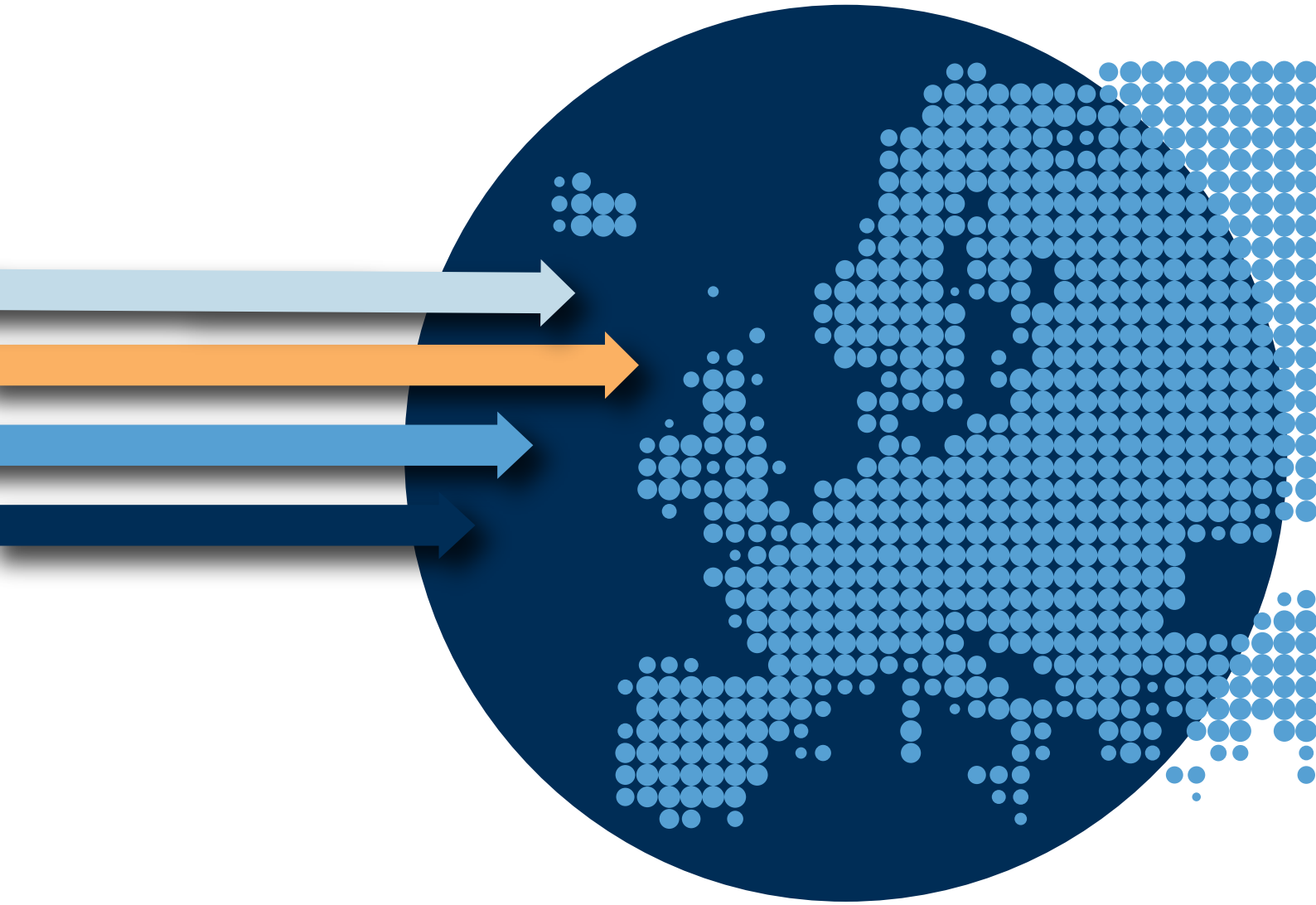
COMPARATOR REPORT ON PATIENT ACCESS TO CANCER MEDICINES IN EUROPE REVISITED



BENGT JÖNSSON
THOMAS HOFMARCHER
PETER LINDGREN
NILS WILKING

IHE REPORT
2016:4

COMPARATOR REPORT ON PATIENT ACCESS TO CANCER MEDICINES IN EUROPE REVISITED

Authors:
Bengt Jönsson, PhD, professor emeritus
Stockholm School of Economics, Stockholm, Sweden

Thomas Hofmarcher, MSc
The Swedish Institute for Health Economics, Lund Sweden
Lund University, Lund, Sweden

Peter Lindgren, PhD, associate professor
The Swedish Institute for Health Economics, Lund, Sweden
Karolinska Institutet, Stockholm, Sweden

Nils Wilking, MD, PhD, associate professor
Senior strategic advisor cancer, Skåne University Hospital Lund/Malmö, Sweden
Karolinska Institutet, Stockholm, Sweden

IHE Report 2016:4
e-ISSN 1651-8187

The report can be downloaded from IHE's website www.ihe.se

Please cite this report as:
Jönsson, B., Hofmarcher, T., Lindgren, P., Wilking, N. Comparator report on patient access to cancer medicines in Europe revisited. IHE Report 2016:4, IHE: Lund.

Content

Foreword

This report is an update of a report we published in 2005 on differences between European countries in patients´ access to new cancer drugs. The background to that report was the introduction of some important new cancer medicines in the late 1990s, and the rapid increase in the costs for cancer medicines that followed after that. We recognized the need for oncologists and health economists to work together to address the issues that this new field of medical innovation created. Most important is that the increase in costs as well as the new science behind and the value of the new treatment opportunities for patients could not be seen in isolation if the objective is to develop rational policies to make best use of the new opportunities. We have thus continued to work together to study the development in cancer science and how it is translated into clinical practice, including the economic consequences and benefits for patients.

In the first report we examined the ten-year period from 1995-2004 to understand the driving factors behind changes in medical oncology, and how new drugs were introduced and used in different countries. We looked into the availability of data to describe the situation, and developed a methodology for comparing access using the available data. Not surprisingly, everybody did not agree with our methods and results, and also pointed out shortcomings in the data we used. However, we noticed that we had defined the important questions, and many studies followed that challenged and complemented our findings, comparing selected groups of countries, medicines, and time periods, using mainly the same data sources, but with different definitions of access.

In this report we do a follow-up of the development for the ten-year period 2005-2014 with, in principle, the same method that we used in the first study. This has the advantage that we now can gain insight into what has happened over a twenty-year period with significant scientific and clinical progress in oncology. We are also using the same type of data, which has advantages, but also creates some frustration because we had expected more progress in collecting and publishing of data that support documentation and analysis of one of the most important changes in contemporary medicine. We still lack patient specific data to assess which patients that get what treatments, and with what outcome, that can be used for international comparative studies. But in the same way as we need to make decisions about the use of new cancer medicines before we know their actual value for different patients, we need to make policy decisions based on what we know about access, costs and outcome in different countries.

This is not a study with an answer to a single question and neither with a single answer to a specific question. We leave to the reader to investigate what can be learned from the report. But there are a few things that are noticeable. One is the lack of relevant data, which should be addressed. The second is that we yet have not seen any explosion in the costs for cancer care, but mainly a shift from cost for inpatient care to new cancer drugs. Spending on cancer does not reflect the burden of disease measured as share of total mortality or disability adjusted life years. You may also note from comparing this and the previous report that we do

not think that HTA plays the significant role for access that we predicted ten years ago. The main reason is that regulatory pivotal clinical trials do not provide the data for such assessment early in development. Instead we see a much more intense discussion about initial pricing at launch of new cancer medicines, and the need for follow up data in clinical practice for assessment of value and payment by outcome.

Equal access to cancer medicines remains a challenge in Europe and requires flexible pricing and reimbursement approaches that reflect the affordability levels of the different countries. Unequal access should have consequences for outcome, but we have not tried to directly link data on access to outcome in a statistical analysis. We may make a new attempt to see what the results look like in a later analysis.

Finally, while we discuss policy implications and potential measures to improve access, we have no prescriptions for specific solutions. We think that rational access policies must be developed at the country level. This does not mean that collaboration and exchange of information between EU member states is discouraged. But centralized European solutions will by default focus on prices, and it is obvious that the issues are too complicated for price control to be a solution.

We would like to thank Thomas Hofmarcher and Peter Lindgren for excellent research support for this updated version of the report, and Per Troin at IMS for assisting us in defining, extracting and interpretation of the data on the sales of cancer medicines 2005-2014. We would also like to thank Claire Machin at EFPIA for help in organizing and managing the project, and to the five pharmaceutical companies AstraZenca, J&J, MSD, Novartis and Roche that funded the project through a grant to IHE.

Stockholm 15 June, 2016

Bengt Jönsson

Nils Wilking

List of Abbreviations

ALL	Acute Lymphatic Leukaemia
AML	Acute Myeloid Leukaemia
ASCO	American Society of Clinical Oncology
ASMR	Amélioration du Service Médical Rendu (Improvement of Medical Benefit assessment)
AMNOG	Arzneimittelmarkt-Neuordnungsgesetz (Pharmaceuticals Market Reorganisation Act)
ATC	Anatomical Therapeutic Chemical classification
CML	Chronic Myeloid Leukaemia
CRC	Colorectal Cancer
CT	Computerized Tomographic Scanning
DDD	Defined Daily Dose, used to standardize the comparison of drug usage between different drugs or between different health care environments
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
ESMO-MCBS	ESMO Magnitude of Clinical Benefit Scale
GDP	Gross Domestic Product
GIST	Gastrointestinal Stromal Tumours
HTA	Health Technology Assessment
HER2	Human Epidermal Growth-factor Receptor 2
IGF1	Insulin-like Growth Factor 1
MRI	Magnetic Resonance Imaging
NCE	New Chemical Entity
NCCN	National Comprehensive Cancer Network
NSCLC	Non-Small Cell Lung Cancer
PET	Positron Emission Tomography
PDGF	Platelet-Derived Growth Factor
PPP	Purchasing Power Parity
RCC	Renal Cell Carcinoma
SEER	the Surveillance, Epidemiology, and End Result database in the US
TLV	Tandvårds- och Läkemedelförmånsverket (The Dental and Pharmaceutical Benefits Board)
VEGF	Vascular Endothelial Growth Factor

Country abbreviations:

AT	Austria
BE	Belgium
BG	Bulgaria
HR	Croatia
CH	Switzerland
CY	Cyprus
CZ	Czech Republic
DK	Denmark
EE	Estonia
FI	Finland
FR	France
DE	Germany
EL	Greece
HU	Hungary
IE	Ireland
IS	Iceland
IT	Italy
LV	Latvia
LT	Lithuania
LU	Luxembourg
MT	Malta
NL	Netherlands
NO	Norway
PL	Poland
PT	Portugal
RO	Romania
SK	Slovakia
SI	Slovenia
ES	Spain
SE	Sweden
UK	United Kingdom
EU-27	27 member states of the European Union before the accession of Croatia
EU-28	28 member states of the European Union

Executive summary

- Cancer incidence continues to rise across Europe. Cancer incidence totalled 2.707 million cases in Europe in 2012, up by about 30 per cent compared to 1995. Demographic factors (population growth and population aging) have spurred this development.
- Advances in diagnostics, medical treatment and screening have helped bring mortality rates down in relative terms. In 2012 the burden of cancer disease was second greatest with more than one in four deaths due to cancer.
- Spending on cancer does not reflect the burden of disease. Though the sales of cancer drugs have more than doubled between 2005 and 2014, the direct health cost of cancer has remained more or less flat around 6.0 per cent of total health expenditure over the last twenty years. A major contributing factor is the shift from in-patient to ambulatory and home care. This trend has been supported by the development of less toxic cancer medicines, oral agents and supportive drugs.
- There is a great difference between European countries with a six-fold difference in spending on cancer care per capita in 2014.
- There is a lack of systematically collected data on spending in cancer care to provide detailed estimates of health care spending on cancer in all European countries. Better data is needed in particular about private and public direct costs of cancer outside the health care system and about indirect costs (productivity loss) due to morbidity. This is necessary to be able to develop rational policies for access to new medicines as well as for assessing the efficiency of established treatments.
- Given the opposite trajectories of the direct health cost and the productivity loss due to premature mortality between 1995 and 2014, it seems likely that the direct health cost of cancer had surpassed the indirect cost of cancer by 2014.
- The future development of the economic burden of cancer is intertwined with the future development in cancer incidence, mortality, and survival, as well as the investments made in prevention, diagnostics, and treatment of cancer. While the relative disease burden of cancer is increasing, there is still no sign of a dramatic increase in the health spending on cancer as share of total health spending.
- Cancer care is changing fast in Europe. The latest development in cancer treatment is activating the body's own immune system to attack the tumour. Immuno-oncology has rapidly become standard of care in metastatic malignant melanoma and is studied in a number of other tumour types.
- Cancer treatment today is characterized by a multimodal therapy approach including surgery, radiotherapy and an increasing number of anti-tumour drugs. Optimal care of cancer patients requires multidisciplinary teams.
- Improved diagnostic methods and screening programs have facilitated early detection of tumours, which has led to improved cure rates in some cancer forms.
- Most anti-tumour drugs are introduced in patients with late stage- or metastatic disease. This may lead to improvements in survival, but the precise magnitude of that effect is

seldom known when the drug is first introduced. This development encourages payers and manufacturers to explore innovative pay for performance models to manage uncertainty about value. New diagnostic tools with functional imaging are increasingly used to evaluate effects of therapy and could further support this shift towards outcome based payment models.

- During the last 20 years, 98 NCEs belonging to the ATC groups L1 and L2A or B have been approved, 95 of these according to the EMA centralized procedure. There is a trend towards an increased number of cancer drug approvals in recent years.
- In Europe, sales of cancer drugs were € 8.0 billion in 2005 and € 19.8 billion in 2014.
- During the study period, there have been marked shifts among the top 10 selling drugs. Of the top 5 drugs in 2005, two are no longer in the top 10 in 2014 (docetaxel and oxaliplatin) and one (paclitaxel) is now at the far end of the list. Trastuzumab has almost doubled its share as No1 on the list, and several new agents are listed, e.g. bevacizumab and lenalidomide.
- Countries in Eastern and Southern Europe, with low GDP per capita, have sales at around 1/3 of sales in countries in Western Europe, both in 2005 and in 2014.
- Among the top 5 drugs in 2014, three have recently lost exclusivity, or will in the near future (trastuzumab, rituximab and imatinib). At the same time, uptake of new treatments is slow. The newest drugs (launched within the last three years) make up only 8% of the total average sales, varying between 4% and 11% per year in different countries, with the higher share in richer countries.
- Access to cancer drugs, especially new innovative drugs, varies in Europe and is mainly related to the countries' economic strength. This has not changed over time.
- There are significant variations in access also in different countries of similar economic strength, indicating opportunities for improvement through policies aiming at evidence based and cost-effective cancer care.
- Low national income and health care spending per capita are major obstacles for access to new cancer drugs. New cancer drugs are traded at an international market, and while the absolute price per unit is similar, the relative price is higher for countries with lower income. Parallel trade and international reference pricing limits the opportunities for price differentiation.
- There is an argument for a differentiated pricing in Europe to improve patients' access. A two-part tariff, including price volume agreements and different prices for different uses is common in many markets characterized by large investments (for instance transport, energy and telecoms) and could potentially help improve the situation. The division of competence between the EU member states and the EU institutions makes it difficult to agree at the European level on how this should be applied in practice. Decentralized solutions and flexible payment mechanisms in line with what is developed for health services are more likely to satisfy the different goals of patients, providers and payers in different member states, while at the same time provide incentives for the development of innovative medicines.
- The value of current and future cancer treatments should be at the core of the European debate. A number of initiatives have been launched to assist in determining the value of

new cancer medicines. Value as defined by ESMO-MCBS and actual uptake is connected, although not statistically significantly so. ESMO-MCBS also correlates with HTA assessments in France and Germany, but does not correlate well with assessments in Sweden. However, the assessment of value and cost-effectiveness needs to become more integrated and iterative to take into account new data over time.

- Early HTA advice and relative effectiveness assessments have been introduced as methods to make sure that the industry's efforts align with national priorities and that relevant information for assessment of patient benefit and value is provided for payers at time of launch. However, there will always be uncertainty about the value of a new drug at the time point when there is sufficient information about safety and efficacy to make a positive decision about market authorization.
- Market access agreements can be seen both as a response to the uncertainty around effectiveness of new and potentially valuable cancer drugs, and as a response to the demand for lower and more differentiated prices. A simple agreement on an undisclosed discount can both be seen as a correction for the uncertainty about the projected effectiveness, and as an adjustment of the price (price discrimination) to improve cost-effectiveness and/or affordability to gain a positive reimbursement decision in a specific market.
- Market access agreements are part of a trend towards more sophisticated strategies from public payers to commission health care from private providers. While this has been developed for the commissioning of services, the general knowledge about how to handle these types of contracts can be transferred to designing new contracts for medicines as well. When medicines are used in combination with diagnostics, and several medicines may be used in the same treatment process, the commissioning becomes more like a service commission than a single product commissioning. Cancer is the obvious field for application of this new approach to buying and paying for new medicines.

1 The burden and cost of cancer in Europe 1995–2014

Summary

- Cancer incidence totaled 2.707 million cases in Europe in 2012, up by about 30 percent compared to 1995. Demographic factors (population growth and population aging) have spurred this development. Even in their absence, cancer incidence would have still been on the rise in nearly all countries.
- Cancer mortality totaled 1.319 million deaths in Europe in 2012, up by 11 percent compared to 1995. Taking into account the demographic factors, cancer mortality decreased in nearly every single country.
- The central factors that drove a wedge between the trends in incidence and mortality are advances in diagnostics, medical treatment, and screening. This development was paralleled by a steady rise in cancer survival rates. Yet disparities remain between wealthier countries with higher survival rates and poorer countries with lower survival rates.
- Cancer is the disease group which caused the second greatest disease burden in terms of DALY (18 percent in 2000 and 19 percent in 2012) after cardiovascular diseases. More than one in four deaths was due to cancer in 2012.
- The direct health cost of cancer amounted to €87.9 billion in Europe in 2014, accounting for 6.0 percent of total health expenditure. This equals a 67 percent increase compared to 1995 (€52.7 billion in 2014 prices). Even though health spending on cancer has been increasing continuously since 1995, this happened not primarily because a greater share of total health expenditure was devoted to cancer, but rather because overall health spending increased.
- Per capita health spending on cancer increased from €107 to €169 in Europe between 1995 and 2014 (in 2014 prices). This masks large differences among countries. In 2014 it ranged from €53 in Romania to €311 in Luxembourg (PPP-adjusted); without adjustment for PPP it ranged from €27 in Romania to €441 in Switzerland.
- The largest component of the direct health cost of cancer is inpatient care accounting for more than half of all costs. At least since 2000 inpatient days of cancer patients have been declining in a process of moving treatment to ambulatory care and home care. However, this pattern is not specific to cancer patients and reflects a general trend in health care provision.
- Cancer drug sales doubled from €9.5 billion to €19.8 billion in Europe between 2005 and 2014 (in 2014 prices). The share of costs of cancer drugs on the direct health cost of cancer increased from 12 percent in 2005 to 23 percent in 2014. In most of the poorer countries this share was close to or above 30 percent in 2014. A striking divide in per capita spending on cancer drugs remains though. Poorer countries spent between €10-25 per capita on cancer drugs and wealthier ones between €35-70 in 2014.
- Direct costs of cancer outside the health care system are not well documented, and thus it is difficult to judge how they have developed. Increasing cancer incidence and survival among the elderly may have put additional pressure on both public resources (social care) and private resources (informal care).
- The indirect cost of cancer exceeded the direct health cost in Europe in 1995. Productivity loss due to premature mortality decreased from €57.1 to €50.7 billion between 1995 and

2014, as result of a decline in mortality during working age. Productivity loss due to morbidity is more difficult to assess, but it is smaller in size. Given the opposite trajectories of the direct health cost and the productivity loss due to premature mortality between 1995 and 2014, it seems likely that the direct health cost of cancer had surpassed the indirect cost of cancer by 2014.

- The future development of the economic burden of cancer is intertwined with the future development in cancer incidence, mortality, and survival, as well as the investments made in prevention, diagnostics, and treatment of cancer. While the relative disease burden of cancer is increasing, there is still no sign of a dramatic increase in the health spending on cancer as share of total health spending. However, there are significant shifts in the composition of the economic burden of cancer.

1.1 Health burden of cancer

The World Health Organization (WHO) defines cancer in the following way [1]:

> *Cancer is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumours and neoplasms. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs. This process is referred to as metastasis. Metastases are the major cause of death from cancer.*

Cancer is generally classified as an aging-associated disease, yet it affects people in all ages. This becomes evident in Figure 1. It shows how all newly diagnosed cancer cases in Europe in 2012 are distributed across different age groups. During childhood, adolescence, and even up to the age of 40 years cancer is a comparatively rare phenomenon. Above that age the disease becomes increasingly more prevalent. What seems like a leveling off around the age of 65 years in Figure 1 is a consequence of a lower number of people at that age. If the cancer cases were to be standardized by population size, a continuous increase with age would be evident. Nonetheless, in 2012 almost one third of all cases were diagnosed in people aged 75 years or older, lending credibility to the notion of cancer as an aging-associated disease.

Figure 1 also draws attention to somewhat different cancer patterns in men and women. Between around the ages of 15 to 55 years women seem to get the edge on men in terms of newly diagnosed cases, whereas the reverse is true at older ages. The reason for this is that common cancer types in women, such as breast cancer and cervical cancer, occur at comparatively younger ages than the most common cancer type in men, prostate cancer.

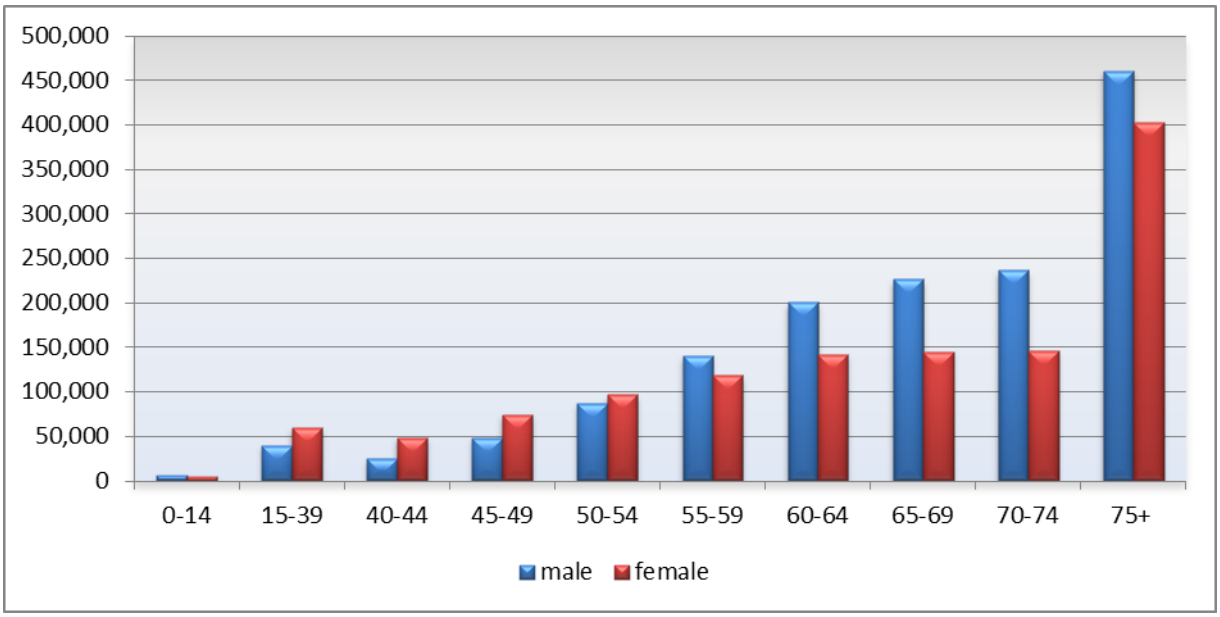


FIGURE 1: NUMBER OF NEW CANCER CASES BY AGE GROUP AND GENDER IN EUROPE, 2012 [2]

Notes: Cancer is defined according to International Classification of Diseases 10th revision (ICD-10) as C00-C97/C44.
The underlying estimate for France includes only metropolitan France.

To understand and analyze the burden of cancer the following sections draw heavily on epidemiological measures, such as incidence and mortality. The data for these measures were collected from databases and studies that were conducted under the auspices of the International Agency for Research on Cancer (IARC)[1]. Nevertheless it should be noted that the methods to estimate country-specific incidence and mortality figures changed slightly over time, and care should be taken when interpreting time trends. Incidence data come usually from national or regional cancer registries and only in two countries (Greece and Hungary) they had to be estimated solely based on data from neighboring countries throughout the whole time period considered. On the other hand, mortality data are available for all countries from the WHO mortality database. Whenever national estimates are based on regional data or estimated based on neighboring countries, this kind of lower data quality is indicated in the figures below.

The unit of analysis in this report is Europe, defined as the 28 member states of the European Union (EU-28) plus Iceland, Norway, and Switzerland. Whenever Europe refers to another composition of countries (e.g. inclusion of additional countries in Eastern Europe or on the Balkan; or exclusion of countries due to lack of data) this is noted in the report. In 1995

[1] Available from: http://www.iarc.fr/

Europe's population encompassed 493 million people and by 2014 it had grown to 520 million people.

1.1.1 Incidence

Cancer incidence refers to all newly diagnosed cases of cancer within a given year in a certain geographical area. In all of Europe[2] the estimated cancer incidence[3] was 2.609 million (1.2 million women, 1.4 million men) in 1995 [3]. Until 2012 this number had swelled by 31 percent to 3.414 million cases (1.603 million women, 1.810 million men) [4]. Using the main definition of Europe applied in this report, the estimated cancer incidence was 2.707 million cases (1.237 million women, 1.470 million men) in 2012 [2]. Even though there are no detailed country-level data available for 1995, it is clear from the overall figures that incidence must also have increased distinctly compared to 1995 in this narrower definition of Europe.

What explains this increase in absolute incidence figures between 1995 and 2012?

- Population growth: The total population in Europe grew by 5 percent from 493 to 519 million people [5]. Yet even in terms of cancer cases per inhabitant, the number of newly diagnosed cases went up; see the section on crude rates below.
- Population aging: The elderly account for a growing share of the total population, e.g., the share of people aged 65 years and older increased from 15 to 18 percent [5]. From Figure 1 it is clear that the risk of getting cancer increases at old age, and thus a growing share of elderly gives rise to more cancer cases. The question of what happens if the effect of population aging is taken into account is addressed in the section on age-standardized rates in the Appendix.
- Risk factors: Some lifestyle factors such as overweight/obesity (which are linked to, inter alia, colorectal cancer) have increased during the last decades in Europe, while smoking rates (which are linked to, inter alia, lung cancer) have started to decline [6]. However, there might be considerable time lags between the onset of exposure to risk factors and the development of cancer. For instance, taking the case of declining smoking rates, it will take a few decades before this change finds an expression in decreasing lung cancer incidence. In men lung cancer incidence stabilized already in the recent decade in some countries paralleling a stagnation or downturn in smoking rates in the 1980s and 1990s, whereas the incidence in women is strongly on the rise as a result of increasing smoking rates at least until the 1980s.
- Screening: Population screening programs for breast, prostate, cervical and colorectal cancer have become more common [7]. This higher screening activity might have led to the detection of more cancer cases rather than a true increase in the number of new cases.

[2] This includes all EU-28 member states but Cyprus, as well as Iceland, Norway, Switzerland, all remaining Balkan states, Belarus, Moldova, Ukraine, and Russia.
[3] All cancer sites but non-melanoma skin (ICD-10 C00-C97/C44).

- The epidemiological development in other diseases influences cancer incidence. For instance, the decline in mortality rates from cardiovascular diseases in recent decades implies that more people reach an advanced age. This leaves more people at risk of getting cancer [8].

While the overall number of new cancer cases has been increasing, the pace of the increase was not uniform across all different cancer types. As a consequence, the share of different cancer types has shifted markedly – some have become more and others less common in relative terms; see Table 1. In both men and women, the five most common cancer types accounted for around 60 percent of all cases in both 1995 and 2012. The most common cancer type in men was lung cancer in 1995 but in 2012 it was prostate cancer, which recorded a massive climb from representing every ninth cancer case in 1995 to almost every fourth cancer case 18 years later. However, it remains unclear to what extent the increasing trends in prostate cancer incidence indicate true risk and how much is due to detection of latent disease [9]. Breast cancer remained by far the most common cancer type in women, and lung cancer edged up to the third place.

TABLE 1: SHARE OF TOP 5 NEWLY DIAGNOSED CANCER TYPES IN EUROPE* BY GENDER, 1995–2012 [3, 4]

1995		men	2012
1st Lung cancer	22%	1st Prostate cancer	23%
2nd Colorectal cancer	12%	2nd Lung cancer	16%
3rd Prostate cancer	11%	3rd Colorectal cancer	13%
4th Stomach cancer	9%	4th Bladder cancer	6%
5th Bladder cancer	7%	5th Stomach cancer	5%
1995		women	2012
1st Breast cancer	26%	1st Breast cancer	29%
2nd Colorectal cancer	14%	2nd Colorectal cancer	13%
3rd Stomach cancer	7%	3rd Lung cancer	7%
4th Lung cancer	6%	4th Corpus uteri cancer	6%
5th Cervix uteri cancer	6%	5th Ovary cancer	4%

Notes: *Europe includes the EU-28 (except Cyprus in 1995), Iceland, Norway, Switzerland, all remaining Balkan states, Belarus, Moldova, Ukraine, and Russia.

1.1.1.1 Crude rates

Age-standardized rates are conceptually a neat way of comparing countries, but they are less relevant for fiscal policy-making in the health area. Countries with an older population have, ceteris paribus, more cancer cases to take care of and hence face a greater fiscal challenge. Crude rates are therefore a more helpful measure in this regard.

Figure 2 shows crude rates for cancer incidence for all cancers combined and for both sexes. Among those countries for which data are available in 1995, Italy, Germany, and the UK had

the highest incidence rates with over 460 cases per 100,000 inhabitants, and Bulgaria, Lithuania, and Malta had the lowest ones with around or below 300 cases per 100,000 inhabitants. In 2012 Denmark, Germany, and Italy recorded the highest rates with around or over 600 cases per 100,000 inhabitants, and Greece, Romania, and Cyprus the lowest rates with around or below 400 cases per 100,000 inhabitants. It is also evident that all countries experienced distinct increases in the incidence rates between 1995 and 2012.

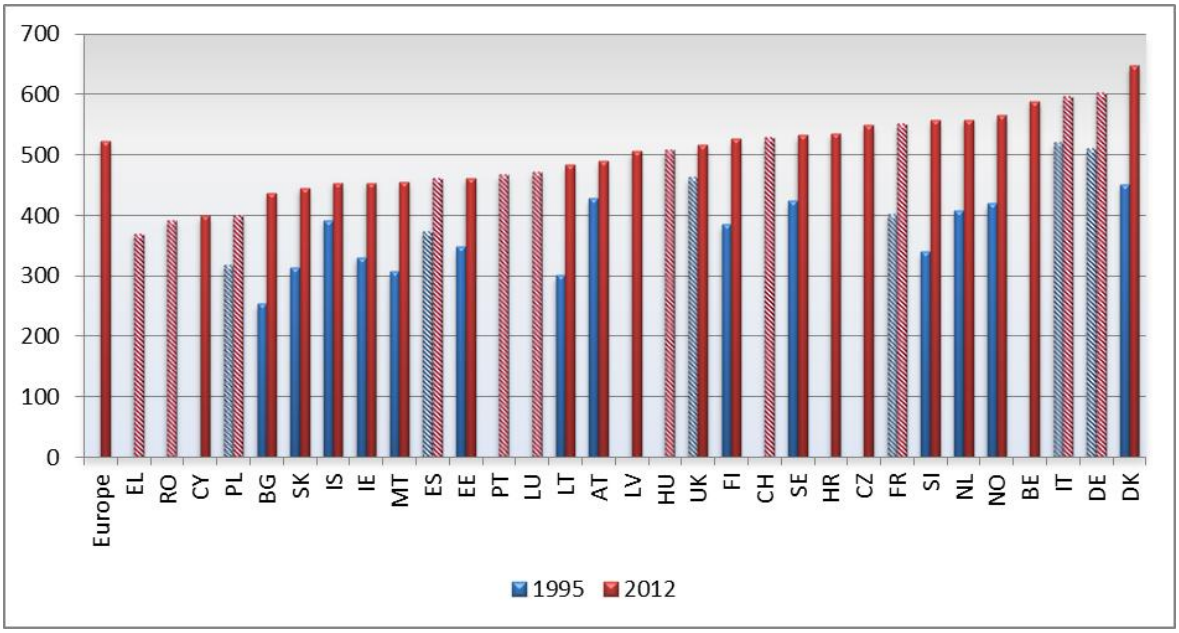


FIGURE 2: ESTIMATED NUMBER OF CANCER INCIDENCE CASES PER 100,000 INHABITANTS (CRUDE RATES FOR BOTH SEXES), 1995–2012 [2, 10]

Notes: Hatched bars indicate that national estimates are based on regional data or based on neighboring countries.
Estimates include all cancers combined, excluding non-melanoma skin cancer (ICD-10 C00-C97/C44).
BE, HR, CY, CZ, EL, HU, LV, LU, PT, RO, CH in 1995 are missing due to lack of data on incidence cases.
Incidence cases in 1995 were based on regional data in Germany (Hamburg, Saarland), France (Doubs, Haut-Rhin, Hérault, Isère, Manche, Somme, Tarn), Italy (Umbria, Veneto), Poland (Lower Silesia), Spain (Balearic Islands, Basque country, La Rioja, Navarre, Region of Murcia), and the UK (East of England, Northern Ireland, Scotland, Wales) and scaled-up to the national level based on population data from Eurostat.
The incidence estimates for France refer to metropolitan France.

To assess the development over time in a more transparent and comparable way, the relative change in crude rates between 1995 and 2012 can be computed. Figure 3 plots this relative change against the purchasing power parity (PPP) adjusted gross domestic product (GDP) per capita in 2004. The year 2004 was chosen as a rough proxy for how affluent countries were on average during this 18 year period, which in turn is indicative of how many resources that potentially could have been allocated to cancer care.

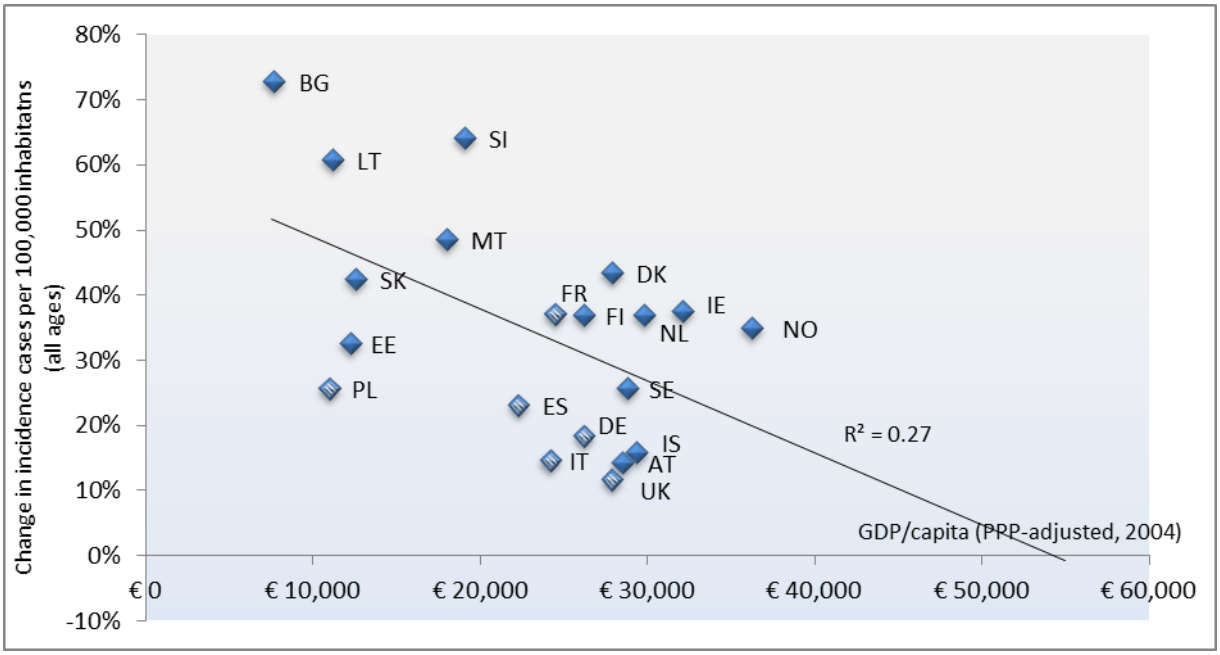


FIGURE 3: ESTIMATED CHANGE IN THE NUMBER OF CANCER INCIDENCE CASES PER 100,000 INHABITANTS (CRUDE RATES FOR BOTH SEXES) BETWEEN 1995–2012 (Y-AXIS) AND PPP-ADJUSTED GDP PER CAPITA IN 2004 (X-AXIS), [2, 10, 11]

Notes: see Figure 2.
Hatched dots indicate that national estimates are based on regional data.
The incidence estimates for France refer to metropolitan France, while the GDP estimate refers to all of France.
The regression line does not take into account underlying population sizes, i.e. each country is weighted equally.

From Figure 3 it is evident that the increases in crude cancer incidence rates between 1995 and 2012 ranged from 10 percent in the UK to 75 percent in Bulgaria. A weak negative association is noticeable between the magnitude of the increase and a country's GDP per capita. This suggests that incidence rates in wealthier countries increased less than in poorer countries. Nevertheless there is a great amount of dispersion, since a country like Slovakia recorded an increase of about 40 percent just as Denmark did, even though Denmark's GDP per capita was 2.5 times higher. This negative association should not be over-interpreted, since GDP per capita also correlates with the age structure in the population. Population aging occurred in all countries during 1995 and 2012, but in wealthier countries, such as Germany or Italy, it might have taken place at a slower pace than in poorer countries[4]. In turn this would mean that the negative association is a product of quicker population aging in poorer countries that drove up incidence rates. An additional explanation for the negative association is connected to the economic catch-up process of poorer countries. Their economies grew

[4] In the Eastern European countries faster population aging compared to Western or Northern European countries is partly a product of emigration of younger people. This reinforces the share of elderly people in the total population and hence naturally drives up the incidence cases per 100,000 inhabitants.

quickly between 1995 and 2012 which allowed them to invest in modern equipment for diagnostics and might have resulted in the detection of comparatively more cancer cases.

1.1.2 Mortality

Cancer mortality refers to all deaths due to cancer within a given year in a certain geographical area. In all of Europe[5] the estimated cancer mortality[6] in 1995 amounted to 1.624 million deaths (0.7 million women, 0.9 million men) [3]. Until 2012 this number had grown by 8 percent to 1.754 million cases (0.778 million women, 0.975 million men) [4]. Using the main definition of Europe applied in this report, the estimated cancer mortality[7] was 1.319 million deaths (0.579 million women, 0.739 million men) in 2012, up 11 percent from 1.192 million deaths (0.524 million women, 0.668 million men) in 1995[8] [12].

What explains this increase in absolute mortality figures between 1995 and 2012?

- The increase in newly diagnosed cancer cases between 1995 and 2012 means that the number of patients that might eventually die from their cancer increased as well. In the absence of improvements in survival, a higher number of cancer patients would thus automatically imply a higher number of deaths. Hence, the factors explaining the increase in cancer incidence are also important for explaining the cancer mortality figures.
- Population growth: As noted in the previous section on incidence, the population in Europe grew by 5 percent during this period. Thus, this factor alone can explain about half of the increase; see the section on crude rates below.
- Population aging: As noted before, the population has become older and a growing number of elderly people gives rise to more cancer cases, since the risk of getting cancer increases at old age. The section on age-standardized rates in the Appendix shows what would have happened in the absence of population aging.
- The epidemiological development in other leading causes of death, in particular the decline in cardiovascular diseases in recent decades, influences cancer mortality figures. The idea here is that since more people reach an advanced age, this leaves more people at risk of getting cancer and eventually also die from cancer. If this effect of competing causes of death is taken into account, cancer mortality might have decreased [8].

While the overall number of mortality cases has been increasing, this is not true for all different cancer types. As a consequence, the share of different cancer types has shifted

[5] This includes all EU-28 member states but Cyprus, as well as Iceland, Norway, Switzerland, all remaining Balkan states, Belarus, Moldova, Ukraine, and Russia.
[6] All cancer sites but non-melanoma skin (ICD-10 C00-C97/C44).
[7] All cancer sites and human immunodeficiency virus (HIV) disease resulting in malignant neoplasms (ICD-10 C00-C97,B21).
[8] The estimate for 2012 includes data for France from 2011, Iceland from 2009, and Slovenia from 2010; the estimate for 1995 includes data from 2004 for Cyprus.

markedly – some have become more and others less common in relative terms; see Table 2. In both men and women, five cancer types accounted for around 50 to 60 percent of all cancer deaths in both 1995 and 2012. Lung cancer was by far the most common cause of death in men with more than every fourth cancer death attributable to this cancer type in both 1995 and 2012. Breast cancer was the most common cause of death in women with every sixth cancer death attributable to this cancer type in both 1995 and 2012. Death from lung cancer in women has become more common, and according to forecasts it will have become the leading cause of death already by 2015 [13]. Death due to stomach cancer has seen a drop in both men and women, probably stemming from a comparable drop in incidence cases; see Table 1 for comparison.

TABLE 2: SHARE OF TOP 5 FATAL CANCER TYPES IN EUROPE* BY GENDER, 1995–2012 [3, 4]

1995		men	2012
1st Lung cancer	29%	1st Lung cancer	26%
2nd Stomach cancer	10%	2nd Colorectal cancer	12%
3rd Colorectal cancer	10%	3rd Prostate cancer	9%
4th Prostate cancer	8%	4th Stomach cancer	7%
5th (not reported)	-	5th Pancreatic cancer	5%
1995		women	2012
1st Breast cancer	17%	1st Breast cancer	17%
2nd Colorectal cancer	14%	2nd Colorectal cancer	13%
3rd Lung cancer	9%	3rd Lung cancer	13%
4th Stomach cancer	9%	4th Pancreatic cancer	7%
5th (not reported)	-	5th Stomach cancer	6%

Notes: *Europe includes the EU-28 (except Cyprus in 1995), Iceland, Norway, Switzerland, all remaining Balkan states, Belarus, Moldova, Ukraine, and Russia.

To put the figures on cancer mortality into context and to understand the burden of cancer, it is helpful to consider cancer deaths and all deaths together. 5.122 million people died in Europe (excluding Iceland) in 2012 of which 1.323 million deaths were due to cancer. This means that more than one in four deaths was caused by cancer. Figure 4 shows how these deaths are distributed across age. Both the number of cancer deaths and all deaths increase throughout most of the age range before falling off after age 90. Cancer deaths peak at age 75-79 and 80-84 with about 200,000 deaths in each age group. All deaths peak a bit later at age 85-89. Almost half of all cancer deaths occur in people aged 75 years or older, which is naturally higher than the one third of all new cancer cases that are diagnosed in people in this age group.

In Figure 5 cancer deaths are considered in relative terms of all deaths. Here it becomes clear that the share of cancer deaths on all deaths has two peaks. The first one is during childhood

(5 to 15 years) where more than one in five deaths is due to cancer. The second peak occurs between age 55 to 69, causing around 43 to 44 percent of all deaths in this age group.

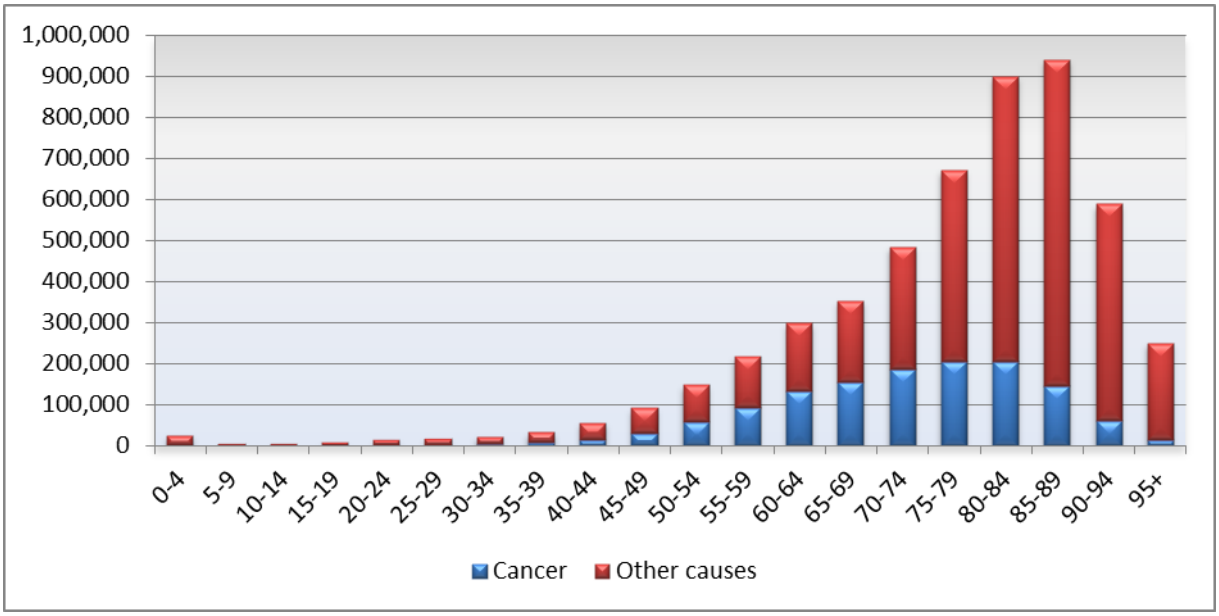


FIGURE 4: NUMBER OF DEATHS BY CAUSE AND AGE GROUP IN EUROPE, 2012 [14]

Notes: Cancer is defined as ICD-10 C00-C97, other causes as all causes of death (A00-Y89) excluding S00-T98 and C00-C97.
Deaths refer to all deaths reported in a country.
The underlying data for Iceland are missing.

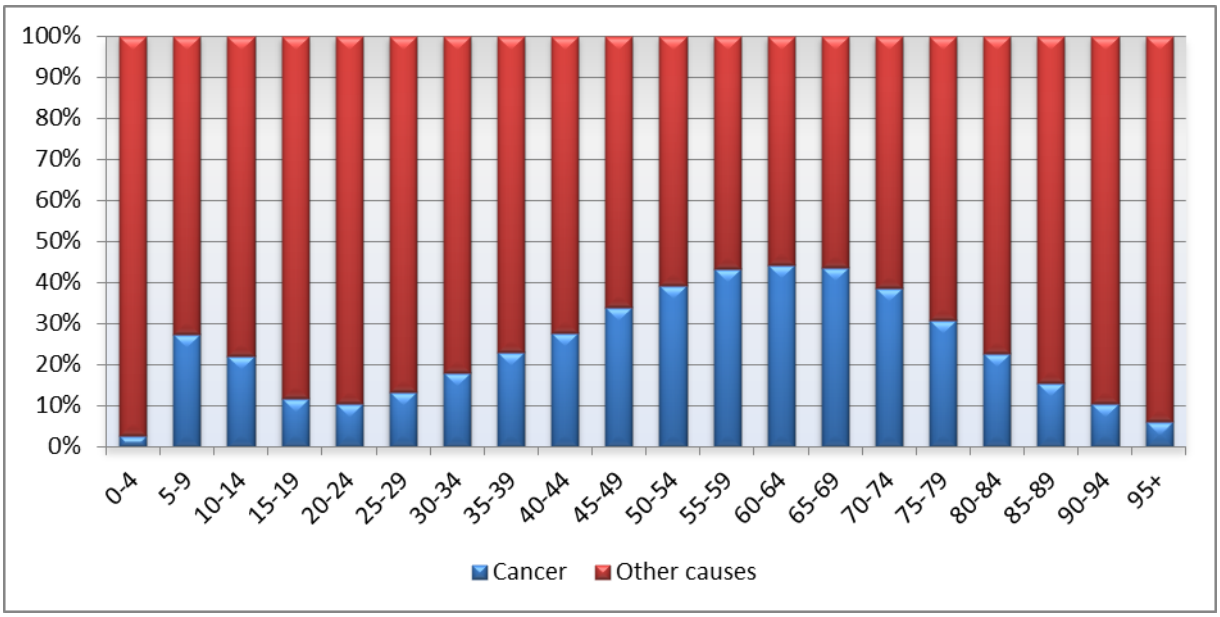


FIGURE 5: SHARE OF DEATHS DUE TO CANCER ON ALL DEATHS BY AGE GROUP IN EUROPE, 2012 [14]

Notes: see **Figure 4**

1.1.2.1 Crude rates

Crude rates for cancer mortality for all cancers combined and for both sexes are shown in Figure 6. In 1995 Hungary and Denmark had the highest mortality rates with over 300 cases per 100,000 inhabitants, and Romania and Iceland had the lowest ones with below 200 cases per 100,000 inhabitants. In 2012 Hungary and Croatia recorded the highest rates with over 300 cases per 100,000 inhabitants, and Cyprus and Ireland the lowest rates with below 200 cases per 100,000 inhabitants. The absolute differences in mortality rates between countries have become smaller over time.

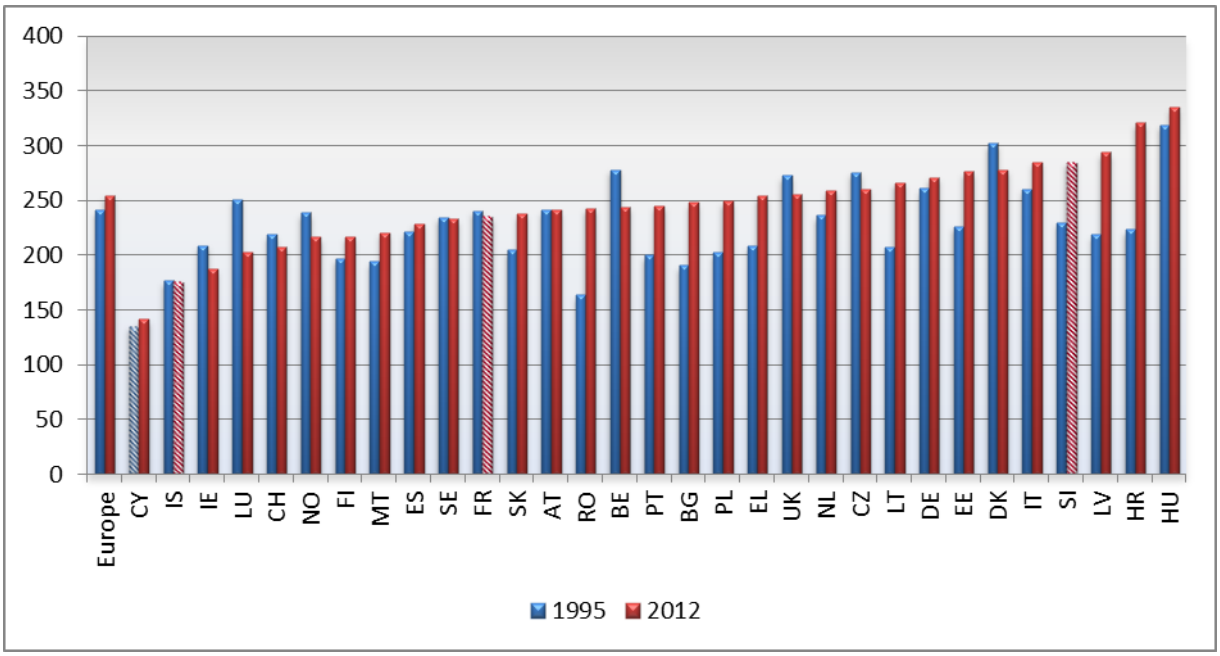


FIGURE 6: ESTIMATED NUMBER OF CANCER MORTALITY CASES PER 100,000 INHABITANTS (CRUDE RATES FOR BOTH SEXES), 1995–2012 [12]

Notes: Cancer is defined as ICD-10 C00-C97,B21.
Hatched bars indicate that data for 1995 for Cyprus refer to 2004; data for 2012 for France refer to 2011, for Slovenia to 2010, and for Iceland to 2009.

Figure 7 shows how mortality crude rates for both sexes (see Figure 6) in all countries changed in relative terms between 1995 and 2012. As before, this change is plotted against the PPP-adjusted GDP per capita in 2004. The first observation is that a majority of countries lies above the zero percent line, indicating that mortality cases per 100,000 inhabitants increased. In all of Europe the increase was 6 percent. However, looking at individual countries the change in mortality rates ranged from a decrease of 20 percent in Luxembourg to an increase of 50 percent in Romania. This result stands in stark contrast to the previous one for age-standardized rates. Age-standardized mortality rates decreased markedly in all countries (but Romania and Bulgaria), whereas crude mortality rates increased in a majority of countries. Since the key difference between age-standardized rates and crude rates is that the effect of

population aging is taken into account in the former concept, it is apparent that population aging is of importance here.

The second observation from Figure 7 is that there seems to be a close negative association between the change in mortality crude rates and GDP per capita. The wealthier the country, the lower the increase was (in fact several of the wealthier ones recorded a decrease); and the poorer the country, the higher the increase was. As cautioned in the previous section on incidence, this association should not be over-interpreted, since GDP per capita could possibly be a proxy for the extent or the pace of population aging. However, different to the pattern in crude incidence rates that increased in all countries, several countries recorded a decrease in crude mortality rates, as Figure 7 shows. Thus, despite the effect of population aging that would push crude mortality rates upwards, some countries were able fight against the odds and decrease the rates. This suggests that other factors than purely demographic ones must have been responsible for that development. The negative association in Figure 7 hints that GDP per capita and with that the absolute amount of potential resources available for health care might have played an important role in keeping increasing mortality rates at bay.

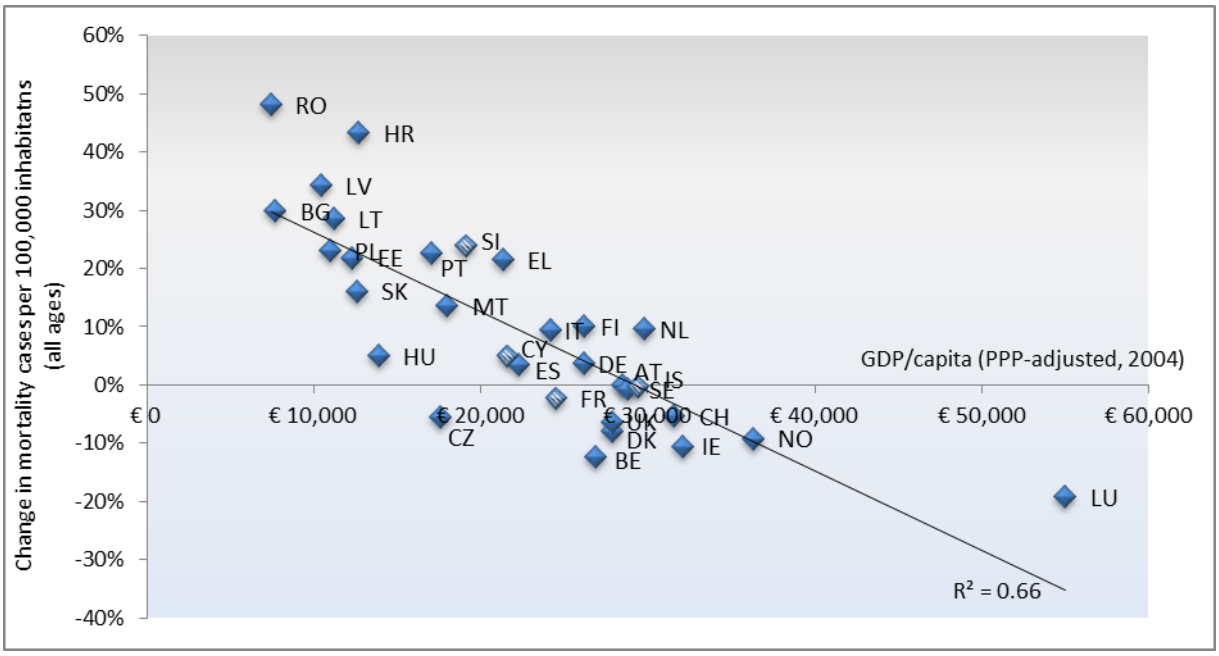


FIGURE 7: ESTIMATED CHANGE IN THE NUMBER OF CANCER MORTALITY CASES PER 100,000 INHABITANTS (CRUDE RATES FOR BOTH SEXES) BETWEEN 1995–2012 (Y-AXIS) AND PPP-ADJUSTED GDP PER CAPITA IN 2004 IN € (X-AXIS), [11, 12]

Notes: Cancer is defined as ICD-10 C00-C97,B21.
Hatched dots indicate that the change in mortality cases is between 1995 and 2011 for France, between 1995 and 2010 for Slovenia, between 1995 and 2009 for Iceland, and between 2004 and 2012 for Cyprus.
The regression line does not take into account underlying population sizes, i.e. each country is weighted equally.

The analysis of cancer incidence and mortality has revealed different trends in their respective development. If measured in absolute numbers, incidence figures increased by 31 percent and mortality figures by 8 percent in (a wider definition of) Europe between 1995 and 2012. From the consideration of age-standardized rates (see Appendix) which took into account the effects of population growth and population aging during this period, it became clear that incidence figures still showed an increase but mortality figures showed a decrease. This discrepancy in the upward trend of cancer incidence and the downward trend of cancer mortality is also reflected by the simultaneous improvement in survival rates; see section 1.1.3 below. The cause behind this development has been summarized as "major advances in cancer management" [15].

