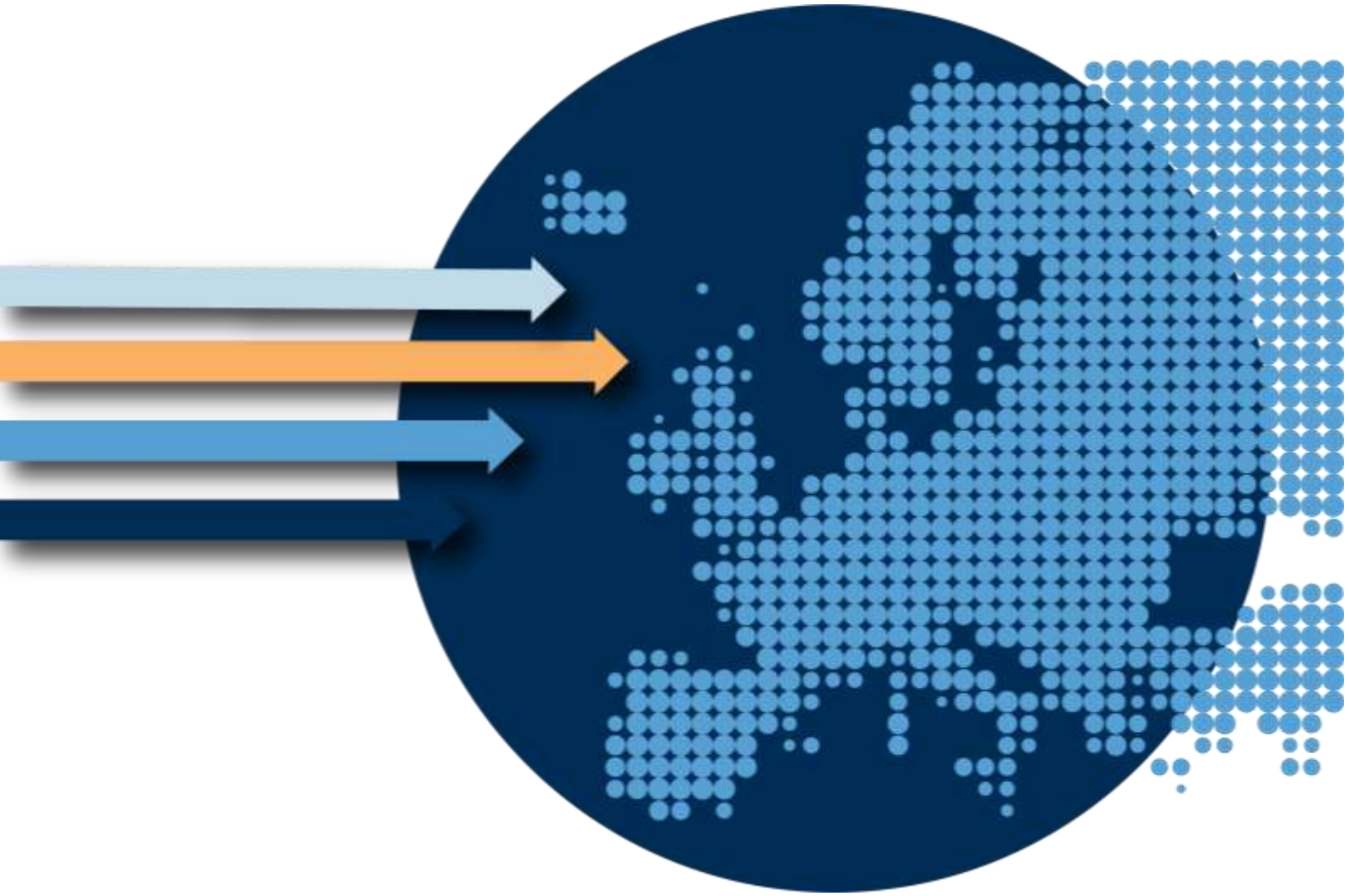
COMPARATOR REPORT ON CANCER IN EUROPE 2019

–DISEASE BURDEN, COSTS AND ACCESS TO MEDICINES



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2019:7

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Foreword

Cancer care remains one of the most intensely discussed health policy issues in Europe. Demographic factors such as an ageing population, in part driven by advancements in other medical fields, have led to an increased disease burden caused by cancer, both to patients and to the health care system as a whole. At the same time, there has been significant scientific advancements made, in some cases transforming cancer from a fatal to a chronic disease which in turn introduces new challenges that need to be addressed.

In this report, which is an update of several reports published between 2005 and 2016 on differences between European countries in terms of disease burden, costs, and patient access to new cancer medicines, we try to provide an up-to-date and comprehensive description of the burden of cancer across Europe alongside data on differences in access to novel therapies in the region. We also discuss some of the medical trends going forward and highlight some policy issues that will be important to address. We hope that the report can serve as a reference to inform key policy discussions between the different stakeholders in this field.

Anna Gustafsson, Fredrik Moen, and Ulla Wilking provided excellent research support for this report. Jyoti Patel at IQVIA assisted us in extracting and interpreting the data on sales of cancer medicines. We would like to thank Mihai Rotaru at EFPIA for help in organizing and managing the project and the members of the EFPIA Oncology Platform for discussions and comments on the report. We would also like to thank EFPIA for funding the project through a grant to IHE. The responsibility for the analysis and conclusions in this report lies solely with the authors.

Lund, December 2019
Peter Lindgren
Managing Director, IHE

Executive summary

More than one of every four deaths (26%) in Europe is due to cancer. This makes cancer the second leading cause of death behind cardiovascular diseases. Cancer is also the disease group that causes the second greatest disease burden (20% measured in DALYs) after cardiovascular diseases. In several wealthier countries (Denmark, France, the Netherlands, and the UK), cancer has already become the leading cause of death and disease burden. This development is also foreseeable in other European countries.

The number of newly diagnosed cancer cases (incidence) is growing. Cancer incidence increased by around 50 percent from 2.1 million to 3.1 million cases between 1995 and 2018 in Europe. This development is driven by several factors – some of which can be addressed by policy measures. A strong driver of the increase in incidence is population aging, as cancer is an aging-associated disease. Projections show that the forecasted development in population aging (and minor overall population growth) will add 775,000 cases in incidence until 2040 compared to the situation in 2018 in the absence of further improvements in cancer care and prevention.

Around 40–45 percent of all cancer cases are estimated to be preventable. The increasing trend in cancer incidence needs to be met by a stronger focus on primary prevention and screening. All European countries still have great opportunities for improving policies in these areas. Tobacco control is the single most important measure. The Tobacco Products Directive (2014/40/EU) has been a major step in the right direction at the European level, but more needs to be done on the national level. HPV vaccination programs for girls and boys are cost effective but not fully implemented in many countries. A cost-effective use of resources for organized screening programs requires spending on colorectal, cervical, and breast cancer (in this order of priority), whereas the cost-effectiveness of prostate and lung cancer screening is currently not well established.

The total number of deaths from cancer (mortality) is still increasing; between 1995 and 2018 there was a 20 percent increase from 1.2 million to 1.4 million deaths in Europe. However, the increase has been slowing and deaths have actually been decreasing in age groups below 65 years. In the absence of population growth and population aging, cancer mortality would have decreased in almost all countries between 1995 and 2018. Continuous increases in 5-year survival rates for the most common cancer types in all countries are a reflection of this development. Increasing survival explains why mortality increased much less than incidence (20% vs. 50%) between 1995 and 2018. There is a clear pattern of wealthier countries to record higher survival rates than poorer countries.

Cancer research has been fundamental to achieving improvements in survival, by leading to advances in screening, diagnostics, and medical treatment. Research has increased our knowledge about the

human cell and its molecular mechanisms. Medical oncology entered a new phase in the 21st century with novel medicines targeting countless newly-identified molecular targets. Progress in diagnostics has made it easier to predict if a patient is likely to respond to a certain treatment and paved the way for personalized medicine. The latest major development is activating the body's own immune system to attack the tumor. Immunotherapy has become a cornerstone in multiple solid malignancies during the last five years, and over 2,000 clinical trials are currently ongoing. Current data indicate that in some indications a substantial subgroup of patients is likely cured from metastatic disease.

Cancer research has resulted in a distinct increase in the number of approved cancer medicines and indications in recent years. Around ten new medicines were approved by the EMA every year in 2012–2018, compared to around four new medicines in 2001–2011. A considerable share of new medicines has an orphan designation, indicating small patient populations. During the last decade, R&D investment in cancer research by the pharmaceutical industry has grown much quicker than investment by public and private non-profit sources and by far outnumbers the total investment made by the latter sources. Cancer research in Europe might receive greater attention and funding from public sources in the coming years by the new European Commission.

Innovations in cancer treatment can only produce benefits if they reach patients in clinical practice, which requires increases in health care spending. The health expenditure spent on cancer care (direct costs of cancer) doubled from €52 billion to €103 billion in Europe between 1995 and 2018 (in 2018 prices and exchange rates). Per-capita health spending on cancer increased by 86 percent from €105 to €195. The direct costs of cancer per capita differ greatly between countries. Austria, Germany, Switzerland, the three Benelux countries, and France spend the most on cancer care. Countries along the Eastern border of the EU (except Finland) spend the least on cancer care, reflecting their lower overall spending on health care per capita. Differences in per-capita health spending on cancer have become smaller over time due to greater increases in spending in poorer countries. A regular provision of disease-specific health expenditure data (such as in Germany and the Netherlands) is needed to provide unambiguous evidence on the magnitude and development of health care costs.

The indirect costs of cancer decreased by 9 percent from €77 billion to €70 billion in Europe between 1995 and 2018 (in 2018 prices and exchange rates), corresponding to a 15 percent decrease from €156 to €133 per capita. This is a result of a decline in mortality among patients of working age, which has reduced the productivity loss from premature mortality (from €57 billion to €50 billion). The productivity loss from morbidity (€20 billion) has, according to available data, remained stable during this period, but there is a lack of comparable data across countries and over time.

Costs for informal care might be of the same magnitude as the indirect costs from morbidity, but their exact magnitude and development over time is unclear due to lack of suitable data. The fact that the sum of indirect costs and informal care costs might be almost as large as the total health expenditure spent on cancer care in 2018 underlines the importance of applying a societal perspective in the design of policy measures to prevent, detect, and treat cancer.

Three major trends have characterized the development of the direct costs of cancer during the last decades. First, direct costs have generally grown in line with total health expenditure. Around 4–7 percent of total health expenditure are usually spent on cancer, and this share has been relatively stable over time. The increase in direct costs is partly driven by the rising number of cancer patients and partly by more intensive care and increased costs per patient.

The second trend is that cancer care has shifted from an inpatient to an ambulatory setting. Inpatient days, which are comparatively expensive, have partly been substituted by outpatient visits, which are comparatively cheaper. This shift is partly a result of new treatment modalities including new cancer medicines. Oral delivery of cancer medicines has also become more common and enabled patients to receive treatment at home. The potential of further cuts to hospital beds has probably already been exhausted in some countries by now, and this will make it difficult to offset future increases in expenditures on ambulatory care and new cancer medicines.

The third trend is that expenditures on cancer medicines have been increasing. The total expenditure doubled from €14.6 billion to €32.0 billion in Europe between 2008 and 2018 (in 2018 prices and exchange rates). Per-capita spending on medicines increased from €28 to €61. The exact size of these expenditures might however be overestimated due to confidential rebates on medicines which are not accounted for in available sales data. Cancer medicines have accounted for a growing share of the direct costs of cancer. Over one fourth (31 percent) of the direct costs consisted of cancer medicines in 2018, compared to 17 percent in 2008. Cancer medicines have also accounted for a modest but growing share of total pharmaceutical expenditure. The increase in cancer medicine spending is related to factors such as an increasing number of new cancer medicines leading to increased usage (e.g. new patient groups eligible for treatment, use in an adjuvant setting, longer duration of therapy) and higher prices of new medicines.

Patient access to new cancer medicines is much greater in wealthier than in poorer countries, irrespective of measuring access in terms of value or volume. This pattern has not changed over time and is consistent with the one found in the previous Comparator reports. Measured in value, the top spenders in 2018 were Austria, Germany, and Switzerland (around €92 to €108 per capita), whereas Czechia, Latvia, and Poland spent the least (around €13 to €16). Higher rebates on medicines in

poorer countries might exaggerate these differences. Measured in volume, poorer countries recorded a use of around one third to one half of the level of the big 5 countries (France, Germany, Italy, Spain, the UK) and other wealthier countries in a selection of cancer medicines.

The largest country differences in uptake of medicines (measured in volume) were observed in immuno-oncology medicines and in medicines used for multiple myeloma and prostate cancer in 2018. The uptake of immuno-oncology medicines in poorer countries was around 10–20 percent of the level observed in the big 5 and other wealthier countries. This reflects a general pattern of a stronger uptake of the newest cancer medicines in wealthier countries than in poorer countries in all years between 2008 and 2018. Country differences in uptake of mature medicines with a large patient population were comparatively smaller than in newer medicines.

A challenge for access to new medicines is the trade-off between early access and evidence on value to patients. Many cancer medicines lack evidence of additional clinical benefits/value to patients (such as in terms of overall survival) at the time of EMA approval. This creates a demand for follow-up studies of patient outcomes in clinical practice, and mechanisms for adjusting pricing and payments based on the results of such studies. While progress along these lines can be seen, there needs to be improvement in the collection and analysis of real-world data to make them useful for agreements between payers and manufacturers. Such agreements may lead to a faster and more equal uptake and use of innovative medicines that provide most value to patients and health care systems.

Another challenge for access to new medicines is the need to balance adequate reimbursement for value against affordability. A large share of European cancer patients, especially in Eastern Europe, cannot gain access to effective (and potentially cost-effective) medicines due to affordability-related reasons. Novel methods for pricing, valuation, and payment have been proposed to ensure access to recent developments such as CAR T-cell therapies and combination and multi-indication treatments. Better access to relevant data and certain regulatory changes can help to adopt these methods in order to incentivize future innovation for the benefit of patients. The use of biosimilars and generics is an important way to support cost-effective spending on medicines and to create financial scope for investing into innovative and cost-effective medicines that previously seemed unaffordable.

Health care systems need to weigh the costs from investing in different areas of cancer care against the potential improvements in patient outcomes. This will ensure that scarce resources are used in a cost-effective way and provide value-for-money for patients and taxpayers. There is a positive association between health expenditure spent on cancer care and survival, but there are variations in efficiency in cancer care both between and within countries. This indicates opportunities to improve efficiency and outcomes in all countries in Europe.

List of abbreviations

ADC – Antibody-drug conjugate
AI – Artificial intelligence
ALK – Anaplastic lymphoma kinase
ALL – Acute lymphatic leukemia
ASCO – American Society of Clinical Oncology
ATC – Anatomical therapeutic chemical classification
ATMP – Advanced therapy medicinal product
CAR-T cell – Chimeric antigen receptor T cell
CDF – Cancer Drugs Fund
CNS – Central nervous system
CPI – Checkpoint inhibitor
CT – Computed tomography
CTLA-4 – Cytotoxic T-lymphocyte-associated protein 4
DALY – Disability-adjusted life year
DBT – Digital breast tomosynthesis
DDD – Defined daily dose
ECDC – European Centre for Disease Prevention and Control
EGFR – Epidermal growth factor receptor
EMA – European Medicines Agency
EP – European Parliament
ER – Estrogen receptor
ESMO – European Society for Medical Oncology
ESMO-MCBS – ESMO Magnitude of Clinical Benefit Scale
FCM – Friction-cost method
FDA – Food and Drug Administration in the US
FFDM – Full-field digital mammography
FGFR – Fibroblast growth factor receptor
FISH – Fluorescence in situ hybridization
GDP – Gross domestic product
GDPR – General Data Protection Regulation
GIST – Gastrointestinal stromal tumors
HCC – Hepatocellular carcinoma
HCM – Human-capital method
HER2 – Human epidermal growth factor receptor 2
HIV – Human immunodeficiency virus
HPV – Human papillomavirus
HR – Hormone receptor
HTA – Health technology assessment
ICD-10 – International classification of diseases 10th revision
ICER – Incremental cost-effectiveness ratio
ICSS – International cancer survival standard
LDCT - Low-dose computed tomography
MRD - Minimal residual disease
MRI – Magnetic resonance imaging
MSI-H - Microsatellite instability high
NCCP – National cancer control programme
NGS – Next generation sequencing
NHS – National Health Service in the UK
NICE – National Institute for Health and Care Excellence
NSCLC – Non-small cell lung cancer
OECD – Organisation for Economic Co-operation and Development
ORR – Objective response rate
OS – Overall survival
PARP – Poly ADP ribose polymerase
PCR – Polymerase chain reaction
PD-1 – Programmed cell death protein 1
PD-L1 – Programmed death-ligand 1
PET – Positron emission tomography
PFS – Progression-free survival
PPP – Purchasing power parity
PRO – Patient-reported outcome
PROTAC – Proteolysis-targeting chimeras
PYWLL – Potential years of working life lost
QALY – Quality-adjusted life year
R&D – Research and development
RCT – Randomized controlled trial
RWD – Real-world data
SHA – System of Health Accounts
SWD – Standard weekly dose, used to standardize drug usage to enable comparisons between different medicines
TLV – The Swedish Dental and Pharmaceutical Benefits Board
USPSTF – US Preventive Services Task Force
VEGFR – Vascular endothelial growth factor receptor
WHO – World Health Organization

Country abbreviations

AT Austria
BE Belgium
BG Bulgaria
CH Switzerland
CY Cyprus
CZ Czechia
DK Denmark
EE Estonia
ES Spain
EU-28 the 28 member states of the European Union before Brexit
FI Finland
FR France
DE Germany
EL Greece
HR Croatia
HU Hungary
IE Ireland
IS Iceland
IT Italy
LT Lithuania
LU Luxembourg
LV Latvia
MT Malta
NL Netherlands
NO Norway
PL Poland
PT Portugal
RO Romania
SE Sweden
SI Slovenia
SK Slovakia
UK United Kingdom
US United States

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1. Introduction

Cancer is the collective name of a group of over 100 diseases that are characterized by uncontrolled growth and division of cells. The most common types in Europe are breast cancer, prostate cancer, colorectal cancer, and lung cancer. Cancer affects people of all ages. However, the risk of getting cancer increases dramatically with age, because the cellular repair mechanisms become less effective as a person grows older and because of an accumulation of and exposure to risks[1] that increase over a person's lifetime [1].

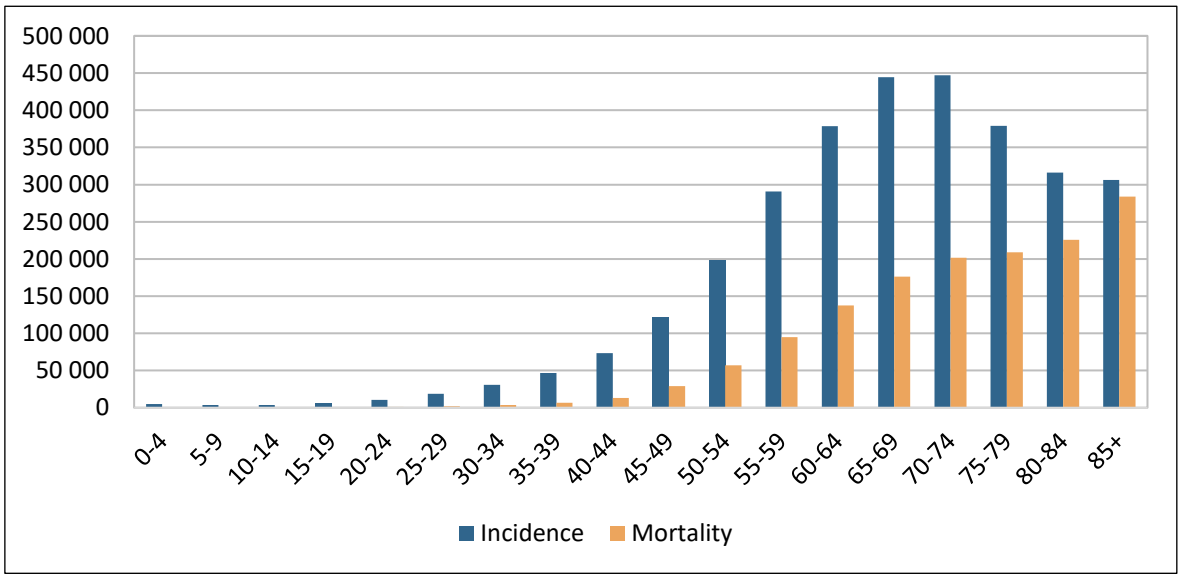

Figure 1: Number of cases of cancer incidence and mortality in Europe, 2018

Notes: Europe includes the EU-28, IS, NO, and CH. Cancer refers to all cancer sites but non-melanoma skin cancer (ICD-10 C00-C97/C44). Source: [2].

Figure 1 shows why cancer is considered an aging-associated disease. The number of newly diagnosed cases (incidence) is very low in children and young adults, but after age 40 it increases rapidly. Similarly, the number of cancer deaths (mortality) rises with age. In 2018, three out of five incidence cases (61%) and three out of four mortality cases (76%) occurred in people aged 65 or older.

The management of cancer represents a major challenge for health care systems in Europe and the rest of the world. The aging population in all countries across Europe means that more and more people are of an age when major cancer types typically develop. Indeed, the total annual number of

[1] These risks include, for instance, tobacco use, alcohol use, unhealthy diet, physical inactivity, infection with carcinogenic viruses (such as human papillomavirus (HPV) and hepatitis B virus) or with helicobacter pylori, air pollution, and ionizing and ultraviolet radiation.

newly diagnosed cancer cases has been rising for a long time. Figure 2 shows that cancer incidence in Europe (defined as EU-28, IS, NO, and CH) has gradually increased by around 50 percent from 2.1 million to 3.1 million cases between 1995 and 2018 [3-8].

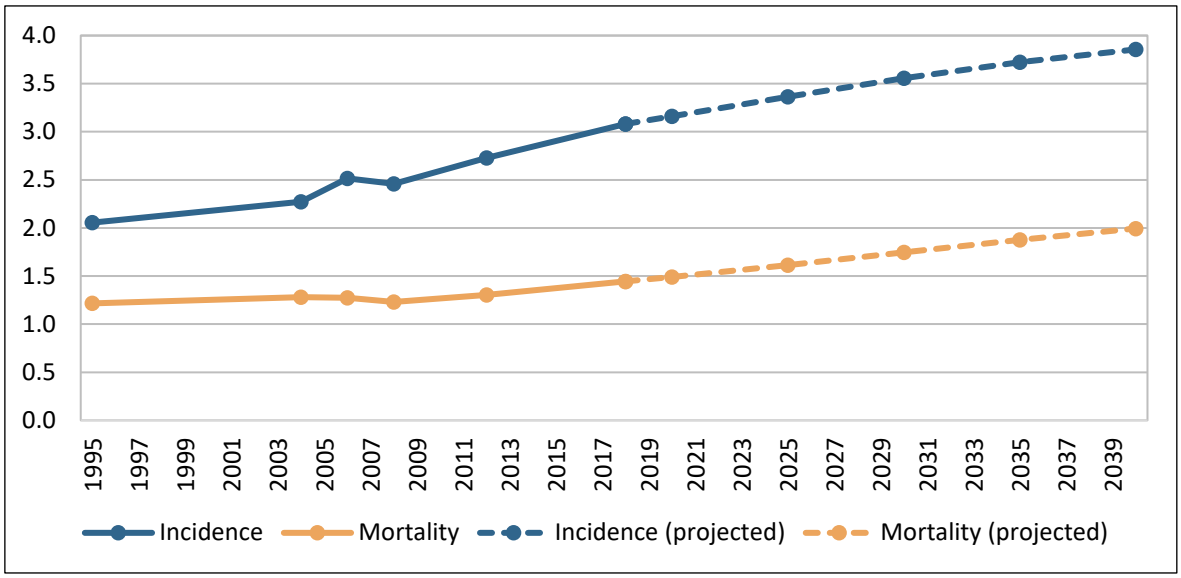

Figure 2: Cancer incidence and mortality (in million cases) in Europe, 1995–2018 and projection of status quo 2020–2040

Notes: Europe includes the EU-28, IS, NO, and CH. Cancer is defined as ICD-10 C00-C97/C44. Source: [3-9].

The increasing trend in cancer incidence has been engaging policy makers for a long time. In the US, the Nixon administration declared "The War on Cancer" already in 1971. In Europe, the European Commission's first "Europe Against Cancer" program was adopted in 1987. The WHO has also persistently called for actions and supported countries to reduce premature mortality from cancer.

Despite increasing cancer incidence, much progress has been achieved in the last decades. Figure 2 shows that cancer mortality in Europe has increased by around 20 percent from 1.2 million to 1.4 million cases between 1995 and 2018. This increase was distinctly lower than the corresponding increase in cancer incidence of 50 percent, leading to a widening gap between incidence and mortality in Figure 2. At the individual level, this development is reflected in increasing survival. Major advances in diagnosis and medical treatment along with screening programs are reasons for this development [10, 11].

Figure 2 also projects what would happen in the absence of further improvements in cancer care and prevention [9]. If the status quo remains (with base year 2018), the forecasted demographic development (population aging and minor overall population growth) will continue to push up incidence and mortality in Europe. In 2040, an estimated 775,000 newly diagnosed cases as well as

550,000 deaths would be added compared to the situation in 2018. This projection makes it clear that further improvements and investment in all areas of cancer care – prevention, screening, diagnosis, treatment – are needed to meet the demographic challenge and to achieve a lasting turnaround in cancer incidence and mortality.

1.1 Purpose and outline of the report

The purpose of this report is to provide decision makers with a clear picture of cancer in Europe in order to support efforts to plan and take action to reduce the burden of cancer. This report is an update of a report published in 2016 [12], which in turn was preceded by several Comparator reports on cancer published since 2005 [13-15]. Similar to the previous report, the geographic scope of this report is Europe, defined as the 28 member states of the European Union (EU-28) and Iceland, Norway, and Switzerland. The exclusion of other countries on the Balkan and in Eastern Europe is due to lack of data. Whenever countries from these regions are included or when countries of the principal 31 countries are missing due to lack of data, this is noted in the report.

The report consists of four main chapters. Chapter 2 analyzes the development of the burden of cancer in recent decades, distinguishing between the disease burden and the economic burden. Chapter 3 reviews recent medical developments in the field of oncology and provides some prospective analysis. Chapter 4 analyzes access to and uptake of cancer medicines. Chapter 5 discusses policy issues in relation to the provision of high-quality cancer care and access to cancer medicines.

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2. Disease burden and economic burden of cancer

2.1 Key messages

- The disease burden of cancer in Europe is high. More than one in four deaths (26%) was due to cancer in 2016. This makes cancer the second leading cause of death behind cardiovascular diseases. Cancer was also the disease group that caused the second greatest disease burden (20%) after cardiovascular diseases.
- The number of newly diagnosed cancer cases is growing. Cancer incidence increased by around 50 percent from 2.1 million to 3.1 million cases between 1995 and 2018 in Europe. Population growth and, more importantly, population aging are strong drivers of this increase. A stronger focus on primary prevention (such as vaccination programs and measures to facilitate the adoption of healthier lifestyles) is needed to achieve a turnaround in cancer incidence.
- Deaths from cancer are still increasing but the increase has slowed and in age groups below 65 years deaths are actually decreasing. Between 1995 and 2018, cancer mortality increased by around 20 percent from 1.2 million to 1.4 million deaths. In the absence of population growth and population aging, cancer mortality would have decreased in almost all countries.
- The 5-year survival rates for the most common cancer types have increased between 1995 and 2014 in all countries. There is a clear pattern of wealthier countries to record higher survival rates than poorer countries. Improvements in all areas of cancer care (screening, diagnostics, treatment, organization of the care process) were important to achieve improvements in survival.
- The health expenditure spent on cancer care (direct costs of cancer) doubled from €52 billion to €103 billion in Europe between 1995 and 2018 (in 2018 prices and exchange rates). Per-capita health spending on cancer increased by 86 percent from €105 to €195. A regular provision of disease-specific health expenditure data (such as in Germany and the Netherlands) is needed to provide unambiguous evidence on the magnitude and development of health care costs.
- The direct costs of cancer per capita differ greatly between countries but differences have become smaller over time. Austria, Germany, Switzerland, the three Benelux countries, and France spend the most on cancer care. Countries along the Eastern border of the EU (except

Finland) spend the least on cancer care, reflecting their lower overall spending on health care per capita.

- Spending on cancer as a share of total health expenditure has been relatively stable over time. Around 4–7 percent of total health expenditure are usually devoted to cancer. However, the composition of the direct costs of cancer has changed in recent decades. Expenditures on inpatient care have declined in relative terms, whereas expenditures on ambulatory care and cancer medicines have increased.
- Expenditures on cancer medicines have increased during recent decades. The total costs of cancer medicines more than doubled between 2008 and 2018 in Europe. Cancer medicines account for a growing share of the direct costs of cancer. Over one fourth (31 percent) of the direct costs consisted of cancer medicines in 2018, compared to 12 percent in 2005, although the exact size of these shares might be overestimated due to confidential rebates on medicines.
- The indirect costs of cancer exceeded the direct costs in 1995 in Europe. The indirect costs decreased by 9 percent from €77 billion to €70 billion in Europe between 1995 and 2018 (in 2018 prices and exchange rates). This is a result of a decline in mortality among patients of working age, which has reduced the productivity loss from premature mortality. The productivity loss from morbidity might have remained stable during this period.
- Costs for informal care might be of the same magnitude as the indirect costs from morbidity, but their exact magnitude and development over time is unclear due to lack of suitable data. Increased treatment of patients in an ambulatory setting and an increased cancer incidence and mortality in older age groups points to a potential future increase in informal care.
- The increase in the direct costs of cancer have to some extent been offset by a decrease in the indirect costs. However, the total costs of cancer keep increasing.

2.2 Epidemiology of cancer

This chapter aims to describe the two key aspects of the burden of cancer – the disease burden (sections 2.2 and 2.3) and the economic burden (section 2.4) – in Europe. The focus is to describe the development of the burden of cancer between 1995 and 2018.

The disease burden of cancer can be characterized by different epidemiological measures, such as incidence, mortality, and survival. Data for these measures come from different sources. Incidence and mortality data are regularly published under the auspices of the International Agency for

Research on Cancer (IARC)[2]. As many European countries lacked national cancer registries in past (and several still do in 2019), incidence and mortality have to be estimated. The methods to estimate country-specific incidence and mortality have changed slightly over time, and care should be taken when interpreting time trends. Survival data for European countries with (regional or national) cancer registries are published by CONCORD[3], a program for worldwide surveillance of cancer survival led by the London School of Hygiene & Tropical Medicine.

2.2.1 Incidence

Cancer incidence refers to the number of new cancer cases diagnosed within a certain year in a specific geographical area. In 1995, the estimated cancer incidence[4] was 2.055 million in Europe[5]; 0.94 million women and 1.11 million men [1]. Until 2018, the corresponding number had increased by 50 percent to 3.081 million; 1.42 million women and 1.66 million men [2].

There are several factors that can help to explain the increase in incidence between 1995 and 2018:

- Population growth: The population of Europe has grown from 495 to 527 million people, an increase by more than six percent [3]. At a constant risk of getting cancer, a positive population growth leads to more cases of cancer. However, cancer incidence has gone up even in per-capita terms; see the section on crude rates below.
- Population aging: As the risk of getting cancer increases with age, an aging population contributes to an increasing number of cancer cases. The share of people aged 60 and older has increased from 20 to 26 percent in Europe [3]. In the Appendix, age-standardized incidence rates are presented, taking into account the effect of an aging population. Although this explains some of the increase in the number of cancer cases, there is still a distinct increase in incidence left unexplained.
- Risk factors: There are certain lifestyle factors linked to cancer that have increased in most European countries during the past decades. Some of them are obesity (linked to, e.g., colorectal cancer and postmenopausal breast cancer), alcohol consumption (linked to, e.g., liver cancer and breast cancer), and exposure to ultraviolet radiation via sunbathing (linked

[2] https://www.iarc.fr/
[3] https://csg.lshtm.ac.uk/
[4] All cancer sites but non-melanoma skin cancer (ICD-10 C00-C97/C44). Non-melanoma skin cancer is commonly excluded from incidence data, as its registration is often incomplete and inaccurate, as it is usually non-fatal and treated in primary care.
[5] This estimate is calculated based on sex-specific growth rates in cancer incidence between 1995 [1] and 2018 [2] in Europe, where Europe is defined as EU-28 (except CY), IS, NO, CH, the remaining Balkan countries, Belarus, Moldova, Russia, and Ukraine.

to, e.g., skin cancer). By contrast, smoking (linked to, e.g., lung cancer) has declined in men and more recently also in women [4]. Declining smoking rates do not immediately translate into decreasing cancer incidence, as there are considerable time lags between the exposure to risk factors and the development of cancer.

- Screening: Nationwide population-based screening programs for breast cancer, cervical cancer, and (since the beginning of the 2010s) colorectal cancer have been implemented in many countries [5, 6]. Opportunistic screening for prostate cancer has also become more common and might have led to the detection of more cases of latent disease that never would have become symptomatic.
- Epidemiological development in other diseases (competing risks of death): People are nowadays surviving previously fatal diseases as a result of improvements in health care and medicine. This is especially true for cardiovascular diseases. As more people reach an advanced age, this leaves more people at risk of getting cancer [7].

2.2.1.1 Crude rates

Crude rates are used to compare countries of different sizes in a comprehensive way. The crude rates are obtained by standardizing the number of cancer cases with the size of the population and are expressed as newly diagnosed cases per 100,000 inhabitants. Crude rates are also a relevant measurement for policy makers to look at, as a growing population per se is not a problem, provided that a growing population entails more income earners and taxpayers.

Figure 3 shows cancer incidence for all cancers combined for both sexes. All countries with available data saw increases in incidence between 1995 and 2018. Among the countries for which data are available for 1995, Italy, Denmark, and Germany had the highest incidence rates with more than 400 cases per 100,000 inhabitants. Bulgaria, Lithuania, and Malta had the lowest incidence rates with around or below 300 cases per 100,000 inhabitants. Italy, Denmark, and Germany remained in the top with more than 600 cases per 100,000 inhabitants in 2018, but the country with the highest crude rate was Hungary. Cyprus, Iceland, and Romania had the lowest crude rates in 2018 with around 400 cases per 100,000 inhabitants.

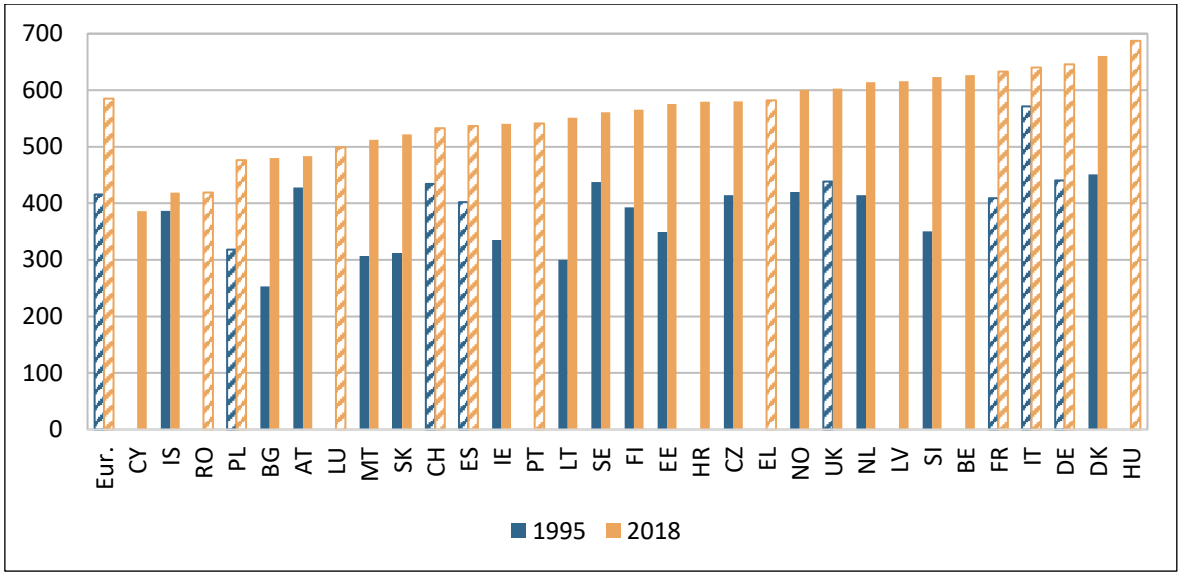

Figure 3: Estimated number of cancer incidence cases per 100,000 inhabitants (crude rates for both sexes), 1995–2018

Notes: Eur. = Europe. Hatched bars indicate that national estimates are based on regional data or neighboring countries. Cancer refers to all cancer sites but non-melanoma skin cancer (ICD-10 C00-C97/C44). BE, HR, CY, EL, HU, LV, LU, PT, RO are missing in 1995 due to lack of data. Incidence cases in 1995 were based on regional data in Germany (North Rhine-Westphalia, Saarland), France (Bas-Rhin, Calvados, Doubs, Haut-Rhin, Herault, Isere, Manche, Somme, Tarn), Italy (Ferrara, FVG, Latina, Liguria, Macerata, Modena, Parma, Ragusa, Romagna, Sassari, South Tyrol, Trento, Tuscany, Umbria, Varese), Spain (Balearic Islands, Basque Country, Girona, Granada, La Rioja, Navarra, Tarragona), and the UK (England, Northern Ireland, Scotland, Wales). Source: [8-11].

To take into account the influence of different age structures between countries or within the same country over time, age-standardized rates can be estimated. Just as crude rates, they are quantified in terms of newly diagnosed cases per 100,000 inhabitants, but in addition they are standardized according to a pre-defined age distribution. Figures A1 and A2 in the Appendix show age-standardized incidence rates separately for men and women. They show that male incidence rates have increased in a majority of countries between 1995 and 2018, but Iceland, Austria, Finland, Poland, Switzerland, Italy, and Czechia recorded slight decreases. By contrast, female incidence rates have increased in all countries, except in Iceland. Even though the gender gap has narrowed over time, female incidence rates were still on average 23 percent lower than male rates in 2018.

2.2.1.2 Incidence by cancer type and age

While the number of new cancer cases has increased during the past decades, the development has not been uniform across all cancer types. As a result, the share of different cancer types has shifted markedly since 1995; see Figures 4 and 5. The eight most common cancer types accounted for around 70 percent of all cases in men and in women in 1995 and 2018.

Among men, the most common cancer type in 1995 was lung cancer with a share of 22 percent of all newly diagnosed cases; see Figure 4. In 2018, lung cancer only accounted for 15 percent of the cases. Prostate cancer surpassed both lung cancer and colorectal cancer with a share of 22 percent in 2018 and has thereby doubled its share since 1995. However, it remains unclear to what extent the massive increase in prostate cancer incidence is driven by detection of latent disease due to the increase in screening. The relative decrease in lung cancer among men between 1995 and 2018 is, as mentioned earlier, likely to be a consequence of the decrease in smoking rates since the 1980s and 1990s.

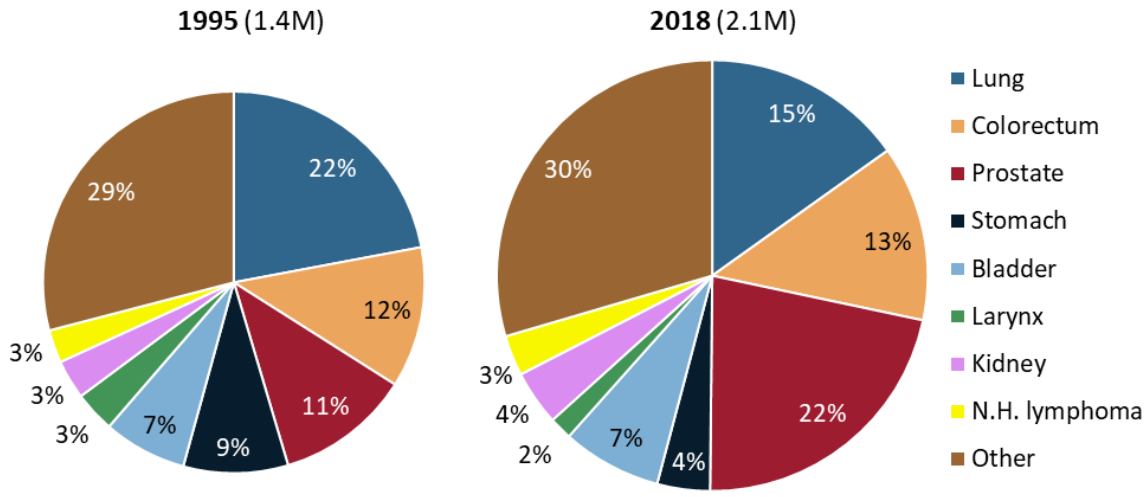

Figure 4: Most common cancer types diagnosed in men in 1995 and their share in 2018, Europe

Notes: Europe includes EU-28 (except CY), IS, NO, CH, the remaining Balkan countries, Belarus, Moldova, Russia, and Ukraine. Source: [1, 8].

Among women, breast cancer was the most common cancer type with 28 percent of all newly diagnosed cases, both in 1995 and in 2018; see Figure 5. Lung cancer incidence increased from five to nine percent and exhibits the opposite development observed in men, probably related to female smoking rates increasing at least until the end of the 1990s in most countries. The incidence rates of stomach cancer and cervical cancer have both been halved from six to three percent, probably related to better diet and cervical screening programs, respectively.

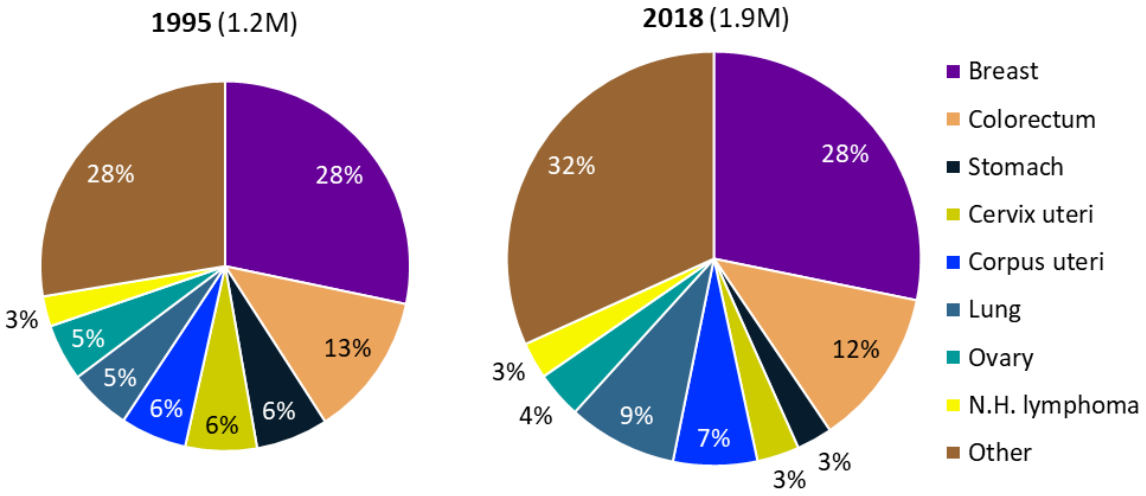

Figure 5: Most common cancer types diagnosed in women in 1995 and their share in 2018, Europe

Notes: see Figure 4.

Cancer incidence has not increased to the same extent in all age groups in recent decades. Figure 6 shows the development of newly diagnosed cases in the Nordic countries between 1995 and 2016; similar data are not available for Europe as a whole due lack of nationwide cancer registries in the past. Overall there was a gradual increase by 50 percent between 1995 and 2016, which is similar to the estimated development in Europe presented above. However, cancer incidence in children (0 to 14 years) remained more or less stable and increased by 30 percent in young adults (15 to 39 years). The age group 40 to 64 years recorded the most rapid increase between 1995 and 2009, but afterwards incidence increased no more. By contrast, cancer incidence in people aged 65 and older has increased continuously. Due to population aging, the latter age group can be expected to continue to be the driving force behind increasing overall cancer incidence in the future.

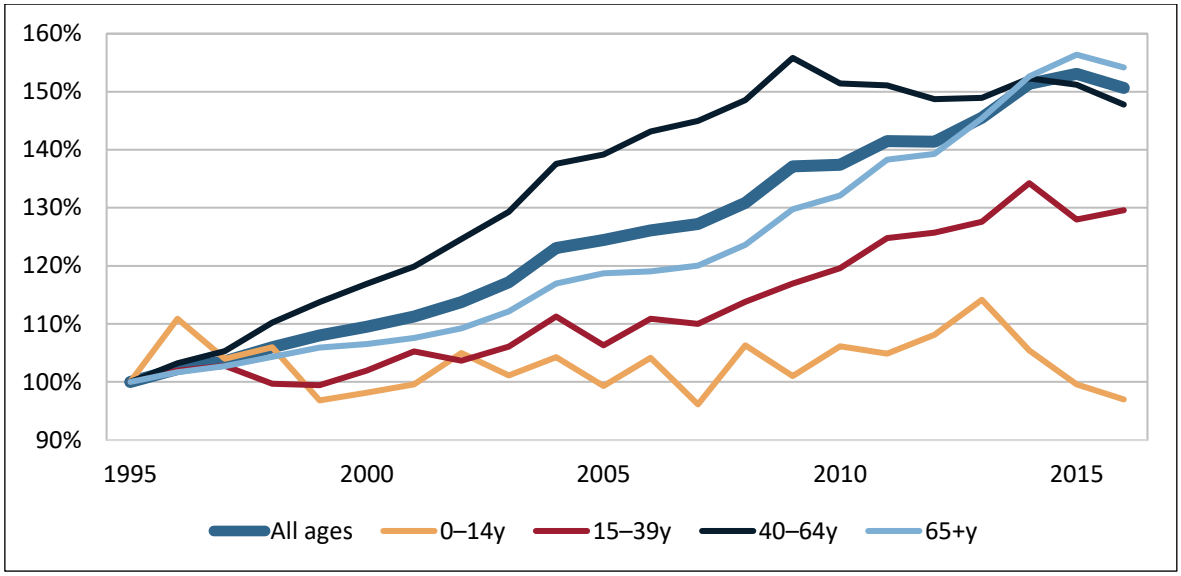

Figure 6: Cancer incidence by age group in the Nordic countries (1995=base year), 1995–2016

Notes: Nordic countries = DK, FI, IS, NO, SE. Cancer is defined as all sites but non-melanoma skin cancer (C00-97/(C44+C46.0)+D09.0-1+D30.1-9+D35.2-4+D41.1-9+D32-33+D42-43+D44.3-5+D45-46+D47.0-1,3-9). The development is based on the total number of cancer cases. Source: [12].

2.2.2 Mortality

Cancer mortality refers to the number of deaths caused by cancer in a certain year in a specific geographical area. In 1995, the estimated cancer mortality[6] was 1.191 million in Europe[7]; 0.52 million women and 0.67 million men [1]. Until 2018, the corresponding number had increased by 21 percent to 1.445 million; 0.63 million women and 0.81 million men [2].

Several factors can help to explain the increase in mortality between 1995 and 2018. As shown above, the number of newly diagnosed cases increased by 50 percent during this period. More new cancer cases imply more deaths if the rate of curing cancer cases (survival) remains constant. This means also that the factors explaining the increase in cancer incidence (the demographic development, the development of lifestyle factors, the introduction of screening programs, and the epidemiological development in other diseases) are important for explaining the increase in cancer mortality. For instance, age-standardized mortality rates, presented in the Appendix, indicate that mortality rates would have decreased in the absence of population aging. Similarly, if the effect of competing causes

[6] All cancer sites (except non-melanoma skin cancer in 2018) and HIV disease resulting in malignant neoplasms (ICD-10 C00-C97,B21).
[7] Data for CY in 1995 is missing.

of death (in particular the decline in deaths from cardiovascular diseases) is taken into account, cancer mortality might have decreased [7].

2.2.2.1 Crude rates

Figure 7 shows crude rates for cancer mortality for all cancers combined for both sexes. Out of the 31 countries, eight countries saw decreases in mortality between 1995 and 2018. In 1995, Hungary and Denmark had the highest mortality rates with more than 300 cases per 100,000 inhabitants. Romania, Iceland, Malta, Bulgaria, and Finland had the lowest rates with less than 200 cases per 100,00 inhabitants. In 2018, Hungary was still among the top two countries with the highest mortality rates of around 340 cases per 100,000 inhabitants along with Croatia. The lowest rates were recorded in Luxembourg, Iceland, Cyprus, and Ireland with less than 200 cases per 100,000 inhabitants.

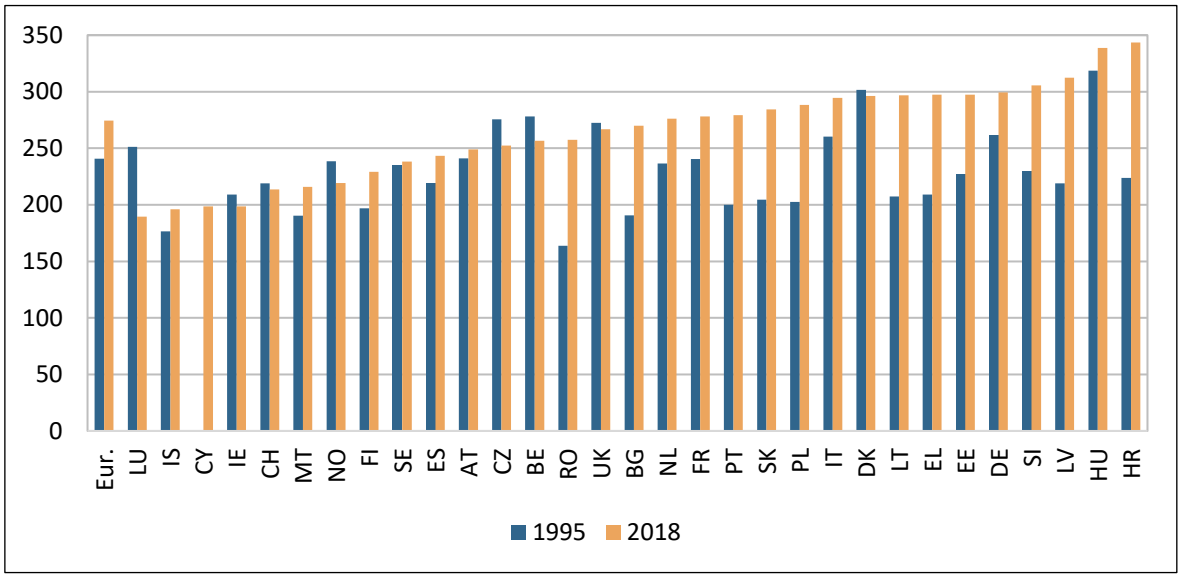

Figure 7: Estimated number of cancer mortality cases per 100,000 inhabitants (crude rates for both sexes), 1995–2018

Notes: Eur. = Europe. Cancer refers to all cancer sites (except non-melanoma skin cancer in 2018) and HIV disease resulting in malignant neoplasms (ICD-10 C00-C97,B21). CY is missing in 1995 due to lack of data.
Source: [8, 13].

Country differences in mortality rates should not be interpreted in isolation. A high mortality rate of a country does not necessarily indicate something about that country's effectiveness of cancer care, rather it could be a result of the country's high incidence rate. For instance, Hungary had the highest incidence rate and the second-highest mortality rate in 2018. Iceland had the second-lowest incidence rate and the second-lowest mortality rate in 2018.

Figures A3 and A4 in the Appendix show age-standardized mortality rates separately for men and women. They show that male mortality rates have decreased in all countries between 1995 and 2018, except in Bulgaria, Greece, and Romania. Similarly, female mortality rates have decreased in all countries, except in Bulgaria, Croatia, Greece, Romania, and Slovakia. As with incidence rates, the gender gap has narrowed over time, but female mortality rates were still on average 39 percent lower than male rates in 2018.

2.2.2.2 Mortality by cancer type and age

While the number of deaths from cancer has increased during the past decades, the development has not been uniform across all cancer types. As a result, the share of different cancer types has shifted markedly since 1995; see Figures 8 and 9. The eight most common cancer types accounted for around 70 percent of all cancer deaths in men and in women in 1995 and 2018.

Among men, lung cancer was the most common fatal cancer type, but its relative share has decreased from 29 percent in 1995 to 25 percent in 2018; see Figure 8. Colorectal cancer comes in second place in these years, and it has increased its share from ten to twelve percent. The share of deaths from prostate cancer has increased slightly and surpassed stomach cancer, which has seen its share decrease over time. Given that prostate cancer deaths increased, the surge in the number of prostate cancer incidence described above was probably not solely due to screening leading to higher detection of latent disease.

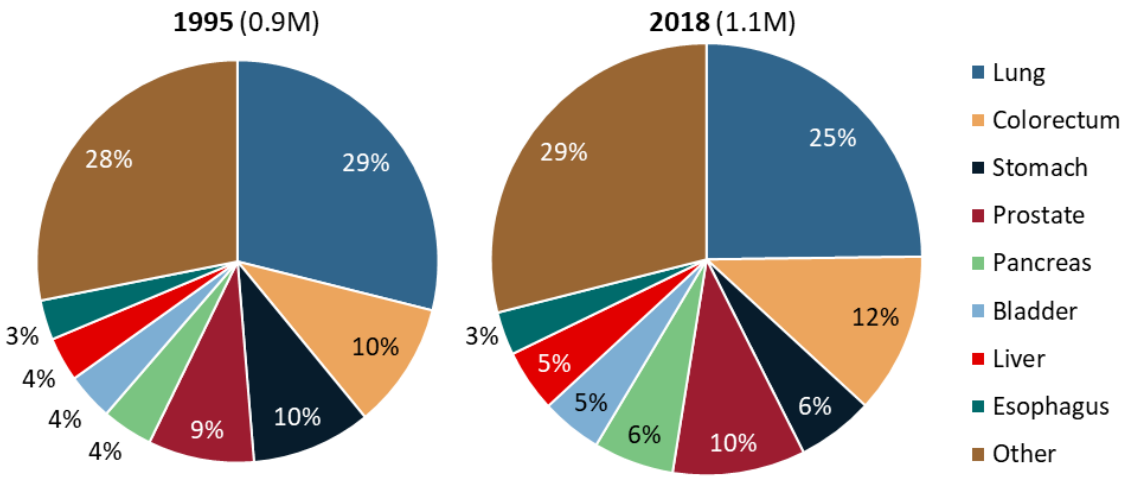

Figure 8: Most common fatal cancer types in men 1995 and their share in 2018, Europe

Notes: see Figure 4.

Among women, breast cancer was the most common fatal cancer type, but its relative share has decreased from 19 percent in 1995 to 16 percent in 2018; see Figure 9. Death due to colorectal cancer was equally common in 1995 and 2018 with 13 percent of all cases. Lung cancer has increased its share from 10 to 14 percent and was the second most common fatal cancer type in 2018. Deaths due to stomach cancer have decreased over time.

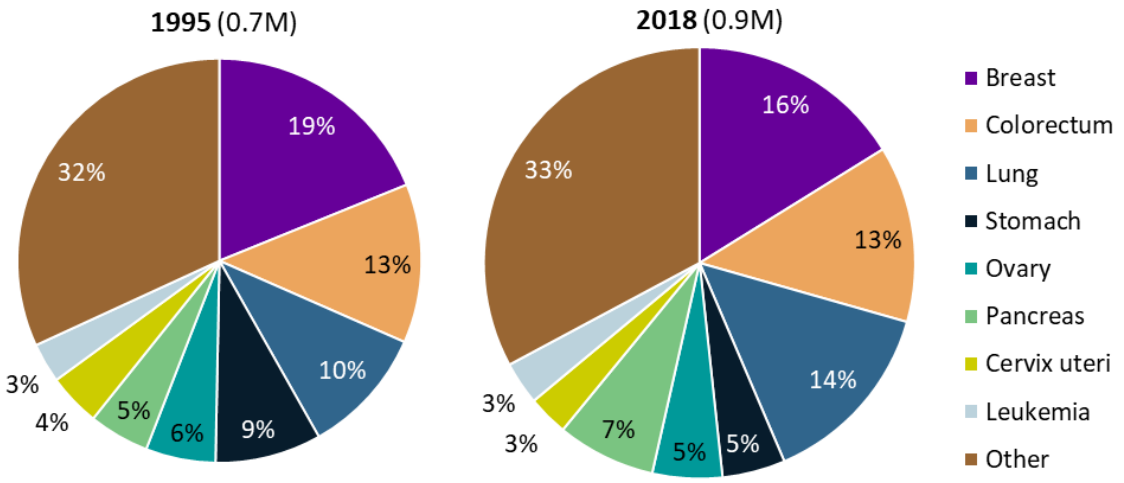

Figure 9: Most common fatal cancer types in women 1995 and their share in 2018, Europe

Notes: see Figure 4.

Cancer mortality has not increased to the same extent in all age groups in recent decades. Figure 10 shows the development of actually recorded (and not estimated as above) cancer deaths in Europe between 1995 and 2017 (or the most recent year). Overall there was a gradual increase by 15 percent between 1995 and 2017. However, all age groups below 65 years recorded decreases. Cancer mortality in children (0 to 14 years) decreased by 50 percent, in young adults (15 to 39 years) by 40 percent, and in people aged 40 to 64 by 10 percent. By contrast, cancer mortality in people aged 65 and older increased by 27 percent. Part of this diverging trend between younger and older age groups might be related to differences in use of treatment options based on patients' age. Population aging and the resulting increase in cancer incidence make it challenging to break the increasing mortality trend in the oldest age group.

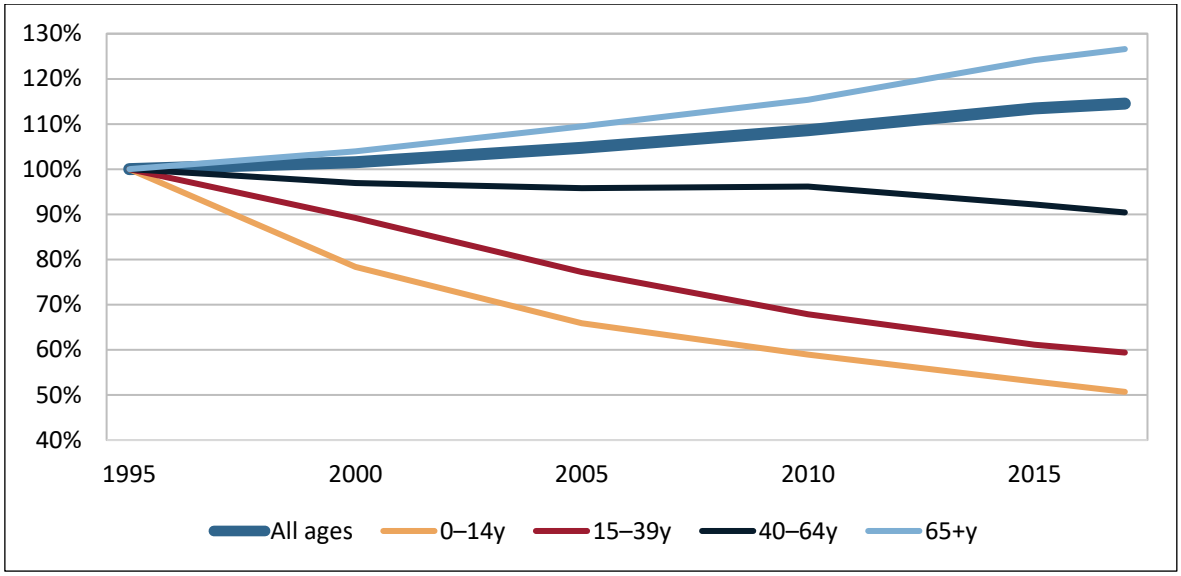

Figure 10: Cancer mortality by age group in Europe (1995=base year), 1995–2017

Notes: The development is based on the total number of cancer deaths. Cancer is defined as C00-97,B21in 1995–2010 and as C00-97 in 2015–2017. Data for 1995 and 2000 include figures for 2004 from CY. Data for 2017 include figures from 2016 for some countries. Source: [13, 14].

2.2.3 Survival

Survival is the concept that connects the two epidemiological measures of incidence and mortality. It measures the share of people that have been diagnosed with cancer in a certain year and that are still alive after a specified period of time. Survival rates are commonly measured in terms of 5-year survival rates, i.e. the share of people diagnosed with cancer in year t that is still alive in year t+5. This means that data on the 5-year survival rate of cancer patients diagnosed in 2019 can only be definitely evaluated after 2024, based on what is called "cohort analysis". However, through alternative methods ("period analysis" and "mixed analysis") a good approximation of the likely result can be estimated [15, 16].

Two adjustments are routinely made to survival rates to receive comparable rates across time and countries. Firstly, net (also called "relative") survival rates rather than gross ("absolute") survival rates are compared. The net survival rate is the ratio of two survival rates: the gross survival rate of cancer patients divided by the expected survival rate of people in the general population with similar age and sex in the same country and calendar year[8] [17]. This adjusts survival rates for the

[8] For instance, assume that the observed share of cancer patients that are alive 5 years after their diagnosis is 60%. This is the gross survival rate. In addition, assume that the 5-year expected survival rate in the general population (with the same age structure, same sex composition and during the same time period) is 80%. The 5-year net survival rate is then 60%/80% = 75%. Thus, of the 40% (100% - 60%) of cancer patients who died

effect of competing causes of death (background mortality) that would otherwise bias comparisons across time and between countries. Thus, net survival rates indicate the hypothetical situation in which cancer is the only cause of death [15]. Secondly, the age structure of cancer patients differs across countries and within countries across time. Since net survival rates for most cancer types vary by age (typically they decrease with age), they are adjusted for age at diagnosis [18]. The International Cancer Survival Standard (ICSS) is typically used to this end.

The CONCORD program has recently started to provide 5-year age-standardized (according to ICSS) net survival rates for all European countries with (regional or national) cancer registries. The CONCORD-2 program estimated survival rates for ten cancer types diagnosed during 1995–2009 and followed up to December 31, 2009 [18]. The CONCORD-3 program extended the analysis to 18 cancer types diagnosed during 2000–2014 and followed up to December 31, 2014 [19]. Survival rates are not available for every calendar year, only in groups of five years.

Figure 11 shows the development of the 5-year net survival rate of colon cancer patients. In 2010–2014, the survival ranged from 51% in Croatia to 68% in Belgium and Iceland (the 72% estimate in Cyprus has a low reliability). There is a rather clear pattern of wealthier countries to record higher survival rates, whereas poorer countries record lower rates. Noteworthy exceptions to this pattern are the UK, Ireland, and Denmark which recorded lower rates than Slovenia. Between the periods 1995–1999 and 2010–2014 all countries recorded improvements. The biggest improvements in absolute terms were recorded in Slovenia and Latvia (from relatively low levels) and in Germany (from a relatively high level). Improvements between 2005–2009 and 2010–2014 have been comparatively small in most countries.

within 5 years after diagnosis, 25% (100% - 75%) can be expected to have died from cancer and the remaining 15% (75% - 60%) from other causes.

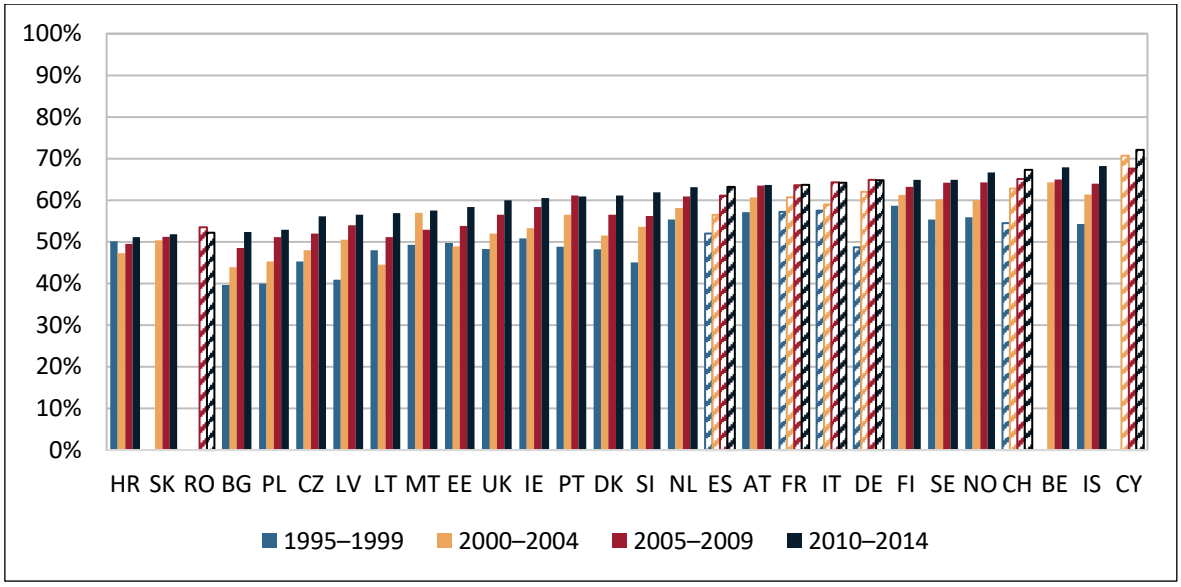

Figure 11: 5-year age-standardized net survival rates for colon cancer in adult patients (15–99 years), 1995–2014

Notes: Hatched bars in CH, DE, ES, FR, IT, and RO indicate that national estimates are based on regional data. Hatched bars in CY indicate less reliable estimates. EL, HU, and LU are missing due to lack of data.
Source: [18, 19].

Figure 12 shows the development of the 5-year net survival rate of female breast cancer patients. In 2010–2014, the survival ranged from 74% in Lithuania to 89% in Finland, Iceland, and Sweden (the 93% estimate in Cyprus has a low reliability). Compared to colon cancer, many countries achieved comparatively similar survival, as 16 countries are in the range of 85% to 89%. There is again a clear pattern of higher survival in wealthier countries (except Ireland) and lower survival in poorer countries. However, several poorer countries (Estonia, Latvia, Malta, Portugal, Slovenia) achieved significant improvements between 1995–1999 and 2010–2014 in absolute terms. Similar to colon cancer, improvements between 2005–2009 and 2010–2014 have been comparatively small in all countries.

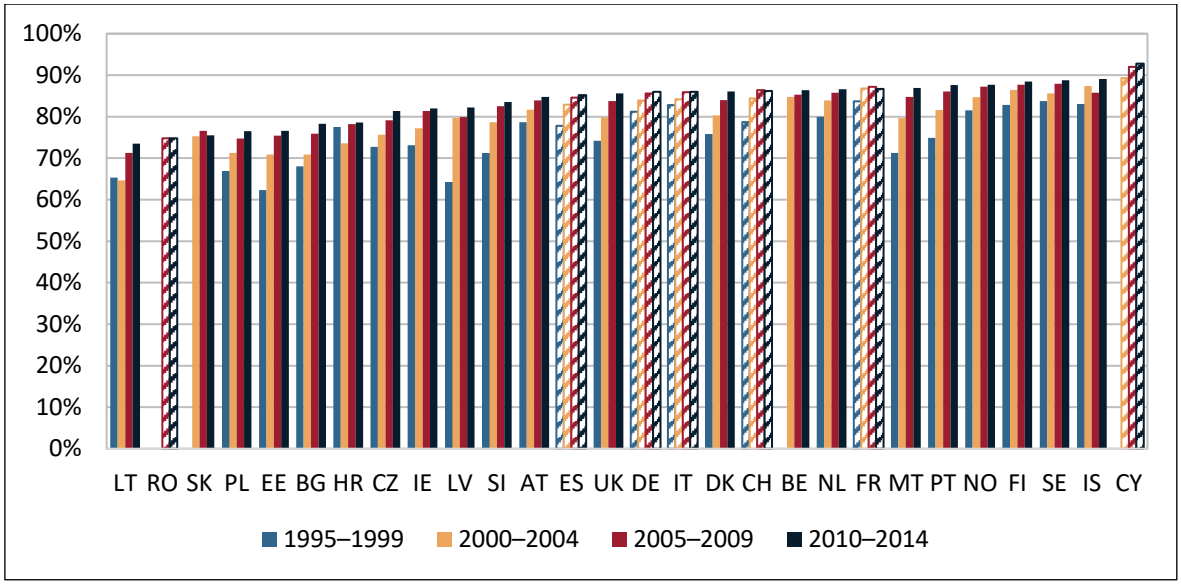

Figure 12: 5-year age-standardized net survival rates for breast cancer in female adult patients (15–99 years), 1995–2014

Notes: see Figure 11.

Figures A5 to A9 in the Appendix present the development in survival rates for additional cancer types (lung cancer, prostate cancer, malignant melanoma, lymphoid cancers (which include multiple myeloma), ovarian cancer) in line with the cancer medicines considered in Chapter 4. A similar pattern as in colon cancer and breast cancer is observable. The highest survival rates are typically observed in wealthier countries, in particular in the Nordic countries (except Denmark), Switzerland, Germany, and Belgium. Bulgaria, Romania, Poland, Croatia, and Slovakia tend to have the lowest survival rates. Country differences in survival rates in 2010–2014 were especially high in lung cancer. By contrast, many countries recorded similar survival rates in prostate cancer and malignant melanoma. Improvements between 1995–1999 (or 2000–2004) and 2010–2014 were typically recorded in all countries and cancer types. However, the improvements between 2005–2009 and 2010–2014 were small (except in lung cancer).

The paucity of survival data for years after 2014 for European countries (provided from a single source) is unsatisfactory. As described in Chapters 3 and 4, many new cancer medicines were approved after 2014 and have quickly become standard of care. Notably, a new class of medicines (immuno-oncology medicines) have been launched on a broad basis in several different indications. Some long-term clinical trials have demonstrated major improvements in survival. For instance, the combination of nivolumab and ipilimumab for the treatment of previously untreated stage III or IV melanoma resulted in a 5-year survival rate of 52%, compared to a survival rate of around 5% ten years ago in this patient group [20]. The use of pembrolizumab in advanced non-small cell lung cancer also significantly increased the 5-year survival rate [21].

2.3 Burden of disease

To understand the extent of the burden of cancer in relation to other diseases two measures are used. The first measure is the number of deaths due to cancer in comparison to the total number of deaths. The second measure is the number of Disability Adjusted Life Years (DALYs) that cancer and other diseases cause.

2.3.1 Deaths

In 2016, 5.244 million people died in Europe, of which 1.365 million died of cancer. This means that over one fourth (26 percent) of all deaths were due to cancer. This made cancer the second leading cause of death behind cardiovascular diseases (36 percent of all deaths). The countries where cancer deaths exceeded deaths due to cardiovascular diseases were Denmark (30 vs. 24 percent), France (28 vs. 24 percent), the Netherlands (31 vs. 26 percent), and the UK (28 vs. 26 percent). There is also a tendency of a larger share of cancer deaths (and a smaller share of cardiovascular deaths) in wealthier countries than in poorer countries.

