



Diet, nutrition, physical activity and **skin cancer**

2019

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WORLD CANCER RESEARCH FUND NETWORK

OUR VISION

We want to live in a world where no one develops a preventable cancer.

OUR MISSION

We champion the latest and most authoritative scientific research from around the world on cancer prevention and survival through diet, weight and physical activity, so that we can help people make informed choices to reduce their cancer risk.

As a network, we influence policy at the highest level and are trusted advisors to governments and to other official bodies from around the world.

OUR NETWORK

World Cancer Research Fund International is a not-for-profit organisation that leads and unifies a network of cancer charities with a global reach, dedicated to the prevention of cancer through diet, weight and physical activity.

The World Cancer Research Fund network of charities is based in Europe, the Americas and Asia, giving us a global voice to inform people about cancer prevention.

OUR CONTINUOUS UPDATE PROJECT (CUP)

The Continuous Update Project (CUP) is World Cancer Research Fund Network's ongoing programme to analyse cancer prevention and survival research related to diet, nutrition and physical activity from all over the world. Among experts worldwide it is a trusted, authoritative scientific resource which informs current guidelines and policy on cancer prevention and survival.

Scientific research from around the world is continually added to the CUP's unique database, which is held and systematically reviewed by a team at Imperial College London. An independent panel of experts carries out ongoing evaluations of this evidence, and their findings form the basis of the WCRF Network's Cancer Prevention Recommendations (see **inside back cover**).

Through this process, the CUP ensures that everyone, including policymakers, health professionals and members of the public, has access to the most up-to-date information on how to reduce the risk of developing cancer.

The launch of World Cancer Research Fund Network's Third Expert Report, *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*, in 2018 brings together the very latest research from the CUP's review of the accumulated evidence on cancer prevention and survival related to diet, nutrition and physical activity. **Diet, nutrition, physical activity and skin cancer** is one of many parts that make up the CUP Third Expert Report; for a full list of contents see **dietandcancerreport.org**

The CUP is led and managed by World Cancer Research Fund International in partnership with the American Institute for Cancer Research, on behalf of World Cancer Research Fund UK, Wereld Kanker Onderzoek Fonds and World Cancer Research Fund HK.

HOW TO CITE THIS REPORT

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Key

See **Glossary** for definitions of terms highlighted in *italics*.

References to other parts of the Third Expert Report are highlighted in **purple**.

EXECUTIVE SUMMARY

Background and context

Skin cancers can be divided into two main groups: *melanoma* and *non-melanoma*.

In 2018, melanoma accounted for about 22 per cent of skin cancer diagnoses, and non-melanoma tumours accounted for about 78 per cent of skin cancer diagnoses [1]. The most common non-melanoma tumours are *basal cell carcinoma* and *squamous cell carcinoma*.

Melanoma of the skin is the 19th most commonly occurring cancer in men and women, with nearly 300,000 new cases worldwide in 2018. Non-melanoma skin cancer is more common, with more than 1 million cases diagnosed in 2018; however, this is likely to be an underestimate. The number of people diagnosed per year with either type of skin cancer is projected to increase over the next 20 years [2].

In this report from our Continuous Update Project (CUP) – the world’s largest source of scientific research on cancer prevention and survivorship through diet, weight and physical activity – we analyse global research on how certain lifestyle factors affect the risk of developing skin cancer. This includes new studies as well as those included in the 2007 Second Expert Report, *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective* [3]. This report forms part of the WCRF/AICR Third Expert Report, *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*.

In addition to the findings in this report, there are other established causes of skin cancer. These include the following:

1. Radiation

- The primary cause of skin cancer is ultraviolet radiation from sunlight.
- Both the duration and severity of exposure is important: there is a *dose-response* relationship between the number of sunburn episodes during any life period (childhood, adolescence or adulthood) and the risk of melanoma [4].

2. Medication

- Taking the medications that are needed after having an organ transplant is associated with an increased risk of squamous cell carcinoma, a type of skin cancer.

3. Infection

- Infection of the skin by human papilloma virus (HPV) can lead to squamous cell carcinoma.
- People living with HIV/AIDS are at increased risk of squamous cell carcinoma. Kaposi’s sarcoma, a type of cancer which can involve the skin, is a characteristic complication of advanced AIDS.

4. Occupational exposure

- Being exposed to certain chemicals used in the plastic and chemical industries is associated with an increased risk of melanoma.

5. Genetics and family history

- Some rare mutations in specific genes can lead to skin cancer.
- Having a family history of skin cancer increases the risk of skin cancer.

6. Skin pigmentation

- Skin cancer is more common in lighter-skinned populations than in darker-skinned populations.

How the research was conducted

The global scientific research on diet, weight, physical activity and the risk of skin cancer was systematically gathered and analysed, and then independently assessed by a panel of leading international scientists in order to draw conclusions about which of these factors increase or decrease the risk of developing skin cancer. This new report includes all new relevant studies as well as studies included in our 2007 Second Expert Report [3]. In total, this new report analysed 55 studies from around the world, comprising more than 13 million adults, and over 56,000 cases of non-melanoma skin cancer and 27,000 cases of malignant melanoma. To ensure consistency, the methodology for the CUP remains largely unchanged from that used for our 2007 Second Expert Report [3]. A summary of the mechanisms underpinning all the findings can be found in the **Evidence and judgements** section of this report.

The panel judged the evidence and drew conclusions in March 2017. The conclusions drawn form part of the [Third Expert Report](#).

Findings

There is strong evidence that:

- consuming arsenic in drinking water increases the risk of skin cancer (unspecified)
- consuming high-dose beta-carotene supplements is unlikely to have a substantial effect on the risk of non-melanoma skin cancer
- being tall increases the risk of malignant melanoma

There is limited evidence that:

- consuming coffee might decrease the risk of malignant melanoma in women
- consuming coffee might decrease the risk of basal cell carcinoma
- consuming alcoholic drinks might increase the risk of malignant melanoma and basal cell carcinoma
- being tall might increase the risk of basal cell carcinoma
- greater birthweight might increase the risk of malignant melanoma

Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active and eating a healthy diet. The Cancer Prevention Recommendations are listed on the inside back cover of this report, with full details available in [Recommendations and public health and policy implications](#).

References

- [1] Ferlay J, Ervik M, Lam F, et al. *Global Cancer Observatory: Cancer Today*, 2018. Accessed: 24/10/2018. Available from: <https://gco.iarc.fr/tomorrow>.
- [2] Ferlay J, Ervik M, Lam F, et al. *Global Cancer Observatory: Cancer Tomorrow*, 2018. Accessed: 24/10/2018. Available from: <https://gco.iarc.fr/tomorrow>.
- [3] World Cancer Research Fund/American Institute for Cancer Research, *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*, 2007: Washington, DC: AICR.
- [4] Dennis LK, Vanbeek MJ, Beane Freeman LE, et al. Sunburns and risk of cutaneous melanoma: does age matter? A comprehensive meta-analysis. *Annals of Epidemiology* 2008; 18: 614–27.

2019	DIET, NUTRITION, PHYSICAL ACTIVITY AND SKIN CANCER		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		
	Probable		Arsenic in drinking water¹ (unspecified skin cancer) Adult attained height² (MM)
LIMITED EVIDENCE	Limited – suggestive	Coffee (BCC; MM [women])	Alcoholic drinks (BCC; MM) Adult attained height ^{2,3} (BCC) Birthweight ^{3,4} (MM)
	Limited – no conclusion	Potatoes, non-starchy vegetables, fruits, milk, coffee (MM [men], SCC), decaffeinated coffee, tea, alcoholic drinks (SCC), total fat, cholesterol, protein, retinol in the diet and/or supplements, beta-carotene in the diet (MM; NMSC), vitamin D, selenium, caffeine physical activity, body fatness, adult attained height (SCC), patterns of diet, meat, processed meat, fish, oily fish, offal, poultry, eggs, all vegetables, multivitamin supplements, folate, pyridoxine B ₆ , cobalamin B ₁₂ , lycopene, lutein and zeaxanthin, vitamin A, vitamin C, vitamin E, carotenoids, alpha-carotene, energy intake	
STRONG EVIDENCE	Substantial effect on risk unlikely	High-dose beta-carotene supplements⁵ (NMSC)	

BCC, basal cell carcinoma; MM, malignant melanoma; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma.

- 1 The International Agency for Research on Cancer (IARC) has judged arsenic and inorganic arsenic compounds to be carcinogenic to humans (Group 1) [5]. Drinking water contaminated with arsenic is also classed separately as a human carcinogen (Group 1) [5]. Water can become contaminated by arsenic as a result of natural deposits present in the earth, volcanic activity, or agricultural, mining and industrial practices. Countries particularly affected by higher levels of arsenic in drinking water include Bangladesh, China and India.
- 2 Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and nutritional factors affecting growth during the period from preconception to completion of growth in length.
- 3 The evidence shows that, in general, the taller people are during adulthood and the more people weighed at birth, the higher their risk of some cancers. A better understanding of the developmental factors that underpin the associations between greater growth and cancer risk is needed.
- 4 Birthweight is a marker for prenatal growth, reflecting a combination of factors including foetal nutrition, and is also a predictor of later growth and maturation.
- 5 The evidence for beta-carotene and non-melanoma skin cancer is derived from one study on plasma levels, as well as two studies on high-dose supplement use (50 milligrams per day and 50 milligrams per day on alternate days).

1. Summary of Panel judgements

Overall the Panel notes the strength of evidence that greater adult attained height increases the risk of *malignant melanoma* and that consuming arsenic in drinking water increases the risk of skin cancer (unspecified).

The Continuous Update Project (CUP) Panel judges as follows:

Probable evidence

Arsenic in drinking water: Consuming arsenic in drinking water is probably a cause of skin cancer (unspecified).

