Priority Medicines for Europe and the World "A Public Health Approach to Innovation"

> Update on 2004 Background Paper Written by Warren Kaplan

## Background Paper 6.5 Cancer and Cancer Therapeutics

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## What's new since 2004

- Targeted therapies: While previous research on targeted therapies has identified a number of single agents that are safe and can shrink tumours, research during 2004/2005 showed that an increasing number of targeted therapies in combination with chemotherapy are effective against common cancers.
  - Now targeted agents have also shown benefit as monotherapy. One such example, is anaplastic lymphoma kinase (*ALK*) gene-mutated, non-small cell lung cancer, where the pace of research progress in this area has been remarkable.
  - One agent, vismodegib, marks the first FDA approval of a drug that targets the hedgehog signaling pathway, which plays an important role in tissue growth and repair. The drug is also being tested in clinical trials for colorectal, stomach, and pancreatic cancers.
- A potentially useful strategy for conquering resistant tumors is to attack more than one target in a molecular pathway that is critical for tumor survival and growth. This can be achieved through use of multi-targeted drugs, such as the new agents regorafenib, which has benefited patients with treatment-resistant GI stromal tumors (GISTs) and metastatic colorectal cancer; crizotinib, which has shown promising activity against neuroblastoma and anaplastic large-cell lymphoma (ALCL) in children; and cabozantinib, which seems to slow progression of medullary thyroid carcinoma. An alternative approach is to treat patients with two or more drugs that target the same pathway
- FDA approves first vaccine to prevent HPV infection The most significant advance in 2005 was the U.S. Food and Drug Administration (FDA) approval of the first vaccine to prevent infection with human papillomavirus (HPV), a virus present in virtually all cervical cancers. The vaccine, Gardasil®, was shown to be 100% effective in preventing HPV 16-and 18-related cervical precancers in women who were not previously exposed to these strains of the virus. These strains together account for approximately 70% of cervical cancer cases worldwide. In January 2013, the GAVI Alliance announced it would provide HPV vaccine as part of its portfolio.
- Reductions in breast cancer incidence appear to be associated with the declining use of hormone replacement therapy (HRT) in menopausal women. The use of HRT declined beginning in 2002, following a report from the National Institutes of Health-sponsored Women's Health Initiative that linked the use of estrogen plus progestin during and after menopause with a number of adverse effects, including an increased risk for invasive breast cancer.
- The monoclonal antibody bevacizumab (Avastin®) has been an important treatment for patients with advanced colorectal and non-small cell lung cancers. In February 2008, the FDA approved the drug—in combination with the chemotherapy drug paclitaxel (Taxol®)—for women with previously untreated metastatic breast cancer. The US breast cancer approval was conditional and the approval was recently withdrawn for this indication. Avastin is still approved for breast cancer in the EU but since the US FDA questioned its risk/benefits profile and asked for withdrawal of

the marketing application for this indication, Avastin utilization for the treatment of breast cancer in the EU has decreased.

- First targeted treatment for gastric cancer: In 2009, Herceptin®, which is widely used to treat HER2-positive breast cancer, was proven effective in stomach cancer. A large clinical trial found that adding trastuzumab to standard chemotherapy for advanced gastric (stomach) cancer increased survival by 26 percent in patients whose tumours overexpressed the HER2 receptor.
- Vaccine Approved for Treating Advanced Prostate Cancer: In 2010, the FDA approved Sipuleucel-T (Provenge®), a cancer vaccine for metastatic hormone-refractory prostate cancer. Unlike a preventive vaccine, which is given to stimulate the immune system to fight off infections and prevent disease, this is a true **therapeutic vaccine** that boosts the body's immune system to attack cancer cells in the body. See also Section 7.4.
- The entire cancer therapeutics field is moving more toward targeted therapies and immunotherapy. The monoclonal antibody ipilimumab was approved by the FDA in March 2011 to treat patients with late-stage melanoma that has spread or cannot be removed by surgery. This is an area of high unmet medical need. On 1 February 2012, Health Canada approved ipilimumab for "treatment of unresectable or metastatic melanoma in patients who have failed or do not tolerate other systemic therapy for advanced disease." <u>http://en.wikipedia.org/wiki/Ipilimumab cite note-8</u> Ipilimumab was approved in both the UK and European Union (EU), for second line treatment of metastatic melanoma in November 2012.
- Those needing further information should review the American Society of Clinical Oncology annual "Progress against Cancer" brochures at <u>http://www.cancerprogress.net/latest\_advances.html</u>

## **Executive Summary**

#### **Burden of Disease**

It has been estimated that over one-quarter of the global burden of cancer incidence occurs in Europe, despite the fact that persons living in Europe comprise only approximately oneeighth of the world's population. Within Europe, for all the countries considered, improvement in age-adjusted death rates are more marked in men than women, with however notable disparities. There is a disparity in cancer mortality between central European post- 2004 accession countries (particularly Poland) and countries of the EU15. This was seen in the early 2000s and is not projected to have closed, at least in proportional terms, over recent years.

The global burden of cancer doubled between 1975 and 2000 and is expected to double again by 2020 and nearly triple by 2030. Cancer burden in many countries in societal and economic transition from a communicable to a non-communicable epidemiology and demography is a net burden between reductions in infection-related cancers and increases in new cases that are more associated with reproductive, dietary, and hormonal factors

#### **Treatment Options**

The wide range of cancer treatments and associated services reflects the biological diversity of cancer. For most solid tumours if the cancer is at a relatively early stage of development, surgery is the most standard and effective form of initial cancer treatment, but this is largely augmented by radiation therapy to the tumour bed and some form of systemic therapy. As cancers progress, treatments typically include radiation, combination chemotherapy regimens, in hormone-regulated tumours, hormone ablation therapy, and where appropriate targeted therapies. The stage of cancer at diagnosis, the rate of progression, and the treatment options vary significantly with the type of cancer a patient presents with.

## **Pipeline of Potential Products**

- The therapeutic pipeline is dynamic and significant private sector funding is being put into the cancer R&D system.
- The distribution of therapeutics in clinical trials across cancer types seems to correlate with the incidence of those cancer types reasonably well, suggesting that the pharmaceutical industry is appropriately matching its resources to the size of the market. Recent regulatory approvals significantly impacted approaches to management of lung cancer and increased treatment options in several cancers that have been previously hard to treat such as colorectal cancer. The emerging group of targeted therapies has opened up opportunities for a personalized approach to cancer treatment based on the characteristics of the individual tumour at the time of diagnosis. This area represents a significant focus of current research initiatives and ongoing clinical trials, raising the question of how this may impact future clinical trials design as well as regulatory approval processes.

## **Introduction to the Background Paper**

When the original (2004) Background paper was written, malignant tumours were responsible for 12% of the nearly 56 million deaths worldwide from all causes and over 6 million died specifically from some type of malignant tumour. Indeed, cancer had emerged as a major public health problem in developing countries, matching its effect in industrialized nations. In the European Union (EU) at that time, lung cancer was the principal cause of death in men (25% of all male cancer deaths) followed by colorectal and prostate cancers. In women, the three major causes of death were breast cancer (16% of all female deaths), colorectal (12%) and lung cancer (9%).

At that time, there was a large and dynamic pipeline of products. Further, at that time, the distribution of therapeutics in clinical trials across cancer types seems to correlate with the incidence of those cancer types reasonably well, suggesting that the pharmaceutical industry is appropriately matching its resources to the size of the market. The European Union did not match the private or public funding levels of the United States with regard to cancer therapeutic research and development.

## 1. Introduction to cancer

Cancers are caused by combined genetic and non-genetic changes induced by environmental factors that trigger inappropriate activation or inactivation of specific genes leading to neoplastic transformations, or abnormal cell growth. There is a lack of information about key cellular events that occur in early stages of cancer development as well as environmental factors and internal cues that trigger these changes.

Advances in molecular epidemiology are allowing researchers the possibility of simultaneously identifying multiple changes affecting the genome and extra-genomic environment of normal, precursor and cancer cells as well as their link to the environment. It should be now possible to define which genetic and other alterations, or combinations thereof, can be interpreted as reliable biomarkers of exposures. By identifying changes associated with tumour cells and surrogate tissues associated with specific known and suspected environmental risk factors, it may be possible to identify particularly high-risk individuals and potentially design an efficient strategy for cancer prevention.

## 2. Introduction to cancer therapeutics

Cancer' is therefore a generic term used to describe a group of at least a hundred diseases that occur when malignant forms of abnormal cell growth develop in one or more body organs. Cancer arises after a series of genetic mutations remove the normal checks on cell growth. These cancer cells continue to divide and grow to produce tumours. Cancer cells can invade adjacent structures and spread via the lymph or blood to distant organs. Some of the biological mechanisms that change a normal cell into a cancer cell are known while others are not yet known.

Cancer differs from most other diseases in that it can develop at any stage in life and in any body organ. No two cancer cases behave exactly alike. Some may follow an aggressive course, with the cancer growing rapidly. Other types grow slowly or may remain dormant for years. Very high cure rates can be achieved for some types of cancers, but for others the cure rates are disappointingly low and await improved methods of detection and treatment. The wide range of cancer treatments and associated services reflects the biological diversity of cancer. The most common stage of cancer at diagnosis, the rate of progression, and the treatment options vary significantly with the type of cancer a patient presents.

It is estimated that about 80% of cancers are due to environment or lifestyle, and therefore are potentially preventable.<sup>1</sup> The risk factors for some cancers have been clearly identified, but for others further research is needed. Based on current evidence, at least 30% of future cancer cases are preventable by comprehensive and carefully considered action, taken now.<sup>2</sup>

The cancer treatment that a patient receives is determined by the stage of cancer at diagnosis, the type and location of the cancer, the standard medical practices and treatment guidelines in the patient's country,<sup>3</sup> and the ability of the patient to pay for treatment (through national or private insurance or otherwise). For most solid tumours, if the cancer is at a relatively early stage of development, surgery is the most standard and effective form of initial cancer treatment. This is often combined with radiation therapy to the tumour bed and systemic therapy as the goal is curative treatment. As cancers progress, treatments typically include radiation, chemotherapy, in hormone-regulated tumours, and hormone ablation therapy. Targeted therapy is becoming increasingly available in appropriate cases. See Section 7.3.

Multiple metastases (in various locations) and the overall tumour load ultimately limit surgical removal and the effectiveness of anti-cancer drugs. When cancers recur and spread beyond the initial site or region, systemic treatment is necessary and the goal of this treatment is no longer curative. Chemotherapy is the most prevalent form of systemic treatment, because it can reach and destroy cancer cells throughout the body, although the blood-brain barrier often limits effectiveness in the case of brain metastases. Chemotherapy may be used alone or in combination with other forms of treatment such as radiation therapy to specific metastatic sites. Hormone-regulated tumours, such as certain breast and prostate cancers use the body's natural hormones to grow, and they are often more responsive to hormone-based treatments that chemotherapy. As in the case of chemotherapy, tumours can become increasingly resistant to standard treatments. Certain cancers can be resistant to systemic treatments at the time of diagnosis. Other cancers become resistant over a period of months or years. Overall, 30% to 80% of cancers can become refractory.<sup>4, 5, 6</sup>

As there are over 100 cancer types, when discussing specific cancers in this updated Background Paper, we will concentrate on breast cancer, lung cancer, colorectal, and prostate cancers, which are the top four highest incidence cancers in Europe (combined men and women). See Figure 6.5.3.

## 3. What are the Epidemiological Trends for Europe and the World?

## 3.1 Cancer in Europe

It has been estimated that over one-quarter of the global burden of cancer incidence occurs in Europe, despite the fact that persons living in Europe comprise only approximately one-eighth of the world's population.<sup>7</sup>

The most recent comprehensive data we have is for 2008 (<u>http://eu-cancer.iarc.fr/EUCAN/</u><u>Country.aspx?ISOCountryCd=930</u>). The WHO GLOBOCAN project, the aim of which is to provide contemporary estimates of the incidence, mortality, and prevalence from major type of cancers at national level, for 184 countries of the world will update their 2008 data in mid-2013 (too late for publication of this Report). Nevertheless, for the EU27 in 2008, a "league table" for men ranked by incidence (age-standardized per 100 000 persons) is shown in Figure 6.5.1, for women the league table ranked by incidence is Figure 6.5.2 and the combined (men and women) league table ranked by incidence is shown in Figure 6.5.3.





Source: EUCAN Factsheets | European Union (27). Available at <u>http://eu-cancer.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=930</u>

Figure 6.5.2: Incidence, mortality, and prevalence from major type of cancers, for the EU27 women in 2008



Source: EUCAN Factsheets | European Union (27). Available at <u>http://eu-cancer.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=930</u>





Source: EUCAN Factsheets | European Union (27). Available at <u>http://eu-cancer.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=930</u>

In 2012, in the EU-27 over 700 000 men and over 550 000 women were estimated to have died of cancer. These numbers are slightly higher than those recorded for 2007 (increase in 1.5% in men and 2% in women). The age-adjusted cancer mortality rates are expected to substantially improve (in a positive trend) between 2007 to 2012 from 153.5/100 000 men in 2007 to 138.7/100 000 men in 2012 (drop of 9.6%) and from 90.6/100 000 women to 84.7/100 000 women (drop of 6.5%). <sup>8</sup>

In men, improvements in age-adjusted mortality rates (between 2007 to 2012) are also expected significant reductions for five cancer sites: stomach (-20%), leukemias (-11%), lung and prostate (-10%), and colorectal (-27%) cancers. In women in the same five-year period, mortality rates from these individual sites considered are predicted to decline in the following cancers: stomach (-23%), leukemias (-12%), uterus and colorectum (-11%), and breast (-29%), while increases in lung (+7%) and pancreatic (+3%) cancer mortality rates are expected.<sup>8</sup>

Within Europe, for all the countries considered, improvement in age-adjusted death rates are more marked in men than women, with however notable disparities. In men, estimated improvements in the period from 2000 to 2012 were 21% in France, Germany, and Italy, 18% in Spain, 15% in the UK, and 11% in Poland.<sup>8</sup>

There is a disparity in cancer mortality between Central European post- 2004 EU accession countries (particularly Poland) and countries of the EU15. This was seen in the early 2000s and is not projected to have closed, at least in proportional terms, over recent years. See Figure 6.5.4 (where "EU 12" represents approximately the central EU accession countries post-2004). Data from the European Detailed Mortality Database (<u>http://data.euro.who.int/dmdb/</u>).



Figure 6.5.4: Mortality rates from cancers in Europe

Source: Data extracted from the European Detailed Mortality Database (<u>http://data.euro.who.int/dmdb/</u>)

For women, the improvement in all-cancer mortality rates in the period 2000–2012 was estimated to be 15% for Germany, 11%–12% for France, Italy, Spain and the UK and 7% in Poland. Thus, for women also, the disparity between the already higher rates in countries like Poland and the other EU15 countries is likely to widen.<sup>8</sup>

From trends in mortality rates by cancer site from 1970 onward for various countries considered, some patterns emerge, although disparities in mortality continue to persist.<sup>8,9</sup> For instance:

- There is a generalized unfavorable trend in pancreatic cancer mortality rates, with a leveling off in recent periods, at least in men;<sup>10</sup>
- The contrasting trends between sexes in lung cancer mortality rates, with increases in women and improvements in men from the 1990s onward, and the exceptionally high rates in certain EU 12 countries;
- The continuing steady declines in (cervix) uterine cancers, without evidence of closing the gap between the higher rates in certain EU 12 countries and the other countries;
- The declines in prostate cancer rates with again a less favorable picture for men in some EU12 countries.