Viewed holistically, cancer management refers to all the actions that are taken in the cancer patient pathway. It encompasses primary prevention, screening, diagnostics, and treatment with curative and palliative intent [16]. Although it is not completely clear by how much each of these components of cancer management contributed to the observed discrepancy in the trends between incidence and mortality, the following deductions can be made:

- Primary prevention: This includes measures such as efforts to decrease smoking rates, promote healthier dietary habits and physical activity, lower air pollution, implement more comprehensive vaccination programs against hepatitis B virus infection to prevent liver cancer, and more comprehensive vaccination programs against human papillomavirus (HPV) for girls/women to mainly prevent cervical cancer and for boys/men to prevent HPV-related anal, neck and oropharyngeal cancers. Since these measures aim at preventing cancer from occurring in the first place (i.e. they contribute to decrease cancer incidence), this component of cancer management cannot be part of the explanation for the different trends.
- Screening: The roll-out of population screening programs for certain major cancer types in many countries during the 2000s might have led to the detection of a larger share of cancer cases at an early stage [17-19]. Since the curability at an early stage is higher than at an advanced stage, screening programs would be expected to moderate the increase in deaths from these cancer types. Additionally, mass screening has, e.g. for prostate cancer, led to the detection of latent disease cases. This phenomenon has inflated incidence but since the disease is latent, mortality from it is, by definition, zero. Thus, screening forms a component of cancer management that can offer some explanation for certain cancer types that influence the overall development in all cancers.
- Diagnostics: The aim of diagnostics is to locate the cancer and determine its spread. During the last decades the introduction of computed tomography (CT) scanners, magnetic resonance imaging (MRI) scanners, and positron emission tomography–computed tomography (PET-CT) scanners has improved the possibilities of accurate diagnostics. Since the investment costs for such medical equipment is high, availability of and access to it differs between countries and might explain some of the country-

level differences. As is the case for screening, improved diagnostics 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 can thus explain some part of the diverging trend between incidence and mortality. Based on mortality data from the United States during 2000-2009 it has been shown that better diagnostics explains indeed some of the observed decline there [20].

- Treatment: Cancer is usually initially treated with surgery or radiation therapy with curative intent and sometimes preceded by neoadjuvant systemic therapy (which encompasses chemotherapy, hormonal therapy, immunotherapy, and molecularly targeted therapy). In many cases it is succeeded by adjuvant systemic therapy. Radiation therapy, as well as systemic therapy and to some extent surgery, is also extensively used in palliative care. Both the availability of radiation therapy machines and the availability of effective cancer drugs for systemic therapy have been improving during the last decades. New therapy modalities such as molecularly targeted therapy and immunotherapy have been developed and increasingly used; see chapter 2 and 3 in this report. This enabled not only access to more effective treatments but also allowed for a wider share of patients to be eligible for drug treatment. As stated above, screening and diagnostics can only unfold their positive effects on cancer mortality if they are followed up by appropriate medical treatment. But also advances in medical treatment itself affect mortality. Based on mortality data from the United States during 2000–2009 it has been shown that the introduction of novel cancer drugs explains indeed some of the observed decline there [20]. A study drawing on Dutch mortality data during 1960–2008 also presented suggestive evidence on a connection between the introduction of novel cancer drugs and declining cancer mortality [21]. Consequently, medical treatment as the central component of cancer management can also offer some explanation for the different trends in incidence and mortality.

1.1.3 Survival

Survival is the central 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 reflect both how early cancers are being detected and the effectiveness of cancer treatment [22].

Survival rates are often measured in terms of 5-year survival rates, i.e. the share of people diagnosed with cancer in some 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 2015 can only be evaluated after 2020 with this method called “cohort analysis”. There are however other methods (“period analysis” and “mixed analysis”) available to circumvent this problem [23, 24].

Two adjustments are usually made to survival rates to receive comparable figures across countries. Firstly, relative survival rates rather than absolute survival rates are compared. The relative survival rate is the ratio of two survival rates: the absolute survival rate of cancer patients divided by the expected survival rate of the general population with corresponding age structure and gender mix in the same country (or region) and calendar year[9] [25]. This adjusts survival rates for the effect of competing causes of death that could bias comparisons between countries. Thus relative survival rates indicate the hypothetical situation in which cancer is the only cause of death [23, 26]. Secondly, the age structure of cancer patients differs between countries, and also relative survival rates vary by age (typically they decrease with age) for most cancer types. Therefore, relative survival rates are adjusted for age [26].

Comparable data on cancer survival for European countries are collected and provided by EUROCARE, the EUROpean CAncer REgistry-based study on survival and care of cancer patients. The projects EUROCARE-3, EUROCARE-4, and EUROCARE-5 cover cancer patients diagnosed between 1990 and 2007. The data availability has been improving over the years. The latest project, EUROCARE-5, provided survival rates for Iceland, Norway, Switzerland, and 23 of the EU-28 member states, only Cyprus, Greece, Hungary, Luxembourg, and Romania are missing. Even the coverage of the total population has been improving over time in countries with cancer registries that originally only covered certain regions. In EUROCARE-5 survival rates are only based on regional data in Belgium, France, Germany, Italy, Poland, Portugal, Spain, and Switzerland [15, 27].

Even though comprehensive country-specific data for different cancer types have been published [15, 27], the accompanying online databases[10] provide greater detail and are used for the analysis below. Survival rates for all cancers combined are presented below. Survival rates for the four most common cancer types, lung cancer, colorectal cancer, breast cancer, and prostate cancer, as well as the long-term trend in survival rates for selected countries are presented in the Appendix. The outcome measure is the 5-year age-adjusted relative survival rate in adult patients (age ≥15 years).

The average 5-year relative survival rate for all cancer types combined was 54 percent in Europe for cancers diagnosed between 2000 and 2007. The rates varied from 40 percent in Bulgaria to 64 percent in Sweden; see Figure 8. There is a rather clear pattern of wealthier countries to record higher survival rates, whereas poorer countries record lower rates.

[9] For instance, let's assume that the observed share of cancer patients that are alive 5 years after their diagnosis is 60%. This is the absolute survival rate. Then, in addition, assume that the 5-year expected survival rate in the general population (with the same age structure, the same gender mix and during the same time period) is 80%. The 5-year relative survival rate is then 60%/80% = 75%. Thus, of the 40% (100% – 60%) of cancer patients who died 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.

[10] Available from: http://www.eurocare.it/ (accessed January 19, 2016)

Noteworthy exceptions to this pattern are the UK and Denmark whose survival rates are below the European average. Regarding the development over time between 1990–1994 and 2000–2007 improvements have been achieved in all countries.

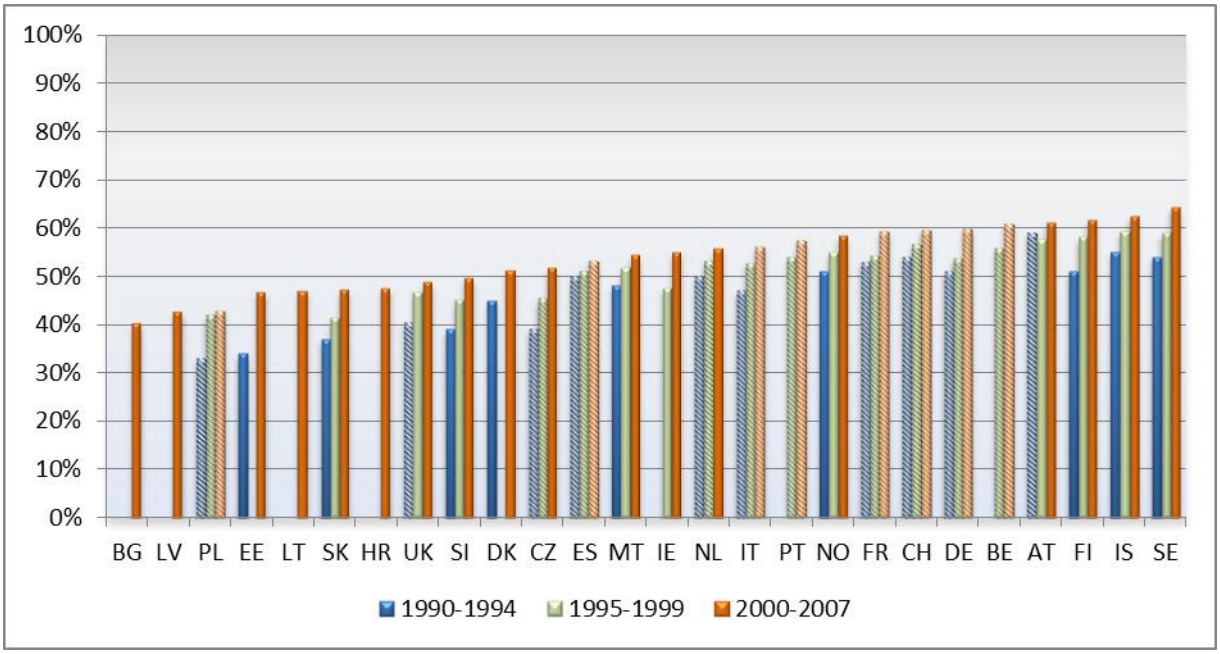


FIGURE 8: 5-YEAR AGE-ADJUSTED RELATIVE SURVIVAL RATES FOR ALL CANCERS IN PATIENTS AGED ≥15 YEARS, 1990–2007 [15, 27]

Notes: Hatched bars indicate that national estimates are based on regional data.
The survival rates for the UK are calculated as the arithmetic average of the rates from England, Northern Ireland, Scotland, and Wales (in 1990-1994 only from England, Scotland, and Wales).
CY, EL, HU, LU, and RO are missing due to lack of data.

Despite survival rates being a central measure of how well cancer care is functioning in a country, there are considerable time lags involved in the publication of data. The lack of up-to-date data means that causal inferences have to be made carefully, because the current quality of cancer care can only be judged retrospectively in a few years from now, when the survival rates of today's patients can be evaluated. This constitutes a challenge for informing health policy makers as well as patients [16].

1.1.4 Burden of disease

One crude measure to quantify the health burden of a disease like cancer is to look at the number of deaths due to this disease. However, there are many non-fatal diseases and health conditions that also represent a huge health burden to society. To take into account both elements of a disease, i.e. the impact on people's lives living with this disease (morbidity) and premature death due to this disease (mortality), another more advanced measure is needed. A measure that fulfills this requirement is Disability Adjusted Life Years (DALYs). It has been

developed for the WHO. Alternative measures are years of potential life lost (YPLL), although this one disregards the morbidity burden, and quality-adjusted life years (QALYs), for which no comparable country-level data across the whole disease spectrum are available.

One DALY represents one lost year of "healthy" life. 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 measurement of the gap between the current health state of the population and an ideal health 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 Life Lost (YLL) due to premature death caused by the disease or health condition, and Years Lost due to Disability (YLD) for people living with the disease or health condition [28]. Comparable country-level data are available for 2000 and 2012[11].

Table 3 provides an overview of the disease burden in Europe and its development between 2000 and 2012. Several trends are noteworthy. Firstly, in the bottom row it can be seen that the total disease burden decreased both in absolute terms from 159 to 155 million DALYs and even stronger in per capita terms from 319 to 298 DALYs per 1,000 inhabitants. Secondly, cancer (defined as malignant neoplasms) is the disease group which caused the second greatest burden after cardiovascular diseases. Thirdly, the order of the five disease groups and health conditions causing the greatest burden remained unchanged between 2000 and 2012. Fourthly, despite remaining the disease group with the greatest burden, cardiovascular diseases' share of the total disease burden decreased markedly from 25 to 21 percent between 2000 and 2012. This is due to substantial decreases in mortality in cardiovascular diseases during this period [29]. If this trend continues, it will not be before long that cancer (which increased its share from 18 to 19 percent) will represent the disease group with the greatest burden. It should be noted though that even the burden of cancer decreased marginally in per capita terms from 59 to 58 DALYs per 1,000 inhabitants; in absolute terms the burden increased slightly.

[11] Note that these data were published in 2014. They are not comparable to earlier burden of disease data from the WHO for the years 2000 and 2004, in which social value weights (age-weighting and discounting) were applied [28].

TABLE 3: DISEASE BURDEN OF THE TOP 5 DISEASE GROUPS IN EUROPE, 2000–2012 [30]

	2000				2012			
	Total DALYs ('000)	DALYs/ 1,000 inhab	Share	Share of YLL	Total DALYs ('000)	DALYs/ 1,000 inhab	Share	Share of YLL
1st Cardiovascular diseases	39,112	78	25%	93%	32,500	62	21%	90%
2nd Cancer	29,375	59	18%	97%	30,228	58	19%	97%
3rd Mental and behavioral disorders	17,571	35	11%	8%	18,150	35	12%	8%
4th Injuries	15,692	31	10%	63%	13,853	27	9%	52%
5th Musculoskeletal diseases	11,908	24	7%	3%	13,080	25	8%	3%
All disease groups	159,223	319	100%	63%	155,304	298	100%	59%

Since DALYs are composed of a morbidity component (YLD) and a mortality component (YLL), it is possible to look at the composition of the disease burden. This provides more insights into the nature of diseases; see Table 3. For instance, among the top five disease groups, the mortality component in mental and behavioral disorders (such as unipolar depressive disorders or alcohol use disorders) as well as in musculoskeletal diseases (such as back and neck pain) represents less than 10 percent of the burden. For injuries the mortality component represents half of the disease burden, and for cardiovascular diseases about 90 percent. For cancer the mortality component accounts for 97 percent of the disease burden and the morbidity component for the remaining 3 percent. Thus, the disease burden of cancer is effectively solely caused by premature death.

Regarding the disease burden of the most common cancer types different trends are noticeable in Table 4 between 2000 and 2012. Cancers of the lung, trachea, and bronchus, which mainly are related to smoking, caused the greatest burden and their share increased slightly. Colorectal cancer was in the second position and showed no signs of decline, whereas the burden of breast cancer in the third position decreased slightly. Among other cancer types noteworthy changes of the burden were recorded for pancreatic cancer which increased, and stomach cancer which decreased. The disease burden of all cancer types is dominated by the mortality component. This is especially true for cancer types with low survival chances (e.g. pancreatic or lung cancer) where it amounts to 99 percent. In cancer types with good survival chances (e.g. prostate and breast cancer) the morbidity component constitutes a relatively larger share of up to 10 percent.

TABLE 4: DISEASE BURDEN OF THE TOP 10 CANCERS (MALIGNANT NEOPLASMS) IN EUROPE, 2000–2012 [30]

2000					2012				
	Total DALYs ('000)	DALYs/ 1,000 inhab	Share	Share of YLL		Total DALYs ('000)	DALYs/ 1,000 inhab	Share	Share of YLL
1st Trachea, bronchus, lung	6,144	12	20.9%	99%	1st Trachea, bronchus, lung	6,611	13	21.9%	99%
2nd Colorectal	3,387	7	11.5%	97%	2nd Colorectal	3,492	7	11.6%	96%
3rd Breast	2,760	6	9.4%	93%	3rd Breast	2,598	5	8.6%	91%
4th Stomach	1,733	3	5.9%	98%	4th Pancreatic	1,780	3	5.9%	99%
5th Lymphomas, multiple myeloma	1,414	3	4.8%	98%	5th Prostate	1,420	3	4.7%	90%
6th Pancreatic	1,398	3	4.8%	99%	6th Stomach	1,394	3	4.6%	98%
7th Prostate	1,327	3	4.5%	93%	7th Lymphomas, multiple myeloma	1,355	3	4.5%	98%
8th Leukemia	1,062	2	3.6%	98%	8th Liver	1,137	2	3.8%	99%
9th Liver	1,000	2	3.4%	99%	9th Leukemia	1,027	2	3.4%	98%
10th Mouth & oropharynx	938	2	3.2%	98%	10th Mouth & oropharynx	940	2	3.1%	98%
Cancer	29,375	59	100%	97%	Cancer	30,228	58	100%	97%

In comparisons across countries and time a lower total number of DALYs of a certain disease is equivalent to a lower disease burden. However, a lower burden of a certain disease in a specific country does not necessarily imply that this is the result of better medical treatment in this country. In the case of cancer, a lower disease burden in a country might also reflect a younger population, better primary prevention (e.g. reflected by lower smoking rates, healthier dietary habits, more physical activity, lower air pollution, vaccination programs against hepatitis B virus infection, vaccination programs against HPV for girls/women and boys/men), and more comprehensive screening activities.

In Figure 9 the disease burden of cancer is compared between all countries. As already shown in Table 3, in Europe the burden was 59 DALYs per 1,000 inhabitants in 2000 and decreased slightly to 58 DALYs per 1,000 inhabitants in 2012. Among all countries Hungary has by far had the highest burden in both years with almost 90 DALYs per 1,000 inhabitants which is partly a reflection of its high mortality rates. Cyprus on the other hand has had a burden that was only one third of that in Hungary with 30 DALYs, by far the lowest burden among all countries. Notable increases occurred in Croatia, Latvia, Malta, Portugal, and Romania, whereas larger reductions were recorded in the Czech Republic and Ireland.

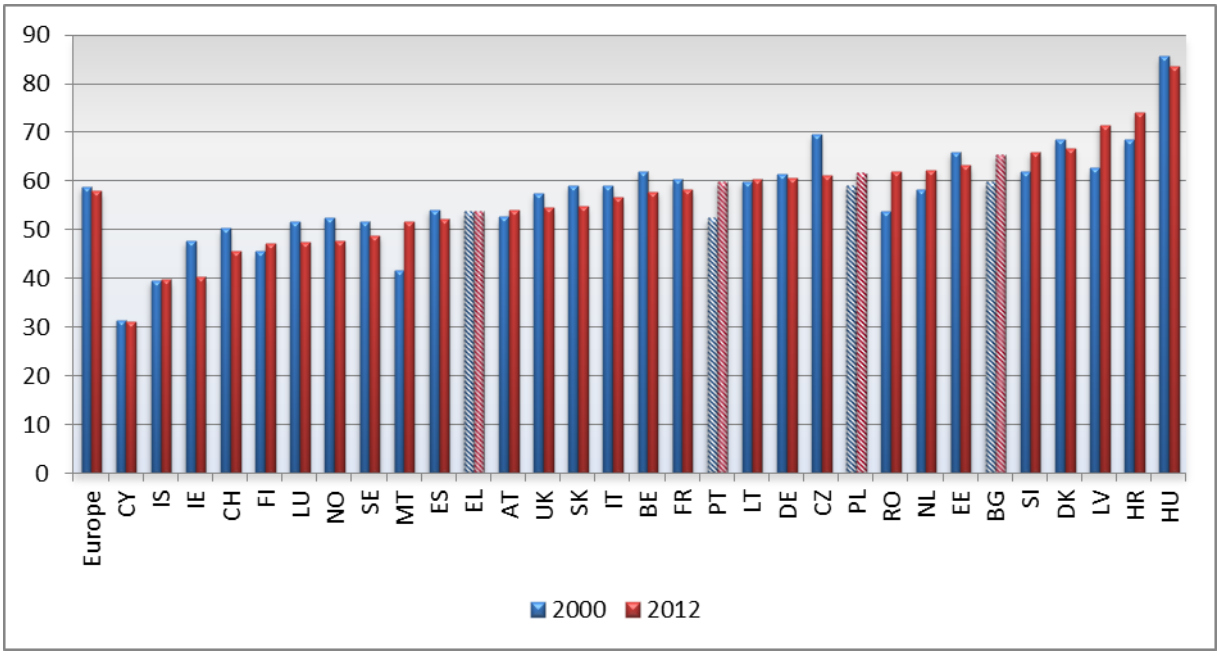


FIGURE 9: ESTIMATED DALYS CAUSED BY CANCER (MALIGNANT NEOPLASMS) PER 1,000 INHABITANTS, 2000–2012 [30]

Notes: Hatched bars indicate that estimates are based on country data and/or nationally representative sample death registration or surveillance, and not based on nationally representative death registration data.

1.2 Economic burden of cancer

The economic burden of cancer is comprised of direct costs that are borne by the health care system (henceforth called direct health costs), direct costs outside the health care system, and indirect costs in terms of productivity loss of cancer patients. The development of the economic burden is partly a reflection of the development in cancer incidence and cancer mortality. For instance, rising incidence pushes up the costs of diagnostics and treatment, whereas declining mortality (in patients in working age) reduces productivity loss. Progress in cancer care, such as the introduction of new imaging techniques for diagnosis and new treatment modalities, also affects the development of the economic burden since technological innovations typically come at a higher cost.

The diagnosis and treatment of cancer are resource-intensive tasks. Medical equipment, such as CT, MRI and PET-CT scanners, is used to locate and radiation therapy machines to treat the cancer. Surgeons, radiologists, and oncologists perform surgery on the tumors, radiation therapy and/or systemic therapy (chemotherapy, hormonal therapy, immunotherapy, and molecularly targeted therapy) with the help of nurses, after pathologists have examined the nature of the cancer. Modern cancer care also includes psychosocial care and rehabilitation. Thus, a lot of different resources within and outside the health care system are allocated to

cancer care. All these resources are summarized as the direct cost of cancer [31]. Note that both publicly paid resources (taxpayers' money and/or social security contributions spent on the health care system) and privately paid resources (private health insurance and out-of-pocket payments for health care visits or drugs) are the sources of expenditure on cancer care. It is also important to keep in mind that the direct costs of cancer only present the quantitative measure of how many resources that have been devoted to fight the disease. In order for this monetary input to yield benefits to patients, the allocation of the resources and the organization of cancer care are critical [32].

Cancers causes also direct costs that fall beyond the remit of the health care system. Patients with cancer are increasingly treated outside hospitals in ambulatory care, which creates a need for social support services. These are often not classified as health care costs, and thus the magnitude of these costs may be difficult to assess. The same is the case for many private expenses that relate to goods and services consumed as a consequence of the cancer.

Services by relatives and friends should also be included, since these services are important complements to other services. For example, they include time to accompany the patient for treatments, or care for the patient at home. If these services had not been provided, other services would have been needed to replace them. It is often possible to collect data on time inputs from informal caregivers, but the valuation or pricing of these time inputs is not obvious. Totally ignoring these informal care costs is not an option either because it would mean that informal care is not assigned any value or opportunity cost. Thus, it is important to include these costs in the calculation of the resource use due to cancer.

Patients that die during working age that otherwise would have continued to work until retirement give rise to mortality-induced productivity loss. Patients that need to reduce working hours or stop working altogether as a consequence of the disease and/or its treatment give rise to morbidity-induced productivity loss. Productivity loss from these different sources is summarized as the indirect cost of cancer [31].

The economic burden of cancer has also a time dimension on the patient level. Costs related to incidence are incurred during the first months or year after diagnosis. They encompass direct costs for diagnosis and initial treatment, informal care, and indirect costs arising from morbidity-induced productivity loss. Costs related to mortality are incurred during the last months of life. They encompass direct costs for renewed treatment attempts and/or palliative care of advanced disease, informal care, and indirect costs arising from mortality-induced productivity loss. Direct and indirect costs vary with the age of the patients. For children with cancer, costs of informal care may be high since the parents need to devote many hours of support. Since parents are of working age, there will be both hours lost from work and hours

lost from reduced leisure activities. For elderly patients with a number of co-morbidities, the assignment of informal care specifically to cancer is a methodological issue.

The aims of the following sections are (1) to determine the economic burden of cancer in all countries and Europe as a whole for the latest possible year (2014), (2) to describe the development over time between 1995 and 2014, as well as (3) to compare the estimates with those from previous studies. Before focusing on the resources spent specifically on cancer within the health care system, it is useful to provide an overview of countries' economic preconditions and the resources devoted to health care in general.

1.2.1.1 Economic preconditions and spending on health

The development of the total health expenditure in Europe as a whole is shown in Table 5. In 1995 total health expenditure amounted to €640 billion and more than doubled to €1,454 billion in 2014. If these figures are adjusted for inflation, then the total health expenditure in 1995 amounted to €921 billion, and thus the increase until 2014 was 58 percent in real terms. Similarly, per capita expenditure more than doubled between 1995 and 2014 from €1,297 to €2,793, but in real terms the increase was 50 percent. A description of the underlying development of GDP per capita and the total health expenditure as a share of GDP is provided in the Appendix.

TABLE 5: TOTAL HEALTH EXPENDITURE IN EUROPE, 1995–2014 [5, 11, 33-36]

	1995	2000	2005	2010	2014	Change 1995–2014
Total health expenditure (in billion €)	640.0	833.8	1,106.2	1,343.2	1,453.5	127%
… adjusted for inflation	920.5	1,098.8	1,316.9	1,442.7	1,453.5	58%
Total health expenditure per capita (in €)	1,297	1,672	2,182	2,602	2,793	115%
… adjusted for inflation	1,866	2,203	2,598	2,795	2,793	50%

Notes: Total health expenditure in 2014 was calculated with GDP data from 2014 and the share of total health expenditure on GDP from 2013.
The underlying GDP data are based on ESA 95. The 2014 values are calculated by applying the nominal growth rate between 2013 and 2014 based on ESA 2010 to the 2013 values.
The adjustment for inflation was carried out with country-specific inflation rates. The 1995 estimates could only be adjusted for inflation between 1996 (for BG between 1997 and for HR and RO between 1998) and 2014 due to lack of data. For Switzerland the same inflation rate as in Austria was assumed for 1996 and 2000.

1.2.1.2 Data on health expenditure

The calculation of the direct cost of cancer that are borne by the health care system in the following section uses a country's total expenditure on health as a starting point to estimate

what share of it is spent on cancer. It is therefore necessary to briefly define total expenditure on health. The WHO together with the Organisation for Economic Co-operation and Development (OECD) developed a framework called System of Health Accounts (SHA) to calculate health expenditures in a harmonized way. All countries considered in this report use the SHA framework. According to this framework the "total expenditure on health"[12] (ICHA[13] code HC1-HC9+HCR1) refers to the final consumption of health goods and services, i.e., current expenditure on health, plus capital investment in health care infrastructure [37]. Current expenditure on health (HC1-HC9) includes services of curative care, services of rehabilitative care, services of long-term nursing care, ancillary services to health care, medical goods dispensed to outpatients, services of prevention and public health, health administration and health insurance, and expenditure on services not allocated by function. Note that expenditures from both public and private sources are included. Despite this common framework the OECD cautions that the comparability of data is imperfect, since some different practices regarding the treatment of capital expenditure and the inclusion of long-term care in health or social expenditure have not been completely resolved [6].

The SHA framework enables a breakdown of expenditure by the above-mentioned functions (services of curative care, etc.), by financing agent (public or private sources) and by provider (e.g. hospitals). However, it does not enable a breakdown by disease. The OECD has for many years pushed for an extension of the SHA framework to include the calculation of health expenditure by disease [38]. The advantage with such a methodology is that the sum of expenditures across all diseases equals the total expenditure on health. This restriction does not necessarily hold in cost of illness studies due to the possibility of double counting of expenditures[14]. Nevertheless a challenge is that certain kinds of expenditure are difficult to allocate to particular diseases [39].

The extent of the lack of disease-specific health expenditure data is exemplified in the following example. In 2011 the WHO attempted to estimate the cost of major non-communicable diseases using disease-specific health accounts [39]. Out of the over 130 countries that reported total expenditure on health using the SHA framework, only 13 countries could provide a complete disease-specific dataset which in most cases only covered a single year. The lack of this kind of data is a major limitation for policy making in the health area. It would give policy makers a clear idea on how much resources are spent on different

[12] Note that the expression "total health expenditure" is used synonymously with "total expenditure on health" in this report.
[13] International classification for health accounts (ICHA)
[14] The restriction holds if calculations are based on main diagnosis. However, this would then only allow calculating the health costs of patients with cancer as a main diagnosis, but not the health costs of cancer. This is because costs for patients that have cancer, but for whom cancer is not the main diagnosis, are allocated to the disease constituting the main diagnosis instead. Yet this means also that the health costs of patients with cancer as a main diagnosis include costs that actually arise from the treatment of other diseases (co-morbidities).

diseases, how the spending evolves over time, and most of all how targeted disease-specific expenditures relate to patient outcomes.

1.3 Direct cost of cancer

The direct cost of cancer that falls within the remit of the health care system includes public and private expenditure on services provided by the health care system during the whole chain of care. It comprises expenditures for primary prevention measures, screening programs, diagnosis, treatment (including cancer drugs), rehabilitation and palliative care. Thus, the direct cost of cancer in this section represents a subset of the total expenditure on health, i.e. the direct health cost of cancer, as defined in the previous section.

Comparative studies on the cost of cancer are rare. A lack of data on the consumption of cancer care resources and their prices are limitations for the conduct of such studies [40]. The only studies that attempted to estimate the direct health cost of cancer for most countries in Europe or the EU member states are the previous Comparator reports [41-43], and two studies by Luengo-Fernandez and colleagues published in 2013 and 2015 (henceforth called LF-2013-study and LF-2015-study or together LF-studies) [44, 45]. The estimation of the cost in the LF-studies relies on a cost-of-illness approach in which the direct health cost is the sum of estimates for some pre-defined cost categories. The Comparator reports on the other hand tried to estimate the direct health cost more in line with the idea of disease-specific health accounts proposed by the OECD [38]. Further methodological differences are discussed below when the results of this report are compared with the results from previous studies.

1.3.1.1 Methodology

In this report the method applied to estimate the direct health cost of cancer in Europe is the same as in the previous Comparator reports. The starting point is a country's GDP based on data from Eurostat. Then GDP is multiplied with the share of total expenditure on health of GDP based on data from the WHO to receive the total expenditure on health. The next step is to determine the cancer-specific health expenditure as a share of total expenditure on health for each country. In the final step the results from the two previous steps are combined to receive the direct health cost of cancer for each country and also Europe as a whole.

The main argument for this approach is that it provides the best guarantee against both underestimations and overestimations. It is also an approach where data from different types of studies can be used for the estimation of the share of cancer-specific health expenditures. It is neither dependent on a predetermined definition of which types of health expenditures to include.

The key step is the estimation of the cancer-specific share of total health expenditure. Country-specific data were gathered from reports and studies from the WHO, the OECD, national ministries of health, national statistical offices, academic research organizations, national cancer societies, as well as studies in peer-reviewed journals. For those countries that provide disease-specific health expenditure data, estimates of both the cost of cancer and the relative share could be obtained directly. For other countries cancer-specific cost-of-illness studies were available. Yet most of these studies left out relevant cost categories, such as screening or long-term care, resulting in an underestimation of the true costs. If the estimate was based on a cost-of-illness study, attention was paid to include all relevant cost categories (even if the study itself did not classify certain categories as part of the direct health costs) and exclude cost categories not part of total health expenditures such as publicly funded research on cancer. In total, national estimates for 20 countries could be obtained this way. For the 11 countries for which no data were found, extrapolations were performed based on geographical proximity and similarity in GDP per capita. Note that all extrapolations were only based on countries for which national estimates were found. The detailed estimation of the cancer-specific share of each country is described in the Appendix.

Even though the direct health cost in this report is estimated for the years between 1995 and 2014, the underlying national shares of cancer-specific health expenditure pertain to years between 2002 and 2013. The use of older cancer-specific shares does not necessarily limit the validity of the estimate for, e.g., year 2014. If the cancer-specific share remained constant between the year that the estimate refers to and 2014, then an exact result for the direct health cost could still be obtained. An increase (decrease) in the cancer-specific share between the year that the estimate refers to and 2014 would lead to an underestimation (overestimation) of the direct health cost. Changes in the cancer-specific share over time are examined in section 1.3.2 for a handful of countries that provide estimates for several years. There it is shown that this share is rather constant over time.

The estimate of the direct health cost refers to neoplasms defined as ICD-10 C00-D48. This includes malignant neoplasms (C00-C97), in situ neoplasms (D00-D09), benign neoplasms (D10-D36) and neoplasms of uncertain or unknown behavior (D37-D48). Cancer commonly only refers to malignant neoplasms. Here cancer is instead equated with neoplasms. This broader definition of cancer was used since most countries with disease-specific health expenditure data only report the cost of neoplasms. In addition, in some cost-of-illness studies it was not clear whether “cancer” only referred to malignant neoplasms or to some broader definition. As a result, the direct health costs in this report are likely to be underestimated since some national estimates for the cancer-specific share of total health expenditure only include the cost of malignant neoplasms and/or specifically note that the cost of benign neoplasms are excluded. The magnitude of this issue can be illustrated on the basis of data

from Germany, which is the only country that provides a detailed break-down of disease-specific health expenditure data. Of all health expenditure spent on neoplasms (C00-D48) in 2008, 85.6 percent were spent on malignant neoplasm (C00-C97), 9.1 percent on benign neoplasms (D10-D36) and the remaining 5.4 percent on in situ neoplasms (D00-D09) as well as neoplasms of uncertain or unknown behavior (D37-D48) [46].

1.3.1.2 Results

The results of the estimation of the direct health cost of cancer in 2014 are shown in Table 6. As already illustrated before, total health expenditure as a share of GDP differ widely between countries. The share ranged from 5.3 percent in Romania to 12.9 percent in the Netherlands. In Europe as a whole it was 10.1 percent, which implies total health expenditure of €1,454 billion.

Poorer countries spend a smaller share of GDP on health. This amplifies differences in total health expenditure per capita compared to differences in GDP per capita. The top spenders were Luxembourg, Switzerland, Norway, and the Netherlands with more than €4,200 per capita, followed by Central and Western European countries and the Nordic countries. Most of the Southern European countries spent around €1,600 to €2,200 per capita. The countries on the eastern border of the EU spent the least with Romania and Bulgaria having spent less than €1,000 per capita. The top spender, Luxembourg, spent more than six times more on health per capita than the lowest spender, Romania. Note that these figures are adjusted for differences in purchasing power parity (PPP). In unadjusted terms, there was a eighteen-fold difference in health spending per capita between the highest and lowest spender, Switzerland (€7,105) and Romania (€395); see Table A1 in the Appendix.

TABLE 6: TOTAL HEALTH EXPENDITURE AND ESTIMATED DIRECT HEALTH COST OF CANCER IN EUROPE (ADJUSTED FOR PPP), 2014

	Total health expenditure			Direct health cost of cancer		
	% of GDP	total (million €, PPP)	per capita (€, PPP)	% of THE	total (million €, PPP)	per capita (€, PPP)
Austria	11.0%	31,678	3,716	6.5%*	2,059	242
Belgium	11.2%	38,750	3,465	6.2%*	2,415	216
Bulgaria	7.6%	6,904	960	6.8%*	466	65
Croatia	7.3%	4,919	1,161	6.9%*	337	80
Cyprus	7.4%	1,405	1,636	6.3%	88	103
Czech Republic	7.2%	16,398	1,559	5.4%	885	84
Denmark	10.6%	19,542	3,461	4.5%	879	156
Estonia	5.7%	1,500	1,124	5.8%	87	65
Finland	9.4%	14,775	2,706	4.4%	650	119
France	11.7%	216,787	3,275	6.2%	13,441	203
Germany	11.3%	309,380	3,757	6.8%	21,038	255
Greece	9.8%	20,939	1,945	6.5%	1,361	126
Hungary	8.0%	14,345	1,455	7.0%	1,004	102
Iceland	9.1%	923	2,821	3.8%	35	107
Ireland	8.9%	14,002	3,040	5.0%*	700	152
Italy	9.1%	141,385	2,308	6.7%	9,473	155
Latvia	5.7%	2,077	1,043	6.2%*	128	64
Lithuania	6.2%	3,677	1,252	6.2%*	226	77
Luxembourg	7.1%	2,785	4,990	6.2%*	174	311
Malta	8.7%	870	2,033	6.5%*	57	132
Netherlands	12.9%	71,863	4,260	5.7%	4,096	243
Norway	9.6%	23,991	4,672	3.4%	816	159
Poland	6.7%	46,628	1,212	6.5%	3,031	79
Portugal	9.7%	20,395	1,957	3.9%	795	76
Romania	5.3%	15,533	783	6.8%*	1,048	53
Slovakia	8.2%	9,095	1,682	6.2%*	564	104
Slovenia	9.2%	4,230	2,051	6.7%	283	137
Spain	8.9%	102,776	2,238	5.8%	5,961	130
Sweden	9.7%	31,168	3,213	6.8%	2,119	219
Switzerland	11.5%	38,239	4,708	6.2%	2,371	292
United Kingdom	9.1%	165,950	2,566	5.0%	8,298	128
Europe	10.1%†	1,453,522‡	2,793	6.0%§	87,895‡	169

Notes: GDP = gross domestic product, PPP = purchasing power parity, THE = total health expenditure.
THE in 2014 was calculated with GDP data from 2014 and the share of THE on GDP from 2013 [33].
The underlying GDP data are based on ESA 95. The 2014 values are calculated by applying the nominal growth rate between 2013 and 2014 based on ESA 2010 to the 2013 values [11, 34, 36].
Source for THE on cancer: own estimate based on national sources; see Appendix for methodology.
* Estimated share based on data from similar countries; see Appendix for methodology.
† The estimate is calculated as THE of all countries (not adjusted for PPP) divided by total GDP.
‡ The sum of all PPP-adjusted national estimates does not equal the estimate for Europe, because the different shares of GDP spent on THE, and the different shares of THE spent on cancer, respectively, change the weighting of the national estimates.
§ The estimate is calculated as THE on cancer of all countries (not adjusted for PPP) divided by THE.

Column 5 in Table 6 shows the key variable to estimate the direct health cost of cancer, viz. the cancer-specific share of total health expenditure. This share was highest in Hungary with 7.0 percent and lowest in Norway with 3.4 percent. Viewed as a single entity, the share in Europe stood at 6.0 percent, which puts the direct health cost of cancer to €87.9 billion in 2014.

There is no clear tendency that poorer countries would devote a larger or smaller share of their total health expenditure to cancer compared with wealthier countries. As a consequence, country differences in per capita spending on cancer mirror to some extent the differences in overall health spending. There is neither a clear geographical pattern in differences of this share of cancer-specific health expenditure. This finding is somewhat surprising, since it would seem plausible that countries with a higher cancer burden are forced to spend more, given that they have a larger number of patients to take care of. This is, e.g., the case in Denmark and Norway which have among the highest incidence rates (both in terms of crude rates and age-standardized rates) but spend less on cancer than Sweden which has lower incidence rates. One reason for this observation could be measurement error, since several country estimates of the share of cancer-specific health expenditure are clearly underestimated, as described in the Appendix.

The direct health cost of cancer per capita was €169 in Europe. After adjusting for differences in PPP, it was highest in Luxembourg with €311, followed by Central and Western European countries including Sweden where it exceeded €200. In Southern European countries (except Portugal and Croatia) the direct health cost was between €160 and €100. In all countries on the eastern border of the EU (except Slovakia) the direct health cost fell short of €100. It was lowest in Romania with €53, which is almost six times lower than in Luxembourg. Not taking into account price differentials, the direct health cost in the top spending country, Switzerland (€441), was sixteen times higher than in the least spending one, Romania (€27); see Table A1 in the Appendix. Figure 10 illustrates the point that differences in the direct health cost of cancer between countries become smaller once adjusted for price differentials. Nonetheless, great disparities in the level of spending on cancer remain.

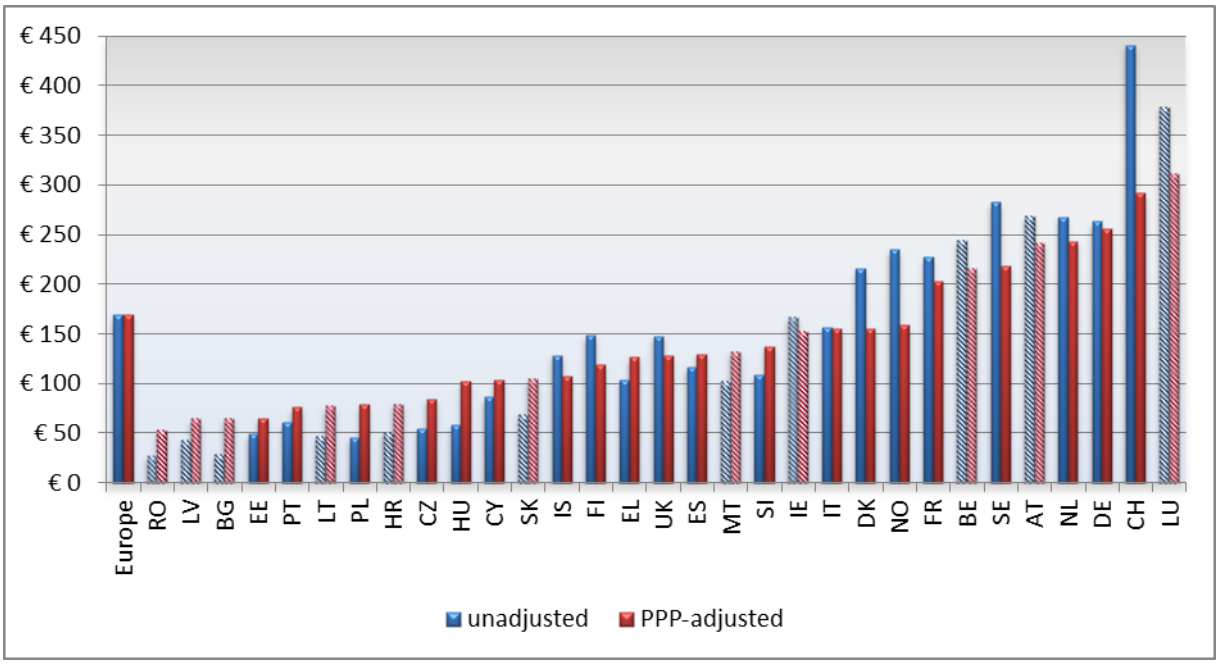


FIGURE 10: DIRECT HEALTH COST OF CANCER PER CAPITA, 2014

Notes: Hatched bars indicate that the direct health cost is estimated based on data from similar countries; see Appendix for methodology.
Sources: see Table 6

The composition of the direct cost of cancer is analyzed in more detail in the Appendix. There, the distribution of the costs across cancer types and cost categories is presented along with evidence on the distribution of the costs across stages of cancer and from diagnosis to death.

1.3.1 Comparison with previous results

The previous Comparator reports estimated the direct health cost of cancer that is attributable to the health care system in Europe to €120 per capita in 2002/03 and €125 per capita in 2004 based on selection of 19 European countries [41, 42]. The latest Comparator report estimated it to €148 per capita in 2007 for the same sample of countries (excluding Croatia, Cyprus, and Malta) as in this report [43]. In this report the estimate for Europe is €169 per capita in 2014.

The obtained results can also be contrasted with the ones from the recent LF-studies [44]. The LF-studies estimated the direct health cost of cancer for every member state of the EU and the EU as a whole. The LF-2013-study (LF-2015-study) put the direct health cost of cancer in the EU to €51.0 billion in 2009 (€57.5 billion in 2012). In this report it is estimated to €83.1 billion in 2014, after excluding Iceland, Norway, and Switzerland, which is 63 (45) percent higher. In per capita terms the LF-studies yielded an estimate of €102 (€114), whereas in this

report it is €164 (for the EU-28) which is 61 (44) percent higher. What are the reasons for this discrepancy?

- The estimation of the direct health costs in the LF-studies follows a cost-of-illness approach which pre-defined five cost categories, viz. primary care, outpatient care, accident and emergency, inpatient care, drugs. For each category, data on health care utilization are combined with health care unit costs. This bottom-up approach fails to include other relevant cost categories such as screening and primary prevention measures as well as cost items in the ambulatory setting for which there is no disease-specific registration. This leads to an underestimation of the true costs. By contrast, in this report a top-down approach is applied which is more in line with the idea of disease-specific health accounts proposed by the OECD [38]. Here the risk of failing to include all relevant costs is smaller. The failure to include all relevant costs in the LF-studies is also reflected in the lower cancer-specific shares of total health expenditure in these studies compared to the results in this report. For instance, for Germany the LF-studies estimate a 5 percent share of cancer-specific health expenditure in both 2009 and 2012, whereas the estimate provided by the German Federal Statistical Office is 5.8 percent in 2008 (€15.466 billion spent on ICD-10 C00-C97 in relation to total health expenditure of €264.798 billion [33, 46]). This leads ultimately to the estimation of a cancer-specific share of 4 (5) percent for the whole EU in the LF-studies, whereas it is 6.0 percent in this report. The relative difference between these two estimates is 50 (20) percent.
- In the LF-studies cancer is defined according to ICD-10 C00-C97, i.e. malignant neoplasms. In this report cancer is defined according to ICD-10 C00-D48, i.e. neoplasms, which was the only viable option given the nature of the underlying national data. In Germany malignant neoplasms (C00-C97) accounted for 85.6 percent of all expenditure on neoplasms (C00-D48) in 2008 [46]. If this distribution of costs were similar in other countries, the use of the broader definition of cancer could potentially explain around 17 percent of the discrepancy in the direct health costs. However, some national estimates used in this report did not include benign neoplasms and/or probably only referred to malignant neoplasms. This implies that the discrepancy due to different definitions of cancer is likely to be smaller than 17 percent.
- The estimate of the LF-studies refers to the year 2009 (2012), whereas in this report the reference year is 2014. The increase in general inflation (HICP) between 2009 (2012) and 2014 in the whole EU-28 was 10.3 (2.1) percent, although in the category “health” (CP06) it was only 7.7 (1.5) percent [35].
- The LF-2013-study does not include Croatia for which the direct health costs are estimated to be €337 million in this report, equaling a 0.7 percent difference.

1.3.2 Development of the direct cost over time

There are no studies tracking the development of the direct health cost of cancer in Europe over time, probably due to a lack of data. As described above, it was impossible to obtain information on this matter for 11 countries even for single year for this report. For many other

countries estimates are only available for a single year. However, there are a few countries that provide a time series of the health expenditure on cancer; see Table 7.

TABLE 7: DEVELOPMENT OF THE CANCER-SPECIFIC SHARE OF TOTAL HEALTH EXPENDITURE IN SELECTED COUNTRIES, 2002–2012

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Germany	6.0%		6.7%		6.9%		6.8%				
Netherlands		4.6%		4.3%		5.0%				5.7%	
Poland								6.2%	6.4%	6.5%	
Spain					5.6%	5.1%	5.8%				
United Kingdom		5.1%	5.2%	5.3%	5.0%	5.2%	5.1%	5.3%	5.0%	5.0%	5.0%

Notes: For the sources and the methodology of the calculation of the shares for each country see Appendix. For the United Kingdom the estimate in year X refers to the budget year X/X+1; for instance the estimate in 2003 refers to the budget year 2003/2004. Note that there were some methodological changes that might affect the comparability of the estimates for the UK over time.

Data for Germany show that the cancer-specific share of total health expenditures increased from 6.0 percent in 2002 to 6.7 percent in 2004 and remained at this level until 2008. In the Netherlands the share decreased from 4.6 percent in 2003 to 4.3 percent in 2005, before bouncing back to 5.0 percent in 2007 and further rising to 5.7 percent in 2011. In Poland there was a slight increase between 2009 and 2011. In Spain the share was 5.6 percent in 2006 and dropped to 5.1 percent in 2007 before bouncing back to 5.8 percent in 2008. In the United Kingdom the share remained stable at around 5 percent between 2003/2004 and 2012/2013. In sum, the cancer-specific share remained mostly stable[15] or increased slightly during the 2000s and the beginning of the 2010s.

A stable pattern in the cancer-specific share for a much longer period has been observed in the United States. There the share has been very close to 5 percent from 1963 to 1995 [47]. In 2010 the cost of cancer care was estimated to $124.57 billion [48], and total health expenditure amounted to $2,555.4 billion [33], which equals a share of 4.9 percent. Thus, the cancer-specific share has remained virtually unchanged between 1995 and 2010, whereas total health expenditure as a share of GDP increased from 13 to 17 percent during this period [33].

Given these results, the use of older estimates for the cancer-specific share of total health expenditures (dating back as far as 2004 for the calculation of the direct health cost in some countries in this report), should not seriously bias the estimates of the direct health cost of cancer in 2014. In fact, the limited evidence of a slight upward trend suggests that the direct health costs in 2014 are probably slightly underestimated. By the same argument, these results indicate that the estimates can even be used to calculate the direct health cost of cancer in preceding years.

[15] Note that a stable share of health expenditure on cancer in a time of increasing overall health expenditure implies that the total amount spent on cancer increases in line with other health expenditures.

Using the same methodology outlined above and incorporating the results of Table 7, the direct health costs of cancer have also been calculated for the years 1995, 2000, 2005, and 2010. The results are shown in Figure 11 for the total amount of health expenditures on cancer and in Figure 12 for the expenditures per capita in Europe. Measured in current prices the direct health cost of cancer in Europe amounted to €37.5 billion in 1995 and more than doubled to €87.9 billion in 2014, equaling an increase of 134 percent. If inflation is taken into account, the direct health cost in 1995 amounted to €52.7 billion and the increase between 1995 and 2014 equals 67 percent. In per capita terms the direct health cost increased from €76 in 1995 to €169 in 2014, equaling an increase of 122 percent (measured in current prices). Taking into account inflation, the direct health cost in 1995 was €107 and the increase between 1995 and 2014 equals 58 percent. The corresponding country-specific results are summarized in Table A2–A5 in the Appendix.

Figure 11 and Figure 12 also show that the direct health cost of cancer remained constant between 2010 and 2014, if measured in 2014 prices. By construction of the estimates, this reflects the use of a constant cancer-specific share of health expenditures together with a slight decline in health spending as a share of GDP (from 10.3 to 10.1 percent) and a minor increase in GDP.

Since the same cancer-specific share of health expenditure was used for many countries in all calculations between 1995 and 2014, the recorded increases are similar to the ones presented in Table 5 for the development of total health expenditure. For instance, the increase in per capita health expenditure in 2014 prices was 50 percent, whereas the corresponding increase in per capita spending on cancer was 58 percent. The reason for the slightly higher increases in the measures of the direct health cost of cancer is that the cancer-specific share of health expenditure increased somewhat throughout this period; see Table 7.

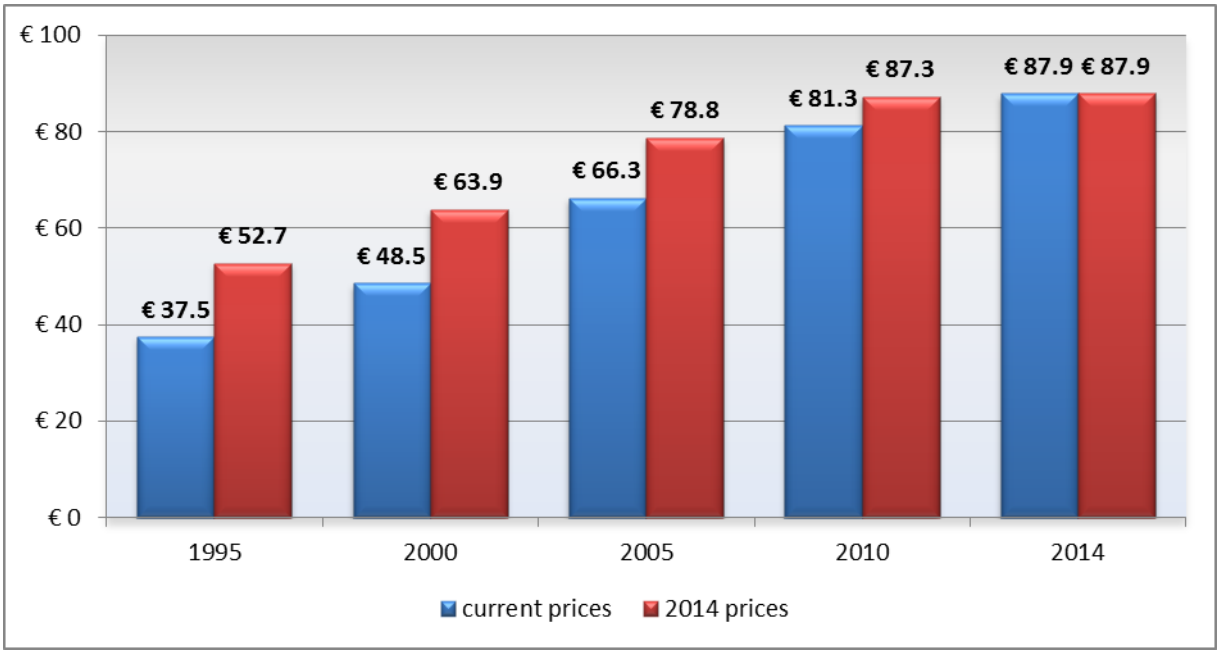


FIGURE 11: TOTAL DIRECT HEALTH COST OF CANCER IN EUROPE (IN BILLION €), 1995–2014

Notes: Data for total health expenditure come from the WHO [33]. Total health expenditure in 2014 was calculated with GDP data from 2014 and the share of total health expenditure on GDP from 2013.
The GDP data are based on ESA 95. The 2014 values are calculated by applying the nominal growth rate between 2013 and 2014 based on ESA 2010 to the 2013 values [11, 34, 36].
The shares of cancer-specific health expenditures are based on Table 6 and Table 7.
The adjustment for inflation was carried out with country-specific inflation rates [35]. The 1995 estimates could only be adjusted for inflation between 1996 (for BG between 1997 and for HR and RO between 1998) and 2014 due to lack of data. For Switzerland the same inflation rate as in Austria was assumed for 1996 and 2000.

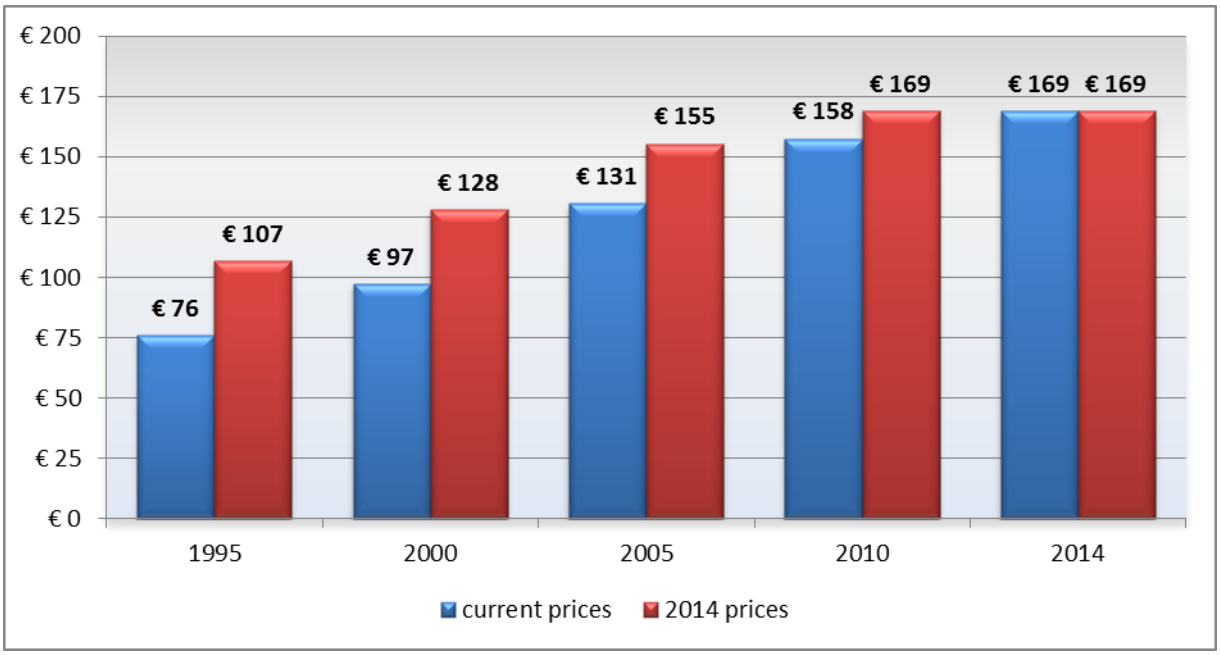


FIGURE 12: DIRECT HEALTH COST OF CANCER PER CAPITA IN EUROPE (IN €), 1995–2014

Notes: see Figure 11

An interesting observation from the development of the direct health cost of cancer over time is that its magnitude is somewhat similar to the development in cancer incidence. As described above, the total number of newly diagnosed cases (cancer incidence) increased by 31 percent between 1995 and 2012 in Europe[16]. The total direct health cost of cancer (measured in 2014 prices) increased by 67 percent between 1995 and 2014; see Figure 11. Thus, the sheer increase in the number of cancer patients seems to be one likely explanatory factor of the observed increase in the direct health cost of cancer. As cancer incidence, in crude terms, is still on the rise due to the demographic development and an increasing prevalence of some risk factors, the total direct health cost will thus probably continue to increase in the future.

There are also a number of other factors that can help to explain the increase in the direct health cost of cancer over time and have implications for the future development:

- More resources were spent on both screening (e.g. population-based breast screening programs were rolled out in many countries) and primary prevention (e.g. HPV vaccination programs for girls and boys were rolled out in many countries) in recent years. They will be further extended to cover more cancer types (e.g. several countries already introduced population-based screening for colorectal cancer; possibly screening for lung cancer will be introduced as well). These measures increase the cost in the short and medium run, but are supposed to decrease it in the long run.
- Since survival has been increasing, more patients require care for a longer time. This might mostly affect the cost 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 the prevention of recurrence will go up.
- New cancer therapies, such as targeted cancer therapy and immunotherapy, allow a greater share of patients to be treated. In addition, new cancer drugs come at a high price which has led to substantial expenditure increases on drugs in recent years; see section 1.4 on the cost of cancer drugs. This trend seems likely to continue and will push up direct health costs.
- There is a shift from intravenous to oral delivery methods of cancer drugs. As more patients can receive treatment at home, this could potentially decrease the cost of inpatient and ambulatory care.
- Due to earlier detection, improved diagnostics, new cancer drugs, as well as other improved treatment modalities, cancer care has become more effective. Improved care enables shorter hospital stays, entails fewer side effects, and results in quicker recovery and potentially fewer recurrences. This might in turn lower total direct health costs through decreasing the demand for other medical services, such as inpatient care [49].

[16] These figures include even all remaining Balkan states, Belarus, Moldova, Ukraine, and Russia.

1.3.3 Spending on cancer and patient outcomes

In the discussion of the direct health cost of cancer a pivotal point is to be able to relate costs to measurable and relevant outcomes. In general, the amount of health expenditure spent on cancer can be viewed as a crude measure for input in the "production" of patient outcomes. The cancer expenditure thus set the framework for producing health, i.e. trying to achieve high survival rates and also to reduce the incidence of cancer.