Adult attained height: Developmental factors leading to greater growth in length in childhood (marked by adult attained height) are probably a cause of malignant melanoma.

Limited – suggestive evidence

Coffee:

- The evidence suggesting that consuming coffee decreases the risk of basal cell carcinoma is limited.
- The evidence suggesting that consuming coffee decreases the risk of malignant melanoma in women is limited.

Alcohol:

- The evidence suggesting that consuming alcoholic drinks increases the risk of basal cell carcinoma is limited.
- The evidence suggesting that consuming alcoholic drinks increases the risk of malignant melanoma is limited.

Adult attained height: The evidence suggesting that the developmental factors leading to greater growth in length in childhood (marked by adult attained height) increase the risk of basal cell carcinoma is limited.

Birthweight: The evidence suggesting that the factors leading to greater birthweight, or its consequences, increase the risk of malignant melanoma is limited.

Substantial effect on risk unlikely

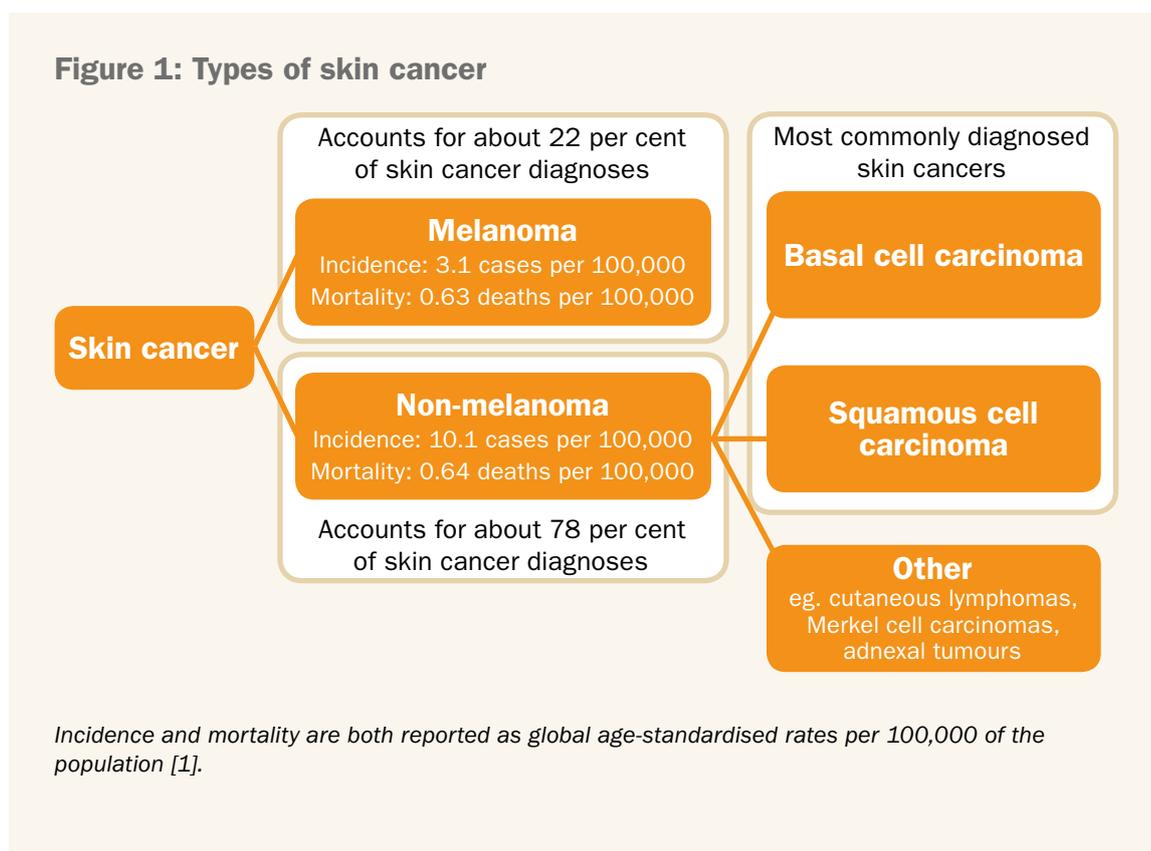
High-dose beta-carotene supplements: Consuming high-dose beta-carotene supplements is unlikely to have a substantial effect on the risk of non-melanoma skin cancer.

For a full description of the definitions of, and criteria for, the terminology of ‘convincing’, ‘probable’, ‘limited – suggestive’, ‘limited – no conclusion’ and ‘substantial effect on risk unlikely’, see **Appendix**.

2. Trends, incidence and survival

The skin is one of the largest organs in terms of surface area and weight. Skin comprises three primary layers – *epidermis*, *dermis* and *subcutaneous layer* – and each has specific functions. The outer layer, the epidermis, is the primary barrier between the body and the environment and contains specialised epithelial cells called *keratinocytes* and pigment-producing *melanocytes*, as well as some immune cell types. The dermis is a structural layer that includes blood and lymph vessels, sweat glands and immune cells. The subcutaneous layer is mainly composed of fat cells.

Skin cancers can be divided into two main groups: *melanoma* and *non-melanoma* (see **Figure 1**). In 2018, melanoma accounted for about 22 per cent of skin cancer diagnoses [1]. Melanoma arises from melanocytes, in the lowest layer of the epidermis. Non-melanoma tumours accounted for about 78 per cent of skin cancer diagnoses in 2018 [1] (also see **Box 1**); the most common non-melanoma tumours are *basal cell carcinoma* and *squamous cell carcinoma*. These cancers arise from the middle and upper layers of the epidermis.



Incidence

Melanoma of the skin is the 19th most commonly occurring cancer in men and women, with nearly 300,000 new cases worldwide in 2018 [1]. The highest age-standardised rates of melanoma are seen in Australia and New Zealand for men, and in Denmark and New Zealand for women. When both sexes are combined, the highest rates are seen in Australia (33.6 cases per 100,000 of the population) and New Zealand (33.3 cases per

100,000 of the population) [1]. New Zealand has the highest age-standardised mortality rate, at 4.8 deaths per 100,000 of the population.

Non-melanoma skin cancer is the fifth most commonly occurring cancer in men and women, with over 1 million diagnoses worldwide in 2018 [1], although this is likely to be an underestimate (see **Box 1**). The rates of non-melanoma skin cancer are also highest in Australia and New Zealand, and at 147.5 cases per 100,000 and 138.4 per 100,000 respectively, are much higher than those for melanoma. Papua New Guinea has the highest age-standardised mortality rate from non-melanoma skin cancer at 7.2 deaths per 100,000 of the population [1].

Improved screening for both melanoma and non-melanoma is thought to contribute to the higher rates in Australia and New Zealand (see **Box 1**). The high rates observed are also due in part to these countries' latitude, their proximity to a hole in the ozone layer above Antarctica, meaning that ultraviolet (UV) radiation is not filtered as effectively as in other regions [6], and in part to migration of non-native people to this area.

For more information on the incidence of cancer around the world, see [Cancer trends](#).

Trends

The rates of melanoma have been increasing over the last 20 years [7]. The time frame is longer for some cancer registries. The increase is more pronounced in *high-income countries*, such as the USA, Australia and New Zealand (see **Box 1**). Data from *low- and middle-income countries* generally do not demonstrate a clear increase over time. For data from specific cancer registries around the world, please see the Global Cancer Observatory: Cancer Over Time [7].

In the next 20 years, the number of new cases of melanoma is projected to increase to over 450,000 incident cases per year [2]. An increase in non-melanoma cases is also projected, to nearly 2 million cases diagnosed per year by 2040 [2].

Survival

Survival rates for melanoma skin cancer are higher than for many other cancers. For example, in Australia between 2010 and 2014, people diagnosed with melanoma skin cancer had a 91 per cent chance (89 per cent for men and 94 per cent for women) of surviving for 5 years compared with the general population. *Survival rate* has increased over time, and in Australia between 1986 to 1990 and 2011 to 2015, the 5-year *relative survival* from melanoma skin cancer improved from 88 per cent to 91 per cent [8]. Survival from melanoma is also high in New Zealand, where the 5-year *cumulative relative survival* of melanoma cancer patients diagnosed between 1994 and 2011 was 90 per cent [9].

The survival rate is influenced by the stage at which melanoma is diagnosed: for instance in the USA, 5-year survival for localised melanoma is 98.4 per cent, whereas for metastatic melanoma 5-year survival is 22.5 per cent [10].

There are large differences in survival rates between ethnicities. Data from the US Surveillance, Epidemiology, and End Results (SEER) Program show that for diagnoses between 2008 and 2014, the 5-year survival rate for melanoma was 93.8 per cent for people from white populations and 66.3 per cent for people from African-American populations [11]. This may be because a diagnosis of advanced disease is more likely for African-Americans than for white people [12]. As for other cancers, the causes of this disparity are likely to be multifactorial [13–15].

The data on survival from melanoma in low- and middle-income countries are limited.

Data from the Global Cancer Observatory show that mortality is low for non-melanoma skin cancer, with a global age-standardised mortality rate of 0.64 deaths per 100,000 of the population [1]. Most cases, especially if diagnosed at an early stage, are not fatal.

Box 1: Cancer incidence and survival.

The cancer incidence rates and figures given here are those reported by cancer registries, now established in many countries. These registries record cases of cancer that have been diagnosed. However, many cases of cancer are not identified or recorded: some countries do not have cancer registries, regions of some countries have few or no records, records in countries suffering war or other disruption are bound to be incomplete and some people with cancer do not consult a physician. Altogether, this means that the actual incidence of cancer is probably higher than the figures given here.

Survival rates are generally higher in high-income countries and other parts of the world where there are established services for screening and early detection of cancer together with well-established treatment facilities. Survival is often a function of the stage at which a cancer is detected, diagnosed and treated.

