is a necessary but not sufficient cause of the comparatively rare adult T-cell leukaemia/lymphoma (see Chapter 2.2). HTLV-1 causes leukaemia in about 5% of people infected with the virus. Although HTLV-1 is endemic in parts of Japan, South America, Papua New Guinea, Africa, and the Middle East, it is hardly ever found elsewhere.

With respect to broader environmental associations, systematic trends with frequently used proxies of exposure are rarely observed

Fig. 5.20.2. Diagnostic distribution of haematological malignancies classified by the International Classification of Diseases for Oncology, third edition (ICD-O-3). Data from the Haematological Malignancy Research Network (HMRN) for 2004–2016 (*n* = 29 329). DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; NOS, not otherwise specified.



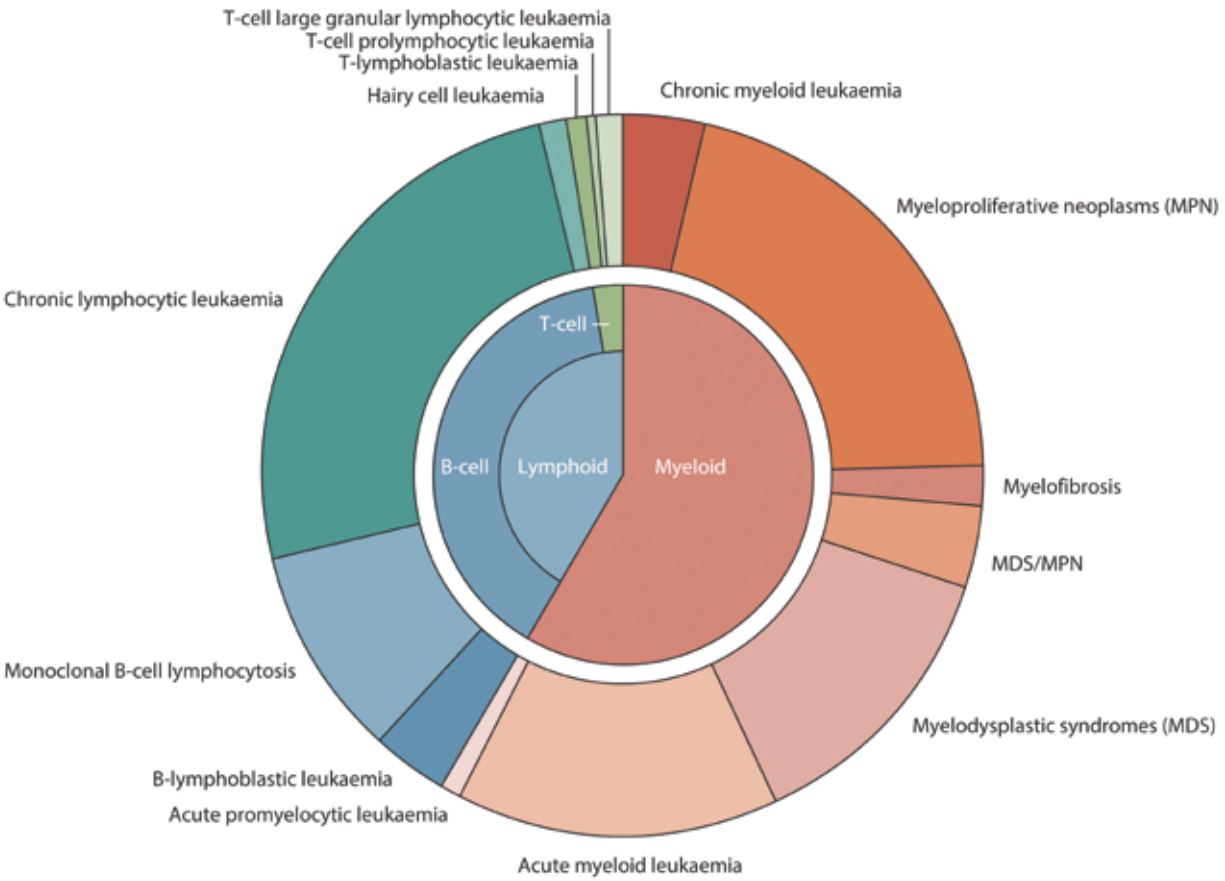
for leukaemias, in contrast to many other cancer types. For example, in high-income countries the incidence of several common cancer types tends to vary with regularly used markers of socioeconomic status or lifestyle, including education level, income, and deprivation level, for reasons that are related either to etiology – exemplified by lung cancer and smoking, or cervical cancer and human papillomavirus (HPV) infection – or to detection, as illustrated by colon cancer and screening. The consistency of such observations often helps to target public health interventions and policies that aim either to prevent the development of disease (see Chapter 6.1) or to detect it at an early stage (see Chapter 6.6).

However, for the leukaemias, coherent patterns of this type are rarely observed. Findings from epidemiological studies examining the potential etiological role of specific risk factors, such as exposure to antibiotics, non-ionizing radiation, or hair dyes, often produce results that are weak and inconsistent. An extensive up-to-date review of all the evidence relating to the environmental determinants of leukaemia in children and adults can be found in the latest edition of *Cancer Epidemiology and Prevention* [18].

As with environmental determinants, certain genetic features that predispose towards leukaemia have long been known. Perhaps the most notable is male sex, which is generally associated with an increased risk across the age spectrum (Fig. 5.20.4). In addition, certain congenital disorders are strongly associated with the subsequent development of the acute leukaemias, usually those occurring in children, adolescents, or young adults. Examples are the association of Down syndrome with AML and ALL and of Fanconi anaemia and other bone marrow failure syndromes with myelodysplastic syndromes and AML.

In contrast to knowledge about environmental determinants, knowledge relating to the genetic determinants of several leukaemia subtypes has increased markedly over the past 5 years. This increase is, at least in part, due to the advent of new genomic technologies and their growing accessibility to the wider scientific community. As a result, the number of predisposition syndromes recognized to be associated with certain leukaemia subtypes, particularly (but not exclusively) those of the myeloid lineage, has increased considerably. Knowledge in this area is advancing rapidly. A chapter on myeloid neoplasms with germline predisposition (inherited and de novo) is, for the first time, included in the

Fig. 5.20.3. Diagnostic distribution of leukaemias (including monoclonal B-cell lymphocytosis) classified by the International Classification of Diseases for Oncology, third edition (ICD-O-3). Data from the Haematological Malignancy Research Network (HMRN) for 2004–2016 (*n* = 11 231).



most recent WHO classification, and associations between genetic conditions and lymphoid leukaemias, notably B-cell ALL, are also discussed in the relevant chapters [1].

Genomics, survival, and treatment

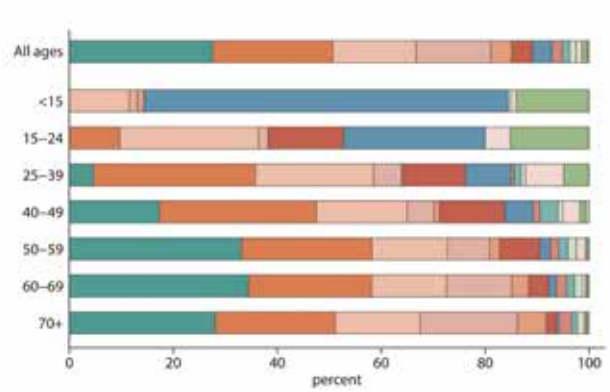
The leukaemias have led the field of cancer genomics. In the 1960s, the Philadelphia translocation was discovered in chronic myeloid leukaemia (CML), a subtype of myeloproliferative neoplasms. This discovery eventually resulted in the development of the first targeted therapy in cancer, a BCR-ABL tyrosine kinase inhibitor, which has transformed outcomes in CML [19].

Chromosomal analysis, undertaken through either classical or molecular techniques, has been part of routine clinical practice for many decades [1]. However, these methods have limitations. Conventional cytogenetics are limited to detecting structural changes at a chromosome level, whereas smaller abnormalities such as point mutations are not detectable, and molecular cytogenetics can only be targeted at known abnormalities.

Accordingly, new techniques that have been developed in the past 15 years are increasingly being used for the diagnosis, classification, and prognostication of the leukaemias. These include DNA sequencing and array-based platforms with next-generation sequencing, which currently provides the greatest genomic resolution (see Chapter 3.2). Recent studies using these techniques are revealing the complexity of many leukaemia subtypes [20–23], many of which – unlike the single chromosomal translocation and resulting aberrant fusion protein in CML – have complex pathogenic pathways. Although next-generation sequencing and other techniques are rapidly becoming part of routine diagnostic practice in some settings, the incorporation of this information in other settings, particularly in low-income countries, remains challenging.

The scientific advances that have led to improvements in survival for some leukaemia subtypes are a major success story. In high-income countries, survival rates for paediatric B-cell ALL now exceed 90%, and survival rates for acute promyelocytic leukaemia, a subtype of AML, are about 80%. Tyrosine kinase inhibitors have transformed CML from a comparatively rare fatal cancer to a long-term condition

Fig. 5.20.4. Incidence proportions of leukaemias (excluding monoclonal B-cell lymphocytosis) distributed by subtype within age strata, age-standardized (world, 2000–2025) rates per 100 000, and 5-year overall survival (OS) and relative survival (RS). Sex rate ratio is male rate divided by female rate. Data from the Haematological Malignancy Research Network (HMRN) for 2004–2016, followed up September 2018.



	Total	Males	Females	Sex rate ratio	5-year OS	5-year RS
All ages	14.82	18.51	11.72	1.58	50.4	63.5
<15	1.02	1.06	0.99	1.07	84.2	84.3
15–24	0.45	0.51	0.38	1.36	77.7	77.9
25–39	0.94	0.98	0.89	1.11	70.1	70.4
40–49	1.04	1.19	0.89	1.34	78.3	79.2
50–59	2.20	2.72	1.67	1.63	73.8	76.3
60–69	3.34	4.37	2.35	1.86	61.5	66.7
70+	5.85	7.67	4.55	1.68	34.9	50.8

	Number			Age (median)			Age standardised rate per 100,000				5-year	
	N	Males	Females	N	Males	Females	Total	Males	Females	Sex rate ratio	OS	RS
Total	11231	6472	4759	71.5	70.6	72.7	14.82	18.51	11.72	1.58	50.4	63.5
Chronic lymphocytic leukaemia (CLL)	3096	1935	1161	71.6	70.1	74.2	3.77	5.21	2.51	2.08	66.4	84.1
Myeloproliferative neoplasms (MPN)	2597	1222	1375	71.3	69.7	72.5	3.32	3.41	3.26	1.04	71.9	92.1
Acute myeloid leukaemia (AML)	1799	1003	796	72.0	71.7	72.7	2.39	2.88	1.99	1.45	11.7	13.2
Myelodysplastic syndromes (MDS)	1612	1059	553	75.9	75.9	76.0	1.81	2.66	1.55	2.32	20.9	27.6
MDS/MPN	453	298	155	76.6	76.0	78.4	0.49	0.74	0.30	2.48	14.0	18.8
Chronic myeloid leukaemia (CML)	448	256	192	59.3	58.1	61.9	0.72	0.87	0.58	1.50	76.2	87.3
B-lymphoblastic leukaemia (B-ALL)	421	226	195	12.4	14.8	9.20	1.10	1.16	1.03	1.12	64.2	66.7
Myelofibrosis	225	133	92	73.8	72.0	75.6	0.26	0.35	0.19	1.16	41.1	53.4
Hairy cell leukaemia (HCL)	153	117	36	67.8	65.2	74.9	0.21	0.35	0.07	4.70	77.8	93.3
T-cell large granular lymphocytic leukaemia (T-LGLL)	152	69	83	71.3	71.0	71.9	0.19	0.20	0.19	1.01	62.9	63.7
Acute promyelocytic leukaemia (APL)	116	58	58	50.5	52.3	50.0	0.22	0.22	0.21	1.05	60.0	62.8
T-lymphoblastic leukaemia (T-ALL)	115	77	38	19.1	16.9	28.0	0.30	0.41	0.18	2.25	17.6	20.9
T-cell prolymphocytic leukaemia (T-PLL)	44	19	25	76.9	75	78.3	0.05	0.05	0.05	1.07	74.8	88.8

with a survival rate that approaches that of the general population. Such progress has redirected the research efforts to other types of leukaemia, and to other cancer types.

However, despite these improvements, the outlook for older people and those with aggressive subtypes remains poor. Contemporary estimates of 5-year overall survival and relative survival from the HMRN population-based patient cohort are shown in Fig. 5.20.4, both by age strata for all subtypes combined and by major subtype by all ages combined. The corresponding relative survival curves are shown in Fig. 5.20.6.

Although some subtypes of AML are potentially curable with intensive chemotherapy, over the past three decades there has been little improvement for the majority of AML patients. The 5-year relative survival for AML in the HMRN population-based data is 13.2%. For AML, the median age at diagnosis is about 70 years. Although the frequency of curative therapy is relatively high in younger patients, who often comprise the focus of clinical trials involving ALLs as well as AMLs, the inability of some patients, notably older patients, to tolerate intensive chemotherapy regimens remains problematic.

The increased application of genomic technologies is leading to the development of new targeted agents, including monoclonal antibodies. However, at present, most of these agents still need to be used in conjunction with intensive chemotherapy, so little progress has been made to date for the treatment of patients who cannot tolerate such regimens [24].

In contrast, the outlook for patients with more indolent leukaemias, including CLL (5-year relative survival, 84.1%) and the myeloproliferative neoplasms (5-year relative survival, 92.1%), is relatively good, despite the fact that these cancers are currently incurable. The pathways of patients with these more chronic cancers often follow a remitting–relapsing course, with patients being monitored until chemotherapy treatment is required, and some never receiving treatment at all.

Prevention and early detection

In recent decades, advances in molecular biology and therapy have transformed the landscape for several leukaemia subtypes. However, in general this progress has not been matched by similar insights into the etiological determinants of the majority of leukaemias. In such circumstances, the development of preventive strategies that will affect the total burden of leukaemia

is challenging. However, it is clear that reduction in population exposures to well-known leukaemogenic agents such as polycyclic aromatic hydrocarbons should be pursued. In addition, radiological diagnostic and therapeutic procedures involving ionizing radiation should be used only when clinically required, and at the lowest possible doses.

With respect to the potential impact on high-risk groups, more careful monitoring of individuals with recognized leukaemia predisposition syndromes or other genetic susceptibilities is one area where improvements could be made. For example, the onset of bone marrow failure, a prelude to AML, could perhaps be detected at an earlier stage, enabling pre-emptive haematopoietic stem cell transplantation to be undertaken.

However, in situations where primary prevention is not possible, early detection and improved treatments tend to be the major focus. In this respect, the landscape for the leukaemias is changing rapidly, with new diagnostic technologies and less toxic targeted novel agents emerging, providing considerable promise for the future.

Fig. 5.20.5. Sex rate ratios (male rate divided by female rate) for subtypes of myelodysplastic syndromes and acute myeloid leukaemia (AML).

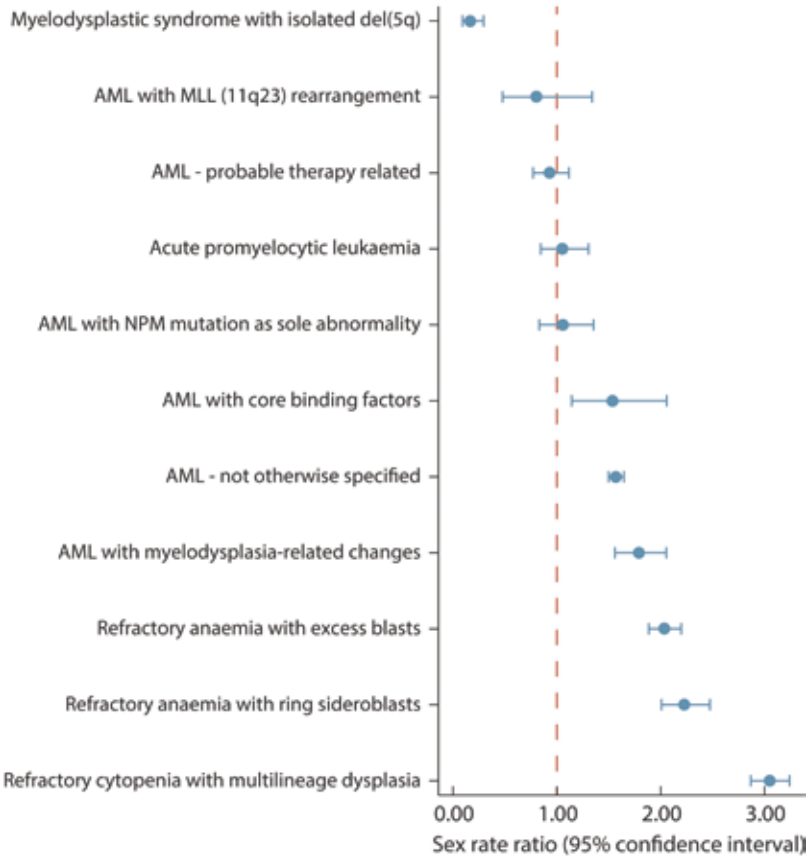
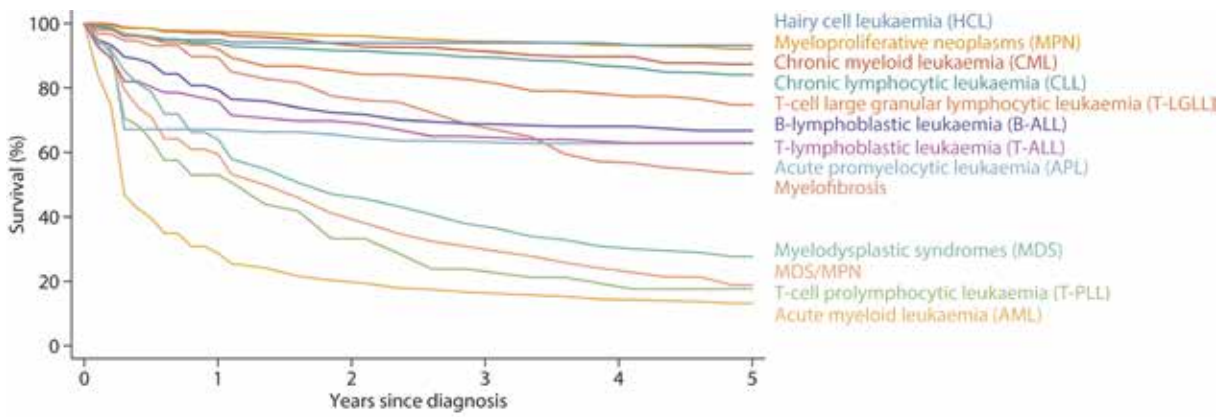


Fig. 5.20.6. Relative survival curves for leukaemias classified by the International Classification of Diseases for Oncology, third edition (ICD-O-3). Data from the Haematological Malignancy Research Network (HMRN) for 2004–2016, followed up September 2018.



References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors (2017). WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: International Agency for Research on Cancer (WHO Classification of Tumours series, revised 4th edition). Available from: http://publications.iarc.fr/556.
2. Piller G (2001). Leukaemia – a brief historical review from ancient times to 1950. Br J Haematol. 112(2):282–92. https://doi.org/10.1046/j.1365-2141.2001.02411.x PMID:11167820
3. Jaffe ES, Harris NL, Stein H, Vardiman JW, editors (2001). Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon, France: International Agency for Research on Cancer (WHO Classification of Tumours series, 3rd edition).
4. Cronin KA, Lake AJ, Scott S, Sherman RL, Noone A-M, Howlader N, et al. (2018). Annual report to the nation on the status of cancer, part I: national cancer statistics. Cancer. 124(13):2785–800. https://doi.org/10.1002/cncr.31551 PMID:29786848
5. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al.; CONCORD Working Group (2018). Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 391(10125):1023–75. https://doi.org/10.1016/S0140-6736(17)33326-3 PMID:29395269
6. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593
7. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. (2016). The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 127(20):2391–405. https://doi.org/10.1182/blood-2016-03-643544 PMID:27069254
8. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. (2016). The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 127(20):2375–90. https://doi.org/10.1182/blood-2016-01-643569 PMID:26980727
9. Ruhl J, Adamo M, Dickie L (2015). Hematopoietic and lymphoid neoplasm coding manual. Bethesda (MD), USA: National Cancer Institute.
10. HAEMACARE Working Group (2010). Manual for coding and reporting haematological malignancies. Tumori. 96(4):i–A32. PMID:20968151
11. Miranda-Filho A, Piñeros M, Ferlay J, Soerjomataram I, Monnereau A, Bray F (2018). Epidemiological patterns of leukaemia in 184 countries: a population-based study. Lancet Haematol. 5(1):e14–24. https://doi.org/10.1016/S2352-3026(17)30232-6 PMID:29304322
12. Juliusson G, Lazarevic V, Hörstedt A-S, Hagberg O, Höglund M; Swedish Acute Leukemia Registry Group (2012). Acute myeloid leukemia in the real world: why population-based registries are needed. Blood. 119(17):3890–9. https://doi.org/10.1182/blood-2011-12-379008 PMID:22383796
13. Østgård LSG, Nørgaard JM, Raaschou-Jensen KK, Pedersen RS, Rønnov-Jessen D, Pedersen PT, et al. (2016). The Danish National Acute Leukemia Registry. Clin Epidemiol. 8:553–60. https://doi.org/10.2147/CLEP.S99460 PMID:27822099
14. Smith A, Howell D, Crouch S, Painter D, Blase J, Wang HI, et al. (2018). Cohort profile: the Haematological Malignancy Research Network (HMRN); a UK population-based patient cohort. Int J Epidemiol. 47(3):700–700g. https://doi.org/10.1093/ije/dyy044 PMID:29618056
15. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR (2016). 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin. 66(6):443–59. https://doi.org/10.3322/caac.21357 PMID:27618563
16. Morton LM, Slager SL, Cerhan JR, Wang SS, Vajdic CM, Skibola CF, et al. (2014). Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014(48):130–44. https://doi.org/10.1093/jncimonographs/lgu013 PMID:25174034
17. Roman E, Smith A, Appleton S, Crouch S, Kelly R, Kinsey S, et al. (2016). Myeloid malignancies in the real-world: occurrence, progression and survival in the UK's population-based Haematological Malignancy Research Network 2004–15. Cancer Epidemiol. 42:186–98. https://doi.org/10.1016/j.canep.2016.03.011 PMID:27090942
18. Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, editors (2018). Cancer epidemiology and prevention. 4th ed. New York (NY), USA: Oxford University Press.
19. Apperley JF (2015). Chronic myeloid leukaemia. Lancet. 385(9976):1447–59. https://doi.org/10.1016/S0140-6736(13)62120-0 PMID:25484026
20. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, et al. (2016). Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med. 374(23):2209–21. https://doi.org/10.1056/NEJMoa1516192 PMID:27276561
21. Papaemmanuil E, Gerstung M, Malcovati L, Tauro S, Gundem G, Van Loo P, et al.; Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium (2013). Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 122(22):3616–27, quiz 3699. https://doi.org/10.1182/blood-2013-08-518886 PMID:24030381
22. Strefford JC (2015). The genomic landscape of chronic lymphocytic leukaemia: biological and clinical implications. Br J Haematol. 169(1):14–31. https://doi.org/10.1111/bjh.13254 PMID:25496136
23. Vainchenker W, Kralovics R (2017). Genetic basis and molecular pathophysiology of classical myeloproliferative neoplasms. Blood. 129(6):667–79. https://doi.org/10.1182/blood-2016-10-695940 PMID:28028029
24. Dombret H, Gardin C (2016). An update of current treatments for adult acute myeloid leukemia. Blood. 127(1):53–61. https://doi.org/10.1182/blood-2015-08-604520 PMID:26660429

WHO Report on Cancer: Setting priorities, investing wisely and providing care for all

André M. Ilbawi

Background and rationale

Over the past two decades, there has been rapid progress in the understanding of cancer prevention and treatment. Cancer now features in global development targets, including the United Nations 2030 Sustainable Development Goals, and is a critical element of universal health coverage.

However, the reality for cancer patients suggests that progress has been inadequate and inequitable, particularly in low- and middle-income countries. At the current rate, global targets to reduce premature mortality will not be achieved. Exacerbating the problem, the number of new cancer cases is projected to double over the next two or three decades. The greatest impact of cancer and the fastest increase in the cancer burden will be in low- and middle-income countries, many of which are ill-equipped to cope with the current burden.

The time is now to set the cancer policy agenda promoting health for all, consistent with universal health coverage and the Sustainable Development Goals. Implementation of evidence-based cancer policies will shift the trajectory and save millions of lives each year. Governments expressed their commitment to accelerate action through the 2017 World Health Assembly resolution on cancer prevention and control (WHA70.12). As part of resolution WHA70.12, governments specifically requested WHO, in collaboration with IARC, to produce a global report on cancer, a landmark document intended to shape the global agenda and highlight priority actions.

Aim and scope

The *WHO Report on Cancer: Setting priorities, investing wisely and providing care for all* provides evidence-based public health- and policy-oriented guidance on cancer, based on the latest available evidence and international experience. The report catalyses global collaboration and provides guidance on next steps to improve cancer control in countries.

The aim of the *WHO Report on Cancer* is to set the agenda for accelerated action on evidence-based, comprehensive cancer control programmes and to raise awareness about cancer as a preventable and controllable public health priority globally.

The scope of the *WHO Report on Cancer* is to:

- present the cancer burden and trends, and the social and economic impact of the disease;
- inform policy-makers about the need to prioritize investment in cancer, and provide recommendations on the way forward;
- describe effective public health strategies to mitigate common risk factors for cancer;
- provide the most up-to-date evidence on effective cancer control programmes for all resource levels, with a focus on access and equity;
- facilitate evidence-based decision-making by policy-makers in selecting a basic cancer control package relevant for their national context.
- highlight the importance of cancer registries and other information systems; and
- draw attention to cancer research to better understand the causes of cancer, to evaluate interventions, and to formulate a research agenda to develop new policies and programmes.

The primary target audience for the *WHO Report on Cancer* is policy-makers. The report is also intended for a broad multisectoral audience, including nongovernmental organizations, philanthropic foundations, academic institutions, and private sector entities. It is global in its reach, providing clear guidance for policy-makers in all settings.

Link to IARC *World Cancer Report*

The *WHO Report on Cancer* is a complement to the existing IARC *World Cancer Reports*, which provide extensive details and scientific background on cancer patterns and causes and tested preventive interventions. This new IARC *World Cancer Report* comprehensively presents the most up-to-date science in cancer prevention.

The *WHO Report on Cancer* translates this structured evidence and other scientific findings into actionable policies and programmes. This has been achieved by promoting clear linkages between the two documents and integration of content. The *WHO Report on Cancer* summarizes the current state of the science to advance understanding of how the science of cancer informs policy. In effect, the new IARC *World Cancer Report* and the *WHO Report*

on Cancer have complementary roles, respectively summarizing the evidence and promoting evidence-based policies, based on the highest quality science.

Next steps

Before global release of the *WHO Report on Cancer*, the report underwent regional consultations to ensure that it presents the perspectives of stakeholders around the world and summarizes the best global understanding of cancer policies. The work does not stop with the release of the report; there will be spin-off products and broad dissemination strategies. The success of the *WHO Report on Cancer* will be measured by its impact in shifting the global dialogue, supporting the formulation and implementation of effective cancer policies, and changing the trajectory of cancer for communities around the world.

6 The basis for, and outcomes from, prevention strategies

The burden of death from the multiple different cancer types can be decreased in all communities and countries. Cancer incidence can be reduced by decreasing or eliminating exposure to carcinogens in multiple contexts. Success in reducing the incidence of smoking-related cancers in some countries indicates a range of measures that may be researched for their efficacy in other situations. Interventions to change behaviour related to nutrition, exercise, and weight gain are being actively researched. Vaccination is effective for some cancers caused by infectious agents. Deaths from sporadic cancer may be decreased through chemoprevention and diagnosis of early-stage disease by screening and emerging molecular methods of early diagnosis. An increased risk of cancer may be indicated by family history and can be addressed by monitoring the affected individuals. The extent to which the options summarized here are realized across national boundaries warrants continuing research.

Tobacco cessation: the WHO perspective

Cessation support can more than double the chance of successfully quitting

Tobacco use, particularly cigarette smoking, remains the leading preventable cause of death from cancer and other conditions worldwide. In 2017, about 8 million people died from a tobacco-related disease [1,2]. The global costs of smoking are equivalent to 18% of what countries spend on health care [3].

Globally, there are 1.1 billion adult smokers and at least 303 million users of smokeless tobacco [4], many of whom say they want, or intend, to quit [5,6]. Although this is encouraging, the availability of tobacco cessation support worldwide remains low, and many people do not have adequate cessation support available to them. Currently, only about 30% of the world's population have access to appropriate tobacco cessation services [6].

Over the past decade, countries have made substantial progress in establishing evidence-based and cost-effective tobacco control measures. In numerous countries, many indoor public spaces are now smoke-free, warnings about the dangers of tobacco use appear on packaging and in mass media messages, higher tobacco product prices and taxes have reduced the affordability of tobacco products, and tobacco product advertising, promotion, and sponsorship have been prohibited.

All of these efforts have contributed to reduced demand for tobacco products and have increased existing tobacco users' intention to quit. On average, across countries where the Global Adult Tobacco Survey has been conducted, more than 60% of smokers indicated that they intend to quit, and more than 40% had attempted to quit in the 12 months preceding the survey (Fig. P1.1). Tobacco cessation support services complement countries' tobacco control measures and can contribute to reducing the prevalence of tobacco use.

Nicotine, a pharmacologically active drug that occurs naturally in the tobacco plant, is highly addictive and is delivered rapidly to the brain after the inhalation or ingestion of tobacco products or the use of non-tobacco products that contain nicotine [7]. Nicotine is so addictive that the autonomy over smoking of one quarter of adolescents starts to diminish after smoking just three or four cigarettes, and after smoking five packs (i.e. 100 cigarettes), nearly 60% are dependent [8]. Most people who use tobacco regularly do so because they are addicted to nicotine, and they can therefore benefit greatly from a range of effective tobacco cessation interventions. It is estimated that the highest-level cessation policies, adopted in 14 countries from 2007 to 2014, will result in about 1.5 million fewer future tobacco-related deaths up to 2030 [9].

The health benefits of quitting tobacco

The risk of death due to tobacco use begins to decrease soon after quitting. Current evidence suggests that the risk of death due to ischaemic heart disease is halved within 5 years of quitting, and the risk of stroke returns to that of a never-smoker within 5–15 years. The risk of death due to lung cancer is reduced by 30–50% within 10 years of quitting smoking [10].

People who quit tobacco can live longer, healthier, and more productive lives. Quitting smoking at any time in life is likely to extend life expectancy; for example, quitting at age 30 years can add up to

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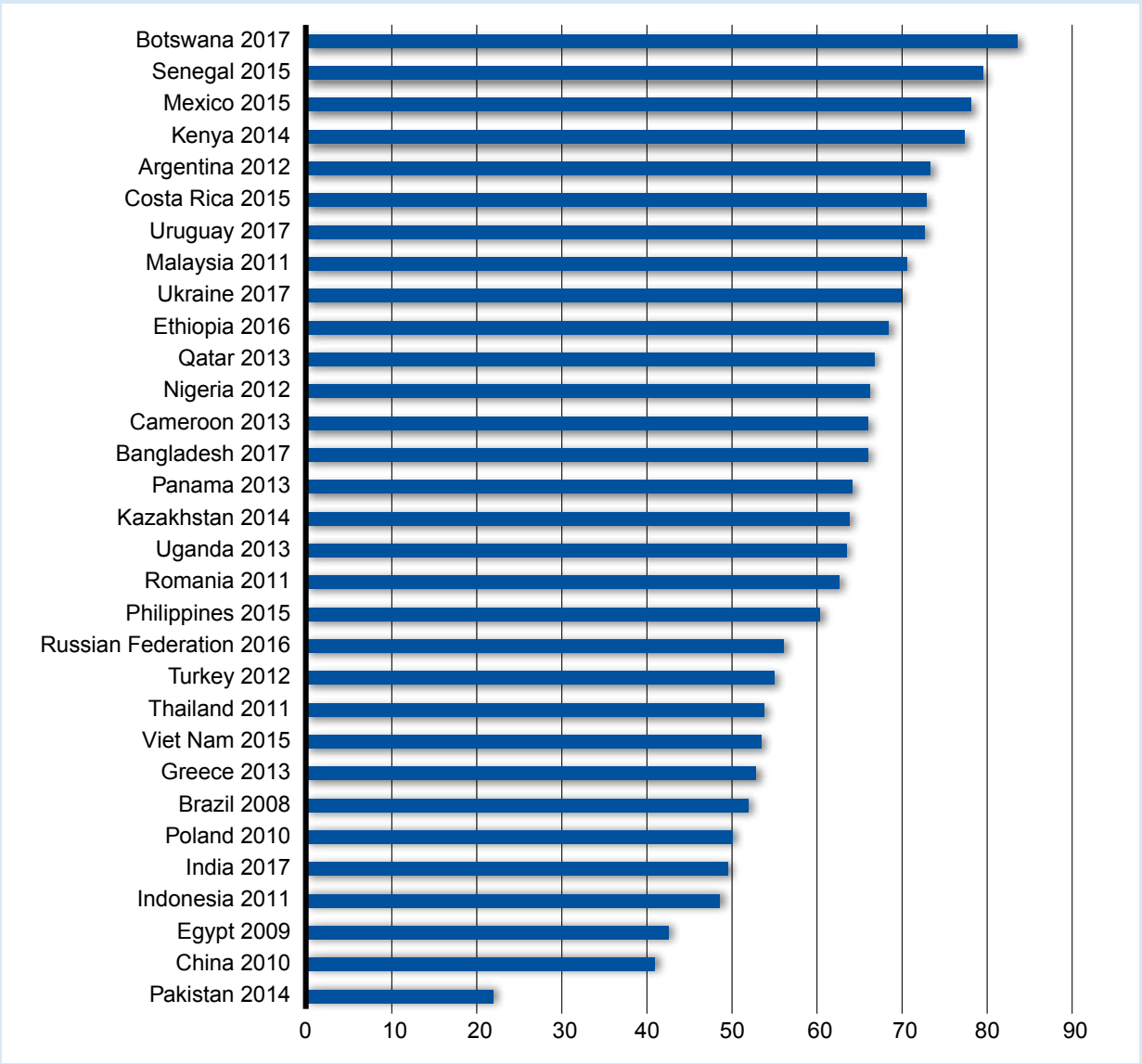
- The success of tobacco control policies has increased the demand for support to quit tobacco use.
- Without cessation assistance, only 4% of attempts to quit tobacco succeed.
- Proven cessation medications and professional support can double a tobacco user's chance of successfully quitting.
- Several different approaches have been developed to help people stop using tobacco. These vary in terms of intensity, cost, and effectiveness, and can broadly be categorized as behavioural or pharmacological interventions.
- Tobacco cessation support should be made readily accessible in order to have a greater impact on reducing the prevalence of tobacco use.

Fig. P1.1. Proportion of current smokers who intend to quit (countries with Global Adult Tobacco Survey data [4], various years). Proportions include those who indicated they were thinking of quitting in the next month, within the next 12 months, or sometime in the future.



10 years of life expectancy. Even at age 50 years, quitting results in an average of 6 years of life expectancy gained [11]. Hence, it is never too late to gain the health benefits of quitting tobacco use. The life years gained can also be expected to be lived in better health, because the diseases caused by tobacco use are commonly chronic and debilitating and lead to years of diminished quality of life. Therefore, quitting can reduce the health-care costs associated with long-term illness while also increasing the years of economically and socially productive life.

Policy actions recommended by WHO

Following the Political Declaration on the prevention and control of noncommunicable diseases (NCDs) adopted by the United Nations General Assembly in 2011, WHO developed nine voluntary global targets to reduce global mortality from the four main NCDs – cardiovascular diseases, cancer, chronic lung diseases, and diabetes – and accelerate action against the leading risk factors for NCDs. The agreed target for tobacco control is a 30% relative reduction in the prevalence of current (daily and occasional) tobacco use in people aged 15 years and older between 2010 and 2025, which was endorsed by the World Health Assembly in May 2013. To achieve this target, it is essential not only to prevent the uptake of tobacco use but also to ensure that

more tobacco users quit. Several highly effective and inexpensive interventions exist to help make this happen, as summarized below.

The importance of helping current tobacco users quit is reflected in the WHO Global Action Plan for the Prevention and Control of NCDs 2013–2020 [12]. The Global Action Plan lists a menu of "best buys" and cost-effective policy options for countries to address the NCD burden. These include the recommendation that countries should provide cost-covered, effective, and population-wide cessation support, including brief advice, national toll-free quitline services, and mCessation (a mobile phone-based intervention providing text messages supporting individual efforts to stop smoking), to all those who want to quit [12].

Despite these commitments, progress towards best-practice cessation support in countries is slow compared with progress on other WHO-recommended policy measures, such as smoke-free places and bans on tobacco advertising, promotion, and sponsorship.

Effective cessation interventions are available

A wide choice of behavioural and pharmacological tobacco cessation interventions is available. Without cessation assistance, only 4% of attempts to quit tobacco succeed [13]. Proven cessation medications and professional support can double a tobacco user's chance of successfully quitting [14]. Several different approaches have been developed to help people stop using tobacco (Table P1.1). These vary in terms of intensity, cost, and effectiveness, and can broadly be categorized as behavioural or pharmacological interventions.

Behavioural interventions

Although behavioural interventions for tobacco cessation are generally low-cost, they can be very effective. Brief advice from health professionals as part of their routine consultations or interactions is an approach that makes use of existing health-care systems. When a tobacco user visits a primary or specialized care service, this presents an opportunity for the health-care worker to offer and provide them with personalized counselling. Brief advice is a key

Table P1.1. Types of tobacco cessation interventions

Behavioural interventions	Population-level approaches	Brief advice	Advice to stop using tobacco, usually taking only a few minutes, is given to all tobacco users during the course of a routine consultation and/or interaction with a physician or health-care worker.
		Quitlines	A national toll-free quitline is a telephone counselling service that can provide both proactive and reactive counselling. A reactive quitline provides an immediate response to a call initiated by the tobacco user, but only responds to incoming calls. A proactive quitline involves setting up a schedule of follow-up calls to tobacco users to provide ongoing support.
		mCessation	Tobacco cessation interventions are delivered via mobile phone text messaging. Mobile technologies provide the opportunity to expand access to a wider population, and text messaging can provide personalized tobacco cessation support in an efficient and cost-effective manner.
	Individual specialist approaches	Intensive behavioural support	Behaviour support refers to multiple sessions of individual or group counselling aimed at helping people stop their tobacco use. It includes all cessation assistance that imparts knowledge about tobacco use and quitting, and provides support and resources to develop skills and strategies for changing behaviour.
		Cessation clinics	In many countries, clinics specializing in tobacco cessation services are available. These clinics offer intensive behavioural support and, where appropriate, medications or advice on the provision of medications, delivered by specially trained practitioners.
Pharmacological interventions	Nicotine replacement therapies (NRTs)		NRTs are available in several forms, including gum, lozenges, patches, inhalers, and nasal spray. These cessation tools reduce cravings and withdrawal symptoms by providing a low, controlled dose of nicotine without the toxins found in cigarettes. The doses of NRT are gradually reduced over time to help the tobacco user wean off nicotine by getting used to less and less stimulation.
	Non-nicotine pharmacotherapies		These include medications such as bupropion, varenicline, and cytisine. These pharmacotherapies reduce cravings and withdrawal symptoms and decrease the pleasurable effects of cigarettes and other tobacco products.

means of motivating people who might not otherwise seek tobacco cessation support and encouraging them to quit, and thus it is an essential component of tobacco cessation services. Countries can easily train physicians and health-care workers to provide brief advice effectively to the population they serve.

Toll-free quitlines are a convenient way for tobacco users who are ready to quit to access brief and potentially intensive behavioural counselling. People who use quitlines increase their absolute quit rate by 4 percentage points, which represents a doubling of success in quitting compared with those who attempt to quit without assistance [14]. This rate can be further increased if the quitline is proactive and counsellors make follow-up calls to potential tobacco quitters.

With the advent and spread of mobile phone technologies, people who want to quit can now be accessed not only through telephone calls but also via text messages. Text message interventions can increase the absolute quit rate by 4% [15].

Pharmacological interventions

Pharmacotherapy cessation interventions include nicotine replacement therapies (NRTs) as well as medications that do not contain nicotine but act to alleviate tobacco withdrawal symptoms. Both forms of therapy are effective aids to help people to quit tobacco use. The efficacy of pharmacotherapies is generally high, and compared with people who do not use an intervention, increases in the absolute quit rate can range from 6% for a single type of NRT to almost 15% for varenicline [16]. Combining more than one type of NRT (patches and a faster-acting form) can also increase the effectiveness of NRTs (see "Combined NRT" in Fig. P1.2).

Both behavioural cessation support and pharmacotherapies are effective in helping people to quit tobacco use (Fig. P1.2). However, combining both behavioural and pharmacological interventions is more effective and can double the chances of successfully quitting [16].

Mechanisms for developing tobacco cessation support

Implementing tobacco cessation measures alongside other tobacco control policies maximizes their impact

Tobacco cessation support has optimal effect when implemented in conjunction with other demand-reduction tobacco control policies, such as raising tobacco taxes, establishing smoke-free environments, banning tobacco advertising, promotion, and sponsorship, printing large pictorial health warning labels on tobacco packages, and delivering anti-tobacco mass media campaigns. In turn, these tobacco control measures promote tobacco cessation by encouraging quitting and creating a supportive environment. A good example of synergizing efforts is to include the local mCessation register portal/number or quitline number on cigarette and tobacco packs and in mass media anti-tobacco campaigns; this can significantly increase the demand for tobacco cessation services [17].

Using existing infrastructure to develop cessation support is feasible and affordable

Integrating brief advice into existing primary health-care systems is one of the first actions that countries can take to develop tobacco cessation support. Guidelines for implementation of Article 14 of the WHO Framework Convention on Tobacco Control recommend that countries adopt a stepwise approach to develop and strengthen national tobacco cessation systems as rapidly and cost-effectively as possible [18]. Much of the needed infrastructure for promoting tobacco cessation measures, such as a primary health-care system, already exists in most countries, making such promotion not only feasible but also affordable. Therefore, every country can use its existing systems and resources to ensure that tobacco users at least receive brief advice (Fig. P1.3).

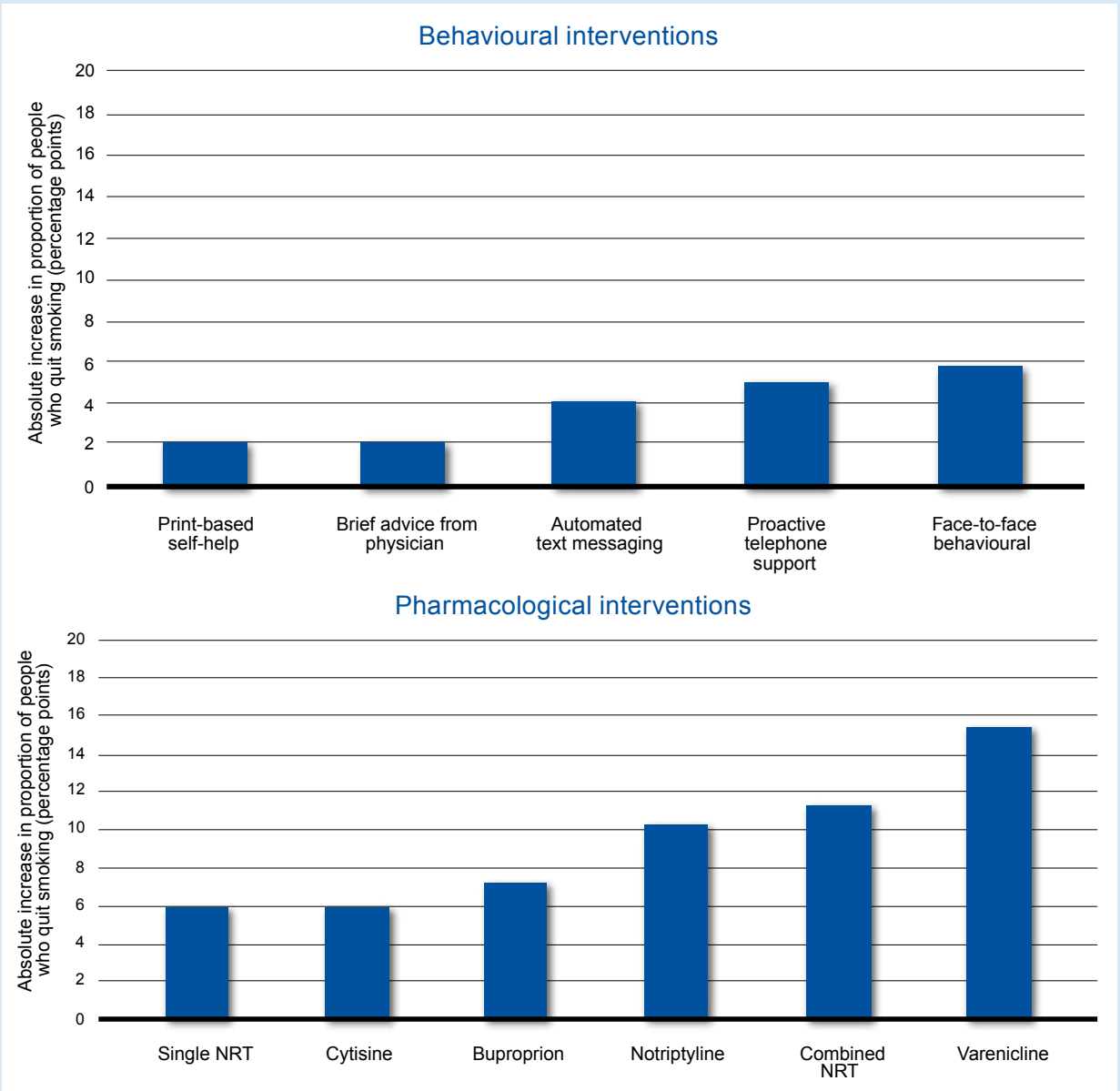
Incorporating brief advice into existing health-care programmes has the potential to reach more than 80% of all tobacco users in a country each year if delivered routinely and widely across a health-care system [19]. Tobacco cessation interventions should be integrated into any existing health programmes in primary care where feasible, as well as disease- and population-specific programmes such as national tuberculosis programmes [20], NCD programmes, oral health programmes [21], HIV/AIDS programmes, mental health programmes, and programmes addressing the needs of women's, children's, and adolescents' health. In particular, there has been a major drive globally to integrate cessation services into tuberculosis programmes and into sexual and reproductive health programmes. Both of these programmes reach populations at particular risk from the harms of tobacco and present an opportunity to address tobacco dependence when people make (potentially rare) contact with the health system.

Countries should also consider leveraging existing infrastructure to provide wide-reaching intensive behavioural support for tobacco users. Many countries have existing call centres and substance abuse or other health-related hotlines that can be expanded to provide tobacco quitline services.

Provide comprehensive tobacco cessation support and treatment when resources allow

The cost and effectiveness of different cessation approaches vary, and therefore the affordability of the different approaches varies across low-, middle-, and high-income countries. Overall, almost all population-level behavioural interventions are globally affordable, whereas intensive face-to-face therapy is affordable for middle- and high-income countries [16].

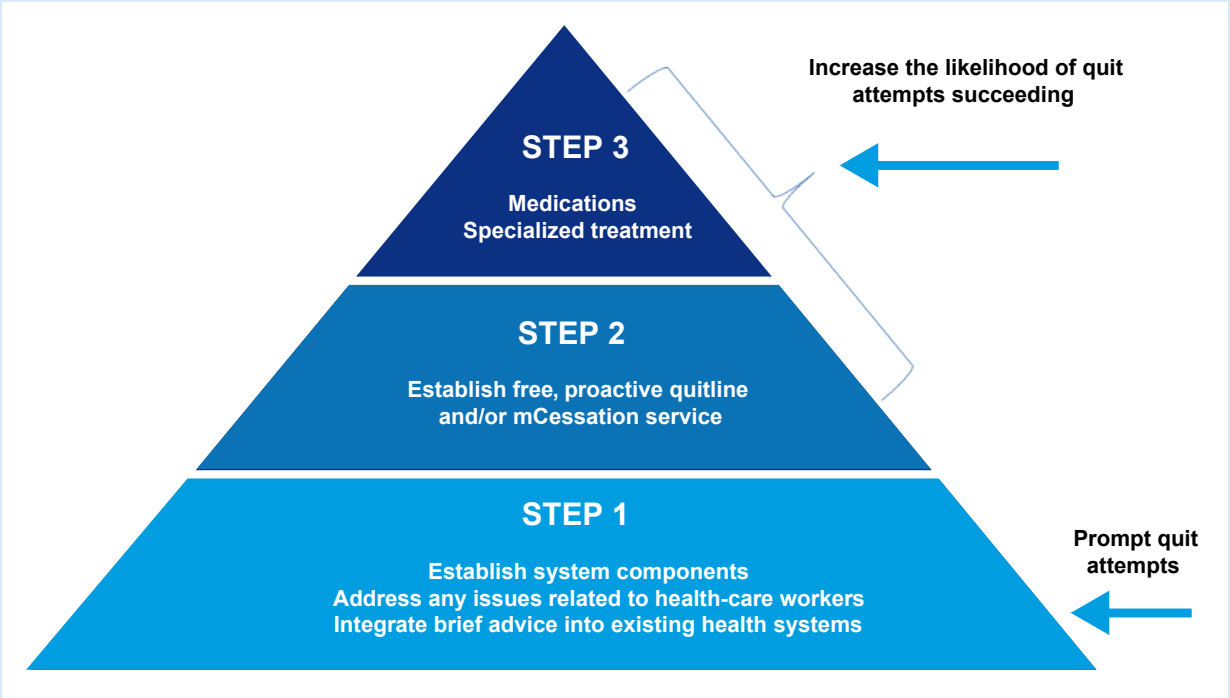
Fig. P1.2. Increased proportion of people who abstain from smoking for 6 months or more due to a specific intervention. Each bar represents the findings of a meta-analysis, and the strength of evidence associated with each study will vary. The vertical axis represents the projected percentage point increase in 6–12-month abstinence compared with no intervention. The authors adjusted the published percentage point increase in 6–12-month abstinence to allow for direct comparison between each intervention where the meta-analyses did not use a comparator equivalent to "no intervention". Assessments were based on the published effectiveness of the comparison intervention through a consensus [16]. NRT, nicotine replacement therapy.



If resources allow, countries should provide tobacco users with the highest level of support to facilitate a successful quit attempt. Countries may follow a stepwise approach to develop their tobacco cessation support systems (Fig. P1.3).

Combining behavioural and pharmacological interventions is the most effective way to quit, but uptake of interventions also relies on people's preferences, which is likely to vary across different social and cultural contexts. Tobacco users may prefer using multiple tobacco cessation interventions, including health education materials, advice from health professionals, counselling (individual, group, or telephone), pharmacological therapy, and other cessation services via text messaging or online tools [22,23]. Providing a diverse range of tobacco cessation support options, as often as possible, is also important to ensure maximal uptake and effectiveness (Table P1.2).

Fig. P1.3. Stepwise approach to developing and strengthening national tobacco cessation systems.



E-cigarettes and other products promoted as "cessation aids"

In recent years the tobacco industry (and other non-tobacco commercial actors, such as those manufacturing e-cigarettes) has introduced a wide array of products, the majority of which simulate the act of smoking while typically delivering nicotine. There are currently three broad categories of these products:

- Electronic nicotine delivery systems (ENDS), which are sometimes referred to as e-cigarettes, are devices that heat a liquid to create an aerosol that is inhaled by the user. The liquid contains nicotine (but not tobacco) and other chemicals that may be toxic to people's health.
- Electronic non-nicotine delivery systems (ENNDS) are similar to ENDS, but the heated solution delivered as an aerosol through the device does not generally contain nicotine.
- Heated tobacco products (HTPs) are tobacco products that produce aerosols containing nicotine and toxic chemicals upon heating of the tobacco or activation of a device containing the tobacco. These aerosols are inhaled by users during a process of sucking or smoking involving a device. They contain nicotine and non-tobacco additives, and are often flavoured. The tobacco may be in the form of specially designed cigarettes (e.g. "heat sticks", "Neo sticks") or pods or plugs.