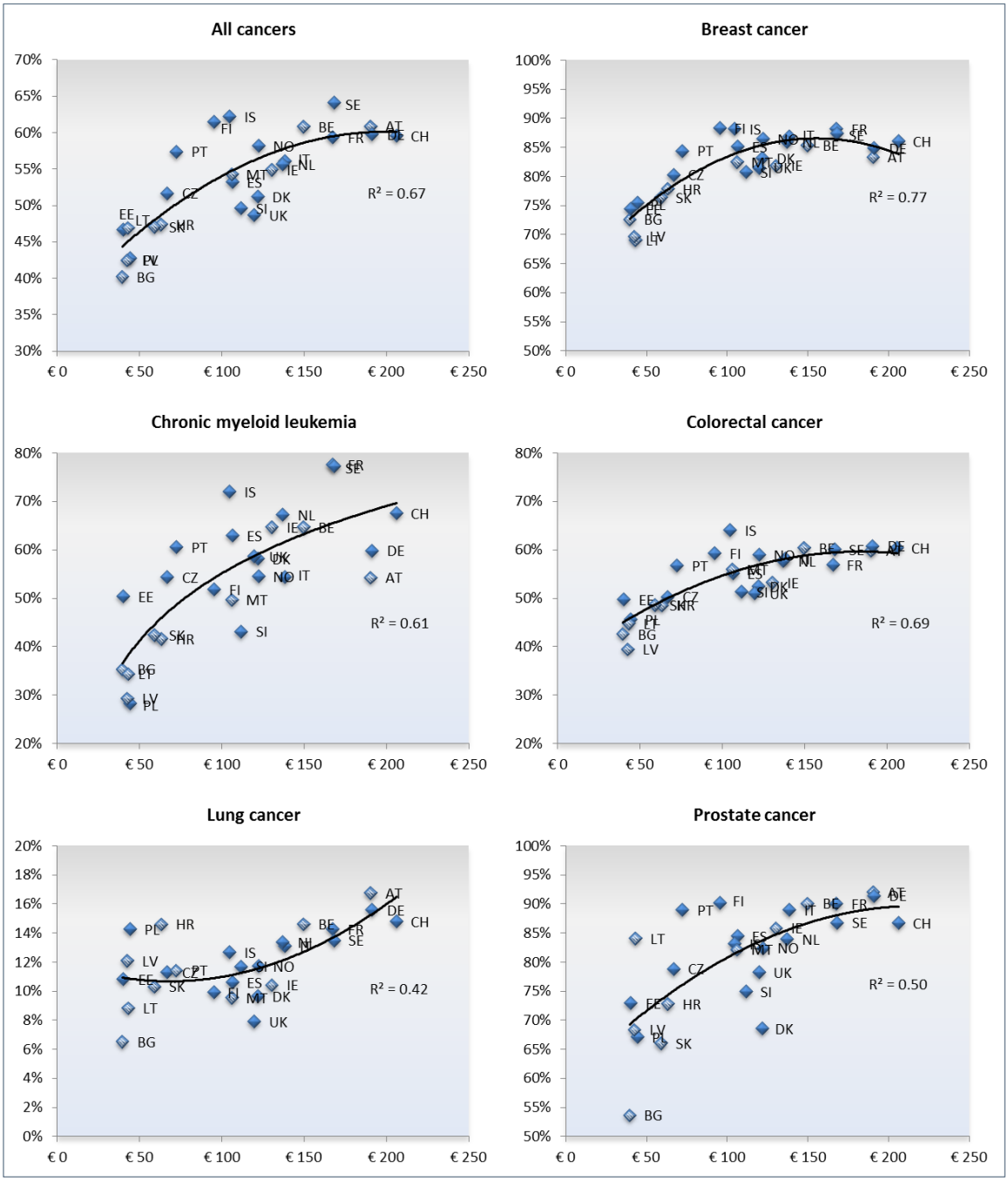


FIGURE 13: RELATIONSHIP BETWEEN CANCER EXPENDITURE PER CAPITA (PPP-ADJUSTED) IN 2005 AND 5-YEAR RELATIVE SURVIVAL RATES FOR DIFFERENT CANCER TYPES DURING 2000–2007, [15]

Notes: Hatched dots indicate that the national estimate for cancer expenditure is based on data from similar countries; see Appendix for methodology.
CY, EL, HU, LU, and RO are missing due to lack of data on survival rates.

Figure 13 shows how the estimated per capita expenditure on cancer (adjusted for PPP) relate to the 5-year survival rates of all cancers combined and five different cancer types in each country[17] (see Figure 8 and Figures A7–A11 in the Appendix). Cancer-specific health expenditures refer to the year 2005 and the survival rates to the period 2000–2007. Apart from the dots representing individual countries, each graph contains a trend line. The following two implications can be derived from the observed pattern in Figure 13. Note, however, that this pattern could potentially also be driven by some third factor that is related to both the amount of cancer-specific health expenditure and survival rates, such as the level of education in the country.

- Sufficient spending on cancer is a prerequisite for achieving high survival rates. The upward sloping trend lines in Figure 13 show that countries with lower spending tend to record lower survival rates, and countries with higher spending tend to record higher survival rates. For all cancers combined but also for several specific cancer types, the correlation between per capita spending on cancer and survival rates is strong. This is indicated by the close fit of the quadratic trend lines in Figure 13. This is particularly true in the case of breast cancer but also for colorectal cancer. This suggests that per-capita spending is especially important for achieving high survival rates for these two cancer types. For prostate cancer and lung cancer the correlation between these two measures of input and output of cancer care is somewhat lower, as the countries do not line up as neatly along the trend lines as for the other cancer types. For instance, despite similar per capita spending on cancer in Denmark and Italy, the survival rates for prostate cancer in Denmark are 20 percentage points lower than in Italy. In the same way, Poland and France have similar survival rates for lung cancer but spending is three times higher in France than in Poland.
- The relationship between spending on cancer and survival rates could be non-linear. For all considered cancers types the quadratic trend line is increasing and has a concave shape, i.e. survival improves at a decreasing rate with higher spending. Put another way, each additional euro spent on cancer care seems to improve survival rates, but the improvements per each additional euro spent become smaller the more euros that have already been spent. The only exception to this pattern is lung cancer for which the trend line is also increasing but has a convex shape, i.e. survival improves at an increasing rate with higher spending. Note, however, that a linear trend line instead of the quadratic one provides also a high goodness of fit for all analyzed cancer types. Thus, it must not be the case that survival really improves at a decreasing or increasing rate with spending, but rather a constant rate.

[17] The OECD has previously made a similar analysis but used total health expenditure per capita instead of cancer expenditure per capita [22]. The result of this analysis is similar to the one presented here, since the cancer-specific share of total health expenditure appears largely unrelated to the absolute amount of total health expenditure; see Table 6.

1.4 Cost of cancer drugs

The cost of cancer drugs is a hotly debated issue. Especially in the United States the focus has been on the increasing cancer drug prices and resultant unsustainable out-of-pocket expenditure for uninsured patients as well as many patients with insurance who have to pay large portions themselves [50-54]. In Europe the situation is somewhat different, as public payers (governments or sickness funds) cover the vast majority of the cost of cancer care for the whole population [55]. As emphasized in the section on the composition of the direct cost of cancer in the Appendix, studies on the direct health cost of cancer do provide figures for the share of cancer drugs on the direct health cost. Yet most often this only covers cancer drugs dispensed as prescription drugs, whereas cancer drugs administered in a hospital setting are included in inpatient care costs. To single out the cost of cancer drugs in inpatient care is most often impossible.

In this section new country-specific sales data obtained from the IMS Health MIDAS database are presented and analyzed. The data include all drugs with ATC code L1 (antineoplastic agents), L2 (endocrine therapy), and four agents from L4 (immunosuppressants), belimumab, lenalidomide, pomalidomide, and thalidomide. The data cover the years 2005 to 2014 and comprise all cancer drugs sold to hospitals and retail. Note that this selection of drugs does not cover all drugs used in the treatment of cancer patients. Drugs used for control of pain and side effects of cancer drugs are not included. However, many of the high volume drugs used by cancer patients have a very low price, and the underestimation of the true cost of drugs used in the treatment of cancer patients is thus limited.

There are some minor caveats in the data that should be kept in mind when interpreting levels and trends across countries. Firstly, data for Estonia, Latvia, Luxembourg, and Greece only comprise retail sales, but not hospital sales, throughout the whole period[18]. Secondly, complete data for Ireland (from 2006) and Portugal (from 2010) are not available for the whole period. Thirdly, no data have been obtained for Cyprus, Iceland, and Malta. Fourthly, sales data are based on ex-manufacturer prices. Ex-manufacturer prices do not represent actual final sales prices, since drugs are granted (secret) discounts in most health systems. As a consequence, the use of sales data based on ex-manufacturer prices overestimates the cost of cancer drugs[19]. Fifthly, there might be parallel trade of drugs in some countries that can run in

[18] Data on retail sales might be underreported in those and other 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 IMS data as those data are based on sales by wholesalers.
[19] This shortcoming can be overcome by considering sales in terms of volume instead of value. The analysis using sales in volume terms is carried out in chapter 3 in this report.

both directions (import and export) and that is not captured by the data and would bias country-specific results.

In general, the cost of cancer drugs can be considered (1) in absolute terms, (2) in relation to the overall development of health expenditure, as well as (3) in relation to health expenditure on cancer. Below only the aggregate cost of all cancer drugs for Europe and the individual countries are analyzed. More in-depth analyses on specific drugs and therapeutic areas are carried out in Chapter 3 in this report. Note that differences in country-specific prices of cancer drugs explain some of the variation in drug sales between countries. Since all drug sales are measured in euro, changes in the exchange rate affect the development of the value of drug sales in the countries outside the euro area with floating currencies (Croatia, Czech Republic, Iceland, Hungary, Norway, Poland, Romania, Sweden, Switzerland, and UK)[20]. However, if the cost of cancer drugs is measured in relative terms, as outlined above, exchange rate effects are not a concern. Further methodological aspects about the measurement and comparison of drug sales data are discussed in the beginning of chapter 3.

Since the focus of this section is the aggregate cost of all cancer drugs for Europe and individual countries, data for 1995 to 2004 that are partly used in chapter 3 are not analyzed in this section for the following reasons. First of all, these data leave out sales of the four agents with ATC code L4. More importantly, data for most of the Eastern European countries are missing for the period 1995 to 1998. Even for the period 1999 to 2004 sales in several countries comprise only retail sales. Additionally, there are breaks in the time series of several countries that complicate a valid comparison.

1.4.1 Development of the cost of cancer drugs in absolute terms

Figure 14 shows that the total cancer drug sales in Europe amounted to €9.5 billion (€8.0 billion in 2005 prices) in 2005 and more than doubled during the following nine years to €19.8 billion in 2014. Both in 2005 and 2014 the big 5 accounted for almost 75 percent of all sales (compared to a share of 60 percent in 2005 and 61 percent in 2014 on the total European population). France was the biggest spender on cancer drugs in 2005 but was surpassed by Germany in 2014 which then stood for a quarter of the value of all cancer drug sales in Europe. The country-specific results both in terms of total sales and per capita sales for the years 2005, 2010, and 2014 are summarized in Table A2–A5 in the Appendix.

[20] Bulgaria (since 2007) and Denmark (since 1999) pegged their national currencies to the euro. The seven countries that joined the euro area between 2007 and 2015 all had their national currencies pegged to the euro since at least 2005 without any major devaluations or appreciations taking place. The only exception is Slovakia that devalued its currency twice in 2007 and 2008 before joining the euro area in 2009 [56].

The strong increase in sales between 2005 and 2014 is not only the product of higher prices of newly introduced drugs. Even if the prices of drugs had been constant during this period, rising incidence of cancer would have implied an increase in sales due to growing patient numbers. The effect of increased survival and reduced mortality resulted also in an increased number of prevalent cases that need long-term chemotherapy. Moreover, new cancer drugs had been introduced that addressed unmet needs and allowed a greater share of patients to be treated.

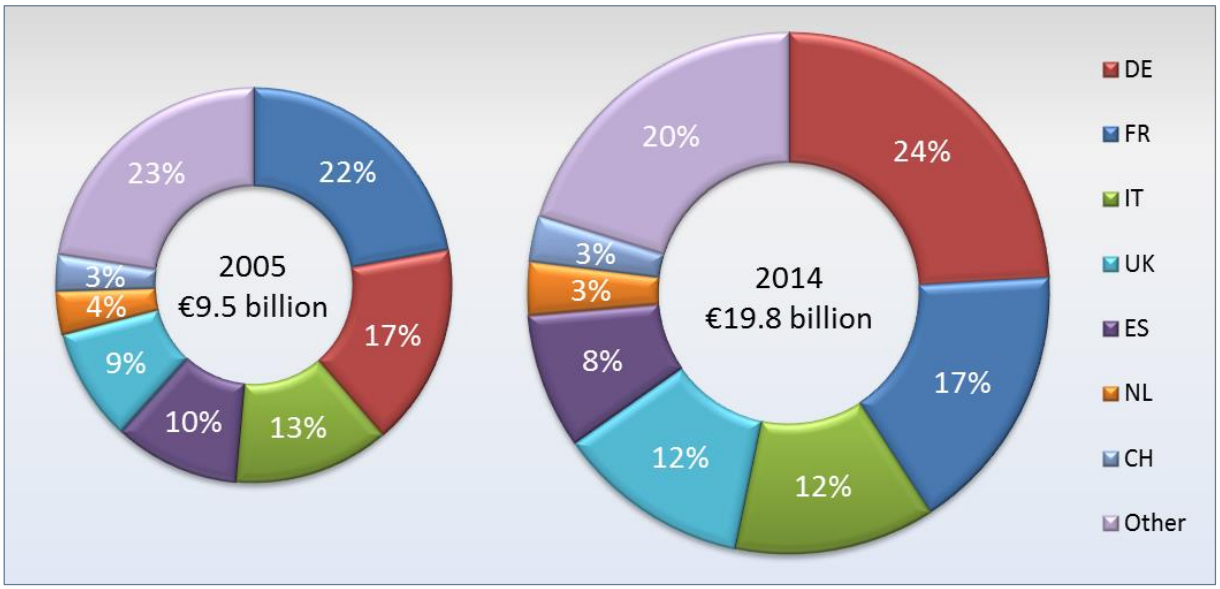


FIGURE 14: TOTAL COST OF CANCER DRUGS IN EUROPE AND COUNTRY-SPECIFIC SHARES (IN 2014 PRICES), 2005–2014 [35, 57]

Notes: The underlying value for 2005 for IE is from 2006 and for PT from 2010. Data for EE, LV, LU, and EL only comprise retail sales. CY, IS, and MT are missing due to lack of data.

The three graphs in Figure 15 show how cancer drug sales per capita evolved between 2005 and 2014 (not taking into account inflation) in individual countries. The countries are divided into three groups; wealthier countries, the big 5, and poorer countries. In all countries there was a fast growth in cancer drug sales between 2005 and 2008. In Austria, Italy, and the UK there was no slowdown after the onset of the economic crisis in 2008 and in Germany growth accelerated actually after that. By contrast, in Denmark, the Netherlands, and Sweden drugs sales remained at a constant level between 2008 and 2012 and picked up again afterwards. In Ireland and Switzerland sales started to increase again from 2011. In France and Spain drug sales peaked in 2008 and 2010, respectively, and then declined until 2012. By 2014 neither of the two countries had reached the previous highs.

Even the poorer countries fared differently. In Bulgaria, Romania, and Poland there was no noticeable slowdown in the increase of cancer drug sales after the onset of the economic

crisis. In Hungary drug sales stagnated between 2009 and 2013 but edged up again in 2014, but in Estonia the stagnation in retail sales stretched until 2014. In the Czech Republic the increase in cancer drug sales slowed after 2008, reached a peak in 2011 and dipped until 2014.

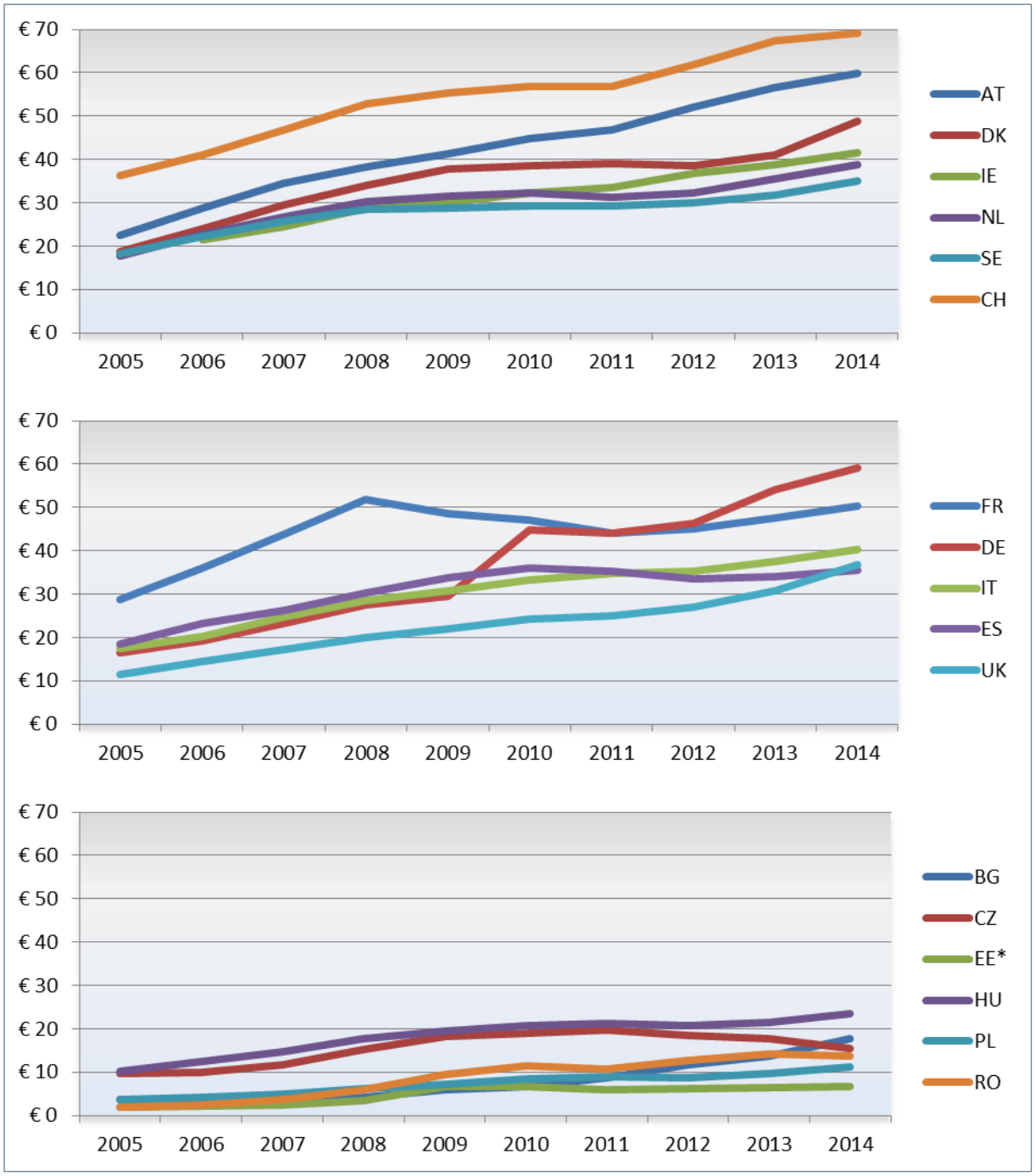


FIGURE 15: COST OF CANCER DRUGS PER CAPITA (IN CURRENT PRICES) IN SELECTED COUNTRIES, 2005–2014 [57, 58]

Notes: * Data for EE only comprise retail sales.

Figure 16 compares cancer drug sales per capita in 2005 and 2014 (adjusted for inflation) in each country. In Europe as a whole, cancer drug sales in per capita terms doubled from €19 (€16 in 2005 prices) in 2005 to €38 in 2014. Despite the economic crisis all countries recorded an increase between 2005 and 2014, except Portugal for which the 2005 value is the deflated 2010 sales figure as well as Greece and Luxembourg for both of which only retail sales are available. The biggest increases in spending in absolute terms between 2005 and 2014 were recorded in Germany (from €19 to €59), Austria (€27 to €60), and Switzerland (€38 to €69); the smallest increases in Lithuania (from €2.9 to €5.6), the Czech Republic (€12.0 to €15.4), and Poland (€4.8 to €11.3).

The top spenders in 2014 were Switzerland, Austria, and Germany that spent between €60-70 per capita on cancer drugs. The second biggest spender in 2005, France, dropped to fourth place. At the other end of the spending scale are countries for which only retail sales (and no hospital sales) of cancer drugs are available. Among the countries with complete data Lithuania spent the least in 2014 with €5.6 (but increased from €2.9 in 2005) followed by Poland with €11.3 (increased from €4.8 in 2005) and Romania with €13.8. Romania spent the least in 2005 with €2.8.

Figure 16 reveals also a clear tendency of wealthier countries to spend more on cancer drugs in per capita terms than poorer countries. As mentioned before, differential pricing of cancer drugs between countries partly exaggerates the extent of this tendency.

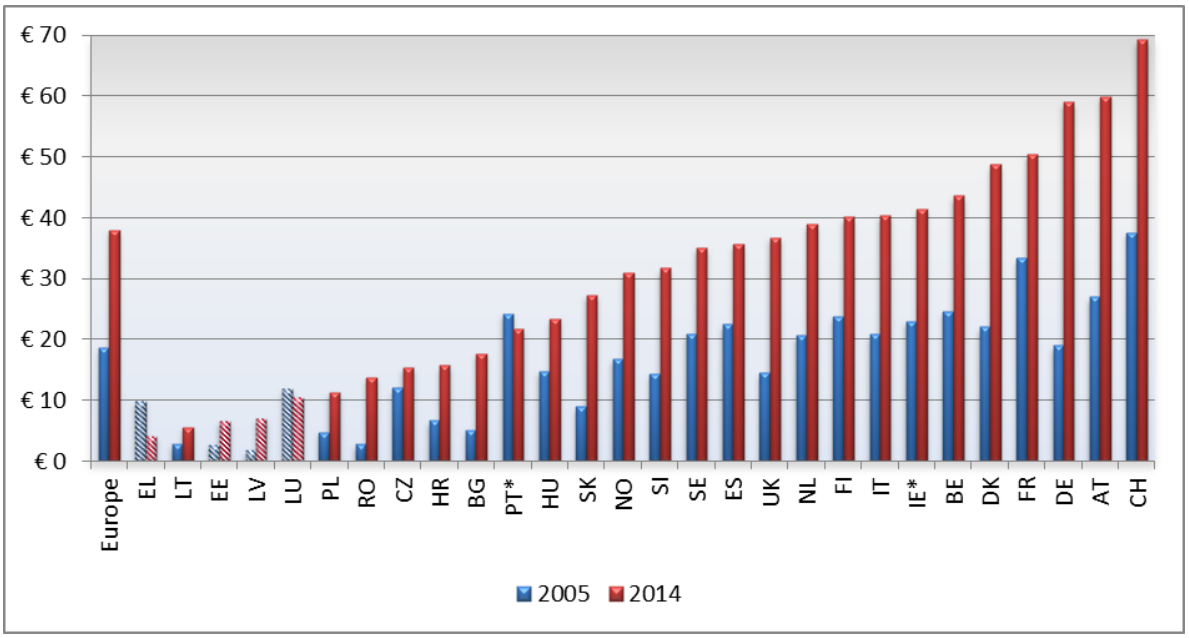


FIGURE 16: COST OF CANCER DRUGS PER CAPITA (IN 2014 PRICES), 2005–2014 [35, 57, 58]

Notes: Hatched bars indicate that data for EE, LV, LU, and EL only comprise retail sales.
* The value for 2005 for IE is from 2006 and for PT from 2010.
CY, IS, and MT are missing due to lack of data.

1.4.2 Development of the cost of cancer drugs in relative terms

The development of the cost of cancer drugs can also be considered in relative terms. Figure 17 shows the annual average growth rate of cancer drug sales between 2005 and 2014. The annual average growth rate of total health expenditure during the same time period serves as a comparison[21]. Note that the growth rates are calculated based on total cancer drug sales and total health expenditure (thus not per capita). The latter two measures had been inflated to 2014 prices to get comparable real growth rates. The results show that the annual growth rate in total health expenditure was 1 percent in Europe, whereas the annual growth rate in cancer drug sales was 9 percent. This pattern is also prevalent at the country level. The growth in cancer drug sales greatly outpaced the growth in total health expenditure in all countries but Luxembourg and Greece for which the growth rates of cancer drugs only refer to retail sales.

Total health expenditure increased in almost all countries between 2005 and 2014, except in some Southern European countries as well as in Iceland, Hungary, and the UK. As already shown above in absolute terms in Figure 16, cancer drug sales increased in all countries with complete data. The highest relative increase in cancer drug sales was recorded in Romania with an average annual growth rate of 18 percent. In Latvia (retail sales), Bulgaria, Slovakia, Germany, and the UK, the average annual growth rate also exceeded 10 percent.

[21] An alternative comparison measure would be total pharmaceutical expenditure. However, the data on pharmaceutical expenditure provided by the OECD only include 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 instead [6]. The OECD estimates that its measure for pharmaceutical expenditure underestimates the real total pharmaceutical expenditure by some 15 percent. Nonetheless, in cancer patients a far greater share of drugs is administered at hospitals than dispensed via retail. Of course this share depends on the health care organization in each country, but data from the IMS Health MIDAS database point towards a much greater underestimation than 15 percent in the case of cancer drugs. For instance, in Ireland retail sales of cancer drugs amounted to €25 million in 2005 but the combined retail and hospital sales in 2006 amounted to €91 million. Similarly, in Portugal retail sales in 2009 amounted to €4 million but combined sales in 2010 amounted to €240 million [57]. This issue inhibits a valid calculation of the share of cancer drug expenditure on the OECD's measure for total pharmaceutical expenditure.

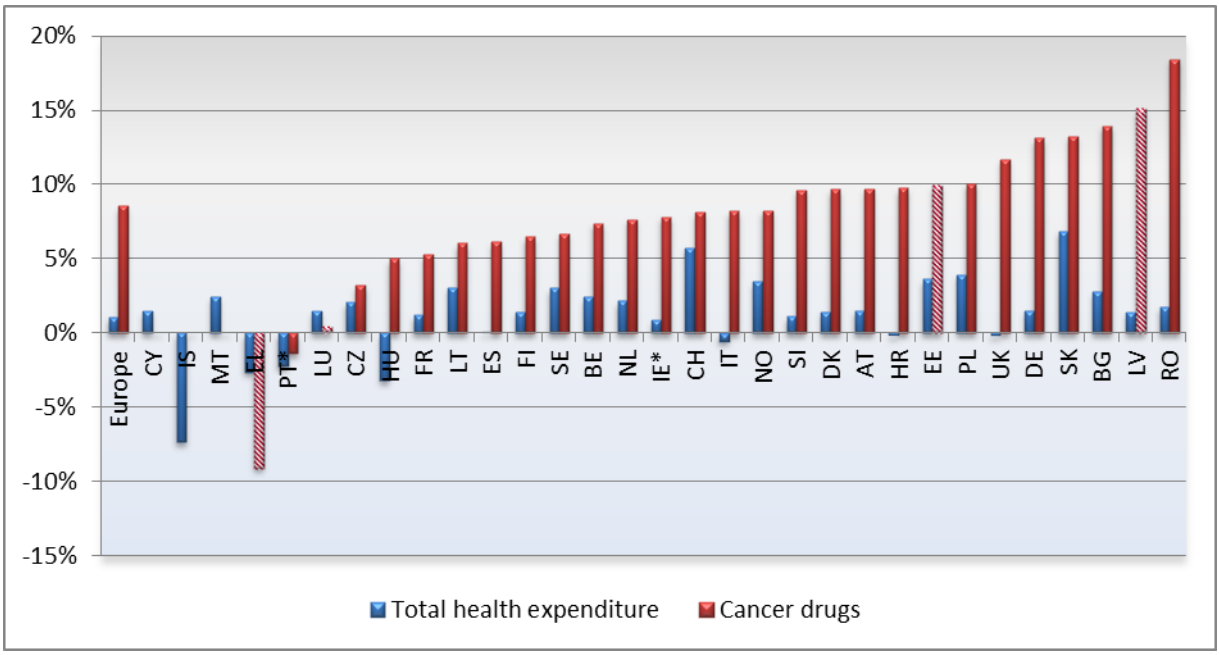


FIGURE 17: ANNUAL AVERAGE GROWTH RATES IN TOTAL HEALTH EXPENDITURE AND COST OF CANCER DRUGS (IN 2014 PRICES) BETWEEN 2005 AND 2014, [33-36, 57]

Notes: Hatched bars indicate that data for cancer drugs for EE, LV, LU, and EL only comprise retail sales.
* Both growth rates in IE are between 2006 and 2014, and in PT between 2010 and 2014.
There is no growth rate of the cost of cancer drugs in CY, IS, and MT due to lack of data.

The final measure to put the cost of cancer drugs into perspective is to calculate their share on the direct health cost of cancer. The direct health cost of cancer has been calculated for the year 2014 in section 1.3; see also Table A1 in the Appendix. The share of cancer drugs on the estimated direct health cost is shown in Figure 18. In Europe as a whole this share amounted to 23 percent. On the one hand, this estimate might be slightly underestimated since sales data for Cyprus and Malta are not included and for Estonia, Greece, Latvia, and Luxembourg only retail sales data are included. On the other hand, the use of ex-manufacturer prices leads to an overestimation.

There is great variation in the share of cancer drugs on the direct health costs between countries. In Bulgaria and Romania cancer drugs accounted for more than half of all health expenditure on cancer. Also in other poorer countries this share tended to be higher than in wealthier countries, with the exception of Lithuania. In wealthier countries cancer drugs accounted for slightly more than 20 percent of the direct health cost of cancer. An explanation for this pattern of higher shares in poorer countries is the difference in relative prices of cancer care services and cancer drugs. Cancer care services reflect lower domestic price levels, whereas the price of cancer drugs mostly lies within a common price corridor and reflects higher international price levels.

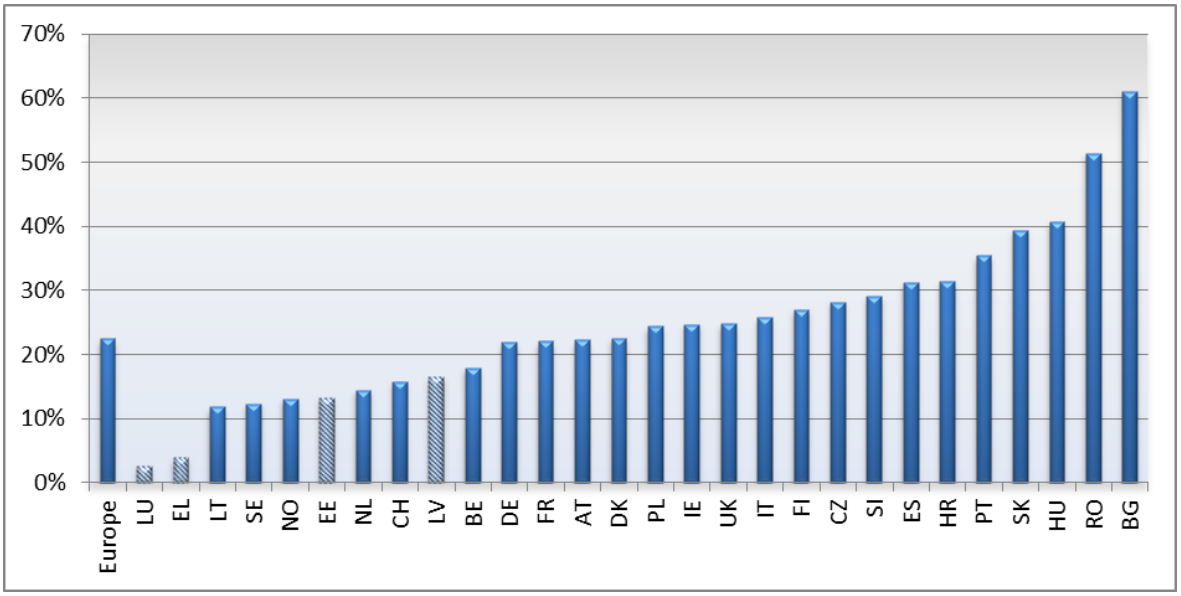


FIGURE 18: SHARE OF THE COST OF CANCER DRUGS ON THE DIRECT HEALTH COST OF CANCER, 2014 [57]

Notes: Hatched bars indicate that data for EE, LV, LU, and EL only comprise retail sales.
CY, IS, and MT are missing due to lack of data on cancer drug sales.

The findings from Figure 18 can also be compared with previous studies. The LF-2013-study (LF-2015-study) estimated the share of cancer drugs on total health expenditure on cancer to be 27 (26) percent in the EU-27 (EU-28) in 2009 (2012) [44]. These estimates are 3-4 percentage points higher than the estimate in this report. The higher shares stem mainly from the different calculation of the total health expenditure on cancer, as explained above. In the first Comparator report the share of the cost of cancer drugs was estimated to be 9 percent of the total health expenditure on cancer in 2002/2003 [41]. In the follow up Comparator reports this share was estimated to be 13 percent in 2004 [42], and 18 percent in 2007 [43]. Against the backdrop of these previous results, cancer drugs seem to represent a growing share of the direct cost of cancer.

Based on the calculation of the direct health cost of cancer in Europe over time in section 1.3, the argument of a growing share of the cost of cancer drugs on the direct cost can be reassessed for the period 2005 to 2014. Figure 19 shows that the cost of cancer drugs amounted to €8.0 billion in 2005 measured in current prices (€9.5 billion measured in 2014 prices). Given that the total direct cost of cancer was €66.3 (€78.8) billion that year, this equals a share of 12 percent. Until 2010 this share had increased to 20 percent, and eventually reached 23 percent in 2014.

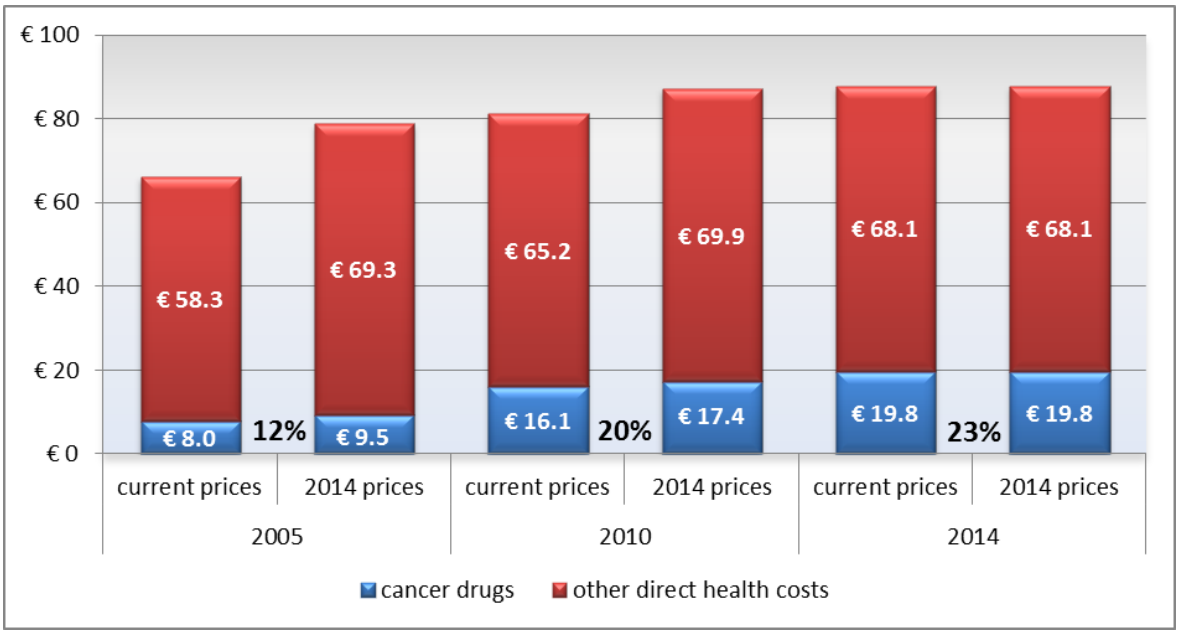


FIGURE 19: COMPONENTS OF THE DIRECT HEALTH COST OF CANCER IN EUROPE (IN BILLION €), 2005–2014 [57]

Notes: The adjustment for inflation was carried out with country-specific inflation rates [35].

Despite the increasing share of cancer drugs on the direct health cost of cancer since 2002/2003, Table 7 provided evidence of a relatively stable or at best slightly increasing share of cancer-specific expenditure on total health expenditure. Thus, it seems that increased expenditure on cancer drugs were paralleled by a reduction or at least a slower increase in other direct health costs. The analysis in the Appendix on the composition of the direct cost of cancer points out a puzzle piece that could potentially help to explain this finding. Inpatient care constitutes the lion's share of the health expenditure on cancer; see Figure A14. At least since the year 2000 inpatient days of cancer patients have been trending downwards in the populous countries; see Figure A15. In countries like Germany, Poland, or the Czech Republic they declined even faster than the overall trend of declining inpatient days in all diagnoses. Thus, the savings from fewer inpatient days might have to some extent compensated for the additional expenditure on cancer drugs. As a result, the cancer-specific expenditure on total health expenditure remained mostly unchanged.

This shifting trend in the composition of the direct health cost of cancer should, however, be interpreted with some caution. A reduction in the number of inpatient days does not automatically imply a decrease in the cost for inpatient care, since the cost per inpatient day could have gone up. Nonetheless, there is a gain in opportunity costs from fewer inpatient days of cancer patients since it frees up hospital beds for other patients. Moreover, it might be the case that some costs for the increased management of patients in ambulatory care instead

of inpatient care are not accounted for in the statistics, which would lead to an underestimation of the total direct health cost of cancer.

In sum, cancer drug sales in Europe have been rising at a fast pace between 2005 and 2014. Especially between 2005 and 2008 every country recorded swift increases in sales. The following economic crisis hampered this development in a majority of countries. But by 2013 cancer drug sales had picked up again strongly in most countries and seemed set to continue to increase. In comparison, the increasing overall development of health expenditure was much slower between 2005 and 2014. This is also an important reason for why the share of cancer drugs on the direct health cost of cancer has increased strongly. In 2014 it had reached 23 percent in Europe; ten years before it was 12 percent. In most of the poorer countries the share of cancer drugs is distinctly higher than in the wealthier countries. Nonetheless, there is still a rather striking divide in per capita spending on cancer drugs between wealthier and poorer countries in Europe. In 2014 poorer countries spent mostly between €10-25 per capita on cancer drugs, whereas wealthier countries spent between €35-70.

1.5 Indirect cost of cancer

The economic cost of cancer extends beyond the remit of the health care system. If a societal perspective is applied, indirect costs arise in addition to direct costs. Ignoring these costs can lead to suboptimal policy decisions from a societal perspective [59]. The indirect cost of cancer refers to productivity loss of cancer patients and represents foregone labor market earnings from three different causes. Firstly, productivity loss due to premature mortality arises in patients who die during working age and who otherwise would have continued to work until retirement age. Secondly, productivity loss arises due to temporary absence from work (sickness absenteeism) of patients in the labor force who are forced to take a hiatus from work while they receive care and fight the diseases. Thirdly, productivity loss arises due to permanent absence from work (permanent incapacity/disability) of patients in the labor force who cannot continue to work due to the disease and are forced to retire early. The latter two causes of productivity loss are often summarized under the term productivity loss due to morbidity.

Even though there is a broad agreement on the importance of indirect costs, there is less agreement on the exact methodology to calculate these costs. Two different methodologies are commonly used to calculate the productivity loss; the human-capital method and the friction-cost method. The human-capital method takes the patient's perspective and counts any hour not worked as an hour lost. By contrast, the friction-cost method takes the employer's perspective and counts only those hours not worked as lost until another employee takes over the patient's work [60]. If the human-capital method is used there is further disagreement over

whether public spending on sick leave and early retirement benefits should be included in addition to lost labor income, since they only represent so-called transfer payments from the general taxpayer to the cancer patient without altering the use of resources [61]. The choice of the method has an important influence on the size of the indirect costs. If the friction-cost method is used, the estimated costs will typically be much smaller compared to when the human-capital method is used [62, 63].

1.5.1 Results from previous studies

The availability of studies on the indirect cost of cancer in different European countries has improved in recent years. They show to which extent different components give rise to indirect costs. Moreover, they provide insight into how large the indirect costs are in relation to the direct costs. Similar to studies on the direct cost of cancer, studies on the indirect cost do not always include all relevant components due to data limitations.

The only studies to date that calculated the indirect cost of cancer in the EU in a comprehensive manner are the LF-studies described in section 1.3.1. They included all relevant components, productivity loss due to premature mortality, sickness absence, and early retirement. They estimated the indirect cost of cancer to be €52.0 (€62.0) billion in the EU-27 (EU-28) in 2009 (2012) [44, 45]. Compared to the estimated direct health cost of cancer of €83.1 billion in the EU-28 in 2014 in this report, the indirect cost seems to be smaller than the direct health cost. Even after taking into account the methodological differences (the use of a broader definition of cancer in this report, inflation between 2009 (2012) and 2014, inclusion of Croatia), the indirect cost of cancer would probably not exceed the direct cost of cancer in 2014. However, the LF-studies used the friction-cost method to calculate productivity loss due to sickness absence and early retirement. The LF-2013-study notes that the use of the human-capital method would have increased indirect costs by €7 billion to €59 billion in 2009. This would bring the indirect costs closer to the direct health costs.

Another study by Hanly, et al. (2015) put the productivity loss due to premature mortality to €71.3 billion in 2008 in the EU-28 (excluding Greece) [64]. This is much higher than the estimate in both the LF-2013-study (€42.6 billion in 2009) and the LF-2015 study (€50.2 billion in 2012) even though all three studies used the human-capital method for the calculation. Thus based on this study it would seem very likely that the indirect cost of cancer is at least as large as the direct health cost in Europe.

1.5.1.1 Share of indirect costs on the total costs

The few European studies that looked at the share of indirect costs on the total costs of cancer are summarized in Table 8. The LF-2015-study for the EU-28 estimated that the indirect costs accounted for around 52 percent of the total costs of cancer[22], and direct costs for the remaining 48 percent in 2012. Similarly, the LF-2013 study for the EU-27 estimated that indirect costs are equally large as direct costs. The individual member states did not deviate too far from this aggregate value. Only in Finland and Italy did the direct costs (around 60 percent) markedly outweigh the indirect costs. By contrast, Denmark, Lithuania, and Portugal were the only member states where the share of indirect costs was around 70 percent. Country-specific studies for France (for 2004), Poland (for 2009), and Spain (for 2003) yielded somewhat similar results. In those studies indirect costs accounted for 61-65 percent of the total costs. In a study for Sweden for the year 2004 the share of indirect costs was just as large as the share of direct costs. In sum, the indirect cost seems to be at least as large as the direct cost of cancer. This means that a great part of the economic burden of cancer falls outside the remit of the health care system.

[22] Note here that the total costs of cancer do not include costs for informal care which have been included in the LF-studies.

TABLE 8: OVERVIEW OF EUROPEAN STUDIES ON THE DIRECT AND INDIRECT COST OF CANCER

Country & Year	Types of direct costs included	Types of indirect costs included	Share of direct costs	Share of indirect costs
EU-28 2012 [45]	Inpatient care, outpatient care, drugs, primary care, emergency care	Productivity loss (premature mortality (HCM), sickness absence (FCM), early retirement (FCM))	48%*	52%*
EU-27 2009 [44]	Inpatient care, outpatient care, drugs, primary care, emergency care	Productivity loss (premature mortality (HCM), sickness absence (FCM), early retirement (FCM))	50%*	50%*
France 2004 [65]	Inpatient care, outpatient care, screening programs, primary prevention	Productivity loss (premature mortality (HCM), sickness absence (FCM))	39%	61%
Poland 2009 [66-68]	Inpatient care, outpatient care, palliative and hospice care, screening, rehabilitation, nursing and care services, other services, prescription drugs	Productivity loss (premature mortality (HCM), sickness absence (HCM), early retirement (HCM))	35%	65%
Spain 2003 [69]	Inpatient care, ambulatory care (including chemotherapy)	Productivity loss (premature mortality (HCM), sickness absence (HCM), early retirement (HCM))	36%	64%
Sweden 2004 [70, 71]	Care, drugs, screening programs, primary prevention	Productivity loss (premature mortality, sickness absence, early retirement)	50%	50%

Notes: FCM = friction-cost method; HCM = human-capital method.
* Costs for informal care are excluded in this calculation to provide comparable figures.
The direct cost in France, Poland, and Sweden was (re-)calculated according to the methodology outlined in the Appendix.
An exchange rate of PLN 1 = EUR 0.23 was applied in the calculation of the direct cost in Poland in 2009.

European studies that looked at the share of indirect costs on the total costs of specific cancer types are summarized Table 9. Even though the share of the indirect costs on the total costs of all cancers has been estimated to 50 percent in the EU-27 in the LF-2013-study, it differs greatly between different cancer types. For lung cancer, the share of the indirect costs is 72 percent of the total costs, whereas for prostate cancer this share is only 17 percent. Breast cancer (43 percent share of the indirect costs) and colorectal cancer (46 percent) fall somewhere in between. Two studies for Belgium and Sweden that estimated the share of the indirect costs in breast cancer found this share to exceed 70 percent. Another study for Sweden for pancreatic cancer estimated that the share of the indirect costs (not including productivity loss due to early retirement) was 95 percent in patients aged younger than 65 years. A study for the UK for skin cancer found that indirect and direct costs are equally large.

TABLE 9: OVERVIEW OF EUROPEAN STUDIES ON THE DIRECT AND INDIRECT COST OF SPECIFIC CANCER TYPES

Country & Year	Cancer type	Types of direct costs included	Types of indirect costs included	Share of direct costs	Share of indirect costs
EU-27 2009 [44]*	Breast Colorectal Lung Prostate	Inpatient care, outpatient care, drugs, primary care, emergency care	Productivity loss (premature mortality (HCM), sickness absence (FCM), early retirement (FCM))	57%* 54%* 28%* 83%*	43%* 46%* 72%* 17%*
Belgium 1998 [72]	Breast	Health care	Productivity loss (premature mortality (HCM), morbidity (HCM))	11%	89%
Sweden 2002 [73]	Breast	Inpatient care, ambulatory care drugs, screening	Productivity loss (premature mortality (HCM), sickness absence (HCM), early retirement (HCM))	30%	70%
Sweden 2009 [74]	Pancreatic	Inpatient care, outpatient care	Productivity loss (premature mortality (HCM), sickness absence (HCM))	5%†	95%†
UK 2002 [75]	Skin	GP consultations, inpatient care, day cases, outpatient attendances, patient fees	Productivity loss (premature mortality (HCM), sickness absence (HCM))	50%	50%

Notes: FCM = friction-cost method; HCM = human-capital method.
* Costs for informal care are excluded in this calculation to provide comparable figures.
† Only refers to patients aged <65 years. The direct cost was calculated as the average of the value for men and women.

Taken together, there is a pattern of distinctly higher shares of indirect costs on total costs in cancer types with low survival rates (lung cancer and pancreatic cancer). This stems mainly from higher productivity loss due to premature mortality in these cancer types. Another factor is the age at which patients are diagnosed and die, since patients above retirement age do not incur productivity loss. For instance, prostate cancer patients are typically older than patients with breast or lung cancer. Since many of them are already retired at the time of diagnosis and even more so at the time of death productivity loss is comparatively small. The composition of the indirect cost of all cancers and four major cancer types is analyzed in more detail in the Appendix.

1.5.2 Development of the indirect cost over time

Studies on the development of the indirect cost of cancer in European countries over time could not be found. The aim of this section is to provide a rough idea on the development. The review of the studies above showed that productivity loss due to premature mortality is the major component of the indirect cost of cancer (see also the section on the composition of the indirect cost of cancer in the Appendix). The key measure to estimate this kind of productivity loss is years of potential life lost (YPLL) during working age. The working age is commonly assumed to stretch from age 15 to age 64 inclusive.

The following steps were taken to calculate YPLL during working age. Age-specific cancer deaths were obtained from IARC's WHO mortality database for each country [12]. There, deaths are grouped into five-year age intervals. To calculate YPLL, all deaths in an age interval were assumed to occur in the middle of that interval. Thus, for instance, a death in the age interval 25-29 years was assumed to occur at age 27.5 and result in 37.5 YPLL (i.e. retirement age 65 years minus age at death 27.5 years). The deaths in each age interval were then multiplied with the respective YPLL. Finally, YPLL were summed over all age intervals as well as female and male cases. YPLL were calculated for all cancers and also for the major cancer types.

Even though YPLL during working age form the basis of the calculation of productivity loss from premature mortality, there is a general criticism of the restriction 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 not captured. Also the assumption of a uniform retirement age of 65 years across countries and sexes is imperfect. In some countries the statutory retirement age is above or below 65 years and the effective retirement age might also deviate from the statutory one [76]. As explained above, for the calculations in this report the same age interval is considered in each country and all periods. This guarantees a transparent approach and facilitates the interpretation of the results.

Figure 20 compares the total number of YPLL in Europe in the years 1995 and 2012. In 1995 3.8 million YPLL during working age were lost. Until 2012 this number had decreased by 16 percent to 3.2 million YPLL. This decline occurred despite a growing population in the age range 15-64 years; it increased from 331 million people in 1995 by 4 percent to 345 million people in 2012 [5]. If standardized by population size, then the YPLL lost in Europe decreased by 20 percent from 1,148 to 923 YPLL per 100,000 inhabitants aged 15-64.

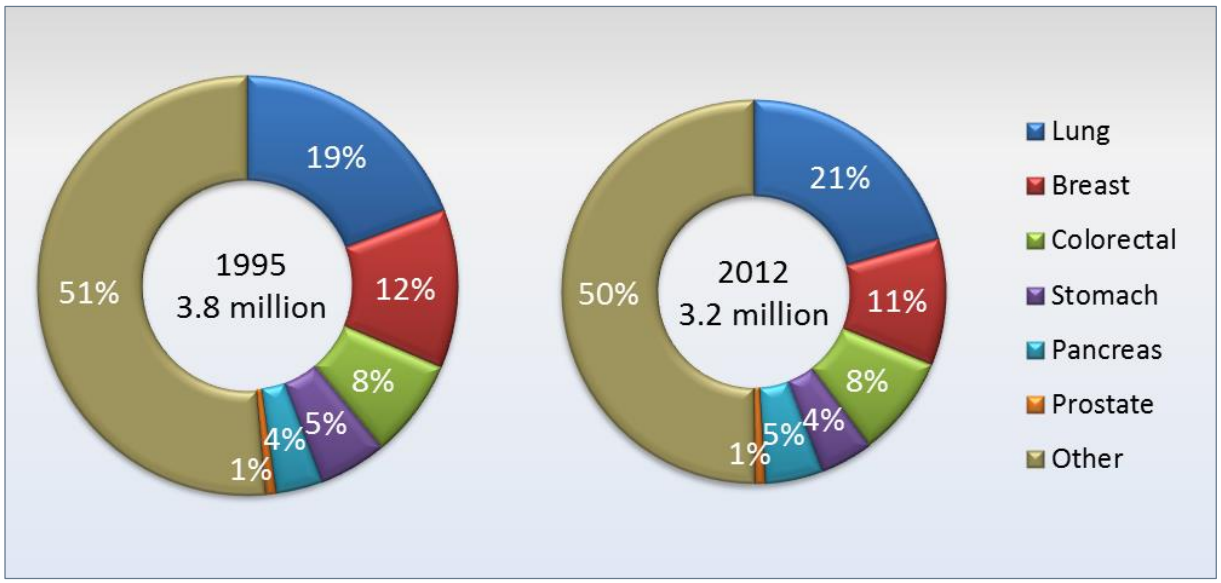


FIGURE 20: YEARS OF POTENTIAL LIFE LOST (YPLL) DURING WORKING AGE DUE TO CANCER IN EUROPE, 1995–2012 [12]

Notes: Cancer is defined as ICD-10 C00-C97,B21, lung as C33-34, breast as C50, colorectal as C18-21, stomach as C16, pancreatic as C25, and prostate as C61.
The 1995 estimate includes data for Cyprus from 2004.
The 2012 estimate includes data for France from 2011, for Slovenia from 2010, and for Iceland from 2009.
In 1995 no pancreatic cancer cases for Latvia are included due to missing data.
Working age stretches from 15-64 years inclusive.
Deaths were assumed to occur in the middle of the five-year age intervals.

Six common cancer types accounted for half of all YPLL during working age in 1995 and 2012; see Figure 20. Lung cancer is the most important cause of YPLL followed by breast cancer and colorectal cancer. The reason for the small share of prostate cancer can again be explained by the advanced age at death of prostate cancer patients as well as the high survival rates. Despite the overall decrease in YPLL between 1995 and 2012 the proportions of the cancer types remained broadly stable.

On the country level there are great variations in terms of YPLL during working age; see Figure 21. Sweden recorded the lowest number of YPLL in 1995 (about 830 YPLL per 100,000 inhabitants aged 15-64) and Cyprus in 2012 (about 500 YPLL). The highest number of YPLL was recorded in Hungary in both 1995 (about 2,000 YPLL) and 2012 (about 1,600 YPLL). Despite these variations in the level of YPLL, the number of YPLL decreased markedly in all countries, except in Portugal, Greece, and Romania where it remained stable. The result for specific cancer types was similar to the overall pattern in observed in Europe in Figure 20. Lung cancer causes the most YPLL followed by breast cancer, whereas YPLL caused by prostate cancer are comparatively very small. The decrease in YPLL between 1995 and 2012 was more or less proportional across all cancer types in every country.

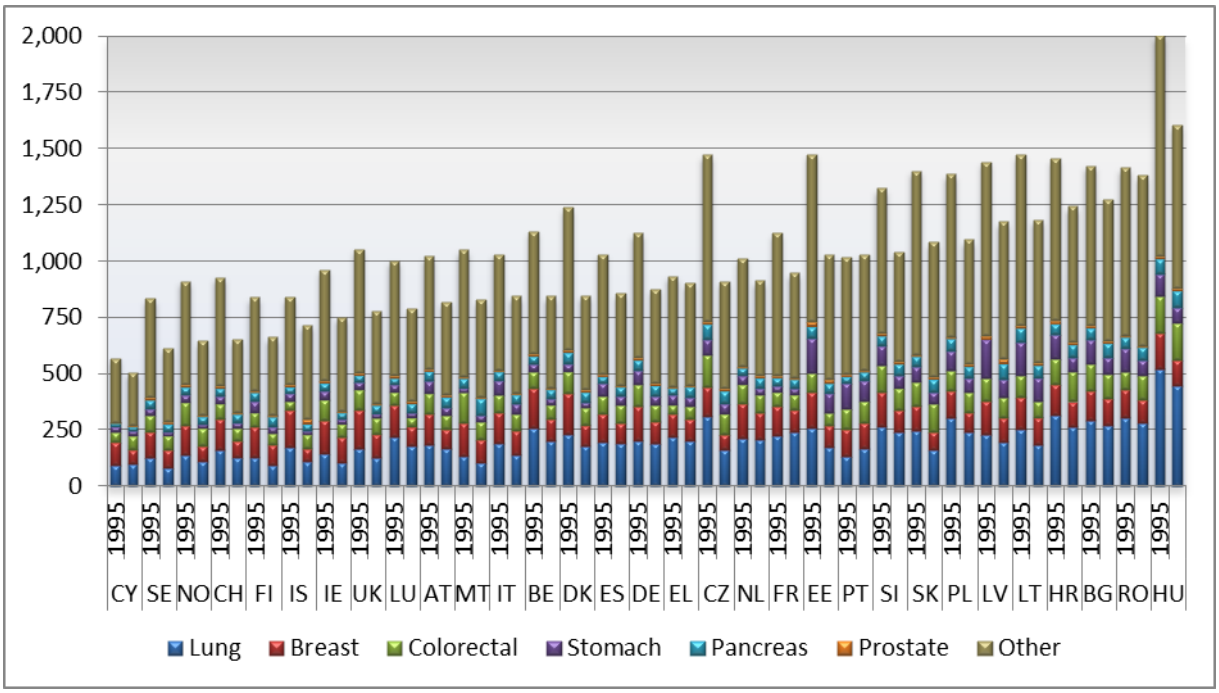


FIGURE 21: YEARS OF POTENTIAL LIFE LOST (YPLL) DURING WORKING AGE DUE TO CANCER PER 100,000 INHABITANTS AGED 15-64, 1995–2012 [5, 12]

Notes: see Figure 20

Using the human-capital method, the productivity loss due to premature mortality is calculated below. To do so, the YPLL have to be combined with annual earnings and adjusted for the employment rate. Gender-specific mean annual earnings from employment for all countries are only available for the year 2010 [77], but have been adjusted for inflation to 2014 prices [35]. Gender-specific employment rates in the age group 15-64 years are applied [78], implicitly assuming a uniform employment rate during the whole age interval. Since the death of a cancer patient in working age implies the loss of a whole stream of future earnings, they have to be discounted. In line with common practice in health economic evaluation, a 3.5 percent annual discount rate is assumed. A zero real growth rate in future earnings is assumed.

Figure 22 shows how the productivity loss due to premature mortality in Europe evolved between 1995 and 2014. It amounted to €57.1 billion in 1995 and remained constant until 2000, but started to decline afterwards to €50.7 billion in 2014 (all measured in 2014 prices). This equals an 11 percent decline. Measured in per capita, the productivity loss decreased from €115 by 15 percent to €98 (in 2014 prices). The corresponding country-specific results are summarized in Table A2–A3 in the Appendix.

Another observation from Figure 22 is the gender-specific composition of the productivity loss. Throughout the whole period women's share on the productivity loss is much lower than men's share. The three reasons for this pattern are a lower number of YPLL, lower earnings,

and a lower employment rate in women compared to men. The consideration of the composition by gender reveals also that the overall decline stems solely from a decrease in productivity loss in men. The reason for this is that the employment rate in men remained more or less constant between 1995 and 2014, whereas the YPLL decreased. Rising female labor market participation especially in the Western and Southern European countries during this period counteracted the decrease in YPLL, since only deaths by people in employment constitute a loss.