Despite improvements in breast cancer mortality over most recent periods in Europe and the United States, breast cancer is still the leading cancer mortality in women in the EU as a whole, as well as in France, Germany, Italy, and Spain, while lung cancer is the leading cancer mortality site in the UK. In relative terms, younger women (20–49 years) are those who have shown the greatest reductions in breast cancer mortality rates between 2000 to 2004 and 2005 to 2009 (minus 13%) in the EU.<sup>8,11, 12</sup>

The interpretation of the favorable pattern in breast cancer rates in the EU has raised several controversies, in particular as concerns the role of mammographic screening. In general, many important risk factors for breast cancer, including menstrual and reproductive factors, physical activity, and obesity have not changed favorably. This and the spread of mammographic screening, either spontaneous or organized, have led to increases in breast cancer incidence rates up to the early 2000s. Subsequent declines in incidence rates have been attributed, at least in part, to decreased use of hormone replacement therapy. Apart from lung cancer in women and pancreatic cancer, the fall in mortality from major cancers in major European countries and the EU essentially reflects the decline in tobacco smoking in men and the continuing progress in cancer prevention, early detection, and treatment.<sup>8</sup>

#### 3.1.1 Rare cancers

In Europe, any spotlight on high impact cancers such as breast, lung, prostate and colorectal cancers must keep in focus also the rare cancers. There are about 500 000 new cases per year in the EU27 of "rare cancers" (For definitions see <u>http://www.rarecare.eu/default.asp</u>). About 4 300 000 patients are living today in the European Union with a diagnosis of a rare cancer - 24% of the total cancer prevalence. Five-year survival rates become worse as the patient gets older. Across all ages, five-year survival is 48% for rare and 64% for more common cancers. <sup>13</sup> About 30% of Europeans with a rare cancer have one of the particularly rare forms that affect less than one per 100 000, and this is important because low incidence is a major obstacle to conducting clinical trials to develop effective treatments.<sup>13</sup> See also Chapter 6.19 on Rare Diseases.

## 3.1.2 Paediatric/childhood Cancers

All paediatric cancers are rare diseases and fall under the Commission policy framework on rare diseases. The strategic objectives are described in Commission Communication COM(2008)679/2 on Rare diseases: Europe's challenges (http://ec.europa.eu/health/ ph threats/non com/docs/rare com en.pdf) and Council Recommendation of 8 June 2009 on action the field diseases (http://eur-lex.europa.eu/LexUriServ/ an in of rare LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF). Each year 15 000 children and adolescents in Europe are diagnosed with cancer. One third of all childhood cancers are leukaemias, of which acute lymphocytic leukaemia (ALL) and acute myelogenous leukaemia (AML) are most common. Brain and other nervous system cancers make up about one fifth of childhood cancers. Although over the past 50 years the progress in the treatment of childhood cancers has been enormous, still around 25% of all patients die of their disease. See Appendix 6.5.1

In the period from 2006 to 2010, on average three in 100 000 children died from cancer in the EU, but in most countries in Northern and Western Europe, childhood cancer mortality is below this level. In the countries in Southern and Eastern Europe, the ratio is higher.

Romania has the highest childhood cancer mortality rate. The comparison between the various countries in Europe only includes malignant types of cancer.

Figure 6.5.5 (extracted from a Dutch publication Statistics Netherlands, at http://www.cbs.nl/en-GB/menu/home/default.htm) shows the death rate (per 100 000 children: 0-14 yrs)) in the EU, 2006-2010





Source: Eurostat

Source: Dutch publication Statistics Netherlands, at http://www.cbs.nl/en-GB/menu/home/default.htm

Survival rates have improved to 80% with the latest treatment regiments in developed countries. However, 60 000 children in developing countries die each year from cancers that are often curable. Overall survival for children in 1990s was 64% in Eastern and 75% in Western Europe with differences between regions for all tumour groups. <sup>14</sup> A study showed that the annual government health care expenditure per capita correlated well with the estimated survival rates of children with cancer. The survival rates were calculated as 5% to 50%, 50% to 70% and more than 70% in those which spend less than US\$ 100, US\$ 100, and

more than US\$ 1000, respectively. <sup>15</sup> Access to care and research in childhood cancer as a "rare" tumour is also highly critical to closing the gaps in survival in children with cancer at European and global level.<sup>16, 17, 18</sup> In this context, for both adults and children, there is a need for research in survivorship issues as the long-term side-effects of cancer therapies is an important research subject. In addition, quality of life issues such as end of life care and palliative therapy are worthy of research.

Each year 175 000 childhood cancers are expected at global level. A recent report surveyed European paediatric oncologists.<sup>19</sup> Briefly, we summarize the findings as follows:

- Countries with a larger oncology burden, such as those in Eastern Europe, tended not to collaborate in research with those with a better developed research structure, and this in turn affected the care they were able to give young patients.
- National situations with regard to paediatric oncologic facilities, resources, research grants for young scientists, and hospital space were quite different.
- In Italy, nearly 50 centres specialized in paediatric haematology and oncology, and a there was a lack of coordination between research laboratories and clinics.
- The authors also found large differences in the provision of information on childhood cancer, with variations in the involvement of parental organizations, the use of digital media, and the adoption of a common national standard for information provision.
- The authors called for adequate long-term EU funding to support a Europe-wide clinical trials network for paediatric oncology.

## 3.1.3 Trends in cancer survival

Trends in cancer survival vary across the EU.<sup>20</sup> Berrino et al determined that as of 2009, the relative excess risk of death was 28% higher in Eastern Europe (based on data from the Czech Republic) than Central Europe (based on data from Austria, Belgium, France, Germany, the Netherlands and Switzerland); the relative excess risk of death was 60% higher for patients aged 55–99 years than those aged 15–54 years, and male cancer patients had a significantly higher risk of dying than women.<sup>21</sup> Such data are inherently subject to interpretation and controversy. It is possible that differences between Eastern and Western States have persisted largely because of fewer resources for healthcare services and recent dysfunction in health care systems of Eastern States. Survival differences for relatively uncommon treatable cancers such as testicular cancer and Hodgkin's disease, and for cancers with very poor prognosis, tend to be less marked than the disparities observed for common breast, cervical, and colorectal cancers.

As an example of the data generated, Coleman et al. collected data from population-based cancer registries in 12 jurisdictions in Australia, Canada, Sweden, Norway, Denmark, and the UK for 2.4 million adults diagnosed with primary colorectal, lung, breast (for women), or ovarian cancer during 1995–2007, with follow-up to 31 Dec 31 2007.<sup>22</sup>

Relative survival improved during 1995 to 2007 for all four cancers in all jurisdictions. Survival was persistently higher in Australia, Canada, and Sweden, intermediate in Norway, and lower in Denmark, England, Northern Ireland, and Wales, particularly in the first year after diagnosis and for patients aged 65 years and older. Trends in cancer incidence and mortality were broadly consistent with these trends in survival. It was asserted that these patterns were consistent with later diagnosis or differences in treatment, particularly in Denmark and the UK, and in patients aged 65 years and older.<sup>22</sup>

The idea of using cancer survival as a means of measuring the effectiveness of health care systems is a major topic of research and discussion and is somewhat challenging. We will not dwell on this subject for the Report but note the following brief points:

- It appears that when factors likely to influence survival statistics are similar across medical facilities, or when data on these factors are available, survival statistics might bring insights into the respective roles of detection and treatment. When comparing countries, it would be prudent to collect country-specific cancer survival data as well as incidence and mortality data.
- One should also consider the multiple factors unrelated to health system performance that could influence survival data. It may well be that joint interpretation of survival, incidence, prevalence, and mortality is the best guide to policy for prevention, screening, treatment, and the organization of health care systems.
- When countries are compared, because of the complexity and intricacy of factors influencing survival statistics (including the fact that health systems differ in many ways), many factors not associated with performance can influence variations in survival.

**Incidence-related factors:** Earlier detection of cancer from which patient will die (lead-time bias); detection of non-life-threatening cancer (length-time bias and over-diagnosis); and detection of cancer precursor lesions.

**Cancer registries**: Cancer definition (e.g. classification used); population coverage; completeness of cancer case ascertainment; registration of newly diagnosed cases; cases registered after death from cancer and unknown date of diagnosis (death certificate only); and registration of cancer recurrence instead of cancer diagnosis.

**Patient-related factors:** Age, gender, genetic background; socioeconomic status, education; race, ethnic origin; comorbidity; and mortality from other causes (competing causes of death).

Cancer-related factors: stage at diagnosis; anatomical site of cancer; and dancer capacity to invade surrounding and distant tissues.

**Health system factors:** ability of early detection methods and screening programmes to prevent cancer occurrence and/or occurrence of advanced cancer; alertness of health professionals (attention to signs and symptoms possibly associated with cancer); and availability, access to, and quality of diagnostics, classification of cancers, supportive and follow-up care.

**Organizational efficiency**: speed and quality of work-up of positive early detection (screening) tests, clinical signs, and symptoms; referral to specialized services; and health facility's patient load.

Survival differences could also be due to differences in exposure to cancer risk factors. For instance, obesity is associated with breast cancers of worse prognosis that are less sensitive to treatment. If the prevalence of obesity in adult women in one country is twice as high as in another, this might play a role in the dissimilarity in breast cancer survival.

## 3.2 Global Perspective

We note the comprehensive global and regional examination of cancer to date is the World Cancer Report, updated for 2008.<sup>23</sup> We also note the WHO GLOBOCAN project, the aim of which is to provide contemporary estimates of the incidence, mortality, prevalence, and disability-adjusted life years (DALYs) from major type of cancers at national level, for 184 countries of the world.

The 2008 World Cancer Report shows that the global burden of cancer doubled between 1975 and 2000 and is expected to double again by 2020 and nearly triple by 2030.<sup>23</sup> The report estimates that there were some 12 million new cancer diagnoses worldwide in 2008, based on the most recently available data, and that an estimated seven million people will die from the disease. The projected numbers for the year 2030 are 20 million to 26 million new cancer diagnoses and 13 million to 17 million cancer deaths.<sup>6</sup> In large measure, this a function of increased life expectancy generally and of better and earlier diagnostic procedures.<sup>24</sup> There are interesting relationships between cancer and country development index (CDI). In the highest human development index (HDI) [http://hdr.undp.org/en/statistics/] regions in 2008, cancers of the female breast, lung, colorectum, and prostate accounted for half the overall cancer burden; whereas in medium HDI regions, cancers of the oesophagus, stomach, and liver were also common, and together these seven cancers comprised 62% of the total cancer burden in medium to very high HDI areas.

In low HDI regions, cervical cancer was more common than both breast cancer and liver cancer. Nine different cancers were the most commonly diagnosed in men across 184 countries, with cancers of the prostate, lung, and liver being the most common. Breast and cervical cancers were the most common in women.

In medium and high HDI settings, decreases in cervical and stomach cancer incidence seem to be offset by increases in the incidence of cancers of the female breast, prostate, and colorectum. See Figure 6.5.6, taken from Bray et al.<sup>25</sup>

If the cancer-specific and sex-specific trends estimated in this study continue, an increase in the incidence of all-cancer cases is predicted from 12.7 million new cases in 2008 to 22.2 million by 2030. This data on the cancer-HDI association suggest that cancer burden in many countries in societal and economic transition from a communicable to a non-communicable epidemiology and demography is a net burden between reductions in infection-related cancers and increases in new cases that are more associated with reproductive, dietary, smoking and hormonal factors. Targeted interventions can lead to a decrease in the projected increases in cancer burden through effective primary prevention strategies, alongside the implementation of vaccination, early detection, and effective treatment programmes.<sup>25</sup>





Source: 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. Note: map shows only the countries included in the analysis.

## 3.3 Specific cancers

The high impact cancers of the EU with respect to incidence, prevalence, and mortality are summarized in Figures 6.5.1-6.5.3 above.

## 3.3.1 Tobacco-driven Lung cancer: Europe and the World

Tobacco is the primary driver for development of lung cancer. Within the 27 countries of the European Union, the highest European age-standardized incidence rates for 2008 are

estimated to be in Hungary for men (around 115 cases per 100 000) and Denmark for women (around 51 cases per 100 000), while the lowest rates are in Sweden for males (around 27 cases per 100 000) and Cyprus for females (around 7 cases per 100 000).<sup>26</sup>

Lung cancer has been the most common cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total). The majority of the cases now occur in the developing countries (55%). Lung cancer is still the most common cancer in men worldwide (1.1 million cases, 16.5% of the total), with high rates in Central-Eastern and Southern Europe, Northern America, and Eastern Asia. Very low rates are still estimated in Middle and Western Africa. In females, incidence rates are generally lower, but worldwide lung cancer is now the fourth most frequent cancer of women (516 000 cases, 8.5% of all cancers) and the second most common cause of death from cancer (427 000 deaths, 12.8% of the total).

The highest incidence rate is observed in North America (where lung cancer it is now the second most frequent cancer in women), and the lowest in central Africa (15th most frequent cancer). Because of its high fatality (the ratio of mortality to incidence is 0.86) and the lack of variability in survival in developed and developing countries, the highest and lowest mortality rates are estimated in the same regions, both in men and women.<sup>26,27</sup>

#### 3.3.2 Breast cancer: Europe and the World

Within the 27 countries of the European Union (EU27), the highest female breast cancer European age-standardized mortality rates for 2008 were estimated to be in Ireland (31.1 deaths per 100 000 women), while the lowest were in Spain (18.4 deaths per 100 000 women).<sup>26</sup> Non-metastatic breast cancer is by far the most frequent cancer among women with an estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all cancers), and ranks second overall (10.9% of all cancers).<sup>26,28</sup>

Incidence rates vary from 19.3 per 100 000 women in Eastern Africa to 89.7 per 100 000 women in Western Europe, and are high (greater than 80 per 100 000) in developed regions of the world (except Japan) and low (less than 40 per 100 000) in most of the developing regions. As a result, breast cancer ranks as the fifth cause of death from cancer overall (458 000 deaths), but it is still the most frequent cause of cancer death in women in both developing (269 000 deaths, 12.7% of total) and developed regions, where the estimated 189 000 deaths is almost equal to the estimated number of deaths from lung cancer (188 000 deaths).

<u>Metastatic or advanced breast cancer</u> is the presence of disease at distant sites such as the bone, liver, or lung. The true prevalence of metastatic disease is high because some women live with the disease for many years. Since 1990, there has been an overall increase in incidence rates of about 1.5% annually. It is considered incurable. In women who receive no treatment for metastatic disease, the median survival from diagnosis of metastases is 12 months.

#### 3.3.3 Prostate cancer: Europe and the World

Prostate cancer is the second most frequently diagnosed cancer of men (899 000 new cases, 13.6% of the total). Nearly three-quarters of the registered cases occur in developed countries (644 000 cases). Within the 27 countries of the European Union (EU-27), the highest European age-standardized incidence rates for 2008 are in Ireland (183.2 new cases per 100 000) and the lowest in Greece (27.9 cases per 100 000).

Incidence rates of prostate cancer vary by more than 25-fold worldwide, the highest rates are in Australia and New Zealand (104.2 per 100 000), Western and Northern Europe, and Northern America largely because the practice of prostate specific antigen (PSA) testing and subsequent biopsy has become widespread in those regions. Within the era of PSA testing, an estimated 16% of men will receive a diagnosis of prostate cancer sometime during their lifetime and about 2.2 million American men are estimated to be living with prostate cancer.<sup>29</sup> The lowest age-standardized incidence rate is estimated in South-Central Asia (4.1 per 100 000).<sup>26</sup>

Incidence rates are relatively high in certain developing regions such as the Caribbean, South America, and sub-Saharan Africa. The likelihood of prostate cancer increases with age, particularly starting at around age 45 years. Autopsy studies found that as many as 75% of men 85 years and older have prostate cancer at the time of death. With an estimated 258 000 deaths in 2008, prostate cancer is the sixth leading cause of death from cancer in men (6.1% of the total).