These products are aggressively marketed or promoted as "cleaner" alternatives to conventional cigarettes, as smoking cessation aids, or as "reduced risk" products (see Chapter 2.1). They have proliferated in several markets around the globe and present a unique challenge to

Table P1.2. Examples of minimal, expanded, and advanced cessation interventions[a]

Minimal	Expanded	Advanced
Brief advice integrated into primary care services	**Brief advice** integrated into primary care and hospital services	**Brief advice** integrated into primary care, hospital, and specialized services
	Quitline: toll-free quitline provided	**Quitline:** toll-free quitline provided
	mCessation: text messaging	**mCessation:** text messaging
		Specialized tobacco dependence treatment services: behavioural counselling and/or medication

[a] All countries should implement, at a minimum, brief advice. Once this is well established, countries can apply expanded and advanced measures, subject to the availability of resources.

regulators. Although some of these products have lower emissions than conventional cigarettes, they are not risk-free, and the long-term impact on health and mortality is still unknown. There is insufficient independent evidence to support the use of these products as a population-level tobacco cessation intervention to help people quit use of conventional tobacco (Table P1.3). HTPs contain tobacco, and the use of these products constitutes tobacco use, thereby contributing to the burden of tobacco in countries where they are sold. In addition, some studies do not support the claims that these products are less harmful relative to conventional tobacco products [24,25].

There remains a great deal of uncertainty surrounding the risks associated with ENDS (Table P1.4). Although some have been shown to help smokers quit conventional smoking under certain conditions [26,27], the evidence is inconclusive [28–30]. There have been only a limited number of randomized controlled trials and longitudinal studies investigating the role of ENDS as potential cessation aids offered to a population, and their conclusions are equivocal [28,30].

Two systematic reviews – which were published in 2016 and 2017, respectively – established that no conclusions could be drawn from the available studies [28,30]. This is consistent with the conclusion of the 2018 review by the National Academies of Sciences, Engineering, and Medicine of the evidence on ENDS (referred to as e-cigarettes in this and the subsequent reports): "Overall, there is limited evidence that e-cigarettes may be effective aids to promote smoking cessation" [31].

In contrast, a randomized controlled trial of e-cigarettes versus NRT concluded that e-cigarettes were more effective for smoking cessation than NRT when both products were accompanied by behavioural support, based on a 1-year abstinence rate of 18.0%

Table P1.3. Questions and summaries of the evidence for heated tobacco products (HTPs)

Question	Summary of the evidence
Do HTPs contain harmful chemicals?	From available evidence, we know that many of the harmful chemicals that are generated by HTPs are similar to those generated by conventional cigarettes, but generally at lower levels [46,47]. However, there is also some evidence that there are new chemicals in HTPs that are not present in the emissions of conventional cigarettes, and that could have some degree of toxicity and associated harm [24].
Are HTPs less harmful than cigarettes?	To date, the available evidence demonstrates that exposure to harmful and potentially harmful chemicals from these products may be lower relative to cigarettes [48] (but higher compared with electronic nicotine delivery systems [ENDS]). However, the evidence does not show that these products will reduce tobacco-related diseases, or that they are exclusively used as substitutes for cigarettes. If they attract users who were not previously tobacco users, their overall impact on health would be negative.
Are HTPs useful as a cessation aid?	HTPs are tobacco products and, therefore, even if a tobacco user converts from the use of conventional cigarettes to HTPs, this would not constitute cessation. Claims that smokers switch from conventional cigarettes to exclusive use of HTPs are unsubstantiated [49]. Further independent studies are needed to gather more information and inform policy options.

Table P1.4. Questions and summaries of the evidence for electronic nicotine delivery systems (ENDS)

Question	Summary of the evidence
What are the consequences of taking up ENDS use at a younger age?	Recent surveys in the USA and some European countries have shown marked increases in ENDS use among young people [50]. Between 2011 and 2018 in the USA, rates of e-cigarette use in young people increased from 1.5% to a staggering 20.8% [44]. Young people who use ENDS are exposed to nicotine, which can have long-term effects on the developing brain, and there is a risk of nicotine addiction, given that tobacco product use is primarily established in adolescence [37]. Furthermore, there is a growing body of evidence in some settings that never-smoker minors who use ENDS at least double their chance of starting to smoke cigarettes later in life [51,52].
What is the harm of ENDS relative to conventional cigarettes?	ENDS' aerosols are likely to be less toxic than cigarettes, but there is insufficient evidence to quantify the precise level of risk associated with them [39]. Also, many factors will have an impact on the relative risk associated with their use, for example the amount of nicotine and other toxicants in the heated liquid.
What are the health effects associated with ENDS?	ENDS pose risks to users and non-users [39]. There is insufficient evidence to quantify this risk, and the long-term effects of exposure to ENDS' toxic emissions are unknown [39,50]. In addition to risks associated with emissions of ENDS, there are also risks of physical injury brought about by fires or explosions related to ENDS devices [53].
Do ENDS help smokers quit tobacco?	The effectiveness of ENDS as a smoking cessation aid is still being debated. To date, in part due to the diversity of ENDS products and the low certainty surrounding many studies, the potential for ENDS to play a role as a population-level tobacco cessation intervention is unclear [28–30].

in the e-cigarette group compared with 9.9% in the NRT group [32]. However, the study has several limitations. For example, although people who were assigned to the e-cigarette group were more likely to abstain from using traditional cigarettes compared with those who were assigned to the NRT group, 80% of people in the e-cigarette group continued to use e-cigarettes 1 year after the study started, whereas only 9% of those in the NRT group continued to use NRTs at 1 year. In most countries where e-cigarettes are available, the majority of users of e-cigarettes continue to use e-cigarettes and conventional cigarettes concurrently, which has little or no beneficial impact on health risk and effects [33].

Some reviews have also suggested that use of e-cigarettes could in fact hinder smoking cessation [34]. Furthermore, beyond the scope of cessation, novel and emerging tobacco and nicotine products are increasingly being taken up by never-users of tobacco [35]. These products therefore play an important role in expanding the market of nicotine users, with a high associated risk of addiction, particularly in children and adolescents.

WHO does not endorse ENDS as cessation aids

The scientific evidence on e-cigarettes as cessation aids is inconclusive, and there is a lack of clarity as to whether these products have any role to play in smoking cessation. There are also real concerns about the risk they pose to nonsmokers who start to use them, especially young people. Unlike for the tried and tested nicotine and non-nicotine pharmacotherapies that are known to help people quit tobacco use, WHO does not endorse e-cigarettes as cessation aids.

As ENDS are increasingly introduced to the market, careful monitoring of cessation rates is vital. The possibility of tobacco industry interference in tobacco cessation efforts through misinformation about the potential benefits of these products – which are presented as alternatives but in most cases are complementary to the use of conventional tobacco products – is a present and real threat (Box P1.1 and Box P1.2).

Conclusions

A wide range of proven behavioural and pharmacological cessation interventions can be used to support tobacco users to quit, but currently only about 30% of the world's population have access to comprehensive tobacco cessation services. Countries – in particular low- and middle-income countries, where the majority of tobacco users in the world live – should implement these proven tobacco cessation measures, alongside other tobacco control policies, to maximize their impact on reducing the prevalence of tobacco use and the risk of death from all tobacco-related diseases, including cancer.

Resources are finite. In order for tobacco cessation interventions to reach as many tobacco users as possible at the lowest achievable cost and have the most impact, governments should prioritize population-wide tobacco cessation approaches as recommended by the WHO Global Action Plan for the Prevention and Control of NCDs 2013–2020: integrating brief advice into primary care, providing national toll-free quitline services, and making mCessation support available. If resources allow, countries should also provide tobacco users with combined behavioural and pharmacological interventions to facilitate a successful quit attempt.

Box P1.1. Excerpt on electronic nicotine delivery systems (ENDS) from the WHO Director-General's Commentary in *The Lancet* [54].

Much has been written and said about the potential of electronic nicotine delivery systems (ENDS) such as e-cigarettes to help tobacco users quit [31,36–38]. Although tobacco and related industries promote these products as tools for quitting, the evidence does not support their use as part of population-based cessation strategies. The aerosols of ENDS contain toxic chemicals that are harmful to both users and non-users and are, therefore, products that come with health risks of their own [31,39]. And in combination with smoking, which is the practice with the majority of ENDS users, the health effects of two or more products are combined [35]. ENDS on their own are associated with increased risk of cardiovascular diseases [40] and lung disorders [41] and adverse effects on the development of the fetus during pregnancy [37]. For adolescents, the addictive nature of nicotine can lead to dependence and may harm adolescent brain development, including reduced activity in the prefrontal cortex [42,43]. Use of ENDS could also lead to a new generation of nicotine and tobacco users, as seen in some countries [44], especially given how these products are marketed to young people [37]. Although the specific level of risk associated with ENDS has not yet been conclusively estimated, ENDS are undoubtedly harmful, should be strictly regulated, and, most importantly, must be kept away from children. It is also incorrect to think that heated tobacco products are the answer, as they simply move tobacco users from one harmful tobacco product to another.

To truly help tobacco users quit and to strengthen global tobacco control, governments need to scale up policies and interventions that we know work. Tried and tested interventions, such as nicotine and non-nicotine pharmacotherapies, should be promoted for cessation.

Box P1.2. Summary on electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) and cessation, from the seventh report of the WHO Study Group on Tobacco Product Regulation [45].

ENDS are a heterogeneous class of products, with various profiles of nicotine and non-nicotine toxicants, which depend on factors including their construction, power, liquid constituents, nicotine concentration, and user behaviour. The amount of nicotine delivered can range from none to doses that exceed those delivered by tobacco cigarettes in the same number of puffs. Nicotine from ENDS reaches users' blood faster than from most types of nicotine replacement therapy (NRT), and, at least with some ENDS, at higher concentrations. ENDS could be effective in cessation for some smokers under some circumstances, while, for other smokers, in different circumstances, it might have the opposite effect. Whether an ENDS has beneficial or detrimental effects on smoking cessation appears to depend on the technology, the motivation and consumer behaviour of the ENDS user, the type of smoker who seeks ENDS use, and the regulatory environment for ENDS and tobacco use.

Translating the evidence into a potential role of ENDS and ENNDS in smoking cessation is difficult. The evidence does not allow a blanket policy recommendation for or against general use of ENDS and ENNDS as cessation aids.

References

1. IHME (2018). Findings from the Global Burden of Disease Study 2017. Seattle (WA), USA: Institute for Health Metrics and Evaluation. Available from: http://www.healthdata.org/policy-report/findings-global-burden-disease-study-2017.
2. WHO (2019). WHO report on the global tobacco epidemic, 2019: offer help to quit tobacco use. Geneva, Switzerland: World Health Organization. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/tobacco/global_report/en/.
3. WHO (2018). WHO global report on trends in prevalence of tobacco smoking 2000–2025. 2nd ed. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/tobacco/publications/surveillance/trends-tobacco-smoking-second-edition/en/.
4. Asma S, Mackay J, Song SY, Zhao L, Morton J, Palipudi KM, et al. (2015). The GATS atlas: Global Adult Tobacco Survey. Atlanta (GA), USA: CDC Foundation. Available from: http://gatsatlas.org/.
5. GBD 2016 Risk Factors Collaborators (2017). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 390(10100):1345–422. https://doi.org/10.1016/S0140-6736(17)32366-8 PMID:28919119
6. WHO (2017). WHO report on the global tobacco epidemic, 2017: monitoring tobacco use and prevention policies. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/tobacco/global_report/2017/en/.
7. CDC (1994). Preventing tobacco use among young people: a report of the Surgeon General. Atlanta (GA), USA: Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/mmwr/PDF/rr/rr4304.pdf.
8. Ursprung WW, DiFranza JR (2010). The loss of autonomy over smoking in relation to lifetime cigarette consumption. Addict Behav. 35(1):14–8. https://doi.org/10.1016/j.addbeh.2009.08.001 PMID:19717241
9. Levy DT, Yuan Z, Luo Y, Mays D (2018). Seven years of progress in tobacco control: an evaluation of the effect of nations meeting the highest level MPOWER measures between 2007 and 2014. Tob Control. 27(1):50–7. https://doi.org/10.1136/tobaccocontrol-2016-053381 PMID:27956650
10. DHHS (1990). The health benefits of smoking cessation: a report of the Surgeon General. Rockville (MD), USA: Department of Health and Human Services. Available from: https://profiles.nlm.nih.gov/ps/access/NNBBCT.pdf.
11. Doll R, Peto R, Boreham J, Sutherland I (2004). Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 328(7455):1519–27. https://doi.org/10.1136/bmj.38142.554479.AE PMID:15213107
12. WHO (2013). Global action plan for the prevention and control of noncommunicable diseases 2013–2020. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/nmh/events/ncd_action_plan/en.
13. Cohen S, Lichtenstein E, Prochaska JO, Rossi JS, Gritz ER, Carr CR, et al. (1989). Debunking myths about self-quitting. Evidence from 10 prospective studies of persons who attempt to quit smoking by themselves. Am Psychol. 44(11):1355–65. https://doi.org/10.1037/0003-066X.44.11.1355 PMID:2589730
14. Stead LF, Hartmann-Boyce J, Perera R, Lancaster T (2013). Telephone counselling for smoking cessation. Cochrane Database Syst Rev. (8):CD002850. https://doi.org/10.1002/14651858.CD002850.pub3 PMID:23934971
15. Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y (2016). Mobile phone-based interventions for smoking cessation. Cochrane Database Syst Rev. (4):CD006611. https://doi.org/10.1002/14651858.CD006611.pub4 PMID:27060875
16. West R, Raw M, McNeill A, Stead L, Aveyard P, Bitton J, et al. (2015). Health-care interventions to promote and assist tobacco cessation: a review of efficacy, effectiveness and affordability for use in national guideline development. Addiction. 110(9):1388–403. https://doi.org/10.1111/add.12998 PMID:26031929
17. Park J, Minh LN, Shin SH, Oh JK, Yun EH, Lee DH, et al. (2019). Influence of new tobacco control policies and campaigns on Quitline call volume in Korea. Tob Induc Dis. 17:21. https://doi.org/10.18332/tid/104674 PMID:31582932
18. WHO (2010). Guidelines for implementation of Article 14 of the WHO Framework Convention on Tobacco Control. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/fctc/guidelines/adopted/article_14/en/.

19. WHO (2008). WHO report on the global tobacco epidemic, 2008: the MPOWER package. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/tobacco/mpower/2008/en/.

20. WHO (2007). A WHO/the Union monograph on TB and tobacco control: joining efforts to control two related global epidemics. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/tobacco/resources/publications/tb_tobac_monograph.pdf.

21. WHO (2017). WHO monograph on tobacco cessation and oral health integration. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/bitstream/handle/10665/255692/9789241512671-eng.pdf?sequence=1.

22. Cox LS, Cupertino AP, Tercyak KP (2011). Interest in participating in smoking cessation treatment among Latino primary care patients. J Clin Psychol Med Settings. 18(4):392–9. https://doi.org/10.1007/s10880-011-9259-y PMID:21984387

23. Ybarra ML, Bağci Bosi AT, Bilir N, Holtrop JS, Korchmaros J, Emri S (2011). Interest in technology-based and traditional smoking cessation programs among adult smokers in Ankara, Turkey. Tob Induc Dis. 9(10):10. https://doi.org/10.1186/1617-9625-9-10 PMID:21806793

24. Glantz SA (2018). Heated tobacco products: the example of IQOS. Tob Control. 27(Suppl 1):s1–6. https://doi.org/10.1136/tobaccocontrol-2018-054601 PMID:30352841

25. TPSAC (2018). Tobacco Products Scientific Advisory Committee. Washington (DC), USA: Food and Drug Administration. Available from: https://www.fda.gov/advisory-committees/committees-and-meeting-materials/tobacco-products-scientific-advisory-committee.

26. Rahman MA, Hann N, Wilson A, Mnatzaganian G, Worrall-Carter L (2015). E-cigarettes and smoking cessation: evidence from a systematic review and meta-analysis. PLoS One. 10(3):e0122544. https://doi.org/10.1371/journal.pone.0122544 PMID:25822251

27. Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P (2016). Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. (9):CD010216. https://doi.org/10.1002/14651858.CD010216.pub3 PMID:27622384

28. Malas M, van der Temple J, Schwartz R, Minichiello A, Lightfoot C, Noormohamed A, et al. (2016). Electronic cigarettes for smoking cessation: a systematic review. Nicotine Tob Res. 18(10):1926–36. https://doi.org/10.1093/ntr/ntw119 PMID:27113014

29. Khoudigian S, Devji T, Lytvyn L, Campbell K, Hopkins R, O'Reilly D (2016). The efficacy and short-term effects of electronic cigarettes as a method for smoking cessation: a systematic review and a meta-analysis. Int J Public Health. 61(2):257–67. https://doi.org/10.1007/s00038-016-0786-z PMID:26825455

30. El Dib R, Suzumura EA, Akl EA, Gomaa H, Agarwal A, Chang Y, et al. (2017). Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis. BMJ Open. 7(2):e012680. https://doi.org/10.1136/bmjopen-2016-012680 PMID:28235965

31. National Academies of Sciences, Engineering, and Medicine (2018). Public health consequences of e-cigarettes. Washington (DC), USA: National Academies Press. https://doi.org/10.17226/24952

32. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. (2019). A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med. 380(7):629–37. https://doi.org/10.1056/NEJMoa1808779 PMID:30699054

33. Robertson L, Hoek J, Blank ML, Richards R, Ling P, Popova L (2019). Dual use of electronic nicotine delivery systems (ENDS) and smoked tobacco: a qualitative analysis. Tob Control. 28(1):13–9. https://doi.org/10.1136/tobaccocontrol-2017-054070 PMID:29419488

34. Kalkhoran S, Glantz SA (2016). E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. Lancet Respir Med. 4(2):116–28. https://doi.org/10.1016/S2213-2600(15)00521-4 PMID:26776875

35. Wang JB, Olgin JE, Nah G, Vittinghoff E, Cataldo JK, Pletcher MJ, et al. (2018). Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study. PLoS One. 13(7):e0198681. https://doi.org/10.1371/journal.pone.0198681 PMID:30044773

36. WHO (2016). Electronic nicotine delivery systems and/or electronic non nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/tobacco/industry/product_regulation/BackgroundPapersENDS4_4November.pdf?ua=1.

37. WHO (2016). Electronic nicotine delivery systems and electronic non-nicotine delivery systems (ENDS/ENNDS). Report by WHO. Conference of the Parties to the WHO Framework Convention on Tobacco Control, seventh session, FCTC/COP/7/11. Available from: https://www.who.int/fctc/cop/cop7/FCTC_COP_7_11_EN.pdf.

38. McNeill A, Brose LS, Calder R, Bauld L, Robson D (2019). Vaping in England, an evidence update, February 2019. A report commissioned by Public Health England. London, UK: Public Health England. Available from: https://www.gov.uk/government/publications/vaping-in-england-an-evidence-update-february-2019.

39. WHO (2014). Electronic nicotine delivery systems. Report by WHO. Conference of the Parties to the WHO Framework Convention on Tobacco Control, sixth session, FCTC/COP/6/10 Rev.1. Available from: https://apps.who.int/iris/handle/10665/147110.

40. Alzahrani T, Pena I, Temesgen N, Glantz SA (2018). Association between electronic cigarette use and myocardial infarction. Am J Prev Med. 55(4):455–61. https://doi.org/10.1016/j.amepre.2018.05.004 PMID:30166079

41. Wills TA, Pagano I, Williams RJ, Tam EK (2019). E-cigarette use and respiratory disorder in an adult sample. Drug Alcohol Depend. 194:363–70. https://doi.org/10.1016/j.drugalcdep.2018.10.004 PMID:30472577

42. England LJ, Aagaard K, Bloch M, Conway K, Cosgrove K, Grana R, et al. (2017). Developmental toxicity of nicotine: a transdisciplinary synthesis and implications for emerging tobacco products. Neurosci Biobehav Rev. 72:176–89. https://doi.org/10.1016/j.neubiorev.2016.11.013 PMID:27890689

43. Morean ME, Krishnan-Sarin S, O'Malley SS (2018). Assessing nicotine dependence in adolescent E-cigarette users: the 4-item Patient-Reported Outcomes Measurement Information System (PROMIS) Nicotine Dependence Item Bank for electronic cigarettes. Drug Alcohol Depend. 188:60–3. https://doi.org/10.1016/j.drugalcdep.2018.03.029 PMID:29753155

44. Cullen KA, Ambrose BK, Gentzke AS, Apelberg BJ, Jamal A, King BA (2018). Notes from the field: use of electronic cigarettes and any tobacco product among middle and high school students – United States, 2011–2018. MMWR Morb Mortal Wkly Rep. 67(45):1276–7. https://doi.org/10.15585/mmwr.mm6745a5 PMID:30439875

45. WHO (2019). WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: seventh report of a WHO study group. Geneva, Switzerland: World Health Organization (WHO Technical Report Series, No. 1015). Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/publications-detail/who-study-group-on-tobacco-product-regulation-report-on-the-scientific-basis-of-tobacco-product-regulation-seventh-report-of-a-who-study-group.

46. Simonavicius E, McNeill A, Shahab L, Brose LS (2019). Heat-not-burn tobacco products: a systematic literature review. Tob Control. 28(5):582–94. https://doi.org/10.1136/tobaccocontrol-2018-054419 PMID:30181382

47. Auer R, Concha-Lozano N, Jacot-Sadowski I, Cornuz J, Berthet A (2017). Heat-not-burn tobacco cigarettes: smoke by any other name. JAMA Intern Med. 177(7):1050–2. https://doi.org/10.1001/jamainternmed.2017.1419 PMID:28531246

48. Committee on Toxicity, Carcinogenicity and Mutagenicity of Chemicals in Food, Consumer Products and the Environment (2017). Statement on the toxicological evaluation of novel heat-not-burn tobacco products. Assessment made for UK Department of Health and Public Health England. Available from: https://cot.food.gov.uk/sites/default/files/heat_not_burn_tobacco_statement.pdf.

49. WHO (2017). Heated tobacco products (HTPs) information sheet. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/tobacco/publications/prod_regulation/heated-tobacco-products/en/.

50. Perikleous EP, Steiropoulos P, Paraskakis E, Constantinidis TC, Nena E (2018). E-cigarette use among adolescents: an overview of the literature and future perspectives. Front Public Health. 6:86. https://doi.org/10.3389/fpubh.2018.00086 PMID:29632856

51. Berry KM, Fetterman JL, Benjamin EJ, Bhatnagar A, Barrington-Trimis JL, Leventhal AM, et al. (2019). Association of electronic cigarette use with subsequent initiation of tobacco cigarettes in US youths. JAMA Netw Open. 2(2):e187794. https://doi.org/10.1001/jamanetworkopen.2018.7794 PMID:30707232

52. Chaffee BW, Watkins SL, Glantz SA (2018). Electronic cigarette use and progression from experimentation to established smoking. Pediatrics. 141(4):4. https://doi.org/10.1542/peds.2017-3594 PMID:29507167

53. Rossheim ME, Livingston MD, Soule EK, Zeraye HA, Thombs DL (2019). Electronic cigarette explosion and burn injuries, US Emergency Departments 2015–2017. Tob Control. 28(4):472–4. https://doi.org/10.1136/tobaccocontrol-2018-054518 PMID:30219795

54. Ghebreyesus TA (2019). Progress in beating the tobacco epidemic. Lancet. 394(10198):548–9. https://doi.org/10.1016/S0140-6736(19)31730-1 PMID:31371094

6.1 Changing behaviour
The need for sustainable implementation

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SUMMARY

- Prevention strategies over the past 5 years have made strides in cancer prevention through the modification of various causal pathways.
- Two of the most notable successes in prevention have been through tobacco control and vaccination policies.
- Despite advances in evidence-based interventions, widespread implementation of these prevention strategies varies between countries.
- For effective prevention practices, the cultural context, measurement strategies, and sustainability for implementation must be considered.

The burden of death from the multiple different cancer types can be reduced in all communities and countries by implementing evidence-based prevention and treatment strategies. The incidence of cancer can be reduced by decreasing or eliminating exposure to carcinogens in multiple contexts and by maximizing adherence to a lifestyle that lowers risk. Success in reducing the incidence of smoking-related cancers is well established but varies by country. Interventions to change behaviour related to nutrition, physical activity, and energy balance could achieve comparable benefit. Vaccination is effective in preventing some cancers caused by infectious agents. Variations in the implementation of prevention strategies across countries and the benefits that extend beyond individual countries deserve further study.

Scope of the preventive approach

There has been a renewed focus on the increasing global cancer burden, which rose to an estimated 18.1 million new cases and 9.6 million deaths in 2018 [1]. Currently, a growing emphasis is on how to increase the availability of evidence-based prevention and treatment strategies [2].

With respect to primary prevention, the nine principles of prevention associated with effective programmes are still relevant to ensure that the approach will be effective. Interventions must include the following characteristics: they should (i) be comprehensive, (ii) be appropriately timed, (iii) use varied teaching methods, (iv) have sufficient dosage, (v) be administered by well-trained staff, (vi) provide opportunities for positive relationships, (vii) be socioculturally relevant, (viii) be theory-driven, and (ix) include outcome evaluation.

Population health and prevention strategies have evolved over the past 50 years, with an increasing awareness that the social context drives exposures and health habits. Evolving from the Lalonde report in Canada in 1974 [3] and the *Healthy People* report in the USA in 1979 [4], the focus on health equity and reducing disparities in disease burden has taken centre stage in the past decade. In 2009, Australia established a National Preventative Health Taskforce with the intention of Australia becoming the world's healthiest country by 2020 [5]. Similarly, the USA expanded the *Healthy People* goals with targets to reduce disparities by 2020 [6], and some progress has been reported [7].

Globally, the most notable successes in prevention have been in two contrasting domains. The first is in tobacco control. In 2008, WHO identified the MPOWER measures (Fig. 6.1.1), a set of six cost-effective and high-impact changes that help countries reduce demand for tobacco. More than half of the world's countries have implemented at least one MPOWER measure at the highest level of achievement [8].

In addition, the WHO Framework Convention on Tobacco Control, which is implemented variably by country, has led to increases in regulatory approaches to reduce cigarette smoking, resulting in a decline in lung cancer mortality [9]. However, this decline is restricted to high-income countries, and the prevalence of smoking and the rates of lung cancer remain high in low- and middle-income countries [9]. In many countries, a broad spectrum of prevention research is occurring, with a

Fig. 6.1.1. The MPOWER measures, established by WHO to help reduce demand for tobacco.

focus remaining on tobacco control. In Australia, cigarette taxes have increased by 12.5% each year since 2016, and there is a plan to continue the increase for another 2 years [10]. Tobacco taxes are a proven strategy to reduce the prevalence of smoking, particularly in adolescents and groups with low socioeconomic status. In addition, in Canada graphic warning labels about the harms of smoking have had a significant impact on the prevalence of smoking and on quit attempts [11].

The second notable success in prevention is in vaccination programmes, particularly those for hepatitis B virus (HBV) and for human papillomavirus (HPV). Uptake of HBV vaccination has resulted in reductions in incidence of liver disease and deaths from liver cancer [12]. In many high- and middle-income countries, rates of delivering the HBV vaccine on time are fairly high (> 80%); in contrast, in many low-income countries, rates of adherence to vaccination schedules are lower [13]. Variations in childhood HBV vaccination schedule and population coverage are shown in Fig. 6.1.2.

These inequalities emphasize the continued need to strengthen the infrastructure for immunization systems, especially in low-income countries. Such approaches have been successful. For example, the Maldives has sustained an immunization programme that trains health workers across the country on various aspects of immunization and surveillance. These workers combine the work of health professionals with community engagement and strong public awareness [14].

There is overwhelming evidence that HPVs are responsible for diverse preventable cancer types (see Chapter 2.2), accounting for an estimated 4.5% of all new cancer cases worldwide [15]. HPV vaccines have been determined to provide safe and durable protection against these tumorigenic viruses [16]. Strong evidence of reduced incidence of early cervical lesions [17] and follow-up evidence of population benefits [18] with HPV vaccination led to changes in cervical cancer screening guidelines [18]. As a result, Australia has moved to vaginal HPV testing every 5 years, which consequently saves lives and reduces the patient burden and costs of prevention programmes [19].

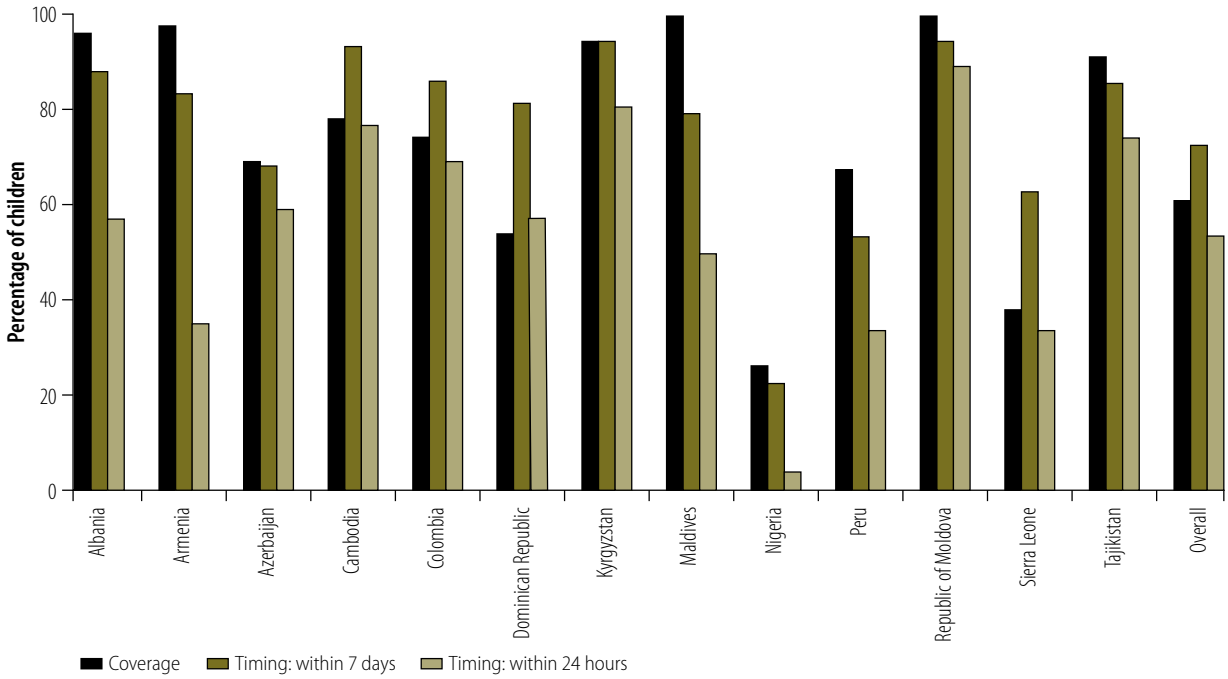
However, despite compelling objective evidence of the benefit of HPV vaccines, vaccination rates and policies differ markedly by country (see Chapter 6.3). Personal reasons for low vaccination rates include: needing more information, no recommendation by physician, confusion about the age requirement, and the perception that the vaccine will encourage sexual promiscuity. It has been shown that physician recommendation [20] and widespread vaccine availability [21] are major factors in achieving high vaccination rates. Discussing HPV vaccination at every well-child checkup for children starting at about age 9 years as well as implementing school-based vaccination programmes could help to increase acceptance of the vaccine and increase vaccination rates.

In addition, there are established effective approaches to screening for the prevention and early detection of colorectal cancer, which is the third most commonly diagnosed cancer worldwide. In some countries, there have been promising improvements

FUNDAMENTALS

- During the past 40 years, rates have decreased for some cancer types, but they have increased for other cancer types. Cancer remains a leading cause of death worldwide.
- Behaviour is central to the etiology and management of cancer prevention and outcomes. This allows for several avenues for targeted and sustained interventions.
- Successful preventive interventions have focused on tobacco use, vaccinations, nutrition, and physical activity.
- However, successful preventive interventions are not effective without sustainable implementation strategies that are widespread and scalable.
- Sustainable implementation requires organizing and maximizing community assets and resources, institutionalizing policies and practices within communities and organizations, considering the context and infrastructure of the community, and involving a multiplicity of stakeholders who can develop long-term buy-in and support.

Fig. 6.1.2. Coverage and timing of birth dose of hepatitis B virus (HBV) vaccine for children aged 12–60 months in 13 countries with national vaccination schedules that include a vaccine dose at birth, 2005–2014. Coverage is the percentage of children receiving the birth dose of HBV vaccine. Timing of vaccination is the percentage of children receiving the birth dose within 7 days of birth and within 24 hours of birth.



in population screening rates after the establishment of countrywide colorectal cancer screening programmes. Mathematical modelling studies have shown that screening by colonoscopy is potentially highly cost-effective at combatting colorectal cancer in countries in sub-Saharan Africa [22].

In addition to these notable prevention strategies, other countries have implemented successful programmes that are showing progress in improving various public health initiatives. For example, in Brazil conditional cash transfer programmes (which provide low-income families with cash conditional on investments in health and education) have been shown to increase the odds of children's visits for preventive services and vaccinations [23].

Childhood obesity is a global public health problem with consequences such as premature cardiovascular disease and premature mortality [24]. Adolescent obesity increases the risk of several cancer types. Although trends from data suggest that the prevalence of childhood obesity has plateaued in some countries, groups with low socioeconomic status face a disproportionate impact, including in populations in South Asia [25].

No countrywide programmes against childhood obesity are currently being implemented, but some interventions are showing promise. One example is a school-based programme evaluated in urban Pakistan that demonstrated favourable trends in blood pressure and body mass index at follow-up [26]. Cost-effective school-based programmes have been implemented successfully in Australia and in groups with low socioeconomic status [27]. Although these programmes show promise in the field of physical activity, proper implementation requires scaling up through a transdisciplinary approach.

An established driver of childhood and adolescent obesity is consumption of sugar-sweetened beverages (see Chapter 2.6). In Mexico, an excise tax of 1 peso per litre on sugar-sweetened beverages, which was successfully implemented on 1 January 2014, resulted in a 5.5% reduction in purchases of taxed beverages in 2014 and a 9.7% reduction in 2015 [28].

Broader application of effective prevention strategies to address these top public health initiatives must move beyond tobacco control and singular interventions. Applying the principles of implementation science to evidence-based interventions will speed up the translation of research into practice and the achievement of the global benefit of a reduced disease burden. Implementation science provides a framework to study and identify the effective strategies to move from research to practice [29].

Background information required before implementation

Defining evidence-based interventions is a necessary first step for the implementation of effective prevention strategies. Evidence-based health care can provide access to

more and higher-quality information on what works, resulting in a higher likelihood of successful programmes and policies being implemented, greater workforce productivity, and more efficient use of public and private resources [30].

Despite the gold standard provided by timely implementation of these evidence-based interventions, much less attention has been focused on how to effectively implement these practices [30]. A useful framework ties the evidence-based strategies to implementation science for effective uptake, dissemination, and scale-up. The context for the preventive interventions (e.g. public health or clinical systems, regulatory strategies, or community- or group-based interventions, such as in the workplace, at schools, and at childcare centres) must be considered when identifying strategies for implementation [31].

In addition to the characteristics of the intervention, the capacity of the public health infrastructure and the health delivery system to implement and sustain a prevention strategy is fundamental to the success of the intervention. In the setting of tobacco control, partners of WHO assess the commitment and organizational structure for implementing evidence-based tobacco control programmes. For other interventions, including vaccination programmes, the underlying structure of health systems and the goals of access to universal health coverage are integral to the programme's success. Universal access to health care is important for the delivery of the preventive intervention and also for cancer care and outcomes of care [32].

Considerations for national campaigns

A common tension of implementing prevention strategies is the trade-off of population-wide coverage versus targeting prevention to the groups at highest risk.

Vaccination programmes and taxation on cigarettes demonstrate the value of population-wide strategies. For example, national campaigns engage public awareness to support the changes in culture that have removed the acceptability of indoor smoke exposure (and indoor smoking). These campaigns are most effective when the messages are reinforced by health-care providers and by other structural changes, including restricting access to cigarettes or putting in place workplace policies, facilities, and practices.

However, for national, population-wide campaigns, the components of health literacy and cultural context within a country must be considered [33]. For example, Australia has led the world with simple messages about sun protection [34], which have been complemented by professional education, mass media messaging, and environmental modifications, resulting in population-wide changes in beliefs about sun exposure and prevention (see Chapter 5.8). As a result, the incidence of and mortality from melanoma have fallen [35].

Fig. 6.1.3. A poster about human papillomavirus (HPV) vaccination in the Sinhala language, in Sri Lanka.

of a programme to achieve its goals and the desired population health outcomes. Often, interventions are adapted to fit in a new applied context, and the study of this process shows promise to inform broader prevention goals. Specifically, interventions that address children's nutrition, physical activity, and energy balance can be adapted to diverse school settings and student populations to align with local relevance and account for the norms and culture within schools [36]. Similarly, the components of programmes that lead to sustainability are now considered within frameworks that may help to bring prevention to broader populations [37].

Public health capacity is a key variable that underpins the successful implementation of programmes. When evaluating and implementing a programme, cues can be taken from other strategies that have proven effective in building capacity [38].

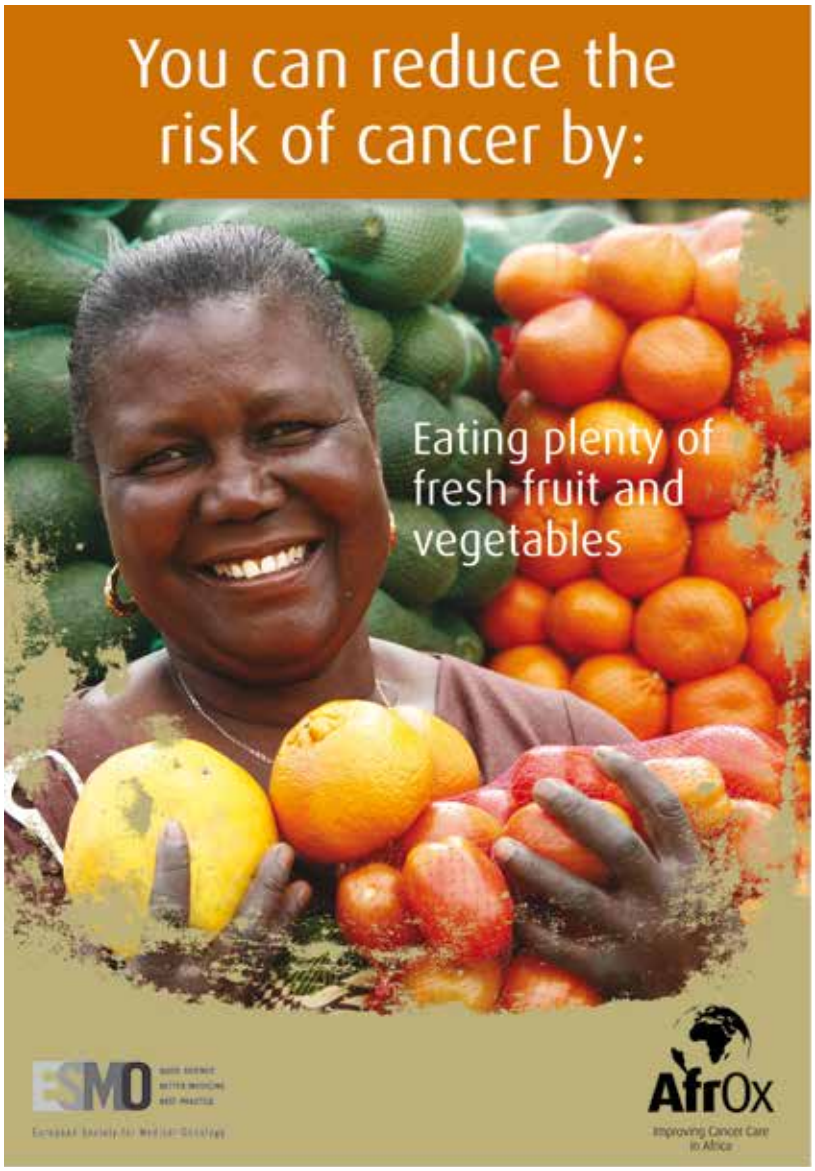
Finally, approaches to measuring and evaluating the success of interventions (and their component parts) must be defined and assessed within the constraints of real-world delivery. Using appropriate measures in the context of implementation models bring a sharper focus to quantification of the impact of programmes [30].

Health behavioural interventions, such as prevention, should follow the dimensions of the RE-AIM framework (i.e. reach, efficacy, adoption, implementation, and maintenance). To ensure that preventive interventions are effective, a focus must be placed on the maintenance and sustainability of the intervention. Furthermore, given the clear role that policy and environmental approaches play in ensuring population-level access to prevention, increased research illustrating a more systematic increase in implementation of these approaches is critical, although such research is rarely funded.

In the past 5 years there has been an increasing emphasis on implementation science research, which is the study of methods to promote the integration of research findings and evidence into health-care policy and practice [39]. Implementation science seeks to understand the behaviour of health-care professionals and other stakeholders as a key variable in the sustainable uptake, adoption, and implementation of evidence-based interventions. The field of implementation science offers innovative approaches to identify, understand, and develop strategies for overcoming barriers to the adoption, adaptation, integration, scale-up, and sustainability of evidence-based interventions, tools, policies, and guidelines. Expanding the focus of implementation science to include policy research could be very fruitful.

Brownson et al. [40] summarized lessons learned related to population-level prevention of chronic disease, including several that are relevant

Fig. 6.1.4. A poster about healthy nutrition from the Cancer Prevention 4 Africa campaign, which is designed to improve people's understanding about the early signs of cancer and how simple lifestyle changes can greatly reduce the likelihood of developing many cancer types.



to implementation science in cancer prevention specifically: (i) start with environmental and policy interventions as the key to initiating and sustaining systematic change, (ii) think across multiple levels of influence, (iii) make better use of existing tools for implementation, (iv) understand the local context and politics, (v) build new and non-traditional partnerships, (vi) address health disparities, and (vii) conduct more and better policy research. These lessons deserve particular attention in terms of identifying untapped levers for increasing implementation of the evidence base for cancer prevention.

When planning to scale up interventions for wider population coverage, questions arise, such as the strength of the evidence base, the ability to deliver the intervention at low cost, the approaches to monitoring the consistency or integrity of the delivery of the intervention, and outcomes across levels of health system (health-care provider or health department) and individuals. Key questions include the following:

- How does the intervention align with local needs and provide available resources for feasible monitoring strategies?
- Will additional technical assistance be needed for broader implementation?
- How is this developed, delivered, and sustained?
- How flexible can and must the intervention be?
- What are the measures of organizational success and of overall outcome?

Conclusions

Numerous effective prevention strategies have been evaluated over the past 5 years. Vaccination and tobacco control strategies have been shown to be scalable and effective in widespread implementation. However, there is continuing development in the areas of nutrition and physical activity, among other prevention strategies. For the development of effective programming, the cultural context, measurement strategies, and sustainability for implementation must be considered.

Future priorities in the area of changing behaviour include:

- identifying the components of interventions that are key to sustained change, and those that are most readily adapted to fit a population group;
- a clearer understanding of when prevention strategies are not adequate and should be abandoned or replaced;
- a greater use of implementation science to move from research to broader application of prevention strategies;
- maintaining programmes for the sustained achievement of desirable goals and population outcomes; and
- a better understanding of the benefits of prevention through the leading modifiable risk factors and the benefits that extend beyond individual countries.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593
2. Sullivan R, Peppercorn J, Sikora K, Zalcberg J, Meropol NJ, Amir E, et al. (2011). Delivering affordable cancer care in high-income countries. Lancet Oncol. 12(10):933–80. https://doi.org/10.1016/S1470-2045(11)70141-3 PMID:21958503
3. Lalonde M (1974). Social values and public health. Can J Public Health. 65(4):260–8. PMID:4849733
4. DHEW (1979). Healthy people: the Surgeon General's report on health promotion and disease prevention. Washington (DC), USA: Department of Health, Education, and Welfare. Available from: https://profiles.nlm.nih.gov/ps/access/NNBBGK.pdf.
5. National Preventative Health Taskforce (2009). Australia: the healthiest country by 2020. National Preventative Health Strategy – the roadmap for action. Canberra: Commonwealth of Australia.
6. Koh HK, Graham G, Glied SA (2011). Reducing racial and ethnic disparities: the action plan from the Department of Health and Human Services. Health Aff (Millwood). 30(10):1822–9. https://doi.org/10.1377/hlthaff.2011.0673 PMID:21976322
7. NCHS (2016). Healthy People 2020 midcourse review. Hyattsville (MD), USA: National Center for Health Statistics. Available from: https://www.cdc.gov/nchs/healthy_people/hp2020/hp2020_midcourse_review.htm.
8. WHO (2015). WHO report on the global tobacco epidemic, 2015: raising taxes on tobacco. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/tobacco/global_report/2015/en/.
9. Islami F, Torre LA, Jemal A (2015). Global trends of lung cancer mortality and smoking prevalence. Transl Lung Cancer Res. 4(4):327–38. https://doi.org/10.3978/j.issn.2218-6751.2015.08.04 PMID:26380174
10. Kirby T (2016). Australia tax increases to price cigarettes out of reach. Lancet Oncol. 17(6):e228. https://doi.org/10.1016/S1470-2045(16)30136-X PMID:27183848
11. Azagba S, Sharaf MF (2013). The effect of graphic cigarette warning labels on smoking behavior: evidence from the Canadian experience. Nicotine Tob Res. 15(3):708–17. https://doi.org/10.1093/ntr/nts194 PMID:22990228
12. Chiang CJ, Yang YW, You SL, Lai MS, Chen CJ (2013). Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. JAMA. 310(9):974–6. https://doi.org/10.1001/jama.2013.276701 PMID:24002285

13. Schweitzer A, Akmatov MK, Krause G (2017). Hepatitis B vaccination timing: results from demographic health surveys in 47 countries. Bull World Health Organ. 95(3):199–209G. https://doi.org/10.2471/BLT.16.178822 PMID:28250533

14. WHO (2017). Expanded Programme on Immunization (EPI) fact sheet: Maldives 2017. Geneva, Switzerland: World Health Organization. Available from: http://origin.searo.who.int/immunization/data/maldives_2017.pdf.

15. de Martel C, Plummer M, Vignat J, Franceschi S (2017). Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 141(4):664–70. https://doi.org/10.1002/ijc.30716 PMID:28369882

16. Huh WK, Joura EA, Giuliano AR, Iversen OE, de Andrade RP, Ault KA, et al. (2017). Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. Lancet. 390(10108):2143–59. https://doi.org/10.1016/S0140-6736(17)31821-4 PMID:28886907

17. Brotherton JM, Gertig DM, May C, Chappell G, Saville M (2016). HPV vaccine impact in Australian women: ready for an HPV-based screening program. Med J Aust. 204(5):184, e1. https://doi.org/10.5694/mja15.01038 PMID:26985843

18. Medical Services Advisory Committee (2013). National Cervical Screening Program Renewal: evidence review. Canberra: Commonwealth of Australia. Available from: http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/E6A211A6FFC29E2CCA257CED007FB678/$File/Review%20of%20Evidence%20notated%2013.06.14.pdf.

19. Simms KT, Laprise JF, Smith MA, Lew JB, Caruana M, Brisson M, et al. (2016). Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: a comparative modelling analysis. Lancet Public Health. 1(2):e66–75.https://doi.org/10.1016/S2468-2667(16)30019-6 PMID:29253419

20. Holman DM, Benard V, Roland KB, Watson M, Liddon N, Stokley S (2014). Barriers to human papillomavirus vaccination among US adolescents: a systematic review of the literature. JAMA Pediatr. 168(1):76–82. https://doi.org/10.1001/jamapediatrics.2013.2752 PMID:24276343

21. Walling EB, Benzoni N, Dornfeld J, Bhandari R, Sisk BA, Garbutt J, et al. (2016). Interventions to improve HPV vaccine uptake: a systematic review. Pediatrics. 138(1):e20153863. https://doi.org/10.1542/peds.2015-3863 PMID:27296865

22. Ginsberg GM, Lauer JA, Zelle S, Baeten S, Baltussen R (2012). Cost effectiveness of strategies to combat breast, cervical, and colorectal cancer in sub-Saharan Africa and South East Asia: mathematical modelling study. BMJ. 344:e614. https://doi.org/10.1136/bmj.e614 PMID:22389347

23. Shei A, Costa F, Reis MG, Ko AI (2014). The impact of Brazil's Bolsa Família conditional cash transfer program on children's health care utilization and health outcomes. BMC Int Health Hum Rights. 14(1):10. https://doi.org/10.1186/1472-698X-14-10 PMID:24690131

24. Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker HC (2010). Childhood obesity, other cardiovascular risk factors, and premature death. N Engl J Med. 362(6):485–93. https://doi.org/10.1056/NEJMoa0904130 PMID:20147714

25. Jafar TH, Qadri Z, Islam M, Hatcher J, Bhutta ZA, Chaturvedi N (2008). Rise in childhood obesity with persistently high rates of undernutrition among urban school-aged Indo-Asian children. Arch Dis Child. 93(5):373–8. https://doi.org/10.1136/adc.2007.125641 PMID:17942586

26. Almas A, Islam M, Jafar TH (2013). School-based physical activity programme in pre-adolescent girls (9-11 years): a feasibility trial in Karachi, Pakistan. Arch Dis Child. 98(7):515–9. https://doi.org/10.1136/archdischild-2012-303242 PMID:23661575

27. Craike M, Wiesner G, Hilland TA, Bengoechea EG (2018). Interventions to improve physical activity among socioeconomically disadvantaged groups: an umbrella review. Int J Behav Nutr Phys Act. 15(1):43. https://doi.org/10.1186/s12966-018-0676-2 PMID:29764488

28. Colchero MA, Rivera-Dommarco J, Popkin BM, Ng SW (2017). In Mexico, evidence of sustained consumer response two years after implementing a sugar-sweetened beverage tax. Health Aff (Millwood). 36(3):564–71.https://doi.org/10.1377/hlthaff.2016.1231 PMID:28228484

29. Emmons KM, Colditz GA (2017). Realizing the potential of cancer prevention – the role of implementation science. N Engl J Med. 376(10):986–90. https://doi.org/10.1056/NEJMsb1609101 PMID:28273020

30. Brownson RC, Colditz GA, Proctor EK, editors (2018). Dissemination and implementation research in health: translating science to practice. 2nd ed. New York (NY), USA: Oxford University Press.

31. Lobb R, Colditz GA (2013). Implementation science and its application to population health. Annu Rev Public Health. 34(1):235–51. https://doi.org/10.1146/annurev-publhealth-031912-114444 PMID:23297655

32. Colditz GA, Emmons KM (2016). The role of universal health coverage in reducing cancer deaths and disparities. Lancet. 388(10045):638–40. https://doi.org/10.1016/S0140-6736(16)30376-2 PMID:27236343

33. Kaufman J, Ames H, Bosch-Capblanch X, Cartier Y, Cliff J, Glenton C, et al. (2017). The comprehensive 'Communicate to Vaccinate' taxonomy of communication interventions for childhood vaccination in routine and campaign contexts. BMC Public Health. 17(1):423. https://doi.org/10.1186/s12889-017-4320-x PMID:28486956

34. Montague M, Borland R, Sinclair C (2001). Slip! Slop! Slap! and SunSmart, 1980-2000: skin cancer control and 20 years of population-based campaigning. Health Educ Behav. 28(3):290–305. https://doi.org/10.1177/109019810102800304 PMID:11380050

35. Hill D, Marks R (2008). Health promotion programs for melanoma prevention: screw or spring? Arch Dermatol. 144(4):538–40. https://doi.org/10.1001/archderm.144.4.538 PMID:18427051

36. Lee RM, Gortmaker SL (2018). Health dissemination and implementation within schools. In: Brownson RC, Colditz GA, Proctor EK, editors. Dissemination and implementation research in health: translating science to practice. 2nd ed. New York (NY), USA: Oxford University Press; pp. 401–16.