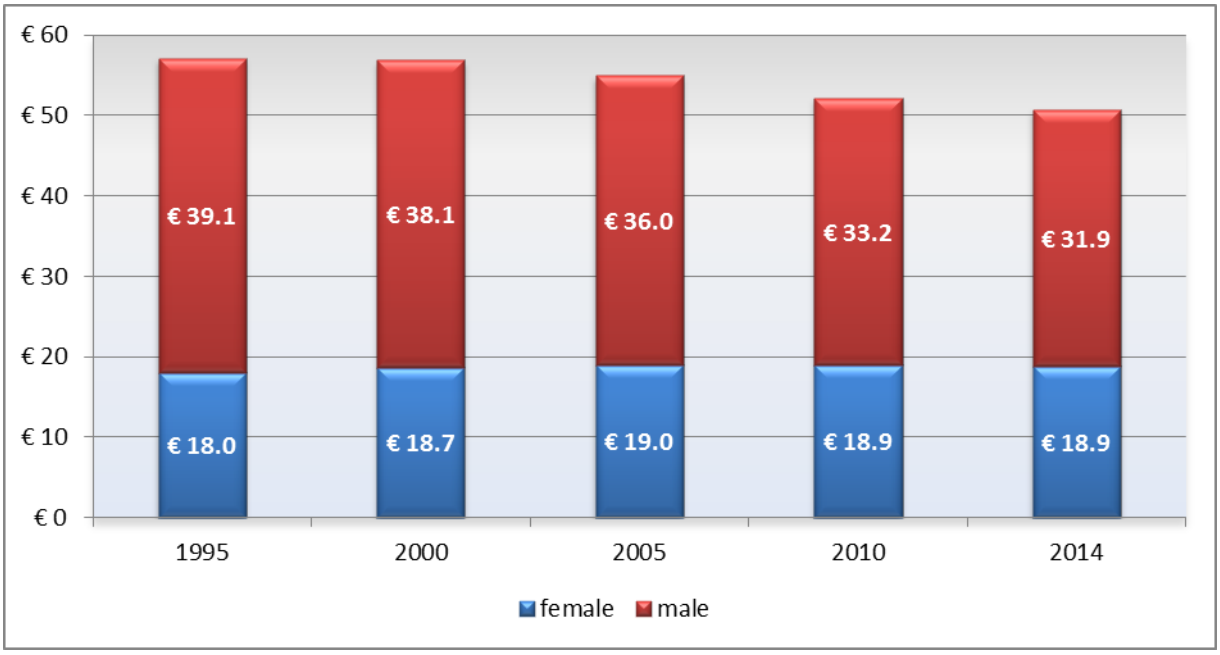


FIGURE 22: PRODUCTIVITY LOSS DUE TO PREMATURE MORTALITY FROM CANCER IN EUROPE (IN BILLION €; IN 2014 PRICES), 1995–2014

Notes: Cancer is defined as ICD-10 C00-C97,B21.
The 1995 and 2000 estimates include mortality data for Cyprus from 2004. The 2005 estimate includes mortality data for Portugal from 2007. The 2010 estimate includes mortality data for Iceland from 2009. The 2014 estimate includes mortality data for HR, CZ, FI, DE, HU, LT, LU, NL, NO, PL, PT, ES, SE, CH, UK from 2013, for BE, BG, CY, DK, EE, EL, IE, IT, LV, RO from 2012, for FR from 2011, for SI from 2010, and for IS from 2009 [12].
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 [78].
Earnings in all years are from 2010 [77], and have been adjusted for inflation to 2014 prices [35].

In sum, the following conclusions about the past and future development of the indirect cost of cancer over time can be made:

- Cancer mortality in the age group 40-64 years has decreased by 20 percent in Europe between 1995 and 2012, if standardized by population size. This development is also reflected in the reduction of YPLL during working age from 3.8 to 3.2 million YPLL. As a result the productivity loss due to premature mortality has declined. This trend will continue as cancer survival increases. Owing to the way productivity loss is calculated, rising (female) labor market participation, rising real wages, and potentially higher

retirement age might however partially offset or even balance future reductions in YPLL.

- The development in the other two components of the indirect cost of cancer is uncertain, due to lack of data. The increase in cancer incidence (in absolute terms) probably pushed up the productivity loss due to sickness absence and also due to early retirement. Since cancer incidence is set to increase, these two sources of productivity loss will most likely increase on the overall level. However, on the patient level advances in treatment result in shorter spells of sickness absence (due to quicker recovery and fewer side effects) and increase the chances to continue to work. These improvements mitigate the increase in productivity loss due to morbidity.

The results from the calculation of cancer mortality-induced productivity loss (ICD-10 C00-C97,B21) can also be compared to the estimates of the direct health cost of cancer (ICD-10 C00-D48) in Europe; see Figure 23 for total costs and Figure 24 for per capita costs. The direct health cost amounted to €53 billion in 1995 and the productivity loss due to premature mortality to €57 billion. Since there is also productivity loss due to morbidity, the indirect cost of cancer in 1995 evidently exceeded the direct health cost. During the years until 2014 the direct health cost and the mortality-induced productivity loss followed opposite trajectories. The former increased by 67 percent to €88 billion while the latter decreased by 11 percent to €51 billion. Given that productivity loss due to morbidity is typically smaller than productivity loss due to mortality, it seems very likely that the direct health cost of cancer had surpassed the indirect cost by 2014 or even already by 2010. It is also noteworthy that the absolute reduction in mortality-induced productivity loss between 2005 and 2014 equaled almost half of the simultaneous increase in costs of cancer drugs.

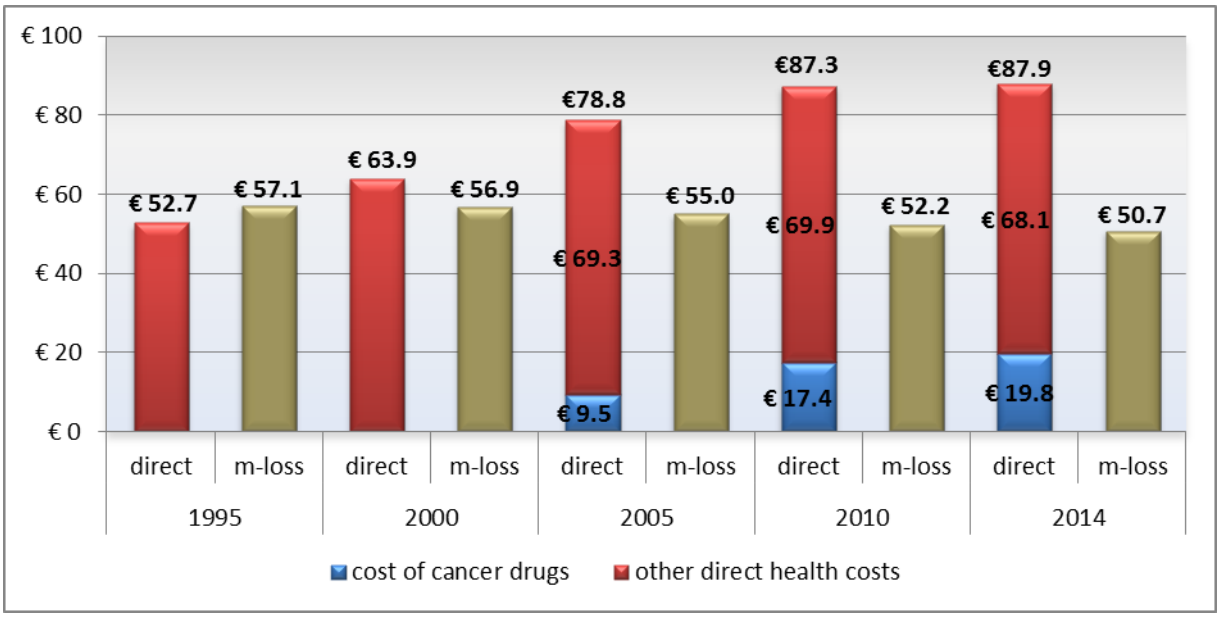


FIGURE 23: COMPONENTS OF THE ECONOMIC BURDEN OF CANCER IN EUROPE (IN BILLION €; 2014 PRICES), 1995–2014

Notes: "direct" = direct health cost of cancer; "m-loss" = productivity loss due to premature mortality from cancer during working age.
Cancer is defined as ICD-10 C00-D48 for direct health costs, and C00-C97,B21 for productivity loss.
For calculations see Figure 11, Figure 19, and Figure 22.

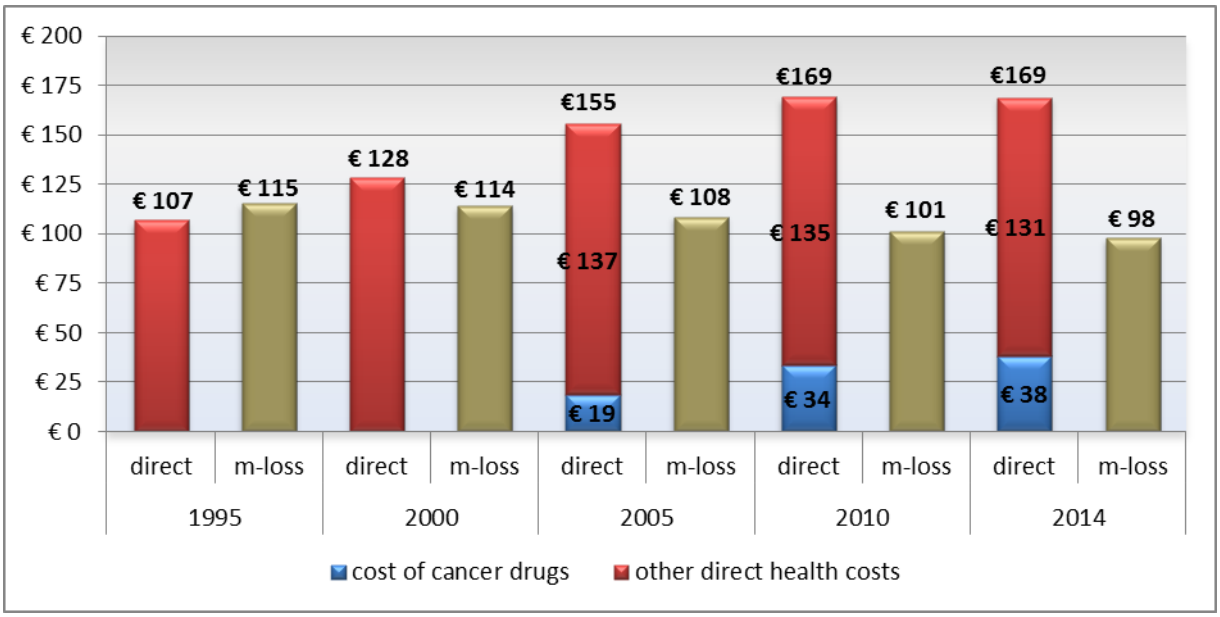


FIGURE 24: COMPONENTS OF THE ECONOMIC BURDEN OF CANCER IN EUROPE (PER CAPITA; IN €; 2014 PRICES), 1995–2014

Notes: see Figure 23

1.6 Conclusion

The aim of this chapter was to provide evidence on the development of the two cornerstones of the cancer burden (the health burden and the economic burden) in Europe over the last two decades. In the following, the findings are summarized and some forward-looking conclusions derived based on past trends.

Cancer is a disease that affects people in all ages, yet mainly people aged over 50. In Europe the estimated cancer incidence totaled 2.707 million cases in 2012, which was about 30 percent higher than in 1995. Overall population growth during this period can only explain some part of this increase. A more fundamental demographic factor behind this increase is population aging. Even if both of these two demographic factors are taken into account, there is still an increase observable in nearly all countries. An increase in some risk factors related to lifestyle, such as obesity, and more extensive screening activities might offer additional explanations for the observed increase in cancer incidence. Also, the positive epidemiological development in other major diseases, such as cardiovascular diseases, implies that more people reach an advanced age at which the risk of getting cancer is higher. These factors together with the demographic changes will probably render it difficult to achieve a turnaround in the trend of increasing cancer incidence in the near future.

Cancer mortality has increased by 11 percent between 1995 and 2012, claiming an estimated 1.319 million deaths in Europe in 2012. After taking into account population growth the overall increase becomes smaller, and in some countries it becomes clear that cancer mortality had in fact decreased. If in addition population aging is taken into account, nearly every single country recorded a decrease in cancer mortality. Thus, in the absence of the demographic development, cancer mortality by and large declined in a period during which an increasing number of people was diagnosed with cancer.

This discrepancy in the upward trend of cancer incidence and the downward trend of cancer mortality is reflected in the development of survival rates. Between 1990 and 2007 there was a steady increase in cancer survival rates in all countries, yet disparities remain between wealthier countries with higher survival rates and poorer countries with lower survival rates. In a majority of countries half of all cancer patients still live 5 years after receiving their diagnosis. The steady increase in survival rates has been observed since the 1960s in the Nordic countries and continued even after 2007. “Major advances in cancer management” have been cited as the raison d'être for this improvement in survival [15]. The central factors that drove a wedge between the trends in incidence and mortality are advances in diagnostics and medical treatment. Due to its limited scope in the past, the role of screening in providing an additional explanation is limited, but it will grow in importance in the coming years

following rollouts of population-based screening programs of certain major cancer types in many countries.

Cancer was the disease group that caused the second greatest burden of disease, measured in DALYs, after cardiovascular diseases in Europe in both 2000 and 2012. In absolute terms DALYs caused by cancer increased between 2000 and 2012, but in per capita terms there was a slight decrease from 59 to 58 DALYs per 1,000 inhabitants. Due to significant successes in reducing mortality in cardiovascular diseases, their share of the total disease burden decreased from 25 to 21 percent between 2000 and 2012. At the same time, the share of cancer increased from 18 to 19 percent. If this trend continues, cancer will become the disease group causing the greatest burden of disease in the coming years. The diseases burden of cancer in terms of mortality is also high, given that more than one in four deaths in Europe was due to cancer in 2012.

The economic burden of cancer is comprised of direct costs inside and outside the health care system and indirect costs in terms of productivity loss due to morbidity and premature mortality. The estimated direct health cost of cancer amounted to €87.9 billion in Europe in 2014, accounting for 6.0 percent of the total expenditure on health. This share stands in stark contrast to the 19 percent share of the total burden of all diseases that cancer caused and also to the 26 percent share of all deaths due to cancer in 2012. Health spending on cancer per capita ranged from €53 in Romania to €311 in Luxembourg in 2014 if price differentials (PPP-adjusted) are taken into account; if not, then the gap increases to €27 in Romania and €441 in Switzerland. Sufficient spending on cancer is a prerequisite for achieving high survival rates. Countries with lower per capita health spending on cancer in 2005 tended to record lower survival rates during the period 2000–2007, and countries with higher spending tended to record higher survival rates.

Health spending on cancer in Europe has increased continuously since 1995, from €107 per capita in 1995 to €155 in 2005 and €169 in 2014 (all measured in 2014 prices). This equals an increase of 58 percent between 1995 and 2014. Total health spending on cancer increased from €52.7 billion in 1995 by 67 percent to €87.9 billion in 2014 (all measured in 2014 prices). This increase happened not primarily because a greater share of the total expenditure on health was devoted to cancer, but rather because overall health spending increased. Furthermore, this increase in health costs should be considered against the backdrop of the simultaneous increase in the total number of newly diagnosed cases (cancer incidence), which was about half as large.

The largest component of the direct health cost of cancer is inpatient care accounting for more than half of all costs. Despite the increase in cancer incidence, inpatient days of cancer patients have been declining at least since 2000. However, this pattern is not specific to cancer

patients and reflects a general trend in health care provision with fewer inpatient days and (in some countries) more day cases. The share of total health expenditure devoted to cancer did not decline during the 2000s though, but rather remained constant or increased slightly.

The development in the use of cancer drugs might offer some explanation for this observation. Cancer drug sales doubled from €9.5 billion to €19.8 billion in Europe between 2005 and 2014 (measured in 2014 prices). The share of costs of cancer drugs on the direct health cost of cancer increased from 12 percent in 2005 to 23 percent in 2014. In most of the poorer countries this share was close to or above 30 percent in 2014. A striking divide in per capita spending on cancer drugs remained though. Poorer countries spent mostly between €10-25 per capita on cancer drugs and wealthier countries mostly between €35-70 in 2014. The strong increase in costs of cancer drugs is linked to higher prices of newly introduced drugs and greater patient numbers, due to increased cancer incidence, and more prevalent cases that need long-term chemotherapy. Moreover, new cancer drugs had been introduced that addressed unmet needs and allowed a greater share of patients to be treated.

The indirect cost of cancer is comprised of productivity loss of patients of working age. Productivity loss due to premature mortality amounted to €57.1 billion in 1995 and decreased by 11 percent to €50.7 billion until in 2014 (all measured in 2014 prices) as result of a decline in mortality during working age and a compression of cancer deaths towards older ages. In per capita terms, this type of productivity loss decreased from €115 by 15 percent to €98 (in 2014 prices). Productivity loss due to morbidity is more difficult to assess, but its size is typically (significantly) smaller than that of productivity loss due to premature mortality. As a consequence, the indirect cost of cancer exceeded the direct health cost in 1995. Given the opposite trajectories of the direct health cost and the productivity loss due to premature mortality between 1995 and 2014, it seems likely that the direct health cost of cancer had surpassed the indirect cost of cancer by 2014. These indirect costs must not be forgotten when assessing the economic burden of cancer to society. Ignoring them 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 is intertwined with the future development in cancer incidence, mortality, and survival, as well as the investments made in prevention, diagnostics, and treatment of cancer. While the relative disease burden of cancer is increasing, there is still no sign of a dramatic increase in health spending on cancer as share of total health spending. However, there are significant shifts in the composition of the economic burden of cancer.

Indirect costs have fallen below the direct health costs, and might be reduced further in relative terms. The number of life years lost due to cancer for the population of working age is

decreasing. However, with higher real wages, greater labor force participation, and potentially higher retirement age, the monetary value of indirect costs will not be reduced significantly, but rather balance the reduction in years lost. Indirect costs due to morbidity are smaller, but might increase as a result of increasing incidence and improved survival on the overall level. By contrast, increased treatment of patients in ambulatory care and improved medical treatment with fewer side effects make it possible for a larger share of patients to continue to work during treatment and rehabilitation.

Direct costs outside the health care system are not very well documented, and thus it is difficult to judge how they will develop. Nevertheless, increasing cancer incidence and survival among the elderly may put additional pressure on both public resources (mostly in the form of social care) and private resources (in the form of informal care) outside the health care system.

1.7 References chapter 1

1. World Health Organization. Cancer [August 23, 2015]. Available from: http://www.who.int/cancer/en/.
2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11: International Agency for Research on Cancer; 2013 [August 12, 2015]. Available from: http://globocan.iarc.fr.
3. Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. Eur J Cancer. 2002;38(1):99-166.
4. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403.
5. Eurostat. Population on 1 January by five years age group and sex [demo_pjangroup] [January 22, 2016]. Available from: http://ec.europa.eu/eurostat/.
6. OECD. Health at a Glance: Europe 2014: OECD Publishing; 2014.
7. von Karsa L, Anttila A, Ronco G, Ponti A, Malila N, Arbyn M, et al. Cancer screening in the European Union. Report on the Implementation of the Council Recommen-dation on cancer screening – First Report. European Commission, editor2008.
8. Honoré BE, Lleras-Muney A. Bounds in Competing Risks Models and the War on Cancer. Econometrica. 2006;74(6):1675-98.
9. Bray F, Lortet-Tieulent J, Ferlay J, Forman D, Auvinen A. Prostate cancer incidence and mortality trends in 37 European countries: an overview. Eur J Cancer. 2010;46(17):3040-52.
10. Steliarova-Foucher E, O'Callaghan M, Ferlay J, Masuyer E, Forman D, Comber H, et al. European Cancer Observatory: Cancer Incidence, Mortality, Prevalence and Survival in Europe. Version 1.0 (September 2012). European Network of Cancer Registries, International Agency for Research on Cancer; 2012 [August 15, 2015]. Available from: http://eco.iarc.fr.
11. Eurostat. Main GDP aggregates per capita [nama_10_pc] [January 22, 2016]. Available from: http://ec.europa.eu/eurostat/.
12. International Agency for Research on Cancer. WHO cancer mortality database [January 18, 2016]. Available from: http://www-dep.iarc.fr/WHOdb/WHOdb.htm.
13. Malvezzi M, Bertuccio P, Rosso T, Rota M, Levi F, La Vecchia C, et al. European cancer mortality predictions for the year 2015: does lung cancer have the highest death rate in EU women? Ann Oncol. 2015;26(4):779-86.
14. Eurostat. Causes of death - Deaths by country of residence and occurrence [hlth_cd_aro] [February 1, 2016]. Available from: http://ec.europa.eu/eurostat/.
15. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. Lancet Oncol. 2014;15(1):23-34.
16. Hofmarcher T, Jönsson B, Wilking N. Access to high-quality oncology care across Europe. IHE Report. 2014;2, IHE: Lund.
17. Altobelli E, Lattanzi A. Breast cancer in European Union: an update of screening programmes as of March 2014 (review). Int J Oncol. 2014;45(5):1785-92.
18. Altobelli E, Lattanzi A. Cervical carcinoma in the European Union: an update on disease burden, screening program state of activation, and coverage as of March 2014. Int J Gynecol Cancer. 2015;25(3):474-83.
19. Altobelli E, Lattanzi A, Paduano R, Varassi G, di Orio F. Colorectal cancer prevention in Europe: burden of disease and status of screening programs. Prev Med. 2014;62:132-41.
20. Lichtenberg FR. Has Medical Innovation Reduced Cancer Mortality? CESifo Economic Studies. 2014;60(1):135-77.

21. Uyl-de Groot CA, de Groot S, Steenhoek A. The economics of improved cancer survival rates: better outcomes, higher costs. Expert Rev Pharmacoecon Outcomes Res. 2010;10(3):283-92.

22. OECD. Cancer Care: Assuring Quality to Improve Survival: OECD Publishing; 2013.

23. Brenner H. Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis. Lancet. 2002;360(9340):1131-5.

24. Brenner H, Spix C. Combining cohort and period methods for retrospective time trend analyses of long-term cancer patient survival rates. Br J Cancer. 2003;89(7):1260-5.

25. Henson DE, Ries LA. The relative survival rate. Cancer. 1995;76(10):1687-8.

26. Verdecchia A, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, et al. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. Lancet Oncol. 2007;8(9):784-96.

27. Berrino F, De Angelis R, Sant M, Rosso S, Bielska-Lasota M, Coebergh JW, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study. Lancet Oncol. 2007;8(9):773-83.

28. World Health Organization. Metrics: Disability-Adjusted Life Year (DALY) [August 27, 2015]. Available from: http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/.

29. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J. 2014;35(42):2950-9.

30. World Health Organization. Global Health Estimates Summary Tables: Disease Burden - Estimates for 2000–2012. 2014 [August 11, 2015]. Available from: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html.

31. Guinness L. Counting the costs. In: Guinness L, Wiseman V, editors. Introduction to Health Economics. Understanding Public Health. 2nd ed. Maidenhead, England: Open University Press; 2011.

32. Uyl-de Groot CA, de Vries EGE, Jaap Verweij J, Sullivan R. Dispelling the myths around cancer care delivery: It's not all about costs. Journal of Cancer Policy. 2014;2:22–9.

33. World Health Organization. Global Health Expenditure Database [February 11, 2016]. Available from: http://apps.who.int/nha/database.

34. Eurostat. GDP and main components (output, expenditure and income) [nama_10_gdp] [January 22, 2016]. Available from: http://ec.europa.eu/eurostat/.

35. Eurostat. HICP (2005 = 100) - annual data (average index and rate of change) [prc_hicp_aind] [January 22, 2016]. Available from: http://ec.europa.eu/eurostat/.

36. Eurostat. GDP and main components - Current prices [nama_gdp_c] [February 11, 2016]. Available from: http://ec.europa.eu/eurostat/.

37. OECD. OECD Health Statistics 2015 - Definitions, Sources and Methods - Health Expenditure and Financing [September 24, 2015]. Available from: http://www.oecd.org/els/health-systems/health-data.htm.

38. OECD. Estimating Expenditure by Disease, Age and Gender under the System of Health Accounts (SHA) Framework [September 24, 2015]. Available from: http://www.oecd.org/els/health-systems/estimating-expenditure-by-disease-age-and-gender.htm.

39. Garg CC, Evans DB. What is the Impact of Noncommunicable Diseases on National Health Expenditures: A Synthesis of Available Data. Geneva: WHO - Department of Health Systems Financing; 2011.

40. Lipscomb J, Yabroff KR, Hornbrook MC, Gigli A, Francisci S, Krahn M, et al. Comparing cancer care, outcomes, and costs across health systems: charting the course. J Natl Cancer Inst Monogr. 2013;2013(46):124-30.

41. Wilking N, Jönsson B. A pan-European comparison regarding patient access to cancer drugs. Stockholm: Karolinska Institutet in collaboration with Stockholm School of Economics; 2005.

42. Jönsson B, Wilking N. A global comparison regarding patient access to cancer drugs. Ann Oncol. 2007;18 Suppl 3:iii1-iii77.

43. Wilking N, Jönsson B, Högberg D, Justo N. Comparator Report on Patient Access to Cancer Drugs in Europe. Karolinska Institutet & Stockholm School of Economics & i3 Innovus, 2009 [January 22, 2016]. Available from: http://www.comparatorreports.se/.

44. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncol. 2013;14(12):1165-74.

45. Leal J, Luengo-Fernandez R, Sullivan R, Witjes JA. Economic Burden of Bladder Cancer Across the European Union. Eur Urol. 2015.

46. Federal Statistical Office (Destatis - Statistisches Bundesamt). Krankheitskosten: Deutschland, Jahre, Krankheitsdiagnosen 2002-2008 [Medical Expenses: Germany, years, disease diagnoses 2002-2008] (Table 23631-0001) [September 14, 2015]. Available from: https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Gesundheit/Krankheitskosten/Krankheitskosten.html.

47. Bosanquet N, Sikora K. The economics of cancer care in the UK. Lancet Oncol. 2004;5(9):568-74.

48. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst. 2011;103(2):117-28.

49. Civan A, Koksal B. The effect of newer drugs on health spending: do they really increase the costs? Health Econ. 2010;19(5):581-95.

50. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood. 2013;121(22):4439-42.

51. Kantarjian H, Rajkumar SV. Why are cancer drugs so expensive in the United States, and what are the solutions? Mayo Clin Proc. 2015;90(4):500-4.

52. Kantarjian H, Steensma D, Rius Sanjuan J, Elshaug A, Light D. High cancer drug prices in the United States: reasons and proposed solutions. J Oncol Pract. 2014;10(4):e208-11.

53. Siddiqui M, Rajkumar SV. The high cost of cancer drugs and what we can do about it. Mayo Clin Proc. 2012;87(10):935-43.

54. Tefferi A, Kantarjian H, Rajkumar SV, Baker LH, Abkowitz JL, Adamson JW, et al. In Support of a Patient-Driven Initiative and Petition to Lower the High Price of Cancer Drugs. Mayo Clin Proc. 2015;90(8):996-1000.

55. Drummond MF, Mason AR. European perspective on the costs and cost-effectiveness of cancer therapies. J Clin Oncol. 2007;25(2):191-5.

56. European Commission. What is ERM II? [October 13, 2015]. Available from: http://ec.europa.eu/economy_finance/euro/adoption/erm2/index_en.htm.

57. IMS Health MIDAS database.

58. Eurostat. Population on 1 January by age and sex [demo_pjan] [January 27, 2016]. Available from: http://ec.europa.eu/eurostat/.

59. Lidgren M, Wilking N, Jonsson B, Rehnberg C. Resource use and costs associated with different states of breast cancer. Int J Technol Assess Health Care. 2007;23(2):223-31.

60. van den Hout WB. The value of productivity: human-capital versus friction-cost method. Ann Rheum Dis. 2010;69 Suppl 1:i89-91.

61. World Health Organization. WHO guide to identifying the economic consequences of disease and injury. Geneva: WHO; 2009.

62. Hanly P, Timmons A, Walsh PM, Sharp L. Breast and prostate cancer productivity costs: a comparison of the human capital approach and the friction cost approach. Value Health. 2012;15(3):429-36.

63. Pearce AM, Hanly P, Timmons A, Walsh PM, O'Neill C, O'Sullivan E, et al. Productivity Losses Associated with Head and Neck Cancer Using the Human Capital and Friction Cost Approaches. Appl Health Econ Health Policy. 2015;13(4):359-67.

64. Hanly P, Soerjomataram I, Sharp L. Measuring the societal burden of cancer: the cost of lost productivity due to premature cancer-related mortality in Europe. Int J Cancer. 2015;136(4):E136-45.

65. National Cancer Institute (INCa - Institut National du Cancer). Analyse économique des coûts du cancer en France [Economic Analysis of the Cost of Cancer in France]. Paris: INCa; 2007.

66. Macioch T, Hermanowski T. The indirect costs of cancer-related absenteeism in the workplace in Poland. J Occup Environ Med. 2011;53(12):1472-7.

67. Ministry of Health - Department of Drug Policy and Pharmacy. Informacja Ministerstwa Zdrowia na temat leczenia chorób onkologicznych [Information of the Ministry of Health on the treatment of oncological diseases]. Warsaw. January 5, 2011.

68. National Health Fund (NFZ - Narodowy Fundusz Zdrowia). Realizacja świadczeń onkologicznych 2009 - 2011 [Realization of benefits in oncology 2009 - 2011].

69. Antoñanzas F, Oliva J, Velasco M, Zozaya N, Lorente R, López-Bastida J. Costes directos e indirectos del cáncer en España [Direct and indirect costs of cancer in Spain]. Cuadernos Económicos de ICE. 2006;72:280-309.

70. National Board of Health and Welfare (Socialstyrelsen) and Swedish Association of Local Authorities and Regions (SKL - Sveriges Kommuner och Landsting). Öppna jämförelser 2014 – Cancersjukvård – Jämförelser mellan landsting [Comparisons 2014 – Cancer Care – Comparisons between regions]. Stockholm: Socialstyrelsen & SKL; 2014.

71. Swedish Cancer Society (Cancerfonden). Cancerfondsrapporten 2006 [The report of the Swedish Cancer Society 2006]. Stockholm: Swedish Cancer Society (Cancerfonden); 2006.

72. Broekx S, Den Hond E, Torfs R, Remacle A, Mertens R, D'Hooghe T, et al. The costs of breast cancer prior to and following diagnosis. Eur J Health Econ. 2011;12(4):311-7.

73. Lidgren M, Wilking N, Jonsson B. Cost of breast cancer in Sweden in 2002. Eur J Health Econ. 2007;8(1):5-15.

74. Tingstedt B, Andersson E, Flink A, Bolin K, Lindgren B, Andersson R. Pancreatic cancer, healthcare cost, and loss of productivity: a register-based approach. World J Surg. 2011;35(10):2298-305.

75. Morris S, Cox B, Bosanquet N. Cost of skin cancer in England. Eur J Health Econ. 2009;10(3):267-73.

76. OECD. Ageing and Employment Policies - Statistics on average effective age of retirement [January 29, 2016]. Available from: http://www.oecd.org/els/public-pensions/ageingandemploymentpolicies-statisticsonaverageeffectiveageofretirement.htm.

77. Eurostat. Structure of earnings survey: annual earnings [earn_ses_annual] [January 29, 2016]. Available from: http://ec.europa.eu/eurostat/.

78. Eurostat. Employment rates by sex, age and citizenship (%) [lfsa_ergan] [January 29, 2016]. Available from: http://ec.europa.eu/eurostat/.

79. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol. 2007;18(3):581-92.

80. Lortet-Tieulent J, Renteria E, Sharp L, Weiderpass E, Comber H, Baas P, et al. Convergence of decreasing male and increasing female incidence rates in major tobacco-related cancers in Europe in 1988-2010. Eur J Cancer. 2015;51(9):1144-63.

81. Arnold M, Karim-Kos HE, Coebergh JW, Byrnes G, Antilla A, Ferlay J, et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. Eur J Cancer. 2015;51(9):1164-87.

82. Bray FI, Weiderpass E. Lung cancer mortality trends in 36 European countries: secular trends and birth cohort patterns by sex and region 1970-2007. Int J Cancer. 2010;126(6):1454-66.

83. Autier P, Boniol M, La Vecchia C, Vatten L, Gavin A, Hery C, et al. Disparities in breast cancer mortality trends between 30 European countries: retrospective trend analysis of WHO mortality database. BMJ. 2010;341:c3620.

84. Bosetti C, Levi F, Rosato V, Bertuccio P, Lucchini F, Negri E, et al. Recent trends in colorectal cancer mortality in Europe. Int J Cancer. 2011;129(1):180-91.

85. Weiderpass E, Antoine J, Bray FI, Oh JK, Arbyn M. Trends in corpus uteri cancer mortality in member states of the European Union. Eur J Cancer. 2014;50(9):1675-84.

86. Levi F, Lucchini F, Gonzalez JR, Fernandez E, Negri E, La Vecchia C. Monitoring falls in gastric cancer mortality in Europe. Ann Oncol. 2004;15(2):338-45.

87. Engholm G, Ferlay J, Christensen N, Kejs AMT, Johannesen TB, Khan S, et al. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 7.2 (16.12.2015): Association of the Nordic Cancer Registries, Danish Cancer Society; [January 19, 2016]. Available from: http://www-dep.iarc.fr/NORDCAN/english/frame.asp.

88. Wilking N, Högberg D, Jönsson B. Benchmarking report of lung cancer care in selected European Countries. Karolinska Institutet & i3 Innovus, 2008 [October 25, 2015]. Available from: http://www.comparatorreports.se/.

89. Lichtenberg FR. Are Increasing 5-Year Survival Rates Evidence of Success Against Cancer? A Reexamination Using Data from the U.S. and Australia. Forum for Health Economics & Policy. 2010;13(2).

90. Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? JAMA. 2000;283(22):2975-8.

91. Maringe C, Walters S, Butler J, Coleman MP, Hacker N, Hanna L, et al. Stage at diagnosis and ovarian cancer survival: evidence from the International Cancer Benchmarking Partnership. Gynecol Oncol. 2012;127(1):75-82.

92. Maringe C, Walters S, Rachet B, Butler J, Fields T, Finan P, et al. Stage at diagnosis and colorectal cancer survival in six high-income countries: a population-based study of patients diagnosed during 2000-2007. Acta Oncol. 2013;52(5):919-32.

93. Walters S, Maringe C, Butler J, Rachet B, Barrett-Lee P, Bergh J, et al. Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: a population-based study. Br J Cancer. 2013;108(5):1195-208.

94. Walters S, Maringe C, Coleman MP, Peake MD, Butler J, Young N, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. Thorax. 2013;68(6):551-64.

95. Kalseth J, Halsteinli V, Halvorsen T, Kalseth B, Anthun K, Peltola M, et al. Costs of cancer in the Nordic countries - A comparative study of health care costs and public income loss compensation payments related to cancer in the Nordic countries in 2007. Trondheim: SINTEF Technology and Society; 2011.

96. Lai T, Habicht T, Kahur K, Reinap M, Kiivet R, van Ginneken E. Estonia: Health system review. Health Systems in Transition. 2013;15(6):1–196.

97. Mäklin S, Rissanen P. Kostnader för cancer [Cost of cancer]. Helsinki: Cancer Society of Finland (Cancerorganisationerna); 2006.

98. Chevreul K. Colorectal cancer in France. Eur J Health Econ. 2010;10 Suppl 1:S15-20.

99. Ministry of Health. National Action Plan on Cancer, 2011-2015 [September 16, 2015]. Available from: http://www.anticancer.gov.gr/.

100. Francisci S, Guzzinati S, Mezzetti M, Crocetti E, Giusti F, Miccinesi G, et al. Cost profiles of colorectal cancer patients in Italy based on individual patterns of care. BMC Cancer. 2013;13:329.

101. National Institute for Public Health and the Environment (RIVM - Rijksinstituut voor Volksgezondheid en Milieu). Cost of Illness database 2013 [September 16, 2015]. Available from: https://www.volksgezondheidenzorg.info/cost-of-illness.

102. Ruszkowski J. Colorectal cancer management in Poland: current improvements and future challenges. Eur J Health Econ. 2010;10 Suppl 1:S57-63.

103. Araujo A, Barata F, Barroso S, Cortes P, Damasceno M, Parreira A, et al. Custo do tratamento do cancro em Portugal [Cost of cancer care in Portugal]. Acta Med Port. 2009;22(5):525-36.

104. Lopez-Bastida J, Serrano-Aguilar P, Duque-Gonzalez B. [Socioeconomic costs of cardiovascular disease and cancer in the Canary Islands (Spain) in 1998]. Gac Sanit. 2003;17(3):210-7.

105. Pastor M, Gisbert R. Evolució de la participació dels plans directors en la despesa i en el pressupost sanitari del CatSalut. Any 2008 [Evolution of participation plans on spending and the health budget of the Catalan Health Service (CatSalut). Year 2008]. In: Departament de Salut - Direcció General de

Planificació i Avaluació, editor. Estudis d'Economia de la Salut (Volum III) [Health Economics Studies (Volume III)]. Barcelona: Generalitat de Catalunya - Departament de Salut; 2010. p. 9-39.

106. OECD. Health at a Glance: Europe 2010: OECD Publishing; 2010.

107. Lundqvist A, Andersson E, Steen Carlsson K. Kostnader för cancer i Sverige idag och år 2040 [Cost of cancer in Sweden today and 2040]. IHE rapport. 2016 (forthcoming); IHE: Lund.

108. Wieser S, Tomonaga Y, Riguzzi M, Fischer B, Telser H, Pletscher M, et al. Die Kosten der nichtübertragbaren Krankheiten in der Schweiz [The cost of non-communicable diseases in Switzerland]. Winterthur, Switzerland: Winterthurer Institut für Gesundheitsökonomie, ZHAW; Institut für Sozial- und Präventivmedizin, UZH; Polynomics, 2014.

109. NHS Networks. Programme Budgeting Aggregate PCT Expenditure for all programmes and subcategories for financial years 2003/04 to 2012/13 [September 15, 2015]. Available from: https://www.networks.nhs.uk/nhs-networks/health-investment-network/news/2012-13-programme-budgeting-data-is-now-available.

110. Williamson S. Co-payment schemes - when patients pay for high cost drugs. Hospital Pharmacist. 2008;15:154.

111. Eurostat. Hospital days of in-patients [hlth_co_hosday] [October 9, 2015]. Available from: http://ec.europa.eu/eurostat/.

112. Eurostat. Hospital discharges by diagnosis, day cases, per 100 000 inhabitants [hlth_co_disch4] [October 9, 2015]. Available from: http://ec.europa.eu/eurostat/.

113. Fourcade RO, Benedict A, Black LK, Stokes ME, Alcaraz A, Castro R. Treatment costs of prostate cancer in the first year after diagnosis: a short-term cost of illness study for France, Germany, Italy, Spain and the UK. BJU Int. 2010;105(1):49-56.

114. Ivanauskiene R, Domeikiene A, Kregzdyte R, Milasauskiene Z, Padaiga Z. The cost of newly diagnosed breast cancer in Lithuania, 2011. Medicina (Kaunas). 2015;51(1):63-8.

115. Haug U, Engel S, Verheyen F, Linder R. Estimating colorectal cancer treatment costs: a pragmatic approach exemplified by health insurance data from Germany. PLoS One. 2014;9(2):e88407.

116. Chastek B, Harley C, Kallich J, Newcomer L, Paoli CJ, Teitelbaum AH. Health care costs for patients with cancer at the end of life. J Oncol Pract. 2012;8(6):75s-80s.

117. Kelly RJ, Smith TJ. Delivering maximum clinical benefit at an affordable price: engaging stakeholders in cancer care. Lancet Oncol. 2014;15(3):e112-8.

118. Lewin SN, Buttin BM, Powell MA, Gibb RK, Rader JS, Mutch DG, et al. Resource utilization for ovarian cancer patients at the end of life: how much is too much? Gynecol Oncol. 2005;99(2):261-6.

119. Obermeyer Z, Makar M, Abujaber S, Dominici F, Block S, Cutler DM. Association between the Medicare hospice benefit and health care utilization and costs for patients with poor-prognosis cancer. JAMA. 2014;312(18):1888-96.

2 Medical review

Summary

- Cancer treatment today is characterized by a multimodal therapy approach including surgery, radiotherapy and an increasing number of anti-tumour drugs. Optimal care of cancer patients requires multidisciplinary teams; surgeons, radiotherapists, medical oncologists, diagnostic radiologists, pathologists, specialized nurses and psychosocial support.
- Most anti-tumour drugs are introduced in patients with late stage- or metastatic disease. This may lead to improvements in survival, but the magnitude of that effect is seldom known when the drug is first introduced, as surrogate end-points are often used. Effects in late stage disease may translate to increased cure rates in conjunction with surgery or with a curative intent as first-line treatment.
- Anti-tumour drugs are generally cell toxic (kill all rapid growing cells, not only cancer cells), and have often severe side effects. The progress in molecular medicine has led to the development of new agents targeting cancer specific cell mechanisms, and generally with less and different toxicity profile.
- There has also been an introduction of an increasing number of compounds with a focus on improving the quality of life for patients – supportive drugs.
- Improved diagnostic methods and screening programs have facilitated early detection of tumours, which has led to improved cure rates in some cancer forms.
- The decreased toxicity of new agents, the trend towards oral agents, and the use of supportive drugs have resulted in an increased number of day-care treatments or treatments taken at home.
- It is already possible to predict if a patient is likely to respond to treatments by different molecular markers, and gene/protein analyses of tumour cells will likely improve accuracy in the treatment offered to individual patients.
- New diagnostic tools with functional imaging are increasingly used to evaluate effects of therapy.
- The medical treatment of cancer has developed and expanded from chemotherapy and hormonal treatment to therapies targeting cell-signalling pathways. Drugs in this area include small molecules like tyrosine kinases inhibitors, or monoclonal antibodies like trastuzumab. These treatment modalities, developed over many decades, are now established back-bones of modern cancer therapy. The latest development in cancer treatment is activating the body's own immune system to attack the tumour. This treatment approach has shown important effects in metastatic malignant skin melanoma and lung cancer, and has rapidly become standard of care in these tumours and is now studied in a number of other tumour types.

2.1 Understanding the biology of tumour cells

The development of invasive cancer is a process with many steps, with an accumulation of genetic changes occurring over a long time period (5-20 years). Intense research has increased 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 markers. Progress in molecular medicine has led to increased understanding of cancer evolution and cancer cells characterization and defects in DNA repair mechanisms, leading to an accumulation of genetic defects. Furthermore, increased knowledge of cancer biology has reduced use of highly cell-toxic treatments and increased use of agents, targeting pathways in the cell [1].

The main areas of drug mechanisms of action in oncology (Figure 1):

- Targeting of the cell cycle and apoptosis, DNA replication/transcription and repair [1, 2]
- Inhibition of hormones, growth factors and cell signalling pathways [1] [3, 4]
- Inhibition of angiogenesis [5]
- Immunotherapy [6, 7]

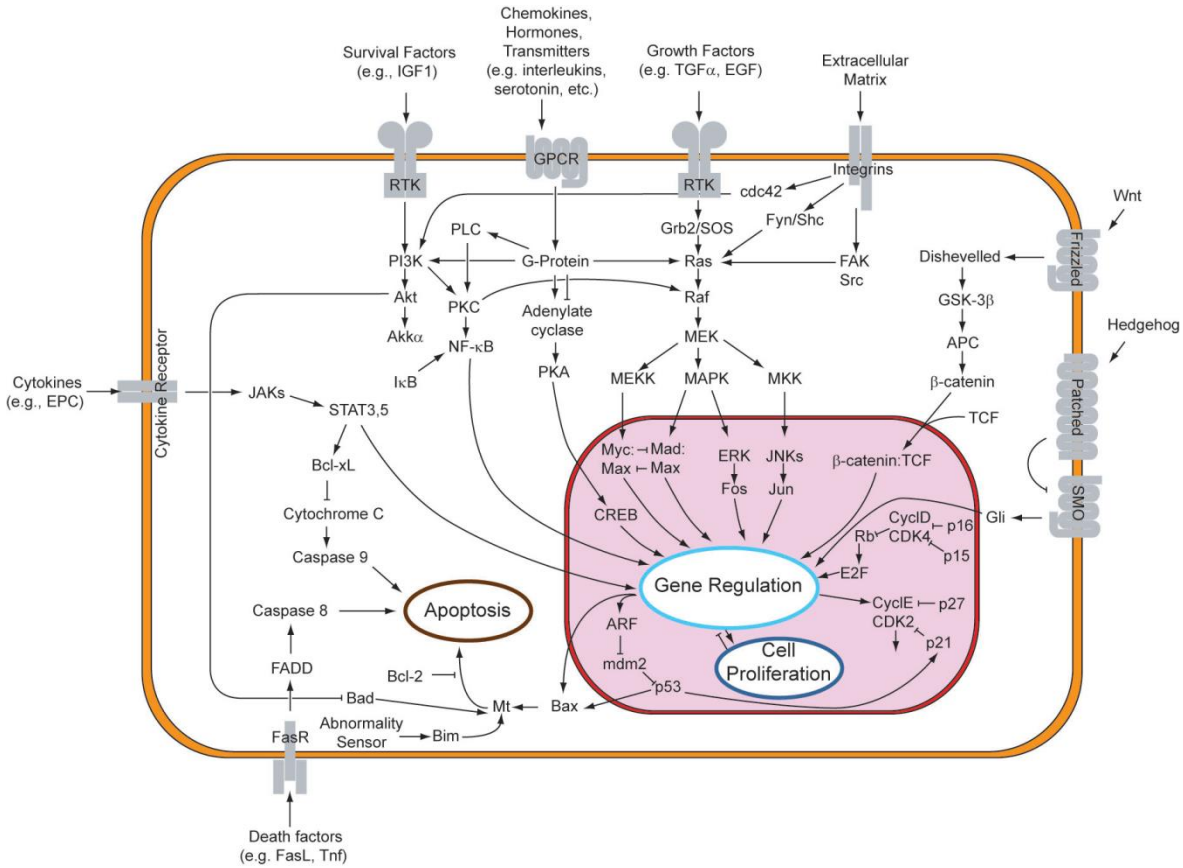


FIGURE 1: SIMPLISTIC CELL SIGNALING PATHWAYS

2.2 Targeting of the cell cycle and apoptosis, DNA replication/transcription and repair

Most chemotherapeutic agents act by inhibiting DNA replication. Although, the mechanisms of action of some older chemotherapeutic agents still remain unclear. In 1984, it was shown that anthracyclines, one of the most effective class of compounds in conventional chemotherapy at the time, worked by inhibiting topoisomerase activity [2]. This discovery started the work towards finding other agents with similar mechanisms of action. In the 1990ies, the topoisomerase inhibitors irinotecan and topotecan were introduced with significant clinical impact in – for instance – colorectal cancer (CRC) [8]. During the 1990ies the role of microtubules in cell division, proliferation and chemotaxis made way for several new agents; taxans (paclitaxel and docetaxel), and vinca alkaloids (vinblastine, vincristine, and vinorelbine), both derived from plant toxins. Since their introduction in the 1990ies, these agents have increased the survival in a variety of cancers, as lung cancer, breast cancer and ovarian cancer.

Antimetabolite agents have been introduced during the last decade, e.g. gemcitabine in pancreatic and lung cancer [9], and pemetrexed in non-small cell lung cancer (NSCLC) [10]. Capecitabine is an antimetabolite in oral formulation, with a wide range of indications, making it possible to take the treatment at home.

2.3 Targeting hormones, growth factors, and cell signalling pathways

Intracellular signal transduction pathways are activated by e.g. proteins, amino acids and lipids. The binding to matched receptors activates various enzyme systems, ultimately resulting in changes in protein synthesis, cellular behaviour or growth.

The endocrine drugs were the first treatments with a molecular target. Interfering with the production of hormones or blocking their action has become cornerstones in the treatment of both breast- and prostate cancer. Tamoxifen, acting by blocking oestrogen stimulation of cells, was the first hormonal drug to be widely used in breast cancer. Since its introduction in the 1970ies, tamoxifen has proved valuable in the treatment of metastatic breast cancer, as well as for adjuvant treatment after surgery, decreasing the risk of relapse with 50%, providing a long term effect on survival of [11, 12]. The efficacy and relatively low toxicity of tamoxifen has led to the development of a large number of new classes of hormonal agents for the treatment of hormone sensitive breast cancer. A number of aromatase inhibitors, blocking the non-ovarian esterogen synthesis, are used in post-menopausal women (e.g. anastrozole, letrozole and exemestane). Other agents with similar mechanisms of action (e.g. fulvestrant, palbociclib) provide valuable therapeutic options in metastatic breast cancer [13].

In prostate cancer, anti-androgens (e.g. flutamide, bicalutamide and nilutamide) are alternatives to testicular ablation. Additionally, gonadotrophin releasing hormone analogues (e.g. goserelin, leuprolide), blocking the production of testosterone, are used to achieve chemical castration [14]. The latest development in prostate cancer includes drugs that block the intra-tumoural synthesis of androgens in patients with hormone refractory disease. These drugs, abiraterone and enzalutamid, were initially approved in patients progressing on first line chemotherapy (docetaxel) but are now approved pre-chemotherapy in patients developing hormone refractory disease [15, 16].

Growth factors play an important role in stimulating cell growth during cell development and are essential in cell populations where constant proliferation and tissue renewal is required (e.g. skin, bone marrow and intestine). Growth factors stimulate cell growth by binding to cell surface receptors, starting a cascade of activity of specific enzymes in the cell. Many cancers overexpress growth factor receptors and/or have aberrations in the related gene leading to defects in the signal transduction, resulting in rapid growth as well as invasion of normal tissue [17]. Most research efforts have focused on families of growth factors and their receptors, such as the Epidermal Growth Factor Receptor (EGFR), including Human Epidermal Growth-factor Receptor 2 (HER2), Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF) and Insulin-like Growth Factor 1 (IGF-1). Also, downstream signalling factors have shown to be interesting targets; the enzymes PI3K, MEK/MAPK, and the protein mTOR [1].

There are two main groups of agents that have demonstrated efficacy in interfering with growth factor signalling; monoclonal antibodies, and small molecules blocking the receptor and/or tyrosine kinases, the first step in most signal transductions. In the 1970ies, the hybridoma technique enabled mass production of antibodies with a single binding site. The first clinical trials were conducted using murine antibodies (from mice) targeting tumour cell surface structures (antigens). Unfortunately, the results did not meet the expectations, largely because of low target specificity of the antibodies. The development of antibodies with major parts of the molecule of human origin and only the binding fraction being murine (humanised antibody) has overcome these problems. The high specificity and, in general, low toxicity of antibodies makes them attractive therapeutic options [51].

Cetuximab, a monoclonal antibody developed against EGFR, has demonstrated efficacy in metastatic CRC by increasing time to disease progression [18]. In combination with radiotherapy, cetuximab has also demonstrated efficacy in patients with advanced head and neck tumours [19]. Erlotinib has demonstrated efficacy and increased survival as monotherapy in NSCLC, and gefitinib has demonstrated efficacy in a subset of patients with the same disease [20]. The latest drug to be approved in CRC is panitumumab, targeting

EGFR. This is also a monoclonal antibody directed against EGFR, although the effect is only seen in a subpopulation of patients with a non-mutated version of the oncogene KRAS, wild type, wKRAS [21]. Cetuximab has now the same indication in CRC [21]. Treatment with the monoclonal antibody trastuzumab directed against HER2 led to marked prolonged survival in metastatic breast cancer [4, 22]. Adjuvant treatment with trastuzumab results in an approximately 50% reduction in recurrence rates in patients with HER2-positive breast cancer [23, 24]. The dual HER2 blockade with trastuzumab and pertuzumab has been shown to be superior to trastuzumab alone in the metastatic setting and has now become standard of care [25].

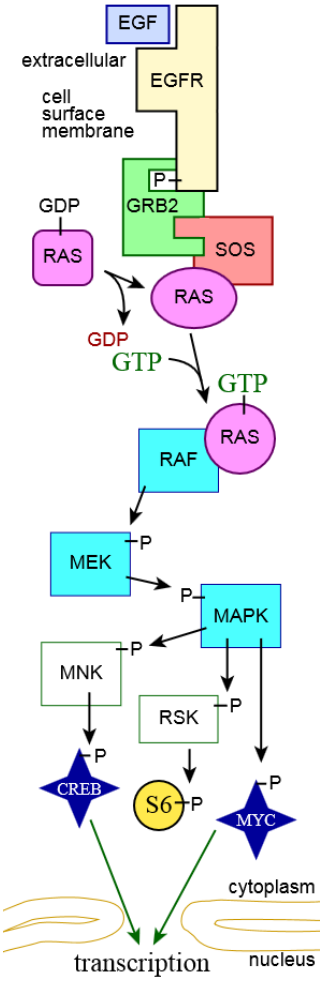


FIGURE 2: EGFR SIGNAL TRANSDUCTION PATHWAY

The trastuzumab – emtansine, T-DM1 (monoclonal antibody linked with a strong cytotoxic agent) combination is used for the treatment of metastatic breast cancer [26]. Lapatinib, a small molecule interaction with both HER2 and EGFR (HER1) is also in clinical use [27].

Chronic myeloid leukaemia (CML) was the first malignant disease, for which a characteristic genetic abnormality, the Philadelphia chromosome, was described [28]. In the 1980ies, the genetic alteration was identified as the BCR-ABL fusion gene and the protein it encodes was established as the cause of activation of CML [29]. Imatinib, an agent inhibiting BCR-ABL activity, results in complete responses in 80% of patients [30]. Unfortunately, resistance to imatinib occurs, but the mechanisms of resistance have been clarified and an agent restoring sensitivity to imatinib in 14 of the 15 resistance mechanisms described has already been developed [31]. For patients with tumours resistant to imatinib there are new therapeutic options including dasatinib and nilotinib [32, 33]. These drugs are now also approved as first line treatment. Imatinib also inhibits another cell enzyme, C-KIT, which is mutated in 95% of patients with gastrointestinal stromal tumours (GIST). Treatment with imatinib results in long-lasting tumour regression [34] and has been an enormous step forward, since the disease does not respond to conventional chemotherapy.

The agents that inhibit growth factors and their signal transduction pathways represent a new class of anti-tumour agents and their place in the clinical setting continues to evolve. In some cases like GIST and renal cell cancer (RCC), for which there are no active chemotherapy alternatives, they are first-line options [35]. In other tumour forms it remains to be seen if these agents will replace conventional chemotherapy as first-line treatment. Data support the concept of combining these agents with radiotherapy and chemotherapy and combining agents inhibiting different pathways (e.g. bevacizumab [targeting VEGF] in combination with erlotinib [targeting EGFR] in both RCC and NSCLC [36]. However, the additive value of combining drug therapies that target the same pathway or sequential use of these drug therapies is yet to be determined. Although, in breast cancer the use of dual HER2 blockade (targeting different sites of HER2) with trastuzumab and pertuzumab is now standard of care in the metastatic setting [25].

Another key challenge with these agents, as with conventional chemotherapy, is to predict responders. The clinical trials and initial introduction of gefitinib illustrate the complexity of clinical trials in different patient populations, the value of continued follow-up, and the potential of today's biological research. The first studies of gefitinib in lung cancer indicated high response rates in the Japanese population that subsequently were not consistently seen in other patient populations. Further analysis indicated that certain subgroups (non-smokers, female patients with tumours of particular histological characteristics) were more likely to respond to treatment [37]. Genetic analysis identified mutations in EGFR in lung cancer patients correlating to response to gefitinib [38].

Other drugs are vemurafenib and later dabrafenib introduced in BRAF mutated malignant skin melanomas, with 50-80% tumour regression and 20% progression free at 3-years follow-up [39, 40].

2.4 Inhibiting angiogenesis

The development of new blood vessels, angiogenesis, is an important normal physiological function, especially during pregnancy, growth, inflammation and wound healing. The regulation of angiogenesis is complex, with stimulating and inhibiting factors that, under normal conditions, are kept in balance. It has long been recognised that some tumours are highly vascularised. However, it was not until the 1970s that Professor Judah Folkman hypothesised that tumours need angiogenesis for their continued growth [5]. We now know that tumours will not grow beyond 1-2 mm without the development of blood vessels. The point at which the tumour starts producing pro-angiogenic factors (angiogenic switch) is believed to be one of the most important steps in transforming these dormant tumours into rapidly growing tumours with metastatic potential [41].

Several growth factors are involved in angiogenesis but VEGF has been identified as the most important. Both monoclonal antibodies targeting VEGF receptor and tyrosine kinase inhibitors targeting the VEGF pathway have been developed. Bevacizumab, a monoclonal antibody against VEGF, has increased survival rates in patients with metastatic CRC and NSCLC [42, 43]. Preliminary data indicated an effect in breast cancer, and the drug was approved both in the US and in EU for the use in metastatic breast cancer. The US approval has been withdrawn, as the first results, based on the surrogate end-point progression free survival could not be translated into improved overall survival [44, 45].

In renal cancer bevacizumab extends the period of stable disease [46]. Studies has also shown efficacy of bevacizumab in ovarian and cervical carcinoma [47, 48]. Bevacizumab represents an important breakthrough in cancer therapy as it is the first agent in this new class of drugs showing efficacy in a range of tumours. Two agents sorafenib and sunitinib malate, inhibiting tyrosine kinase targeting the VEGF pathway, have demonstrated efficacy in a variety of tumours [49]. However, it has been difficult to translate improvement in progression free survival (PFS) based on the use of these drugs, to gains in over-all survival (OS). Furthermore, continuous low-dose chemotherapy (rather than the conventional high-dose intermittent dosing) has effect on tumour angiogenesis [50].

2.5 Immunotherapy

The stimulation of human immune system responses has long been a promising approach of cancer therapy, although until recently, immunotherapeutic drugs had provided very limited

clinical effect. In years 2010-2011 a true revolution in the treatment of metastatic malignant skin melanoma was seen with the approval of the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibitor. The CTLA-4 receptor inhibitors block the natural immunological response to tumours. The drug induces anti-tumour activity characterized by durable responses and long term overall survival. A large pooled OS analysis of >1800 ipilimumab-treated patients showed a plateau in the OS curve at ~3 years, with follow-up to 10 years. Median OS values and 1-year OS are consistent with phase 3 trials in real-world observational studies [52]. This data has established ipilimumab as a standard of care for melanoma. Another new aspect of treatment with immuno-oncology agents is the novel adverse event profile as compared with targeted therapies. Ipilimumab may induce certain severe immune related side effects like colitis and pituitary dysfunction. Still, ipilimumab represents the first breakthrough in the now very rapidly expanding area of immuno-oncology.

In 2015 a new class of drugs blocking Programmed cell death protein 1 (PD-1) was approved. The PD-1 inhibitors activate the immune system to attack tumours. PD-1 drugs were approved in 2015 in the EU for melanoma and NSCLC adenocarcinoma. In 2016 PD-1 drugs have received approval for renal cancer, and further indications are expected, alone or in combinations.

An important benefit of using an immuno-oncology approach to treatment is that these agents target the immune system and not the cancer, and therefore have the potential of adaptable and durable control across a variety of tumour types [53].

2.6 Companion diagnostics

Tumour status of receptors and genes or proteins can be determined with a diagnostic test, thereby making testing of patients an important step in eligibility for treatment. The proportion of patients with a positive status is for BRAF 50% in metastatic melanoma, for EGFR 10-35% (depending on ethnicity) in NSCLC, for wKRAS 50% in CRC, and for HER2 14% in breast cancer [54, 55]. The importance of companion diagnostics can be illustrated by HER2 positive breast cancer and trastuzumab treatment. In an interesting comparison between treating only patients with HER2 positive breast cancer with trastuzumab versus treating an unselected patient population, 23,586 breast cancer patients would have been required to detect similar survival differences in the studies instead of the 469 patients included in the pivotal studies [56]. There are some important aspects related to use of companion diagnostics for selection of patients for a certain treatment. The technical aspects relates to sensitivity and specificity of methodologies and cut-off levels. The methods may change over time as knowledge increases, and cut-off levels may change [57]. Other aspects are tumour heterogeneity and retesting of recurrences [58].