Because PSA testing has a much greater effect on incidence than on mortality, there is less variation in mortality rates worldwide (10-fold) than is observed for incidence (25-fold), and the number of deaths from prostate cancer is almost the same in developed and developing regions. Mortality rates are generally high in predominantly black populations (26.3 per 100 000 for the Caribbean and sub-Saharan Africa), very low in Asia (2.5 per 100 000 in Eastern Asia) and intermediate in Europe and Oceania.<sup>26</sup>

## 3.3.4 Colorectal Cancer: Europe and the World

Colorectal cancer incidence rates have overall increased in Britain since the mid-1970s. For men, European age-standardized incidence rates have increased by 27% between 1975 and 1977 and 2007 and 2009, with most of this increase occurring between the mid-1970s and late 1990s. For women, the rise is much smaller, with rates increasing by 8% between 1975 and 1977 and from 2007 to 2009.<sup>26</sup>

Within the 27 countries of the European Union, the highest European age-standardized incidence rates for 2008 are estimated to be in Slovakia for men (around 91 cases per 100 000) and Denmark for women (50 cases per 100 000), while the lowest rates are in Greece for both sexes (around 24 cases per 100 000 for men and 17 per 100 000 for females). The incidence rate varies up to 10-fold between countries with the highest rates and those with the lowest rates. It ranges from more than 40 per 100 000 people in the United States, Australia, New Zealand, and Western Europe to less than 5 per 100 000 in Africa and some parts of Asia. <sup>30</sup>

Colorectal cancer is a major cause of morbidity and mortality throughout the world. It accounts for over 9% of all cancer incidence.<sup>30</sup> <u>http://www.ncbi.nlm.nih.gov/pmc/articles/</u>

<u>PMC2796096/ - r22191-2</u>It is the third most common cancer worldwide and the fourth most common cause of death.<u>http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2796096/ - r22191-2</u>It affects men and women almost equally. Countries with the highest incidence rates include Australia, New Zealand, Canada, the United States, and parts of Europe. The countries with the lowest risk include China, India, and parts of Africa and South America. The developed world accounts for over 63% of all cases.<sup>30</sup>

Much of the geographical variation in incidence across the world can be attributed to differences in diet, particularly the consumption of red and processed meat, fibre and alcohol, as well as excess bodyweight and lack of physical activity. Countries that have had a rapid 'westernization' of diet, such as Japan, have seen a rapid increase in the incidence of colorectal cancer. <sup>31</sup> Epidemiological studies report a rapid increase in risk for colorectal cancer in migrants moving from low- to high-risk countries.<sup>30,31</sup>

## 4. What is the Control Strategy? Is There an Effective Package of Control Methods

#### Assembled Into a "Control Strategy" for most Epidemiological Settings?

In 2008, the World Health Assembly passed resolution WHA61.14 endorsing the Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases. <sup>32</sup> The Action Plan set out six objectives, actions to be implemented over the six-year period from 2008 to 2013, and performance indicators to guide the work of WHO at national, regional, and global levels with a particular focus on low - and middle-income countries and vulnerable populations. Member States have committed to national non-communicable diseases (NCD) plans by the end of 2013.

Cancer control is a population-based public health strategy. The aim of cancer control is a reduction in both the incidence of the disease and the associated morbidity and mortality where possible, as well as improved quality of life for cancer patients. Significant advances in our ability to diagnose, screen and detect cancers earlier as well as improved understanding of the etiology and biology of cancer have led to significant improvements in cancer survival over the past decades. This had led to increasingly effective cancer therapies, which add to the ability to tackle more cancer types and individual cancers in a more targeted manner. Advances continue to be made across the disciplines of surgery, radiation therapy and systemic therapy; for example, the development of the human papillomavirus vaccine (HPV), immunotherapy (ipilumimab for melanoma), and survival improvements in patients with chronic myelocytic leukemia using imatinib mesylate (Gleevec ®). <sup>33</sup> See below for more recent advances in this area, Section 7.

We searched the WHO Global Health Observatory data repository, which provides access to over 50 datasets on priority health topics.<sup>34</sup> At the national level, many countries have established comprehensive national cancer control programs. The Communication from the Commission of 2009 on Action against Cancer pledges that by the end of the Partnership in 2013 all EU Member States will have adopted integrated cancer plans. <sup>35</sup>

A recent systematic assessment of the National Cancer Control Plans available in Europe in 2009 showed that despite the growing number of plans in Europe (19 in the 31 countries studied), significant differences remain between them. A major source of concern is the fact that in many cases, elements crucial to a health systems approach and to the efficacy of the plans such as financing, resource allocation, or governance were missing or inadequate.<sup>36</sup> For those interested in national cancer control programmes, see <u>https://spiral.imperial.ac.uk/</u><u>bitstream/10044/1/4204/1/Cancer%20Control%20vf2.pdf</u>.<sup>37</sup>

In developing countries in particular, where a large proportion of cancers are detected late in the course of the disease, efforts to achieve earlier diagnosis and delivery of adequate palliative care and pain relief deserve urgent attention. A comprehensive national cancer control strategy would be required for any country for the following reasons:

- People are going to continue to develop cancer and die from it
- Cancer control is unique in its complexity, involving a range of diseases and a diversity of service providers it cannot be achieved by any single organization or by government alone
- Effective and efficient use of limited resources is crucial
- Establishing an alliance of organizations and health professionals, both government and non-government, is critical if action is to be cost-effective
- It is important to act now, before the full impact of the ageing population is felt by the health care system

## 4.1 **Prevention**

Cancer prevention should be a key element in all cancer control programs. Cancer prevention focuses not only on factors that increase a person's chances of developing cancer (such as smoking), but also on protective factors such as a healthy diet and physical activity. Exposure to risk factors (e.g. increase in melanoma incidence and the need to avoid sunburn) is generally the result of a complex range of behavioral, social, economic, environmental, and cultural factors that are not easy to change so that efforts to reduce the incidence of lifestyle-related cancers require a comprehensive approach.

Geographical patterns of cancer arise because the prevalences of risk factors differ in a given population. Studies of geographical differences and of migrant populations (i.e. their adoption of the cancer patterns of the host country) provided a cornerstone that established the role of environmental and lifestyle factors in the causation of cancer. Nevertheless, cancer differs from other noncommunicable diseases in that specific risk factors for a number of major cancer sites remain poorly defined. <sup>38</sup>

It is important to recognize that cancer in low- and medium-HDI countries (See Figure 6.4.5 above) is not simply due to their adoption of the social and behavioral conditions found in the high- and very high-HDI countries. Perhaps the best example for which cancer-specific actions are needed is chronic infections. Infections are estimated to explain approximately 16% of cancers globally; however, in developing countries infections explain 22.9% of cancers. <sup>39</sup> The major contributors to cancer are infections with hepatitis B and C viruses (HBV and HCV), HPVs, and *Helicobacter pylori*. Consequently, several of the most common cancers (e.g. liver, stomach, and cervix) in Africa, Asia, and South America are related to an infection.<sup>39</sup>

Ignoring the substantial cancer burden related to infection would be a failure to address preventable causes of cancer in many parts of the world. Other infections that are of lesser global significance can have a serious impact on a local or regional level. These infections can also be addressed by available interventions including the combined role of Kaposi sarcoma herpes virus and HIV in Kaposi sarcoma in sub-Saharan Africa and the role of liver flukes in cholangiocarcinoma in parts of Asia.<sup>39</sup>

Other categories of risk factors can also be addressed.<sup>38</sup> These include environmental and occupational agents: reduction in exposure to aflatoxins, indoor air pollution, radon, arsenic, and excess sunlight; and regulatory protection of workers in certain industries.<sup>40</sup> Such preventive measures will be priorities in some regions even though the impact on global cancer incidence will be comparatively modest.

The shared environmental and behavioral risk factors for noncommunicable diseases make an important contribution to the global cancer burden. In addition to the global impact of tobacco on cancer in multiple organs, alcohol is associated with cancers of the liver, larynx, esophagus, pharynx, breast, and colorectum. Also, reducing the consumption of sugar should help control obesity and overweight, which are risk factors for cancers of the esophagus, breast, colorectum, endometrium, kidney, and pancreas. As mentioned above, for some cancers, the challenge is to implement established interventions, and for other cancers the research priority should be to identify prevention strategies. Tobacco consumption probably remains the most important avoidable cancer risk. In the twentieth century, approximately 100 million people worldwide died from tobacco-associated diseases (cancer, chronic obstructive lung disease, heart disease and stroke).

## 4.2 Early Detection and Screening

Early detection means detecting cancer prior to the development of symptoms or as soon as is practicable after the development of symptoms. Its aim is to detect the cancer when it is localized to the body organ of origin, before it has time to spread to other parts of the body.

Early detection is only part of a wider strategy including diagnosis, treatment, and followupwhich can involve strategies to promote early presentation, including education about signs and symptoms and improved access to primary care.<sup>27</sup> Early detection of cancer prior to the development of symptoms occurs through screening.

## 4.3 Diagnosis and Treatment

Diagnosis involves clinical assessment and a range of investigations, such as endoscopy, imaging, histopathology, cytology, and laboratory studies. Diagnostic tests are also important in identifying the extent to which the cancer may have spread (known as 'staging'). Cancer staging is necessary for determining options for treatment and assessing likely prognosis.

The cancer treatment that a patient receives is determined in large part by the stage of cancer at diagnosis. For most solid tumours, surgery is the most standard and effective form of initial cancer treatment. As cancers progress, treatments typically include radiation, chemotherapy, and in hormone-regulated tumours, hormone ablation therapy. A comprehensive review would also focus on support, rehabilitation and palliative care but this Priority Medicines Report concentrates on pharmacotherapies and these vitally important subject cannot be reviewed here. For further information see Review of Rehabilitation Intervention in Palliative Care for Cancer Patients.<sup>41</sup>

It is just as challenging to summarize an enormous literature on treatment options in this short review. We use the summaries provided by the United States National Cancer Institute (NCI) as a (US-FDA centric) template for this overview. See <u>http://www.cancer.gov/cancertopics/factsheet/cancer-advances-in-focus.</u>

Overall:

- Combination chemotherapy is now standard in the treatment of many cancers and has contributed to increasing survival and cure rates. For example, the introduction of combination chemotherapy containing cisplatin led to cure rates for testicular cancer of approximately 95%. Treatment for this disease has become so effective that 80% of patients with metastatic testicular cancer can now be cured. Thirty-five years ago, 95% of these patients died, usually within 1 year of diagnosis.
- Thus far, three cancer prevention vaccines have been approved by the U.S. Food and Drug Administration (FDA). One of these vaccines, the hepatitis B virus vaccine, has the potential to prevent some forms of liver cancer. The other two vaccines are directed against human papillomavirus (HPV) types 16 and 18 and have the potential to prevent approximately 70% of cervical cancers and some other HPV-associated cancers. Significantly, responding to demand from developing countries, the GAVI Alliance announced in November 2011 that it would take the first steps towards the introduction of human papillomavirus (HPV) and rubella vaccines at US\$ 5 per dose, which is significantly lower than the general retail price of USError! Hyperlink reference not valid.. See GAVI FAQ: Appendix 6.5.2
- In 2010, the FDA approved the first cancer treatment vaccine. This vaccine can be used to treat advanced prostate cancer. Several other cancer treatment vaccines are being tested in large-scale clinical trials, including vaccines for the treatment of non-small cell lung cancer, pancreatic cancer, ovarian cancer, melanoma, and multiple myeloma.
- Therapies that target the specific molecular changes that cause cells to become cancerous and processes that are required for continuous cancer cell growth and survival are in use. To date, the FDA has approved approximately 30 molecularly targeted agents for cancer-related indications, including trastuzumab and three different aromatase inhibitors for breast cancer; imatinib mesylate for chronic myelogenous leukemia and gastrointestinal stromal cell tumours (GIST); sunitinib for advanced kidney cancer and imatinib-resistant GIST; bevacizumab for advanced colorectal, non-small cell lung, and kidney cancers; and bortezomib for multiple myeloma and a type of non-Hodgkin lymphoma. See Section 7.
- Refined radiation therapy techniques, such as three-dimensional conformal radiation therapy, stereotactic radiosurgery, and brachytherapy (radioactive seeds), which are designed to deliver high doses of radiation to tumours while minimizing the doses delivered to nearby healthy tissue, are now widely used. These advances have resulted in greater tissue, organ, and limb preservation.
- Effective therapies to control the side effects of cancer and its treatment, including pain, mouth sores, nausea, and vomiting are available.

## 4.3.1 Tobacco related cancers: Lung cancer

The following summaries are extracted from Autier et al. 2011, and Gatta et al. 2011.<sup>12,13</sup> There are some seemingly basic questions that still remain unanswered.

- We do not know whether intensifying the chemotherapy dose increases survival in small cell lung cancer, and it may increase treatment-related toxicity.
- First-line platinum-based regimens improve survival in people with unresectable non-small cell lung cancer compared with older, non-platinum agents, but we do not know whether platinum-based chemotherapy is more effective than non-platinum third-generation chemotherapeutic agents.
- Adding chemotherapy to thoracic irradiation may improve survival at 2 to 5 years in people with unresectable non-small cell lung cancer compared with thoracic irradiation alone, but increases adverse effects.
- Targeted therapy with gefitinib or erlotinib does not increase survival when used as first-line palliative therapy in people with unresectable non-small cell lung cancer. But there are now subgroups defined who can be treated initially with targeted agents alone
- Adding thoracic irradiation to chemotherapy improves survival in people with limited-stage small cell lung cancer, but may increase complications.

## 4.3.2 Breast Cancer (non-metastatic)

- Breast-conserving surgery (lumpectomy) followed by local radiation therapy has replaced mastectomy as the preferred surgical approach for treating early-stage breast cancer.
- Combination chemotherapy is a standard of care in the adjuvant treatment of operable breast cancer. The goal of this systemic therapy is to eradicate cancer cells that may have spread beyond the breast. Neoadjuvant chemotherapy, or chemotherapy given before surgery to reduce the size of the tumour and to increase the chance of breast-conserving surgery, is also an option.
- Hormonal therapy with selective estrogen receptor modulators (SERMs)<sup>i</sup> (such as tamoxifen) and aromatase inhibitors is now standard in the treatment of women with estrogen receptor-positive breast cancer, both as adjuvant therapy and in the treatment of advanced disease. Aromatase inhibitors block estrogen production by the body.
- Tamoxifen and another SERM, raloxifene, have been approved by the FDA as treatments to reduce the risk of breast cancer in women who have an increased risk of developing the disease.
- The monoclonal antibody trastuzumab is an accepted treatment for breast cancers that overproduce a protein called human epidermal growth factor receptor 2, or HER2. This protein is produced in abnormally high amounts by about 20% of breast tumours. Breast cancers that overproduce HER2 tend to be more aggressive and are more likely to recur. Trastuzumab targets the HER2 protein specifically, and this antibody, in conjunction with adjuvant chemotherapy, can lower the risk of

<sup>&</sup>lt;sup>i</sup> Selective estrogen receptor modulators block the effects of estrogen in the breast tissue. If estrogen isn't attached to a breast cell, the cell doesn't receive estrogen's signals to grow and multiply. There are three SERMs: tamoxifen (also called tamoxifen citrate; brand name: Nolvadex) Evista (chemical name: raloxifene) Fareston (chemical name: toremifene)

recurrence of HER2-overproducing breast cancers by about 50% in comparison with chemotherapy alone.

- Several breast cancer susceptibility genes have now been identified, including *BRCA1*, *BRCA2*, *TP53*, and *PTEN/MMAC1*. Approximately 60% of women with an inherited mutation in *BRCA1* or *BRCA2* will develop breast cancer sometime during their lives, compared with about 12% of women in the general population. Women with inherited *BRCA1* or *BRCA2* gene mutations also have an increased risk of ovarian cancer.
- The prevalence of ductal carcinoma in situ (DCIS) has dramatically increased since the widespread adoption of screening mammography. Because DCIS is considered to be a potential precursor of invasive breast cancer, it has been treated aggressively with local therapy. The potential for pre-operative (neoadjuvant) therapy is being actively explored using a variety of agents (e.g. lapatinib U.S. clinical trials: NCT00555152).