37. Shelton RC, Cooper BR, Stirman SW (2018). The sustainability of evidence-based interventions and practices in public health and health care. Annu Rev Public Health. 39(1):55–76. https://doi.org/10.1146/annurev-publhealth-040617-014731 PMID:29328872

38. Leeman J, Calancie L, Hartman MA, Escoffery CT, Herrmann AK, Tague LE, et al. (2015). What strategies are used to build practitioners' capacity to implement community-based interventions and are they effective?: a systematic review. Implement Sci. 10(1):80. https://doi.org/10.1186/s13012-015-0272-7 PMID:26018220

39. DHHS (2016). Dissemination and implementation research in health, PAR-16-238. Washington (DC), USA; Department of Health and Human Services. Available from: https://grants.nih.gov/grants/guide/pa-files/par-16-238.html.

40. Brownson RC, Haire-Joshu D, Luke DA (2006). Shaping the context of health: a review of environmental and policy approaches in the prevention of chronic diseases. Annu Rev Public Health. 27(1):341–70. https://doi.org/10.1146/annurev.publhealth.27.021405.102137 PMID:16533121

6.2 Improving diet and nutrition, physical activity, and body weight

From evidence to practice

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Christine Friedenreich (reviewer)
Martin Wiseman (reviewer)

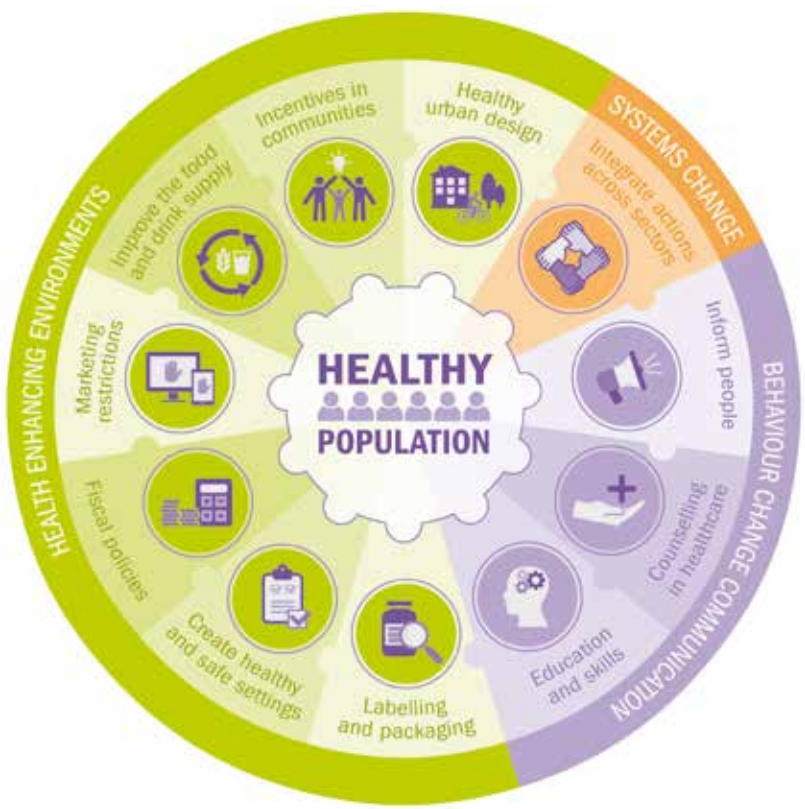
SUMMARY

- There is now clear evidence that the greatest change in diet and physical activity across a population can be achieved when population-wide approaches, such as policy specification, are combined with individually targeted approaches.
- Approaches to changing diet and physical activity should take into consideration health-enhancing environments, behaviour change communications, and systems change.
- Government regulatory measures, such as product nutrient specification, and fiscal interventions can be used to successfully affect dietary patterns, but industry opposition can influence the design of optimal programmes.
- Educational approaches and awareness-raising strategies can motivate and support people to change their behaviour, but their impact on dietary intake alone is small and may be lowest in vulnerable groups.
- No single intervention can address the challenge of achieving healthy dietary patterns.

Behavioural risk factors for cancer, such as diet and physical activity, are influenced by underlying social determinants, including economic, political, environmental, and cultural factors; global efforts to reduce the burden of cancer need to take account of these social determinants in order to produce equitable changes in health and well-being [1]. The NOURISHING framework and the new Driving Action framework from World Cancer Research Fund International [2] (Fig. 6.2.1) highlight the importance of using comprehensive approaches that take into consideration health-enhancing environments, behaviour change communications, and systems change. Health services, including cancer screening programmes, can contribute to national efforts [3].

Single strategies, such as those focusing on communications and

Fig. 6.2.1. The Driving Action framework from World Cancer Research Fund International.



education, have limited effects and can be associated with increases in health inequalities. A comprehensive community approach to changing health behaviours has been demonstrated historically in the North Karelia Project in Finland, which showed significant reductions in cardiovascular outcomes, followed by reductions in cancer mortality, arising from "the correct theory base, comprehensive work with the population, and much hard work in the community" [4].

There is a growing evidence base on the impact of behaviour change communications and programmes, which include individual-level counselling by health professionals, education, and social support, such as demonstrated by the diabetes prevention programmes. However, these approaches tend to be intensive and may have low generalizability, especially in the most vulnerable communities [5]. There is now clear evidence that the greatest change in diet and physical activity across a population can be achieved when population-wide approaches, such as policy specification, are combined with individually targeted approaches.

Although evidence from trials, modelling (i.e. theoretical analysis estimated from existing data), and practical experience can guide action for effective change, the implementation of effective intervention policies is dependent on government knowledge, the capacity and will to act, and the governance structures to translate evidence into practice. In addition, actions have to take account of the local context and the specific needs of the population (see Chapter 6.1).

Diet and nutrition

Food

For cancer prevention, both dietary quantities (i.e. appropriate energy intake) and diet quality are important. Plant-based dietary patterns – with an emphasis on whole grains, vegetables, fruits, and beans, and limited intake of red meat, processed meat, sugar, ultra-processed foods, sugar-sweetened beverages, and alcoholic beverages – are desirable (see Chapter 2.6).

It is clear that multiple factors, beyond personal decision-making, influence food choice and dietary patterns, including sociocultural background, lifestyle patterns, and economic and commercial pressures. Therefore, to achieve equitable, secure, sustainable, and optimal dietary intake, wider environmental factors need to be embraced in addition to individually focused approaches.

Fig. 6.2.2. Vegetables and fruits at a market in France.

FUNDAMENTALS

- Although evidence from trials, modelling (i.e. theoretical analysis estimated from existing data), and practical experience can guide action for effective change, the implementation of effective and equitable intervention policies, such as a sugar tax, is dependent on government action.
- Natural experiments can provide useful evidence for intervention planning and policy development.
- Evidence from comprehensive community programmes suggests that a combination of behavioural theory, commitment, and national and local action are key factors in the design of programmes and policies.
- When implementing programmes that were successful in other regions, care needs to be taken to consider the local context and the specific needs of the population.
- Most research evidence has short- to medium-term outcomes, and more research is needed on programme sustainability, reach, and long-term outcomes to assess the impact of programmes and policies on cancer outcomes across all population groups.

No single intervention can address the challenge of achieving healthy dietary patterns.

Hawkes et al. [6] described four mechanisms through which food policies can have an impact on diet throughout the life-course: (i) providing an enabling environment for the learning of healthy preferences in childhood (because preferences are often persistent and resistant to change); (ii) identifying and overcoming barriers to the expression of healthy preferences, such as strategies related to physical

resources, information, and skills; (iii) approaches that encourage people to reassess existing unhealthy preferences at the point of purchase through changes in price, availability, and presentation (sometimes referred to as choice architecture); and (iv) the ability to stimulate food-systems response so that changes made by one action, such as mandatory nutrition labelling, have an impact elsewhere in the food environment, for example product reformulation.

For decades, nutrition programmes have focused primarily on behaviour change communications such as education programmes, food labelling information (e.g. traffic-light labelling), and skills (e.g. food preparation). These are considered to be important strategies to support people to practically implement advice, to help frame public understanding, and to generate support for healthy public policy, but their impact on dietary intake alone is small and may be lowest in vulnerable groups. More recently, many countries have developed voluntary codes of practice in conjunction with the food industry, for example reduction in sugar intake, but these have not been demonstrated to achieve desirable levels of change.

Increasingly, it is recognized that government regulatory measures, such as product nutrient specification, and fiscal interventions can be used to successfully affect dietary patterns, but industry opposition can influence the design of optimal programmes. Actions by governments should be monitored, and accountability mechanisms should be in place at the local, national, and international levels [7]. Fiscal incentives and disincentives, such as food prices, subsidies, and financial rewards and penalties, are considered to be positive approaches in changing dietary behaviours, notably when implemented as part of an integrated package of mutually reinforcing activities, such as education and marketing. However, the level of financial impact needed to improve health outcomes needs to be carefully assessed. Implementing regulations for food composition (e.g. maximum limits) and standards for product availability (e.g. trans fatty acids and salt) for use in food marketing and procurement (such as in local and national government catering settings, worksites, nurseries, schools, and food assistance programmes), accompanied by mandatory labelling, can have a significant effect on population dietary patterns [8]. The impact is likely to be greatest when regulatory rather than voluntary approaches are used [9].

Beverages

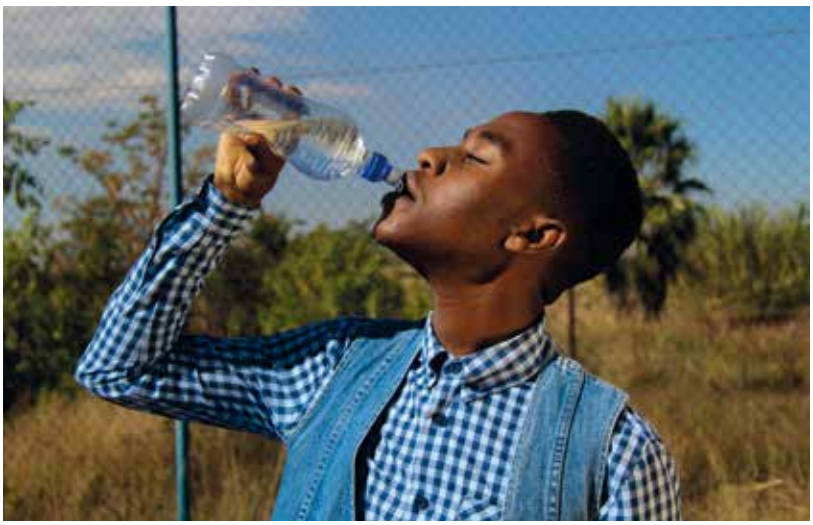
Caloric beverages can make a significant contribution to excess energy intake and the development of weight gain, or may decrease appetite for more nutrient-dense foods, thus decreasing dietary quality. In addition, alcoholic beverages are of concern because of the established association between alcohol consumption and the incidence of cancer at several sites (see Chapter 2.3).

Sugar-sweetened beverages

Consumption of sugar-sweetened beverages is associated with weight gain, overweight, and obesity, which increase the risk of cancer. Health promotion efforts – including nutrient regulations in schools, bans on vending machines, nutrition education, and provision of access to safe drinking-water – have been associated with modest reductions in consumption in many countries. However, intakes remain high, notably in children (compared with adults) and in groups with lower socioeconomic status. Sales of sugar-sweetened beverages are continuing to increase in low- and middle-income countries; this is most likely to be related to the low cost, large unit size, and marketing.

Recent efforts have focused on the additional, population-wide strategy of introducing taxes on sugar-sweetened beverages, with the aims of decreasing consumption, encouraging beverage companies to reformulate their products, and generating income to support public health. Taxes are commonly identified as the single most important policy approach for reducing intakes of sugar-sweetened beverages. Although taxes are financially regressive for low-income groups, this financial impact can be balanced by using tax revenues to reduce the prices of healthier food options [10]. It is estimated that in 2018 at least 26 countries had introduced a sugar tax, with a significant impact on purchases. For example, in 2014 Mexico introduced an

Fig. 6.2.3. A young man in South Africa drinking water. Reducing consumption of sugar-sweetened beverages is a positive step towards a healthier diet.



excise tax of 10% on sugar-sweetened beverages, accompanied by campaigns to raise awareness of the association between consumption of sugar-sweetened beverages and diabetes; this was followed by an average decrease of 7.6% in purchases of taxed beverages in 2014 and 2015 [11].

Alcohol

Reviews of approaches to reduce alcohol consumption indicate that the most cost-effective strategies include taxes that increase prices, restrictions on the physical availability of alcohol, drink–driving laws, brief interventions with at-risk drinkers, and the treatment of drinkers with alcohol dependence [12].

Data from natural experiments suggest that the level of price restriction is important and that similar interventions can have different effects depending on context and culture [13]. The effects are influenced by availability and licensing, acceptability of alcohol use within society, marketing (including sponsorship), and labelling information (i.e. alcohol content, calories, serving size). Changing consumer attitudes and norms about alcohol consumption and garnering support for comprehensive policy approaches may be challenging in contexts where knowledge levels about the association between alcohol consumption and cancer risk are low [14]. Opportunities to provide warning labels related to cancer are considered to be a useful avenue to raise awareness of cancer risk, although such approaches are not supported by the alcohol industry.

At the individual level, opportunistic screening (assessment of alcohol consumption) in primary care and other health-care settings, followed by brief interventions, is an effective approach, which has been demonstrated to have a moderate effect on reducing alcohol consumption and increasing the number of people drinking alcohol below levels associated with increased risk. Brief interventions with multiple contacts or follow-up sessions appear to be the most effective [15].

The approaches considered to be the least effective in decreasing alcohol consumption are education in schools, public service announcements, and voluntary regulation by the alcohol industry [16].

Physical activity

Consistent with the new Driving Action policy framework from World Cancer Research Fund International [2], evidence suggests that health-enhancing environments and behaviour change communications are key components for increasing physical activity. In addition, a systems approach is needed to provide a structural framework for national and local action. Examples include government policies that ensure adequate and affordable access to and use of natural environments for activity, recreation, and play.

A 2012 review of physical activity interventions around the world reported that initiatives to promote physical activity can have increased effectiveness when health agencies form partnerships and coordinate efforts with several stakeholders: schools; businesses; policy, advocacy, nutrition, recreation, planning, and transport agencies; and health-care organizations [17]. Positive effects were also reported from environmental and policy approaches that include the creation or enhancement of access to places to be active, through infrastructural initiatives such as community-scale and street-scale urban design and land use, an active transport policy and practices, and community-wide policies and planning [17].

The same review recommended the informational approaches of community-wide and mass media campaigns, as well as short messages about physical activity targeting key community sites. Given the importance of social support, behavioural and social approaches are effective for increasing physical activity within communities, neighbourhoods, and worksites. For children, school-based strategies that encompass physical education, classroom activities, after-school sports, and active transport can produce positive impacts. A key message from the review is that although individuals need to be informed and motivated to adopt physical activity, the public health priority should be to ensure that environments are safe and supportive of health and well-being. In

Fig. 6.2.4. Young men playing football on the beach in Rio de Janeiro, Brazil.

Fig. 6.2.5. Women and girls participating in a free public yoga course held every December morning in Yangon, Myanmar.

addition, the authors noted that to properly support initiatives for the promotion of physical activity, workforces need to be trained in physical activity and health, core public health disciplines, and methods of intersectoral collaboration [17].

More recently, a review of intervention studies in low- and middle-income countries highlighted that although the number of interventions is increasing, the challenge is greater because the prevalence of physical inactivity is higher in urban versus rural communities at a time when there is a rising global trend towards urbanization [18]. The review of intervention studies in low- and middle-income countries, including examples from the Islamic Republic of Iran, China, India, South Africa, and Vanuatu, reported an increasing number of promising approaches, including community-wide campaigns (e.g. using multiple communication media to raise programme awareness), strategies that include social support (e.g. walking groups), and school-based programmes, although not all of these approaches were found to be effective.

There is increasing evidence of the effectiveness of community-wide policies and planning to enhance physical activity in built environments, such as limiting street access to cars, increasing access to cyclists and pedestrians, and improving walkability, especially when combined with promotional efforts. In addition, although most countries have adopted national physical activity policies and plans, major challenges with implementation are evident. In low- and middle-income countries, resources to scale up effective interventions and train workforces in physical activity will compete with other healthcare demands.

Sedentary behaviour

Research on changing sedentary behaviour (i.e. time spent sitting) in the workplace, during leisure time, commuting, and in the household is relatively recent (see Chapter 2.7). Several reviews have highlighted that interventions that target both physical activity and sedentary behaviour are generally ineffective in changing time spent sitting [19]. This finding underlines the importance of an intervention having a primary aim of reducing sedentary behaviour; otherwise, effects on this outcome tend to be small.

Current evidence from behaviour change studies indicates that environmental restructuring, persuasion, education, and training generally show promise in reducing sedentary behaviour. A recent systematic review evaluated the evidence from randomized controlled trials on the effectiveness of workplace interventions to reduce time spent sitting at work [20]. The review concluded that sit–stand desks are effective in reducing sitting time at work, total sitting time, and duration of sitting bouts. In addition, short breaks (1–2 minutes

Fig. 6.2.6. Using a standing workstation effectively reduces sitting time at work.

every 30 minutes) were more effective than long breaks (two 15-minute breaks per workday) in the short term. Computer prompting resulted in decreases in the average number and duration of sitting bouts lasting 30 minutes or more [20].

In randomized controlled trials, interventions to reduce non-occupational sedentary behaviour have been shown to be effective in adults. The current evidence suggests that use of technology to reduce sedentary time (e.g. alerting the user to accumulated time spent sedentary), use of specific behaviour change techniques (e.g. self-monitoring), or a combination of both are characteristics of effective programmes [21]. Reduced television viewing, computer use, and total transport-related sitting time and the use of smart technologies need further investigation, and these are promising areas for further investigation.

Obesity

Excess body fat results from an imbalance between energy consumed from food and beverages and energy expenditure, notably through physical activity. Data from weight-loss studies clearly show that energy intake is the most important driver for achieving changes in energy balance, although physical activity is also important. Review-level evidence demonstrates that combined diet plus physical activity interventions can result in a loss of 8–11% of body weight within 6 months, whereas moderate- to high–intensity interventions without reduction in energy intake achieve a loss of about 2–3% of body weight within the same period [22]. Physical activity is considered particularly helpful in maintenance of weight loss.

The global burden of obesity highlights an urgent need to identify and implement policies that will have an impact on prevention and management. To date, no country has reversed the obesity epidemic in its population, and evidence on effective national programmes is lacking. Much of the work in this arena has been focused on tackling childhood obesity, given the burden of noncommunicable diseases that are now presenting in adolescence. However, many children who are overweight also have parents who are overweight, and the adult world shapes what children see and respond to. Societal actions that have favourable impacts on vulnerable groups of all ages and backgrounds offer the greatest potential for equitable effects.

Tackling obesity is more complex than addressing either energy intake or energy expenditure, and there are no simple solutions. Approaches that tackle both environmental factors, which support or undermine the ability of people to participate in healthful behaviours, and individual action are desirable. Roberto et al. [23] highlighted how food environments exploit people's biological, psychological, social, and economic vulnerabilities, making it easier for them to eat processed foods and follow unhealthy dietary patterns (see Chapter 2.6). This situation reinforces preferences and demands for foods of poor nutritional quality, thus maintaining unhealthy food environments.

Approaches by governments to address obesity have tended to focus on one or two target areas and lack the comprehensive approach needed for sustainable behaviour change. It is clear that relevant policy actions for addressing obesity need to be identified in a systematic manner. The Food Environment Policy Index [24], which offers a useful tool for developing consensus for action, has been used in Thailand, New Zealand, Australia, and England. For example, in England the top-priority policy actions identified for government were those that affect both children and adults: (i) control the advertising of unhealthy foods to children; (ii) implement the levy on sugary beverages; (iii) reduce the sugar, fat, and salt content in processed foods; (iv) monitor school and nursery food standards; (v) prioritize health and the environment in the 25-year Food and Farming Plan; (vi) adopt a national food action plan; (vii) monitor the food environment; (viii) apply buying standards to all public institutions; (ix) strengthen planning laws to discourage less-healthy food offers; and (x) evaluate food-related programmes and policies [25].

The combined forces of regulatory actions from governments and increased efforts from industry and civil society will be necessary to address obesity (see Chapter 6.9). Public advocacy efforts [26] (including those from cancer organizations) are considered to be a key component in creating demand and support for effective obesity policies and in mitigating reaction against their implementation. Important issues for obesity coalitions to address include challenges from the food and beverage industry and ways to avoid stigmatization by insensitive programmes and campaigns, and thus lose support for obesity programmes by civil society.

References

1. Marmot M (2018). Diet, cancer, and NCD prevention. Lancet Oncol. 19(7):863–4. https://doi.org/10.1016/S1470-2045(18)30382-6 PMID:29803702

2. World Cancer Research Fund International (2018). Driving action to prevent cancer and other non-communicable diseases: a new policy framework for promoting healthy diets, physical activity, breastfeeding and reducing alcohol consumption. Available from: https://www.wcrf.org/sites/default/files/driving-action.pdf.

3. Anderson AS, Mackison D, Boath C, Steele R (2013). Promoting changes in diet and physical activity in breast and colorectal cancer screening settings: an unexplored opportunity for endorsing healthy behaviors. Cancer Prev Res (Phila). 6(3):165–72. https://doi.org/10.1158/1940-6207.CAPR-12-0385 PMID:23324132

4. Puska P, Vartiainen E, Nissinen A, Laatikainen T, Jousilahti P (2016). Background, principles, implementation, and general experiences of the North Karelia Project. Glob Heart. 11(2):173–8. https://doi.org/10.1016/j.gheart.2016.04.010 PMID:27242083

5. Aziz Z, Absetz P, Oldroyd J, Pronk NP, Oldenburg B (2015). A systematic review of real-world diabetes prevention programs: learnings from the last 15 years. Implement Sci. 10(1):172. https://doi.org/10.1186/s13012-015-0354-6 PMID:26670418

6. Hawkes C, Smith TG, Jewell J, Wardle J, Hammond RA, Friel S, et al. (2015). Smart food policies for obesity prevention. Lancet. 385(9985):2410–21. https://doi.org/10.1016/S0140-6736(14)61745-1 PMID:25703109

7. Swinburn B, Kraak V, Rutter H, Vandevijvere S, Lobstein T, Sacks G, et al. (2015). Strengthening of accountability systems to create healthy food environments and reduce global obesity. Lancet. 385(9986):2534–45. https://doi.org/10.1016/S0140-6736(14)61747-5 PMID:25703108

8. Mytton OT, Clarke D, Rayner M (2012). Taxing unhealthy food and drinks to improve health. BMJ. 344:e2931. https://doi.org/10.1136/bmj.e2931 PMID:22589522

9. Mozaffarian D, Angell SY, Lang T, Rivera JA (2018). Role of government policy in nutrition – barriers to and opportunities for healthier eating. BMJ. 361:k2426. https://doi.org/10.1136/bmj.k2426 PMID:29898890

10. Knai C, James L, Petticrew M, Eastmure E, Durand MA, Mays N (2017). An evaluation of a public–private partnership to reduce artificial trans fatty acids in England, 2011–16. Eur J Public Health. 27(4):605–8. https://doi.org/10.1093/eurpub/ckx002 PMID:28339665

11. Álvarez-Sánchez C, Contento I, Jiménez-Aguilar A, Koch P, Gray HL, Guerra LA, et al. (2018). Does the Mexican sugar-sweetened beverage tax have a signaling effect? ENSANUT 2016. PLoS One. 13(8):e0199337. https://doi.org/10.1371/journal.pone.0199337 PMID:30133438

12. Alcohol and Public Policy Group (2010). Alcohol: no ordinary commodity – a summary of the second edition. Addiction. 105(5):769–79. https://doi.org/10.1111/j.1360-0443.2010.02945.x PMID:20331569

13. Nelson JP, McNall AD (2017). What happens to drinking when alcohol policy changes? A review of five natural experiments for alcohol taxes, prices, and availability. Eur J Health Econ. 18(4):417–34. https://doi.org/10.1007/s10198-016-0795-0 PMID:27055901

14. Buykx P, Li J, Gavens L, Hooper L, Lovatt M, Gomes de Matos E, et al. (2016). Public awareness of the link between alcohol and cancer in England in 2015: a population-based survey. BMC Public Health. 16(1):1194. https://doi.org/10.1186/s12889-016-3855-6 PMID:27899099

15. Álvarez-Bueno C, Rodríguez-Martín B, García-Ortiz L, Gómez-Marcos MÁ, Martínez-Vizcaíno V (2015). Effectiveness of brief interventions in primary health care settings to decrease alcohol consumption by adult non-dependent drinkers: a systematic review of systematic reviews. Prev Med. 76(Suppl):S33–8. https://doi.org/10.1016/j.ypmed.2014.12.010 PMID:25514547

16. WHO (2011). Reducing risks and preventing disease: population-wide interventions. In: Global status report on noncommunicable diseases 2010. Geneva, Switzerland: World Health Organization; pp. 47–60.

17. Heath GW, Parra DC, Sarmiento OL, Andersen LB, Owen N, Goenka S, et al.; *Lancet* Physical Activity Series Working Group (2012). Evidence-based intervention in physical activity: lessons from around the world. Lancet. 380(9838):272–81. https://doi.org/10.1016/S0140-6736(12)60816-2 PMID:22818939

18. Sallis JF, Bull F, Guthold R, Heath GW, Inoue S, Kelly P, et al.; *Lancet* Physical Activity Series 2 Executive Committee (2016). Progress in physical activity over the Olympic quadrennium. Lancet. 388(10051):1325–36. https://doi.org/10.1016/S0140-6736(16)30581-5 PMID:27475270

19. Howlett N, Trivedi D, Troop NA, Chater AM (2019). Are physical activity interventions for healthy inactive adults effective in promoting behavior change and maintenance, and which behavior change techniques are effective? A systematic review and meta-analysis. Transl Behav Med. 9(1):147–57. https://doi.org/10.1093/tbm/iby010 PMID:29506209

20. Shrestha N, Kukkonen-Harjula KT, Verbeek JH, Ijaz S, Hermans V, Pedisic Z (2018). Workplace interventions for reducing sitting at work. Cochrane Database Syst Rev. (6):CD010912. https://doi.org/10.1002/14651858.CD010912.pub4 PMID:29926475

21. Thraen-Borowski KM, Ellingson LD, Meyer JD, Cadmus-Bertram L (2017). Nonworksite interventions to reduce sedentary behavior among adults: a systematic review. Transl J Am Coll Sports Med. 2(12):68–78. PMID:28993817

22. Chin SH, Kahathuduwa CN, Binks M (2016). Physical activity and obesity: what we know and what we need to know. Obes Rev. 17(12):1226–44. https://doi.org/10.1111/obr.12460 PMID:27743411

23. Roberto CA, Swinburn B, Hawkes C, Huang TT, Costa SA, Ashe M, et al. (2015). Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. Lancet. 385(9985):2400–9. https://doi.org/10.1016/S0140-6736(14)61744-X PMID:25703111

24. Swinburn B, Sacks G, Vandevijvere S, Kumanyika S, Lobstein T, Neal B, et al.; INFORMAS (2013). INFORMAS (International Network for Food and Obesity/non-communicable diseases Research, Monitoring and Action Support): overview and key principles. Obes Rev. 14(Suppl 1):1–12. https://doi.org/10.1111/obr.12087 PMID:24074206

25. Watson F, Taylor A, Rayner M, Lobstein T, Hinks R (2018). Priority actions for addressing the obesity epidemic in England. Public Health Nutr. 21(5):1002–10. https://doi.org/10.1017/S1368980017003500 PMID:29233230

26. Huang TT, Cawley JH, Ashe M, Costa SA, Frerichs LM, Zwicker L, et al. (2015). Mobilisation of public support for policy actions to prevent obesity. Lancet. 385(9985):2422–31. https://doi.org/10.1016/S0140-6736(14)61743-8 PMID:25703113

6.3 Vaccination
The prospect of eliminating some cancer types

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SUMMARY

- Hepatitis B virus (HBV) infection is very common in some areas of the world. In 2016, an estimated 292 million people were living with chronic HBV infection worldwide. HBV infection is also responsible for approximately 1 million deaths per year.
- Highly effective vaccines against HBV infection have been available since 1982. By 2016, 185 countries had introduced HBV vaccination, and vaccination coverage in children had reached 87% globally.
- HBV vaccination of babies at birth is necessary to prevent mother-to-child transmission, but more than half of the world's children fail to receive a birth dose.
- Thirteen high-risk human papillomavirus (HPV) types, particularly HPV type 16, cause cervical cancer (about 570 000 new cases per year in 2018) and anal cancer, and substantial fractions of cancers of the vulva, vagina, penis, and oropharynx.
- Three prophylactic vaccines, consisting of empty viral capsids of HPV types 16 and 18, alone or with an additional two or seven types, have been available since 2006. By 2018, 85 countries had established HPV vaccination programmes.
- Comprehensive data document the safety and high efficacy of HPV vaccines, especially in adolescent girls, who are the priority target for HPV vaccination.
- Anti-vaccination campaigns and the relatively high cost, coupled with the necessarily protracted time frame to cancer prevention, hamper adequate coverage and universal implementation of HPV vaccination.

A notable fraction of cancer cases in humans (~15%) are caused by infections [1], and these are largely amenable to effective preventive interventions. Among the most important infections associated with cancers are human papillomavirus (HPV), *Helicobacter pylori* (see Chapters 2.2 and 5.4), hepatitis B virus (HBV), and hepatitis C virus (HCV). To date, only cancers related to HPV and HBV can be prevented through vaccination. Because of the long latency between the occurrence of infection and the diagnosis of cancer, data on efficacy against invasive cancers remain limited, but findings on precancerous lesions and viral end-points are extremely favourable and robust.

Chronic infection with HBV is one of the most important causes of liver cancer, particularly in highly endemic areas such as sub-Saharan Africa, the Amazon basin, China, the Republic of Korea, and countries in South-East Asia [2]. In 2018, there were an estimated 841 000 new cases of liver cancer and 781 000 deaths from liver cancer worldwide [3]. Vaccines against HBV have been available for several decades, and their efficacy in preventing chronic HBV infection and liver cancer has been clearly demonstrated in children and adolescents. It is expected that HBV vaccination will nearly eliminate HBV-associated liver cancer in many areas when the vaccinated populations reach adulthood [4].

HPV is the most common sexually transmitted virus. Infection typically resolves asymptomatically within 1–2 years, but certain types of HPV (called oncogenic types) can cause cancers of the cervix, anus, vulva, vagina, penis, and oropharynx over extended time periods in individuals in whom HPV infection is not cleared by the immune system. Highly effective vaccines have been available since 2006 to prevent infection by HPV16 and HPV18, which are the most oncogenic types and are responsible for most HPV-related cancers. Recently, a vaccine has become available that also targets oncogenic types HPV31, 33, 45, 52, and 58.

The efficacy and cost–effectiveness of the HPV vaccine are greatest in previously unexposed women. Therefore, HPV vaccination is preferentially recommended for pre-adolescent girls. By 2018, 85

countries had established HPV vaccination programmes [5]. However, most girls in low- and middle-income countries, who are at highest risk of cervical cancer, are not yet immunized [6]. HPV vaccines are efficacious at preventing infections and lesions not only in the cervix but also at other anatomical sites where they have been investigated, but only global high-coverage mass vaccination programmes are expected to reduce the incidence of and mortality from cancers associated with vaccine-targeted HPV types in the next few decades [7].

This chapter summarizes the epidemiological features of HBV and HPV infections and the performance of vaccines against these infections and the associated cancers, with a focus on the large amounts of data that have accumulated in the past 5 years.

Hepatitis B virus

Hepatitis B virus and liver cancer

HBV is a highly contagious DNA virus that is transmitted by exposure to HBV-contaminated blood and other body fluids, including semen and vaginal fluids [8]. The virus is transmitted from mother to infant and from child to child, as well as by unsafe injections, sexual contact, and blood transfusions. Perinatal transmission from infected mothers to their newborn babies or from one child to another is very common in highly endemic areas, and HBV can also be transmitted by fomites [8]. HBV infection is a major global health problem. In 2016, an estimated 292 million people were chronically infected with HBV, i.e. about 3.9% (uncertainty interval, 3.4–4.6%) of the world's population [9].

Chronic HBV infection, through persistent inflammation, liver necrosis, and regenerative proliferation, may eventually lead to cirrhosis and hepatocellular carcinoma. About 80% of hepatocellular carcinomas develop in cirrhotic livers. The risk of chronic HBV infection is greatest if transmission occurs during birth and early childhood. Overall, up to 40% of men and 15% of women with a perinatally acquired HBV infection will die of liver cirrhosis or hepatocellular carcinoma [10].

In high-risk areas, HBV is responsible for 50–80% of cases of liver cancer [11].The attributable fractions for liver cancers due to HBV and HCV vary substantially by country (Fig. 6.3.1) [2]. HBV causes about two thirds of liver cancer cases in less-developed countries but only about one quarter of cases in more-developed countries. For HCV-attributable cases, the pattern is nearly opposite.

Hepatitis B virus vaccine

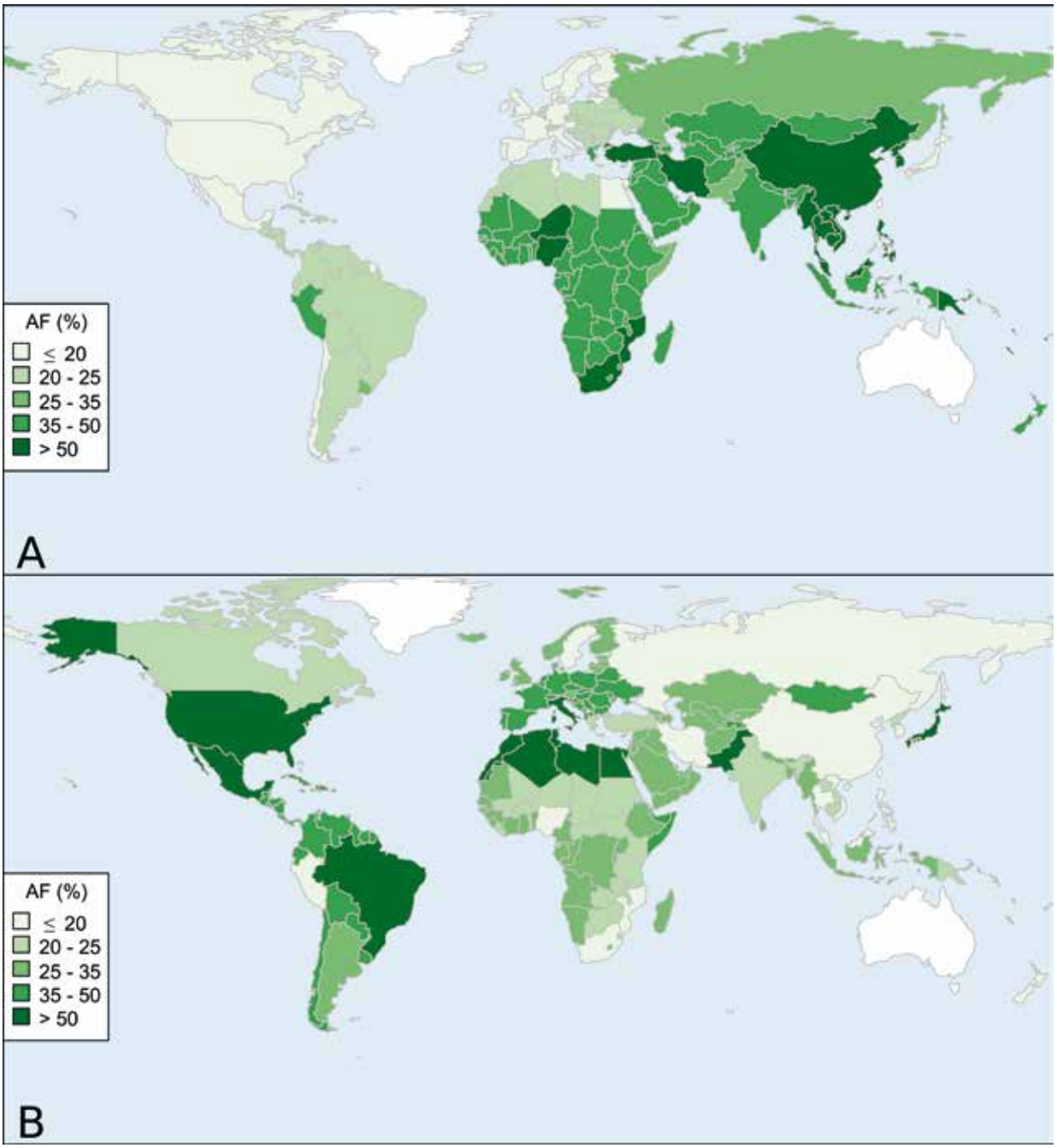
The HBV vaccine was the first vaccine designed to prevent a major human cancer type [12]. A highly effective vaccine has been available since 1982, but worldwide vaccination only ramped up after GAVI, the Vaccine Alliance, started supporting HBV vaccine in 2001 [8]. The current vaccine is a recombinant HBV surface antigen (HBsAg) produced in yeast or mammalian cells into which the HBsAg gene is inserted using plasmids. The vaccine, administered as a three-dose series, is highly safe and 95% effective in preventing HBV infection and its chronic consequences. In settings with a high prevalence of HBV infection, the first dose should be given to newborn babies as soon as possible after birth, to prevent mother-to-child transmission.

The introduction of HBV vaccination programmes has resulted in a decrease in the incidence of HBV infection and hepatocellular carcinoma [10] (see Chapter 5.6). In Taiwan, China, where a nationwide HBV vaccination programme for newborn babies was started in 1983, the proportion of children who were seropositive for HBsAg decreased from 10% before the vaccination programme started to 0.5% in 2009 [13]. The reduction in prevalence was accompanied by a 70% reduction in the incidence of liver cancer in children and adolescents [14].

FUNDAMENTALS

- In some low-income countries, up to one third of all cases of cancer are directly associated with various infections. This offers the prospect of prevention through vaccination.
- The hepatitis B virus (HBV) vaccine was the first vaccine designed to prevent a major human cancer type. The vaccine can safely and effectively be administered simultaneously with many other routine childhood immunizations.
- One of the first nationwide HBV vaccination programmes was implemented in Taiwan, China, and has resulted in a marked decrease in the incidence of hepatocellular carcinoma.
- Prevention of chronic HBV infection through vaccination is anticipated to result in decreases in the rates of liver cancer, but several decades will be required to confirm this outcome.
- Prophylactic human papillomavirus (HPV) vaccines were initially developed to prevent infection with a small number of oncogenic HPV types. The scope and effectiveness of such vaccines has improved, by expanding the range of types covered and because of unforeseen cross-protection against related types.
- Nationwide HPV vaccination of adolescent girls (in some cases, together with boys) in some countries is now recognized as offering, in combination with cervical screening, the prospect of the elimination of cervical cancer as a public health problem.
- HPV vaccination can also prevent a fraction of cases of cancer of the anus, vulva, vagina, penis, and oropharynx.

Fig. 6.3.1. Attributable fraction (AF) for liver cancers due to (A) hepatitis B virus (HBV) and (B) hepatitis C virus (HCV).



In the USA, the incidence of acute HBV infection decreased by 81% between 1990 and 2006 [15].

By 2016, 185 countries had introduced HBV vaccination, and three-dose vaccination coverage in children had reached 87% globally [9]. There have been favourable trends in HBV vaccine coverage in all WHO regions (Fig. 6.3.3), with a major increase in coverage at the beginning of the 21st century [4]. In 2016, vaccine coverage was still low (≤ 80%) in some high-risk populations, such as in Kenya, the Central African Republic, Chad, Gabon, Mali, Nigeria, Haiti, Guatemala, Iraq, the Syrian Arab Republic, and Papua New Guinea [9].

The recommended introduction of universal HBV vaccination of babies at birth has been successful in far fewer countries. In 2016, coverage of birth dose of HBV vaccine

Fig. 6.3.2. An eight-week-old baby is vaccinated against eight antigens, including hepatitis B virus (HBV), at the Madarounfa Health Centre in Niger.

was estimated to be 46% globally and only 10% in sub-Saharan Africa [9,16]. The United Nations included combating viral hepatitis in the Sustainable Development Goals, with the target of achieving 90% global coverage of birth dose by 2030. Because of the increasing efficacy and the decreasing cost of antiviral treatments for HBV and HCV infection, WHO also has an aim of identifying and treating at least 80% of chronic carriers of HBV and HCV infections by 2030 [9].

Human papillomaviruses

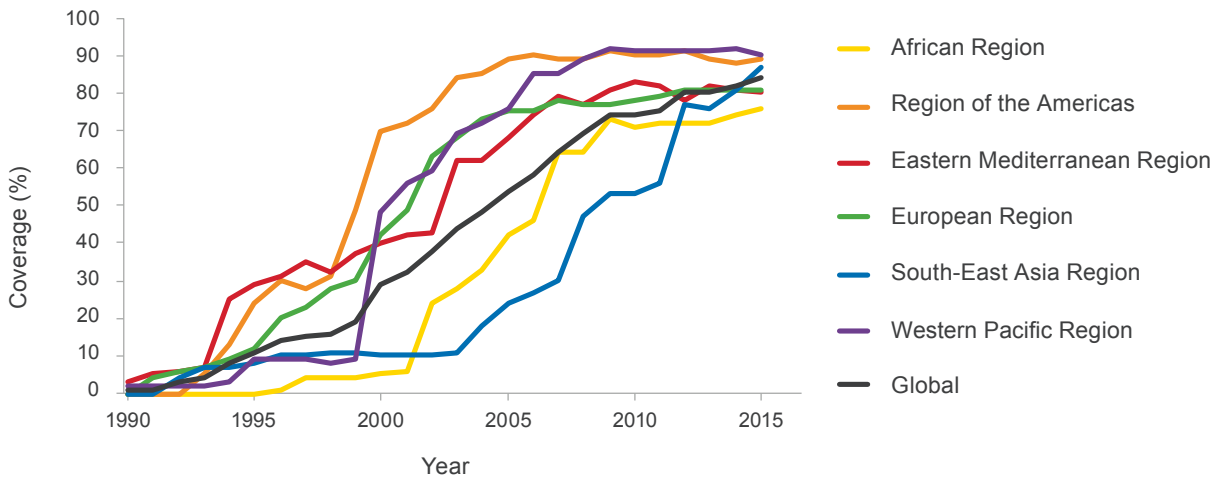
Human papillomaviruses and cancer

HPV is a sexually transmitted infection that is acquired by most women and men shortly after the onset of sexual activity. HPV infection is considered a necessary cause of cervical cancer (see Chapter 5.10). In 2018, there were an estimated 570 000 new cases of cervical cancer and 311 000 deaths from cervical cancer worldwide, 95% of which occurred in less-developed countries [3]. Multiple epidemiological studies over the past three decades have confirmed the carcinogenicity of 13 oncogenic types in cervical cancer (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and probably 68). Types HPV16 and HPV18 are detectable in about 70% of cervical cancers, with little variation around the world [17].

Substantial fractions of other cancer types, including cancers of the anus (88%), vulva and vagina (41%), penis (50%), and oropharynx (30%), are also attributable to HPV, nearly always due to type HPV16 [17]. The relative importance of HPV in oropharyngeal cancer is much greater in more-developed countries in which the prevalence of tobacco use has been declining. Non-cervical cancers account for about 100 000 HPV-related cases per year globally. The incidence of HPV-associated cancers is especially high in immunodeficient individuals, especially anal cancer in HIV-positive men who have sex with men.

The natural history and molecular mechanisms involved in HPV carcinogenesis are best understood in the cervix [7]. The most common morphological manifestation of HPV infection consists of minor epithelial abnormalities (equivocal and low-grade cellular changes). In a minority of women (~10%) in whom the infection is not cleared by the immune

Fig. 6.3.3. Three-dose hepatitis B virus (HBV) vaccine coverage, by WHO region, 1990–2015.



system, precancerous lesions (advanced intraepithelial neoplasia) can develop. If these lesions are not treated, they can lead to cervical cancer after many years, usually decades.

Human papillomavirus vaccines

Three subunit vaccines against HPV are currently available. All are composed of virus-like particles and are produced by expression of the HPV L1 gene in insect cells or yeast. The bivalent vaccine is against HPV16 and HPV18. The quadrivalent vaccine also includes HPV6 and HPV11, which are the cause of most genital warts, and the more recent nonavalent vaccine also targets HPV31, 33, 45, 52, and 58.

HPV vaccines also differ by the adjuvant. An alum adjuvant is used in the quadrivalent and nonavalent vaccines, and a complex adjuvant system (ASO4) consisting of monophosphoryl lipid A and alum is used in the bivalent vaccine.

Vaccine efficacy and safety

A systematic review [18] combined published and unpublished findings from 26 randomized controlled trials that included a placebo or other vaccine control arm and involved a total of 73 428 women, mainly aged 15–26 years, with a follow-up of 1.3–8 years.

Vaccine efficacy and the corresponding 95% confidence intervals (CIs) against cervical intraepithelial neoplasia grade 2 and above (CIN2+), and adenocarcinoma in situ were evaluated by computing risks in the vaccination group versus the control group separately by women's HPV DNA status, i.e. the presence of oncogenic HPV infection at vaccination. In HPV-negative women aged 15–26 years, vaccines reduced the risk of CIN2+ associated with HPV16/18 from 164 to 2 per 10 000 (vaccine efficacy, 99%; 95% CI, 95–100%). Vaccine efficacy was about 90% also for relatively rare adenocarcinoma in situ (Table 6.3.1). Among all young women, regardless of baseline HPV status, the risk of CIN2+ associated with HPV16/18 fell from 341 to 157 per 10 000 (vaccine efficacy, 54%; 95% CI, 43–63%). Reductions in risk for the most severe precancer (CIN3+) were consistent with those for CIN2+ [18].

Vaccines also prevented CIN2+ in HPV-negative women vaccinated at age 24–45 years. However, the protection against HPV16/18-associated CIN2+ of all women, regardless of baseline HPV status, was weaker than that in younger women and was not statistically significant (vaccine efficacy, 26%; 95% CI, −5% to 48%); the lower frequency of CIN2+ in this age group was noted [18].

The risk of serious adverse events, including autoimmune diseases, was similar in the vaccinated and control groups (relative risk, 0.94; 95% CI, 0.72–1.06) [18]. Total death rates were similar (11 per 10 000 in the control group and 14 per 10 000 in the HPV vaccinated group), and no pattern in the cause or timing of death was detected. In addition, HPV vaccines did not significantly increase the risk of miscarriage, pregnancy termination, congenital abnormality, or stillbirth [18]. The effectiveness [19] and safety [20] of HPV vaccines continue to be monitored in many countries

Table 6.3.1. Efficacy of human papillomavirus (HPV) vaccines in women aged 15–26 years who were negative for oncogenic HPV infection at vaccination

Outcome	Anticipated absolute effects[a] (95% CI)		Vaccine efficacy (%) (95% CI)[c]	Number of participants (number of studies)
	Risk with placebo (per 10 000)	Risk with HPV vaccination[b] (per 10 000)		
CIN2+ associated with HPV16/18 Follow-up: 3–5 years	164	2 (0 to 8)	99 (95 to 100)	23 676 (3 RCTs)
CIN3+ associated with HPV16/18 Follow-up: 3–5 years	70	0 (0 to 7)	99 (90 to 100)	20 214 (2 RCTs)
AIS associated with HPV16/18 Follow-up: 3–5 years	9	0 (0 to 7)	90 (18 to 99)	20 214 (2 RCTs)
Any CIN2+ irrespective of HPV type, bivalent or quadrivalent vaccine Follow-up: 2–6 years	287	106 (72 to 158)	63 (45 to 75)	25 180 (5 RCTs)
Any CIN3+ irrespective of HPV type, bivalent or quadrivalent vaccine Follow-up: 3.5–4 years	109	23 (4 to 120)	79 (−10 to 96)	20 719 (3 RCTs)
Any AIS irrespective of HPV type Follow-up: 3–5 years	10	0 (0 to 8)	90 (24 to 99)	20 214 (2 RCTs)

AIS, adenocarcinoma in situ; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 and above; HPV, human papillomavirus, RCTs, randomized controlled trials.

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). When risk in the vaccinated group is zero, the 95% CI is computed using an exact binomial method.

[b] Assumed risk calculated from the sum of control group event rates.

[c] Vaccine efficacy (%) = (1 − relative risk)*100.

through population-based surveillance systems, ad hoc studies, and follow-up of trial participants.

The most recently licensed nonavalent HPV vaccine (not included in the systematic review [18]) was compared with the quadrivalent HPV vaccine in a randomized trial involving 14 215 women aged 15–26 years. The nonavalent HPV vaccine prevented infection and precancers related to HPV31, 33, 45, 52, and 58 and generated an antibody response to HPV6, 11, 16, and 18 that was non-inferior to that generated by the quadrivalent HPV vaccine [21]. In HPV-uninfected women, the efficacy of the nonavalent vaccine against CIN2+ associated with the nine targeted oncogenic HPV types was 100% (95% CI, 70.4–100%).

Both trial data [18] and population-based studies [22] demonstrate that the bivalent vaccine induces substantial and significant cross-protection against HPV31, 33, and 45 at least. Preliminary findings also suggest that the vaccines can prevent HPV infection in the entire anogenital tract and in the mouth [23].

Doses

The initial recommendation for HPV vaccination was a three-dose schedule for everybody. A significant development to improve population coverage was the endorsement by WHO in 2014 of two-dose instead of three-dose schedules up to age 15 years, supported by stronger immune responses in children and adolescents than in young women [24]. One-dose-only vaccination could greatly further augment the feasibility and affordability of mass vaccination (see Chapter 4.4). The earliest non-randomized evidence that one dose of vaccine could provide durable protection against HPV infection came from the Costa Rica Vaccine Trial [25]. The antibody levels after one dose, although lower than the levels elicited by three doses, were 9 times as high as the levels elicited by natural infection. A formal randomized controlled trial and other complementary studies to further document the long-term non-inferiority of one dose are under way [25].

Immunization rates

Between 2006 and 2014, 64 countries implemented national HPV vaccination programmes, but vaccine uptake varies widely across and within countries [6].

Nearly all European countries offer HPV vaccination [26]. The average time between first vaccine authorization and universal mass vaccination was 36 months, ranging from 5 months in Spain to 117 months in Croatia. The target age is generally 12–13 years, but some countries recommended starting at older ages or including several birth cohorts in the first rounds. Immunization rates ranged from 14.1% in Bulgaria to 85.9% in the United Kingdom. Coverage of less than 30% was reported in eastern European countries, Greece, and France, but the accuracy of vaccination monitoring also varies greatly in Europe [26].

In the USA, the HPV vaccines were recommended for girls in 2006 and for boys in 2011, but uptake has been slow compared with that for other adolescent vaccines [27]. According to a nationwide database of medical billings, in 2014 cumulative vaccination coverage of one or more doses by age 18 years was 53.3% in girls and 30.3% in boys. Although coverage is still lower in boys, the ramp-up in vaccination in boys was quicker than that in girls, which indicates good acceptability. Immunization rates were found to be substantially affected by area of residence and type of health insurance. Vaccination at later than age 12 years was frequent among girls in the USA, and vaccination is administered by a variety of providers: paediatricians, family doctors, and gynaecologists.

In Australia, 80.1% of girls and 74.1% of boys aged 15 years had been fully vaccinated in 2015–2016, thanks to an especially strong societal advocacy and a close interaction between school-based vaccination and active recall of girls and boys who had missed a dose in school [28].