2.7 Advances in diagnostic techniques

Radiology has come to play a key role in oncology, not only as a diagnostic tool but also as a method of evaluating efficacy of treatment by measuring progression or regression of tumours and metastatic lesions. The introduction of new radiological methods in the 1980ies and 1990ies; Computerized Tomographic Scanning (CT) and Magnetic Resonance Imaging (MRI) have greatly improved the diagnostic accuracy. Ultrasound is also useful and bone scintigraphy provides an overall picture of bone. Currently, Positron Emission Tomography (PET) in combination with CT (PET/CT) is introduced in clinical practice with the advantage of being more sensitive in differentiating between viable and non-viable tumour tissue [59].

Advances in molecular medicine, e.g. gene- and protein profiling techniques, have contributed to increased understanding of cell and cancer biology and has also provided more accurate classification of various tumour forms. By analysing the gene expression of a wide range of tumours, it has been possible to identify genes that provide tumour-specific characteristics. In some cases it is also possible to predict if an individual tumour will respond to certain treatments. Pharmacogenomics has become an important field in cancer research and drug development. In the future pharmacogenomics together with analyses of tumours, determining potential response to treatment (chemo sensitivity tests), will most certainly be used in the clinical setting [54].

Less than 2% of human diseases are caused by aberration in one gene (monogenic), the rest are caused by multiple gene aberrations or by changes in the proteins they encode [60, 61]. The deciphering of the entire human proteome is underway and will undoubtedly shed new light on disease mechanisms and reveal possible targets for intervention. Already, the individual protein patterns of different tumour types are being mapped and have demonstrated that patients with a specific type of cancer have certain protein patterns present in blood [62].

Liquid biopsy, i.e. collecting blood from cancer patients, has the potential of detecting circulating tumour cells and/or cell free tumour, ctDNA. This rapidly evolving technology will probably play a major role in the future of cancer diagnosis and treatment [63]

2.8 Advances in supportive drug treatment

Supportive drugs enable intensified treatment schedules and improved quality of life for patients suffering adverse symptoms of the cancer or the treatment. Patients with metastatic disease, treated with chemotherapy, often develop fatigue, low levels of red blood cells (anaemia), decreased white blood cell counts (neutropenia) pain and nausea [64, 65].

The fatigue of cancer patients is often multifactorial: It may be related to side effects of treatment or psychological stress. Many tumours also secrete substances (cytokines) that may

cause fatigue. However, fatigue is primarily caused by anaemia. Traditionally, anaemia has been treated with blood transfusions, but drugs (e.g. epoetin alpha, epoetin beta, erythropoetin) increase the production of red blood cells reducing the need of blood transfusions. In addition, chemotherapy is often associated with bone marrow depression which lead to anaemia, neutropenia and thrombocytopenia which may delay/reduce consecutive doses of treatment. The development of erythropoietin, G-CSF (filgrastim, pegfilgrastim), broad spectrum antibiotics and platelet transfusion techniques has decreased morbidity and mortality, and has also enabled intensified treatment schedules with increased cure rates [66].

There are also several agents that prevent nausea (e.g. ondansetron, granisetron). Bisphosphonates (e.g. pamidronat, zoledronic acid), and RANKL (denosumab), reduce the risk of skeletal events (fractures) as well as providing relief of pain caused by skeletal metastases [67].

2.9 Advances towards curing cancer

Although cancer is a common disease, affecting roughly every third person during their lifetime, approximately 50-60% of patients diagnosed with cancer will be ‘cured’ or will die from other causes. Progress in medical treatment of cancer has been made in almost every area. In most tumours, stepwise and relatively modest improvements have over time resulted in impressive increases in the proportion of patients considered cured [68]. For instance, the overall breast cancer mortality in the USA and the UK was reduced by 25% from the 1980ies to the year 2000 [69]. This progress is to some extent the result of screening programs, enabling earlier detection of the disease, but it is also a true reduction in mortality due to important improvements in treatments. Anthracycline based poly-chemo therapy reduces the annual breast cancer death rate by about 40% for women younger than 50 years and by about 20% for those in the age of 50-69 years [70]. Additional use of 5 years tamoxifen treatment in oestrogen receptor positive (ER-positive) disease results in a reduction of the annual breast cancer death rate by 31%. There is now a discussion about prolonging this treatment to 10 years, but the effect is not entirely clear [12, 71]. Improved chemotherapeutic regimens have increased survival further and recently, adjuvant treatment with the monoclonal antibody trastuzumab in patients with HER2-positive disease has shown a 50% decreased relapse risk and a 33% reduced mortality risk [23]. In CRC adjuvant chemotherapy has reduced mortality with 20-30% and chemotherapy in the metastatic setting has four-folded average survival, from 5 to 20 months [72-74]. In other diseases like aggressive Non-Hodgkin’s Lymphoma (NHL), the combination of CHOP (cyclophosphamide/hydroxydaunorubicin/oncovin/ predisone or prednisolone) and rituximab results in a five year survival rate of 58% in patients over 60 years of age and a 3-year overall survival of 93% in patients under 61 years of age

[75, 76]. Significant improvements in the outcome of NHL, CML and multiple myeloma (MM) has been described based on epidemiological data [77-80].

These publications represent epidemiological support for the value of innovative drugs in oncology and haematology. Similar support for treatment effects at a population level has been reported from Norway with a significant improvement in the outcome for patients with advanced NSCLC, linked to the introduction of palliative chemotherapy [81].

In other areas of oncology, such as testicular cancer and Hodgkin's disease, the changes in cure rates have been sudden and dramatic. With the introduction of the MOPP regimen (nitrogen mustard, vincristine, procarbazine and prednisone) in 1967, cure rates of over 50% were obtained in patients with advanced Hodgkin's disease [82]. This was a milestone in medical oncology, proving the ability of cure even in advanced stages of the disease. Since then, even higher cure rates (90%) have been obtained using new combinations of chemotherapy [83]. In testicular cancer, the prognosis has turned from one of the worst to one of the best among the oncological diagnoses. The introduction of cisplatin in the 1970ies was an immediate breakthrough in the treatment of testicular cancer [84]. The addition of chemotherapy agents to surgery and local radiotherapy has further increased cure rates in patients with metastatic testicular cancer [85]. However, it is important to note that breast cancer is a much more common disease; the number of patients cured of breast cancer far exceeds the number of patients cured of testicular cancer and Hodgkin's disease put together.

2.10 Advances towards the prevention of cancer

Epidemiological research has shown that cancer risk is associated with various external and lifestyle factors such as smoking, alcohol consumption, obesity, exercise habits and exposure to certain viruses. For example, it has been known for more than 50 years that smoking increases the risk of developing many cancers, especially lung cancer. Very little has been done in order to change smoking habits, which has resulted in the global epidemic of lung cancer we see. The strong relationship between hormone exposure and breast cancer was the rationale for the first chemoprevention trials with tamoxifen in women with an increased genetic risk of breast cancer. The women were found to benefit from treatment with tamoxifen (50% risk reduction) [86]. In the USA FDA has approved the use of tamoxifen as a preventive agent in high-risk patients. Recently, raloxifene (Selective Estrogen Receptor Modulator, SERM) has proved as efficient as tamoxifen as a preventive agent and with less side effects [87]. Several breast cancer prevention studies with aromatase inhibitors have also been performed [88]. Other agents that have potential preventive effect are non-steroidal anti-inflammatory drugs in CRC [89], and with variable results finasteride in prostate cancer [90] and statins in breast cancer [91]. The first vaccines against human papilloma virus (HPV) -the

cause of the vast majority of cervical cancers –were introduced in 2005 [92]. There are also studies on preventive effect of metformin, which have shown contradictive results [93]. Hepatitis B vaccinations may reduce the risk of liver cancer [94]

The fact that there are agents that can be used for prevention of cancer is in itself an important milestone in oncology. The area of cancer prevention is complex and involves political as well as medical measures. From a medical perspective, the main challenge is finding preventive agents/measures that are non-toxic and well tolerated. As costs for cancer treatments continue to increase the cost-saving of preventive measures will become more interesting.

2.11 Clinical effectiveness

Clinical effectiveness is a measure of the extent to which a particular intervention works in clinical use. If the intervention is shown to be effective in clinical studies (efficacy), effectiveness studies include different aspects of efficiency and safety from the perspective of the individual patient and the wider community. Clinical effectiveness is studied using data from real life (clinical practice).

Evaluation of usage in clinical practice can show which treatments that will work—and what remains unknown, and clinical effectiveness studies are also important to define areas where more research is needed.

Tumor heterogeneity is a key challenge when treatments are entering clinical practice as the methods of investigating tumors in clinical practice may differ from those in clinical trials. Tumor development from primary tumor to recurrence may include selection of clones that may be treatment related. This is rarely discovered in clinical trials and large cohorts may be required.

Co-morbidities may affect proposed treatments and outcome of treatments, and the sequence and combinations of treatments differ from the strict programs of clinical trials. Side-effects resulting in dose reductions will also reduce the amount of drug reaching the target.

Anti-tumor treatment guidelines are based on results from clinical studies. The adherence to guidelines and outcome of compliance is rarely evaluated. Many oncology drugs are approved on the surrogate end-point PFS, although there is no support of this translating to OS benefit [95, 96]. Thus, it is important to continue to study outcome, also after finalization of clinical trials.

2.12 Summary and conclusion

Traditional anti-tumour drugs have been cell toxic, with often severe side effects. The progress in molecular medicine has enabled the development of new agents targeting specific cell mechanisms, generally with less side-effects and different toxicity profiles compared to cytotoxic drugs. These targets include:

- Cell cycle and apoptosis, DNA replication/transcription and repair, as the traditional cytotoxic agents.
- Hormones, growth factors, and cell cell signalling pathways, as small molecules and monoclonal antibodies.
- Angiogenesis, targeting specific angiogenetic growth factors.
- Immunotherapy, targeting immune response in normal cells to cancer cells.

It is possible to predict if a patient is likely to respond to treatments by different molecular markers. Gene/protein analyses of tumours are likely to improve accuracy in the treatment offered to individual patients in the near future.

Improved diagnostic methods have facilitated detection of tumours, and consequently, improving cure rates. There is an increased use of diagnostic tools, including functional imaging for early evaluation of therapy effects.

The conclusion of the latest development of medical oncology is that we do see substantial improvements in survival in many tumour forms, based on the increase molecular knowledge. At the same time diagnosis and selection of patients for each treatment is complex and costly. To continue pursuing this road of molecular medical oncology (precision medicine) we need to investigate the value of the survival benefits for all new treatments and combinations.

2.13 References chapter 2

1. Hanahan, D. and R.A. Weinberg, *Hallmarks of cancer: the next generation.* Cell, 2011. 144(5): p. 646-74.
2. Tewey, K.M., et al., *Adriamycin-induced DNA damage mediated by mammalian DNA topoisomerase II.* Science, 1984. 226(4673): p. 466-8.
3. Slamon, D.J., et al., *Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene.* Science, 1987. 235(4785): p. 177-82.
4. Slamon, D.J., et al., *Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.* N Engl J Med, 2001. 344(11): p. 783-92.
5. Folkman, J., *Tumor angiogenesis: therapeutic implications.* N Engl J Med, 1971. 285(21): p. 1182-6.
6. Di Giacomo, A.M., et al., *Therapeutic efficacy of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with metastatic melanoma unresponsive to prior systemic treatments: clinical and immunological evidence from three patient cases.* Cancer Immunol Immunother, 2009. 58(8): p. 1297-306.
7. Weber, J., et al., *A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma.* Clin Cancer Res, 2009. 15(17): p. 5591-8.
8. FDA. *Irinotecan approval*. 1998; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/20571s8ltr.pdf.
9. Rothenberg, M.L., et al., *A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer.* Ann Oncol, 1996. 7(4): p. 347-53.
10. Hanna, N., et al., *Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy.* J Clin Oncol, 2004. 22(9): p. 1589-97.
11. Davies, C., et al., *Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials.* Lancet, 2011. 378(9793): p. 771-84.
12. Davies, C., et al., *Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial.* Lancet, 2013. 381(9869): p. 805-16.
13. Rugo, H.S., R.B. Rumble, and H.J. Burstein, *Endocrine Therapy for Hormone Receptor Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline Summary.* J Oncol Pract, 2016.
14. van den Bergh, R.C., et al., *Role of Hormonal Treatment in Prostate Cancer Patients with Nonmetastatic Disease Recurrence After Local Curative Treatment: A Systematic Review.* Eur Urol, 2015.
15. de Bono, J.S., et al., *Abiraterone and increased survival in metastatic prostate cancer.* N Engl J Med, 2011. 364(21): p. 1995-2005.
16. Tombal, B., et al., *Long-term Efficacy and Safety of Enzalutamide Monotherapy in Hormone-naive Prostate Cancer: 1- and 2-Year Open-label Follow-up Results.* Eur Urol, 2015. 68(5): p. 787-94.
17. Witsch, E., M. Sela, and Y. Yarden, *Roles for growth factors in cancer progression.* Physiology (Bethesda), 2010. 25(2): p. 85-101.
18. Lenz, H.J., *Cetuximab in the management of colorectal cancer.* Biologics, 2007. 1(2): p. 77-91.
19. Bonner, J.A., et al., *Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival.* Lancet Oncol, 2010. 11(1): p. 21-8.
20. Shepherd, F.A., et al., *Erlotinib in previously treated non-small-cell lung cancer.* N Engl J Med, 2005. 353(2): p. 123-32.
21. Di Nicolantonio, F., et al., *Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer.* J Clin Oncol, 2008. 26(35): p. 5705-12.

22. Marty, M., et al., *Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group.* J Clin Oncol, 2005. 23(19): p. 4265-74.

23. Slamon, D., Eiermann, W, Robert, NJ, Giermek, J, Martin, M, Jasiowka, M, Mackey, JR, Chan, A, Liu, M-C, Pinter, T, Valero, V, Falkson, C, Fornander, T, Shiftan, TA, Bensfia, S, Hitier, S, Xu, N, Bée-Munteanu, V, Drevot, P, Press, MF, Crown, J, . *Ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer*. in *San Antonio Breast Cancer Symposium*. 2015. San Antonio Texas, USA.

24. Slamon, D., et al., *Adjuvant trastuzumab in HER2-positive breast cancer.* N Engl J Med, 2011. 365(14): p. 1273-83.

25. Swain, S.M., et al., *Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer.* N Engl J Med, 2015. 372(8): p. 724-34.

26. Shen, K., et al., *Safety and Efficacy of Trastuzumab Emtansine in Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: a Meta-analysis.* Sci Rep, 2016. 6: p. 23262.

27. Nelson, M.H. and C.R. Dolder, *Lapatinib: a novel dual tyrosine kinase inhibitor with activity in solid tumors.* Ann Pharmacother, 2006. 40(2): p. 261-9.

28. Nowell, P.C., *The minute chromosome (Phl) in chronic granulocytic leukemia.* Blut, 1962. 8: p. 65-6.

29. Melo, J.V., *The diversity of BCR-ABL fusion proteins and their relationship to leukemia phenotype.* Blood, 1996. 88(7): p. 2375-84.

30. O'Brien, S.G., et al., *Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia.* N Engl J Med, 2003. 348(11): p. 994-1004.

31. Shah, N.P., et al., *Overriding imatinib resistance with a novel ABL kinase inhibitor.* Science, 2004. 305(5682): p. 399-401.

32. Talpaz, M., et al., *Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias.* N Engl J Med, 2006. 354(24): p. 2531-41.

33. Emole, J., T. Talabi, and J. Pinilla-Ibarz, *Update on the management of Philadelphia chromosome positive chronic myelogenous leukemia: role of nilotinib.* Biologics, 2016. 10: p. 23-31.

34. Demetri, G.D., et al., *Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors.* N Engl J Med, 2002. 347(7): p. 472-80.

35. Hainsworth, J.D., et al., *Treatment of metastatic renal cell carcinoma with a combination of bevacizumab and erlotinib.* J Clin Oncol, 2005. 23(31): p. 7889-96.

36. Herbst, R.S., et al., *Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer.* J Clin Oncol, 2005. 23(11): p. 2544-55.

37. Miller, V.A., et al., *Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer.* J Clin Oncol, 2004. 22(6): p. 1103-9.

38. Pao, W., V.A. Miller, and M.G. Kris, *'Targeting' the epidermal growth factor receptor tyrosine kinase with gefitinib (Iressa) in non-small cell lung cancer (NSCLC).* Semin Cancer Biol, 2004. 14(1): p. 33-40.

39. Bollag, G., et al., *Vemurafenib: the first drug approved for BRAF-mutant cancer.* Nat Rev Drug Discov, 2012. 11(11): p. 873-86.

40. Long, G.V., et al., *Overall Survival and Durable Responses in Patients With BRAF V600-Mutant Metastatic Melanoma Receiving Dabrafenib Combined With Trametinib.* J Clin Oncol, 2016.

41. Hanahan, D. and J. Folkman, *Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis.* Cell, 1996. 86(3): p. 353-64.

42. Hurwitz, H., et al., *Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.* N Engl J Med, 2004. 350(23): p. 2335-42.

43. Horn, L., et al., *Phase II study of cisplatin plus etoposide and bevacizumab for previously untreated, extensive-stage small-cell lung cancer: Eastern Cooperative Oncology Group Study E3501.* J Clin Oncol, 2009. 27(35): p. 6006-11.

44. Hayes, D.F., K. Miller, and G. Sledge, *Angiogenesis as targeted breast cancer therapy.* Breast, 2007. 16 Suppl 2: p. S17-9.

45. Dienstmann, R., et al., *Benefit-risk assessment of bevacizumab in the treatment of breast cancer.* Drug Saf, 2012. 35(1): p. 15-25.

46. Minguet, J., et al., *Targeted therapies for treatment of renal cell carcinoma: recent advances and future perspectives.* Cancer Chemother Pharmacol, 2015. 76(2): p. 219-33.

47. Oza, A.M., et al., *Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial.* Lancet Oncol, 2015. 16(8): p. 928-36.

48. Bizzarri, N., et al., *Bevacizumab for the treatment of cervical cancer.* Expert Opin Biol Ther, 2016. 16(3): p. 407-19.

49. Leite de Oliveira, R., A. Hamm, and M. Mazzone, *Growing tumor vessels: more than one way to skin a cat - implications for angiogenesis targeted cancer therapies.* Mol Aspects Med, 2011. 32(2): p. 71-87.

50. Wang, J., et al., *Paclitaxel at ultra low concentrations inhibits angiogenesis without affecting cellular microtubule assembly.* Anticancer Drugs, 2003. 14(1): p. 13-9.

51. Yagami, H., et al., *Monoclonal antibodies based on hybridoma technology.* Pharm Pat Anal, 2013. 2(2): p. 249-63.

52. Schadendorf, D., et al., *Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma.* J Clin Oncol, 2015. 33(17): p. 1889-94.

53. Mahoney, K.M., P.D. Rennert, and G.J. Freeman, *Combination cancer immunotherapy and new immunomodulatory targets.* Nat Rev Drug Discov, 2015. 14(8): p. 561-84.

54. Ong, F.S., et al., *Personalized medicine and pharmacogenetic biomarkers: progress in molecular oncology testing.* Expert Rev Mol Diagn, 2012. 12(6): p. 593-602.

55. Ryden, L., et al., *Reproducibility of human epidermal growth factor receptor 2 analysis in primary breast cancer: a national survey performed at pathology departments in Sweden.* Acta Oncol, 2009. 48(6): p. 860-6.

56. Simon, R. and A. Maitournam, *Evaluating the efficiency of targeted designs for randomized clinical trials.* Clin Cancer Res, 2004. 10(20): p. 6759-63.

57. Calhoun, B.C. and L.C. Collins, *Predictive markers in breast cancer: An update on ER and HER2 testing and reporting.* Semin Diagn Pathol, 2015. 32(5): p. 362-9.

58. Wilking, U., et al., *HER2 status in a population-derived breast cancer cohort: discordances during tumor progression.* Breast Cancer Res Treat, 2011. 125(2): p. 553-61.

59. Petersen, H., et al., *FDG PET/CT in cancer: comparison of actual use with literature-based recommendations.* Eur J Nucl Med Mol Imaging, 2016. 43(4): p. 695-706.

60. Goodspeed, A., et al., *Tumor-Derived Cell Lines as Molecular Models of Cancer Pharmacogenomics.* Mol Cancer Res, 2016. 14(1): p. 3-13.

61. Debniak, T. and J. Lubinski, *Principles of genetic predisposition to malignancies.* Hered Cancer Clin Pract, 2008. 6(2): p. 69-72.

62. Sallam, R.M., *Proteomics in cancer biomarkers discovery: challenges and applications.* Dis Markers, 2015. 2015: p. 321370.

63. Syn, N.L., et al., *Evolving landscape of tumor molecular profiling for personalized cancer therapy: a comprehensive review.* Expert Opin Drug Metab Toxicol, 2016.

64. Bruera, E. and J.A. Paice, *Cancer pain management: safe and effective use of opioids.* Am Soc Clin Oncol Educ Book, 2015: p. e593-9.

65. Hesketh, P.J., et al., *Antiemetics: American Society of Clinical Oncology Focused Guideline Update.* J Clin Oncol, 2016. 34(4): p. 381-6.

66. Smith, T.J., et al., *Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update.* J Clin Oncol, 2015. 33(28): p. 3199-212.

67. Wang, Z., et al., *Systematic literature review and network meta-analysis comparing bone-targeted agents for the prevention of skeletal-related events in cancer patients with bone metastasis.* Oncologist, 2015. 20(4): p. 440-9.

68. Ferlay, J., et al., *Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012.* Int J Cancer, 2015. 136(5): p. E359-86.

69. Peto, R., et al., *UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years.* Lancet, 2000. 355(9217): p. 1822.

70. Peto, R., et al., *Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials.* Lancet, 2012. 379(9814): p. 432-44.

71. Dowsett, M., et al., *Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials.* Lancet, 2015. 386(10001): p. 1341-52.

72. Wolmark, N., et al., *The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03.* J Clin Oncol, 1993. 11(10): p. 1879-87.

73. *Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators.* Lancet, 1995. 345(8955): p. 939-44.

74. Andre, T., et al., *Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer.* N Engl J Med, 2004. 350(23): p. 2343-51.

75. Pfreundschuh, M., et al., *CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group.* Lancet Oncol, 2006. 7(5): p. 379-91.

76. Feugier, P., et al., *Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte.* J Clin Oncol, 2005. 23(18): p. 4117-26.

77. Pulte, D., A. Gondos, and H. Brenner, *Expected long-term survival of older patients diagnosed with non-Hodgkin lymphoma in 2008-2012.* Cancer Epidemiol, 2012. 36(1): p. e19-25.

78. Pulte, D., et al., *Trends in survival of multiple myeloma patients in Germany and the United States in the first decade of the 21st century.* Br J Haematol, 2015.

79. Pulte, D., et al., *Survival of patients with chronic myelocytic leukemia: comparisons of estimates from clinical trial settings and population-based cancer registries.* Oncologist, 2011. 16(5): p. 663-71.

80. Bjorkholm, M., et al., *Success story of targeted therapy in chronic myeloid leukemia: a population-based study of patients diagnosed in Sweden from 1973 to 2008.* J Clin Oncol, 2011. 29(18): p. 2514-20.

81. von Plessen, C., et al., *Effectiveness of third-generation chemotherapy on the survival of patients with advanced non-small cell lung cancer in Norway: a national study.* Thorax, 2008. 63(10): p. 866-71.

82. Devita, V.T., Jr., A.A. Serpick, and P.P. Carbone, *Combination chemotherapy in the treatment of advanced Hodgkin's disease.* Ann Intern Med, 1970. 73(6): p. 881-95.

83. Diehl, V., et al., *Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease.* N Engl J Med, 2003. 348(24): p. 2386-95.

84. Einhorn, L.H. and J. Donohue, *Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer.* Ann Intern Med, 1977. 87(3): p. 293-8.

85. Kvammen, O., et al., *Long-term Relative Survival after Diagnosis of Testicular Germ Cell Tumor.* Cancer Epidemiol Biomarkers Prev, 2016. 25(5): p. 773-9.

86. Fisher, B., et al., *Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study.* J Natl Cancer Inst, 1998. 90(18): p. 1371-88.

87. Vogel, V.G., et al., *Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial.* Jama, 2006. 295(23): p. 2727-41.

88. Ahmad, I. and Shagufta, *Recent developments in steroidal and nonsteroidal aromatase inhibitors for the chemoprevention of estrogen-dependent breast cancer.* Eur J Med Chem, 2015. 102: p. 375-86.

89. Bains, S.J., et al., *Aspirin As Secondary Prevention in Patients With Colorectal Cancer: An Unselected Population-Based Study.* J Clin Oncol, 2016.

90. Bosland, M.C., *Is There a Future for Chemoprevention of Prostate Cancer?* Cancer Prev Res (Phila), 2016.

91. Borgquist, S., et al., *Statin Use and Breast Cancer Risk in the Nurses' Health Study.* Cancer Epidemiol Biomarkers Prev, 2016. 25(1): p. 201-6.

92. Drolet, M., et al., *Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis.* Lancet Infect Dis, 2015. 15(5): p. 565-80.

93. Gong, Z., et al., *Diabetes, metformin and incidence of and death from invasive cancer in postmenopausal women: Results from the women's health initiative.* Int J Cancer, 2016. 138(8): p. 1915-27.

94. Chang, M.H., et al., *Long-Term Effects of Hepatitis B Immunization of Infants in Preventing Liver Cancer.* Gastroenterology, 2016.

95. Kim, C. and V. Prasad, *Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent Overall Survival: An Analysis of 5 Years of US Food and Drug Administration Approvals.* JAMA Intern Med, 2015: p. 1-2.

96. Prasad, V., et al., *The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-analyses.* JAMA Intern Med, 2015. 175(8): p. 1389-98.

3 Access to oncology drugs 2005 – 2014

Summary

- During the last 20 years, 98 NCEs belonging to the ATC groups L1 and L2A or B have been approved, 95 of these according to the EMA centralized procedure. In addition, three drugs belonging to ATC group L4X were approved for use in cancer. There is a trend towards more approval in recent years.
- In Europe, sales of cancer drugs were € 8.0 billion in 2005 and € 19.8 billion in 2014. Seven countries (France, Germany, Italy, Netherlands, Spain, Switzerland, and the UK) accounted for around 80% of all sales, both in 2005 and in 2014. France had the highest sales on cancer drugs in 2005 but was passed by Germany in 2014.
- During the study period, there have been marked shifts among the top 10 selling drugs. Of the top 5 drugs in 2005, two are no longer of the top 10 in 2014 (docetaxel and oxaliplatin) and one (paclitaxel) is now at the far end of the list. Trastuzumab has almost doubled its share as No1 on the list, and several new agents are listed, e.g. bevacizumab and lenalidomide.
- Among the top 5 drugs in 2014, three have recently lost exclusivity, or will in the near future (trastuzumab, rituximab and imatinib).
- The newest drugs (launched within the last three years) make up only 8% of the total average sales, varying between 4% and 11% per year in different countries, with the higher share in richer countries.
- Countries in Eastern and Southern Europe, with low GDP per capita, have sales at around 1/3 of sales in countries in Western Europe, both in 2005 and in 2014.
- Access to cancer drugs, especially new innovative drugs, varies in Europe and is mainly related to the countries' economic status, and this has not changed over time.
- There are significant variations in access in different countries of similar economic power, indicating opportunities for improvement through policies aiming at evidence based as well as cost-effective cancer care.

3.1 Definitions of access to cancer drugs and methodological aspects

Full access to cancer drugs is attained when every patient that may benefit will receive the relevant drug. Studies on the access of patients to cancer drugs can cover numerous themes, either using patient-level data or regional/country-level data. On the patient level two common research areas are physician adherence to guidelines and patient compliance to treatment. Physicians determine usage of drugs that will impact patient access to drugs. Many countries have national treatment guidelines. At the same time physicians are bound by local therapeutic recommendations and traditions and budgetary constraints. Due to information asymmetry between physicians and patients, and different views on best practice, physicians can deviate from the recommended treatment in the guidelines [1, 2]. On the other hand, how much of the drug a patient eventually ends up taking can be partly determined by the patient

him/herself, although the majority of cancer drugs are administered as infusions or injections at hospitals, which means compliance is less of an issue. However, in oral cancer therapy when patients are taking drugs at home, compliance is imperfect, especially in long-term treatments. Studies have shown that patient compliance with oral cancer therapy may vary between 16-100 percent [3].

Individual patient data are optimal for studies of drug access, since usage can be related to information about the patient and the diagnosis. If such data is available it can be aggregated to a population level providing increased knowledge on usage patterns, length of usage, doses used, side effects of treatment, etc. The obvious advantage of using this data has been an ongoing discussion for many years, however, rarely available even within a single country. Access is often studied using regional comparisons of usage and costs. Such studies can indicate variations in access, but have shortcomings as evidence for policy development. Variations or similarities in use between countries may mask both under- and over-consumptions. Comparisons between countries can be carried out if variations in prices and health system characteristics are small.

Studying access at the international level has additional complications. Comparable patient level data, which includes all relevant variables, are generally missing. In the absence of patient-level data, one has to rely on country-level measures as proxy for patient access to cancer drugs. This approach has been used in previous Comparator reports [4]. It is also the approach adopted in this report. In this context access to cancer drugs is equated with market uptake, i.e. utilization measured in terms of total sales of cancer drugs in a country during a specific period of time. Comparisons of market uptake between countries are challenging as, for instance, cancer drug prices and the population base varies. The most important methodological aspects and strengths and weakness of different approaches to measure market uptake are discussed in this chapter. [5].

3.1.1 Definition of cancer drugs

In the ATC classification system cancer drugs belong to group L, i.e. antineoplastic and immunomodulating agents, with the subgroups L1 for antineoplastic agents (chemotherapy and targeted cancer drugs), L2 for endocrine therapy, L3 for immunostimulants, and L4 for immunosuppressants. Several drugs 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 L1) and only 20 percent of interferon alpha 2a and 2b (in subgroup L3) are used for cancer treatment and the remainder for other diseases [6]. This needs to be adjusted for to estimate cancer-related drug sales.

Furthermore, the number of approved indications in the cancer area of a specific cancer drug can vary between countries that might explain some of the differences in utilization. For instance, sunitinib was initially approved by 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 reimburse sunitinib for all indications, and the time period between EMA approval and first drugs sold differed and sales data cannot show the distribution between different indications, which makes access interpretation difficult [7],

3.1.1.1 Grouping of cancer drugs

Apart from considering the utilization of a specific drug, a common theme in market uptake studies is to divide cancer drugs into two or more groups and compare access for the different groups. Cancer drugs might be grouped according to:

- Vintage: Comparing older and newer drugs (defined by year of marketing authorization or first sales)
- Degree of innovation: Comparing innovative and non-innovative drugs, or novel and incremental innovation drugs. The FDA has implemented the breakthrough therapy designation, which should help bring new needed products to the market faster. However, it has been noted that it is difficult to define innovation without reference to outcome or therapeutic value [8]. The classification according to the five-tier innovation scale used by the French transparency commission (TC) is one example [9]. The early benefit assessment in accordance with the Act on the Reform of the Market for Medicinal Products (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) is another example of classification of innovation based on outcome.
- Classification according to therapeutic value. This is closely linked to classification according to innovation. Different systems for classification have been proposed by ESMO, ASCO and others, see chapter 4 for a more in-depth discussion.
- Drug type: Comparing different ATC subgroups
- Drug type: Comparing drugs for conventional chemotherapy and targeted cancer therapy
- Drug type: Comparing drugs for biologic therapy (large molecules) and non-biologic therapy (small molecules) and also the new immune therapy drugs.
- Classification according to size of target population (orphan drugs)

3.1.2 Measurements of sales of cancer drugs

The utilization of cancer drugs can be measured in value terms (e.g. in euros) or in volume terms (often in milligrams (mg) and sometimes in Defined Daily Dose (DDD)). Measuring sales in value terms enables aggregations, such as total spending on all cancer drugs or

spending on drugs used in a specific indication. It also enables comparisons of spending on cancer drugs in relation to spending on other resources used for cancer care; see section 1.5. This method has however some shortcomings:

- Since sales have to be compared on a common currency basis (in euros), nominal sales figures in countries with a different currency will be subject to exchange rate fluctuations. Even in countries with a common currency (euro area), prices of one and the same drug can differ and higher sales in a country might simply reflect higher national drug prices rather than higher utilization in volume terms. A further complication arises with hospital drugs usage, as the true price might be unknown due to confidential rebates granted. Managed entry agreements might also complicate the determination of the true drug price.
- Older drugs, such as paclitaxel and docetaxel, gone off patent with generics available are sold at much lower prices compared to patent-protected newer drugs. As a consequence, the share of older drugs on total drug sales might appear to be small, even though their utilization measured in volume terms might be considerable. Another aspect in relation to old generic drugs is the price level of generic drugs in different countries as well as pricing of previously patented drugs when they become generic. There are also examples of large price increases in the generic market when competition is decreased within a certain market segment.

Measuring sales in volume terms eliminates the problem of price effects between countries and cancer drugs over time. Therefore, cancer drug utilization is often measured on a weight basis in milligrams. However, this method has other shortcomings:

- Each drug can only be compared separately. An aggregation of different drugs would assign equal weights to large volume and small volume cancer drugs and thus bias the result.
- Since national treatment guidelines differ, variations in dosage and treatment duration might explain some of the differences in utilization between countries.
- The volume size(s) of vials of a specific drug can differ between countries and affect utilization. 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.

An alternative measure of volume is to express uptake in terms of the number of daily defined doses (DDD). The DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is a statistical measure, and should not be confused with a recommended prescribed dose. The number of DDD used can be obtained by dividing the total volume with the DDD for the drug under study. In this way, the DDD provide a fixed unit of measurement independent of price and dosage form (e.g. tablet strength), and allow for simultaneous comparison of drugs which may have radically different dosing schemes and schedules, e.g. with their basic doses being expressed in mg and g. There are several issues that need to be kept in mind when using this measurement procedure:

- Not all drugs have a DDD defined due to dosing being very individual. This is true for a number of antineoplastic agents.
- When the recommended dose refers to body weight, an adult is considered to be a person of 70 kg. This is true also for drugs used in children.
- As a treatment episode can have different number of treatment days the DDD the DDD is not directly a measure of number of treated patients.
- DDD definitions may change over time, which is important to take into consideration when comparing results from different sources.

Measurements in value terms and volume terms equalize some of their respective shortcomings and each method yields informative results on its own. Provided detailed data are available, a comprehensive analysis should apply a pragmatic approach and present results for both methods.

3.1.3 Sales related to incidence, mortality and prevalance

In order to provide comparable figures on cancer drug utilization in different countries, sales of cancer drugs should be related to the population size. The two possible options are total population or by cancer defined by cancer incidence, mortality or prevalence.

Sales related to total population is reported as euros or milligrams per 100,000 inhabitants. Data on total population size are readily available and easy to interpret. However, this type of adaptation disregards the epidemiologic of cancer in a country and therefore disregards the actual need and demand for cancer care. For instance, a country with an older population has, ceteris paribus, a higher number of cancer cases compared to a country with a younger population. Given equal drug utilization per cancer case in either country, the country with the older population will record higher sales per 100,000 inhabitants simply because of a higher number of cancer cases.

Sales related to cancer incidence are reported as euros or milligrams per diagnosed cancer case. This measure takes cancer care into account, since treatment costs are partly concentrated to the years after diagnosis; see section 1.4.4. Cancer incidence is sensitive to the extent of screening activities. More comprehensive screening in a country might result in the detection of a relatively high number of less advanced cases in need of no or little drug treatment. As a consequence, such a country will, ceteris paribus, appear to have a lower level of drug utilization per cancer case than a country with little screening. It is also important to compare the same indication. Another problem is the complete absence of data on cancer incidence in many countries.

Sales related to cancer mortality are reported as euros or milligrams per cancer death. Even this measure takes cancer care into account, since treatment costs are partly concentrated to

the last years in life; see section 1.4.4. Another advantage of using mortality is that almost all cancer drugs 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. Furthermore, the data availability on cancer mortality is relatively good. The shortcoming of this approach is linked to the way survival influences mortality. As shown in section 1.1.3., survival rates and hence mortality figures vary greatly between countries. In countries with high survival rates (and relatively few mortality cases) a presumably high amount of cancer drugs (which might be one reason for the high survival rates) would be related to a small number of mortality cases, resulting in high utilization figures. By contrast, in countries with low survival rates (and many mortality cases) a presumably small amount of cancer drugs would be related to a high number of mortality cases, resulting in low utilization. As a consequence, this method might exaggerate differences between countries with high and low survival. However, when a drug has a specific indication in the palliative treatment of only one diagnosis, this has been the preferred method to compare access and uptake in our reports.

Sales related to cancer prevalence are reported as euros or milligrams per prevalent cancer case. The problem with this method is the lack of data on prevalent cases. Also the definition of cancer prevalence is problematic, as it could encompass all people who ever had a diagnosis of cancer or all people with a diagnosis during, e.g., the last five years. In either case many patients are not treated with cancer drugs anymore and therefore the connection to cancer care is less pronounced.

Measures for cancer drug sales and population size should correspond to the same year. If instead sales data, stretching over several years, is related to, e.g., incident cases in a certain reference year, year-on-year changes in utilization might only reflect changes in incidence cases rather than real changes in utilization. In times of increasing cancer incidence, the use of incident cases from a single reference year will bias utilization figures downwards/upwards in all years before/after the reference year. The magnitude of the bias will differ between countries related to development in cancer incidence.

3.1.4 Sales related to date of launch

Another possible standardization to sales figures in international comparisons is the date of launch of a drug. Launch can refer to the date of marketing authorization or the date of first sales of a drug in a country. This means that utilization is not compared on the basis of sales in a certain quarter or year, but rather according to the time passed since the drug was launched in each respective country (such as 13 quarters after launch). However, if the discrepancy between dates of launch is small and/or if annual (rather than quarterly) sales figures are compared differences may not be obvious. This is also the case for mature drugs

that have been sold for a decade or so, as the influence of the date of launch naturally diminishes over time.

Usually it takes time for knowledge of a new drug to diffuse in clinical practice and not least to be included into treatment guidelines. Comparisons can inform on the speed of market uptake from launch and show how responsive national health care systems are in adopting a new drug. The disadvantage with this standardization is that it conceals the effect of a delayed launch. In Europe waiting times between EMA marketing authorization and national pricing and reimbursement decisions are important barriers to timely patient access to new drugs [7].

3.2 Definitions used in and results from earlier studies

In a report for the Swedish research-based pharmaceutical industry (LIF) the share of sales of "innovative" cancer drugs in the fourth quarter of 2012 was studied based on IMS Health data [10]. The result showed that Poland and Germany have a similar share with 29 and 30 percent, respectively, of sales related to newer drugs, and France and Sweden showing higher proportions with 40 and 41 percent, respectively. However, these results have to be interpreted with caution as an arbitrary choice was made of what constitutes an "innovative" cancer drug. Only a selection of drugs that had been issued between 2001 and 2012 were attributed the label "innovative". Furthermore, solely looking at the share of sales of new and old drugs conveys limited information about access to drugs. If, for instance, the total amount of drug sales was small, then access to drugs was restricted, but this kind of information was disregarded in the study.

In another report in 2010 by UK's national cancer director, cancer drug usage was assessed through calculating the drug volume sold (in milligrams) per capita [11]. The analysis was based on IMS Health data supplemented with manufacturer data covering sales between April 2008 and March 2009. Cancer drugs were grouped into three groups by time of launch (within the last 5 years, 6-10 years, 10+ years) and a fourth group for hormonal drugs. Countries were ranked according to sold volume per capita. Highest usage was recorded in France followed by Germany and Sweden in each of the three time-of-launch-specific groups.

Thirdly, a report prepared for the Belgian presidency of the Council of the EU in 2010 measured the uptake of "innovative" medicines (i.e. also other than cancer drugs) through sales measured in Euros per 100,000 inhabitants in 2009 based on IMS Health data [12]. The report contrasted sales figures with the number of available innovative medicines in each country. The findings were that the uptake of innovative medicines had no apparent link with availability across EU countries. For instance, in France 44 innovative medicines were available and in Sweden 43, but French sales figures of some 2.6 million Euros per 100,000 inhabitants were twice as high as Swedish sales with about 1.2 million Euros. In Germany 47

innovative drugs were available and 33 in Poland; the differences in sales were huge with some 1.5 million Euros per 100,000 inhabitants in Germany and a mere 0.2 million Euros in Poland.

Finally, in an earlier report by Wilking and Jönsson, in turn an update of of their 2005 report, the market uptake of cancer drugs was analyzed during the period 1998-2008 based on IMS Health data [13]. Drugs were grouped into four categories according to their period of launch (earlier than 1999, 1999-2002, 2003-2005 and 2006-2007). Overall, old drugs launched before 1999 constituted around two thirds of total sales in 2007 in Germany and France, 70 percent in Sweden and around 75 percent in Poland. Level and speed of drug uptake was also investigated for selected drugs that are used in the treatment of colorectal cancer (CRC) and non-small cell lung cancer (NSCLC). For drugs for CRC France is, by far the best performer both in terms of level and speed of uptake. Germany and Sweden show similar levels of uptake for well-established drugs, but for more recently released drugs Germany shows higher levels of uptake. Poland is worst in terms of level of uptake, with population-standardized sales being at best 5 times lower than France and 3 times lower than Germany or Sweden for drugs that have been available for a longer time. For recently released drugs Polish sales are effectively inexistent. For NSCLS the same picture emerged. France showed a quick uptake and comparatively high levels of drug usage. Germany performed slightly better than Sweden and especially for recently approved drugs. Polish uptake of NSCLS drugs available for a longer time was lower than in Sweden and Germany and for newer drugs the level of uptake was only marginal in Poland.

TABLE 1: OVERVIEW OF RECENT STUDIES OF MARKET UPTAKE OF CANCER DRUGS

Author	Methodology	Result
Opticom International Research AB (2013) [10]	Share of sales of innovative cancer drugs on total sales in Euros in the fourth quarter of 2012; Note: only a selection of approved between 2001 and 2012 were considered "innovative"	**Share of innovative cancer drugs:** Sweden: 41% France: 40% Germany: 30% Poland: 29%
Richards, M. (2010) [11]	Drug volume sold (in milligrams) per capita between April 2008 and March 2009; Three groups of cancer drugs by time of launch (within the last 5 years, 6-10 years, 10+ years) and a fourth group for hormonal drugs	**Ranking according to highest uptake in any of the three groups:** 1. France 2. Germany 3. Sweden Ranking for hormonal drugs: 1. Germany 2. France 3. Sweden
Annemans, L., Arickx, F., Belle, O., Boers, K., Bogaert, M., Callens, S., et al. (2010) [12]	Sales of "innovative medicines" (i.e. also other than cancer drugs) in Euros per 100,000 inhabitants in 2009; Number of available innovative drugs	France: 44 innovative drugs available; sales of 2.6 million € per 100,000 inhabitants Germany: 47 drugs, 1.5 million € Sweden: 43 drugs, 1.2 million € Poland: 33 drugs, 0.2 million €
Wilking, N., Jönsson, B., Högberg, D., Justo, N. (2009) [13]	Share of sales of new cancer drugs on total sales in Euros in 2007; Four groups of cancer drugs by time of launch (earlier than 1999, 1999-2002, 2003-2005 and 2006-2007) Level and speed of uptake for selected cancer drugs for specific cancer types; Level of uptake in 2007 measured in volume sold per 100,000 inhabitants; Speed of uptake from 1998 or start of launch until 2007	**Share of new cancer drugs (launched 1999-2007) (approx.):** France: 33% Germany: 33% Sweden: 30% Poland: 25% **Non-small cell lung cancer:** Level of uptake of established drugs: 1. France 2. Germany 3. Sweden 4. Poland Level of uptake of new drugs: 1. France 2. Germany 3. Sweden 4. Poland **Colorectal cancer:** Level of uptake of established drugs: 1. France 2. Germany & Sweden 3. Poland Level of uptake of new drugs: 1. France 2. Germany 3. Sweden 4. Poland

3.3 Materials and methods used in this study

In this section we describe the methodological choices made for the analyses presented in this report.

3.3.1 Data sources

Four principal sources have been used for the analyses in this section:

- Data on characteristics of approved drugs have been collected from the EMA database on drug approvals. Decisions up to the end of year 2015 were included [14].
- Data on quarterly volumes and sales for individual drugs were taken from the IMS MIDAS database [15]. We had access to data for years 2005 up to 2014, with the exception of Portugal and Ireland where hospital sales were missing for parts of the period (Ireland prior to 2006 and Portugal prior to 2010). We included drugs from the ATC groups L1, L2A and B and selected drugs from L4X (belimumab, lenalidomide, pomalidomide, thalidomide). For some analyses we complement these data with results from the previous comparator report, and the 2009 update, stretching back to 1995 [4, 13].
- Country-specific incidence and mortality figures were based on data from EUCAN. Estimates are for the year 2012 [16].
- DDD are from the official definitions by the WHO [17].

3.3.2 Definitions of access

We have used three main approaches to analyze access in this report: When comparing total consumption and vintage for all cancer drugs or sub-groups of cancer drugs defined according to the site of the cancer we used aggregated sales figures expressed in € at market price levels. Sales were based on ex-manufacturer prices; when comparing countries or groups of countries, sales were expressed per case.

When studying uptake of single drugs, we express this as g per case.

To allow for aggregation and comparisons of drugs with different administration forms or dosing, uptake was expressed as the number of DDD per case. The number of cases in each country were based on the number of deaths from the diagnosis, based on estimates from EUCAN.

3.3.3 Geographic scope

Analyses have been conducted for the EU member states excluding countries with no or limited data in the MIDAS dataset (Cyprus, Estonia, Latvia, Lithuania, Luxembourg, Malta) and adding Norway and Switzerland. The 24 countries were divided into three groups based

on their GDP per capita at market prices (consistent with how sales are reported) in 2014, see Table 2. Note that with this classification, the "big five" countries France, Germany, Italy, Spain and UK forms the middle group.

TABLE 2: GROUPING OF COUNTRIES

Upper tier GDP/capita (36,000 – 73,400 €)	**Mid tier GDP/capita** (22,800 – 35,400 €)	**Lower tier GDP/capita** (5,800 – 18,100 €)
Austria	France	Bulgaria
Belgium	Germany	Croatia
Denmark	Italy	Czech Republic
Finland	Spain	Greece
Ireland	The UK	Hungary
The Netherlands		Poland
Norway		Portugal
Sweden		Slovakia
Switzerland		Slovenia
		Romania
Total GDP (billion €)*		
3 356	9 943	1 371
Share of EU population**		
15%	61%	23%

*In 2014; **In 2014, including Norway and Switzerland

Source. Eurostat.

3.4 Cancer drugs

In this study we will analyze all cancer drugs, as well as undertake specific analyses for certain indications (see below). In the last 20 years, 98 NCEs belonging to the ATC groups L1 and L2A or B have been approved, 95 of these according to the EMA centralized procedure. In addition, three drugs belonging to ATC group L4X were approved for use in cancer. A summary of the approved drug can be found in Table 3. As can be seen in Figure , there has been a marked increase in the number of approved drugs within the field of oncology over time, with 2015 being the year with the largest number of approved drugs to date, with 15 drugs receiving marketing authorization in the EU.

TABLE 3: APPROVED DRUGS IN ONCOLOGY 1995 – 2015 (EMA 1 FEB 2016)

Year	Common name	Organ	Class	Orphan drug	Monoclonal antibody	Companion diagnostic
1995	gemcitabine	lung	Chemo	No	No	No
	docetaxel	breast	Chemo	No	No	No
1996	toremifene	breast	Targeted	No	No	No
	anastrozole	breast	Hormon	No	No	No
	bicalutamide	prostate	Hormon	No	No	No
	doxorubicin	breast	Chemo	No	No	No
	topotecan	lung	Chemo	No	No	No
1998	rituximab	lymphoma	Targeted	No	Yes	No
	irinotecan	colorectal	Chemo	No	No	No
1999	temozolomide	glioblastoma	Chemo	No	No	No
2000	trastuzumab	breast	Targeted	No	Yes	Yes
	doxorubicin	breast	Chemo	No	No	No
	alitretinoin	sarcoma	Chemo	No	No	No
2001	imatinib	leukaemia	Targeted	No	No	Yes
	capecitabine	sarcoma	Chemo	No	No	No
	bexarotene	lymphoma	Chemo	No	No	No
	cytarabine	lymphoma	Chemo	No	No	No
	temoporfin	head and neck	Chemo	No	No	No
2002	arsenic trioxide	leukaemia	Chemo	No	No	No
2003	busulfan		Chemo	No	No	No
2004	bortezomib	myeloma	Targeted	No	No	No
	cetuximab	colorectal	Targeted	No	Yes	Yes
	fulvestrant	breast	Hormon	No	No	No
	cladribine	leukaemia	Chemo	No	No	No
	mitotane	adrenal carcinoma	Chemo	No	No	No
	pemetrexed	lung	Chemo	No	No	No
	anagrelide		Chemo	Yes	No	No
2005	bevacizumab	colorectal	Targeted	No	Yes	No
	erlotinib	lung	Targeted	No	No	Yes
2006	sorafenib	renal	Targeted	Yes	No	No
	sunitinib	renal	Targeted	No	No	No
	dasatinib	leukaemia	Targeted	Yes	No	Yes
	clofarabine	leukaemia	Chemo	Yes	No	No
2007	nilotinib	leukaemia	Targeted	Yes	No	Yes
	temsirolimus	renal	Targeted	Yes	No	No
	panitumumab	colorectal	Targeted	No	Yes	Yes
	docetaxel	breast	Chemo	No	No	No
	hydroxycarbamide		Chemo	Yes	No	No
	nelarabine	leukaemia	Chemo	Yes	No	No
	lenalidomide	myeloma		Yes	No	No
	trabectedin	ovarian	Chemo	Yes	No	No
2008	lapatinib	breast	Targeted	No	No	Yes
	paclitaxel	breast	Chemo	No	No	No
	azacitidine	leukaemia	Chemo	Yes	No	No
	thalidomide	myeloma		Yes	No	No

2009	catumaxomab	carcinoma	Targeted	No	Yes	No
	gefitinib	lung	Targeted	No	No	Yes
	everolimus	breast	Targeted	No	No	No
	vinflunine	urothelial	Targeted	No	No	No
	degarelix	prostate	Hormon	No	No	No
2010	ofatumumab	leukaemia	Targeted	Yes	Yes	No
	pazopanib	renal	Targeted	No	No	No
	thiotepa		Chemo	Yes	No	No
	topotecan	lung	Chemo	No	No	No
2011	ipilimumab	melanoma	Targeted	No	Yes	No
	everolimus	renal	Targeted	Yes	No	No
	abiraterone	prostate	Hormon	No	No	No
	tegafur / gimeracil / oteracil	gastric	Chemo	No	No	No
	cabazitaxel	prostate	Chemo	No	No	No
	eribulin	breast	Chemo	No	No	No
2012	vandetanib	thyroid	Targeted	No	No	No
	vemurafenib	melanoma	Targeted	No	No	Yes
	ruxolitinib		Targeted	No	No	No
	axitinib	renal	Targeted	No	No	No
	crizotinib	lung	Targeted	No	No	Yes
	brentuximab vedotin	lymphoma	Targeted	Yes	Yes	No
	mercaptopurine	leukaemia	Chemo	Yes	No	No
	pixantrone dimaleate	lymphoma	Chemo	No	No	No
	decitabine	leukaemia	Chemo	Yes	No	No
2013	aflibercept	colorectal	Targeted	No	No	No
	pertuzumab	breast	Targeted	No	Yes	Yes
	bosutinib	leukaemia	Targeted	Yes	No	No
	enzalutamide	prostate	Targeted	No	No	No
	ponatinib	leukaemia	Targeted	Yes	No	No
	vismodegib	basal-cell	Targeted	No	No	No
	dabrafenib	melanoma	Targeted	No	No	Yes
	regorafenib	colorectal	Targeted	No	No	No
	afatinib	lung	Targeted	No	No	No
	trastuzumab emtansine	breast	Targeted	No	Yes	Yes
2014	cabozantinib	thyroid	Targeted	Yes	No	No
	trametinib	melanoma	Targeted	No	No	No
	obinutuzumab	leukaemia	Targeted	Yes	Yes	No
	idelalisib	leukaemia	Targeted	No	No	No
	ibrutinib	lymphoma	Targeted	Yes	No	No
	nintedanib	lung	Targeted	No	No	No
	olaparib	ovarian	Targeted	Yes	No	No
2014	ramucirumab	gastric	Targeted	Yes	Yes	No
2015	nintedanib		Targeted	Yes	No	No
	ceritinib	lung	Targeted	No	No	No
	lenvatinib	thyroid	Targeted	Yes	No	No
	dinutuximab	neuroblastoma	Targeted	Yes	Yes	No
	sonidegib	basal-cell	Targeted	No	No	No

2015	panobinostat	myeloma	Targeted	Yes	No	No
	nivolumab	melanoma	Immuno	No	Yes	No
	pembrolizumab	melanoma	Immuno	No	Yes	No
	nivolumab	lung	Immuno	No	Yes	No
	sonidegib	basal-cell	Targeted	No	No	No
	dinutuximab	neuroblastoma	Targeted	Yes	Yes	No
	panobinostat	myeloma	Targeted	Yes	No	No
	carfilzomib	myeloma	Targeted	Yes	No	No
	cobimetinib	melanoma	Targeted	No	No	No
	blinatumomab	leukaemia	Immuno	Yes	Yes	No

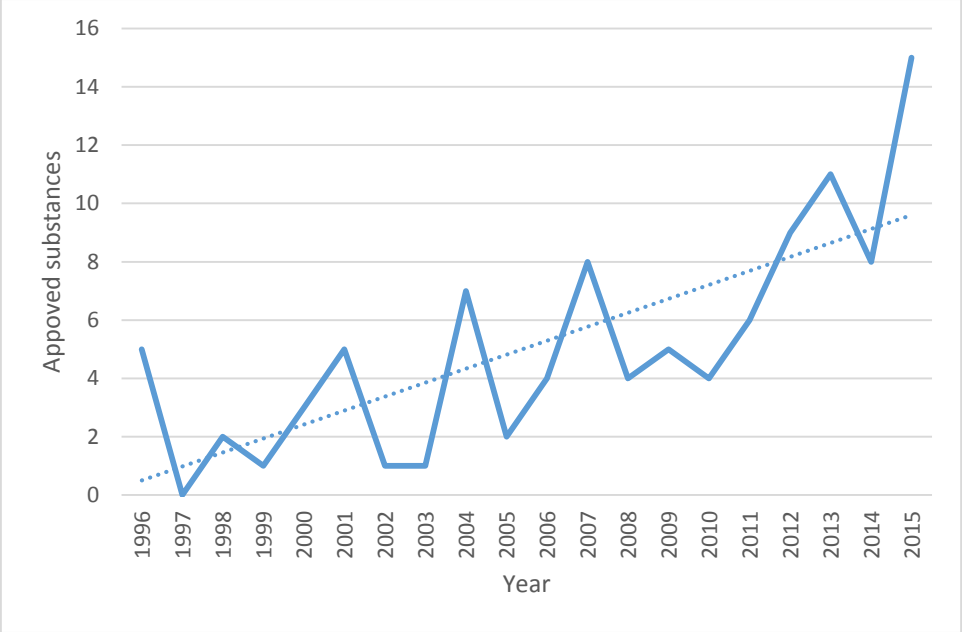


FIGURE 1: NUMBER OF APPROVED DRUGS/INDICATIONS OVER TIME.

Drugs used in leukemia represent the largest share of approved drugs with 16 new approvals during the time period studied. In breast cancer 13 drugs were approved, and 10 each were approved for lung cancer and myeloma. Lymphoma, colorectal cancer and renal cancer (6 drugs each) and prostate cancer (5 drugs) represented other areas with several new drugs approved.

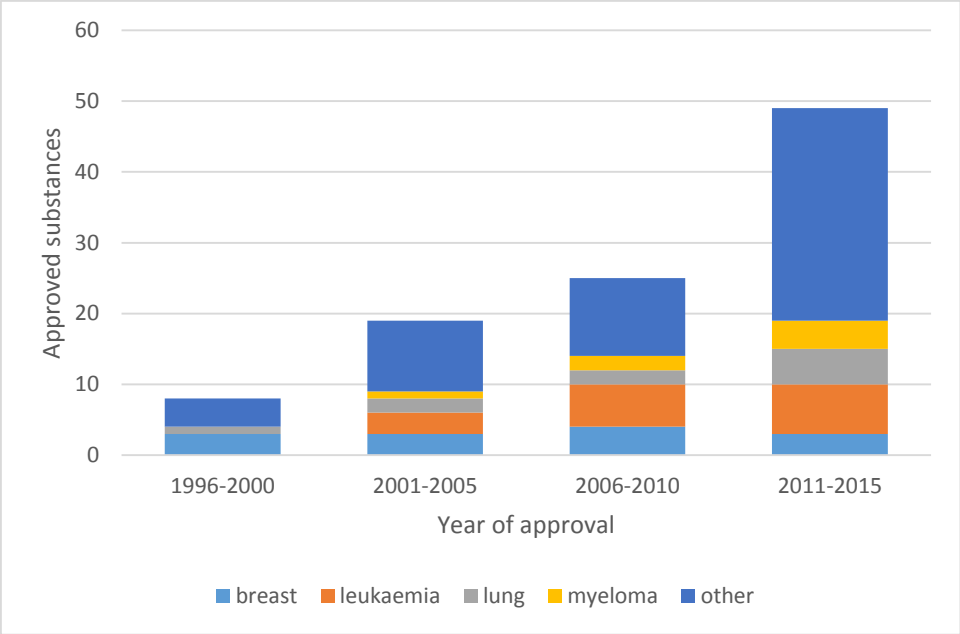


FIGURE 2: NUMBER OF APPROVED DRUGS/INDICATIONS BY TYPE OF CANCER.

As was described in chapter 2.2, there has been a shift from chemotherapy to more and more drugs being targeted therapies. This is clearly seen in with a majority of drugs approved during the last five years being targeted therapies. A recent development is the immunotherapies, with 4 drugs entering the market in recent years.