Non-melanoma skin cancer represents a particular challenge for estimating incidence and survival. Non-melanoma skin cancer is often not tracked by cancer registries, or registrations of this cancer are often incomplete, such as with the Surveillance, Epidemiology and End Results (SEER) Program in the USA [16], because most cases are successfully treated via surgery or ablation. Due to these factors, it is likely that the reported global incidence of non-melanoma skin cancer is an underestimate [17, 18]. Non-melanoma skin cancer is usually omitted from comparative rankings of the most common cancers. (In the **Cancer trends section of the Third Expert Report, non-melanoma skin cancer is not part of the rankings listed.)**

3. Pathogenesis

Exposure to UV radiation is the primary cause of skin cancer. The role of sun damage is supported by the association between measures of sun sensitivity and skin cancer incidence, which is higher in people who have pale skin that burns without tanning, blue eyes and red hair [19–21]. Both the duration and severity of exposure is important: there is a *dose–response relationship* between the number of sunburn episodes during any life period (childhood, adolescence or adulthood) and the risk of *melanoma* [4].

UV radiation can induce cellular changes consistent with the *hallmarks of cancer*, including inducing *genomic instability* and *mutation*, resisting cell death, activating sustained proliferative signalling and cell growth, as well as initiating tumour-promoting inflammatory responses [22]. See also [The cancer process](#), sections 1.2.3 and 1.3.2.4.

UV radiation can directly damage *DNA* by affecting bonding between adjacent pyrimidines [23]. The most commonly studied mutation, particularly associated with *non-melanoma skin cancer*, is in the *p53* gene. Faults in this gene affect the normal processes by which damaged cells are removed (*apoptosis*). UV radiation can also damage DNA indirectly through the generation of *reactive oxygen species* (ROS), which can cause mutations [24].

UV radiation and UV radiation-induced *oxidative stress* both activate specific signalling pathways, including *MAP kinases*, that lead to changes in cell survival, cell cycle regulation and ultimately, uncontrolled cell growth [25]. In addition, ROS-mediated activation of the NF-κB and STAT3 pathways perpetuates the chronic inflammatory response [25, 26]. Chronic *inflammation* helps generate an environment conducive to cancer development and progression [22] and is associated with progression from *actinic keratosis* to squamous cell carcinoma [25].

COX-2, an enzyme involved in the production of *prostanoids*, has also been implicated in the promotion and progression of skin cancers [27]. COX-2 expression is stimulated by UV radiation. The downstream signalling can result in sustained cellular proliferation, inhibition of apoptosis, inflammation and immunosuppression and can promote *metastasis* through *epithelial-mesenchymal transition* [27].

HPV may also have an indirect role in non-melanoma skin cancer *pathogenesis* [28]. HPV in the skin may facilitate UV radiation-induced *carcinogenesis* by interfering with normal cellular repair and clearance processes [29]. A wide variety of HPV subtypes have been associated with non-melanoma skin cancer [30].

Overall, UV radiation has a range of effects on skin cells, affecting several metabolic pathways that together create a cellular microenvironment conducive to the development and progression of cancer. These effects may be modulated by genetic factors [31].

4. Other established causes

Other established causes of skin cancer include the following:

Radiation

Over-exposure to UV radiation (mainly from sunlight, but also from UV-emitting tanning devices) is the primary cause of *melanoma* and *non-melanoma* skin cancers [21, 32]. For further detail, see **Pathogenesis**.

Medication

Immune suppression medication following organ transplantation is associated with an increased risk of skin cancers, especially *squamous cell carcinoma* [33].

Infection

HPV can cause squamous cell carcinomas of the skin, especially in immunocompromised people [33]. People living with HIV/AIDS, who are immunocompromised, are also at increased risk of squamous cell carcinoma. Kaposi's sarcoma, which is otherwise rare, is a characteristic complication of advanced AIDS.

Occupational exposure

Exposure to polychlorinated biphenyls (chemicals used in the plastic and chemical industries) has also been strongly associated with an elevated risk for melanoma [34].

Genetics and family history

There are some rare, high-penetrance genetic mutations known to cause melanoma, such as mutations in the CDKN2A gene, but these do not make a large contribution to the total number of melanoma cases [35]. People who have a family history of melanoma are predisposed to this cancer [36–38].

Skin pigmentation

There is an inverse relationship between risk of skin cancer and skin pigmentation, with highest risks observed in populations with the fairest skin. This is likely due to lower production of the protective skin pigment *melanin* [21].

5. Interpretation of the evidence

5.1 General

For general considerations that may affect interpretation of the evidence, see [Judging the evidence](#).

'Relative risk' (RR) is used in this report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

5.2 Specific

Confounding. Sun exposure is an important *confounder*.

Classification. *Melanoma* and *non-melanoma* skin cancers may have different causes; this would explain *heterogeneity* between studies that do not distinguish between these two types. Non-melanoma skin cancer is not always recorded by cancer registries and may therefore be underestimated in reports.

6. Methodology

To ensure consistency with evidence collected and analysed for the 2007 Second Expert Report [3], the methodology for reviewing the epidemiological evidence in the CUP remains largely unchanged. However, on the basis of the experience of conducting the *systematic literature reviews* (SLRs) for the 2007 Second Expert Report, some modifications were made to the methodology. The updated literature search was restricted to Medline and included only *randomised controlled trials*, cohort and *nested case-control studies*.

Owing to their methodological limitations, *case-control* and *ecological studies* were not analysed in the CUP Skin SLR 2017, apart from those for arsenic in drinking water, for which evidence from the International Agency for Research on Cancer (IARC) monograph [5] and strong mechanistic evidence were used as an upgrading factor.

Dose–response meta-analyses were possible for coffee, alcoholic drinks, adult attained height and birthweight, and where possible are presented by skin cancer subtype. Although it was not possible to conduct stratified analyses by skin pigmentation, information on *adjustments* for skin pigmentation by individual studies and from pooled and published meta-analyses were taken into account during Panel discussions.

Studies reporting mean difference as a measure of association were not included in the CUP Skin SLR 2017, as relative risks estimated from mean differences are not adjusted for *confounders*, and thus are not comparable with adjusted relative risks from other studies.

Non-linear meta-analysis is applied when the data suggest that the dose–response curve is non-linear and when a threshold or plateau of effect is detected that might be of interest. Exploratory non-linear dose–response meta-analyses were conducted only when there were five or more studies with three or more categories of exposure.

For this report, where possible, skin cancer subtypes (malignant *melanoma* and *non-melanoma skin cancer*, including *basal cell carcinoma* and *squamous cell carcinoma*) were reviewed separately.

The CUP Skin SLR 2017 included studies published up to 19 April 2016.



The Panel judged the evidence and drew conclusions in March 2017. The conclusions drawn form part of the Third Expert Report.

For more information on the methodology, see [Judging the evidence](#) and the full [CUP Skin SLR 2017](#).

6.1 Mechanistic evidence

The summary of the mechanisms included in this report were produced by the International Agency for Research on Cancer (IARC) and reviewed by CUP Panel members. The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. The mechanisms sections cover the primary hypotheses that currently prevail and are not based on a systematic or exhaustive search of the literature. For further information on general processes involved in the development of cancer, see [The cancer process](#). A brief summary is given of possible mechanisms for arsenic in drinking water, coffee, alcoholic drinks, adult attained height and birthweight.

7. Evidence and judgements

The following sections summarise the evidence identified in the [CUP Skin SLR 2017](#) and provide a comparison with the findings and the Panel's conclusions from the 2007 Second Expert Report [3]. They also include a brief description of the potential *biological mechanisms* for each exposure.

For information on the criteria for grading the epidemiological evidence, see the **Appendix** on page 47 of this report. References to studies added as part of the CUP have been included; for details of references to other studies from the 2007 Second Expert Report, see [CUP Skin SLR 2017](#).

Where possible, the evidence is presented separately for different subtypes of skin cancer.

7.1 Arsenic in drinking water

(Also see [CUP Skin SLR 2017: Section 4.1.2.7.2](#))

The evidence for drinking water contaminated with arsenic and risk of skin cancer is presented in the following subsections.

The most compelling data were from ecological studies [5]. Generally, this type of study design produces evidence from which it is not possible to draw robust conclusions. However, for arsenic in drinking water (as an exposure), ecological studies arguably provide the most useful type of evidence. If, as is likely, the same water source supplies the whole population in a region, regional variation will overwhelm individual differences in drinking behaviours. This design also substantially reduces measurement error.

The CUP identified one new study (one publication [39]), giving a total of three studies (three publications) reviewing the evidence for arsenic in drinking water and risk of skin cancer (see [CUP Skin SLR 2017](#), section 4.1.2.7.2 for a full list of references). Highest versus lowest or *dose-response meta-analyses* could not be conducted in the CUP due to variability in arsenic exposure assessment across studies. The evidence is from individual published *cohort studies*. The Panel also considered evidence from a published IARC review of *case-control* and *ecological studies* on consumption of arsenic in drinking water and skin cancer [5].

Of the three cohort studies identified, one study, conducted in areas of Taiwan where arseniasis is hyperendemic, reported a *statistically significant* increased risk of skin cancer when comparing the highest with the lowest arsenic concentration in drinking water [40]. No statistically significant increase or decrease in risk was observed in two other studies from populations with low levels of exposure to arsenic in drinking water [39, 41].

Most studies *adjusted* or accounted for age and sex. One study [39] adjusted for measures of sun exposure and sensitivity.

The findings of the published cohort studies are summarised in **Table 1** (for more detailed information see [CUP Skin SLR 2017](#), section 4.1.2.7.2).