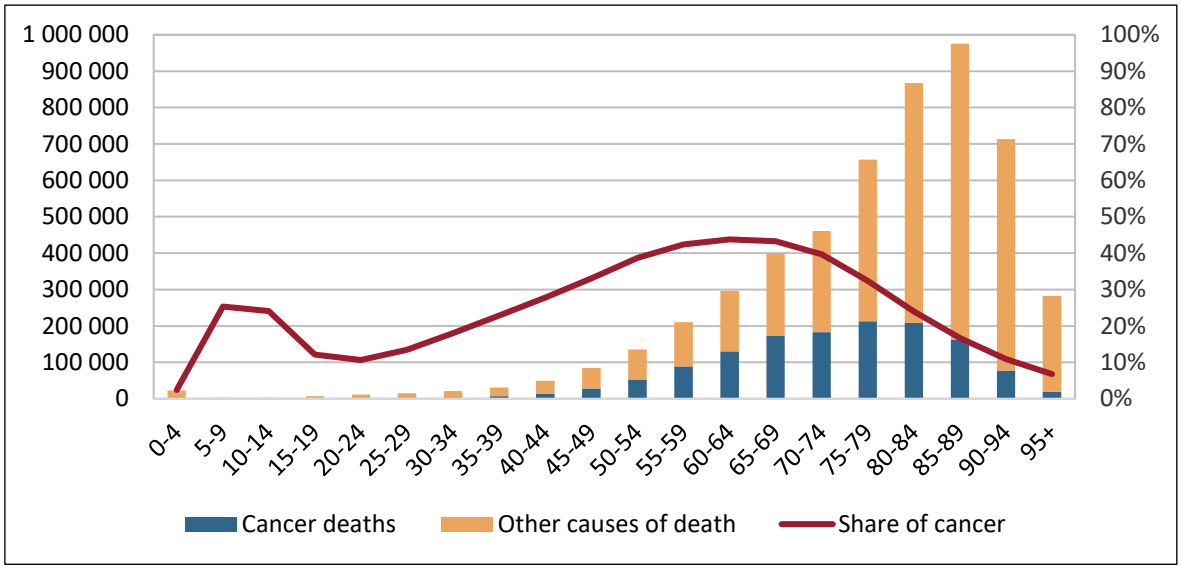

Figure 13: Number of deaths by cause (left scale) and cancer deaths as share of total deaths (right scale) by age group in Europe, 2016

Notes: Cancer is defined as ICD-10 C00-C97 and other causes as all causes of death (A00-Y89) excluding S00-T98 and C00-C97. Deaths refer to all deaths reported in a country. Source: [14].

Figure 13 shows how cancer deaths were distributed across age groups in 2016. Both cancer deaths and other causes of deaths increase throughout most of the age range before starting to decline after the age of 90. Cancer deaths peak at ages 75–79 and 80–84 with more than 200,000 deaths in each age group. The peak of all deaths occurs in the age group 85–89 with almost one million deaths.

Looking at cancer deaths relative to all deaths there are two peaks in the share of cancer deaths. The first one is during childhood (ages 5 to 15) where more than one in five deaths (22 percent) is due to cancer. The second peak occurs between ages 60 and 69 where around 43 percent of all deaths are due to cancer.

2.3.2 DALYs

DALYs, developed by the WHO, are a comprehensive measure of the disease burden.[9] They take into account the morbidity aspect (the impact of a disease on people's daily lives) and the mortality aspect (premature death due to the disease). In comparisons of the disease burden across disease groups, such a comprehensive measure is important as many diseases are not fatal but can still cause a great burden to society and health systems.

One DALY represents one year of "healthy" life lost [22]. The sum of all DALYs across a country's population represents the burden of disease in that country. It can be thought of as a measure of the gap between the current health state of a population and the ideal situation in which the entire population lives to an advanced age, free of disease and disability. DALYs for a specific disease or health condition are computed as the sum of two components; Years of Lost Life (YLL) due to premature death caused by the disease or health condition and Years of Lost Life to Disability (YLD) for people living with the disease or health condition.

Figure 14 presents an overview of the disease burden measured in DALYs in Europe in 2000 and 2016 [23]. Several changes are notable between the two years. First, the total number of DALYs has decreased from 157.5 to 154.3 million (despite the population growth during the period), indicating a healthier population. Secondly, cardiovascular diseases caused the greatest share of DALYs, but their share decreased from 25 to 21 percent. Cancer (defined as malignant neoplasms) caused the second-greatest share of DALYs, and it increased its share from 19 to 20 percent. This pattern can be attributed to a substantially decreased mortality in cardiovascular diseases during this period [24]. Cancer might soon surpass cardiovascular diseases and become the disease group causing the greatest burden; it has already done so in mostly wealthier countries (Belgium, Denmark, France, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Slovenia, Spain, Switzerland, and the UK).

[9] An alternative measure is Years of Potential Life Lost, but this one fails to take morbidity into account. Another measure is Quality-Adjusted Life Years, for which no comparable country-level data across the disease spectrum are available.

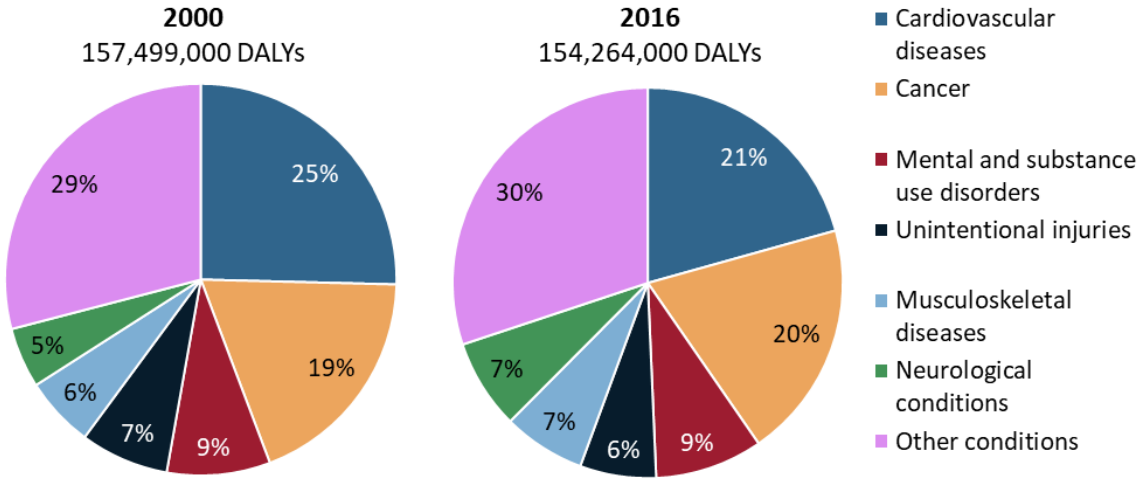

Figure 14: Disease burden of the largest disease groups in Europe, 2000 & 2016 [23]

Table 1 lists the ten cancer types that caused the greatest disease burden, in terms of DALYs, in 2000 and 2016. The bottom row of the table shows that the total burden of cancer has increased slightly between 2000 and 2016, but it decreased in per-capita terms. Cancers of the trachea, bronchus, and lung (mainly related to smoking) top the list in both years. Colorectal cancer comes in second place in both years. Breast cancer in third place and stomach cancer, slipping from fourth to seventh place, were the only major cancer type that significantly decreased in terms of total number of DALYs.

Table 1: Disease burden of the top 10 cancer types in Europe, 2000 & 2016 [23]

	2000					2016			
	Total DALYs ('000)	DALYs / 1,000 inhab	Share of total	Share of YLL		Total DALYs ('000)	DALYs / 1,000 inhab	Share of total	Share of YLL
1st Trachea, bronchus, lung	6,197	12	21%	99%	1st Trachea, bronchus, lung	6,621	13	22%	99%
2nd Colorectal	3,419	7	12%	97%	2nd Colorectal	3,501	7	12%	96%
3rd Breast	2,757	6	9%	95%	3rd Breast	2,560	5	8%	93%
4th Stomach	1,787	4	6%	98%	4th Pancreatic	1,851	4	6%	99%
5th Lymphomas, mul. myeloma	1,470	3	5%	97%	5th Prostate	1,460	3	5%	90%
6th Pancreatic	1,407	3	5%	99%	6th Lymphomas, mul. myeloma	1,423	3	5%	96%
7th Prostate	1,358	3	5%	92%	7th Stomach	1,377	3	5%	98%
8th Leukemia	1,102	2	4%	97%	8th Liver	1,185	2	4%	99%
9th Brain and nervous system	1,090	2	4%	99%	9th Brain and nervous system	1,165	2	4%	98%
10th Liver	1,005	2	3%	99%	10th Leukemia	1,051	2	3%	96%
All cancers	29,708	60	100%	97%	All cancers	30,398	58	100%	97%

When taking a closer look at the two components of DALYs - the mortality component YLL and the morbidity component YLD - it is possible to distinguish the nature of the disease burden. In both 2000 and 2016 mortality accounted for 97 percent of the disease burden and morbidity for the remaining three percent. For cancer types with relatively low survival (e.g. lung cancer and pancreatic cancer) mortality accounted for almost 100 percent. By comparison, in cancer types with relatively high survival (e.g. prostate cancer and breast cancer), the morbidity component accounted for a share of up to ten percent.

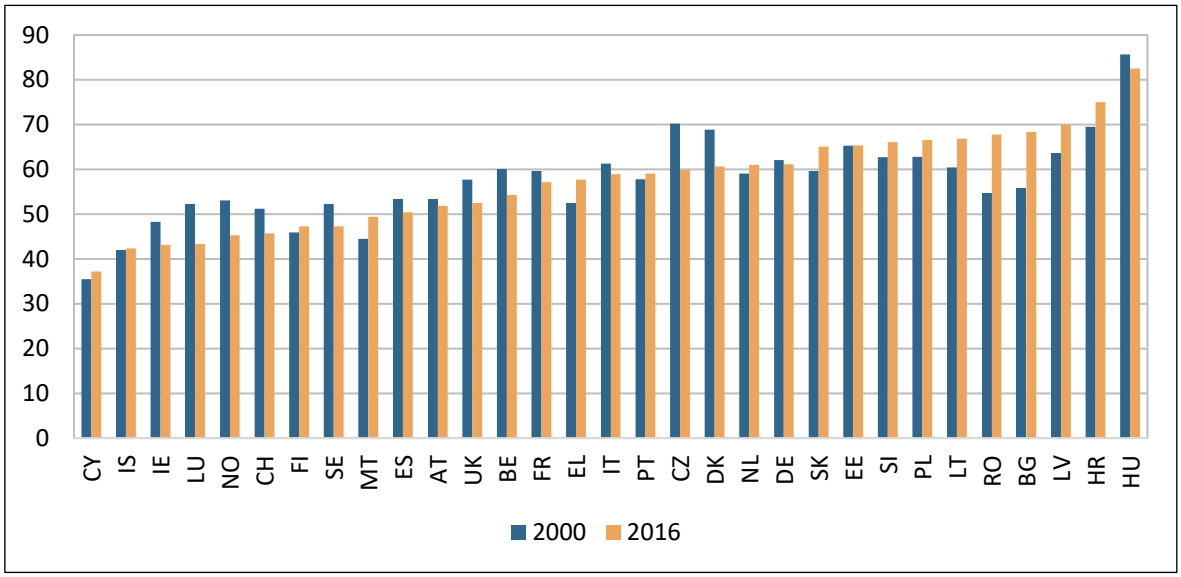

Figure 15: DALYs caused by cancer per 1,000 inhabitants, 2000 & 2016 [23]

Figure 15 shows the disease burden of cancer in different countries in 2000 and 2016. Hungary had by far the highest burden with 86 DALYs (year 2000) and 82 DALYs (year 2016) per 1,000 inhabitants. The country with the lowest disease burden was Cyprus with less than 40 DALYs in both years. The disease burden of cancer has decreased in about half of the countries (the biggest absolute reductions occurred in Czechia, Luxembourg, Denmark, and Norway), while it increased or remained stable in the other half of the countries (the biggest absolute increases occurred in Bulgaria and Romania).

2.3.3 Explanations for recent trends

The analysis of cancer incidence and cancer mortality revealed different trends. Measured in absolute numbers, incidence increased by around 50 percent and mortality by around 20 percent in Europe between 1995 and 2018. In the absence of the demographic development (positive population growth and population aging), incidence rates would still have increased in most countries, whereas mortality rates would have decreased in most countries. This discrepancy in the development of incidence and

mortality is reflected in the simultaneous improvement in survival rates of different cancer types. The cause behind this development has been attributed to “major advances in cancer management” [25, 26].

Cancer management refers to all the actions that are taken in the cancer patient pathway. It encompasses primary prevention, screening, diagnosis, and treatment with curative and palliative intent [27]. To pin down the exact contribution of each of these components is impossible, but a few conclusions can nevertheless be drawn.

2.3.3.1 Primary prevention

Primary prevention refers to measures that aim to decrease modifiable risk factors attributable to cancer. These risk factors include, among others, cigarette smoking, alcohol consumption, excess body weight, and exposure to ultraviolet radiation. As primary prevention measures aim at preventing cancer from occurring in the first place, these measures can only influence the level of cancer incidence, but they cannot help to explain the diverging trends in incidence and mortality.

Figure 16 shows estimates of the cancer cases (incidence) that were attributable to 17 different risk factors in the US in 2014 [28]. All risk factors together are estimated to be attributable to 42 percent of all cancer incidence cases. Cigarette smoking accounted for the highest portion of preventable cancer cases (19 percent), followed by excess body weight (7.8 percent), alcohol consumption (5.6 percent), and ultraviolet radiation (4.7 percent). The same study also estimated the share of preventable cancer cases for different cancer types; see Figure 16. It estimated that all cases (100%) of cervical cancer and Kaposi sarcoma are attributable to modifiable risk factors. Of the 26 cancer types considered, 15 types had a preventable share of over 50 percent of all cases.

The role that the health care system can play in reducing risk factors depends on the type of risk factor. Figure 16 shows that most risk factors are related to certain lifestyles (smoking, eating and drinking habits, etc.). Public campaigns can help to raise awareness around these risk factors. Excise taxes can help to change consumption patterns. Smoking bans in restaurants and public spaces can help to reduce tobacco consumption. In case of the six infections listed in Figure 16, the health care system can play a bigger role. The implementation of comprehensive vaccination programs is important. Vaccination against the hepatitis B virus can prevent liver cancer. Vaccination against HPV in both girls/women and boys/men can prevent cancers of the cervix, vagina, vulva, anus, neck & oropharynx, and penis. The treatment to cure hepatitis C virus infection can prevent liver cancer. Needle exchange programs can prevent the spread of HIV infection.

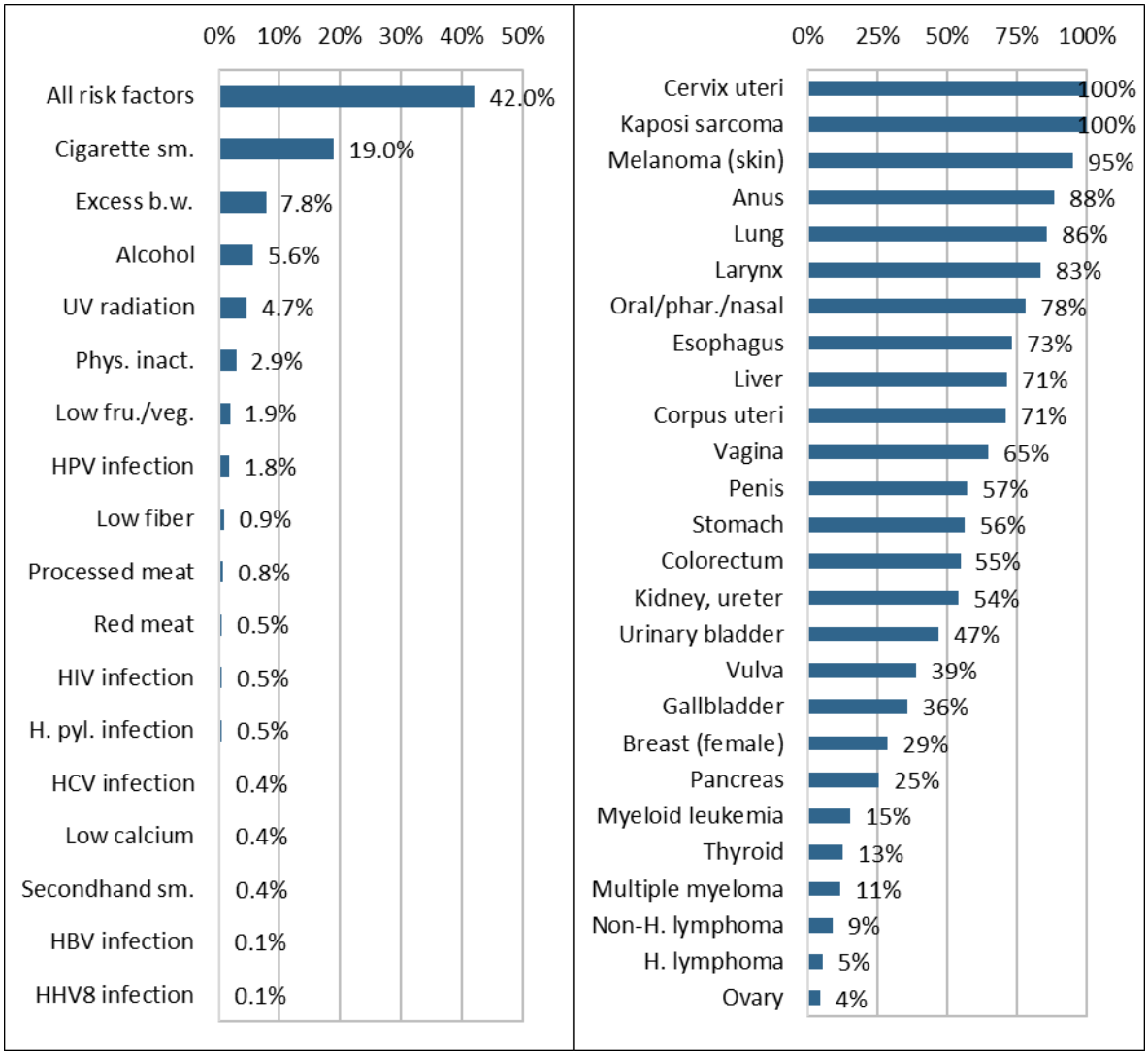

Figure 16: Estimated share of cancer incidence cases attributable to risk factors by risk factor and by cancer type of both sexes aged ≥ 30 years in the US, 2014

Notes: b.w. = body weight; UV = ultraviolet radiation; Phys. inact. = physical inactivity; fru./veg. = fruit and vegetable consumption; HPV = human papillomavirus; HIV = human immunodeficiency viruses; H. pyl. = Helicobacter pylori; HCV = hepatitis C virus; sm. = smoking; HBV = hepatitis B virus; HHV8 = human herpes virus type 8; phar. = pharynx; H. lymphoma = Hodgkin lymphoma; N-H. lymphoma = non-Hodgkin lymphoma. Kidney also includes renal pelvis and ureter, and lung includes bronchus and trachea. Cancer is defined as all cancer types excluding nonmelanoma skin cancer. Source: [28].

2.3.3.2 Screening

Screening (secondary prevention of cancer) aims to detect a cancer in the earliest stages, before the onset of signs and symptoms. The roll-out of population-based screening programs for cervical cancer and breast cancer in the 1990s and 2000s in most countries in Europe might have led to the detection of a larger share of cancer cases at an early stage [29-31]. The same is true for the roll-out of population-based screening programs for colorectal cancer in the 2010s. To give an example, after

the introduction of a population-based screening program for colorectal cancer in March 2014 in Denmark, the number of newly diagnosed cases of colorectal cancer suddenly surged by 20 percent between 2013 and 2014 [10]. This distinct increase in Denmark is probably a result of a larger number of early detected cases. Since curability at an early stage is higher than at an advanced stage, screening programs can improve survival even in the absence of changes in the effectiveness of actual treatment.[10] Furthermore, unorganized mass screening has – especially for prostate cancer – led to the detection of many cases of latent disease that never would have become symptomatic [32]. This phenomenon has inflated incidence but since the disease is latent, mortality is very low.

The description above shows that screening can explain part of the diverging trends in incidence and mortality. However, it is important to remember that established screening methods are only available for a handful of (rather common) cancer types. It should also be noted that the steady increase in survival rates for breast cancer and colorectal cancer over the last decades set in long before the now established screening methods were implemented.

2.3.3.3 Diagnostics

Diagnostics also contributes to the observed development in Europe. The aim of diagnostics is to locate the cancer, to determine its spread, and to examine its nature. During the last decades, the introduction of CT and MRI scanners as well as PET-CT scanners has improved the possibilities of accurate diagnosis. Since the investment costs for such medical equipment is high, availability of and access to it differs between and within countries and might explain some country-level differences. In addition, molecular prognostic/predictive testing, for instance to examine HER2 status in breast cancer, has become more common. As is the case with screening, an improved diagnosis provides better preconditions for successful medical treatment, but it alone does not yield any benefit except knowledge on the nature of the cancer. In this sense, better diagnostics has certainly contributed to more effective medical treatment and thus can explain some part of the diverging trend between incidence and mortality. Based on mortality data from the US during 2000–2009, it has been shown that better diagnostics explains indeed some of the observed decline [33].

[10] For instance, a country might have an incidence rate of 500 cases per 100,000 inhabitants. If screening efforts are low, 50% of newly diagnosed cases are cured and 50% die, whereas with high screening efforts 60% can be cured and 40% die. Low (high) screening efforts will lead to a mortality rate of 250 (200) cases per 100,000 inhabitants. Thus, a lower mortality rate need not be the result of being more effective in treating each and every cancer case – it could solely be the result of having a larger share of early-stage cases that are "easier" to cure.

2.3.3.4 Treatment

The treatment of cancer is usually initiated with surgery or radiation therapy with curative intent and sometimes preceded by neoadjuvant therapy. Afterwards it is treated with adjuvant systemic therapy (i.e. chemotherapy, hormonal therapy, immunotherapy, and molecularly targeted therapy). Radiation therapy, systemic therapy, and to some extent surgery are also extensively used in palliative care. The availability of radiation therapy machines and the availability of effective cancer medicines for systemic therapy have been improving during the last decades. New therapy modalities such as molecularly targeted therapy and immunotherapy have been developed and are being increasingly used (see Chapters 3 and 4). For instance, for the US it has been shown that the introduction of novel cancer medicines explains some of the observed decline in cancer mortality in 2000–2009 [33]. A Dutch study also presented evidence on the connection between the introduction of novel cancer medicines and declining cancer mortality in the Netherlands in 1960–2008 [34].

As noted above, screening and diagnostics can only unfold their potential to reduce cancer mortality if they are accompanied by appropriate medical treatment. Nonetheless, advances in medical treatment have also improved survival rates in their own right. This can be assessed by looking at stage-specific survival rates, in order to separate the influence of screening and diagnostics from medical treatment. For breast, colorectal, lung, and ovarian cancer different studies focusing on wealthier European countries have shown that stage at diagnosis explains some of the differences in survival rates between countries. Yet they also showed that differences persist even when stage-specific survival rates are compared [35-38]. This suggests that better medical treatment can explain part of the improvements in survival and the diverging trends in incidence and mortality.

2.3.3.5 Organization of care

Cancer management in Europe has seen some notable organizational changes during the last decades. For instance, Denmark was an earlier adopter of so-called standardized care processes (“kræftpakker” or “pakkeforløb for kræft”) for some cancer types in 2007. These standardized care processes span over the whole patient pathway from diagnosis to treatment and follow-up as well as rehabilitation and palliative care [39]. They are supposed to ensure that all patients receive high-quality care regardless of where in the country they live. High-quality care in this context means, among others, access to modern equipment for diagnostics and treatment, access to new cancer medicines, and timely access to treatment after diagnosis. The introduction of standardized care processes in Denmark coincides with the time when Denmark started to close the gap in survival rates to other wealthier countries [40].

2.4 Economic burden of cancer

The economic burden of cancer consists of two parts; direct and indirect costs. Direct costs are costs of resource consumption arising from the disease. These are expenditures borne by the health care system related to primary prevention, screening, diagnosis, treatment, rehabilitation, and palliative care. Formally provided social support services and informal care in terms of help with transportation and support at home from relatives and friends are also a part of the direct costs.[11] Indirect costs are costs of productivity loss arising from the disease. They consist of productivity loss from reduced ability to work in the labor market and from premature death of people in working age.

The development of the economic burden partly reflects the development of the disease burden. The growing number of diagnosed cancer cases increases the direct costs for diagnostics and treatment. Better cancer care might decrease the number of cancer deaths (in patients in working age) and thereby reduce mortality-induced productivity loss. Progress in cancer care, such as new imaging techniques for diagnosis, new treatment modalities, and additional screening programs, also affects the development of the economic burden. This usually increases the direct costs, as technological innovations tend to come at a higher cost and/or expand the share of patients benefiting from them.

The economic burden of cancer also has a time dimension on the patient level. Costs related to incidence are incurred during the first months or year after diagnosis. These costs encompass direct costs for diagnosis, initial treatment, and informal care, and indirect costs from morbidity-induced productivity loss. By contrast, costs related to mortality are incurred during the last months in life. These costs encompass directs costs for renewed treatment and/or palliative care of advanced disease and informal care, and indirect costs from mortality-induced productivity loss.

The aim of this section is to estimate the economic burden of cancer in Europe and to describe the development between 1995 and 2018.

2.4.1 Direct costs

The care process of cancer patients requires many different resources. To locate the cancer, medical equipment, such as CT, MRI, and PET-CT scanners, are used. Pathologists and diagnostic radiologists examine the nature of the cancer. Surgeons, radiologists, medical oncologists, and hematologists assisted by nurses perform surgery on the tumors and initiate radiation therapy and/or

[11] The difference between the value of productivity loss of a relative or friend who has to leave work to take care of the patient and the value of the informal care provided would constitute an indirect cost. In reality, most informal care is provided by relatives who in many cases have reached retirement age.

systemic therapy (chemotherapy, hormonal therapy, immunotherapy, and molecularly targeted therapy). Modern cancer care also includes psychosocial care and rehabilitation. Other cornerstones of cancer care are screening programs and primary prevention measures, such as HPV vaccination programs and public campaigns promoting a healthy lifestyle. Informal care provided by relatives and friends during the care process is also very important.

The direct costs of cancer constitute the sum of the resources mentioned above [41], although informal care might be considered a separate category. These costs encompass mostly resources within the health care system but also some resources outside of it (e.g. social care services). Both publicly paid resources (financed by tax money and/or social security contributions spent on the health care system) and privately paid resources (out-of-pocket payments for health care visits and medication, but also private health insurance) are part of the direct costs. When comparing the direct costs of cancer between countries, it should be remembered that these costs only represent a single number of the monetary value of all resources used. In order for the monetary inputs to yield the highest benefits to patients, the allocation and organization of resources is pivotal [42].

2.4.1.1 Methodology

The estimation of the direct costs of cancer has been carried out using the same method as in the previous comparator reports [11, 43-45]. The estimation follows a top-down approach. Starting with a country's gross domestic product (GDP; measured in euros, PPP-euros, or national currencies), the share of total health expenditure is used to obtain the total health expenditure.[12] Then the share of health expenditure spent on cancer care is determined to obtain cancer-specific health expenditure.

This top-down approach is in line with the idea of disease-specific health accounts that is proposed by the OECD [52]. The main argument for the top-down approach (instead of a bottom-up approach based on resource use of a few selected resource categories) is that it provides the best guarantee against both under- and overestimations. Data from different types of studies can be used for estimating the share of cancer-specific health expenditure, without having to depend on a pre-

[12] Data for GDP are obtained from Eurostat [46, 47], whereas data for the share of total health expenditure are obtained from the OECD and the WHO [48-50]. The calculation of the total health expenditure is carried out by the national statistical offices according to the System of Health Accounts (SHA), a common framework developed by the WHO and the OECD. Total health expenditure (actually called "current expenditure on health") are defined as the final consumption of health goods and services. Expenditure from both public and private sources are included. Despite the common framework, the OECD cautions that the comparability of the data is imperfect, since some different practices regarding the classification of long-term cars as either health expenditure or social expenditure have not been completely resolved [51].

determined definition of which types of health expenditure to include. When using a top-down approach, cancer-specific health expenditure represent a subset[13] of the total health expenditure.

The development of the total health expenditure in Europe as a whole is shown in Table 2. In 1995, total health expenditure amounted to €624 billion and more than doubled to €1,666 billion in 2018. If these figures are adjusted for inflation until 2018 and based on exchange rates in 2018, the total health expenditure in 1995 amounted to €888 billion, corresponding to an increase of 88 percent until 2018. Similarly, expenditure per capita more than doubled between 1995 and 2018 from €1,261 to €3,163. After adjusting for inflation and exchange rates there was still an increase of 76 percent. Total health expenditure as a share of GDP have increased from 8% in 1995 to 10% in 2018.

Table 2: Total health expenditure in Europe, 1995–2018

	1995	2000	2005	2010	2015	2018	Change 1995–2018	Mean annual change
Current prices (in billion €)	624	815	1,076	1,323	1,579	1,666	167%	4.4%
2018 prices (in billion €)	888	1,065	1,288	1,469	1,581	1,666	88%	2.8%
Current prices per capita (in €)	1,261	1,633	2,122	2,563	3,024	3,163	151%	4.1%
2018 prices per capita (in €)	1,794	2,134	2,542	2,847	3,027	3,163	76%	2.5%
Share of GDP	8.1%	8.0%	8.8%	9.7%	10.0%	9.9%		

Notes: Total health expenditure in 2018 were calculated based on GDP data from 2018 and on estimates of the share of total health expenditure from 2018 or the latest available year. The adjustment for inflation was carried out with country-specific inflation rates. The 1995 estimates could only be adjusted for inflation between 1996 and 2018 due to lack of data. Missing annual inflation rates for BG (1996; 3%), HR (1996–1997; 3%), and CH (1996–2004; 1%) were imputed. Source: [47-50, 53].

Health expenditure broken down into disease-specific expenditure are not routinely provided by national statistical offices. Therefore, the key factor to calculate the cancer-specific share of health expenditure must be obtained from other sources. In line with the previous Comparator reports, reports and studies from national ministries of health, national statistical offices, research institutes, national cancer societies, and peer-reviewed journals were reviewed. Section A.1.4 in the Appendix provides a description of all identified studies that assessed the direct costs of cancer for each country.

[13] Cancer causes also direct costs that fall beyond the remit of the health care system. Cancer patients are increasingly treated outside hospitals in ambulatory care, which created a need for social support services. These direct costs are often not classified as health care costs, and thus the magnitude of these costs is difficult to assess.

Ideally, we would require estimates of cancer-specific health expenditure for every country and every year between 1995 and 2018. However, national estimates for only 20 countries could be found. For eight of these countries, information of the cancer-specific health expenditure was available for more than one year and provided by the same source. In these countries, the shares of cancer-specific health expenditure remained mostly stable (Finland, Germany, Norway, Poland, UK) or increased slightly (Czechia, France, Netherlands) during the 2000s and the 2010s; see Table 3. For instance, in Germany the share was 6.3% in 2002 and between 2004 and 2015 it was around 7.0%, whereas in the Netherlands the share increased from 4.7% in 2003 to 6.9% in 2015. A stable pattern of the cancer-specific share for a much longer period has been observed in the United States, where it was close to 5% between 1963 and 1995 [54]. In 2010, the cost of cancer care was estimated to be $124.57 billion [55], and total health expenditure amounted to $2,555.4 billion [49], corresponding to a share of 4.9%. Thus, the cancer-specific share in the US was virtually identical in 1995 and 2010, but, just as in Europe, the total health expenditure as a share of GDP increased during this period.

Table 3: Cancer-specific share (in %) of total health expenditure in selected countries

	2002	‘03	‘04	‘05	‘06	‘07	‘08	‘09	‘10	‘11	‘12	‘13	‘14	‘15	‘16	‘17
CZ								5.7		7.0						
FI			4.1										4.0			
FR												6.2	6.5	6.7	6.8	7.1
DE	6.3		6.9		7.2		7.1							6.8		
NL		4.7		4.8		5.5				6.2				6.9		
NO										4.5	4.2	4.3	4.2			
PL								6.7	6.9	7.0						
UK		4.9	5.1	5.2	5.0	5.1	5.1	5.3	5.0	4.9	5.0					

Notes: For the sources and the calculations of the shares see section A.1.4 in the Appendix. For the UK, the estimate in year X refers to the budget year X/X+1.

For 12 countries, information on the cancer-specific share of health expenditure was only available for a single year (e.g. for 2015 for Spain). Given the above observation of rather stable cancer-specific shares of total health expenditure in European countries, the use of shares from a single year for all years from 1995 to 2018 should yield a valid approximation of the real costs. If there were a slight upward trend in the share during this period, the national estimates of the direct costs for the years preceding (succeeding) the year that the original estimates refer to, would be slightly overestimated (underestimated). For the eight countries with estimates for multiple years, the cancer-specific share that was closest to the year in question was used (e.g. the Finnish estimate for 2004 was applied to the years 1995, 2000, and 2005, while the estimate for 2014 was applied to the years 2010, 2015, and 2018). Finally, for the eleven countries for which no data were found, extrapolations based on the shares from other countries (selected based on geographical proximity and similarity in

GDP per capita) were made. Note that all extrapolations were only based on countries for which national estimates were found.

Another methodological challenge is the use of different definitions of cancer in the reviewed studies. While some studies focused only on malignant neoplasms (ICD-10 C00-C97), others used a broader definition (ICD-10 C00-D48), which includes in situ neoplasms (D00-D09), benign neoplasms (D10-D36), and neoplasms of uncertain or unknown behavior (D37-D48). In this section, we equate cancer with neoplasms. Since some studies only focused on malignant neoplasms, it is likely that the direct costs in this section are underestimated.[14]

The direct costs are calculated in euros (€) to facilitate a comparison between countries. As the estimates cover the period from 1995 to 2018, the effects of a general increase in prices (inflation) and of fluctuating exchange rates must be taken into account. The main results are therefore presented in 2018 price levels and exchange rates. To take into account different price levels between countries, in some comparisons costs are adjusted for differences in purchasing power parity (PPP).

2.4.1.2 Results

The top-down approach to estimate the direct costs of cancer in all countries for the year 2018 is illustrated in Table 4. Data on GDP and the share devoted to total health expenditure form the starting point. Countries differed greatly on how much of GDP that is spent on health care. Cyprus, Estonia, Hungary, Latvia, Lithuania, Luxembourg, Poland, Romania, and Slovakia spent less than seven percent on health care. By contrast, France, Germany, Sweden, and Switzerland spent eleven percent or more on health care. Together with differences in GDP this meant that per-capita health spending ranged from just below €1,000 in Romania to almost €6,000 in Switzerland (after adjusting for PPP). In Europe as a whole, health expenditure as a share of GDP were 9.9% and per-capita spending was €3,163.

Table 4: Total health expenditure and direct costs of cancer (adjusted for PPP), 2018

	Total health expenditure			Direct costs of cancer		
	% of GDP	total (million €, PPP)	per capita (€, PPP)	% of THE	total (million €, PPP)	per capita (€, PPP)
Austria	10.3%	35,930	4,060	6.4%*	2,300	260
Belgium	10.4%	42,261	3,703	6.9%*	2,930	257
Bulgaria	8.2%	8,992	1,276	7.1%*	634	90

[14] The magnitude of this issue can be illustrated on the basis of data from Germany. Of all health expenditures spent on neoplasms (C00-D48) in 2015, 87% were spent on malignant neoplasm (C00-C97) and the rest on other neoplasms (D00-D48) [56].

Croatia	7.2%	5,720	1,398	6.8%*	386	94
Cyprus	6.9%	1,601	1,844	6.3%	101	116
Czechia	7.5%	22,295	2,095	7.0%	1,561	147
Denmark	10.5%	23,690	4,094	4.8%	1,137	197
Estonia	6.4%	2,139	1,619	5.8%	124	94
Finland	9.1%	17,029	3,091	4.0%	681	124
France	11.2%	240,872	3,583	7.1%	17,102	254
Germany	11.2%	350,039	4,222	6.8%	23,803	287
Greece	7.8%	17,641	1,648	6.5%	1,147	107
Hungary	6.6%	13,992	1,431	7.1%	993	102
Iceland	8.3%	1,197	3,394	3.8%	45	129
Ireland	7.0%	20,101	4,132	5.0%*	1,005	207
Italy	8.8%	157,031	2,600	6.7%	10,521	174
Latvia	5.9%	2,457	1,273	6.4%*	157	81
Lithuania	6.8%	4,752	1,694	6.4%*	304	108
Luxembourg	5.4%	2,586	4,245	6.9%*	179	294
Malta	9.3%	1,356	2,816	6.5%*	88	183
Netherlands	9.9%	68,338	3,966	6.9%	4,715	274
Norway	10.2%	25,140	4,735	4.2%	1,056	199
Poland	6.3%	53,013	1,377	7.0%	3,711	96
Portugal	9.1%	21,893	2,129	5.4%	1,182	115
Romania	5.0%	19,376	991	7.1%*	1,366	70
Slovakia	6.7%	8,805	1,615	7.1%*	621	114
Slovenia	7.9%	4,446	2,145	6.4%	285	137
Spain	8.9%	117,031	2,507	4.9%	5,735	123
Sweden	11.0%	41,970	4,128	3.7%	1,553	153
Switzerland	12.2%	50,041	5,860	6.0%	3,002	352
UK	9.8%	209,243	3,145	5.0%	10,462	157
Europe	9.9%	1,665,542†	3,163	6.2%	102,607†	195

Notes: GDP = gross domestic product, PPP = purchasing power parity, THE = total health expenditure. *Estimated share based on data from similar countries; see section A.1.4 in the Appendix for the methodology. † The sum of all PPP-adjusted national estimates does not equal the estimate for Europe, as the different shares of GDP spent on THE and the different shares of THE spent on cancer change the weighting of the national estimates. The estimate for Europe is the sum of the non-PPP adjusted national estimates. Source for THE: see Table 2. Source for direct costs of cancer: own estimate based on national sources; see section A.1.4 in the Appendix for the methodology.

Table 4 also shows that the share of total health expenditure that is spent on cancer care differed between countries. It ranged from four percent or less in Finland, Iceland, and Sweden to seven percent or more in Bulgaria, Czechia, France, Hungary, Poland, Romania, and Slovakia. However, there is no clear tendency that poorer countries would devote a larger or a smaller share of their total health expenditure to cancer compared with wealthier countries; see also Figure A10 in the Appendix. There is neither a clear tendency that the share devoted to cancer is related to the disease

burden; see Figure A11 in the Appendix. Per-capita health spending on cancer ranged from below €100 in Bulgaria, Croatia, Estonia, Latvia, Poland, and Romania to €352 in Switzerland (after adjusting for PPP). In Europe as a whole, the share of health expenditure spent on cancer was 6.2% and translated into per-capita health spending of €195.

Differences between countries in per-capita health spending on cancer (direct costs) in 2018 are also illustrated in Figure 17. Switzerland, Germany, Austria, the Benelux countries, and France spent the most on cancer – between €250 and €350 (PPP-adjusted). The Nordic countries, Ireland, the UK, Malta, Italy, Spain, Czechia, and Slovenia spent between €125 and €200 (PPP-adjusted). Countries on the Eastern border of the EU spent the least. The lowest spending country, Romania (€70), spent only a fifth of the highest spending country, Switzerland (€352), on cancer. If price differentials are not taken into account, the direct costs of cancer in the highest spending country, Switzerland (€511), were fourteen times higher than in the lowest spending country, Romania (€36).

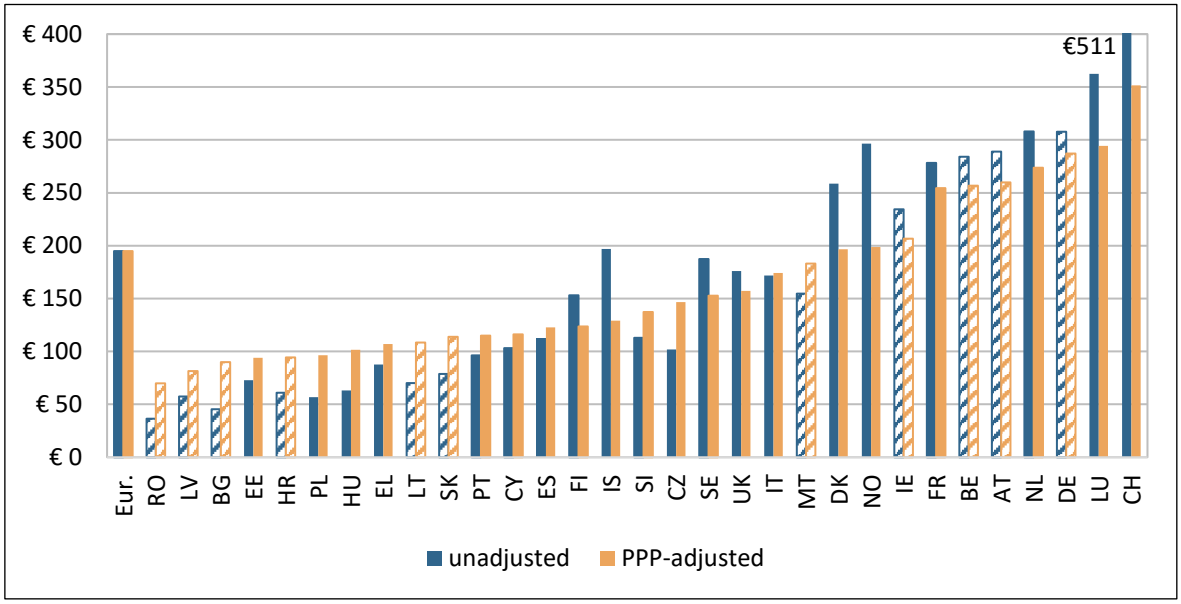

Figure 17: Direct costs of cancer per capita (in €), 2018

Notes: Hatched bars indicate that the direct costs are estimated based on data from similar countries; see Appendix for methodology. The blue bar for CH is truncated - its true size is €511. Source: see Table 4.

Even though the direct costs of cancer differed greatly between countries in 2018, the country differences were even greater in 1995; see Figure 18. Romania, Bulgaria, Poland, and the Baltic countries spent less than €10 on cancer (in non-PPP adjusted terms), whereas Switzerland spent over €200 on cancer. There was a 77-fold difference between the lowest spending country (Romania) and the highest spending country (Switzerland), and after taking into account price differentials there was still a 14-fold difference. Per-capita health spending on cancer thus increased more rapidly in the poorer countries on the Eastern border of the EU than in the other countries between 1995 and 2018.

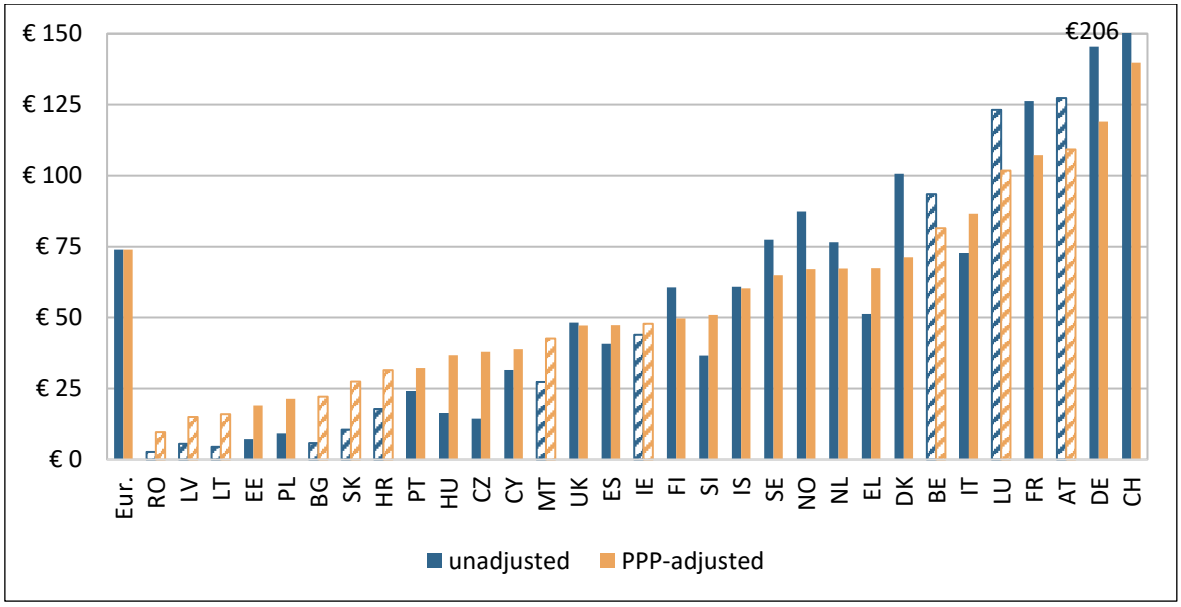

Figure 18: Direct costs of cancer per capita (in €), 1995

Notes and source: see Table 4. The blue bar for CH is truncated - its true size is €206.

The development of the direct costs of cancer in Europe as a whole is shown in Figure 19. Measured in current prices and exchange rates, total health expenditure spent on cancer amounted to €36.5 billion in 1995 and almost tripled (181% increase) to €102.6 billion in 2018. Adjusting for inflation and applying constant exchange rates, the direct costs amounted to €51.9 billion in 1995 and then doubled (98% increase) until 2018. It is noticeable that the growth in the direct costs of cancer slowed somewhat during the last ten years (potentially related to the economic crisis starting in 2008); between 1995 and 2005 costs increased by €26 billion but between 2005 and 2015 they increased by €18 billion.

Figure 20 shows the same information as Figure 19 but provides numbers in per-capita terms. In 1995, the health expenditure spent on cancer amounted to €74 per capita and increased to €195 per capita until 2018, equaling a 164% increase. After adjusting for inflation and applying constant exchange rates, the direct costs amounted to €105 in 1995 and increased by 86% until 2018.

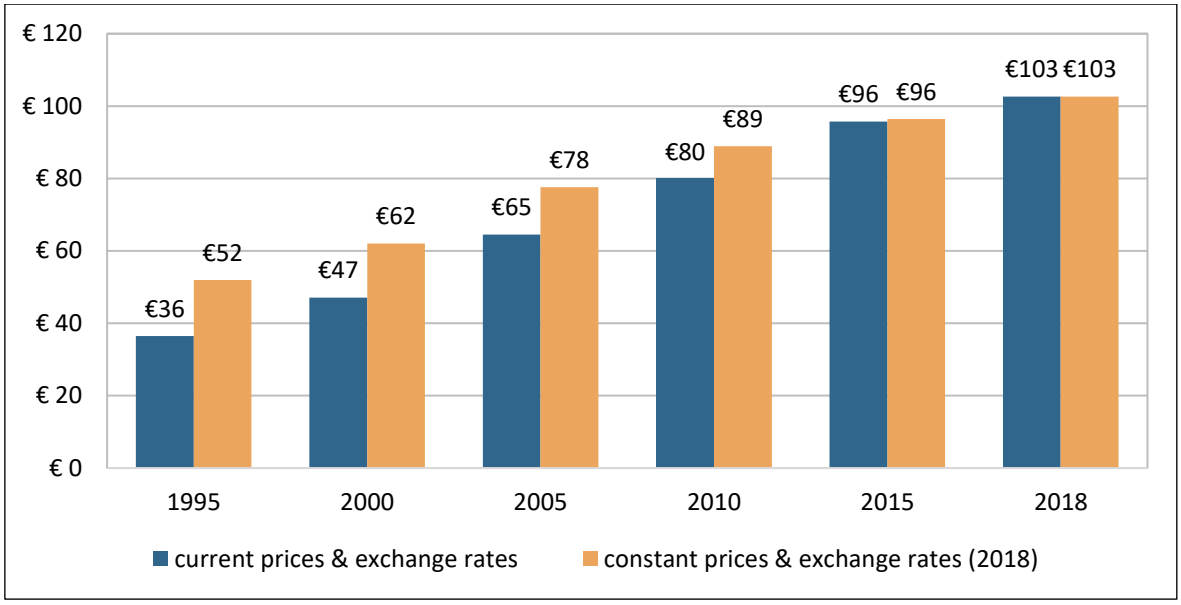

Figure 19: Direct costs of cancer in Europe (in billion €), 1995–2018

Notes: The adjustment for inflation was carried out with country-specific inflation rates. The 1995 estimates could only be adjusted for inflation between 1996 and 2018 due to lack of data. Source: [53, 57] and see Table 2 and Table 4.

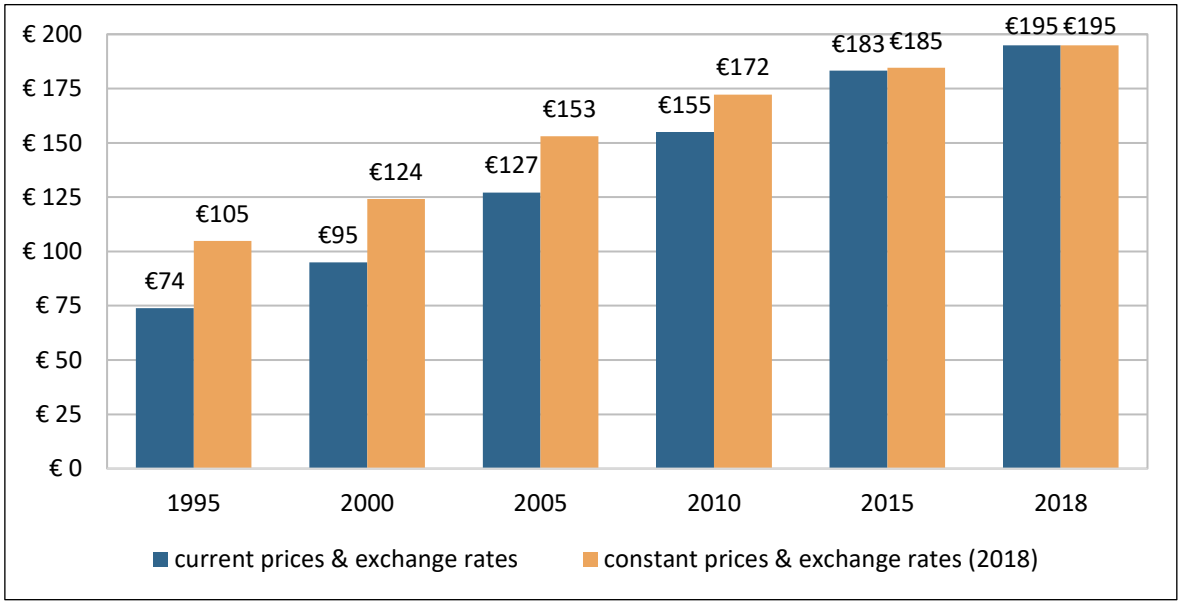

Figure 20: Direct costs of cancer per capita in Europe (in €), 1995–2018

Notes and source: see Figure 19.

By construction of the estimates of the direct costs of cancer in this report, the development of the direct costs (Figures 19 and 20) is closely related to the overall development of the total health expenditure (Table 2). The pattern of increasing direct costs of cancer between 1995 and 2018 is a consequence of increased spending on health care rather than an increased share of health care resources devoted to cancer care. However, there are a range of important factors that can help to

explain (1) the overall increase in the direct costs, and (2) why the share of health care resources devoted to cancer care remained relatively stable. These factors, listed below, have also implications for the future development of the direct costs of cancer:

- The description of the burden of cancer in section 2.2.1 showed that the number of newly diagnosed cancer cases increased by about 50% between 1995 and 2018. This sheer increase in the number of cancer patients might be one important explanatory factor of the observed increase in the direct costs (98% in constant prices and exchange rates). As cancer incidence, in crude terms, is predicted to increase further in the future due to the demographic development and an increasing prevalence of some risk factors, the direct costs will probably continue to increase.
- Since survival has increased (see section 2.2.3), some patients have required care for a longer time. This affects mostly the costs of long-term care and rehabilitation but also of ambulatory care, as the number of regular medical check-ups for the monitoring of disease progression and of recurrence increases.
- More resources have been spent on screening (e.g. population-based breast cancer screening programs were rolled out during this period; cervical cancer screening programs had been rolled out before in some cases) and on primary prevention (e.g. HPV vaccination programs mostly for girls were rolled out in the 2010s). This trend will continue in the future, as additional screening programs will be added (currently for colorectal cancer, but in the future possibly also for lung cancer) and boys will be covered by HPV vaccination programs. The implementation of these measures increases the direct costs in the short and medium run but can be expected to decrease the costs in the long run.
- The development of personalized/precision medicine involves a growing role of molecular testing, increases the treatment options for patients, and reduces the exposure to the costs and side effects of non-effective treatments. But this development requires investments in facilities for testing, which adds to the direct costs of cancer [58].
- Cancer care has become more effective as new and improved treatment modalities have been introduced (see Chapter 3). In many cases, these improvements enable shorter hospital stays, entail fewer side effects, and result in quicker recovery and potentially fewer recurrences [59]. For instance, the introduction of antiemetic medicines in the early 1990s meant that patients no longer had to suffer from vomiting and nausea due to treatment with cytostatic agents. This meant that more patients could be shifted from inpatient care to ambulatory care. Thus, more effective cancer care might have increased the demand for some medical

services (especially cancer medicines) but decreased the demand for other services (especially inpatient care); see section 2.4.1.3.

- There has been a shift from intravenous to oral delivery methods of cancer medicines (see Figure 45 in Chapter 4). As more patients could receive treatment at home, this might have decreased the demand for inpatient care and ambulatory care. However, the introduction of cancer immunotherapy works against this trend, as it requires intravenous delivery methods.
- New cancer therapies, such as targeted therapy and immunotherapy, come at a higher price, which has led to substantial increases in expenditures on medicines (see Chapter 4). New therapies have also allowed new patient groups to be treated. This has increased the direct costs and is likely to continue in the foreseeable future.

2.4.1.3 Composition of the direct costs

Despite the overall increase in the direct costs of cancer between 1995 and 2018 documented in the previous section, the different types of direct costs did not uniformly follow the same pattern. In Europe, inpatient care has accounted for the by far largest share of the direct costs of cancer [11]. This includes costs for surgery, but also part of the costs for diagnostics, radiation therapy, systemic therapy, and medical staff. Outpatient care (ambulatory care at hospitals) used to play a much smaller role. This includes costs for diagnostics, radiation therapy, systemic therapy, and medical staff. Palliative care and nursing services usually account for a small share. The same is true for costs for screening and primary prevention measures.

Figure 21 shows the distribution of the direct costs of cancer across different cost categories in Finland in 2004 and 2014. During this period, the total direct costs increased from €506 to €775 million (in nominal prices) [60], whereas the share of the direct costs on the total health expenditure remained unchanged with 4.1% and 4.0%, respectively. Inpatient care was by far the largest cost category in 2004, but its share on the total costs almost halved until 2014. In 2014, ambulatory care provided by hospitals was the largest cost category. In addition, the share of outpatient medications nearly doubled between 2004 and 2014. The other cost categories grew mostly in line with the overall increase in the direct costs.

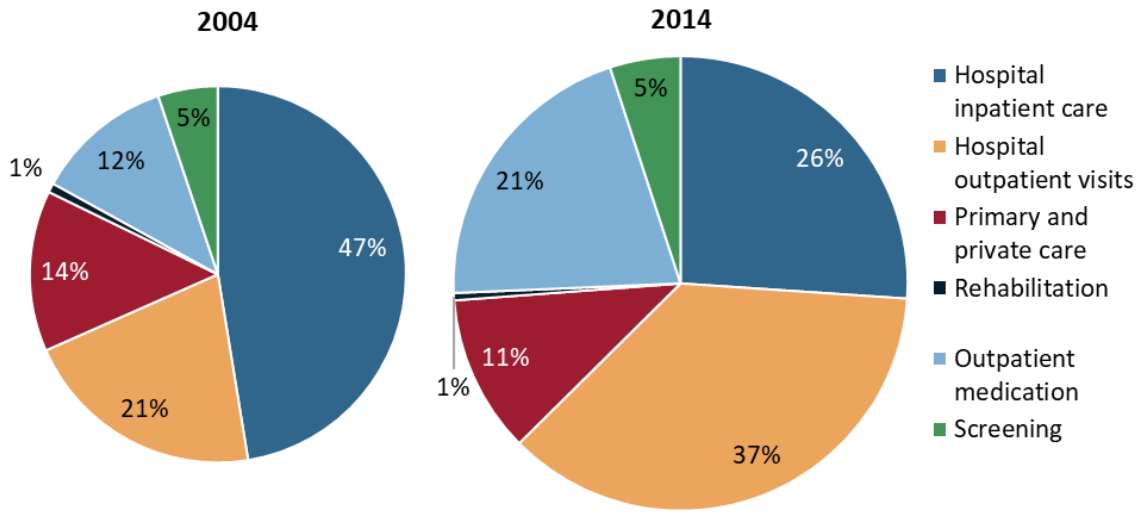

Figure 21: Composition of the direct costs of cancer in Finland, 2004 & 2014 [60]

The Finnish example highlights three major trends that have characterized the shifting composition of the direct costs of cancer [61]:

- The direct costs have increased, but they grew mostly in line with total health expenditure. The increase is partly driven by the rising number of cancer patients but also by more intensive care and increased costs per patient.
- Cancer care has shifted from an inpatient to an ambulatory setting (see section 2.4.1.4). Inpatient days, which are comparatively expensive, have partly been substituted by outpatient visits, which are comparatively cheaper. This shift is a result of the development of new treatment modalities. Newer cancer medicines with different side effects can more easily be administrated in ambulatory care (as an intravenous infusion). Oral delivery of cancer medicines has become more common, which has enabled more patients to receive treatment at home.
- Expenditure on cancer medicines are increasing (see section 2.4.1.5). This is related to factors leading to increased usage (due to, e.g., increasing number of new cancer medicines, more cancer patients, new patient groups eligible for treatment, use in an adjuvant setting, longer duration of therapy) and to higher prices (see also Chapter 4).

2.4.1.4 Inpatient and ambulatory care

The rapid relative decline in costs for inpatient care observed in Finland (see Figure 21) was probably shared by most other European countries. Figure 22 shows the development of the number of bed days (i.e. overnight stays of hospitalized patients) and the number of day cases (i.e. patients who are

formally admitted to the hospital but then discharged on the same day) between 2000 and 2017 in a few selected European countries. Both the development for cancer patients (top figures) and the general development for all patients (bottom figures) are shown. This provides insights into whether the development in the number of cancer patients simply reflects a general shift in the organization of health care (e.g. from inpatient care to ambulatory care) in a country, or whether there is a disconnection between the overall trend and the specific trend in cancer patients. Note that comparable data for visits in ambulatory care (i.e. outpatient visits) are not available.

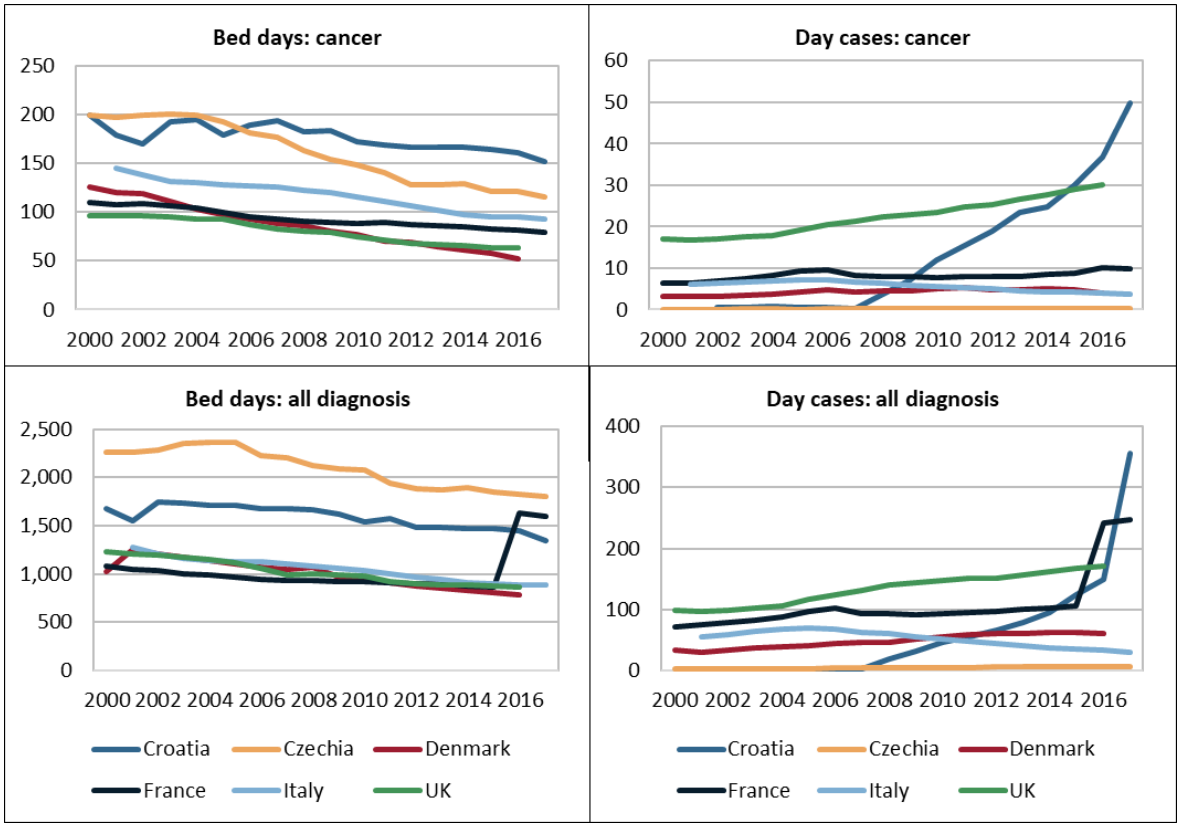

Figure 22: Bed days (left figures) and day cases (right figures) spent in hospitals per 1,000 inhabitants, 2000–2017

Notes: "All diagnoses" refers to ICD-10 A00-Z99/V00-Y98+Z38 and "cancer" to ICD-10 C00-D48. There are some breaks in the time series, notably in France in 2016. Sources: [62-64].

Figure 22 shows a clear downward trend in the number of bed days (standardized by population size) and a simultaneous upward (or constant) trend in number of day cases (standardized by population size) in the selected countries between 2000 and 2017. This pattern is observable both in cancer patients and in all patients. The number of bed days among cancer patients was approximately halved during this period in all countries. This represented a stronger decline than on the overall level. This suggests that inpatient days in cancer patients decreased even though the number of cancer patients increased during this period. Shorter hospital stays in the form of day cases are one expression of this development, but the largest chunk of patients has most likely been shifted to ambulatory care.

However, a reduction in the number of inpatient days does not automatically imply a decrease in costs of inpatient care, since the cost per inpatient day increase over time. Nonetheless, fewer inpatient days of cancer patients free up hospital beds for other patients.

2.4.1.5 Cancer medicines

The prices of individual cancer medicines and the total expenditure on all cancer medicines are two frequently debated topics. In the US, increasing prices have resulted in unsustainable out-of-pocket expenditure for both uninsured and insured patients who must pay a large portion themselves [65-69]. In Europe, the debate focuses more on the sustainability of the increasing total public expenditure on cancer medicines, since public payers (governments or sickness funds) cover the vast majority of the cost of cancer care (including cancer medicines) for the whole population [70].

Total sales of cancer medicines increased from €12.9 billion to €32.0 billion (in current prices) between 2008 and 2018 in Europe [71]. In per-capita terms, sales increased from €25 to €61 (in current prices). Chapter 4 describes this development in more detail and also discusses limitations of cancer medicine sales data, which often do not take into account confidential rebates leading to an overestimation. The development of the costs of cancer medicines should not be considered in isolation, as cancer medicines are part of the direct costs of cancer. Below, the total costs of cancer medicines are considered in relation to the direct costs of cancer.

Figure 23 compares the mean annual growth rate of cancer medicine sales between 2008 and 2018 with the mean annual growth rate of the direct costs of cancer during the same period. The annual growth rate in direct costs was 1.7 percent in Europe, whereas the annual growth rate in cancer medicine sales was 7.9 percent. Note that the growth rates are calculated based on per-capita costs which are expressed in 2018 price levels and exchange rates. It is also interesting to note that the annual growth rate in direct costs (1.7%) was equally large as the annual growth rate in the number of newly diagnosed cancer cases (1.7%, in per capita terms) in Europe between 2008 and 2018.

The pattern of much faster growth in cancer medicine costs than total direct costs is observable in most countries in Figure 23. The direct costs increased in all countries between 2008 and 2018, except in Greece, Luxembourg, Italy, and Croatia, and cancer medicine sales also increased in all countries (with complete data), except in Czechia. Czechia is the only country (with complete data) where direct costs grew faster than expenditures for cancer medicines. The highest relative increase in cancer medicine sales was recorded in Bulgaria with a mean annual growth rate of 21 percent; Bulgaria also recorded the highest relative increase in total health expenditure (7 percent). Lithuania,

Norway, Latvia (between 2014 and 2018), and Germany all had annual growth rates in cancer medicine sales of more than 10 percent.

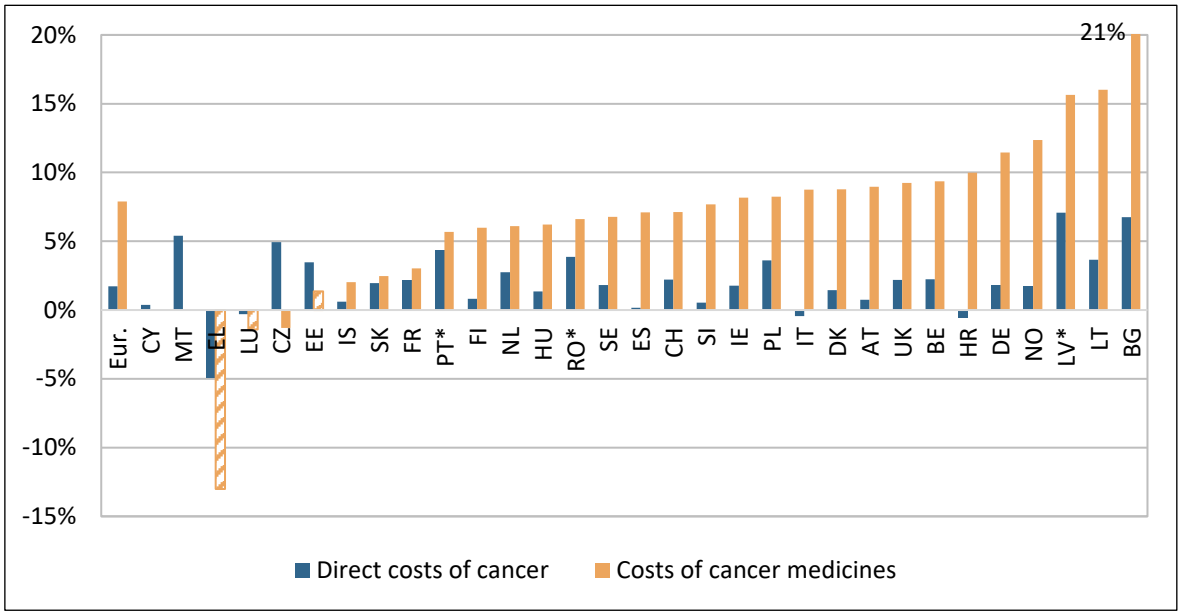

Figure 23: Mean annual growth rates in direct costs of cancer and cost of cancer medicines (per capita; in 2018 prices & exchange rates) between 2008 and 2018

Notes: Eur. = Europe. Hatched bars indicate that data for cancer medicines for EE, EL, and LU only comprise retail sales. * Both growth rates in PT are between 2010 and 2018, in RO between 2009 and 2018, and in LV between 2014 and 2018. There is no growth rate of medicine costs in CY and MT due to lack of data. The orange bar for BG is truncated - its true size is 21%.

As the costs of cancer medicines grew faster than the total direct costs, the share of cancer medicines on the direct costs increased. Figure 24 shows that this share was 31 percent in Europe in 2018, up from 17 percent in 2008.[15] This share varies also a lot between countries. It increased in all countries (with complete data) between 2008 and 2018, except in Czechia, where the share decreased from 29 to 16 percent, and in Slovakia, where the share was almost unchanged at around 38 percent. Cancer medicines accounted for more than half of the direct costs in Bulgaria (68%), Hungary, Croatia, and Spain in 2018. In Norway, the Netherlands, and Switzerland they accounted for less than 25 percent. Poorer countries (except Czechia, Poland, and Lithuania) tend to spend a larger share on medicines than wealthier countries (except Spain and Italy in 2018). One reason for this pattern is that there is a greater difference in relative prices of cancer care services (e.g. physicians, nurses) and cancer medicines in poorer countries. Cancer care services reflect lower domestic price levels, whereas the

[15] The use of IQVIA invoice prices (which often do not take into account rebates) leads to an overestimation of these shares. In the aggregate shares for Europe, medicine sales data from Cyprus and Malta are not included and for Estonia, Greece, and Luxembourg only retail sales are included.

price of cancer medicines mostly lies within a common price corridor and reflects higher international price levels.

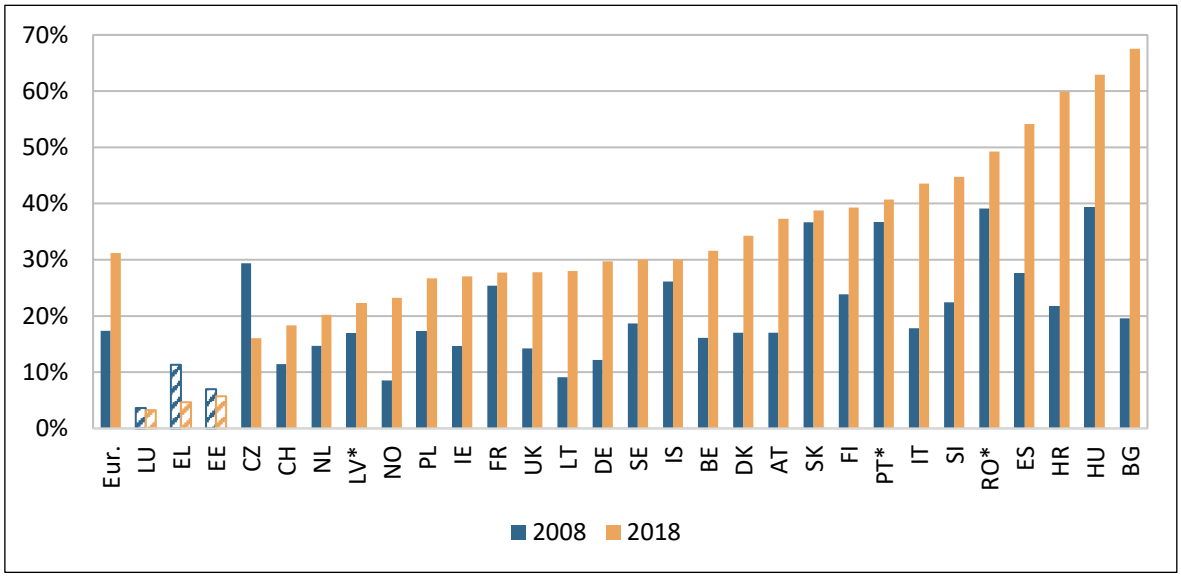

Figure 24: Share of the cost of cancer medicines on the direct costs of cancer, 2008 & 2018

Notes: Eur. = Europe. Hatched bars indicate that data for cancer medicines for EE, EL, and LU only comprise retail sales. * The share in 2008 for PT is from 2010, for RO from 2009, and for LV from 2014. CY and MT are missing due to lack of data on cancer medicine sales.

The findings in Figure 24 can be compared to the results from previous Comparator reports. In the first Comparator report, the share of cancer medicine costs in Europe was estimated to be nine percent of the direct costs of cancer in 2002/2003 [44]. In the follow up Comparator reports, this share was estimated to be 13 percent in 2004 [43], 18 percent in 2007 [45], and 23 percent in 2014 [11].

Figure 25 summarizes the costs of cancer medicines and the direct costs of cancer in Europe. As shown in the previous Comparator report [11], the cost of cancer medicines amounted to around €8.0 billion in 2005 (€9.6 billion measured in 2018 prices and exchange rates), corresponding to a 12 percent share of cancer medicines on the direct costs. By 2010, this share had increased to 20 percent, and by 2015 to 23 percent. It eventually reached 31 percent in 2018. Thus, cancer medicines have been representing a fast-growing share of the direct costs of cancer.