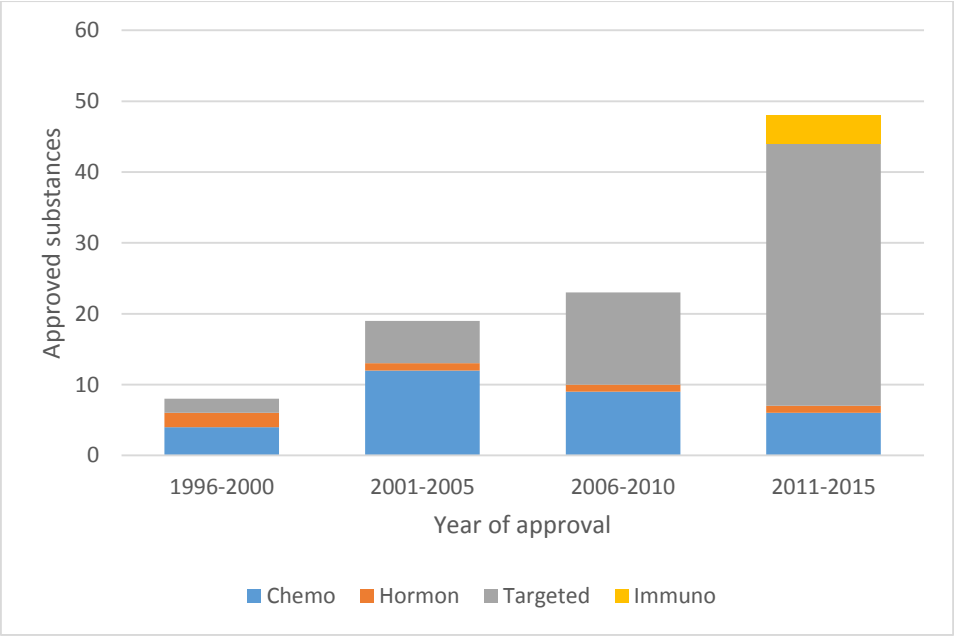


FIGURE 3: NUMBER OF APPROVALS BY TYPE OF THERAPY.

Drugs from ATC group L4X not included.

Figure 4 and Figure 5 illustrate two other trends: The increasing role of monoclonal antibodies in contrast to small molecules and an increasing number of drugs approved with an

orphan designation[23]. 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.

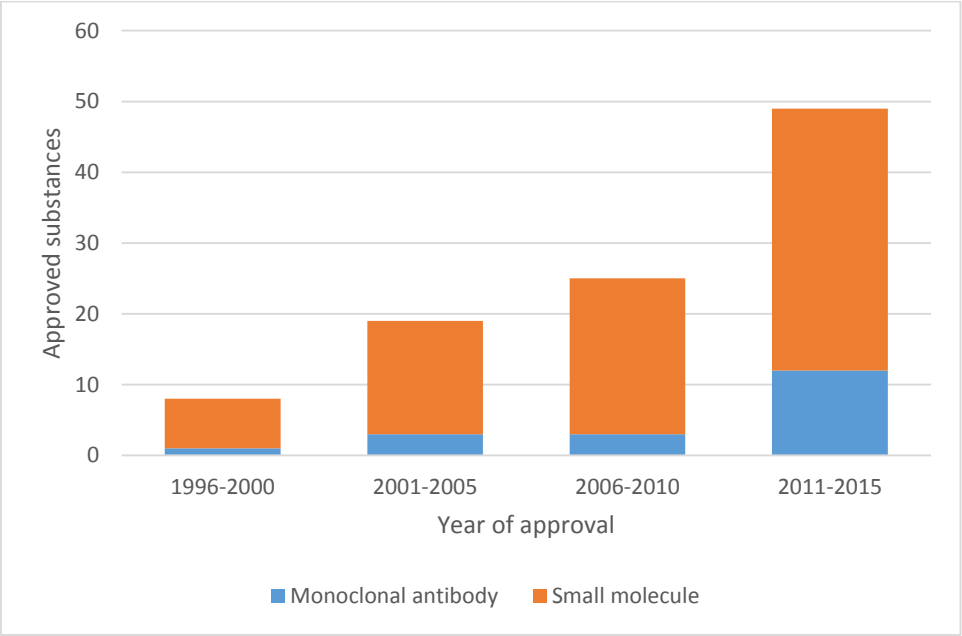


FIGURE 4. NUMBER OF APPROVED DRUGS/INDICATIONS BY TYPE OF MOLECULE.

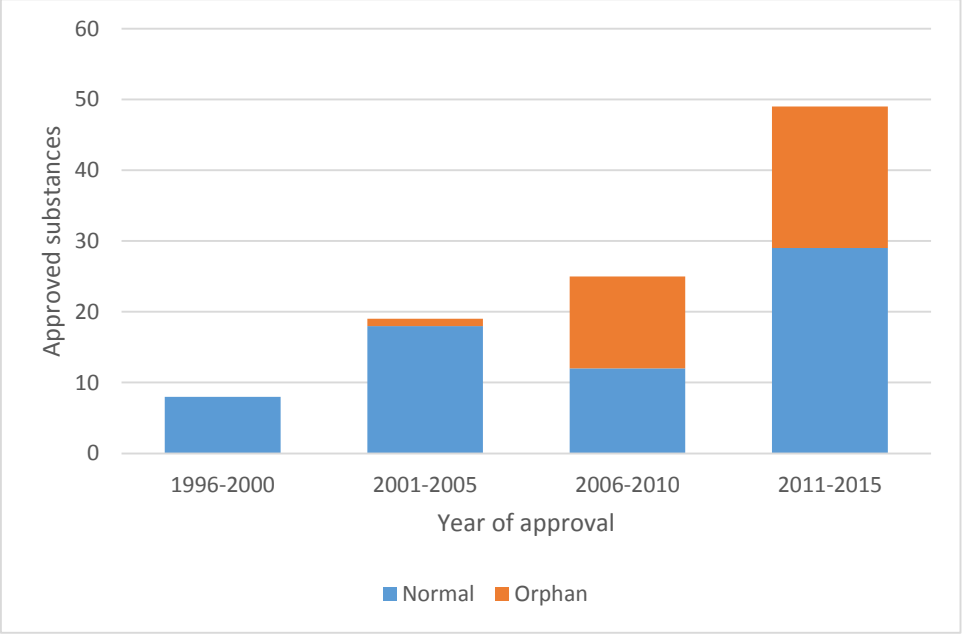


FIGURE 5. NUMBER OF APPROVED DRUGS/INDICATIONS RECEIVING AN ORPHAN DRUG DESIGNATION.

[23] To qualify for this, the drug must be intended for a disease that is life-threatening or chronically debilitating; the prevalence of the condition 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) and no satisfactory treatment be available.

3.5 Top-selling drugs

Based on ex-manufacturer list prices, the total sales of drugs used in oncology was 8.0 billion € in 2005, growing to 19.8 billion € in 2014. [24] It can be noted that a small number of drugs make up the majority of sales: The 10 largest drugs in terms of sales in 2005 made up 59% of total sales. In 2014 the corresponding number was 52%.

TABLE 4. TOP 10 DRUGS BY MARKET SHARE 1995 - 2014 – ALL COUNTRIES.

1995		2000		2005		2014	
Molecule	Share of total sales	Molecule	Share of total sales	Molecule	Share of total sales	Molecule	Share of total sales
Goserelin	9,7%	Paclitaxel	11,0%	Imatinib	9,3%	Trastuzumab	8,9%
Leuprorelin	8,9%	Leuprorelin	7,6%	Rituximab	7,1%	Rituximab	8,2%*
Calcium folinate	8,4%	Goserelin	7,5%	Docetaxel	6,5%	Bevacizumab	8,1%
Tamoxifen	8,4%	Docetaxel	5,3%	Paclitaxel	5,7%	Imatinib	5,9%
Flutamide	6,1%	Gemcitabine	4,9%	Oxaliplatin	5,6%	Lenalidomide	4,7%
Interferon alfa-2a	5,9%	Bicalutamide	4,4%	Trastuzumab	5,4%	Abiraterone acetate	4,4%
Triptorelin	5,3%	Triptorelin	4,3%	Anastrozole	5,3%	Pemetrexed	3,5%
Carboplatin	4,7%	Carboplatin	3,5%	Bicalutamide	5,3%	Bortezomib	3,3%
Epirubicin	4,7%	Irinotecan	3,5%	Leuprorelin	4,5%	Leuprorelin	2,6%
Paclitaxel	4,4%	Tamoxifen	3,4%	Goserelin	4,2%	Paclitaxel	2,5%
Total	**66.7%**	**Total**	**55.4%**	**Total**	**58.9%**	**Total**	**52.0%**

*Also includes sales outside oncology, approximately 20% of value globally

Over time, there have been marked shifts among the top 10 sellers (see Table 4). Paclitaxel and Leuprorelin are the only drug on top 10 both 1995 and 2014. Paclitaxel on place 10 both years, and place 1 in 2000 and place 4 in 2005. Leuprorelin number 2 in 1995 and 2005, and number 9 in 2005 and 2014. Only three drugs on top 10 in 1995, is on the list 2005, Goserelin, Leuprorelin and Paclitaxel. 5 drugs from top 10 in 2005 remain in 2014.

Looking further back, the top selling drug in 1995 Goserelin has moved downwards to third place in 2000 and 10th place in 2005. Leuprorelin has seen a similar shift. This is an effect both of loss of patent, leading to lower prices due to competition from generics and therefore a smaller share of sales (in value) and of replacement by new drugs. Trastuzumab has almost doubled its share and several new agents have entered the list, e.g. bevacizumab and lenalidomide. It's interesting to note that among the top 5 drugs in 2014, three have recently

[24] These numbers likely constitutes an overestimation of the true cost of oncology drugs as they don't take rebates into consideration. Some drugs are also used in other indications.

lost exclusivity in the market or are about to do so in the near future (trastuzumab, rituximab and imatinib).

3.6 Vintage

Figure 6 shows the share of sales attributable to drugs launched within the last three years, between three and five years ago and more than five years ago. Sales of drugs launched in the preceding three years was roughly 1.1 billion € per year, this number has been fairly stable over time with the exception of the last two years where the contribution to costs has been larger. As a proportion of sales, the newest drugs (launched within the last three years) have made up 8% of the total sales on average, varying between 4% and 11% per year. Drugs launched 3 to 5 years ago made up another 8% of the total sales on average, but with a slightly wider distribution (3% to 15%).

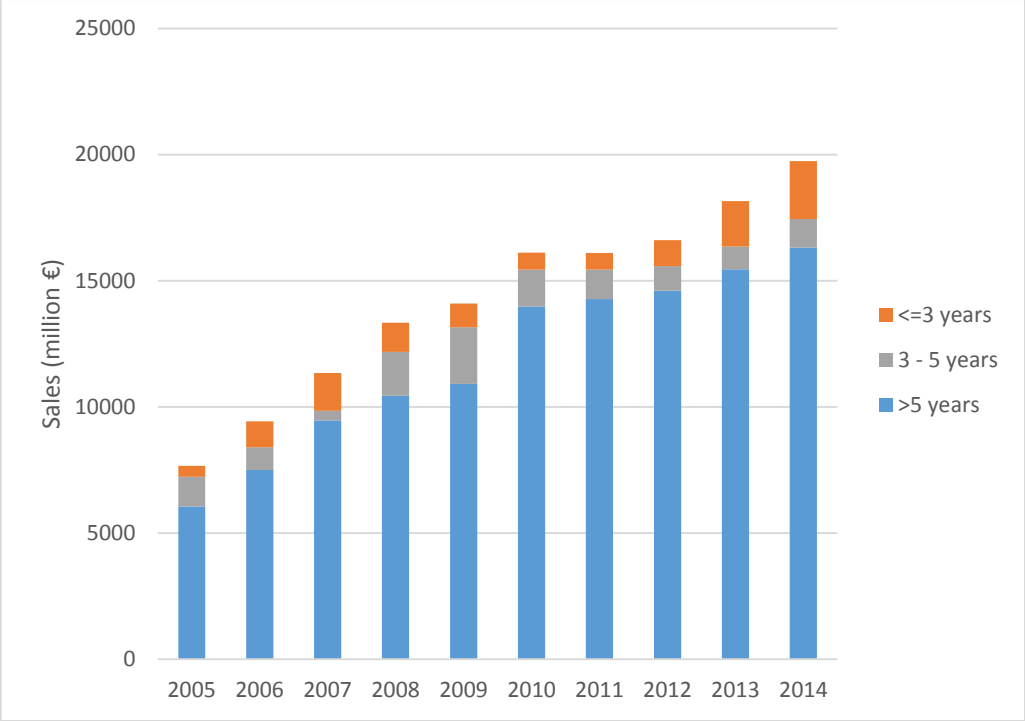


FIGURE 6. SALES OF ONCOLOGY DRUGS BY TIME SINCE LAUNCH.

Figure 7 show sales of oncology drugs per 100,000 inhabitants in the three groups of countries. The upper and mid-tier countries are fairly similar in terms of both absolute levels and the share of sales of newer drugs. Part of the explanation is that Germany and France (classified in tier 2) have the highest and third highest expenditures per capita of all countries The lower income countries have markedly lower sales overall, with barely any sales of newer drugs. Total sales per 100 000 inhabitants are only a third of that in the richer countries. The population in these countries is 119 million people or 24 % of the EU population.

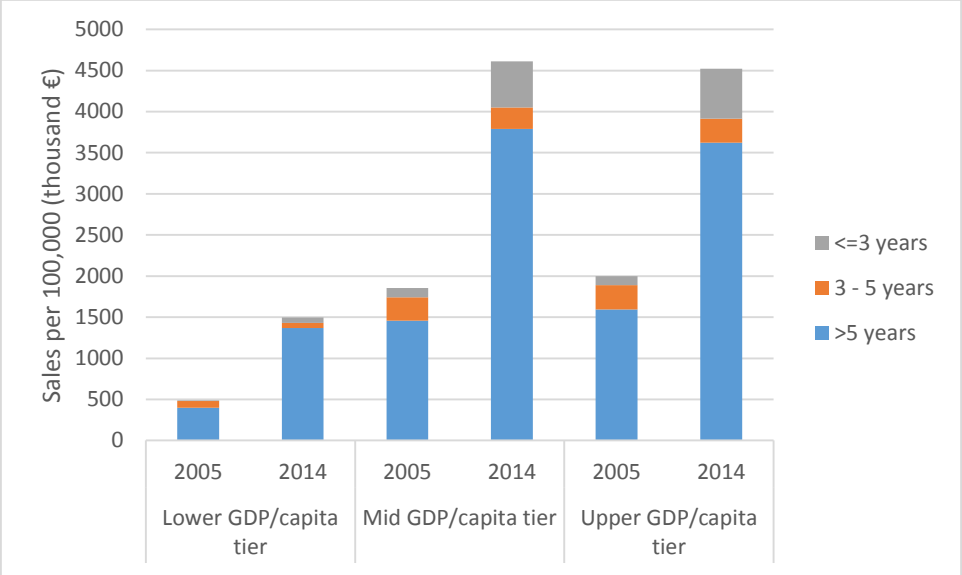


FIGURE 7. SALES OF ONCOLOGY DRUGS PER 100,000 INHABITANTS BY TIME SINCE LAUNCH BY ECONOMIC STATUS

3.7 Uptake in selected therapeutic areas

In this section of the report we describe the uptake of new drugs in six therapeutic areas where a number of new agents have been introduced during the time period studied. The main therapeutic areas and drugs included are:

- Breast cancer; HER2+ (eribulin, fulvestrant, lapatinib, pertuzumab, trastuzumab, trastuzumab emtansine)
- Chronic myeloid leukemia (imatinib, dasatinib, nilotinib)
- Colorectal cancer (bevacizumab, cetuximab, panitumumab)
- Lung cancer (erlotinib, pemetrexed, crizotinib, gefitinib)
- Melanoma (ipilimumab, vemurafenib, dabrafenib)
- Multiple myeloma (bortezomib, lenalidomide, thalidomide)

These drugs account for 48% of the total sales of cancer drugs based on sales in 2014. As can be seen in Table 5, they constitute the drugs with most sales within each of the selected indications. One indication with several new drugs on the market that wasn't included here is prostate cancer. This is due to the fact that the new drugs have very recent approvals and we therefore have only limited follow-up data.

For breast cancer, we also include data on the aromatase inhibitors who also were included in the previous report. They provide an nice illustration of the development over the life cycle of a class of drugs. In a separate section we also present life cycle data on the taxanes.

TABLE 5: SALES (EU + NO & CH IN 2014) FOR PATENT PROTECTED DRUGS USED IN SELECTED INDICATIONS

Indication	Substance	Sales (Million €)
Breast cancer	**Trastuzumab**	1765,8
	nab-Paclitaxel*	156,2
	Everolimus*	364,2
	Fulvestrant	198,6
	Pertuzumab	156,7
	Trastuzumab Emtansine	109,1
	Lapatinib	85,9
	Eribulin	67,0
Colorectal cancer	**Bevacizumab**	1595,4
	Cetuximab	446,1
	Panitumumab	158,6
Chronic myeloid leukemia	**Imatinib**	1169,8
	Nilotinib	342,3
	Dasatinib	313,5
Lung cancer	**Pemetrexed**	683,9
	Erlotinib	257,0
	Gefitinib	128,9
	Crizotinib	65,6
Malignant melanoma	**Ipilimumab**	421,2
	Vemurafenib	170,1
	Dabrafenib	79,4
Multiple myeloma	**Lenalidomide**	4549,0
	Bortezomib	645,4
	Thalidomide	267,4

Substances in bold are included in the review below.

*Used in several indications

Uptake is defined as the number of DDD per case, with the number of deaths from the specific indication as the definition of a case. DDD per case was chosen over volume in mg, as differences in dosing would make comparisons between drugs difficult to interpret. Using value has similar problems as prices differ. Nevertheless, we show some data by value to illustrate the cost impact.

3.7.1 Breast cancer

Breast cancer remains the most drug intensive area of oncology as pointed out in chapter 2. During the last 25 years we have seen the introduction of new chemotherapy agents; the taxanes and lately eribulin. The taxanes have established themselves as backbones in both the adjuvant setting and in the treatment of advanced breast cancer. Both taxanes alternatively paclitaxel and docetaxel have gone off patent so it is therefore of special interest to analyze uptake and use also after the patents expired. Eribulin is the only new chemotherapeutic agent to enter the arena of breast cancer treatment in the last decades, however it has only indication in late stages of advanced metastatic breast cancer treatment.

During the same time period, since early 1990ies, the aromatase inhibitors anastrazol, letrozol and exemestane, have become new and valuable components in the treatment of metastatic as well as early breast cancer. These drugs are now also off patent and therefore, similar to the taxanes, interesting to study from a life cycle perspective. Fulvestrant, an oestrogen receptor down regulator, is only indicated in metastatic hormone sensitive breast cancer.

The introduction of trastuzumab in 1998 (in the US and in Switzerland; in EU in 2000) marked the starting point of a revolution in the treatment of HER2+ breast cancer, which is found in about 15% of patients with early breast cancer and in about 25% in patients with metastatic breast cancer. The introduction in metastatic breast cancer was followed by an adjuvant indication in 2006. There are now several more alternatives in the treatment of metastatic HER2+ breast cancer including lapatinib, pertuzumab and trastuzumab emtansine.

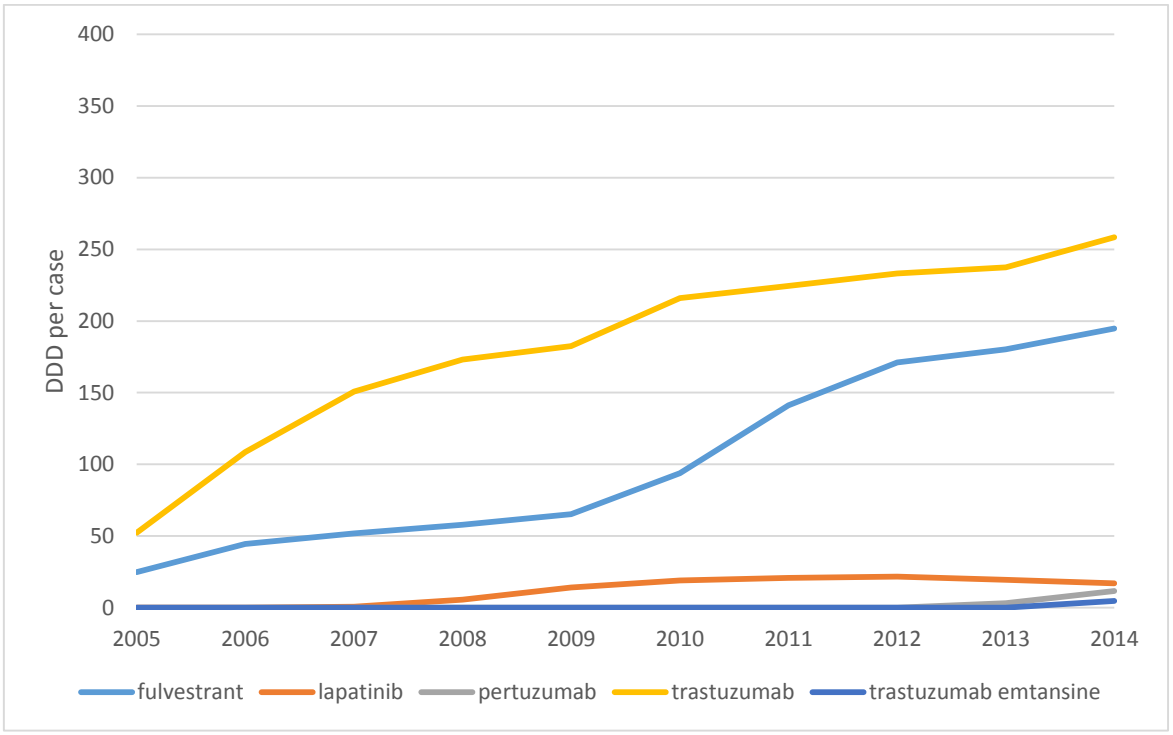


FIGURE 8. UPTAKE OF DRUGS IN BREAST CANCER EXPRESSED AS DDD PER CASE OF BREAST CANCER DEATH – ALL COUNTRIES

Eribulin omitted as it lacks a DDD.

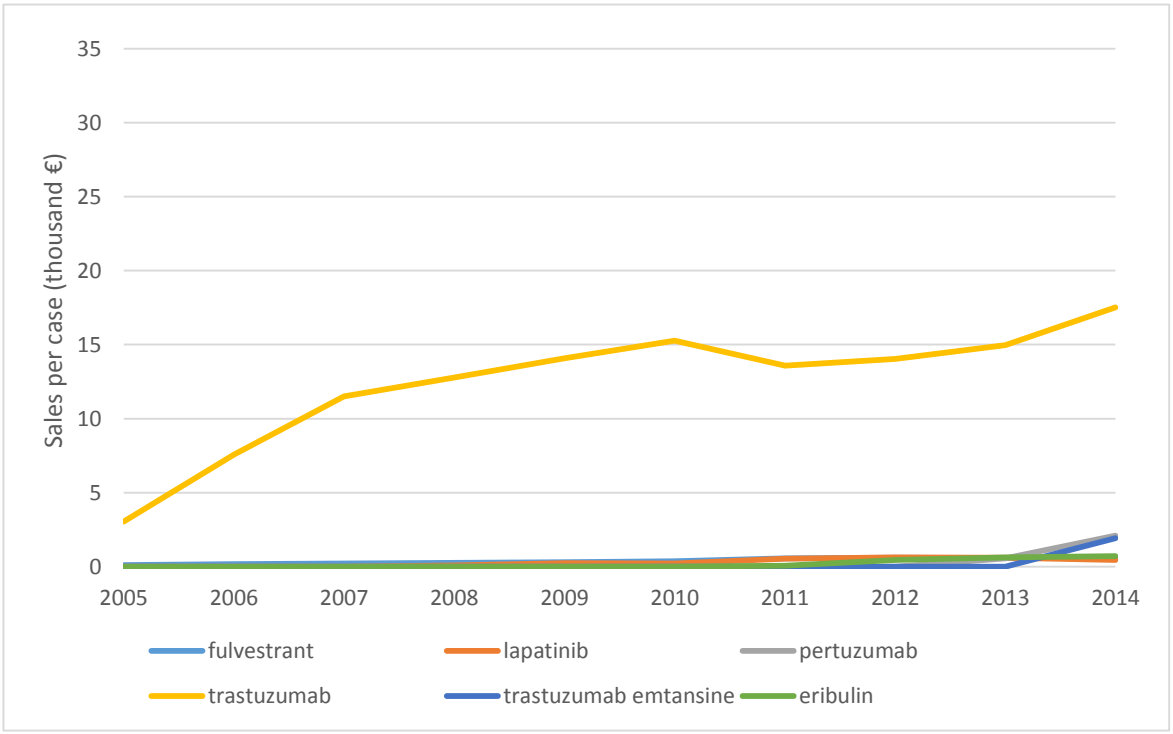


FIGURE 9. UPTAKE OF DRUGS IN BREAST CANCER EXPRESSED AS THOUSAND € PER CASE OF BREAST CANCER DEATH – ALL COUNTRIES

The increase in euro per case between 2005 and 2014 is only fourfold compare to the five-fold increase in DDD. This indicates a modest reduction in price and cost per treated patient. Since the sales figures do not include rebates, the reduction in price and costs per patient may be greater in practice.

As can be seen, trastuzumab is the "back-bone" of HER2+ therapy. It is an established first line therapy both for early HER2+ breast cancer and for metastatic HER2+ disease. Lapatinib has played a role as second line therapy in the metastatic situation upon progression on trastuzumab, but has been largely replaced by new treatment options. This decrease in usage of lapatinib is both related to new emerging therapeutic alternatives, but also to failure to demonstrate added medical value in pivotal trials. The new HER+ drug options include combination therapy with trastuzumab and pertuzumab in first line metastatic disease and trastuzumab emtansine upon progression.

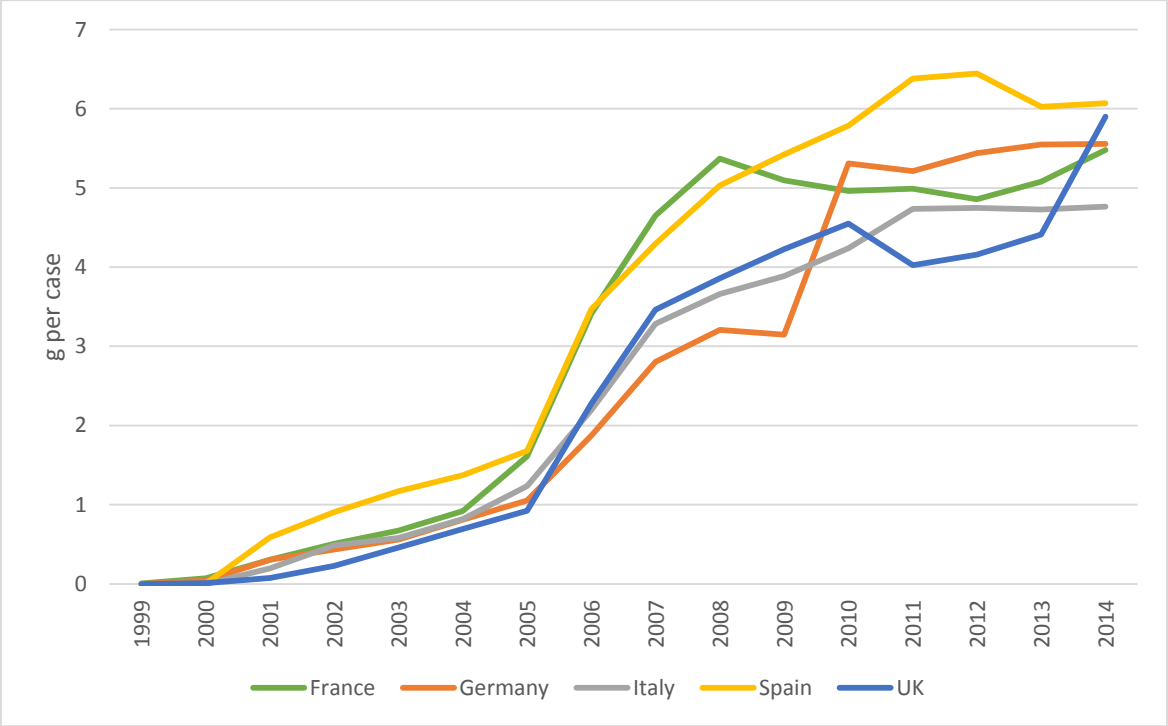


FIGURE 10. UPTAKE OF TRASTUZUMAB EXPRESSED AS G PER BREAST CANCER DEATH IN THE FIVE LARGEST COUNTRIES

As can be seen in Figure 10 and 11, uptake of trastuzumab increased dramatically in 2005 - 2006 when in the drug was approved for use in the adjuvant setting.

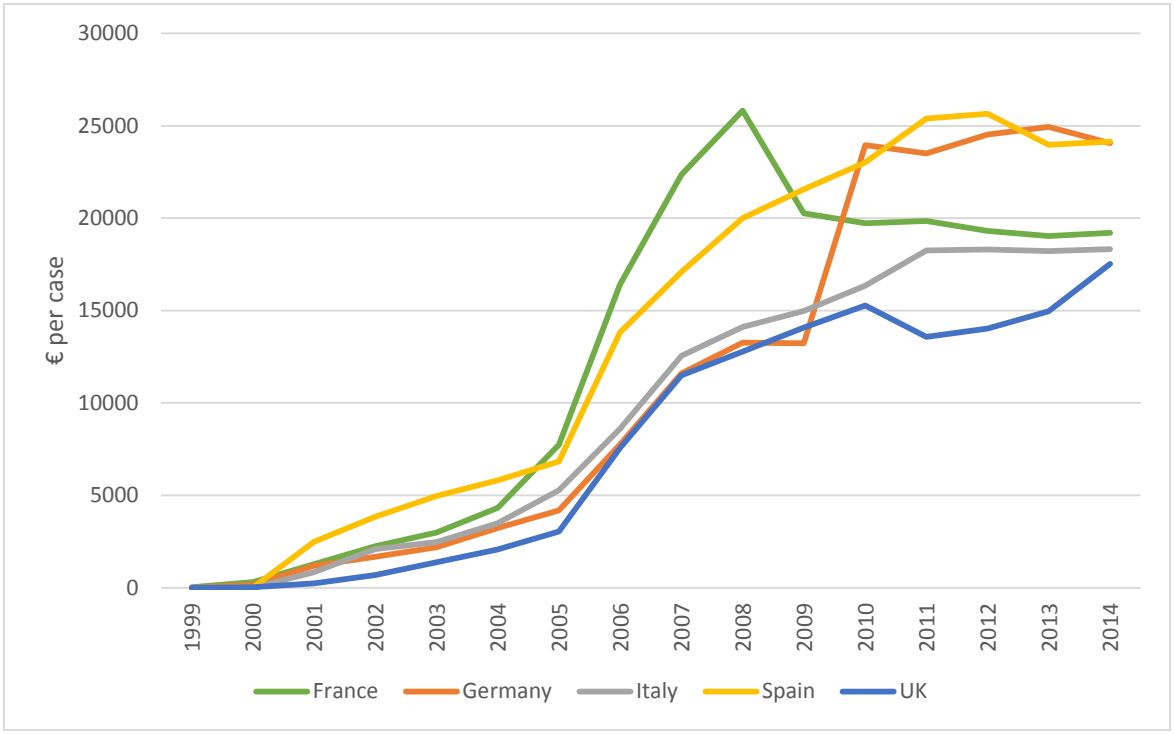


FIGURE 11. UPTAKE OF TRASTUZUMAB EXPRESSED AS € PER BREAST CANCER DEATH IN THE FIVE LARGEST COUNTRIES

Figure 12 shows increased use of trastuzumab in all countries during the period, although use is linked to income. Pertuzumab and trastuzumab emtansine is barely used at all in the lower income countries. Lapatinib is less common in the highest income tier based on less positive outcomes data. This has, as pointed out, led to an increased use of the new HER2+ drugs in particular pertuzumab.

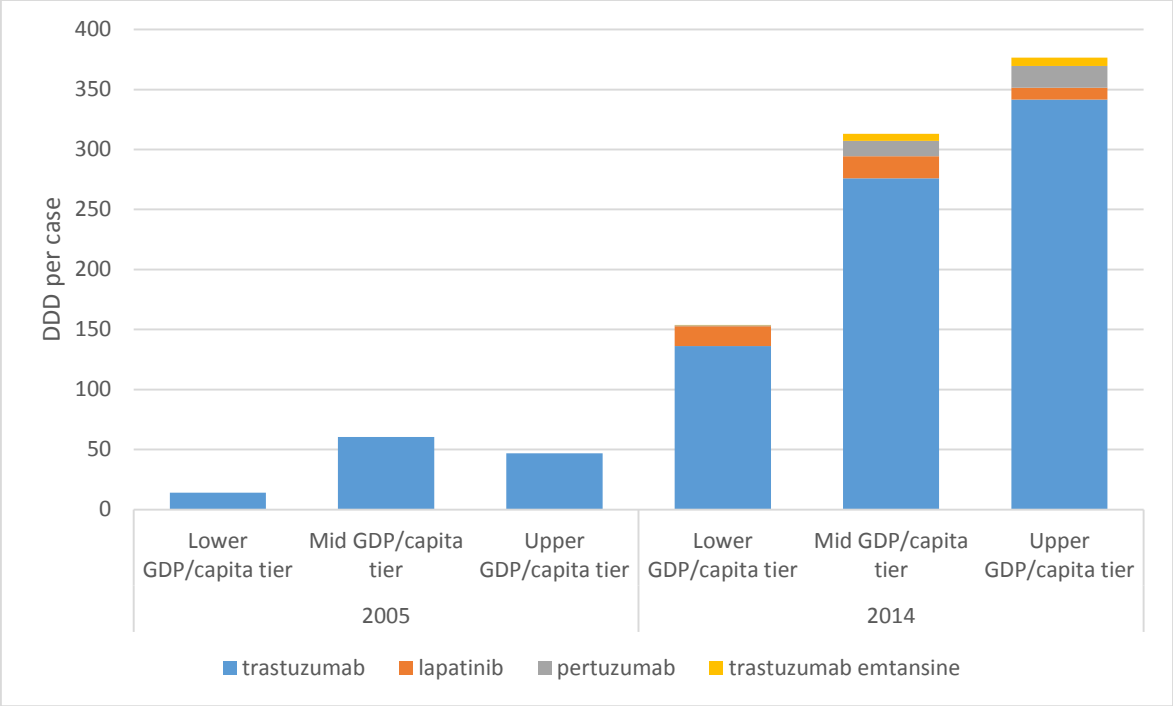


FIGURE 12. COMPARISON OF UPTAKE OF HER2+ BREAST CANCER DRUGS BETWEEN GROUPS OF COUNTRIES (DEFINED BY GDP/PER CAPITA)

Eribulin omitted as it lacks a DDD.

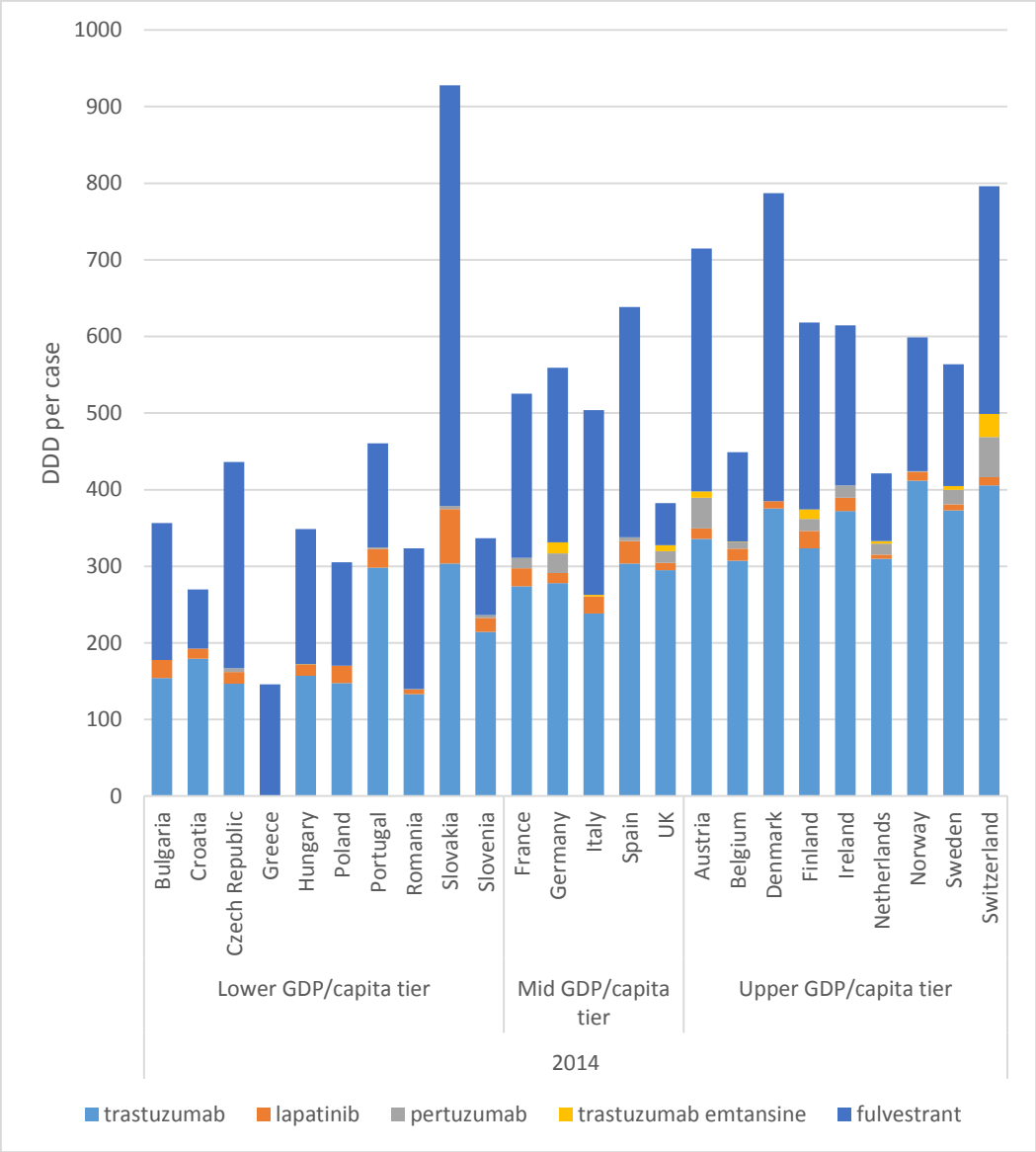


FIGURE 13. USE OF HER2+ BREAST CANCER DRUGS IN 2014

Eribulin omitted as it lacks a DDD.

As can be seen in Figure 13 there are large variations between countries with similar income, both in total use and in what drugs are being chosen. Portugal and Slovakia have a drug usage more similar to that of the richer countries, though Lapatinib seems to be more popular.

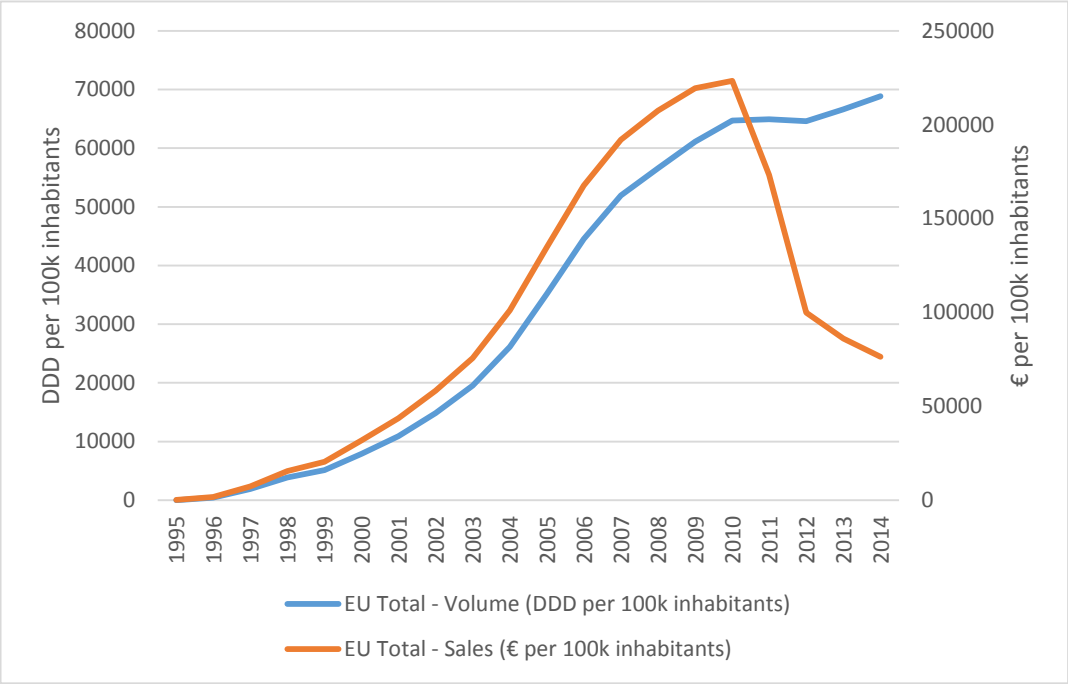


FIGURE 14. USE OF AROMATASE INHIBITORS OVER TIME

Figure 14 illustrates the development how the use of aromatase inhibitors (anastrozole, exemestane, formestane and letrozole), have increased over time. Following the loss of exclusivity, the overall cost have been decreasing in spite of the continued increase in use. As illustrated in Figure 15 there are still very large variations in use between countries irrespective of their economic status.

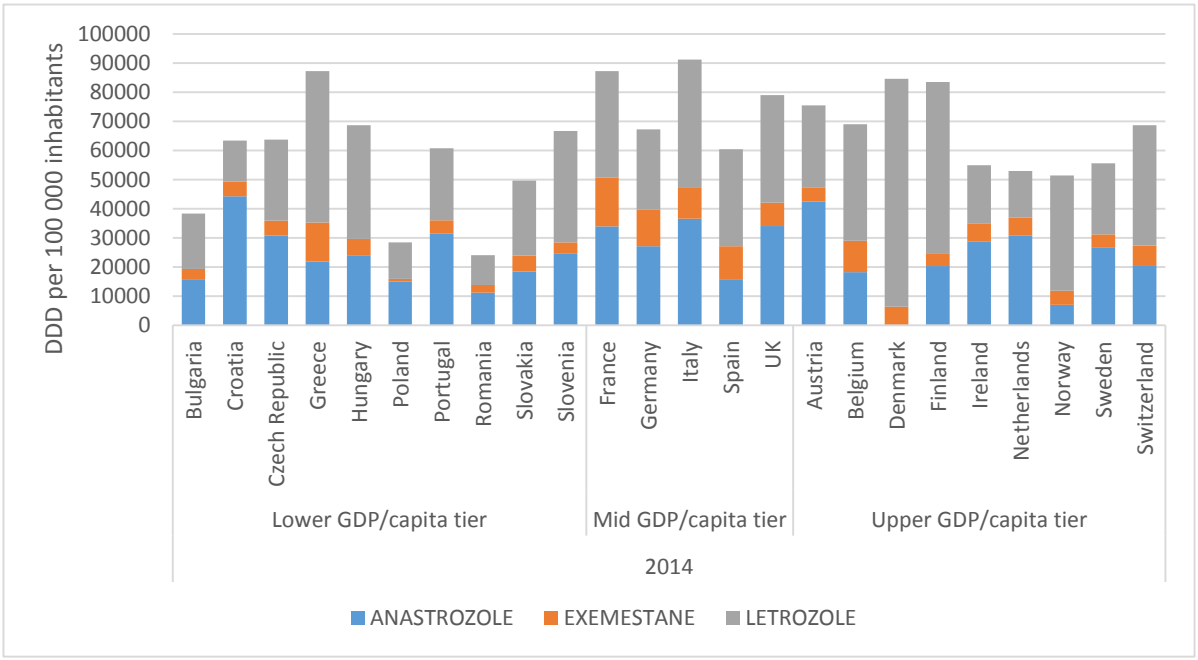


FIGURE 15. USE OF AROMATASE INHIBITORS IN 2014

3.7.2 Chronic myeloid leukemia

CML is a rare form of leukemia where the outcome has changed dramatically over the last two decades. Bone marrow and stem cell transplantation changed the outcome for younger patients already in the 1990ies, but it was with the introduction of imatinib that the most dramatic change in outcome appeared. Most patient diagnosed with CML who receive treatment with imatinib or any of the second generation drugs like dasatinib and nilotinib, will now have a normal or near normal life expectancy.

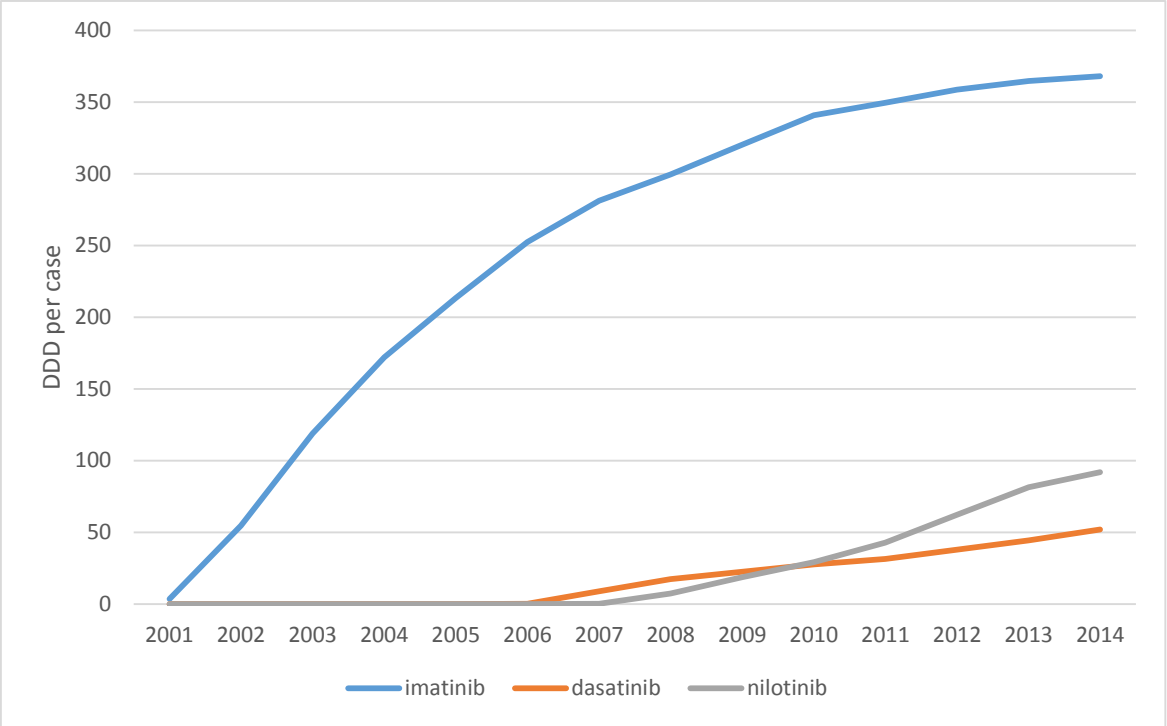


FIGURE 16. UPTAKE OF DRUGS IN CML EXPRESSED AS DDD PER CASE OF DEATH IN LEUKEMIA – ALL COUNTRIES

Imatinib was relatively fast established as first line standard of care in CML. Dasatinib and nilotinib were initially introduced as second line options in 2007 and 2008 respectively, but are (since year 2011) also established first line options.

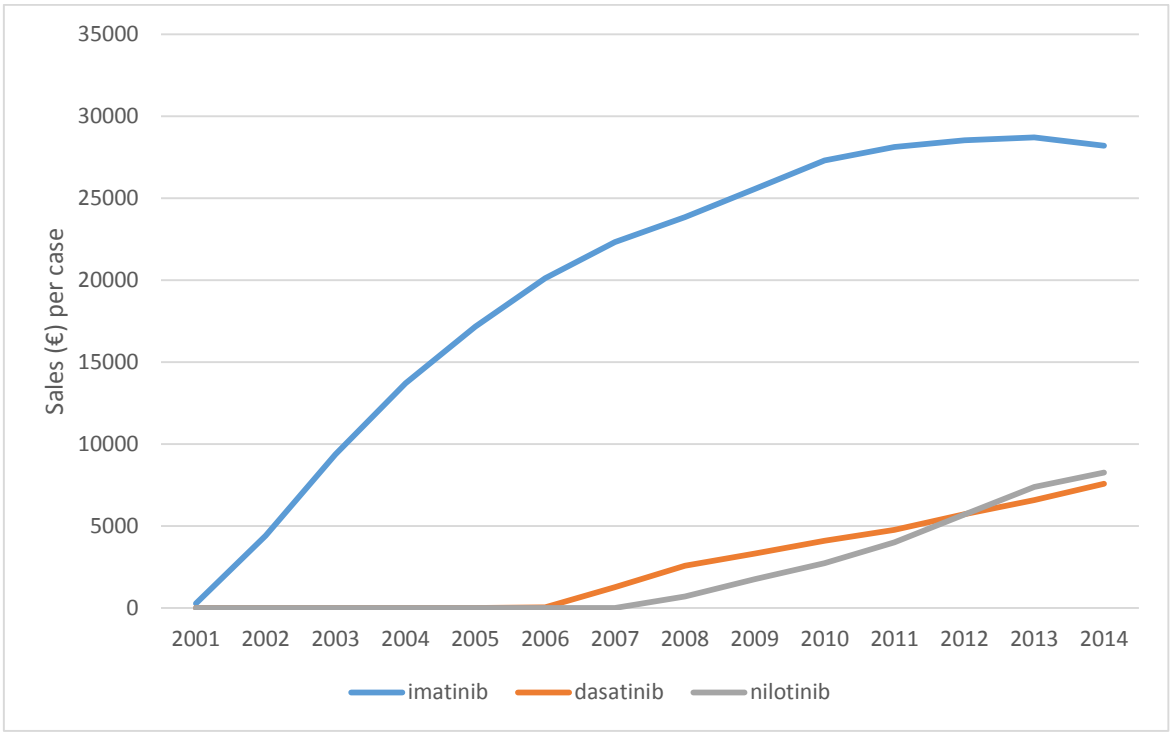


FIGURE 17. UPTAKE OF DRUGS IN CML EXPRESSED AS € PER CASE OF DEATH IN LEUKEMIA – ALL COUNTRIES

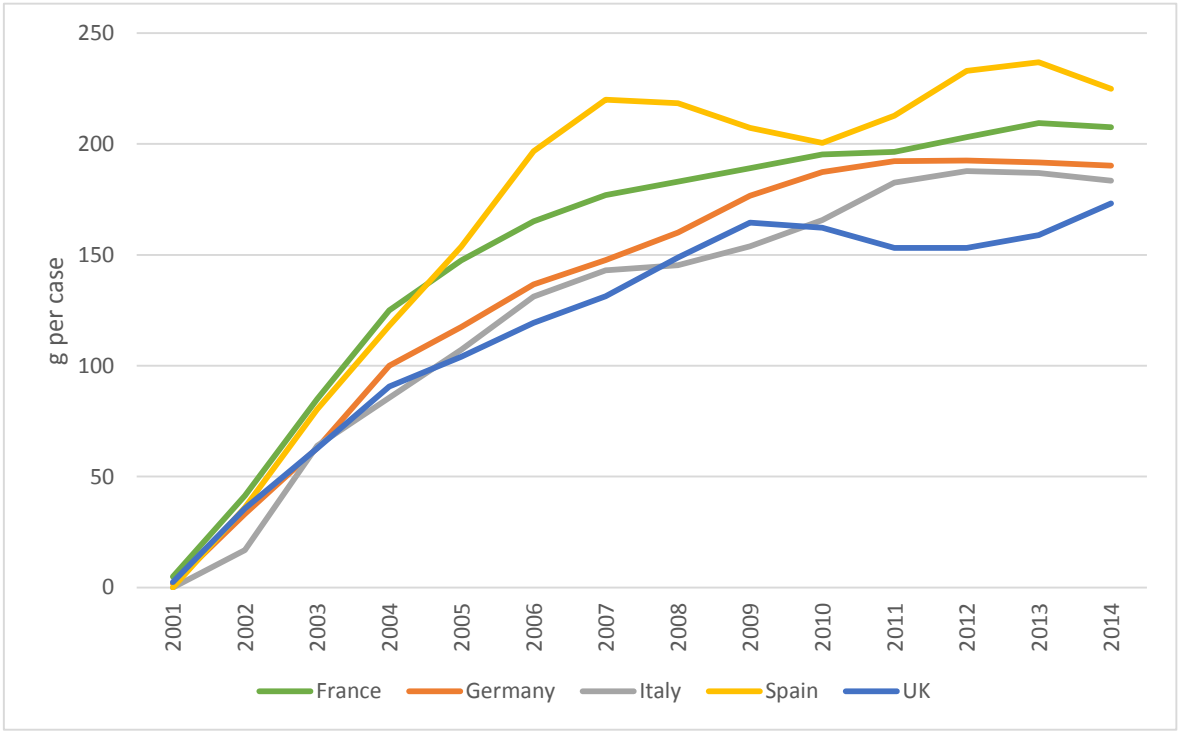


FIGURE 18. UPTAKE OF IMATINIB EXPRESSED AS G PER CML DEATH IN THE FIVE LARGEST COUNTRIES

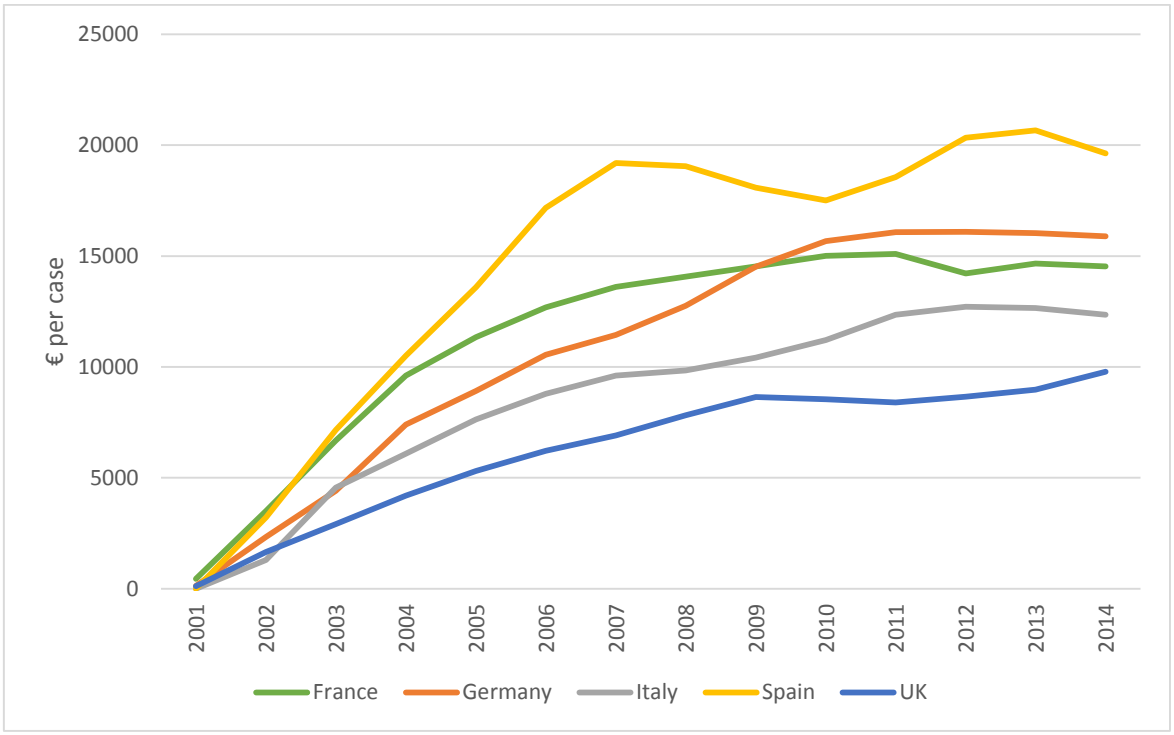


FIGURE 19. UPTAKE OF IMATINIB EXPRESSED AS € PER CML DEATH IN THE FIVE LARGEST COUNTRIES

The uptake of imatinib differs between the five largest countries. Based on observations from a Swedish study treatment in the elderly patients may differ between countries. Older patients may not be treated even if they tolerate treatment as well as younger patients. As seen in the Swedish study, the survival improvement seem related to the introduction of imatinib is only seen in age groups offered treatment and is absent in older patients not being offered therapy with imatinib [18].

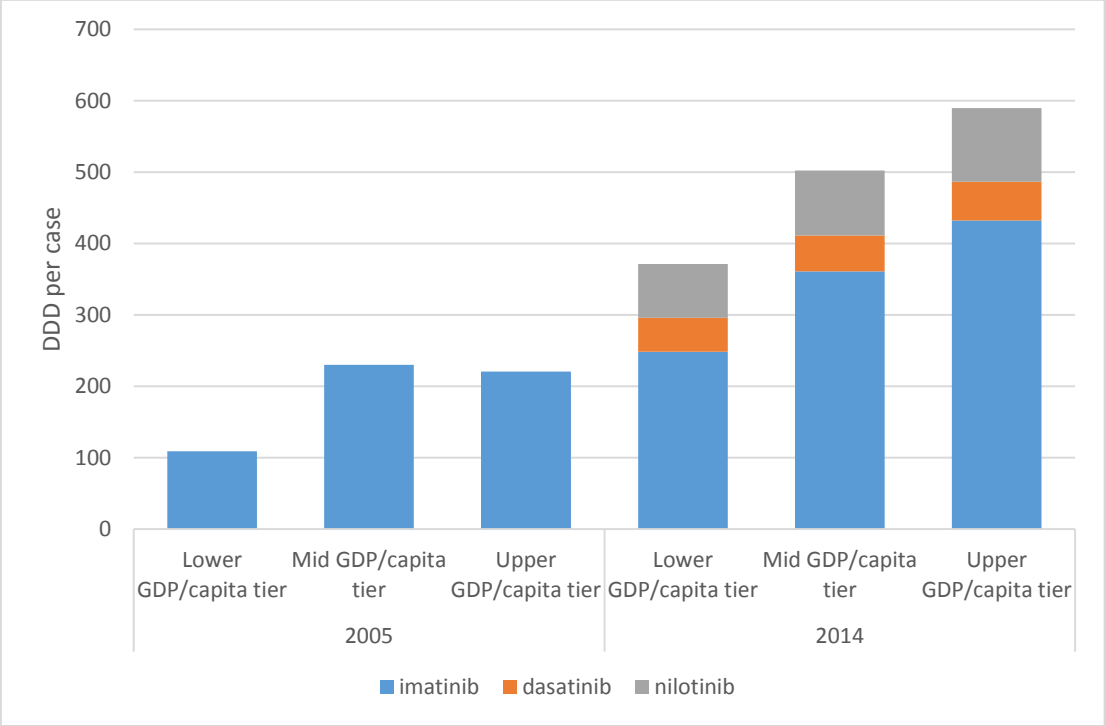


FIGURE 20. COMPARISON OF UPTAKE OF CML DRUGS BETWEEN GROUPS OF COUNTRIES (DEFINED BY GDP/PER CAPITA)

It is of interest to note the usage in Lower GDP/ capita tier is about 2/3 of that in the upper tier indicating a relative high access to CML drugs in all included populations compared to many other diagnoses. Also interesting to note that newer drugs have taken about the same market share in all three groups of countries. Though there is variation between countries, in particular in the lower income countries (Figure 21), this seems to be smaller than e.g. for breast cancer. Some variation may also be explained by underreporting of sales in some countries.