National programmes exist in many low-income countries in Latin America, but not yet in India, China, and most countries in Africa [6]. Bhutan, Malaysia, and Rwanda pioneered the implementation of HPV vaccination [24] before GAVI started supporting HPV vaccine in 2012. Since then, more than 30 GAVI-eligible countries have started implementing vaccination [29] and have achieved good levels of participation (> 70%) in the targeted girls [30]. However, the GAVI target of vaccinating 40 million girls in the lowest-income countries by 2020 is considered to be at risk, because of a slow ramp-up from demonstration projects to national programmes and because of challenges with the supply of vaccines [5].

Conclusions

Despite the effectiveness and safety of HPV vaccines, anti-vaccination campaigns and the relatively high cost, coupled with the delayed benefits of anti-cancer vaccines, hamper the universal implementation of HPV vaccination. There are projected to be 770 000 new cases of cervical cancer per year by 2040 [3]. To seize a unique opportunity to tackle a major disease in women, in 2018 the WHO Director-General, Dr Tedros Adhanom Ghebreyesus, made a call for coordinated global action against cervical cancer.

Modelling studies are being done to identify the best vaccination and screening strategy to eliminate cervical cancer as a public health problem [31]. The higher the pre-vaccination prevalence of HPV infection, the more difficult HPV elimination will be [32]. Fortunately, if coverage is equal, herd protection is predictably stronger against a sexually transmitted virus like HPV than it is against airborne and foodborne infections [33].

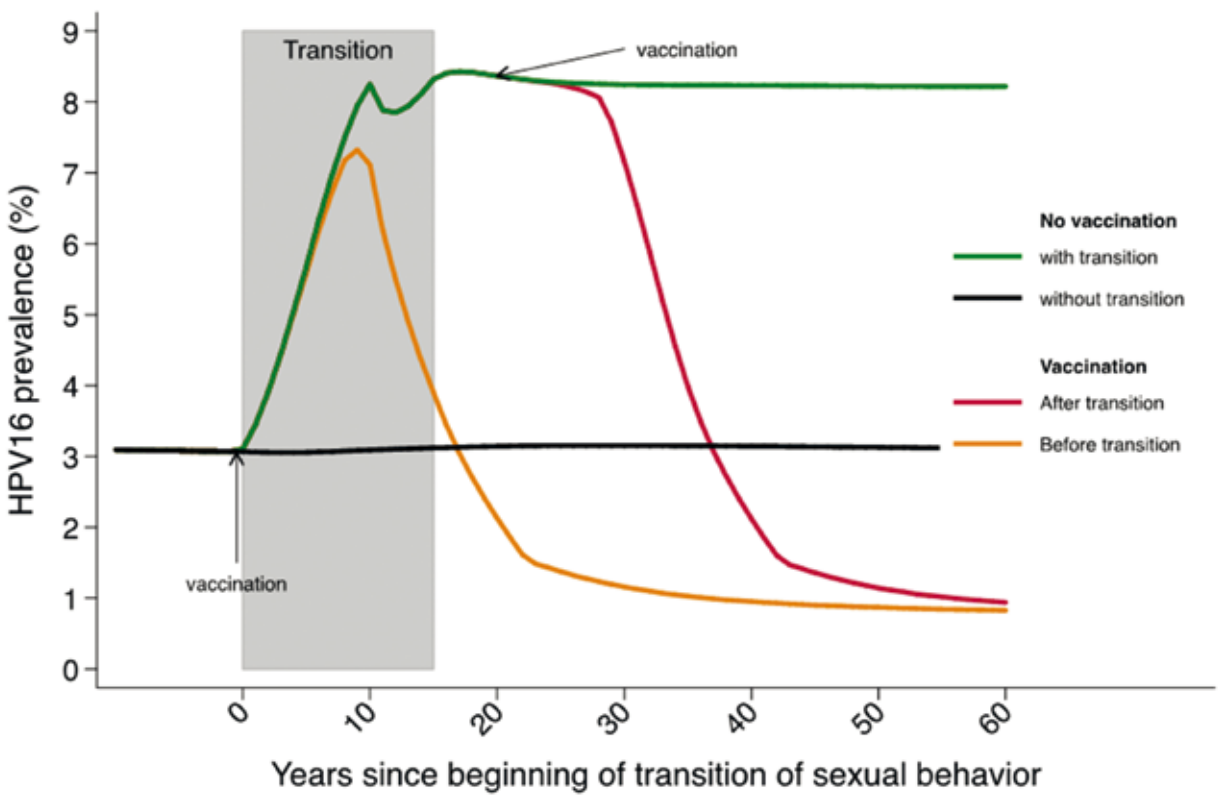
In the absence of vaccination, the prevalence of HPV16 infection may increase in populations in less-developed countries, as a

result of the transition from traditional to gender-similar age-related sexual behaviour, i.e. the sexual pattern that is most conducive to rapid spread of the infection in young people. A prompt introduction of HPV vaccination before the transition of sexual behaviour would decrease the prevalence of HPV16 infection, whereas introduction of vaccination after the transition would mean that vaccination will take longer to decrease the prevalence of HPV16 infection by the same amount (Fig. 6.3.4) [32].

Key factors to improve HPV vaccination coverage include educating communities – including adolescents, families, and health workers – and better addressing organizational and programme factors responsible for vaccine delivery and completion. The implementation of additional strategies to increase population-level protection, such as vaccinating older women or men, would be dependent on greatly reduced vaccine prices. Offering vaccination to multiple cohorts of girls, for example up to age 15 years or 18 years, is very cost-effective, even at current vaccine prices, and accelerates cervical cancer prevention. Beyond a certain age, vaccination remains attractive but has limited return, because of the age-related accumulation of persistent HPV infections whose fate is not ameliorated by the vaccines [34]. Gender-neutral vaccination is highly desirable to eliminate HPV from a population more rapidly, but it is less cost-effective than increasing the coverage or the number of birth cohorts in girls [33].

Because there are currently only two manufacturers of vaccines, a shortage of vaccines is threatening the global action of WHO [5]. Therefore, more abundant availability of fair-priced HPV vaccines greatly depends on the advent of new manufacturers in developing countries. Multivalent vaccines are ideal, but bivalent vaccines would be welcome, because of the preponderant role of HPV16/18 in the onset of HPV-associated cancer in the cervix and at other sites [17].

Fig. 6.3.4. Expected variations of vaccination effectiveness according to pre-vaccination HPV prevalence in women and changes in sexual behaviour. Changes in the prevalence of HPV16 among women aged 20–34 years in relation to the number of years since the beginning of a population's transition from traditional to gender-similar age-related sexual behaviour and the introduction of vaccination among girls aged 11 years (with an assumption of 70% coverage) before and after the transition. The shaded area shows an assumption of a 15-year transition period. The arrows show the approximate timing of the introduction of vaccination, before or after the transition. Traditional sexual behaviour indicates a population in which genders have different age-specific sexual activity rates and a wide gap in ages (e.g. an average of 5.6 years, as observed in India) of spouses or cohabitating sexual partners. Gender-similar sexual behaviour indicates a population in which genders have similar age-specific sexual activity rates and a narrow gap in ages (e.g. an average of 2.1 years, as observed in the USA) of spouses or cohabitating sexual partners.



References

1. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S (2016). Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 4(9):e609–16. https://doi.org/10.1016/S2214-109X(16)30143-7 PMID:27470177

2. Maucort-Boulch D, de Martel C, Franceschi S, Plummer M (2018). Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. Int J Cancer. 142(12):2471–7. https://doi.org/10.1002/ijc.31280 PMID:29388206

3. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. (2018). Global Cancer Observatory. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/.

4. WHO (2017). Global hepatitis report 2017. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/.

5. WHO (2018). Meeting of the Strategic Advisory Group of Experts on Immunization, October 2018 – conclusions and recommendations. Wkly Epidemiol Rec. 93(49):661–79. Available from: https://apps.who.int/iris/handle/10665/276545.

6. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, et al. (2016). Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. Lancet Glob Health. 4(7):e453–63. https://doi.org/10.1016/S2214-109X(16)30099-7 PMID:27340003

7. Schiffman M, Doorbar J, Wentzensen N, de Sanjosé S, Fakhry C, Monk BJ, et al. (2016). Carcinogenic human papillomavirus infection. Nat Rev Dis Primers. 2:16086. https://doi.org/10.1038/nrdp.2016.86 PMID:27905473

8. IARC (2012). Biological agents. IARC Monogr Eval Carcinog Risks Hum. 100B:1–441. Available from: http://publications.iarc.fr/119 PMID:23189750

9. Razavi-Shearer D, Gamkrelidze I, Nguyen MH, Chen D-S, Van Damme P, Abbas Z, et al.; Polaris Observatory Collaborators (2018). Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol. 3(6):383–403. https://doi.org/10.1016/S2468-1253(18)30056-6 PMID:29599078

10. Trépo C, Chan HL, Lok A (2014). Hepatitis B virus infection. Lancet. 384(9959):2053–63. https://doi.org/10.1016/S0140-6736(14)60220-8 PMID:24954675

11. de Martel C, Maucort-Boulch D, Plummer M, Franceschi S (2015). World-wide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma. Hepatology. 62(4):1190–200. https://doi.org/10.1002/hep.27969 PMID:26146815

12. WHO (2009). Hepatitis B vaccines: WHO position paper. Wkly Epidemiol Rec. 84(40):405–19. PMID:19817017

13. Ni YH, Chang MH, Wu JF, Hsu HY, Chen HL, Chen DS (2012). Minimization of hepatitis B infection by a 25-year universal vaccination program. J Hepatol. 57(4):730–5. https://doi.org/10.1016/j.jhep.2012.05.021 PMID:22668640

14. Chang MH, You SL, Chen CJ, Liu CJ, Lee CM, Lin SM, et al.; Taiwan Hepatoma Study Group (2009). Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. J Natl Cancer Inst. 101(19):1348–55. https://doi.org/10.1093/jnci/djp288 PMID:19759364

15. Wasley A, Grytdal S, Gallagher K; Centers for Disease Control and Prevention (CDC) (2008). Surveillance for acute viral hepatitis – United States, 2006. MMWR Surveill Summ. 57(2):1–24. PMID:18354374

16. Li X, Dumolard L, Patel M, Gacic-Dobo M, Hennessey K (2018). Implementation of hepatitis B birth dose vaccination – worldwide, 2016. Wkly Epidemiol Rec. 93(7):61–72. PMID:29450989

17. de Martel C, Plummer M, Vignat J, Franceschi S (2017). Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 141(4):664–70. https://doi.org/10.1002/ijc.30716 PMID:28369882

18. Arbyn M, Xu L, Simoens C, Martin-Hirsch PP (2018). Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database Syst Rev. (5):CD009069. https://doi.org/10.1002/14651858.CD009069.pub3 PMID:29740819

19. Drolet M, Bénard É, Boily MC, Ali H, Baandrup L, Bauer H, et al. (2015). Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis. 15(5):565–80. https://doi.org/10.1016/S1473-3099(14)71073-4 PMID:25744474

20. WHO (2017). Human papillomavirus vaccines: WHO position paper, May 2017. Wkly Epidemiol Rec. 92(19):241–68. PMID:28530369

21. Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, et al.; Broad Spectrum HPV Vaccine Study (2015). A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 372(8):711–23. https://doi.org/10.1056/NEJMoa1405044 PMID:25693011

22. Kavanagh K, Pollock KG, Cuschieri K, Palmer T, Cameron RL, Watt C, et al. (2017). Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. Lancet Infect Dis. 17(12):1293–302. https://doi.org/10.1016/S1473-3099(17)30468-1 PMID:28965955

23. Beachler DC, Jenkins G, Safaeian M, Kreimer AR, Wentzensen N (2016). Natural acquired immunity against subsequent genital human papillomavirus infection: a systematic review and meta-analysis. J Infect Dis. 213(9):1444–54. https://doi.org/10.1093/infdis/jiv753 PMID:26690341

24. Brotherton JM, Jit M, Gravitt PE, Brisson M, Kreimer AR, Pai SI, et al. (2016). Eurogin Roadmap 2015: how has HPV knowledge changed our practice: vaccines. Int J Cancer. 139(3):510–7. https://doi.org/10.1002/ijc.30063 PMID:26916230

25. Kreimer AR, Herrero R, Sampson JN, Porras C, Lowy DR, Schiller JT, et al.; Costa Rica HPV Vaccine Trial (CVT) Group (2018). Evidence for single-dose protection by the bivalent HPV vaccine – review of the Costa Rica HPV vaccine trial and future research studies. Vaccine. 36(32 Pt A):4774–82. https://doi.org/10.1016/j.vaccine.2017.12.078 PMID:29366703

26. Sheikh S, Biundo E, Courcier S, Damm O, Launay O, Maes E, et al. (2018). A report on the status of vaccination in Europe. Vaccine. 36(33):4979–92. https://doi.org/10.1016/j.vaccine.2018.06.044 PMID:30037416

27. Gargano JW, Zhou F, Stokley S, Markowitz LE (2018). Human papillomavirus vaccination in commercially-insured vaccine-eligible males and females, United States, 2007–2014. Vaccine. 36(23):3381–6. https://doi.org/10.1016/j.vaccine.2018.03.045 PMID:29735321

28. Brotherton JM, Winch KL, Bicknell L, Chappell G, Saville M (2017). HPV vaccine coverage is increasing in Australia. Med J Aust. 206(6):262. https://doi.org/10.5694/mja16.00958 PMID:28359009

29. GAVI (2018). Gavi welcomes call for coordinated global action against cervical cancer. 19 May 2018. Available from: https://www.gavi.org/library/news/statements/2018/gavi-welcomes-call-for-coordinated-global-action-against-cervical-cancer/.

30. Gallagher KE, Howard N, Kabakama S, Mounier-Jack S, Griffiths UK, Feletto M, et al. (2017). Lessons learnt from human papillomavirus (HPV) vaccination in 45 low- and middle-income countries. PLoS One. 12(6):e0177773. https://doi.org/10.1371/journal.pone.0177773 PMID:28575074

31. Brisson M, Bénard É, Drolet M, Bogaards JA, Baussano I, Vänskä S, et al. (2016). Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. Lancet Public Health. 1(1):e8–17. https://doi.org/10.1016/S2468-2667(16)30001-9 PMID:29253379

32. Baussano I, Lazzarato F, Brisson M, Franceschi S (2016). Human papillomavirus vaccination at a time of changing sexual behavior. Emerg Infect Dis. 22(1):18–23. https://doi.org/10.3201/eid2201.150791 PMID:26691673

33. Baussano I, Lazzarato F, Ronco G, Franceschi S (2018). Impacts of human papillomavirus vaccination for different populations: a modeling study. Int J Cancer. 143(5):1086–92. https://doi.org/10.1002/ijc.31409 PMID:29603224

34. Hildesheim A, Gonzalez P, Kreimer AR, Wacholder S, Schussler J, Rodriguez AC, et al.; Costa Rica HPV Vaccine Trial (CVT) Group (2016). Impact of human papillomavirus (HPV) 16 and 18 vaccination on prevalent infections and rates of cervical lesions after excisional treatment. Am J Obstet Gynecol. 215(2):212.e1–15. https://doi.org/10.1016/j.ajog.2016.02.021 PMID:26892991

6.4 Preventive therapy
Certain interventions clearly established

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SUMMARY

- For women at high risk of breast cancer, reductions of 30–70% in the incidence of breast cancer can be achieved with use of anti-estrogenic agents.
- Widespread use of low-dose aspirin for 10 years between ages 50 years and 65 years could have a major impact on cancer incidence and mortality.
- Many other agents, including some medicines used for other purposes and some food components, seem promising for cancer prevention but have not been fully evaluated in humans.
- Good short-term biomarkers for response to treatment are needed to efficiently evaluate new agents.

Cancer prevention is a large field comprising lifestyle changes to reduce risk, screening interventions to detect early lesions, and preventive interventions aimed at more actively interrupting the carcinogenic pathway. Although tobacco use is clearly the strongest known avoidable cause of cancer [1], only therapeutic interventions to reduce risk are considered in this chapter.

Compared with cardiovascular disease, for which preventive treatments are firmly established, the development of therapies to prevent cancer is still in its infancy. This partly reflects the fact that cancers are more heterogeneous and biologically complex than cardiovascular disease, and the causal pathways are less well understood. Good biomarkers for identifying individuals at increased risk of specific cancer types are also missing, and even less is known about factors that are predictive of response to specific treatments.

Interventions have been divided into four groups: those for which there is good evidence of efficacy, those with findings that are promising but not fully convincing, those for which there is a substantial amount of evidence of no benefit, and those for which there is good evidence of harm.

Breast cancer

Breast cancer prevention has been facilitated by the fact that studies of the treatment of existing cancers can also provide reliable evidence for a preventive effect on new tumours in the contralateral breast.

Tamoxifen

The Cancer Research Campaign II (CRC-II) trial provided the first evidence of a preventive effect for tamoxifen [2]. A subsequent meta-analysis of 20 randomized clinical trials of 5 years of treatment with tamoxifen as adjuvant therapy in about 15 000 women overall documented a reduction of about one third in contralateral breast tumours [3]. Four prevention trials have subsequently confirmed this finding in high-risk women without breast cancer (Table 6.4.1).

Overall, these trials show a 38% reduction in breast cancer incidence [4], as a result of a 50% reduction for estrogen receptor (ER)-positive breast cancers but no effect for ER-negative tumours. Two of these trials with long-term follow-up have shown that the protection persists long after stopping use of the medication [5,6]. In the International Breast Cancer Intervention Study I (IBIS-I) trial, 5 years of treatment with tamoxifen resulted in a greater reduction in the incidence of breast cancer in the 10–20-year follow-up period than in the first 10 years of follow-up (cumulative risk, 4.6% vs 6.3% in years 0–10, 3.3% vs 6.3% in years 10–20) (Fig. 6.4.1).

The two major side-effects of tamoxifen are endometrial cancer and venous thromboembolism (Table 6.4.2). Endometrial cancer was increased in postmenopausal women by about 2.5-fold above the baseline rate of about 60 per 100 000 per year at age 60 years, whereas venous thromboembolism occurred about twice as often in the tamoxifen arm compared with placebo. Less serious but more common side-effects of tamoxifen include vasomotor symptoms such as hot flushes and night sweats, and gynaecological symptoms such as bleeding and uterine polyps. Topical formulations of tamoxifen

Table 6.4.1. Established therapeutic agents for cancer prevention

Agent	Type of study	Relevant references	Number evaluated	Key findings
Aspirin	RCTs and observational studies	[17,18,21]	69 224 in RCTs 52 926 in case–control studies	7–10% reduction in all-cancer incidence and 9–12% in mortality for 10-year use. Mostly for colorectal, stomach, and oesophageal cancer (30% each), with smaller and less certain reductions for breast, prostate, and lung cancer (5–15%)
Oral contraceptives	Meta-analysis of 17 case–control studies and 7 cohort studies	[15]	> 20 000 cases	27% reduction for ovarian cancer for any use; > 50% reduction for > 10-year use
Anti-estrogenic compounds for breast cancer prevention				
Selective estrogen-receptor modulators				
Tamoxifen	4 RCTs in women at high risk	[5,6]	28 193	33% reduction for all breast cancer, based on 44% reduction for ER+ invasive and no effect for ER− breast cancer
Raloxifene	3 RCTs (1 vs tamoxifen in women at high risk)	[7,8]	37 296	34% reduction overall, with 56% reduction for ER+ invasive breast cancer; 25% less effective than tamoxifen in direct comparison in women at high risk
Lasofoxifene	1 RCT in women with osteoporosis	[4,9]	8856	79% reduction for all breast cancer for higher dose; 18% reduction for lower dose
Arzoxifene	1 RCT in women with osteoporosis	[4]	9354	58% reduction for all breast cancer; 70% reduction for ER+ breast cancer
Aromatase inhibitors				
Anastrozole	1 RCT in women at high risk; contralateral tumours in RCTs in adjuvant setting	[13]	3864	53% reduction for all breast cancer; 58% reduction for ER+ invasive breast cancer
Exemestane	1 RCT in women at high risk; RCT of contralateral tumours in adjuvant setting	[12]	4560	53% reduction for all breast cancer; 73% reduction for ER+ invasive breast cancer

ER, estrogen receptor; RCTs, randomized controlled trials.

FUNDAMENTALS

- "Preventive therapy" has been widely adopted as an appropriately focused term to address many interventions, anticipated or established, once referred to as "chemoprevention".
- Over recent decades, evidence of preventive benefit from clinical trials has largely involved drugs rather than micronutrients or supplements.
- Confidence to introduce preventive therapy is markedly increased if relevant mechanistic data are available.
- Some reduction in risk of cancer associated with consumption of fruits and vegetables is evident, but the relative impact of particular food items has not become clear.
- Particular micronutrients and supplements for cancer prevention have been subject to large clinical trials, but few, if any, benefits have emerged, and evidence of increased risk has accrued.
- When available, integration of preventive therapy involving particular drugs with other initiatives including screening represents the broadest basis for reducing cancer incidence.

metabolites applied directly to the breast are now under study, with the hope that the local dose will be high enough to maintain its preventive effects but the reduction in systemic dose will limit its side-effects.

Other selective estrogen-receptor modulators

The effects of three other selective ER modulators (SERMs) on breast cancer risk have now been evaluated. Raloxifene is a second-generation SERM originally developed to prevent osteoporosis in postmenopausal women. It has estrogenic effects on bone and lipid metabolism, and anti-estrogenic effects on the endometrium and breast tissue. Because of this tissue selectivity, raloxifene has fewer side-effects than tamoxifen.

Trials in women with osteoporosis suggested larger effects for raloxifene than for tamoxifen [7], but a direct comparison in the Study of Tamoxifen and Raloxifene (STAR) trial found that the reduction in breast cancer risk for raloxifene was about 25% less than that for tamoxifen [8]. However, no excess of endometrial cancer or other gynaecological problems were observed, and raloxifene may be more acceptable than tamoxifen for postmenopausal women, because it is already widely used to treat and prevent osteoporosis.

Fig. 6.4.1. Long-term effect of tamoxifen treatment on cumulative incidence of breast cancer over time in the International Breast Cancer Intervention Study I (IBIS-I) trial. Solid lines indicate all breast cancers, and dashed lines indicate invasive estrogen receptor (ER)-positive breast cancers.

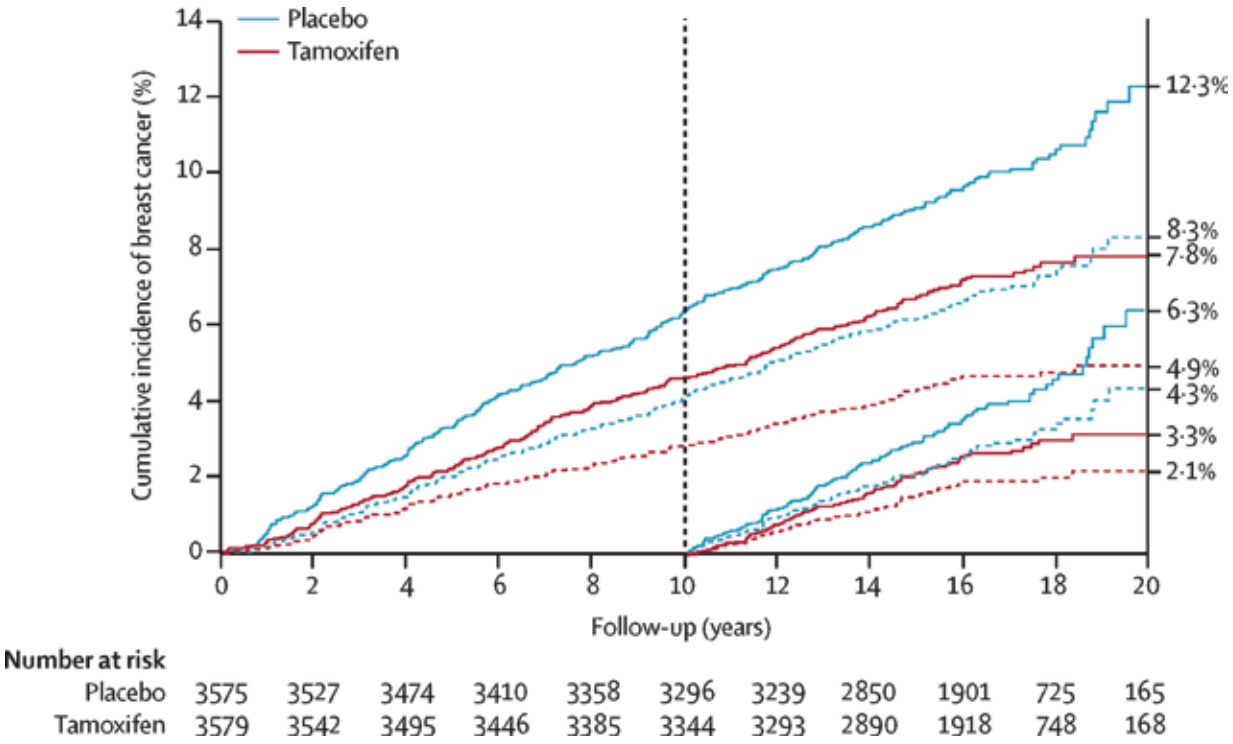


Table 6.4.2. Potential common or major side-effects of pharmacological agents considered for cancer prevention

Agent	Side-effect	Findings
Tamoxifen/SERMs	Endometrial cancer	2–3-fold increase, except with raloxifene
	Venous thromboembolic events	73% increase overall; smaller increase with raloxifene
	Vasomotor symptoms	20% increase during treatment; no effect subsequently
Aromatase inhibitors	Bone fractures	50% increase in adjuvant trials without baseline bone density scan; non-significant 11% increase in prevention studies with baseline identification and treatment of women with low bone density
	Musculoskeletal symptoms, arthralgia	Increase from 58% in placebo to 64% with anastrozole (10% relative increase)
	Carpal tunnel syndrome	3.6-fold increase in adjuvant setting vs tamoxifen (3% vs 1%); 58% increase in prevention setting (3% vs 2%)
	Vasomotor symptoms	15% increase overall; 20% increase in severe symptoms
	Vaginal dryness, dyspareunia, loss of libido	20% increase in prevention setting vs placebo (19% vs 16%); 3-fold increase in adjuvant setting vs tamoxifen (1% vs 0.3%)
LHRH agonist	Bone loss, menopausal symptoms	7% loss in bone mineral density at lumbar spine; substantial increase in vasomotor symptoms
Aspirin/NSAIDs	Gastrointestinal bleeding	Increase of ~50%, mostly in initial period after starting treatment
	Haemorrhagic stroke	35% increase, but larger reduction in occlusive stokes; net decrease in incidence, but increase in fatal events

LHRH, luteinizing hormone-releasing hormone; NSAIDs, non-steroidal anti-inflammatory drugs; SERMs, selective estrogen-receptor modulators.

Two other SERMs – lasofoxifene [4,9] and arzoxifene [4] – have been investigated again in postmenopausal women with osteoporosis, with reduction in the incidence of fractures as the primary end-point. For both agents, a reduction in the incidence of breast cancer was found that was larger than has been seen for tamoxifen (Table 6.4.1). Lasofoxifene was also associated with reductions in the incidence of fractures, heart disease, and strokes [9], suggesting that it could be an ideal preventive agent, but the manufacturer is not pursuing the licensing of this drug for any of these indications.

Aromatase inhibitors

The third-generation aromatase inhibitors anastrozole, letrozole, and exemestane have all been found to be more effective than tamoxifen for the treatment of ER-positive breast cancer in postmenopausal women [10] and are now routinely used for this indication. In these trials, the incidence of contralateral breast tumours, a good surrogate for new cancers, was also reduced by a further 50% compared with tamoxifen [11].

Two large breast cancer prevention trials have reported on the use of aromatase inhibitors in high-risk women without breast cancer. The Mammary Prevention 3 (MAP3) trial randomized 4560 postmenopausal women to either exemestane or placebo for 5 years and found a 65% reduction in invasive breast cancers [12]. No reduction was observed for ER-negative disease, but the effect on ER-positive disease was even greater than the overall effect (hazard ratio, 0.27; 95% confidence interval, 0.12–0.60; $P < 0.001$). However, these conclusions are limited by the short median follow-up period of 35 months.

The IBIS-II trial compared anastrozole with placebo in 3864 postmenopausal women at increased risk of breast cancer. After a median follow-up of 5 years, a 53% reduction in invasive breast cancer and ductal carcinoma in situ combined (primary end-point) was seen (hazard ratio, 0.47; 95% confidence interval, 0.32–0.68; $P < 0.0001$) [13], which was similar to the results reported in the MAP3 trial. For ER-positive invasive cancer, the reduction was 58%, but – as in the MAP3 trial – no effect was found for ER-negative breast cancer. Vasomotor and musculoskeletal side-effects were increased with both agents, but only by 10–15%, and these adverse events were also reported by many women who received placebo (64% for anastrozole vs 58% for placebo in the IBIS-II trial). This illustrates the need to have a placebo arm to accurately assess subjective side-effects. Blinded long-term follow-up is continuing in IBIS-II, so that the long-term efficacy and side-effects of anastrozole can be evaluated.

Overall, the reported reductions in breast cancer incidence for both exemestane and anastrozole were larger than those seen for tamoxifen or raloxifene, and indicate that these two drugs are attractive options for breast cancer prevention in postmenopausal women at high risk. Although both SERMs and aromatase inhibitors increase menopausal symptoms, SERMs also increase the incidence of endometrial cancer and thromboembolic events, whereas aromatase inhibitors increase the incidence of fractures and musculoskeletal symptoms (Table 6.4.2). The fracture risk seems to be largely controlled by a baseline dual-energy X-ray absorptiometry (DEXA) scan and use of bisphosphonates in women with low bone density [13].

For premenopausal women, the only well-studied option remains tamoxifen, although a small randomized trial in 75 women has examined a combination of the luteinizing hormone-releasing hormone (LHRH) agonist goserelin with raloxifene in women at high risk [14]. A 4.7% absolute reduction in breast density was seen after 2 years of treatment, but this was not maintained after treatment completion, and no data are available on reduction in cancer risk.

None of these agents have had an effect on ER-negative breast cancer; this remains an unmet need.

Ovarian cancer

Although no randomized trials have been conducted, there is clear evidence from case–control and cohort studies that use of oral contraceptives has a large protective effect for ovarian cancer. In an overview of 24 such studies, Havrilesky et al. demonstrated a 27% reduction for any use and a 57% reduction for more than 10 years of use [15]. Oral contraceptives have impacts on other cancer types, including a small increase in the risk of breast cancer and cervical cancer but larger reductions in the risk of endometrial cancer and colorectal cancer [16].

Aspirin and other non-steroidal anti-inflammatory drugs

There is now overwhelming evidence for a reduction of about one third in colorectal cancer incidence and mortality from long-term regular aspirin use [17]. Beneficial effects of a similar size have been seen for oesophageal cancer and stomach cancer, and smaller, less convincing reductions of 5–15% have recently also been found for lung cancer, breast cancer, and prostate cancer (Table 6.4.3) [18], but there appears to be little or no effect on other major cancer sites. Long-term use of about 10 years was estimated to reduce overall cancer incidence by about 9% in men and 7% in women, and overall cancer mortality by 13% in men and 9% in women (Table 6.4.3) [18]. The relative impact appears to be similar between the sexes, but the overall effects are greater for men because these cancer types are relatively more common in men.

Gastrointestinal and cerebral bleeding are the most important harms associated with aspirin use,

Table 6.4.3. Estimated impact of 10 years of aspirin use for individuals aged 50–70 years on percentage reduction in 15-year incidence and 20-year mortality from six cancer sites affected by aspirin use, and for all cancers separately for men and women

Site	Reduction in incidence (%)	Reduction in mortality (%)
Colorectum	35	40
Oesophagus	30	50
Stomach	30	35
Breast	10	5
Prostate	10	15
Lung	5	15
Overall – men	9	13
Overall – women	7	9

and their risk and fatality rate increase with age [19]. Use of prophylactic aspirin in the general population aged 50–65 years is likely to be beneficial when the reduction in risk of cancer and cardiovascular disease and the risk of excess bleeding are all considered. The benefit–risk ratio is highly favourable for the general population for both men and women and is about 5:1 for serious events and at least 7:1 for deaths [18]. Markers that identify individuals most likely to benefit would enable treatment to be more focused, and this is a current research priority. The United States Preventive Services Task Force currently supports the use of aspirin for those at increased risk of cardiovascular disease or colorectal cancer [20].

The effects of daily use of aspirin on cancer incidence are not apparent until at least 3 years after the start of use (Fig. 6.4.2), with a relative reduction in incidence after that time for all cancers of about 24% [21]. Some benefits appear to be sustained for several years after treatment cessation in long-term users. Relative reductions in cancer incidence appear to be similar in men and women [21], although data are less extensive for women and men have a higher incidence of the cancer types for which the incidence is reduced by aspirin use, leading to greater absolute reductions.

The impact of aspirin use on cancer mortality appears to be larger than that for incidence, suggesting an anti-metastatic effect as well as a separate effect on incidence [22,23]. The mechanisms that mediate these effects are currently not established, and trials are under way to examine aspirin as an adjuvant treatment for individuals with colorectal, stomach, oesophageal, breast, and prostate cancer [24].

Data on other non-steroidal anti-inflammatory drugs, such as ibuprofen, sulindac, or celecoxib, are less extensive, and there are no trials with long-term follow-up, except for studies of colorectal adenomas. However, observational studies have found similar overall effects on cancer incidence [22].

Other agents

Vaccination against human papillomavirus (HPV) has proven to be highly effective in reducing precursor lesions for cervical cancer and is very likely to prevent cervical cancer and other HPV-related cancers (see Chapter 6.3).

Many studies have suggested a protective effect of consumption of fruits and vegetables, with a stronger effect for vegetables [25]. Specific potentially active components include sulforaphane, which is found in cruciferous vegetables, and lycopene, which is found at particularly high levels in cooked tomatoes but is also found in other fruits and vegetables. Both sulforaphane and lycopene have been linked to reduced risk of prostate cancer [26,27].

Several spices have also been put forward as having protective effects. Curcumin, which comes from turmeric, has been the most studied, but there is still very limited evidence in humans for cancer prevention [28]. Of the many hundreds of other compounds that have been studied [29], those that have received the most attention are resveratrol (which is found mostly in red wine and berries) [30], green tea polyphenols [31], and pomegranate juice [32], but again convincing evidence of efficacy in humans is lacking.

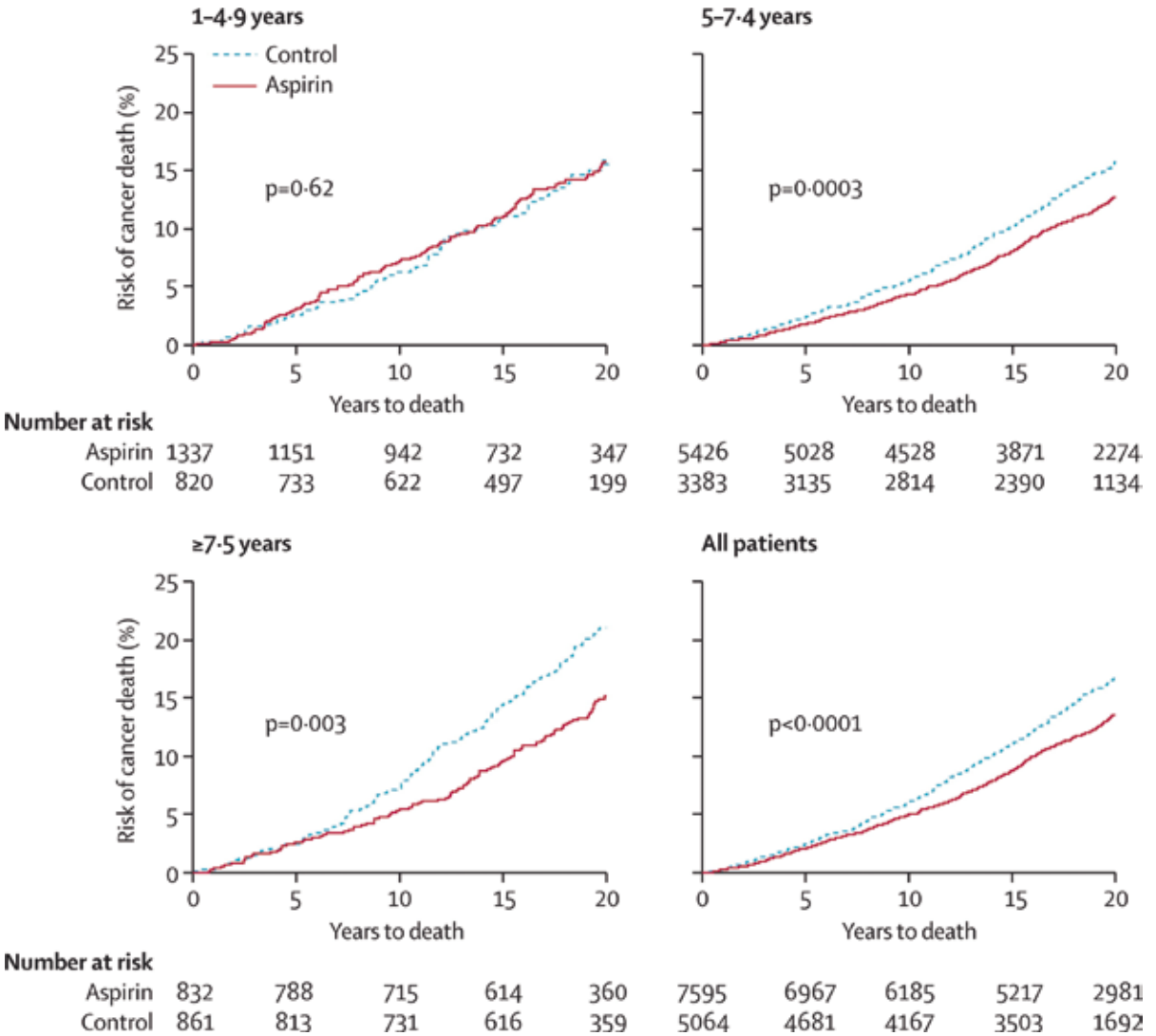
Reports on vitamin D with or without calcium are very mixed, with no compelling evidence for benefit at any cancer site [33].

Agents that have not worked

Epidemiological and laboratory evidence suggested a potential anti-cancer effect of vitamin A, β-carotene, and their analogues. Despite randomized evidence of a benefit of β-carotene, vitamin E, and selenium in a severely deficient population in Linxian, China [34], subsequent studies in Europe and North America have been negative. Two large studies of β-carotene in heavy smokers and in workers exposed to asbestos found that it actually led to increases in the incidence of lung cancer [35,36], and one found an increase in all-cause mortality [35]. An overview of all randomized trials of β-carotene confirmed an increase in the incidence of lung cancer and also found an increase in the incidence of stomach cancer but no significant effect on other cancer types, either individually or overall [37].

Vitamin E and selenium were thought to have a beneficial effect on prostate cancer, on the basis of laboratory and epidemiological studies [38], but randomized trials have been negative. In particular, neither selenium nor vitamin E supplementation reduced the incidence of prostate

Fig. 6.4.2. Impact of aspirin use on cancer mortality by scheduled duration of treatment.



cancer in the Selenium and Vitamin E Cancer Prevention Trial (SELECT), in which prostate cancer was the primary end-point, and Klein et al. [39] reported that the incidence of prostate cancer increased by 17% with vitamin E supplementation. Other studies have not shown any effects of supplementation on the incidence of prostate cancer, colorectal cancer, or cause-specific mortality.

The use of 5α-reductase inhibitors either for prevention or for management of early prostate cancer has produced complex outcomes, with substantial reductions in disease of low Gleason grade but an apparent increase in high-grade cancers in both the Prostate Cancer Prevention Trial (PCPT) [40], which investigated finasteride, and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial [41], which assessed dutasteride.

There has also been much interest in the role of statins for cancer prevention, but the overall evidence is largely negative [42].

Conclusions and challenges

Despite its early stage of development, important discoveries have already been made for preventive therapy. Of these, low-dose aspirin stands out as having the largest potential impact on the population at large. This is because it has a major effect on three common gastrointestinal cancer types – colorectal, stomach, and oesophageal cancer – and potentially provides small reductions in three other major cancer types: lung, breast, and prostate cancer. However, questions still remain about aspirin's optimal dose, duration, efficacy, safety, and impact on different subtypes of specific cancers, and more research is needed.

In terms of relative overall importance for cancer prevention, tobacco cessation remains the most important factor. Parkin et al. estimated that

tobacco use is responsible for 19% of all new cancer cases but calculated that no other activity is responsible for more than 10% of cancers [1]. The estimate that 7–10% of cancers could be avoided with daily use of low-dose aspirin for 10 years between ages 50 years and 65 years, with a larger reduction of 9–13% for mortality [18], makes this a key element of any cancer prevention strategy.

However, several major challenges remain. Key among these is to find ways to encourage more widespread use of agents with established utility. Uptake of tamoxifen in women at high risk of breast cancer is only 10–20% [43], and much of this low uptake is due to a lack of knowledge and interest in prevention from health professionals. Aspirin has had earlier recommendations from professional bodies against using it in the general population [44]. However, those recommendations were based on comparing cardiovascular benefits with risks of bleeding, and now need to be updated in view of the much larger benefits seen for cancer prevention than for cardiovascular disease. These benefits have only been reported more recently, largely because they were not apparent until after 3–5 years of aspirin use. Education of both health professionals and the general public about the benefits of therapeutic prevention needs to be a major goal and activity.

Also, activities to promote preventive therapy need to be integrated with those to encourage a healthy lifestyle. Neither of these alone will eliminate cancer, and adoption of one does not preclude the need for the other.

References

1. Parkin DM, Boyd L, Walker LC (2011). 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 105(Suppl 2):S77–81. https://doi.org/10.1038/bjc.2011.489 PMID:22158327
2. Cuzick J, Baum M (1985). Tamoxifen and contralateral breast cancer. Lancet. 2(8449):282. https://doi.org/10.1016/S0140-6736(85)90338-1 PMID:2862460
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 365(9472):1687–717. https://doi.org/10.1016/S0140-6736(05)66544-0 PMID:15894097
4. Cuzick J, Sestak I, Bonanni B, Costantino JP, Cummings S, DeCensi A, et al.; SERM Chemoprevention of Breast Cancer Overview Group (2013). Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet. 381(9880):1827–34. https://doi.org/10.1016/S0140-6736(13)60140-3 PMID:23639488
5. Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M (2007). Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst. 99(4):283–90. https://doi.org/10.1093/jnci/djk050 PMID:17312305
6. Cuzick J, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A, et al.; IBIS-I Investigators (2015). Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol. 16(1):67–75. https://doi.org/10.1016/S1470-2045(14)71171-4 PMID:25497694
7. Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, et al.; Raloxifene Use for The Heart (RUTH) Trial Investigators (2006). Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med. 355(2):125–37. https://doi.org/10.1056/NEJMoa062462 PMID:16837676
8. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al.; National Surgical Adjuvant Breast and Bowel Project (2010). Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 trial: preventing breast cancer. Cancer Prev Res (Phila). 3(6):696–706. https://doi.org/10.1158/1940-6207.CAPR-10-0076 PMID:20404000
9. Cummings SR, Ensrud K, Delmas PD, LaCroix AZ, Vukicevic S, Reid DM, et al.; PEARL Study Investigators (2010). Lasofoxifene in postmenopausal women with osteoporosis. N Engl J Med. 362(8):686–96. https://doi.org/10.1056/NEJMoa0808692 PMID:20181970
10. Dowsett M, Cuzick J, Ingle J, Coates A, Forbes J, Bliss J, et al. (2010). Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol. 28(3):509–18. https://doi.org/10.1200/JCO.2009.23.1274 PMID:19949017
11. Cuzick J (2005). Aromatase inhibitors for breast cancer prevention. J Clin Oncol. 23(8):1636–43. https://doi.org/10.1200/JCO.2005.11.027 PMID:15755971
12. Goss PE, Ingle JN, Alés-Martínez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, et al.; NCIC CTG MAP.3 Study Investigators (2011). Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 364(25):2381–91. https://doi.org/10.1056/NEJMoa1103507 PMID:21639806
13. Cuzick J, Sestak I, Forbes JF, Dowsett M, Knox J, Cawthorn S, et al.; IBIS-II investigators (2014). Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet. 383(9922):1041–8. https://doi.org/10.1016/S0140-6736(13)62292-8 PMID:24333009
14. Howell A, Ashcroft L, Fallowfield L, Eccles DM, Eeles RA, Ward A, et al. (2018). RAZOR: a phase II open randomized trial of screening plus goserelin and raloxifene versus screening alone in premenopausal women at increased risk of breast cancer. Cancer Epidemiol Biomarkers Prev. 27(1):58–66. https://doi.org/10.1158/1055-9965.EPI-17-0158 PMID:29097444
15. Havrilesky LJ, Moorman PG, Lowery WJ, Gierisch JM, Coeytaux RR, Urrutia RP, et al. (2013). Oral contraceptive pills as primary prevention for ovarian cancer: a systematic review and meta-analysis. Obstet Gynecol. 122(1):139–47. https://doi.org/10.1097/AOG.0b013e318291c235 PMID:23743450
16. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, et al. (2013). Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev. 22(11):1931–43. https://doi.org/10.1158/1055-9965.EPI-13-0298 PMID:24014598
17. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW (2011). Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 377(9759):31–41. https://doi.org/10.1016/S0140-6736(10)62110-1 PMID:21144578

18. Cuzick J, Thorat MA, Bosetti C, Brown PH, Burn J, Cook NR, et al. (2015). Estimates of benefits and harms of prophylactic use of aspirin in the general population. Ann Oncol. 26(1):47–57. https://doi.org/10.1093/annonc/mdu225 PMID:25096604

19. Thorat MA, Cuzick J (2015). Prophylactic use of aspirin: systematic review of harms and approaches to mitigation in the general population. Eur J Epidemiol. 30(1):5–18. https://doi.org/10.1007/s10654-014-9971-7 PMID:25421783

20. Chubak J, Whitlock EP, Williams SB, Kamineni A, Burda BU, Buist DSM, et al. (2016). Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. Preventive Services Task Force. Ann Intern Med. 164(12):814–25. https://doi.org/10.7326/M15-2117 PMID:27064482

21. Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G, et al. (2012). Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet. 379(9826):1602–12. https://doi.org/10.1016/S0140-6736(11)61720-0 PMID:22440946

22. Chan AT, Ogino S, Fuchs CS (2009). Aspirin use and survival after diagnosis of colorectal cancer. JAMA. 302(6):649–58. https://doi.org/10.1001/jama.2009.1112 PMID:19671906

23. Holmes MD, Chen WY, Li L, Hertzmark E, Spiegelman D, Hankinson SE (2010). Aspirin intake and survival after breast cancer. J Clin Oncol. 28(9):1467–72. https://doi.org/10.1200/JCO.2009.22.7918 PMID:20159825

24. Coyle C, Cafferty FH, Rowley S, MacKenzie M, Berkman L, Gupta S, et al.; Add-Aspirin investigators (2016). ADD-ASPIRIN: a phase III, double-blind, placebo controlled, randomised trial assessing the effects of aspirin on disease recurrence and survival after primary therapy in common non-metastatic solid tumours. Contemp Clin Trials. 51:56–64. https://doi.org/10.1016/j.cct.2016.10.004 PMID:27777129

25. Negri E, La Vecchia C, Franceschi S, D'Avanzo B, Parazzini F (1991). Vegetable and fruit consumption and cancer risk. Int J Cancer. 48(3):350–4. https://doi.org/10.1002/ijc.2910480307 PMID:2040528

26. Juge N, Mithen RF, Traka M (2007). Molecular basis for chemoprevention by sulforaphane: a comprehensive review. Cell Mol Life Sci. 64(9):1105–27. https://doi.org/10.1007/s00018-007-6484-5 PMID:17396224

27. Chen P, Zhang W, Wang X, Zhao K, Negi DS, Zhuo L, et al. (2015). Lycopene and risk of prostate cancer: a systematic review and meta-analysis. Medicine (Baltimore). 94(33):e1260. https://doi.org/10.1097/MD.0000000000001260 PMID:26287411

28. Devassy JG, Nwachukwu ID, Jones PJ (2015). Curcumin and cancer: barriers to obtaining a health claim. Nutr Rev. 73(3):155–65. https://doi.org/10.1093/nutrit/nuu064 PMID:26024538

29. Hackshaw-McGeagh LE, Perry RE, Leach VA, Qandil S, Jeffreys M, Martin RM, et al. (2015). A systematic review of dietary, nutritional, and physical activity interventions for the prevention of prostate cancer progression and mortality. Cancer Causes Control. 26(11):1521–50. https://doi.org/10.1007/s10552-015-0659-4 PMID:26354897

30. Gescher A, Steward WP, Brown K (2013). Resveratrol in the management of human cancer: how strong is the clinical evidence? Ann N Y Acad Sci. 1290(1):12–20. https://doi.org/10.1111/nyas.12205 PMID:23855461

31. Li MJ, Yin YC, Wang J, Jiang YF (2014). Green tea compounds in breast cancer prevention and treatment. World J Clin Oncol. 5(3):520–8. https://doi.org/10.5306/wjco.v5.i3.520 PMID:25114865

32. Malik A, Afaq F, Sarfaraz S, Adhami VM, Syed DN, Mukhtar H (2005). Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer. Proc Natl Acad Sci U S A. 102(41):14813–8. https://doi.org/10.1073/pnas.0505870102 PMID:16192356

33. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Krstic G, Wetterslev J, et al. (2014). Vitamin D supplementation for prevention of cancer in adults. Cochrane Database Syst Rev. (6):CD007469. https://doi.org/10.1002/14651858.CD007469.pub2 PMID:24953955

34. Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, et al. (1993). Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst. 85(18):1483–92. https://doi.org/10.1093/jnci/85.18.1483 PMID:8360931

35. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. (1996). Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med. 334(18):1150–5. https://doi.org/10.1056/NEJM199605023341802 PMID:8602180

36. Albanes D, Heinonen OP, Taylor PR, Virtamo J, Edwards BK, Rautalahti M, et al. (1996). Alpha-tocopherol and beta-carotene supplements and lung cancer incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study: effects of base-line characteristics and study compliance. J Natl Cancer Inst. 88(21):1560–70. https://doi.org/10.1093/jnci/88.21.1560 PMID:8901854

37. Druesne-Pecollo N, Latino-Martel P, Norat T, Barrandon E, Bertrais S, Galan P, et al. (2010). Beta-carotene supplementation and cancer risk: a systematic review and metaanalysis of randomized controlled trials. Int J Cancer. 127(1):172–84. https://doi.org/10.1002/ijc.25008 PMID:19876916

38. Pak RW, Lanteri VJ, Scheuch JR, Sawczuk IS (2002). Review of vitamin E and selenium in the prevention of prostate cancer: implications of the Selenium and Vitamin E Chemoprevention Trial. Integr Cancer Ther. 1(4):338–44. https://doi.org/10.1177/1534735402238186 PMID:14664728

39. Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. (2011). Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 306(14):1549–56. https://doi.org/10.1001/jama.2011.1437 PMID:21990298

40. Thompson IM Jr, Goodman PJ, Tangen CM, Parnes HL, Minasian LM, Godley PA, et al. (2013). Long-term survival of participants in the Prostate Cancer Prevention Trial. N Engl J Med. 369(7):603–10. https://doi.org/10.1056/NEJMoa1215932 PMID:23944298

41. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, et al.; REDUCE Study Group (2010). Effect of dutasteride on the risk of prostate cancer. N Engl J Med. 362(13):1192–202. https://doi.org/10.1056/NEJMoa0908127 PMID:20357281

42. Emberson JR, Kearney PM, Blackwell L, Newman C, Reith C, Bhala N, et al.; Cholesterol Treatment Trialists' (CTT) Collaboration (2012). Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS One. 7(1):e29849. PMID:22276132

43. Hackett J, Thorneloe R, Side L, Wolf M, Horne R, Cuzick J, et al. (2018). Uptake of breast cancer preventive therapy in the UK: results from a multicentre prospective survey and qualitative interviews. Breast Cancer Res Treat. 170(3):633–40. https://doi.org/10.1007/s10549-018-4775-1 PMID:29687178

44. Thun MJ, Jacobs EJ, Patrono C (2012). The role of aspirin in cancer prevention. Nat Rev Clin Oncol. 9(5):259–67. https://doi.org/10.1038/nrclinonc.2011.199 PMID:22473097

6.5 Managing people with high and moderate genetic risk

Genomic tools to promote effective cancer risk reduction

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SUMMARY

- The identification of individuals and families with hereditary cancer is an important opportunity for cancer prevention.
- Cancer risk-reducing interventions (e.g. lifestyle changes, enhanced surveillance, chemoprevention, and prophylactic surgery) are available, and identification of the causative germline genetic variant is key to the development of rational management guidelines according to specific cancer risks.
- Recent advances in diagnostic tools using multigene panel testing have enabled the simultaneous and more affordable analysis of multiple cancer predisposition genes.
- Health system, ethnic, and socioeconomic disparities in access to risk assessment still exist, especially in low- and middle-income countries, and add to the complexity of enabling universal access to this important strategy to reduce the global cancer burden. These disparities must be addressed to ensure that all benefits of incorporating genetic or genomic information into an individual's clinical care are attained at a global level.