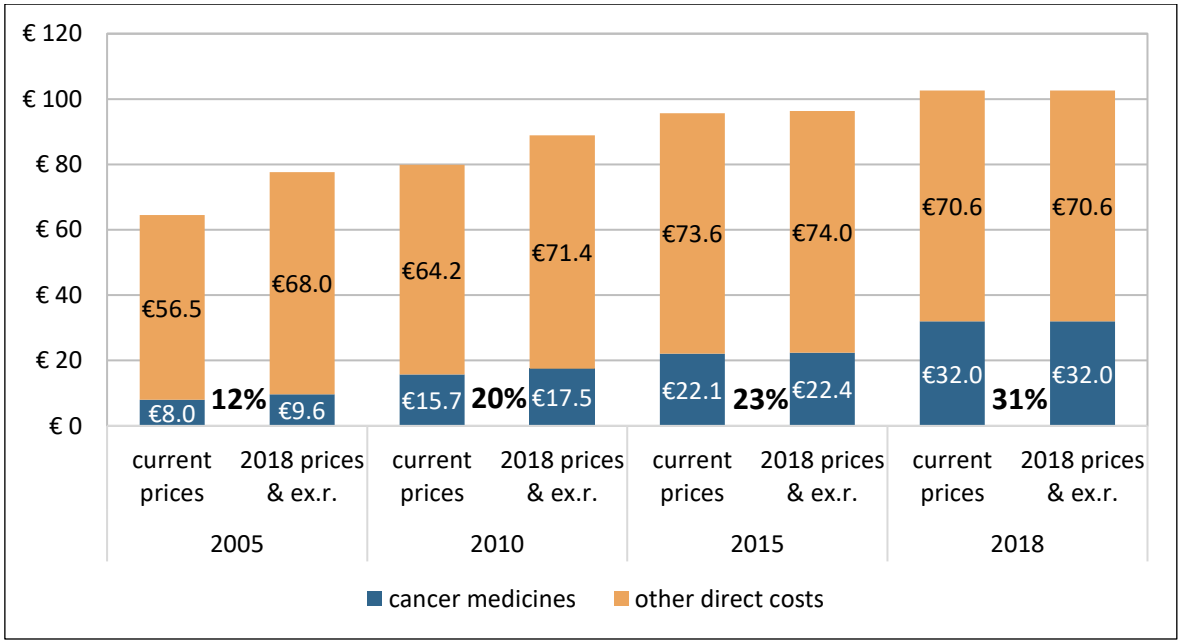

Figure 25: Components of the direct costs of cancer in Europe (in billion €), 2005–2018

Notes: Data on cancer medicines in 2005 are missing for IS.

Despite the increasing share of cancer medicines on the direct costs since at least 2002/2003, Table 3 in section 2.4.1.1 provides evidence of a relatively stable share of cancer-specific expenditure on the total health expenditure. The increased expenditure on cancer medicines must have been paralleled by a reduction or a slower increase in other direct costs. The analysis of the composition of the direct costs of cancer in section 2.4.1.3 pointed to reductions in expenditures on inpatient care as an explanation. At least since the year 2000, inpatients days of cancer patients have been trending downwards (see Figure 22). Savings from fewer inpatient days might, to some extent, have compensated for the additional expenditures on cancer medicines.

2.4.1.6 Informal care

Informal care refers to the services provided by relatives and friends. These services are important complements to other formal services. For instance, they include the time to accompany the patient to the hospital to receive treatment, or care for the patient at home. If these services had not been provided informally, formal services would have been needed to replace them. This means that the work by informal caregivers entails an opportunity cost, which should be assigned a value.

The assessment of informal care is challenging. Even if it were possible to collect data on time inputs from informal caregivers, the valuation or pricing of these time inputs is not obvious; two possibilities are to use minimum wages or mean salary of social care workers. If informal caregivers use their leisure time to provide support (e.g. a retired person supports her spouse) or whether they

are compelled to reduce working hours (e.g. a working parent supports his child) has also implications for the value of informal care. It would thus be necessary to know who the informal caregiver is.

Two previous estimates have put the informal care costs for cancer patients to €23.2 billion in 2009 in the EU-27 and to €23.9 billion in 2012 in the EU-28 (defining cancer as malignant neoplasms) [72, 73]. These estimates assumed that only patients severely limited in daily activities or who were terminally ill would receive informal care. They were only based on patients aged 50 and older, and on non-imputed data from half of the countries included. Thus, these estimates are fairly crude and probably underestimate the true size of the informal care costs.

The development of the extent of informal care over time is difficult to judge. Increased treatment of patients in an ambulatory setting might raise the need of relatives and friends to take the cancer patient repeatedly to the hospital. The increase in cancer incidence and mortality in the older age groups also indicates a potential increase in informal care. If increased length of survival entails a prolonged state of being in poor (rather than good) health for some patients, they require informal support for a longer time. All of these factors point to future increases in the need and costs of informal care [74]. Further studies are needed to document this, to make it possible to have a comprehensive view of the total cost of cancer to society.

2.4.2 Indirect costs

The indirect costs of cancer are composed of productivity loss due to foregone labor market earnings of cancer patients based on three different reasons [41]. First, productivity loss from premature mortality arises from patients who die during working age and who otherwise would have continued to work until retirement age. Second, productivity loss arises from temporary absence from work (sickness absence) of patients in the labor force who are compelled to take a hiatus from work while receiving treatment and care. Third, productivity loss arises from the permanent discontinuation of work (permanent incapacity/disability) of patients in the labor force who have to quit their job due to the disease and have to retire early. The latter two reasons of productivity loss are commonly summarized under the term productivity loss from morbidity.

2.4.2.1 Methodology

Even though there is broad agreement on the importance of indirect costs, there is less agreement on the exact methodology to calculate them. Two different methodologies are commonly used to calculate the productivity loss; the human-capital method (HCM) and the friction-cost method

(FCM). The HCM takes the patient's perspective and counts any hour not worked as an hour lost. By contrast, the FCM takes the employer's perspective and counts only those hours not worked as lost until another employee takes over the patient's work [75]. The FCM method rests on the unrealistic assumption that there are unemployed persons that can quickly replace cancer patients who temporarily or permanently leave the labor market. The choice of the method has an important impact on the size of the indirect costs. If the FCM is used, the estimated costs are typically much smaller than when the HCM is used [76].

In line with the previous Comparator reports, we estimate the productivity loss from premature mortality based on the HCM. This type of productivity loss represents the present value of the future earnings that a person who dies would have been expected to receive.[16] Using the HCM, the first step is to calculate the potential years of working life lost (PYWLL). If a death occurs during working age, which is assumed to stretch from age 15 to 64 inclusive,[17] it causes a certain number of PYWLL. Information on age-specific deaths for each country was obtained from the WHO for the years 1995 to 2010 and from Eurostat for 2015 and 2018 (or the latest available year) [13, 14]. As deaths are grouped into five-year age intervals, all deaths in an age interval are assumed to occur in the middle of that interval.[18] In the final step, the PYWLL are combined with annual earnings and adjusted for the employment rate.[19] Since the death of a person in working age implies the loss of a whole stream of future earnings, we apply a 3.5% annual discount rate in line with common practice in health economic evaluation. A zero real growth rate in future earnings is assumed.

The estimation of the productivity loss from morbidity is more challenging due to lack of European datasets that cover relevant parameters on diseases-specific sick leaves and reasons for early retirement. An attempt to estimate this type of productivity loss (comprising sickness absence and

[16] Unpaid work of homemakers or volunteering is thus not included.
[17] Even though PYWLL form the basis of the calculation of productivity loss from premature mortality, there is a general criticism of the approach to count only deaths during working age. While a value is attached to the death of a 15 or 64-year-old person, the death of a 14 or 65-year-old person is disregarded. Moreover, the assumption of a uniform retirement age of 65 years across the European countries and across men and women is imperfect. Some countries have statutory retirement ages above or below 65 years, and there are often options to retire earlier after a certain number of years of contribution or in exchange for a lower pension. The actual retirement age might also deviate from the statutory one [77]. In the calculations in this report, working age is uniformly defined in each country and all periods. This guarantees a transparent approach and facilitates the interpretation of the results.
[18] For instance, a death in the age interval 35-39 years is assumed to occur at age 37.5 and result in 27.5 PYWLL (= retirement age of 65 years minus age at death of 37.5 years). One additional step that is sometimes taken is to correct the PYWLL in each age interval for the general risk of death in each age group to take into account the likelihood of reaching retirement age. In line with the previous Comparator reports, we do not correct for this.
[19] Sex-specific mean annual earnings from employment for all countries were obtained for the year 2014 [78], and adjusted for inflation to 2018 prices [53], as well as corrected for changes in exchange rates to 2018 levels [57]. Sex-specific employment rates in the age group 15–64 years were applied [79], implicitly assuming a uniform employment rate during the whole age interval.

permanent incapacity/disability) for the EU-27 countries has been made by Luengo-Fernandez et al. (2013) [73]. This study used the FCM in the main analysis but provided information on how the results (for the joint EU-27 estimate) would change if the HCM were applied. Based on these results we use a conversion factor of 1.7 to translate country-specific results from the FCM to the HCM.[20] Luengo-Fernandez et al. (2013) only provide information for a single year (2009). A study for Finland provides better insights into the development of the productivity loss from morbidity between 2004 and 2014 [60]. It found that expenditures on disability pensions decreased from €80 to €76 million (in current prices) during this period, whereas expenditures on sickness benefits increased from €46 to €58 million. In sum, there was a slight increase in the productivity loss from morbidity from €126 to €134 million, but once adjusted for inflation [53], this turns into a 13 percent decrease from €154 to €134 million (measured in 2014 prices). Based on this observation from Finland, we assume that the total costs of productivity loss from morbidity (with base year 2009 but adjusted for preceding/subsequent changes in inflation and exchange rates) remained constant between 1995 and 2018 in all countries.[21]

In line with the section on direct costs, cancer in this section is defined as neoplasms (ICD-10 C00-D48). Productivity loss from mortality for malignant neoplasms (C00-C97) would only be slightly smaller than for neoplasms, as cancer mortality from in situ neoplasms and benign neoplasms is (close to) zero. In the calculations of the productivity loss from morbidity, we apply a country-specific scaling factor (around 1.02) to adjust the results from Luengo-Fernandez et al. (2013) for malignant neoplasms to neoplasms, based on the observed difference in productivity loss from mortality in 2010 using these two definitions of cancer.

2.4.2.2 Results

The development of the total number of PYWLL in Europe between 1995 and 2018 is shown in Figure 26. There was continuous reduction from 2.91 million PYWLL in men and women in 1995 to 2.29 million PYWLL in 2018, corresponding to 21 percent decrease. This decline occurred despite a growing population in the age range 15–64 years; it increased from 331 million people in 1995 by three percent to 341 million people in 2018 [3]. The reason for the reduction in PYWLL is the underlying decrease in cancer mortality. As shown in section 2.2.2., there was a 12 percent (-16% in

[20] A French study of respiratory cancers yielded a conversion factor of 2.6 for productivity loss from morbidity [80], while two Irish studies for breast and prostate cancer and head & neck cancer yielded conversion factors of 13 and 24, respectively [81, 82]. The large differences in conversion factors is a result of differences in parameter choices (e.g. length of the friction period or discounting of future earnings) in the calculations.
[21] For HR we used an estimate from [72] for the productivity loss. For IS and NO we imputed data based on per-capita costs in SE but adjusted for differences in mean annual earnings in 2010 [78], and for CH we used data from AT in a similar manner.

men and -5% in women) reduction in the number of deaths between 1995 and 2018 in the age group 15–64 years. This was a result of a shift of deaths towards older ages due to increased survival.

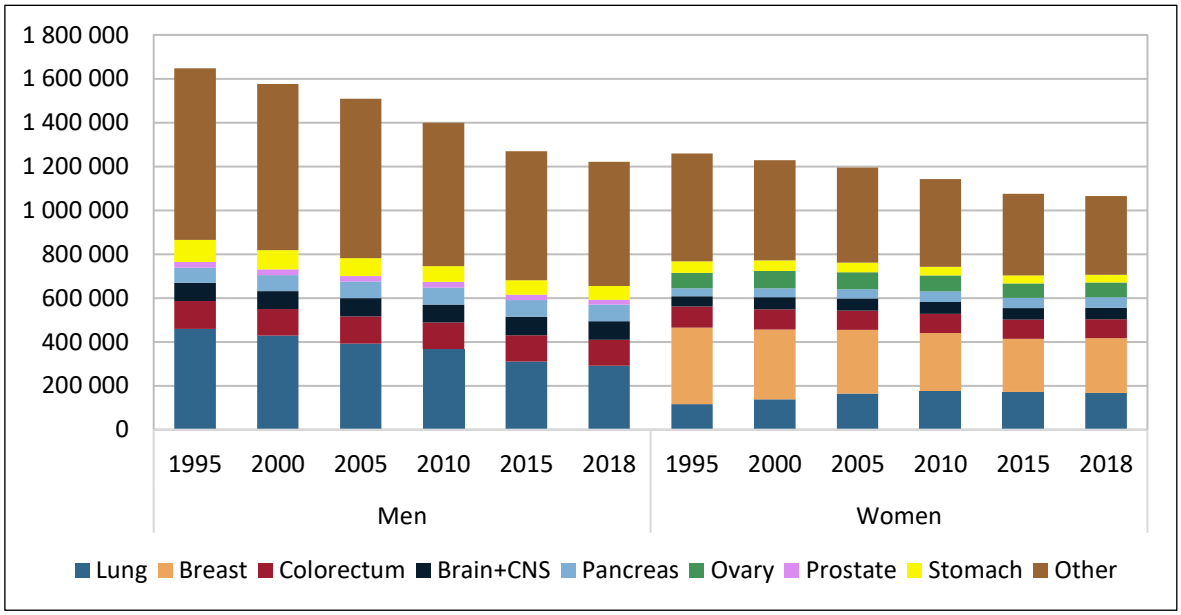

Figure 26: Number of PYWLL due to cancer in Europe, 1995–2018

Notes: PYWLL = potential years of working life lost. Cancer is defined as C00-D48, lung as C33-34, breast as C50, colorectum as C18-21, brain + central nervous system (CNS) as C70-72, pancreas as C25, ovary as C56, prostate as C61, and stomach as C16. Working age stretches from 15 to 64 years inclusive. The estimates for 1995 and 2000 include data for CY from 2004. In 1995, data for pancreas is missing for LV, for brain+CNS for LV, PL, and RO, and for ovary for BG, EE, LV, LT, LU, PL, and RO. In 2000, data for ovary is missing for BG. Source: [13, 14].

Figure 26 also highlights differences in PYWLL between men and women. During the entire period, the number of PYWLL was higher in men than in women. Lung cancer caused the greatest share of PYWLL in men throughout the period, whereas in women breast cancer caused the greatest share. PYWLL caused by the eight cancer types in Figure 26 decreased mostly proportionally to the overall trend. However, PYWLL caused by brain+CNS cancer and pancreatic cancer remained stable in both men and women, and lung and ovarian cancer also did not decrease in women. This is partly related to the small improvements in survival in these cancer types during this period.

The development in the number of PYWLL on the country level is shown in Figure 27. Hungary, Estonia, Czechia, Lithuania, and Croatia recorded the highest number of PYWLL with more than 1,100 per 100,000 inhabitants aged 15–64 in 1995. Cyprus, Iceland, Sweden, and Finland recorded the lowest number of PYWLL in 1995 with less than 650 per 100,000 inhabitants aged 15–64. In 2018, Hungary and Romania were the only countries to record PYWLL over 1,000 per 100,000 inhabitants aged 15–64. The lowest numbers were recorded in Iceland and Cyprus with less than 400 PYWLL. Figure 27 also shows that the number of PYWLL markedly decreased in all countries

between 1995 and 2018, except in Greece, Portugal, and Romania where it remained stable. The strongest decrease in both absolute and relative terms was observed in Czechia.

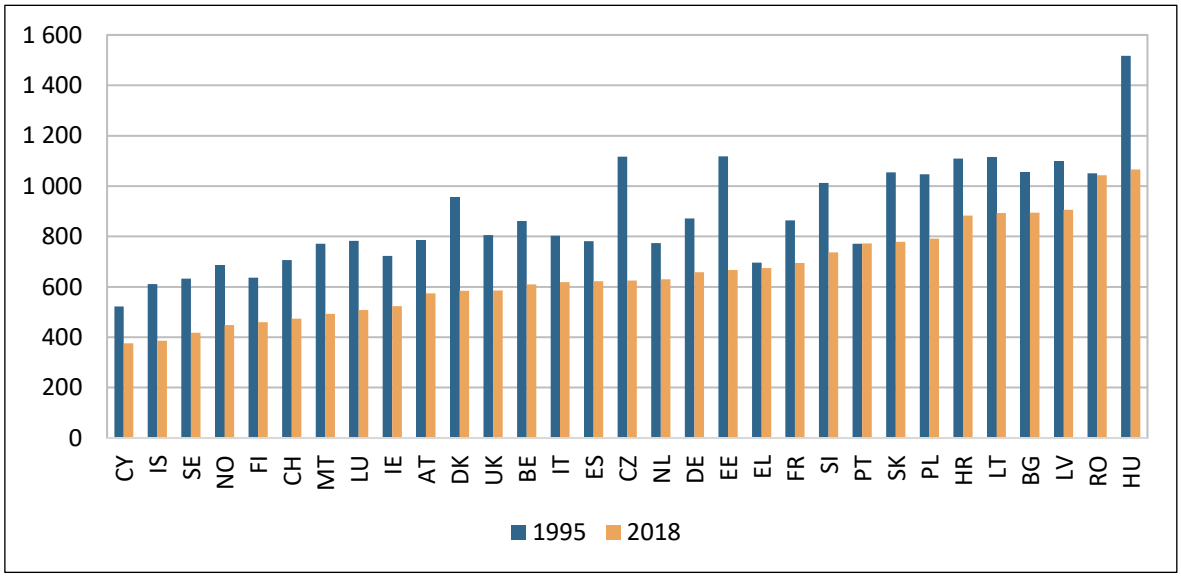

Figure 27: Number of PYWLL due to cancer (per 100,000 inhabitants aged 15–64), 1995 & 2018

Notes and source: see Figure 26.

The development of the indirect costs of cancer between 1995 and 2018 in Europe as a whole is shown in Figure 28. The productivity loss from premature mortality amounted to €57.0 billion in 1995 and declined continuously to €48.8 billion in 2015 (all measured in 2018 prices and exchange rates). Between 2015 and 2018 this type of productivity loss increased slightly by €0.8 billion to €49.6 billion, which is a product of increasing (female) employment rates during this period. Over the whole period, the productivity loss from premature mortality declined by 13 percent. Another observation from Figure 28 is the sex-specific composition of the productivity loss from premature mortality. Throughout the whole period, women's share of the productivity loss was lower than men's share, which is a result of women's lower number of PYWLL, lower employment rates, and lower earnings. The productivity loss also remained stable at around €18–19 billion in women during the whole period, as rising employment rates offset the reductions in PYWLL. The productivity loss from morbidity amounted to €20.4 billion and remained constant between 1995 and 2018 according to the methodological assumptions described above.

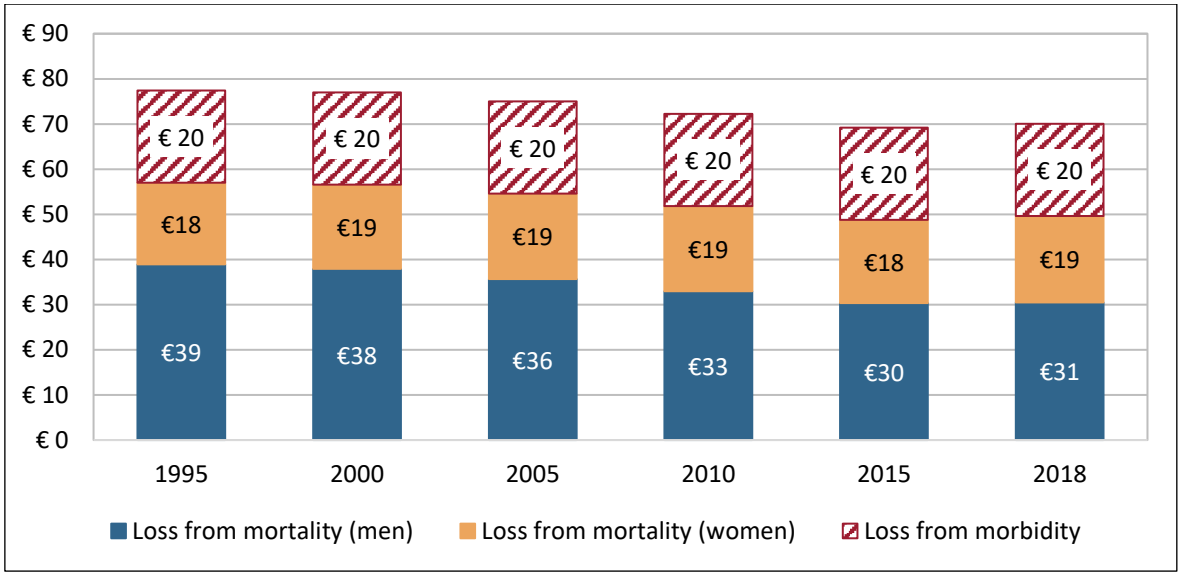

Figure 28: Indirect costs of cancer in Europe (in billion €; 2018 prices & exchange rate), 1995–2018

Notes: "Loss from mortality" and "Loss from morbidity" refer to productivity loss from premature mortality and morbidity, respectively. Hatched bars indicate crude and uncertain estimates. Earnings in all years are based on 2014 values [78], which have been adjusted for inflation and changes in exchange rates to 2018 levels [53, 57]. The 1995 estimate includes employment rates for BG from 2000, HR 2002, CY 1999, CZ 1997, EE 1997, HU 1996, LV 1998, LT 1998, MT 2000, PL 1997, RO 1997, SK 1998, SI 1996, CH 1996. The 2000 estimate includes employment rates for HR from 2002 [79].

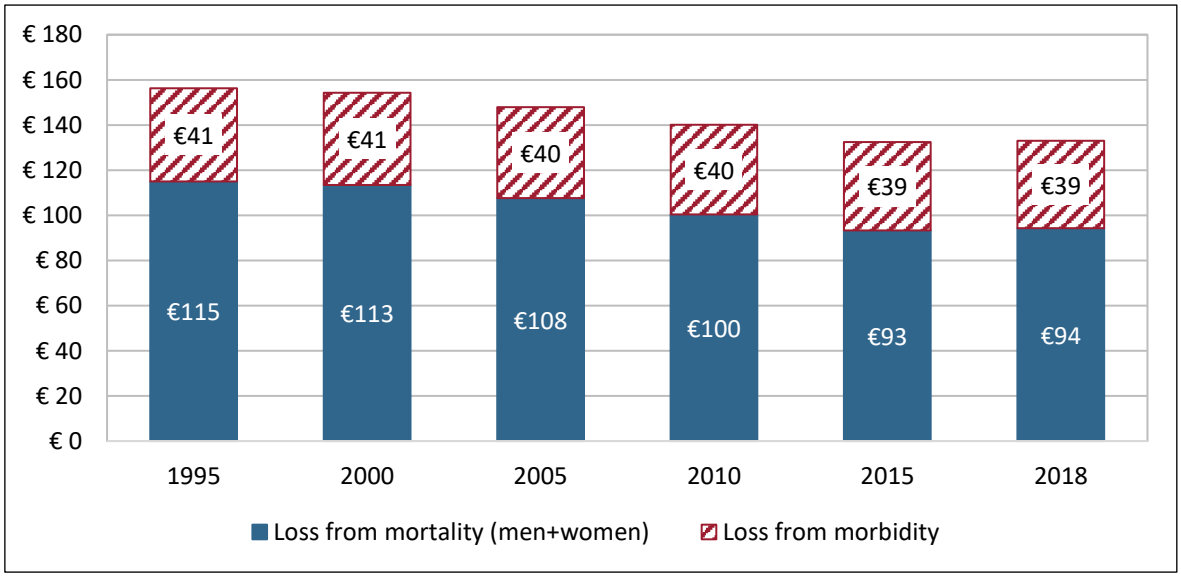

Figure 29: Indirect costs of cancer per capita in Europe (in €; 2018 prices & exchange rates), 1995–2018

Notes and source: see Figure 28.

Figure 29 shows the indirect costs of cancer in per-capita terms for Europe. They declined from €156 in 1995 (comprised of €115 for mortality-related and €41 for morbidity-related productivity loss) to

€132 in 2015, before they increased again to €133 in 2018. Over the whole period, the indirect costs declined by 15 percent (-18 percent for mortality-related and -6 percent for morbidity-related productivity loss).

The results above indicate that productivity loss from premature mortality is much larger than productivity loss from morbidity. This is in line with many studies on the indirect costs cancer, which have been summarized in the previous Comparator report [11]. Based on the results above, the following conclusions about the past and future development of the two components of the indirect costs of cancer can be drawn:

- Cancer mortality has decreased by 20 percent between 1995 and 2018 in people of working age in Europe, even though cancer incidence most likely increased in this age group during this period. This is a result of more patients living longer with the disease. This development is reflected in the reduction of the number of PYWLL from 2.91 to 2.29 million. As a result, the productivity loss from premature mortality has declined. This trend will continue in the future as long as survival in people of working age keeps increasing.
- The exact development of productivity loss from morbidity is more uncertain. The likely increase in cancer incidence in people of working age has probably increased the loss from temporary absence from work (as was the case in Finland where expenditures on sickness benefits increased). Shorter spells of sickness absence due to quicker recovery and fewer side effects of newer treatment modalities might however have moderated this increase. If newer and more effective treatments have increased the chances of patients to return to work, the loss from permanent discontinuation of work will have decreased (as was the case in Finland where expenditures on disability pensions did not increase). Even though cancer incidence is expected to increase further, productivity loss from morbidity might remain stable in the foreseeable future as long as the treatment of cancer keeps improving.

2.4.3 Total costs

Direct costs (including informal care costs) and indirect costs represent the economic burden of cancer (the total costs). The economic burden extends beyond the remit of the health care system. A societal perspective requires that indirect costs and costs for informal care are included. Ignoring these substantial costs can lead to suboptimal policy decisions from a societal perspective [83].

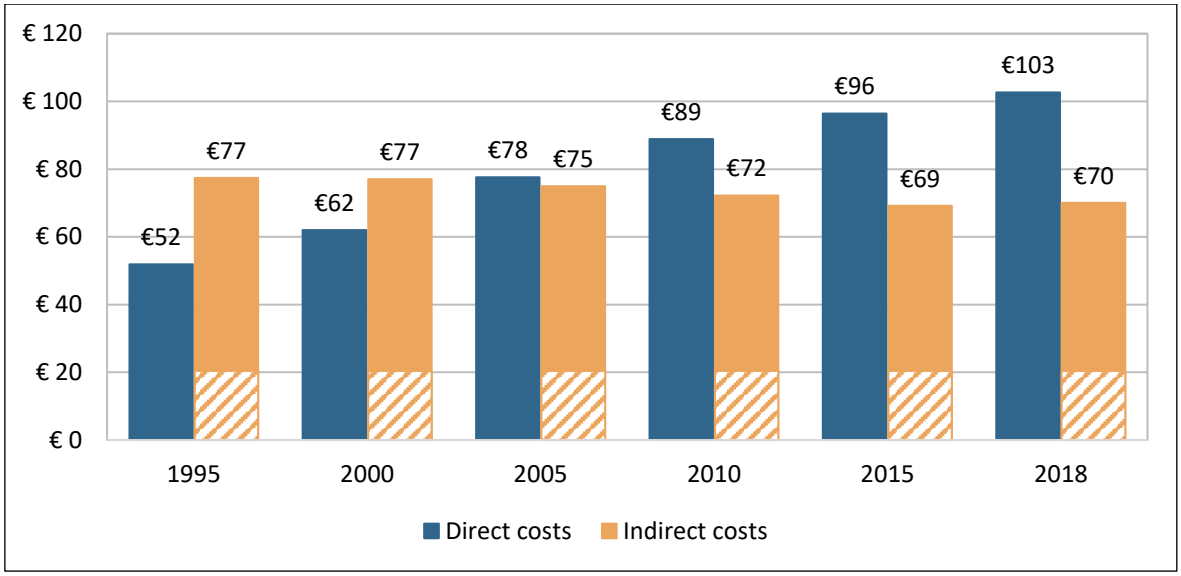

Figure 30: Economic burden of cancer in Europe (in billion €; 2018 prices & exchange rates), 1995–2018

Notes: Cancer is defined as neoplasms (C00-D48). The hatched part of the indirect costs indicates uncertain estimates of the size of productivity loss from morbidity. See Figure 19 and Figure 28 for further details on the calculations.

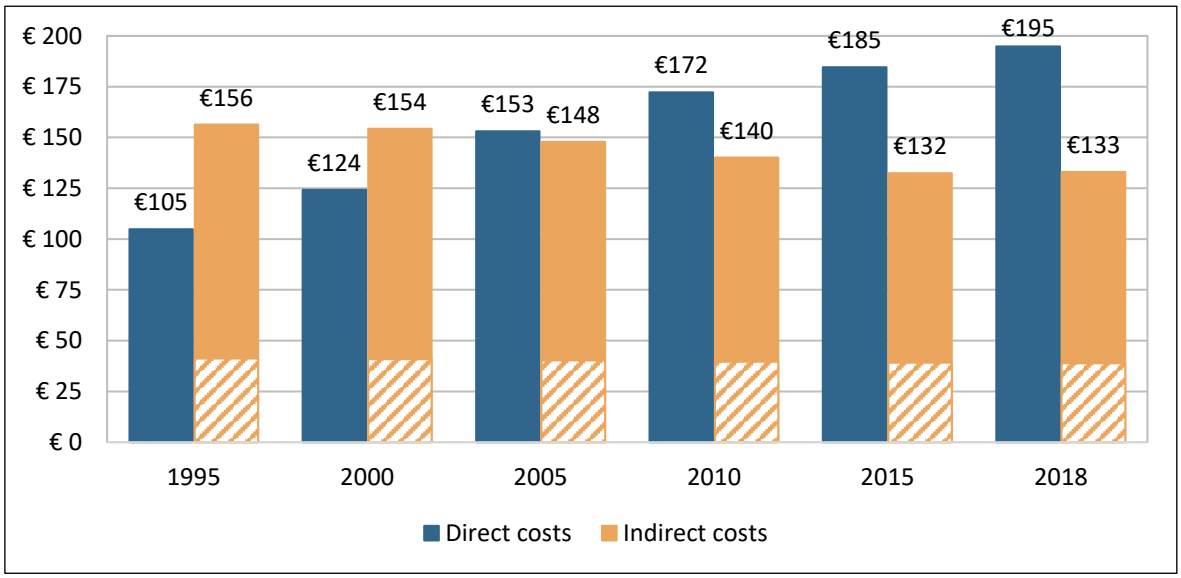

Figure 31: Economic burden of cancer per capita in Europe (in €; 2018 prices & exchange rates), 1995–2018

Notes: see Figure 30.

The economic burden of cancer in Europe is summarized in Figure 30 (total figures) and in Figure 31 (per-capita figures). In 1995, the direct costs (not including informal care costs) amounted to €51.9 billion (€105 per capita) and were exceeded by the indirect costs with €77.4 billion (€156). In the years until 2018, direct costs and indirect costs developed in opposite directions. While direct

costs grew continuously and amounted to €102.6 billion (€195 per capita) in 2018, indirect costs decreased to €70.0 billion (€133).

Figure 32 summarizes the development of the economic burden of cancer in the European countries separately; see also Tables A1 and A2 in the Appendix. It is evident that most countries experienced a similar pattern between 1995 and 2018, consisting of an increase in direct costs (typically by 60–150 percent in wealthier countries, and more than 200 percent in poorer countries) and a decrease in indirect costs (typically by 15–30 percent in wealthier countries, and 0–10 percent in poorer countries). Notable exceptions to this pattern are Bulgaria, Croatia, Latvia, Lithuania, and Portugal which did not record a decrease in indirect costs over the period. Greece recorded a very low increase in the direct costs (16 percent) over the period.

The analysis of the economic burden of cancer highlights that a focus on the costs of cancer that are borne by the health care system is too narrow. Only considering direct costs, there was an increase of 98 percent in total costs (86 percent in per-capita costs) between 1995 and 2018 in Europe, corresponding to a mean annual growth rate of 3.0% (2.7%). It should be kept in mind that (1) there was a parallel increase in the number of new cancer cases of around 50 percent during this period, and (2) limited evidence shows that health spending on cancer grew mostly in line with the overall spending on health. Notably, the results show that the increased health spending on cancer care was partly offset by reductions in other costs, as evidenced by the 9 percent decline in total indirect costs (15 percent in per-capita costs), corresponding to a mean annual growth rate of -0.4% (-0.7%). Most importantly, patients benefited greatly as the 5-year survival rate of most cancer types typically increased in all countries.

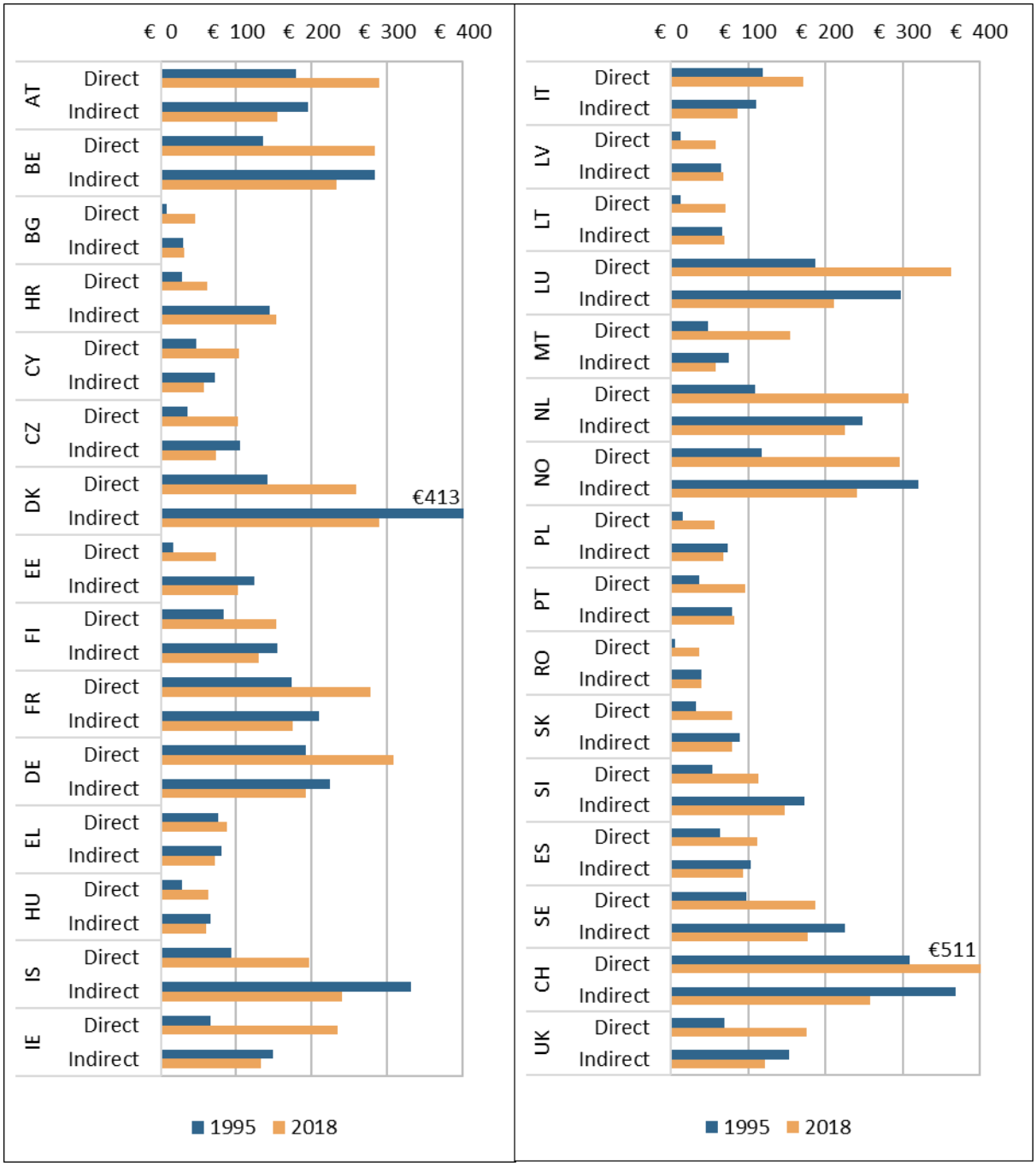

Figure 32: Economic burden of cancer per capita (in €; 2018 prices & exchange rates), 1995 & 2018

Notes: see Figure 30. The blue bar for indirect costs in DK is truncated – its true size is €413, and the true size of the orange bar for direct costs in CH is €511.

2.5 Summary and conclusions

The disease burden of cancer is high. More than one in four deaths (26%) was due to cancer in Europe in 2016. This makes cancer the second leading cause of death behind cardiovascular diseases. In

Denmark, France, the Netherlands, and the UK, cancer was the leading cause of death. Measured in DALYs, cancer was the disease group that caused the second greatest disease burden (20%) after cardiovascular diseases in 2016, but in most wealthier countries it caused the greatest disease burden. If the significant reductions in cardiovascular diseases continue as in the past, cancer will very soon become the leading disease group in terms of disease burden in Europe.

The number of newly diagnosed cancer cases is growing. Cancer incidence increased by around 50 percent from 2.1 million to 3.1 million cases between 1995 and 2018 in Europe. Overall population growth during this period explains a small part of this increase. A more fundamental demographic factor behind this development is population aging. However, a marked increase in cancer incidence in all countries, except in Iceland, remains even after taking into account the demographic changes between 1995 and 2018. An increase in some risk factors related to lifestyle, such as obesity, as well as more extensive screening activities (since the 1990s) offer additional explanations. The positive development in other major diseases, such as cardiovascular diseases, entails more people reaching an advanced age at which the risk of getting cancer is higher.

A stronger focus on effective primary prevention measures is needed to achieve a turnaround in cancer incidence. A recent study for the US showed that over 40 percent of all new cancer cases are attributable to modifiable risk factors. The situation is probably similar in Europe. Health care systems should foster the implementation of comprehensive vaccination programs (HPV vaccination for girls and boys, but also vaccination against the hepatitis B virus), try to eliminate the hepatitis C virus to prevent liver cancer, and offer needle exchange programs. In addition, the adoption of a healthy lifestyle needs to be promoted and incentivized, possibly through excise taxes and smoking bans.

Deaths from cancer are still increasing but the increase has slowed and in age groups below 65 years deaths are actually decreasing. Between 1995 and 2018, cancer mortality increased by around 20 percent from 1.2 million to 1.4 million deaths. After taking into account the growing population during this period, several countries recorded decreases in cancer mortality. In the absence of both population growth and population aging, cancer mortality would have decreased in all countries, except in Bulgaria, Greece, and Romania.

Improvements in survival explain the dissimilarity in the magnitudes of the overall increases in cancer incidence and cancer mortality. The 5-year survival rates for all considered cancer types have increased between 1995 and 2014 in all countries. Improvements in survival between the periods 2005–2009 and 2010–2014 were smaller compared to previous periods. There is a clear pattern of wealthier countries to record higher survival rates than poorer countries.

Improvements in all areas of cancer care were important to achieve improvements in survival. Advances in diagnostics are important to better understand the nature and spread of the cancer to be able to deliver effective treatment. More effective treatment modalities have been introduced that can meet patient needs. Since the start of the roll-out of population-based screening programs (for cervical cancer and for breast cancer) in the 1990s and 2000s, they too contribute to increased survival by detecting more cases at an early stage. The roll-out of colorectal cancer screening programs in the 2010s in several countries will support this development. A good organization of all parts of cancer care, e.g. through standardized care processes, can ensure that all patients receive high-quality care.

The advances in cancer care could not have been achieved without adequate investment into prevention, diagnostics, treatment, and rehabilitation. The health expenditure spent on cancer care (direct costs of cancer) increased from €52 billion to €103 billion in Europe between 1995 and 2018 (in 2018 prices and exchange rates). This equals a 98 percent increase, yet it should be recalled that the number of newly diagnosed patients increased by around 50 percent during the same period. Per-capita health spending on cancer increased by 86 percent from €105 to €195.

The direct costs of cancer differ greatly between countries. In 2018, health spending on cancer ranged from €70 in Romania to €352 in Switzerland if price differentials (PPP-adjustment) are taken into account; if not, then the gap increases to €36 in Romania and €511 in Switzerland. In general, Austria, Germany, Switzerland, the three Benelux countries, and France spent the most on cancer. Countries along the Eastern border of the EU (except Finland) spent the least on cancer. However, country differences in health spending on cancer have grown smaller over time. This is mostly a result of stronger increases in overall health spending in poorer countries.

The health expenditure on cancer increased mostly in line with the overall increase in health expenditure. Even though the data in support of this observation only come from a handful of countries, it shows that health spending on cancer hardly outpaced overall health spending. However, total health expenditure increased from around eight to ten percent of GDP in Europe between 1995 and 2018. Around 4–7 percent of total health expenditure are usually devoted to cancer. In order to provide unambiguous evidence on the magnitude and development of health care costs of all disease groups, national statistical authorities and health ministries should follow the Dutch and German example and provide disease-specific health expenditure data on a regular basis.

The composition of the direct costs of cancer has changed in recent decades. Historically, expenditures on inpatient care (irrespective of whether expenditures on cancer medicines administered during the inpatient stay are included or not) have dominated the direct costs. At least

since 2000, inpatient days of cancer patients have been trending downwards as part of a process of moving treatment to ambulatory care and treatment at home. This shift was made possible through the development of new treatment modalities, which can be administered more easily. The direct costs of cancer are nowadays dominated by expenditures on ambulatory care and cancer medicines.

Expenditures on cancer medicines have increased during recent decades. The total costs of cancer medicines more than doubled between 2008 and 2018 in Europe. The increase in the costs of cancer medicines (7.9 percent per year) greatly exceeded the simultaneous increase in the direct costs of cancer (1.7 percent per year) in Europe between 2008 and 2018. This pattern was also observable in virtually all countries. As a result, cancer medicines accounted for a growing share of the direct costs of cancer. Over one fourth (31 percent) of the direct costs consisted of cancer medicines in 2018. The previous Comparator reports showed that this share was 9 percent in 2002/2003 and 12 percent in 2005, while it was 20 percent in 2010 before reaching 23 percent in 2015. However, the exact size of these shares might be overestimated due to confidential rebates on medicines.

Informal care by relatives and friends is an important complement to other formal services. Two previous estimates have put the informal care costs for cancer patients to €23 billion in 2009 in the EU-27 and to €24 billion in 2012 in the EU-28, but they might underestimate the true costs. Increased treatment of patients in an ambulatory setting might raise the need of relatives and friends to take the cancer patient repeatedly to the hospital. The increase in cancer incidence and mortality in older age groups also points to a potential future increase in informal care.

The indirect costs of cancer exceeded the direct costs in 1995 in Europe and in most individual countries. The indirect costs decreased from €77 billion to €70 billion in Europe between 1995 and 2018 (in 2018 prices and exchange rates). This equals a 9 percent decrease and is a result of a decline in mortality among patients of working age, which has reduced the productivity loss from premature mortality. The productivity loss from morbidity (resulting from sickness absence and early retirement/disability) might have remained stable despite increasing patient numbers, as newer treatment modalities enabled shorter spells of sickness (due to fewer side effects).

The decline in the indirect costs shows that the economic benefits from increased health spending on cancer care have mostly fallen outside the health care system. However, the availability of adequate data to evaluate the size and the development of both indirect costs and informal care costs remains a major challenge. The lack of data is especially serious given that some national authorities in Europe that are responsible for health technology assessment (HTA) apply a societal perspective. The inability to estimate these costs properly can lead to suboptimal decisions in the design of policy measures to prevent, detect, and treat cancer from a societal perspective.

The future development of the economic burden of cancer in Europe is closely linked to the future development of the disease burden. The continuous increase in the number of newly diagnosed patients presents a challenge for all health care systems. Further investment in all areas of cancer care – prevention, diagnostics, treatment, rehabilitation – as well as an effective and efficient organization are required to meet this challenge.

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3. The present and future of cancer diagnostics and medical treatment

3.1 Key messages

- Cancer prevention has had a long history of slow progress and lack of implementation. Major obstacles are linked to awareness and education. R&D in cancer prevention has mostly relied on public funding. Better biological understanding of the carcinogenic process may identify new targets for cancer prevention.
- Screening is recommended for breast, cervical, colorectal, and lung cancer as mortality can be reduced. However, the specific design of the screening programs determines the value and cost-effectiveness. Screening for prostate cancer results in many false positive and false negative diagnoses depending on the screening method. Pancreatic, liver, and bladder cancer are examples of diseases for which reliable and practical risk-based screening tests are needed. Blood tests are in development and can potentially detect many types of asymptomatic cancers.
- Progress in diagnostics has made it easier to predict if a patient is likely to respond to a certain treatment. New technologies can help to characterize changes in genes and unravel novel targets that are druggable. New tests are developed that can assess relevant markers in blood. Identifying appropriate patients for a future complex landscape of different combinations of therapies and cell-based therapies will require extensive testing. This will increase the up-front costs for treatment and thus must be compensated by improvements in outcome and/or reduction of side effects.
- Countless targets for cancer treatment have been identified. Over 40 small molecules are currently in use for targeting protein kinases involved in cancer. Although tyrosine kinase inhibitors were not the magic bullets as they had been anticipated to be at the arrival of imatinib, they have provided significant value in multiple indications. Most of these drugs are used in late-stage or metastatic disease. Active research areas are their use in the adjuvant setting and their use in combination with immune checkpoint inhibitors.
- Antibodies are in many ways ideal cancer drugs. Over 30 antibodies are currently in use in oncology/hematology, and over 300 are in clinical development. Emerging areas are ADCs, bispecific, multispecific, and oligoclonal antibodies, nanobodies, and antibody mimetics.

- Immunotherapy has become a cornerstone in multiple solid malignancies during the last five years, and over 2,000 clinical trials are currently ongoing. The position of these therapies has moved to front line therapy in several indications and even to adjuvant approvals in high risk patients with melanoma. Immunotherapy is still in its infancy and most patients do not respond to these agents. Better biomarkers are needed to facilitate patient selection.
- Most of the human proteome is currently not "druggable". Novel drug classes such as gene editing/therapy, oncolytic virotherapy, siRNA/RNA interference, cell-based therapies, and PROTACs are likely to enable targeting of several of the proteome targets that have been out of reach so far. Notably, cell-based therapies have recently been approved in hematological malignancies.
- The increasing amount of patient data collected enables but also necessitates the use of AI. AI is already used in clinical care for imaging analysis and in drug development. AI can improve quality of care and reduce stress for physicians by assisting in treatment decisions. Rigorous validation of AI in different datasets to prove performance and viable solutions to ensure patient integrity and confidentiality are needed before widespread clinical use.
- More patient groups have become eligible for drug treatment, but the number of patients in each group has become smaller. In some cases, treatments are approved on phase II trial data and on PFS in the metastatic setting, which increases the need for clinical effectiveness studies in order to ensure effectiveness in clinical practice and value-for-money.

3.2 Background

The development of invasive cancer is a process with many steps, with an accumulation of genetic changes that in most cases likely occur over a long time period (5–20 years). There are many genetic changes in cells in our body every day, but they are in most cases stopped by the cell's own protection systems. The requirement for a cell to change into a cancer cell is a combination of many events happening at the same time [1]. Research has increased our knowledge about the human cell and its molecular mechanisms, and medical oncology entered a new phase in the 21st century with new drugs targeting different molecular targets. Progress in molecular medicine increased our understanding of cancer evolution, cancer cells characterization, and defects in DNA repair mechanisms; see Figure 33.

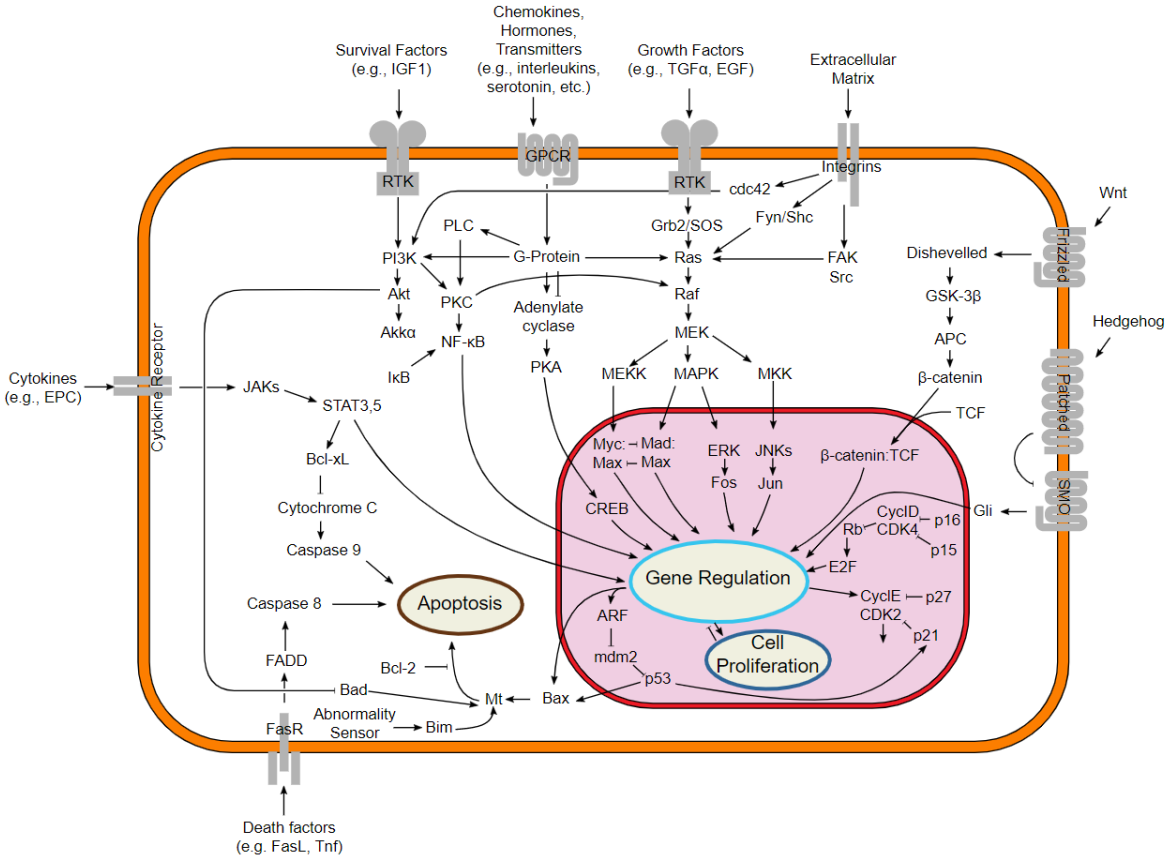

Figure 33: The basics of cancer – simplistic cell signaling pathways [2]

This chapter focuses first on present and future trends in two areas cancer care; prevention (section 3.3) and screening (section 3.4). Afterwards it addresses various aspects of treatment. The first aspect (section 3.5) concerns diagnostics and biomarkers. In some cases, it is already possible to predict if a patient is likely to respond to treatments using different molecular markers, and these markers will likely improve the accuracy of the treatment offered to individual patients.

The second aspect (section 3.6) concerns different targets in cancer treatment. Increased knowledge of cancer biology has reduced the use of highly cell-toxic treatments (chemotherapy targeting all fast-dividing cells) and increased the use of agents targeting specific proteins/pathways in the cell [1]. The latest major development is activating the body's own immune system to attack the tumor.

The third aspect (section 3.7) concerns machine learning and artificial intelligence, which has recently started to be used in oncology, in particular for imaging analysis in digital pathology. The final aspect concerns the use of surrogate endpoints in clinical studies (section 3.8) and clinical effectiveness and real-world data (section 3.9). Real-world data is essential to learn about the value of new treatments in clinical practice.

3.3 Cancer prevention

Prevention science has matured over the last 30 years, shifting from primarily descriptive studies that suggested prevention's potential [3], to interventional studies that prove the power of preventive measures. This development is based on improved understanding of the events that initiate and promote oncogenesis. This has provided insight into how germline genetics interact with somatic molecular and cellular-related drivers in this process [4].

Preventable cancer risks including unhealthy lifestyle choices, such as physical inactivity and tobacco use, and consequent health outcomes, such as obesity, are unacceptably common, particularly among people with low socioeconomic status; see Figure 34. These few factors are linked to more than 50% of preventable cancers [5]. This area of cancer prevention is still faced with major obstacles linked to public awareness and education.

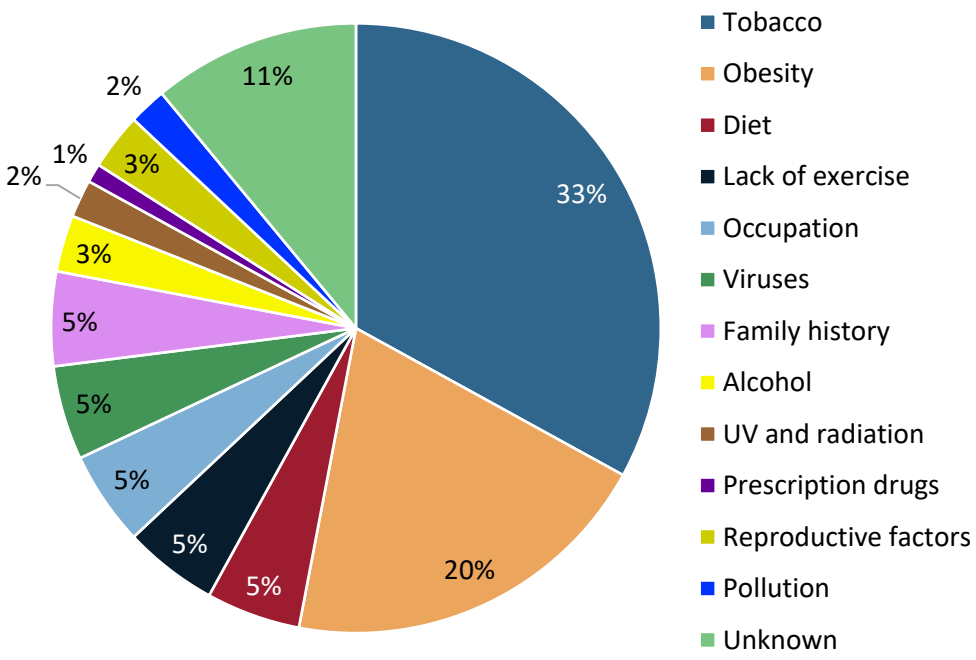

Figure 34: Distribution of preventable cancer-related factors [6]

Technological advances, such as bio-monitors and mobile devices with health applications, have the potential to improve the quality of individuals' health and health care systems. Real-time assessments can promote communication with individuals at risk and much knowledge can be gained.

Another driver in the development of cancer prevention is the resistance of advanced/recurrent cancers to therapy. Furthermore, cancer interception via early detection and intervention may halt neoplastic progression that could later progress to refractory cancer.

3.3.1 Molecular profiling

The rate-limiting step in cancer prevention has been our limited in-depth understanding of the biology of cancer risk (e.g. obesity) and precancer progression. This contrasts with the extensive study of cancer biology, driving breakthrough advances in precision therapy and immunotherapy over the last decades.

Current data suggest that cancer develops as a consequence of progressive genomic and epigenomic alterations [7, 8], some of which can drive immune escape and occur in the context of an inflammatory microenvironment. For instance, HCC precursor progression was recently mechanistically linked to defects in adaptive immunity [9-12].

The relationship between inflammation and cancer is complicated, with features of inflammation that range from adaptive to maladaptive [13]. In general, chronic inflammation has long been implicated in the genesis and promotion of tumors following inflammatory lung, bowel, and liver disease. Such studies suggest that immune-based intervention may have value when applied in a preventive context, potentially “normalizing” the immune suppressive environment where the neoplastic cells are “rejected” by a productive immune infiltrate.

Specific strains of gut and intra-tumoral bacteria induce an immunosuppressive microenvironment favoring oncogenic progression [14]. Ablation of the microbiome with antibiotics reshapes the tumor microenvironment, inducing T-cell activation, improving immune surveillance, and increasing sensitivity to immune interception [15, 16], while depletion of the gut microbiome promote the efficacy of immunotherapy in established tumor models [17]. Age-associated changes in gut microbes may be a mechanism of age-related cancer [18]. Recent studies have identified microbiome genomic signatures associated with precancer progression [19, 20].

The use of liquid biopsies for cancer detection and monitoring is rapidly changing standards of care. Owing to improved sensitivity, low levels of circulating tumor DNA can be detected among patients with early-stage cancer [21], suggesting the potential of blood-based molecular screening for early, preinvasive stages of neoplasia from a variety of tissues. Circulating tumor DNA may also reflect the genetic profile of the tumor and the ability to detect and characterize it may therefore be of prognostic and therapeutic value [22, 23]. Relative to solid-tissue biopsy, blood-based biopsy could

provide (i) less biased detection of genomic alterations [24, 25], and (ii) less invasive detection of genomic alterations [26, 27].

3.3.2 Breast cancer

Long-term randomized controlled trials (RCTs) showed that raloxifene, a common osteoporosis drug, prevented breast cancer to the same degree (but with fewer serious side effects) as tamoxifen, which is FDA approved in this setting. Raloxifene, also approved as well as aromatase inhibitors, retained 76% of tamoxifen's efficacy in preventing invasive disease and incidence curves approached that of tamoxifen in preventing non-invasive disease, with significantly less endometrial cancer with raloxifene use [28, 29]. The problem with breast cancer prevention based on antiestrogens and aromatase inhibitors has been the limited acceptance from patients due to cumbersome side effects. Molecular profiling may identify subgroups of women where the risk-harm balance is in favor of medical prevention.

3.3.3 Colorectal cancer

The available data on intestinal carcinogenesis and precancers has come mainly from hereditary colorectal cancer syndromes, which recapitulate the two major pathways in sporadic colorectal cancer: chromosomal instability (non-hypermutant) and mismatch repair deficiency (hypermutant). Preventive agent trials in the colorectal adenoma-carcinoma model have produced major advances. Aspirin is an example of a repurposed preventive compound with consistent 20% to 30% reductions in colorectal adenoma incidence and colorectal cancer risk and mortality in a large array of observational and experimental studies. Clinical benefit has been established in RCTs in the sporadic and Lynch syndrome setting. Regular aspirin use may also complement the benefits of screening. The USPSTF (US Preventive Services Task Force) has recommended aspirin in individuals aged 50–59 and a 10% 10-year risk for cardiovascular events, noting additional benefits of reductions in colorectal cancer with long-term use. The balance of benefits and harms may change substantially with age, because the risk of major bleeding increases with age. For that reason, the USPSTF rated the evidence "Insufficient" (I) for people aged 70 or older.

3.3.4 Vaccination and treatment of infection

The microbial genesis of several types of cancer (e.g. HPV and cancers of the cervix, anus, genital tract, and oropharynx; hepatitis B and C and hepatocellular carcinoma; helicobacter pylori and gastric cancer; HIV and AIDS-defining malignancies; etc.) have been identified. Thus, cancer prevention can focus on actions that reduce the risk of exposure, such as vaccination against the offending

organism and promptly identifying and treating infections. Immune prevention efforts, such as the administration of vaccines directed against HPV or hepatitis B, are most effectively applied in unexposed children and young people, as they are directed at preventing the initial infection.

3.4 Cancer screening

The purpose of screening is to prevent death from cancer by reducing the incidence of advanced disease and introduce therapy at the early stages of disease. The potential is greatest for cancers that have a natural history allowing for the detection and treatment of precursor lesions. The effectiveness of a population-level screening program is measured based on the degree of reduction in disease-specific mortality that can be accomplished with an acceptable balance of benefit to harm [30].

3.4.1 Breast cancer

Screening and treatment have contributed substantially to declining mortality in breast cancer [31, 32]. In its most recent comprehensive review of the efficacy and effectiveness of breast cancer screening, including RCTs and observational analyses of modern studies, the International Agency for Research on Cancer concluded that incidence-based cohort studies indicate reductions in breast cancer mortality of approximately 40% among women aged 50–69 who attend screening, 32% for women aged 45–49, and 17% for those aged 40–44 [33].

Breast imaging technology has evolved since the introduction of mammography, from film to digital image receptors. Currently, full-field digital mammography (FFDM) is rapidly being replaced by digital breast tomosynthesis (DBT), also known as 3-dimenisonal (3D) mammography [34]. Digital mammography has a performance similar to that of film-screen mammography in women aged 50–79; however, sensitivity is improved in women aged 40–49 because of the higher prevalence of mammographic breast density, but at a cost of reduced specificity [35].

The unique feature of DBT is the ability to take images of the breast from different angles to produce both 2D and pseudo-3D images of the breast. Studies indicate that DBT has superior, or at least equivalent, performance compared with 2D mammography in terms of both sensitivity and specificity and appears to have some additional advantages compared with FFDM in screening performance among women with mammographic dense breasts [36, 37]. A large prospective trial comparing FFDM versus DBT has been launched to determine whether DBT is superior to FFDM in reducing the detection rate of advanced breast cancer [38].

3.4.2 Cervical cancer

Cervical cancer deaths have declined since the mid-20th century. This decline has been linked to the introduction of cervical cancer screening not based on prospective RCTs but mainly to a change in care patterns [39].

The USPSTF recommendation statement for women at risk for cervical cancer was updated in 2018 but remained similar to the 2012 guidelines, with the exception that high-risk HPV testing alone every five years is an additional option for women aged 30–65 [40, 41]. It is expected that high-risk HPV testing alone will replace cervical smear screening in this age group and potentially for some women younger than 30 years. Guidance for high-risk HPV testing alone has been issued by a consortium of organizations, but it remains currently unclear whether and how soon high-risk HPV testing alone will become broadly acceptable and accessible [42, 43]. The impact of the HPV vaccines on cervical cancer will in the future likely influence screening for the disease.

3.4.3 Colorectal cancer

In the US, a decline in colorectal cancer deaths in the past two decades has been observed. This decline has been linked to RCTs on screening and related to a broad introduction of screening [44].

A recent analysis indicated that people born around 1990 have twice the risk of colon cancer and four times the risk of rectal cancer compared to people born around 1950, who have the lowest risk. Deaths have also been increasing in people younger than 55 years at an annual rate of approximately 1% between 2005 and 2014 [44-46]. These observations may lead to a re-evaluation of age limits for colorectal cancer screening.

3.4.4 Lung cancer

Modern lung cancer screening with low-dose computed tomography (LDCT) was first recommended by the American Cancer Society and the USPSTF in 2013. In Europe, lung cancer screening has not yet been implemented on a broad scale, but there is now strong recommendation at a European level to implement lung cancer screening in the coming years [47-49]. It will take some years before the influence of lung cancer screening on lung cancer mortality rates will be evident because of the slow pace at which risk assessment and screening referral are integrated into national population-based screening programs.

Recent recommendations to increase the threshold of a positive scan from 4 to 6 mm may contribute to reduced overdiagnosis by reducing the detection of a high volume of mostly benign nodules that may also include some non-progressive malignancies [50-52].

3.4.5 Prostate cancer

The present view in the US as well as in Europe is that decisions about prostate cancer screening should be individualized in men aged 55–69 after a discussion of the potential benefits and harms of screening, and should be handled keeping in mind each individual's situation [53]. Different markers are being assessed for screening of prostate cancer. The implementation of new markers will depend on their sensitivity/specificity and cost-effectiveness.

3.5 Diagnostics and biomarkers

The field of diagnostics has rapidly developed in the last decade, with improved technologies to assess DNA/mRNA and other genomic alterations with approved drugs. Older inexpensive testing technologies such as polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) based assays are increasingly being replaced by more complex methods that enable assessment of a large number of genes simultaneously (next generation sequencing (NGS) panels) as tumor material is frequently scarce and there is a need for assessment of multiple alterations for approved agents and further alterations to identify patients for clinical trials with candidate drugs. The performance and the reporting from different NGS platforms are not identical as they use different technologies, different bioinformatics, and annotation. However, comparisons of NGS platforms currently reveal that overall the results are fairly similar [54].

PCR testing will likely continue in indications where there are only a few actionable genetic alterations, and broad PCR panels – covering alterations across multiple genes – may provide a useful alternative in patients who are not eligible for clinical trials and in countries/indications where the cost of NGS testing is prohibitive. The advantages of PCR testing are that (i) it tends to be specific in amplification of target sequence of DNA fragment [55, 56], (ii) it is cheap and readily accessible [55, 56], (iii) it has a rapid turnaround time [55, 56], and (iv) it is recommended by some guidelines for linking diseases to FDA-approved targeted therapies [57]. The drawbacks of PCR testing are that (i) prior information about the target sequence is necessary in order to generate the primers that will allow its selective amplification [58], (ii) contamination can lead to false results [58], (iii) mistakes can happen due to Taq polymerase [59], and (iv) there is a potential for over-representation of certain fragments (multiple replicates of the same sequence) [60].

Liquid biopsy assessment of alterations in single genes have been available for a few years. Decreasing costs of NGS and improved bioinformatics capabilities have also enabled the development of large mutation panels for use in liquid biopsies. This is increasingly incorporated in clinical trials but also in selecting patients in clinical care when it is challenging to take biopsies. The highest clinical utility for liquid biopsy assessment is currently in patients where there is a need to understand resistance mechanisms associated with acquired mutations, in particular in non-small-cell lung cancer which is challenging to re-biopsy. Sensitivity of liquid biopsy testing limits its utility in patients with metastatic disease where sensitivity is still in the 75–85% range [61]. Efforts are ongoing to assess the value of monitoring and early prediction of response/lack of response in the metastatic setting using various technologies and by assessing different circulating factors ranging from circulating tumor cells, exosomes to detection of mutations in cdDNA, miRNA, and proteins [62-64], and it could be that in the future we will see this clinically implemented in some situations. However, significant efforts are being made to develop tests that may provide clinical value in early stage disease [65-67] and even early detection by combining different parameters or assessing DNA methylation [68-70]. The sensitivity to detect, in particular, stage I cancers is still limited although it could be argued that patients with detectable disease by liquid biopsy may have a worse prognosis. The initial field where liquid biopsy assessment will prove a role in earlier stages of disease will be in detecting minimal residual disease (MRD). Patients with MRD are likely to benefit from further antitumoral treatment and there will likely be several drug approvals based on MRD as defined by liquid biopsy assessment in the future [64, 71].

Gene expression analysis has also proven valuable in some indications (breast, colon, prostate, renal) but with varied clinical implementation, except in early stage ER-positive breast cancer. Multiple assays have been developed for prognostic and predictive use, but data show that the algorithms for each assay classify patients somewhat differently, making comparisons difficult [72, 73]. Thus, a key learning is that robust validation is required and that claims should be made only based on available data for each assay. RNA-SEQ is also increasingly being incorporated in large NGS panels, as it provides orthogonal information to mutation analysis.

Assays are also being developed using urine, saliva, and stool samples. The commercial test Cologuard represents a major advance in non-invasive screening of colorectal cancer with a specificity of 87% [74], and we will likely see similar tests brought forward for other indications. Such tests may be composite tests including many different variables ranging from assessment of nucleic acids to the microbiome, which in some situations appear to be relevant from a disease perspective.

The introduction of immunotherapy has led to extensive research in predictive biomarkers; see also section 3.6.3. Microsatellite instability high (MSI-H) [75-77] has been approved by regulatory authorities (e.g. FDA). Other markers, such as tumor mutational burden, are being validated and many further markers, such as IFN-γ signature [78], TGF-β [79], presence of stromal immune cells [80], T-cell receptor repertoire, neoantigen epitope, and prediction of immunogenicity of such epitopes, MHC class I expression, HLA haplotype [81], mutations in JAK1/JAK2, beta-2 microglobulin [82], and NF1 [83], gene expression algorithms [84], and even gut microbiome [85], are being assessed for their predictive ability. Further understanding of driver mutations/oncogenic pathways and potential immune escape mechanisms associated with such alterations is also warranted, as data indicate that for instance activation of many oncogenic pathways appears to lead to immune escape [86-89]. The coming years will require substantial efforts to define and validate biomarkers for patient selection for these therapies.

In clinical oncology, the coming years will require inclusion of a wealth of biomarkers in finding patients eligible for targeted therapy and to individualize treatment. Most likely we will also see further refinements with digital pathology and image analysis combined with mutation and RNA SEQ data to provide more refined predictive and prognostic estimates. Single-cell analysis for the characterization of immune and tumor cells may also become integrated, as bulk analysis of biopsy material will provide estimates that represent the “average” of the content, but the structural elements of the tumor is not captured [90]. It should be emphasized that testing with NGS technology is expensive which is limiting uptake. Finding cost-effective testing alternatives will be key to helping patients get the personalized therapies of the future [91].

3.6 Targets in cancer treatment

3.6.1 Small molecular targeted drugs

The human genome encodes more than 500 protein kinases. Mutations, overexpression, and dysregulation of some of these kinases have been identified as involved with cancer initiation and progression; see Figure 35.

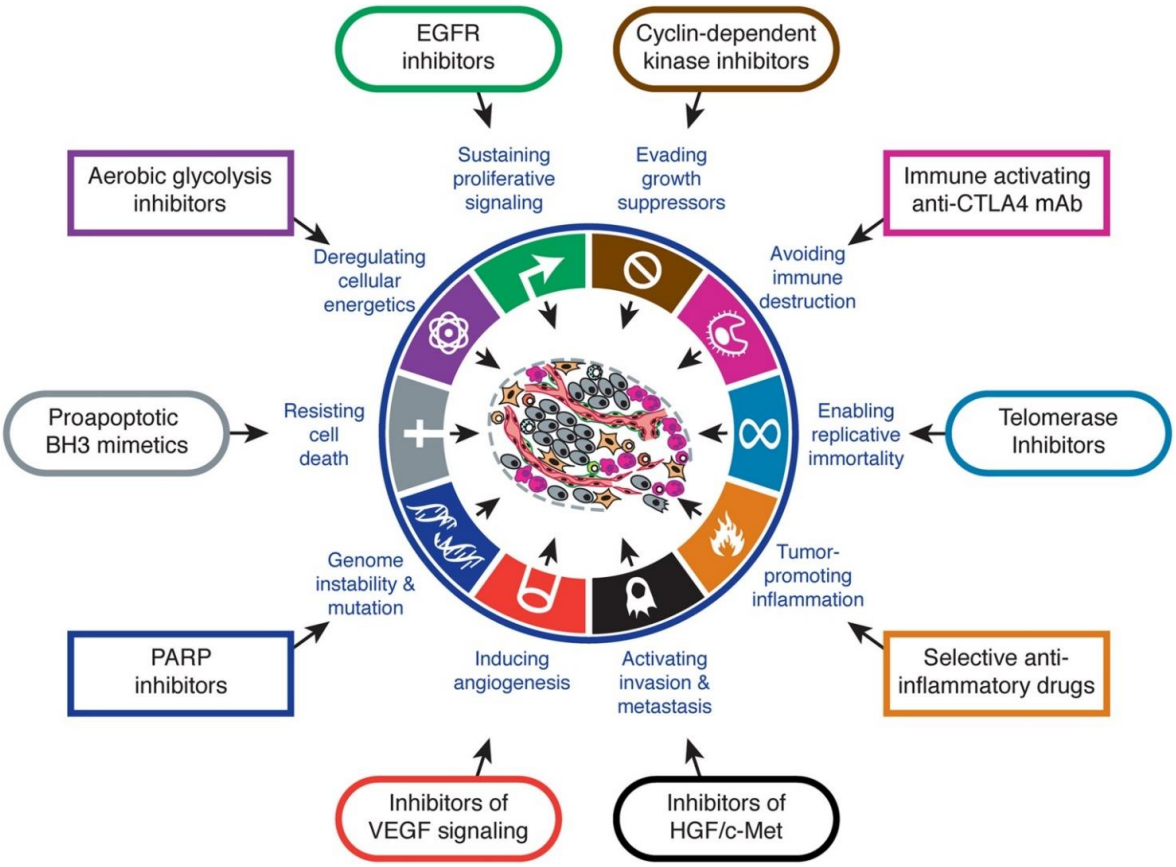

Figure 35: Different targets in modern cancer drugs [1]

There are currently 43 approved kinase inhibitors used in oncology/hematology. Although tyrosine kinase inhibitors were not the magic bullets as they had been anticipated to be at the arrival of imatinib, they have provided significant value in multiple indications, predominantly in lung cancer, melanoma, bladder cancer, GIST, and hematological indications. The most common driver mutations (EGFR, HER2, ALK, FGFR, BRAF) can be targeted by tyrosine kinase inhibitors. There has been a clear trend of novel agents with higher potency for original driver mutations but also activity in gate keeper mutations (that are associated with resistance) and improved selectivity to replace older agents. For instance, osimertinib has rapidly become a frontline therapy in EGFR-mutant non-small cell lung cancer, as it is a potent inhibitor of the most common EGFR alterations but also EGFR T790M, the most common alteration associated with resistance to the earlier EGFR inhibitors such as gefitinib and erlotinib. Similar examples exist in other alterations such as ALK.