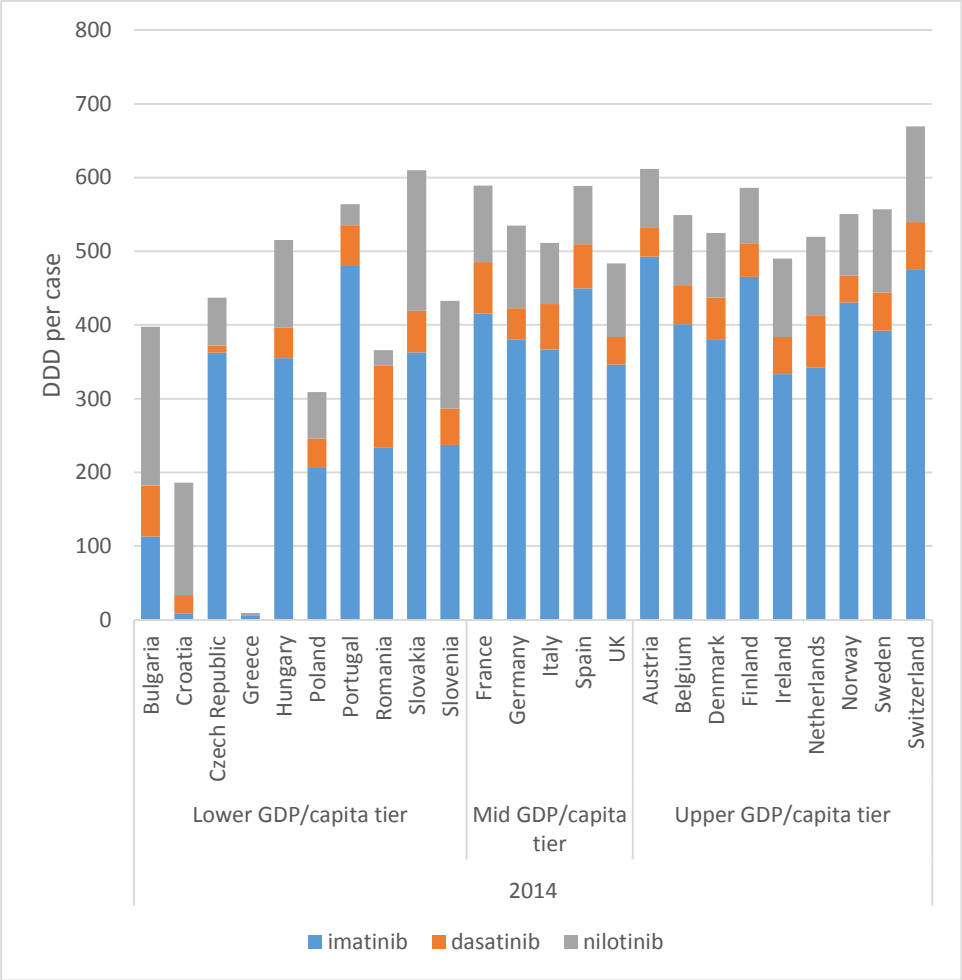


FIGURE 21. USE OF CML DRUGS IN 2014

3.7.3 Colorectal cancer

Surgery remains the back bone in the treatment of colorectal cancer but medical treatment has come to play a more important role over time. 5 fluorouracil (5-FU) based chemotherapy remains the cornerstone both in the adjuvant and in the metastatic setting. 5-FU in combination with either irinotecan or oxaliplatin prolonged survival in metastatic colorectal cancer patients when introduced during the 1990ies and the development of new drug combinations and schedules have further improved outcome. This development have continued after the change of the millennium and colorectal cancer is the major indication for three drugs introduced since 2005; bevacizumab and cetuximab introduced 2005, and panitumumab introduced in 2008. A problem when interpreting the data on use of the first two drugs is that they are also indicated for other indications. Bevacizumab has several other indications including lung-, renal-, breast- and ovarian cancer and some usage in not approved indications like brain tumours. Cetuximab is also approved for the treatment of head and neck cancer, while panitumumab is only indicated in metastatic colorectal cancer.

In colorectal cancer these drugs are used in the metastatic situation. None of the new drugs, bevacizumab, cetuximab and panitumumab, have had significant effects in the adjuvant setting based on several large clinical trials.

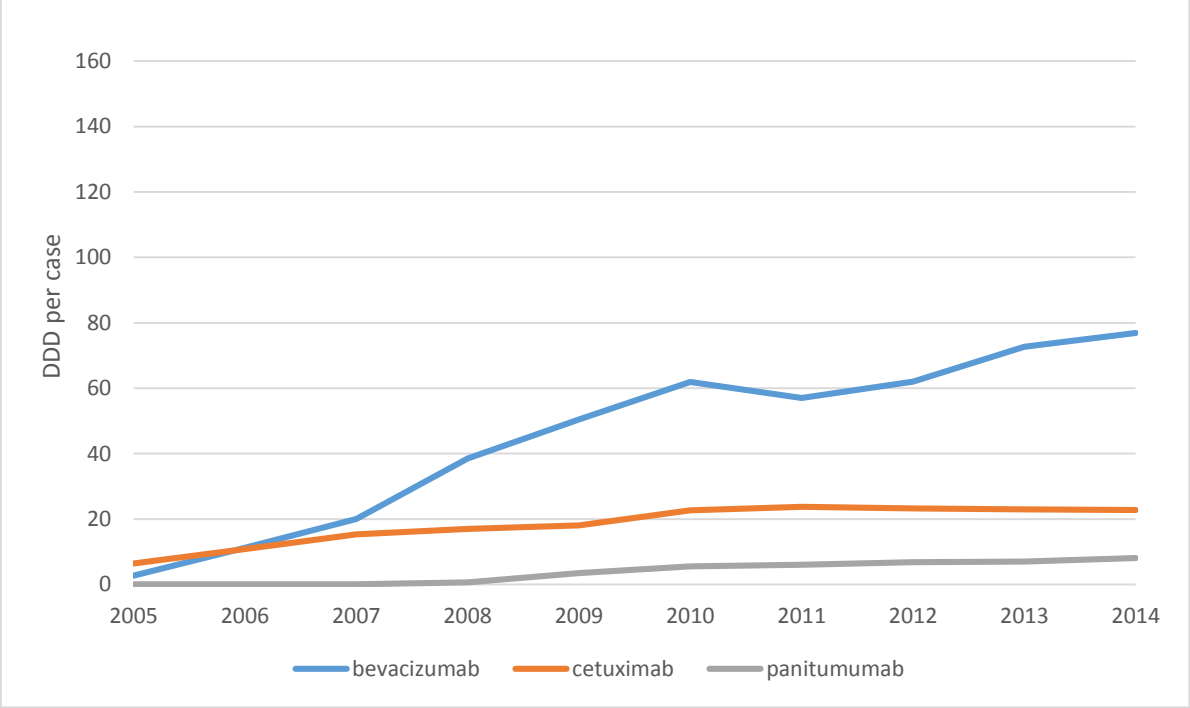


FIGURE 22. UPTAKE OF DRUGS IN COLORECTAL CANCER EXPRESSED AS DDD PER CASE OF DEATH FROM COLORECTAL CANCER – ALL COUNTRIES

Since 2012 the increased uptake of bevacizumab may be related to the additional approved indications in ovarian cancer and cervical cancer.

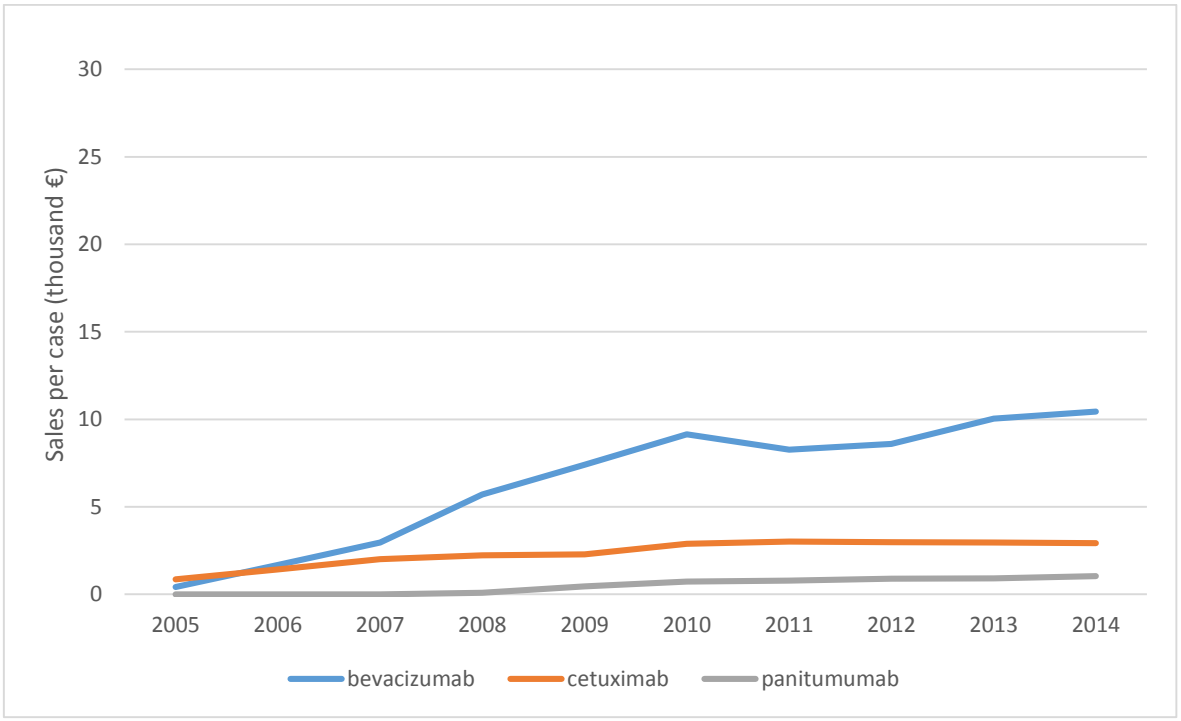


FIGURE 23. UPTAKE OF DRUGS IN COLORECTAL CANCER EXPRESSED AS € PER CASE OF DEATH FROM COLORECTAL CANCER – ALL COUNTRIES

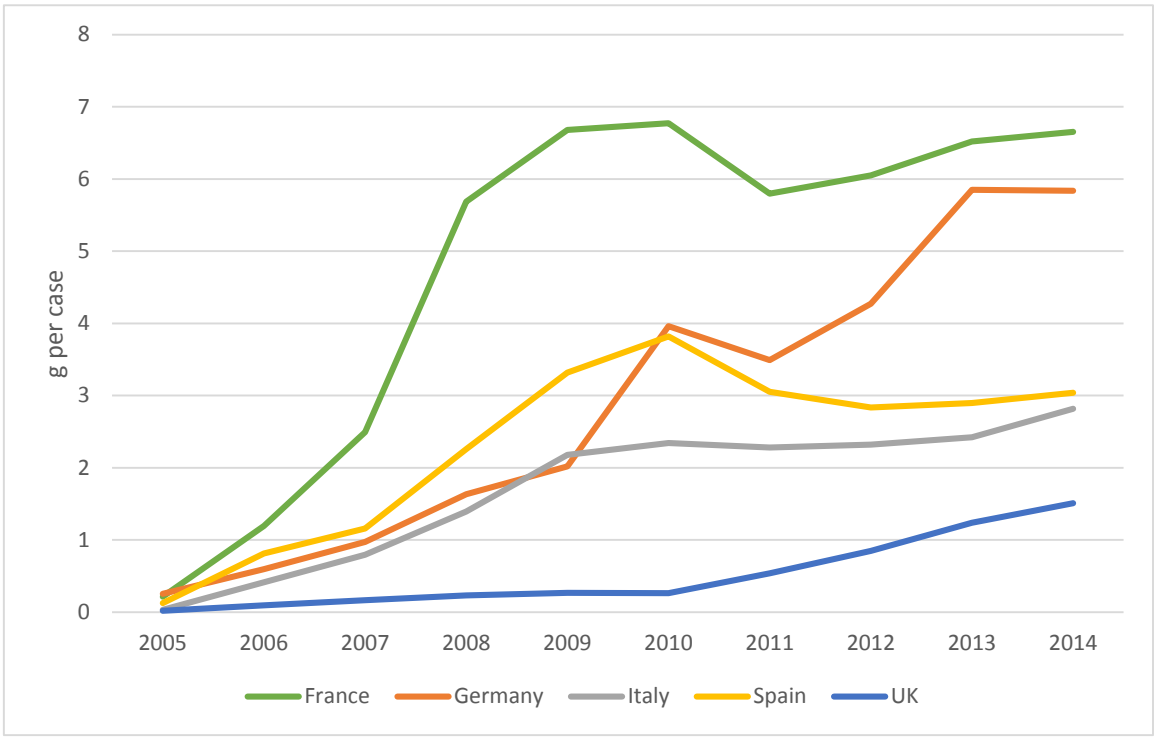


FIGURE 24. UPTAKE OF BEVACIZUMAB EXPRESSED AS G PER CASE IN THE FIVE LARGEST COUNTRIES

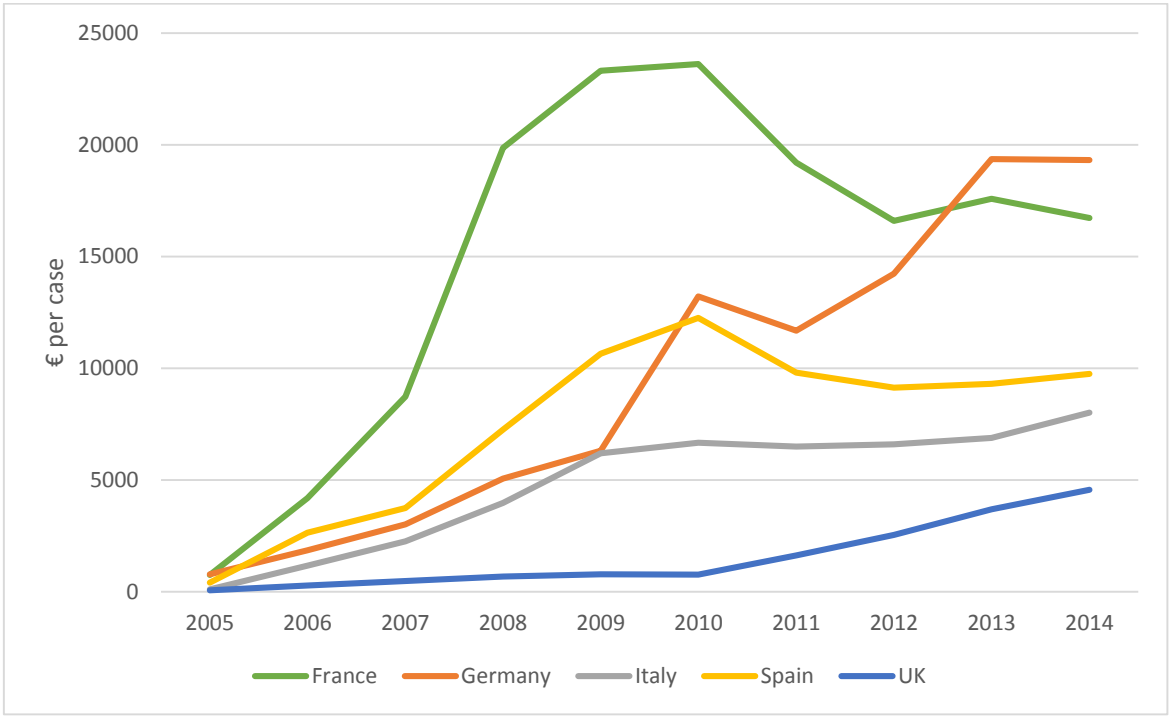


FIGURE 25. UPTAKE OF BEVACIZUMAB EXPRESSED AS € PER CASE IN THE FIVE LARGEST COUNTRIES

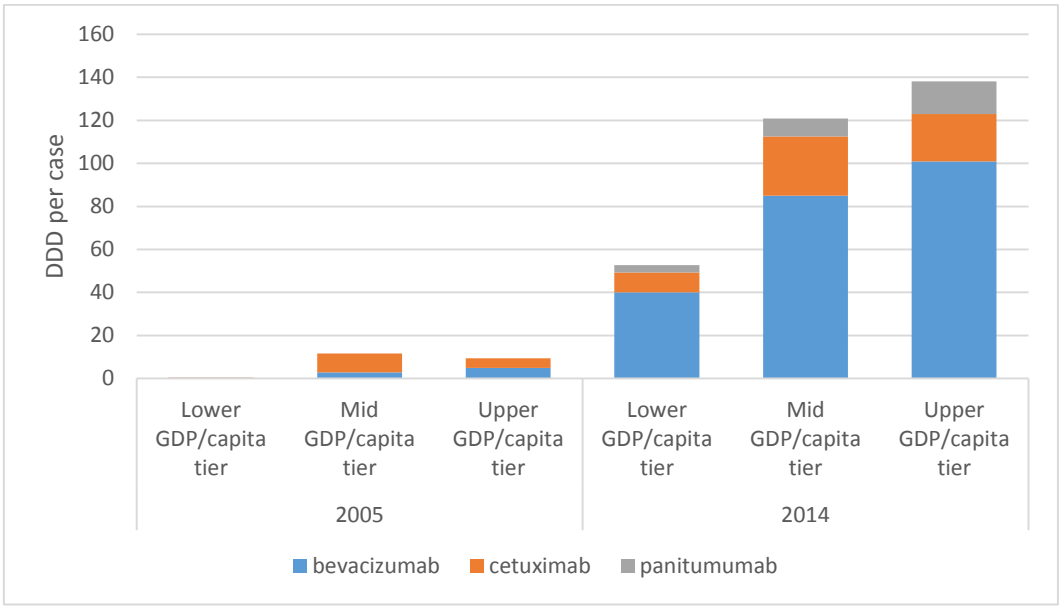


FIGURE 26. COMPARISON OF UPTAKE OF COLORECTAL CANCER DRUGS BETWEEN GROUPS OF COUNTRIES (DEFINED BY GDP/PER CAPITA)

In colorectal cancer the usage is Lower GDP/ capita tier is just 1/3 of that in Mid and Upper tier in contrast to the situation in CML. There are very large variations within each income group.

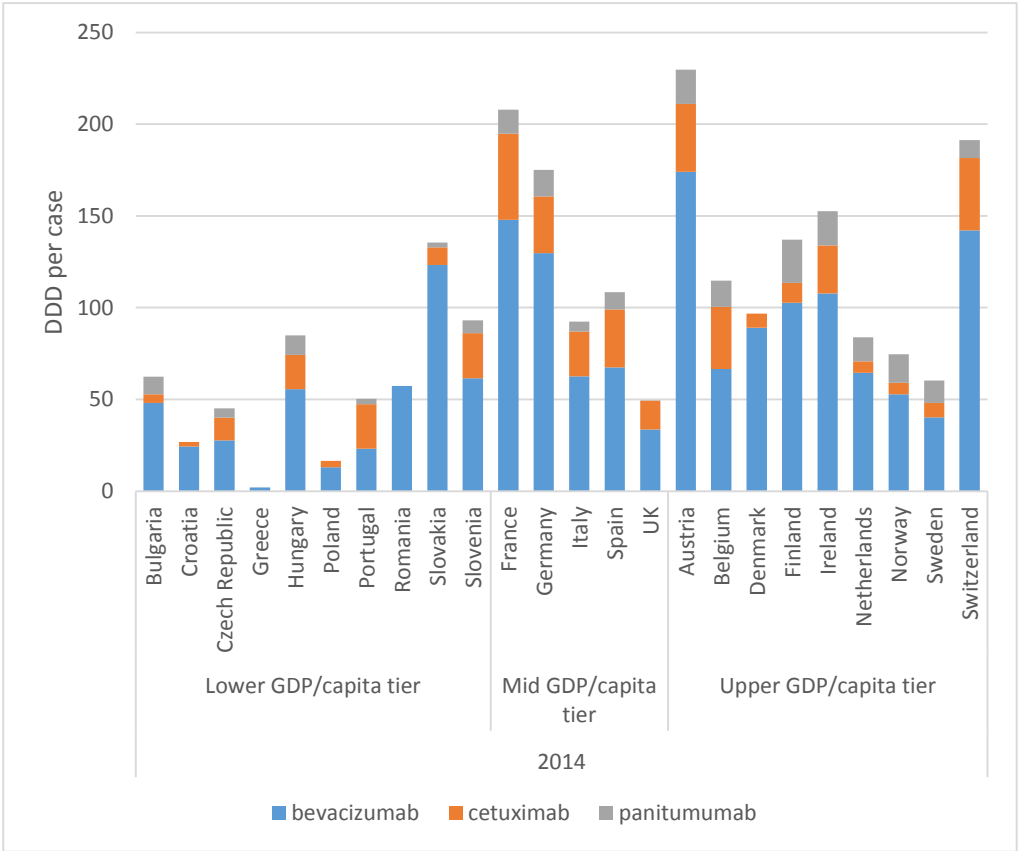


FIGURE 27. USE OF COLORECTAL CANCER DRUGS IN 2014

3.7.4 Lung cancer

In many parts of EU, medical treatment of lung cancer, had no major role in the treatment of the disease or any impact on outcome until the mid 1990ies. With the introduction of platinum (cis- or carboplatin) based combinations with either taxanes (pacli- or docetaxel), gemcitabine or vinorelbine, a marked improvement was seen in the metastatic setting. Platinum based therapy was also shown to significantly improve outcome in the adjuvant setting. The introduction of pemetrexed further established the role of chemotherapy.

A new era in the treatment of lung cancer came with drugs targeting signaling pathways like the EGFR and ALK fusion protein pathways. These new drugs, erlotinib, gefitinib and most recently crizotinib, have now changed the therapeutic landscape for many lung cancer patients. 2015 also marked the introduction of immuno-oncology in the treatment of lung cancer.

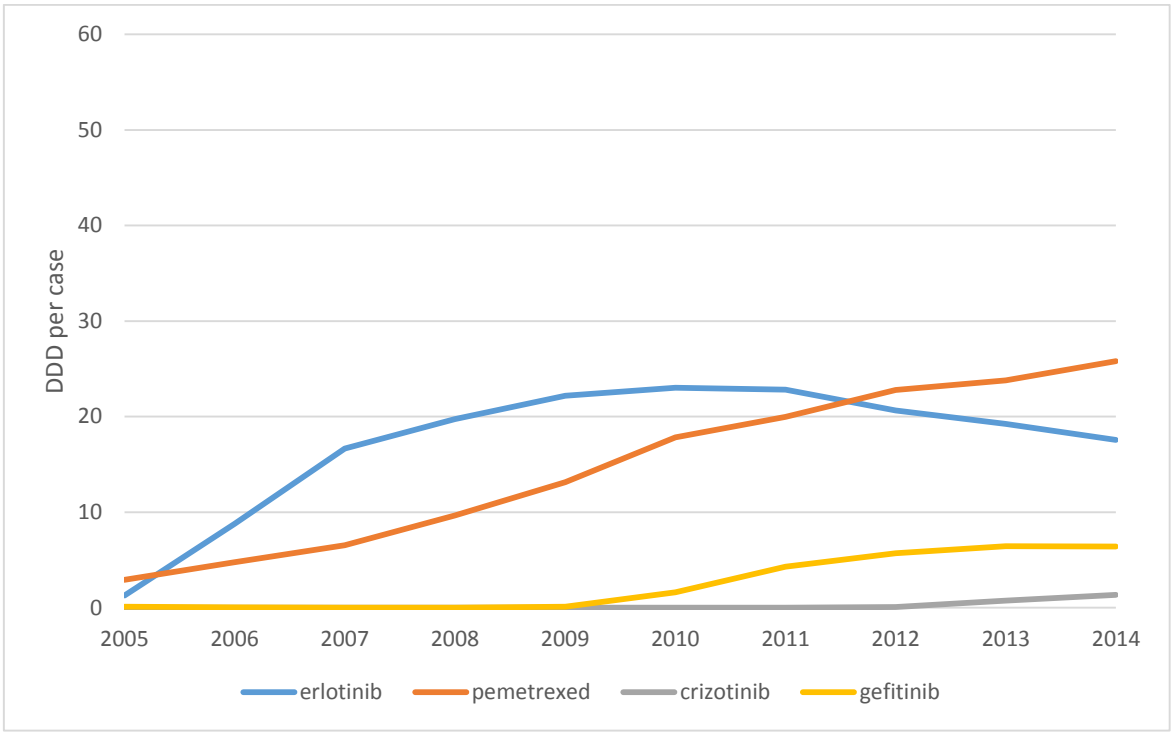


FIGURE 28. UPTAKE OF DRUGS IN LUNG CANCER EXPRESSED AS DDD PER CASE OF DEATH FROM LUNG CANCER – ALL COUNTRIES

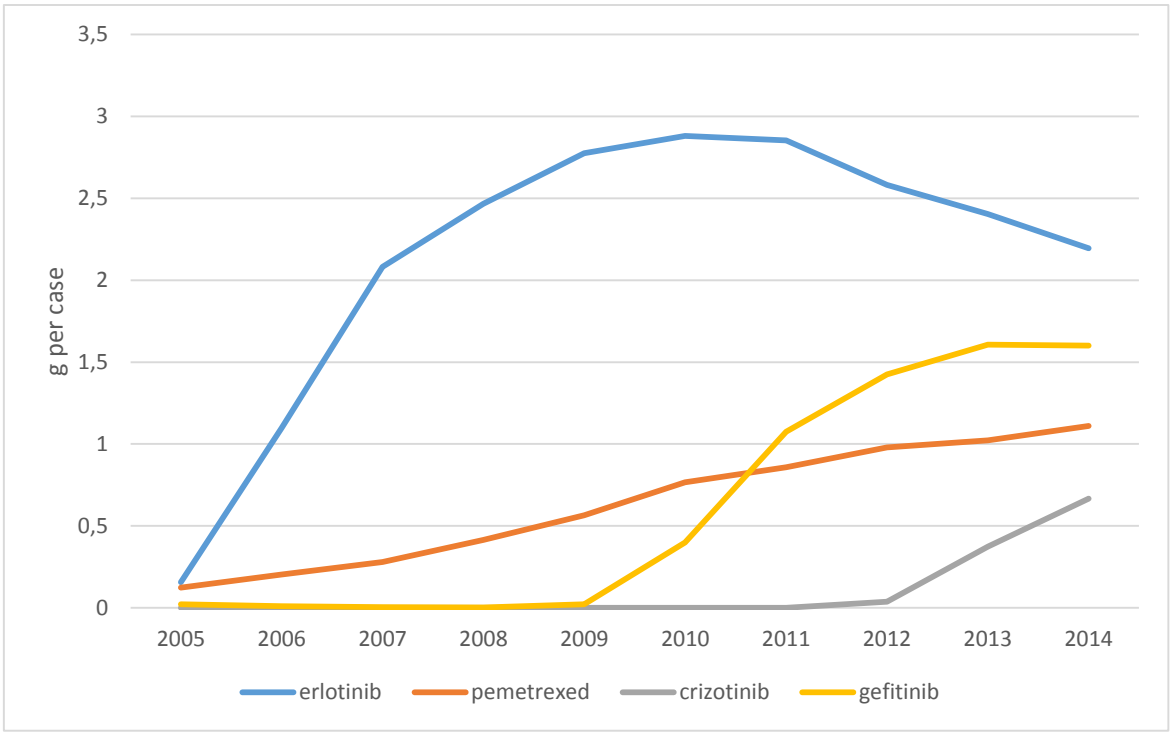


FIGURE 29: UPTAKE OF DRUGS IN LUNG CANCER EXPRESSED AS G PER CASE OF DEATH FROM LUNG CANCER – ALL COUNTRIES

The drugs selected for these comparisons are all introduced after year 2000. Pemetrexed has its major indication linked to a certain histological subtype, and erlotinib and gefitinib use is based on analysis of the EGFR status in the tumour. It is estimated that 10-35% of the patients depending on the populations studied have mutations that may indicate activity of these drugs. Crizotinib is indicated in a small lung cancer population i.e. patients with ALK protein positive tumours. This means that the use of erlotinib, gefitinib and crizotinib should be linked the biomarker analysis. The latest development in oncology includes activating the body's own immune system in the treatment of cancer. Immuno-oncology has rapidly become standard of care in metastatic malignant melanoma and progress is also ongoing in a number of other tumour types including lung cancer. Therapies such as nivolumab are not yet included in this analysis as they only became available to patients recently.

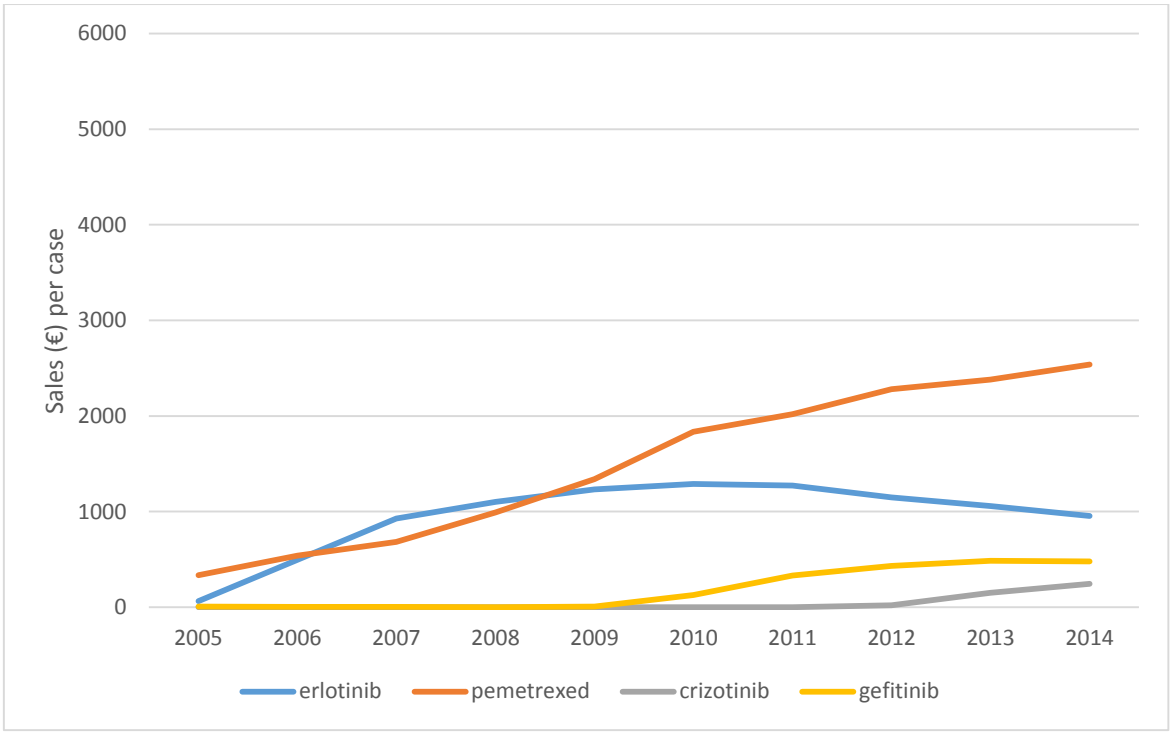


FIGURE 30. UPTAKE OF DRUGS IN LUNG CANCER EXPRESSED AS € PER CASE OF DEATH FROM LUNG CANCER – ALL COUNTRIES

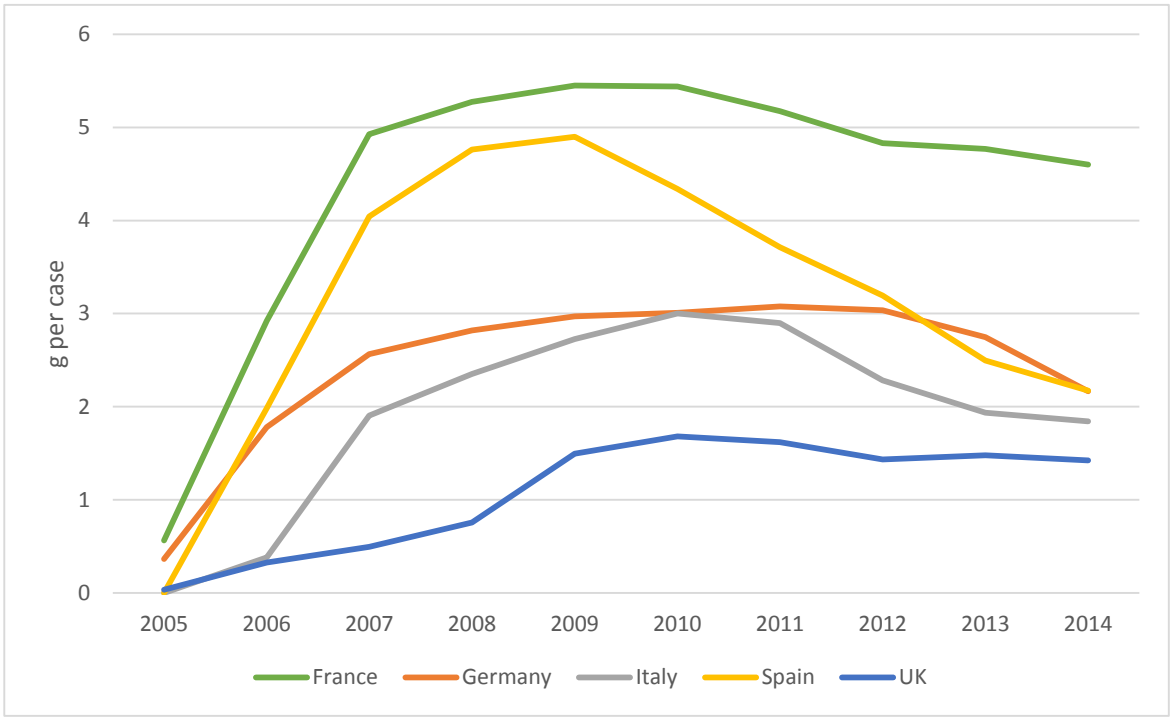


FIGURE 31. UPTAKE OF ERLOTINIB EXPRESSED AS G PER CASE IN THE FIVE LARGEST COUNTRIES

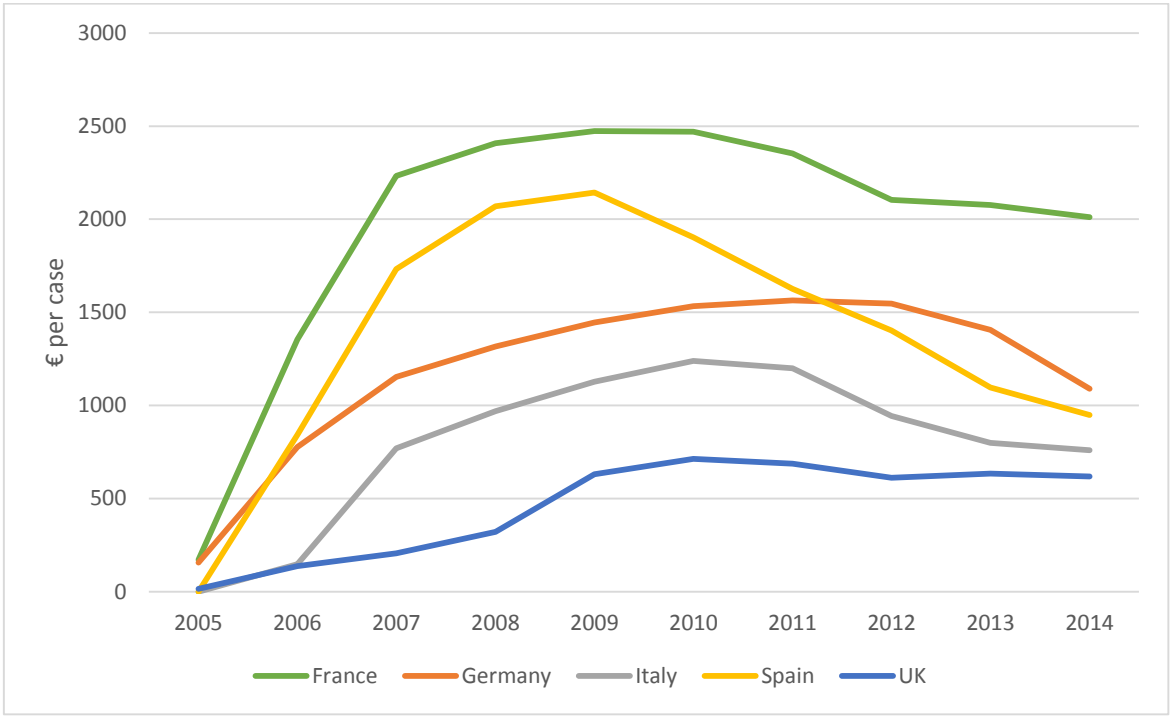


FIGURE 32. UPTAKE OF ERLOTINIB EXPRESSED AS € PER CASE IN THE FIVE LARGEST COUNTRIES

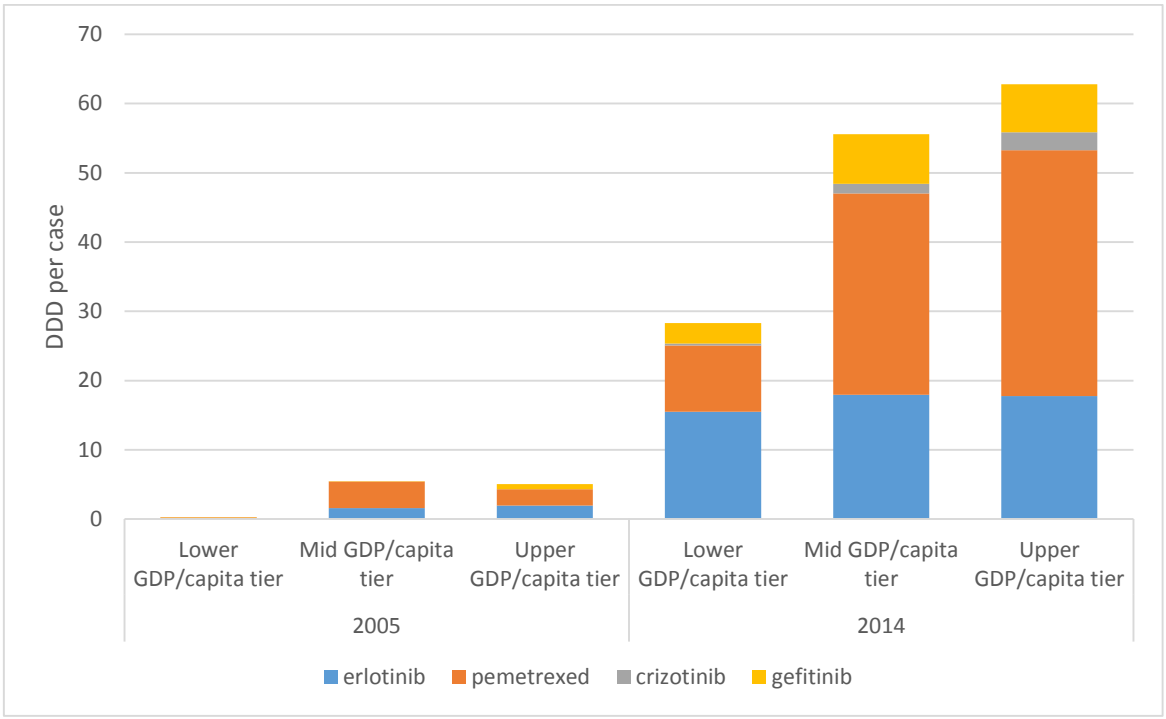


FIGURE 33. COMPARISON OF UPTAKE OF LUNG CANCER DRUGS BETWEEN GROUPS OF COUNTRIES (DEFINED BY GDP/PER CAPITA)

The income gradient is very clear when considering the uptake of pemetrexed, crizotinib and gefitinib while erlotinib seems to be used equally across the three groups of countries. There is considerable variation between the groups, with Portugal and Slovakia being among the highest users of newer drugs overall, together with France and Switzerland.

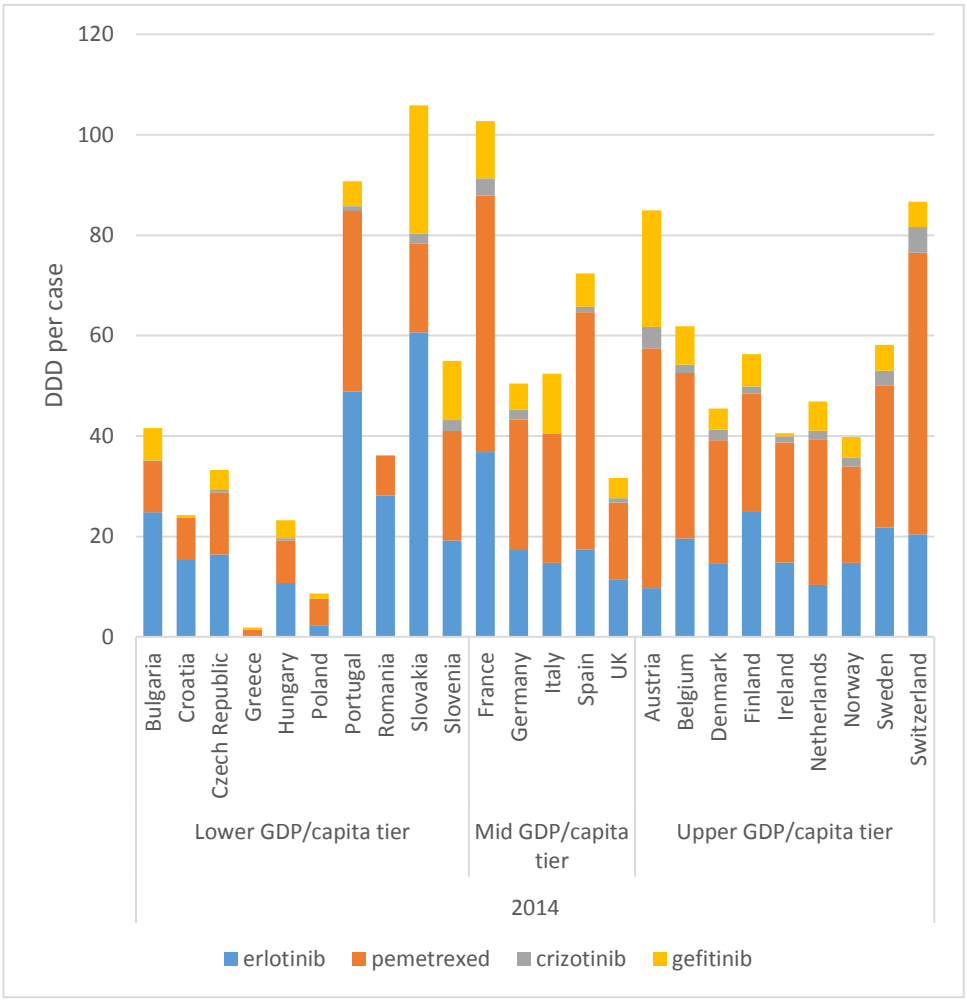


FIGURE 34. USE OF LUNG CANCER DRUGS IN 2014

3.7.5 Malignant melanoma

Metastatic malignant melanoma was for long considered a disease with a very poor outcome. Chemotherapy had only limited effects in controlling the disease with no major impact on overall survival. Interferons played a minor role in the metastatic, as well as in the adjuvant setting, however the effects were limited and the toxicity profile troublesome. Experimental immunotherapy had been shown to impact outcome of the disease in selected patients, but these therapies could not be expanded to larger patient populations due to their complexity and costs.

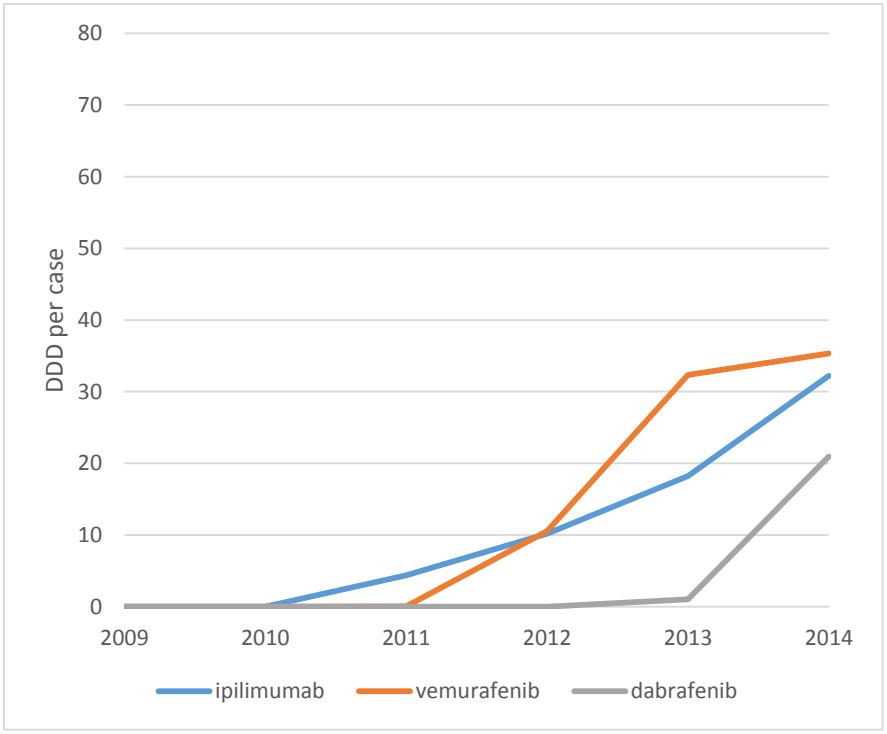


FIGURE 35. UPTAKE OF DRUGS IN MELANOMA EXPRESSED AS DDD PER CASE OF MELANOMA DEATH – ALL COUNTRIES

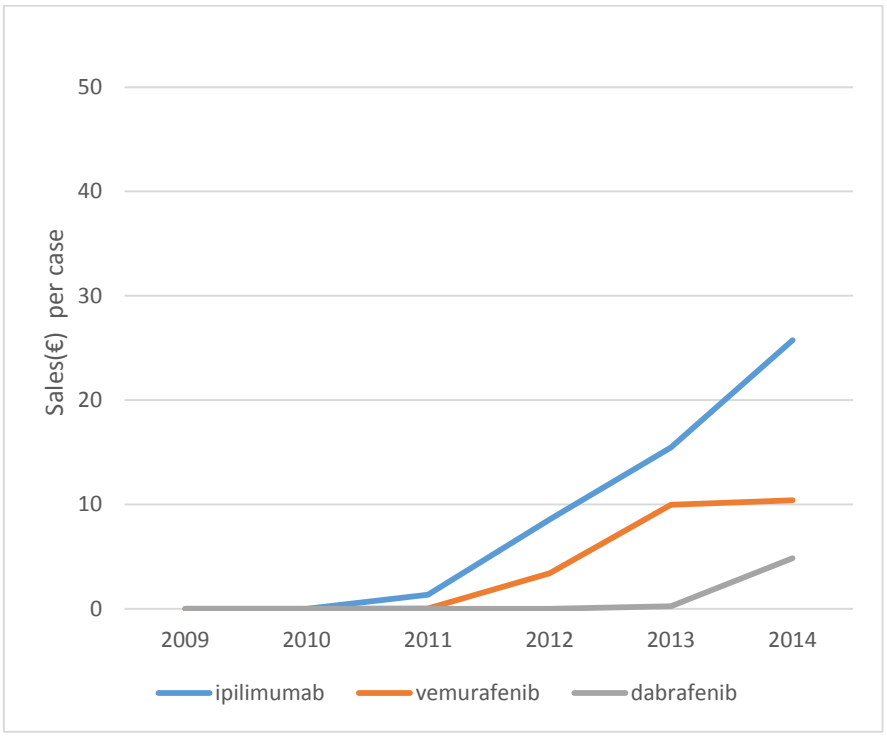


FIGURE 36. UPTAKE OF DRUGS IN MELANOMA EXPRESSED AS € PER CASE OF MELANOMA DEATH – ALL COUNTRIES

2010-2011 marked a revolution in the treatment of metastatic malignant melanoma. Two new drugs (initially vemurafenib and later dabrafenib) were introduced in BRAF mutated tumours, with 50-80% tumour regression. Many of these responses were short-lasting, still in a certain proportion of patients long term tumour control was achieved.

Ipilimumab was the first immune-oncology drug to be introduced. These drugs acts on the CTLA-4 receptor blocking the natural immunological response to tumours. The drugs induces relatively low up-front anti-tumour activity, in fact a number of patients initially have increased tumour growths i.e. progression in traditional terms, but later show a marked anti-tumour activity and long term disease stabilization (>20% at 7 years). A complicating factor with ipilimumab is the toxicity panorama. Ipilimumab may induce certain severe immune related side effects like colitis and pituitary dysfunction. Still ipilimumab represents the first breakthrough in the now very rapidly expanding area of immune-oncology.

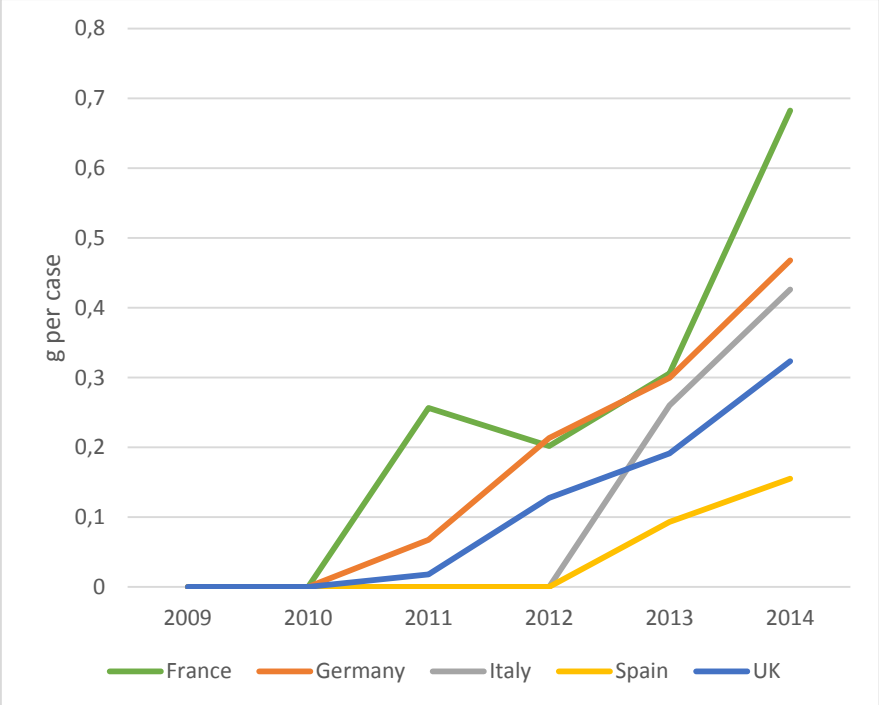


FIGURE 37. UPTAKE OF IPILIMUMAB EXPRESSED AS G PER CASE OF DEATH FROM MELANOMA IN THE FIVE LARGEST COUNTRIES

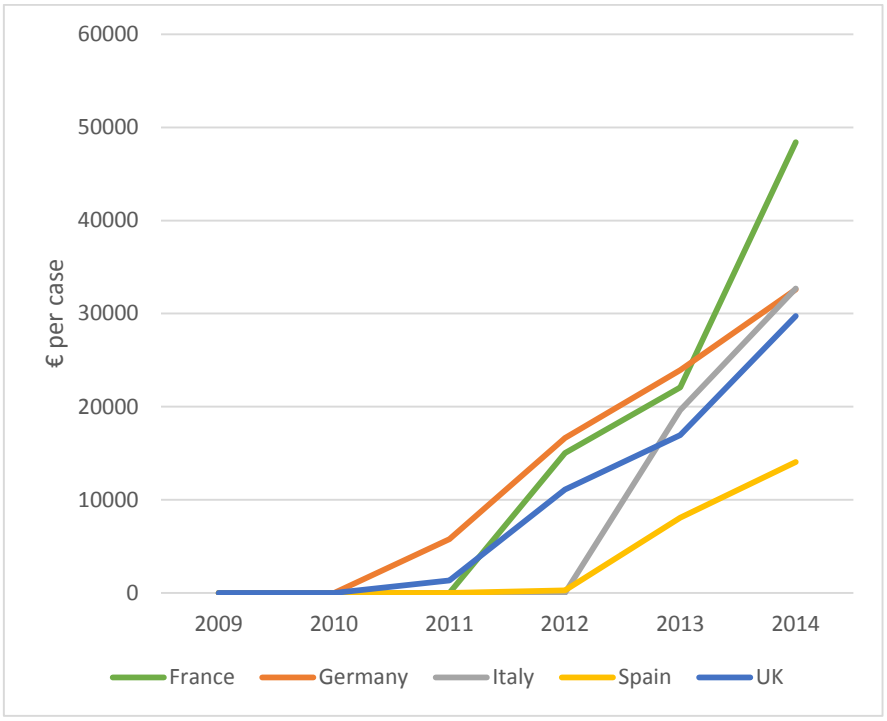


FIGURE 38. UPTAKE OF IPILIMUMAB EXPRESSED AS € PER CASE OF DEATH FROM MELANOMA IN THE FIVE LARGEST COUNTRIES

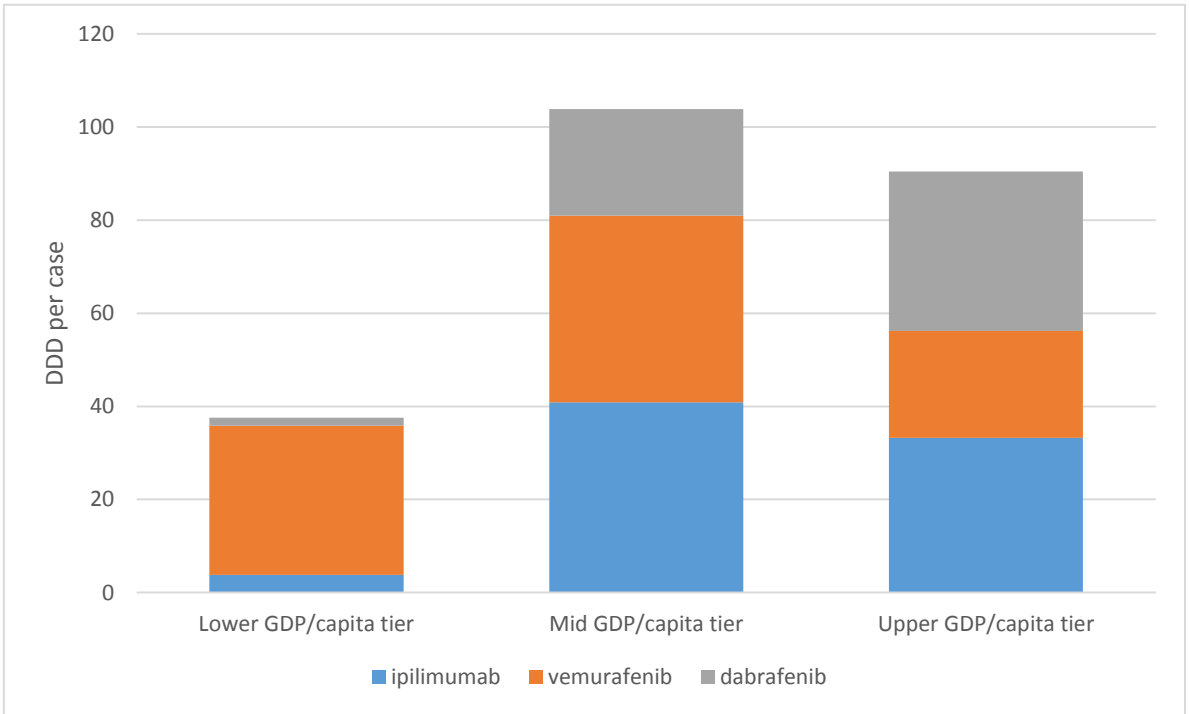


FIGURE 39. COMPARISON OF UPTAKE OF MELANOMA DRUGS BETWEEN GROUPS OF COUNTRIES (DEFINED BY GDP/PER CAPITA) IN 2014

In the treatment of metastatic malignant melanoma a somewhat surprising finding is observed in that the Mid GDP/ capita tier has significantly higher sales than the Upper GDP/ capita tier. This is driven primarily by high usage in France, and could be linked to the fact that more patients are referred to large Comprehensive Cancer Centers thus having access to front line treatment of melanoma at an earlier state than if referred to regular cancer centers.

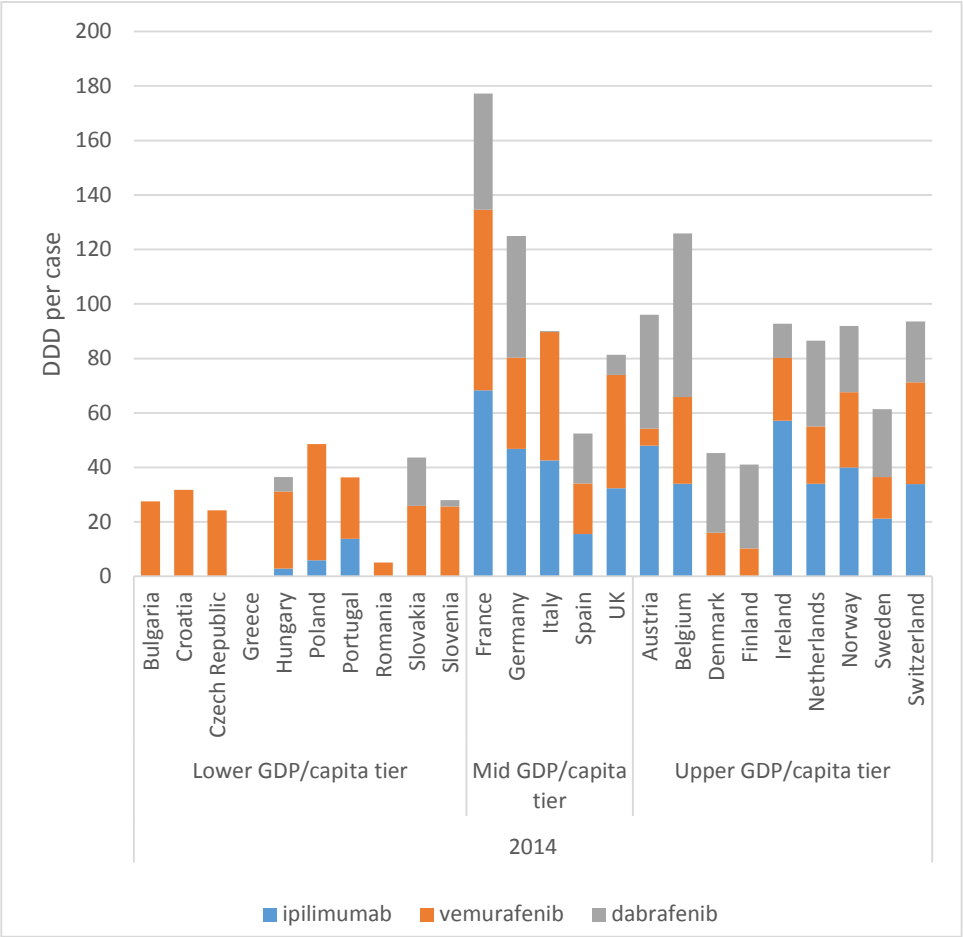


FIGURE 40. USE OF MELANOMA DRUGS IN 2014

3.7.6 Multiple myeloma

Multiple myeloma still remains an incurable disease in most patients. However, major advances have been seen in the treatment with the introduction of new drugs that both induce disease control for long periods of time, but also extend survival.