#### 4.3.3 Metastatic breast cancer

- Hormonal treatment using tamoxifen or progestins may be preferable to chemotherapy as first-line treatment in women with estrogen receptor-positive disease.
- First-line chemotherapy is associated with an objective tumour response in 40% to 60% of women, of median duration of 6 to 12 months. Complete remission may occur in some women, whereas others show little or no response.
- The optimum duration of chemotherapy is unknown. Increasing the dose may increase serious adverse effects without prolonging survival.
- Taxane-based chemotherapy may increase tumour response and survival compared with some non-taxane regimens as second-line treatment. No clear benefit has been found in first-line treatment.
- Targeted therapies as m-TOR inhibitors (i.e. everolimus) are now being used in combination with other therapies (e.g. exemestane) to treat metastatic breast cancer

## 4.3.4 Prostate Cancer/ PSA Screening

Due to the widespread implementation of prostate specific antigen (PSA) screening in the United States, more than 90 percent of all prostate cancers are diagnosed at an early stage. Whether this earlier detection actually reduces the number of prostate cancer deaths was studied in two randomized clinical trials in the NIH-sponsored Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trial and the European Study of Screening for Prostate Cancer (ESRPC). The PLCO trial had at least 44% of participants in the control arm already PSAtested prior to being randomized into the study. This United States study has been unable to demonstrate any difference in prostate cancer mortality between the two arms of the study. The ERSPC trial has published its 11-year follow-up results (New England Journal of Medicine, 15 March 2012). They demonstrate, as they had in their original findings, that screening does significantly reduce death from prostate cancer by at least 20% but that PSAbased screening "was associated with a high risk of overdiagnosis".<sup>42</sup> However, this benefit came at a cost because many more cancers were diagnosed and treated in the screened group than in the control (unscreened) group. These findings suggest that PSA screening can lead to the diagnosis and treatment of some prostate cancers that will not cause symptoms or threaten a man's life, phenomena known as overdiagnosis and overtreatment (i.e.

unnecessary treatment). The major side effects of prostate cancer treatment include urinary incontinence and sexual impotence.

Summary of progress in prostate cancer:

- Advances in the treatment of prostate cancer include new surgical approaches and improvements in radiotherapy. In addition, laparoscopic and robot-assisted surgical methods are also widely used, although evidence of their superiority to open prostatectomy is lacking. Furthermore, clinical researchers have refined a radiotherapy technique known as brachytherapy, which involves the implantation of small sources of radioactivity (radioactive seeds) into the prostate.
- Advances in hormonal therapy for prostate cancer have included the development of gonadotropin-releasing hormone (GnRH) agonists, which inhibit the pituitary gland's ability to stimulate the testes to make testosterone. Other GnRH agonists used today include goserelin, triptorelin, and histrelin. Additional prostate cancer treatments that interfere with the production or activity of male hormones and are used today include the drugs degarelix, flutamide, bicalutamide, nilutamide, and ketoconazole.
- Recent progress in our understanding of the pathogenesis of advanced prostate cancer has heralded a new era in treatment. Numerous agents now populate the treatment landscape (i.e. hormonal treatments for advanced disease -abiraterone and elazutamide- and an impressive number of novel agents are in development.
- Advances have also been made in chemotherapy for prostate cancer. In 2004, results from two large NIH-sponsored clinical trials showed that use of the drug docetaxel can prolong the survival of men who have advanced prostate cancer that no longer responds to hormonal therapy. Another drug, cabazitaxel, approved in 2010, improves the survival of men whose prostate cancer no longer responds to docetaxel.
- In 2010, the FDA approved sipuleucel T, a cancer treatment vaccine that improves the survival of men with advanced prostate cancer. This vaccine is created using a patient's own immune cells. The cells are removed from the patient's body, activated, and then infused into the patient's bloodstream to boost the immune response to his cancer.
- In 2003, the NIH-sponsored Prostate Cancer Prevention Trial demonstrated that hormonal therapy with finasteride, a drug approved for the treatment of benign prostatic hyperplasia (a noncancerous enlargement of the prostate), reduced the risk of developing prostate cancer by 25%. <sup>43</sup> This was the first study to show that a drug could be used to prevent this disease. In 2010, a similar drug, dutasteride, was also found to reduce the risk of prostate cancer in men at higher than average risk for the disease. <sup>44</sup>

## 4.3.5 Colorectal Cancer:

- Colorectal cancer surgical techniques and survival after surgery have improved over the past 15 years. Surgery can cure about 90% of colorectal cancers when they are found early.
- Researchers began testing drug combinations with flurouracil (5-FU) as early as the 1980s, and, in the mid-1990s, the combination of 5-FU and leucovorin became standard adjuvant treatment for patients with stage III colon cancer. The addition of oxaliplatin to 5-FU and leucovorin was later found to improve survival compared with 5-FU and leucovorin alone. A newer drug, capecitabine, is an alternative to 5-FU

and leucovorin. Capecitabine is sometimes combined with oxaliplatin as well. Capecitabine is taken by mouth, whereas 5-FU must be given intravenously. For some patients whose cancer has metastasized, the drug irinotecan may also be part of chemotherapy.

- Radiation therapy is not standard treatment for patients with colorectal cancer, but patients with stage II or stage III rectal cancer may receive neoadjuvant radiation plus chemotherapy in addition to adjuvant chemotherapy. If a patient does not receive neoadjuvant radiation therapy, he or she may be treated with adjuvant radiation therapy plus chemotherapy.
- The targeted therapies cetuximab and panitumumab can extend survival or slow tumour growth, respectively, for some patients with advanced colorectal cancer. Recent genetic studies have identified a subset of patients who do not benefit from these drugs, sparing them unnecessary treatment.
- The targeted therapy bevacizumab (Avastin®) blocks the growth of new blood vessels to tumours. Studies have shown that bevacizumab can help extend survival for some patients with metastatic colorectal cancer.

## 4.4 Histology and segmentation

By necessity, the Background paper is focused on therapeutic interventions, including targeted therapies. Nonetheless, understanding cancer growth, classification, and prognostic factors requires new methods in tumor segmentation and histology. In part this is because many tumours are a complex intermixing of cellular tissue types: incorporating cancer cells, fibroblastic stromal tissue, and inactive fibrosis. Quantitative proportions and distributions of the various tissue types are useful to understand in some detail. Any review of this subject is well beyond the scope of the Background paper. We cite two examples.

Scanning hardware and viewing software can digitize samples of stained pathological tissue excised from a patient. Image analysis algorithms can be employed to assist in analyzing these digital samples, increasing the speed and efficiency with which pathology samples are examined in the clinic. Traditionally these algorithms have focused on simple quantification (e.g. cell counting or stain enhancement), but the most recent developments have focused on developing quantitative disease signatures for different tissue types.

In conventional pathological diagnosis even with serial sections of a good quality, it is difficult, if not impossible, to grasp the three-dimensional (3D) structure of cancer lesions in a complex microenvironment under a microscope. Recent advance in 3D imaging technology allow clinicians to inspect the details of tumor architecture.<sup>45</sup>

# 5. What is Known of the Affordability, Feasibility, and Sustainability of the Control Strategy?

## 5.1 NCD Global monitoring framework

A draft comprehensive global monitoring framework, including indicators, and a set of voluntary global targets for the prevention and control of noncommunicable diseases was developed from a WHO meeting of Member States in November 2012 <u>http://apps.who.int/gb/NCDs/pdf/A\_NCD\_INF1-en.pdf</u>. Many of the proposed sets of monitoring indicators are relevant for our present purpose.

The global monitoring framework including the proposed set of indicators, is intended to provide internationally comparable assessments of the status of NCD trends over time and help to benchmark the situation in individual countries against others in the same region or in the same development category.

Some of these indicators might be rated "best buys" as being very cost-effective. For instance, it is estimated that 2.3 million deaths annually, or 3.8% of all global deaths, are attributed to alcohol consumption, from which more than half are due to NCDs including cancers and cardiovascular diseases. Tracking alcohol consumption is important as the risk of most alcohol-attributable health conditions is correlated with the overall levels of alcohol consumption with no evidence of a threshold effect for cancers and hypertension.

Tracking dietary fat intake is important as this has been linked to increased risk of obesity, coronary heart disease and certain types of cancer. Tracking inadequate consumption of fruit and vegetables is important as adequate amounts reduces the risk for cardiovascular diseases, stomach cancer, and colorectal cancer. Tobacco smoking is estimated to cause about 71% of lung cancer deaths. Hepatitis V virus (HBV) results in liver cirrhosis and in total it is estimated that 600 000 people die each year from chronic HBV infections, mainly from cirrhosis and liver cancer. A safe effective vaccine to prevent chronic infection with HBV is available and is recommended by the WHO to be included in national infant vaccination programmes. Preventing liver cancer via hepatitis B vaccination is classified as a "best buy" by the WHO. Human papilloma virus (HPV) vaccination to prevent cervical cancer is potentially very cost effective if it can be made available at below US\$ 10 per vaccinated girl.

## 5.2 Overall Economic Burden: Europe and the World

Cancer costs European countries  $\in$ 124 billion (£99 billion) every year, according to the first estimate of the full economic burden of the disease in the EU. <sup>46</sup> Lung cancer incurred the biggest total cost, amounting to  $\in$ 19 billion (£15 billion). This was mostly the result of losses caused by patients dying prematurely. For healthcare alone, the most expensive disease was breast cancer. At  $\in$ 6 billion (£5 billion), it was responsible for 13% of cancer healthcare costs. Direct healthcare costs were also calculated for each of the 27 countries included in the research.

Data shows that Lithuania spent the least on cancer healthcare, around €7550 (£6026) per patient with a per capita cost of €32 (£25.50) per person per year. Germany had the highest healthcare cost, spending an average of €28 269 (£22 563) on every cancer case. It had a per-

capita expenditure of €165 (£132). The UK spent €17 619 (£14 062) per case and €88 (£70) per head of population. See also Figure 6.5.7.





Source: D. Fukumura, R.K. Jain Imaging angiogenesis and the microenvironment APMIS, 116 (2008), pp. 695–715

In 2008, researchers gathered global burden of disease data from the WHO for 17 different types of cancer, and 15 foremost causes of death. Death and disability is responsible for the loss of 85 million DALY years. To reduce this death toll by one DALY, the WHO recommends investing as much as three times per capita Gross Domestic Product (GDP) to make an intervention cost-effective. Cancer has the largest economic impact from premature death and disability when compared to all global causes of death. <sup>47</sup> Cancer accounted for close to US\$ 1 trillion in economic losses from premature death and disability in 2009. The economic burden from cancer, at US\$ 895 billion, is nearly 20% more than heart disease's toll (US\$ 753 billion). These figures do not include direct medical costs, which might double the amounts.

It has recently been estimated that it would cost US\$ 1.8 billion to reduce exposure to key risk factors like smoking, drinking, and poor diet (US\$ 0.6 billion for smoking/ US\$ 0.4 billion for diet/exercise and US\$ 0.8 billion for alcohol). <sup>48</sup>

Alone, cancers of the bronchus, lung and trachea already cost the global economy nearly US\$ 180 billion annually. It is estimated that 8 million people will die prematurely because of tobacco smoking by 2030, with four-fifths of these deaths occurring in low- to middle-income countries - approximately 30% of those deaths will be from cancer. It is estimated that passive smoking (second hand smoke) in the workplace kills about 200 000 people annually.<sup>47,49</sup>

In the United States alone, based on growth and ageing of the United States population, medical expenditures for cancer in the year 2020 are projected to reach at least US\$ 158 billion (in 2010 dollars) — an increase of 27% over 2010.<sup>50</sup> If newly developed tools for cancer diagnosis, treatment, and follow-up continue to be more expensive, medical expenditures for cancer could reach as high as US\$ 207 billion. In 2010, medical costs associated with cancer were projected to reach US\$ 124.6 billion, with the highest costs associated with breast cancer (US\$ 16.5 billion), followed by colorectal cancer (US\$ 14 billion), lymphoma (US\$ 12 billion), lung cancer (US\$ 12 billion) and prostate cancer (US\$ 12 billion).

## 5.3 Affordability /Availability

More than 70% of all cancer deaths occurred in low- and middle income countries (LMICs). The high cost and poor availability of cancer treatment are significant barriers to access in many LMICs. See Appendix 6.5.3. The issue is not restricted to LMICs. In the context of a National cancer control policy (See above, Section 5.1), a commitment to monitor availability and possibly affordability would be very much needed. The high cost of cancer medicines generally remains a significant question related to the future of healthcare management and its impact on pharmaceutical pricing strategies for emerging treatments that are focused on precision, targeted agents (See Section 7.3) and often times in combination with other novel or existing treatments.

## 5.3.1 The complex issue of "Companion diagnostics"

The cost of diagnostics is a major issue and challenge for many of the new "personalized" treatments. Regulators and insurers are asking cancer medicine developers to market, or a least use, companion tests to pinpoint which patients are most likely to benefit from a drug, thereby sparing other patients from needless side effects and expense.

The U.S. FDA issued guidance to the industry on companion diagnostics in July 2011, asserting that if safe and effective use of a therapeutic depends on a diagnostic, then FDA generally will require approval or clearance of the diagnostic at the same time that FDA approves the therapeutic.<sup>51</sup> As of January 2013, the final FDA guidance on this subject has not yet been formulated. The European Medicines Association (EMA) has yet to put forth specific guidance regarding companion diagnostics.

There are numerous economic, scientific and regulatory obstacles to developing companion diagnostics. As the diagnostic may not often be reimbursed in many markets around the world and if the patient cannot access the diagnostic, they will not be able to access the treatment. It is a significant gap that will need to be addressed to ensure that the right patient is benefiting from the right medicine reducing overall healthcare costs to payers and national healthcare systems.

Also, it may not be known what to test for to predict a drug's effectiveness, or this information is not available and they don't find out until near the end of the drug's clinical trials. Moreover, coordinating development and approval of a drug and a test — by two separate companies reviewed by two FDA divisions — can raise the cost of drug development if not done well. Pharmaceutical companies can spend hundreds of millions of dollars to develop a drug, then can reap billions of dollars a year in sales with high profit margins. Diagnostic companies typically spend several million dollars to develop a test, with

annual revenues also around that level, and low profit margins. For pharmaceutical companies, the risk is that a test can lower sales of their drugs by restricting use to a fraction of potential patients. For diagnostic companies, there is a risk of developing a test in advance for a drug that may never reach the market.

#### 5.3.2 Essential NCD medicines and basic technologies to treat major NCDs

The draft comprehensive global monitoring framework, including indicators, and a set of voluntary global targets for the prevention and control of noncommunicable diseases mentioned previously (<u>http://apps.who.int/gb/NCDs/pdf/A\_NCD\_INF1-en.pdf</u>) contains a comprehensive monitoring framework, one of the indicators being "availability of basic technologies and generic essential medicines required to treat major NCDs in public and private sector facilities, including primary care facilities." The minimum list of medicines would include: medicines (at least aspirin), a statin, an angiotensin converting enzyme inhibitor, thiazide diuretic, a long acting calcium channel blocker, metformin, insulin, a bronchodilator, and a steroid inhalant. Technologies would include at least a blood pressure measurement device, a weighing scale, blood sugar, and blood cholesterol measurement devices with strips and urine strips for albumin assay.

## 6. Why Does the Disease Burden Persist?

Cancer is a multidimensional condition, and it is caused by both hereditary and environmental factors. Changing, and disparities in, incidence must be set against the backdrop of improvements in health and life expectancy, the changing demographies and public health improvements in hygiene, sanitation, and combating infectious diseases.