Hereditary cancer is caused predominantly by one (or, rarely, more than one) moderately or highly penetrant pathogenic or likely pathogenic (P/LP) germline variant in a cancer predisposition gene (see Chapter 3.2). The identification of individuals and families with hereditary cancer is an important opportunity for cancer prevention [1].

About 5–10% of all solid tumours and haematological malignancies are associated with P/LP germline variants in cancer predisposition genes [2,3]. Carriers of such variants have significantly higher risks of developing multiple cancer types, often at an early age, compared with the general population. Therefore, these cases contribute a significant proportion of the cancer burden worldwide, given that lifetime cancer risks in these individuals may reach up to 80% (e.g. for hereditary breast and ovarian cancer syndrome) or even close to 100% (e.g. for Li–Fraumeni syndrome).

Genetic/genomic cancer risk assessment (GCRA) is standard-of-care medical practice that uses genetic and genomic tools to identify individuals and families with increased risk of cancer. This enables early and frequent screening to detect smaller, more curable cancers, and to propose cancer prevention measures (Box 6.5.1). Despite such high risks and the availability of cancer risk-reducing interventions (e.g. lifestyle changes, enhanced surveillance, chemoprevention, and prophylactic surgery [4]), there are still health system, ethnic, and socioeconomic disparities in access to risk assessment, especially in low- and middle-income countries [5].

The phenotypic effect is heterogeneous for most variants associated with hereditary cancer. Genetic variants can be classified according to their frequency and the associated risk of cancer (Fig. 6.5.1). In addition, there are geographical, population-derived differences in variant type and frequency among different regions of the world, and founder mutations account for a substantial fraction of the cancer burden in certain regions (Table 6.5.2). Therefore, characterization of the mutational landscape of cancer predisposition genes and variant penetrance is of great importance.

Although specific cancer predisposition syndromes are clearly identified (Table 6.5.1), phenotypic overlap exists among several of them (Fig. 6.5.2) [5]. Most P/LP germline variants are inherited, but in some cancer predisposition syndromes, such as Li–Fraumeni syndrome and familial adenomatous polyposis, de novo mutations in *TP53* and *APC*, respectively, have been described in 5–10% of affected patients [6]. As tumour genetic testing becomes more common, previously unrecognized germline mutations will be detected, and the percentage of cancers accounted for by high or moderate genetic risk as a result of de novo mutations will be better understood.

Box 6.5.1. Components of genetic/genomic cancer risk assessment (GCRA), indicating the most common features of pre- and post-test counselling.

Pre-test counselling

- Initial assessment and engagement with patient.
- Document patient and family history of cancer; perform physical examination whenever necessary.
- Assess psychosocial and interpersonal dynamics (communication within family) and support system; discuss cultural beliefs.
- Discuss basic principles of cancer genetics (including medical, genetic, and technical information); describe features of hereditary cancer syndromes, and consider factors that limit interpretation and assessment.
- Assess mutation probabilities and empirical cancer risks.
- Discuss genetic testing process, potential test outcomes, cost, turnaround time, and insurance coverage.
- Develop genetic testing strategies and facilitate informed consent, and assess and address psychological, cultural, communication, and ethical issues. Anticipate potential cancer risk management options according to test result.
- Ensure protection of anonymity, privacy, and confidentiality, and facilitate communicating genetic information to at-risk family members and/or medical caregivers.
- Discuss alternatives to genetic testing.
- Anticipate increasing referrals from patients participating in direct-to-consumer testing schemes and those with a possible germline mutation detected on tumour testing.

Post-test counselling

- Disclose, interpret, and communicate test results.
- Address psychological and ethical concerns.
- Identify at-risk family members who would also benefit from genetic testing and/or increased screening or preventive care.
- Discuss communication of results to at-risk family members (strategies, resources, and barriers).
- Arrange contacts and resources for patient and at-risk family members.
- Develop personalized risk management plan by applying evidence-based guidelines.
- Propose empirical risk screening and prevention recommendations in setting of uninformative genetic test results.
- Identify research options or clinical trials appropriate to patients and at-risk family members when applicable.
- Summarize and disseminate personalized risk management plan with patient and patient-authorized care providers.

Recent advances in diagnostic tools using multigene panel testing have enabled the identification of previously unidentified genotype–phenotype relationships and the simultaneous and more affordable analysis of multiple cancer predisposition genes, with shorter testing turnaround times and a higher yield in the identification of disease-causing variants. Despite these advances, important challenges arise from multigene panel testing. These include uncertain clinical actionability of P/LP variants identified in genes with moderate penetrance,

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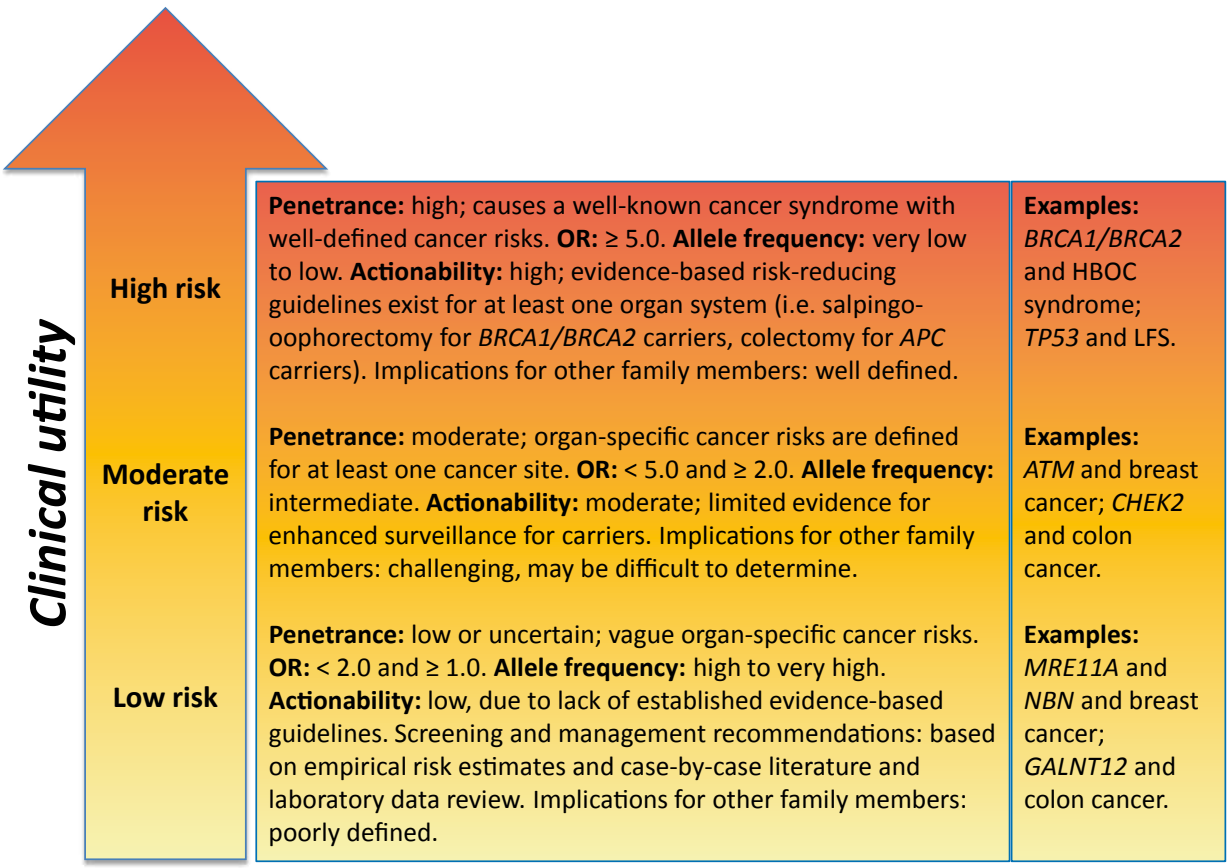
- About 5–10% of all solid tumours and haematological malignancies are associated with inherited predisposition from moderately or highly penetrant pathogenic or likely pathogenic germline variants. An estimated 1.7 million new cases of hereditary cancer were diagnosed worldwide in 2018.
- There is significant heterogeneity in cancer risks associated with pathogenic or likely pathogenic variants in cancer predisposition genes, and management differs according to the penetrance of each variant. Phenotypic overlap is common and is observed for multiple genes.
- Advances in sequencing technology have enhanced knowledge about the genes and pathogenic or likely pathogenic variants associated with hereditary cancer and have increased access to more affordable and comprehensive genetic testing.
- Options are available for cancer risk reduction in carriers, including lifestyle changes, enhanced surveillance, chemoprevention, and risk-reduction surgery. However, evidence on the efficacy and cost–effectiveness of these interventions has been generated only for high-penetrance genes such as *BRCA1* and *BRCA2*, and most guidelines cite inadequate evidence for some or all aspects of management for moderate-risk gene variants, for which more work is needed to calibrate risks and interventions.
- Genetic/genomic cancer risk assessment is a standard-of-care multidisciplinary process that ideally involves genetic counselling, experienced cancer risk consultants, and medical/surgical risk management teams.
- Despite major advances in the field, the remaining challenges include difficulties in the breadth of variants and their curation, limited accuracy of the associated risk estimation and establishment of clinical utility, limited access to professional genetic counselling and testing, and the need for professional education about genetics and genomics and training of multidisciplinary teams.

Fig. 6.5.1. Genetic risk categories in hereditary cancer and their characterization according to penetrance, actionability, screening and management recommendations, and implications for family members. Clinical utility increases with higher cancer risk predisposition; the gradient in the arrow denotes the potential significant overlap between the categories. Odds ratios are presented as estimates of the generalized odds over the baseline population for organ-specific cancer risk. More studies, especially on genes in the low- and moderate-risk categories, are needed to better clarify the associated cancer risks and penetrance. It is important to note that penetrance and expressivity can widely vary with specific mutations within the same gene. HBOC syndrome, hereditary breast and ovarian cancer syndrome; LFS, Li–Fraumeni syndrome; OR, odds ratio.



or in newly identified or very rare genes for which validation studies are required, and the pervasive conundrum of variants of uncertain significance. Another complication is that causality of observed moderate- or low-risk variants is difficult to infer, and many are simply an incidental finding with respect to a given patient's history of cancer [7].

Scope of the preventive approach in cancer genomics

Moderately or highly penetrant P/LP germline variants have been described in individuals with most, if not all, tumour types. On the basis of cancer incidence statistics for solid tumours and assuming that 10% are hereditary, an estimated 1.7 million new cases of hereditary cancer were diagnosed worldwide in 2018 (http://gco.iarc.fr). The identification of cancer patients with genetic predisposition can influence oncological management and can direct screening and prevention strategies to ameliorate the risk of second primary tumours. Critically, cascade testing of relatives for a familial mutation has the greatest potential to enhance cancer prevention and improve the cost–benefit ratio for society, as well as enable the avoidance of cancer mortality and treatment-related morbidity for individuals [8,9].

Considering the prevalence of hereditary cancer and its effects in terms of cancer risks and prevention, it is noteworthy that only a few countries address this issue in their strategic plans for cancer control. In the World Cancer Declaration Progress Report 2016, only Bermuda, France, and Greece formally included GCRA among their strategies to reduce cancer risks (https://www.uicc.org/wcd-report). Nationwide guidelines and/or government programmes of GCRA and genetic testing have been established in some countries, including Canada, France, the United Kingdom, and the USA [10].

Table 6.5.1. Common cancer predisposition syndromes, associated genes, and phenotype

Hereditary cancer syndrome	Associated gene(s)	Most commonly associated tumours	Additional/distinctive findings
Ataxia telangiectasia	*ATM*	Leukaemia, breast cancer, pancreatic cancer	Ataxia, telangiectasias, recessive inheritance; female carriers at increased risk of breast cancer
Cowden syndrome	*PTEN*	Breast cancer, thyroid cancer, colorectal cancer, endometrial cancer	Macrocephaly, Lhermitte–Duclos disease, acral keratosis, trichilemmomas, papillomatous papules; developmental delay and/or autism spectrum disorders
Familial adenomatous polyposis, attenuated and classic forms	*APC*	Colorectal cancer, pancreatic cancer, gastric cancer, thyroid cancer, desmoid tumours, tumours of the central nervous system, hepatoblastoma	Osteomas, dental abnormalities, congenital hypertrophy of the retinal pigment epithelium, benign cutaneous lesions
Gorlin syndrome	*PTCH*	Basal cell carcinoma, medulloblastoma, ovarian tumours	Pits in palms and soles, macrocephaly and prominent forehead keratocystic odontogenic tumours, cardiac and ovarian fibromas, calcified falx cerebri
Li–Fraumeni syndrome	*TP53*	Breast cancer (ER+ and HER2+), sarcomas, tumours of the central nervous system, adrenocortical carcinoma	
Hereditary breast and ovarian cancer syndrome	*BRCA1/BRCA2*	Breast cancer, ovarian cancer, prostate cancer, melanoma, pancreatic cancer	Biallelic mutations in *BRCA2* cause Fanconi syndrome
	BRIP1, *RAD51C*, *RAD51D*	Ovarian cancer	
	BRCA1, *BRCA2*, *PALB2*, *RAD51D*?	Triple-negative breast cancer	Includes both high-risk and moderate-risk genes
	ATM, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*	Male breast cancer	
Hereditary diffuse gastric cancer	*CDH1*	Diffuse gastric cancer, lobular breast cancer, colorectal cancer	
Juvenile polyposis syndrome	*BMPR1A*, *SMAD4*	Colorectal and small intestine cancer, pancreatic cancer, gastric cancer	Hamartomatous polyps
Lynch syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	Colon and small intestine, gastric, hepatobiliary, endometrial, ovarian, pancreatic, and ureteral tumours	
Melanoma–pancreatic cancer syndrome	*CDKN2*, *CDK4*	Pancreatic cancer, melanoma	
Multiple endocrine neoplasia type 1 (MEN1)	*MEN1*	Pancreatic cancer, pituitary and parathyroid tumours, well-differentiated endocrine tumours of the gastroenteropancreatic tract, carcinoid and adrenal tumours	Familial isolated hyperparathyroidism, facial angiofibromas, collagenomas, lipomas, meningiomas, ependymomas, leiomyomas
Multiple endocrine neoplasia type 2 (MEN2)	*RET*	Medullary thyroid carcinoma, pheochromocytoma, benign thyroid tumours	Mucocutaneous neuromas, gastrointestinal symptoms, muscular hypotonia, Marfanoid habitus
MUTYH-associated polyposis (MAP)	*MUTYH*	Colorectal (polyps) and small intestine cancers	Recessive inheritance; carriers may be at increased risk of colon cancer
Peutz–Jeghers syndrome	*STK11*	Colon cancer (polyps), breast cancer, ovarian cancer, pancreatic cancer, gastric cancer, endometrial and cervical carcinoma	Hyperpigmented lesions, Peutz–Jeghers polyps
Von Hippel–Lindau syndrome	*VHL*	Haemangioblastoma, clear cell renal cell carcinoma, pheochromocytoma, endolymphatic sac tumours	Retinal angiomas; renal, pancreatic, and genital cysts

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

Differences between countries in effective implementation of GCRA

In high-income countries, progress in the detection and diagnosis of hereditary cancer in the past 20 years has been enormous and well documented [5]. Important discoveries about the biology of hereditary cancers have resulted in efforts to increase the awareness and education of both the general public and health-care professionals, as well as the discovery of targeted treatments for hereditary cancers, and even the development of public policies. These, in turn, have enabled early – and often presymptomatic – detection of carriers, prompt and effective intervention, and thus effective reduction of the cancer burden in families with hereditary cancer.

However, this progress has reached only part of the world's population. In many countries, diagnoses still rely on overt clinical signs, which appear late in the course of disease, and access to periodic cancer screening methods, predictive genetic testing, and appropriate therapeutic options remains limited (see Chapter 1.3). Therefore, the proportion of potentially curable tumours at diagnosis is decreased in lower-income countries, especially in patients who rely solely on public health-care systems. The incidence and mortality rates of several cancer types (e.g. breast cancer and endometrial cancer) have been correlated with the Human Development Index (HDI) level of a country; decreases in mortality-to-incidence ratios have been observed with increments in HDI level, probably resulting from better access to cancer screening, diagnosis, and treatment [11,12].

In addition to regional economic and social constraints, an important barrier is lack of awareness of hereditary cancer and of the cancer prevention opportunities that result from proper GCRA. An additional challenge is the limited availability of GCRA practitioners. GCRA training resources to address the need for a skilled workforce include programmes such as the American Society of Clinical Oncology (ASCO) University curricula and the Cancer Genomics Education Program at City of Hope (https://www.cityofhope.org/education/health-professional-education/cancer-genomics-education-program).

Hereditary cancer syndromes also have distinct clinical patterns and distribution globally. One of the main factors to explain such differences is the occurrence of specific founder mutations at higher frequency in certain geographical regions or populations, leading to large clusters of specific inherited cancers (Table 6.5.2), in addition to the geographical differences in cancer detection rate, registration, diagnosis, prevention initiatives, and management [13–16]. Only a few national cancer institutions in low- and middle-income countries have formulated coordinated programmes towards the identification and management of patients with inherited cancers.

Table 6.5.2. Hereditary cancer in different populations: examples of founder mutations identified in selected cancer predisposition genes

Continent	Country	Gene	Mutation(s)	Details	Reference
Africa	Algeria, Morocco, and Tunisia	*BRCA1*	c.798_799delTT	22% of *BRCA1* mutations in North African families	[35]
	South Africa	*BRCA1* *BRCA2*	c.1374delC, c.2641G>T c.7934delG	77.8% of mutation carriers had 1 of the 3 Afrikaner founder mutations	[36]
North America	Canada	*MSH2*	c.942+3A>T	27% of Lynch syndrome mutations in families from Newfoundland	[37]
	Mexico	*BRCA1*	Exon 9–12 del	35% and 29% of the *BRCA*-associated cases of ovarian cancer and breast cancer, respectively	[38]
South America	Brazil	*TP53*	c.1010G>A	70–80% of *TP53* mutations in patients with breast cancer in Brazil	[13]
Asia	China	*MSH2*	c.1452_1455del	21% of Lynch syndrome mutations in Guangdong	[37]
	Palestine	*TP53*	c.541G>A	2% of women with early-onset breast cancer in one study	[39]
Europe	Denmark	*MLH1*	c.1667+2_1667+8del7ins4	25% of Lynch syndrome mutations in Amsterdam	[37]
	Portugal	*BRCA2*	c.156_157insAlu	37.9% of *BRCA2* pathogenic variants in Portuguese families	[40]
	Germany	*VHL*	c.T292C, c.T334C	Observed in families from the Black Forest and east central regions	[41]
Oceania	Australia	*BRCA1*	c.3331_3334del	Also recurrent in Hispanic populations, Europe, the United Kingdom, and the USA	[15]
	Australia	*BRCA2*	c.6275_6276del	Also recurrent in the United Kingdom, Belgium, Spain, the Netherlands, and North America	[15]

Models for implementation of GCRA

The high cost of diagnostic cancer gene sequencing has historically been a barrier to access, although costs associated with newer methodologies (high-throughput massively parallel or next-generation sequencing) are decreasing significantly. Intrinsic to the identification and management of patients with hereditary cancer is the complexity of interpreting and communicating the genetic information as well as the desirability for a multidisciplinary approach in patient care. Different models have been proposed to provide comprehensive GCRA, including the following three.

Integrated nationwide reference centres provide GCRA, genetic testing, and long-term management of patients and families with hereditary cancer in specialized networks. There are examples of such networks in the United Kingdom (within specialist genetic services of the National Health System), France (in the national health-care system), and Canada (http://ocp.cancercare.on.ca/cms/One.aspx?portalId=77515&pageId=10051) [17].

The community of practice approach relies on the collaboration of academic centres with community-based providers in practice networks, leveraging their practice with the experience and the multidisciplinary nature of academic programmes [5,18,19].

In integrated GCRA, consultations and/or referrals are embedded in pathology services or oncology practices. For example, a reflexive statement may be included in the pathology report (e.g. *BRCA* mutation testing is suggested in all high-grade serous ovarian cancers) and/or electronic medical record. Genetic counsellors may be embedded in oncology clinics to identify eligible patients and provide point-of-service GCRA during oncology visits [19,20].

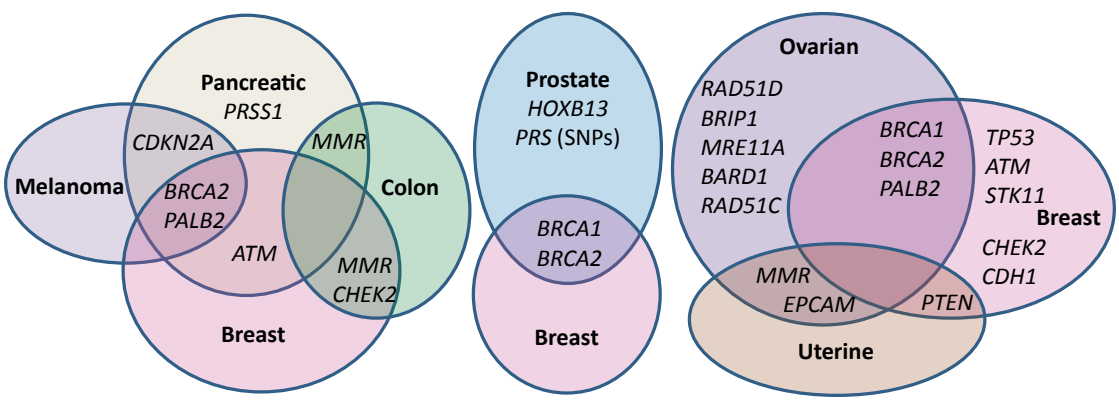
These established models are being challenged by (i) the practice shift from single-gene testing to multigene panel testing, thus increasing the complexity of risk interpretation and communication; (ii) the expansion of direct-to-consumer genetic testing platforms, which offer, but do not require, genetic counselling; and (iii) the increasing identification of germline hereditary cancer predisposition through genomic tumour analysis, which provides unsolicited and previously unsuspected diagnoses of hereditary cancer. Furthermore, the availability of targeted drug therapies has created a medical necessity and increased the frequency of germline genetic testing in a treatment-focused context; however, inclusion of personal and family counselling has not been emphasized.

Whatever the approach, several studies indicate that genetic testing rates are still low and a significant proportion of patients with hereditary cancer remain undetected; this is the main argument in favour of proposing population-based genetic testing for high-risk variants, regardless of clinical or pathological features. However, robust evidence for the cost–effectiveness and feasibility of such practices is still lacking outside populations with a high frequency of founder mutations in hereditary cancer. Finally, there are numerous initiatives to increase the low rate of cascade testing to identify at-risk relatives [21–23].

Management of patients with hereditary cancer

In the past two decades, major advances have occurred in the diagnosis and management of patients with hereditary cancer [5,7]. The advent and decreasing costs of next-generation sequencing have resulted in the development of multigene panel testing and a significant expansion of knowledge about the genes involved and the degree of phenotypic overlap among them (Fig. 6.5.2). In addition, incidental (unrelated to the respective phenotype) but clinically important findings have become increasingly common, such as those identified through tumour genetic testing and those that do not match the clinical picture (e.g. the presence of a P/LP germline variant in a mismatch repair gene in a proband with no personal and/or family history of colon cancer) [24–26].

Fig. 6.5.2. Phenotypic overlap of solid tumours observed in association with germline pathogenic or likely pathogenic variants in cancer predisposition genes. SNPs, single-nucleotide polymorphisms.



Compared with sequential single-gene testing, multigene panel testing is more efficient in identifying a P/LP variant, less expensive, and faster, and it also identifies variants in intermediate-penetrance (moderate- or low-risk) genes. For these reasons, next-generation sequencing is often regarded as an increasingly economical diagnostic tool, with the potential to democratize access to effective risk assessment and cancer prevention.

However, for many of the genes included in multigene panel testing, there are still limited data on cancer-specific penetrance, and therefore screening or risk-reducing interventions are less established (Box 6.5.2). As a result, clinical management of patients harbouring a P/LP variant in a moderate-penetrance gene or a newly identified gene with little associated information can be very challenging. The guidelines of the National Comprehensive Cancer Network change every year in response to this dynamic. Furthermore, the identification of a P/LP variant in a moderate-penetrance gene may not necessarily be associated with causality of the phenotype that motivated testing. In these situations, a critical review of results of genetic testing in light of the family history of cancer and segregation analyses may add to the interpretation of the significance of the results.

Multigene panel testing has also resulted more often in the identification of unexpected, phenotype-unrelated P/LP variants. Apart from the question of causality, one has to consider the incomplete knowledge of allelic heterogeneity and genotype–phenotype associations in these situations. A recent study showed that carriers of germline *TP53* mutations identified by multigene panel testing had fewer tumours in childhood, had an older median age at first cancer diagnosis, and less often met established testing criteria for Li–Fraumeni syndrome, compared with those identified by single-gene testing [27]. These findings are likely to result in a revision of the phenotype and genetic testing criteria for Li–Fraumeni syndrome.

The definition of the penetrance of variants has also been shown to be of great importance in cascade testing of a patient's relatives. As demonstrated recently, residual cancer risk for relatives who test negative for a familial P/LP variant is inversely proportional to variant penetrance and is influenced by family history of cancer. Therefore, negative results of familial testing for high-penetrance variants have a higher negative predictive value than those for low-penetrance variants, and counselling of a relative who is unaffected by cancer and has a P/LP germline variant in a low-penetrance gene should take into account family history of cancer [28].

Another challenge that arises as a consequence of the improved diagnostic capacity is the frequent identification of variants of uncertain significance; this is an especially frequent occurrence in populations that are less well represented. Despite multiple efforts to standardize the process of variant calling, discordant classifications among different laboratories are still fairly common. In a study of 518 patients (603 genetic variants) tested in more than one laboratory, the interpretation differed among the laboratories for 155 (26%) of the variants [29].

In addition to variant calling, disclosure of a result of variants of uncertain significance is a challenge both for the patient and for the clinician, because the result does not have an associated clinical utility. To overcome this challenge, efforts should be directed towards reclassification of variants of uncertain significance, but that process usually takes years, and when it is available, patient contact and counselling may be difficult.

Taken together, the benefits and challenges of multigene panel

Box 6.5.2. Different levels of information and clinical utility of results of multigene panel testing, according to the genes harbouring pathogenic or likely pathogenic variants.

Genes associated with a well-known cancer predisposition syndrome

- Highest cancer risks
- High-penetrance, low-frequency alleles
- Risk well defined for most associated cancers
- Screening and management guidelines well defined
- Clear implications for family members

Genes not associated with a well-known syndrome but well known/researched

- Moderate to high cancer risks
- Moderate-penetrance and high- or moderate-frequency alleles
- Risk fairly well defined for some but not all cancers
- Screening and management guidelines dependent on test results and family history
- Implications for family members less well defined

Recently described genes

- Cancer risks not well defined (usually moderate or low)
- Management guidelines not well defined
- Implications for family members not clear
- Frequent variants of uncertain significance
- May not change medical management

testing underscore the importance of genetic counselling and taking a family history of cancer – an affordable tool that can still drive patient care and data-sharing initiatives in providing clinically useful genetic information [8,26].

Finally, although the benefit of risk-reducing mastectomy and salpingo-oophorectomy for *BRCA* mutation carriers is well established, there have also been important advances in evidence to support cancer risk-reducing strategies in other scenarios. The most emblematic example is that of Li–Fraumeni syndrome (OMIM no. 151623), one of the most aggressive cancer predisposition syndromes, which is described and characterized by a high and early-onset risk of cancer. The disease is caused by germline *TP53* mutations, and carriers have an estimated lifetime risk of 80% (males) to 100% (females) of developing at least one malignancy. In a recent study of 214 families with Li–Fraumeni syndrome, 4% of carriers developed a malignancy in the first year of life, 41% were diagnosed with cancer by age 18 years, and 40% developed second neoplasms [30]. In another study of 286 carriers from 107 families, the cumulative cancer incidence was 50% by age 31 years in females and 50% by age 46 years in males, and nearly 100% by age 70 years for the entire cohort [31].

Recently, survival benefits from intensive cancer screening in patients with Li–Fraumeni syndrome have been reported, and this has completely changed the approach towards managing affected families. In 2004, a clinical surveillance protocol using physical examination and frequent biochemical and imaging studies was introduced in three tertiary care centres in North America. An 11-year follow-up showed that 5-year overall survival was significantly higher in individuals undergoing surveillance than in those not undergoing surveillance. This result shows that long-term compliance with surveillance for early tumour detection in patients with Li–Fraumeni syndrome is effective [32]. Similar strategies have been applied in other countries, and although results from screening are positive overall, there are still limited data on the effect on mortality and a lack of consensus on the best long-term follow-up protocol [33].

A very recent advance is the development of polygenic risk scores that combine information on multiple single-nucleotide polymorphisms, which are associated with very modest risk individually. As these tools are clinically validated, they will refine the capacity to predict risk and apply tailored interventions [34].

Current challenges, and interventions to overcome barriers

The identification and management of patients with hereditary cancer should be regarded as a public health concern, because public health plays an important role in ensuring access to interventions that can prevent disease. The timely identification of patients with hereditary cancer and their at-risk relatives can drastically change the management of individuals who have already been diagnosed with cancer, and enables the implementation of cancer prevention strategies or early detection options among at-risk relatives who are unaffected by cancer.

However, to ensure that all benefits of incorporating genetic or genomic information into an individual's clinical care are attained at a global level, several barriers must still be overcome. Actions suggested to reduce such barriers include, but are not restricted to, the following:

- Invest in the education of healthcare providers, to reduce variability in knowledge about hereditary cancer and to qualify them to provide genetic services. Inform and empower patients with hereditary cancer, to enhance the adherence to and effectiveness of interventions to reduce cancer risk. These actions aim at a reduction of the harms that have been reported as a result of lack of access to adequate genetic testing, inaccurate interpretation of results, or failure to tailor risk-reducing interventions appropriately.
- Address the challenge of a limited workforce in GCRA through the development of tailored initiatives aimed at increasing access to service provision for at-risk individuals.
- Improve the quality of care (i.e. accuracy of genetic testing and interpretation of results) through research efforts, data sharing, training of multidisciplinary teams, and regulatory actions. This includes (i) in-depth study of the clinical utility (i.e. associated cancer risks and appropriate screening and risk-reducing options) of P/LP variants in moderate-penetrance genes and in newly identified genes; (ii) in-depth study of the clinical significance of unexpected, phenotype-unrelated findings obtained by multigene panel testing; and (iii) characterization of the mutational landscape and associated phenotypes in populations or countries with reduced access to genetic risk assessment and, thus, very limited available information.
- Invest in population-specific research to better define the landscape of genetic variants (individually or in combination) that significantly influence cancer risk.
- Develop public policies aimed at increasing access to GCRA and management, including genetic counselling, testing, risk-reducing interventions, and targeted cancer therapies whenever applicable.

References

1. Rodriguez JL, Thomas CC, Massetti GM, Duquette D, Avner L, Iskander J, et al. (2016). CDC grand rounds: family history and genomics as tools for cancer prevention and control. MMWR Morb Mortal Wkly Rep. 65(46):1291–4. https://doi.org/10.15585/mmwr.mm6546a3 PMID:27880748

2. Euhus DM, Robinson L (2013). Genetic predisposition syndromes and their management. Surg Clin North Am. 93(2):341–62. https://doi.org/10.1016/j.suc.2013.01.005 PMID:23464690

3. Desai AV, Perpich M, Godley LA (2017). Clinical assessment and diagnosis of germline predisposition to hematopoietic malignancies: the University of Chicago experience. Front Pediatr. 5:252. https://doi.org/10.3389/fped.2017.00252 PMID:29270394

4. Daly MB, Pilarski R, Berry M, Buys SS, Farmer M, Friedman S, et al. (2017). NCCN guidelines insights: genetic/familial high-risk assessment: breast and ovarian, version 2.2017. J Natl Compr Canc Netw. 15(1):9–20. https://doi.org/10.6004/jnccn.2017.0003 PMID:28040716

5. Weitzel JN, Blazer KR, MacDonald DJ, Culver JO, Offit K (2011). Genetics, genomics, and cancer risk assessment: state of the art and future directions in the era of personalized medicine. CA Cancer J Clin. 61(5):327–59. https://doi.org/10.3322/caac.20128 PMID:21858794

6. Acuna-Hidalgo R, Veltman JA, Hoischen A (2016). New insights into the generation and role of de novo mutations in health and disease. Genome Biol. 17(1):241. https://doi.org/10.1186/s13059-016-1110-1 PMID:27894357

7. Slavin TP, Niell-Swiller M, Solomon I, Nehoray B, Rybak C, Blazer KR, et al. (2015). Clinical application of multigene panels: challenges of next-generation counseling and cancer risk management. Front Oncol. 5:208. https://doi.org/10.3389/fonc.2015.00208 PMID:26484312

8. George R, Kovak K, Cox SL (2015). Aligning policy to promote cascade genetic screening for prevention and early diagnosis of heritable diseases. J Genet Couns. 24(3):388–99. https://doi.org/10.1007/s10897-014-9805-5 PMID:25577298

9. Tuffaha HW, Mitchell A, Ward RL, Connelly L, Butler JRG, Norris S, et al. (2018). Cost-effectiveness analysis of germ-line *BRCA* testing in women with breast cancer and cascade testing in family members of mutation carriers. Genet Med. 20(9):985–94. https://doi.org/10.1038/gim.2017.231 PMID:29300376

10. Green RF, Ari M, Kolor K, Dotson WD, Bowen S, Habarta N, et al. (2019). Evaluating the role of public health in implementation of genomics-related recommendations: a case study of hereditary cancers using the CDC Science Impact Framework. Genet Med. 21(1):28–37. https://doi.org/10.1038/s41436-018-0028-2 PMID:29907802

11. Liedke PE, Finkelstein DM, Szymonifka J, Barrios CH, Chavarri-Guerra Y, Bines J, et al. (2014). Outcomes of breast cancer in Brazil related to health care coverage: a retrospective cohort study. Cancer Epidemiol Biomarkers Prev. 23(1):126–33. https://doi.org/10.1158/1055-9965.EPI-13-0693 PMID:24165578

12. Martínez-Mesa J, Werutsky G, Michiels S, Pereira Filho CAS, Dueñas-González A, Zarba JJ, et al. (2017). Exploring disparities in incidence and mortality rates of breast and gynecologic cancers according to the Human Development Index in the Pan-American region. Public Health. 149:81–8. https://doi.org/10.1016/j.puhe.2017.04.017 PMID:28577441

13. Achatz MI, Zambetti GP (2016). The inherited p53 mutation in the Brazilian population. Cold Spring Harb Perspect Med. 6(12):a026195. https://doi.org/10.1101/cshperspect.a026195 PMID:27663983

14. Foulkes WD, Knoppers BM, Turnbull C (2016). Population genetic testing for cancer susceptibility: founder mutations to genomes. Nat Rev Clin Oncol. 13(1):41–54. https://doi.org/10.1038/nrclinonc.2015.173 PMID:26483301

15. Rebbeck TR, Friebel TM, Friedman E, Hamann U, Huo D, Kwong A, et al.; EMBRACE; GEMO Study Collaborators; HEBON (2018). Mutational spectrum in a worldwide study of 29,700 families with *BRCA1* or *BRCA2* mutations. Hum Mutat. 39(5):593–620. https://doi.org/10.1002/humu.23406 PMID:29446198

16. Bray F, Jemal A, Grey N, Ferlay J, Forman D (2012). Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. Lancet Oncol. 13(8):790–801. https://doi.org/10.1016/S1470-2045(12)70211-5 PMID:22658655

17. Gadzicki D, Evans DG, Harris H, Julian-Reynier C, Nippert I, Schmidtke J, et al. (2011). Genetic testing for familial/hereditary breast cancer – comparison of guidelines and recommendations from the UK, France, the Netherlands and Germany. J Community Genet. 2(2):53–69. https://doi.org/10.1007/s12687-011-0042-4 PMID:22109790

18. Blazer KR, Christie C, Uman G, Weitzel JN (2012). Impact of web-based case conferencing on cancer genetics training outcomes for community-based clinicians. J Cancer Educ. 27(2):217–25. https://doi.org/10.1007/s13187-012-0313-8 PMID:22328115

19. McCuaig JM, Stockley TL, Shaw P, Fung-Kee-Fung M, Altman AD, Bentley J, et al.; BRCA TtoT Community of Practice (2018). Evolution of genetic assessment for BRCA-associated gynaecologic malignancies: a Canadian multisociety roadmap. J Med Genet. 55(9):571–7. https://doi.org/10.1136/jmedgenet-2018-105472 PMID:30042185

20. Kentwell M, Dow E, Antill Y, Wrede CD, McNally O, Higgs E, et al. (2017). Mainstreaming cancer genetics: a model integrating germline *BRCA* testing into routine ovarian cancer clinics. Gynecol Oncol. 145(1):130–6. https://doi.org/10.1016/j.ygyno.2017.01.030 PMID:28162234

21. Slavin TP, Banks KC, Chudova D, Oxnard GR, Odegaard JI, Nagy RJ, et al. (2018). Identification of incidental germline mutations in patients with advanced solid tumors who underwent cell-free circulating tumor DNA sequencing. J Clin Oncol. [Epub ahead of print] https://doi.org/10.1200/JCO.18.00328 PMID:30339520

22. Manchanda R, Legood R (2018). Population based germline testing for primary cancer prevention. Oncotarget. 9(69):33062–3. https://doi.org/10.18632/oncotarget.25995 PMID:30237851

23. Caswell-Jin JL, Zimmer AD, Stedden W, Kingham KE, Zhou AY, Kurian AW (2019). Cascade genetic testing of relatives for hereditary cancer risk: results of an online initiative. J Natl Cancer Inst. 111(1):95–8. https://doi.org/10.1093/jnci/djy147 PMID:30239769

24. Yurgelun MB, Allen B, Kaldate RR, Bowles KR, Judkins T, Kaushik P, et al. (2015). Identification of a variety of mutations in cancer predisposition genes in patients with suspected Lynch syndrome. Gastroenterology. 149(3):604–13.e20. https://doi.org/10.1053/j.gastro.2015.05.006 PMID:25980754

25. Roberts ME, Jackson SA, Susswein LR, Zeinomar N, Ma X, Marshall ML, et al. (2018). *MSH6* and *PMS2* germ-line pathogenic variants implicated in Lynch syndrome are associated with breast cancer. Genet Med. 20(10):1167–74. https://doi.org/10.1038/gim.2017.254 PMID:29345684

26. Graffeo R, Livraghi L, Pagani O, Goldhirsch A, Partridge AH, Garber JE (2016). Time to incorporate germline multigene panel testing into breast and ovarian cancer patient care. Breast Cancer Res Treat. 160(3):393–410. https://doi.org/10.1007/s10549-016-4003-9 PMID:27734215

27. Rana HQ, Gelman R, LaDuca H, McFarland R, Dalton E, Thompson J, et al. (2018). Differences in *TP53* mutation carrier phenotypes emerge from panel-based testing. J Natl Cancer Inst. 110(8):863–70. https://doi.org/10.1093/jnci/djy001 PMID:29529297

28. Lee AJ, Cunningham AP, Tischkowitz M, Simard J, Pharoah PD, Easton DF, et al. (2016). Incorporating truncating variants in *PALB2*, *CHEK2*, and *ATM* into the BOADICEA breast cancer risk model. Genet Med. 18(12):1190–8. https://doi.org/10.1038/gim.2016.31 PMID:27464310

29. Balmaña J, Digiovanni L, Gaddam P, Walsh MF, Joseph V, Stadler ZK, et al. (2016). Conflicting interpretation of genetic variants and cancer risk by commercial laboratories as assessed by the Prospective Registry of Multiplex Testing. J Clin Oncol. 34(34):4071–8. https://doi.org/10.1200/JCO.2016.68.4316 PMID:27621404

30. Bougeard G, Renaux-Petel M, Flaman JM, Charbonnier C, Fermey P, Belotti M, et al. (2015). Revisiting Li-Fraumeni syndrome from *TP53* mutation carriers. J Clin Oncol. 33(21):2345–52. https://doi.org/10.1200/JCO.2014.59.5728 PMID:26014290

31. Mai PL, Khincha PP, Loud JT, DeCastro RM, Bremer RC, Peters JA, et al. (2017). Prevalence of cancer at baseline screening in the National Cancer Institute Li-Fraumeni syndrome cohort. JAMA Oncol. 3(12):1640–5. https://doi.org/10.1001/jamaoncol.2017.1350 PMID:28772286

32. Villani A, Shore A, Wasserman JD, Stephens D, Kim RH, Druker H, et al. (2016). Biochemical and imaging surveillance in germline *TP53* mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. Lancet Oncol. 17(9):1295–305. https://doi.org/10.1016/S1470-2045(16)30249-2 PMID:27501770

33. Asdahl PH, Ojha RP, Hasle H (2017). Cancer screening in Li-Fraumeni syndrome. JAMA Oncol. 3(12):1645–6. https://doi.org/10.1001/jamaoncol.2017.2459 PMID:28772307

34. Mavaddat N, Michailidou K, Dennis J, Lush M, Fachal L, Lee A, et al.; ABCTB Investigators; kConFab/AOCS Investigators; NBCS Collaborators (2019). Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. Am J Hum Genet. 104(1):21–34. https://doi.org/10.1016/j.ajhg.2018.11.002 PMID:30554720

35. Laraqui A, Uhrhammer N, Rhaffouli HE, Sekhsokh Y, Lahlou-Amine I, Bajjou T, et al. (2015). *BRCA* genetic screening in Middle Eastern and North African: mutational spectrum and founder *BRCA1* mutation (c.798_799delTT) in North African. Dis Markers. 2015:194293. https://doi.org/10.1155/2015/194293 PMID:25814778

36. Seymour HJ, Wainstein T, Macaulay S, Haw T, Krause A (2016). Breast cancer in high-risk Afrikaner families: is *BRCA* founder mutation testing sufficient? S Afr Med J. 106(3):264–7. https://doi.org/10.7196/SAMJ.2016.v106i3.10285 PMID:26915939

37. Ponti G, Castellsagué E, Ruini C, Percesepe A, Tomasi A (2015). Mismatch repair genes founder mutations and cancer susceptibility in Lynch syndrome. Clin Genet. 87(6):507–16. https://doi.org/10.1111/cge.12529 PMID:25345868

38. Villarreal-Garza C, Alvarez-Gómez RM, Pérez-Plasencia C, Herrera LA, Herzog J, Castillo D, et al. (2015). Significant clinical impact of recurrent *BRCA1* and *BRCA2* mutations in Mexico. Cancer. 121(3):372–8. https://doi.org/10.1002/cncr.29058 PMID:25236687

39. Lolas Hamameh S, Renbaum P, Kamal L, Dweik D, Salahat M, Jaraysa T, et al. (2017). Genomic analysis of inherited breast cancer among Palestinian women: genetic heterogeneity and a founder mutation in *TP53*. Int J Cancer. 141(4):750–6. https://doi.org/10.1002/ijc.30771 PMID:28486781

40. Peixoto A, Santos C, Pinheiro M, Pinto P, Soares MJ, Rocha P, et al. (2011). International distribution and age estimation of the Portuguese *BRCA2* c.156_157insAlu founder mutation. Breast Cancer Res Treat. 127(3):671–9. https://doi.org/10.1007/s10549-010-1036-3 PMID:20652400

41. Nielsen SM, Rhodes L, Blanco I, Chung WK, Eng C, Maher ER, et al. (2016). Von Hippel-Lindau disease: genetics and role of genetic counseling in a multiple neoplasia syndrome. J Clin Oncol. 34(18):2172–81. https://doi.org/10.1200/JCO.2015.65.6140 PMID:27114602

6.6 Screening
From biology to public health

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SUMMARY

- Early detection of cancer is a critical component of cancer control. In addition to reduction of mortality from a specific cancer type, a proper approach to cancer screening should ensure that the harms do not outweigh the benefits.
- A linear evolution has been the underlying concept of carcinogenesis. However, a better understanding of tumour biology would help to broaden cancer screening coverage while reducing the overdiagnosis of indolent tumours and the underdiagnosis of interval cancers.
- Alternative screening algorithms should not only overcome the challenges of morphology-based diagnosis but also help to improve adherence in the context of population-based screening, to reduce the gap in mortality reduction between high-income countries and low- and middle-income countries.
- After decades of research and development, only screening for cervical cancer, breast cancer, and colorectal cancer has been successfully implemented, generally in high-income countries.
- Observer-dependent techniques are limited by inter-observer variability in the interpretation of findings and by errors in sampling techniques for microscopic analysis.
- The hallmarks of cancer may offer a new approach to cancer screening by combining oncoproteins, cell damage markers, and epigenetic markers.
- Cost–effectiveness analyses on organization of cervical cancer and breast cancer screening report variable results depending on the assumptions in the models.

The available evidence consistently shows that survival rates are significantly higher for cancers that are detected at early stages and properly treated than for advanced cancers [1]. Early detection of cancer is achievable either by earlier diagnosis in symptomatic patients or by systematic screening of asymptomatic individuals. Although prolonged survival is a desired outcome for the evaluation of treatment, reduction of mortality from a specific cancer is the primary objective for cancer screening [2].

The principles of screening for disease proposed by Wilson and Jungner [3] have been regularly used to analyse the progress of implementation of organized cancer screening [4,5]. More recently, dos Santos Silva summarized the essential components of successful cancer screening as a suitable disease, a suitable screening test, and a suitable screening programme [2]. These proposed principles highlight the need to detect the disease at a preclinical stage and provide timely treatment to reduce the associated mortality, the need for screening tests with good accuracy, and the need for population-based screening programmes with quality assurance and access to confirmatory diagnosis and treatment, among other characteristics (Box 6.6.1).

Cancer screening programmes aim to comply with these principles. However, recent research has revealed more clearly that cancer screening is a complex scenario in which there are both benefits and harms, and that in some instances the harms may outweigh the benefits or the determination of whether the benefits outweigh the harms can be made only by the individual patient [4]. After decades of research and development, only screening for cervical cancer, breast cancer, and colorectal cancer has been successfully implemented, generally in high-income countries [6–8], whereas screening for other cancer types, such as prostate cancer, lung cancer, and stomach cancer, continues to be debated [4]. In low- and middle-income countries, where the burden of cancer mortality is growing, there has been no significant progress in the implementation of cancer screening [9].

Contradictory results from both clinical research and effectiveness research have promoted an intense

scientific debate about the valid methods for the assessment and evaluation of cancer screening [10], as well as about alternative approaches for programme organization to pursue a better balance between diagnostic accuracy and treatment rates [11,12]. The uncertainty derived from this controversy can be reduced only by progressively understanding tumour biology, the factors associated with successful screening, and technology development as a binding element between cancer biology and public health programmes. This chapter reviews the contribution and potential use of knowledge about these elements as a means to improve early detection of cancer.

Biological bases of screening

Natural history of the disease

A linear model with consecutive steps explains carcinogenesis from initiation to invasion [13]. The clonal evolution theory states that a first mutation in a driver gene induces abnormal cell proliferation; a second mutation contributes to abnormal cell division and the alteration of cellular architecture, resulting in benign tumours or identifiable precancerous conditions; and subsequent mutations produce the final transformation to a cell with invasive capacity [13].

With this approach, actionable models of carcinogenesis are best expressed by the progress of cervical intraepithelial neoplasia to invasive cervical cancer and the development of adenomatous polyps that progress to invasive cancer of the colon [5]. However, the approach is also proposed in the development of cutaneous naevi to melanoma, the progression of Barrett oesophagus to oesophageal adenocarcinoma, and the progression of ductal adenocarcinomas in the pancreas and the breast [5,13,14].

In this context, dysplasia is the ideal surrogate marker for cancer, and its detection in asymptomatic individuals is seen as the best way to intervene in the natural history of the disease [4,15]. However, the use of morphological features for the diagnosis of pre-neoplastic lesions poses the inherent challenge of accessing the target organ [15]. In addition, breast cancer, prostate cancer, and lung cancer have revealed great heterogeneity of disease, with controversial results in mortality reduction by screening [5].

The existence for the same cancer type of indolent, less aggressive (slow-progressing), and aggressive tumours is currently one of the biggest challenges for cancer screening, given the possibility of overdiagnosis of tumours without clinical significance and, at the same time, the difficulty of detecting lethal tumours in early phases (interval cancers). Furthermore, the identification of only a limited number of driver genes, the discouraging results of mutation-targeted therapies on overall survival, and the variable progression of precancerous lesions, most of which return spontaneously, challenge the theory of successive linear somatic mutations as the only route of carcinogenesis [5,14,16].

Next-generation sequencing has shown for a single tumour thousands of genetic alterations not contained in germlines, and has enabled a better understanding of the roles of these alterations not only by differentiating driver genes from passenger genes but also by elucidating the role of epigenetic alterations involved in malignant cellular transformation. Moreover, recent publications have highlighted the role of the tissue and tumour microenvironment [16] and have proposed new approaches to better explain tumour heterogeneity and the onset of aggressive tumours over a short period, such as the concept of the field effect, which suggests multiple initiating cells with independent evolution [17]. In addition, alternative models of clonal evolution suggest branched and punctuated evolutions; branched evolution entails multiple clonal lineages evolving in parallel and cellular cooperation via paracrine interactions, and the model of punctuated evolution states that many anomalies involving genomic instability could rapidly occur, reshaping the entire genome from one or two dominant clones [18] (Fig. 6.6.1).

The new theories enable a better understanding of tumour diversity. Srivastava et al. have argued that the difference between indolent and aggressive tumours may not rely exclusively on the characteristics of tumour cells, but is instead determined by interactions among the host, environmental exposures, and neoplasia [14]. Therefore, understanding these interactions could determine

FUNDAMENTALS

- The essential components of successful cancer screening are a suitable disease, a suitable screening test, and a suitable screening programme. Although there is relative consensus about these principles of screening, improved knowledge about the critical components is required.
- The natural history of the disease does not enable an understanding of the differences between indolent, less aggressive, and aggressive tumours. This challenge can lead to both overtreatment and undertreatment of cancers detected by screening.
- Improved knowledge of tumour biology warrants new approaches in developing screening tests or in combining screening tests in alternative algorithms to improve the accuracy and reliability.
- The experience in both high-income countries and low- and middle-income countries on implementation of cancer screening has furthered innovative programmatic approaches that are suited to different levels of resources and contexts.

Box 6.6.1. Principles of cancer screening.