The most recent years have also seen the approval of drugs in very rare alterations such as NTRK, where clinical trials have become feasible only with the introduction of broad mutation panels. Other kinases have also in more recent years been targeted successfully: Multiple CDK4/6 inhibitors have for instance demonstrated significant value in ER-positive breast cancer in combination with endocrine therapy and are now first-line option for many patients with metastatic disease [92].

Ongoing studies are assessing these agents in further indications. PI3K inhibition has succeeded after moving from pan PI3K inhibitors to more isoform selective PI3K inhibitors and there are now four approved agents covering all PI3K, but the beta isoform and the number of indications are expected to increase.

An important area under investigation is whether these agents will show efficacy in the adjuvant setting. The data reported so far has been somewhat conflicting but the picture that is emerging is that potent agents at sufficient dose appear to provide benefit. So far, there are approvals for dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) in high risk BRAF-mutant melanoma [93], imatinib is approved for high risk patients with GIST tumors [94], and sunitinib is approved for high risk patients with renal cancer in the US but not Europe based on positive data supporting prolonged disease free survival but no overall survival difference (data immature).[22] In HER2-positive disease, neratinib is approved as extended adjuvant therapy after trastuzumab treatment based on positive data from the Extenet study [98]. However, a previous large study assessing lapatinib as adjuvant therapy in various combinations with trastuzumab was negative [99]. The reasons for the different outcomes for neratinib compared to lapatinib in the adjuvant setting is unclear but may relate to the study design where neratinib was given after trastuzumab adjuvant therapy had been ended. In EGFR-mutant lung cancer, studies with the older EGFR-targeted therapies have not resulted in approvals but a recent meta-analysis of 11 studies strongly suggests that there is a benefit from EGFR-targeted therapy with hazard ratios of about 0.6 for both disease free survival and overall survival compared with patients that did not receive any treatment [100]. There are ongoing adjuvant studies with osimertinib, and it would not be surprising if those studies will be positive with substantial benefit and increased survival based on the level of benefit seen in the metastatic setting. There are also ongoing adjuvant studies with ALK inhibitors. For other rarer targets, adjuvant studies may be challenging from a feasibility perspective and they would require global efforts in order to include the number of patients required.

Another area that is being explored is the combination of tyrosine kinase inhibitors with immune checkpoint inhibitors and with other types of agents. The most compelling combination data that has been presented so far has been the combination of axitinib with pembrolizumab in first line renal cancer. This combination was recently approved based on the Keynote-426 study [101]. Other combinations have had issues with toxicity that to some extent has been unexpected: durvalumab in

[22] The approval was based on positive results from the S-TRAK study [95], but a previous large adjuvant study comparing both sunitinib and sorafenib with placebo was negative [96]. The difference between these two studies appears to be a higher drug exposure in the S-TRAK study. Supporting this hypothesis, is data for a pazopanib, a similar agent. An adjuvant study with pazopanib in renal cancer was overall negative but importantly, a benefit was seen in a subset of patients treated with a higher dose [97].

combination with osimertinib was for instance associated with pneumonitis [102], tremelimumab and sunitinib was associated with renal failure [103], nivolumab and crizotinib [104] and pazopanib [105] was associated with hepatic toxicity. The final role of combinations of tyrosine kinase inhibitors with immune checkpoint inhibitors is unclear at this point. Tyrosine kinase inhibitors are also tested in combination with for instance VEGFR inhibitors such as ramucirumab in EGFR-mutated lung cancer where the combination was superior to monotherapy erlotinib [106]. A combination of gefitinib (an EGFR inhibitor) with chemotherapy has also been shown to be superior to monotherapy gefitinib in lung cancer [107].

The coming years will see the approval of new agents for targets for which there is currently no available therapy. Highly compelling data has recently been presented for RET inhibitors for patients with RET fusions [108], MET inhibitors for patients with cMET exon 14 skipping mutations [109], EGFR inhibitors with efficacy in exon 20 insertions [110, 111], and agents active in ROS1 G2032R, the most common mutation associated with resistance to current ROS1 inhibitors [112, 113]. Furthermore, there are more than 150 new tyrosine kinase inhibitors in clinical trials and many molecules are in pre-clinical development [114].

3.6.2 Antibodies, bispecific and multispecific antibodies, antibody conjugates, and nanobodies

Antibodies constitute a cornerstone of modern cancer therapy and are in many ways ideal cancer drugs by their high specificity, biological background, favorable pharmacokinetics, and potential for multiple mode of actions depending on construction and binding epitope. Antibodies have been developed against both ligands and receptors. They have been designed so that the binding of the antibody can shut down or activate the signaling of a receptor due to a conformational change, inhibit ligand binding, inhibit receptor dimerization, or to predominantly activate the immune system to kill the cell they are binding to or as in the case of immune checkpoint inhibitors, modulation of the immune system itself. There are currently over 30 approved antibodies in oncology/hematology with approvals ranging from late stage metastatic to adjuvant setting and from monotherapy to combination with other therapies. Antibodies have over the years had a higher rate of success compared with small molecular drugs when assessing the rate of candidate drugs entering phase I to regulatory approval with an overall rate of about one in five compared with one in eight [115], which has triggered significant investments. There are currently over 300 antibodies targeting cancer in clinical development and more than 30 in phase III [116]. Although some have targets that already have approved antibodies (not least immune checkpoint inhibitor targets) many have new targets, identified through advances in the biological understanding of cancer.

About 60 of the antibodies in early and late stages of development are antibody-drug conjugates (ADCs) [117]. ADCs consist of monoclonal antibodies that are linked to cytotoxic chemicals by a synthetic linker. The idea is to enable highly selective delivery of a cytotoxic agent that is cleaved off when internalized, thereby increasing the anti-tumor efficacy but at the same time also decreasing the off-target toxicity that is usually significant for cytotoxic therapies. There are already four approved ADCs (trastuzumab emtansine, brentuximab vedotin, gemtuzumab ozogamicin, inotuzumab ozogamicin), but new ADCs have recently reported impressive efficacy data in both breast cancer [118] and bladder cancer [119], and we should thus expect multiple new approvals in this class of drugs. The development of novel cytotoxic payloads and improved linkers may also enable improved safety profiles, as systemic toxicity has remained an issue with the currently approved agents [117]. There are also antibodies in development where the attached payload consists of immune toxins or a radioisotope (radioimmunoconjugates).

Another emerging area within the antibody field are antibodies with two different binding epitopes, so-called bispecific antibodies. There are currently two bispecific antibodies approved in oncology: blinatumomab which binds to two proteins, CD19 on the surface of B-lineage cells and CD3 on T cells – essentially bringing these cells closer and thereby increasing the chance of T cells killing the leukemic cells, and catumaxomab which binds to CD3 and EPCAM. Another approximately 50 bispecific antibodies are in clinical development. There are also multispecific and oligoclonal antibodies in development, but these have not yet entered late stage clinical trials in oncology [120].

Yet another emerging field relating to antibodies are so-called nanobodies and antibody mimetics. Nanobodies are fragments of antibodies consisting of a single monomeric variable antibody domain. Like an antibody, it can thereby bind selectively to a specific antigen. The potential advantage of a nanobody is that it is much smaller and has a lower molecular weight (12–15kDa) than common antibodies (150–160 kDa). Penetration to the interstitial space is thus higher. It also lacks the immune activating region of an antibody, which is advantageous in some (but not all) contexts. The first approval for a nanobody came in 2018 [121], and although it was not in oncology (caplacizumab in acquired thrombotic thrombocytopenic purpura) it represents an important milestone. Multiple nanobodies and antibody mimetic are in development in oncology and it is reasonable to assume that some will result in approvals in the coming years.

3.6.3 Immuno-oncology

In less than a decade immunotherapy has become a cornerstone of cancer therapy; see Figure 36 a for schematic description of the first targets, CTLA-4 and PD-1. Current data indicate that in some indications a substantial subgroup of patients is likely cured from metastatic disease [122].

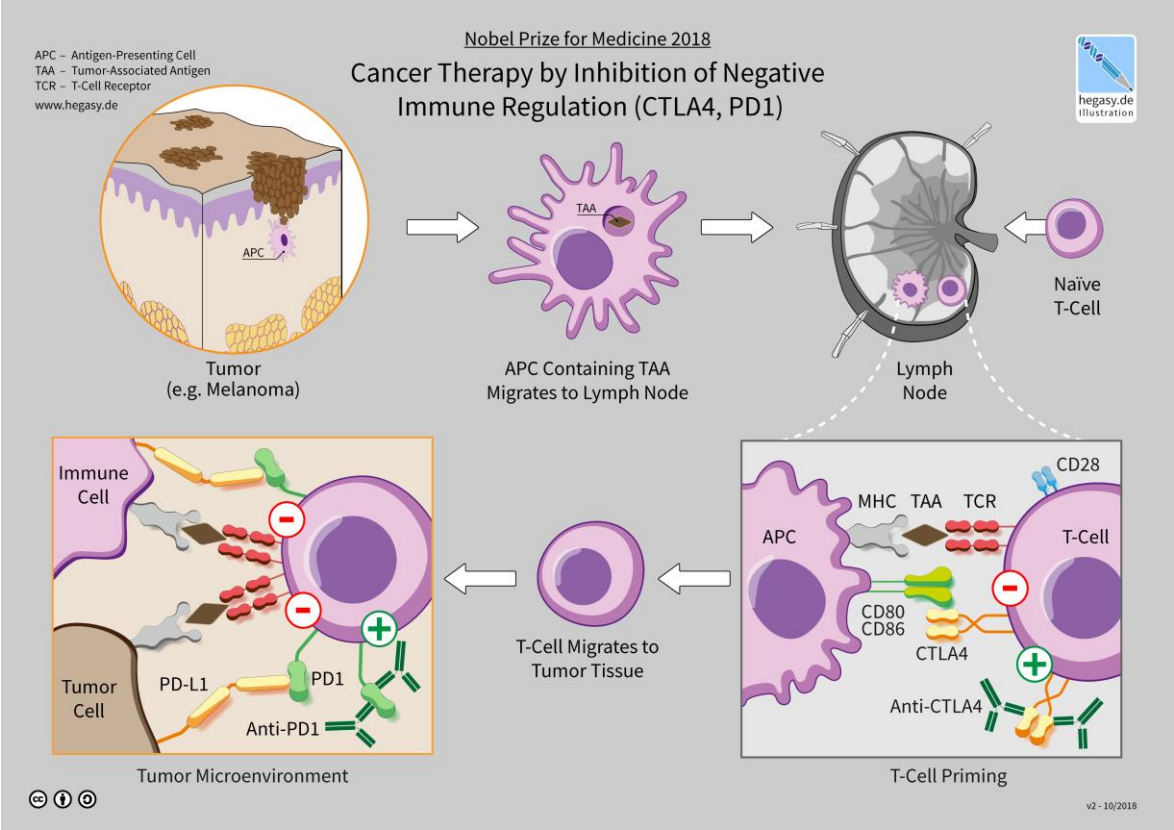

Figure 36: CTLA-4 and PD-1 – the first targets for immuno-oncology [123]

Immune checkpoint inhibitor antibodies against CTLA-4 (ipilumumab), PD-1 (pembrolizumab, nivolumab, cemiplimab), and PD-L1 (atezolizumab, durvalumab, avelumab) have been approved across multiple solid malignancies (melanoma, squamous NSCLC, adenocarcinoma (NSCLC), urothelial cancer, head and neck cancer, renal cancer, colorectal cancer, Hodgkin lymphoma, PMBCL, gastric adenocarcinoma, cervical cancer, cutaneous squamous carcinoma, Merkel cell carcinoma, and most recently esophageal cancer). The position of these therapies has also moved rapidly to front line therapy in several indications and even to adjuvant approvals in high risk patients with melanoma. Interestingly, an indication agnostic approval has also been granted by the FDA in patients with MSI-H status, as these patients have a higher likelihood of benefit from PD-1 targeted therapy [124].

The introduction of these agents has opened up a wealth of studies to assess the added value of different combinations with these agents. Currently, there is a trend that a subset of patients appears to benefit most from monotherapy with these agents while another subset derives most benefit from combination with standard chemotherapy. The approved combination of PD-1 and CTLA-4 antibodies has proven to be more efficacious than either agent alone in for instance melanoma, but toxicity has been problematic, limiting use so far.

It should be emphasized that immunotherapy is still in its infancy. Most patients do not respond to these agents [125]; see Figure 37. Biomarkers (see section 3.5) to help select patients appropriately need significant further work to make sure that eligible patients (the blue line in Figure 37) and patients who respond to treatment (the yellow line in Figure 37) lie as close to each other as possible.

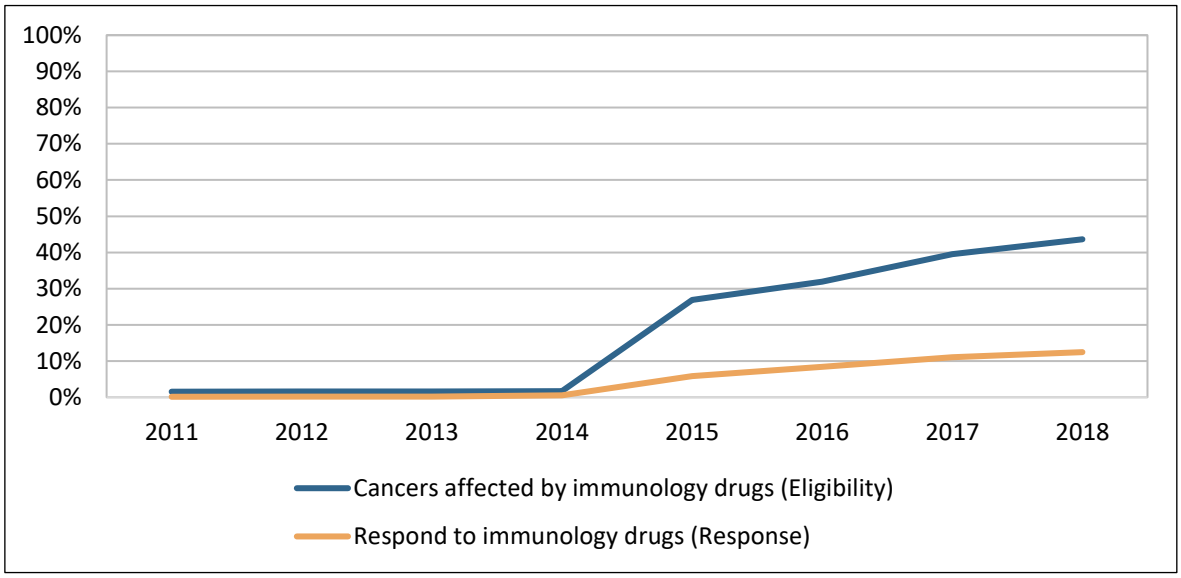

Figure 37: Share of cancer patients who may benefit from and respond to checkpoint inhibitor immunology drugs in the US [125]

An ongoing and future challenge will be to elucidate the value of different combinations and selecting patients appropriately. In September 2018, there were 2,250 clinical trials assessing PD-1/PD-L1 agents either alone (monotherapy; 534 trials) or in combination with other therapies (1,716 trials), such as standard chemotherapies, immuno-oncology doublets, and targeted therapy [126]; see Figure 38. These combination therapies covered at least 240 different targets. There is also a rapidly growing number of agents in the immuno-oncology pipeline with 3,394 reported agents in 2018 [127]. New agents have a variety of mode of action with targets ranging from surface-bound immune checkpoint molecules such as TIM-3, OX40, LAG-3, TIGIT, PROCR, and PDPN [128] as well as soluble factors such as TGFβ [79]. Other agents target Tregs [80] and the reprogramming of tumor-associated macrophages [129]. Many of these agents are targeting subgroups of patients based on biomarkers. There are many efforts to understand the differences between tumors based on genomic analysis and analysis of stromal immune cells, but our understanding is still limited. Data indicate however that there are several main subgroups with different characteristics: IFNγ dominant, inflammatory, lymphocyte depleted, immunologically cold, TGFβ dominant, and a subgroup characterized by a "wound healing" signature [78]. Although specific targets are not necessarily restricted to these subgroups, it is reasonable to expect that different combination therapies will be best suited in

subgroups of patients. Emerging data are also indicating that it may be preferable to "normalize" rather than amplify anti-tumor immunity [130].

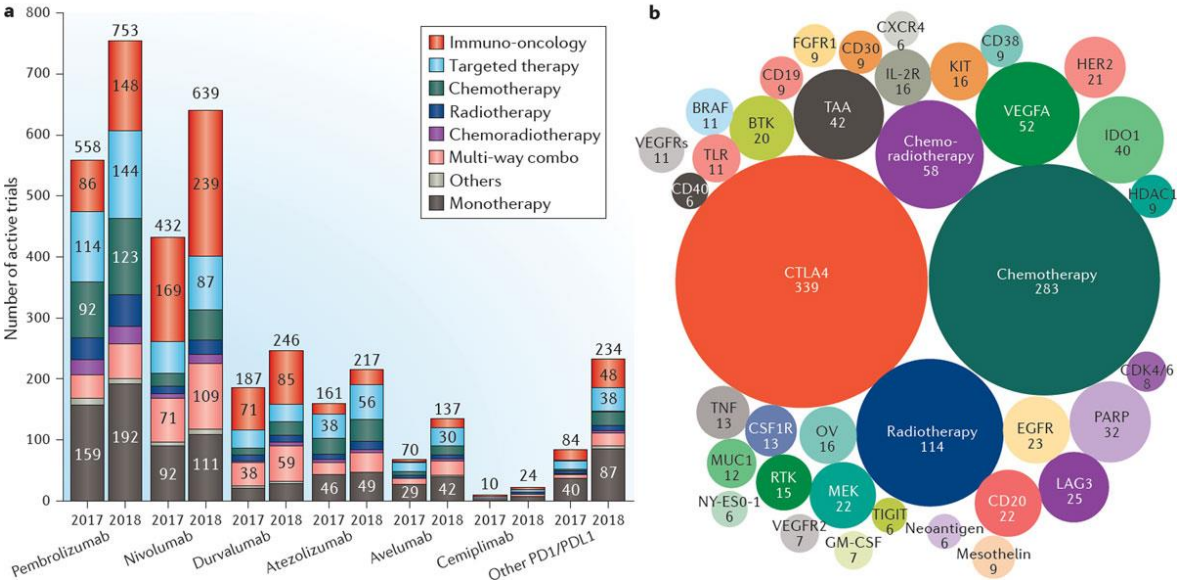

Figure 38: The immuno-oncology trial landscape in September 2018

Notes: (a) 2,250 active trials testing anti-PD-1/PD-L1 agents in 2018 compared with 1,502 trials in 2017, (b) 1,332 trials testing anti-PD-1/PD-L1 agents in combination with the top 38 targets. Source: [126].

There are multiple examples of successful and promising combinations such as pembrolizumab in combination with axitinib in renal cancer [101], oncolytic viral therapy with talimogene laherparepvec in combination with pembrolizumab in advanced melanoma [131], the bispecific antibody M7824 (PD-L1 and TGFβ) in heavily pre-treated patients [79], a CD47 antibody in combination with rituximab (CD20) [132], a bispecific antibody of PD-L1 and CD47 [133], but also trials that despite compelling pre-clinical evidence have failed such as IDO1 inhibitor in combination with pembrolizumab [134]. However, as mentioned in section 3.6.1, some combinations have not been possible to take forward due to toxicity.

The success of PD-1/PD-L1 and CTLA-4 targeted antibodies has highlighted the importance and potential of our immune systems in oncology. It has also validated immune escape as a phenomenon and that it is possible to target and reverse immune escape in some patients.

Future challenges include improved biomarkers to enable patient selection. Finding the optimal combinations will also be a significant challenge and it must be expected that not all of the combinations currently tested will lead to approvals. Since the immune system has the ability to remember and destroy new tumor clones as they emerge, immunotherapy is likely to become a cornerstone in almost all areas of oncology. Immunotherapies have rapidly moved to first line therapy in multiple indications and importantly initial adjuvant studies (melanoma) have been positive.

Recent data in the neoadjuvant setting also indicate that response rates appear to be high compared to the metastatic setting although toxicity of doublet CTLA-4 and PD-1 targeted therapy appears also to be associated with more adverse effects in the neoadjuvant compared to the metastatic setting [135]. Multiple adjuvant trials are ongoing in several indications in solid tumors. If these trials are positive, the case for screening in several malignancies will become stronger – partly in order to identify patients that can potentially be cured by immunotherapy but also to find patients early when the risk of recurrence is so low that no therapy is indicated. Positive adjuvant studies will also open up new indications in patients who have recurred after adjuvant immunotherapy. A potential future scenario is also that immunotherapy may be more effective in the neoadjuvant (i.e. prior or without surgery) than the adjuvant setting (post-surgery).

Immune modulation, provided that the therapies have a good safety profile, may also become important in the prevention of cancer as our immune systems change with aging, which is likely a strong contributing factor to the high incidence of cancer in the elderly.

3.6.4 Cell-based therapies

There are currently two approved CD19-targeted CAR T-cell therapies. Both platforms (axicabtagene ciloleucel and tisagenlecleucel) are approved for B cell lymphoma after two or more lines of systemic therapy. Tisagenlecleucel is also approved for acute lymphatic leukemia (ALL) in late relapses. Response rates are impressive in these heavily pre-treated patients but there are also complexities with these agents. Some patients experience cytokine release syndrome and transient neurological adverse events. Importantly, treatment can lead to B cell aplasia which requires maintenance therapy of intravenous immunoglobulins from normal donors (as all B cells express CD19).

Many further cell-based therapies are in development. Alternative CD19-targeted CAR-Ts such as JCAR017 [136] are likely to become approved within the near future. CAR-Ts with other targets that can potentially expand the use to other indications such as BMCA, CD20, CD22, CD30, CD33, CD123, WT1, GPC3, CD38, MUC1, mesothelin, GD2, and neoantigens are being explored [127]. Some of these have already demonstrated clinical efficacy, e.g. CAR-Ts with CD22 in ALL [137], CD30 in Hodgkin lymphoma [138], BMCA in multiple myeloma [139], CD123 in myelodysplastic syndrome [140]. There are also multiple efforts to design safer and more effective CAR-T strategies. Gene editing methodology could potentially enable deletion of HLA and endogenous T cell receptors in T cells expressing the CAR-T construct, which could be used for any patient whose cancer would express the target of the CAR-T [141]. Gene editing has also been used to make the CAR-Ts without PD-1 expression and to secrete antibodies against PD-L1 or secrete other immune modulating agents

locally in the tumor that may help overcome potential resistance mechanisms [142-144]. Other efforts are directed to strategies to switch off CAR-Ts in order to help patients who develop severe toxicities [145, 146].

Other types of cell therapy such as T cells engineered to express T cell receptors with known specificity, tumor-reactive or tumor infiltrating T cells isolated and expanded from cancer patients, hematopoietic stem cells, polyclonal tumor-reactive T cells isolated from the tumor, NK cells, NKT cells, and dendritic cells are also being explored. Evidence is supporting clinical efficacy for some of these alternative concepts to CAR-Ts.

There have been doubts concerning the role of cell-based therapies in solid tumors as there is no antigen that is consistently expressed in a similar way to CD19 in B-cell malignancies and due to a different tumor stroma. Recent data indicate however a future role of cell-based therapies also in solid tumors, as responses have been seen in synovial sarcoma and impressive PFS (but stable disease only) in heavily pre-treated patients using tumor antigens that are expressed in a fair proportion of patients in some indications [147]. Other forms of cell-based therapies have also demonstrated clinical efficacy in solid tumors; tumor infiltrating lymphocytes (TILs) in melanoma has reported an overall response rate of 42% [148], and adoptive transfer with neoantigen-specific T cells has led to objective clinical responses in patients with metastatic cholangiocarcinoma, colorectal, cervical, and triple-negative breast cancer [149-151]. In the coming years we will most likely see several cell-based therapy approvals also in solid malignancies. Multiple factors, including identification/validation of targets, solving CMC/logistics, and costs and efficacy of other types of therapies will determine the ultimate role of cell therapy in solid malignancies.

3.6.5 Challenging-to-drug targets

Although the last two decades have seen a wealth of novel agents targeting kinases and immune checkpoints, most of our proteome is currently not “druggable” [152], and many interesting targets that are common in cancer have remained elusive. Common drivers such as RAS, MYC, and other transcription factors have proved difficult to drug owing to large protein–protein interaction interfaces and/or lack of deep protein pockets and a complex biology with mechanisms of action requiring association with many co-factors. Recently a KRAS-G12C-targeted molecule showed clinical efficacy, which constitutes a major breakthrough that hopefully can be taken through to approval shortly [153].

Novel drug classes such as gene editing/therapy, oncolytic virotherapy, siRNA/RNA interference, cell-based therapy, and proteolysis-targeting chimeras (PROTACs) are likely to enable targeting of

several of the proteome targets that have been out of reach so far [154]. The first gene therapy was approved in 2019 (onasemnogene abeparvovec-xioi) and although not in an oncology indication, it represents a milestone in medicine and theoretically oncology is not out of reach for this class of agents. There is currently only one FDA/EMA-approved oncolytic virotherapy (talimogene laherparepvec) but other platforms are in development, including combinations with immune checkpoint inhibitors [155]. RNA interference is also rapidly developing after years of challenges with a first approval in 2017 (patisiran) [156], and other candidate drugs with proof of concept [157] (although not yet in oncology). PROTACs is a novel class of compounds that tag specific proteins for degradation. Although challenges remain with PROTACs before they are in the clinic, there is substantial evidence supporting the concept and importantly it has been revealed that the mode of action of thalidomide at least in part functions as a PROTAC [158]. Immunotherapy approaches may also enable targeting tumors with some of these alterations, for instance T cell transfer therapy targeting mutant KRAS has been demonstrated to be effective [150]. Thus, there are reasons to be optimistic concerning the targets that have been elusive so far – these should be considered as challenging-to-drug but not undruggable.

3.7 Machine learning and artificial intelligence

Health care is becoming increasingly rich in data generated from patients, health care records are transitioning to digital format, and new technologies like NGS are providing detailed genomic/molecular characteristics of patients. Furthermore, imaging and pathology is used in digital format and wearable technologies are starting to enable capturing data from patients that have previously not been possible – ranging from vital parameters to the spoken word. The amount of data generated requires computer-assisted analysis in the form of artificial intelligence (AI)/deep learning in order to make sense and develop understandable output that can help clinicians and patients in a meaningful way. Machine learning has been applied to image analysis and current data support that it can have a high accuracy in diagnosis of various medical conditions [159]. In cancer, it has been applied to for instance diagnosis of melanoma, where the performance was similar to trained dermatologists [160], or better [161, 162]. Machine learning has also been applied to various areas of radiology imaging including mammography interpretation [163], thoracic screening imaging [164], and as a tool to help improve monitoring and control [165]. The application of AI/deep learning to radiology is clearly starting to show interesting results, not least as it may assist in decreasing the interobserver variability of radiology assessments.

In digital pathology, AI has demonstrated accurately mitosis detection, characterization of histologic features such as nuclei, tubules and epithelium, count events, and characterization and classification

of tissue [166-168]. Deep learning has also helped to identify some features that are currently not used and that may be prognostic, such as stromal features [169], tumor-adjacent benign tissue in prostate cancer [170], and nuclear shape/orientation [171]. Deep learning in digital pathology has also been shown to be able to predict specific genomic/molecular characteristics such as mutations in lung cancer [172], MSI status [173], and ER status [174]. For some parameters in pathology such as determination of grade, there is substantial interobserver variability [175]. One of the most likely first broad clinical uses of deep learning in digital pathology will be the standardization of such parameters. Deep learning is also being applied to the large genomic datasets with annotated clinical outcome data that are being built [176-178].

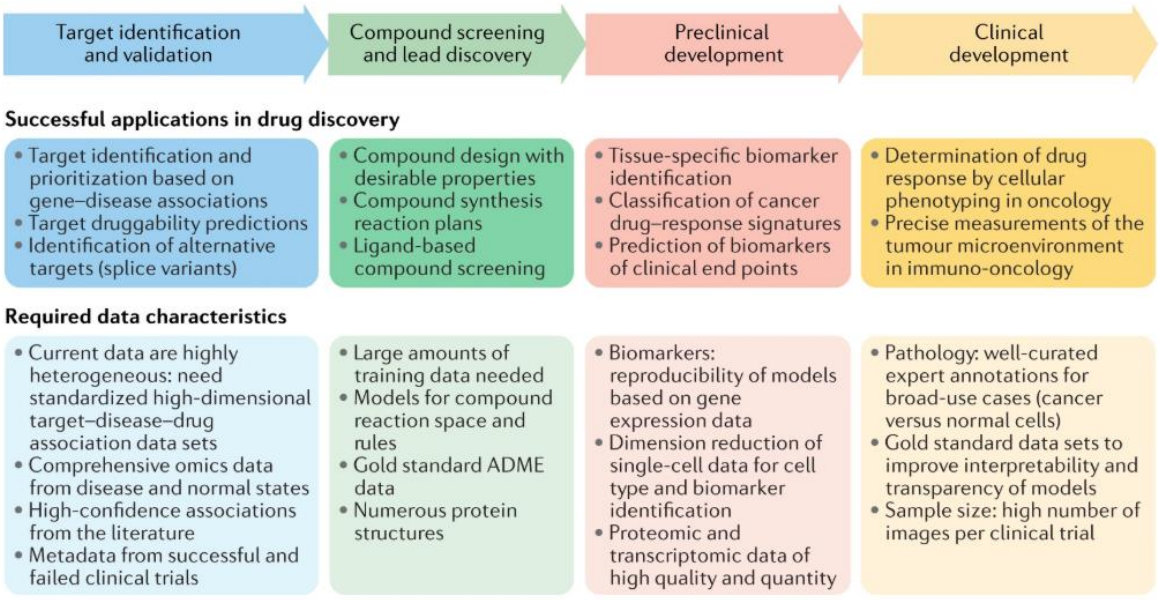

Figure 39: Application of AI in drug development [179]

AI is also being applied to other areas of oncology. Drug development in oncology is cumbersome and slow, and although there have been many breakthroughs related to improved understanding of cancer biology, the success rates for screened molecules is still lower than 10% [180]. With low success rates and long development times there is a strong interest in applying deep learning to various steps of the drug development process [181]. Machine learning is now increasingly being applied to almost all stages of drug discovery and development as well as biomarker and clinical follow up data; see Figure 39. In drug discovery, it is being tested for target identification and validation primarily based on gene-disease associations [182-184], but also on target druggability prediction [185-187]. In compound screening and lead discovery, it has been applied to compound design and ligand-based compound screening [188]. In preclinical development, it is being applied to biomarker identification, predictive signatures [189], and prediction of future clinical endpoints

[190]. In clinical development, it is being applied to digital pathology and biomarker assessments as described above.

In the coming years, AI will be included in various aspects of clinical care and drug development. Applying AI to imaging analysis in radiology, skin diseases/retina, and digital pathology will help to standardize and potentially also to improve assessments. It can also improve quality of care and reduce stress for physicians by assisting in treatment decisions. AI analysis of data from wearable technologies also has the potential to improve quality of care by identifying situations where the patient is in need of medical assistance and by providing more granular information on a patient's symptoms and quality of life. The major clinical advance will likely be the merger of data from genomic, digital pathology, imaging, health records, and wearables, but interoperability of different datasets will be a challenge. It should also be emphasized that the successful application of AI to these areas will require large and high-quality clinical datasets, as the quality of the datasets determines the performance of the final results. Many of the efforts using AI in clinical medicine have so far not been assessed for reproducibility and the complete artificial algorithm code is provided in a minority of publications [191]. Rigorous validation in different datasets to prove performance will be key before clinical use. Another key aspect for the application of these products in clinical care is to respect patient integrity and confidentiality in line with privacy regulations such as GDPR. Unlike the application of AI to many technology products where consumer data are used without much concern for privacy, inappropriate use in health care will be detrimental and may severely damage and delay the integration of these technologies in clinical care. Thus, the use requires extra attention to ethics and privacy.

3.8 Surrogate endpoints in clinical studies

Most anti-tumor drugs are introduced in patients with late-stage or metastatic disease. Their use may lead to improved survival, but the magnitude of the effect is seldom known when the drug is first introduced, as surrogate endpoints, such as progression free survival (PFS) and objective response rate (ORR), are often used in clinical trials. Surrogate endpoints trade the advantage of reducing the time needed to conduct clinical trials (and hence accelerating patient access to new treatment options) for the disadvantage of greater uncertainty regarding patient-centered outcomes (e.g. overall survival (OS) and quality of life). Analyzing trials of 188 indications of 107 cancer medicines approved by the FDA in the US between 2006 and 2017, a recent study showed that the use of ORR or PFS as the primary endpoint was associated with 19 months or 11 months, respectively, shorter study duration compared to using OS [192]. This can be compared to the average development time of a medicine – from early clinical trials to drug approval – of about 6 to 15 years in the US [193].

There is an ongoing discussion about suitable endpoints for drug approvals. In general, the use of ORR alone is not enough, and the use of PFS is only suitable if it is strongly associated with OS. Surrogate endpoints are essential in certain settings, e.g. when the assessment of OS takes several years (e.g. early-stage prostate cancer) and when crossover and the number of lines of therapy administered after the study drug can dilute the chances of demonstrating clinically relevant effects on OS [194-197]. It is important to note that in late-stage disease PFS and OS may not differ much [198]. A statistically significant increase in PFS with borderline clinical relevance (less than 2 months) that does not translate into a similar or larger impact on OS is not useful. However, it might happen that there is a modest median PFS benefit but a substantial effect on OS. For instance, in the pivotal study for ipilimumab there was no benefit in median PFS but a significant median OS benefit of close to 4 months difference favoring ipilimumab, with a continuous survival advantage and 20 percent survival at 7–8 years follow-up [199, 200].

Many recent drugs target rare alterations. In fact, 87 percent of drug usage aims at fewer than 10,000 patients globally [201]. In these small indications it is not feasible to perform large-scale randomized phase III clinical trials to gain regulatory approval. Instead, approvals have to be based on smaller phase II trials using PFS as primary endpoint, in order to not delay patient access to these drugs. Furthermore, tumor heterogeneity is a challenge when treatments are entering clinical practice. Tumor development is also an important difficulty which may include selection of clones that can be treatment related. Thus, demonstrating OS advantage can be very challenging in heavily pre-treated patients, and PFS may be a more useful endpoint. Also, evasion of immune response can be difficult to study as patient groups are small and heterogenous.

Ways to improve the robustness of the demonstration of clinical benefit compared to historical controls include the development of “synthetic” control arms, based on data from clinical registries capturing outcome. In theory, this may also become an option for other drugs with more common targets provided that the synthetic-control-arm data are robust and from high-quality sources.

3.9 Clinical effectiveness and real-world evidence

If a new drug demonstrates efficacy in an RCT, it means that the drug works under controlled conditions and pre-defined endpoints. A patient treated in clinical practice does not generally fit the inclusion and exclusion criteria of clinical trials and is often older and has more co-morbidities. Treatments for co-morbidities, such as beta blockers, may affect the outcome of cancer treatment [202-204]. Side effects resulting in dose reductions will reduce the amount of drug reaching the target, which may influence outcome. Furthermore, the sequence and combinations of treatments

differ often from the strict protocols of clinical trials. The adherence to guidelines (based on results from clinical studies) and outcome in relation to compliance is rarely evaluated.

The discrepancy in treatment between any RCT and clinical practice is the main argument for conducting clinical effectiveness studies. These studies include different aspects of effectiveness and safety from the perspective of the individual patient, the health care system, and of the broader society. Clinical effectiveness studies use data from clinical practice, usually extracted from patient charts (real-world data, RWD). An example of a successful use of RWD in oncology is avelumab, which was granted accelerated access by the FDA in the US based on an open-label, single-arm study, supported by RWD [205].

Clinical effectiveness studies can demonstrate which treatments work in practice and show outcome and long-term effects in different patient groups. They may also reveal unknown aspects which necessitate further research. The amount of data collected for each patient may be very high, and the methods for analyses will require large databases and AI support. Significant efforts are being made to generate very large datasets of patients with clinical follow-up data and extensive genomic profiling data [206, 207]. These efforts are likely to enable novel ways to identify what therapy/ies to give to subsets of patients. Importantly, these datasets may become valuable for drug development, as they can function as synthetic control arms in novel therapies and be used for the expansion of labels to different subgroups that are not included in pivotal trials. Provided that these datasets include relevant variables and high rates of completeness of data for each patient, they will also enable higher quality RWD that can support good medical practice as well as reimbursement.

In the Nordic and some other European countries, there are national high-quality registries with data on cancer diagnoses and deaths on all cancer patients. Other countries have regional/local registries, with information on diagnosis and deaths, but they have generally lower coverage compared to the above-mentioned national registries. Unfortunately, all registries contain little data on treatments; this data has so far been collected retrospectively. Even though publications using RWD at really high standards exist [208], the lack of prospective registration will always lower quality. The value of each treatment will be difficult to record, as treatments are given in combinations and sequences. Establishing the value of each treatment will be even more difficult if not enough data are recorded.

Electronic health records will simplify the transfer of data to registries, as the data transfer can be done automatically. There are however many challenges with the interoperability between databases and data privacy. In Sweden, it is possible to collect data and RWD can be collected prospectively from all consenting patients. By contrast, in Germany it is not allowed to link data [205].

Patient-reported outcomes (PROs) are also one factor to consider in terms of RWD, as it has been shown that PRO data collection may affect outcome [209, 210]. Although very important, it is outside of the scope of this report to evaluate this important field of oncology.

Patients, clinicians, pharmaceutical companies, and the society as a whole all want new and more effective drugs to reach the patient as soon as possible. It is essential to follow the outcomes of these treatments when used in clinical practice in order to ensure effectiveness and value-for-money. This should be a prerequisite for any new drug. RWD is important and "(o)nly by working together to build awareness and infrastructure, to foster alignment across policies and to develop standards and skills, can health data truly be used to its full potential and transform the way in which cancer care is delivered", as previously acknowledged in an EFPIA report [205].

3.10 Summary and conclusions

Cancer prevention has had a long history of slow progress and lack of implementation. This is probably linked to the fact that more than half of all preventable cases (which themselves constitute about 40–45 percent of all cancer cases) are linked to unhealthy lifestyles. Cancer prevention is still faced with major obstacles linked to awareness and education. R&D in cancer prevention has not garnered much interest from the pharmaceutical industry, possibly due to the temporal and fiscal challenges inherent in preventive device and drug development [211]. Most progress in this field are results from public funding, which is limited due to competing priorities in basic cancer science and treatment. As a result, few well-funded investigators are vested in prevention and screening research. However, a recent article clarifies the pharmaceutical industry's perspective on the field and its potential [212]. Better biological understanding of the carcinogenic process may identify new targets for cancer prevention.

Screening is recommended for breast, cervical, colorectal, and lung cancer as mortality can be reduced. However, the specific design of the screening programs determines the value and cost-effectiveness. Screening for prostate cancer is uncertain, as testing may cause both false positive and false negative diagnoses depending on the screening method. New directions in functional breast cancer screening are now used in women with significant mammographic breast density [213, 214]. Blood tests on circulating DNA are in development and can potentially detect many types of asymptomatic cancers [215]. Pancreatic, liver, and bladder cancer are examples of diseases for which reliable and practical risk-based screening tests are needed. Screening for less common cancer types may be possible but demands highly accurate tests and well-defined and acceptable diagnostic and treatment approaches.

The field of diagnostics has rapidly developed in the last decade. In some cases, it is already possible to predict if a patient is likely to respond to a certain treatment using different molecular markers. New technologies such as NGS can help to characterize changes in genes and unravel novel targets that are druggable. Testing is evolving from single markers to broad panels covering markers with approved drugs but also markers that can enable patients to participate in ongoing clinical trials with drugs in development. Testing has so far mainly involved assessment of tumor material requiring surgical or needle biopsies. New tests are increasingly being developed that can assess many relevant markers in blood, which poses little risk for the patient and may enable monitoring over time, but inclusion into standard of care of such tests will require high sensitivity and specificity. Identifying appropriate patients for a future complex landscape of different combinations of therapies and cell-based therapies will also require extensive testing. This will increase the up-front costs for treatment and thus must be compensated by improvements in outcome and/or reduction of side effects. Modern testing is also costly, which limits its use in many regions of the world.

Countless targets for cancer treatment have been identified. Over 40 small molecules are currently in use for targeting protein kinases involved in cancer. Although tyrosine kinase inhibitors were not the magic bullets as they had been anticipated to be at the arrival of imatinib, they have provided significant value in multiple indications. Most of these drugs are used in patients with late-stage or metastatic disease. An important area under investigation is whether these agents will show efficacy in the adjuvant setting. The data reported so far has been somewhat conflicting but the picture that is emerging is that potent agents at sufficient dose appear to provide benefit. Another area that is being explored is the combination of tyrosine kinase inhibitors with immune checkpoint inhibitors and with other types of agents. The coming years will see the approval of new agents for targets for which there is currently no available therapy. There are more than 150 new tyrosine kinase inhibitors in clinical trials and many molecules are in pre-clinical development.

Antibodies constitute a cornerstone of modern cancer therapy and are in many ways ideal cancer drugs. There are currently over 30 approved antibodies in oncology/hematology with approvals ranging from late-stage metastatic to adjuvant setting and from monotherapy to combination with other therapies. Antibodies have over the years had a higher rate of success compared with small molecular drugs when assessing the rate of candidate drugs entering phase I to regulatory approval. There are currently over 300 antibodies targeting cancer in clinical development and more than 30 in phase III. About 60 of the antibodies in early and late stages of development are ADCs. Another emerging area are antibodies with two different binding epitopes, so-called bispecific antibodies. Multispecific and oligoclonal antibodies are also in development. Nanobodies and antibody mimetics are another promising alternative in oncology, which might see approvals in the coming years.

Immunotherapy has become a cornerstone in cancer therapy during the last five years. Current data indicate that in some indications a substantial subgroup of patients is likely cured from metastatic disease. Immunotherapies have been approved across multiple solid malignancies. The position of these therapies has also moved rapidly to front line therapy in several indications and even to adjuvant approvals in high risk patients with melanoma. Despite this development, immunotherapy is still in its infancy. Most patients do not respond to these agents. Better biomarkers are needed to facilitate patient selection. Another challenge is to determine the value of different combinations of agents. Over 2,000 clinical trials assessing immunotherapies either alone or in combination with other targets are currently ongoing.

Although the last two decades have witnessed the launch of many novel agents targeting kinases and immune checkpoints, most of our proteome is currently not “druggable”. Novel drug classes such as gene editing/therapy, oncolytic virotherapy, siRNA/RNA interference, cell-based therapies, and PROTACs are likely to enable targeting of several of the proteome targets that have been out of reach so far. Notably, cell-based therapies have recently emerged in hematological malignancies. Currently there are two approved CAR T-cell therapies, which have shown great response rates in some patients but also come along with potentially severe side effects. Cell-based therapies in solid tumors are also studied.

Health care is becoming increasingly rich in the data that is generated from patients. The amount of data requires computer-assisted analysis in the form of AI/deep learning. In the coming years, AI will be included in various aspects of clinical care and drug development. Applying AI to imaging analysis in radiology, skin diseases/retina, and digital pathology will help to standardize and potentially also to improve assessments. It can also improve quality of care and reduce stress for physicians by assisting in treatment decisions. AI analysis of data from wearable technologies also has the potential to improve quality of care by identifying situations where the patient is in need of medical assistance. A successful application of AI will require large and high-quality clinical datasets. Rigorous validation in different datasets to prove performance will be key before clinical use. Patient integrity and confidentiality also need to be addressed before widespread clinical use.

In recent years, more and more patient groups have become eligible for drug treatment. Targeted therapies are being developed for patients with sometimes very rare alterations and in some cases treatments are only approved on phase II trial data and on PFS in the metastatic setting. It is thus increasingly important to collect data from patients in clinical practice (RWD) and to follow the results of each treatment using relevant outcomes (safety, OS). Patients are also increasingly treated with many different drugs in combinations and in sequence. It is essential to follow the outcomes of

these treatments when used in clinical practice in order to ensure effectiveness and value-for-money. This should be a prerequisite for any new drug.

3.11 References

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4. Access to and uptake of cancer medicines

4.1 Key messages

- There has been a distinct increase in the number of approved cancer medicines and indications in recent years. Around ten new medicines per year were approved by the EMA between 2012 and 2018. Targeted medicines and since 2015 immuno-oncology medicines are behind the increase in the number of new cancer medicines. A considerable share of new medicines has an orphan designation.
- The total costs of cancer medicines more than doubled between 2008 and 2018 in Europe. Total cancer medicine sales increased from €12.9 billion (€14.6 billion in 2018 prices and exchange rates) to €32.0 billion between 2008 and 2018. In per-capita terms, sales increased from €25 (€28) to €61.
- Patient access to cancer medicines (measured in total sales) was much greater in wealthier countries than in poorer countries. The top spenders in 2018 were Austria, Germany, and Switzerland (around €92 to €108 per capita), whereas Czechia, Latvia, and Poland spent the least (around €13 to €16). Higher rebates on medicines in poorer countries might exaggerate these differences.
- Cancer medicines accounted for a modest but growing share of total pharmaceutical sales. Around 9–14 percent of total pharmaceutical expenditure were spent on cancer medicines in 2015 in some wealthier countries, compared to around 5–7 percent in 2005. Cancer medicines also accounted for a growing share of the direct costs of cancer and reached almost one third (31 percent) in 2018.
- A small number of cancer medicines make up the majority of sales in Europe. The top 10 medicines in terms of sales stood for 55 percent of total sales in 2008 and for 45 percent in 2018. However, the composition of the top-selling medicines changed quickly over time. Of the top 10 in 2008, there were only three medicines left in the top 10 in 2018.
- There is a stronger uptake of the newest cancer medicines (approved within the last two years) in wealthier countries than in poorer countries in all years between 2008 and 2018. The economic crisis seemed to have slowed the uptake of the newest cancer medicines only temporarily.
- Uptake of new cancer medicines, measured in volume, also varies between countries. Differences in uptake relate to countries' economic status; higher uptake in wealthier

countries and lower uptake in poorer countries. This pattern has not changed over time and is consistent with the one found in the previous Comparator reports.

- Poorer countries recorded around one third to one half of the level of uptake (in volume) of the big 5 countries and the wealthier countries. Among the big 5, the UK showed a consistent pattern of the lowest level of uptake across seven considered cancer types and immunotherapy. France and Germany had the highest level of uptake among the big 5.
- The largest country differences in uptake were observed in immuno-oncology medicines and in medicines used for multiple myeloma and prostate cancer in 2018. The uptake of immuno-oncology medicines in poorer countries was around 10–20 percent of the level observed in the big 5 and the wealthier countries, which might also reflect differences in how well health care systems were prepared for the introduction of this new form of treatment.
- The smallest country differences in uptake were observed in medicines used for lung cancer in 2018. In addition, country differences in the uptake of mature medicines with a large patient population were comparatively smaller than in newer medicines.

4.2 Data sources

Cancer medicines are a cornerstone in cancer therapy. This chapter analyzes access to and uptake of these medicines in countries across Europe.

Three principal sources have been used for the analysis in this chapter:

- Data on quarterly sales (in euros) and volumes (in milligrams) for individual cancer medicines were obtained from the MIDAS database maintained by IQVIA [1]. We had access to data for the years from 2008 until 2018 comprising medicines sold to hospitals and retail. We included cancer medicines from the ATC groups L01 (antineoplastic agents) and L02 (endocrine therapy), as well as five medicines from L04 (alemtuzumab, lenalidomide, pomalidomide, siltuximab, thalidomide).[23] The data cover the EU-28 member states (except Cyprus and Malta), Bosnia and Herzegovina [24], Iceland [25], Norway, Serbia [26], and

[23] Note that this selection of medicines does not cover all medicines used in the treatment of cancer patients. Medicines used for control of pain and side effects of cancer medicines are not included. However, many of the high-volume medicines given to cancer patients (e.g. antiemetic drugs) have a very low price, and the underestimation of the true costs of medicines used in the treatment of cancer patients is thus limited.
[24] Data for Bosnia and Herzegovina are available since 2011, but we exclude this country, as reliable statistics on fundamental measures such as population and GDP are not available.
[25] Data from Iceland were obtained from Icelandic Drug Market.
[26] Data for Serbia are available since 2011, but they only cover retail sales. We exclude Serbia for this reason.

Switzerland.[27] Sales data are based on IQVIA invoice prices, which often do not represent actual final sales prices, since medicines are granted confidential rebates to public payers in most European health systems. Consequently, the use of sales data based on invoice prices overestimates the cost of cancer medicines.[28] Medicines dispensed via retail can contain a profit margin, which is not included in the data and hence leads to an underestimation of the cost of some cancer medicines.

- Data on different characteristics of cancer medicines have been collected from the database on authorized medicines of the European Medicines Agency (EMA). Decisions up to the end of year 2018 were included [2].

- Country-specific cancer mortality figures for the year 2018 were obtained from the European Cancer Information System (ECIS) [3]. Population data come from Eurostat [4].

4.3 Measurement of access and uptake

Full access to cancer medicines is attained when every patient that may benefit will receive the relevant medicine [5]. If individual-level data are available, medicine usage can be related to information about the patient and the diagnosis. The data can then be aggregated to the country level providing knowledge on therapy patterns, length of usage, doses used, side effects of treatment, etc. However, this kind of data is rarely available even within a single country or for a single year.

Studying patient access at the international level is even more challenging. Comparable patient-level data, which includes all relevant variables, are generally missing. In the absence of patient-level data, country-level measures have to be used as a proxy for patient access to cancer medicines. This approach has been used in previous Comparator reports [6-9]. It is also the approach adopted in this report. In this context, access to cancer medicines is equated with market uptake, i.e. usage measured as total annual sales, in volume and value, of cancer medicines in a country.

[27] There are some minor caveats in the data in the MIDAS database. Estonia, Greece, and Luxembourg lack hospital sales throughout the whole period and Portugal for 2008–2009, whereas Latvia lacks retail sales for 2008–2012 (and lacks reliable data for 2013) and Romania for 2008. Romanian hospital sales in milligram are lacking for the whole period. Lithuanian sales data might be underreported in some years. Furthermore, data on retail sales might be underreported in some countries. For instance, in Austria an increasing number of pharmaceutical companies deliver products directly to pharmacies and not via wholesalers. These direct sales are not captured by MIDAS data, as MIDAS data are based on sales by wholesalers. Moreover, there might be parallel trade of medicines in some countries that can run in both directions (import and export) and that is not captured by the data and would bias country-specific results.
[28] This shortcoming can be overcome by considering sales in terms of volume instead of value.

4.3.1 Methodology

There are different approaches to measure market uptake [5]. Each approach has strengths and weaknesses, which are discussed below. In order to strike a balance between strengths and weaknesses, we adopted two main approaches in this chapter. First, when comparing total usage of all cancer medicines or sub-groups of cancer medicines, we used aggregated sales figures expressed in euros (€) at current price levels.[29] Sales were based on IQVIA invoice prices, which do not include confidential rebates. When comparing countries or groups of countries, sales were standardized by cases of cancer deaths or by 100,000 inhabitants. Second, when studying uptake of a single medicine, we expressed this as milligrams (mg) per case of cancer death or per 100,000 inhabitants, adjusted for the standard weekly dose. The latter measure indicates the number of patients treated with the reported sales volume.

Measuring usage of cancer medicines in value terms (e.g. in euros) enables aggregations, such as total spending on all cancer medicines or spending on medicines used in a specific indication. It also enables comparisons of spending on cancer medicines in relation to spending on other resources used for cancer care; see section 2.4. A limitation of this approach is that a common currency (€) is needed, which means that sales figures in countries with other currencies make it necessary to define an exchange rate. The choice of the exchange rate, for instance based on current values or PPP-adjusted values, will determine the relative position. Exchange rates may also fluctuate over time. Even in countries with a common currency (euro area), prices of one and the same medicine can differ and higher sales in one country might simply reflect higher national medicine prices rather than higher usage in volume terms. A further complication arises with hospital drugs, as the true price might be unknown due to confidential rebates granted. The size of these rebates might also vary between countries and over time.[30] The same is true for medicines dispensed via retail as pharmacy margins may vary, although such margins have a small impact on the total price of new medicines. Managed entry agreements also complicate the determination of the true drug price. Another complication is that medicines typically experience large drops in prices when they go off patent and generics become available. Even though the usage of off-patent drugs might still be high in volume terms, sales data would indicate low usage compared to patent-protected drugs.

Measuring usage of cancer medicines in volume terms (e.g. in milligrams) eliminates the problem of varying medicine prices, rebates, and exchange rates between countries and over time. A limitation

[29] In line with the previous Comparator reports, we did not adjust for exchange rate fluctuations or purchasing power differences.
[30] For instance, the estimated overall refund in Sweden in 2017 was 29% of total cancer medicine sales. A recent analysis showed that rebates might vary quite considerably across European countries [10].

of this approach is that medicines can only be compared individually. An aggregation of different medicines would mean that large volume and small volume medicines are bunched together.[31] Varying volume sizes of vials of a specific medicine across countries are another factor that can bias comparisons of usage. For instance, the entire content of large volume vials might not be used, as drug doses are given according to body surface area or weight of patients. Another complication is that national treatment guidelines might differ. Even though the EMA provides a recommended dose for each medicine, variations in dosage and treatment duration might explain some of the differences in usage between countries.

Irrespective of measuring usage in value or volume terms, a factor that complicates the analysis of market uptake based on IQVIA sales data is stockpiling. A certain portion of the initial sales of new products is often used to create inventory in the health care system, which leads to an overestimation of market uptake. Older products may experience decreases in inventory, and their market uptake may therefore be underestimated.

In order to provide comparable figures on usage of cancer medicines in different countries, sales have to be related to population size. Relating sales to the total population (€ or mg per 100,000 inhabitants) is one option. Data on total population size are readily available and easy to interpret. However, this type of standardization disregards the disease burden of cancer in a country and therefore ignores the actual need and demand for cancer care. Relating sales to cancer mortality (€ or mg per cancer deaths) or cancer incidence[32] (€ or mg per newly diagnosed cases) addresses this shortcoming. This chapter relies mostly on sales relating to cancer mortality, as most cancer medicines are used – especially during the first part of their life-cycle – for the treatment of advanced disease, i.e. they are used in a population that cannot be cured and will die of their cancer.[33] For medicines with a single indication, usage can be related to mortality in this specific indication. When a medicine or a class of medicines have several indications in different cancer sites this is more

[31] An alternative measure of usage in volume terms is the number of defined daily doses (DDD). It standardizes the dosage of medicines and thus enables an aggregation across medicines. However, the WHO does not provide DDD for virtually all cancer medicines (ATC group L01).

[32] A standardization based on cancer incidence is sensitive to the extent of false positive diagnosis and screening activities, as countries with more screening might have a higher share of early stage cancers which require little or no drug treatment. The absence of complete and reliable data on cancer incidence in many countries is another challenge.

[33] The shortcoming of this approach is linked to the way survival influences mortality. Survival and mortality figures vary greatly between European countries. In countries with high survival (and relatively few mortality cases) a presumably high amount of cancer medicines (which might be one reason for high survival) would be related to a small number of mortality cases, resulting in high market uptake. By contrast, in countries with low survival (and many mortality cases) a presumably small amount of cancer medicines would be related to a high number of mortality cases, resulting in low market uptake. Thus, this standardization might exaggerate differences between countries with high and low survival.

problematic.[34] Even though it would be desirable to standardize annual sales data with annual mortality data, sales in all years between 2008 and 2018 are standardized with mortality estimates for 2018 in this chapter due to lack of data for all years and countries.[35] Cancer mortality in Europe did not change much though between 2008 and 2018 as shown in Figure 10 in section 2.2.2.

4.3.2 Geographic scope

The analysis in this chapter encompasses the greatest possible number of European countries. This includes the 28 EU member states, excluding countries with no data (Cyprus and Malta) or limited data (Estonia, Greece, Luxembourg) in the MIDAS database, and adding Iceland, Norway, and Switzerland.

Table 5: Grouping of countries

Lower tier GDP/capita (€5,800 – €17,600)	**Mid tier GDP/capita** (€22,000 – €35,000)	**Upper tier GDP/capita** (€35,300 – €77,600)
Bulgaria	France	Austria
Croatia	Germany	Belgium
Czechia	Italy	Denmark
Hungary	Spain	Finland
Latvia	UK	Iceland
Lithuania		Ireland
Poland		Netherlands
Portugal		Norway
Romania		Sweden
Slovakia		Switzerland
Slovenia		
Share of total population in 2013 (504 million)		
22%	63%	15%
Share of total GDP in 2013 (€14,249 billion)		
9%	68%	24%

Source: Eurostat [4, 11, 12].

Sales data are presented for three levels of aggregation. The European level includes the 26 countries with complete data and even the three countries with limited data. The second level is based on

[34] In such cases, usage can be related to mortality in the primary indication of a medicine. However, the fact that a medicine might be introduced for different indications at varying times and speed in different countries can bias the results.

[35] Using a single reference year (2018) for mortality cases means that year-on-year changes in usage also reflect changes in mortality rather than real changes in usage. In times of decreasing cancer mortality, the use of mortality cases from a single reference year will bias usage upwards/downwards in all years before/after the reference year. The magnitude of the bias will differ between countries if the development in mortality differs.

countries' economic strength. The 26 countries with complete data are divided into three groups based on their GDP per capita at market prices (consistent with how sales are reported) in 2013; see Table 5. Note that with this classification, the "big five" countries France, Germany, Italy, Spain, and the UK form the middle group. The third level of analysis is the country level, where the 26 countries with complete data are compared.

As it is not always possible to portray the development of sales data over the entire period between 2008 and 2018, some comparisons are limited comparing specific years – mostly 2008, 2013, and 2018. These three years also cover different economic circumstances in Europe – pre-crisis, crisis, and post-crisis.

4.4 Cancer medicines

4.4.1 Definition of cancer medicines

In the ATC classification system cancer medicines belong to group L, i.e. antineoplastic and immunomodulating agents, with the subgroups L01 for antineoplastic agents (chemotherapy and targeted cancer medicines), L02 for endocrine therapy, L03 for immunostimulants, and L04 for immunosuppressants. Several medicines in this group do not have exclusive indication for the treatment of cancer. For instance, in Switzerland it was estimated that 60 percent of the sold units of cyclophosphamide (in subgroup L01) and only 20 percent of interferon alpha 2a and 2b (in subgroup L03) are used for cancer treatment and the remainder for other diseases [13]. In order to precisely estimate cancer-related medicine sales, the usage of every single medicine in diseases other than cancer would need to be estimated and subtracted.

A cancer medicine can have several indications in the cancer area. This is an issue in international comparisons, as differences in reimbursement between indications might explain some of the differences in usage between countries. For instance, sunitinib was initially approved by the EMA in July 2006 for the use in gastrointestinal stromal tumor and metastatic renal cell carcinoma. Sunitinib received a third indication (pancreatic neuroendocrine tumors) in October 2010. Not every European country reimbursed sunitinib for all indications, but IQVIA sales data do not show the distribution of sales between different indications, which makes a clear-cut interpretation of access for different patient groups difficult [14].

4.4.2 Grouping of cancer medicines

Cancer medicines might be grouped in different ways in order to study access. Some common classifications are:

- ATC subgroups
- Medicines for conventional chemotherapy and targeted cancer therapy
- Medicines for biologic therapy (large molecules), non-biologic therapy (small molecules), and immunotherapy
- Indication (breast cancer, lung cancer, etc.)
- Size of target population (orphan drugs)
- Vintage (older vs. newer medicines)
- Degree of innovation (innovative vs. non-innovative medicines; novel vs. incremental innovation medicines): The FDA has implemented a breakthrough therapy designation, which should facilitate faster market access for new needed products. However, it has been noted that it is difficult to define innovation without reference to outcome or therapeutic value [15]. The classification according to the five-tier innovation scale used by the French transparency commission is one example [16].
- Therapeutic value: This is closely linked to a classification according to innovation. Different systems for classification have been proposed by ESMO, ASCO and others; see Chapter 4 in the 2016 Comparator report for a more in-depth discussion [6].

4.4.3 EMA-approved cancer medicines

The EMA has been responsible for the scientific evaluation of centralized marketing authorization applications of medicines since 1995. Once granted by the European Commission, the centralized marketing authorization is valid in all EU member states, Iceland, Liechtenstein, and Norway. Table 6 lists all 118 cancer medicines belonging to ATC groups L01, L02, and L04 that were granted centralized marketing authorization between 1995 and 2018. Medicines with identical active substances have only been included at their first instance of marketing authorization.

Table 6: Centrally approved cancer medicines by the EMA, 1995–2018

Year	Chemical name	Cancer type	Orphan drug	Class	Mono-clonal antibody	Route of administration
1995	docetaxel	breast, lung (2000), prostate (before 2005), gastric adenocarcinoma (2006), head & neck (2006)	No	Chemo	No	IV
1996	toremifene	breast	No	Hormone	No	Oral
1996	topotecan	ovarian, lung (2005), cervical (2006)	No	Chemo	No	IV, Oral
1998	rituximab	lymphoma, leukemia (2009)	No	Targeted	Yes	IV
1999	temozolomide	glioma, glioblastoma	No	Chemo	No	IV, Oral
2000	trastuzumab	breast, stomach (2009)	No	Targeted	Yes	IV, SC
2000	alitretinoin	Kaposi's sarcoma	No	Chemo	No	Topical
2001	capecitabine	colorectal, breast (before 2006), stomach (2007)	No	Chemo	No	Oral
2001	bexarotene	lymphoma	No	Chemo	No	Oral
2001	alemtuzumab	leukemia	No	Targeted	Yes	IV
2001	temoporfin	head & neck	No	Chemo	No	IV
2001	imatinib	leukemia, GIST	No	Targeted	No	Oral
2002	arsenic trioxide	leukemia	Yes	Chemo	No	IV
2003	celecoxib	colorectal	No	Targeted	No	Oral
2004	fulvestrant	breast	No	Hormone	No	IM
2004	bortezomib	multiple myeloma	No	Targeted	No	IV, SC
2004	mitotane	adrenal cortex	Yes	Chemo	No	Oral
2004	cetuximab	colorectal, head & neck (2006)	No	Targeted	Yes	IV
2004	pemetrexed	lung, mesothelioma	No	Chemo	No	IV
2005	bevacizumab	colorectal, breast (2007), lung (2007), renal (2008), ovarian (2011), cervical (2015)	No	Targeted	Yes	IV
2005	erlotinib	lung, pancreatic (2006)	No	Targeted	No	Oral
2006	clofarabine	leukemia	No	Chemo	No	IV
2006	sorafenib	renal, hepatocellular (2007)	Yes	Targeted	No	Oral
2006	sunitinib	renal, GIST, neuroendocrine (2010)	No	Targeted	No	Oral
2006	dasatinib	leukemia	No	Targeted	No	Oral
2007	lenalidomide	multiple myeloma, leukemia (2013), lymphoma (2016)	Yes	Targeted	No	Oral
2007	nelarabine	leukemia	Yes	Chemo	No	IV
2007	5-aminolevulinic acid hydrochloride	glioma	Yes	Chemo	No	Oral
2007	trabectedin	sarcoma, ovarian (2009)	Yes	Chemo	No	IV
2007	nilotinib	leukemia	Yes	Targeted	No	Oral
2007	temsirolimus	renal, lymphoma (2009)	Yes	Targeted	No	IV
2007	panitumumab	colorectal	No	Targeted	Yes	IV
2008	thalidomide	multiple myeloma	Yes	Targeted	No	Oral
2008	lapatinib	breast	No	Targeted	No	Oral
2008	azacitidine	leukemia	No	Chemo	No	IV, SC
2009	degarelix	prostate	No	Hormone	No	SC

2009	catumaxomab	cancer-caused ascites	No	Targeted	Yes	IP injection
2009	gefitinib	lung	No	Targeted	No	Oral
2009	everolimus	renal, pancreatic (2011), breast (2012), neuroendocrine (2016)	No	Targeted	No	Oral
2009	vinflunine	urothelial	No	Chemo	No	IV
2010	ofatumumab	leukemia	Yes	Targeted	Yes	IV
2010	pazopanib	renal	No	Targeted	No	Oral
2011	tegafur / gimeracil / oteracil	stomach	No	Chemo	No	Oral
2011	cabazitaxel	prostate	No	Chemo	No	IV
2011	eribulin	breast, liposarcoma (2016)	No	Chemo	No	IV
2011	ipilimumab	melanoma	No	Immuno (CPI)	Yes	IV
2011	abiraterone	prostate	No	Hormone	No	Oral
2012	vandetanib	thyroid	No	Targeted	No	Oral
2012	vemurafenib	melanoma	No	Targeted	No	Oral
2012	pixantrone	lymphoma	No	Chemo	No	IV
2012	ruxolitinib	myeloproliferative	No	Targeted	No	Oral, Topical
2012	axitinib	renal	No	Targeted	No	Oral
2012	decitabine	leukemia	Yes	Chemo	No	IV
2012	crizotinib	lung	No	Targeted	No	Oral
2012	brentuximab vedotin	lymphoma	Yes	Targeted	Yes	IV
2013	aflibercept	colorectal	No	Targeted	No	IV
2013	pertuzumab	breast	No	Targeted	Yes	IV
2013	bosutinib	leukemia	No	Targeted	No	Oral
2013	enzalutamide	prostate	No	Hormone	No	Oral
2013	ponatinib	leukemia	Yes	Targeted	No	Oral
2013	vismodegib	basal-cell	No	Targeted	No	Oral
2013	pomalidomide	multiple myeloma	Yes	Targeted	No	Oral
2013	dabrafenib	melanoma	No	Targeted	No	Oral
2013	regorafenib	colorectal	No	Targeted	No	Oral
2013	afatinib	lung	No	Targeted	No	Oral
2013	trastuzumab emtansine	breast	No	Targeted	Yes	IV
2014	cabozantinib	thyroid, renal (2016), hepatocellular (2018)	Yes	Targeted	No	Oral
2014	siltuximab	Castleman disease	Yes	Targeted	Yes	IV
2014	trametinib	melanoma	No	Targeted	No	Oral
2014	obinutuzumab	leukemia	Yes	Targeted	Yes	IV
2014	idelalisib	lymphoma, leukemia	No	Targeted	No	Oral
2014	ibrutinib	lymphoma, leukemia	Yes	Targeted	No	Oral
2014	nintedanib	lung	No	Targeted	No	Oral
2014	olaparib	ovarian	No	Targeted	No	Oral
2014	ramucirumab	stomach	No	Targeted	Yes	IV
2015	ceritinib	lung	No	Targeted	No	Oral
2015	lenvatinib	thyroid	No	Targeted	No	Oral
2015	nivolumab	melanoma, lung (2015), renal (2016), lymphoma (2016),	No	Immuno (CPI)	Yes	IV

2015	pembrolizumab	head & neck (2017), urothelial (2017) melanoma, lung (2016), lymphoma (2017), urothelial (2017)	No	Immuno (CPI)	Yes	IV
2015	dinutuximab	neuroblastoma	No	Targeted	Yes	IV
2015	sonidegib	basal-cell	No	Targeted	No	Oral
2015	panobinostat	multiple myeloma	Yes	Targeted	No	Oral
2015	carfilzomib	multiple myeloma	Yes	Targeted	No	IV
2015	cobimetinib	melanoma	No	Targeted	No	Oral
2015	blinatumomab	leukemia	Yes	Targeted	Yes	IV
2015	talimogene laherparepvec	melanoma	No	Chemo	No	Injection
2016	pegaspargase	leukemia	No	Chemo	No	IM, IV
2016	osimertinib	lung	No	Targeted	No	Oral
2016	necitumumab	lung	No	Targeted	Yes	IV
2016	trifluridine / tipiracil	colorectal	No	Chemo	No	Oral
2016	elotuzumab	multiple myeloma	No	Targeted	Yes	IV
2016	olaratumab	sarcoma	Yes	Targeted	Yes	IV
2016	palbociclib	breast	No	Targeted	No	Oral
2016	ixazomib	multiple myeloma	Yes	Targeted	No	Oral
2016	venetoclax	leukemia	No	Targeted	No	Oral
2017	alectinib	lung	No	Targeted	No	Oral
2017	daratumumab	multiple myeloma	Yes	Targeted	Yes	IV
2017	dinutuximab beta	neuroblastoma	Yes	Targeted	Yes	IV
2017	inotuzumab ozogamicin	leukemia	Yes	Targeted	Yes	IV
2017	ribociclib	breast	No	Targeted	No	Oral
2017	tivozanib	renal	No	Targeted	No	Oral
2017	avelumab	neuroendocrine	Yes	Immuno (CPI)	Yes	IV
2017	midostaurin	leukemia	Yes	Targeted	No	Oral
2017	atezolizumab	urothelial, lung	No	Immuno (CPI)	Yes	IV
2017	padeliporfin	prostate	No	Chemo	No	IV
2017	niraparib	ovarian	Yes	Targeted	No	Oral
2018	gemtuzumab ozogamicin	leukemia	Yes	Targeted	Yes	IV
2018	rucaparib	ovarian	No	Targeted	No	Oral
2018	tisagenlecleucel	leukemia, lymphoma	Yes	Immuno (CAR-T)	No	IV
2018	axicabtagene ciloleucel*	lymphoma	Yes	Immuno (CAR-T)	No	IV
2018	cytarabine / daunorubicin	leukemia	Yes	Chemo	No	IV
2018	neratinib*	breast	No	Targeted	No	Oral
2018	encorafenib	melanoma	No	Targeted	No	Oral
2018	binimetinib	melanoma	No	Targeted	No	Oral
2018	durvalumab	lung	No	Immuno (CPI)	Yes	IV
2018	abemaciclib	breast	No	Targeted	No	Oral

2018	brigatinib	lung	No	Targeted	No	Oral
2018	mogamulizumab*	Sezary syndrome, mycosis fungoides	Yes	Targeted	Yes	IV

Notes: CPI = checkpoint inhibitor; CAR-T = chimeric antigen receptor T cell; IV=intravenous injection or infusion; SC=subcutaneous injection; IM=intramuscular injection; IP=intraperitoneal injection. *There were no sales of these medicines in any country in 2018. Lenalidomide, pomalidomide, and thalidomide are classified as targeted medicines, but they are in fact immunosuppressants.

Figure 40 displays the year in which the 118 cancer medicines were approved. There has been a marked increase in the number of approved medicines over time, although this increase was not steady. Three distinct periods can be identified. Between 1995 and 2000, at most two new cancer medicines were approved per year. Between 2001 and 2011, the average number of approved medicines per year fluctuated around four. Afterwards there was a significant increase to around ten approved medicines per year between 2012 and 2018. Figure 40 also shows the development of the number of approved indications per year (in total 164 indications of the 118 medicines), as several medicines have multiple indications. Especially two CPI therapies (nivolumab and pembrolizumab) have been indicated in many cancer types after their first approval in 2015.