Table 1: Summary of cohort studies for consumption of arsenic in drinking water and the risk of skin cancer

Study	Increment/ contrast	Sex	RR (95% CI)	No. of cases (No. of participants)
High-exposure area				
South-western Taiwan cohort, 1989–1992 [40]	0.71 to 1.1 vs 0 mg per litre	Men and women	Skin cancer 8.69 (1.08-65.50)	26 (654)
Low-exposure area				
Danish Diet, Cancer and Health cohort [39]	Per 1 µg per litre Time-weighted average exposure	Men and women	MM IRR 0.80 (0.59-1.08)	147 (56,378)
	Per 1 µg per litre Time-weighted average exposure		NMSC IRR 0.99 (0.94-1.06)	1,010 (56,378)
Cohort of Mormons, USA¹ [41]	≥ 5,000 vs < 1,000 ppb-years	Men	MM SMR 0.83 (0.17-2.43)	3 (2,092)
		Women	MM SMR 1.82 (0.50-4.66)	4 (1,966)

¹The Lewis Cohort study [41] is a retrospective cohort study of mortality.

Abbreviations: IRR, incident rate ratio; MM, malignant melanoma; NMSC, non-melanoma skin cancer; ppb, parts per billion; SMR, standardised mortality ratio.



Published pooled analyses and meta-analyses

No published *pooled analyses* and no published meta-analyses on consumption of arsenic in drinking water and the risk of skin cancer were identified. One published review from IARC [5] of case-control and ecological studies on arsenic intake and skin cancer was identified. For the full results of these studies, please see [CUP Skin SLR 2017](#), Appendix 4. In summary, four of six case-control studies reported a statistically significant increased risk of non-melanoma skin cancer or of skin cancer (histological type not specified); and of 17 ecological studies, in which the outcomes were mostly skin cancer and histological type was not specified, most reported a significant increased risk.

Mechanisms

The mechanisms linking arsenic in drinking water with cancer development are poorly understood. Experimental studies suggest that arsenic exhibits tumour-promoting properties by inducing oxidative DNA damage, activating transcription factors and modulating the expression of genes involved in cell growth [42, 43]. It is currently uncertain, however, whether these mechanisms are applicable specifically to skin cancer.

CUP Panel's conclusion

Overall, the evidence was generally consistent. A statistically significant increased risk of skin cancer with consumption of arsenic in drinking water was reported in one study from a high-exposure area. Results were not significant in the other two studies; however, there were very few cases of malignant melanoma. The IARC review of case-control and ecological studies supported the evidence from the cohort studies. No dose–response meta-analysis was possible in the CUP. In addition, arsenic is judged a ‘Group 1’ carcinogen¹ by IARC [5]. There is evidence for plausible mechanisms operating in humans.

Consumption of arsenic in drinking water is probably a cause of skin cancer (unspecified).

¹ The CUP Panel noted the strength of the evidence from IARC judging arsenic as a ‘Group 1’ carcinogen, and this evidence acts as a special upgrading factor (see the **Appendix**).

7.2 Coffee

(Also see [CUP Skin SLR 2017: Section 3.6.1](#))

As part of the CUP, seven new studies (six publications [44–49]) were identified, giving a total of 11 studies (11 publications) reviewing the evidence for coffee consumption and risk of skin cancer (for a full list of references see [CUP Skin SLR 2017](#), tables 8 and 9).

Malignant melanoma

When comparing highest versus lowest consumption of coffee, six of nine comparisons (eight studies) reported decreased risks, of which three were significant (see [CUP Skin SLR 2017](#), figure 4).

Seven studies were included in the CUP *dose–response meta-analysis* [44–46, 49, 50], which comprised 6,401 cases of malignant *melanoma*. No significant association was observed: RR 0.96 (95% CI 0.92-1.00). Moderate *heterogeneity* was observed: $I^2 = 50\%$. See [CUP Skin SLR 2017](#), figure 5 and table 6.

There was no evidence of *publication bias* but visual inspection of the funnel plot showed some asymmetry driven by one study [50] that reported a decreased risk. When this study was excluded from the dose–response meta-analysis, there was no substantial change to the overall estimate.

There was no evidence of a non-linear association ($p = 0.54$).

When stratified by sex, a significant 9 per cent decreased risk was observed for women (RR 0.91 [95% CI 0.86-0.96]) but no significant association was observed for men (RR 1.03 [95% CI 0.97-1.10]); see **Table 2** and also figure 7 in [CUP Skin SLR 2017](#). Stratification by geographical location, duration of follow-up, number of cases, publication year and level of adjustment showed no significant association. A *statistically significant* inverse association was found in studies with fewer than 15 years of follow-up (RR 0.96 [95% CI 0.93-0.99]). See [CUP Skin SLR 2017](#), table 6.

Table 2: Summary of CUP stratified dose–response meta-analyses of coffee consumption and risk of malignant melanoma

Analysis	Increment	Sex	RR (95% CI)	I^2	No. of studies	No. of cases
CUP analysis	Per cup of coffee per day	All	0.96 (0.92-1.00)	50%	7	6,401
		Men	1.03 (0.97-1.10)	0%	2	818
		Women	0.91 (0.86-0.96)	36%	4	1,830



The level of *adjustment* for skin type and exposure to sunlight or UV radiation varied between studies. Four studies (two publications [45, 46]) adjusted for sun exposure and skin type characteristics, one study adjusted for erythemal UV exposure [44] and two studies did not adjust for any variable related to pigmentation or radiation exposure [49, 50]. See tables 6 and 8 in the [CUP Skin SLR 2017](#).

One study was not included in any CUP analyses as it did not provide a risk estimate [51].

No significant association was reported in the 2007 Second Expert Report [3], in which two studies were meta-analysed. Five new studies were included in the CUP analysis and 6,310 more cases of malignant melanoma.

Published pooled analyses and meta-analyses

Two publications contained meta-analyses of coffee consumption and risk of malignant melanoma [52, 53]. Both publications reported significant decreased risk when comparing highest versus lowest categories of consumption. No significant associations were observed in the dose–response analyses; see **Table 3**. All cohort studies in both published meta-analyses were also included in the CUP analysis.

Table 3: Summary of published meta-analyses of coffee consumption and the risk of malignant melanoma

Study	Increment/ contrast	RR (95% CI)	I ² , p value	No. of studies	No. of cases
Liu et al. 2016¹ [52]	Caffeinated coffee per one cup per day	0.96 (0.91-1.00)	-	Cohort: 7	5,737
	Highest versus lowest categories of consumption	0.84 (0.71-0.99)	57%		
Wang et al. 2016² [53]	Total coffee intake per one cup per day	0.97 (0.93-1.00)	-	Cohort: 6 Case-control: 1	6,094
	Highest versus lowest categories of consumption	0.83 (0.72-0.97)	51%, 0.048	Cohort: 7	5,660

Specific adjustments for skin sensitivity or sun exposure

1. In this meta-analysis, two studies did not adjust for any measures of skin sensitivity or sun exposure, three studies adjusted for multiple measures of skin sensitivity and sun exposure, and one study adjusted for ‘July erythemal exposure’. For full details, please see the original papers.
2. In this meta-analysis, two studies did not adjust for any measures of skin sensitivity or sun exposure, four studies adjusted for multiple measures of skin sensitivity and sun exposure, and one study adjusted for ‘July erythemal exposure’. The case-control study adjusted for multiple measures of skin sensitivity and sun exposure. For full details, please see the original papers.

Basal cell carcinoma

When comparing highest versus lowest levels of coffee consumption, four of six comparisons (five studies) reported a decreased risk of *basal cell carcinoma*, of which two were statistically significant (see [CUP Skin SLR 2017](#), figure 4).

Three studies (two publications [47, 48]; 23,109 cases of basal cell carcinoma) were included in the CUP dose–response meta-analysis. A significant 4 per cent decreased risk per cup of coffee per day was reported (RR 0.96 [95% CI 0.94-0.97]). There was no evidence of heterogeneity, $I^2 = 0\%$, $p = 0.75$; see [CUP Skin SLR 2017](#), figure 5.

Two studies adjusted for measures of skin sensitivity and sun exposure, and one study adjusted for skin sensitivity; see table 8 in the [CUP Skin SLR 2017](#).

No meta-analysis was possible for the 2007 Second Expert Report [3].

Published pooled analyses and meta-analyses

One publication [54] conducted a meta-analysis of three *cohort studies* and one case-control study (23,750 cases of basal cell carcinoma). When comparing highest with lowest categories of intake, a significant 17 per cent decreased risk was reported (RR 0.83 [95% CI 0.76-0.91]; see [CUP Skin SLR 2017](#), table 7). In this meta-analysis, two of the cohort studies and the case-control study adjusted for sun exposure; please see original paper for details. All three cohort studies were included in the CUP analysis.

Mechanisms

The exact biological mechanisms linking coffee consumption to malignant melanoma and basal cell carcinoma are uncertain. Coffee drinking provides exposure to a range of biologically active compounds, many of which have been demonstrated in *in vitro* and animal studies to have *antioxidant* and anti-tumorigenic properties. These include high levels of certain phenolic *phytochemicals*, such as the antioxidants caffeic acid and chlorogenic acid, and natural diterpenes, such as cafestol and kahweol, which have been shown to inhibit changes in *DNA methylation* [55], induce *apoptosis*, and have antioxidative and anti-inflammatory effects [56–59].

CUP Panel's conclusion

Malignant melanoma

The evidence for consumption of coffee and decreased risk of melanoma was limited but generally consistent. The CUP dose–response meta-analysis showed no significant association, with moderate heterogeneity. Stratification by sex showed a significant decreased risk in women but not in men. Other published meta-analyses supported the findings from the CUP. There is evidence for plausible mechanisms operating in humans.

The evidence suggesting that consumption of coffee decreases the risk of malignant melanoma in women is limited.