Since many cancers are due to environment or lifestyle, increases in certain cancer types (primarily lung, oral, and pharyngeal cancers) can be anticipated in countries where smoking and obesity has not been controlled. Common to many NCDs, including cancer, is the fact that many of the preventative measures involve behavioural change and these are, by their very nature, difficult to implement and sustain in a population-based manner.

A serious challenge for the future is the ageing of the population, with dramatic increases in the number of people over the age of 65 as well as increases in the number of people over the age of 80, a population that has received little attention. Due to the increase in the total population, as well as the increased cancer risk associated with ageing, we would expect the number of cancer diagnoses in Europe to continue to increase, while there will be concomitant declines in cancer mortality rates. To be sure, ageing is not the only reason why cancer incidence might rise over time. Heightened efforts in screening, diagnosis, education, basic research, tobacco control (especially among women), and other public health interventions will be required.

# 7. What can be Learned from Past/Current Research into Pharmaceutical Interventions for this Condition?

## 7.1 Vaccines

Cancer chemoprevention refers to the use of pharmacological agents to inhibit, delay, or reverse the multi-step process of carcinogenesis. Epidemiological studies suggest a protective role of several agents in reducing the risk of cancer. Vaccines targeting infections with hepatitis B virus, a risk factor for hepatocellular cancer, and human papillomavirus, a risk factor for cervical cancer, are considered major clinical cancer chemoprevention successes.

Nevertheless, the broad translation of chemoprevention to the clinic is not yet a reality. Cancer is a comparatively infrequent event, and clinically overt cancer usually takes many years to develop. Clinical trials to test the effectiveness of chemopreventive agents therefore require large study populations and a long-term commitment of resources. The availability of biomarkers as surrogate end points for clinical disease would allow smaller trials of shorter duration, facilitating clinical research into chemoprevention. In this regard, it is useful to talk about the risk benefit ratio of vaccines and of cancer therapeutics generally.

In Europe, part of the mandate of the Committee for Medicinal Products for Human Use (CHMP) is to assess risks and benefits of authorized medicines on behalf of the European Medicines Agency (EMA). In 2007, the CHMP revised its guidance and included quantitative risk-benefit analyses in the regulatory agenda.<sup>52</sup> Although no specific method was recommended, several risk-benefit analysis (RBA) features were noted as being of value, including 1) all important benefits and medically serious risks are identified; and 2) the risks and benefits are weighted according to their relative importance and the strength of the evidence available.

Many payers now use health technology assessments (HTAs) to weigh the additional expense of a new drug against the increase in effectiveness it delivers over the current standard of care. The standard bearer for such assessments has been the UK's National Institute for Health and Clinical Excellence (NICE), which uses the quality-adjusted life year, or QALY, to compare the value and/or health gain of a new product against a comparator drug. Drugs that NICE considers have a QALY of over £30 000 (US\$ 49 000) rarely receive reimbursement. <sup>53</sup>

## 7.2 **Personalized medicine and biomarkers**

Genomic technologies, especially next-generation or massively parallel sequencing, has allowed study designs involving understanding gene sequences to be done more quickly while potential lowering the cost and increased the throughput of analyzing tumors. There exists also an information technology structure that allows massive amounts of data to be processed and managed. Arguably, this "era" of personalized medicine in cancer began when in 1998 the FDA approved the use of trastuzumab in metastatic breast cancer patients whose tumors were human epidermal growth factor receptor (HER) 2-positive. The FDA has approved at least 11 tests that either predict response to specific medications or risk of recurrence in malignancies like non-small cell lung cancer (NSCLC), colon, breast, and

gastric cancer, and chronic myelogenous leukemia The tests, using a variety of methods, can identify a host of biochemical changes in cancer, including somatic and inherited mutations, polymorphisms, gene expression, amplification or copy number variations, and protein overexpression, loss, mutations and copy number variations as well as other biomarkers.

As an example of how "personalized medicine' is changing the regulatory environment, the FDA in 2011 approved Roche's vemurafenib to treat patients with metastatic or inoperable melanoma whose tumors test positive for a specific gene mutation (BRAF V600E mutation). FDA coupled approval of the drug with a companion diagnostic. Also in 2011, Pfizer's crizotinib was approved to treat late stage lung cancer, along with a diagnostic to detect abnormal anaplastic lymphoma kinase (ALK) gene expression.

Implementation of these "personalized" medicines is very complex from a drug development as well as from a regulatory perspective and pharmaceutical companies will have to factor in development of diagnostics for identified predictive biomarkers as an investment in this approach.

## 7.3 Targeted Therapy

Today's emerging targeted therapies are designed to destroy specific cancerous cells and leave healthy cells intact. Targeted therapies are per definition likely to be more effective at earlier stage where the driver for the tumour growth is the particular target. At later stage disease many mechanisms drive growth. One of the more recent examples includes imatinib mesylate

(Gleevec® in the United States, Glivec® outside the United States), which is a specific inhibitor for tyrosine kinase in Philadelphia chromosome positive chronic myeloid leukemia (CML) and gastrointestinal stromal tumours (GIST). Gleevec® serves a defined but small population, and this is the case with targeted therapies. Thus, the trend in targeted therapy is towards many niched treatments rather than sweeping standard therapies as we have had with chemotherapy. Other drugs work in a similar way, including erlotinib (Tarceva®) for a form of lung cancer, bevacizumab (Avastin®) for breast, colorectal and other cancers, and sunitinib (Sutent®) for renal cell carcinoma and gastrointestinal sarcoma.

In principle, targeted therapies can be tailored to the genetic mechanisms responsible for a particular patient's tumour. Therefore, one could control a particular cancer's runaway growth properties, thus controlling the growth of the malignancy in the body and causing the cancer to exist chronically within the body. There are, however, tremendous hurdles to overcome. Most tumours grow by multiple mechanisms so that preventing one such mechanism might not be enough and since cancer cells mutate rapidly, tumours can evolve resistance, sometimes very quickly, and neighboring cells in a tumour might be different and not susceptible to the same drug. The vemurafenib/crizotinib examples, cited above in Section 7.2, show that 'personalized medicines' might overcome this issue, given the importance of specific genetic biomarkers.

The first molecular target for targeted cancer therapy was the cellular receptor for the female sex hormone estrogen, which many breast cancers require for growth. When estrogen binds to the estrogen receptor (ER) inside cells, the resulting hormone-receptor complex activates the expression of specific genes, including genes involved in cell growth and proliferation.

Research has shown that interfering with estrogen's ability to stimulate the growth of breast cancer cells that have these receptors (ER-positive breast cancer cells) is an effective treatment approach. Several drugs that interfere with estrogen binding to the ER have been approved by the FDA for the treatment of ER-positive breast cancer. These include selective estrogen receptor modulators (SERMs), including tamoxifen and toremifene (Fareston®), which bind to the ER and prevent estrogen binding.

Another drug, fulvestrant (Faslodex®), binds to the ER and promotes its destruction, thereby reducing ER levels inside cells. Aromatase inhibitors (AIs) are another class of targeted drugs that interfere with estrogen's ability to promote the growth of ER-positive breast cancers. The enzyme aromatase is necessary to produce estrogen in the body. Blocking the activity of aromatase lowers estrogen levels and inhibits the growth of cancers that need estrogen to grow. Aromatase inhibitors are used mostly in women who have reached menopause because the ovaries of premenopausal women can produce enough aromatase to override the inhibition. Three AIs have been approved by the FDA for the treatment of ER-positive breast cancer: Anastrozole (Arimidex®), exemestane (Aromasin®), and letrozole (Femara®).

## 7.3.1 A note on Immunotherapy

We briefly only mention a few points about this subject, as a review of this type cannot be fully comprehensive. One of the new trends in the development of cancer therapy has been the involvement of the body's immune system, which is our primary defense mechanism against disease. The general idea is to develop new therapies that direct our immune system response against cancer cells, which results in their destruction through a natural and highly effective system. This is in contrast to chemotherapy, which destroys normal and cancer cells.

Provenge (sipuleucel-t) in Section 7.3, is but one example. Another is ipilimumab (see Table 6.4D), a monoclonal antibody inhibitor of a protein call CTLA-4 which keeps Cytotoxic T lymphocytes "in check" through one of the body's mechanisms. Through its mechanism of action, it frees one of the natural restrictions put on the immune system to allow for targeting of malignant melanoma cells to great success.

Adoptive cell therapy (ACT), which is the administration of a patient's own (autologous) or donor (allogeneic) anti-tumour lymphocytes following a lymphodepleting preparative regimen, has emerged as an effective treatment for patients with metastatic melanoma. Studies have demonstrated that normal human lymphocytes can be genetically engineered to recognize cancer antigens and mediate cancer regression in vivo has opened opportunities for enhancing and extending the ACT approach to patients with a wide variety of cancer types. <sup>54</sup>

Therapeutic antibodies (Table 6.4A) currently provide clinical benefit to patients with cancer and have been established as 'standard of care' agents for several highly prevalent human cancers. The next generation of unconjugated antibody therapies will undoubtedly yield many effective new treatments for cancer over the next decade. These advances will arise from the identification and validation of new targets, the manipulation of tumour–host microenvironment interactions, and the optimization of antibody structure to promote the amplification of antitumour immune responses.<sup>55</sup>

## 7.3.2 Examples of targeted therapies

Some targeted therapies block specific enzymes and growth factor receptors involved in cancer cell proliferation. These drugs are sometimes called signal transduction inhibitors. See Table 6.4.A. Note that all the names of the medicines in the following Tables are hyperlinked to the NCI clinical trial database at <u>www.cancer.gov</u>.

Therapy	Indication (FDA)	Mode of Action
Imatinib mesylate	variety of cancers	targets several members of a class of proteins
(Gleevec®)		called tyrosine kinase enzymes that participate in
		signal transduction
Dasatinib	approved to treat some patients	
(Sprycel®).	with chronic myelogenous	
	leukemia (CLL) or acute	
	lymphoblastic leukemia (ALL)	
Nilotinib	approved to treat some patients	small-molecule tyrosine kinase inhibitor
<u>(Tasigna®)</u>	with CML	
Bosutinib	CML	small-molecule tyrosine kinase inhibitor.
(Bosulif®)		
<u>Trastuzumab</u>	certain types of breast cancer	antibody that binds to the human epidermal
(Herceptin®)		growth factor receptor 2 (HER-2). HER-2
Pertuzumab	used in combination with	Antibody likely prevents HER-2 from sending
<u>(Perjeta™)</u>	trastuzumab and docetaxel to treat	growth signals and induces the immune system to
	metastatic breast cancer that	attack HER-2-expressing cells.
	expresses HER-2	
<u>Lapatinib</u>	advanced or metastatic breast	small-molecule drug inhibits several tyrosine
(Tykerb®)	cancer.	kinases, including the tyrosine kinase activity of
		HER-2.
<u>Gefitinib</u>	advanced non-small cell lung	inhibitsstyrosine kinases of epidermal growth
(Iressa®)	cancer.	factor receptor (EGFR)
<u>Erlotinib</u>	metastatic non-small cell lung	inhibits the tyrosine kinase activity of EGFR,
<u>(Tarceva®)</u>	cancer and pancreatic cancer	
<u>Cetuximab</u>	squamous cell carcinoma of the	Antibody binds to the external portion of EGFR,
(Erbitux®)	head and neck or colorectal cancer.	thereby preventing the receptor from being
		activated by growth signals,
<u>Panitumumab</u>	metastatic colon cancer.	Antibody binds to EGFR and prevents it from
(Vectibix®)		sending growth signals.
<u>Temsirolimus</u>	advanced renal cell carcinoma.	specific inhibitor of a serine/threonine kinase
(Torisel®)		called mTOR that is activated in tumour cells
<u>Everolimus</u>	advanced kidney cancer	binds to a protein called immunophilin FK
(Afinitor®)		binding protein-12, forming a complex that in
		turn binds to and inhibits the mTOR kinase.
<u>Vandetanib</u>	metastatic medullary thyroid cancer	binds to and blocks the growth-promoting activity
<u>(Caprelsa®)</u>		of several tyrosine kinase enzymes,
<u>Vemurafenib</u>	inoperable or metastatic melanoma.	blocks the activity of a permanently activated
(Zelboraf®)		mutant form of the serine/threonine kinase BRAF
		(known as BRAF V600E).
<u>Crizotinib</u>	locally advanced or metastatic non-	inhibits the tyrosine kinase activity of a fusion
<u>(Xalkori®)</u>	small cell lung cancer.	protein called EML4-ALK, resulting in decreased
		tumour cell growth

 Table 6.5.1a: Signal Transduction Inhibitors in clinical trials (as of March 2013)

Other targeted therapies modify the function of proteins that regulate gene expression and other cellular functions. (Table 6.5.1.b)

Table 6.5.1.b: Regulators of gene expression and cell function in clinical trials (as of March 2013)

Therapy	Indication (FDA)	Mode of Action
<u>Vorinostat</u> ( <u>Zolinza®</u> )	cutaneous T-cell lymphoma (CTCL)	inhibits the activity histone deacetylases (HDACs), HDAC inhibitors can induce tumour cell differentiation, cell cycle arrest, and apoptosis.
<u>Romidepsin</u> (Istodax®)	CTCL	inhibits members of one class of HDACs and induces tumour cell apoptosis.
<u>Bexarotene</u> ( <u>Targretin®</u> )	CTCL	retinoids, which are chemically related to vitamin A. Bexarotene binds selectively to, and thereby activates, retinoid X receptors. Once activated, these nuclear proteins act in concert with retinoic acid receptors to regulate the expression of genes that control cell growth, differentiation, survival, and death.
<u>Alitretinoin</u> (Panretin®)	cutaneous lesions in patients with AIDS- related Kaposi sarcoma	binds to both retinoic acid receptors and retinoid X receptors.
<u>Tretinoin</u> (Vesanoid®)	induction of remission in certain patients with acute promyelocytic leukemia.	retinoid binds to and thereby activates retinoic acid receptors.

Other targeted therapies block the growth of blood vessels to tumours (angiogenesis). To grow beyond a certain size, tumours must obtain a blood supply to get the oxygen and nutrients needed for continued growth. Treatments that interfere with angiogenesis may block tumour growth. Table 6.5.1.c.

Therapy	Indication (FDA)	Mode of Action
<u>Bevacizumab</u>	glioblastoma. non-small cell lung	binds to VEGF and prevents it from
(Avastin®)	cancer, metastatic colorectal cancer,	interacting with receptors on
	and metastatic kidney cancer.	endothelial cells,
Ziv-aflibercept	metastatic colorectal cancer	By binding to VEGF, ziv-aflibercept
<u>(Zaltrap®)</u>		prevents it from interacting with
		receptors on endothelial cells,
<u>Sorafenib</u>	advanced renal cell carcinoma and	blocks an enzyme that is involved in cell
(Nexavar®)	some cases of hepatocellular carcinoma	growth and division.
	-	-
Sunitinib	metastatic renal cell carcinoma,	small-molecule tyrosine kinase inhibitor
(Sutent®)	gastrointestinal stromal tumour	
<u>Pazopanib</u>	advanced renal cell carcinoma and	small-molecule inhibitor of several
(Votrient®)	advanced <u>soft tissue sarcoma</u>	tyrosine kinases,
Regorafenib	metastatic colorectal cancer	small-molecule inhibitor of several
(Stivarga®)		tyrosine kinases that are involved in
<u> </u>		angiogenesis and tumour cell growth,
<u>Cabozantinib</u>	metastatic medullary thyroid cancer.	small-molecule inhibitor of several
(Cometriq <sup>TM</sup> )		tyrosine kinases

Table 6.5.1.c: Angiogenesis and growth factor antagonists in clinical trials (as of March 2013)

Some targeted therapies act by helping the immune system to destroy cancer cells. Table 6.5.1.d

Table 6.5.1.d: Immunomodulators	s in clinical	trials (as	of March 2013)
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Therapy	Indication (FDA)	Mode of Action
<u>Rituximab</u>	B-cell <u>non-Hodgkin</u>	CD20 that is found on B cells. When
<u>(Rituxan®)</u>	<u>lymphoma</u> chronic	rituximab binds to these cells, it triggers an
	lymphocytic leukemia (CLL).	immune response that results in their
		destruction.
<u>Alemtuzumab</u> ( <u>Campath®)</u>	B-cell CLL.	antibody directed against CD52, a protein found on the surface of normal and malignant B and T cells and many other cells of the immune system. Binding triggers an immune response that destroys the cells
<u>Ofatumumab</u> ( <u>Arzerra®)</u>	CLL	antibody is directed against the B-cell CD20 cell surface antigen.
<u>Ipilimumab</u> <u>(Yervoy™)</u>	metastatic melanoma	By inhibiting CTLA-4, ipilimumab stimulates the immune system to attack melanoma cells.