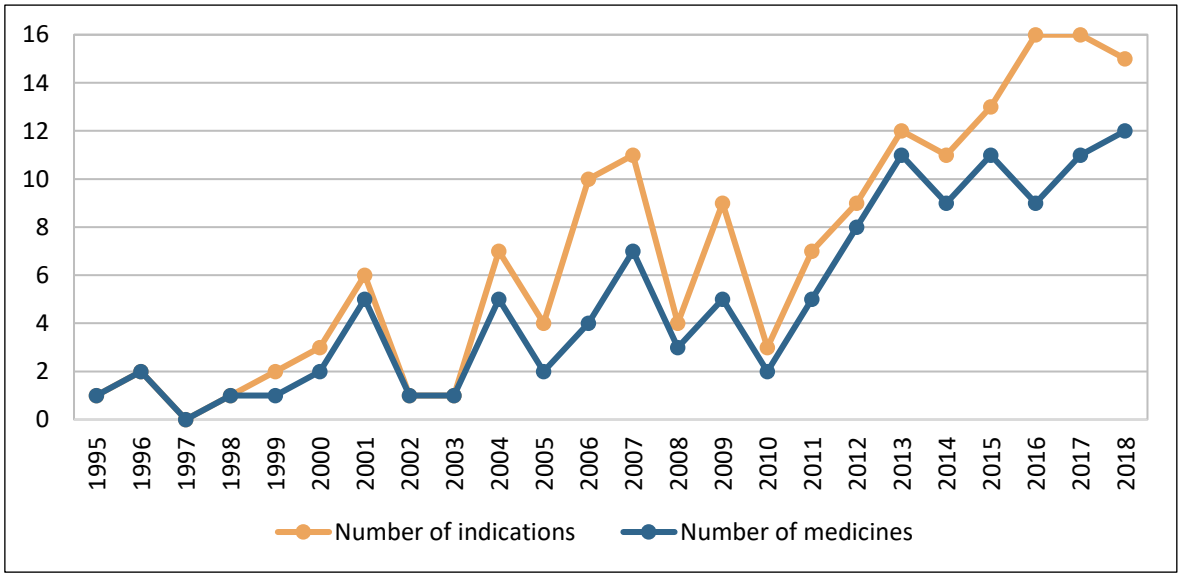


Figure 40: Number of EMA-approved cancer medicines and indications, 1995–2018

Medicines for many different indications have been introduced between 1995 and 2018; see Figure 41. Medicines used in leukemia represented the largest area with 25 medicines approved of which 21 medicines had leukemia as the main indication at time of approval. There were 18 approved medicines (12 as main indication) used in lung cancer, however most of these approvals occurred after 2010. There were 15 approved medicines (12 as main indication) used in breast cancer, and 12 medicines (7 as main indication) used in lymphoma. The 10 medicines (all as main indication) for malignant melanoma were all approved after 2010. Renal cancer (10 medicines; 7 as main

indication), multiple myeloma (9 medicines, all as main indication), and colorectal cancer (8 medicines, all as main indication) represented other areas with significant numbers of approvals.

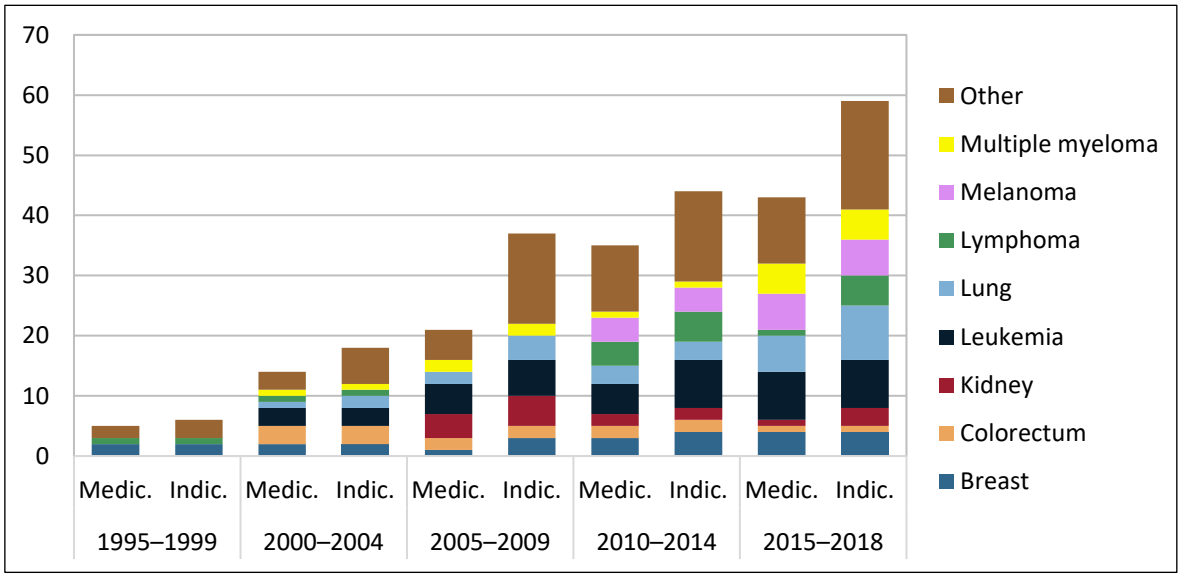


Figure 41: Number of EMA-approved medicines and indications by cancer type

Notes: The first column shows the number medicines ("Medic.") by main indication at time of initial drug approval; in cases of multiple indications at initial approval, the most commonly used indication was chosen. The second column shows the number of approved indications ("Indic.") by cancer type; see also Table 6.

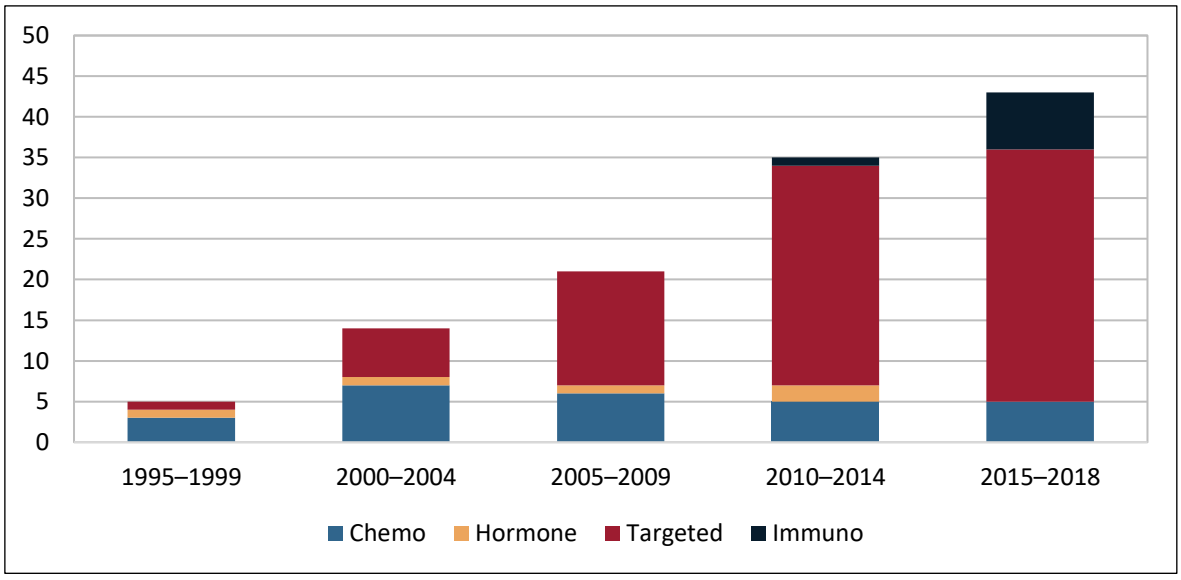


Figure 42: Number of EMA-approved medicines by type of therapy

As described in Chapter 3, since the turn of the millennium there has been a profound shift from chemotherapy to targeted therapies. More recently, medicines for immunotherapy have been introduced. This is clearly seen in Figure 42. The whole increase in the number of cancer medicines

between 1995 and 2018 was essentially driven by targeted medicines and since 2015 also by medicines for immunotherapy (CPI and CAR T-cell therapies).

Figure 43 and Figure 44 illustrate two other trends – the increasing role of monoclonal antibodies in contrast to small molecules (29% of all approvals 2010–2018 compared to 18% 1995–2009) and an increasing number of medicines approved with an orphan designation[36] (32% 2010–2018 compared to 25% 1995–2009). This shows that there has been an increased activity in developing treatment for smaller indications that could for instance be defined by a specific genotype. Smaller indications mean that fewer cancer patients can benefit from them, but they might offer greater benefit for this particular set of patients.

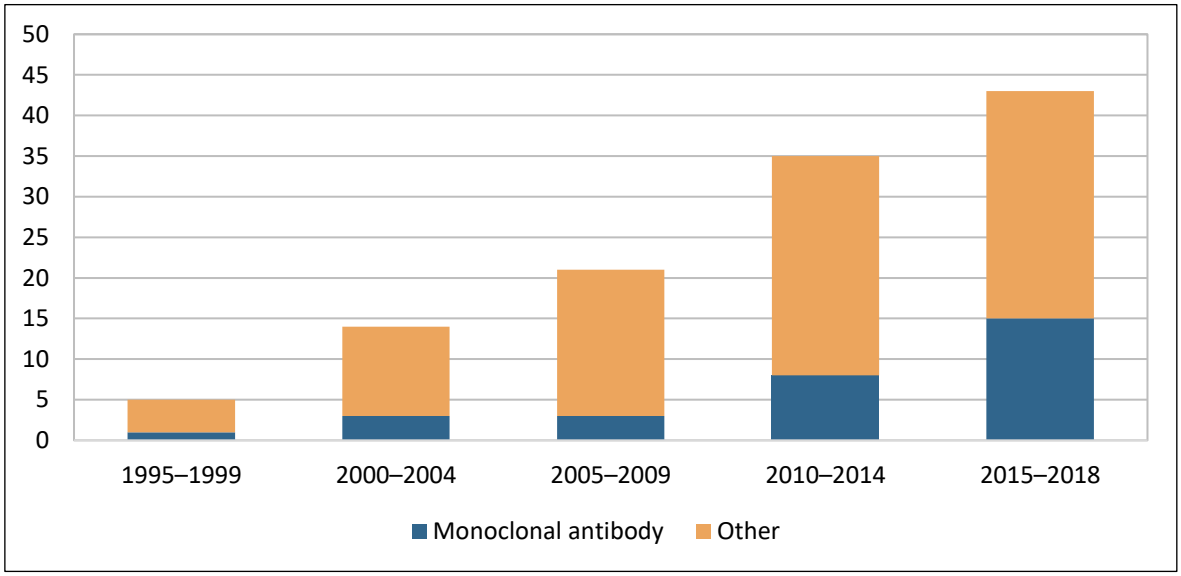


Figure 43: Number of EMA-approved medicines by type of molecule

[36] To qualify for orphan designation, a medicine (i) must be intended for a disease that is life-threatening or chronically debilitating, (ii) the prevalence of the disease must be less than 5 in 10,000 (or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development), (iii) no satisfactory treatment of the disease is available.

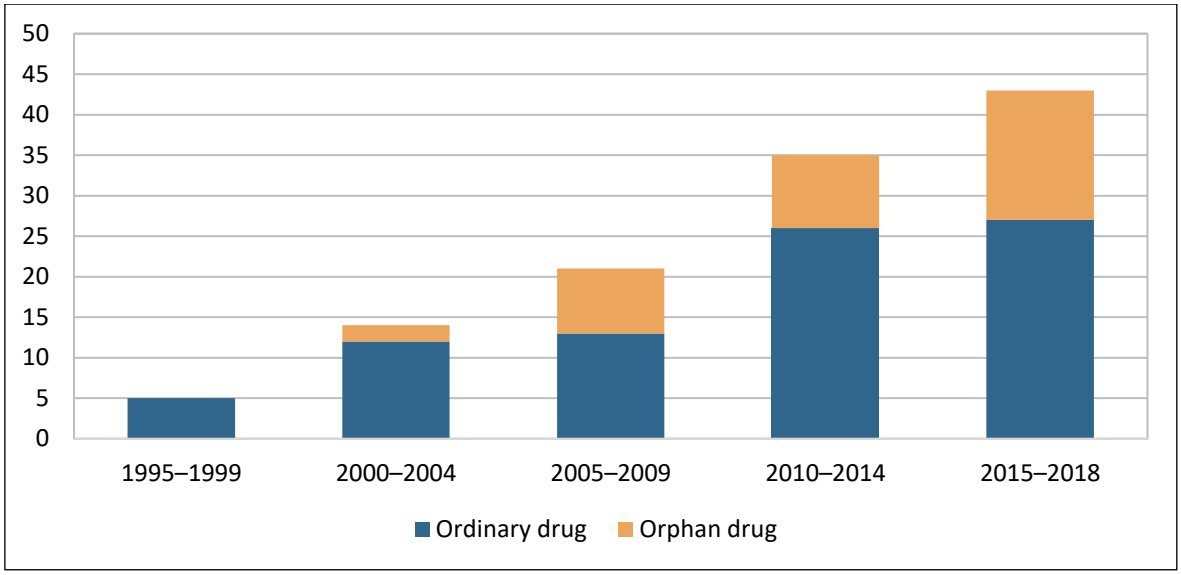


Figure 44: Number of EMA-approved medicines by orphan drug designation

Figure 45 displays a trend relevant for the analysis of costs associated with the administration of medicines. Medicines approved before 2000 were mostly administered intravenously, which required prolonged ambulatory care visits or even inpatient stays due to a need to monitor side effects. With the increasing introduction of medicines for targeted therapy, oral administration has become more common, except for medicines with monoclonal antibodies. The introduction of medicines for immunotherapy has worked against the trend of increasing oral administration, as they are administered intravenously.

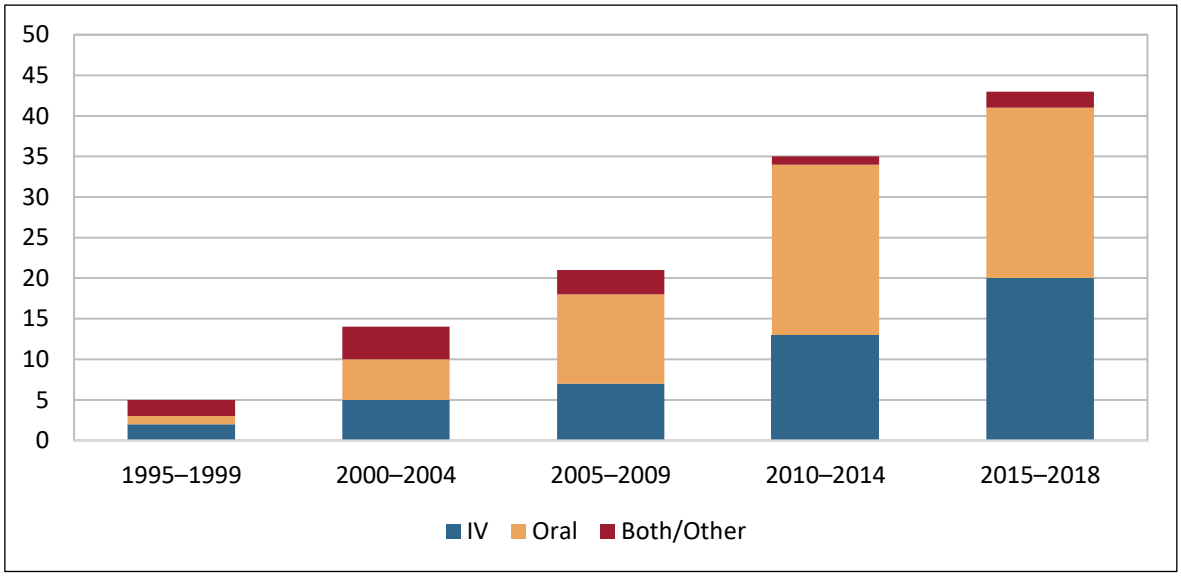


Figure 45: Number of EMA-approved medicines by route of administration

4.5 Costs

This section focuses on the total expenditure on cancer medicines between 2008 and 2018, whereas section 4.7 focuses more on individual medicines. The total cost of cancer medicines can be considered (1) in absolute terms and (2) in relation to, e.g., total health expenditure, health expenditure on cancer care, and total pharmaceutical expenditure.

4.5.1 Costs of cancer medicines in absolute terms

Figure 46 shows that total cancer medicine sales in Europe went up from €12.9 billion to €32.0 billion (in current prices) between 2008 and 2018. In per-capita terms, sales increased from €25 to €61. Thus, the costs more than doubled between these years. Taking into account inflation and using exchanges rates from 2018, the costs in 2008 amounted to €14.6 billion (€28 per capita). Thus, even in real terms the costs of cancer medicines more than doubled to €32.0 billion until 2018. The big 5 countries accounted for almost 75 percent of all sales in both years (their share of the population in Europe is just over 60 percent). France was the single biggest spender in 2008 with 25 percent, followed by Germany with 17 percent, and Italy with 13 percent. In 2018, Germany had surpassed France and accounted for 24 percent of the European cancer medicines sales. The country-specific total sales and per-capita sales for all years are summarized in Tables A3 and A4 in the Appendix.

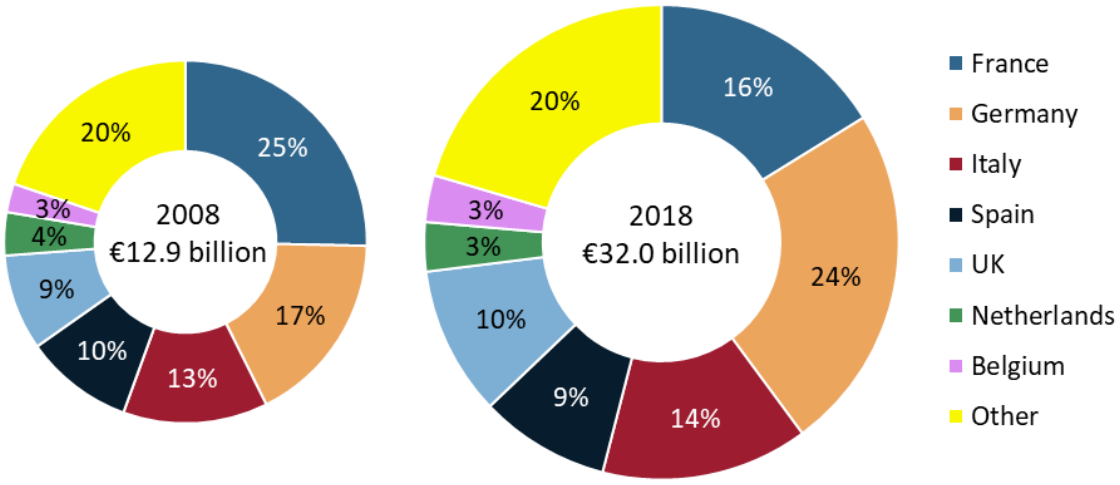


Figure 46: Total cost of cancer medicines (in current prices) in Europe and country-specific shares, 2008 & 2018

The strong increase in sales between 2008 and 2018 is a product of several factors:

- Higher prices of newly introduced medicines, i.e. cost per treatment

- Rising number of cancer patients, i.e. incidence (see Chapter 2)
- Increasing survival and decreasing mortality leading to a growing number of prevalent cases needing long-term chemotherapy and more rounds of treatment (e.g. four lines of therapy whereas in the past patients died after the second line)
- Increasing number of approved cancer medicines and indications (see section 4.4.3)
- Introduction of cancer medicines for previously untreated patient groups (e.g. metastatic castration-resistant prostate cancer)
- Introduction of cancer medicines that are increasingly used in an adjuvant setting instead of just in a palliative setting (see Chapter 3)
- Increasing use of combination therapies (see Chapters 3 and 5)

Figure 47 (consisting of 5 graphs) shows how cancer medicine sales per capita have evolved between 2008 and 2018 in current prices; i.e. the numbers are not adjusted for inflation and are subject to exchange rate fluctuations. The countries are divided into five groups; non-Nordic upper tier, Nordic, the big five, two groups of lower-tier countries. All countries have seen a growth in medicine sales between 2008 and 2018. Austria, Germany, Switzerland (partly due to exchange rate fluctuations), and Belgium have seen the greatest growth in cancer medicine sales in absolute terms. Except for Denmark, which also saw a steep increase, the development among the Nordic countries was remarkably similar. France sticks out as it had the highest sales of all countries in 2008 but then experienced decreases which might be related to price reductions imposed just after the economic crisis to control public health spending – it took until 2015 for sales to exceed those seen in 2008. The UK kept increasing until 2015 before it started decreasing (partly due to exchange rate fluctuations and changes to the Cancer Drugs Fund in England [17]), yet it turned around again in 2017. In the lower-tier countries, the level of sales was about one third of that in the richer countries throughout the whole period. Except for Bulgaria, most countries had fairly constant sales between 2008 and 2014, probably as a result of tight budgets during the economic crisis. After 2014, countries such as Slovenia, Portugal, Lithuania, Hungary, and Croatia saw a robust growth until 2018, whereas Czechia, Poland, Romania, and Slovakia continued to have a similar level of per-capita sales as in 2014.

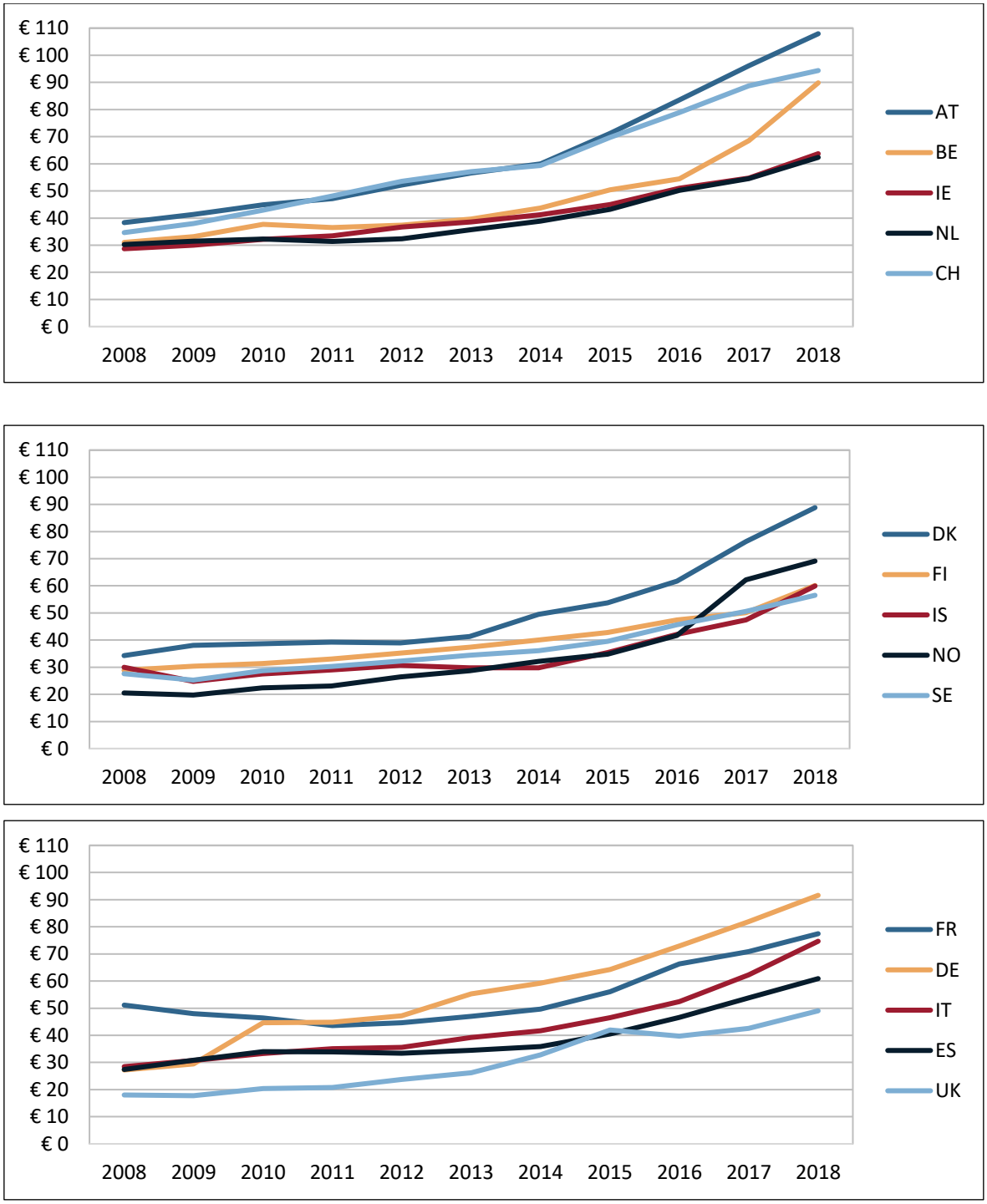
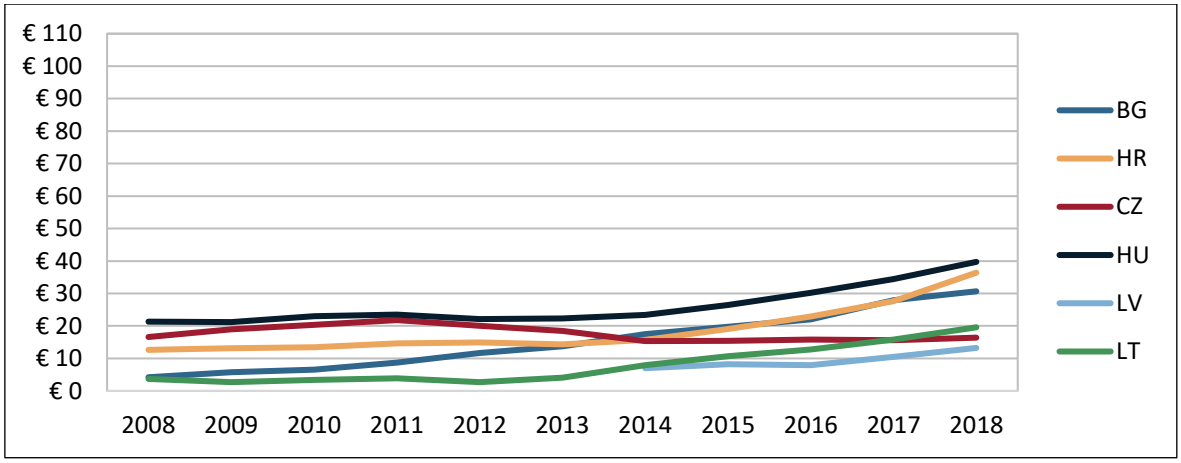


Figure 47: Cost of cancer medicines per capita (in € in current prices), 2008–2018



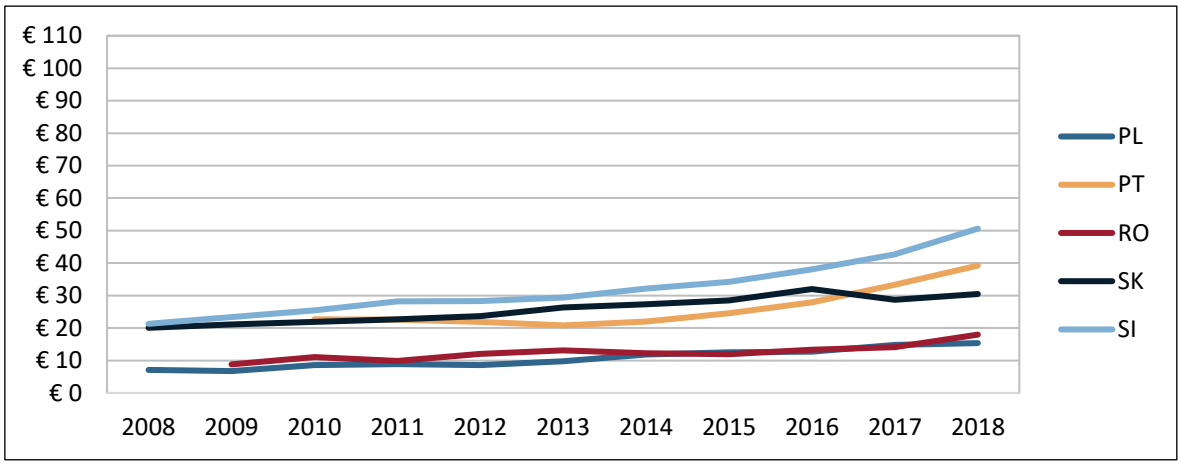


Figure 47 (cont.): Cost of cancer medicines per capita (in € in current prices), 2008–2018

Figure 48 compares the costs of cancer medicines per capita (adjusted for inflation and in 2018 exchange rates) in each country in 2008 and 2018. In Europe as a whole, the costs of cancer medicines per capita doubled from €28 to €61. Costs increased in all countries with complete data, except for Czechia. The biggest increases in spending in absolute terms between 2008 and 2018 were recorded in Austria (from €46 to €108) and Germany (from €31 to €92). The smallest absolute increases in costs per capita were observed in Slovakia (from €24 to €30) and in Poland (from €7 to €15).

The top spenders in 2018 were Austria, Switzerland, Germany, Belgium, and Denmark with around €90–110 per capita spent on cancer medicines. France dropped from being the biggest spender in 2008 to sixth place in 2018. At the other end of the spending scale are countries for which only retail sales (and no hospital sales) of cancer medicines are available. Among the countries with complete data, Latvia spent the least in 2018 with €13 (but increased from €7 in 2014) followed by Poland with €15 (increased from €7 in 2008) and Czechia with €16 (decreased by €2 since 2008).

Figure 48 reveals also a clear pattern of wealthier countries to spend distinctly more on cancer medicines per capita than poorer countries. The differences between wealthier and poorer countries might be exaggerated as poorer countries receive higher rebates on cancer medicines to make them affordable for them.

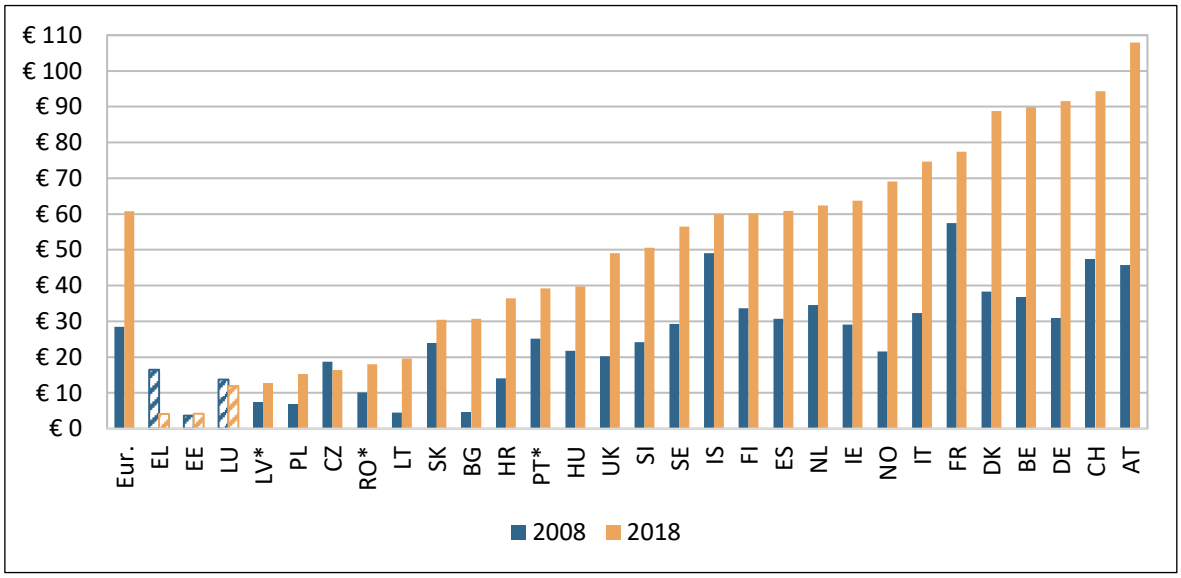


Figure 48: Cost of cancer medicines per capita (in 2018 price levels and exchange rates), 2008 & 2018

Notes: Eur. = Europe. Hatched bars indicate that data for EE, EL, and LU only comprise retail sales. CY and MT are missing due to lack of data. * The values in 2008 are from 2014 for LV, from 2009 for RO, and from 2010 for PT.

4.5.2 Costs of cancer medicines in relative terms

The development of the cost of cancer medicines in relation to the direct costs of cancer has already been discussed in section 2.4.1.5. The main takeaway of this comparison is that the share of cancer medicine costs on the direct costs is increasing. Figure 49 illustrates this again using the country grouping defined above. In Europe, the share increased from 17 percent in 2008 to 31 percent in 2018. The share in the big five countries (mid tier) closely followed the European pattern. Upper-tier countries spend a lower share on cancer medicines than mid-tier countries, and lower-tier countries spend a higher share on cancer medicines. As explained in section 2.4.1.5, the difference between wealthier and poorer countries is a reflection of greater relative differences in domestic prices of cancer care services (e.g. physicians, nurses) and international prices of cancer medicines in poorer countries.

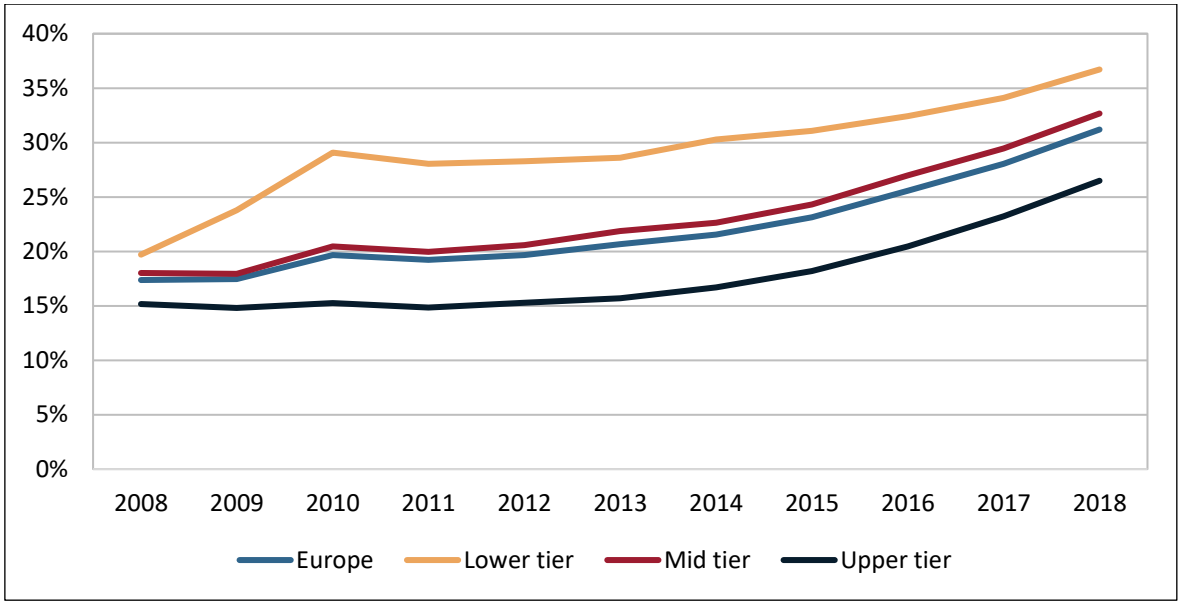


Figure 49: Share of the cost of cancer medicines on the direct costs of cancer, 2008–2018

Cancer medicines account for a modest but growing share of total pharmaceutical sales. Figure 50 exemplifies this based on data for France, Germany, Sweden, and the UK.[37] Between 1995 and 2001, cancer medicines accounted for 3–4% of total pharmaceutical sales. After the introduction of the first major targeted therapies in around 2000, cancer medicines' share started to increase. In 2015, this share was highest in France and Germany with 14% and lower in the UK (12%) and Sweden (9%). After 2015, cancer medicines' share continued to expand to 12% in 2018 in Sweden.

[37] This measure could not be calculated in a comparable way for other countries. OECD data on total pharmaceutical expenditure include only pharmaceuticals used in ambulatory care, prescription drugs, and over-the-counter drugs, but they exclude drugs used in hospitals, as the latter is included in inpatient care expenditure. In cancer patients, a far greater share of medicines is administered at hospitals than dispensed via retail, even though the exact share depends on the health care organization in each country. Data from the MIDAS database show for instance that in France retail sales of cancer medicines amounted to €2.0 billion and hospital sales to €3.2 billion in 2018. This issue inhibits a valid calculation of the share of cancer medicine expenditure on the OECD's measure for total pharmaceutical expenditure.

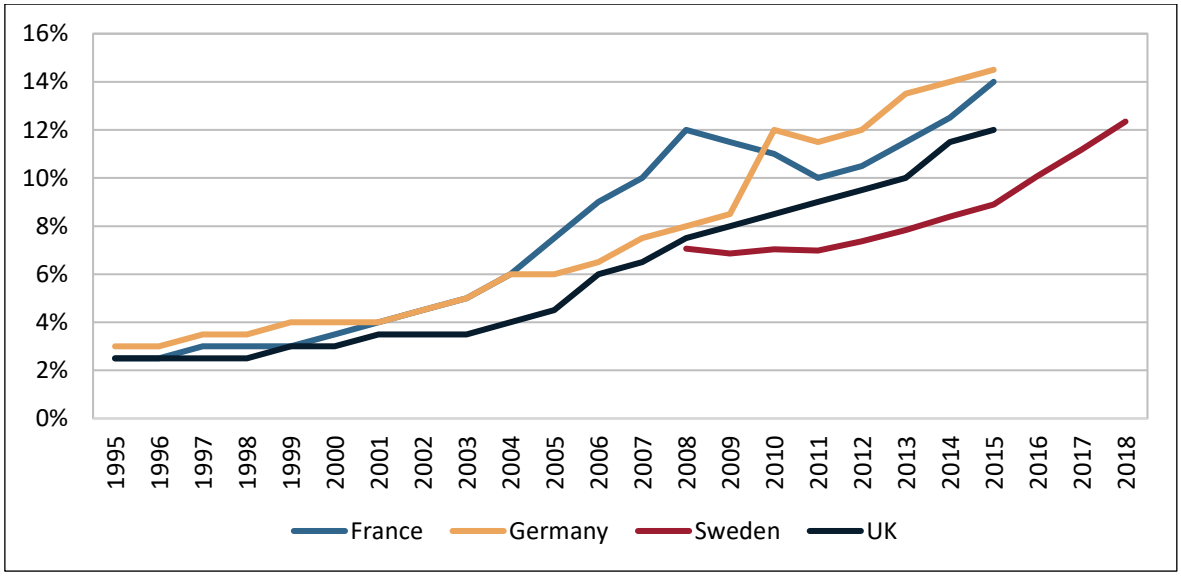


Figure 50: Share of cancer medicine expenditure on total pharmaceutical expenditure in selected countries, 1995–2018

Notes: Data for SE combine cancer medicines sales from the MIDAS database [1] and total pharmaceutical expenditure from the Swedish eHealth Agency. Source for FR, DE, UK: [18].

4.6 Vintage

4.6.1 Top-selling cancer medicines

Around 200 different cancer medicines (with unique active substances) have been sold at least in some quantity in some European country in 2018. However, a small number of medicines make up the majority of sales. The top 10 medicines in terms of sales in 2008 made up 55 percent of total sales; see Table 7. In 2018, the corresponding number was 45 percent. This noteworthy drop is probably a result of the strong increase in the number of approved cancer medicines since 2012 (see Figure 40) and the availability of generics.

Table 7: Top ten medicines by market share 2008–2018, Europe

2008		2012		2015		2018	
Medicine	Share of total sales	Medicine	Share of total sales	Medicine	Share of total sales	Medicine	Share of total sales
Trastuzumab	10.1%	Trastuzumab	10.4%	Trastuzumab	8.2%	Lenalidomide	6.2%
Rituximab	7.5%	Rituximab	9.2%	Bevacizumab	7.8%	Nivolumab	5.8%
Imatinib	7.1%	Bevacizumab	8.0%	Rituximab	7.6%	Trastuzumab	5.6%
Bevacizumab	6.7%	Imatinib	7.1%	Imatinib	5.3%	Pembrolizumab	5.2%
Docetaxel	5.8%	Lenalidomide	4.7%	Lenalidomide	5.3%	Bevacizumab	4.9%
Anastrozole	4.2%	Pemetrexed	3.7%	Abiraterone	3.9%	Rituximab	4.8%

Oxaliplatin	3.9%	Bortezomib	3.1%	Pemetrexed	3.1%	Enzalutamide	3.5%
Bicalutamide	3.5%	Leuprorelin	3.0%	Bortezomib	3.1%	Ibrutinib	3.4%
Leuprorelin	3.3%	Cetuximab	2.8%	Paclitaxel	2.4%	Abiraterone	3.2%
Paclitaxel	3.0%	Paclitaxel	2.5%	Enzalutamide	2.4%	Palbociclib	2.7%
Total	55.1%	Total	54.5%	Total	49.0%	Total	45.2%

Notes: Sales of rituximab also include usage outside oncology; approximately 20% of value.

There have been marked shifts among the top 10 selling medicines in Europe over time. Table 7 shows that of the top 10 in 2008, there are only three medicines left in 2018; trastuzumab, rituximab, and bevacizumab. Similarly, of the top 10 in 2012, there are only four medicines left in 2018; lenalidomide, trastuzumab, rituximab, and bevacizumab.

Trastuzumab, which lost its patent in 2014, topped the list from 2008 to 2015, but between 2012 and 2018 its share of sales was almost halved. Imatinib, which lost its patent in 2016, experienced a similar halving of its share between 2015 and 2018. Two immunotherapy medicines, nivolumab and pembrolizumab, which both were approved in 2015, made up 11 percent of sales in 2018.

Since the European picture is dominated by the big five countries, Table 8 and Table 9 look separately at the lower-tier and the upper-tier countries, respectively. As shown before, countries in the lower-tier group spend much less (in per-capita terms) on cancer medicines. However, the top 10 most sold medicines are surprisingly similar compared to the European picture. For instance, the top 10 in 2018 are identical, except for sunitinib instead of palbociclib. The two immunotherapy medicines, nivolumab and pembrolizumab, made up 9 percent of sales – lower than the 11 percent in Europe.

Table 8: Top ten medicines by market share 2008–2018, lower-tier countries

2008		2012		2015		2018	
Medicine	Share of total sales	Medicine	Share of total sales	Medicine	Share of total sales	Medicine	Share of total sales
Imatinib	9.9%	Trastuzumab	12.8%	Trastuzumab	10.8%	Trastuzumab	7.5%
Trastuzumab	9.3%	Rituximab	11.5%	Bevacizumab	9.6%	Bevacizumab	6.8%
Docetaxel	6.4%	Imatinib	10.0%	Rituximab	8.5%	Rituximab	5.0%
Rituximab	6.3%	Bevacizumab	8.6%	Imatinib	6.9%	Lenalidomide	4.7%
Bevacizumab	5.5%	Sunitinib	4.4%	Sunitinib	4.0%	Nivolumab	4.4%
Goserelin	4.5%	Capecitabine	3.6%	Bortezomib	3.8%	Pembrolizumab	4.3%
Anastrozole	4.2%	Bortezomib	3.3%	Nilotinib	3.2%	Ibrutinib	3.4%
Gemcitabine	4.1%	Leuprorelin	2.5%	Lenalidomide	3.1%	Abiraterone	3.1%
Letrozole	3.5%	Erlotinib	2.5%	Everolimus	2.4%	Sunitinib	2.9%
Paclitaxel	3.4%	Cetuximab	2.2%	Cetuximab	2.4%	Enzalutamide	2.8%
Total	57.0%	Total	61.3%	Total	54.6%	Total	44.8%

The top 10 medicines in the countries in the upper-tier group are also similar to the European picture; see Table 9. Noteworthy differences are that ipilimumab, one of the first major immunotherapies, was in the top 10 in 2015 but not in Europe. Nivolumab and pembrolizumab made up 13 percent of sales in 2018. This might indicate that upper-tier countries tended to introduce immunotherapies relatively faster and use it to a greater extent. Another example for such a pattern is daratumumab, which was approved in 2017 and was already in the top 10 in 2018.

Table 9: Top ten medicines by market share 2008–2018, upper-tier countries

2008		2012		2015		2018	
Medicine	Share of total sales	Medicine	Share of total sales	Medicine	Share of total sales	Medicine	Share of total sales
Trastuzumab	10.5%	Trastuzumab	11.6%	Trastuzumab	8.8%	Pembrolizumab	7.2%
Rituximab	8.9%	Rituximab	10.3%	Rituximab	8.4%	Lenalidomide	7.2%
Imatinib	6.7%	Bevacizumab	8.0%	Bevacizumab	7.7%	Nivolumab	6.1%
Docetaxel	6.5%	Imatinib	6.8%	Lenalidomide	6.5%	Trastuzumab	5.7%
Bevacizumab	6.2%	Lenalidomide	5.4%	Imatinib	5.1%	Rituximab	5.4%
Oxaliplatin	4.3%	Pemetrexed	4.0%	Abiraterone	3.9%	Bevacizumab	4.7%
Bicalutamide	4.3%	Bortezomib	3.8%	Bortezomib	3.8%	Enzalutamide	4.7%
Anastrozole	3.5%	Docetaxel	3.1%	Pemetrexed	3.6%	Palbociclib	3.0%
Goserelin	3.4%	Leuprorelin	2.7%	Enzalutamide	3.1%	Ibrutinib	3.0%
Leuprorelin	3.4%	Abiraterone	2.6%	Ipilimumab	2.5%	Daratumumab	2.8%
Total	57.8%	Total	58.3%	Total	53.4%	Total	49.7%

4.6.2 Recently approved cancer medicines

Figure 51 shows cancer medicine sales broken down by year of EMA approval in Europe. The share of both the most recently approved medicines (within the last two years) and somewhat older medicines (approved between three and five years ago) has varied greatly between 2008 and 2018. The newest medicines had a share of 8 percent in 2008, but after the outbreak of the economic crisis their share reached a minimum of 3 percent in 2010 and 2011. Afterwards, the newest medicines expanded their share again and stood for over 10 percent of sales in 2015–2017 and 8 percent in 2018. A similar U-pattern can be observed for somewhat older medicines which had a share of 16 percent in 2008, bottomed out in 2013 at 6 percent and peaked in 2018 at 30 percent. Note that all shares are also influenced by how many new medicines that have been approved.

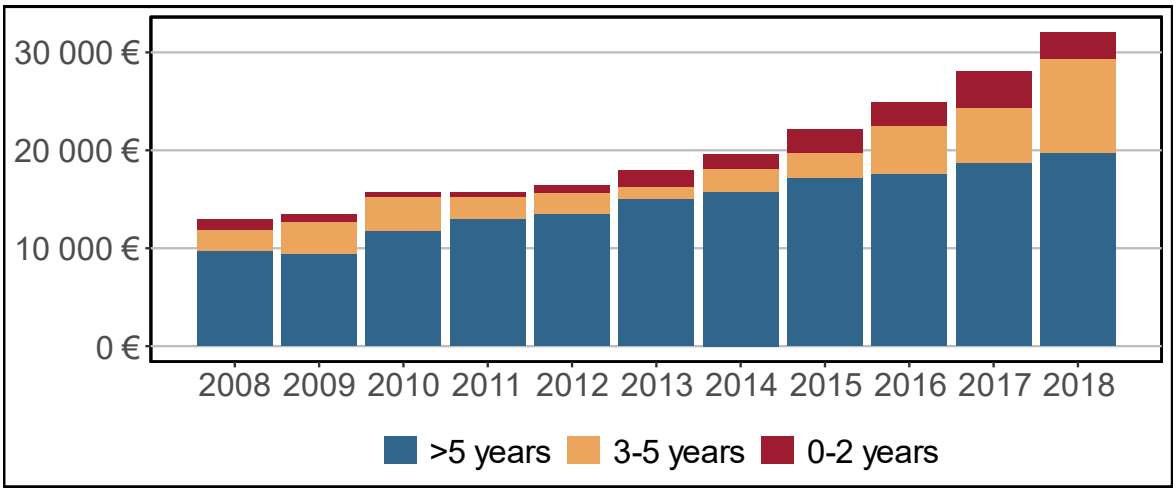


Figure 51: Sales of cancer medicines (in million €) by time since EMA approval in Europe

Figure 52 shows cancer medicine sales broken down by year of EMA approval in the three groups of countries. The upper-tier and mid-tier countries are fairly similar in terms of both absolute levels of sales and the share of newer medicines. The U-pattern of larger sales of newer medicines before the economic crisis (2008), smaller sales during the crisis (2013), and again larger sales after the crisis (2018) are clearly visible. The lower-tier countries, which spend around a third of the amount of the other country groups on cancer medicines, also exhibit a U-pattern, although it is more difficult to see. They spent 6 percent on the newest medicines in 2008 and 3 percent in 2018, compared to 9 percent in mid-tier countries in both of these years, and 8 percent and 10 percent in upper-tier countries.

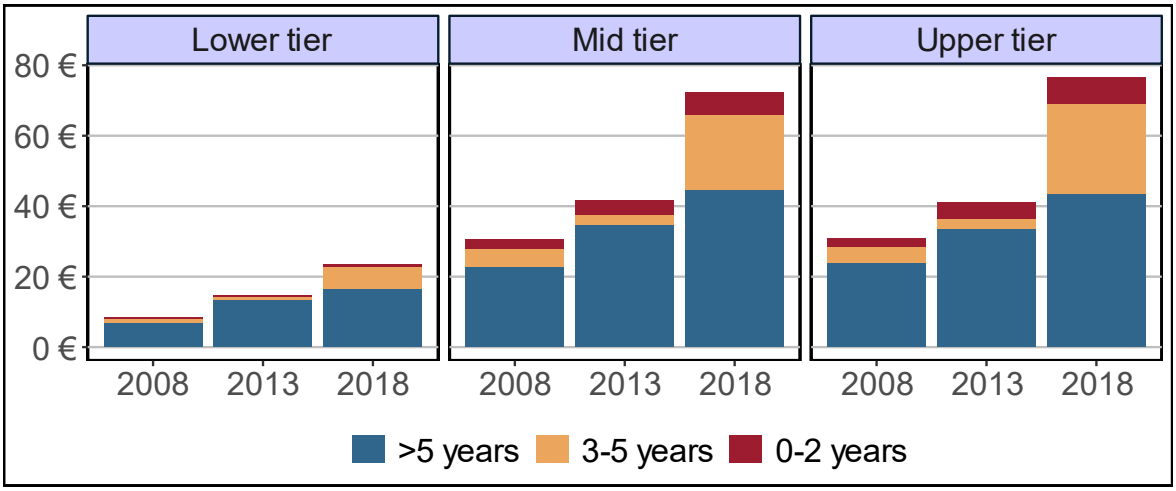


Figure 52: Sales of cancer medicines (in € per capita) by time since EMA approval and group of country

Figure 53 shows cancer medicine sales broken down by type of therapy in Europe. Sales of older medicines naturally declined over time, due to a combination of expired patents and replacement by

newer medicines. The sales of chemotherapies approved in 1995 and later was stable in absolute terms between 2008 and 2018. Targeted cancer therapies accounted for most sales in all years between 2008 and 2018 and their share kept expanding. Immunotherapy medicines have also increased their sales, especially after 2015 when two major medicines were approved. The same is true for hormone therapy medicines, where two major medicines were approved in 2011 and 2013.

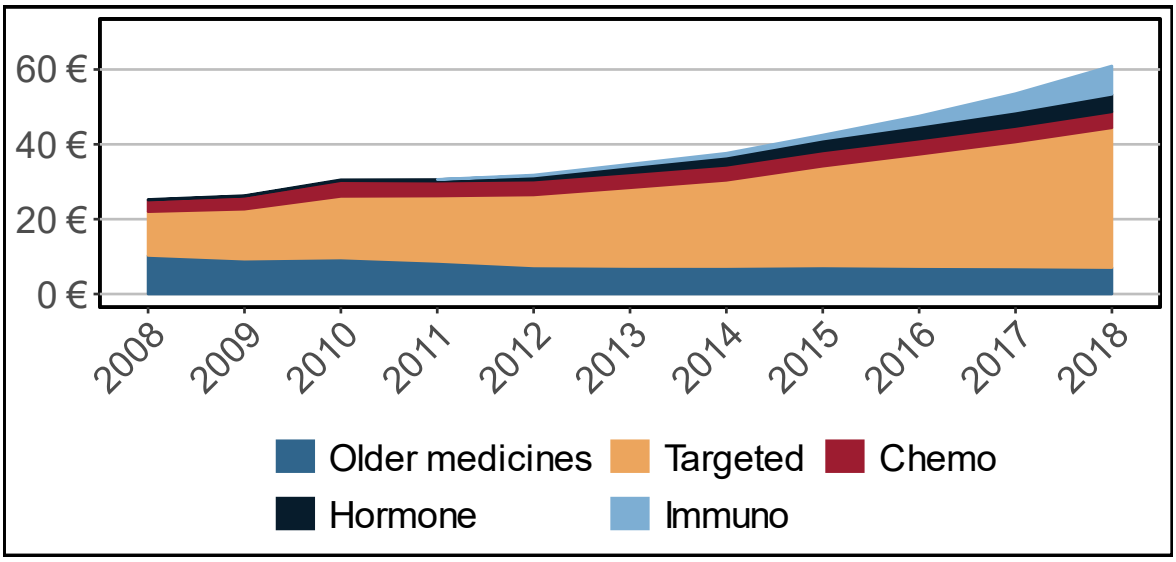


Figure 53: Sales of cancer medicines (in € per capita) by type of therapy in Europe

Notes: "Older medicines" are medicines not approved by the EMA after 1995 (see Table 6).

4.7 Uptake in selected therapeutic areas

This section illustrates the uptake of medicines in different therapeutic areas where a number of new agents have been introduced during the time period studied. We consider the following medicines in the four cancer types that constitute the largest number of newly diagnosed cases:

- Breast cancer: palbociclib, pertuzumab, ribociclib, trastuzumab, trastuzumab emtansine
- Colorectal cancer: bevacizumab, cetuximab, panitumumab
- Lung cancer: afatinib, crizotinib, erlotinib, gefitinib, osimertinib, pemetrexed
- Prostate cancer: abiraterone, enzalutamide

We also consider the following cancer types for which a stream of new medicines has been introduced during the 2010s:

- Malignant melanoma: cobimetinib, dabrafenib, ipilimumab, trametinib, vemurafenib
- Multiple myeloma: bortezomib, carfilzomib, daratumumab, lenalidomide, pomalidomide

- Ovarian cancer: niraparib, olaparib

Lastly, we consider medicines for immunotherapy that have started to enter the market in the 2010s:

- Immunotherapy: atezolizumab, ipilimumab, nivolumab, pembrolizumab

The choice of the inclusion or exclusion of different medicines for each cancer type in the analysis was partly informed by their relevance in terms of sales volume in 2018; see Table 10.

Uptake is defined as (1) the number of euros (€), (2) milligram (mg), or (3) standard weekly dose (SWD) per 100,000 inhabitants or per case, using the number of deaths of the considered cancer type as the definition of a case. A list of the SWD for each cancer medicine considered is provided in Table A5 in the Appendix.

Table 10: Sales of cancer medicines by cancer type in Europe, 2018

Cancer type	Chemical name	Sales (million €)	Year of EMA approval
Breast cancer	trastuzumab	1803.2	2000
	palbociclib	854.3	2016
	pertuzumab	847.9	2013
	trastuzumab emtansine	334.9	2013
	fulvestrant	278.0	2004
	docetaxel	246.0	1995
	eribulin	91.6	2011
	ribociclib	60.6	2017
	lapatinib	47.0	2008
	abemaciclib	0.5	2018
	toremifene	0.1	1996
Colorectal cancer	bevacizumab	1565.5	2005
	cetuximab	419.5	2004
	panitumumab	243.4	2007
	trifluridine / tipiracil	124.6	2016
	capecitabine	107.7	2001
	aflibercept	57.0	2013
	regorafenib	51.5	2013
	celecoxib	0	2003
Lung cancer	pemetrexed	562.8	2004
	osimertinib	250.9	2016
	crizotinib	157.1	2012
	afatinib	115.9	2013
	gefitinib	108.2	2009
	erlotinib	105.0	2005

	alectinib	97.3	2017
	durvalumab	27.1	2018
	ceritinib	27.0	2015
	nintedanib	25.6	2014
	necitumumab	0.8	2016
	brigatinib	0.0	2018
Prostate cancer	enzalutamide	1105.9	2013
	abiraterone	1029.9	2011
	cabazitaxel	176.4	2011
	degarelix	44.9	2009
	padeliporfin	0.0	2017
Malignant melanoma	nivolumab	1846.1	2015
	pembrolizumab	1670.0	2015
	dabrafenib	414.1	2013
	trametinib	290.2	2014
	ipilimumab	259.7	2011
	vemurafenib	79.2	2012
	cobimetinib	42.5	2015
	talimogene laherparepvec	9.0	2015
	binimetinib	1.2	2018
	encorafenib	1.1	2018
Multiple myeloma	lenalidomide	1987.3	2007
	daratumumab	620.8	2017
	bortezomib	602.6	2004
	pomalidomide	399.2	2013
	carfilzomib	264.8	2015
	ixazomib	98.7	2016
	elotuzumab	49.5	2016
	thalidomide	25.0	2008
	panobinostat	12.1	2015
Ovarian cancer	olaparib	160.8	2014
	niraparib	69.9	2017
	topotecan	18.8	1996
	rucaparib	0.0	2018
Immunotherapy	nivolumab	1846.1	2015
	pembrolizumab	1670.0	2015
	ipilimumab	259.7	2011
	atezolizumab	143.6	2017
	durvalumab	27.1	2018
	avelumab	25.9	2017
	tisagenlecleucel	3.8	2018

4.7.1 Breast cancer

HER2-positive breast cancer represents about 15 percent of primary breast cancer cases. Before the introduction of trastuzumab in 1998 (2000 in the EU), HER2-positive disease was linked to poor outcome. This changed dramatically first with the introduction of trastuzumab in metastatic disease and then in 2006 with the adjuvant introduction. In 2013, pertuzumab was introduced in combination with trastuzumab, resulting in a significant prolongation of survival. At the same time trastuzumab emtansine was introduced as a second line HER2-positive medication following trastuzumab failure, thus expanding the therapeutic arsenal in HER2-positive breast cancer (see Chapter 2 in the 2016-Comparator report [6]). As of 2018, biosimilars of trastuzumab have been introduced and this will change the overall cost of breast cancer treatment. The most recent advances in breast cancer have been the introduction of CDK 4/6 inhibitors (abemaciclib, palbociclib, and ribociclib) in HR-positive, HER2-negative metastatic breast cancer in 2016-18 (see Chapter 3). As HR-positive, HER2-negative metastatic cancer represents around 75 percent of all metastatic breast cancer patients, the use of these medicines will probably expand over the coming years, especially with recent data showing prolonged survival [19, 20].

Medicine costs in breast cancer are still dominated by trastuzumab; see Figure 54. There is a relatively rapid and uniform uptake of newer medicines in 2018 in all upper-tier and mid-tier countries (this is also true over time for pertuzumab; see Figure 55), whereas the introduction has been much slower and unequal in lower-tier countries with almost no access in some instances; see Figure 56 and Figure 57. In Figure 54 it is also interesting to note that in 2018 spending on drug treatment for HER2-positive patients was three times higher than for HER2-negative patients, even though the former group only encompasses around one fifth of all patients. This is due to medicine use in adjuvant therapy of HER2-positive patients and much longer time of these medicines in the market.

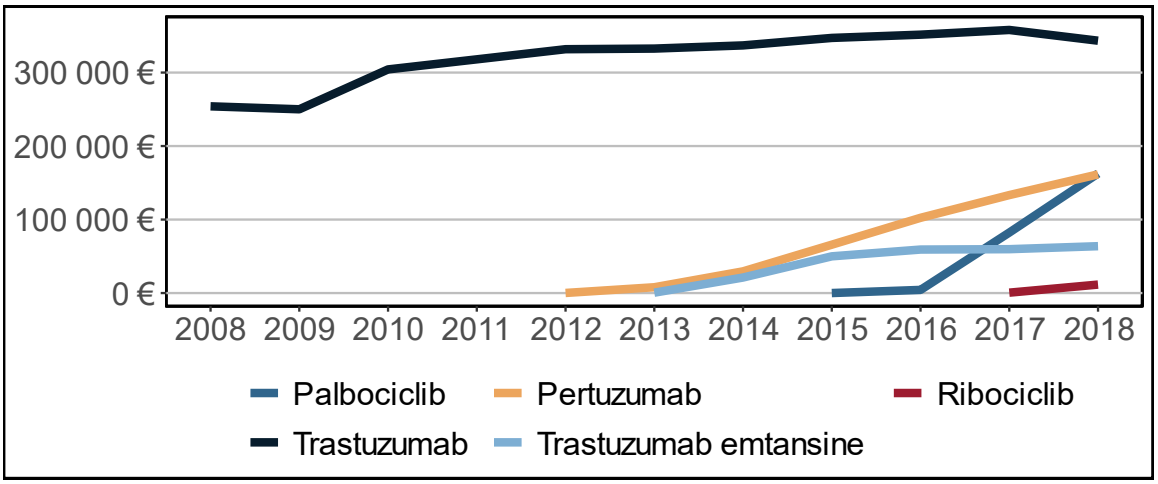


Figure 54: Uptake of medicines in breast cancer expressed as sales per 100,000 inhabitants – Europe

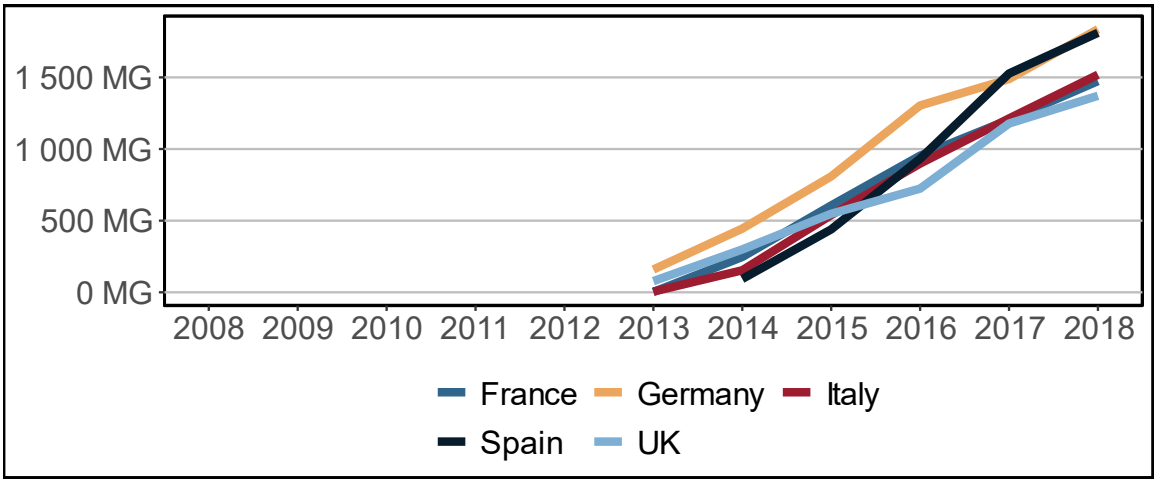


Figure 55: Uptake of pertuzumab expressed as sales in mg per case – Big 5

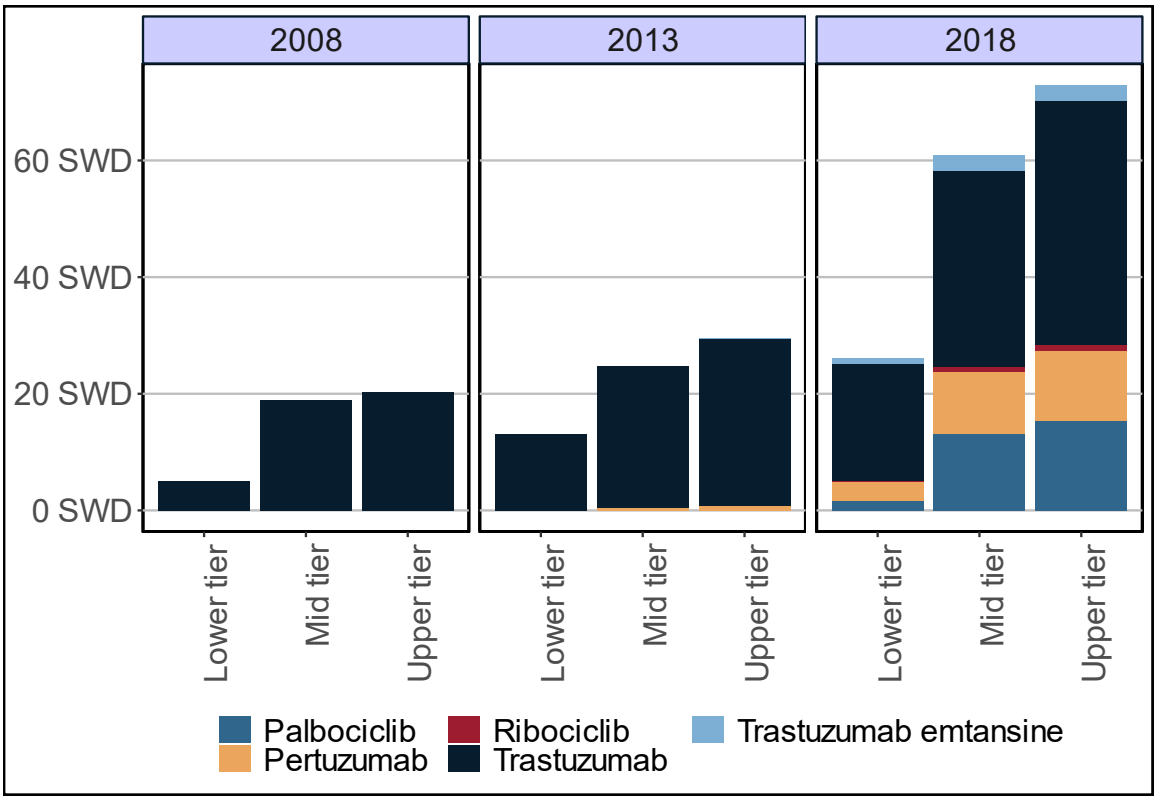


Figure 56: Uptake of medicines in breast cancer expressed as sales in SWD per case – groups of countries

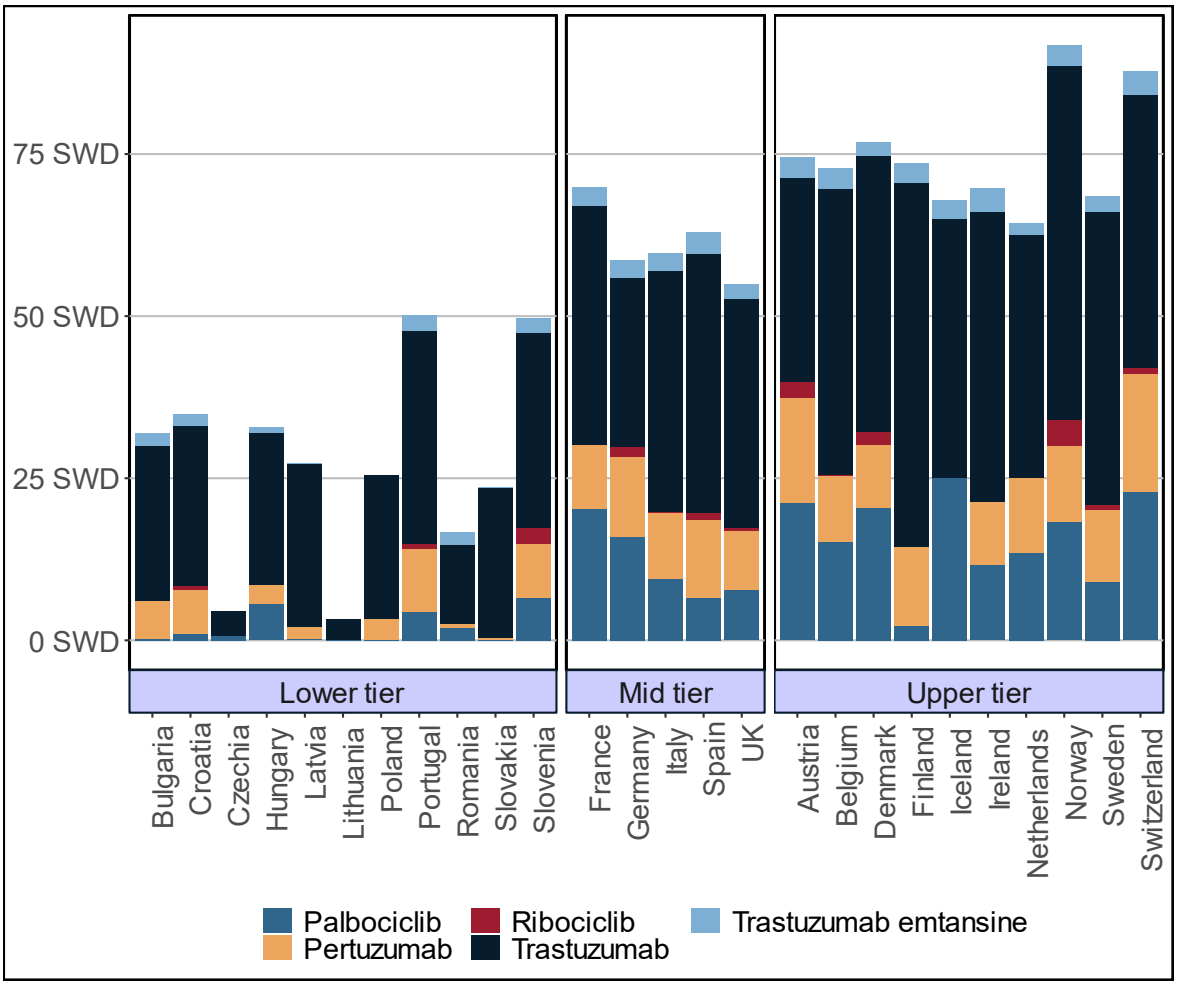


Figure 57: Uptake of medicines in breast cancer expressed as sales in SWD per case, 2018

Notes: Data for pertuzumab for Iceland are omitted.

4.7.2 Colorectal cancer

Even though key medicines for colorectal cancer like bevacizumab and cetuximab have been on the market for 15 years, and panitumumab for 10 years (see Chapter 2 in the 2016-Comparator report [6]), there are still marked differences in use between countries; see Figures 58 to 61. It should also be noted that bevacizumab and to some extent cetuximab are also used in other indications than colorectal cancer. Usage of bevacizumab in each mid-tier country has been relatively stable over the last 10 years, but there have been huge variations with a more than a 10-fold higher usage in France and Germany compared to the UK. Between 2013 and 2018, usage of all three medicines was stable in the upper-tier and the mid-tier countries, while it still increased somewhat in the lower-tier countries. It is of interest to note that in countries where there has been a formal HTA evaluation of these medicines, like in the UK and Sweden, the use of especially bevacizumab is low. The variation

in lower-tier countries is also marked, yet the usage of bevacizumab in most countries in 2018 is well above the usage in the UK for example.