Basal cell carcinoma

The evidence for consumption of coffee and decreased risk of basal cell carcinoma was limited but generally consistent. The CUP dose–response meta-analysis showed a significant decreased risk, with no evidence of heterogeneity. This was supported by findings from another published meta-analysis. There is evidence for plausible mechanisms operating in humans.

The evidence suggesting that consumption of coffee decreases the risk of basal cell carcinoma is limited.

7.3 Alcoholic drinks

(Also see *CUP Skin SLR 2017*: Sections 3.7.1, 3.7.1.1, 3.7.1.2, 3.7.1.3, and 3.7.1.4)

Alcohol as ethanol. As part of the CUP 8 new studies (8 publications [44, 60–66]) were identified, giving a total of 17 studies (17 publications) reviewing the evidence for consumption of alcohol as ethanol and risk of skin cancer (for a full list of references, see *CUP Skin SLR 2017*, tables 17 and 18).

Specific alcohol drinks. As part of the CUP five new studies (six publications [60–62, 64, 66, 67]) were identified with respect to beer, giving a total of nine studies (nine publications); five new studies (five publications [60–62, 64, 66]) were identified as part of the CUP with respect to wine, giving a total of eight studies (seven publications); and five new studies (five publications [60–62, 64, 66]) were identified as part of the CUP with respect to spirits, giving a total of seven studies (six publications). For a full list of references see *CUP Skin SLR 2017*, tables 19, 20 and 21.

Malignant melanoma

Alcohol as ethanol

When comparing the highest with the lowest categories of total alcohol intake, all six studies reported increased risks of malignant *melanoma*, of which three were significant (see *CUP Skin SLR 2017*, figure 15).

Six studies (six publications [44, 60, 62, 63, 65, 68]) were included in the CUP *dose–response meta-analysis*, comprising 7,367 cases of malignant *melanoma*. A significant 8 per cent increased risk per 10 grams of alcohol (as ethanol) consumed per day (RR 1.08 [95% CI 1.03-1.13]) was found. High and significant *heterogeneity* was observed ($I^2 = 66%$, $p = 0.01$). See *CUP Skin SLR 2017*, figure 16.

One study [44], contributing the most weight to the meta-analysis, had a risk estimate close to 1 (RR 1.02 [95% CI 0.99-1.05]). During influence analysis, heterogeneity was significantly reduced ($I^2 = 5%$) when this study was omitted, while the summary risk estimate remained robust and similar to the original analysis (RR 1.10 [95% CI 1.06-1.14]).

There was no evidence of *publication bias* ($p_{\text{Egger's}} = 0.142$); however, visual inspection of the funnel plot showed asymmetry with an absence of small studies on the left hand side (see [CUP Skin SLR 2017](#), figure 17). There was evidence of a *non-linear association* ($p < 0.0001$) at lower levels of intake (no intake to less than 10 grams of alcohol, as ethanol, per day), but the dose–response plateaued at higher levels of consumption; see [CUP Skin SLR 2017](#), figure 18 and associated table.

When stratified by sex, a significant increased risk was observed in women (RR 1.09 [95% CI 1.03-1.16]); see [CUP Skin SLR 2017](#), table 15.

Two studies [62, 68] were *adjusted* for various measures of skin sensitivity, two studies [60, 65] were adjusted for a range of potentially confounding factors but not skin sensitivity, and two studies [44, 63] were only minimally adjusted (for age and sex). For details of adjustments for each study, see table 17 in the [CUP Skin SLR 2017](#).

One study [69] reported a standardised incidence ratio and was not included in CUP analysis. This study reported no association between malignant melanoma and alcohol dependence.

The CUP findings are similar to those from the 2007 Second Expert Report [3]; however, in 2007 fewer studies were meta-analysed and no significant association was observed (RR 1.18 [95% CI 0.99-1.40]). In the CUP analysis four additional studies and 10 times as many cases of malignant melanoma were included.

Published pooled analyses and meta-analyses

Two publications [70, 71] that conducted meta-analyses of alcohol consumption and risk of malignant melanoma were identified via the CUP. At all levels of drinking, increased risks were reported; see **Table 4**.



Table 4: Summary of CUP meta-analysis and published meta-analyses of alcohol consumption and the risk of malignant melanoma

Analysis	Increment/contrast	RR (95% CI)	I ² , p value	No. of studies	No. of cases
CUP analysis	Per 10 grams of alcohol (as ethanol) per day	1.08 (1.03-1.13)	66%	6	7,367
Bagnardi et al. 2015^{1,2} [70]	Light drinking (≤ 12.5 grams per day) vs no or occasional drinking	1.25 (1.13-1.38)	0%	2	2,666
	Moderate drinking (12.5–50 grams per day) vs no or occasional drinking	1.27 (1.13-1.42)	0%		
Rota et al. 2014^{2,3} [71]	Any alcohol drinking vs no or occasional drinking	1.26 (1.19-1.35)	0%, 0.657	2	2,666
	Light alcohol drinking (≤ 1 drink per day) vs no or occasional drinking	1.25 (1.15-1.35)	0%, 0.847		
	Moderate to heavy alcohol drinking (> 1 drink per day) vs no or occasional drinking	1.29 (1.17-1.43)	0%, 0.370		

Specific adjustments for skin sensitivity or sun exposure

1. The meta-analysis reported that one study adjusted for measures of skin sensitivity and sun exposure. For details, please see original paper.
2. The same two cohorts were used for Bagnardi et al. 2015 [70] and Rota et al. 2014 [71].
3. The meta-analysis reported that one study adjusted for measures of sun exposure. For details, please see original paper.

Specific alcoholic drinks

Beer, wine and spirits. Four studies provided 11 results across the exposures of beer, wine, and spirits. Ten results reported positive associations, of which three were statistically significant (see CUP Skin SLR 2017, tables 19, 20 and 21). One study [62] adjusted for a measure of skin sensitivity.

In a historical cohort study of beer and malignant melanoma risk, a non-significant positive association between Danish brewery workers (employed for at least six months between 1939 to 1963) and risk of malignant melanoma compared with the general Danish population was reported: SIR 1.12 (0.83-1.48) [72].

Other alcoholic drinks. A Norwegian prospective study reported an IRR of 0.60 (0.30–1.20) in men (47 cases) and an IRR of 1.70 (0.90-3.20) in women (61 cases) when comparing consumption of wine or liquor with no consumption [50].

Basal cell carcinoma

Alcohol as ethanol

When comparing the highest versus the lowest categories of total alcohol intake, four out of five comparisons (seven studies) reported positive associations, of which one was statistically significant. One comparison reported no association [73]. See [CUP Skin SLR 2017](#), figure 20.

Nine studies (seven publications) were included in the CUP dose–response meta-analysis, which comprised 3,349 cases of *basal cell carcinoma*. No significant association was observed per 10 grams of alcohol (as ethanol) per day (RR 1.04 [95% CI 0.99-1.10]; see [CUP Skin SLR 2017](#), figure 21). There was evidence of high and significant heterogeneity: $I^2 = 68\%$, $p = 0.004$. In sensitivity analysis, when one study [74] investigating monozygotic twins was excluded, there was no significant effect on the summary estimate (RR 1.05 [95% CI 1.00-1.10]). The excluded study assumed the twins had similar sun exposure throughout childhood.

Egger's test showed no evidence of publication or small study bias.

There was evidence of a non-linear relationship ($p < 0.0001$) at lower levels of intake (in the range of no intake to less than 10 grams of alcohol, as ethanol, per day) but was mainly flat at higher levels of consumption; see [CUP Skin SLR 2017](#), figure 25 and associated table.

When stratified by sex, a significant positive association was observed for women (RR 1.08 [95% CI 1.04-1.12]; see [CUP Skin SLR 2017](#), figure 23). When stratified by geographical location a significant positive association was reported for North America (RR 1.10 [95% CI 1.02-1.17]), but not Europe or Australia. Stratification by number of cases showed no significant associations. See [CUP Skin SLR 2017](#), table 15.

Six studies (four publications [61, 64, 66, 73]) adjusted for multiple markers of sun sensitivity, one study [75] adjusted for hair colour, and one study [74] adjusted for sunlight. For details, see table 17 in the [CUP Skin SLR 2017](#).

The results from the CUP analysis are similar to those from the 2007 Second Expert Report [3], where no significant association was reported. Seven more studies were included in the CUP analysis, with over 1,800 more cases of basal cell carcinoma.

Specific alcoholic drinks

Beer, wine and spirits. From six studies (five publications [61, 64, 66, 74, 76]) there were eight significant positive associations and one significant inverse association across the exposures of beer, wine and spirits (see [CUP Skin SLR 2017](#), tables 19, 20 and 21). Three results reported no association (RR = 1.00) [61, 76] (see [CUP Skin SLR 2017](#), tables 19 and 20). All studies except the Finnish Adult Twin Cohort [74] adjusted for a measure of skin sensitivity.

Mechanisms

The mechanisms of action for an effect of chronic alcohol consumption on the development of malignant melanoma are not well elucidated. *Acetaldehyde*, a highly toxic metabolite of ethanol oxidation, can interfere with *DNA* synthesis and repair, which may result in the development of cancer. Higher ethanol consumption can also induce *oxidative stress* through increased production of *reactive oxygen species*, which are *genotoxic* and *carcinogenic* [77]. Alcohol may also affect hormone metabolism or interfere with retinoid metabolism and with *DNA* repair mechanisms [78]. Limited experimental evidence in animal models suggests that the consumption of alcohol stimulates melanoma angiogenesis and tumour progression [79].

CUP Panel's conclusion

Malignant melanoma

The evidence for consumption of alcoholic drinks and increased risk of malignant melanoma was limited but generally consistent. The CUP dose–response meta-analysis reported a significant increased risk, with high heterogeneity. There was evidence of a non-linear relationship at lower levels of intake. The direction of association was maintained when stratified by sex but remained significant only in women. Results from other published meta-analyses also reported positive associations; studies contained in these meta-analyses were also included in the CUP meta-analysis. Prospective cohort studies investigating individual alcoholic drinks generally reported increased risks with increased intake. In addition, alcoholic drinks are judged as a ‘Group 1’ carcinogen by IARC [80]. There is evidence of plausible mechanisms operating in humans.