Another class of targeted therapies includes monoclonal antibodies that deliver toxic molecules to cancer cells specifically. Table 6.5.1.e

Therapy	Indication (FDA)	Mode of Action
Tositumomab and	B-cell non-Hodgkin	mixture of monoclonal antibodies that
1311-tositumomab	lymphoma.	recognize the CD20 molecule. Some of the
(Bexxar®)		antibodies in the mixture are linked to a
		radioactive substance called iodine-131.
Ibritumomab tiuxetan	B-cell non-Hodgkin	monoclonal antibody directed against CD20
<u>(Zevalin®)</u>	lymphoma	that is linked to a molecule that can bind
		radioisotopes such as indium-111 or yttrium-
		90
Denileukin diftitox	CTCL	interleukin-2 (IL-2) protein sequences fused
<u>(Ontak®)</u>		to diphtheria toxin. The drug binds to cell
		surface IL-2 receptors, directing the
		cytotoxic action of the diphtheria toxin to
		these cells.
Brentuximab vedotin	systemic anaplastic large	monoclonal antibody directed against a
(Adcetris®).	cell lymphoma and	molecule called CD30, which is found on
	Hodgkin lymphoma	some lymphoma cells, linked to a drug
		called monomethyl auristatin E (MMAE).

 Table 6.5.1.e: Site-specific targeted monoclonal antibodies

Nevertheless, targeted therapies have some limitations. Chief among these is the potential for cells to develop resistance to them. In some patients who have developed resistance to imatinib, for example, a mutation in the BCR-ABL gene has arisen that changes the shape of the protein so that it no longer binds this drug as well. In most cases, another targeted therapy that could overcome this resistance is not available. It is for this reason that targeted therapies may work best in combination, either with other targeted therapies or with more traditional therapies.

## 7.4 Tumour Vaccines: Therapeutic versus preventive vaccines

Anti-tumour vaccines are effective in preventing a subsequent tumour challenge in animals — this is a well-substantiated observation established through tumour-challenge animal model experiments in which, immunization against a tumour antigen (e.g. a protein) is followed by a challenge with a lethal dose of a transplantable tumour. Vaccines being tested in these models range from those consisting of live, irradiated or genetically modified tumour cells, proteins, peptides or naked DNA. In mice, effective immunity is often elicited and a successful pre-immunization against almost any kind of tumour seems to be feasible as a preventative measure.<sup>56</sup>

The U.S. Food and Drug Administration (FDA) has approved two vaccines, Gardasil® and Cervarix®, that protect against infection by the two types of HPV—types 16 and 18HPV types 16 and/or 18 also cause some vaginal, vulvar, anal, penile, and oropharyngeal cancers. In addition, Gardasil® protects against infection by two additional HPV types, 6 and 11,

which are responsible for about 90 percent of all cases of genital warts in males and females but do not cause cervical cancer. The FDA has also approved a cancer preventive vaccine that protects against HBV infection. The following are links to the NCI site listing the various clinical trials for preventative vaccines against <u>Cervical Cancer</u> and <u>Solid Tumours</u>.

However, therapeutic immunization in the setting of established, chronic disease such as breast cancer, colorectal cancer and the like has been much less successful. Transfer of experimental results with preventative vaccines to the clinical setting and the prospect of curing cancer with therapeutic vaccines are in principle seen as feasible goals. There are many clinical trials but the results achieved so far, however, have been poor; partial responses are rare and complete responses extremely rare. Only in a few patients has the progression of previously growing tumours been halted and prolonged survivals observed.<sup>57</sup>

The FDA has approved immunotherapeutic cancer treatment vaccine for certain men with metastatic prostate cancer called Sipuleucel-T (Provenge<sup>®</sup>). This vaccine is made specially for each man – it is not mass produced. To make it, white blood cells are removed from the patient's blood over a few hours while he is hooked up to a special machine. The cells are then sent to a lab, where they are exposed to a protein from prostate cancer cells called *prostatic acid phosphatase* (PAP). The cells are then sent back to the doctor's office or hospital, where they are given back to the patient by vein (IV). In the body, the cells help other immune system cells to attack the prostate cancer.

Researchers are developing treatment vaccines against many types of cancer and testing them in clinical trials. Cancer treatment vaccines are designed to work by activating B cells and killer T cells and directing them to recognize and act against specific types of cancer. They do this by introducing one or more molecules known as antigens into the body, usually by injection. An antigen is a substance that stimulates a specific immune response. An antigen can be a protein or another type of molecule found on the surface of or inside a cell. The list below shows the types of cancer that are being targeted in active cancer prevention or treatment clinical trials using vaccines. The names are linked to the NCI clinical trials website <u>www.cancer.gov</u>.

#### Active Clinical Trials of Cancer Treatment Vaccines by Type of Cancer:

Brain Tumours; Breast Cancer; Cervical Cancer; Hodgkin Lymphoma; Kidney Cancer; Leukemia; Lung Cancer; Melanoma; Multiple Myeloma; Non-Hodgkin Lymphoma; Pancreatic Cancer; Prostate Cancer; Solid Tumours.

## 8. The Cancer pipeline

More oncology drugs are available in the United States, and the costs for a higher share of these medicines are reimbursed. The evidence-based approach, which includes health technology assessment, adopted by European systems has improved the affordability of drugs in Europe that are considered to be cost-effective. Regulatory approval in Europe does not imply reimbursement, as the evidence threshold for reimbursement is higher than in the United States. In general, regulatory approval for oncology drugs is faster in the United States than in Europe.<sup>58</sup>

We looked at the United States pharmaceutical industry association (PhRMA) website <sup>59</sup> and tallied the total number of therapeutics for all types of cancer. We had found 317 distinct drugs in 2003. The pharmaceutical industry now has 887 distinct cancer drugs in development, which is over 30% of its entire portfolio of new drug candidates according to PhRMA.<sup>60</sup> The industry is putting much research and development resources in cancer therapeutics.

However, the business reality is that since there are fewer cancer patients than there are people with chronic conditions like elevated cholesterol. Moreover, many cancer patients unfortunately do not live very long, therefore the prices of medicines needed to support the industry's oncology sector current size, structure and profits must be substantially higher. Therefore, pressures on health systems in light of the ageing population and increase in prevalence of NCDs means that countries will need to develop robust mechanisms for assessing relative benefit to society. The national cancer control policies (See above, Section 4) provides a useful framework for governments to set priorities.

Figure 6.5.8 shows the total number of medicines for various cancers in the U.S. pipeline as of 2012 (PhRMA). Many medicines are found in more than one cancer category. The majority of medicines are for approximately 10 cancers: leukemias, breast, prostate, colorectal, melanoma, ovarian, pancreatic, kidney, liver, and lymphomas. This cross-sectional 'snapshot' shows that there are more medicines in Phase II trials than Phase I and, as expected, less in Phase III. As one might also expect, the number of medicines in the pipeline generally for some cancers (CNS, nasopharyngeal, orofacial and so on) are quite low. See Annex 6.5.1.



Figure 6.5.8: Number of cancer medicines in each phase of R&D (United States) as a function of type of cancer

Do these myriads of cancer medicines bear any relationship to the size of the cancer market? One could expect that, regardless of whether supported by the public or private sectors, the number of therapeutics are ultimately driven by the size of the cancer market.

However, possibly the opposite is going on – with our increasing learning on mutations that can be targeted, the patient population with specific mutations will be small, much smaller than the formerly developed cytotoxic drugs that were given to all patients with a cancer in one specific organ. This is true also for small cancer types that are increasingly being targeted by the pharmaceutical industry with specific drugs.

We ranked various cancers according to their mortality in the United States (combined male and female, all races: mortality per 100 000 persons average between 2004 and 2009 and age adjusted to the 2000 USA standard population. <sup>61</sup>

Using the PhRMA dataset, above, for a given cancer type we predicted the number of medicines in the pipeline by scaling the total number of medicines in Phase I, II or III to a measure of the aged-adjusted mortality of the that cancer type.<sup>ii</sup> Specifically, our scalar was:

Source: PhRMA

<sup>&</sup>lt;sup>ii</sup> It may well be that, given the chronic and often insidious (i.e. asymptomatic) nature of some cancers, we should use incidence or, better, prevalence as a better estimator of the cancer burden. The incentives for R&D with regard to treating newly diagnosed patients may be very different from those for supporting long-term survivors. We

(adjusted mortality rate of cancer X/total mortality rate of all cancers). Thus, if the total number of medicines for all cancers in Phase I is 100, and the breast cancer mortality scalar is 0.10, we predict there should be 10 medicines for breast cancer (100 \* (0.10)) in Phase I if cancer research and development (R&D) is driven entirely by the "market" (i.e. the integrated death rate of breast cancer averaged over several years).

Figures 6.5.9, 6.5.10, and 6.5.11 show the actual number of cancer medicines in the three phases and the predicted number of cancer medicines based on the total cancer medicines in each phase and the scalar (mortality rate of cancer X/total mortality rate of all cancers). The qualitative prediction, aside from lung cancer, appears quite good for Phase I but then becomes progressively less predictive in Phase III. Remarkably and consistently, there seem to be fewer medicines for lung cancer than one would predict from knowledge of the lung cancer mortality rate.

Figure 6.5.9: Actual number of medicines and predicted number based on mortality rate of different cancers



Source: U.S. Clinical Trials Database at http://www.clinicaltrials.gov

have used mortality data, however, because cancers are often, but not invariably, fatal and it was more readily available than prevalence.

Figure 6.5.10: Actual number of medicines and predicted number based on mortality rate of different cancers



Source: U.S. Clinical Trials Database at http://www.clinicaltrials.gov





Source: U.S. Clinical Trials Database at http://www.clinicaltrials.gov

We repeated this using the United States clinical trials database<sup>62</sup> and would expect similar results.

Figure 6.5.12 shows the relationship between the actual number of cancer trials as of late 2011 (X axis: total cancer trials = 14 058; all phases) in the database for various cancers and

the predicted number of clinical trials (scaled based on the United States mortality rates, as cited above) for these cancers.<sup>iii</sup>



Figure 6.5.12: Actual and predicted number of cancer trials

Source: U.S. Clinical Trials Database at http://www.clinicaltrials.gov

The relatively "poor showing" for lung or bronchus cancers is, unsurprisingly, consistent with the analysis of medicines in the pipeline. We are not able to explain this apparent discrepancy between the high mortality for lung cancer and the relatively few clinical trials and new medicines for this condition. We cannot distinguish between targeted therapies and more generalized chemotherapies in this analysis.

The principal, and rebuttable, presumption of this brief analysis is that mortality rate is a proxy for "market size" and these Figures in particular show a remarkably consistent relationship between the number of medicines (whether targeted or 'personalized" or chemotherapeutic) in clinical trials for a given cancer and mortality rate (e.g. size of the market) of that cancer -a proposition that makes intuitive sense. The glaring exception is lung cancer.

It appears from this crude analysis that the pharmaceutical industry is correctly judging their efforts and that overall drug development for most cancers in the public and private sectors is roughly congruent with the mortality (e.g. "market") for that cancer. Various cancers *might* 

<sup>&</sup>lt;sup>iii</sup> These figures show the data as a continuous function but they are not, as the data are discrete and could also be shown as a series of vertical bar graphs. The connected points are, however, easier to visualize. The clinical trials are **interventional trials only** but may include procedures and devices as well as pharmaceuticals. We made no attempt to exclude trials for devices and procedures.

be underrepresented or overrepresented (melanoma, pancreas) based on "market" but the limits of the data cannot suggest a more nuanced statement.

#### Text Box: Transforming Treatment of Cancer

Gleevec®, also marketed internationally as Glivec and sometimes referred to by its chemical name imatinib, was initially approved for use by the U.S. Food and Drug Administration (FDA) in 2001 for the treatment of chronic myelogenous leukemia (CML), a rare form of cancer that affects certain types of white blood cells. Imatinib acts by specifically inhibiting a receptor tyrosine kinase enzyme that is characteristic of particular cancer cells, rather than non-specifically inhibiting and killing all rapidly dividing cells. By 2011, Gleevec® had been FDA approved to treat ten different cancers. Currently, scientists continue to study the drug's effectiveness not only in various cancers, but also in other diseases, such as stroke (Su *et al.*, 2008).

It has had a phenomenal success rate against CML. In one of the first clinical studies described in the medical literature, it was reported that "[c]omplete hematologic responses were observed in 53 of 54 patients with CML treated with daily dosage of 300 mg or more and typically occurred in the first four weeks of therapy" (Druker *et al.*, 2001). In the case of CML, patients have too many immature white blood cells in their bone marrow and blood, a complete hematologic response occurs when the patient's white blood cell count returns to within normal range. More recently, Druker *et al.* found that, after 60 months of Gleevec® therapy, 98% of patients had shown a complete hematologic response. Also at 60 months, the estimated overall survival rate for patients was 89% with a relapse rate of only about 17% (Druker *et al.*, 2006).

Arguably, Gleevec® has transformed CML treatment. In the past, the only options patients had were either bone marrow transplantation, which had serious side effects and was often fatal (and only about 20% to 25% of patients were eligible for the procedure because of age or other factors), or daily interferon infusions. The latter also had serious side effects and, moreover, was not a cure but merely a way to prolong survival. Thus, before Gleevec®, only 30% of patients with CML survived for even five years after being diagnosed (Pray 2008).

Gleevec® may be an exceptional case, and the same success may not be achieved with other cancers. Significantly, unlike most other cancers, which are caused by complex interacting factors and therefore have many potential therapeutic targets, CML is caused by a single aberrant protein related to a consistent chromosomal translocation. The Gleevec® story is a good example of how knowledge of the biological functioning of a cell can lead to life-saving medical treatment (Pray 2008).

Pray, L. (2008) Gleevec: the breakthrough in cancer treatment. Nature Education 1(1) http://www.nature.com/scitable/topicpage/gleevec-the-breakthrough-in-cancer-treatment-565

Su, E. J., *et al.* Activation of PDGF-CC by tissue plasminogen activator impairs blood-brain barrier integrity during ischemic stroke. *Nature Medicine* **14**, 731–737 (2008) doi:10.1038/nm1787

Druker, B. J., *et al.* Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *New England Journal of Medicine* **344**, 1031–1037 (2001)

## 9. Funding for Cancer R&D

Cancer research has a multi-billion Euro global network covering most domains of science and including all manner of research funders from industry to government and philanthropic funders.<sup>63</sup> Europe and the USA account for the majority of global cancer funding with a combined spend of over  $\in$ 8 billion per annum, compared to circa  $\in$ 3 billion for the rest of the world. Despite different absolute spends Australia, Canada, and Japan have broadly similar per capita spending (this similarity remains regardless of comparative denominator (e.g. GDP) at  $\in$ 7.93,  $\in$ 8.27 and  $\in$ 7.88, respectively.<sup>63</sup> In comparison, Europe as a whole only spends  $\in$ 5.79, however, when one views European cancer research spend as only those original EU15 Member States then this figure dramatically rises to  $\in$ 8.20. At  $\in$ 17.98 per capita, USA funding is one of the highest in the world along with the UK, which spends some  $\in$ 18.5 per capita ( $\in$ 13.18 of this comes directly from funding organizations and the remainder flows through infrastructure funding to the university and healthcare systems).<sup>63</sup>

## 9.1 Europe

The next Framework Programme for Research and Innovation (2014 –2020) is Horizon2020. It is designed to address the major societal that need translational action, including "Health, demographic change, and well-being" theme. With a proposed budget of €80.8 billion over seven years, it will unite all EU funding in research and innovation in a single programme and support every stage of the innovation ecosystem "from research to retail".