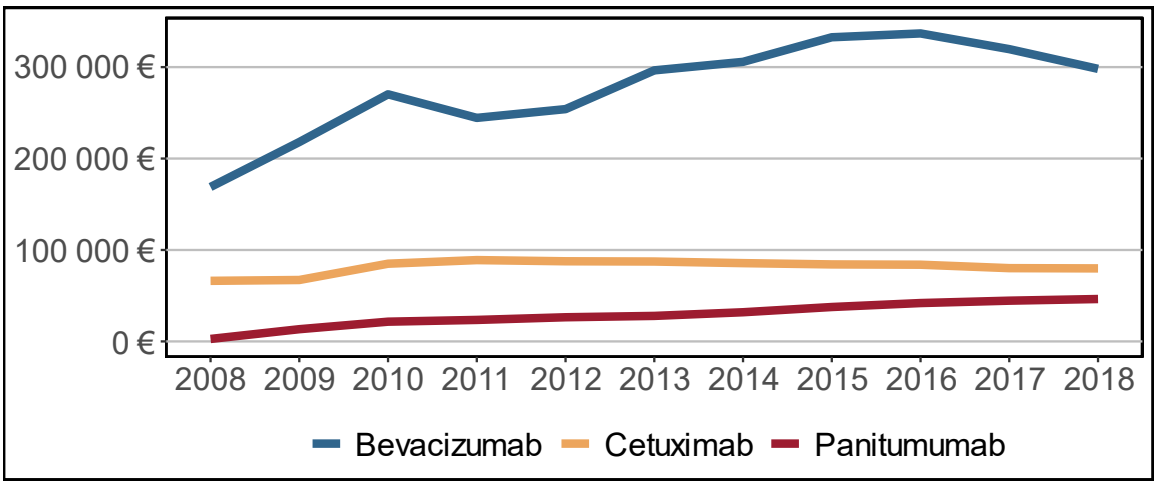


Figure 58: Uptake of medicines in colorectal cancer expressed as sales per 100,000 inhabitants – Europe

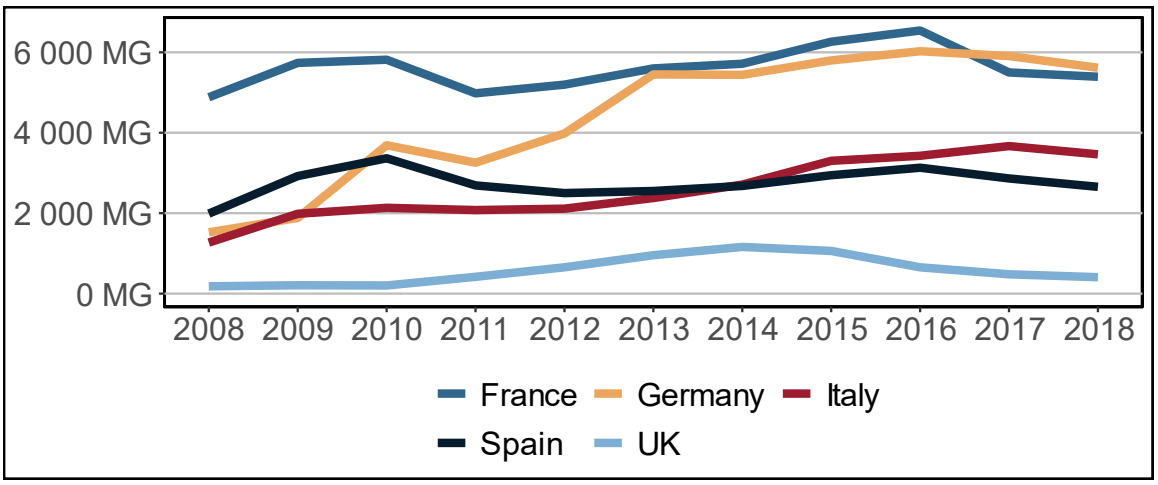


Figure 59: Uptake of bevacizumab expressed as sales in mg per case – Big 5

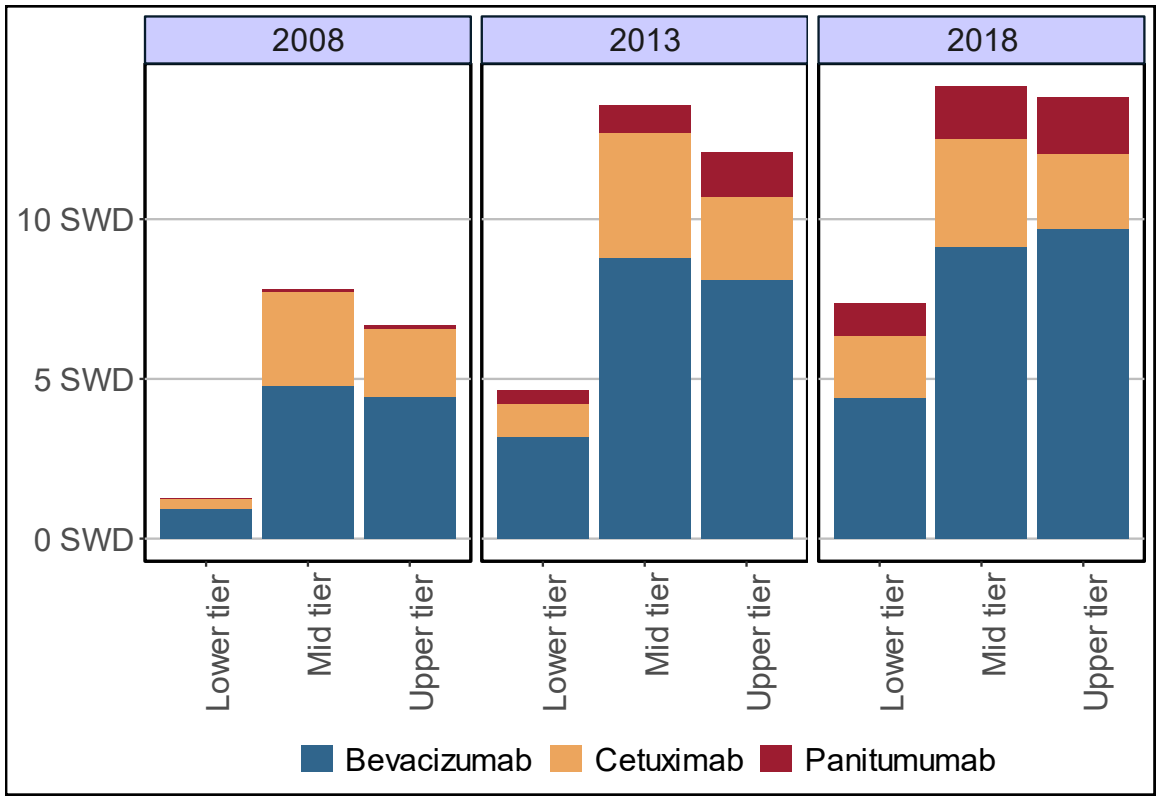


Figure 60: Uptake of medicines in colorectal cancer expressed as sales in SWD per case – groups of countries

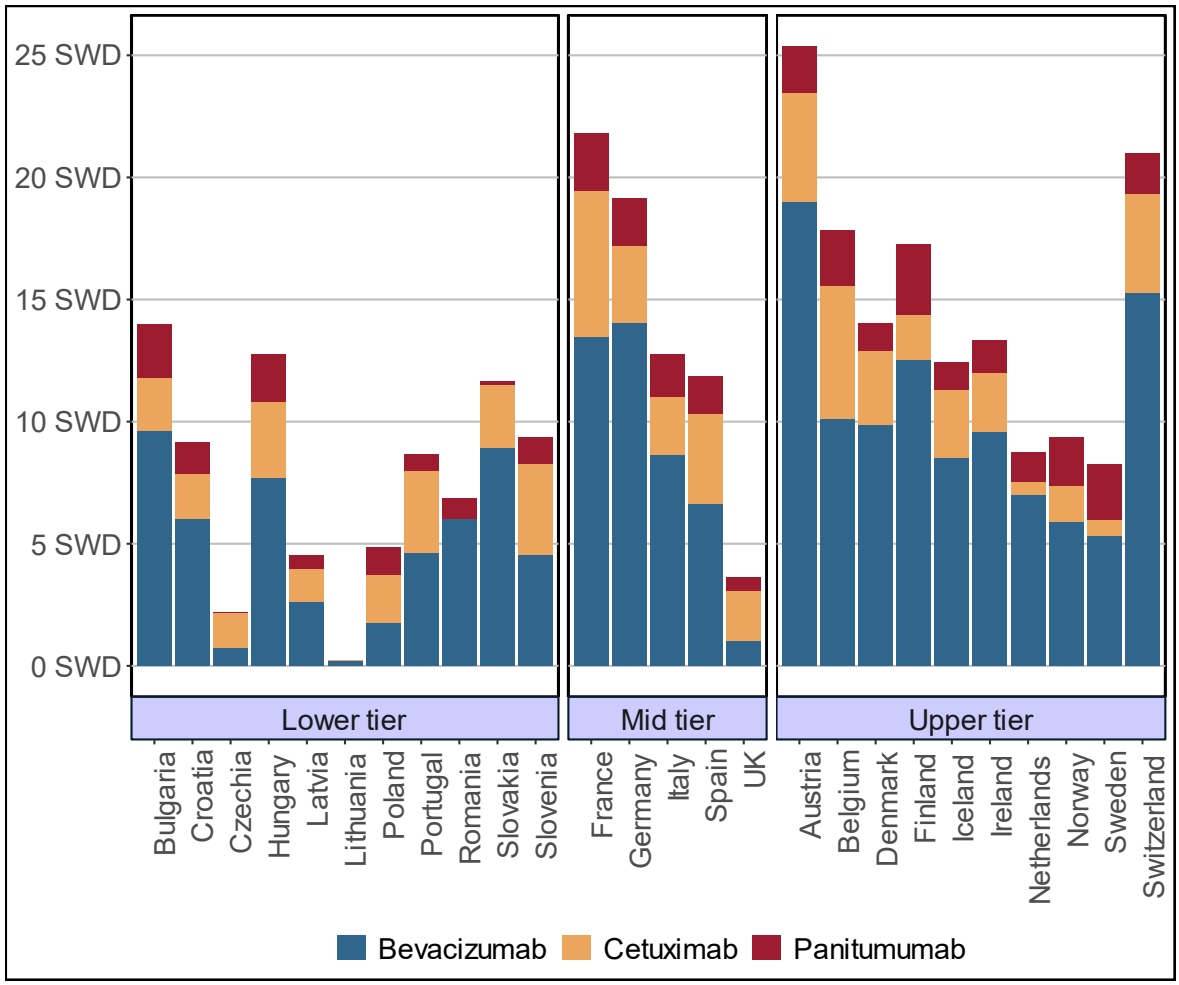


Figure 61: Uptake of medicines in colorectal cancer expressed as sales in SWD per case, 2018

4.7.3 Lung cancer

Lung cancer treatment has changed dramatically over the last decade from being dominated by chemotherapy alone to a disease area with medicines targeting the EGFR receptor as well as the ALK receptor (see Chapter 3). Immunotherapy has also rapidly become standard of care since its introduction in lung cancer treatment in 2015-16 (see Chapter 3).

The use of lung cancer medicines targeting EGFR or ALK varies to a great extent; see Figures 62 to 65. Among the mid-tier countries, France has had a total usage of these medicines per case that is three times that of the UK in 2018. The uptake of, for instance, crizotinib also follows this pattern in the mid-tier countries. There are similar variations seen in lower-tier and upper-tier countries, with some lower-tier countries having access to, for instance, erlotinib at a level of most mid-tier and upper-tier countries. This may also relate to lower-tier countries having a larger burden of lung cancer compared to some mid-tier and upper-tier countries, thereby having a greater focus on lung cancer

care. Undisclosed rebates may also play a role in some lower-tier countries, which may have enabled a relatively high access at a relatively low cost.

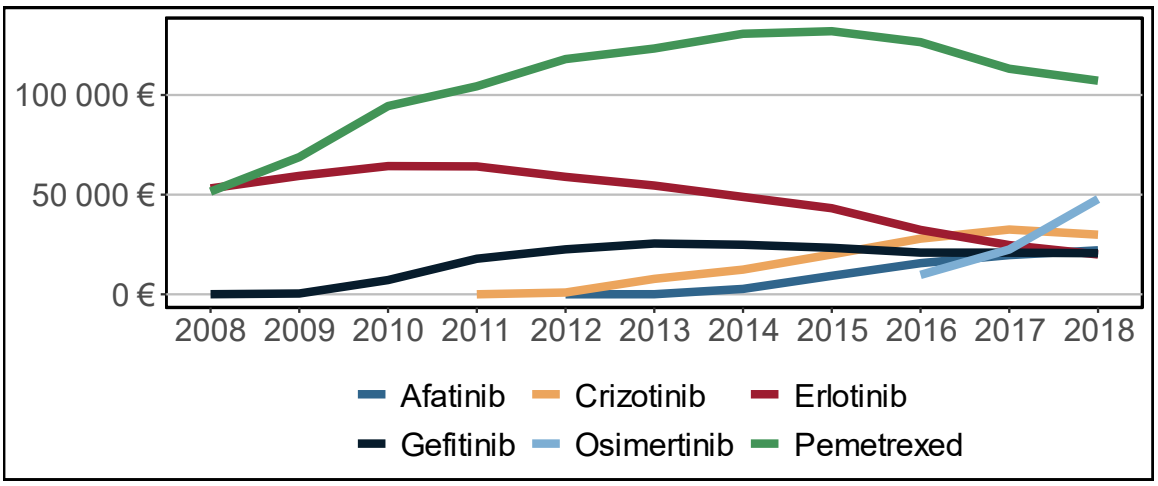


Figure 62: Uptake of medicines in lung cancer expressed as sales per 100,000 inhabitants – Europe

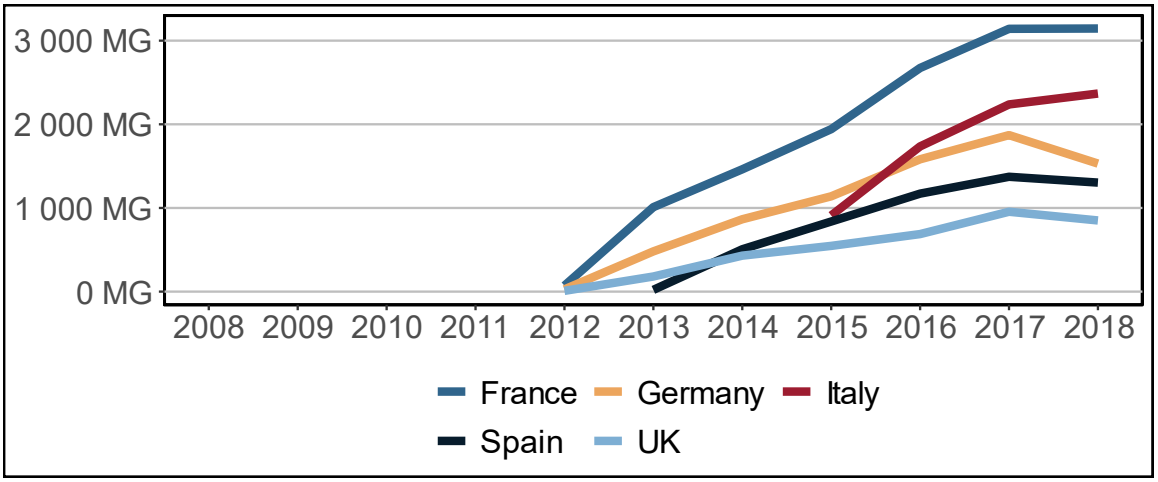


Figure 63: Uptake of crizotinib expressed as sales in mg per case – Big 5

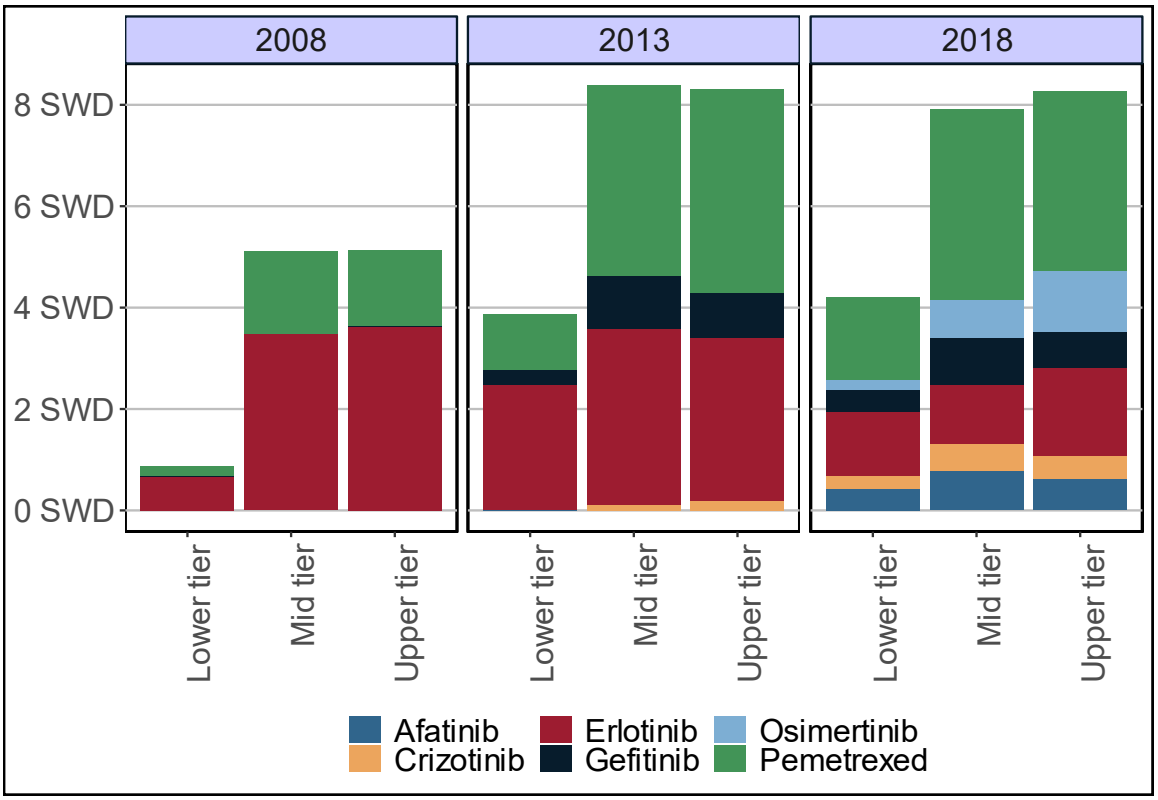


Figure 64: Uptake of medicines in lung cancer expressed as sales in SWD per case – groups of countries

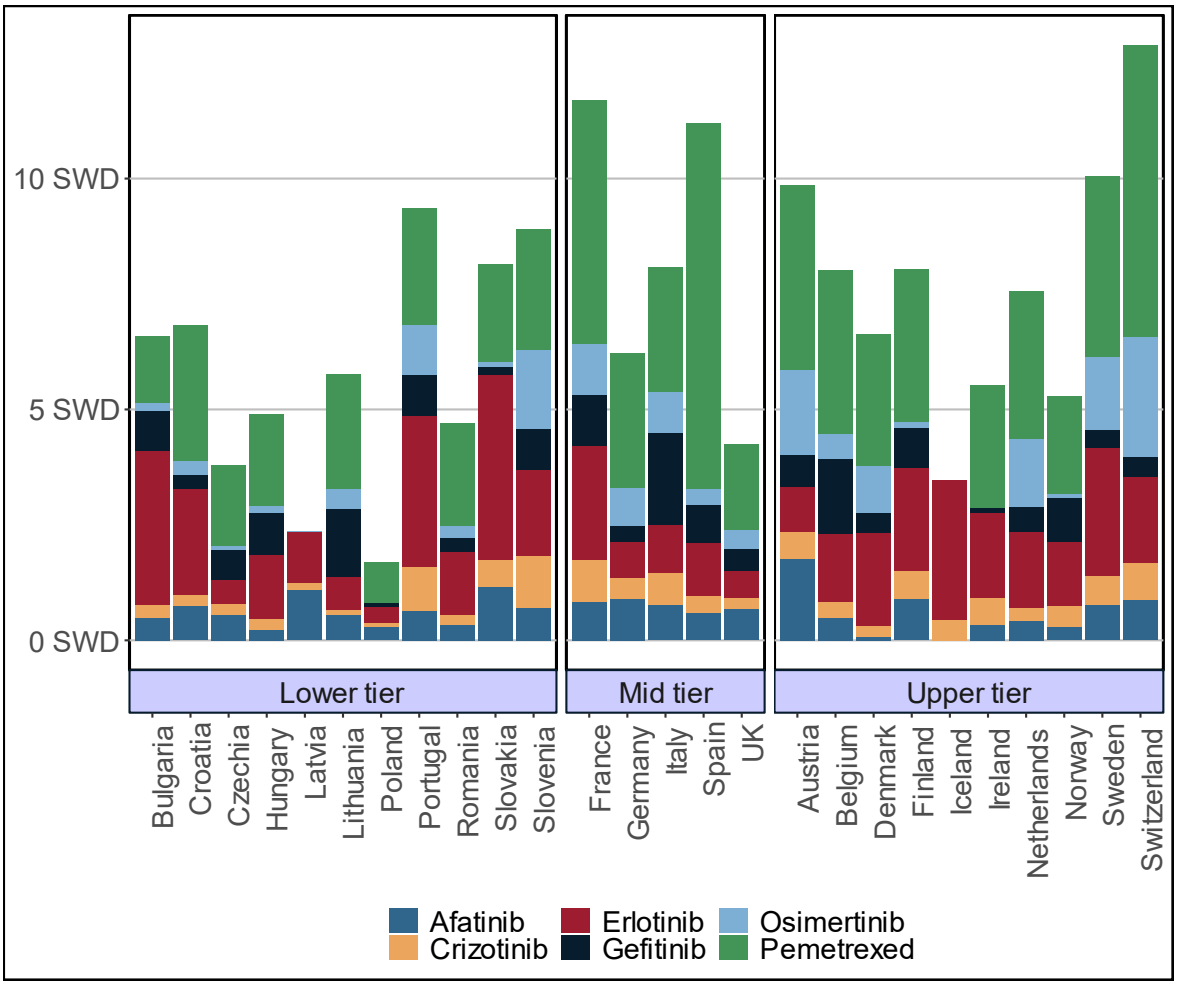


Figure 65: Uptake of medicines in lung cancer expressed as sales in SWD per case, 2018

Notes: Data for pemetrexed for Iceland are omitted.

4.7.4 Prostate cancer

The introduction of new medicines in castration-resistant prostate cancer started in 2011 with the approval of abiraterone. This was followed in 2013 by the approval of enzalutamide. Studies of both medicines have shown survival gains of 4–6 months (see Chapter 2 in the 2016-Comparator report [6]).

Sales of both medicines have been increasing since their introduction, although sales of abiraterone were stable between 2013 and 2017; see Figures 66 to 68. In most lower-tier and mid-tier countries, there was an equal distribution between the usage of these two medicines in 2018; see Figure 69. Most upper-tier countries had a higher usage of enzalutamide than abiraterone in 2018, but it is unclear if this is a reflection of the extension of the indication of enzalutamide to non-metastatic castration-resistant prostate cancer in September 2018. In general, usage of both medicines was much

higher in upper-tier and mid-tier countries (except in Spain and the UK) compared to lower-tier countries in 2018.

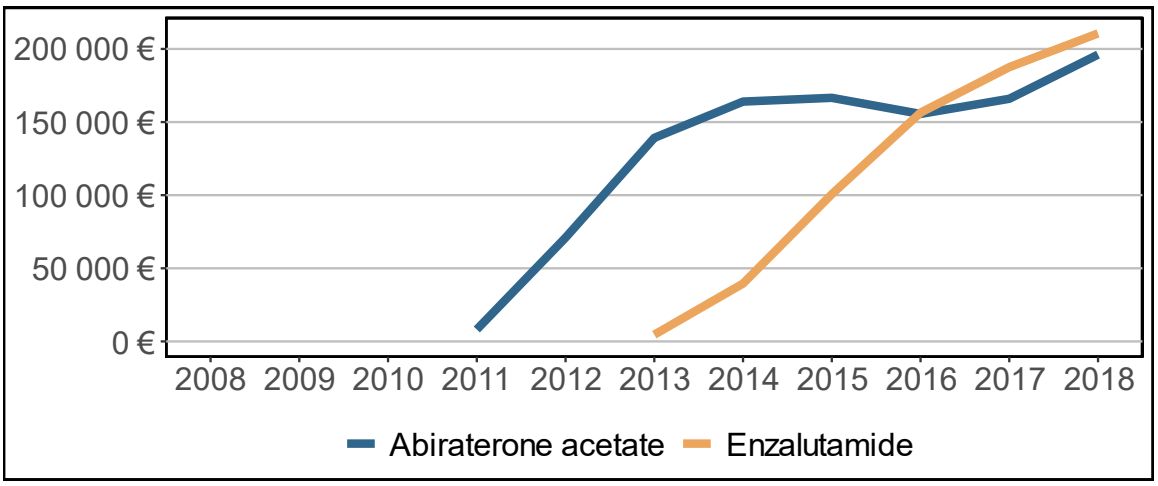


Figure 66: Uptake of medicines in prostate cancer expressed as sales per 100,000 inhabitants – Europe

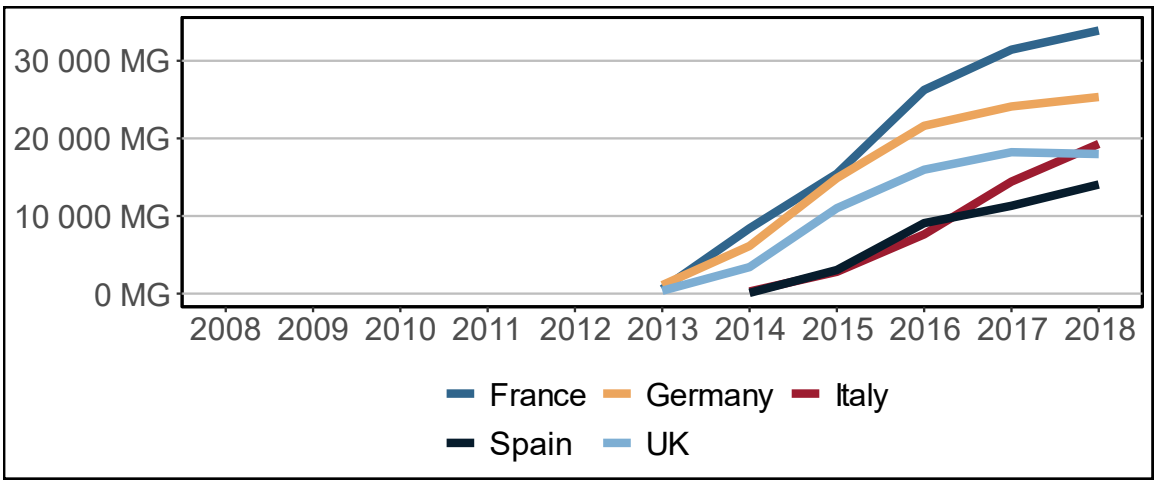


Figure 67: Uptake of enzalutamide expressed as sales in mg per case – Big 5

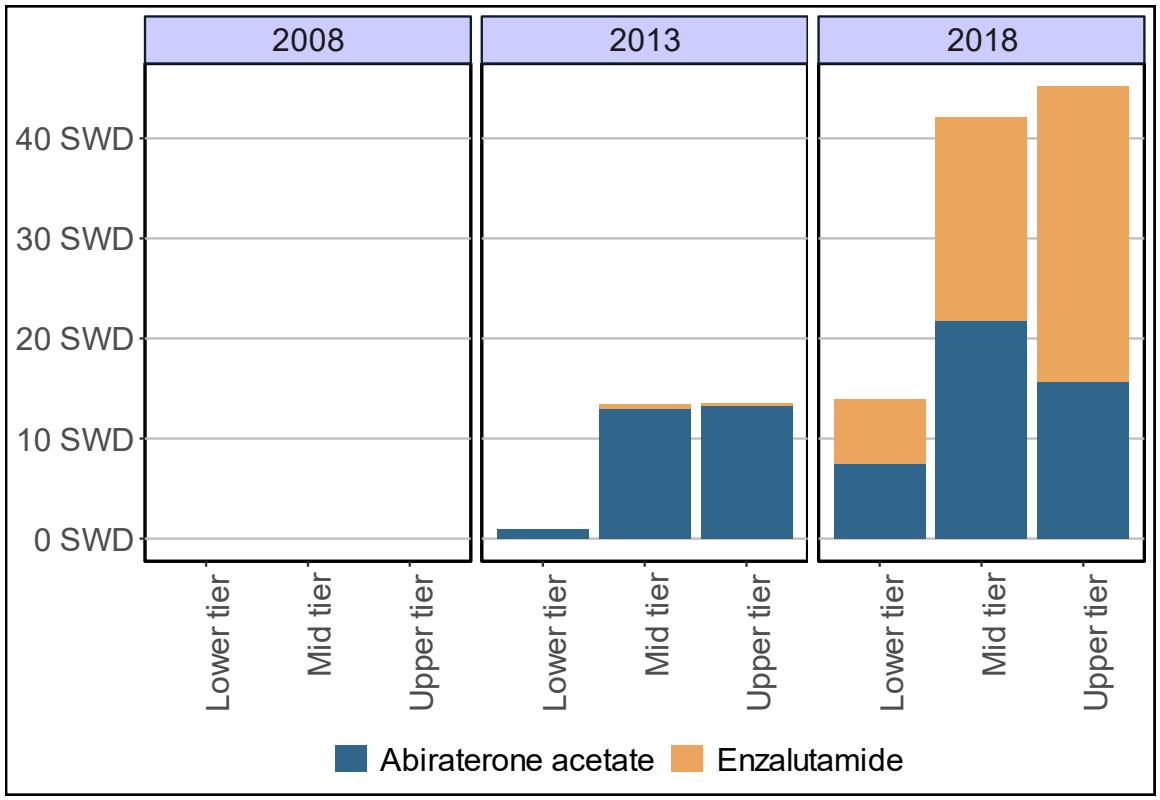


Figure 68: Uptake of medicines in prostate cancer expressed as sales in SWD per case – groups of countries

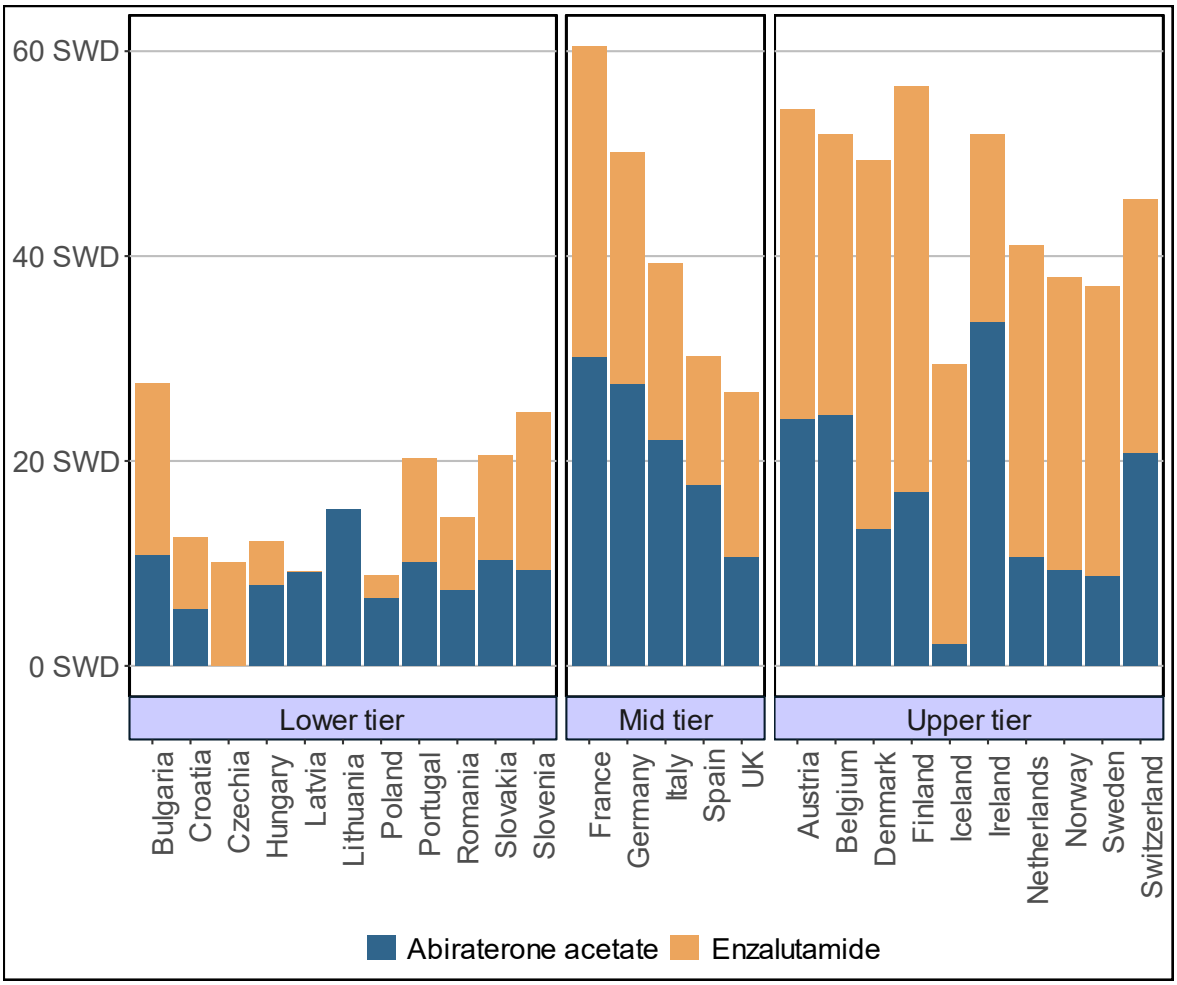


Figure 69: Uptake of medicines in prostate cancer expressed as sales in SWD per case, 2018

4.7.5 Malignant melanoma

New medicines targeting CTLA-4, PD-1, and mutated BRAF have meant a revolution for patients with metastatic malignant melanoma (see Chapter 2 in the 2016-Comparator report [6]). Ipilimumab was first introduced in 2011 and then in 2015-16 replaced by PD-1 medicines (nivolumab and pembrolizumab). This replacement was mainly based on the more positive side effect profile of PD-1 medicines. In 2016, ipilimumab was again introduced in combination with PD-1 medicines showing clinical benefit for about one third of the patients. The use of the combination resulted in both added costs and increased severe toxicity, but also in a marked improvement of 5-year survival [21]. For patients with BRAF mutations, vemurafenib was introduced in 2011 and to a great extent replaced by dabrafenib which was introduced in 2013. MEK inhibitors (cobimetinib and trametinib) in combination with BRAF inhibitors were approved in 2014-15; see Figure 70.

Ipilimumab can serve as an example for new melanoma medicines (for other immunotherapy medicines like nivolumab and pembrolizumab see section 4.7.8); see Figures 71 to 75. It had high uptake in most upper-tier countries, with the exceptions of Finland, Norway, and Sweden. Among the mid-tier countries, Spain and the UK had a relatively low uptake, whereas in all lower-tier countries uptake was low or very low. BRAF and MEK inhibitors had a more equal uptake in mid-tier and upper-tier countries, where the level of usage was twice as high compared to lower-tier countries in 2018; see Figures 76 and 77. However, there are major variations within the country groups, especially among the upper-tier countries. For instance, Austria had a level of access about 2-3 times that of Finland, Iceland, and Norway in 2018. Among the mid-tier countries, the UK had the lowest level of access.

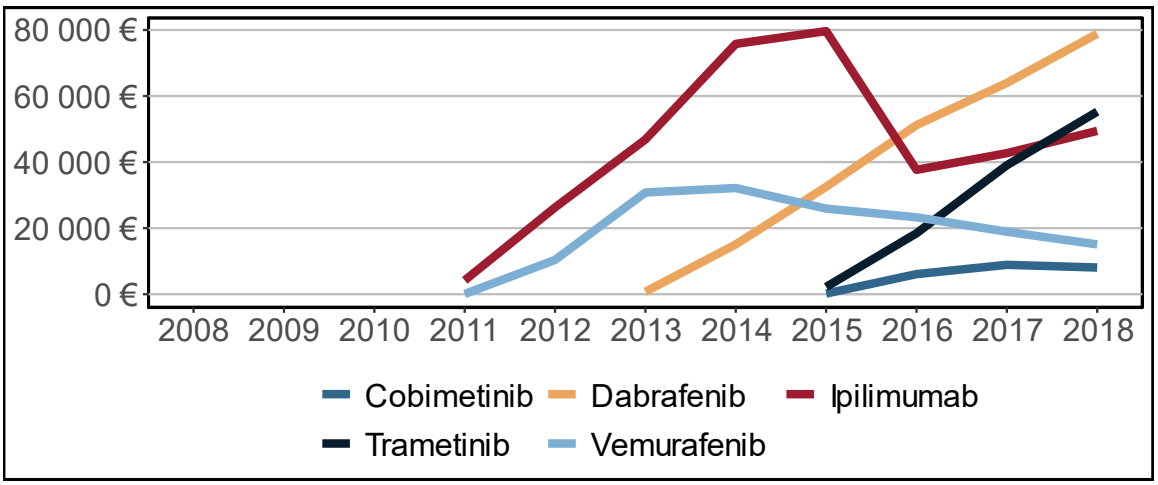


Figure 70: Uptake of medicines in malignant melanoma expressed as sales per 100,000 inhabitants – Europe

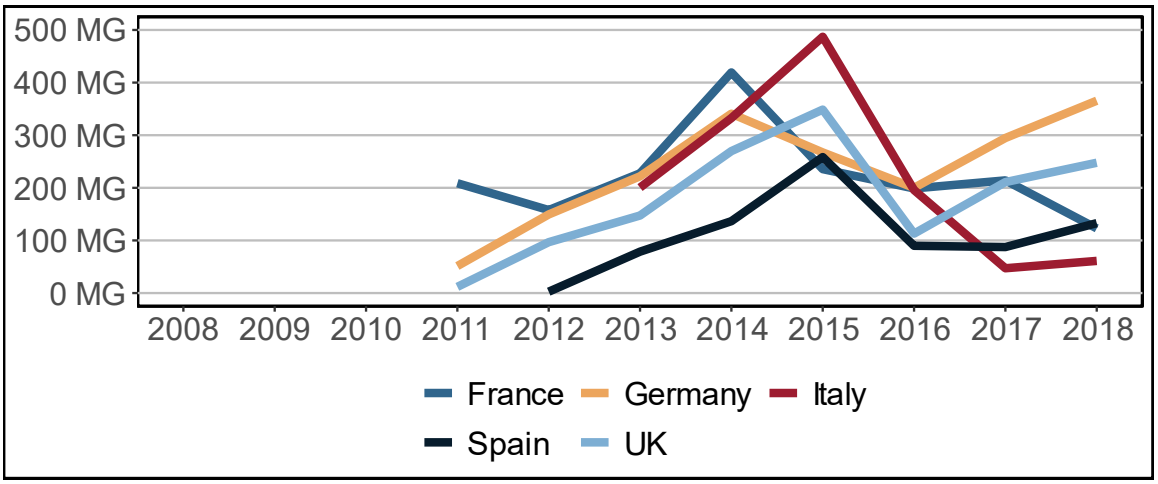


Figure 71: Uptake of ipilimumab expressed as sales in mg per case – Big 5

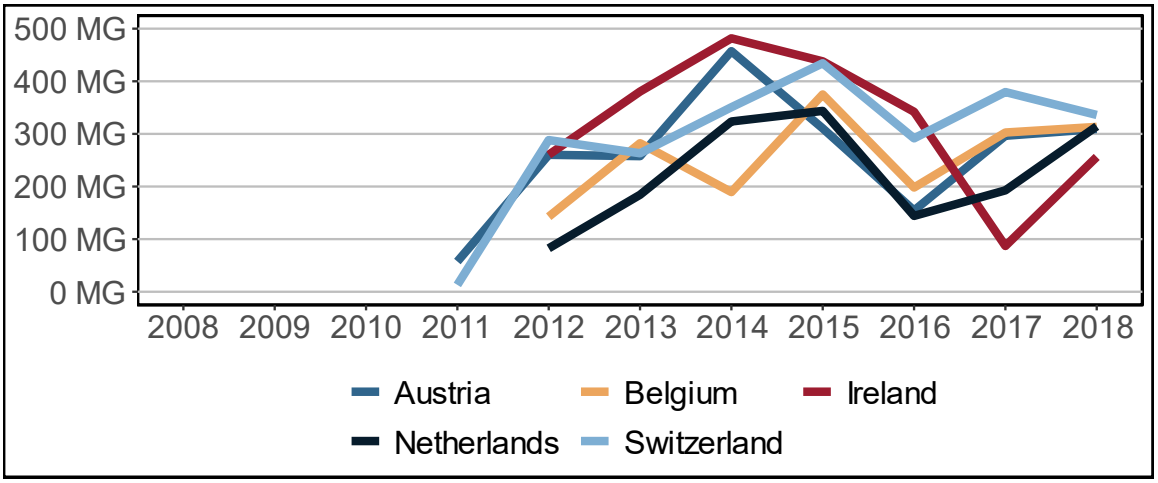


Figure 72: Uptake of ipilimumab expressed as sales in mg per case – Upper-tier 1

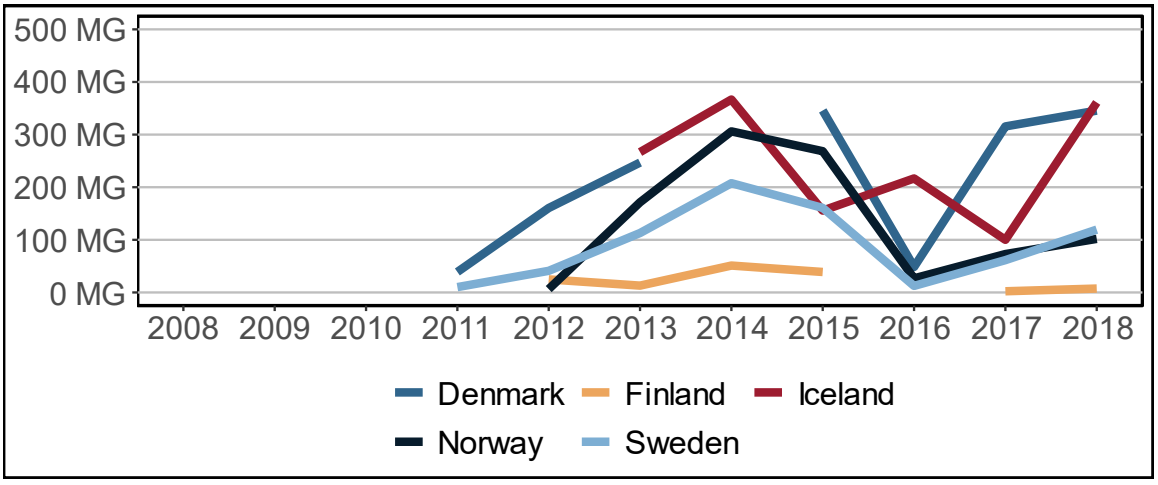


Figure 73: Uptake of ipilimumab expressed as sales in mg per case – Upper-tier 2

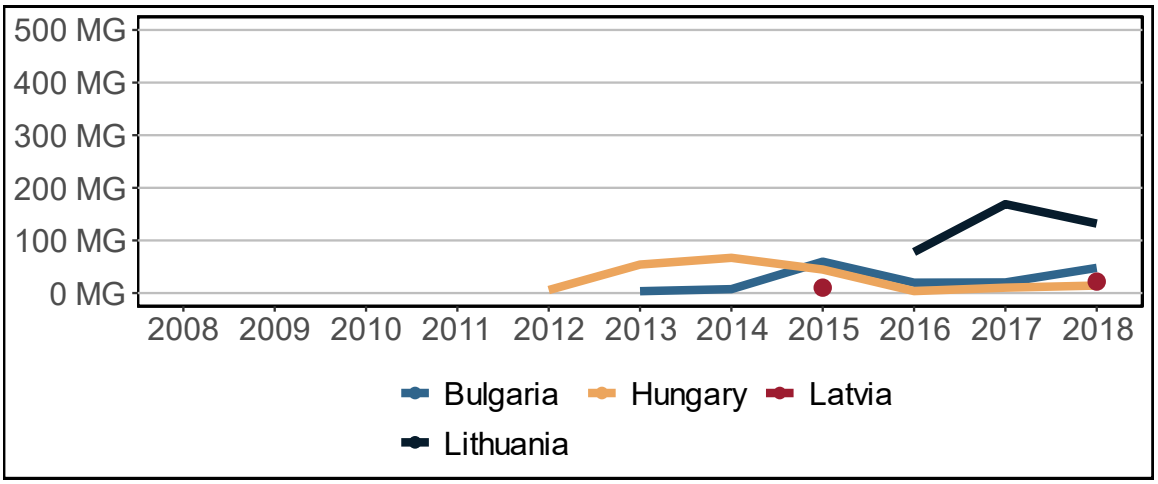


Figure 74: Uptake of ipilimumab expressed as sales in mg per case – Lower-tier 1

Notes: No sales of ipilimumab in Croatia and Czechia until 2018.

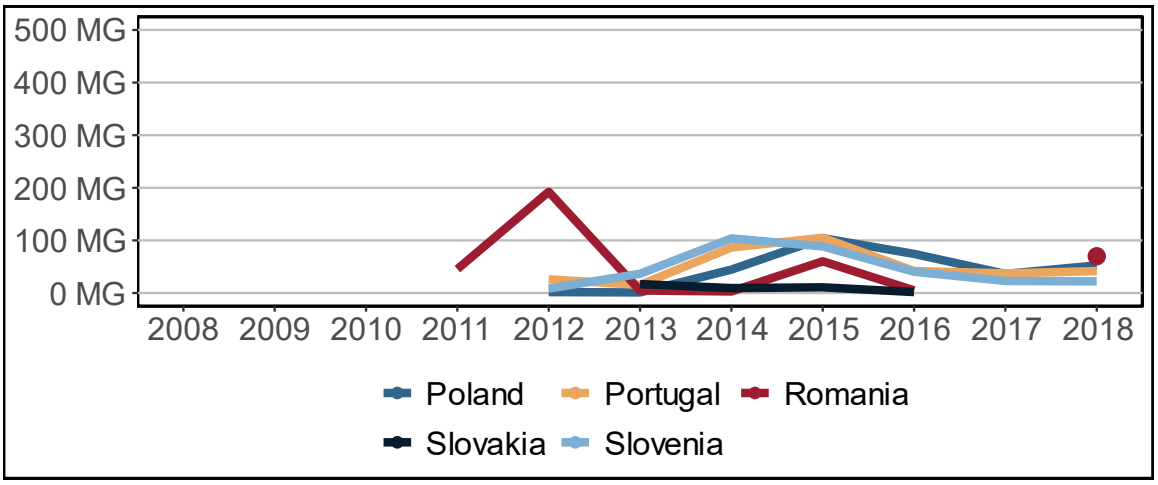


Figure 75: Uptake of ipilimumab expressed as sales in mg per case – Lower-tier 2

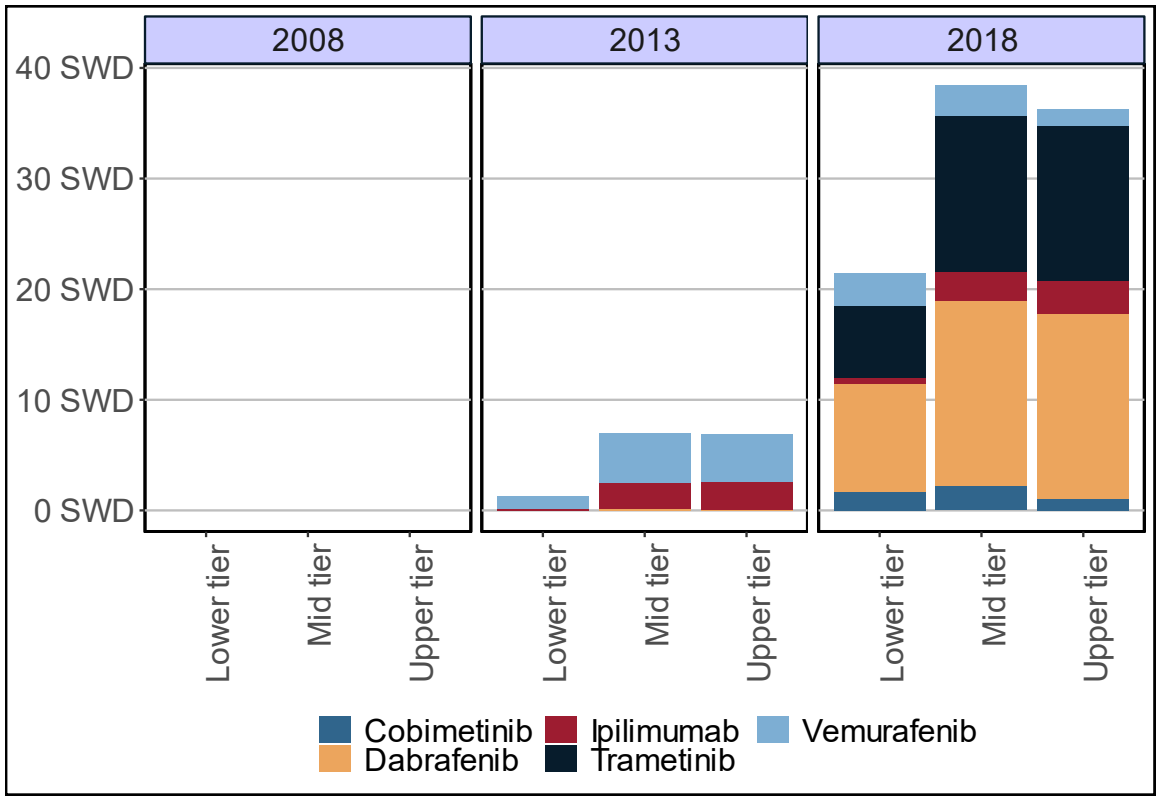


Figure 76: Uptake of medicines in malignant melanoma expressed as sales in SWD per case – groups of countries

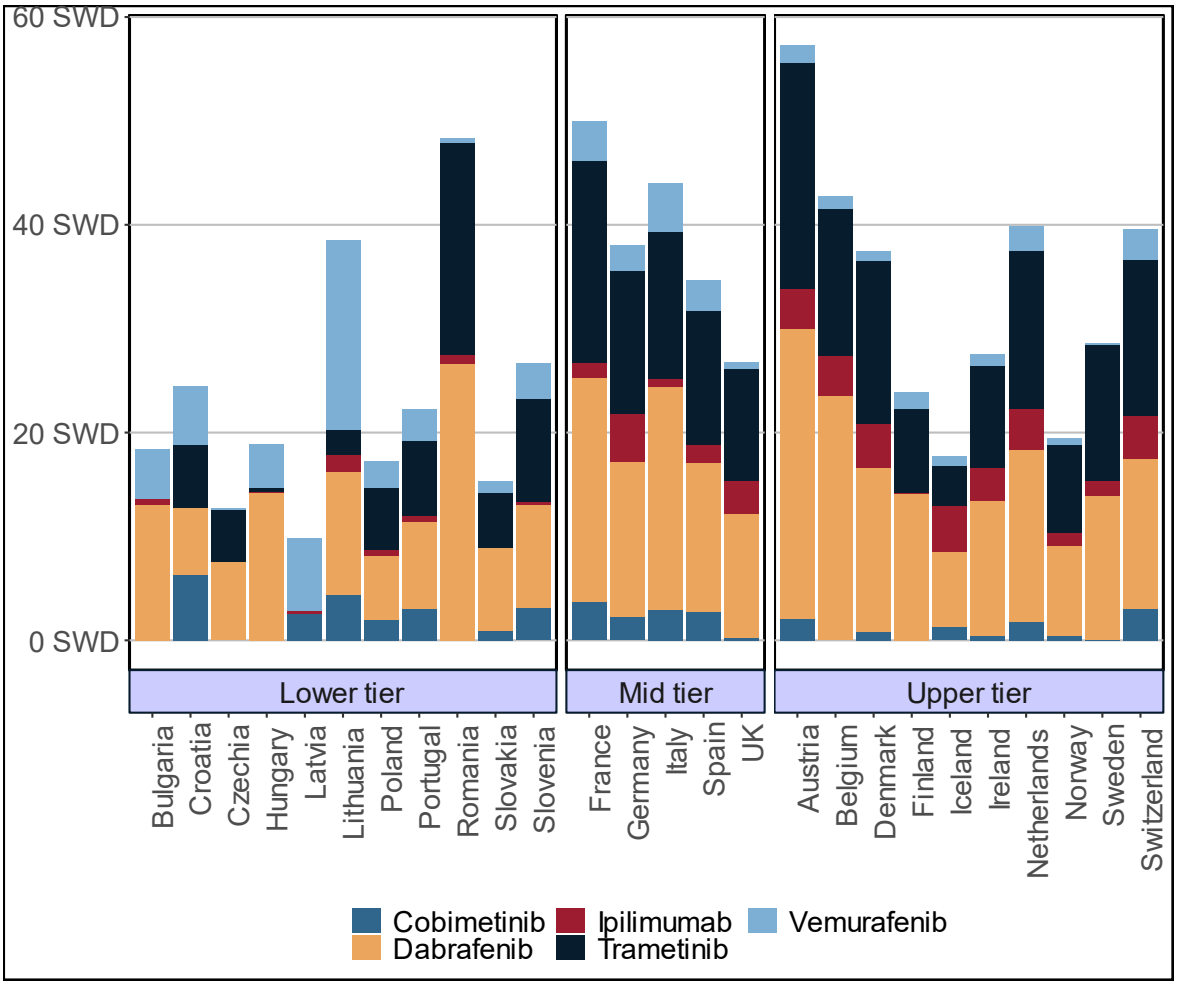


Figure 77: Uptake of medicines in malignant melanoma expressed as sales in SWD per case, 2018

4.7.6 Multiple myeloma

Multiple myeloma represents a disease where effective medicines for both disease control and symptom control are key for quality of life and survival (see Chapter 2 in the 2016-Comparator report [6]).

Usage of the first "backbone" medicine in multiple myeloma, bortezomib, has been relatively stable over the last 10 years, while lenalidomide has become another "backbone" in myeloma therapy in many countries; see Figures 78 to 81. The introduction of lenalidomide over time has been relatively uniform in the mid-tier countries, with small changes in usage between 2010 and 2014 and steadily increasing usage afterwards. The overall usage of myeloma medicines per case was much higher in the upper-tier countries in 2018 compared to the mid-tier countries, reflecting a rapid uptake of newer medicines like pomalidomide, carfilzomib, and daratumumab. Note that the high usage of daratumumab in Denmark is probably owed to the fact that it was partly developed there, leading to

high medical knowledge early on. In general, the use of myeloma medicines was low or very low in the lower-tier countries in 2018, constituting perhaps the largest inequality in access to cancer medicines of all cancer types considered in this report.

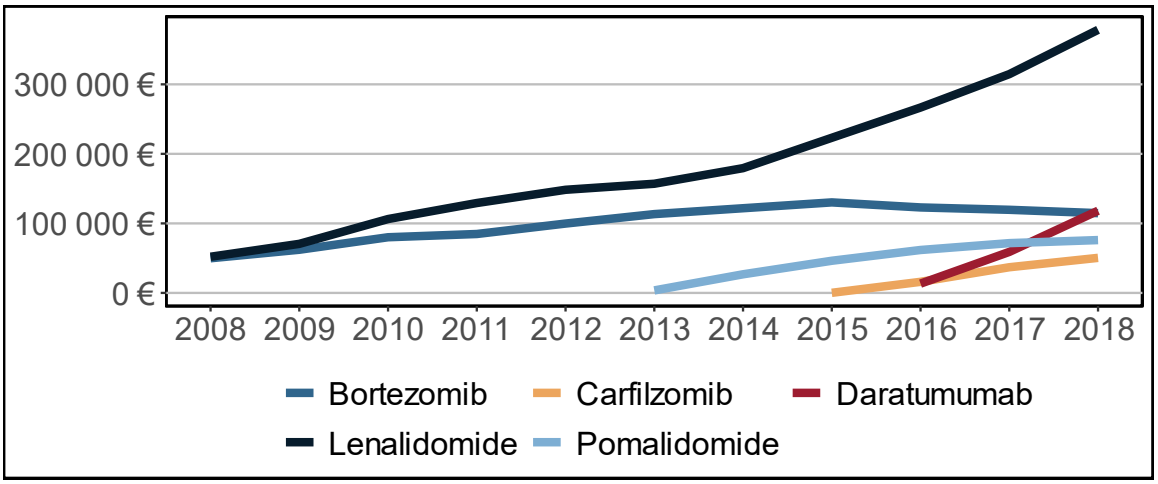


Figure 78: Uptake of medicines in multiple myeloma expressed as sales per 100,000 inhabitants – Europe

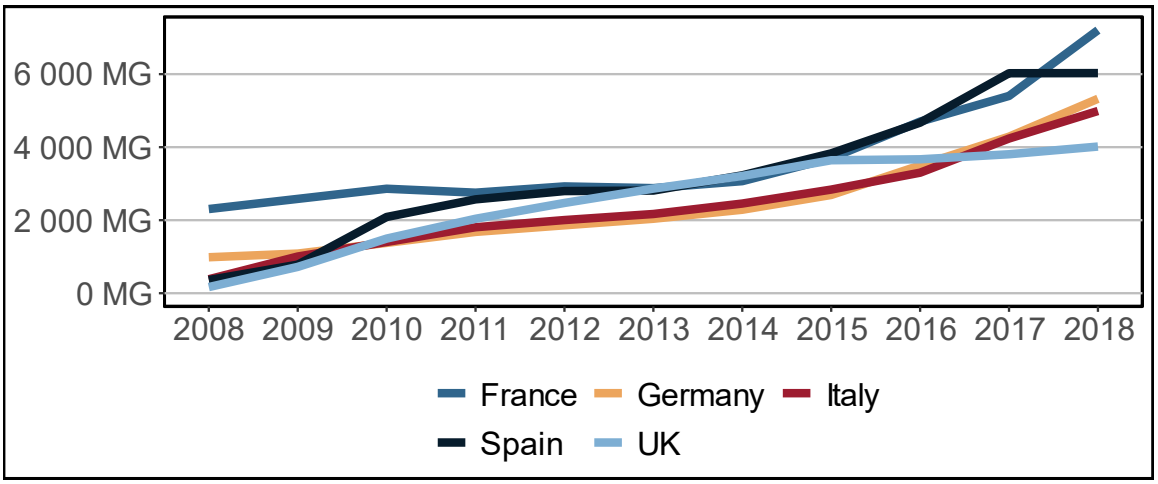


Figure 79: Uptake of lenalidomide expressed as sales in mg per case – Big 5

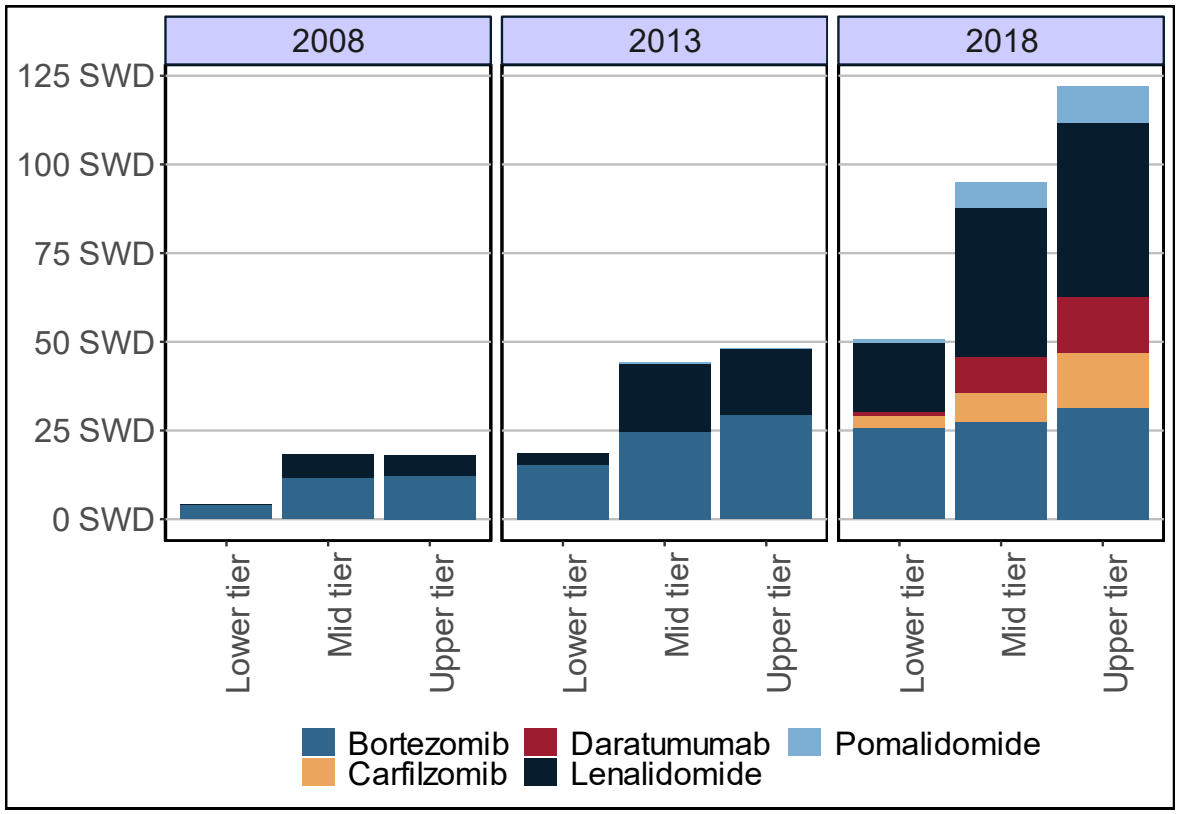


Figure 80: Uptake of medicines in multiple myeloma expressed as sales in SWD per case – groups of countries

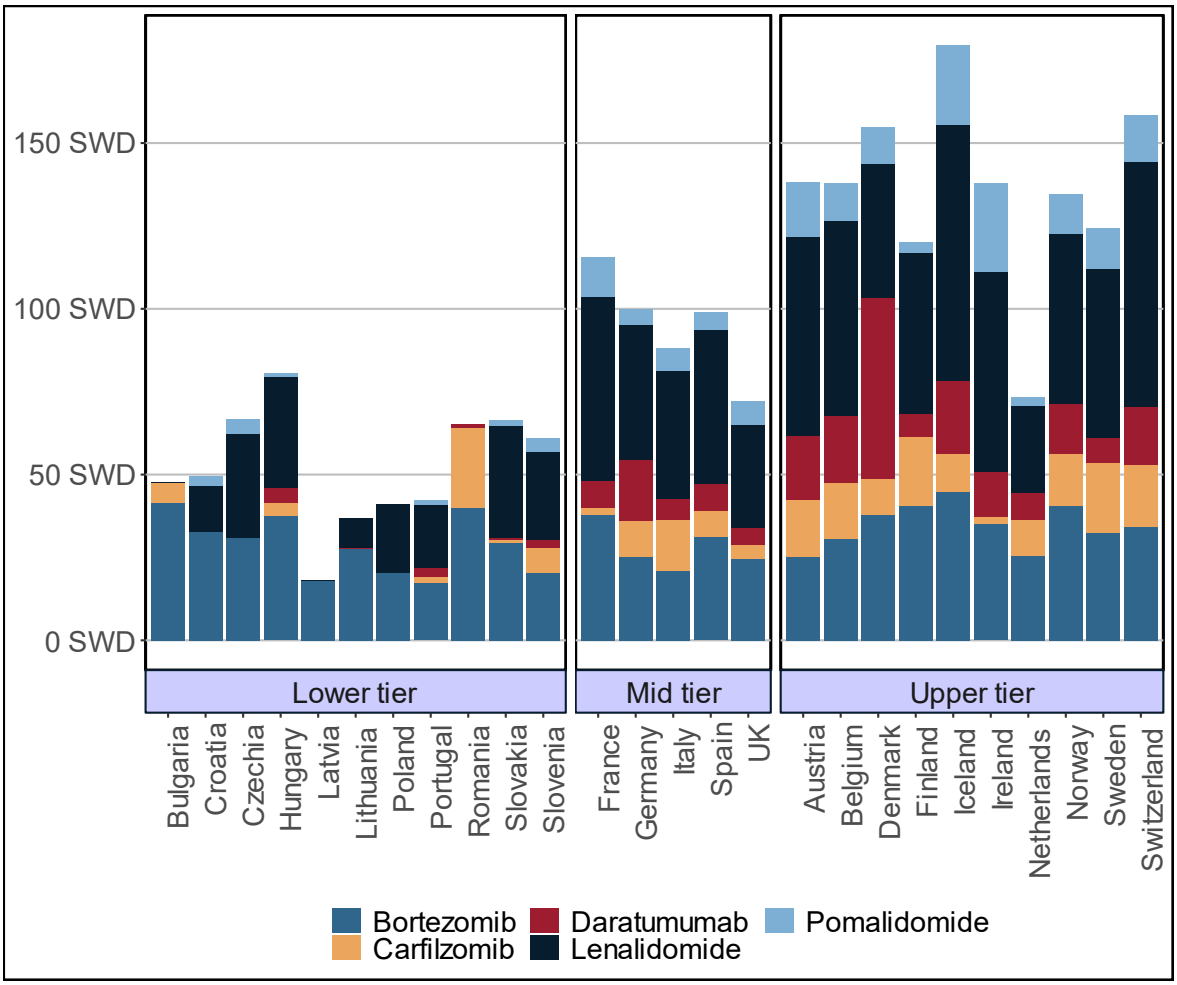


Figure 81: Uptake of medicines in multiple myeloma expressed as sales in SWD per case, 2018

4.7.7 Ovarian cancer

The first PARP inhibitor for BRCA-mutated ovarian cancer was olaparib, introduced in 2014, followed by niraparib in 2017 and by rucaparib in 2018 (see Chapter 3). PARP inhibitors have in 2019 also been approved for BRCA-mutated breast cancer. Uptake of PARP inhibitors has been very varied, with some upper-tier countries like Finland having a very low uptake, while some lower-tier countries have a higher uptake (Slovenia had the highest uptake) in 2018; see Figures 82 to 84. In the mid-tier countries, uptake has been similar, except for a low uptake in the UK.

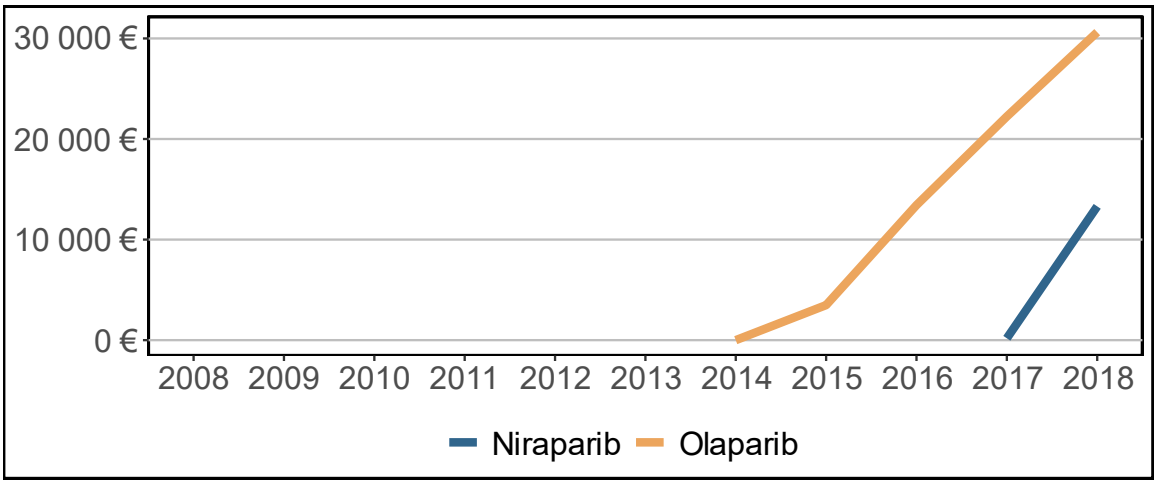


Figure 82: Uptake of medicines in ovarian cancer expressed as sales per 100,000 inhabitants – Europe

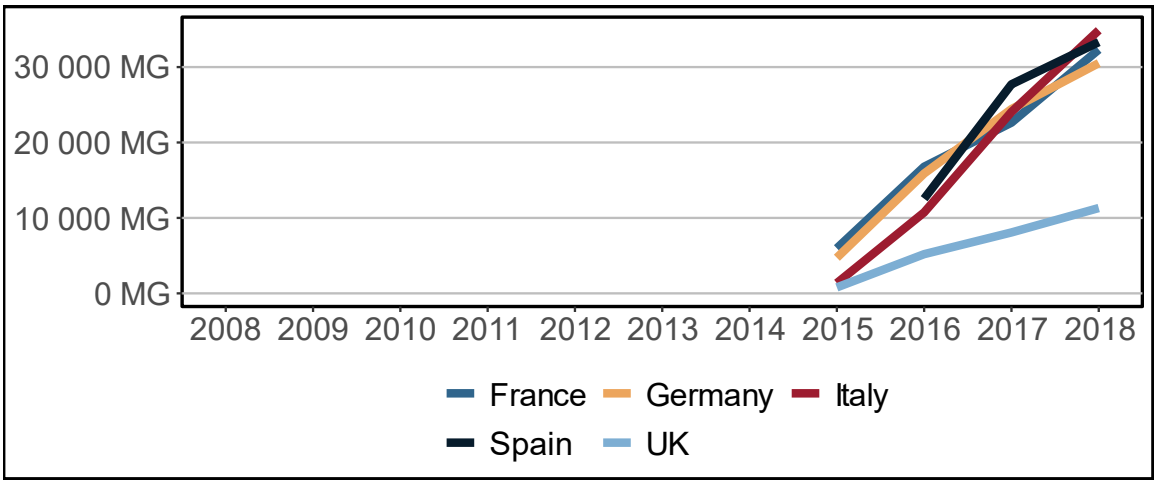


Figure 83: Uptake of olaparib expressed as sales in mg per case – Big 5

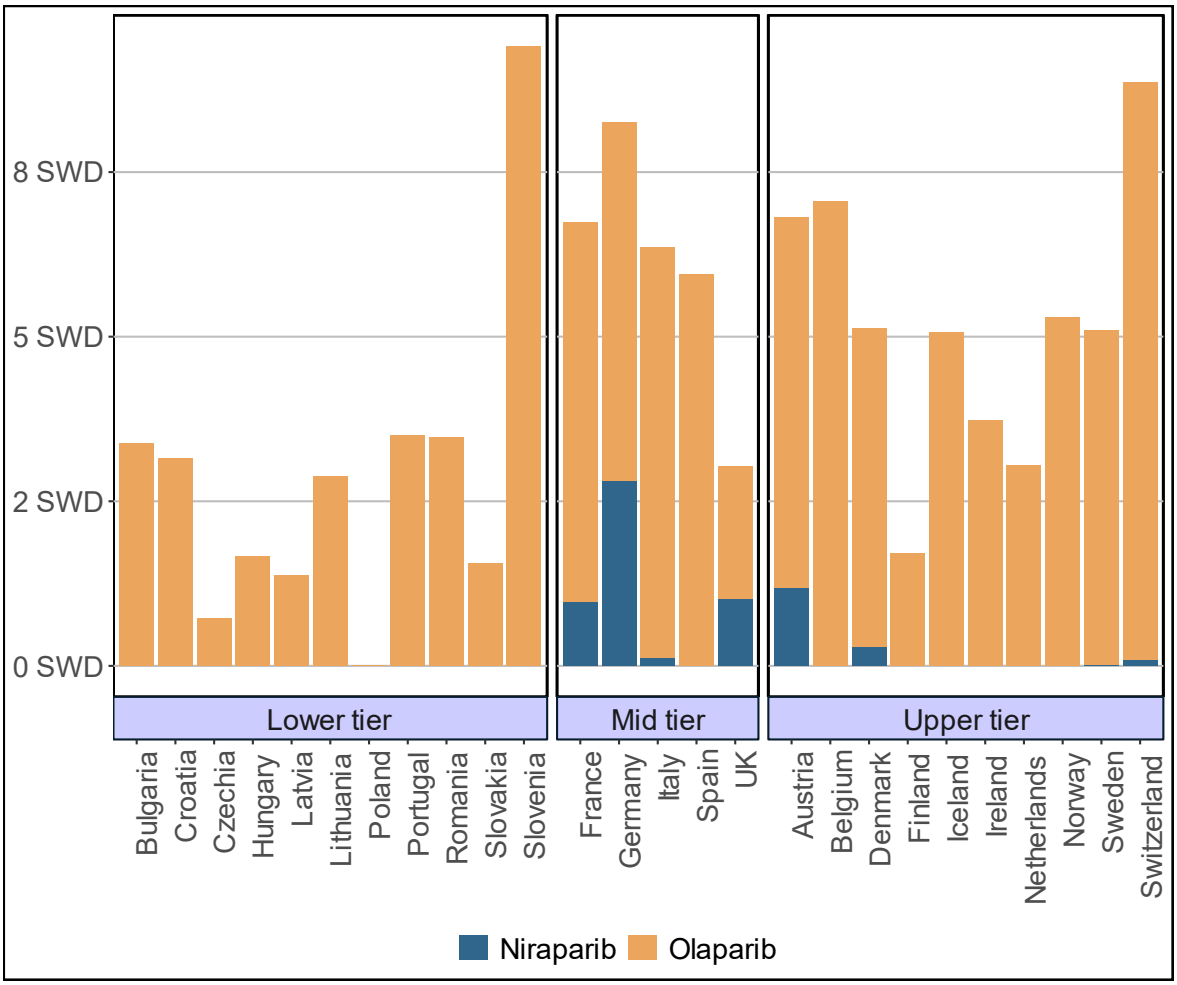


Figure 84: Uptake of medicines in ovarian cancer expressed as sales in SWD per case, 2018

4.7.8 Immunotherapy

Immuno-oncology started with the introduction of ipilimumab in 2011 but took off with the introduction of the less toxic and more effective PD-1 medicines, nivolumab and pembrolizumab, in 2015 (see Chapter 3). Later PD-L1 medicines (atezolizumab and avelumab in 2017 and durvalumab in 2018) have been added to the immuno-oncology arsenal; see Figures 85 to 89. In general, access to immuno-oncology medicines is much higher in upper-tier and mid-tier countries compared lower-tier countries which only have 10–20% of the former's access levels. There is however relatively large variation between the mid-tier countries with lower access in Spain and the UK, and also between the upper-tier countries with very low access in Finland (similar to lower-tier countries).