The evidence suggesting that consumption of alcoholic drinks increases the risk of malignant melanoma is limited.

Basal cell carcinoma

The evidence for consumption of alcoholic drinks and increased risk of basal cell carcinoma was limited but generally showed positive associations. The CUP dose–response meta-analysis reported no significant association, with high heterogeneity. There was evidence of a non-linear relationship at lower levels of intake. Stratification tended to attenuate the association, but the direction was maintained for most analyses. Results from prospective cohort studies investigating individual alcoholic drinks generally reported increased risks with increased intakes. In addition, alcoholic drinks are judged as a ‘Group 1’ carcinogen by IARC [80]. There is evidence of plausible mechanisms operating in humans.

The evidence suggesting that consumption of alcoholic drinks increases the risk of basal cell carcinoma is limited.

7.4 High-dose beta-carotene supplements

(Also see [CUP Skin SLR 2017: Section 5.5.1.2](#))

The evidence for beta-carotene plasma levels and supplementation with beta-carotene (alone) and the risk of *non-melanoma skin cancer* is presented in the following section.

No new studies were identified as part of the CUP reviewing the evidence for high-dose beta-carotene supplements and risk of non-melanoma skin cancer (for a full list of references see [CUP Skin SLR 2017](#), section 5.5.1.2). Highest versus lowest and *dose-response meta-analyses* could not be conducted.

Plasma beta-carotene

One published *nested case-control study* was identified, in which there was no *statistically significant* association between plasma beta-carotene concentration and the risk of non-melanoma skin cancer (RR 0.97 [95% CI 0.69-1.37]) for ≥ 23.29 versus ≤ 7.28 micrograms per 100 millilitres of plasma beta-carotene among subjects assigned to placebo [81]. This study did not adjust for measures of skin sensitivity or sun exposure.

Published pooled analyses and meta-analyses

No published *pooled analyses* and no published meta-analyses on plasma beta-carotene and the risk of non-melanoma skin cancer were identified.

High-dose beta-carotene supplements

Two randomised controlled trials (*RCTs*) on supplements of beta-carotene alone and the risk of non-melanoma skin cancer were identified. A summary of the results from these trials is presented in **Table 5**. In both, analyses stratified by smoking did not show any significant effects [82, 83]. One study adjusted for skin type and the other did not adjust for any measure of skin sensitivity or sun exposure. See [CUP Skin SLR 2017](#), table 28.

Table 5: Summary of published randomised controlled trials for beta-carotene supplements and the risk of non-melanoma skin cancer

Study	Contrast	Sex	RR (95% CI)	Length of intervention (years)	No. of cases treatment/placebo (No. of participants)
Physicians Health Study [82]	50 mg every other day vs placebo	Men	0.98 (0.92-1.05)	12	1,786/1,821 (22,071)
Beta Carotene Trial 1983–89 [83]	50 mg/day vs placebo	Men and women	1.04 (0.89-1.21)	5	362/340 (1,805)



Published pooled analyses and meta-analyses

No published pooled analyses were identified. One published meta-analysis on consumption of beta-carotene supplements and the risk of non-melanoma skin cancer has been identified, which included four RCTs and reported no statistically significant effect [84]; see **Table 6**.

Table 6: Summary of published meta-analyses for high-dose beta-carotene supplements and the risk of non-melanoma skin cancer

Analysis	Contrast	RR (95% CI)	Heterogeneity p-value	No. of studies	No. of cases
Druesne-Pecollo et al. 2010¹ [84]	Supplemented with beta-carotene (no upper limit) vs placebo	0.99 (0.93-1.05)	0.52	4	4,447
	Supplemented with beta-carotene (alone) vs placebo	0.99 (0.93-1.06)	0.17	2	3,870
	Supplemented with beta-carotene (combined with other antioxidants) vs placebo	0.98 (0.83-1.15)	0.55	2	577
	Supplemented with beta-carotene (with doses of 20 to 30 milligrams per day) vs placebo	0.99 (0.93-1.05)	0.36	3	4,315
	Supplemented with beta-carotene (in populations with majority men) vs placebo	0.97 (0.91-1.03)	0.46	3	4,119
	Supplemented with beta-carotene (in populations with majority women) vs placebo	1.18 (0.97-1.45)	0.53	2	395

Specific adjustments for skin sensitivity or sun exposure

1. The review article did not provide information on adjustments made in each trial. For details please see original trials.

Note: All four RCTs included in this meta-analysis [84] were identified as part of the CUP: one [82] is included in the evidence summary above, two [85, 86] are included in the [CUP Skin SLR 2017](#) in section 5.5.18 under *Multivitamin supplements* and one [87] disaggregated the outcome of non-melanoma skin cancer into basal cell carcinoma and squamous cell carcinoma and so is not included in the evidence summary above (see table 28 in the [CUP Skin SLR 2017](#)).

Mechanisms

This judgement requires the absence of strong and plausible experimental evidence; hence, no mechanisms are presented.

CUP Panel's conclusion

There is strong evidence on beta-carotene from two good-quality RCTs on supplements and one nested case-control study on plasma levels, which all fail to demonstrate an effect on or association with the risk of non-melanoma skin cancer. There was no evidence of an adverse or protective effect for non-melanoma cancer using supplements at doses of 50 milligrams either daily or on alternate days. A published meta-analysis found no associations between beta-carotene supplementation (various regimens) and risk of non-melanoma skin cancer.

Consuming high-dose beta-carotene supplements is unlikely to have a substantial effect on the risk of non-melanoma skin cancer.

7.5 Adult attained height

(Also see [CUP Skin SLR 2017: Section 8.3.1](#))

The evidence for adult attained height and the risk of malignant *melanoma* and *basal cell carcinoma* is presented in the following subsections.

As part of the CUP 16 new studies (11 publications [88–98]) were identified, giving a total of 20 studies (18 publications) reviewing the evidence for adult attained height and risk of skin cancer (for a full list of references see [CUP Skin SLR 2017](#), tables 59 and 60).

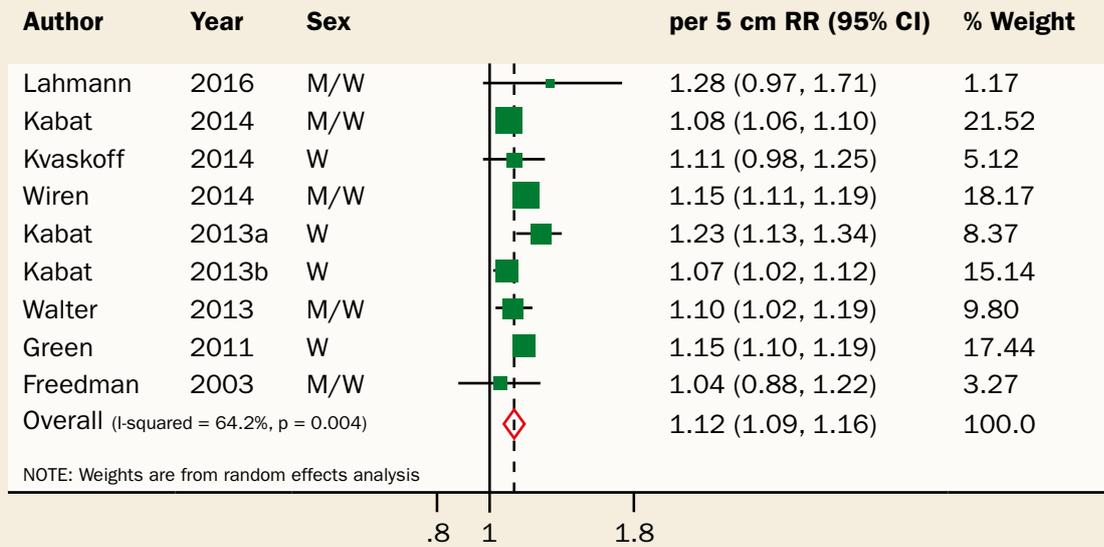
Malignant melanoma

Three studies [68, 90, 99] were included in the CUP highest versus lowest analysis. One study reported significant positive associations for both men and women [99]; see [CUP Skin SLR 2017](#), figure 67.

Fifteen studies were included in the *dose–response meta-analysis*, which showed a *statistically significant* 12 per cent increased risk of malignant melanoma per 5 centimetres increase in height (RR 1.12 [95% CI 1.09-1.16]; $n = 13,020$) (see **Figure 2**). High heterogeneity was observed ($I^2 = 64\%$), which was due to the size of effect rather than the direction of effect (see [CUP Skin SLR 2017](#), figure 68). There was no evidence of small study bias with *Egger's test* ($p = 0.31$). However, the funnel plot showed asymmetry that was driven by a higher than expected increased risk in a small Norwegian study (28 cases; see [CUP Skin SLR 2017](#), figure 69) [88].



Figure 2: CUP dose–response meta-analysis for the risk of malignant melanoma, per 5 centimetre increase in height



Source: Lahmann, 2016 [88]; Kabat, 2014 [89]; Kvaskoff, 2014 [90]; Wiren, 2014 [91]; Kabat, 2013a [92]; Kabat, 2013b [93]; Walter, 2013 [94]; Green, 2011 [96]; Freedman, 2003 [68].