## 9.1.1 P 7: Final work programme: Cancer

See reference 64 and 65

The Seventh Framework Programme for Research and Technological Development (FP7, 2007–2013) has dedicated over €1.1 billion to cancer research, using a variety of funding mechanisms including collaborative research, frontier research, mobility programmes, public-private partnerships, and coordination of national research activities to strengthen the innovative translation of research discoveries to clinical application. With regard to cancers, research is supposed to focus on identification and validation of drug targets; prevention, early diagnosis, prognosis and treatment biomarkers; as well as on assessment of various preventive, diagnostic, prognostic, and therapeutic interventions. We note that the clinical trials to be supported will have to be registered in a publicly accessible clinical trials registry and their results published in peer-reviewed journals. Significantly, "patient advocacy groups which can contribute to the quality, feasibility and impact of clinical trials, may be involved where appropriate." For this subject, the requested EU contribution per project shall not exceed €6 million.<sup>65</sup>

The European Commission is also partnering with the European pharmaceutical industry to fund research via the Innovative Medicines Initiative (IMI), through which close to  $\in$ 80 million (of which  $\in$ 38 million is from FP7) have been devoted to cancer therapeutics research.

For example, in the Sixth and Seventh Framework Programmes (FP6, FP7), 22 projects focused on child and adolescent cancers and were supported with a total budget of close to €150 million, €75 million of which was in FP7. Several projects focused on specific cancers,

for example Ewing's sarcoma, leukaemia, and lymphoma. Others aimed to reduce the longterm side effects of cancer therapy in survivors. Many research groups focused on environmental factors in childhood that may lead to increased cancer risk. Others work on improving cancer therapies for children and on developing drugs for paediatric use. Appendix 6.5.1

The priority setting for the Health Work Programme (2013) –the last annual call for proposals of the Cooperation Programme in FP7– is intended to "respond to the major health-related socio-economic and societal challenges" in view of the Europe 2020 Strategy. Two topics focused on clinical trials in cancer research and one on cancer immune system calling for projects focusing on cell, antibody, or molecule-based immunotherapy and therapeutic cancer vaccines. In all three the requested EU contribution per project shall not exceed  $\epsilon$ 6 million. Regarding the clinical trials topics, the first one called for "trials to combat or prevent metastases in patients with solid cancer" and the second one for "supportive and palliative care clinical trials and observational studies". We note that the clinical trials to be supported will have to be registered in a publicly accessible clinical trials registry and their results published in peer-reviewed journals. Significantly, "patient advocacy groups which can contribute to the quality, feasibility and impact of clinical trials, may be involved where appropriate".

A third topic is supportive and palliative care clinical trials and observational studies. As above, the clinical trials to be supported need to be registered in a publicly accessible clinical trials and patient advocacy groups can contribute to the quality, feasibility and impact of clinical trials, "may be involved where appropriate." <sup>62</sup> The requested EU contribution per project is similar to the above.

Palliative and supportive care was proposed in order to complement a growing portfolio of projects focusing on quality-of-life research funded by the 7th Framework Programme of the EC, such as:

a) *PanCareSurFup: PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies,* a consortium of 16 European institutions, , to carry out research studies into late effects of treatment for cancer, to establish guidelines for follow-up, and to disseminate the results and provide training and workshops for stakeholders. <u>http://www.pancaresurfup.eu/</u>.

b) *EURO IMPACT*, a project developing an educational and research training framework, aimed at monitoring and improving the quality of palliative care. <u>http://www.euro-impact.eu/.</u>

c) *PRISMA: Reflecting the Positive diveRsities of European prlorities for reSearch and Measurement in end of life cAre,* a project that focused on mapping differences in end of life care and culture, comparing cancer end of life care research across, Europe and beyond, and developing measurement and quality indicators and online resources to support end-of life care and research.

d) *OPCARE9: Optimising clinical care in the last days of life,* provided comprehensive 'state of the art' in the field of care in the last days of life, developed new research protocols a list of resources and quality indicators for measuring care in the last days of life <u>http://www.liv.ac.uk/opcare9/index.htm</u>.

Notwithstanding, funding for cancer research in Europe is split almost 50:50 between philanthropic and governmental sources. In Europe the majority of the spending is concentrated (>90%) in the original 15 Member States, a situation that remains unchanged since the original Report. Contributing some  $\in$ 10 million to European spending was also trans-European research funders such as the EORTC. <sup>66</sup>

According to the EC, annual total EU cancer research investments in 2012were as follows:  $\in 2$  billion in governments and charity;  $\in 1.4$  billion in national health systems and universities; and  $\in 1.8$  billion in industry. See Appendix 6.5.4.

Estimates of cancer research spend by the major pharmaceutical companies can underestimate total global spending by omitting small and medium enterprises (SMEs) and biotech firms and current spending on pivotal Phase III clinical trials. However, an estimated gross figures of just over €3 billion per year suggests that the private sector is responsible for around a quarter of global investment in cancer research.<sup>66</sup>

To put the industry expenditure into perspective, in 2004 global pharmaceutical research and development (R&D) expenditures reached €41 billion (about US\$ 56 billion) with around 7% of this flowing into cancer research.<sup>63</sup> Indeed Europe attracts some 45.9% of total pharmaceutical R&D expenditure (CMR International, 2006b).<sup>66</sup>

Despite an average annual expenditure of approximately  $\in$ 150 million since FP6, EU efforts represent only 3.5% of the total expenditure of cancer research in the EU's 27 Member States , showing that the bulk of research in this field is funded at the national level. See Appendix 6.5.4.<sup>64</sup> The European cancer research arena is characterized by a significant degree of fragmentation and diversity (e.g. multiplicity of support mechanisms, funding bodies, barriers between disciplines, suboptimal critical mass). The necessity to better coordinate cancer research throughout Europe, which requires a strong commitment from the scientific community, is now largely recognized.

In a study completed in 2006, the USA outspent Europe three to five times as a percentage of GDP or per capita.<sup>67</sup> However, the regions have radically different systems and processes for disbursing funds. Europe (in particular the original EU15 Member States) channels a substantial amount of funding for cancer research through its university and/or healthcare systems. This accounts for between 21% and 44% of overall spending depending on the Member State. In comparison, public cancer research funding in the USA is almost entirely through federal and other philanthropic organizations. Indeed despite the majority of public funding in cancer research being concentrated in a few major funding organizations across Europe (80% funds come from just 18 funders) the overall complexity of investment streams, particularly through so called infrastructure funds into healthcare systems and universities makes the development of cancer funding policies difficult.<sup>66</sup>

## 9.1.2 Horizon 2020: The importance of palliative care

Regarding Horizon 2020, exact details of cancer funding is still in process, and first calls are not yet published. For Horizon 2020 one important area is studies around palliative care. There are some examples related to palliative care research:

a. PanCareSureFup: *PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies* is a consortium of 16 European institutions, funded by the

7<sup>th</sup> Framework Programme of the EC, to carry out research studies into late effects of treatment for cancer, to establish guidelines for follow-up, and to disseminate the results and provide training and workshops for stakeholders. <u>http://www.pancaresurfup.eu/</u>

- b. IMPACT: EURO IMPACT is developing an educational and research training framework, aimed at monitoring and improving the quality of palliative care. <u>http://www.euro-impact.eu/</u>
- c. PRISM: coordinating research on end-of life care
- d. OPCARE: Optimising clinical care in the last days of life

www.ecancermedicalscience.3 com ecancer 2011, 5:210

Estimates have been made of the financial resources being applied to paediatric oncology research worldwide in 2008. The estimate was about US\$ 1.23 billion, of which an estimated 53% was from public or federal sources (US\$ 656 million), 27% from private, non-profit sources (US\$ 328 million) and 20% (US\$ 245 million) from industry. The low level of funding in many countries coupled to the very small contribution by the private sector is a major concern.

## 9.2 The United States

One of the unique features of the U.S. National Cancer Act in 1971 was the creation of dedicated cancer research funding (National Cancer Institute) with bypass budget authority directly to the President without need for NIH or other authorisation. USA funding of cancer research has taken a radically different direction from Europe. The funding for cancer research has seen the budget allocation grow dramatically since 2000.

While the NCI has remained the core source of cancer research funding in the USA over the years many governmental and philanthropic funders have also joined. In comparison to Europe, where the contribution of governmental and philanthropic funding is almost equal, governmental funding in the USA (mostly through the NCI) accounts for over 90% of the total spending with a total funded portfolio of research of about \$2.91 billion (about €2.21 billion) in fiscal year 2011. About 80% of the total NCI accounted-for research funding for 2011 is relegated to eleven cancers (see Figure 6.5.13).<sup>68</sup>



Figure 6.5.13: Cumulative percentage of total NCI funding in fiscal year 2011

Using the NCI accounted-for research funding <sup>36</sup>, we did a similar unvariate scalar analysis as in the Figures above to "predict' the level of funding for various cancers if the funding was based on the mortality rate in the United States. Results are shown in Figure 6.5.14. Based on its large mortality, lung cancer seems under-represented in terms of funding and thus, clinical trials, and by extension, medicines in the pipeline.

Source: NCI Funded Research Portfolio. <u>http://fundedresearch.cancer.gov/search/funded?action=full&fy=PUB2011&type=site</u>





In terms of per capita spend or as a proportion of GDP, the USA enjoys one of the highest levels of funding in the world, only bettered by the UK which has seen substantial levels of growth in funding (faster even than the USA). However, the gap between allocation and spending is growing representing a real downward pressure on available funds due to the increased cost per unit of research. <sup>69</sup>

The impact of regulatory policy on research funding and productivity remains a critical issue for all countries. As Europe has recently discovered, changes to regulatory policy can have a dramatic effect on the cost of research. <sup>70</sup> Over the last decade the increasing regulation across all domains (e.g. clinical trials, healthcare data, human tissue) has led to an increase in the unit cost of research.

## 10. Ways Forward from a Public Health Viewpoint with Regard to Public Funding

## 10.1 Gaps Between Current Research and Potential Research Issues which Could Make a Difference.

The therapeutic pipeline is dynamic and significant private sector funding is being put into the cancer R&D system. There remain gaps between current and potential issues that could make a difference.

- Basic knowledge of cancer etiology and potential links with other NCDs and or infectious diseases such as HIV-AIDs.
- Basic knowledge of cancer and resistance to therapy. There are still many unmet medical needs in cancer treatment and these should be well known to those with the relevant expertise. Single platform pathology processes for improved efficiency in diagnosis
- Getting promising drug candidates for rare cancers "off of the shelf"
  - Notwithstanding the potential significance of pharmacogenomics, large pharmaceutical firms still face substantial pressures to produce medicines targeted at large patient populations. This business reality often deters investments in treatments for rare, life-threatening diseases. In addition, this business strategy often allows drug candidates to remain untested for these rare conditions.
- Point-of-care diagnostics

Point-of-care testing allows patient diagnoses in the doctor's office, an ambulance, or even at home or in the field. With the development of miniaturized devices and wireless communication, the way in which doctors care for patients will change dramatically and the role patients take in their own health care will increase. Lowcost diagnostic imaging devices can be used at the point-of-patient care for disadvantaged and under-served populations in the United States as well as in the developing world. The development of low-cost imaging devices could make affordable diagnostic imaging more widely available, particularly in remote or rural communities and small hospitals that do not have ready access to these technologies.

- Prevention and risk factors:
  - For example, *H. pylori* infection is a well-established risk factor for stomach cancer, and yet optimal *H. pylori* eradication and its impact on stomach cancer incidence remain to be defined. Although HBV is associated with a majority of liver cancer cases worldwide, there are 350 million chronic HBV carriers whom HBV vaccination cannot help and in many HBV-endemic areas, dietary staples are contaminated with aflatoxins, a potent human liver carcinogen.
  - Similarly, research into cancer risk in individuals living with HIV is needed, particularly in relation to their susceptibility to other cancer-associated chronic infections.
  - As breast cancer becomes the most common cancer in women and prostate cancer incidence likewise continues to increase in men, research into the most effective early detection approaches is vital, even in many low-income countries.

## 11. Conclusion: Cancer medicines for Europe and the World?

This Background paper ends with a question and a challenge. Since the 2004 Priority Medicines Report, there has been an unprecedented acceleration of research and development into cancer biology and genetics, cancer therapeutics, biomarkers, and diagnostics, some of the key elements being only briefly mentioned in this Background chapter. Substantial inequalities exist in cancer survival rates across countries (see Section 3.1.3). We can prevent new cancers by reducing risk factors, but strategies are needed to close the gap between developed and developing countries in cancer survival.<sup>71</sup>

In resource-constrained countries without specialized services, cancer could be partially prevented and treated using lessons learned from the public health battle against HIV/AIDS, such as using primary and secondary caregivers to screen and continue treatment, use of generic drugs, and application of regional and global mechanisms for financing and procurement. <sup>68</sup> In those countries with national health insurance, cancer treatment can be included with an emphasis on a benefits package focusing on the least wealthy. Expensive immune and targeted therapies should not only be for those in upper income countries, although we should not be so naïve as to think that these can be made accessible without reducing costs, increasing access to health services, and strengthening health systems in low-and middle-income countries.

The United Nations took the issue of noncommunicable diseases (NCDs) to its high level meeting on 19 September 2011 because of the burden of the disease and high economic cost of NCDs. There was a consensus to continue on working for targets and indicators to fight against NCDs. The recent formal meeting of Member States during 5-7 November 2012 concluded the work on the comprehensive global monitoring framework, including indicators, and set voluntary global targets for the prevention and control of noncommunicable diseases.<sup>69</sup> Nine voluntary global targets and 25 indicators were agreed to have a major progression by 2025 in the prevention and control of noncommunicable diseases. New opportunities are expected from this high level political agenda.<sup>72</sup>

For the EC, in the period 2014 to 2020, one challenge will be to understand the inequalities between EU countries in levels of cancer control and care, including screening and follow-up for breast, cervical and colorectal cancer. Identification and promotion of good practice in prevention, diagnosis, treatment and care of all cancer types, including paediatric cancers, across the EU will be important. In addition, collaborations between EU countries can provide the "economies of scale" needed to manage this condition more effectively across all parts of the health care system.

## References

<sup>1</sup> Doll R and Peto R. The causes of cancer. *Journal of the National Cancer Institute*, 1981, 66: 1191–308.

<sup>&</sup>lt;sup>2</sup> National Cancer Control Programmes: Policies and management guidelines. Geneva, World Health Organization, 1995.