Principles of early disease detection, from Wilson and Jungner (1968) [3]:

1. The condition sought should be an important health problem.
2. There should be a recognizable latent or early symptomatic stage.
3. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
4. There should be an accepted treatment for patients with recognized disease, and treatment should be better at an earlier stage.
5. There should be an agreed policy on whom to treat, for patient care as a whole.
6. There should be a suitable test or examination.
7. The test should be acceptable to the population.
8. Facilities for diagnosis and treatment should be available.
9. Case-finding should be a continuing process and not a "once-and-for-all" project.
10. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

Essential components of successful cancer screening, from dos Santos Silva (1999) [2]:

1. Suitable disease:
   - Detectable preclinical phase
   - Early treatment
   - Relative burden of disease.
2. Suitable screening test:
   - Validity (sensitivity and specificity)
   - Acceptability and costs.
3. Suitable screening programme:
   - There is a clear definition of the target population.
   - The individuals to be screened are identifiable.
   - Measures are available to ensure high coverage and attendance.
   - There are adequate field facilities for collecting the screening material and adequate laboratory facilities to examine it.
   - There is an organized quality control programme to assess the screening material and its interpretation.
   - Adequate facilities exist for diagnosis and appropriate treatment of confirmed neoplastic lesions and for the follow-up of treated individuals.
   - There is a carefully designed referral system for management of any abnormality found.
   - Evaluation and monitoring of the total programme is organized.

the ideal time to effectively use a screening test and significantly reduce the chance of overdiagnosis.

Hallmarks of cancer

Hanahan and Weinberg proposed a set of characteristics of malignant cells as the basis of molecular mechanisms that enable tumour growth and metastatic invasion [19]. They proposed acquired capabilities as the hallmarks of cancer cells, including sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, sustaining angiogenesis, evading immune destruction, reprogramming energy metabolism, and activating invasion and metastasis.

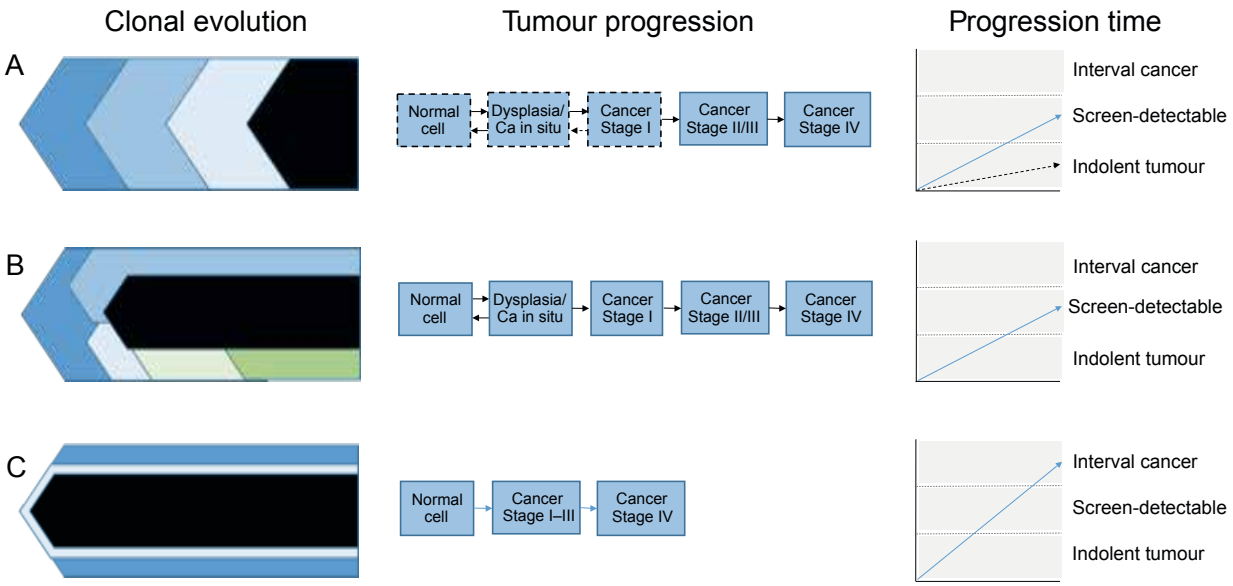
In addition to an improved understanding of cancer biology, the hallmarks of cancer offer an alternative approach to carcinogenesis unrelated to a specific evolutionary model. From this perspective, therapies targeted to precise signalling pathways have been developed irrespective of clinical stage at diagnosis, with the idea that each tumour expresses its hallmark capabilities within a certain clinical and molecular course, which might differ from patient to patient [14].

Although the described hallmarks are distinctive of malignant cells, many of them must be expressed early in the process of carcinogenesis. Accordingly, alterations in cell proliferation and differentiation, anti-growth signalling, and apoptosis have been reported for different precancerous conditions [20]. Therefore, early detection of anomalies in the cell circuits involved has prompted enthusiastic research into cancer screening. However, understanding the molecular profile of premalignant lesions remains challenging, because individual mutations do not follow a consistent pattern between premalignant and malignant states, suggesting a variable order and timing in the process of carcinogenesis [21]. In addition to cellular properties, changes in the surrounding tissue and in the cell microenvironment have been proposed as early indicators of malignant transformation, including pro-inflammatory and immune responses, changes in energy metabolism, and increased angiogenesis.

Screening tests

Cancer diagnosis continues to be morphology-based. Therefore, tissue or cell samples are needed to verify the malignant transformation, and this condition may influence the

Fig. 6.6.1. Models of clonal evolution and tumour progression. The relationship between models of carcinogenesis (clonal evolution with tumours shown in black), tumour progression through clinical stages, and progression time with regard to early detection by screening. A linear evolution of carcinogenesis (A) is more plausible in tumours that have a long sojourn time, progressively transit through clinical stages, and are detectable by screening. However, some tumours that are due to this pattern may have a slow growth rate (even regression) and would not be detected by screening (indolent tumours, shown by the dotted lines). In tumours with branched evolution (B), clones derive from a common ancestor but evolve in parallel. Such tumours may have more rapid progression, but the sojourn time is still long enough to enable their detection by screening. Some tumours have punctuated evolution (C), with a large number of mutations in short periods and one or two clones progressing rapidly. Therefore, they are more difficult to detect by screening (interval cancers).



development of technologies for the early detection of cancer.

To date, the epidemiological axiom favours the combination of a highly sensitive screening test with a highly specific diagnostic test [4]. Despite the low sensitivity of cervical cytology and faecal occult blood tests, the achievements of screening for cervical cancer and colorectal cancer reinforce this approach. Highly frequent screening (i.e. with a short interval) usually rectifies the low sensitivity; however, this is possible only if the disease has a long sojourn time and if it is not difficult to obtain tissue or cell samples, thus resulting in a positive balance between the benefits and the risk [15].

Safe specimen sampling is possible if direct anatomical access is available, as to the skin or the oral cavity, and even for organs that are accessible by endoscopy, such as the stomach. In contrast, the inaccessibility of visceral organs and the potential severity of adverse events associated with invasive procedures highlight the need to confer higher value to the specificity of screening tests, in addition to reassessing their capability to avoid the detection of indolent tumours.

An additional characteristic of morphology-based diagnosis is observer dependency. Most screening tests in use today (Table 6.6.1) seek macroscopic or microscopic visualization of changes related to malignant

Fig. 6.6.2. Safe specimen sampling is possible if direct anatomical access is available, as is the case for skin cancer screening.

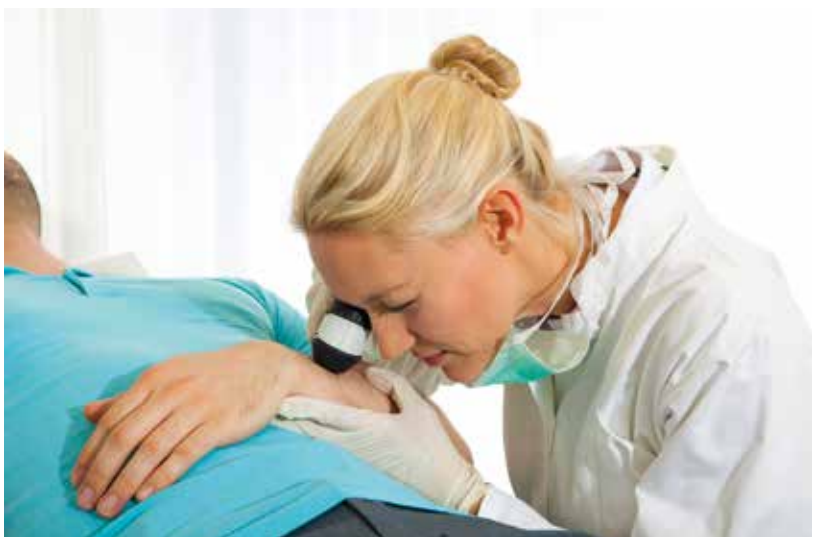


Table 6.6.1. Cancer screening practices

Cancer site	Screening test	Screening interval (years)	Main age range (years)	Mortality reduction?
Image-based screening				
Breast	Mammography	1–3	50–69	Yes
Lung	Low-dose computed tomography (CT)	1–2	55–74[a]	Yes
Stomach	Upper gastrointestinal X-ray series	1–2	≥ 40	Uncertain
Direct or endoscopic visual screening				
Cervix	Visual inspection with acetic acid (VIA)	1–3	30–49	Yes[b]
Oral	Direct visual inspection	1–3	≥ 35[a]	Yes[b]
Colon	Colonoscopy	5–10	50–69	Yes
Colon	Flexible sigmoidoscopy	3–5	55–69	Yes
Stomach	Upper gastrointestinal endoscopy	1–2	40–64	Uncertain
Clinical examination screening				
Breast	Clinical breast examination	1	40–69	Unknown
Breast	Breast self-examination	–	–	No
Cell sampling screening				
Cervix	Cervical cytology	1–3	25–69	Yes[b]
Biomarker-based screening				
Cervix	Human papillomavirus (HPV) testing	3–5	30–65	Yes
Colon	Faecal occult blood test (FOBT)	1–2	50–69	Yes
Stomach	Pepsinogen I/II		40–64	Unknown
Prostate	Prostate-specific antigen (PSA)	1–5	50–74	Uncertain
Liver	α-Fetoprotein (AFP)[c]	Every 6 months	High risk[a]	Uncertain
Ovary	CA125	–	–	No

[a] Restricted to individuals at high risk: tobacco use for lung cancer and oral cancer; chronic hepatitis or cirrhosis for liver cancer.

[b] Limited evidence: VIA, one trial using "screen and treat" in one visit; direct visual inspection, one trial without adjustment by cluster design; cervical cytology, based on observational studies (effectiveness).

[c] Regularly combined with ultrasound.

transformation. Observer-dependent techniques share some limitations, such as variability in the characteristics of premalignant and malignant lesions, inter-observer variability in the interpretation of findings, and errors in sampling techniques for microscopic analysis [15,22]. Although these techniques are complemented by histological verification, the limitations noted must be compensated for with short screening intervals and high reassessment rates.

Currently, research on alternative approaches to cancer screening focuses on functional images and biomarkers of early disease. To date, no single technology has overcome the limitations of anatomical accessibility or diagnostic accuracy and reliability. Therefore, the most likely future scenario would be to combine different tests in diagnostic algorithms to guarantee adequate sensitivity and specificity. However, gains in diagnostic accuracy could be counterbalanced by the effects of such algorithms on the number of visits and patient adherence to clinical protocol [23].

Biomarkers have several advantages for cancer screening, including the possibility of measuring them in body fluids, measuring in quantitative terms, lowering provider dependency, using automated platforms with high throughput, reducing costs by large-scale production, and reducing the number of visits through simultaneous testing in a single specimen [24]. However, most existing biomarkers suffer from limited sensitivity or low specificity for early identification of lesions with high malignant potential. To date, only human papillomavirus (HPV) tests and faecal occult blood tests have solid evidence for reduction of cancer mortality when used as screening tests (Table 6.6.1).

The search for new diagnostic biomarkers requires prolonged processes and faces several challenges, which increase if asymptomatic individuals with low prevalence of disease are envisioned as the target population. The accessibility of body fluids is countered by the lack of specificity to the site of tumour origin and by the low concentration of markers released in the early stages of tumour development [24]. Moreover, mortality reduction as the main research outcome and avoidance of

detection of indolent tumours continue to be major challenges in translating basic research into clinical practice. These limitations are common to tests based on cells, DNA, proteins, and circulating metabolites, which are currently the most widespread research approaches to early detection of cancer.

Some novel approaches to overcome these limitations include combining oncoproteins, cell damage markers, and epigenetic markers to increase specificity to lesions with high malignant potential [25], combining circulating markers with tumour antigens to improve specificity to the site of tumour origin [26], searching for markers in fluids specific to the site of tumour origin [27], and combining functional tests with anatomical images [28]. Thus, new technologies in genomics, proteomics, and metabolomics, as well as the growing number of high-quality biorepositories and a greater capacity for data analysis, are opening up new avenues to search for cancer screening biomarkers.

Furthermore, the use of big databases and machine learning offer new opportunities to improve the accuracy of screening tests (particularly for image-based screening) and to improve individual risk stratification in order to better guide screening protocols.

Screening programmes

Population-based programmes are considered to be essential for successful cancer screening (Box 6.6.1). The main effects expected from such programmes are increased coverage, improved cost–effectiveness, and improved equity. Early studies in Europe showed an inverse relationship between screening coverage and cervical cancer incidence and mortality [29]. However, this relationship is less clear in regions without population-based screening, such as Latin America, where screening coverage has increased but recall attendance after positive screening results remains low [30].

Although mortality rates from cervical cancer are low in Europe, data from programme evaluation in European countries show that population-based screening programmes do not cover most of the region [31] (see Chapter 4.5). Moreover, case–control studies reveal greater effectiveness for organized screening versus opportunistic screening [32,33], but cohort analyses have shown variable results over time, with a greater effect of organized screening on cervical cancer incidence revealed in earlier studies [34,35].

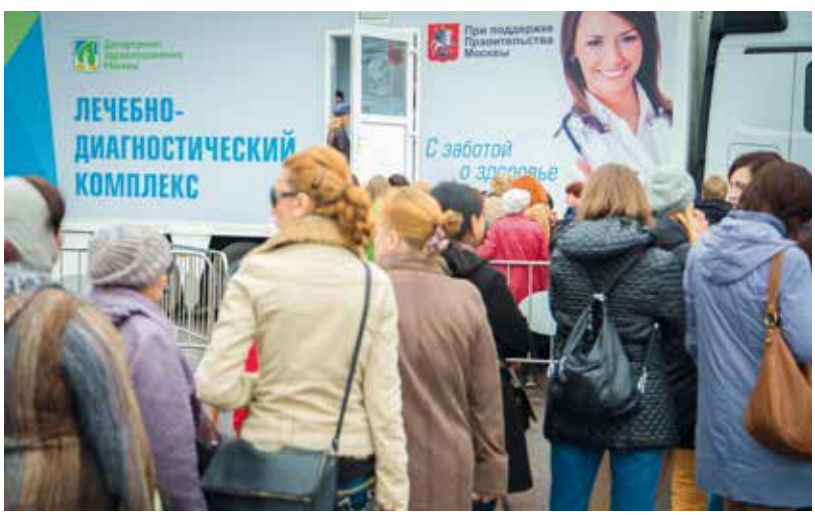
Similarly, cost–effectiveness analyses on organization of cervical cancer (see Chapter 5.10) and breast cancer (see Chapter 5.9) screening report variable results depending on the assumptions in the models. In general, organized screening is more cost-effective than opportunistic screening. However, analyses of the effectiveness of screening reveal no significant differences when data from real scenarios are fed into the models [36,37], as opposed to models with hypothetical scenarios that assume substantially lower participation rates for opportunistic screening [38].

Although the definition of organized and opportunistic screening is not consistent across studies, screening accuracy and excessive use of diagnostics have been identified as major factors that influence cost–effectiveness ratios [36]. Hence, quality assurance plays a central role in minimizing false-negative and false-positive results, and observer-dependent tests present a challenge in this respect. However, the broad concept should be tailored according to the level of resources, because certain quality assurance guidelines from high-income countries propose more than 40 indicators per programme [6–8], a standard that is difficult to meet in most low- and middle-income countries.

In addition to deficient participation and quality, deficient follow-up of positive screening results and reassessment of equivocal results contribute to the lack of mortality reduction in low- and middle-income countries [30], as well as to the higher mortality in socially disadvantaged populations in high-income countries. Cervical cytology screening has reduced mortality from cervical cancer in high-income countries, but short screening intervals and high reassessment rates hinder adherence in women with limited access to health care [30].

The gap in mortality reduction between high-income countries and low- and middle-income countries has invigorated the search for alternative programmatic approaches, accompanied by the introduction of

Fig. 6.6.3. Women waiting at a mobile clinic for free breast cancer screening in Moscow, Russian Federation.



technologies that conform to these approaches. A "screen and treat" approach in one or two visits has been proven to result in a significant reduction in mortality from cervical cancer in low-income settings, either with visual inspection with acetic acid or with HPV testing [39,40]. HPV testing has also enabled self-sampling and the identification of women at higher risk. Self-sampling favours participation in reluctant populations [41], and the identification of women at higher risk has led to a greater reduction in the incidence of cervical cancer [42]. However, the lower specificity must be corrected for by additional visits to triage HPV-positive women (Fig. 6.6.4).

Mammography screening has reduced mortality from breast cancer in high-income countries. However, the requirements for facilities and professional skills are challenges for patient access in low-income settings [43]. Moreover, controversial data on effectiveness, cost–effectiveness, and overdiagnosis have impaired the implementation of mammography screening programmes in low- and middle-income countries. A stepwise approach according to level of resources and health system capacity seems more suited to these scenarios, moving from breast awareness (based on breast self-examination) to a shift of the stage distribution of detected disease towards a lower stage (based on clinical breast examination) and progressive implementation of mammography screening (from hospital-based to population-based) [11].

Recently, stratified screening according to individual risk has been proposed for early detection of breast cancer [44]. This is the underlying concept of HPV testing in cervical cancer screening, and similar approaches have been developed for screening of colorectal cancer (by familial and genetic risk) and lung cancer (by smoking history). Although preliminary data on effectiveness and cost–effectiveness are positive, the ultimate success of the strategy will depend on the predictive capacity of risk assessment and the final impact on mortality reduction.

Conclusions

The connections among disease, screening tests, and screening programmes remain valid. However, in

Fig. 6.6.4. Alternative approaches for cervical cancer screening according to natural history of the disease. ^ Available technologies for self-collection and physician collection. * Visual inspection with acetic acid (VIA) has not reliably demonstrated high specificity.

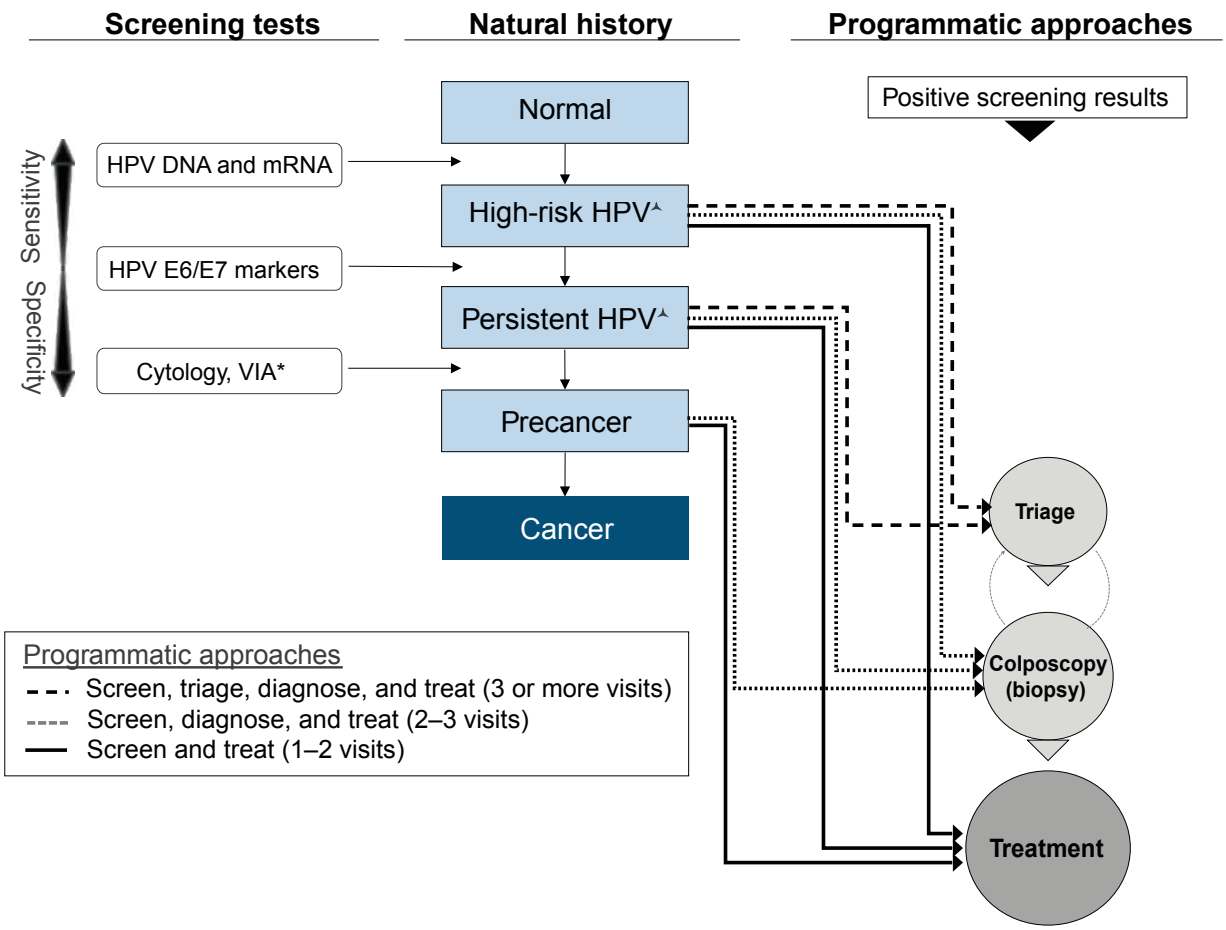
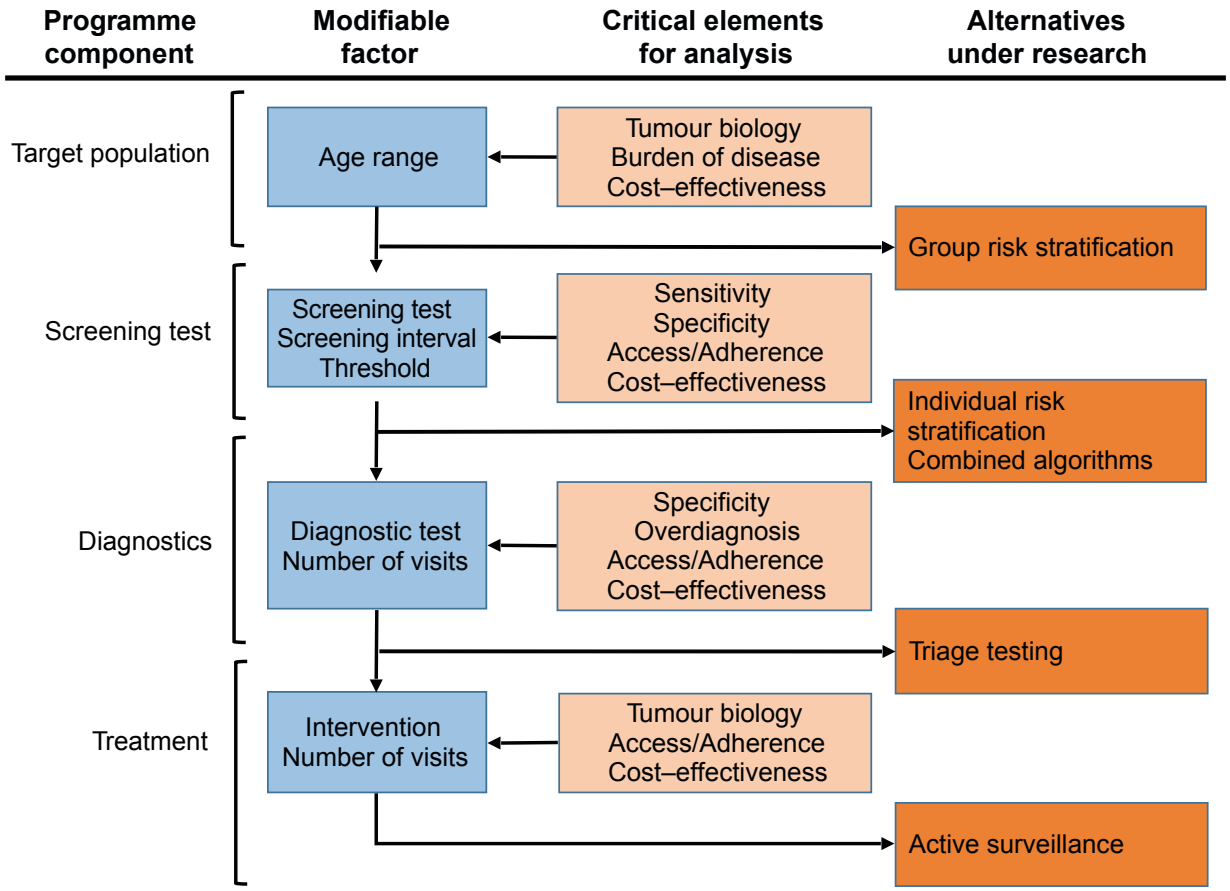


Fig. 6.6.5. Alternative approaches to cancer screening.



understanding tumour biology, the prevailing linear approach to identifying tumours with aggressive behaviour that merit early detection must be overcome. Overdiagnosis of indolent tumours and the morphological basis of cancer diagnosis are the most relevant challenges in searching for alternative approaches to cancer screening. These concepts elicit a change in the traditional epidemiological approach, in which the balance between sensitivity and specificity, as well as the predictive capacity of new technologies, must be reviewed.

Currently, the implementation of cancer screening might be improved by variations in programmatic approaches, including, as necessary, decreased screening intensity, a reduced number of visits for the clinical protocol, increased cut-off points for referrals on diagnostic confirmation, stratified screening according to population risk, and expecting behaviour against lesions that are suspected to be indolent [45] (Fig. 6.6.5). Knowledge accumulated from years of experience, not only in high-income countries but also in low- and middle-income countries, reveals the need to rethink screening programmes on the basis of the level of resources available and the specific conditions of each scenario. Combining programmatic approaches with suitable technologies ensures broader participation and increased treatment rates.

References

1. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al.; CONCORD Working Group (2018). Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 391(10125):1023–75. https://doi.org/10.1016/S0140-6736(17)33326-3 PMID:29395269

2. dos Santos Silva I (1999). Cancer prevention. In: Cancer epidemiology: principles and methods. Lyon, France: International Agency for Research on Cancer; pp. 355–380. Available from: http://publications.iarc.fr/421.

3. Wilson JMG, Jungner G (1968). Principles and practice of screening for disease. Public Health Papers No. 34. Geneva, Switzerland: World Health Organization. Available from: http://whqlibdoc.who.int/php/WHO_PHP_34.pdf.

4. Croswell JM, Ransohoff DF, Kramer BS (2010). Principles of cancer screening: lessons from history and study design issues. Semin Oncol. 37(3):202–15. https://doi.org/10.1053/j.seminoncol.2010.05.006 PMID:20709205

5. Shieh Y, Eklund M, Sawaya GF, Black WC, Kramer BS, Esserman LJ (2016). Population-based screening for cancer: hope and hype. Nat Rev Clin Oncol. 13(9):550–65. https://doi.org/10.1038/nrclinonc.2016.50 PMID:27071351

6. Dimitrova N, Parkinson ZS, Bramesfeld A, Ulutürk A, Bocchi G, López-Alcalde J, et al. (2016). European guidelines for breast cancer screening and diagnosis – the European breast guidelines. Luxembourg: Publications Office of the European Union. Available from: https://doi.org/10.2788/503032.

7. Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al. (2010). European guidelines for quality assurance in cervical cancer screening. Second edition – summary document. Ann Oncol. 21(3):448–58. https://doi.org/10.1093/annonc/mdp471 PMID:20176693

8. von Karsa L, Patnick J, Segnan N, Atkin W, Halloran S, Lansdorp-Vogelaar I, et al.; European Colorectal Cancer Screening Guidelines Working Group (2013). European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. Endoscopy. 45(1):51–9. https://doi.org/10.1055/s-0032-1325997 PMID:23212726

9. Sullivan T, Sullivan R, Ginsburg OM (2015). Screening for cancer: considerations for low- and middle-income countries. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. Disease control priorities. 3rd ed. Vol. 3, Cancer. Washington (DC), USA: World Bank; pp. 211–222.

10. Jacklyn G, Bell K, Hayen A (2017). Assessing the efficacy of cancer screening. Public Health Res Pract. 27(3):e2731727. https://doi.org/10.17061/phrp2731727 PMID:28765860

11. WHO (2014). WHO position paper on mammography screening. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/cancer/publications/mammography_screening/en/.

12. WHO (2013). WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/.

13. Vogelstein B, Kinzler KW (2015). The path to cancer – three strikes and you're out. N Engl J Med. 373(20):1895–8. https://doi.org/10.1056/NEJMp1508811 PMID:26559569

14. Srivastava S, Reid BJ, Ghosh S, Kramer BS (2016). Research needs for understanding the biology of overdiagnosis in cancer screening. J Cell Physiol. 231(9):1870–5. https://doi.org/10.1002/jcp.25227 PMID:26505642

15. Khunger M, Kumar U, Roy HK, Tiwari AK (2014). Dysplasia and cancer screening in 21st century. APMIS. 122(8):674–82. https://doi.org/10.1111/apm.12283 PMID:24910362

16. Brücher BL, Jamall IS (2016). Somatic mutation theory – why it's wrong for most cancers. Cell Physiol Biochem. 38(5):1663–80. https://doi.org/10.1159/000443106 PMID:27160408

17. Lochhead P, Chan AT, Nishihara R, Fuchs CS, Beck AH, Giovannucci E, et al. (2015). Etiologic field effect: reappraisal of the field effect concept in cancer predisposition and progression. Mod Pathol. 28(1):14–29. https://doi.org/10.1038/modpathol.2014.81 PMID:24925058

18. Davis A, Gao R, Navin N (2017). Tumor evolution: linear, branching, neutral or punctuated? Biochim Biophys Acta Rev Cancer. 1867(2):151–61. https://doi.org/10.1016/j.bbcan.2017.01.003 PMID:28110020

19. Hanahan D, Weinberg RA (2011). Hallmarks of cancer: the next generation. Cell. 144(5):646–74. https://doi.org/10.1016/j.cell.2011.02.013 PMID:21376230

20. Srivastava S, Grizzle WE (2010). Biomarkers and the genetics of early neoplastic lesions. Cancer Biomark. 9(1–6):41–64. https://doi.org/10.3233/CBM-2011-0204 PMID:22112469

21. Ryan BM, Faupel-Badger JM (2016). The hallmarks of premalignant conditions: a molecular basis for cancer prevention. Semin Oncol. 43(1):22–35. https://doi.org/10.1053/j.seminoncol.2015.09.007 PMID:26970122

22. Baron JA (2012). Screening for cancer with molecular markers: progress comes with potential problems. Nat Rev Cancer. 12(5):368–71. https://doi.org/10.1038/nrc3260 PMID:22495319

23. Herrero R, Murillo R (2018). Cervical cancer. In: Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, editors. Cancer epidemiology and prevention, 4th ed. New York (NY), USA: Oxford University Press; pp. 925–46.

24. Duffy MJ (2015). Use of biomarkers in screening for cancer. Adv Exp Med Biol. 867:27–39. https://doi.org/10.1007/978-94-017-7215-0_3 PMID:26530358

25. Wentzensen N, Schiffman M, Palmer T, Arbyn M (2016). Triage of HPV positive women in cervical cancer screening. J Clin Virol. 76(Suppl 1):S49–55. https://doi.org/10.1016/j.jcv.2015.11.015 PMID:26643050

26. Cohen JD, Li L, Wang Y, Thoburn C, Afsari B, Danilova L, et al. (2018). Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science. 359(6378):926–30. https://doi.org/10.1126/science.aar3247 PMID:29348365

27. Martin KJ, Fournier MV, Reddy GP, Pardee AB (2010). A need for basic research on fluid-based early detection biomarkers. Cancer Res. 70(13):5203–6. https://doi.org/10.1158/0008-5472.CAN-10-0987 PMID:20587531

28. Minamimoto R, Senda M, Jinnouchi S, Terauchi T, Yoshida T, Inoue T (2015). Detection of breast cancer in an FDG-PET cancer screening program: results of a nationwide Japanese survey. Clin Breast Cancer. 15(2):e139–46. https://doi.org/10.1016/j.clbc.2014.09.008 PMID:25454690

29. Quinn M, Babb P, Jones J, Allen E (1999). Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. BMJ. 318(7188):904–8. https://doi.org/10.1136/bmj.318.7188.904 PMID:10102852

30. Murillo R, Almonte M, Pereira A, Ferrer E, Gamboa OA, Jerónimo J, et al. (2008). Cervical cancer screening programs in Latin America and the Caribbean. Vaccine. 26(Suppl 11):L37–48. https://doi.org/10.1016/j.vaccine.2008.06.013 PMID:18945401

31. Basu P, Ponti A, Anttila A, Ronco G, Senore C, Vale DB, et al. (2018). Status of implementation and organization of cancer screening in the European Union Member States – summary results from the second European screening report. Int J Cancer. 142(1):44–56. https://doi.org/10.1002/ijc.31043 PMID:28940326

32. Makkonen P, Heinävaara S, Sarkeala T, Anttila A (2017). Impact of organized and opportunistic Pap testing on the risk of cervical cancer in young women – a case-control study from Finland. Gynecol Oncol. 147(3):601–6. https://doi.org/10.1016/j.ygyno.2017.09.010 PMID:28942994

33. Nieminen P, Kallio M, Anttila A, Hakama M (1999). Organised vs. spontaneous Pap-smear screening for cervical cancer: a case-control study. Int J Cancer. 83(1):55–8. https://doi.org/10.1002/(SICI)1097-0215(19990924)83:1<55::AID-IJC11>3.0.CO;2-U PMID:10449608

34. Lynge E, Madsen M, Engholm G (1989). Effect of organized screening on incidence and mortality of cervical cancer in Denmark. Cancer Res. 49(8):2157–60. PMID:2702657

35. Ronco G, Pilutti S, Patriarca S, Montanari G, Ghiringhello B, Volante R, et al.; Turin Cervical Screening Working Group (2005). Impact of the introduction of organised screening for cervical cancer in Turin, Italy: cancer incidence by screening history 1992–98. Br J Cancer. 93(3):376–8. https://doi.org/10.1038/sj.bjc.6602705 PMID:16012518

36. de Gelder R, Bulliard JL, de Wolf C, Fracheboud J, Draisma G, Schopper D, et al. (2009). Cost-effectiveness of opportunistic versus organised mammography screening in Switzerland. Eur J Cancer. 45(1):127–38. https://doi.org/10.1016/j.ejca.2008.09.015 PMID:19038540

37. Adab P, McGhee SM, Yanova J, Wong CM, Hedley AJ (2004). Effectiveness and efficiency of opportunistic cervical cancer screening: comparison with organized screening. Med Care. 42(6):600–9. https://doi.org/10.1097/01.mlr.0000128007.04494.29 PMID:15167328

38. Kim JJ, Leung GM, Woo PP, Goldie SJ (2004). Cost-effectiveness of organized versus opportunistic cervical cytology screening in Hong Kong. J Public Health (Oxf). 26(2):130–7. https://doi.org/10.1093/pubmed/fdh138 PMID:15284314

39. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, et al. (2009). HPV screening for cervical cancer in rural India. N Engl J Med. 360(14):1385–94. https://doi.org/10.1056/NEJMoa0808516 PMID:19339719

40. Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S, et al. (2007). Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. Lancet. 370(9585):398–406. https://doi.org/10.1016/S0140-6736(07)61195-7 PMID:17679017

41. Madzima TR, Vahabi M, Lofters A (2017). Emerging role of HPV self-sampling in cervical cancer screening for hard-to-reach women: focused literature review. Can Fam Physician. 63(8):597–601. PMID:28807952

42. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, et al.; International HPV screening working group (2014). Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 383(9916):524–32. https://doi.org/10.1016/S0140-6736(13)62218-7 PMID:24192252

43. Panieri E (2012). Breast cancer screening in developing countries. Best Pract Res Clin Obstet Gynaecol. 26(2):283–90. https://doi.org/10.1016/j.bpobgyn.2011.11.007 PMID:22222136

44. Gray E, Donten A, Karssemeijer N, van Gils C, Evans DG, Astley S, et al. (2017). Evaluation of a stratified national breast screening program in the United Kingdom: an early model-based cost-effectiveness analysis. Value Health. 20(8):1100–9. https://doi.org/10.1016/j.jval.2017.04.012 PMID:28964442

45. Esserman LJ, Thompson IM, Reid B, Nelson P, Ransohoff DF, Welch HG, et al. (2014). Addressing overdiagnosis and overtreatment in cancer: a prescription for change. Lancet Oncol. 15(6):e234–42. https://doi.org/10.1016/S1470-2045(13)70598-9 PMID:24807866

6.7 Circulating DNA and other biomarkers for early diagnosis

Great potential, but challenges recognized

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SUMMARY

- The analysis of tumour-derived products, including circulating cell-free tumour DNA (ctDNA) and related biomarkers, in body fluids is increasingly recognized as an aid in the early diagnosis of malignant disease.
- For application in screening or early diagnosis, ctDNA analysis and related techniques require well-validated tests with exceptionally high sensitivity and specificity.
- Recent approaches have combined the evaluation of soluble tumour biomarkers with ctDNA analysis of cancer-related mutations in multiple genes.
- These technologies face challenges, including low concentrations of ctDNA and other liquid biomarker analytes.
- Progress in technology (e.g. next-generation sequencing) is paving the way for the development of diagnostic tests for early detection of cancer and the introduction of precision medicine into clinical practice.

The analysis of tumour cells and tumour-derived products detectable in blood and other body fluids, which was introduced by Pantel and Alix-Panabieres and has been referred to as a liquid biopsy [1], has garnered substantial interest in recent years (see Chapter 5.12). The family of liquid biopsy analytes includes circulating tumour cells (CTCs), circulating cell-free tumour DNA (ctDNA), circulating non-coding nucleic acids such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), extracellular vesicles, and tumour-educated platelets [2–6].

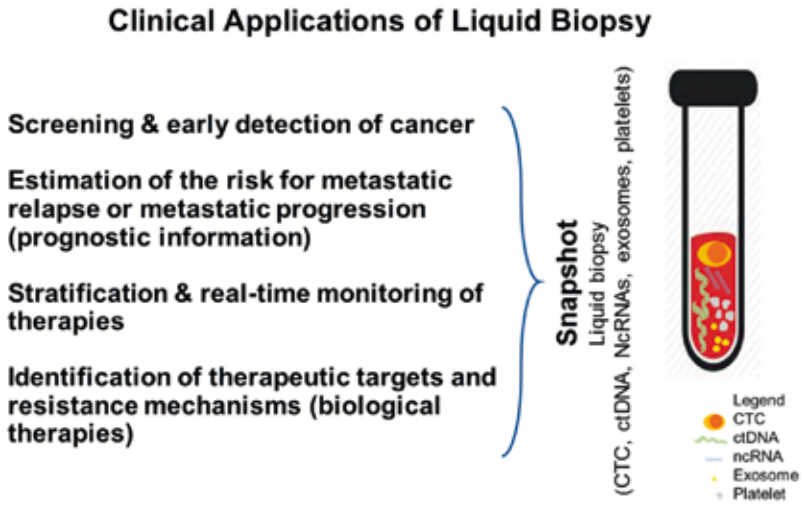
Over the past 10 years, many liquid biopsy tests have been established and validated [3]. Clinical applications of liquid biopsy in patients with early-stage cancer include early detection of small tumours, improved risk assessment (tumour staging), and monitoring of minimal residual disease [7]. Thus, liquid biopsy is set to become an essential element of personalized medicine (Fig. 6.7.1).

This chapter discusses some of the recent highlights on the use of ctDNA and CTCs for early detection and monitoring of cancer.

ctDNA for early detection of cancer

Early detection of cancer in the context of a screening programme for healthy individuals at high risk is a much sought-after goal in cancer research. Current therapeutic strategies, in particular surgery, enable many patients with cancer to be cured, provided the disease is detected early in its anticipated clinical

Fig. 6.7.1. Liquid biopsy in cancer. Schematic representation of the liquid biopsy concept as the analysis of circulating tumour cells (CTCs), circulating cell-free tumour DNA (ctDNA), non-coding RNAs (ncRNAs), exosomes, and tumour-educated platelets in the blood of patients with cancer. Key applications of liquid biopsy are listed.



course. However, metastatic disease remains largely incurable, with very few exceptions, which specifically include testicular cancer or small liver metastases in colon cancer.

Liquid biopsy, as a minimally invasive and easily repeatable method, seems to offer an attractive alternative to invasive tissue biopsies as the current definitive methodology in tumour diagnostics. However, programmes for early detection or screening require well-validated tests with exceptionally high sensitivity and specificity.

In the context of the TRACERx study, Abbosh et al. investigated the potential of ctDNA analysis for early diagnosis and monitoring in patients with non-small cell lung carcinoma (NSCLC). The sequencing of single-nucleotide variants in resected tumour tissue was used to create a patient-specific panel for next-generation sequencing-based ctDNA analysis of plasma collected before surgery. With the detection threshold of at least two tumour-specific single-nucleotide variants, the sensitivity of personalized tests in pre-surgery plasma samples was 97% for lung squamous cell carcinomas but only 19% for lung adenocarcinomas [8]. The authors calculated that a tumour with a diameter of about 2.7 cm (volume, 10 cm^3) would result in a mean ctDNA plasma variant allele frequency of 0.1%. Modern low-dose computed tomography lung screening enables the detection of tumours of diameter 0.4 cm (volume, 0.34 cm^3), which would correspond to a plasma variant allele frequency of 1.8×10^{-4}%, below the detection limit of most current ctDNA technologies [8].

Another aspect is the cost of the patient-tailored next-generation sequencing-based ctDNA approach for the detection of single-nucleotide variants. Abbosh at al. estimated the current cost of targeted ctDNA profiling to be US$ 1750 per patient, which is likely to be too high for routine implementation as a test for population cancer screening [8]. These findings challenge the application of ctDNA analysis for early diagnosis of small cancerous lesions.

The proper choice of markers is also very important. Markers detected and validated in patients with advanced disease, such as CEA, lack specificity and sensitivity for early detection. Concentrations of the marker are lower at early stages of disease than at late stages. In addition, the biology of these two disease states varies; therefore, a late-stage marker may not be suitable to detect small tumours at early stages. Also, blood markers of early lesions may be masked by comorbidities, such as chronic inflammatory diseases [9], as well as by the accumulation of cancer-related mutations with age in healthy individuals [10,11].

These limitations may be illustrated by the recently published work of Cohen et al., who introduced the CancerSeek panel for the detection of the eight most common cancer types [12]. This complex approach combined the evaluation of eight soluble tumour biomarkers, including standard tumour markers such as CEA, with ctDNA analysis of cancer-related mutations in 16 genes. The panel reached an overall median sensitivity of 70%, with specificity of 99% or more, but significant differences in sensitivity were observed among the tumour types analysed, including 98% in ovarian cancer, 60% in lung cancer, and 33% in breast cancer [12]. These findings require validation, ideally in an independent prospectively sampled, pre-diagnostic cohort. Moreover, the study analysed only healthy controls; therefore, the high specificity of the CancerSeek approach requires further validation with non-cancer controls with comorbidities such as inflammatory diseases, which are common in ageing individuals.

ctDNA for monitoring of minimal residual disease in patients with early-stage cancer

Liquid biopsy tests for the detection and monitoring of minimal residual disease in patients with early-stage cancer face similar challenges to tests for early detection, including low concentrations of ctDNA and other liquid biomarker analytes [7].

Tie et al. evaluated the ability of ctDNA analysis to detect minimal residual disease in blood samples obtained from patients with stage II colon cancer after surgical removal of the primary tumour. The method was able to predict recurrence at 36 months with a sensitivity of 48% and a specificity of 100% [13]. In the above-mentioned study of Abbosh et al. in patients with lung cancer, detection of ctDNA mutations that were also present in the respective primary tumour was predictive of relapse in 93% of cases, with a median of 70 days before radiological

FUNDAMENTALS

- The analysis of circulating tumour cells, circulating cell-free tumour DNA, and other tumour-derived products detectable in the blood and other body fluids has been referred to as liquid biopsy.
- Most research has been focused on prognosis and therapy, including real-time assessment of the stage of malignant disease in individual patients.
- Liquid biopsy tests have the potential to aid in the detection of minimal residual disease.
- The presence of circulating tumour cells as potential seeds of distant metastases is highly predictive of metastatic outgrowth and worse outcome in patients with both early-stage and late-stage disease.
- Analysis of therapy-relevant genomic aberrations in circulating tumour cells and circulating cell-free tumour DNA enables the guidance of precision therapy and the prediction of resistance to therapy.

confirmation [8]. Both of these studies demonstrate the feasibility and potential clinical value of ctDNA analysis for monitoring of minimal residual disease. However, ctDNA detection required knowledge of primary tumour-specific mutations, and the mutational spectrum may change during progression from minimal residual disease to overt metastatic disease.

ctDNA analysis without prior knowledge of the genetics of the primary tumour was applied in a recent study of patients with stage I–III lung cancer. Chaudhuri et al. used the highly sensitive cancer personalized profiling by deep sequencing (CAPP-Seq) approach targeting 128 genes that are recurrently mutated in lung cancer. Detection of ctDNA after the initial treatment of the primary tumour was predictive of progression in 72% of patients, with a median of 5.2 months before radiological evidence of disease recurrence. Remarkably, ctDNA was detectable in 94% of patients experiencing recurrence at the "minimal residual disease landmark" time point, which was defined as the first post-treatment blood draw within 4 months of treatment completion [14].

Goh et al. used in vitro and patient-derived xenograft assays to test whether chromosome 1q23.1 amplification was enriched in tumour-initiating cells from patients with breast cancer. Amplification of the region was detected in ctDNA as the average copy-number ratio of three genes (*TUFT1*, *S100A7*, and *S100A8*) relative to a reference gene by droplet digital polymerase chain reaction (PCR). Detection of the amplification in ctDNA samples already at first diagnosis was predictive of relapse within 5 years in 67% of patients with early-stage breast cancer (stage I or II) and within 3 years in 40% of patients with locally advanced breast cancer (stage II or III), with 100% specificity in both cohorts [15].

Taken together, these results demonstrate the power of ctDNA analysis to predict minimal residual disease in patients with cancer.

CTCs for early detection and monitoring of minimal residual disease

Over the past decade, in addition to the measurement of ctDNA, various methods have been developed to detect CTCs in the peripheral blood of patients with cancer [16]. As for any other liquid biopsy analyte, quantification and characterization of CTCs in the blood of patients with cancer at any particular time provides a snapshot of the actual disease status. It has been shown that regular enumeration of CTCs can be used for disease prognosis, diagnosis of minimal residual disease, and monitoring of effectiveness of therapy [17–19].

Although reliable information can easily be obtained in patients with advanced disease, patients with early-stage cancer usually present with very low concentrations of CTCs. Nonetheless, a pooled analysis including data from 3173 patients with non-metastatic breast cancer (stage I–III) provided strong evidence for CTCs as an independent prognostic factor with regard to poor overall, breast cancer-specific, and disease-free survival [20]. Detection of CTCs in patients with breast cancer receiving neoadjuvant therapy is a significant predictor of outcome independent of the response of the primary tumour to therapy [21,22]. This suggests that the presence of CTCs signals the occurrence of clinically relevant minimal residual disease at distant sites.

Currently, most CTC assays rely on epithelial markers such as EpCAM, and most of the CTCs detected are single isolated cells. Despite the relevance of epithelial–mesenchymal transition to cancer, the presence of these "epithelial" CTCs is associated with an unfavourable prognosis in cancer of the breast, prostate, colon, and lung [23]. The clinical relevance of "mesenchymal" CTCs lacking any epithelial markers as well as of CTC clusters is still under investigation, but the additional detection of these subsets of CTCs may improve the early detection of cancer and minimal residual disease. The sensitivity of current CTC assays seems to be too low to enable them to be used for early cancer detection. Only one report has shown that detection of CTCs in the blood of patients with chronic obstructive pulmonary disease was able to predict the occurrence of lung cancer [24].

It has been shown that the presence of CTCs after completion of adjuvant therapy is a predictor of metastatic relapse and poor survival

Fig. 6.7.2. A patient receiving chemotherapy in the context of cancer management. The currently available data suggest improved clinical management based on the power of circulating cell-free tumour DNA (ctDNA) analysis to detect and monitor minimal residual disease in patients with cancer.

[18]. Moreover, information provided by CTCs may extend to the proteomic, transcriptomic, and genomic levels. Although single-cell analysis is challenging, investigations of protein expression and genome-wide studies on single cells are becoming the state of the art [25,26]. Molecular characterization of CTCs provides a powerful tool to assess intrapatient heterogeneity and to obtain information about the clonal origin of CTCs and clonal selection under therapy. The identification of clones that are sensitive and resistant to therapy may provide new insights and potential targets for cancer treatment.

Liquid biopsy beyond ctDNA and CTC analyses

In addition, the analysis of circulating non-coding nucleic acids such as miRNAs and lncRNAs (see Chapter 3.8) is a highly promising liquid biopsy approach [4]. miRNAs and lncRNAs were found to provide additional levels of transcriptional and translational regulation and to be strongly involved in cancer development.

Although levels of upregulation and downregulation of individual miRNAs or lncRNAs are probably insufficient for a reliable test to detect cancer, signatures of 3–6 non-coding RNAs may be powerful and sensitive tools for early detection of cancer (reviewed in [4]). For example, a signature of serum miR-21 and miR-155 was reported as a sensitive and specific biomarker for diagnosis of breast cancer; for miR-21 the receiver operating characteristic (ROC) area under the curve (AUC) value was 0.788, the sensitivity was 66.67%, and the specificity was 88.89%, and for miR-155 the ROC AUC value was 0.749, the sensitivity was 100%, and the specificity was 51.02% [27].

lncRNAs can also be successfully used in diagnostic tests. Tang et al. found that three lncRNAs (LINC01627, LINC01628, and ERICH1-AS1) were upregulated in the plasma of patients with NSCLC compared with healthy individuals. The suggested diagnostic signature could identify NSCLC with high accuracy (AUC, 0.942) [28].

Recently, tumour-educated platelets have emerged as new members of the family of liquid biopsy analytes. External stimuli, such as activation of platelet surface receptors and lipopolysaccharide-mediated platelet activation, induce specific splicing of precursor messenger RNAs (mRNAs) in circulating tumour-educated platelets. The combination of specific splice events in response to external signals and the capacity of platelets to directly ingest (spliced) circulating mRNA can provide tumour-educated platelets with a highly dynamic mRNA repertoire, with potential applicability to cancer diagnostics [6,29].

The first results on the use of tumour-derived exosomes and other extracellular vesicles [30] are promising, and their potential as cancer biomarkers has been explored in multiple studies. However, the lack of standardization of protocols for pre-analytical handling and analytical workflows limits interstudy comparisons and large international multicentre studies [31]. Moreover, the investigation of extracellular vesicles and their content in combination with other liquid biopsy analytes (e.g. CTCs, ctDNA) may provide new opportunities for the development of diagnostic tests [32].

In addition to ctDNA and CTCs, the biomarkers discussed in this chapter provide information not only on tumour cells but also on the tumour microenvironment – such as stromal and immune cells. This additional information may be helpful to detect the body's response to the development of small cancerous lesions, which in turn could be used for early cancer detection.

Technologies for detection of ctDNA and CTCs

Circulating cell-free DNA (cfDNA) in blood plasma is highly fragmented DNA derived mainly from apoptotic cells. The concentration of ctDNA in blood may be less than 0.01% of the total cfDNA concentration, in particular during the early stages of cancer that are relevant to early detection programmes.