When stratified by sex, a statistically significant increased risk was observed in men (RR 1.10 [95% CI 1.05-1.15]) and women (RR 1.12 [95% CI 1.08-1.17]); see [CUP Skin SLR 2017](#), table 57 and figure 70. When stratified by geographic location, a significant increased risk was observed in Europe (RR 1.15 [95% CI 1.12-1.18]) and North America (RR 1.10 [95% CI 1.06-1.14]), but not Australia; see [CUP Skin SLR 2017](#), table 57 and figure 71.

All studies included in the dose–response meta-analysis *adjusted* for age, most conducted analyses stratified by sex and some adjusted for an indicator of skin colour and/or sun exposure. For information on the adjustments made in individual studies, see [CUP Skin SLR 2017](#), table 59.

Two studies were not included in any of the CUP analyses as they did not provide risk estimates [51, 100].

In 2007 it was not possible to conduct a meta-analysis of studies investigating malignant melanoma risk and adult attained height. The studies were too few and of too low quality to be able to draw a conclusion.

Published pooled analyses and meta-analyses

One published pooled analysis on height and the risk of malignant melanoma incidence was identified [91]; this was included in the CUP dose–response meta-analysis. Results from three published pooled analyses [91, 101, 102] on height and malignant melanoma mortality are shown in **Table 7** (also see [CUP Skin SLR 2017](#), table 58). No other published meta-analyses were identified.

Table 7: Summary of published pooled analyses of height and malignant melanoma mortality

Publication	Outcome	Increment	Sex	RR (95% CI)	I ²	No. of studies	No. of deaths
Emerging Risk Factors Collaboration¹ [101]	Malignant melanoma mortality	Per 6.5 cm	Men and women	1.26 (1.12-1.42)	43%	121	679
Asia-Pacific Cohort Studies Collaboration¹ [102]	Malignant melanoma mortality	Per 6 cm	Men	1.44 (1.15-1.79)	-	44	63
			Women	1.04 (0.71-1.52)	-		25
The Metabolic Syndrome and Cancer Project (Me-Can)¹ [91]	Malignant melanoma mortality	Per 5 cm	Men	1.10 (0.99-1.21)	-	7	246
			Women	1.09 (0.92-1.29)	-		102

Specific adjustments for skin sensitivity or sun exposure

1. In this meta-analysis, the authors did not add confounding variables relating to skin sensitivity or sun exposure to the multivariate model used. For details of adjustments made please see original studies.

Basal cell carcinoma

Three studies were identified in the CUP that reported on incidence of basal cell carcinoma [74, 88, 95]; however, one study [74] was subsequently excluded as no increment of height was reported; it was not possible to conduct a meta-analysis of these studies. One study reported a significant 28 per cent increased risk when comparing highest versus lowest quartiles of measured height [88]. The other study reported a significant increased risk in women [95]. See **Table 8** and also section 8.3.1 in the [CUP Skin SLR 2017](#). Both studies adjusted for a measure of skin sensitivity; for details, see table 59 in the [CUP Skin SLR 2017](#).

Table 8: Summary of prospective cohort studies of height and the risk of basal cell carcinoma

Study	Contrast	Sex	RR (95% CI)	No. of cases
Nambour Skin Cancer Study [88]	Highest quartile vs lowest quartile	Men and women	1.28 (1.01-1.62) P-trend = 0.015	344
United States Radiologic Technologists cohort [95]	≥67 vs ≤62 inches	Women	1.64 (1.40-1.93) P-trend < 0.0001	1,786
	≥73 vs ≤67 inches	Men	1.34 (0.94-1.89) P-trend = 0.05	481

Mechanisms

The mechanisms by which higher adult attained height is linked to elevated risks of malignant melanoma and basal cell carcinoma are unclear. Taller people have more skin cells, and thus there is greater opportunity for mutations leading to cancer development [103]. In addition, early life and early adulthood exposures may play a role, such as greater exposure to growth factors including growth hormone and insulin-like growth factors and excess calorie consumption in early life [104, 105].

CUP Panel's conclusion

Malignant melanoma

The evidence was generally consistent and the CUP dose–response meta-analysis showed a statistically significant increased risk of skin cancer with increasing height. There was high heterogeneity, which was due to the size of effect rather than the direction of effect. The significant increased risk remained when stratified by sex and by geographic location for Europe and North America. Two published pooled analyses, not included in the CUP analyses, mainly reported a statistically significant increased risk. There is evidence of plausible mechanisms operating in humans.

Developmental factors leading to greater growth in length in childhood (marked by adult attained height) are probably a cause of malignant melanoma.

Basal cell carcinoma

The evidence for adult attained height and risk of basal cell carcinoma was limited but generally consistent. The CUP identified two cohort studies that both reported increased risks of basal cell carcinoma with greater adult attained height. There is evidence for plausible mechanisms operating in humans.

The evidence suggesting that the developmental factors leading to greater linear growth (marked by adult attained height) increase the risk of basal cell carcinoma is limited.

7.6 Birthweight

(Also see [CUP Skin SLR 2017: Section 8.4.1](#))

The evidence for birthweight and the risk of malignant *melanoma* is presented in the following subsections.

The CUP identified five new studies (five publications [98, 106–110]), giving a total of six studies (six publications) reviewing the evidence for birthweight and risk of skin cancer (for a full list of references see [CUP Skin SLR 2017](#), table 64).

Three studies were included in the CUP highest versus lowest analysis (see figure 73 in the [CUP Skin SLR 2017](#)). All three reported an increased risk with greater birthweight; none were significant.

Five studies were included in the *dose-response meta-analysis* (3,561 cases), which showed a 6 per cent increased risk of malignant melanoma per 500 grams of birth weight (RR 1.06 [95% CI 1.02-1.10]: see [CUP Skin SLR 2017](#), figure 74). There was no evidence of *heterogeneity* ($I^2 = 0\%$). The association ranged from a RR of 1.05 (95% CI 1.00-1.10) when one study [109] was omitted (35 per cent of the weight) to an RR of 1.07 (95% CI 1.02-1.11) when another study [106] was omitted (21 per cent of the weight).

There was no evidence of *publication bias* (Egger's test $p = 0.49$). *Non-linear analysis* was not conducted due to the low number of studies.

Two of the included studies were conducted in women only [98, 106]; when meta-analysed together no significant association was observed (RR 1.05 [95% CI 0.99-1.11]; see [CUP Skin SLR 2017](#), table 62 and figure 76). When stratified by geographical location a significant positive association was observed for Europe (see [CUP Skin SLR 2017](#), figure 77).



Two studies used self-reported birthweight [98, 106]; when meta-analysed on their own, the direction of association was maintained but it was no longer significant: RR 1.05 (95% CI 0.99-1.11) per 500 grams birthweight. A significant positive association was observed for the three studies that used measurements reported in hospital or school health records (RR 1.07 [95% CI 1.01-1.13] per 500 grams birthweight; see [CUP Skin SLR 2017](#), table 62).

One study *adjusted* only for age and calendar period [109], and all other studies used multivariate models. However, none of the studies adjusted for any indicator of skin pigmentation or sun exposure. See table 64 in the [CUP Skin SLR 2017](#).

Only one study [110] was identified for the 2007 Second Expert Report [3], and it was not possible to draw a conclusion based on this single study.

Published pooled and meta-analyses

One published meta-analysis [98] reported a significant 14 per cent increased risk of malignant melanoma per kilogram of birthweight (RR 1.14 [95% CI 1.05-1.24]; see [CUP Skin SLR 2017](#), table 63). This meta-analysis combined results from one *case-control study* and five *cohort studies*; the five cohort studies were included in the CUP dose–response meta-analysis. None of the studies adjusted for any indicator of skin pigmentation or sun exposure; for details, please see the original papers.

Mechanisms

Birthweight is a marker of aspects of the fetal growth environment that may influence the development of cancer in later life, through largely uncharacterised biological pathways. Proposed mechanisms include larger infants having a greater number of susceptible cells and in utero programming of insulin-like growth factors such as IGF-1, which may lead to greater postnatal cellular proliferation [111].

CUP Panel's conclusion

The evidence for greater birthweight and risk of malignant melanoma was limited but generally consistent. The CUP dose–response meta-analysis reported a significant increased risk, with no heterogeneity; however, none of the studies adjusted for an indicator of skin pigmentation or sun exposure. One published meta-analysis, with five studies overlapping with the CUP meta-analysis, also reported a significant increased risk. There is evidence for plausible mechanisms operating in humans.

The evidence suggesting that the factors leading to greater birthweight, or its consequences, increase the risk of malignant melanoma is limited.

8. Comparison with the Second Expert Report

More evidence has accrued since 2007, which made it possible for the Panel to draw more conclusions. There was no change in the judgements for arsenic in drinking water and high-dose beta-carotene supplements, both of which remain ‘strong evidence’ conclusions. For the first time it was possible to draw conclusions related to adult attained height, birthweight, alcoholic drinks and coffee. Two exposures – retinol and selenium supplements – have been downgraded since the 2007 Second Expert Report to ‘limited – no conclusion’, as new evidence has made the relationships less clear. The increase in the amount and quality of the evidence highlighted the need for further research, particularly with reference to controlling for skin pigmentation and exposure to UV radiation.



9. Conclusions

Overall the Panel notes the strength of evidence that greater adult attained height increases the risk of malignant melanoma and consuming arsenic in drinking water increases the risk of skin cancer (unspecified).

The CUP Panel concluded the following:

Probable evidence

Arsenic in drinking water: Consuming arsenic in drinking water is probably a cause of skin cancer (unspecified).

Adult attained height: Developmental factors leading to greater growth in length in childhood (marked by adult attained height) are probably a cause of malignant melanoma.

Limited - suggestive evidence

Coffee:

- The evidence suggesting that consuming coffee decreases the risk of basal cell carcinoma is limited.
- The evidence suggesting that consuming coffee decreases the risk of malignant melanoma in women is limited.