- <sup>3</sup> Sobin et al. TNM classification of malignant tumours, 7<sup>th</sup> edition 2009 John Wiley and Sons
- <sup>4</sup> Textbook of Therapeutics: Drug and Disease Management Seventh Edition edited by Eric T. Herfindal and Dick R. Gourley
- <sup>5</sup>Wiley Textbook of Uncommon Cancer, 2nd Edition D. Raghavan (Editor), M. L. Brecher (Editor), D. H. Johnson (Editor), N. J. Meropol (Editor), P. L. Moots (Editor), J. T. Thigpen (Editor) ISBN: 0-471-92921-2, 776 pages
- <sup>6</sup> E. van der Schueren,, K. Kesteloot, I. Cleemput, Federation of European Cancer Societies. Full Report. 2000. Economic evaluation in cancer care: questions and answers on how to alleviate conflicts between rising needs and expectations and tightening budgets European Journal of Cancer 36 : 13-36.
- <sup>7</sup> Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. 2002. Eur J Cancer 38:99-166.
- <sup>8</sup> Malvezzi; and Bosetti C, Bertuccio P, Levi F et al. The decline in breast cancer mortality in Europe: an update (to 2009). Breast 2012; 21: 77–82.
- <sup>9</sup> Senior K. 2009. Disparities in cancer survival and cancer care across Europe , Lancet Oncology 10 (3): 214–215 at <u>http://dx.doi.org.ezproxy.bu.edu/10.1016/S1470-2045(09)70058-0</u>]; For the EUROCARE-4 report see Eur J Cancer 2009; DOI:10.1016/j.ejca.2008.11.029
- <sup>10</sup> Bosetti C, Bertuccio P, Negri E, La Vecchia C, Zeegers MP, Boffetta P. Pancreatic cancer: overview of descriptive epidemiology. Mol Carcinog 51(1):3-13 (2012), PMID 22162227
- <sup>11</sup> Pelucchi C, Levi F, La Vecchia C. The rise and fall in menopausal hormone therapy and breast cancer incidence. Breast 2010; 19: 198–201.
- <sup>12</sup> Autier P, Boniol M, Gavin A, Vatten LJ. Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database. BMJ, 2011, 343: d4411.
- <sup>13</sup> Gatta G et al., Rare cancers are not so rare: The rare cancer burden in Europe, Eur J Cancer (2011), doi:10.1016/j.ejca.2011.08.008
- <sup>14</sup> Steliorova-Foucher E et al. 2004. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. The Lancet 364 (9451): 2097–2105
- <sup>15</sup> Ribeiro RC, Steliarova-Foucher E, Magrath I, Lemerle J, Eden T, Forget C, Mortara I, Tabah-Fisch I, Divino JJ, Miklavec T, Howard SC, Cavalli F: Baseline status of paediatric oncology care in ten lowincome or mid-income countries receiving My Child Matters support: a descriptive study. Lancet Oncol 9,721–729 (2008);
- <sup>16</sup> Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM: GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr;
- <sup>17</sup> Gatta G, Capocaccia R, Stiller C, Kaatsch P, Berrino F, Terenziani M. Childhood cancer survival trends in Europe: a EUROCARE Working Group study. J Clin Oncol. 2005; 23: 3742–3751.

- <sup>18</sup> Howard SC, Metzger ML, Wilimas J. et al. 2008. Childhood Cancer Epidemiology in low-income countries. Cancer 112: 461–472;
- <sup>19</sup> European Cancer Registry-based study 4 (EUROCARE-4) on survival and care of cancer at , <u>http://www.eurocare.it/Results/tabid/79/Default.aspx#eu4dB</u>
- <sup>20</sup> European Cancer Registry-based study 4 (EUROCARE-4) on survival and care of cancer at , http://www.eurocare.it/Results/tabid/79/Default.aspx#eu4dB
- <sup>21</sup> Berrino F, Verdecchia A, Lutz JM et al. 2009. Comparative cancer survival information in Europe. European J. Cancer 45 (6): 901 –908
- <sup>22</sup> Coleman MP, Quaresma M, Berrino F. et al. 2008. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol. 9(8): 730–756.
- <sup>23</sup> The GLOBOCAN Project, estimated cancer incidence, prevalence, mortality and DALYs Worldwide in 2008, World Health Organization at <u>http://globocan.iarc.fr/</u>
- <sup>24</sup> Bray F, Ren JS, Masuyer E, Ferlay J (2012) Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 10.1002/ijc.27711
- <sup>25</sup> 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.
- <sup>26</sup> BMJ Clinical Evidence, Lung Cancer, November 2010 at http://clinicalevidence.bmj.com/x/systematic-review/1504/overview.html
- <sup>27</sup> European Age-Standardised rates calculated by the Cancer Research UK Statistical Information Team, 2011, using data from GLOBOCAN 2008 v1.2, IARC, version 1.2.<u>http://globocan.iarc.fr</u>
- <sup>28</sup> BMJ Clinical Evidence, Non-metastatic Breast Cancer at <u>http://clinicalevidence.bmj.com.ezproxy.bu.edu/x/systematic-review/0102/overview.html</u>
- <sup>29</sup> Wilt, TJ. BMJ Clinical Review, Clinically localised prostate cancer BMJ 2006;333:1102 at http://dx.doi.org/10.1136/bmj.39022.423588.DE (Published 23 November 2006)
- <sup>30</sup> Haggar FA, Boushey RP. 2009. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg. 22: 191–197.
- <sup>31</sup> Bowel cancer incidence statistics : Cancer Research UK. Available at <u>http://www.cancerresearchuk.org/cancer-info/cancerstats/types/bowel/incidence/</u>
- <sup>32</sup> World Health Assembly Resolution WHA 61.14. Resolution of the 61<sup>st</sup> World Health Assembly: Prevention and Control of Noncommunicable Diseases: Implementation of the Global Strategy at <u>http://www.who.int/nmh/Actionplan-PC-NCD-2008.pdf</u>
- <sup>33</sup>Nadal E., Olavarria E. 2004. Imatinib mesylate (Gleevec/Glivec) a molecular-targeted therapoy for chronic myeloid leukemia and other malignancies. Int. J. Clin. Pract. 58: 511-516
- <sup>34</sup> World Health Organization, Global Health Observatory at <u>http://apps.who.int/gho/data/#</u>).

- <sup>35</sup> COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS on Action Against Cancer: European Partnership, at http://ec.europa.eu/health/ph\_information/dissemination/diseases/docs/com\_2009\_291.en.pdf.
- <sup>36</sup> EPAAC National Cancer Plans Available at <u>http://www.epaac.eu/national-cancer-plans</u>.
- <sup>37</sup> Analysis of National Cancer Control Programmes in Europe. Imperial Collage London Business School. Available at <u>https://spiral.imperial.ac.uk/bitstream/10044/1/4204/1/Cancer%20Control%20vf2.pdf</u>.
- <sup>38</sup> Wild CP. 2012. The Role of Cancer Research in Noncommunicable Disease Control J. Nat. Cancer Inst. 104(14): 1051-1058 first published online July 10, 2012 doi:10.1093/jnci/djs262
- <sup>39</sup> de Martel C, Ferlay J, Franceschi S, et al. 2012. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *The Lancet Oncology*. 13:607–615.
- <sup>40</sup> Cogliano VJ, Baan R, Straif K, et al. 2011. Preventable exposures associated with human cancers. J Natl Cancer Inst. 103:1827–1839.
- <sup>41</sup> Paediatric Palliative Care in Europe Expands JNCI J Natl Cancer Inst (2012) 104(1): 10-11 first published online December 14, 2011 doi:10.1093/jnci/djr537; National Institutes of Health State-ofthe-Science Conference Statement: Symptom Management in Cancer: Pain, Depression, and Fatigue, July 15–17, 2002 J Natl Cancer Inst (2003) 95(15): 1110-1117 doi:10.1093/jnci/djg014; Abe K. 2012. Systematic. Review of Rehabilitation Intervention in Palliative Care for Cancer Patients. J. Palliative Care Med 2:131.
- <sup>42</sup> ERSPC Press Release, March 2102. "Latest findings confirm increased mortality benefit from prostate cancer testing" at http://www.erspc-media.org/PSA screening trials; See also Schröder FH, Hugosson J, Roobol MJ et al. 2009. Screening and Prostate-Cancer Mortality in a Randomized European Study N Engl J Med 360:1320-1328 DOI: 10.1056/NEJMoa0810084 at http://www.nejm.org/doi/full/10.1056/NEJMoa0810084.
- <sup>43</sup> Andriole GL, Crawford ED, Grubb III RL. 2009. Mortality Results from a Randomized Prostate-Cancer Screening Trial N Engl J Med. 360:1310-9 at <u>http://www.nejm.org/doi/pdf/10.1056/NEJMoa0810696</u>.
- <sup>44</sup> Andriole GL, Bostwick DG, Brawley OW et al. 2010. Effect of Dutasteride on the Risk of Prostate Cancer. N Engl J Med 362:1192-202.
- <sup>45</sup> Fukumura D, Jain R.K. Imaging angiogenesis and the microenvironment APMIS, 116 (2008), pp. 695–715
- <sup>46</sup> ESMO Press Release, 28 September 2012 at http://www.esmo.org/no\_cache/viewnews.html?tx\_ttnews[tt\_news]=1617&tx\_ttnews[backPid]=585&cHash=8afba3ebb0ESMO 2012 Press Release: The true costs of cancer in Europe revealed.
- <sup>47</sup> International Agency for Research on Cancer, World Health Organization, World Cancer Report 2008 at <u>http://www.iarc.fr/en/publications/pdfs-online/wcr/2008/</u>
- <sup>48</sup> Global Cancer Burden Infographics at <u>http://www.worldcancerday.org/infographics</u>

- <sup>49</sup> The Global Economic Cost of Cancer, Livestrong Foundation and American Cancer Institute, 2008, at <u>http://www.cancer.org/acs/groups/content/@internationalaffairs/documents/document/acspc-026203.pdf</u>.
- <sup>50</sup> Mariotto AB, Yabroff KR, Shao Y et al. 2011. Projections of the Cost of Cancer Care in the United States: 2010–2020 J. Nat. Cancer Institute doi: 10.1093/jnci/djq495. First published online: January 12, 2011 at http://jnci.oxfordjournals.org.ezproxy.bu.edu/content/early/2011/01/12/jnci.djq495.full
- <sup>51</sup> FDA Draft Guidance, In Vitro Companion Diagnostic Devices at <u>http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocumen</u> <u>ts/UCM262327.pdf</u>
- <sup>52</sup> Risk benefit European Medicine Agency (EMEA) CHMP. Reflection paper on benefit-risk assessment in the context of the evaluation of marketing authorization applications of medicinal products for human use. Available from: <u>http://www.emea.europa.eu/pdfs/human/brmethods/1540407en.pdf</u>
- <sup>53</sup> Nature Biotechnology Editorial "Failure to Launch", <u>http://www.nature.com/nbt/journal/v31/n1/full/nbt.2482.html</u>
- <sup>54</sup> Morgan, R. A. *et al.* Cancer regression in patients after transfer of genetically engineered lymphocytes. Science 314, 126–129 (2006).
- <sup>55</sup> Weiner LM, Surana R, Wang S. 2010. Monoclonal antibodies: versatile platforms for cancer immunotherapy Nature Reviews Immunology 10: 317-327, doi:10.1038/nri2744
- <sup>56</sup> Emens LA. Cancer vaccines: on the threshold of success. Expert Opin Emerg Drugs. 2008 June; 13(2): 295–308.
- <sup>57</sup> Cecco S, Muraro E, Giacomin E, Martorelli D, Lazzarini R, Baldo P, Dolcetti R. Cancer vaccines in phase II/III clinical trials: state of the art and future perspectives. Curr Cancer Drug Targets. 2011 Jan;11(1):85-102.
- <sup>58</sup> Tufts Center for the Study of Drug Development U.S. offers patients faster, greater access to cancer drugs than Europe Volume 14(4) July-August 2012 at <u>http://csdd.tufts.edu/files/uploads/julaug\_2012\_ir\_summary.pdf</u>
- <sup>59</sup> Pharmaceutical Manufacturers Association at http://www.phrma.org
- <sup>60</sup> Pharmaceutical Manufacturers Association. Medicines in Development/Cancer 2012 PhRMA
- <sup>61</sup> National Cancer Institute SEER database at <u>http://seer.cancer.gov/faststats/selections.php?series=data</u>
- 62 U.S. Clinical Trials Database at http://www.clinicaltrials.gov
- <sup>63</sup> Eckhouse S, Lewison G, Sullivan G. Trends in the global funding and activity of cancer research . Molecular Oncology (2008): 20-32
- <sup>64</sup> Van de Loo J-W, Trzaska D, Berkouk K. et al. 2012. Emphasising the European Union's Commitment to Cancer Research: A Helicopter View of the Seventh Framework Programme for Research and Technological Development, The Oncologist,

- <sup>65</sup> European Commission C(2012) 4536 of 09 July 2012) at <u>ftp://ftp.cordis.europa.eu/pub/fp7/health/docs/fp7-health-wp-2013\_en.pdf</u>
- <sup>66</sup> Jungbluth, S., et al., 2007. Europe combating cancer: the EuropeanUnion's commitment to cancer research in the 6th FrameworkProgramme. Molecular Oncology 1, 14–18.
- <sup>67</sup> Eckhouse, S., Sullivan, R., 2006. ASurvey of Public Funding of Cancer Research in the European Union. PLoS Medicine 3 (7).
- <sup>68</sup> NCI Funded Research Portfolio. Available at <u>http://fundedresearch.cancer.gov/search/funded?action=full&fy=PUB2011&type=site</u>).
- <sup>69</sup> Niederhuber, J.E., 2007. A look inside the National Cancer Institute budget process: implications for 2007 and beyond. CancerResearch 67, 3.
- <sup>70</sup> Hartmann, M., Hartmann-Vareillas, F., 2006. The clinical trials Directive: how is it affecting Europe's non-commercial research? PLoS Clinical Trials 1 (2), e13, doi:10.1371/ journal.pctr.0010013.
- <sup>71</sup> Farmer P, Frenk J, Knaul FM. Et al. 2010. Expansion of cancer care and control in countries of low and middle income: a call to action. Lancet 376 (9747): 1186-1193 doi: 10.1016/S0140-6736(10)61152-X. Epub 2010 Aug 13. See also Closing the Cancer Divide, Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries, 2011 2<sup>nd</sup> edition at <u>http://ghsm.hms.harvard.edu/uploads/pdf/ccd\_report\_111027.pdf</u>.
- <sup>72</sup> WHO Formal meeting of Member States to conclude the work on the comprehensive global monitoring framework, including indicators, and a set of voluntary global targets for the prevention and control of noncommunicable diseases Geneva, 5–7 November 2012, A/NCD/2, 21 November 2012 at <u>http://apps.who.int/gb/ncds/</u>

## Annex

Annex 6.5.1: Number of cancer medicines in each phase of R&D (United States) as a function of type of cancer

	Phase I	Phase II	Phase III	SUM
Leukemias	73	65	16	154
Breast	45	71	15	131
Prostate	38	56	13	107
Colorectal	31	43	5	79
Melanoma	30	34	11	75
Ovarian	18	39	10	67
Pancreatic	24	30	8	62
Kidney	16	22	10	48
Liver	17	20	7	44
Lymphomas	36	4	0	40
Small cell lung	9	16	1	26
Bladder cancer	6	13	3	22
Gastric, stomach	4	12	5	21
Brain	5	7	1	13
Thyroid	1	7	2	10
Fallopian tube	1	4	3	8
Cervical	1	4	1	6
Lung cancer	1	2	1	4
Esophagus	3	1	0	4
Adenocarcinoma	2	1	0	3
CNS cancer	3	0	0	3
Nasopharyngeal	0	1	0	1
Orofacial	0	1	0	1
Uterine	0	1	0	1
Vulvovaginal	0	0	1	1
Total	364	454	113	931

Source: PhRMA



## Appendices

Appendix 6.5.1	Childhood and adolescent cancer research : EU funding (2002-2009), (2009) Office for Official Publications of the European Communities
Appendix 6.5.2	HPV vaccines; Frequently Asked Questions June 2012. GAVI Alliance
Appendix 6.5.3	Cancer Medicine Prices in low- and middle- income countries. Management Science for Health.
Appendix 6.5.4	Power Point Slides from European Commission