Researchers have used various targeted DNA sequencing techniques, such as digital PCR (quantitative PCR), BEAMing (beads, emulsion, amplification, magnetics) technology, the safe-sequencing system, CAPP-Seq, and tagged-amplicon deep sequencing [33]. These methods can reach ctDNA detection limits of less than 0.01%. A disadvantage of these technologies is the requirement for detailed prior information on the mutational spectrum of the tumour in the individual patient. This may be a limitation if these techniques are used for cancer screening. Such information is not required if non-targeted next-generation sequencing is applied to investigate ctDNA, enabling the genome-wide analysis of mutations by whole-genome sequencing or whole-exome sequencing. However, the drawbacks of genome-wide ctDNA analyses compared with targeted approaches include the need for higher concentrations of ctDNA and the lower overall assay sensitivity.

In addition to next-generation sequencing-based mutation analysis (see Chapter 3.2), which is the most prominent approach in ctDNA analysis, copy number alteration (CNA) and methylation analyses are garnering substantial interest [34]. Shallow whole-genome sequencing of ctDNA, which enables the cost-effective global assessment of CNAs [35], has introduced the global CNA score as a reliable biomarker associated with active disease and survival in patients with melanoma. Similarly, genome-wide CNA assessment has been used to screen cfDNA for the detection of incipient haematological malignancies in apparently healthy individuals [36].

Epigenomic tumour-specific alterations can be detected in ctDNA and have the potential to serve as biomarkers. Shen et al. demonstrated the ability to identify large-scale tumour-specific ctDNA methylation patterns [37]. The method they established was successfully

applied for cancer detection and classification in a patient cohort across several tumour types [37]. Besides large-scale methylation assessment, smaller panels have the benefit of being less expensive and easier to interpret. Thus, methylation of 12 genes investigated by droplet digital methylation-specific PCR in ctDNA was successfully applied to accurately distinguish between patients with breast cancer and healthy volunteers [38].

Furthermore, the physicochemical properties of methylated DNA assessed as the methylation landscape of cfDNA could be used to accurately discriminate between healthy individuals and patients with cancer (accuracy > 70%) [39]. These recent findings demonstrate the high potential as biomarkers of cfDNA CNA and methylome analyses. However, these findings require further validation in larger cohorts and groups of patients with early-stage cancer or benign disease.

Efficient enrichment of CTCs can be achieved by approaches that exploit the differences between tumour cells and blood cells, including the differential expression of cell membrane proteins (e.g. EpCAM, the most widely used marker for the enrichment of CTCs in blood from patients with carcinoma) as well as different sizes, densities, electric charges, and deformabilities [5,16]. After enrichment, the CTCs are still surrounded by hundreds to thousands of leukocytes, and therefore reliable methods are required to identify a CTC at the single-cell level.

CTCs can be detected by antibodies against membrane and cytoplasmic antigens, including epithelial, mesenchymal, tissue-specific, and tumour-associated markers. Most current CTC assays use the same identification step as the system approved by the United States Food and Drug Administration (FDA) for detecting CTCs in patients with metastatic cancer: cells are fluorescently stained for epithelial keratins as a marker of CTCs, and CD45 is used as a leukocyte exclusion marker.

Fig. 6.7.3. A women having blood drawn. Liquid biopsy is recognized as a means of indicating prognosis for patients with cancer, but its potential is also being explored for the purpose of early diagnosis.

Although some antigens are applicable to various different cancer types (e.g. keratins are suitable for cancers of the breast, colon, and prostate and other epithelial tumours), tissue-specific antigens such as prostate-specific antigen or breast-specific mammaglobin are also suitable.

From discovery to clinical validation and utility

Currently, only two liquid biopsy tests are approved in the USA by the FDA, but not for the early detection of cancer. The FDA approved the above-mentioned system for detecting CTCs in metastatic cancer in 2018 and an *EGFR* mutation test for ctDNA analysis in 2016 [3]. The *EGFR* mutation test can detect *EGFR* gene mutations in patients with NSCLC. Such mutations are present in about 10–20% of patients with NSCLC. The *EGFR* mutation test identifies the presence of 42 specific NSCLC mutations in exons 18–21, including the L858R mutation, exon 19 deletions, and the T790M mutation. On the basis of these data, patients who may benefit from treatment with erlotinib or osimertinib may be selected. However, if such mutations are not detected in the blood, then a tumour biopsy should be performed to determine whether the NSCLC mutations are present. Insofar as the test provides positive results, it may benefit patients who may be too ill or are otherwise unable to provide a tumour specimen for *EGFR* testing.

Blood is a rich source of information through which solid cancers can be detected, classified, and matched to a specific therapy. Different approaches such as ctDNA, non-coding nucleic acids, extracellular vesicles, tumour-educated platelets, or CTC analyses will provide complementary information, depending on the tumour type and the intended clinical use. Despite the potential of individual techniques, each has its own limitations; this leads to the idea of combining different analytes for the early detection of cancer. Technical and clinical validation of assays is very important and can be achieved in independent, international consortia such as the European IMI Cancer-ID network (https://www.cancer-id.eu). Similar to the development of new drugs, the pipeline for the development of new diagnostic tools needs more standardization to bridge the gap between the plethora of published biomarker studies and the paucity of new markers entering clinical practice.

References

1. Pantel K, Alix-Panabières C (2010). Circulating tumour cells in cancer patients: challenges and perspectives. Trends Mol Med. 16(9):398–406. https://doi.org/10.1016/j.molmed.2010.07.001 PMID:20667783
2. Babayan A, Pantel K (2018). Advances in liquid biopsy approaches for early detection and monitoring of cancer. Genome Med. 10(1):21. https://doi.org/10.1186/s13073-018-0533-6 PMID:29558971
3. Kwapisz D (2017). The first liquid biopsy test approved. Is it a new era of mutation testing for non-small cell lung cancer? Ann Transl Med. 5(3):46. https://doi.org/10.21037/atm.2017.01.32 PMID:28251125
4. Anfossi S, Babayan A, Pantel K, Calin GA (2018). Clinical utility of circulating non-coding RNAs – an update. Nat Rev Clin Oncol. 15(9):541–63. https://doi.org/10.1038/s41571-018-0035-x PMID:29784926
5. Poudineh M, Sargent EH, Pantel K, Kelley SO (2018). Profiling circulating tumour cells and other biomarkers of invasive cancers. Nat Biomed Eng. 2(2):72–84. https://doi.org/10.1038/s41551-018-0190-5 PMID:31015625
6. Best MG, Sol N, In 't Veld SGJG, Vancura A, Muller M, Niemeijer AN, et al. (2017). Swarm intelligence-enhanced detection of non-small-cell lung cancer using tumor-educated platelets. Cancer Cell. 32(2):238–252.e9. https://doi.org/10.1016/j.ccell.2017.07.004 PMID:28810146
7. Bardelli A, Pantel K (2017). Liquid biopsies, what we do not know (yet). Cancer Cell. 31(2):172–9. https://doi.org/10.1016/j.ccell.2017.01.002 PMID:28196593
8. Abbosh C, Birkbak NJ, Wilson GA, Jamal-Hanjani M, Constantin T, Salari R, et al.; TRACERx consortium; PEACE consortium (2017). Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. Nature. 545(7655):446–51. https://doi.org/10.1038/nature22364 PMID:28445469
9. Pantel K, Denève E, Nocca D, Coffy A, Vendrell JP, Maudelonde T, et al. (2012). Circulating epithelial cells in patients with benign colon diseases. Clin Chem. 58(5):936–40. https://doi.org/10.1373/clinchem.2011.175570 PMID:22205690
10. Krimmel JD, Schmitt MW, Harrell MI, Agnew KJ, Kennedy SR, Emond MJ, et al. (2016). Ultra-deep sequencing detects ovarian cancer cells in peritoneal fluid and reveals somatic *TP53* mutations in noncancerous tissues. Proc Natl Acad Sci U S A. 113(21):6005–10. https://doi.org/10.1073/pnas.1601311113 PMID:27152024
11. Fernandez-Cuesta L, Perdomo S, Avogbe PH, Leblay N, Delhomme TM, Gaborieau V, et al. (2016). Identification of circulating tumor DNA for the early detection of small-cell lung cancer. EBioMedicine. 10:117–23. https://doi.org/10.1016/j.ebiom.2016.06.032 PMID:27377626
12. Cohen JD, Li L, Wang Y, Thoburn C, Afsari B, Danilova L, et al. (2018). Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science. 359(6378):926–30. https://doi.org/10.1126/science.aar3247 PMID:29348365
13. Tie J, Wang Y, Tomasetti C, Li L, Springer S, Kinde I, et al. (2016). Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. Sci Transl Med. 8(346):346ra92. https://doi.org/10.1126/scitranslmed.aaf6219 PMID:27384348
14. Chaudhuri AA, Chabon JJ, Lovejoy AF, Newman AM, Stehr H, Azad TD, et al. (2017). Early detection of molecular residual disease in localized lung cancer by circulating tumor DNA profiling. Cancer Discov. 7(12):1394–403. https://doi.org/10.1158/2159-8290.CD-17-0716 PMID:28899864
15. Goh JY, Feng M, Wang W, Oguz G, Yatim SMJM, Lee PL, et al. (2017). Chromosome 1q21.3 amplification is a trackable biomarker and actionable target for breast cancer recurrence. Nat Med. 23(11):1319–30. https://doi.org/10.1038/nm.4405 PMID:28967919
16. Alix-Panabières C, Pantel K (2016). Clinical applications of circulating tumor cells and circulating tumor DNA as liquid biopsy. Cancer Discov. 6(5):479–91. https://doi.org/10.1158/2159-8290.CD-15-1483 PMID:26969689
17. Fehm T, Müller V, Alix-Panabières C, Pantel K (2008). Micrometastatic spread in breast cancer: detection, molecular characterization and clinical relevance. Breast Cancer Res. 10(Suppl 1):S1. https://doi.org/10.1186/bcr1869 PMID:19091005
18. Pantel K, Alix-Panabières C, Riethdorf S (2009). Cancer micrometastases. Nat Rev Clin Oncol. 6(6):339–51. https://doi.org/10.1038/nrclinonc.2009.44 PMID:19399023
19. Pantel K, Alix-Panabières C (2013). Real-time liquid biopsy in cancer patients: fact or fiction? Cancer Res. 73(21):6384–8. https://doi.org/10.1158/0008-5472.CAN-13-2030 PMID:24145355
20. Janni WJ, Rack B, Terstappen LWMM, Pierga J-Y, Taran F-A, Fehm T, et al. (2016). Pooled analysis of the prognostic relevance of circulating tumor cells in primary breast cancer. Clin Cancer Res. 22(10):2583–93. https://doi.org/10.1158/1078-0432.CCR-15-1603 PMID:26733614
21. Riethdorf S, Müller V, Loibl S, Nekljudova V, Weber K, Huober J, et al. (2017). Prognostic impact of circulating tumor cells for breast cancer patients treated in the neoadjuvant "Geparquattro" trial. Clin Cancer Res. 23(18):5384–93. https://doi.org/10.1158/1078-0432.CCR-17-0255 PMID:28679772
22. Bidard FC, Michiels S, Riethdorf S, Mueller V, Esserman LJ, Lucci A, et al. (2018). Circulating tumor cells in breast cancer patients treated by neoadjuvant chemotherapy: a meta-analysis. J Natl Cancer Inst. 110(6):560–7. https://doi.org/10.1093/jnci/djy018 PMID:29659933
23. Alix-Panabières C, Mader S, Pantel K (2017). Epithelial-mesenchymal plasticity in circulating tumor cells. J Mol Med (Berl). 95(2):133–42. https://doi.org/10.1007/s00109-016-1500-6 PMID:28013389
24. Ilie M, Hofman V, Long-Mira E, Selva E, Vignaud J-M, Padovani B, et al. (2014). "Sentinel" circulating tumor cells allow early diagnosis of lung cancer in patients with chronic obstructive pulmonary disease. PLoS One. 9(10):e111597. https://doi.org/10.1371/journal.pone.0111597 PMID:25360587
25. Wang D, Bodovitz S (2010). Single cell analysis: the new frontier in 'omics'. Trends Biotechnol. 28(6):281–90. https://doi.org/10.1016/j.tibtech.2010.03.002 PMID:20434785
26. Babayan A, Alawi M, Gormley M, Müller V, Wikman H, McMullin RP, et al. (2016). Comparative study of whole genome amplification and next generation sequencing performance of single cancer cells. Oncotarget. 8(34):56066–80. https://doi.org/10.18632/oncotarget.10701 PMID:28915574
27. Han JG, Jiang YD, Zhang CH, Yang YM, Pang D, Song YN, et al. (2017). A novel panel of serum miR-21/miR-155/miR-365 as a potential diagnostic biomarker for breast cancer. Ann Surg Treat Res. 92(2):55–66. https://doi.org/10.4174/astr.2017.92.2.55 PMID:28203552
28. Tang Q, Ni Z, Cheng Z, Xu J, Yu H, Yin P (2015). Three circulating long non-coding RNAs act as biomarkers for predicting NSCLC. Cell Physiol Biochem. 37(3):1002–9. https://doi.org/10.1159/000430226 PMID:26393913

29. Nilsson RJ, Balaj L, Hulleman E, van Rijn S, Pegtel DM, Walraven M, et al. (2011). Blood platelets contain tumor-derived RNA biomarkers. Blood. 118(13):3680–3. https://doi.org/10.1182/blood-2011-03-344408 PMID:21832279

30. Hoshino A, Costa-Silva B, Shen TL, Rodrigues G, Hashimoto A, Tesic Mark M, et al. (2015). Tumour exosome integrins determine organotropic metastasis. Nature. 527(7578):329–35. https://doi.org/10.1038/nature15756 PMID:26524530

31. Lane RE, Korbie D, Hill MM, Trau M (2018). Extracellular vesicles as circulating cancer biomarkers: opportunities and challenges. Clin Transl Med. 7(1):14. https://doi.org/10.1186/s40169-018-0192-7 PMID:29855735

32. Bracht JWP, Mayo-de-Las-Casas C, Berenguer J, Karachaliou N, Rosell R (2018). The present and future of liquid biopsies in non-small cell lung cancer: combining four biosources for diagnosis, prognosis, prediction, and disease monitoring. Curr Oncol Rep. 20(9):70. https://doi.org/10.1007/s11912-018-0720-z PMID:30030656

33. Heitzer E, Haque IS, Roberts CES, Speicher MR (2019). Current and future perspectives of liquid biopsies in genomics-driven oncology. Nat Rev Genet. 20(2):71–88. https://doi.org/10.1038/s41576-018-0071-5 PMID:30410101

34. Heitzer E, Ulz P, Geigl JB, Speicher MR (2016). Non-invasive detection of genome-wide somatic copy number alterations by liquid biopsies. Mol Oncol. 10(3):494–502. https://doi.org/10.1016/j.molonc.2015.12.004 PMID:26778171

35. Silva S, Danson S, Teare D, Taylor F, Bradford J, McDonagh AJG, et al. (2018). Genome-wide analysis of circulating cell-free DNA copy number detects active melanoma and predicts survival. Clin Chem. 64(9):1338–46. https://doi.org/10.1373/clinchem.2018.290023 PMID:29941468

36. Lenaerts L, Vandenberghe P, Brison N, Che H, Neofytou M, Verheecke M, et al. (2019). Genomewide copy number alteration screening of circulating plasma DNA: potential for the detection of incipient tumors. Ann Oncol. 30(1):85–95. https://doi.org/10.1093/annonc/mdy476 PMID:30371735

37. Shen SY, Singhania R, Fehringer G, Chakravarthy A, Roehrl MHA, Chadwick D, et al. (2018). Sensitive tumour detection and classification using plasma cell-free DNA methylomes. Nature. 563(7732):579–83. https://doi.org/10.1038/s41586-018-0703-0 PMID:30429608

38. Uehiro N, Sato F, Pu F, Tanaka S, Kawashima M, Kawaguchi K, et al. (2016). Circulating cell-free DNA-based epigenetic assay can detect early breast cancer. Breast Cancer Res. 18(1):129. https://doi.org/10.1186/s13058-016-0788-z PMID:27993161

39. Sina AA, Carrascosa LG, Liang Z, Grewal YS, Wardiana A, Shiddiky MJA, et al. (2018). Epigenetically reprogrammed methylation landscape drives the DNA self-assembly and serves as a universal cancer biomarker. Nat Commun. 9(1):4915. https://doi.org/10.1038/s41467-018-07214-w PMID:30514834

6.8 Governmental action to control carcinogen exposure

Multiple options covering diverse scenarios

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SUMMARY

- Governmental action has been effective in reducing exposure to known and suspected carcinogens. These actions can involve legislation, regulation (to eliminate or restrict exposure), enforcement of legislation and regulations, voluntary (non-enforceable) guidelines, incentives, and education campaigns.
- Depending on the legal authority, the basis of regulation can be hazard, exposure, or risk.
- Hazard-based regulation can be effective. Notable examples include reduction of tobacco use and international action to eliminate persistent organic pollutants.
- New methods of toxicity testing are emerging and transforming the science of carcinogen identification. The goal is to identify and evaluate cancer hazards on the basis of data on precancerous effects.
- National and international health agencies are still identifying additional carcinogens.

After research identifies a cause of cancer in humans, primary prevention efforts can be directed towards reducing human exposure. In some cases, people can avoid exposure to an agent that is known or suspected to be a carcinogen through individual choice. Often, however, individuals cannot control – or sometimes do not even know about – their exposure to carcinogens in the air they breathe, the food and water they eat and drink, the places they work, or the products they can afford to buy and use. This opens up a role for national governments and intergovernmental organizations to act in ways that complement individual choices to avoid exposure to carcinogens. These actions can take several forms: legislation, regulation (to eliminate or restrict exposure), enforcement of legislation and regulations, voluntary (non-enforceable) guidelines, incentives, and education campaigns that help individuals make informed choices.

Nongovernmental organizations also develop guidelines, incentives, and education campaigns. Examples include the guideline for primary prevention of cervical cancer from the American Society of Clinical Oncology, reduced insurance premiums for nonsmokers from various insurance organizations, the SunSmart campaign from Cancer Council Australia, and the European Code Against Cancer, which was updated in 2014 (https://cancer-code-europe.iarc.fr/index.php/en/).

Fig. 6.8.1. The European Parliament. After a specific cause of cancer in humans is identified, national governments and intergovernmental organizations can act to prevent or control exposure to the carcinogen.

To provide authoritative, impartial scientific information on agents that are known or suspected to be carcinogens, several national and international health agencies develop evaluations of epidemiological and experimental evidence on carcinogenicity (Table 6.8.1).

This chapter discusses examples of governmental action to control carcinogen exposure, with a focus on developments during the past 5 years. Given the breadth of the subject, this chapter is not a comprehensive global assessment; rather, it aims to provide up-to-date examples of new developments, relevant country experiences, and novel approaches. For a discussion of actions to control cervical cancer and exposure to carcinogenic human papillomavirus (HPV) types, see Chapters 5.10 and 6.4.

Restrictions qualitatively based on hazard

In some cases, the identification of an agent as a known or suspected carcinogen can be sufficient basis for action. Depending on the legal authority, preventive measures can protect vulnerable populations without attempting to quantify acceptable levels of exposure or risk. For example, governments worldwide have acted for several decades to prevent smoking and other exposures to tobacco and tobacco smoke, especially for young people. This chapter describes similar actions in response to the recent identification of other carcinogenic hazards to which there is widespread exposure.

Obesity and overweight

Worldwide, an estimated 640 million adults were obese (body mass index ≥ 30 kg/m^2) in 2014, a 6-fold increase since 1975. An estimated 110 million children and adolescents were obese in 2013, a doubling since 1980. If the people who are overweight (body mass index ≥ 25 kg/m^2 and < 30 kg/m^2) are also considered, the totals are about triple.

In 2016, being obese or overweight was established as a risk factor for cancers of the gastric cardia, gall bladder, pancreas, ovary, and thyroid, and for multiple myeloma and meningioma [1,2]. This added to previous findings for cancers of the colorectum, oesophagus, kidney, postmenopausal breast, and endometrium [3]. When these newly established cancer sites are included, as much as 9% of the cancer burden in women in North America, Europe, and the Middle East may be attributable to obesity.

Table 6.8.1. Some sources of authoritative evaluations of carcinogenicity from government agencies and intergovernmental organizations

Authority	Agency or programme
National authorities	
Australia	National Industrial Chemicals Notification and Assessment Scheme, Department of Health
Canada	Health Canada
USA	Environmental Protection Agency Food and Drug Administration National Institute for Occupational Safety and Health National Toxicology Program *Report on Carcinogens* Occupational Safety and Health Administration Several state health or environmental agencies
International authorities	
European Union	European Chemicals Agency European Food Safety Authority Several national health agencies
World Health Organization	IARC (IARC Monographs programme) International Programme on Chemical Safety Joint Expert Committee on Food Additives (joint with the Food and Agriculture Organization of the United Nations) Joint Meeting on Pesticide Residues (joint with the Food and Agriculture Organization of the United Nations)

FUNDAMENTALS

- Historically, legislative action to reduce carcinogen exposure focused on measures directed towards the prevention of occupational cancer. Over decades, legislation in many countries has been based on recognition of specific chemicals as carcinogens in this context.
- Measures to prevent occupational cancer indicate the scope of relevant initiatives, which include prohibition of certain chemicals, restriction of manufacturing processes to reduce emissions, and mandatory requirements for the use of personal protective equipment.
- Involuntary exposure to carcinogenic pollutants in the air, water, and soil may be limited by the specification of maximum levels of known or suspected carcinogens.
- The extent of possible human exposure to known carcinogens as a result of using consumer products and prescription drugs is usually subject to regulation.
- Governments may intervene in relation to carcinogen exposure that occurs through individual choices.
- In most countries, the sale of tobacco products is limited by regulations on advertising, purchase by children, packaging, and product identification.
- Governments may play a role in education campaigns about, for example, sun exposure and tobacco use.

In the past, obesity was viewed as a matter of personal responsibility that could be controlled through individual choice. Governmental intervention focused on education campaigns and on taxation of unhealthy foods and beverages to urge individuals to adopt healthy lifestyles (see Chapter 6.2). More recently, a wider variety of governmental interventions have been recognized as having value in reducing the prevalence of obesity. A recent survey described worldwide trends towards strengthening existing interventions and introducing novel approaches to reduce the prevalence of obesity (see "Effective modern approaches for the control of obesity") [4]. Many of these approaches could also be applicable to the reduction of exposure to other known or suspected carcinogens. Public health interventions to reduce the prevalence of obesity are likely to accelerate with the recognition that the cancer burden attributable to obesity and overweight is greater than was previously believed.

Ultraviolet-emitting tanning devices

Indoor tanning using ultraviolet-emitting devices, such as sunlamps and sunbeds, is common in many high-income countries. Most of the users are young women. Use of ultraviolet-emitting tanning devices is classified by the IARC Monographs as carcinogenic to humans (Group 1); such devices cause malignant melanoma of the skin and eye. The risks are higher for exposure at younger ages (see Chapter 2.4). Risks of cutaneous melanoma are higher for people who first used tanning devices before about age 30 years (overall relative risk, 1.75). Risks of ocular melanoma are higher for people whose first use was before age 20 years. There is also a positive association with risk of squamous cell

Effective modern approaches for the control of obesity

These approaches for the control of obesity [1] are also applicable to other health concerns.

Stronger taxes

For example, in 2014, the Navajo Nation in the USA imposed higher taxes on sugar-sweetened beverages and foods high in salt, fat, and/or sugar, and eliminated taxes on fresh fruits, vegetables, and nuts. Mexico placed an 8% tax on high-calorie foods in 2013 and a 10% tax on sugar-sweetened beverages in 2014.

Stronger educational messages

For example, in 2012, Western Australia launched a campaign featuring graphic images of obese people coupled with messages about "toxic fat". Evidence from research on anti-tobacco campaigns shows that advertising featuring powerful images and health warnings can affect public opinion.

Labelling

Labelling provides better information on more food products. For example, since 2012, Cameroon has mandated nutritional labelling, and Chile, Ecuador, and the United Kingdom have introduced front-of-package, traffic-light labelling. In the USA, where labels have included trans fat content since 2008, there has been a documented decrease in levels of trans fatty acids in the population.

Built environment

Obstacles to obtaining healthy food include lack of supermarkets, lack of public transportation, and unsafe neighbourhoods. For example, since 2011, Canada has worked with supermarkets to provide nutritious perishable foods to more than 70 000 people living in isolated northern communities.

School-based interventions

Many countries promote healthy meals in schools or restrict the provision of unhealthy foods. Since 2013, at least 19 states in the USA have required schools to provide parents with body mass index assessments of their children.

Restrictions on advertising and marketing

Many countries have long restricted advertising of unhealthy foods directed at children. In addition, some countries are moving towards restricting advertising of certain products aimed at the broader public. For example, France requires advertisements for processed, sweetened, or salted foods to include a government health message.

Restrictions, standards, and bans on specific ingredients

For example, many European countries have adopted legislation that restricts the trans fat content of foods. Also, Ghana has a law to restrict the fat content of meats, and several Pacific island countries have banned the sale or import of certain fatty animal parts.

Screening to target high-risk individuals

For example, Japan has a law that requires adults to have their waist circumference measured annually and compared to population standards. There are fines for employers and local governments that do not meet population health goals, but no penalties for individuals.

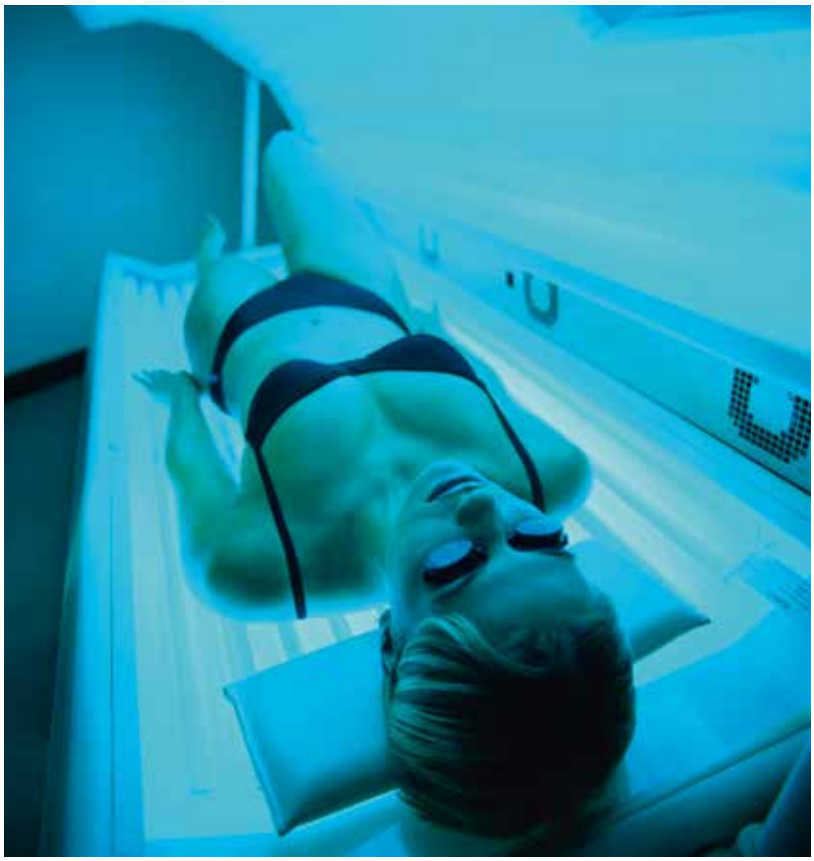
Sustainable agriculture, environment, and healthy food

These are integrated programmes that engage government, multiple private-sector industries, and stakeholders.

Reference

1. Taylor AL, Parento EW, Schmidt LA (2015). The increasing weight of regulation: countries combat the global obesity epidemic. Indiana Law J. 90(1):7.

Fig. 6.8.2. A woman using a sunbed. Brazil was the first country to ban indoor tanning for people of all ages.



carcinoma of the skin, especially for use before age 20 years [5].

Soon after the announcement of the IARC Monographs conclusions, Brazil became the first country to ban indoor tanning for people of all ages, and Australia followed in 2015. In view of the higher susceptibility of younger users, age restriction has been a more common type of action. In Europe, 11 countries ban indoor tanning under age 18 years, as do New Zealand and each province in Canada. In the USA, 17 states ban commercial indoor tanning under age 18 years. Most other states have restrictions for minors, such as bans under age 14–17 years or requirements for parental consent or accompaniment [6]. Research shows that laws with age restrictions are effective in reducing rates of indoor tanning among female students [7].

Mobile phones

Concern about children's health is evident in some actions to reduce exposure from mobile phones. Children hold phones closer to their brains than adults do, and the bone and marrow in children's skulls have higher conductivity. Radiofrequency electromagnetic fields from mobile phones have been classified by the IARC Monographs as possibly carcinogenic to humans (Group 2B), with positive associations for glioma and acoustic neuroma [8].

Although regulation of mobile phone use mostly aims to reduce distractions while driving or in the classroom, some health agencies have acted in response to the possible risk of cancer, citing the IARC Monographs findings. Since 2014, Belgium has banned the sale and advertising of mobile phones designed for children younger than 7 years, and sellers are required to disclose a phone's specific absorption rate of energy [9]. In 2017, the state of California in the USA issued guidance to reduce exposure to energy from mobile phones [10].

Occupational exposures to chemical, physical, and biological agents

Worldwide, an estimated 740 000 people per year die from exposure to carcinogens in the workplace [11] (see Chapter 2.10). Many such cancers occur in high-income countries, because of longer life expectancies. However, exposures can be higher in low- and middle-income countries if there is low compliance with safety norms, if there is weak enforcement of hazard control in workplaces, if worker organizations are not strong enough to ensure compliance with standards, and/or if there is a large informal economy that is not subject to regular inspection [12].

The Globally Harmonized System of Classification and Labelling of Chemicals [13] is becoming an international standard for the communication of chemical hazards. The Globally Harmonized System defines two categories of carcinogenic hazards: known or presumed human carcinogens (Categories 1A and 1B) and suspected human carcinogens (Category 2). The European Chemicals Agency aligned its classification and labelling practices with the Globally Harmonized System in 2011, the United States Occupational Safety and Health Administration in 2012, and the Scientific Committee on Occupational Exposure Limits for the European Union in 2017 [14]. Labelling provides workers with information on the potential hazards of chemicals in the workplace.

Restrictions quantitatively based on levels of exposure or risk

Some laws require a quantitative evaluation of exposure or risk before acting to reduce risks to acceptable levels. Determining what level of risk is acceptable can entail

intense debate, especially when the scientific evidence is inconclusive or when the benefits and costs of exposure reduction accrue to different segments of the population. Government agencies often distinguish between the underlying health science (known as risk assessment) and the legal, political, social, economic, and technical aspects of a decision (known as risk management) [15].

Risk assessment of carcinogens generally proceeds in distinct steps (Fig. 6.8.3): (i) hazard identification determines whether an agent can cause cancer under some conditions; (ii) dose–response assessment describes cancer risk as a function of exposure to the agent; (iii) exposure assessment identifies human exposure pathways and estimates the levels of human exposure; and (iv) risk characterization integrates these steps for a conclusion about cancer risk.

Occupational and environmental exposures

Many government agencies use two approaches to set regulatory limits for known or suspected carcinogens, although specific procedures and terminology differ. Threshold approaches estimate an exposure level below which carcinogenic effects should not occur. Non-threshold approaches derive an exposure–response relationship, often linear, to estimate risk as a function of exposure. Final regulatory limits consider these health-based estimates along with political, socioeconomic, technical, and other considerations, depending on the governing legislation (Fig. 6.8.3).

In 2016, a new law amended the United States Toxic Substances Control Act [16]. This law directs the Environmental Protection Agency to develop risk-based evaluations that consider individuals who may be at greater risk than the general population because of biological susceptibility or higher exposure. The new law also prescribes timelines to accelerate the pace of risk evaluations. Most of the first 10 substances selected to undergo risk evaluation are classified by the Environmental Protection Agency as known or suspected carcinogens.

Exposure and risk assessment of tobacco products

In 2009, a new law authorized the United States Food and Drug Administration to regulate tobacco products. The law mandates several preventive measures that have been successfully implemented in other countries. It also provides a unique risk-based approach for evaluating claims of reduced harm from new or modified tobacco products. Guidance proposed in 2012 describes the need to demonstrate whether a new or modified tobacco product will reduce levels of exposure to hazardous substances or will reduce the risk of tobacco-related disease.

Incorporation of increased understanding and new types of information

Although observational epidemiology has led to the identification of about 100 known human carcinogens, animal bioassays are the primary support for the identification of most suspected carcinogens. In the past decades, the pace of animal bioassays has slowed. The United States National Toxicology Program published its first 200 technical reports during 1976–1982 (a period of 6 years), the next 200 during 1982–1993 (11 years), and the most recent 200 during 1993–2018 (25 years) (https://ntp.niehs.nih.gov/results/pubs/index.html). At the same time, data on cancer mechanisms have become increasingly pivotal, and in the IARC Monographs programme mechanistic data have led to the classification of more than a dozen agents as known human carcinogens (https://monographs.iarc.fr/list-of-classifications-volumes/).

Fig. 6.8.3. The steps involved in risk assessment and risk management.

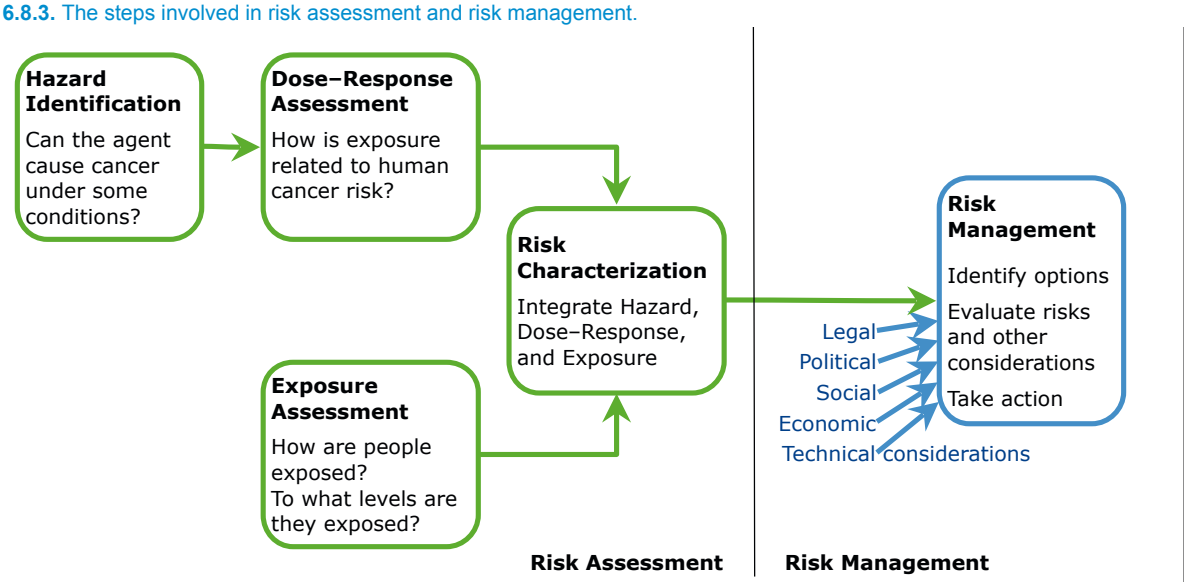


Fig. 6.8.4. The United States Capitol Building. In 2016, the 114th Congress passed a new law on chemical safety to amend and update the Toxic Substances Control Act, which went into force in 1976.

Radically new methods of toxicity testing are emerging to transform or contribute to the science of carcinogen identification. Rather than time-consuming tests of single chemicals in experimental animals, in vitro tests on human cells or cell components are investigating the ability to perturb disease pathways. High-throughput assays can test thousands of chemicals over a wide range of concentrations. Modelling will estimate human intake rates that yield target-tissue concentrations analogous to those that perturb disease pathways in vitro [17]. Pathways can involve multiple agents, some genetic and some environmental [18].

In the realm of exposure assessment, advances in environmental sampling technology, biomarkers, genomics, and informatics are expanding the ability to measure the exposome, which is the totality of environmental exposures received during a lifetime. This will provide data for evaluating interactions between a chemical agent and other chemical and non-chemical stressors, including gene–environment interactions (see Chapter 3.3). These approaches promise to facilitate specific linkages of exposures to biological effects and to indicate molecular pathways involved in carcinogenesis [19,20] (see Chapter 3.11).

The overall goal is to identify and evaluate apical hazards (i.e. observable disease in vivo, such as cancer) on the basis of non-apical data. The research question will shift from whether an agent causes cancer when tested alone as a single agent to whether an agent can contribute to an increased incidence of cancer that can involve multiple risk factors. Full implementation will require a better understanding of human disease pathways, the development of methods to incorporate the new data, characterization of the uncertainties associated with using the new data, and the development of case studies to promote discussion and acceptance among scientists and stakeholders [21]. Acceptance is critical if data on precancerous effects are to support the type of regulation that now requires extensive animal testing or the demonstration of cancer in humans.

In the European Union, the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation has encouraged the replacement of animal testing. The European Union is actively promoting research into the development and validation of alternatives to animal testing. Examples include quantitative structure–activity relationship (QSAR) models for predicting properties of chemicals, and read-across approaches for filling data gaps.

In the USA, Section 4 of the 2016 law that amended the Toxic Substances Control Act directs the Environmental Protection Agency to develop and implement alternative testing methods to reduce vertebrate animal testing. Examples include computational toxicology and bioinformatics, high-throughput screening methods, testing of categories of substances, tiered testing methods, in vitro studies, systems biology, and new methods identified by authoritative validation bodies.

The role of international agreements

International agreements are a means for addressing global health and environmental concerns when governments acting alone cannot achieve the results they seek. International agreements support and guide actions at the national level by articulating general principles and areas of consensus. Details of implementation are a matter for each country.

Fig. 6.8.5. A warning sign about contamination by polychlorinated biphenyls (PCBs), which are listed under the Stockholm Convention on Persistent Organic Pollutants.

Stockholm Convention on Persistent Organic Pollutants

The Stockholm Convention on Persistent Organic Pollutants is a legally binding treaty initiated by the United Nations Environment Programme and adopted in 2001 (http://chm.pops.int/). Countries undertake to eliminate or restrict the production, use, import, and export of persistent organic pollutants, which can cross national boundaries, persist in the environment, bioaccumulate, and harm human health and the environment (see Chapter 2.9). To date, 181 countries plus the European Union have ratified the treaty. There are 28 listed pollutants, most of which are known or suspected human carcinogens (Table 6.8.2).

An example of research translated into governmental action involves perfluorooctanoic acid (PFOA). In 2014, the IARC Monographs classified PFOA as possibly carcinogenic to humans (Group 2B), based in part on evidence of testicular cancer and kidney cancer in humans [22,23]. Subsequently, PFOA, its salts, and PFOA-related compounds were proposed for listing under the Stockholm Convention. In addition to testicular cancer and kidney cancer, the proposal cites thyroid disease, pregnancy-induced hypertension, and high cholesterol as health issues linked to PFOA.

A recent example of national legislative action on persistent organic pollutants is Section 6 of the 2016 law that amended the Toxic Substances Control Act. The law specifies that exposure shall be reduced "to the extent practicable" for certain persistent, bioaccumulative, and toxic substances. The law does not require risk evaluation for these substances, only a reasonable basis to conclude that there is a toxic, persistent, bioaccumulative hazard. This is similar to the treatment of these substances in the European Union, where the aim of REACH is the substitution of persistent, bioaccumulative, and toxic chemicals, and the minimization of exposures in the interim [24].

Table 6.8.2. Persistent organic pollutants listed under the Stockholm Convention

Persistent organic pollutant	IARC Monographs classification[a]
Annex A: Elimination	
Aldrin[b]	Group 2A
Chlordane[b]	Group 2B
Dieldrin[b]	Group 2A
Endrin[b]	Group 3
Heptachlor[b]	Group 2B
Hexachlorobenzene[b]	Group 2B
Mirex[b]	Group 2B
Polychlorinated biphenyls (PCBs)[b]	Group 1
Toxaphene[b]	Group 2B
Chlordecone	Group 2B
Short-chain chlorinated paraffins	Group 2B
Decabromodiphenyl ether (commercial mixture)	–
Technical endosulfan and its related isomers	–
Hexabromobiphenyl	–
Hexabromocyclododecane	–
Hexabromodiphenyl ether and heptabromodiphenyl ether (commercial octabromodiphenyl ether)	–
Hexachlorobutadiene	Group 3
Alpha hexachlorocyclohexane	Group 2B
Beta hexachlorocyclohexane	Group 2B
Lindane	Group 1
Pentachlorobenzene	–
Pentachlorophenol and its salts and esters	Group 1
Polychlorinated naphthalenes	–
Tetrabromodiphenyl ether and pentabromodiphenyl ether (commercial pentabromodiphenyl ether)	–
Annex B: Restriction	
4,4′-Dichlorodiphenyltrichloroethane (DDT)[b]	Group 2A
Perfluorooctane sulfonic acid (PFOS), its salts, and perfluorooctane sulfonyl fluoride	–
Annex C: Unintentional production	
Polychlorinated dibenzo-*para*-dioxins[b]	Group 3
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin	Group 1
Polychlorinated dibenzofurans[b]	Group 3
2,3,4,7,8-Pentachlorodibenzofuran	Group 1
Chemicals proposed for listing	
Dicofol	Group 3
Pentadecafluorooctanoic acid (PFOA), its salts, and PFOA-related compounds	Group 2B
Perfluorohexane sulfonic acid, its salts, and related compounds	–

[a] Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, not classifiable as to its carcinogenicity to humans; –, not evaluated (https://monographs.iarc.fr/agents-classified-by-the-iarc/).

[b] The 12 initial persistent organic pollutants.

WHO Framework Convention on Tobacco Control

The WHO Framework Convention on Tobacco Control is a legally binding treaty initiated by WHO and adopted in 2003 (http://www.who.int/fctc/en/). Concerted international action was undertaken to address the globalization of the tobacco epidemic, given that tobacco use is the leading cause of cancer worldwide. To date, 180 countries plus the European Union have ratified the treaty. The 2018 global progress report on the implementation of the WHO Framework Convention on Tobacco Control documents many national examples of effective action to reduce the prevalence of tobacco use in adults and children [25].

In 2018, a legally binding supplement, the Protocol to Eliminate Illicit Trade in Tobacco Products, was ratified (http://www.who.int/fctc/protocol/en/). The protocol provides tools to prevent illicit trade by securing the supply chain, by establishing an international tracking and tracing system, and through law enforcement and other measures to enable international cooperation.

Disclaimer

The views expressed in this chapter are those of the author and do not necessarily represent the views or the policies of the United States Environmental Protection Agency.

References

1. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group (2016). Body fatness and cancer – viewpoint of the IARC Working Group. N Engl J Med. 375(8):794–8. https://doi.org/10.1056/NEJMsr1606602 PMID:27557308
2. IARC (2018). Absence of excess body fatness. IARC Handb Cancer Prev. 16:1–646. Available from: http://publications.iarc.fr/570.
3. IARC (2002). Weight control and physical activity. IARC Handb Cancer Prev. 6:1–315. Available from: http://publications.iarc.fr/376.
4. Taylor AL, Parento EW, Schmidt LA (2015). The increasing weight of regulation: countries combat the global obesity epidemic. Indiana Law J. 90(1):7.
5. IARC (2012). Radiation. IARC Monogr Eval Carcinog Risks Hum. 100D:1–437. Available from: http://publications.iarc.fr/121 PMID:23189752
6. CDC (2018). Indoor tanning is not safe. Atlanta (GA), USA: Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/cancer/skin/basic_info/indoor_tanning.htm.
7. Guy GP Jr, Berkowitz Z, Jones SE, Olsen EO, Miyamoto JN, Michael SL, et al. (2014). State indoor tanning laws and adolescent indoor tanning. Am J Public Health. 104(4):e69–74. https://doi.org/10.2105/AJPH.2013.301850 PMID:24524515
8. IARC (2013). Non-ionizing radiation, Part 2: Radiofrequency electromagnetic fields. IARC Monogr Eval Carcinog Risks Hum. 102:1–460. Available from: http://publications.iarc.fr/126 PMID:24772662
9. Belgian Federal Public Service Health, Food Chain Safety and Environment (2014). New rules for selling mobile phones. Available from: https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/19099488/FAQ_KBs_mobiele_telefoon_version5_EN.pdf.
10. California Department of Public Health (2017). How to reduce exposure to radiofrequency energy from cell phones. Available from: https://www.cdph.ca.gov/Programs/CCDPHP/DEODC/EHIB/CDPH%20Document%20Library/CellPhone-Guidance.pdf.
11. Hämäläinen P, Takala J, Kiat TB (2017). Global estimates of occupational accidents and work-related illnesses 2017. Singapore: Workplace Safety and Health Institute. Available from: http://www.icohweb.org/site/images/news/pdf/Report%20Global%20Estimates%20of%20Occupational%20Accidents%20and%20Work-related%20Illnesses%202017%20rev1.pdf.
12. Santana VS, Ribeiro FSN (2011). Occupational cancer burden in developing countries and the problem of informal workers. Environ Health. 10(Suppl 1):S10. https://doi.org/10.1186/1476-069X-10-S1-S10 PMID:21489206
13. United Nations (2017). Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Seventh revised edition. Available from: http://www.unece.org/trans/danger/publi/ghs/ghs_rev07/07files_e.html.
14. Scientific Committee on Occupational Exposure Limits (SCOEL) (2017). Methodology for derivation of occupational exposure limits of chemical agents. Luxembourg: Publications Office of the European Union. Available from: https://op.europa.eu/en/publication-detail/-/publication/3c8ef3e0-48fc-11e8-be1d-01aa75ed71a1.
15. National Research Council (1983). Risk assessment in the federal government: managing the process. Washington (DC), USA: National Academies Press. https://doi.org/10.17226/366
16. United States Congress (2016). Frank R. Lautenberg Chemical Safety for the 21st Century Act. Available from: https://www.congress.gov/114/plaws/publ182/PLAW-114publ182.pdf.
17. National Research Council (2007). Toxicity testing in the 21st century: a vision and a strategy. Washington (DC), USA: National Academies Press. https://doi.org/10.17226/11970
18. Goodson WH 3rd, Lowe L, Carpenter DO, Gilbertson M, Manaf Ali A, Lopez de Cerain Salsamendi A, et al. (2015). Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: the challenge ahead. Carcinogenesis. 36(Suppl 1):S254–96. https://doi.org/10.1093/carcin/bgv039 PMID:26106142
19. National Research Council (2012). Exposure science in the 21st century: a vision and a strategy. Washington (DC), USA: National Academies Press. https://doi.org/10.17226/13507
20. Wild CP, Scalbert A, Herceg Z (2013). Measuring the exposome: a powerful basis for evaluating environmental exposures and cancer risk. Environ Mol Mutagen. 54(7):480–99. https://doi.org/10.1002/em.21777 PMID:23681765
21. National Academies of Sciences, Engineering, and Medicine (2017). Using 21st century science to improve risk-related evaluations. Washington (DC), USA: National Academies Press. https://doi.org/10.17226/24635
22. Benbrahim-Tallaa L, Lauby-Secretan B, Loomis D, Guyton KZ, Grosse Y, El Ghissassi F, et al.; International Agency for Research on Cancer Monograph Working Group (2014). Carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone. Lancet Oncol. 15(9):924–5. https://doi.org/10.1016/S1470-2045(14)70316-X PMID:25225686
23. IARC (2017). Some chemicals used as solvents and in polymer manufacture. IARC Monogr Eval Carcinog Risks Hum. 110:1–276. Available from: http://publications.iarc.fr/547
24. ECHA (2018). Management of PBT/vPvB substances under REACH. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/management-of-pbt-vpvb-substances.
25. WHO (2018). Global progress report on implementation of the WHO Framework Convention on Tobacco Control. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/fctc/reporting/WHO-FCTC-2018_global_progress_report.pdf.

6.9 Prevention strategies common to noncommunicable diseases

Focus on tobacco, alcohol, obesity, and physical inactivity

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SUMMARY

- In 2016 there were 40.5 million deaths from noncommunicable diseases worldwide, accounting for 72% of all deaths globally in that year.
- Tobacco use is estimated to cause 22% of cancers worldwide and contributes to multiple other diseases.
- A range of dietary factors, including alcohol consumption, that are implicated in cancer etiology are also relevant to risk of cardiovascular disease, resulting in similar dietary recommendations for both disease types.
- An estimated 24% of disability-adjusted life years lost due to tracheal, bronchial, and lung cancers worldwide are attributable to air pollution (both indoor and outdoor), which also contributes to the burden of cardiovascular disease, stroke, and chronic obstructive pulmonary disease.
- In some high-income countries, the mortality rates of noncommunicable diseases have peaked – particularly with respect to cardiovascular diseases and, possibly, cancer.
- Reducing the prevalence of tobacco smoking is key to reducing the risk of many cancer types as well as other noncommunicable diseases. National cancer control programmes should seek potential synergies with programmes for the prevention of other noncommunicable diseases in relation to alcohol consumption, diet, and physical exercise.

With increases in life expectancy and the growth of populations, more people worldwide are living into the age groups of peak cancer incidence. Many cancer prevention strategies are specific to cancer, such as human papillomavirus (HPV) vaccination. Some strategies for cancer prevention also reduce the risk of other noncommunicable diseases (NCDs).

The United Nations and WHO called for a 25% reduction in premature deaths (i.e. at ages 30–69 years) from NCDs by 2025, compared with 2010, with a slogan of "25 by 25" [1]. This was later modified within the Sustainable Development Goals agenda to an overarching target (Target 3.4) of reducing the total premature mortality from NCDs by one third by 2030, relative to 2015 [2].

Win–win strategies that have benefits across several NCDs are attractive in attempting to reach this goal and are reviewed in this chapter.

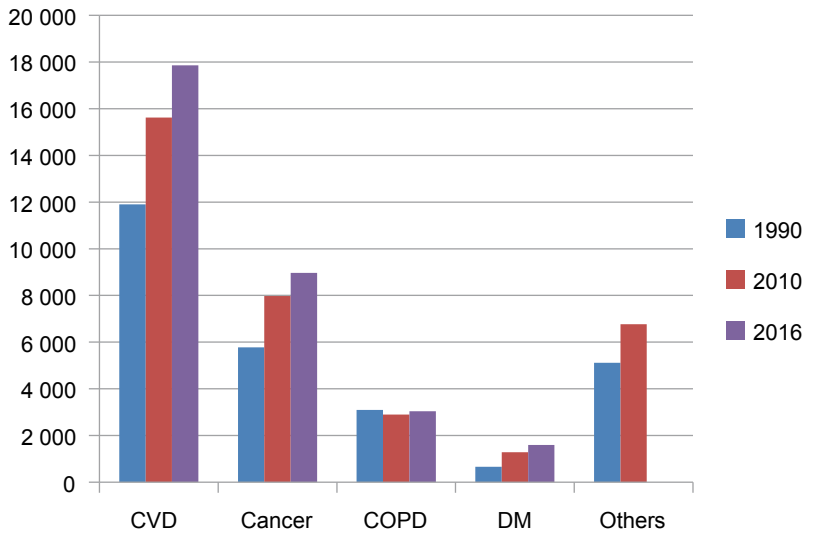
Burden of disease

Four common behavioural risk factors – tobacco use, excess alcohol consumption, unhealthy diet, and lack of physical activity – are relevant to four disease clusters: cancers, cardiovascular diseases, chronic respiratory diseases, and diabetes, which together account for about 78% of global deaths from NCDs [3]. According to WHO estimates, in 2016 there were 40.5 million deaths from NCDs worldwide, accounting for 72% of all deaths globally in that year [3]. About 78% of the NCD-related deaths occurred in low- and middle-income countries, which also had a high proportion of deaths in middle age. This staggering toll of NCDs and premature mortality in low- and middle-income countries reflects the transition in the main causes of death – from maternal and child deaths and infectious and parasitic diseases to NCDs.