Alcohol:

- The evidence suggesting that consuming alcoholic drinks increases the risk of basal cell carcinoma is limited.
- The evidence suggesting that consuming alcoholic drinks increases the risk of malignant melanoma is limited.

Adult attained height: The evidence suggesting that the developmental factors leading to greater growth in length in childhood (marked by adult attained height) increase the risk of basal cell carcinoma is limited.

Birthweight: The evidence suggesting that the factors leading to greater birthweight, or its consequences, increase the risk of malignant melanoma is limited.

Substantial effect on risk unlikely

High-dose beta-carotene supplements: Consuming high-dose beta-carotene supplements is unlikely to have a substantial effect on the risk of *non-melanoma skin cancer*.

For a full description of the definitions of, and criteria for, the terminology of ‘convincing’, ‘probable’, ‘limited – suggestive’, ‘limited – no conclusion’ and ‘substantial effect on risk unlikely’, see the **Appendix**.

The Cancer Prevention Recommendations were reviewed by the CUP Panel and published in 2018. For further details, please see [Recommendations and public health and policy implications](#).

Each conclusion on the likely causal relationship between an exposure and the risk of cancer forms a part of the overall body of evidence that is considered during the process of making Cancer Prevention Recommendations. Any single conclusion does not represent a recommendation in its own right. The 2018 Cancer Prevention Recommendations are based on a synthesis of all these separate conclusions, as well as other relevant evidence.

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Abbreviations

AICR	American Institute for Cancer Research
AIDS	Acquired immune deficiency syndrome
BCC	Basal cell carcinoma
CI	Confidence interval
COX-2	Cyclooxygenase-2
CUP	Continuous Update Project
DNA	Deoxyribonucleic acid
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
IARC	International Agency for Research on Cancer
IGF	Insulin-like growth factor
IRR	Incidence rate ratio
MAP kinase(s)	Mitogen-activated protein kinase(s)
MM	Malignant melanoma
<i>n</i>	Number of cases
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NMSC	Non-melanoma skin cancer
ppb	Parts per billion
RCT	Randomised controlled trial
ROS	Reactive oxygen species
RR	Relative risk
SCC	Squamous cell carcinoma
SIR	Standardised incident ratio
SLR	Systematic literature review
SMR	Standardised mortality ratio
STAT3	Signal transducer and activator of transcription 3
UV	Ultraviolet
WCRF	World Cancer Research Fund

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Appendix: Criteria for grading evidence for cancer prevention

See also [Judging the evidence](#), Section 8.

Adapted from Chapter 3 of the [2007 Second Expert Report](#) [103]. Listed here are the criteria agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are ‘convincing’, ‘probable’, ‘limited – suggestive’, ‘limited – no conclusion’ and ‘substantial effect on risk unlikely’. In effect, the criteria define these terms.

These criteria were used in a modified form for breast cancer survivors (see [CUP Breast cancer survivors report 2014](#)).

CONVINCING (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- No substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.
- Presence of a plausible biological gradient (‘dose–response’) in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

PROBABLE (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies recommendations designed to reduce the risk of cancer.

All of the following are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.
- Evidence for biological plausibility.

LIMITED – SUGGESTIVE

Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws but shows a generally consistent direction of effect. This judgement is broad and includes associations where the evidence falls only slightly below that required to infer a probably causal association through to those where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of cancer; any exceptions to this require special, explicit justification.

All of the following are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

LIMITED – NO CONCLUSION

Evidence is so limited that no firm conclusion can be made. This judgement represents an entry level and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded 'limited – no conclusion' for a number of reasons. The evidence may be limited by the amount of evidence in terms of

the number of studies available, by inconsistency of direction of effect, by methodological flaws (for example, lack of adjustment for known confounders) or by any combination of these factors.

When an exposure is graded 'limited – no conclusion', this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good-quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of cancer. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on cancer risk, this exposure will be judged 'substantial effect on risk unlikely'.

There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the World Cancer Research Fund International website (dietandcancerreport.org). However, such evidence is usually not included in the summaries.

SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)

Evidence is strong enough to support a judgement that a particular food, nutrition or physical activity exposure is unlikely to have a substantial causal relation to a cancer outcome. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high- versus low-exposure categories.
- No substantial unexplained heterogeneity within or between study types or in different populations.
- Good-quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding and selection bias.
- Absence of a demonstrable biological gradient ('dose–response').
- Absence of strong and plausible experimental evidence, from either human studies or relevant animal models, that typical human exposure levels lead to relevant cancer outcomes.

Factors that might misleadingly imply an absence of effect include imprecision of the exposure assessment, insufficient range of exposure in the study population and inadequate statistical power. Defects such as these and in other study design attributes might lead to a false conclusion of no effect.

The presence of a plausible, relevant biological mechanism does not necessarily rule out a judgement of 'substantial effect on risk unlikely'. But the presence of robust evidence from appropriate animal models or humans that a specific mechanism exists or that typical exposures can lead to cancer outcomes argues against such a judgement.

Because of the uncertainty inherent in concluding that an exposure has no effect on risk, the criteria used to judge an exposure 'substantial effect on risk unlikely' are roughly equivalent to the criteria used with at least a 'probable' level of confidence.

Conclusions of 'substantial effect on risk unlikely' with a lower confidence than this would not be helpful and could overlap with judgements of 'limited – suggestive' or 'limited – no conclusion'.

SPECIAL UPGRADING FACTORS

These are factors that form part of the assessment of the evidence that, when present, can upgrade the judgement reached. An exposure that might be deemed a 'limited – suggestive' causal factor in the absence, for example, of a biological gradient, might be upgraded to 'probable' if one were present. The application of these factors (listed below) requires judgement, and the way in which these judgements affect the final conclusion in the matrix are stated.

Factors may include the following:

- Presence of a plausible biological gradient ('dose–response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders.
- Evidence from randomised trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.

Our Cancer Prevention Recommendations

Be a healthy weight

Keep your weight within the healthy range and avoid weight gain in adult life

Be physically active

Be physically active as part of everyday life – walk more and sit less

Eat a diet rich in wholegrains, vegetables, fruit and beans

Make wholegrains, vegetables, fruit, and pulses (legumes) such as beans and lentils a major part of your usual daily diet

Limit consumption of ‘fast foods’ and other processed foods high in fat, starches or sugars

Limiting these foods helps control calorie intake and maintain a healthy weight

Limit consumption of red and processed meat

Eat no more than moderate amounts of red meat, such as beef, pork and lamb.
Eat little, if any, processed meat

Limit consumption of sugar sweetened drinks

Drink mostly water and unsweetened drinks

Limit alcohol consumption

For cancer prevention, it’s best not to drink alcohol

Do not use supplements for cancer prevention

Aim to meet nutritional needs through diet alone

For mothers: breastfeed your baby, if you can

Breastfeeding is good for both mother and baby

After a cancer diagnosis: follow our Recommendations, if you can

Check with your health professional what is right for you

Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk.

Following these Recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.

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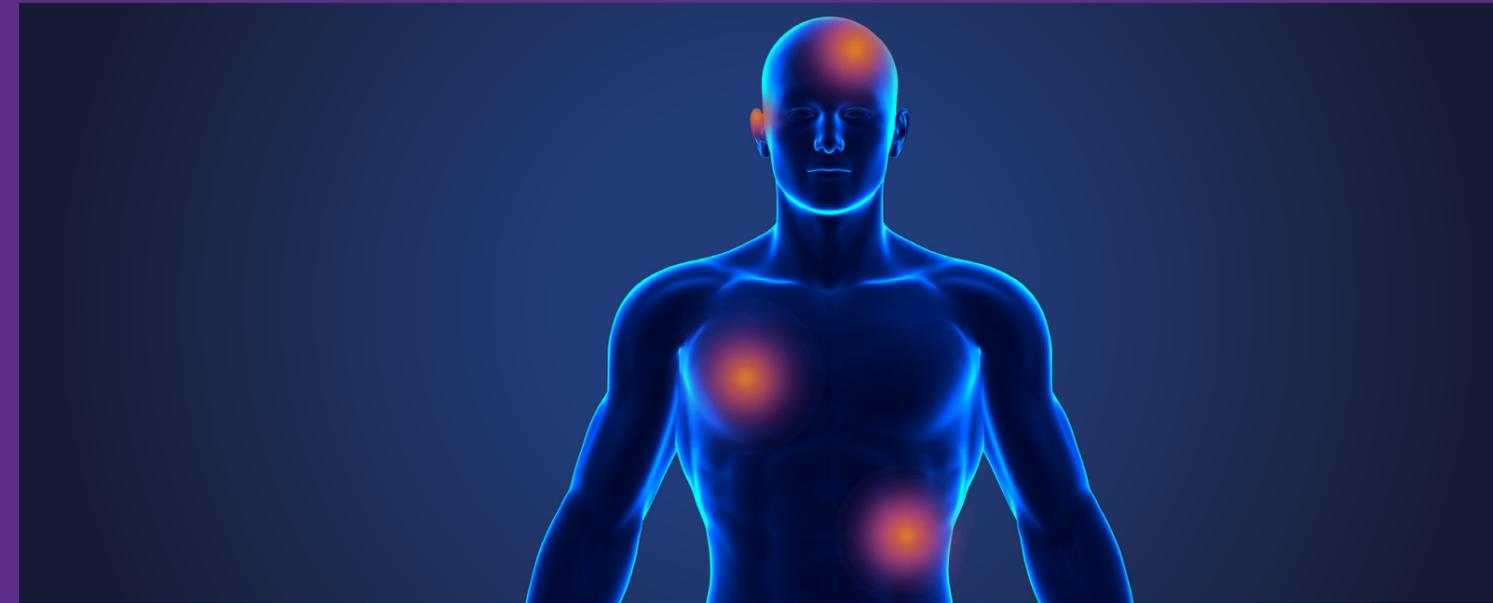
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