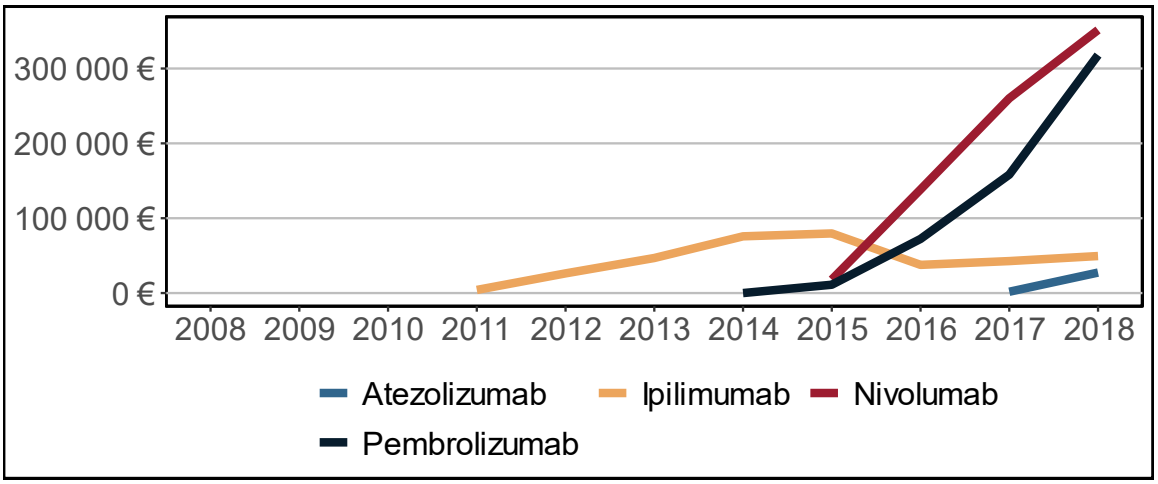


Figure 85: Uptake of immunotherapy medicines expressed as sales per 100,000 inhabitants – Europe

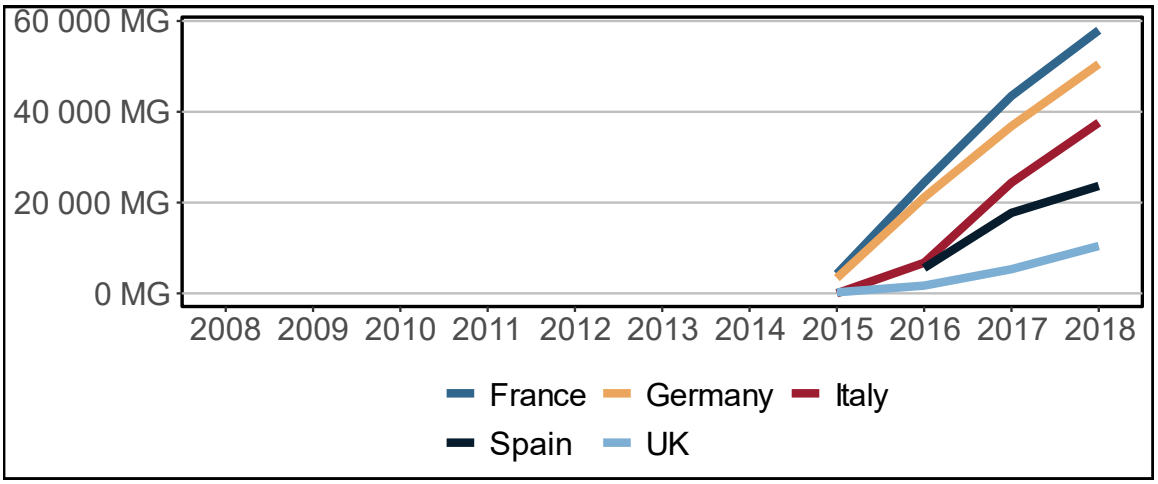


Figure 86: Uptake of nivolumab expressed as sales in mg per 100,000 inhabitants – Big 5

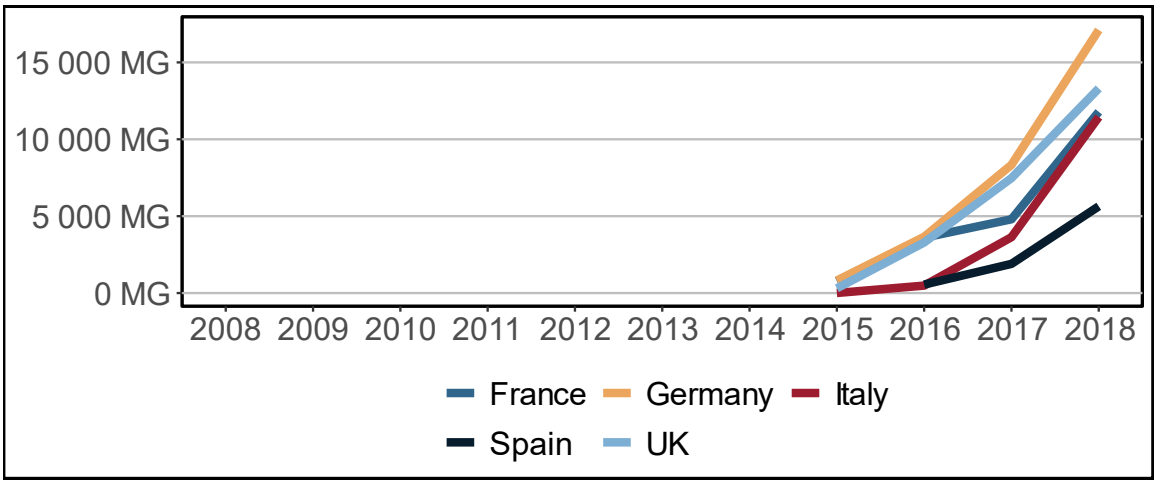


Figure 87: Uptake of pembrolizumab expressed as sales in mg per 100,000 inhabitants – Big 5

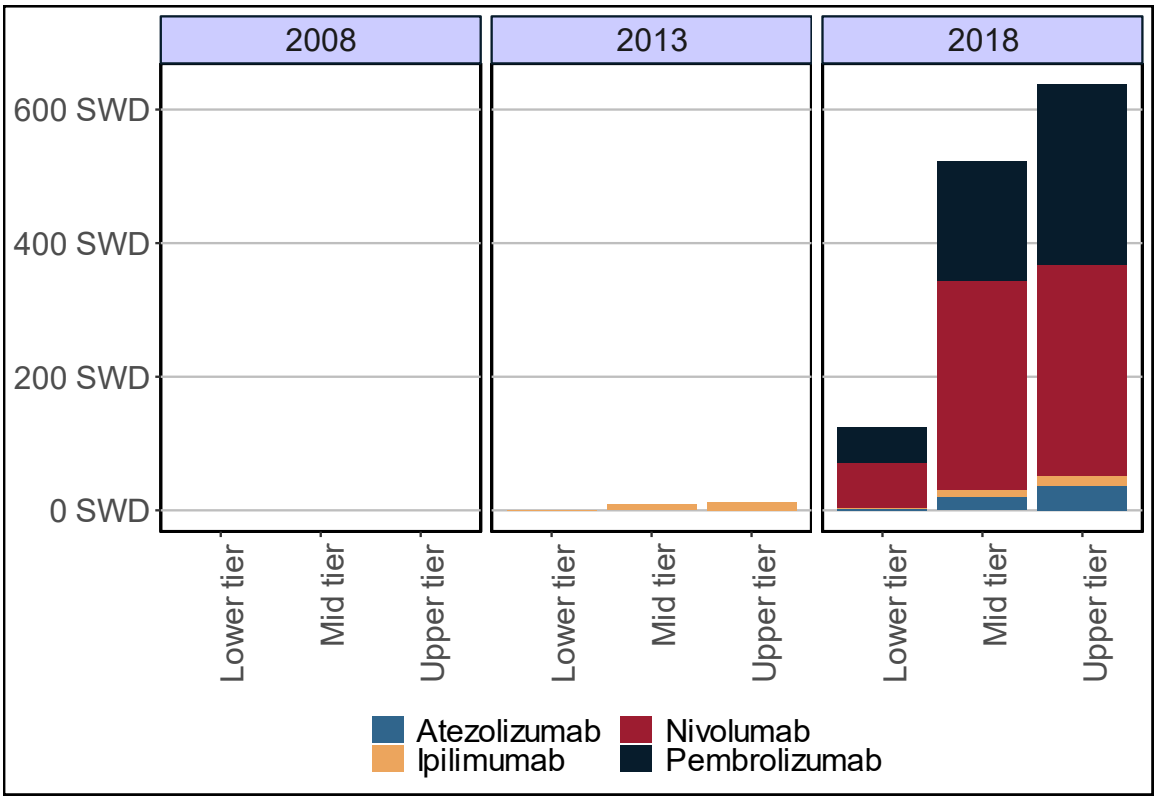


Figure 88: Uptake of immunotherapy medicines expressed as sales in SWD per 100,000 inhabitants – groups of countries

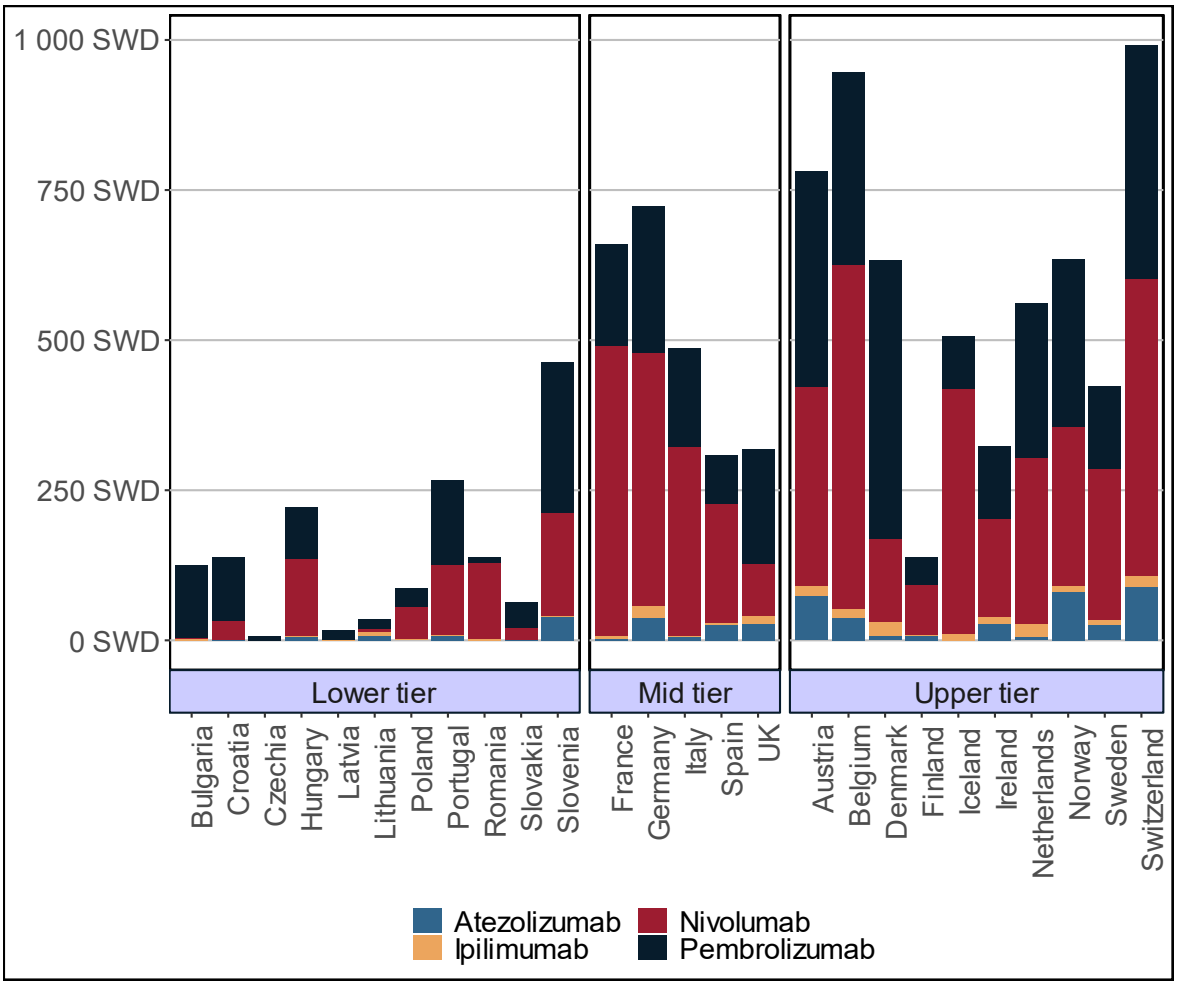


Figure 89: Uptake of immunotherapy medicines expressed as sales in SWD per 100,000 inhabitants, 2018

4.8 Summary and conclusions

Cancer medicines are a cornerstone in both curative and palliative cancer care. Full access to cancer medicines is attained when every patient that may benefit will receive the relevant medicine. In absence of patient-level data, the measurement of adequate access is challenging. Data on the country level can serve as a proxy for patient access, if access is equated with market uptake, i.e. usage measured in volume and value.

There has been a distinct increase in the number of approved cancer medicines and indications since 2012. Between 2001 and 2011, the EMA approved on average four new cancer medicines per year, whereas this number increased to ten medicines per year in 2012 to 2018. The number of indications started to rise already in the mid-2000s and received an additional surge due to an expansion of indications of CPI therapies introduced in 2015. However, over one third (37%) of the medicines

approved 2015–2018 had an orphan designation, compared to one quarter (26%) of those approved 2010–2014.

Targeted medicines and since 2015 immuno-oncology medicines are behind the increase in the number of new cancer medicines and indications. Some indications have seen a greater increase in approved medicines than others. Leukemia represented the largest indication with 25 unique active substances approved between 1995 and 2018. There were 18 approved medicines used in lung cancer, 15 approved medicines in breast cancer, and 12 approved medicines for lymphoma.

The total costs of cancer medicines more than doubled between 2008 and 2018 in Europe. Total cancer medicine sales increased from €12.9 billion to €32.0 billion (in current prices) between 2008 and 2018. In per-capita terms, sales increased from €25 to €61. Taking into account inflation and using exchanges rates from 2018, the costs in 2008 amounted to €14.6 billion (€28 per capita). The strong increase in the costs of cancer medicines is linked to higher prices of newly introduced medicines and greater patient numbers (due to increasing cancer incidence, new medicines for previously untreated patient groups, more prevalent cases that need long-term chemotherapy, increased use in adjuvant treatment).

The costs of cancer medicines increased in all countries between 2008 and 2018, except for Czechia. France, Germany, Italy, Spain, and the UK stood for 75 percent of all sales (compared to around 63 percent of the population) in 2008 and 2018 in Europe. Wealthier countries spend distinctly more on cancer medicines per capita than poorer countries. The top spenders in 2018 were Austria, Germany, and Switzerland (around €92 to €108 per capita), whereas Czechia, Latvia, and Poland spent the least (around €13 to €16). Higher rebates on medicines in poorer countries might exaggerate these differences. Nonetheless, patient access to cancer medicines was much greater in wealthier countries.

Cancer medicines accounted for a modest but growing share of total pharmaceutical sales. Around 9–14 percent of total pharmaceutical expenditure were spent on cancer medicines in 2015 in France, Germany, Sweden, and the UK, compared to around 5–7 percent in 2005. Cancer medicines also accounted for a growing share of the direct costs of cancer. In 2018, almost one third (31 percent) of the direct costs consisted of cancer medicines, up from 17 percent in 2008.

A small number of cancer medicines make up the majority of sales. The top 10 medicines in terms of sales stood for 55 percent of total sales in 2008 and for 45 percent in 2018 in Europe. A remarkable result is that the top 10 most sold medicines are surprisingly similar in the wealthiest countries, the big 5, and the poorer countries. Thus, poorer countries bought a similar mix of medicines even though they spent comparatively little on cancer medicines.

There have been marked shifts among the top 10 selling medicines between 2008 and 2018. Of the top 10 in 2008, there were only three medicines left in 2018; of the top 10 in 2012, only four medicines were left in 2018. Trastuzumab, which lost its patent in 2014, topped the list from 2008 to 2015, but between 2012 and 2018 its share of total sales was almost halved. Imatinib, which lost its patent in 2016, experienced a similar halving of its share between 2015 and 2018. Two immunotherapy medicines, nivolumab and pembrolizumab, which both were approved in 2015, made up 11 percent of sales in 2018.

The newest cancer medicines (approved within the last two years) had a share of 8 percent of total sales in 2008. After the outbreak of the economic crisis, their share bottomed out at 3 percent in 2010–2011 and expanded again to 8 percent until 2018. The same pattern is observable in relatively new cancer medicines (approved within three to five years ago). Wealthier countries spent a larger share on the newest cancer medicines in all years than poorer countries. This indicates a stronger uptake of the newest cancer medicines in wealthier countries.

Uptake of new cancer medicines, measured in volume, varies between countries. Differences in uptake relate to countries' economic status; higher uptake in wealthier countries and lower uptake in poorer countries. This pattern has not changed over time and is consistent with the one found in the previous Comparator reports. Overall, poorer countries recorded around one third to one half of the level of uptake (in volume) of the big 5 and the wealthier countries.

Among the big 5 countries, the UK showed a consistent pattern of the lowest level of uptake across the seven considered cancer types and immunotherapy. France and Germany had the highest level of uptake. These significant variations in uptake in countries of similar economic strength indicate opportunities for improvement through policies aimed at evidence-based and cost-effective cancer care.

The largest country differences in uptake were observed in immuno-oncology medicines and in medicines used for multiple myeloma and prostate cancer in 2018. The uptake of immuno-oncology medicines in poorer countries was around 10–20 percent of the level observed in the big 5 and the wealthier countries, which might also reflect differences in how well health care systems were prepared for the introduction of this new form of treatment. The uptake of medicines in multiple myeloma and prostate cancer was less than one third of the uptake in the wealthier countries.

The smallest country differences in uptake were observed in medicines used for lung cancer in 2018. This may be related to poorer countries having a larger burden of lung cancer compared to wealthier countries, thereby focusing more strongly on lung cancer care. In addition, country differences in the

uptake of mature medicines with a large patient population (trastuzumab, bevacizumab, and pemetrexed) were comparatively smaller than in newer medicines.

A note of caution in interpreting country differences in access to cancer medicines is needed. The data at hand, do not reflect the true final costs of most new cancer medicines in health care systems. Undisclosed rebates in many health care systems and differential pricing in wealthier and poorer countries are a fact. It is also obvious that there is underreporting of sales for some medicines in some countries, especially in poorer countries. The different methods to standardize usage (euros, milligram, or SWD in relation to population or mortality) also have their pros and cons.

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5. Policy issues for improved cancer care

5.1 Key messages

- Research is fundamental for achieving improvements in cancer care. During the last decade, R&D investment in cancer research by the pharmaceutical industry has grown much quicker than investments by public and private non-profit sources. Cancer research in Europe might receive greater attention and funding from public sources in the coming years by the new European Commission.
- Health care systems need to weigh the costs from investing in different areas of cancer care against the potential improvements in patient outcomes. This will ensure that scarce resources are used in a cost-effective and efficient way.
- There is a positive association between health spending on cancer care and survival, but there are variations in efficiency in cancer care both between and within countries. This indicates opportunities to improve efficiency and outcomes in all countries. Improving efficiency and outcomes should be central aims of the planned "Beating Cancer Plan" by the European Commission.
- Important tools for improving efficiency, which most European countries have implemented by now, are (i) a National Cancer Control Programme and (ii) a nationwide population-based cancer registry. However, most countries still lack comprehensive accounts on health care spending on cancer which would allow studies that can link spending and outcomes.
- Primary prevention and screening are two areas where all European countries still have great opportunities for improving policies to reduce cancer incidence and mortality. Stringent measures for tobacco control often only require political willpower but no public money. HPV vaccination programs for girls and boys are cost effective but not fully implemented in many countries. A cost-effective use of resources for screening programs requires spending on colorectal, cervical, and breast cancer (in this priority order), whereas the cost-effectiveness of prostate and lung cancer screening is currently not well established.
- Access to cancer medicines is important for improving patient outcomes. Yet medicines' share on the total health expenditure spent on cancer has been growing. Increasing medicine expenditure have so far been offset by expenditure decreases in other areas (inpatient and ambulatory care), but this possibility will soon be exhausted. In addition, immunotherapy has increased the need for inpatient and ambulatory care for the management of side effects.

- A key challenge for access to new medicines is the trade-off between early access and evidence on value to patients. Many medicines lack evidence of additional clinical benefits/value to patients (such as in terms of overall survival) at the time of EMA approval. There needs to be better monitoring systems to reduce uncertainty over time (via collection of RWD) and to share the risk between payers and manufacturers. This could help in providing faster and more equal access and use of innovative medicines that provide most value to patients and health care systems, and in making access to medicines that have not yet been proven to be cost effective conditional on appropriate follow-up.
- The use of biosimilars and generics is another important way to support cost-effective spending on medicines. Cost savings from using biosimilars and generics create financial scope for investing into innovative and cost-effective medicines that previously seemed unaffordable.
- Another key challenge for access to new medicines is to balance adequate reimbursement for medicines' value against affordability. The affordability and cost-effectiveness of new medicines keeps decreasing due to higher costs per treated patient. A large share of European cancer patients, especially in Eastern Europe, cannot gain access to effective medicines due to high prices and resulting low cost-effectiveness in their health care systems.
- A recent challenge for the valuation and payment of cancer medicines has arisen with the introduction of CAR T-cell therapies. These therapies require only a single treatment and might lead to cure in a large share of patients. Feasible solutions for the valuation (use of a risk elimination premium, mixture cure models, and a higher discount rate) and payment (annuity payments coupled with an outcome-based agreement) have already been proposed.
- Another challenge is the pricing of combination treatments. The value of a drug combination is often less than the sum of the value of each component as a monotherapy. The application of simple rebates risks that companies do not receive the appropriate share of the total price in relation to the value of the treatment, which creates disincentives for future innovation. A potential solution is currently being tested in Sweden.
- The pricing of multi-indication treatments represents another challenge. The application of product-based pricing means that a medicine does not necessarily receive a price in relation to the value it provides in different indications. The solution is to switch to indication-based pricing in order to stimulate research and create appropriate incentives for future innovation. Such a change requires access to better data. Policy makers at both the national and the European level could help drive development in this direction though legislative action.

5.2 Background

Cancer care is a rapidly evolving area of health care. The medical progress reviewed in Chapter 3 demonstrated that a tremendous number of new technologies has been introduced in prevention, diagnostics, and treatment. The review also showed that the near future will see a continuation of this trend which has the potential of bringing great value to patients. However, the focus on the development of treatments for small groups of patients, the need for increased testing for selection of patients for treatment, and a need for combination treatments to achieve optimal outcome also significantly increases the costs per treated patient. Thus, issues related to cost-effectiveness are key for patients access to these new treatment options in different health care systems.

Cancer research is a prerequisite for future advances in cancer care. The first Comparator report in 2005 already highlighted the importance and nature of cancer research [1]. Funding of cancer research comes from different sources. During the last decade, the pharmaceutical industry has become the dominant source of funding for cancer research and development of new products. The return on investment in drug development is determined by the global spending of health care systems on cancer care. The pricing and use of new medicines are an important determinant of the magnitude and direction of the investment. This is discussed in section 5.3.

The analysis in Chapter 2 provided evidence of constant increases in the health expenditures spent on cancer care during the last two decades, but also of decreases in indirect costs related to premature mortality. Health economic analysis is important to inform about the value of new technologies to patients and taxpayers in relation to their costs. Apart from technology adoption, health economic analysis is also important for evaluations of the value-for-money of existing technologies [2]. Increasing efficiency of cancer care in order to both improve patient outcomes and increase value-for-money for patients and taxpayers should be a priority for health policy makers and is discussed in section 5.4.

Chapter 4 showed that spending on cancer medicines has increased greatly during the last decade. Affordability is an issue that might soon restrict patient access to effective (and potentially cost-effective) medicines even in high-income European countries. Two recent trends in cancer oncology are the introduction of CAR T-cell therapies and the increasing use of combination treatments and multi-indication treatments (see section 3.6). In relation to these trends, section 5.5 discusses new approaches for the valuation, pricing, and payment of cancer medicines in order to ensure continued incentives for future innovation and patient access to valuable medicines.

5.3 Cancer research

Research is fundamental for achieving improvements in cancer care. Investments in cancer research are undertaken in an international context and financed by public organizations (governments and the European Commission), private non-profit organizations (cancer charities financed by private donations), and private for-profit organizations (life sciences industry composed of medical technology companies and pharmaceutical companies).

R&D investment in basic research is often financed through public organizations and private donations that fund research activities at universities. R&D investment at a later stage is commonly financed through private companies that also carry out the research activities (clinical trials) in cooperation with the health care sector. Private companies' decision to invest in R&D is based on expected total costs and total revenue, and thus the magnitude and direction of research is dependent on health care systems' spending on new cancer medicines. Public and private funders both cooperate and compete in an international setting, making it difficult to disentangle their respective resources used and their contributions to creating value to patients.

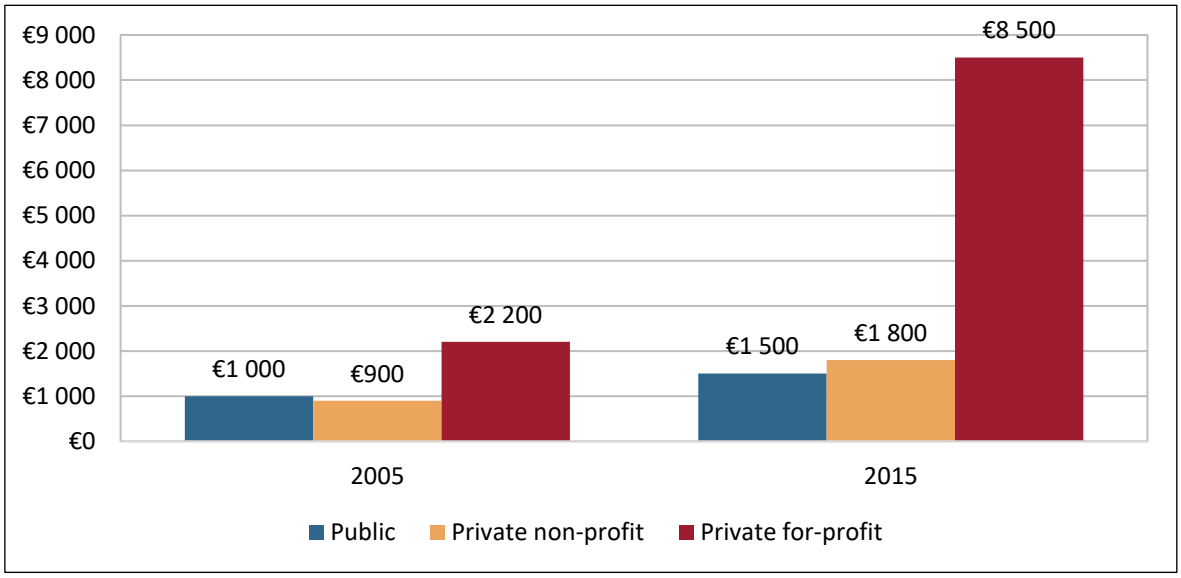

Figure 90: Funding for cancer research in the EU (in million €), 2005 & 2015 (or other available years)

Notes: Private for-profit funding in 2015 was estimated to lie between €8.5 and €13.5 billion. Source: [3].

During the last decade, R&D investment in cancer research by the life sciences industries, particularly the pharmaceutical industry, has grown much quicker than investments by public and private non-profit sources. This is illustrated in Figure 90, which shows rough estimates of public and private funding of cancer research in the EU in 2005 and 2015 [3]. In 2005, public and private non-profit funding was together about as high as private for-profit funding. Until 2015 funding from

all sources increased, but private for-profit funding increased the most and accounted for around three quarters of total funding. The massive increase in R&D spending by the life sciences industries is especially pronounced in the pharmaceutical industry and reflects a general trend not limited to cancer. While total R&D spending by the pharmaceutical industry in Europe was €8 billion in 1990, it more than doubled to €18 billion in 2000, and further increased to €28 billion in 2010 and €35 billion in 2017 [4].

Total global R&D spending by the pharmaceutical industry was USD ($) 179 billion in 2018 [5], of which cancer accounted for $72 billion (assuming a 40% share of total R&D directed to cancer). Half of this spending comes from companies in the US. As a comparison, total spending on public research by the National Institutes of Health (NIH) in the US was $36.6 billion in 2018 [6], of which $6.3 billion went into cancer [7]. The relation between public and industry spending on cancer research is thus about 1 to 6 in both Europe and the US.

The increase in private for-profit spending for cancer research is of great importance for the creation of innovative and valuable medicines for patients. However, it raises questions about the efficiency (see section 5.4.3) and long-term sustainability of this distinct shift in the mix of cancer research funding. All investments in cancer research must be motivated by the value it creates for patients and the health care system. While productivity measured as cost per new cancer medicine that comes to the market declined in the period 1995–2005, it has subsequently increased through an increase in the annual number of new cancer medicines approved [8]. However, the number of patients indicated for newer medicines has decreased which means that the value per patient needs to improve more for these newer medicines to be cost effective.

The nature of cancer research by pharmaceutical companies has also seen some noteworthy changes.

- A recent analysis showed that the number of oncology therapies studied in phase I/II trials and higher was relatively stable with around 500 therapies between 2008 and 2013. From 2013 until 2018, there was a large increase (63%) in the number of therapies studied to 849 in 2018. Targeted small molecule therapies and targeted biologic treatments stood for 91% of all therapies in 2018 and had increased their share since 2008 [9].
- The development of cancer medicines is not evenly spread across all cancer types. It thus does not reflect the burden of cancer in terms cancer incidence. For instance, Figure 41 in section 4.4.3 shows that 21 therapies were approved for leukemia between 2000 and 2018, corresponding to 19% of all approved therapies (113) in this period. This share greatly exceeds leukemia's share of total cancer incidence, which was only around 2–3% in Europe in 2018 [10].

- Competing research activities have become common, as there is no coordination of research. This has led to several cases of cancer medicines being approved in almost identical indications within a short period of time. Two examples are the approval of abiraterone, enzalutamide, and radium Ra223 dichloride in 2011–2013 for metastatic castration-resistant prostate cancer and the approval of palbociclib, ribociclib, and abemaciclib in 2016–2018 for HR-positive, HER2-negative advanced metastatic breast cancer. All of these medicines provide benefits to patients compared to the standard of care ten years ago, whereas this is less true when they are compared to each other. However, it is easier to match a medicine with patient need, as the medicines' adverse event profiles typically differ. In addition, increased competition might put downward pressure on prices.
- New medicines that have reached the market are often indicated for small patient populations (at least at launch). Figure 44 in section 4.4.3 shows a trend towards an increasing number of approved medicines with an orphan designation. However, CPI-based immunotherapies constitute an important exception. Both nivolumab and pembrolizumab have been indicated in many different cancer types since their approval in 2015; newer CPI therapies are also studied in a broad range of indications (see Chapter 3).
- A promising strategy for future research might be a stronger focus on the genetic origin of cancers. In September 2019, the first tumor-agnostic medicine (larotrectinib) received marketing authorization by the EMA for the treatment of solid tumors that display a certain gene fusion [11].

Cancer research in Europe might receive greater attention and funding from public sources in the coming years, which might re-balance the distribution of funding sources shown in Figure 90. At the European level, the newly elected European Parliament (EP) held debates on fighting cancer in the plenary week September 16–19, 2019. There was broad support across the political groups to make cancer a top priority. A special EP committee to fight cancer might also be established. The EP and the Council have also agreed to include cancer research under the Horizon Europe framework (the EU research & innovation investment program running from 2021–2027) which was earlier proposed to have a total budget of €100 billion [12]. In addition, the incoming health commissioner has been tasked to put forward "Europe's Beating Cancer Plan"[38], which indicates that the incoming Commission will continue to focus on fighting cancer.

[38] https://ec.europa.eu/commission/files/stella-kyriakides-mission-letter_en (accessed October 15, 2019)

5.4 Efficiency in cancer care

The review of the disease burden of cancer in section 2.3 showed that the burden in terms of mortality (26% of all deaths are due to cancer) and DALYs (20% of all DALYs are due to cancer) was high in 2016. The high disease burden stands in contrast to the comparatively low share of health care expenditure spent on cancer (around 4–7% in all countries), as shown in section 2.4. The low share of health expenditure in relation to the disease burden indicates a lack of effective treatments that can reduce the burden of cancer. This was historically also the case with ulcer disease, asthma, and cardiovascular diseases before the introduction of effective treatments. Even though health care expenditure spent on cancer might be considered comparatively low, it is still important to focus also on efficient spending of the current health resources.

5.4.1 Measuring efficiency in cancer care

The analysis of efficiency in health care is rooted in the microeconomic theory of the production of health care [13]. A production (or distance) function is used to describe how an output (e.g. a surgery to remove a tumor in a hospital) is produced using inputs (e.g. surgeons, nurses, medical equipment). Efficiency is defined as the ratio of outputs to inputs. If patient outcomes (e.g. survival) are considered instead of outputs, efficiency can be defined as the ratio of outcomes to inputs.

As efficiency is the ratio of outputs (or outcomes) to inputs, increases in efficiency can be achieved in various ways. For instance, if a change to robot-assisted surgery lowers the total number of inputs required to perform the same number of surgeries as before, efficiency has increased. Similarly, if survival of cancer patients increases after a fixed amount of resources has been re-allocated from PSA-screening to colorectal cancer screening, efficiency has increased. These examples also illustrate the fact that efficiency should not be confused with “effectiveness” and “cost containment”, as the former is only concerned about outputs/outcomes and the latter is only concerned about inputs. Furthermore, it should be noted that the concepts of efficiency and cost-effectiveness are closely related. Cost-effectiveness (e.g. costs per life year gained) is essentially the inverse of efficiency if inputs are equated with costs.

Figure 91 shows a simple way of relating inputs (in the form of health expenditure on cancer care; see section 2.4.1 on direct costs) to patient outcomes (defined as 5-year survival; see section 2.2.3) in cancer care. The total amount of health expenditure per capita spent on cancer is a crude measure, but it defines the fundamental boundaries with which health can be produced. Note that cancer-specific health expenditures refer to the year 2010 and survival to the period 2010–2014. Each dot in Figure 91 represents a country, and each graph contains an (unweighted) trend line.

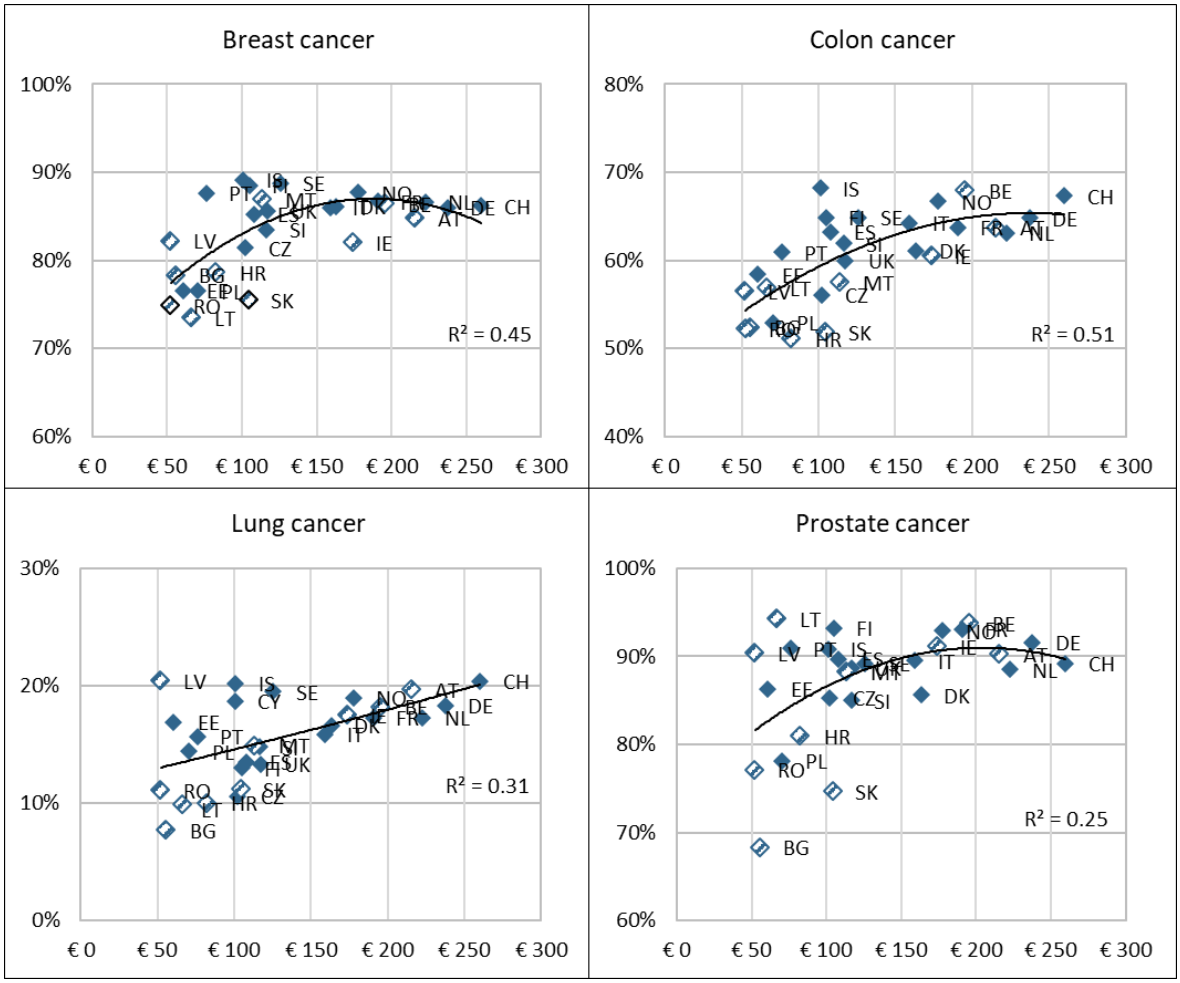

Figure 91: Cancer expenditure (in € per capita, PPP-adjusted) in 2010 and 5-year net survival (in %) in 2010–2014

Notes: Hatched dots indicate that the national estimate for cancer expenditure is based on data from similar countries; see Appendix for methodology. Cancer expenditure refer to total expenditure and not cancer type-specific expenditure. EL, HU, and LU are missing due to lack of survival data. CY is excluded in all cancer types except lung cancer due to low reliability of survival data [14].

Two important observations can be made in Figure 91.[39] First, adequate spending on cancer is a prerequisite for achieving high survival rates. The upward sloping trend lines in all four graphs, representing the four largest cancer types, indicate that countries with lower spending tend to record lower survival rates and countries with higher spending tend to record higher survival rates. The strength of this association differs between the four cancer types. Health spending on cancer seems to be more important for achieving high survival rates in breast cancer and colon cancer than in lung cancer and prostate cancer.

[39] Note that the associations in Figure 91 could potentially also be driven by some third factor (e.g. the level of education in a country) that is related to both the amount of cancer-specific health expenditure and survival.

Second, the relationship between spending on cancer and survival rates could be non-linear. For breast, colon, and prostate cancer, the quadratic trend line is increasing and has a concave shape, i.e. survival improves at a decreasing rate with higher spending. This indicates that each additional euro spent on cancer care improves survival rates, but the improvements for every additional euro spent become smaller the more euros that have already been spent. However, a linear trend line instead of the quadratic one would also provide a relatively high goodness of fit for the considered cancer types, which would indicate that incremental increases in survival do not diminish with additional spending.

Figure 91 also shows great variation in spending on cancer care between countries that achieve similar survival rates. For instance, the Netherlands and Spain both recorded a survival rate of 63 percent in colon cancer, but per-capita spending on cancer in the Netherlands (€223) was twice as high as in Spain (€108). This sort of variation indicates inefficiencies in cancer care, although it is a rather crude way of inferring inefficiencies.

A recent analysis by Althin et al. (2019) provides a more sophisticated analysis of efficiency in cancer care in Europe [15]. In this analysis, technical efficiency in cancer care is examined based on a sample of European countries. Technical inefficiency can take values from just above 0 (very inefficient) to 1 (fully efficient). It indicates how far away countries are from an efficiency frontier, where the frontier indicates the minimum number of inputs required to produce a certain amount of output or level of outcome. The efficiency frontier is based on a comparison of inputs and outputs for the different countries in the sample.

Table 11 summarizes the results in Althin et al (2019), who looked at the efficiency in breast cancer and lung cancer. For breast cancer, the analysis relates inputs (breast cancer screening rates, radiation units, number of oncologists, and use of breast cancer medicines in terms of volume) to 5-year net survival rates (outcomes). The results show that six countries (Czechia, France, Italy, Poland, Slovakia, and Slovenia) have an efficiency score of 1 and are hence efficient. The least efficient countries are Sweden and Denmark with efficiency scores of 0.65. Sweden produces the second-highest survival rate in this sample, but it is still considered inefficient, as Sweden uses more of all inputs than France but achieves the same survival rate as France. If Sweden utilized its inputs in the most efficient way, it would be able to produce the same survival rate with only 65% of the resources used.

Table 11: Technical efficiency in the production of 5-year net survival in breast cancer and lung cancer, 2015

	Breast cancer		Lung cancer	
	Survival (%)	Efficiency score	Survival (%)	Efficiency score
Belgium	82.7	0.82	15.4	0.77
Croatia	76.3	0.97	14.8	0.93
Czechia	78.0	1.00	11.5	0.83
Denmark	81.5	0.65	10.3	0.72
Finland	85.7	0.75	11.5	1.00
France	86.1	1.00	13.8	1.00
Germany	83.6	0.92	15.6	1.00
Ireland	79.0	0.72	11.8	0.75
Italy	85.5	1.00	14.3	0.61
Netherlands	84.5	0.74	13.4	0.85
Poland	71.6	1.00	14.4	1.00
Portugal	83.3	0.89	11.2	0.78
Slovakia	73.9	1.00	-	-
Slovenia	78.7	1.00	10.7	1.00
Spain	82.8	0.99	10.7	0.68
Sweden	86.0	0.65	14.7	0.70
UK	79.2	0.86	9.0	0.54

Notes: Efficiency scores can range from 0 (inefficient) to 1 (efficient). Source: [15].

For lung cancer, the analysis relates inputs (radiation units, number of oncologists, number of pulmectomies, and use of lung cancer medicines in terms of volume) to 5-year net survival rates (outcomes). The results in Table 11 show that five countries (Finland, France, Germany, Poland, and Slovenia) have an efficiency score of 1 and are hence efficient. The least efficient country is the UK with an efficiency score of 0.54. Poland, which used the lowest number of radiation units and the lowest amount of lung cancer medicines, managed to produce an above average survival.

The analysis in Table 11 highlights that (1) countries can achieve good patient outcomes but still operate at an inefficient level, and (2) countries with poorer patient outcomes can still be efficient. To summarize, the aim for health policy in cancer care should be to improve patient outcomes and at the same time to strive to enhance efficiency. Countries that are already operating at a level close to efficiency should continue to invest in cancer care. Countries with inefficient cancer care should also prioritize adjusting their mix of inputs and invest in areas where the greatest efficiency gains can be expected.

5.4.2 Improving efficiency in cancer care

A tool to identify opportunities to improve efficiency is a National Cancer Control Programme (NCCP). According to the WHO, an NCCP should aim to reduce incidence, morbidity, and mortality of cancer and improve the quality of life of cancer patients through the systematic implementation of evidence-based interventions for prevention, early detection, diagnosis, treatment, rehabilitation, and palliative care [16]. By applying a holistic approach (instead of focusing on specific areas), it can support an efficient and rational use of available resources. In practice it might however be difficult to follow the WHO principles as solid evidence on the (cost-)effectiveness of different interventions are often lacking. A recent analysis showed that 25 out the 28 EU countries have an NCCP; only Bulgaria, Croatia, and Slovakia are lacking one [17]. However, NCCPs vary in their scope and goals.

A national population-based cancer registry is necessary (though not sufficient) to monitor the effects of resources devoted cancer care. Without a careful registration of newly diagnosed cases it is impossible to draw conclusions on the effects of disease prevention and on the effectiveness of interventions to increase survival. A national cancer registry also facilitates comparisons of regions within a country and comparisons with other countries. According to the WHO, most of the considered 31 European countries had a national population-based cancer registry in 2014. France, Germany (started to establish a nationwide registry in 2013), Italy, Romania, Spain, and Switzerland (will have a nationwide registry by 2020) had population-based registries that only covered certain parts of the country, while Greece had a national hospital-based registry [18]. A general problem with cancer registries is that they often do not report which treatments are given to different patients and cancer types.

Measures to improve efficiency in cancer care can be found in all areas along the patient pathway and beyond. In the area of primary prevention, measures for tobacco control to reduce tobacco consumption and exposure to tobacco smoke are crucial. Tobacco consumption is the single largest avoidable health risk, and the most significant cause of premature death (mostly due to cancer) in the EU [19]. The share of daily smokers in the adult population (15+ years) in 2017 (or nearest year) ranged from around 10% in Iceland, Norway, and Sweden to 25% in Austria, Greece, Hungary, and Latvia [20]. On the EU level, the Tobacco Products Directive (2014/40/EU) became applicable throughout the EU on May 20, 2016. The Directive lays down rules governing the production, presentation, and sale of tobacco and related products [19]. On the country level, measures such as raising tobacco taxes, implementing laws on smoke-free public spaces, banning advertising, promotion, and sponsorship of tobacco, and implementing cessation programs can be taken.

HPV vaccination programs have been shown to lead to substantial decreases in HPV infections, cervical intraepithelial neoplasia grade 2+, and anogenital wart diagnoses among girls, women, boys, and men [21]. The European Centre for Disease Prevention and Control (ECDC) has already in 2008 summarized evidence on the cost-effectiveness of HPV vaccination for girls/women [22]. It concluded that "*[e]conomic evaluations made to date seem to indicate that HPV vaccination of pre-adolescent girls (with or without catch-up of older age groups) has an acceptable cost-effectiveness profile*." Whereas Belgium, France, and Germany quickly implemented population-based vaccination programs for girls already in 2007, Estonia did so only in 2018 and Poland is the only EU country still lacking a program [23]. In its 2012-report, the ECDC concluded that vaccination programs for boys were "*unlikely to be cost effective in the current economic conditions*" [24], whereas the latest report from 2019 indicated it to be a cost-effective option. Austria was first to adopt the program for boys in 2014, followed by Croatia in 2016, and several other countries in 2018–2019, but most countries are still lacking a program [23].

In the area of screening, the Council of the European Union adopted a recommendation (2003/878/EC) to member states on implementing cancer screening programs for three cancer types; breast, cervical, and colorectal cancer. The recommendation was issued in 2003, but in 2016 only 21 of the 28 EU member states had fully implemented population-based programs for breast cancer, 8 countries a population-based program for cervical cancer, and 5 countries a population-based program for colorectal cancer [25]. This pattern does not fit well with evidence on the cost-effectiveness of such programs. Colorectal cancer screening programs are not only highly cost effective, they might also be cost saving [26, 27]. Screening for cervical cancer has also a favorable cost-effectiveness profile [28], although HPV vaccination might worsen the cost-effectiveness in future generations due to the reduction in the incidence of cervical cancer. Breast cancer screening is considered the least cost effective of the three programs [29]. Prostate cancer screening is widely used but it was not recommended by the Council, since, despite its benefits, it also causes harms through over-detection and over-treatment. The cost-effectiveness of prostate cancer screening is still unclear [30]. Modern lung cancer screening with LDCT might be cost effective (at a rather high cost-effectiveness threshold) in European countries with high smoking prevalence [31], similar to findings for the US [32], but unlike findings for Australia where it was not found to be cost-effective [33].

In the area of diagnostics and treatment, short waiting times and high-quality care are important [34]. There have to be well-defined referral paths (based on patient symptom status) from the general practitioner's office to diagnostic clinics/hospital care. An adequate provision of facilities to provide swift and accurate diagnoses (using CT, MRI, and PET-CT scanners) needs to be well aligned with the number of available pathologists. Similarly, adequate staffing in oncology clinics with health care professionals (surgeons, radiologists, oncologists, hematologists, nurses) needs to be well

aligned with the availability of radiation therapy equipment, cancer medicines, and the number of care places in ambulatory and inpatient care.

5.4.3 Cost-effectiveness of cancer medicines

Cancer medicines constitute a growing share of the total health expenditure devoted to cancer care; see section 4.5.2. Over one fourth (31%) of all cancer-specific health expenditure were spent on medicines in Europe in 2018. However, this development does not seem to have affected the share of total health expenditure spent on cancer. Cancer-specific health expenditure have increased mostly in line with the overall increase in health expenditure in the past decades. An explanation for this trend is that there has been a decrease in the number and length of hospitalizations due to cost-containment in health services. New treatment options in cancer that can be cost-effectively delivered in ambulatory care may also have contributed to the trend. There has, for instance, been a shift from intravenous to oral delivery methods of cancer medicines, especially for medicines approved between 2000 and 2014; see Figure 45 in section 4.4.3. As more patients could receive treatment at home, this might have decreased the demand for inpatient and ambulatory care. Improved management of the side effects of cancer medicines might also have decreased the demand for inpatient and ambulatory care.

The possibility of cost savings in other areas of cancer care (inpatient and ambulatory care) to offset the growing expenditure on cancer medicines might be exhausted soon. As shown in Figure 24 in section 2.4.1.5, cancer medicine expenditures already account for more than half of all cancer-related health expenditure in some countries. The potential of further cuts to hospital beds has probably already been exhausted in some countries. Importantly, the introduction of cancer immunotherapy medicines increases the need for inpatient and ambulatory care again. These medicines are given through intravenous delivery methods at hospitals and they have often more severe side effects than targeted cancer medicines, which requires additional monitoring at hospitals. In addition, CAR T-cell therapies (the first two were approved in 2018) require additional investment in the physical health care infrastructure. Health care professionals require special training and hospitals need to obtain approval to administer these therapies. Patients must be closely monitored for 10 days after treatment for side effects and are advised to stay close to a specialist hospital for at least 4 weeks after treatment.

The aim of increasing efficiency in cancer care entails an increasing focus on the cost-effective use of cancer medicines. The cost-effectiveness of new cancer medicines has always been an important feature for reimbursement decisions in Europe. The development described above will undoubtedly reinforce the focus on the cost-effectiveness in the future. In addition, the increasing number of

medicines, which often are used in combination and sequence, creates more alternative uses of resources which needs to be evaluated in terms of costs and effectiveness.

For new medicines there is a well-known trade-off between providing early access and providing evidence on value to patients [35, 36]. The aim of providing timely access to promising therapies is uncontroversial, but public payers also have to ensure value-for-money for patients and taxpayers. Regulatory approvals of cancer medicines by the EMA naturally have to be made based on clinical data that involve a great amount of uncertainty about the effects in clinical practice. Clinical data used for approval are not always based on RCTs, often because of small patient populations. In addition, outcomes in clinical trials are often based on surrogate endpoints instead of patient-relevant outcomes such as OS [37]; see also section 3.8. Several studies have systematically examined the efficacy of cancer medicines approved by the EMA. An analysis of 48 medicines for 68 indications approved in 2009–2013 showed that most medicines were approved without evidence of benefit on survival (65% of all indications) or quality of life (90%), and even after a post-marketing period of at least three years no conclusive evidence on these outcomes had emerged for 49% of all indications [38]. An analysis of medicines for use in solid tumors approved in 2011–2016 showed that only 21% provided a meaningful clinical benefit (MCB) based on the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) at the time of approval [39]. Another analysis of medicines approved in 2009–2015 with initially ambiguous benefit-risk profiles showed that one third of the medicines lacked evidence on improved survival even after a post-marketing period of at least three years [40].

The development of value scales for cancer medicines, such as ESMO-MCBS, is a sign of the need for additional information for both clinical and policy decisions [41]. Uncertain data at the time of regulatory approval do not imply that a medicine is not cost effective, but it complicates the evaluation of the medicines' cost-effectiveness. Given the uncertainty at launch, there needs to be better monitoring systems to reduce uncertainty over time (such as collection of RWD; see section 3.9) and to share the risk between payers and manufacturers. The willingness to enter into such risk-sharing agreements is also important. The Cancer Drugs Fund (CDF) in England and the Authorization of Temporary Usage (ATU) in France are examples of systems of coverage with evidence development to address the early access vs. evidence trade-off. Section 5.5.1 addresses the special case of uncertainty surrounding CAR T-cell therapies and ways to address it.

There is also a need to establish guidelines and a monitoring system for drug usage over time. This could support the cost-effective use of medicines. Instead of providing equal access to all approved medicines, countries ought to put a stronger focus on providing greater access to the most valuable and cost-effective medicines and make access to medicines that have not yet been proven to be cost

effective conditional on appropriate follow-up. The responsibility for establishing the necessary infrastructure for this cannot be left to industry alone but needs to be shared between stakeholders to achieve economies of scale. Health care systems also need to have established procedures for decommissioning of older treatment options that are no longer cost effective.

The introduction of personal/precision/stratified medicine, which refers to the classification of patients according to disease risk or likely therapeutic response as determined by diagnostic markers, makes it both more important and more difficult to assess the cost-effectiveness of cancer medicine [42]. It makes it more important because there are an increasing number of potential diagnostic/treatment pathways with different costs and outcomes that must be considered. It makes it more difficult because it is not possible to undertake clinical studies of all potential alternatives and thus results will come with a high degree of uncertainty.

A number of targeted therapies with companion diagnostics have been introduced over the last decades (e.g. trastuzumab and HER2-positive breast cancer, crizotinib and ALK-positive NSCLC), but with the introduction of next generation sequencing (NSG) both the number and costs of new tests have increased, as well as the complexity in interpreting and making decisions on the information they provide. The English HTA agency (NICE) has recently provided guidance for use of tumor profiling tests (EndoPredict, IHC4, MammaPrint, and Prosigna; cost of around €250–3000 per test) to guide adjuvant chemotherapy decisions for people with ER-positive HER2-negative and LN-negative early breast cancer [43]. The Swedish HTA agency (TLV) has published recommendations for FoundationOne CDx, an NGS test for changes in 324 genes for guiding treatment of several solid tumors including breast cancer and NSCLC [44]. TLV's conclusion was that no cost-effectiveness study could be performed due to the large number of alternatives, and the recommendation was based on a cost comparison instead. The price of FoundationOne CDx in Sweden was €2,000 per test. In TLV's health economic analysis, the cost of using FoundationOne CDx at the company's price was higher than the cost of standard methods in all evaluated tumor types in situations where MSI was not analyzed or analyzed by immunohistochemistry or PCR. In cases where an initial assessment of MSI with immunohistochemistry was complemented by PCR, the cost of FoundationOne CDx was lower than the cost of standard methods in the NSCLC, breast cancer, and cancer of unknown primary.

With the lack of data for assessment of diagnostic/treatment strategies, it is generally concluded that there is a need for data collection in clinical practice. So far, most health care systems do not record the relevant data. Registries and linkable administrative data sets will become more important, including data on patient and clinician behavior following the results of diagnostic tests and associated patient outcomes.

An important future way to support a cost-effective use of medicines is the use of biosimilars and generics. In 2017, the EMA approved the first biosimilars for rituximab and trastuzumab, followed by the first biosimilar for bevacizumab in 2018 [45]. As shown in Table 7 in section 4.6.1, these three medicines accounted together for around 15% (or €4.9 billion) of the total cancer medicine sales in Europe in 2018. There is thus a large potential of savings if realistic price reductions of 30–60% compared to the original product can be assumed [46]. Figure 92 illustrates the potential cost savings from biosimilars for the three above-mentioned medicines. Based on sales in 2016 (i.e. before the first biosimilars were approved), there are potential cost savings of €2.4 billion in Europe per year if a 45% price reduction is assumed.

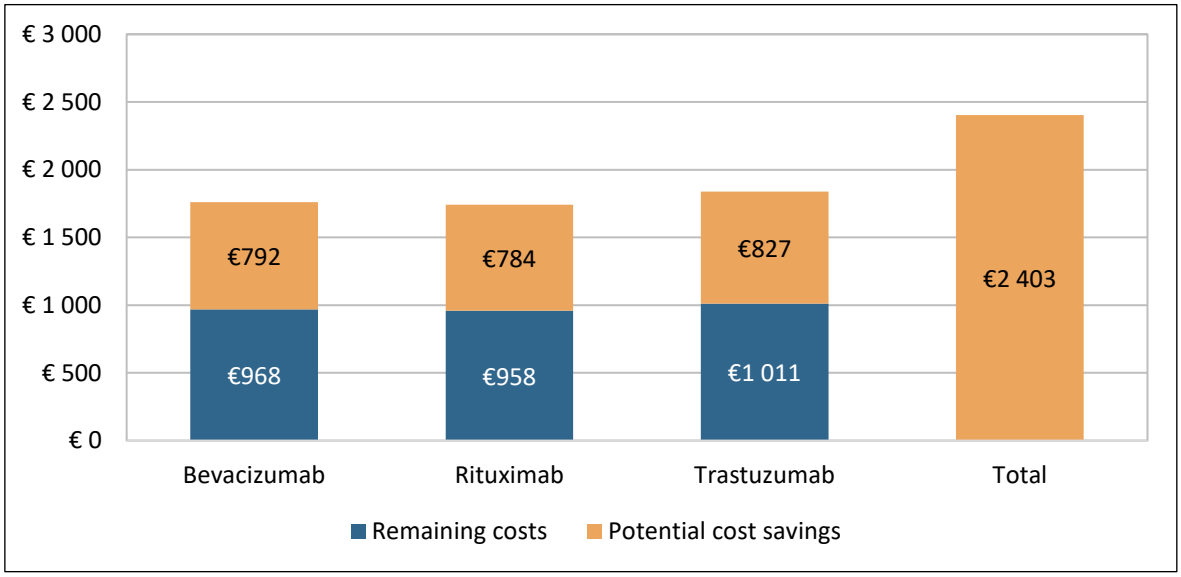

Figure 92: Potential cost savings from biosimilars (in million €) in Europe (based on sales in 2016 and a 45% price reduction)

Source for sales data: [47].

The key will be to introduce biosimilars in clinical practice on a broad basis to fully realize the cost savings. Especially in countries with lower access to these medicines (mostly Eastern Europe), some of the savings will probably be used to treat more patients with these medicines. The remainder of the savings ought to be invested into innovative medicines that are cost effective but that previously seemed unaffordable for a larger share of patients.

5.5 Novel approaches to pricing, valuation, and payment of cancer medicines

Health technology assessment (HTA) of new medicines has become imperative for informing reimbursement and coverage decisions in European countries in recent decades. An economic

evaluation of the new medicine forms a crucial part of the HTA. The price of the new medicine has immediate consequences for the cost-effectiveness and the budget impact of the medicine.

A key challenge for access to new medicines is to balance price, value, and companies' costs for R&D, production, and distribution. The past two decades has seen an unprecedented increase in the development and introduction of effective cancer medicines, and the prices of medicines have also increased over time [9, 48]. Higher prices reduce cost-effectiveness and restrict patient access even if medicines' effectiveness and value also increase. A reason for high prices is the financing of sunk costs for R&D, and today most of the financing for cancer drug development comes from richer countries, predominantly the US, which account for the majority of sales. A lower price that would allow for more use of a medicine in poorer countries or for indications with lower value could still support the financing of fixed costs and of investment in drug development. We can see this reflected in lower prices in Europe than in the US, and greater discounts on list prices for European countries with low income per capita, and different mechanisms for adjusting prices to volumes in non-disclosed contracts with payers.

Patient access to cancer medicines in Europe correlates with countries' economic strength as public payers cannot always afford to reimburse new medicines; see section 4.7 which highlights consistently lower levels of access in poorer countries in Eastern Europe. In the absence of public payers providing access to new medicines, well-off patients may be able access these medicines using their own money (out-of-pocket payments). A recent analysis showed that there was widespread availability of either free or highly subsidized access to new cancer medicines in Western European countries, whereas many medicines (even those on the WHO Model List of Essential Medicines) were either unavailable or only available at full cost to patients in Eastern Europe [49]. This troublesome situation means that a large share of European cancer patients cannot gain access to effective medicines due to due to high prices and resulting low cost-effectiveness in their health care systems. It also means that differences in survival based on socio-economic status might increase in countries with restrictive access to new medicines.

Below we discuss two recent trends in cancer oncology; curative one-off treatments (CAR T-cell therapy) as well as combination treatments and multi-indication treatments. These trends require novel approaches to pricing, valuation, and payment of cancer medicines.

5.5.1 CAR T-cell therapy

August 2018 marked a new era in cancer treatment in Europe with the approval of the first two CAR T-cell therapies; axicabtagene ciloleucel and tisagenlecleucel. These cell-based therapies are

completely different from previous cancer medicines. As opposed to all other types of cancer medicines (chemotherapy, targeted therapy, hormone therapy, CPI-based immunotherapy), CAR T-cell therapies only require a single treatment. In addition, these therapies can be expected to lead to complete remission (i.e. cure) in a large share of patients and thus create long-lasting positive effects on both patient health and health care costs.

CAR T-cell therapies are a rapidly expanding field of research. In March 2019, there were at least 302 active agents for CAR-T being tested in phase I to phase III trials globally, compared to 208 agents just one year before [50]. The expected influx of new agents presents a new challenge to health care systems. A recent report by Persson et al. (2019) has highlighted the main challenges for the valuation and payment of advanced therapy medicinal products (ATMPs) to which CAR T-cell therapies belong [51]. A summary of the main points is provided below.

Current methods for the valuation of medicines are not unfit for the valuation of curative one-off treatments, but they need to be adapted. There are at least three reasons for this:

- Current valuations do not assign a special value for curative therapies. This stands in contrast to studies that have highlighted a higher willingness-to-pay for curative therapies in cancer care and other sectors [52-56]. For instance, a treatment offering a risk reduction of 10 percentage points is valued to be worth more if the initial risk is 10 percent and thus can be eliminated than if the initial risk is 20 percent and thus can be reduced to 10 percent.
- The current method for calculating gains in the number of life years is based on an estimate of a survival function based on survival data from the clinical trial. This technique is not suitable for curative therapies because the proportion of patients who have been cured can be expected to return to the same risk of mortality as the general population. Graphically speaking, this means that the survival curve reaches a plateau instead of trending towards zero. Parametric models (e.g. Weibull, exponential, log-logistic) merely using survival data from the clinical trial are ill-equipped to capture these long-term health effects when estimating the survival function.
- Curative one-off treatments are associated with greater uncertainty than curative continuous treatments. First, there is greater uncertainty about whether the curative effect really persists over time. Second, there is greater uncertainty about future treatment alternatives. For instance, if a second-generation curative treatment is approved three years after the first curative treatment, the true cost for the current non-curative treatment will become three years of current treatment plus the subsequent (currently unknown) curative treatment and not the cost of a life-long treatment with the current non-curative treatment.

The three challenges for an appropriate valuation can be addressed in the following way:

- A risk elimination premium for curative treatments should be applied. This means that a higher cost-effectiveness threshold can be accepted if a treatment leads to cure.
- Mixture cure models should be applied to estimate the long-term health effects. This will better capture the share of patients that are cured and will increase the estimated life years gained (or QALYs) compared to current models. This means that the incremental cost-effectiveness ratio (ICER) will decrease.
- A higher discount rate should be applied to curative one-off treatments than to curative continuous treatments to address greater uncertainty. This means that the ICER will increase as future health gains are discounted more heavily.

The current payment model in health care system characterized by public budgets is not adequate for curative one-off treatments for the following three reasons:

- The current payment model for new medicines is based on payments being made during the time the treatment is given. For curative one-off treatments, this would mean that payment for a large value realized over a long period of time has to be made during a short period of time. This can lead to an affordability barrier, where a medicine can be cost effective but not possible to pay for under the current payment model.
- There is considerable uncertainty regarding what the payer pays for. There may be limited possibilities for making full-fledged RCTs in small patient populations and the approval often takes place at an early stage (i.e. fast track) while the full effects can only be measured after several years.
- Incentives for the introduction of curative one-off treatments can be negatively affected by the fact that the region (or country or sickness fund) paying for the treatment cannot ensure that it receives the positive health care benefits because the patient can move to another region/country/sickness fund.

Several innovative payment models can address these three challenges [57]. First, a separate fund for curative one-off treatments can be established or flexible budgets applied. The CDF in England is an example for a separate fund intended to pay for medicines with great uncertainty, and it also includes outcome-based agreements between the supplier and the NHS to handle uncertainty [58]. In France, Germany, and Italy there is a possibility to expand the budget to pay for innovative treatments that lead to high costs [59]. Second, annuity payments are intended to align payments for the treatment better with the time when the health benefits are realized [60, 61]. The high costs of the treatment thus can be spread out over a longer period which makes them easier to handle for payers. The yearly

payments could also be made conditional on persistence of the health effect. Third, a reinsurance risk pool that is filled by all payers in a country, who contribute with a certain share of their budget, can be established. The pool reimburses payers for selected high-cost medicines. This helps to spread the risk of high payments for single payers.

For the case of CAR T-cell therapies, which are currently characterized by small patient populations, Persson et al. (2019) propose annuity payments with an outcome-based agreement [51]. Through an annuity payment scheme, the costs are split up into yearly payments under a longer period of time. The outcome-based agreement splits the risk of unknown outcomes between the supplier and the payer, which reduces uncertainty regarding future effects and costs. If CAR T-cell therapies were to be developed for larger patient populations, the administrative burden of following up every patient becomes too burdensome. For this case, Persson et al. (2019) propose flexible budgets, which do not require patient follow-up [51]. Such a system might be complemented with a reinsurance risk pool between regions/sickness funds. Uncertainty can be handled through a financial agreement on the national level between the supplier and the payer.

5.5.2 Combination and multi-indication treatments

Combination treatments and multi-indication treatments are two developments in oncology that are expected to grow in the future. The pharmaceutical industry has invested heavily into combination treatments. As described in section 3.6, there were 1,716 clinical trials assessing different combinations of PD-1/PD-L1 agents with other therapies such as standard chemotherapies and targeted therapy in September 2018 [62]. Despite some early setbacks (see section 3.6.3), a number of these combinations are likely to succeed. Similarly, many cancer medicines are effective in multiple indications. More than 50 percent of the major cancer medicines marketed in 2014 were approved in multiple indications, and this share is estimated to grow to 75 percent in 2020 [63]. The dilemma that these products create for the pricing and reimbursement systems is well known [64].

For combination treatments, a central health economic dilemma is how to attribute the value of the combination to its different components. Often, the value of the combination will be less than the sum of the value of each component as a monotherapy; see Figure 93. From a legal perspective, EU competition law prevents two companies to discuss and agree on a common price strategy for a combination. Also, the increasing numbers of combinations and multi-indication treatments in the pipeline risk creating an administrative bottleneck for patient access, as the authorities will constantly have to negotiate and keep track of an ever-growing number of managed entry agreements.

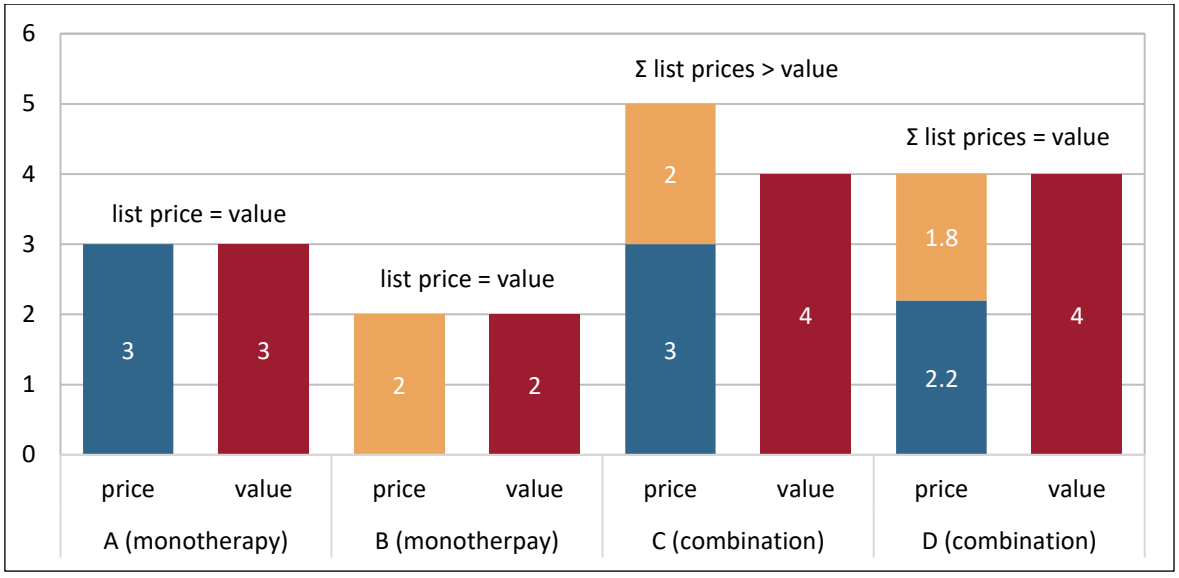

Figure 93: Schematic illustration of the value and price of monotherapy (with either medicine A or B) and combination therapy (C or D consisting of A and B)

For multi-indication treatments, pricing and reimbursement systems with one single price for a particular medicine (product-based pricing) are insufficient to meet the conflicting policy objectives of access, efficiency, and cost control. If the price of a medicine with varying value in multiple indications is set based on the high-value indication, the price may be too high to be cost effective in lower-value indications. As a result, the treatment will not be reimbursed for these indications and patients will not get access to the treatment. Manufactures may be discouraged from applying for regulatory approval in markets where the price is based on the lower-value indication and they may be discouraged from developing new medicines in the long run [64].

So far, few scalable solutions have been forthcoming for combination treatments. In Switzerland, Interpharma piloted a model in 2017, where the industry association facilitated negotiations between payers and the concerned companies to reach an agreement [65]. After negotiating two combination therapies, they concluded that such an approach is too cumbersome and not scalable to the extent needed to meet the R&D pipeline. In France, the authorities set a price unilaterally for the combination of which each company then gets a 50 percent share (in case of two components). Though simple and arguably scalable, the French approach is quite unsatisfactory from a health economic perspective. In every occasion, one of the companies is likely to get less than the "fair" share for the value of the treatment. This will create strange incentives for future innovation and have a detrimental effect on the industry's willingness to bring new combinations to the market.