Cardiovascular diseases are the biggest contributor to NCD-related deaths, followed by cancer, chronic respiratory diseases, and diabetes (Fig. 6.9.1) [3]. High-income countries have a lower burden of maternal and child deaths and infectious diseases, and therefore a higher proportional mortality due to NCDs. However, because low- and middle-income countries have larger population sizes, they have a larger absolute number of deaths due to NCDs.

Surprisingly, age-standardized death rates due to NCDs are also higher in low- and middle-income countries than in high-income countries. For example, rates of cardiovascular disease and death are

Fig. 6.9.1. Global distribution of number of deaths (thousands) within noncommunicable diseases, 1990–2016. COPD, chronic obstructive pulmonary disease; CVD, cardiovascular diseases; DM, diabetes mellitus.



FUNDAMENTALS

- The current toll of noncommunicable diseases and premature mortality in low- and middle-income countries reflects the transition in the main causes of death – from maternal and child deaths and infectious and parasitic diseases to noncommunicable diseases.
- Some risk factors for cancer, such as tobacco use, alcohol consumption, unhealthy diet, and lack of physical activity, also contribute to the burden of other noncommunicable diseases, notably cardiovascular diseases, chronic respiratory diseases, and diabetes.
- Tobacco smoking causes multiple tumour types, respiratory disease, and cardiovascular disease.
- Excess alcohol consumption causes several cancer types and also cardiovascular disease and stroke.
- Policy interventions to reduce the prevalence of these risk factors are likely to be win–win strategies with benefits across several noncommunicable diseases.
- Individual behaviour change should lower personal risk of multiple noncommunicable diseases, including cancer. Primary care workers can be trained to offer advice about the reduction of risk factors as well as about understanding the signs and symptoms of the major noncommunicable diseases, to promote earlier diagnosis and referral for treatment.

substantially higher in low- and middle-income countries even though the prevalence of risk factors is lower [4]. This may reflect the relatively unprepared state of health systems in low- and middle-income countries in responding to this fresh challenge posed by the rapid health transition by providing pharmacological therapies and revascularization to those at risk [4].

The four main disease clusters (cancers, cardiovascular diseases, chronic respiratory diseases, and diabetes) account for a lower proportion of disability-adjusted life years (DALYs) lost compared with NCDs in the neuropsychiatric, musculoskeletal, renal, hearing, and vision clusters.

WHO has estimated that the absolute number and proportion of deaths due to NCDs will increase worldwide, rising to about 70% of all deaths in 2030 [5]. This trend is mainly as a result of increases in the size and age of the world's population, as well as continuing reductions in child mortality and deaths from infectious diseases. Projected increases in the prevalence of risk factors for NCDs also contribute.

Prevalence of risk factors

Behavioural risk factors

The four common behavioural risk factors that contribute to the etiology of NCDs can all be subject to intervention: tobacco use, alcohol consumption, unhealthy diet, and lack of physical activity. All four of these factors contribute to increased cancer incidence and mortality, although for most cancer types there are no readily measurable intermediate non-malignant indicators other than obesity, whereas the prevention of cardiovascular disease and stroke benefits from measurable intermediate indicators, such as blood pressure and hypercholesterolaemia.

Tobacco use is estimated to cause 22% of cancers worldwide, and alcohol consumption 7% [6]. The role of diet and physical activity in cancer may be mediated mainly through obesity or may be at least partially independent. It has been noted that in Asian populations, increased body fat and visceral adiposity pose risks for NCDs at body mass index thresholds that are lower than the conventional criteria [7]; therefore, the associations of diet and physical inactivity with NCDs may have been underestimated in these populations.

It has been particularly difficult to specifically characterize diet as a risk factor for cancer, with the exceptions of contaminants such as aflatoxin contamination of mouldy foods as a cause of liver cancer, and arsenic in drinking-water as a cause of bladder cancer and skin cancer [8]. In the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) 2018 Expert Report, the only other diet–cancer relationship for which the evidence was categorized as *convincing* was between consumption of processed meat and risk of colorectal cancer [8]. However, the WCRF/AICR committee categorized a large number of associations as *probable*, and these directions of association are mostly considered to be the same for risk of cardiovascular disease. Hence, dietary recommendations for cancer and cardiovascular disease largely overlap; they both emphasize consuming a largely plant-based diet and eating whole foods rather than processed foods [8,9].

Air pollution

In recent years, the contribution of air pollution to NCDs has become far more widely appreciated. In 2006, the IARC Monographs classified indoor emissions from household combustion of coal as carcinogenic to humans (Group 1) and indoor emissions from household combustion of biomass fuel (primarily wood) as probably carcinogenic to humans (Group 2A). In 2013, the IARC Monographs classified outdoor air pollution as carcinogenic to humans (Group 1) and estimated that 223 000 deaths per year worldwide (about 15% of all deaths from lung cancer) are attributable to outdoor air pollution.

On the basis of estimates from the Global Burden of Disease Study 2015, The *Lancet* Commission on Pollution and Health estimated that 24% of DALYs lost due to tracheal, bronchial, and lung cancers worldwide are attributable to air pollution, both indoor and outdoor, with a higher burden in low- and middle-income countries [10]. The association of air pollution with cardiovascular disease, stroke, and chronic obstructive pulmonary disease means that much larger numbers of DALYs lost and deaths due to these other NCDs are attributed to air pollution than for cancer. However, reduction in exposure to air pollution would be predicted to reduce the incidence of all four of these NCDs.

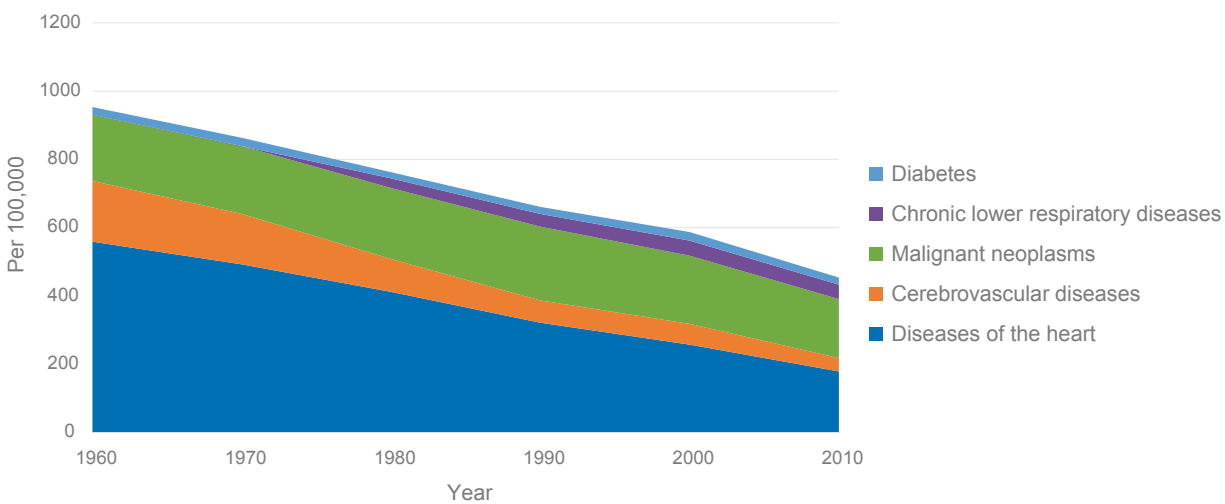
The precise components of air pollution that are causal are not fully identified. Particulates, notably particulate matter with particles of aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), are thought to be mainly responsible for the excess in lung cancer, because these particles can penetrate deeply into the lungs. In addition to particulate matter, airborne gases such as ozone, carbon monoxide, nitrogen dioxide, and sulfur dioxide may be associated with risk of diseases such as asthma, cardiovascular disease, and stroke.

Experience in high-income countries

In some high-income countries, the mortality rates of NCDs have peaked – particularly with respect to cardiovascular diseases and, possibly, cancer. The 60-year trends in the USA (Fig. 6.9.2) show that age-adjusted mortality rates for cardiovascular diseases have decreased by about 75% from a peak in the 1960s, those for cerebrovascular disease have decreased by 78%, and those for cancer have decreased by 17% since 1980 (https://www.cdc.gov/nchs/data/hus/2011/024.pdf).

Similar reductions in the incidence of cardiovascular diseases and of lung cancer in men have been seen in many high-income countries [11]. However, despite these declines in age-adjusted risks, reductions in the absolute number of deaths per

Fig. 6.9.2. Decline in age-adjusted death rates per 100 000 people for major noncommunicable diseases in the USA, 1950–2010.



year are smaller, because of population growth and ageing. The estimates from the Global Burden of Disease Study 2017 of age- and sex-specific rates for deaths and DALYs lost due to NCDs globally demonstrate a substantial reduction in incidence rates, but because of increasing population sizes and population ageing the absolute number of cases continues to increase [12].

Modelling suggests that reductions in the prevalence of risk factors explain about 44–76% of the decline in mortality from coronary heart disease in the USA and other high-income countries, and improved treatments and access to treatments explain about 23–47% of the decline [13]. The causes of the decline in cancer mortality rates in the USA are less well quantified, although a reduction in lung cancer mortality in men as a result of a decrease in the prevalence of smoking is clearly a major contributor. Over the 20th century, mortality rates from cervical cancer decreased dramatically in high-income countries, mainly because of organized cervical cancer screening leading to early detection and treatment [14]. Therefore, the experience in high-income countries suggests that the size of the NCD epidemic is not predetermined, and the challenge for low- and middle-income countries is whether they can intervene sufficiently early to mitigate the epidemic.

However, forecasting of future cancer rates suggests an increasing global burden in the absence of major interventions. The projections from the Global Burden of Disease Study 2017 of the leading causes of years of life lost predict that between 2016 and 2040, cancers of the lung, liver, colorectum, and breast will move up the rankings, as a result of a combination of changes in the prevalence of risk factors, population growth and ageing, and declining mortality from NCDs [15].

Prevention and control of NCDs

A comprehensive NCD control programme should include: (i) policy interventions that assist people to avoid risky behaviours, including international cooperation in tobacco and agricultural policies; (ii) promotion of health literacy, to increase self-efficacy in avoiding risks and maintaining health; and (iii) health services that combine timely and cost-effective management of NCD risk factors and clinically manifest NCDs (Table 6.9.1).

The major priority for cancer prevention is tobacco control (see Chapter 2.1), which could prevent about 29% of all cancer deaths in the USA and also greatly reduce the number of deaths from cardiovascular disease and chronic respiratory disease [16]. Tobacco smoking is the second largest cause of deaths worldwide [10]. Recent experience documents that when the prevalence of smoking declines, there are almost immediate reductions in the incidence of myocardial infarction and hospital admissions for asthma, and the incidence of lung cancer decreases within a decade [17].

The most effective way to reduce tobacco use is by increasing the price of tobacco products (see Chapter 6.1), and the most effective way to do this is by increasing

Table 6.9.1. Opportunities for the prevention, detection, and treatment of noncommunicable diseases in low- and middle-income countries

Category	Prevention	Detection	Treatment
Government policy	Anti-tobacco policy Regulation and labelling of processed foods and high-sugar beverages Planning for safe, healthy environments that promote physical activity and limit transition to sedentary lifestyle Mitigation of harmful effects of alcoholic beverages Reduction in outdoor air pollution; provision of cleaner fuels where indoor air pollution due to burning of coal or biomass occurs	Promotion of awareness of NCDs, signs and symptoms, and need for early detection	Ensure access to affordable essential medicines
Health system	Intersectoral planning for health promotion Training of health personnel, including task-shifting for cancer detection and treatment	Surveillance for risk factor and NCD prevalence Facilities and equipment for low-cost detection of patients who should be referred for cancer workup	Facilities and equipment for affordable treatments Recognition of need for both acute and chronic treatment of NCDs
Clinicians	Counselling of patients in risk factor reduction Treatment for tobacco addiction	Evaluation of intermediate risk factors; lifestyle and drug interventions to lower risk factor profiles Appropriate screening (e.g. HPV detection)	Evidence-based treatment with affordable essential medicines Procedural or surgical interventions if appropriate

HPV, human papillomavirus; NCDs, noncommunicable diseases.

Fig. 6.9.3. This display advertisement from Nepal illustrates one of the many aspects of tobacco control plans.

excise taxes. In both France and South Africa, tripling the price of cigarettes halved cigarette consumption in less than 15 years and doubled tobacco revenues to the state, which could be used to fund other smoking-reduction activities, such as advertising and nicotine replacement therapy [18].

Worldwide, the age-standardized prevalence of daily smoking in 2016 was estimated to be 25% in men and 5.4% in women [19]. Between 1990 and 2015, the global age-standardized prevalence decreased by 28% in men and by 34% in women; there was substantial heterogeneity across countries both in smoking prevalence and in change in prevalence [19]. Implementation of the WHO Framework Convention on Tobacco Control, called for in Target 3a of the United Nations Sustainable Development Goals, is still patchy, and a greatly decreased prevalence of smoking will be required to counter the demographic effects of an increase in the younger age groups that the tobacco industry targets to become new smokers. Increasing the quit rates among current smokers is also critical. Another part of the solution is alternative sources of income for those who are financially dependent on growing tobacco.

The increase in the prevalence of obesity is predicted to result in an increase in cancer incidence and mortality (see Chapter 2.7). This implies that prevention of obesity is a priority for the prevention of cancer, as well as cardiovascular diseases and diabetes. The environment in much of the world has been described as obesogenic because of the increasing availability of lower-cost processed foods, combined with lower levels of daily physical activity.

The evidence shows that sugar-sweetened beverages are important causes of childhood obesity, and substitution of lower-calorie options is associated with weight loss in randomized trials [20,21]. Taxes on sugar-sweetened beverages have been successful in lowering consumption, particularly in Central and South America, and preliminary evidence suggests some reductions in the prevalence of obesity (see Chapter 6.2). However, much larger societal changes will be needed in intersectoral management of agriculture and

Fig. 6.9.4. This poster is part of the “no fast food” campaign in Azerbaijan.

the food supply, as well as urban design to promote healthier transport options. In many countries, the impact of rapid urbanization has meant that these considerations are given a low priority.

Exposure to indoor air pollution has become less prevalent globally but is still highly prevalent in low- and middle-income countries; about 3 billion people worldwide are exposed to household air pollution, which accounts for an estimated 3.5–4 million deaths per year [22]. Exposure to outdoor air pollution has increased substantially in recent decades (see Chapter 2.9). In 2016, an estimated 95% of the world's population lived in areas with ambient $PM_{2.5}$ levels that exceeded the WHO air quality guideline of 10 μg/m^3 for outdoor $PM_{2.5}$ (annual average), and 58% lived in areas with levels that exceeded 35 μg/m^3 [23].

The sources of $PM_{2.5}$ vary substantially geographically. Sand is a major component in North Africa and the Middle East. In India, burning of crop wastes, construction dust, and vehicular emissions combine to create high levels of outdoor air pollution in the growing metropolis of Delhi, which is surrounded by agricultural states. In China, coal-fired power plants, automobiles, and industrial facilities are thought to be the dominant contributors to air pollution in the Beijing–Shanghai corridor [24]. Outdoor air pollution has recently become an issue in several cities in sub-Saharan Africa. Policies that reduce levels of air pollution are urgently needed, to reduce the burden of air pollution-related morbidity and mortality.

Early-life vaccination against hepatitis B virus has sharply reduced the prevalence of chronic hepatitis B virus infection (see Chapter 5.6), and thus the incidence of liver cancer [25]. The recent development of direct-acting antiviral agents that can cure hepatitis C virus infection in more than 95% of people who take a 12-week course offers the potential to remove hepatitis C virus infection as a cause of liver cancer. Reductions in the prevalence of infections with hepatitis B virus and hepatitis C virus will also reduce the incidence of non-cancer liver diseases, such as cirrhosis.

Many of these interventions have been identified by WHO as being cost-effective. A set of 16 "best buys" out of 88 interventions have been selected on the basis of cost–effectiveness and feasibility of implementation [26]. Five of these are policies designed to reduce the prevalence of tobacco use, three are to reduce alcohol consumption, and one aims to increase physical activity. These interventions involve legislative actions, public awareness campaigns, and public health interventions. These steps would be expected to decrease the risk of cancers, cardiovascular diseases, chronic obstructive pulmonary disease, stroke, and diabetes. HPV vaccination and cervical cancer screening are also a "best buy" but would not be predicted to directly alter the risk of other NCDs.

Fig. 6.9.5. Part of the "This Girl Can" campaign from Sport England, which encourages women to get active.

Health system challenges

The global NCD epidemic challenges all health systems, although the challenges vary according to the level of development. In low- and middle-income countries, limited financial protection from the costs of cancer treatment drives many people into bankruptcy. The health-care infrastructure is inadequate to meet the needs, with limited facilities for advanced care and shortages of trained health workers. In general, the health systems are configured to provide acute episodic care and need to be adapted to provide chronic continuous care across multiple disciplines. Although investment in secondary and tertiary hospitals may provide the physical facilities for cancer care, the specialization involved means that economies of scale or clinical experience may not be readily achievable between the treatment of cancer and treatment of other NCDs. This contrasts with the win–win component of a joint approach to reducing the prevalence of risk factors.

In many countries, access to essential drugs is not assured. As a result, some countries, such as India and Thailand, are resorting to compulsory licensing to domestically produce the more expensive cardiovascular or anticancer drugs. Many patients with cancer are deprived of low-cost drugs such as morphine that can provide pain relief; this is due to both national policies and international regulations that restrict the trade in opioid drugs [27].

There is a need to train and deploy non-physician health-care workers in primary care to provide appropriate referral for potential cancer cases in an attempt to detect cancers at an earlier stage. This is a complex endeavour because of a

lack of knowledge in many populations about the signs and symptoms of cancer and its potential to be treated. Necessary diagnostic facilities include imaging, biopsy, and histopathology. Treatment facilities range from outpatient oncology treatments to surgery and/or radiotherapy. Early presentation by patients, along with rapid referral, diagnosis, and treatment initiation, requires substantial specialist staffing. The development of local and regional cancer centres, at three levels (state, capital, and district), is being pioneered by the Tata Trust in India to offer affordable clinical care closer to patients' homes [28]. Telemedicine and mobile phone consultations may be helpful in initial assessment before referral as well as in continuing clinical management.

The costs of acute interventions and chronic care for NCDs, including cancer, are a formidable barrier for patients, governments, and health-care providers. The global movement for universal health coverage means that many countries are adopting policies that provide greater financial protection to people for health care, including the more treatable cancer types [29]. It is essential to ensure that national cancer control programmes actively explore potential synergies with the prevention and acute and chronic care of other NCDs.

References

1. United Nations (2011). Political declaration of the high-level meeting of the General Assembly on the prevention and control of non-communicable diseases. Available from: http://www.un.org/ga/search/view_doc.asp?symbol=A/66/L.1.
2. United Nations (2015). Transforming our world: the 2030 Agenda for Sustainable Development. Available from: https://sustainabledevelopment.un.org/post2015/transformingourworld.
3. WHO (2018). Global health estimates 2016: deaths by cause, age, sex, by country and by region, 2000–2016. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/healthinfo/global_burden_disease/estimates/en/.
4. Yusuf S, Rangarajan S, Teo K, Islam S, Li W, Liu L, et al.; PURE Investigators (2014). Cardiovascular risk and events in 17 low-, middle-, and high-income countries. N Engl J Med. 371(9):818–27. https://doi.org/10.1056/NEJMoa1311890 PMID:25162888
5. Mathers CD, Loncar D (2006). Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 3(11):e442. https://doi.org/10.1371/journal.pmed.0030442 PMID:17132052
6. Institute for Health Metrics and Evaluation (2019). Global Burden of Disease Study 2017 (GBD 2017) data resources: GBD results tool. Available from: http://ghdx.healthdata.org/gbd-results-tool.
7. Krishnaveni GV, Yajnik CS (2017). Developmental origins of diabetes – an Indian perspective. Eur J Clin Nutr. 71(7):865–9. https://doi.org/10.1038/ejcn.2017.87 PMID:28537579
8. WCRF/AICR (2018). Diet, nutrition, physical activity and cancer: a global perspective. Continuous Update Project Expert Report 2018. World Cancer Research Fund/American Institute for Cancer Research. Available from: https://www.wcrf.org/dietandcancer.
9. American Heart Association (2019). The American Heart Association diet and lifestyle recommendations. Available from: https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/aha-diet-and-lifestyle-recommendations.
10. Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu NN, et al. (2018). The *Lancet* Commission on Pollution and Health. Lancet. 391(10119):462–512. https://doi.org/10.1016/S0140-6736(17)32345-0 PMID:29056410
11. Ezzati M, Riboli E (2012). Can noncommunicable diseases be prevented? Lessons from studies of populations and individuals. Science. 337(6101):1482–7. https://doi.org/10.1126/science.1227001 PMID:22997325
12. Kyu HH, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al.; GBD 2017 DALYs and HALE Collaborators (2018). Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 392(10159):1859–922. https://doi.org/10.1016/S0140-6736(18)32335-3 PMID:30415748
13. Ford ES, Capewell S (2011). Proportion of the decline in cardiovascular mortality disease due to prevention versus treatment: public health versus clinical care. Annu Rev Public Health. 32(1):5–22. https://doi.org/10.1146/annurev-publhealth-031210-101211 PMID:21417752
14. Mathew A, George PS (2009). Trends in incidence and mortality rates of squamous cell carcinoma and adenocarcinoma of cervix – worldwide. Asian Pac J Cancer Prev. 10(4):645–50. PMID:19827887
15. Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, et al. (2018). Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. Lancet. 392(10159):2052–90. https://doi.org/10.1016/S0140-6736(18)31694-5 PMID:30340847
16. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. (2018). Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 68(1):31–54. https://doi.org/10.3322/caac.21440 PMID:29160902
17. Glantz S, Gonzalez M (2012). Effective tobacco control is key to rapid progress in reduction of non-communicable diseases. Lancet. 379(9822):1269–71. https://doi.org/10.1016/S0140-6736(11)60615-6 PMID:21963004
18. Jha P, Peto R (2014). Global effects of smoking, of quitting, and of taxing tobacco. N Engl J Med. 370(1):60–8. https://doi.org/10.1056/NEJMra1308383 PMID:24382066
19. GBD 2015 Tobacco Collaborators (2017). Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: a systematic analysis from the Global Burden of Disease Study 2015. Lancet. 389(10082):1885–906. https://doi.org/10.1016/S0140-6736(17)30819-X PMID:28390697

20. de Ruyter JC, Olthof MR, Seidell JC, Katan MB (2012). A trial of sugar-free or sugar-sweetened beverages and body weight in children. N Engl J Med. 367(15):1397–406. https://doi.org/10.1056/NEJMoa1203034 PMID:22998340

21. Ebbeling CB, Feldman HA, Chomitz VR, Antonelli TA, Gortmaker SL, Osganian SK, et al. (2012). A randomized trial of sugar-sweetened beverages and adolescent body weight. N Engl J Med. 367(15):1407–16. https://doi.org/10.1056/NEJMoa1203388 PMID:22998339

22. Gordon SB, Bruce NG, Grigg J, Hibberd PL, Kurmi OP, Lam KB, et al. (2014). Respiratory risks from household air pollution in low and middle income countries. Lancet Respir Med. 2(10):823–60. https://doi.org/10.1016/S2213-2600(14)70168-7 PMID:25193349

23. Shaddick G, Thomas ML, Amini H, Broday D, Cohen A, Frostad J, et al. (2018). Data integration for the assessment of population exposure to ambient air pollution for Global Burden of Disease assessment. Environ Sci Technol. 52(16):9069–78. https://doi.org/10.1021/acs.est.8b02864 PMID:29957991

24. Rohde RA, Muller RA (2015). Air pollution in China: mapping of concentrations and sources. PLoS One. 10(8):e0135749. https://doi.org/10.1371/journal.pone.0135749 PMID:26291610

25. Plymoth A, Viviani S, Hainaut P (2009). Control of hepatocellular carcinoma through hepatitis B vaccination in areas of high endemicity: perspectives for global liver cancer prevention. Cancer Lett. 286(1):15–21. https://doi.org/10.1016/j.canlet.2009.08.024 PMID:19836128

26. WHO (2017). Tackling NCDs: 'best buys' and other recommended interventions for the prevention and control of noncommunicable diseases. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/259232.

27. Knaul FM, Farmer PE, Krakauer EL, De Lima L, Bhadelia A, Jiang Kwete X, et al.; *Lancet* Commission on Palliative Care and Pain Relief Study Group (2018). Alleviating the access abyss in palliative care and pain relief – an imperative of universal health coverage: the *Lancet* Commission report. Lancet. 391(10128):1391–454. https://doi.org/10.1016/S0140-6736(17)32513-8 PMID:29032993

28. Sirohi B, Chalkidou K, Pramesh CS, Anderson BO, Loeher P, El Dewachi O, et al. (2018). Developing institutions for cancer care in low-income and middle-income countries: from cancer units to comprehensive cancer centres. Lancet Oncol. 19(8):e395–406. https://doi.org/10.1016/S1470-2045(18)30342-5 PMID:30102234

29. Frenk J, de Ferranti D (2012). Universal health coverage: good health, good economics. Lancet. 380(9845):862–4. https://doi.org/10.1016/S0140-6736(12)61341-5 PMID:22959372

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Bruce K. Armstrong reports having received personal consultancy fees from Maurice Blackburn Lawyers.

Patricia Ashton-Prolla reports having received personal consultancy fees from AstraZeneca.

Anssi Auvinen reports having received personal consultancy fees from Epid Research Inc. and Merck Sharp & Dohme.

Linda Bauld reports providing expert opinion on tobacco control to the parliaments of the European Union and Iceland, members of the German Bundestag, and several governments.

Julia Brotherton reports that her unit at the Victorian Cytology Service benefited from an unrestricted research grant from Seqirus.

Karen Brown reports that her unit at the University of Leicester benefited from research funding from Indena SpA.

Laia Bruni reports that her unit at the Catalan Institute of Oncology benefits from research funding from Merck and GlaxoSmithKline.

Franco Cavalli reports that his unit at the Oncology Institute of Southern Switzerland benefited from research funding from Roche.

Aaron J. Cohen reports that his unit at the Health Effects Institute benefits from funding from companies that manufacture or market motor vehicles for sale in the USA.

Jack Cuzick reports that his unit at the Wolfson Institute of Preventive Medicine benefits from research funding from AstraZeneca, and reports having received personal consultancy fees in his capacity as a member of an advisory board at Merck.

Diona L. Damian reports receiving non-monetary support from Blackmores Ltd.

Harry J. de Koning reports that his unit, the Department of Public Health at Erasmus University Medical Center, benefits from research funding from SCOR Global Life.

Joanna Didkowska reports that her unit at the Maria Skłodowska-Curie Institute benefits from research funding from Roche Polska, AstraZeneca, and Logistic Speed.

Ronny Drapkin reports having received personal consultancy fees from Repare Therapeutics and from Mersana Therapeutics.

Jessica N. Everett reports that her unit at NYU Langone Health benefits from research funding from Immunovia.

Judy E. Garber reports receiving personal consultancy fees from Helix Pharma and benefiting from research funding from Ambry Genetics.

Gemma Gatta reports that her unit at Istituto Nazionale dei Tumori benefited from research funding from Amgen Dompé.

Adi F. Gazdar (deceased) reported receiving personal consultancy fees from Genentech and Bristol-Myers Squibb.

Charles W. Jameson reports providing expert testimony for plaintiffs in litigation related to glyphosate products and talc products.

Dominique Laurier reports that his unit at the Institute for Radiological Protection and Nuclear Safety benefits from research funding from Areva and EDF.

Alberto Mantovani reports receiving honoraria from Biovelocità, Novartis, Merck, Compugen, Roche, AstraZeneca, and Chiesi.

Francis Mégraud reports that his unit at the University of Bordeaux benefits from research funding from Allergan, reports having benefited from research funding from Biocodex, and reports having received honoraria from Mayoly Spindler.

Klaus Pantel reports that his unit at the Institute of Tumour Biology at University Medical Center Hamburg-Eppendorf benefits from research funding from Janssen and from EU/IMI CANCER-ID EFPIA partners, and reports holding EPO patents No. 2016128125 A1 and application No. 17157020.3 – 1405.

Electra D. Paskett reports that her unit at The Ohio State University benefits from research funding from the Merck Foundation.

David H. Phillips reports receiving personal consultancy fees from the law firm Shook, Hardy & Bacon.

You-Lin Qiao reports having benefited from personal consultancy fees and support for travel, and reports that his unit at the Chinese Academy of Medical Sciences benefited from research support from Merck Sharp & Dohme.

Martin Röösli reports having been an unpaid member of the foundation board of the Swiss Research Foundation for Electricity and Mobile Communication, a non-profit research foundation at ETH Zurich.

Wolfgang A. Schulz reports that his unit at Heinrich Heine University benefited from research support from 4SC.

Nereo Segnan reports that his unit at the Center for Epidemiology and Prevention in Oncology (CPO Piedmont) benefited from equipment support from Medtronic and EndoChoice.

Carlo Senore reports that the University Hospital Città della Salute e della Scienza, where his unit is based, benefited from equipment support from Medtronic and EndoChoice.

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Penelope M. Webb reports that her unit at QIMR Berghofer Medical Research Institute receives funding for a research project from AstraZeneca.

Georg Zeller reports holding shares on the patent EP2955232A1 on “Method for diagnosing colorectal cancer based on analyzing the gut microbiome”.

Sources

Boxes

2.1.1 Reproduced from Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, editors (2018). Cancer epidemiology and prevention. 4th ed. New York (NY), USA: Oxford University Press, Table 11.1, p. 186, by permission of Oxford University Press, USA (www.oup.com).

3.2.1 Thomas Hudson.

4.4.1 Sankar Rengaswamy and Kunnambath Ramadas.

5.10.1 Adapted/translated from Lax SF, Horn LC, Löning T (2016). Categorization of uterine cervix tumors: what's new in the 2014 WHO classification [in German]. Pathologe. 37(6):573–84. https://doi.org/10.1007/s00292-016-0247-8 PMID:27770187, by permission from Springer Nature © 2016.

5.14.1 Adapted from Ulbright TM, Amin MB, Balzer B, Berney DM, Epstein JI, Guo C, et al. (2016). Germ cell tumours. In: Moch H, Humphrey PA, Ulbright TM, Reuter VE, editors. WHO classification of tumours of the urinary system and male genital organs. Lyon, France: International Agency for Research on Cancer (WHO Classification of Tumours series, 4th edition); pp. 189–226.

6.5.1 Adapted from Weitzel JN, Blazer KR, MacDonald DJ, Culver JO, Offit K (2011). Genetics, genomics, and cancer risk assessment: state of the art and future directions in the era of personalized medicine. CA Cancer J Clin. 61(5):327–59. https://doi.org/10.3322/caac.20128 PMID:21858794, with permission from John Wiley & Sons.

6.5.2 Patricia Ashton-Prolla.

6.6.1 Raúl Murillo.

P1.1 Reprinted from Ghebreyesus TA (2019). Progress in beating the tobacco epidemic. Lancet. 394(10198):548–9. https://doi.org/10.1016/S0140-6736(19)31730-1 PMID:31371094, Copyright 2019, with permission from Elsevier.

P1.2 Reprinted from WHO (2019). WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: seventh report of a WHO study group. Geneva, Switzerland: World Health Organization (WHO Technical Report Series, No. 1015). Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/publications-detail/who-study-group-on-tobacco-product-regulation-report-on-the-scientific-basis-of-tobacco-product-regulation-seventh-report-of-a-who-study-group.

Figures

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1.1.1 Reproduced from Cao B, Bray F, Beltrán-Sánchez H, Ginsburg O, Soneji S, Soerjomataram I (2017). Benchmarking life expectancy and cancer mortality: global comparison with cardiovascular disease 1981–2010. BMJ. 357:j2765. https://doi.org/10.1136/bmj.j2765 PMID:28637656

1.1.2 Courtesy of Bochen Cao, Isabelle Soerjomataram, and Freddie Bray. Compiled from WHO Global Health Estimates (https://www.who.int/healthinfo/global_burden_disease/en/).

1.1.3 Reproduced from Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today.

1.1.4 Courtesy of Bochen Cao, Isabelle Soerjomataram, and Freddie Bray. Compiled from Cao B, Bray F, Ilbawi A, Soerjomataram I (2018). Effect on longevity of one-third reduction in premature mortality from non-communicable diseases by 2030: a global analysis of the Sustainable Development Goal health target. Lancet Glob Health. 6(12):e1288–e1296. https://doi.org/10.1016/S2214-109X(18)30411-X PMID:30420032

1.1.5 vicmillon. Courtesy of Pixabay.

1.1.6 iStockphoto.com/PavelSinitcyn.

1.2.1A Compiled from Ferlay J, Colombet M, Bray F (2018). Cancer Incidence in Five Continents, CI5*plus*: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr.

1.2.1B WHO Mortality Database. Available from: http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html.

1.2.2A Compiled from Ferlay J, Colombet M, Bray F (2018). Cancer Incidence in Five Continents, CI5*plus*: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr.

1.2.2B WHO Mortality Database. Available from: http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html.

1.2.3A Compiled from Ferlay J, Colombet M, Bray F (2018). Cancer Incidence in Five Continents, CI5*plus*: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr.

1.2.3B WHO Mortality Database. Available from: http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html.

1.2.4 SoleneC1. Courtesy of Pixabay.

1.2.5A Compiled from Ferlay J, Colombet M, Bray F (2018). Cancer Incidence in Five Continents, CI5*plus*: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr.

1.2.5B WHO Mortality Database. Available from: http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html

1.2.6A Compiled from Ferlay J, Colombet M, Bray F (2018). Cancer Incidence in Five Continents, CI5*plus*: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr.

1.2.6B WHO Mortality Database. Available from: http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html.

1.2.7A Compiled from Ferlay J, Colombet M, Bray F (2018). Cancer Incidence in Five Continents, CI5*plus*: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr.

1.2.7B WHO Mortality Database. Available from: http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html.

1.2.8A Compiled from Ferlay J, Colombet M, Bray F (2018). Cancer Incidence in Five Continents, CI5*plus*: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr.

1.2.8B WHO Mortality Database. Available from: http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html.

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1.2.10A Compiled from Ferlay J, Colombet M, Bray F (2018). Cancer Incidence in Five Continents, CI5*plus*: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr.

1.2.10B WHO Mortality Database. Available from: http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html.

1.3.1 Miranda M. Fidler-Benaoudia and Freddie Bray. Compiled from UNDP Human Development Report Office (2015). What is human development? New York (NY), USA: United Nations Development Programme; pp. 1–10. Available from: http://hdr.undp.org/en/content/what-human-development.

1.3.2–1.3.6 Reproduced from Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today.

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2.3.1 & 2.3.2 Jürgen Rehm, Kevin D. Shield, and Elisabete Weiderpass. Compiled from data in WHO (2018). Global status report on alcohol and health 2018. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/substance_abuse/publications/global_alcohol_report/en/.

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3.3.1 Adapted from Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect. 124(6):713–21. https://doi.org/10.1289/ehp.1509912 PMID:26600562, Reproduced from Environmental Health Perspectives, https://ehp.niehs.nih.gov/15-09912/

3.4.1 Eugenia Dogliotti and Margherita Bignami.

3.6.1 Reproduced from Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, et al.; Ovarian Cancer Association Consortium (2012). Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol. 13(4):385–94. https://doi.org/10.1016/S1470-2045(11)70404-1 PMID:22361336, © 2012 Elsevier Ltd. Published by Elsevier Ltd

3.6.2 Reproduced from Brinton LA, Cook MB, McCormack V, Johnson KC, Olsson H, Casagrande JT, et al.; European Rare Cancer Study Group (2014). Anthropometric and hormonal risk factors for male breast cancer: Male Breast Cancer Pooling Project results. J Natl Cancer Inst. 106(3):djt465. https://doi.org/10.1093/jnci/djt465 PMID:24552677, by permission of Oxford University Press.

3.6.3 Reproduced from Black A, Pinsky PF, Grubb RL 3rd, Falk RT, Hsing AW, Chu L, et al. (2014). Sex steroid hormone metabolism in relation to risk of aggressive prostate cancer. Cancer Epidemiol Biomarkers Prev. 23(11):2374–82. https://doi.org/10.1158/1055-9965.EPI-14-0700 PMID:25178985, Copyright 2014, American Association for Cancer Research.

3.11.1 Reproduced from Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect. 124(6):713–21. https://doi.org/10.1289/ehp.1509912 PMID:26600562, Reproduced from Environmental Health Perspectives, https://ehp.niehs.nih.gov/15-09912/

4.2.1 Reprinted from Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al.; CONCORD Working Group (2018). Global surveillance of trends in cancer survival 2000–2014 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 391(10125):1023–75. https://doi.org/10.1016/S0140-6736(17)33326-3 PMID:29395269, Copyright 2018, with permission from Elsevier.

4.2.2 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM (2010). GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer.

4.5.1–4.5.3 Harry J. de Koning. Compiled from EU-topia (2018). EU-topia: towards improved cancer screening in all of Europe. Available from: www.eu-topia.org; Ponti A, Anttila A, Ronco G, Senore C, Basu P, Segnan N, et al. (2017). Against Cancer. Cancer screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening. Brussels, Belgium: European Commission. Available from: https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf.

4.6.1 Reproduced from Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, et al. (2017). Cancer screening in the United States, 2017: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 67(2):100–21. https://doi.org/10.3322/caac.21392 PMID:28170086, with permission from John Wiley & Sons.

5.1.1 Adi F. Gazdar.

5.1.2 Adi F. Gazdar. Compiled from Langevin SM, Kelsey KT (2017). Clinical epigenetics of lung cancer. In: Laurence J, Van Beusekom M, editors. Translating epigenetics to the clinic. London, UK: Elsevier; pp. 97–133. https://doi.org/10.1016/B978-0-12-800802-7.00005-8; Duruisseaux M, Esteller M (2018). Lung cancer epigenetics: from knowledge to applications. Semin Cancer Biol. 51:116–28. https://doi.org/10.1016/j.semcancer.2017.09.005 PMID:28919484; Gazdar AF, Bunn PA, Minna JD (2017). Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer. 17(12):725–37. https://doi.org/10.1038/nrc.2017.87 PMID:29077690

5.2.1 & 5.2.2 Reproduced from de Martel C, Plummer M, Vignat J, Franceschi S (2017). Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 141(4):664–70. https://doi.org/10.1002/ijc.30716 PMID:28369882, © 2017 International Agency for Research on Cancer (IARC/WHO); licensed by UICC. Open Access.

5.2.3 Reprinted from Leemans CR, Snijders PJF, Brakenhoff RH (2018). The molecular landscape of head and neck cancer. Nat Rev Cancer. 18(5):269–82. https://doi.org/10.1038/nrc.2018.11 PMID:29497144, by permission from Springer Nature © 2018.

5.3.1 Reza Malekzadeh, Christian C. Abnet, and Sanford M. Dawsey.

5.4.1 Compiled from Laurén P (1965). The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 64:31–49. https://doi.org/10.1111/apm.1965.64.1.31 PMID:14320675; Lauwers GY, Carneiro F, Graham DY, Curado MP, Franceschi S, Montgomery E, et al. (2010). Gastric carcinoma. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. Lyon, France: International Agency for Research on Cancer (WHO Classification of Tumours series, 4th edition); pp. 48–58.

5.4.2 Reproduced from Matsuoka T, Yashiro M (2018). Biomarkers of gastric cancer: current topics and future perspective. World J Gastroenterol.24(26):2818–32.https://doi.org/10.3748/wjg.v24.i26.2818 PMID:30018477, © Matsuoka T and Yashiro M, 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

5.5.1 Carlo Senore, Nereo Segnan, and Marc Gunter. Compiled from WCRF/AICR (2018). Diet, nutrition, physical activity and colorectal cancer. Continuous Update Project Expert Report 2018. World Cancer Research Fund/American Institute for Cancer Research. Available from: https://www.aicr.org/continuous-update-project/reports/colorectal-cancer-2017-report.pdf; IARC (2012). Personal habits and indoor combustions. IARC Monogr Eval Carcinog Risks Hum. 100E:1–575. Available from: http://publications.iarc.fr/122 PMID:23193840

5.5.2 Carlo Senore, Nereo Segnan, and Marc Gunter. Compiled from Lauby-Secretan B, Vilahur N, Bianchini F, Guha N, Straif K; International Agency for Research on Cancer Handbook Working Group (2018). The IARC perspective on colorectal cancer screening. N Engl J Med. 378(18):1734–40. https://doi.org/10.1056/NEJMsr1714643 PMID:29580179; Armaroli P, Villain P, Suonio E, Almonte M, Anttila A, Atkin WS, et al. (2015). European Code Against Cancer, 4th edition: cancer screening. Cancer Epidemiol. 39(Suppl 1):S139–52. https://doi.org/10.1016/j.canep.2015.10.021 PMID:26596722

B5.5.1 Reproduced from IARC (2019). Colorectal cancer screening. IARC Handb Cancer Prev. 17:1–300. Available from: http://publications.iarc.fr/573.

5.6.1–5.6.3 Chien-Jen Chen.

B5.6.1 Adapted from Yang HI, Tseng TC, Liu J, Lee MH, Liu CJ, Su TH, et al. (2016). Incorporating serum level of hepatitis B surface antigen or omitting level of hepatitis B virus DNA does not affect calculation of risk for hepatocellular carcinoma in patients without cirrhosis. Clin Gastroenterol Hepatol. 14(3):461–468.e2. https://doi.org/10.1016/j.cgh.2015.10.033 PMID:26598229, Copyright 2016, with permission from Elsevier.

B5.6.2 Compiled from Chiang CJ, Yang YW, You SL, Lai MS, Chen CJ (2013). Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. JAMA. 310(9):974–6. https://doi.org/10.1001/jama.2013.276701 PMID:24002285; Chiang CJ, Yang YW, Chen JD, You SL, Yang HI, Lee MH, et al. (2015). Significant reduction in end-stage liver diseases burden through the national viral hepatitis therapy program in Taiwan. Hepatology. 61(4):1154–62. https://doi.org/10.1002/hep.27630 PMID:25476749

5.7.1 Jessica N. Everett and Diane M. Simeone.

5.8.1 Adapted from Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. (2017). Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 67(6):472–92. https://doi.org/10.3322/caac.21409 PMID:29028110, with permission from John Wiley & Sons; used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, 8th edition (2017), published by Springer International Publishing.

5.9.1 Adapted from Colditz GA, Bohlke K (2014). Priorities for the primary prevention of breast cancer. CA Cancer J Clin. 64(3):186–94. https://doi.org/10.3322/caac.21225 PMID:24647877, with permission from John Wiley & Sons.

5.10.1 Adapted/translated from Lax SF, Horn LC, Löning T (2016). Categorization of uterine cervix tumors: what's new in the 2014 WHO classification [in German]. Pathologe. 37(6):573–84. https://doi.org/10.1007/s00292-016-0247-8 PMID:27770187, by permission from Springer Nature © 2016.

5.10.2 Adapted from Kurman RJ, Carcangiu ML, Herrington S, Young RH, editors (2014). WHO classification of tumours of female reproductive organs. Lyon, France: International Agency for Research on Cancer (WHO Classification of Tumours series, 4th edition).

5.10.3 & 5.10.4 Adapted from Kurman RJ, Carcangiu ML, Herrington S, Young RH, editors (2014). WHO classification of tumours of female reproductive organs. Lyon, France: International Agency for Research on Cancer (WHO Classification of Tumours series, 4th edition); Lax SF, Horn LC, Löning T (2016). Categorization of uterine cervix tumors: what's new in the 2014 WHO classification [in German]. Pathologe. 37(6):573–84. https://doi.org/10.1007/s00292-016-0247-8 PMID:27770187

5.10.5 Reproduced from Bhatla N, Berek J, Cuello M, Denny L, Grenman S, Karunaratne K, et al. (2018). New revised FIGO staging of cervical cancer (2018). Abstract S020.2. Presented at the XXII FIGO World Congress of Gynecology and Obstetrics, Rio de Janeiro, Brazil, 14–19 October 2018. Int J Gynecol Obstet. 143(S3):43–157. https://doi.org/10.1002/ijgo.12584, with permission from John Wiley & Sons.

5.11.1 Penelope M. Webb. Compiled from Getz G, Gabriel SB, Cibulskis K, Lander E, Sivachenko A, Sougnez C, et al.; Cancer Genome Atlas Research Network (2013). Integrated genomic characterization of endometrial carcinoma. Nature. 497(7447):67–73. https://doi.org/10.1038/nature12113 PMID:23636398; McAlpine J, Leon-Castillo A, Bosse T (2018). The rise of a novel classification system for endometrial carcinoma; integration of molecular subclasses. J Pathol. 244(5):538–49. https://doi.org/10.1002/path.5034 PMID:29344951

5.11.2 Penelope M. Webb.

5.12.1 Adapted from Prat J (2012). Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. Virchows Arch. 460(3):237–49. https://doi.org/10.1007/s00428-012-1203-5 PMID:22322322, by permission from Springer Nature © 2012.

5.12.2 Renée Turzanski Fortner and Rudolf Kaaks.

5.19.1 Reproduced from Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors (2017). WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: International Agency for Research on Cancer (WHO Classification of Tumours series, revised 4th edition). Available from: http://publications.iarc.fr/556.

6.3.1 Adapted with permission from Arbyn M, Xu L, Simoens C, Martin-Hirsch PP (2018). Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database Syst Rev. (5):CD009069. https://doi.org/10.1002/14651858.CD009069.pub3 PMID:29740819, John Wiley & Sons, Inc.

6.4.1 & 6.4.2 Adapted from Cuzick J (2017). Preventive therapy for cancer. Lancet Oncol. 18(8):e472–e482. https://doi.org/10.1016/S1470-2045(17)30536-3 PMID:28759386, Copyright 2017, with permission from Elsevier.

6.4.3 Reproduced from Cuzick J, Thorat MA, Bosetti C, Brown PH, Burn J, Cook NR, et al. (2015). Estimates of benefits and harms of prophylactic use of aspirin in the general population. Ann Oncol. 26(1):47–57. https://doi.org/10.1093/annonc/mdu225 PMID:25096604, by permission of Oxford University Press.

6.5.1 Patricia Ashton-Prolla.

6.5.2 Compiled from Achatz MI, Zambetti GP (2016). The inherited p53 mutation in the Brazilian population. Cold Spring Harb Perspect Med. 6(12):a026195. https://doi.org/10.1101/cshperspect.a026195 PMID:27663983; Rebbeck TR, Friebel TM, Friedman E, Hamann U, Huo D, Kwong A, et al.; EMBRACE; GEMO Study Collaborators; HEBON (2018). Mutational spectrum in a worldwide study of 29,700 families with *BRCA1* or *BRCA2* mutations. Hum Mutat. 39(5):593–620. https://doi.org/10.1002/humu.23406 PMID:29446198; Laraqui A, Uhrhammer N, Rhaffouli HE, Sekhsokh Y, Lahlou-Amine I, Bajjou T, et al. (2015). *BRCA* genetic screening in Middle Eastern and North African: mutational spectrum and founder *BRCA1* mutation (c.798_799delTT) in North African. Dis Markers. 2015:194293. https://doi.org/10.1155/2015/194293 PMID:25814778; Seymour HJ, Wainstein T, Macaulay S, Haw T, Krause A (2016). Breast cancer in high-risk Afrikaner families: is *BRCA* founder mutation testing sufficient? S Afr Med J. 106(3):264–7. https://doi.org/10.7196/SAMJ.2016.v106i3.10285 PMID:26915939; Ponti G, Castellsagué E, Ruini C, Percesepe A, Tomasi A (2015). Mismatch repair genes founder mutations and cancer susceptibility in Lynch syndrome. Clin Genet. 87(6):507–16. https://doi.org/10.1111/cge.12529 PMID:25345868; Villarreal-Garza C, Alvarez-Gómez RM, Pérez-Plasencia C, Herrera LA, Herzog J, Castillo D, et al. (2015). Significant clinical impact of recurrent *BRCA1* and *BRCA2* mutations in Mexico. Cancer. 121(3):372–8. https://doi.org/10.1002/cncr.29058 PMID:25236687; Lolas Hamameh S, Renbaum P, Kamal L, Dweik D, Salahat M, Jaraysa T, et al. (2017). Genomic analysis of inherited breast cancer among Palestinian women: genetic heterogeneity and a founder mutation in *TP53*. Int J Cancer. 141(4):750–6. https://doi.org/10.1002/ijc.30771 PMID:28486781; Peixoto A, Santos C, Pinheiro M, Pinto P, Soares MJ, Rocha P, et al. (2011). International distribution and age estimation of the Portuguese *BRCA2* c.156_157insAlu founder mutation. Breast Cancer Res Treat. 127(3):671–9. https://doi.org/10.1007/s10549-010-1036-3 PMID:20652400; Nielsen SM, Rhodes L, Blanco I, Chung WK, Eng C, Maher ER, et al. (2016). Von Hippel-Lindau disease: genetics and role of genetic counseling in a multiple neoplasia syndrome. J Clin Oncol. 34(18):2172–81. https://doi.org/10.1200/JCO.2015.65.6140 PMID:27114602

6.6.1 Raúl Murillo.

6.8.1 Vincent J. Cogliano.

6.8.2 Vincent J. Cogliano. Compiled from Stockholm Convention: http://chm.pops.int/TheConvention/ThePOPs/AllPOPs/tabid/2509/Default.aspx; http://chm.pops.int/TheConvention/ThePOPs/ChemicalsProposedforListing/tabid/2510/Default.aspx.

6.9.1 Reproduced from Hunter DJ, Reddy KS (2013). Noncommunicable diseases. N Engl J Med. 369(14):1336–43. https://doi.org/10.1056/NEJMra1109345 PMID:24088093, Copyright 2013, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

P1.1–P1.4 WHO.

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page 250 Reproduced with permission from CSDH (2008). Closing the gap in a generation: health equity through action on the social determinants of health. Final Report of the Commission on Social Determinants of Health. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/social_determinants/thecommission/finalreport/en/.

World Cancer Report

Cancer research for cancer prevention

Cancer is the second most common cause of death globally, accounting for an estimated 9.6 million deaths in 2018. The 2017 World Health Assembly requested WHO, in collaboration with IARC, to provide a global perspective on all measures that are recognized to limit the burden of cancer. The outcome of this charge – the *WHO Report on Cancer: Setting priorities, investing wisely and providing care for all* – complements the IARC *World Cancer Report* by synthesizing evidence to translate the latest knowledge into actionable policies to support governments.

— Dr Tedros Adhanom Ghebreyesus, Director-General, WHO

In 2014, *World Cancer Report* established that it is implausible to treat our way out of the coming cancer burden: prevention is the only option. Accordingly, this new *World Cancer Report* is totally focused on prevention, and it is the most comprehensive overview of relevant research currently available.

— Dr Christopher P. Wild, IARC Director 2009–2018

This new *World Cancer Report* provides investigators with detailed information across a multidisciplinary spectrum. Equally, *World Cancer Report* provides people in the wider community, no matter where they are located worldwide, with insights into how the cancer types that have for so long affected their communities may now have a lesser impact than was previously thought.

— Dr Elisabete Weiderpass, Director, IARC

“Cancer research for cancer prevention” is not simply a way to describe a particular field of investigation. Far more importantly, these words identify a pathway that may materially reduce the acknowledged burden of cancer faced by humanity. There is, in fact, no other way.

— Professor Bernard W. Stewart, University of New South Wales, Sydney

Highlights of this *World Cancer Report* include:

- Although excess body fatness increases the risk of cancers at various organ sites, including the colon and rectum, the risk may be reduced by intentional weight loss.
- Cancer-causing pollution of air and water are amenable to intervention by technological and regulatory means.
- Cervical cancer may be eliminated as a public health problem by vaccination against human papillomavirus (HPV) infection, even in low-income countries where cervical cancer is the major cancer type.
- In most countries, socioeconomic disparities limit the impact of proven preventive interventions.
- Individual susceptibility to particular cancers is increasingly understood from molecular technology.