The testing of an innovative approach to combination pricing was announced by the Dental and Pharmaceutical Benefits Agency (TLV) in Sweden in July 2019 [66]. The pilot program uses a

technical platform where payers and industry can make contingent commitments, expressing individually to the system their willingness to pay or provide a combination therapy. The solution takes inspiration from the financial market where similar platforms are used for trading of various financial instruments, commodities, etc. The platform provides an infrastructure to implement both simple rebates and price/volume agreements as well as more elaborate outcome-based arrangements. The project has garnered considerable interest, with both industry and payers participating. A first pilot, involving atezolizumab and bevacizumab, will be conducted during fall 2019 to explore how the platform can be incorporated into the Swedish pricing & reimbursement process.

Importantly, this approach has been endorsed by the Swedish Competition Authority. In a statement from May 2019 [67], the Authority recommends that TLV sets up such platform. It adds that the process should be regulated to prevent unilateral actions which could limit competition. The platform should also help reduce the administrative burden for payers and provide an infrastructure to manage the increasing number of agreements. Furthermore, the platform could be used to support the development towards indication-based pricing, where payers and manufacturers need to manage and keep track of multiple, parallel agreements (with different prices and conditions) for the same product.

All emerging solutions require access to data to work. Better data access is needed to effectively support the implementation of both indication-based pricing and pricing of combination treatments. As a minimum, data are needed which can distinguish consumption between various indications and combinations. Much of this infrastructure has to be put in place at the level of the payer (country or regional level). Indeed, the countries which today implement indication-based pricing are countries which have the necessary data infrastructure in place, such as Estonia and Belgium. However, the European Commission could help improve the situation by revising the Commission Implementing Directive (2012/52/EU) laying down measures to facilitate the recognition of medical prescriptions issued in another member state, requiring all prescriptions to incorporate information on indication and whether the medicine is intended to be taken in combination with others. From a pricing policy perspective, national legislation needs to be put in place that allows a product to exist on the market with different prices for different indications and therapeutic regimes (monotherapy or various combinations).

5.6 Summary and conclusions

Research is fundamental for achieving improvements in cancer care. R&D investment in basic research is often financed by public and private non-profit organizations, whereas research at a later stage is commonly financed by private for-profit organizations. During the last decade, R&D

investment in cancer research by the pharmaceutical industry has grown much quicker than investments by public and private non-profit sources. This has resulted in a distinct shift in the mix of cancer research funding which raises questions about efficiency and long-term sustainability. However, cancer research in Europe might receive greater attention and funding from public sources in the coming years by the new European Commission.

A value-based health care system assures that patients and taxpayers receive value-for-money. The aims for health policy in cancer care are therefore no different from those in other disease areas. Health care systems need to weigh the costs from investing in different areas of cancer care against the potential improvements in patient outcomes. This will ensure that scarce resources are used in a cost-effective and efficient way.

How can cancer care be made more efficient? First of all, there is a positive association between health expenditure on cancer care (inputs) and survival (outcomes), but there are variations in efficiency in cancer care both between and within countries. Countries whose cancer care can be considered efficient should continue to invest in cancer care in order to improve outcomes. Countries with inefficient cancer care should also prioritize adjusting their mix of inputs and invest in areas where the greatest efficiency gains can be expected.

Improving efficiency and outcomes should be central aims of the planned “Beating Cancer Plan” by the European Commission. Important tools for identifying opportunities and monitoring efficiency of cancer care are (1) a National Cancer Control Programme that assumes a holistic approach covering all key stages of the disease (prevention, diagnosis, treatment, rehabilitation, and palliative care) and (2) a nationwide population-based cancer registry. Most European countries have implemented both tools by now, although their scope may differ between countries. However, most countries still lack comprehensive accounts on health care spending on cancer which would allow studies that can link spending and outcomes within and between countries.

Primary prevention and screening are two areas where all European countries still have a long way to go. Stringent measures for tobacco control often only require political willpower but no public money. HPV vaccination programs for girls and boys are cost effective but not fully implemented (especially for boys) in many countries. A cost-effective use of resources for screening programs requires spending on colorectal cancer, cervical cancer, and breast cancer (in this priority order), whereas the actual implementation/prioritization has followed the opposite order in most countries. The cost-effectiveness of both prostate cancer screening and lung cancer screening is currently not well established.

Access to cancer medicines is important for improving patient outcomes. Yet medicines constitute a growing share of the total health expenditure spent on cancer care. Increasing medicine expenditure have so far been offset by decreases in expenditure in other areas. A shift from intravenous to oral delivery methods and fewer side effects of targeted therapies has decreased the demand for inpatient and ambulatory care. The possibility to offset increasing medicine expenditure will soon be exhausted. In addition, the introduction of immunotherapy (including CAR T-cell therapy) has again increased the need for care places in inpatient and ambulatory care for the management of side effects.

There will be stronger focus on the cost-effectiveness of new cancer medicines in the future. There is, however, a trade-off between providing early access to new medicines and providing evidence on value to patients based on information from large-scale RCTs. Previous analyses have shown that many medicines approved by the EMA lack evidence of additional value to patients – not just at the time of approval but also during the first years of the post-marketing period. The development of value scales, such as ESMO-MCBS, is a sign of the need for additional information for both clinical and policy decisions. Given uncertain data on effectiveness at the time of approval, there needs to be better monitoring systems to reduce uncertainty over time (via collection of RWD) and to share the risk between payers and manufacturers.

Better monitoring system of medicine usage in clinical practice can support a cost-effective use of medicines. Instead of providing equal access to all approved medicines, countries ought to put a stronger focus on providing greater access to cost-effective medicines and make access to medicines that have not yet been proven to be cost effective conditional on appropriate follow-up. Another important way to support a cost-effective use of medicines is the use of biosimilars and generics. Cost savings from the use of biosimilars and generics create financial scope for investing into innovative medicines that are cost effective but that previously seemed unaffordable for a larger share of patients.

A key challenge for access to new medicines is to balance adequate reimbursement for the value of new medicines against affordability. The affordability and cost-effectiveness of new medicines keeps decreasing due to higher costs per treated patient. A large share of European cancer patients, especially in Eastern Europe, cannot gain access to effective medicines due to high prices and resulting low cost-effectiveness in their health care systems. In the absence of public payers providing access to new medicines, well-off patients may be able to seek access to these medicines using their own money, which will increase socio-economic differences in survival.

A recent development in cancer oncology is the introduction of CAR T-cell therapies. These therapies require only a single treatment and might lead to cure in a large share of patients. However, they come at a high price, necessitate special training of health care professionals, and hospitals need to obtain approval. Therapies consisting of a one-off treatment that leads to cure require an adaption of current methods for valuation and payment. Feasible solutions for the valuation (use of a risk elimination premium, mixture cure models, and a higher discount rate) and payment (annuity payments coupled with an outcome-based agreement) have already been proposed in order to ensure patient access.

Another recent development in cancer oncology is the use of combination treatments and multi-indication treatments. The value of a drug combination is often less than the sum of the value of each component as a monotherapy. Two simple solutions are to apply the same rebate (e.g. 10%) to the price of each component or to determine a price for the combination and then split the price into equal parts for each component. However, this is quite unsatisfactory from a health economic perspective, as companies risk not receiving the appropriate share of the total price in relation to the value of the treatment, which creates disincentives for future innovation. A platform where payers and industry can make contingent commitments, expressing individually their willingness to pay for providing a combination therapy, might be a potential and scalable solution.

Product-based pricing for multi-indication treatments is insufficient to meet the conflicting policy objectives of access, efficiency, and cost control. Instead, indication-based pricing is needed to assign a medicine the correct price in relation to the value it provides in different indications. This is important for stimulating research and creating appropriate incentives for future innovation. However, indication-based pricing requires access to better data and regulatory changes at the national level to enable a product to exist on the market with different prices. At the European level, policy makers could support the development of indication-based pricing through a revision of the Commission Implementing Directive (2012/52/EU) in order to have all prescriptions incorporate information on indication and whether the medicine is intended to be taken in combination with others.

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Appendix

A.1 Chapter 2

A.1.1 Age-standardized incidence rates

Age-standardized incidence rates for men and women are shown in Figures A1 and A2. These rates take into account different population sizes and age structures of the populations, but do not control for other important factors such as the underlying development of risk factors and screening. For instance, countries with more screening programs (e.g. for cervical cancer, breast cancer, colorectal cancer, prostate cancer, or lung cancer) or with higher participation rates in these programs might record higher incidence rates than other countries, because more cancer cases can be detected. In the same manner, an increase in incidence rates over time within a country might reflect higher screening activities leading to the detection of more cancer cases rather than a true increase in the number of new cases.

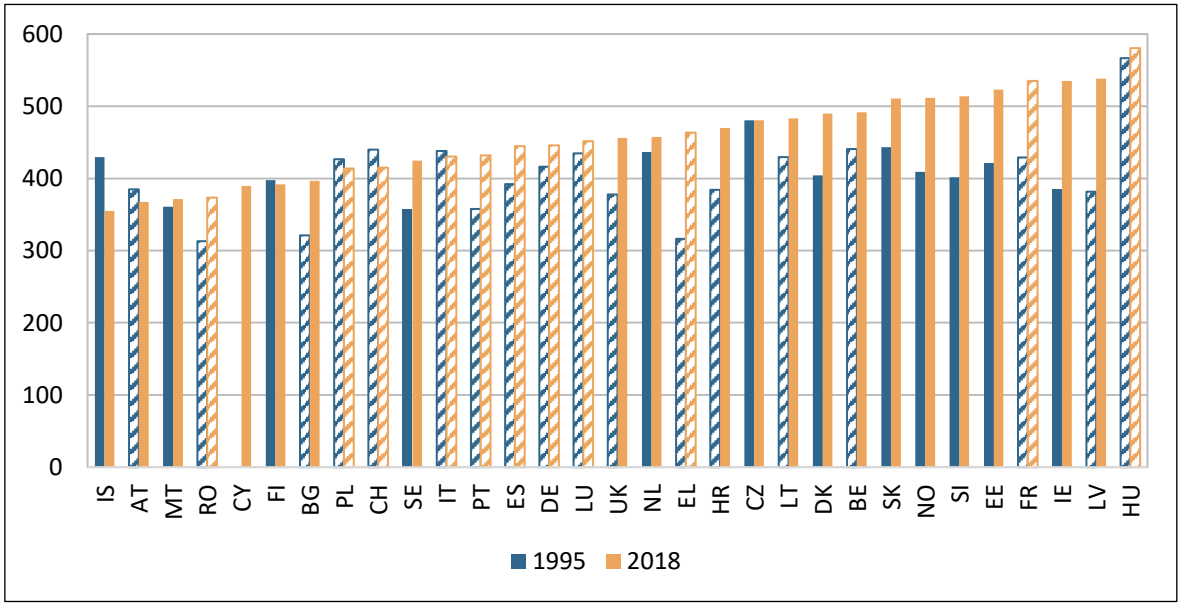

Figure A1: Cancer incidence in men per 100,000 inhabitants (age-standardized rates (Old European standard)), 1995–2018 [1, 2]

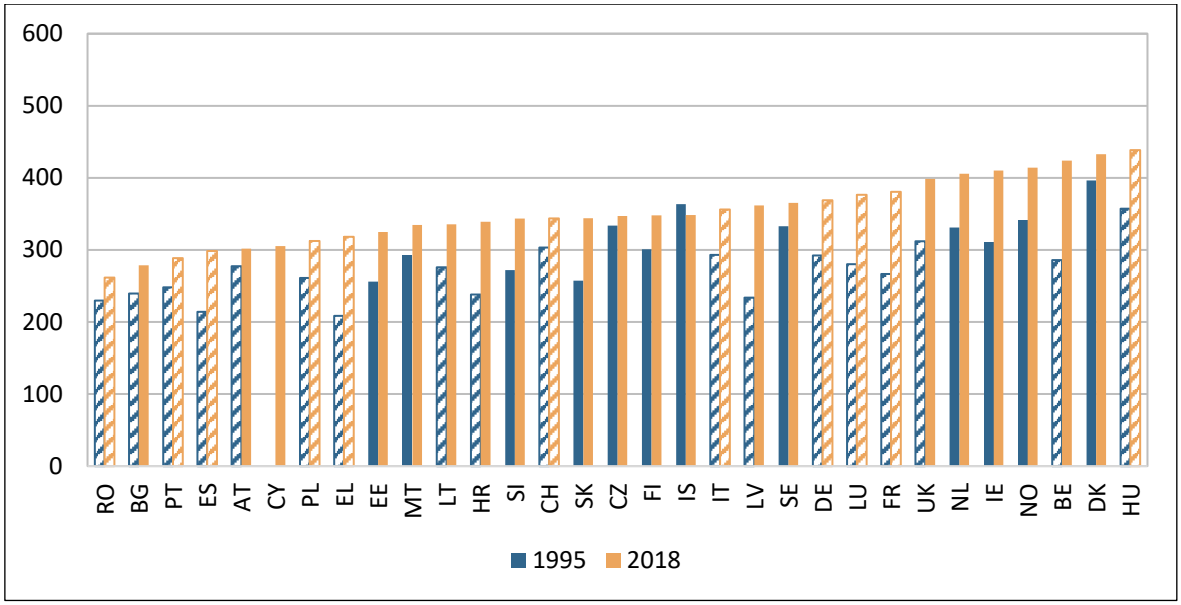

Figure A2: Cancer incidence in women per 100,000 inhabitants (age-standardized rates (Old European standard)), 1995–2018 [1, 2]

A.1.2 Age-standardized mortality rates

Age-standardized mortality rates for men and women are shown in Figures A3 and A4. These rates take into account different population sizes and age structures of the populations, but do not control for other important factors such as screening intensity and effectiveness of treatment.

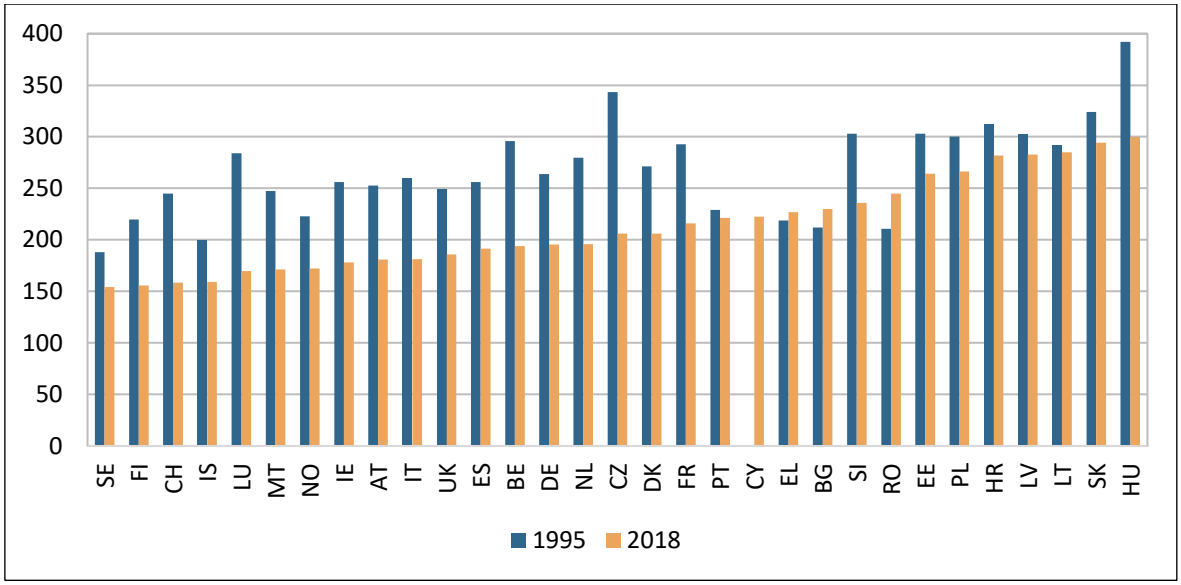

Figure A3: Cancer mortality in men per 100,000 inhabitants (age-standardized rates (Old European standard)), 1995–2018 [1, 2]

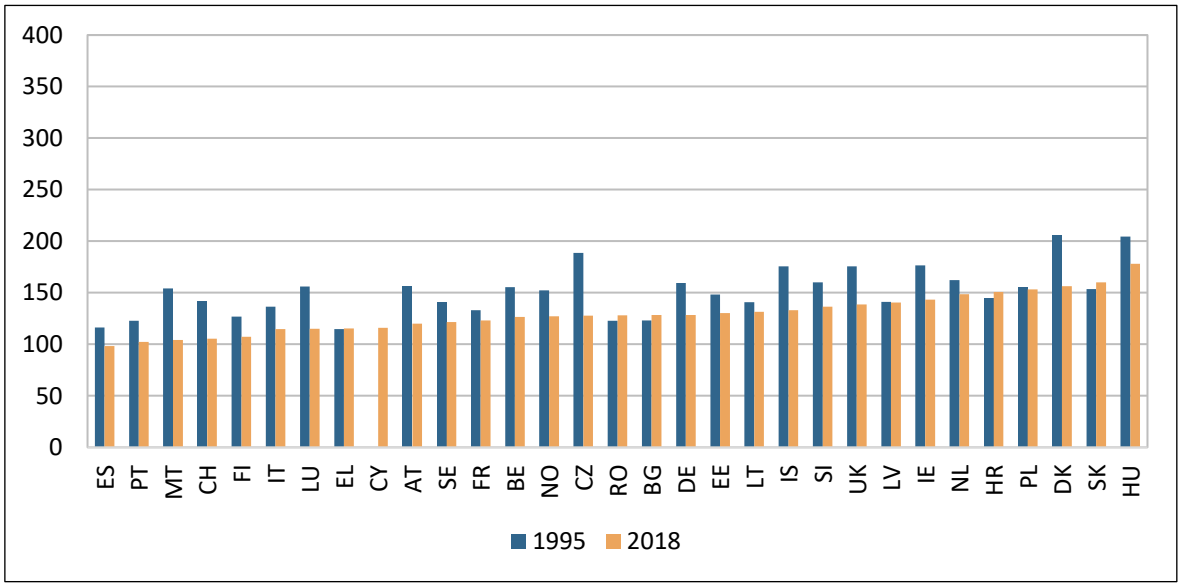

Figure A4: Cancer mortality in women per 100,000 inhabitants (age-standardized rates (Old European standard)), 1995–2018 [1, 2]

A.1.3 Survival rates of selected cancer types

Figures A5 to A9 present 5-year age-standardized net survival rates for two common cancer types (lung cancer, prostate cancer) and three selected cancer types (malignant melanoma, lymphoid cancers (which include multiple myeloma), ovarian cancer).

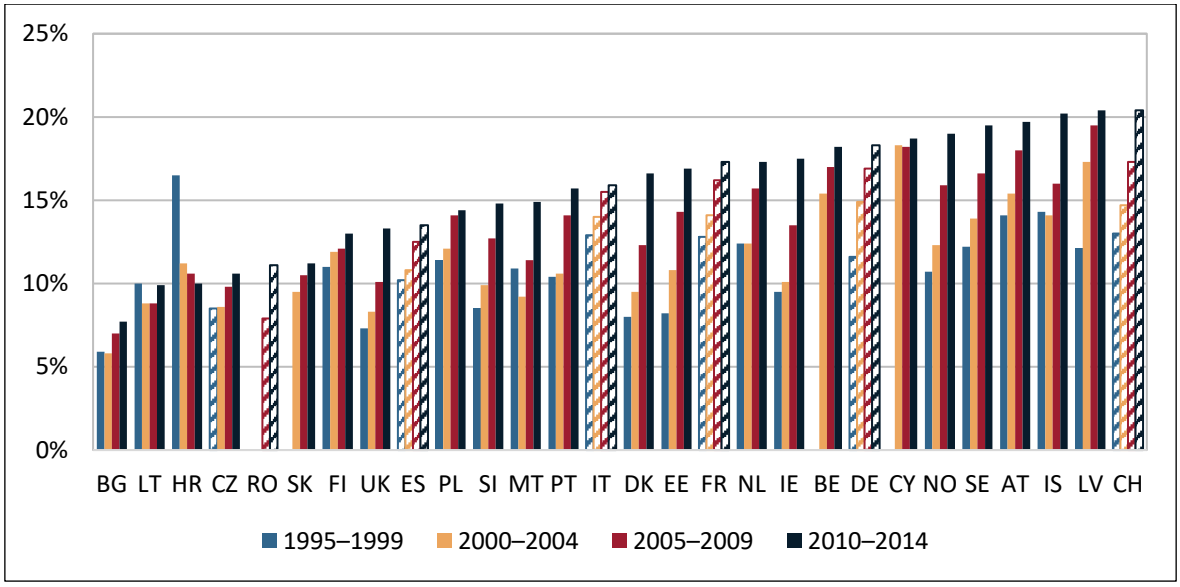

Figure A5: 5-year age-standardized net survival rates for lung cancer in adult patients (15–99 years), 1995–2014

Notes: Hatched bars in CH, DE, ES, FR, IT, and RO indicate that national estimates are based on regional data. Hatched bars in other countries indicate less reliable estimates. EL, HU, and LU are missing due to lack of data. Source: [3, 4].

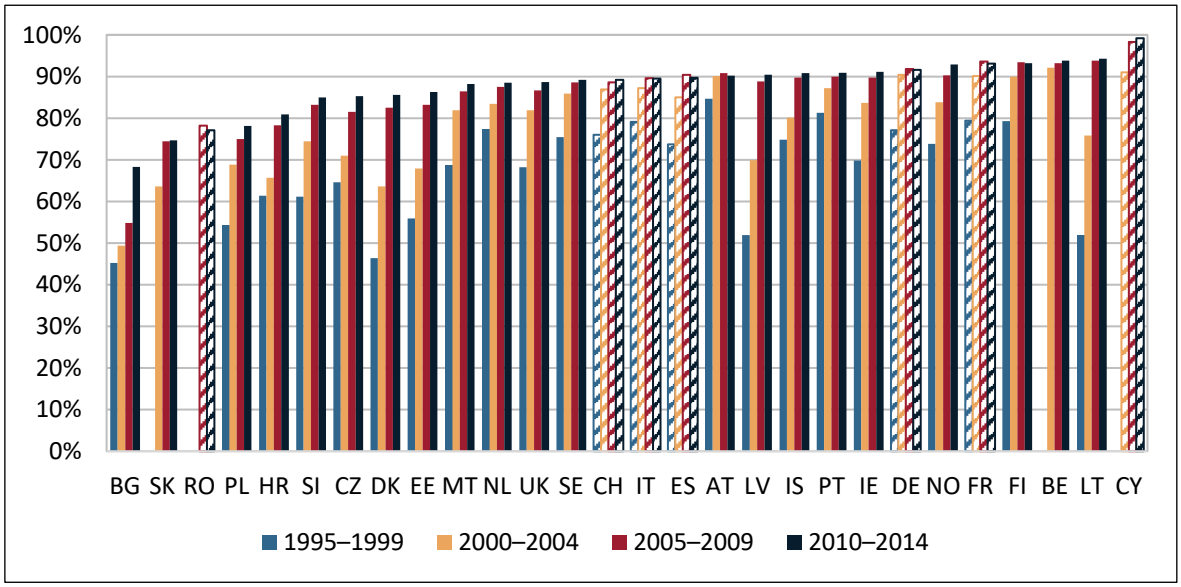

Figure A6: 5-year age-standardized net survival rates for prostate cancer in male adult patients (15–99 years), 1995–2014

Notes: see Figure A5.

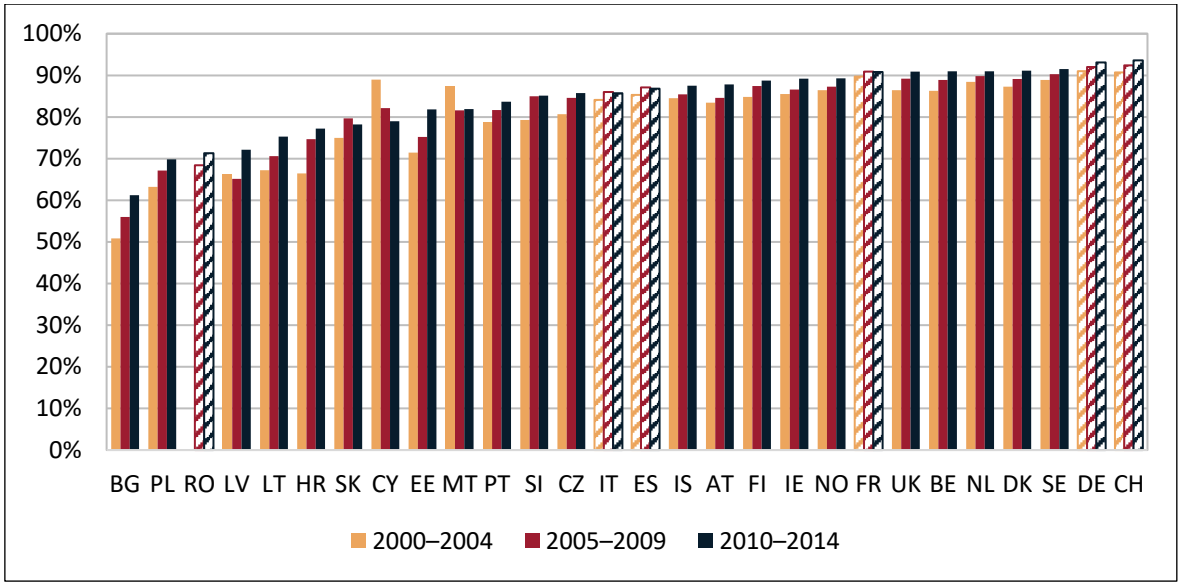

Figure A7: 5-year age-standardized net survival rates for malignant melanoma in adult patients (15–99 years), 1995–2014

Notes: see Figure A5.

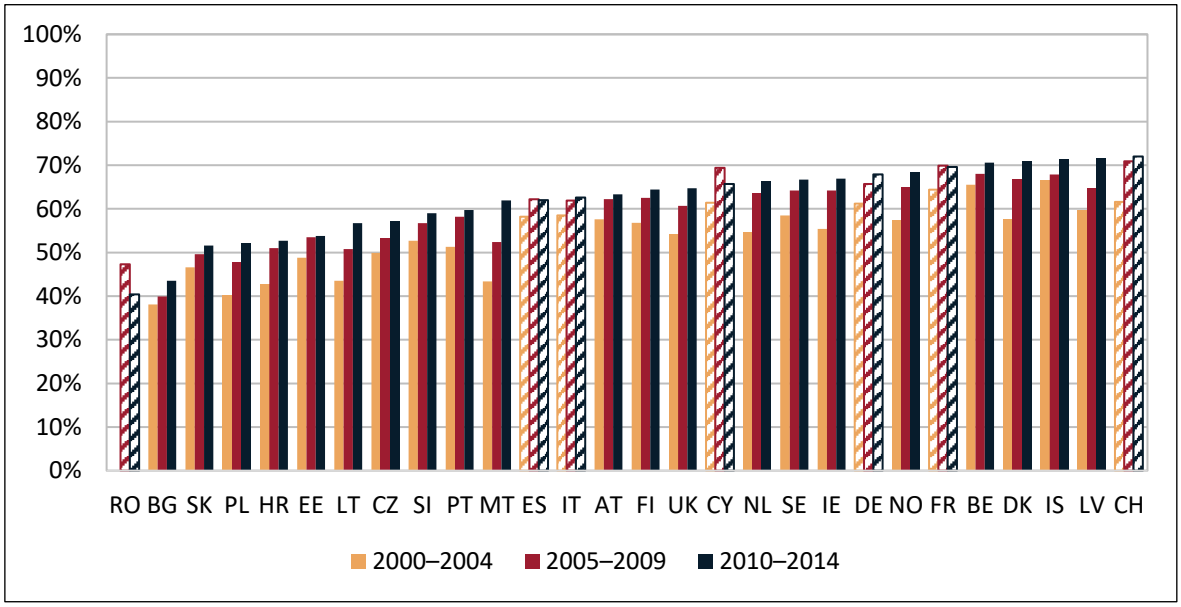

Figure A8: 5-year age-standardized net survival rates for lymphoid cancers in adult patients (15–99 years), 1995–2014

Notes: see Figure A5.

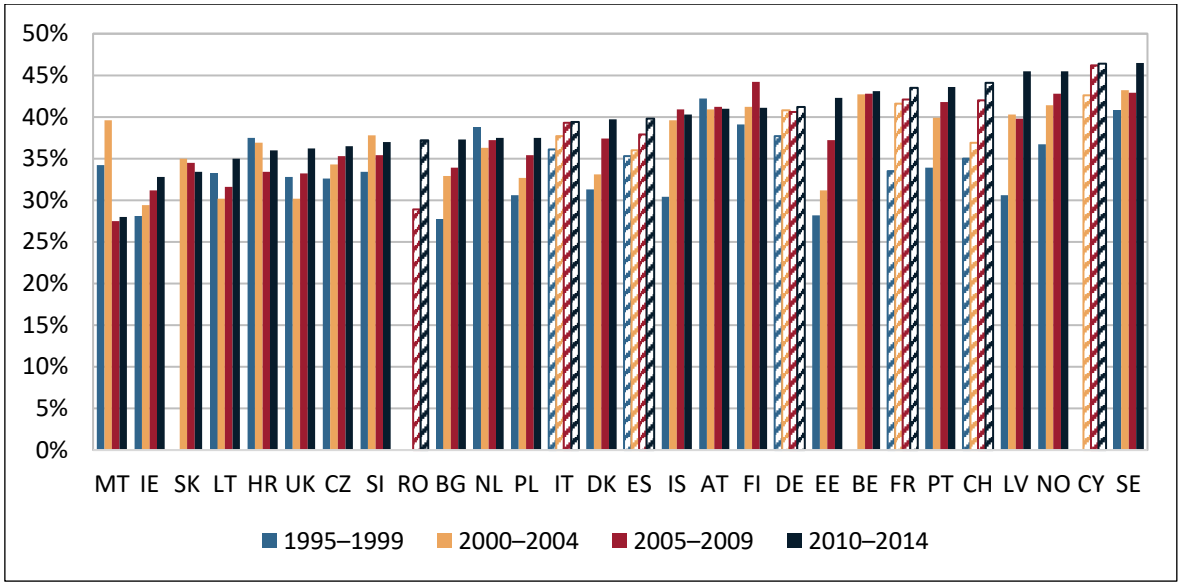

Figure A9: 5-year age-standardized net survival rates for ovarian cancer in female adult patients (15–99 years), 1995–2014

Notes: see Figure A5.

A.1.4 Cancer-specific health expenditure

Most studies identified in the review of national estimates of cancer-specific health expenditure were based on cancer-specific cost-of-illness studies. The completeness in terms of including all relevant sources of expenditure varies. Several studies left out expenditure on primary prevention and long-term care, resulting in an underestimation of the true direct costs. We tried to classify all relevant cost categories in these studies in a common manner, resulting in a re-classification or exclusion of certain categories in some studies.

Austria

The share used is the arithmetic mean of the shares in Germany and Switzerland.

Belgium

The share used is the arithmetic mean of the shares in France, Germany, and the Netherlands.

Bulgaria

The share used is the arithmetic mean of the shares in Hungary and Poland.

Croatia

The share used is the arithmetic mean of the shares in Hungary and Slovenia.

Cyprus

The OECD reports that cancer (not including benign cancers) accounted for 6.3% of total health expenditure in 2010, citing the OECD Questionnaire on Systems of Cancer Care 2010 [5]. In the absence of any other data, 6.3% is used as the best available estimate.

Czechia

Estimates from three sources are available. First, in a discussion paper the WHO estimated the share of cancer-related expenditure on total health expenditure to be 5.5% in 2006 [6]. The WHO's analysis for Czechia was based on data from the OECD. Note that 48% of health expenditure in the disease-specific data for Czechia had initially been unallocated, but in the analysis they were allocated in the same proportions as the allocated expenditure. Second, the OECD reports that cancer (not including benign cancers) accounted for 5.4% of total health expenditure in 2007, citing the OECD Questionnaire on Systems of Cancer Care 2010 [5]. Third, the OECD provides disease-specific estimates for the years 2009 and 2011 under the SHA framework [7]. Expenditures on cancer (ICD-10 C00-D48) were 7.7% (CZK 16.201 billion) and 9.0% (CZK 19.717 billion) of current health expenditure in 2009 and 2011, respectively. However, 35% and 29% of all health expenditures in these years are not allocated to a disease, and the sum of all – allocated and unallocated – expenditures deviates greatly from the official figures in the OECD's main database [8]. Compared to the official current health expenditure in 2009 (CZK 286.641 billion) and in 2011 (CZK 281.431 billion), the cancer expenditure would equal 5.7% and 7.0%, respectively. The latter estimates are used in the analysis.

Denmark

A report by the Center for Health Economic Research (COHERE) estimated the health expenditure for a cancer patient (ICD-10 C00-D48, though some non-malignant types seem to be excluded) based on matching techniques comparing cancer patients to a healthy control group [9]. Patients diagnosed between 2009 and 2013 and followed up until 2014 were included and all prices were adjusted to the price level in 2010. The costs included were expenditure on inpatient care and ambulatory care at hospitals (including medicine use) and on primary care for general practitioner (GP) visits. Expenditure on medicines dispensed outside the hospital, primary prevention measures, screening, and long-term care are missing. The additional health expenditure of a cancer patient amount to DKK 259,960 over a five-year period ranging from one year prior to the diagnosis to three years after it.

However, the costs of DKK 17,710 in the year prior to the cancer diagnosis can, in line with a cost-of-illness approach, not be assigned to cancer as cancer cannot have been the main diagnosis. This puts the costs per patient to DKK 242,250. According to NORDCAN [10], there were 37,438 cancer patients diagnosed in Denmark in 2010. The total costs thus amount to DKK 9,069.4 million, which puts the share of cancer-specific expenditure on the current health expenditure (DKK 187,126 million in 2010 [8]) to 4.8%. This estimate is used in the analysis.

There are two more estimates available with relevant cost categories missing and/or unclear methodology. First, a comparative cost-of-illness study for the Nordic countries estimated that the cancer costs (primary diagnosis ICD-10 C00-C97) in Denmark amounted to DKK 5,989 million in 2007 [11]. These costs include expenditure on hospital treatment (inpatient, day patient, and outpatient activities) (DKK 5,965 million) and prescription medicines (DKK 24 million). Expenditure on primary care, primary prevention measures, screening, and long-term care were not included. The share of cancer-specific expenditure on the current health expenditure (DKK 162,150 million in 2007 [8]) thus amounted to 3.7%. Second, the OECD reports that cancer (not including benign cancers) accounted for 4.5% of total health expenditure in 2008, citing the OECD Questionnaire on Systems of Cancer Care 2010 [5]. It is noted that the data refer to costs in hospitals only.

Estonia

In a discussion paper the WHO estimated the share of cancer-related expenditure on total health expenditure to be 9.4% in 2004 [6]. The WHO's analysis for Estonia was based on personal communication and presentation on Health Expenditures by Patient Characteristics, Luxembourg 2006, Natalja Eigo. Note that the disease-specific allocation of health expenditure was only available for the Estonian Health Insurance Fund which comprised over 62% of total health expenditure. The unallocated health expenditures were allocated in the same proportions as the allocated ones. However, this methodology leads probably to an overestimation of the true share of cancer expenditure, since people with chronic illnesses and retired people were (and still are) subject to lower co-payments in Estonia [12]. If all cancer expenditure were exclusively paid for by the Health Insurance Fund, the share of cancer expenditure on total health expenditure would be about 5.8% (9.4%*62%). But since there are some co-payments, this estimate represents probably an underestimation of the true expenditure. Following the principle of providing conservative estimates, 5.8% is used as the best available estimate.

Finland

A cost-of-illness study covering the period 2004 to 2014 estimated the health expenditure of cancer (ICD-10 C00-C97) to be €506 million in 2004 and €775 million in 2014 [13]. The shares of cancer-specific expenditure on the current health expenditure (€12,347 million in 2004 and €19,479 million in 2014 [8]) thus amount to 4.1% and 4.0%, respectively. The costs include expenditure on inpatient episodes in secondary care (€240 million in 2004 and €202 million in 2014), outpatient visits in secondary care (€106 and €283), inpatient episodes in primary and private care (€70 and €87), rehabilitation (€4 and €4), outpatient medication (€60 and €160), and screening (€26 and €39). All treatment costs are reported as gross costs; i.e. including both the public expenditure and the patient's co-payment or deductible. Medicines administered in secondary care are included in the respective categories. Expenditure on primary prevention measures and long-term care are missing. These estimates are used in the analysis.

There are three more estimates available with relevant cost categories missing and/or unclear methodology. First, a report by the Cancer Society of Finland estimates the health expenditure of cancer (ICD-10 C00-C97) to be €420.1 million in 2004 [14]. The included cost categories and estimates are the same as in the Finnish study above, except that the category of inpatient episodes in primary and private care is missing. Second, a comparative cost-of-illness study for the Nordic countries estimated that the cancer costs (primary diagnosis ICD-10 C00-C97) in Finland amounted to €640.8 million in 2007 [11]. These costs include expenditure on hospital treatment (inpatient, day patient, and outpatient activities) (€501.6 million), prescription medicines (€109.2 million), and screening programs for breast and cervical cancer (€30 million). Expenditure on primary care, primary prevention measures, and long-term care were not included. The share of cancer-specific expenditure on the current health expenditure (€14,602 million in 2007 [8]) thus amounted to 4.4%. Third, the OECD reports that cancer (not including benign cancers) accounted for 4.2% of total health expenditure in 2004, citing the OECD Questionnaire on Systems of Cancer Care 2010 [5]. It is noted that the data do not include all costs related to medicines.

France

Estimates from two sources are available. First, the National Cancer Institute (INCa) estimated the direct cost of cancer to be €11,254 million in 2004 [15] (summary table in English in [16]). These costs include expenditures for inpatient care (€7,185 million), outpatient care (€3,701 million), screening programs (€248 million), and primary prevention (€120 million). Note that publicly funded research (€670 million) is not included, since it is not part of the definition of current health expenditure used in this report. The share of cancer-specific expenditure on the current health

expenditure (€173,201 million in 2004 [8]) thus amounted to 6.5%. Second, the National Health Insurance Fund (CNAM) publishes annual reports on public health expenditures by disease group [17]. The latest publicly available reports cover the period 2013–2017. Public health expenditure on cancer amounted to €15.1 billion in 2013, €16.1 billion in 2014, €16.8 billion in 2015, €17.4 billion in 2016, and €18.4 billion in 2017. The shares of cancer-specific expenditure on the current health expenditure (€242.1 billion in 2013, €248.8 billion in 2014, €251.9 billion in 2015, €256.5 billion in 2016, €259.6 billion in 2017 [8]) thus amount to 6.2%, 6.5%, 6.7%, 6.8%, and 7.1%, respectively. The estimates by CNAM are used in the analysis, although they do not include out-of-pocket payments, which leads to an underestimation of the costs.

Germany

The Federal Statistical Office (Destatis) provides disease-specific health expenditures for selected years under the SHA framework [18, 19]. Expenditures on cancer (ICD-10 C00-D48) amounted to €14.116 billion (6.3% of current health expenditure) in 2002, €15.977 billion (6.9%) in 2004, €17.553 billion (7.2%) in 2006, €18.542 billion (7.1%) in 2008, and €23.002 billion (6.8%) in 2015. These estimates are used in the analysis.

Greece

In its "National Action Plan on Cancer, 2011-2015" the Ministry of Health states that "[i]nformation on the direct costs [of cancer] in Greece is not available, however it is estimated that the cost of treating cancer is around 6.5% of total expenditure on health." [20]. In the absence of any other data, 6.5% is used as the best available estimate.

Hungary

The OECD provides disease-specific estimates for the year 2006 under the SHA framework [7]. Expenditures on cancer (ICD-10 C00-D48) were HUF 134.989 billion, corresponding to a share of 7.1% of current health expenditure (HUF 1,893.601 billion [8]). However, 31% of all health expenditures in 2006 are not allocated to a disease. In the absence of any other data, 7.1% is used as the best available estimate.

Iceland

A comparative cost-of-illness study for the Nordic countries estimated that the cancer costs (primary diagnosis ICD-10 C00-C97) in Iceland amounted to ISK 4,573 million in 2007 [11]. These costs include expenditure on hospital treatment (inpatient, day patient, and outpatient activities) (ISK 3,867 million), prescription medicines (ISK 228 million), and screening programs for breast and cervical

cancer (ISK 479 million). Expenditure on primary care, primary prevention measures, and long-term care were not included. The share of cancer-specific expenditure on the current health expenditure (ISK 118,962 million in 2007 [8]) thus amounted to 3.8%. In the absence of any other data, 3.8% is used as the best available estimate.

Ireland

The share used is the same as in the UK.

Italy

Referring to a publication from the National Institute for Statistics (Istat) from 2011, a study published in BMC Cancer in 2013 provided information on the cost of cancer [21]. According to this study, expenditures on cancer amounted to €7.5 billion and total health expenditure to €110 billion (not specifying a year), resulting in a share of 6.7%. In the absence of any other data, 6.7% is used as the best available estimate.

Latvia

The share used is the arithmetic mean of the shares in Estonia and Poland.

Lithuania

The share used is the arithmetic mean of the shares in Estonia and Poland.

Luxembourg

The share used is the arithmetic mean of the shares in France, Germany, and the Netherlands.

Malta

The share used is the arithmetic mean of the shares in Cyprus, Greece, and Italy.

Netherlands

The National Institute for Public Health and the Environment (RIVM) provides disease-specific health expenditures for selected years under the SHA framework [22]. Expenditures on cancer (ICD-10 C00-D48; ICD-9 140-239) amounted to €2.164 billion in 2003, €2.425 billion in 2005, €3.080 billion in 2007, €4.099 billion in 2011, and €4.925 billion in 2015. The shares of cancer-specific expenditure on the current health expenditure (€46.443 billion in 2003, €50.112 billion in 2005, €56.053 billion in 2007, €66.555 billion in 2011, €71,236 billion in 2015 [8]) thus amount to 4.7%,

4.8%, 5.5%, 6.2%, and 6.9%, respectively. Note that the figures for total health expenditures provided by RIVM are lower than the current health expenditures by the OECD in the years 2003–2011 and higher in 2015. The estimated shares are used in the analysis.

Norway

A cost-of-illness report covering the period 2011 to 2014 estimated the health expenditure of cancer (ICD-10 C00-D48, though some benign neoplasms seem to be excluded) to be NOK 11,137 million in 2011, NOK 10,943 million in 2012, NOK 11,914 million in 2013, and NOK 12,456 million in 2014 [23]. These costs include expenditure on primary care services, specialized health care (private specialized practitioners, day patient care, inpatient care, polyclinical contacts, polyclinical imaging, polyclinical laboratory services), and medicines (including some non-cancer medicines) dispensed at pharmacies. Expenditure on primary prevention measures, screening, and long-term care were not included in the study. Note that "other costs" among the specialized health care expenditure are excluded, since they are not part of the definition of current health expenditure used in this report. The shares of cancer-specific expenditure on the current health expenditure (NOK 245,440 million in 2011, NOK 260,181 million in 2012, NOK 274,246 million in 2013, NOK 293,507 million in 2014 [8]) thus amount to 4.5%, 4.2%, 4.3%, and 4.2%, respectively. These estimates are used in the analysis.

There is one more estimate available with relevant cost categories missing. A comparative cost-of-illness study for the Nordic countries estimated that the cancer costs (primary diagnosis ICD-10 C00-C97) in Norway amounted to NOK 6,782 million in 2007 [11]. These costs include expenditure on hospital treatment (inpatient, day patient, and outpatient activities) (NOK 5,660 million), prescription medicines (NOK 776 million), and screening programs for breast and cervical cancer (NOK 346 million). Expenditure on primary care, primary prevention measures, and long-term care were not included. The share of cancer-specific expenditure on the current health expenditure (NOK 189,209 million in 2007 [8]) thus amounted to 3.6%.

Poland

The National Health Fund (NFZ), responsible for financing public health care, spent PLN 5,539 million on cancer care (ICD-10 C00-C97, D00-D09, D37-D48) in 2009, PLN 5,881 million in 2010, and PLN 6,292 million in 2011 [24]. This includes expenditures for inpatient care (including chemotherapy, hospital wards, therapeutic programs, and radiation therapy), outpatient care, palliative and hospice care, psychiatric care and treatment for addiction, preventive health programs (screening), rehabilitation, nursing and care services, and other services. However, the expenditures for cancer medicines reimbursed under the list of pharmaceutical refund (i.e. cancer medicines

distributed by pharmacies) are not included. In 2009 and 2010, these expenditures amounted to just over PLN 500 million according to the Ministry of Health and the NFZ [25]. Adding these PLN 500 million (in all years) to the expenditures above, yields health expenditure of PLN 6,039 million, PLN 6,381 million, and PLN 6,792 million, respectively. The shares of cancer-specific expenditure on the current health expenditure (PLN 90,385 million in 2009, PLN 92,775 million in 2010, PLN 97,673 million in 2011 [8]) thus amount to 6.7%, 6.9%, and 7.0%, respectively. Note that these estimates do not include private payments for cancer care, yet co-payments for oncology services and cancer medicines are very small compared with other health care provisions in Poland [26]. These estimates are thus used in the analysis.

Portugal

There are two estimates available. First, a cost-of-illness study estimated the "direct medical care expenditures" of cancer to be €565.0 million in 2006 [27]. These expenditures include expenditures on hospitalization, ambulatory care, chemotherapy, radiotherapy, medical consultations, and medicines, whereas expenditures on, e.g., screening and primary prevention are missing. The same study states that "total health cost" amounted to €14,500 million (in 2005), resulting in a share of 3.9%. Updated data from the OECD show that current health expenditure in 2006 were €15,189 million, which means that the cancer-specific share was 3.7%. Second, a cost-of-illness study estimated the direct costs of cancer to be €867.0 million in 2015 (note that most unit costs refer to this year) [28]. The direct costs include expenditures for scheduled and unscheduled outpatient care (€232 million), day hospital sessions for medical treatment (€27 million), radiotherapy sessions (€74 million), hospitalization (€230 million), medicines (€273 million), and primary care (€30 million), whereas expenditures on, e.g., screening and primary prevention are missing. The share of cancer-specific expenditure on the current health expenditure (€16,132 million in 2015 [8]) thus amounted to 5.4%. Estimates from both sources are used in the analysis.

Romania

The share used is the arithmetic mean of the shares in Hungary and Poland.

Slovakia

The share used is the arithmetic mean of the shares in Czechia and Hungary.

Slovenia

There are two estimates available. First, the OECD provides disease-specific estimates for the year 2006 under the SHA framework [7]. Expenditures on cancer (ICD-10 C00-D48) were €157.1 million,

corresponding to a share of 6.4% of current health expenditure (€2,462 million [8]). Only 2% of all health expenditures in 2006 were not allocated to a disease. In the absence of any other data, 6.4% is used as the best available estimate. Second, the OECD reports that cancer (including benign cancers) accounted for 3.4% of total health expenditure in 2008 [5], based on the OECD Disease Expenditure studies. No additional information is provided, which together with the low estimate compared to 2006, makes this estimate doubtful. Therefore, the estimate for 2006 is used in the analysis.

Spain

There are two national estimates available. First, the OECD reports that cancer (not including benign cancers) accounted for 1.9% of total health expenditure in 2003, citing the OECD Questionnaire on Systems of Cancer Care 2010 [5]. Compared to expenditures in similar countries this seems to be an exceptionally low estimate. Second, a cost-of-illness study estimated the direct costs of cancer to be €4,818 million in 2015 [29]. The direct costs include expenditures for hospital care (€2,797 million), cancer medicines (€1,717 million), and primary care (€304 million), whereas expenditures on, e.g., screening and primary prevention are missing. The share of cancer-specific expenditure on the current health expenditure (€98,486 million in 2015 [8]) thus amounted to 4.9%. The latter estimate is used in the analysis.

Sweden

A cost-of-illness study estimated the health expenditure of cancer (ICD-10 C00-C97) to be SEK 15,537 million in 2013 [30]. The costs include expenditure on inpatient care (SEK 6,513 million), specialized outpatient care (SEK 4,145 million), cancer medicines (SEK 2,766 million), screening (SEK 642 million), primary care (SEK 265 million), and palliative care and other care services (SEK 1,207 million). Expenditure on primary prevention measures, screening (PSA), other treatment-related medicines (e.g. antiemetic medicines) and patient fees related health care visits were not included. The share of cancer-specific expenditure on the current health expenditure (SEK 418,490 million in 2013 [8]) thus amounted to 3.7%. This estimate is used in the analysis.

There are three more estimates available with relevant cost categories missing and/or unclear methodology. First, a report by the Swedish Cancer Society estimated the health expenditure of cancer (unclear whether it is ICD-10 C00-C97 or C00-D48) to be SEK 16,830 million in 2004 [31]. These costs include expenditure on care (SEK 14,465 million), medicines (SEK 2,005 million), screening programs (SEK 200 million), and primary prevention (SEK 160 million). Note that publicly funded research (SEK 750 million) is excluded, since it is not part of the definition of current health expenditure used in this report. However, a retrospective analysis on actual sales data showed that medicine costs amounted SEK 1,630 million (SEK 1.530 million for cancer medicines and SEK

100 million for antiemetic medicines) in 2004 [32]. This would reduce the health expenditure in 2004 to SEK 16,455 million. The share of cancer-specific expenditure on the current health expenditure (SEK 290,837 million in 2004 [8, 33]) thus amounted to 5.7%. Second, a comparative cost-of-illness study for the Nordic countries estimated that the cancer costs (primary diagnosis ICD-10 C00-C97) in Sweden amounted to SEK 11,523 million in 2007 [11]. These costs include expenditure on hospital treatment (inpatient, day patient, and outpatient activities) (SEK 8,965 million), prescription medicines (SEK 1,686 million), and screening programs for breast and cervical cancer (SEK 881 million). Expenditure on primary care, primary prevention measures, and long-term care were not included. The share of cancer-specific expenditure on the current health expenditure (SEK 334,084 million in 2007 [8, 33]) thus amounted to 3.4%. Third, the OECD reports that cancer (not including benign cancers) accounted for 3.1% of total health expenditure in 2006, citing the OECD Questionnaire on Systems of Cancer Care 2010 [5]. It is noted that the data refer to costs in hospitals only.

Switzerland

A cost-of-illness study estimated disease-specific health expenditures for 2011 [34]. Expenditures on cancer (ICD-10 C00-D48) amounted to CHF 3.880 billion, whereas total health expenditure amounted to CHF 64.633 billion in 2011 in this study (CHF 66.900 billion of current health expenditure according to the OECD [8]). The share of cancer-specific health expenditure thus amounted to 6.0%. This estimate is used in the analysis.

United Kingdom

The NHS England provides disease-specific expenditure data broken down by 23 so-called "programme budgeting categories" for the financial years 2003/04 to 2012/13 [35]. For instance, the NHS' expenditures on "cancers & tumours" amounted to GBP 5.68 billion in 2012/13, while total NHS expenditures amounted to GBP 94.78 billion. This equals a share of 6.0% for England. However, public expenditures only comprised 83% of the current health expenditure in the UK in 2012 [8]. Assuming that the public share of health expenditures is the same in England and that all cancer expenditures were exclusively paid for by the NHS, cancer expenditures' share on the current health expenditure would be 5.0% (6.0%*83%). Note that these estimates represent an underestimation of the true expenditures, as co-payments for cancer medicines occur [36]. Cancer expenditures for the years 2003/04 to 2011/12 were calculated analogously. In the absence of data covering all of the UK, the estimates for England are used in the analysis.

A.1.5 Correlates with cancer-specific health spending

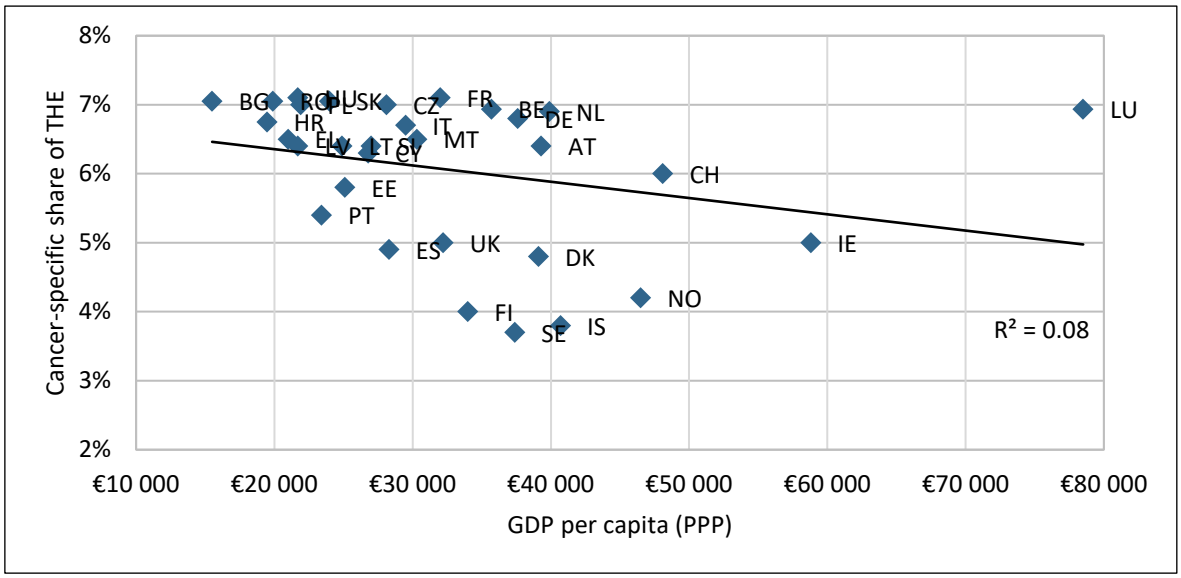

Figure A10: GDP per capita and cancer-specific share of total health expenditure (THE), 2018

Notes: See section A.1.4 in the Appendix for the calculations of the cancer-specific shares. Source: [37].

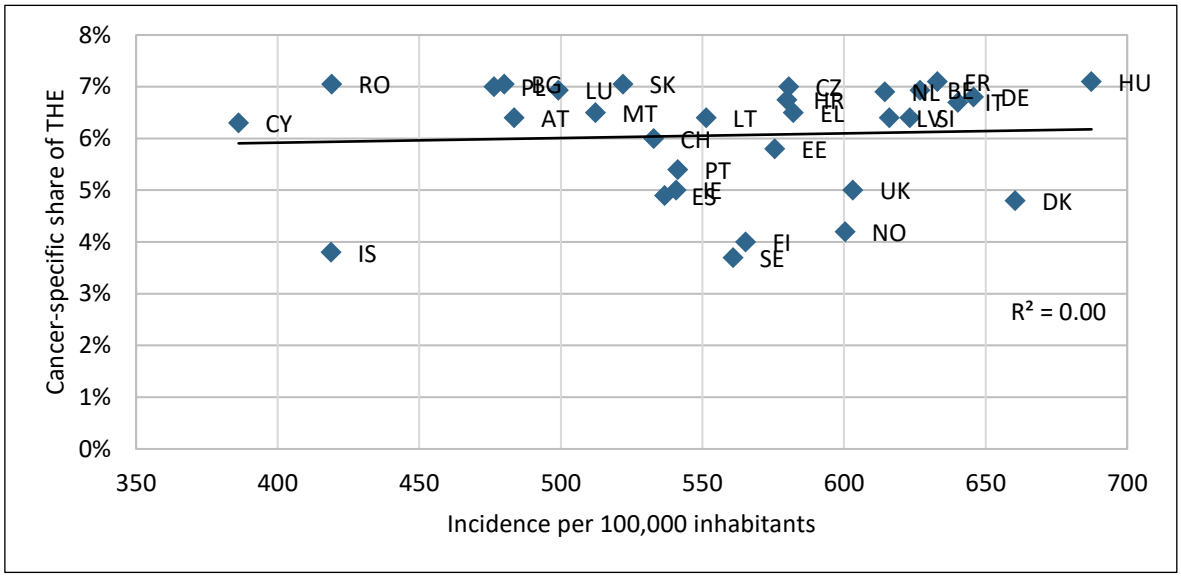

Figure A11: Cancer incidence per 100,000 inhabitants and cancer-specific share of total health expenditure (THE), 2018

Notes: See section A.1.4 in the Appendix for the calculations of the cancer-specific shares. Source: [2].

A.1.6 Summary tables of the economic burden of cancer

Table A1: Economic burden of cancer – total (in million €, 2018 prices and exchange rates), 1995–2018

	1995			2000			2005			2010			2015			2018		
	Direct	Indir.1	Indir.2	Direct	Indir.1	Indir.2	Direct	Indir.1	Indir.2	Direct	Indir.1	Indir.2	Direct	Indir.1	Indir.2	Direct	Indir.1	Indir.2
AT	1,424	1,270	281	1,699	1,219	281	2,068	1,157	281	2,317	1,140	281	2,402	1,093	281	2,553	1,080	281
BE	1,370	1,633	1,244	1,670	1,620	1,244	2,181	1,577	1,244	2,699	1,514	1,244	3,007	1,358	1,244	3,240	1,406	1,244
BG	49	197	49	110	175	49	165	201	49	202	183	49	268	180	49	320	174	49
HR	126	243	427	185	234	427	217	236	427	268	231	427	226	203	427	249	200	427
CY	31	37	9	47	38	9	58	32	9	80	42	9	76	43	9	90	40	9
CZ	361	749	341	431	688	341	597	602	341	850	511	341	955	434	341	1,084	436	341
DK	738	1,430	726	910	1,444	726	1,112	1,291	726	1,304	1,101	726	1,372	934	726	1,499	946	726
EE	24	104	75	34	81	75	50	77	75	66	59	75	84	68	75	96	61	75
FI	424	634	154	509	722	154	672	737	154	748	655	154	838	556	154	844	559	154
FR	10,322	7,904	4,542	11,583	8,499	4,542	13,353	8,577	4,542	15,234	7,859	4,542	17,551	7,130	4,542	18,707	7,116	4,542
DE	15,578	13,886	4,370	17,212	12,585	4,370	20,492	11,320	4,370	22,477	11,662	4,370	23,741	11,371	4,370	25,537	11,516	4,370
EL	802	692	159	955	681	159	1,408	712	159	1,442	693	159	962	575	159	942	607	159
HU	291	591	91	410	631	91	616	609	91	539	513	91	577	506	91	618	497	91
IS	25	49	40	40	50	40	52	45	40	51	45	40	57	44	40	69	44	40
IE	239	425	113	410	557	113	747	535	113	924	466	113	986	509	113	1,139	526	113
IT	6,785	5,963	284	8,695	5,614	284	10,220	5,596	284	10,654	5,162	284	10,195	4,836	284	10,374	4,924	284
LV	30	124	39	45	101	39	78	106	39	80	97	39	94	91	39	111	92	39
LT	46	161	82	81	135	82	110	132	82	141	111	82	166	118	82	196	113	82
LU	77	84	37	116	77	37	169	76	37	209	81	37	226	73	37	221	90	37
MT	18	26	2	25	20	2	37	17	2	40	22	2	61	23	2	74	26	2
NL	1,685	2,441	1,387	2,073	2,910	1,387	2,951	2,761	1,387	4,614	2,769	1,387	5,099	2,484	1,387	5,309	2,485	1,387
NO	511	727	666	771	831	666	1,019	731	666	1,271	683	666	1,504	604	666	1,575	609	666
PL	592	2,058	784	912	1,894	784	1,157	1,819	784	1,663	1,882	784	1,925	1,749	784	2,185	1,775	784

PT	367	599	192	562	680	192	669	704	192	725	673	192	901	607	192	991	655	192
RO	111	731	160	187	686	160	372	625	160	542	617	160	555	577	160	712	598	160
SK	175	307	173	181	283	173	270	284	173	419	261	173	396	257	173	428	257	173
SI	106	204	139	157	187	139	190	185	139	220	180	139	219	166	139	234	166	139
ES	2,528	3,148	950	3,135	3,652	950	4,346	4,034	950	5,255	3,589	950	4,999	3,284	950	5,245	3,440	950
SE	858	1,023	960	1,052	1,046	960	1,316	987	960	1,474	852	960	1,754	819	960	1,907	830	960
CH	2,197	2,114	477	2,545	2,028	477	2,966	1,844	477	3,371	1,798	477	4,084	1,720	477	4,366	1,716	477
UK	4,039	7,409	1,465	5,248	7,232	1,465	7,954	6,955	1,465	9,006	6,371	1,465	11,111	6,350	1,465	11,691	6,633	1,465
Europe	51,929	56,964	20,418	61,988	56,602	20,418	77,614	54,565	20,418	88,886	51,824	20,418	96,390	48,762	20,418	102,607	49,615	20,418

Notes: “Direct” = Direct costs of cancer (see section 2.4.1); “Indir. 1” = Indirect costs of cancer from premature mortality (see section 2.4.2); “Indir. 2” = Indirect costs of cancer from morbidity (see section 2.4.2).

Table A2: Economic burden of cancer – per capita (in €, 2018 prices and exchange rates), 1995–2018

	1995			2000			2005			2010			2015			2018		
	Direct	Indir.1	Indir.2	Direct	Indir.1	Indir.2	Direct	Indir.1	Indir.2	Direct	Indir.1	Indir.2	Direct	Indir.1	Indir.2	Direct	Indir.1	Indir.2
AT	179	160	35	212	152	35	251	141	34	277	136	34	278	127	33	289	122	32
BE	135	161	123	163	158	122	208	151	119	248	140	116	268	121	111	284	123	109
BG	8	23	6	13	21	6	21	26	6	27	25	7	37	25	7	45	25	7
HR	28	52	92	43	52	95	50	55	99	62	54	99	54	48	101	61	49	104
CY	48	57	15	69	55	14	79	44	13	97	52	12	90	51	11	103	46	11
CZ	35	72	33	42	67	33	58	59	33	81	49	33	91	41	32	102	41	32
DK	141	274	139	170	271	136	205	239	134	235	199	132	241	165	128	259	164	126
EE	16	72	52	24	58	53	37	57	55	50	44	56	64	52	57	73	46	57
FI	83	124	30	98	140	30	128	141	29	140	122	29	153	102	28	153	101	28
FR	174	133	77	190	140	75	212	137	72	234	122	71	263	107	68	278	106	68
DE	192	170	54	211	153	53	252	137	53	280	143	53	291	140	54	308	139	53
EL	76	66	15	89	63	15	128	65	14	130	62	14	89	53	15	88	56	15
HU	28	57	9	40	62	9	61	60	9	54	51	9	59	51	9	63	51	9
IS	93	182	149	142	179	143	174	154	136	159	140	125	172	135	121	197	126	115
IE	66	118	31	108	148	30	180	130	27	203	102	25	210	109	24	234	109	23
IT	119	105	5	153	99	5	176	97	5	178	87	5	168	80	5	172	81	5
LV	12	50	16	19	42	16	35	47	17	38	46	18	47	46	20	57	47	20
LT	12	44	22	23	39	23	33	39	24	45	35	26	57	40	28	70	40	29
LU	187	208	91	264	178	85	362	165	80	412	162	74	397	130	65	363	150	61
MT	48	69	5	65	53	5	92	43	5	96	54	5	137	52	5	155	54	4
NL	109	158	90	130	183	87	181	169	85	278	167	84	301	147	82	308	145	81
NO	117	167	153	172	186	149	220	159	145	260	141	139	290	117	129	296	115	126
PL	15	53	20	24	50	21	30	48	21	43	50	21	50	46	21	57	47	21

PT	37	60	19	55	66	19	64	67	18	69	64	18	87	59	18	96	64	19
RO	5	32	7	8	31	7	18	29	7	27	30	8	28	29	8	36	31	8
SK	33	57	32	34	53	32	50	53	32	77	48	32	73	47	32	79	47	32
SI	53	103	70	79	94	70	95	93	70	107	88	68	106	80	67	113	80	67
ES	64	79	24	77	90	23	99	93	22	113	77	21	108	71	20	112	74	20
SE	97	116	109	119	118	108	146	109	107	157	91	104	179	84	99	187	82	95
CH	310	301	68	351	283	67	396	249	64	429	231	62	493	209	58	511	202	56
UK	70	128	25	89	123	25	132	116	24	144	102	24	171	98	23	176	100	22
Europe	105	115	41	124	113	41	153	106	40	172	100	40	185	93	39	195	94	39

Notes: “Direct” = Direct costs of cancer (see section 2.4.1); “Indir. 1” = Indirect costs of cancer from premature mortality (see section 2.4.2); “Indir. 2” = Indirect costs of cancer from morbidity (see section 2.4.2).

Table A3: Cancer drug sales – total (in million €; current prices), 2008–2018

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
AT	318.5	344.9	374.9	394.6	438.7	478.6	510.4	611.1	726.7	843.2	952.3
BE	331.1	356.9	408.4	401.3	414.5	441.9	488.1	566.1	615.5	778.2	1,024.3
BG	31.6	43.2	48.7	64.4	85.2	99.8	126.7	142.2	157.6	198.4	216.2
HR	54.5	56.6	57.8	62.6	63.8	61.2	66.7	80.3	95.9	114.9	149.5
CY	-	-	-	-	-	-	-	-	-	-	-
CZ	171.9	197.2	213.2	228.6	211.0	193.9	161.2	162.5	167.0	165.2	174.0
DK	187.7	209.9	213.9	218.0	217.2	231.7	278.6	304.3	352.2	438.5	513.5
EE	3.8	8.6	8.8	7.7	8.1	8.6	8.6	10.8	11.6	12.8	5.5
FI	153.0	161.7	167.9	177.5	190.1	202.5	218.4	234.1	260.3	275.5	331.4
FR	3,276.3	3,088.6	3,003.4	2,831.5	2,913.1	3,085.8	3,284.2	3,728.2	4,418.4	4,734.5	5,183.7
DE	2,238.5	2,411.7	3,653.4	3,594.4	3,791.9	4,454.9	4,779.3	5,219.7	5,992.2	6,754.3	7,583.9
EL	167.0	167.3	128.9	150.3	90.2	52.9	45.5	46.6	44.5	43.6	43.9
HU	214.7	212.5	229.9	234.2	219.5	220.9	230.7	261.0	296.4	337.9	388.5
IS	9.5	7.9	8.8	9.2	9.8	9.6	9.7	11.6	14.0	16.0	20.9
IE	127.9	135.8	146.4	153.0	168.5	177.8	191.0	210.4	241.1	261.9	307.8
IT	1,669.6	1,813.8	1,973.4	2,080.2	2,114.8	2,342.3	2,534.5	2,826.0	3,183.0	3,774.3	4,516.6
LV	8.1	9.4	5.9	0.9	0.8	1.8	14.0	16.3	15.5	20.5	25.6
LT	11.7	8.6	10.6	11.9	8.1	12.2	23.2	31.2	36.8	44.9	55.0
LU	5.7	5.9	6.2	5.5	5.6	6.2	5.6	5.9	6.0	6.4	7.2
MT	-	-	-	-	-	-	-	-	-	-	-
NL	496.3	518.3	535.0	522.0	541.6	599.4	654.3	730.4	852.5	932.0	1,071.5
NO	97.0	94.7	108.9	113.7	131.7	144.7	164.3	179.6	217.4	327.3	366.0
PL	272.1	257.1	326.1	338.8	327.1	372.2	449.7	475.8	481.9	560.7	583.2
PT	2.8	3.1	240.1	238.8	230.6	218.2	229.4	255.1	288.1	343.4	403.6
RO	54.0	179.9	223.6	200.1	240.9	263.2	244.8	237.6	263.5	276.7	350.9
SK	107.9	113.4	117.8	122.5	128.0	142.6	147.9	154.2	173.6	155.9	165.9
SI	42.8	47.5	52.0	57.8	58.1	60.6	66.3	70.5	78.5	88.1	104.6
ES	1,251.7	1,423.3	1,581.9	1,580.0	1,562.2	1,609.4	1,669.0	1,878.7	2,165.3	2,502.9	2,841.2
SE	253.6	233.7	267.5	285.1	306.0	328.7	348.4	385.5	450.0	505.1	571.9
CH	263.1	292.9	334.0	378.5	426.0	458.8	483.1	574.1	657.2	747.3	800.7
UK	1,107.1	1,101.5	1,273.4	1,309.3	1,506.3	1,672.3	2,113.6	2,725.0	2,596.4	2,800.5	3,249.1
Europe	12,930	13,506	15,721	15,773	16,410	17,953	19,547	22,135	24,859	28,061	32,008

Notes: Sales data are missing for CY and MT. Data for EE, EL, LV (2008–2013), LU, PT (2008–2009), RO (2008) only comprise retail sales but no hospital sales. Source: MIDAS database.

Table A4: Cancer drug sales – per capita (in €; current prices), 2008–2018

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
AT	38	41	45	47	52	57	60	71	84	96	108
BE	31	33	38	36	37	40	44	50	54	69	90
BG	4	6	7	9	12	14	17	20	22	28	31
HR	13	13	13	15	15	14	16	19	23	28	36
CY	-	-	-	-	-	-	-	-	-	-	-
CZ	17	19	20	22	20	18	15	15	16	16	16
DK	34	38	39	39	39	41	50	54	62	76	89
EE	3	6	7	6	6	6	7	8	9	10	4
FI	29	30	31	33	35	37	40	43	47	50	60
FR	51	48	46	44	45	47	50	56	66	71	77
DE	27	29	45	45	47	55	59	64	73	82	92
EL	15	15	12	14	8	5	4	4	4	4	4
HU	21	21	23	23	22	22	23	26	30	34	40
IS	30	25	28	29	31	30	30	35	42	47	60
IE	29	30	32	33	37	39	41	45	51	55	64
IT	28	31	33	35	36	39	42	46	52	62	75
LV	-	-	-	-	-	-	7	8	8	11	13
LT	4	3	3	4	3	4	8	11	13	16	20
LU	12	12	12	11	11	11	10	10	10	11	12
MT	-	-	-	-	-	-	-	-	-	-	-
NL	30	31	32	31	32	36	39	43	50	55	62
NO	20	20	22	23	26	29	32	35	42	62	69
PL	7	7	9	9	9	10	12	13	13	15	15
PT	-	-	23	23	22	21	22	25	28	33	39
RO	-	9	11	10	12	13	12	12	13	14	18
SK	20	21	22	23	24	26	27	28	32	29	30
SI	21	23	25	28	28	29	32	34	38	43	51
ES	27	31	34	34	33	34	36	40	47	54	61
SE	28	25	29	30	32	34	36	40	46	51	57
CH	35	38	43	48	54	57	59	70	79	89	94
UK	18	18	20	21	24	26	33	42	40	43	49
Europe	25	26	30	31	32	35	38	42	47	53	61

Notes: see Table A3.

A.2 Chapter 4

The standard weekly dose (SWD) is based on the recommended dose in milligram (mg) for a standard patient (70–80 kg body weight and body surface 1.7–1.8 m2). Table A5 lists the SWD used for the selected medicines in section 4.7.

Table A5: SWD for selected cancer medicines

Medicine	SWD	Medicine	SWD
abiraterone	7,000	niraparib	2,700
afatinib	280	nivolumab	120
atezolizumab	400	olaparib	5,600
bevacizumab	400	osimertinib	560
bortezomib	3.1	palbociclib	650
carfilzomib	65	panitumumab	240
cetuximab	450	pembrolizumab	70
cobimetinib	315	pemetrexed	300
crizotinib	3,500	pertuzumab	150
dabrafenib	2,100	pomalidomide*	20
daratumumab	560	ribociclib	3,000
enzalutamide	1,120	trametinib	14
erlotinib	700	trastuzumab	200
gefitinib	1,750	trastuzumab emtansine	85
ipilimumab	80	vemurafenib	13,440
lenalidomide	130		

Notes: *For pomalidomide we choose 20 SWD, as it is sometimes administered during 21 days in a 28-day cycle (resulting in 21 SWD) or during 14 days in a 21-day cycle (resulting in 18.7 SWD).

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