Bortezomib represents the first drug introduced in the new era of treatment of multiple myeloma. Thalidomide and later lenalidomide have become other important cornerstones in the treatment additions. At present we see a number of new drugs being developed and introduced in multiple myeloma treatment, thus this area being one of the most research intensive in cancer drug development.

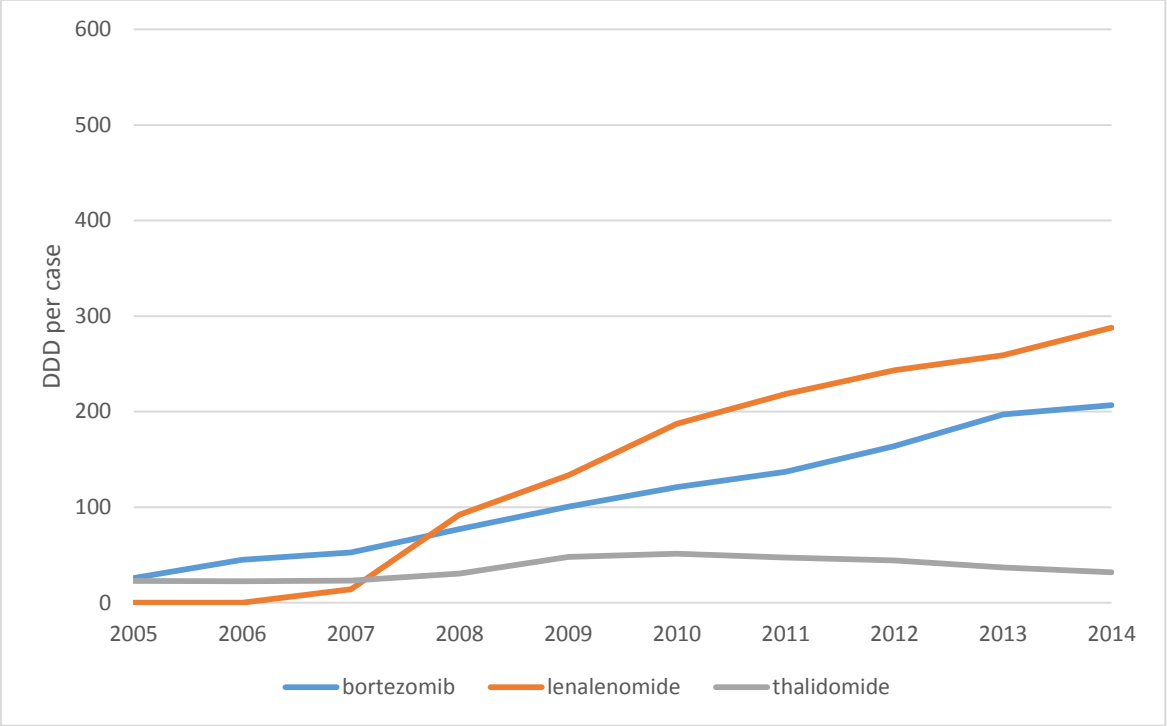


FIGURE 41. UPTAKE OF DRUGS IN MYELOMA EXPRESSED AS DDD PER CASE OF MYELOMA DEATH– ALL COUNTRIES

The introduction of bortezomib in 2004 and the old, previously withdrawn drug thalidomide formally approved in 2008, for the treatment of multiple myeloma represents a major shift in the treatment of this disease. Lenalidomide introduced in 2007, a further development of thalidomide, with less toxicity has now together with bortezomib become standard of care in the treatment of multiple myeloma.

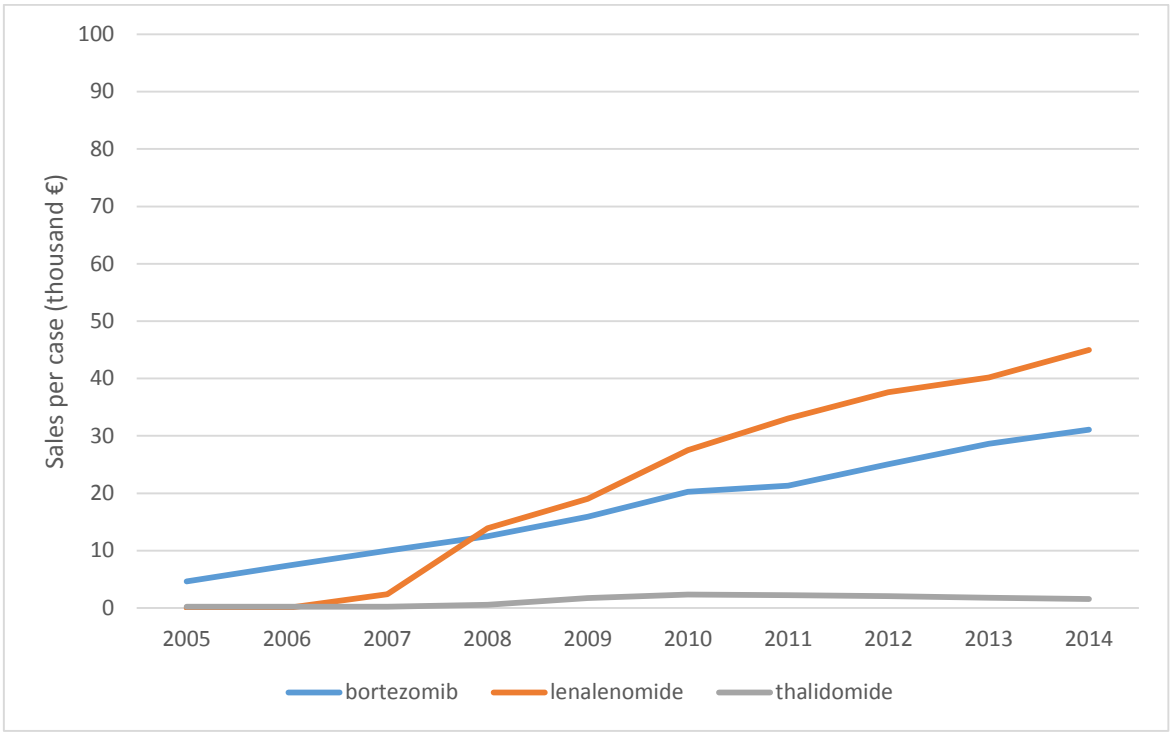


FIGURE 42. UPTAKE OF DRUGS IN MYELOMA EXPRESSED AS € PER CASE OF MYELOMA DEATH– ALL COUNTRIES

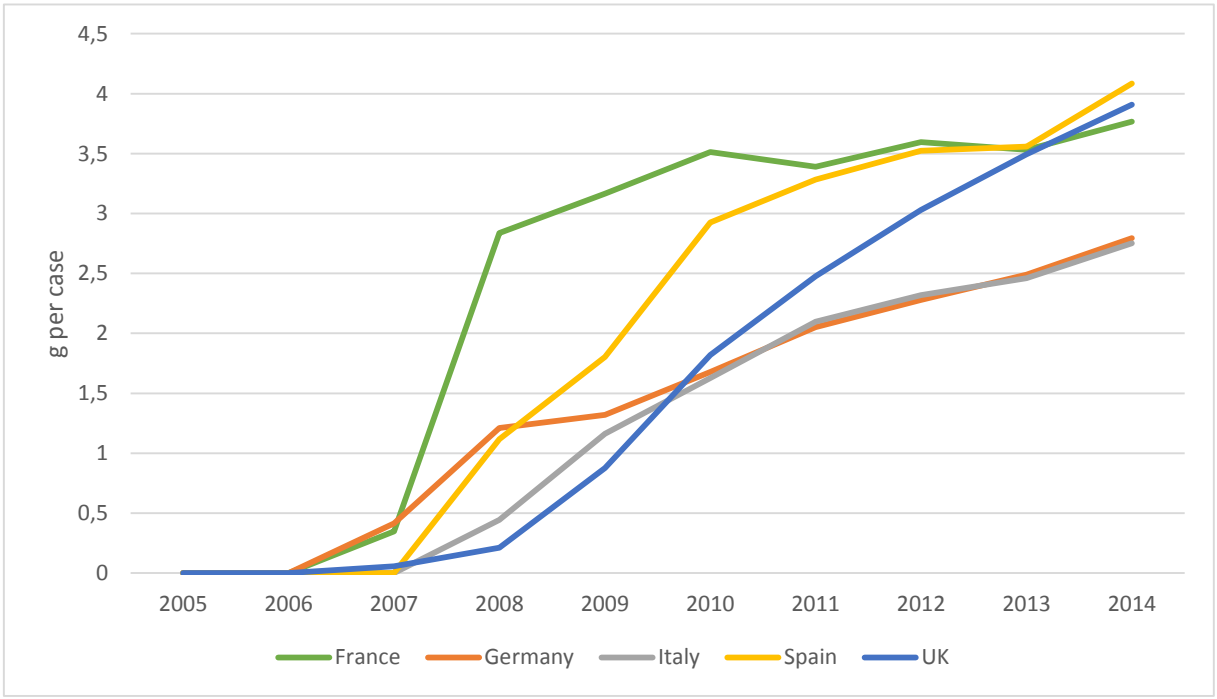


FIGURE 43. UPTAKE OF LENALIDOMIDE EXPRESSED AS G PER CASE IN THE FIVE LARGEST COUNTRIES

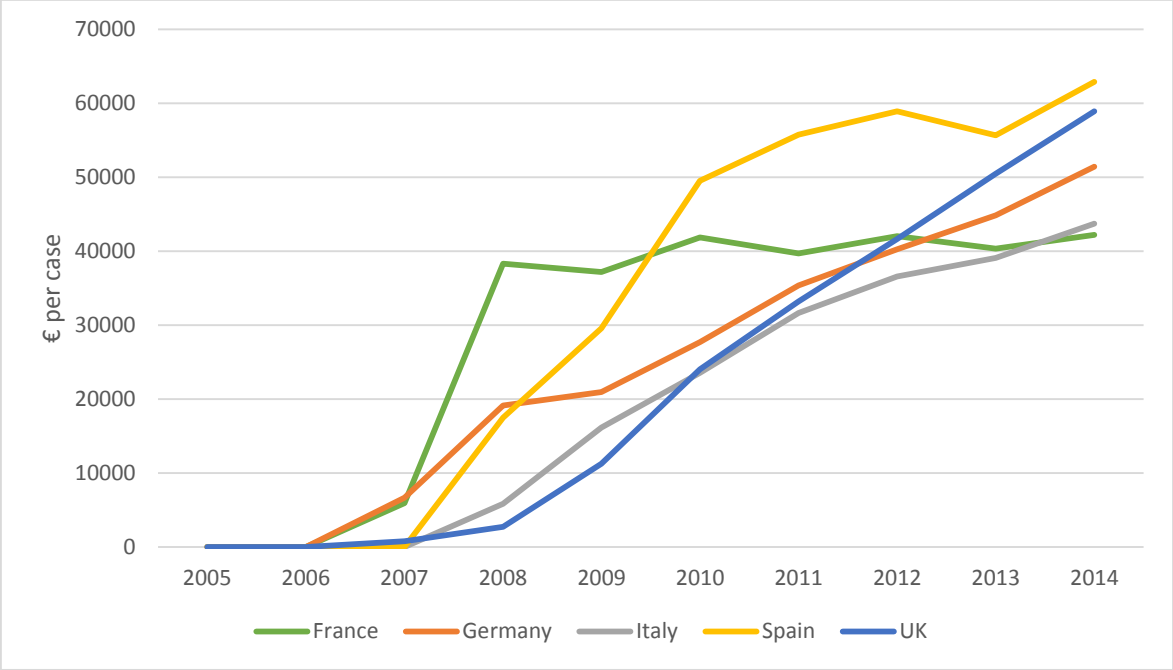


FIGURE 44. UPTAKE OF LENALIDOMIDE EXPRESSED AS € PER CASE IN THE FIVE LARGEST COUNTRIES

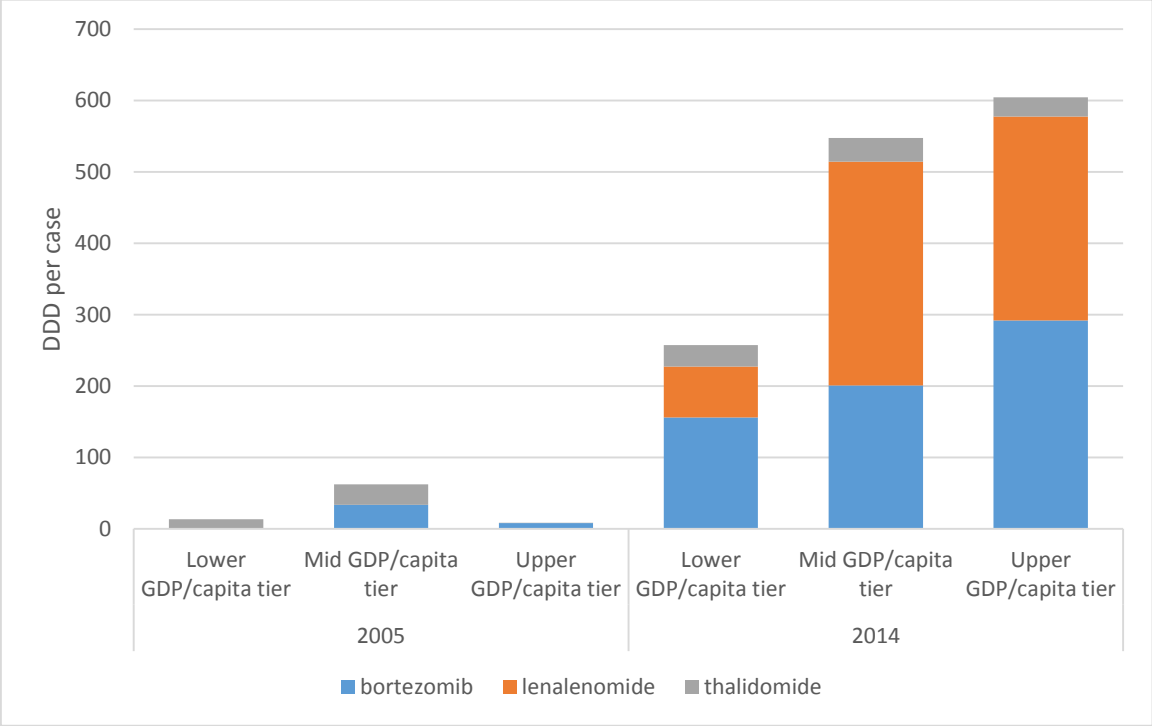


FIGURE 45. COMPARISON OF UPTAKE OF MYELOMA DRUGS BETWEEN GROUPS OF COUNTRIES (DEFINED BY GDP/PER CAPITA)

The mid- and high income groups show similar average use, while the lower income group uses less than half the amount of drug per case. The variation between countries is substantial, both in absolute terms and in which drugs are being used with Ireland standing out with high usage. Denmark in contrast uses very small amount of drugs, on par with Poland.

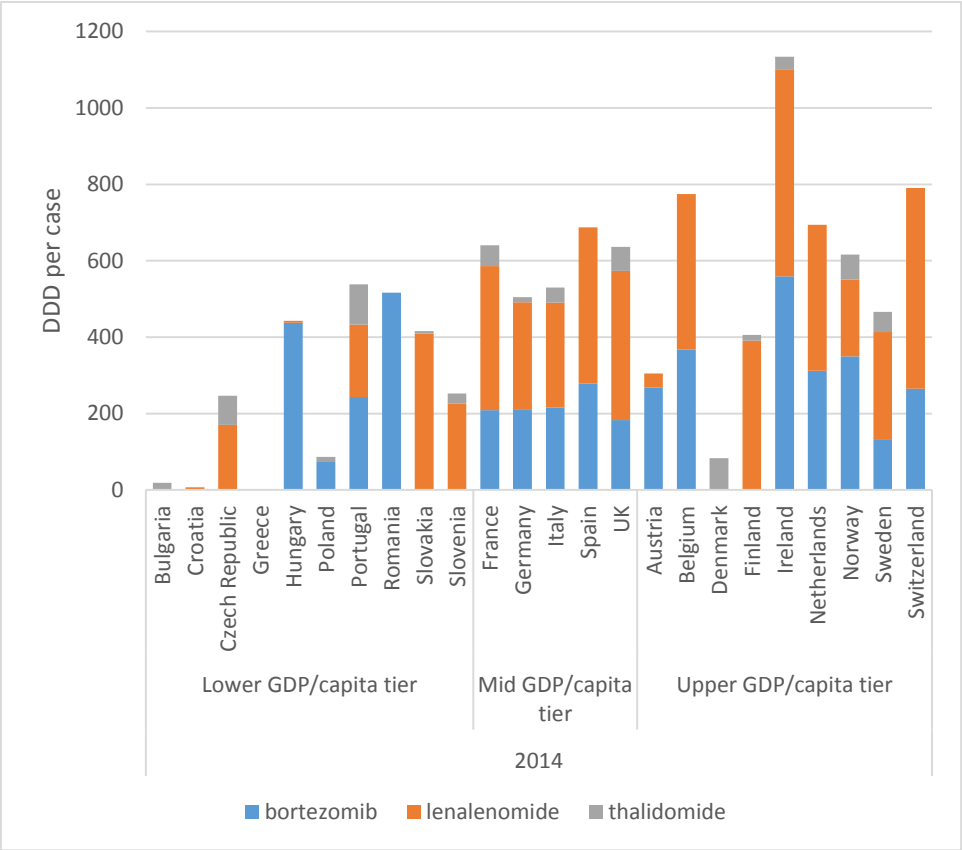


FIGURE 46. USE OF MYELOMA DRUGS IN 2014

3.7.7 Taxanes

Paclitxel (Taxol) and docetaxel (Taxotere) were both introduced and went out of patent during the period we are covering in this report. Paclitaxel was introduced in 1992 and docetaxel in 1995, and the patent expired in 2003 and 2010 respectively. Abraxane, a protein-bound injectable form of paclitaxel was introduced in 2008. While initially indicated for treatment of breast cancer, the taxanes were later used to treat also treat ovarian, lung, pancreatic and other cancers. We will thus in this section look not on uptake and use for a specific type of cancer but focus on the class of drugs called taxanes.[25]

[25] We will not include cabazitaxel (Jevtana) which was introduced in 2011 for treatment of prostate cancer.

Figure 47 shows the total sales in volume (kg) and value for the period 1995-2014 for the countries included in our study.

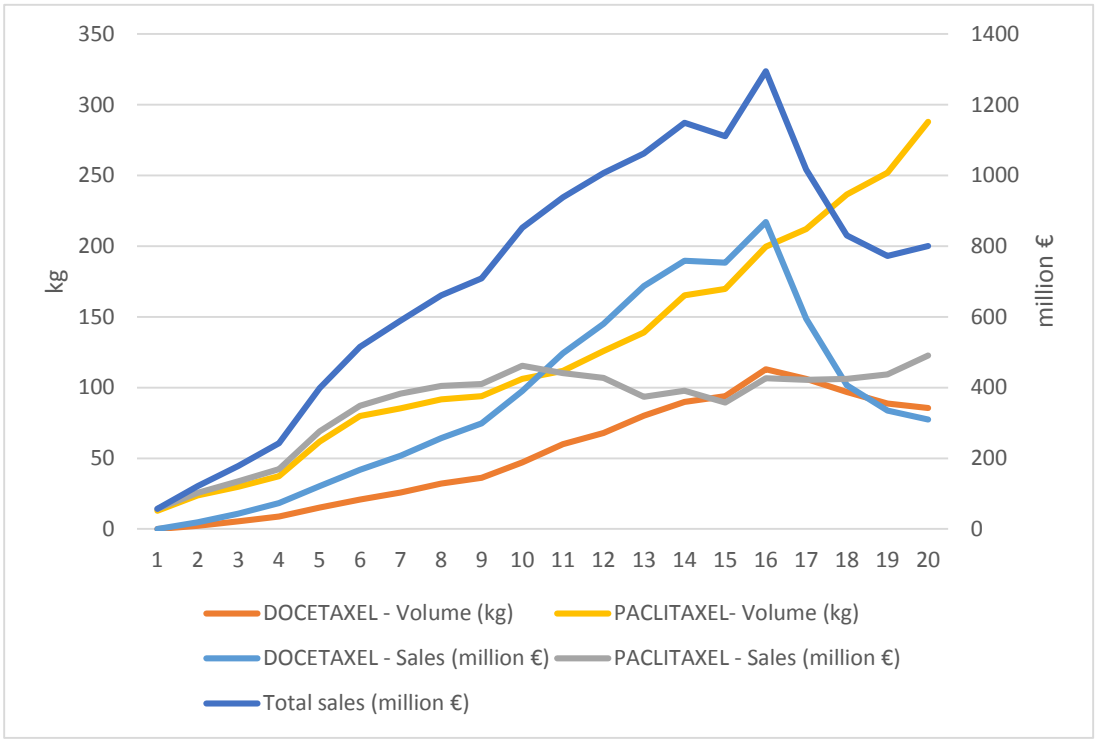


FIGURE 47. USE OF TAXANES IN EU + NORWAY AND SWITZERRLAND

For paclitaxel there is a continuous increase in volume used for the whole period. For docetaxel the continuous increase is broken in 2010, which may be related to the introduction of cabazitaxel and other drugs for treatment of prostate cancer. The reduction in use is also related to the time for patent expiration. After patent expiration, total sales have been reduced from 1300 to 800 million euro annually. For paclitaxel, the total sales in value have been roughly constant since the expiration of the patent in 2003, which may be explained by the introduction of abraxane in 2008.

Figure 48 shows the implicit price, value divided by volume for the two drugs respectively. This is based on list prices and does not take any negotiated discounts into consideration.

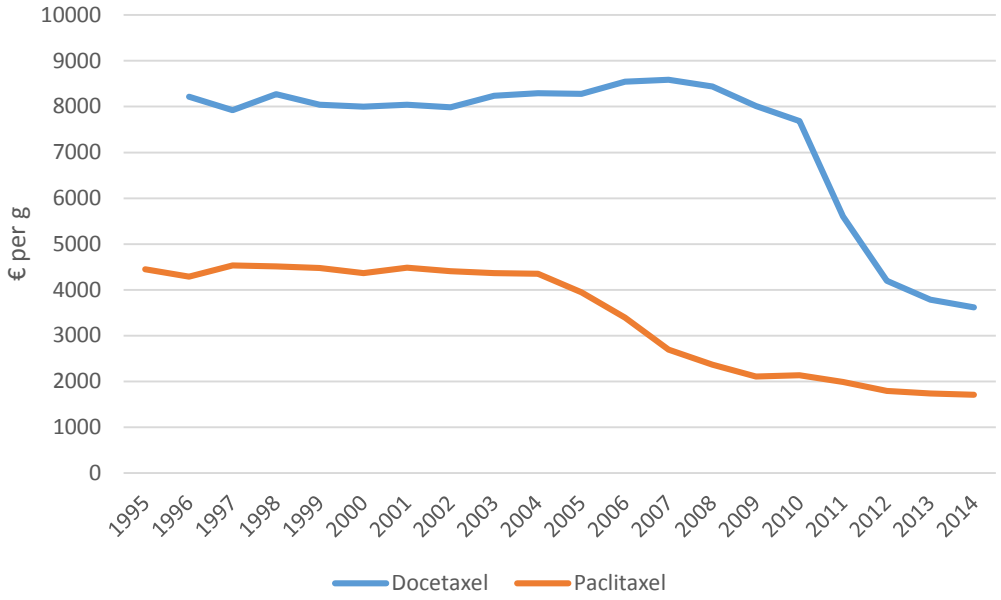


FIGURE 48. IMPLICIT PRICE OF THE TAXANES

The implicit price reveals that docetaxel is about twice as potent as paclitaxel, but taking this into account, the treatment outcome is similar when compared milligram per milligram. Docetaxel shows a more steep price reduction after patent expiration than paclitaxel.

Figure 49 and 50 shows the use of paclitaxel and docetaxel in gram per 100 000 population 1995-2014 in the ”Big 5”.

There are great variations at different time periods. Initially the uptake and use was very similar in Germany, Italy and France. According to data, sale in Spain was not started until 1998. This is probably due to lack of reporting in the statistics, since Spain after that has had the highest use. The use in UK has consistently been lower than in the other countries, and this persists into 2014, when the differences between the other countries is comparably small, indicating a certain consensus in use between these countries.

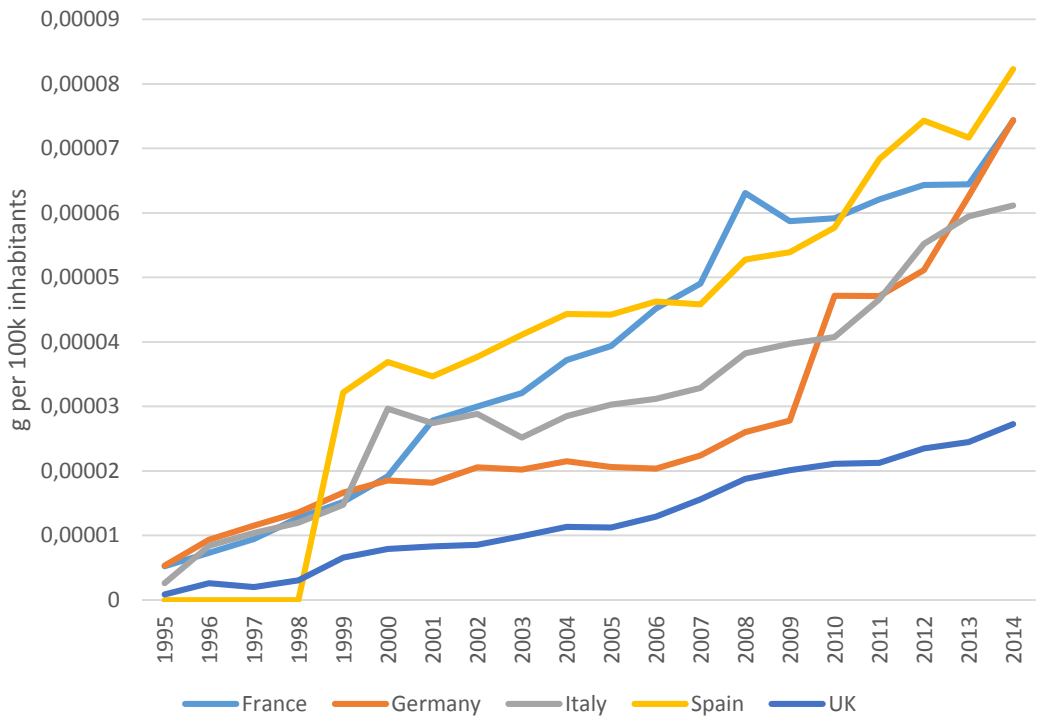


FIGURE 49.USE OF PACLITAXEL IN GRAM PER 100 000 POPULATION 1995-2014 IN FRANCE, GERMANY, ITALY, SPAIN AND UK.

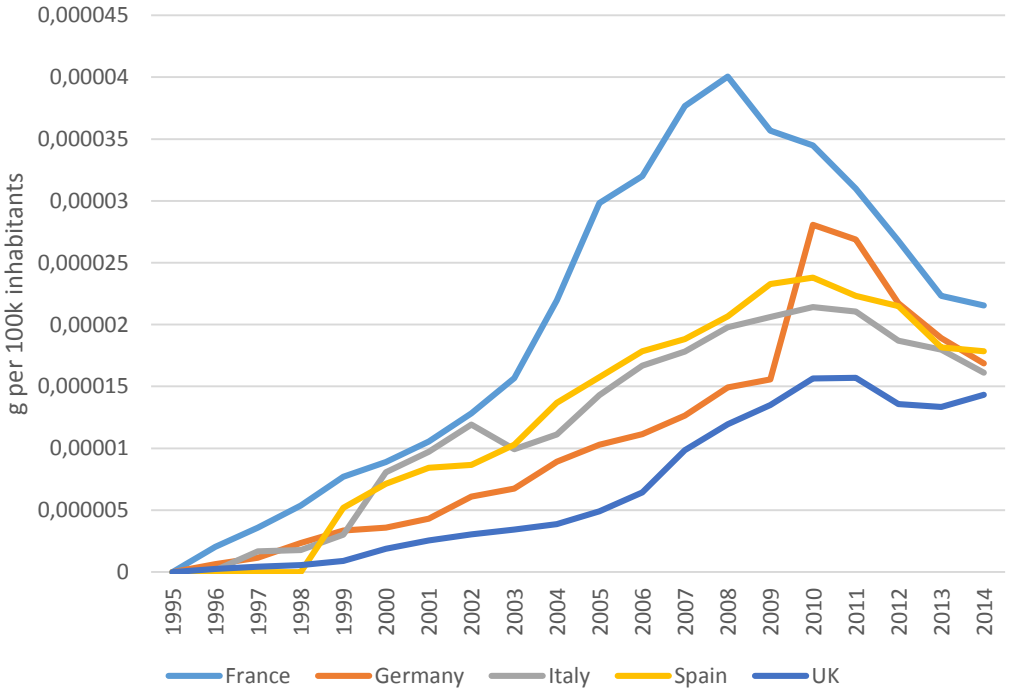


FIGURE 50.USE OF DOCETAXEL IN GRAM PER 100 000 POPULATION 1995-2014 IN FRANCE, GERMANY, ITALY, SPAIN AND UK.

For docetaxel there is the similar pattern as for paclitaxel in the lower use in UK. Remarkable is the rapid increase in use in France from 2002 until 2008, when usage started to decline. In 2004, the usage seems to have converged.

Figure 51 shows the combined sales, taking into account the difference in potency, i.e. the volume of docetaxel has been multiplied by a factor two, for all countries.

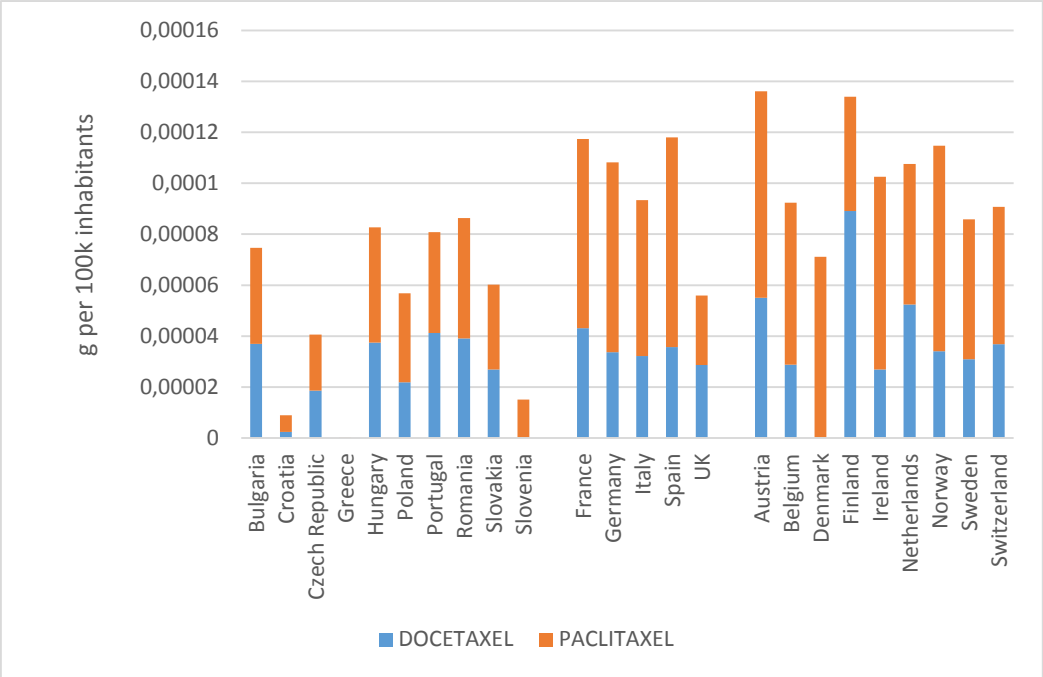


FIGURE 51. USE OF TAXANES IN 2014 (1 MG DOCETAXEL ASSUMED TO EQUAL 2 MG PACLITAXEL)

Figure 51 show that there is still some income gradient in the use of taxanes, despite that they are now generic and available at a relatively low price. Some data for the lower GDP per capita tier may be explained by underreporting. The low use in UK is most significant comparing the other countries.

3.8 Conclusions

Cancer drugs are fundamental in both curative and palliative cancer care. A number of new drugs have improved outcome of cancer over the last decades, both in the curative, adjuvant setting, as well as in the palliative situation.

Sales of cancer drugs in Europe was € 8.0 billion in 2005 and € 19.8 billion in 2014. Both in 2005 and 2014 seven countries (France, Germany, Italy, Netherlands, Spain, Switzerland, and the UK) accounted for around 80% of all sales, while only for 65% of the population. France was the biggest spender on cancer drugs in 2005 but was passed by Germany in 2014.

During the study period, there have been marked shifts among the top 10 selling drugs. Of the top 5 drugs in 2005, two are no longer among the top 10 in 2014 (docetaxel and oxaliplatin) and one (paclitaxel) is now at the bottom of the list. Trastuzumab has almost doubled its share as No1 on the list, and several new agents are listed, e.g. bevacizumab and lenalidomide. It's interesting to note that among the top 5 drugs in 2014, three have recently lost exclusivity or will in the near future (trastuzumab, rituximab and imatinib). The loss of exclusivity of small molecules has been associated with both expanded use and lower cost; it will be interesting to see how this dynamic plays out with the biologicals reaching the end of their patents.

The newest drugs (launched within the last three years) make up only 8% of the total sales, varying between 4% and 11% per year in different countries, with the higher share for richer countries.

Countries in Eastern and Southern Europe with low GDP per capita, have sales at about 1/3 of that in countries in Western Europe, both in 2005 and in 2014.

Access to cancer drugs, especially new innovative drugs, varies in Europe and is mainly depending on the countries' economic status, and this has not changed over time and is consistent with the results in our previous repor. There are also significant variations in access in different countries of similar economic power, indicating opportunities for improvement through policies aimed at evidence based and cost-effective cancer care.

Overall countries with low GDP, and also often more severely affected by the economic crises, have sales at 1/3 to 1/2 of the level observed in countries in the Mid and upper GDP /capita tier. There are exceptions, like CML, where sales/access is at a higher level.

We do not have information about the true costs of most new cancer drugs in individual health care systems. We are fully aware of that there are undisclosed discounts in many/most health care systems and these might also explain differences seen in access for certain

diagnosis for example in CML. It is also obvious that there is underreporting of sales for some drugs in some countries.

Utilization of drugs in certain indications is difficult to assess, as some cancer drugs are used in other indications outside of oncology. Also, many drugs are used in several oncological indications, and therefore, usage will be difficult to estimate within each indication.

When estimating access and utilization, the reference must be used with caution, as the different references (population, incidence, mortality, and prevalence) have their different pros and cons.

3.9 References chapter 3

1. Cabana, M.D., et al., Why don't physicians follow clinical practice guidelines? A framework for improvement. Jama, 1999. 282(15): p. 1458-65.
2. Lemmens, V.E., et al., Mixed adherence to clinical practice guidelines for colorectal cancer in the Southern Netherlands in 2002. Eur J Surg Oncol, 2006. 32(2): p. 168-73.
3. Ruddy, K., E. Mayer, and A. Partridge, Patient adherence and persistence with oral anticancer treatment. CA Cancer J Clin, 2009. 59(1): p. 56-66.
4. Jonsson, B. and N. Wilking, A global comparison regarding patient access to cancer drugs. Ann Oncol, 2007. 18 Suppl 3: p. iii1-iii77.
5. Wilking, N., et al., Oncologicals, in Drug Utilization Research: Methods and Applications, M. Elseviers, et al., Editors. 2016 (forthcoming), Wiley-Blackwell.
6. Fries, R., et al., Helsana Medikamentenstatistik 2013, Onkologie [Helsana Drug Statistics 2013, Oncology]. 2013, Helsana-Gruppe: Zürich.
7. Hofmarcher, T., Jönsson, B., Wilking, N., Access to high-quality oncology care across Europe. IHE Report. 2014:2, IHE: Lund.
8. Steven Morgan, Ruth Lopert,, Devon Greyson Toward a definition of pharmaceutical innovation. Open Medicine 2008;2(1):e4–7
9. ISPOR. France - Pharmaceuticals. October 23, 2015]; Available from: http://www.ispor.org/htaroadmaps/france.asp.
10. Opticom International Research AB, Skillnader i användning av innovativa läkemedel - En internationell jämförande studie på uppdrag av LIF. 2013.
11. Richards, M., Extent and causes of international variations in drug usage - A report for the Secretary of State for Health. 2010.
12. Annemans, L., Arickx, F., Belle, O., Boers, K., Bogaert, M., Callens, S., et al., A call to make valuable innovative medicines accessible in the European Union - Recommendations for a coordinated action to stimulate, measure and valorise pharmaceutical innovation - Background report for the ministerial conference "Innovation and Solidarity on Pharmaceuticals" 23-24 September 2010. 2010, Brussels: Belgian Presidency of the Council of the European Union.
13. Wilking, N., Jönsson, B., Högberg, D., Justo, N., Comparator Report on Patient Access to Cancer Drugs in Europe. 2009, Stockholm: Karolinska Institutet and Stockholm School of Economics.
14. European Medicines Agency, Approved medicines. Available from http://www.ema.europa.eu/ema/
15. IMS Health MIDAS database.
16. Steliarova-Foucher, E., et al. European Cancer Observatory: Cancer Incidence, Mortality, Prevalence and Survival in Europe. Version 1.0 (September 2012). 2012 August 15, 2015]; Available from: http://eco.iarc.fr.
17. WHO Collaborating Centre for Drug Statistics Methodology, ATC/DDD Index 2016. 2016.
18. Björkholm M, Ohm L, Eloranta S et al. Success Story of Targeted Therapy in Chronic Myeloid Leukemia: A Population-Based Study of Patients Diagnosed in Sweden From 1973 to 2008. JCO, 2011. 2514-20.

4 Policy issues for improved access to cancer medicines

Summary

- The relative burden of cancer is increasing over time, while the spending on cancer care is rather stable Spending on cancer drugs is increasing but this is balanced by reductions in spending on inpatient hospital care
- The increase in expenditure of cancer drugs is mainly explained by the introduction of a small number of very important drugs, which account for the majority of sales. Over time the drugs that have been driving this increase in expenditure have changed as older drugs going off patent are replaced with new innovations
- Lack of systematically collected data on spending in cancer care to provide detailed estimates of the health care spending on cancer in all European countries is lacking This is necessary to be able to develop rational policies for access.
- Low national income and health care spending per capita are major obstacles for access to new cancer drugs. New cancer drugs are traded at an international market, and while the absolute price per unit is similar, the relative price is higher for countries with lower income. Parallel trade and international reference pricing limits the opportunities for price discrimination.
- There is an argument for a differentiated pricing for all countries, not preventing patients' access. Such a two-part tariff is common in many markets, but it is difficult to make agreements at the European level on how this should be applied in practice for new cancer drugs.
  - A number of initiatives have been launched to assist in determining the value of new cancer drugs. Value as defined by ESMO-MCBS and actual uptake is connected, although not statistically significantly so. ESMO-MCBS also correlates with HTA assessments in France and Germany, but does not correlate well with assessments in Sweden.
- Early HTA advice and relative effectiveness assessments have been introduced as methods to make sure that these aspects are considered in the early development, and that relevant information for assessment of patient benefit and value is provided for payers at time of launch. However, assessment of value and cost-effectiveness is not a once only assessment at launch, but a process that should cover for the life cycle of the drugs and its different uses.
- Market access agreements can be seen both as a response to the uncertainty around effectiveness of new and potentially valuable cancer drugs, and as a response to demand for lower and more differentiated prices. A simple agreement on an undisclosed discount can both be seen as a correction for the uncertainty about projected effectiveness, and as an adjustment of the price (price discrimination) to improve cost-effectiveness and or affordability to gain a positive reimbursement decision in a specific market.
- Market access agreements are part of a trend towards more sophisticated strategies from public payers to commission health care from private providers. While this has been developed for commissioning of services, the general knowledge about how to handle these types of contracts can be transferred to designing new contracts for medicines as well. When medicines are often used in combination with diagnostics, and several

medicines may be used in the same treatment process, makes commissioning of drugs more like a service commission than a single product commissioning. Cancer is the obvious field for application of this new approach to buying and paying for new medicines

4.1 Burden of cancer and spending on cancer care

The review of the costs and burden of cancer in chapter 1 can be summarized in the following points:

- The burden of cancer in terms of mortality and DALY is far higher than the spending on cancer care
- The relative burden of cancer is increasing over time, while the spending on cancer care is rather stable
- Spending on cancer drugs is increasing but this is balanced by reductions in spending on inpatient hospital care
- Direct health care expenditures have been stable, but indirect costs due to premature mortality have been reduced over time
- There is insufficient granularity in currently available data to systematically follow the effects of changes in cancer care in detail

The low share for health expenditures in relation to burden of cancer is indicating that there is a lack of effective medicines and other treatments that can reduce the burden. This was also the case with ulcer disease, asthma and cardiovascular diseases before the introduction of effective drugs and other treatment. For example, the introduction of preventive measures and treatments reduced cardiovascular mortality by fifty per cent over the last decades. Today, the medicines for these diseases are not anymore on the top-list of best-selling drugs.

There have been important improvements in prevention and treatment of cancer over time, which is reflected by the reduction of life years lost among the working population, as well as a reduction in indirect costs due to loss of production. At the same time cancer incidence is increasing in older ages, partly due to reduction in the burden of cardiovascular disease, and the relative burden of cancer has increased over time.

Over the last twenty years over 100 new cancer drugs have been introduced. It is somewhat surprising that the share of cancer in total health care expenditures has not increased over time. There are several possible explanations for this. While the number of new, innovative drugs has increased, older drugs have gone off patent or been replaced, which has held back the increase in overall costs. A major factor is also the shift from inpatient care to ambulatory care of cancer during the last two decades, made possible by therapeutic advances.

The increase in expenditure of cancer drugs is mainly explained by the introduction of a small number of very important drugs, which account for the majority of sales. Over time the drugs that have been driving this increase in expenditure have changed as older drugs going off patent are replaced with new innovations. Another important observation is that cancer drugs introduced during the last five years, account for less than ten per cent of total cancer drug costs in a given year. Thus, most new cancer drugs have small sales, and a slow uptake.

While we have the overall picture on the total cost of cancer and how it relates to the burden of disease, the data available is far from being sufficient to provide detailed estimates of the health care spending on cancer in all European countries. This is necessary to be able to develop rational policies for access. More detailed studies are needed relating costs of different cancers, treatments and groups of patients. A comparison with the situation at the time of publication of the Karolinska report in 2005, no major improvement in data availability is seen of the cost of cancer over time, and between countries in Europe.

This should be complemented with studies of direct costs for cancer outside the health care system, which will be increasingly important with the growing cancer incidence among the elderly. Such studies also should be able to differentiate costs for cancer and co-morbidities.

While indirect costs related to premature mortality can be calculated rather precisely, data on indirect costs due to morbidity is almost absent. This is a problem when survival increases and cancer becomes more of a “chronic disease”. In a recently published study for Sweden, which has relatively good data, the loss of production due to morbidity accounted for 25 per cent of the total loss of production [1]. Such data is also important in order to trace improvements in treatment that reduces side effects and other burdens of treatment.

Better data on resources used is also important for studies on efficiency of spending on cancer in order to document value for money and potential for improved outcomes through cost-effective spending. When more and more evidence of effectiveness is generated from real world data, improvements in costing data must follow in order to provide better evidence of cost-effectiveness in clinical practice. For traditional modelling studies based on clinical trial data this was less of an issue.

4.2 Access and national health care spending

As shown in this and previous reports, low national income and health care spending per capita are major obstacles for access to new cancer drugs. New cancer drugs are traded at an international market, and while the absolute price per unit is similar (see section on access and price below), the relative price is higher for countries with lower income. Despite the fact that the share of drug expenditure as part of the total spending on cancer is higher in countries

with lower incomes, there is still an issue with access related to big differences in income and health care spending. While Europe has a common market for pharmaceuticals, there is no common health insurance to pay for these. Patients living in countries with lower levels of private and public health insurance have lower access. There is no sign of any change over the last ten years.

Less spending power makes a higher degree of prioritization necessary. It is rational to focus spending on those cancer drugs that offer most value, and are most cost-effective. In the next section we will look more in detail into the question about access and value. It is obvious that there is limited and slow access in low-income countries also for valuable new cancer drugs, as is shown in the diagram below for trastuzumab (breast cancer) and imatinib (leukaemia).

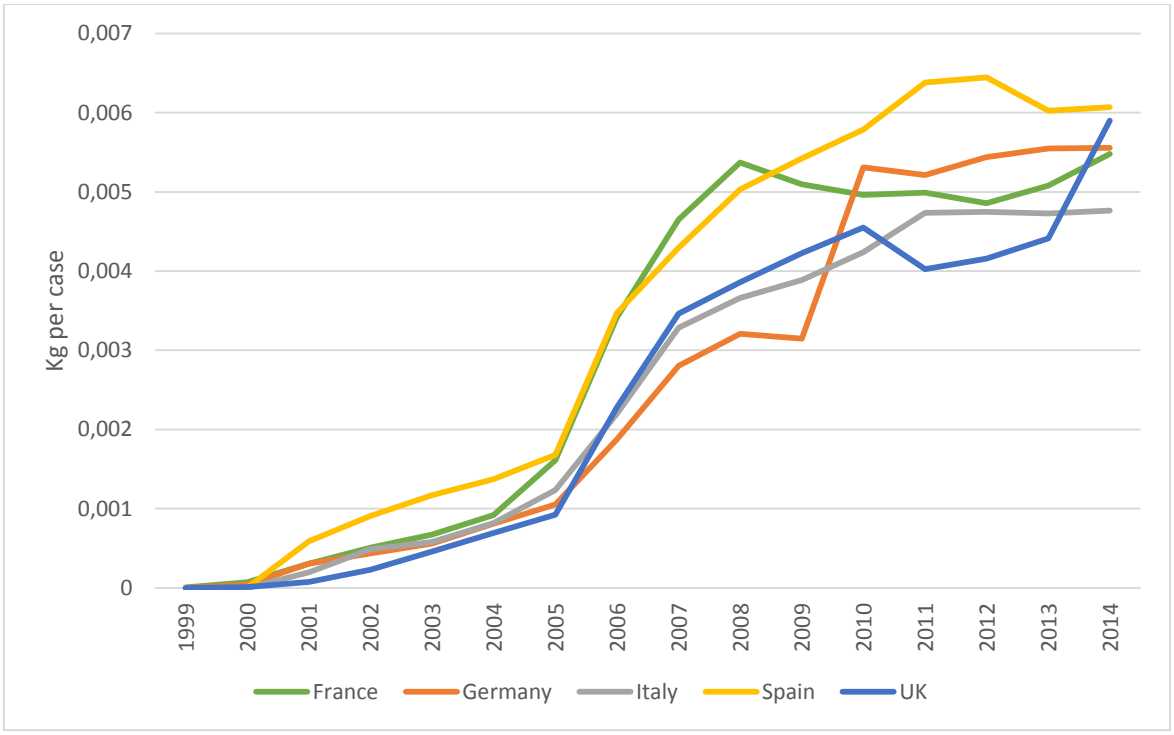


FIGURE 1. UPTAKE OF TRASTZUMAB OVER TIME IN THE "FIVE BIG" IN EUROPE (RELATED TO BREAST CANCER MORTALITY).

Initial rapid uptake in Spain and slow uptake in the UK. German uptake probably underestimated during the initial years due to potential underreporting of hospital sales.

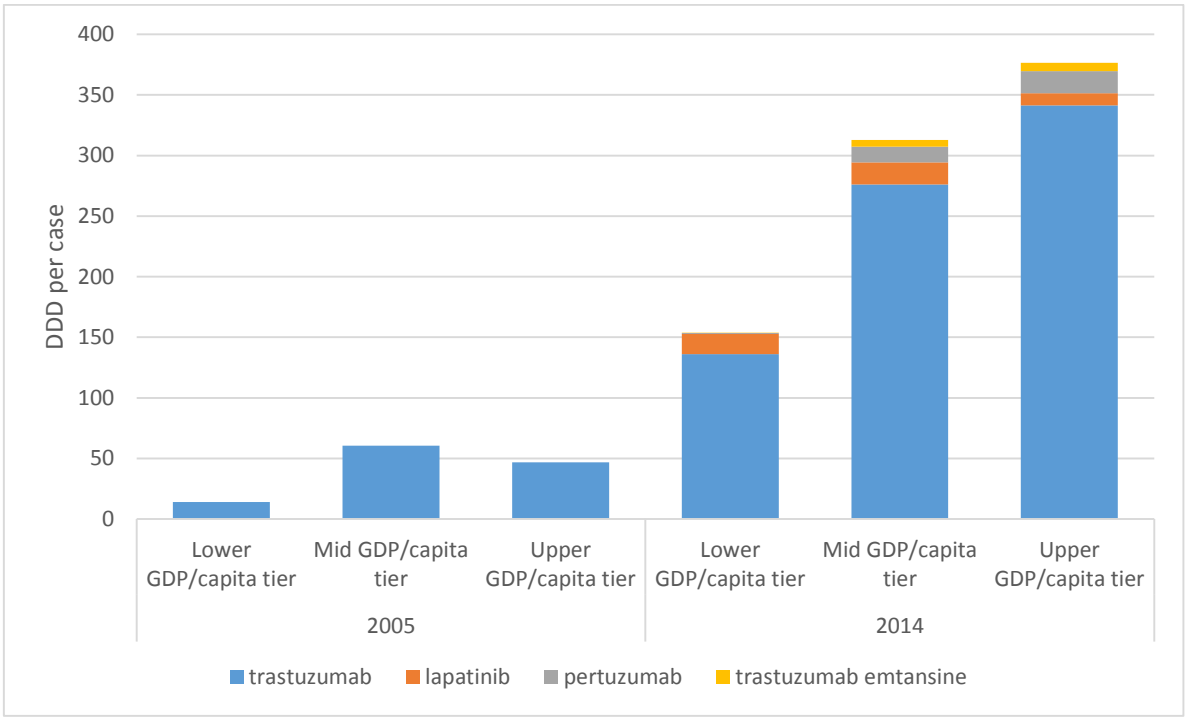


FIGURE 2. THE UPTAKE OF NEW BREAST CANCER DRUGS IS RELATED TO THE LEVEL OF INCOME IN DIFFERENT PARTS OF EUROPE.

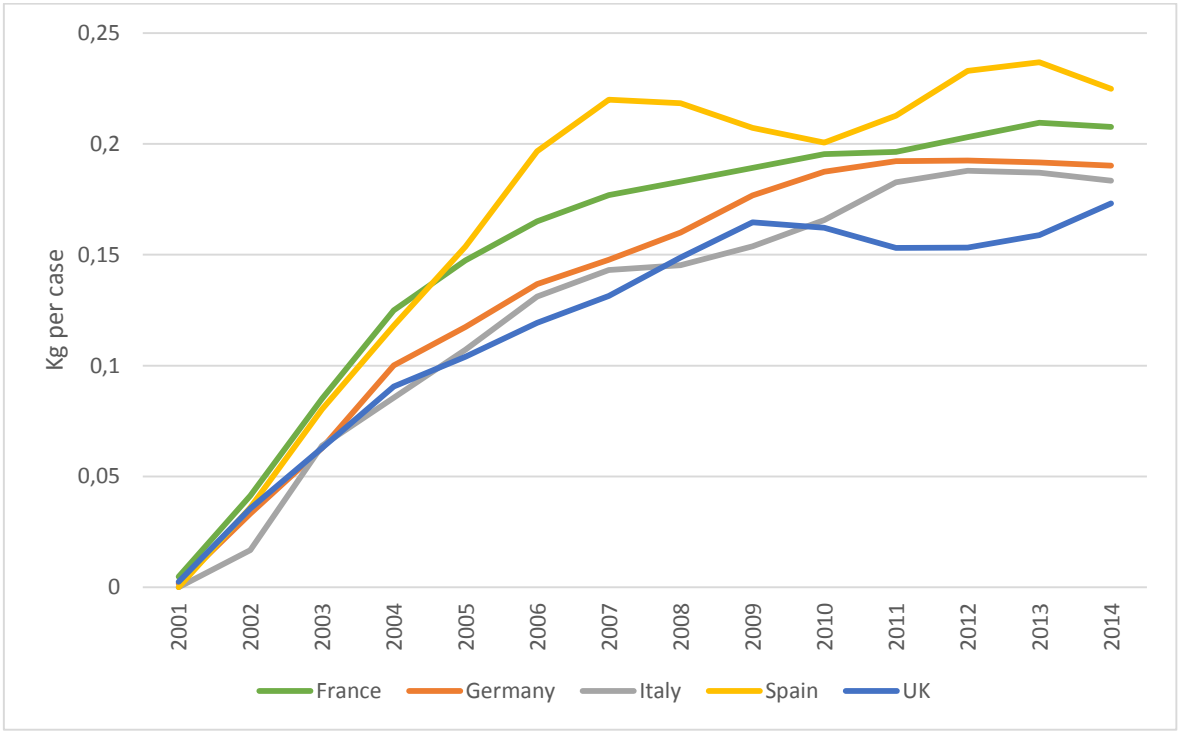


FIGURE 3. UPTAKE OF IMATINIB OVER TIME IN THE "FIVE BIG" IN EUROPE (IN RELATION TO LEUKEMIA MORTALITY).

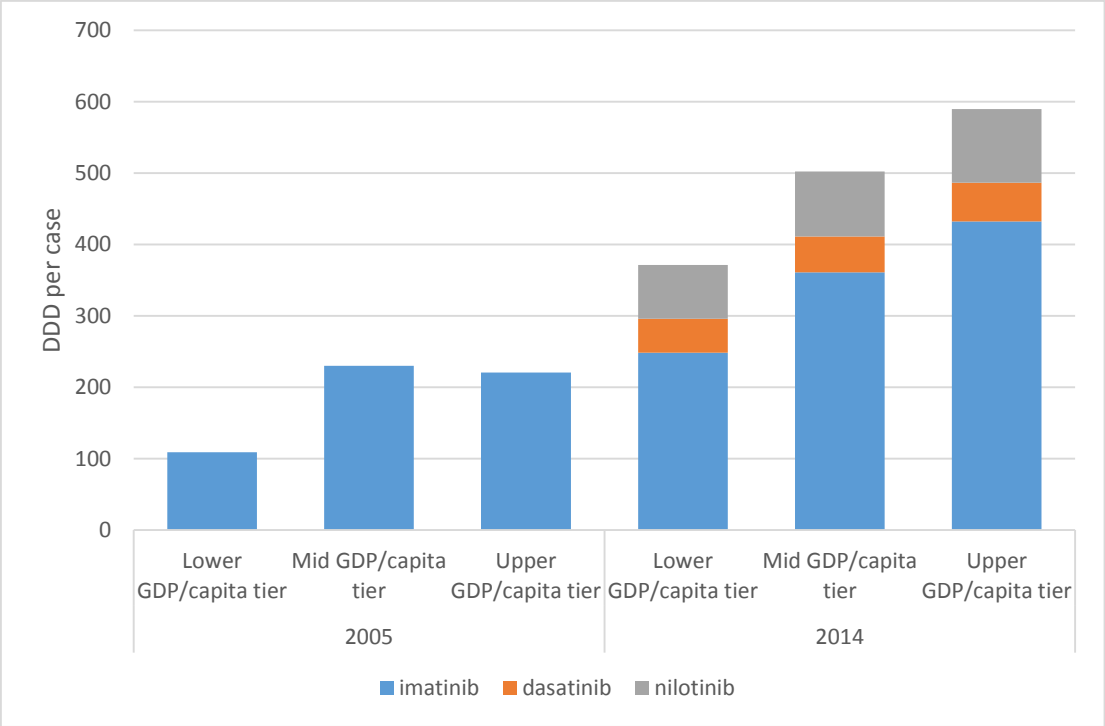


FIGURE 4. THE UPTAKE OF IMATINIB IS RELATED TO THE LEVEL OF INCOME IN DIFFERENT PARTS OF EUROPE, BUT TO A LESSER DEGREE THAN TRASTUZUMAB.

Affordability is an important factor for access, but as in the previous report we show that there are also significant variations in access between countries at similar income levels. This indicates that there are significant opportunities for a more evidence based uptake and use of new cancer drugs. A major limitation with the present data on the use of cancer drugs is that the use cannot be linked to indications and other relevant patient characteristics, and therefore it is impossible to make more precise comparisons of inefficiencies between countries to guide polices for improvement.

Several policy options have been discussed with the aim to reduce the variation in access between countries related to economic factors. The solution would be a more rapid economic growth in countries with lower incomes, but that can only be achieved in the longer term. Many proposed short-term solutions focus on the prices of new cancer drugs. We will discuss pricing issues more in detail in a later section. When considering differences between richer and poorer countries, it is important to recognize that while policies to lower price overall improve the affordability for all countries; it has no specific advantage for countries with lower incomes. You may argue the opposite, that the major beneficiaries of more price control would be the richer countries with the highest use. For a recent proposal on centralized price control in Europe, see Vogler et al [2].

Another alternative is differentiated pricing, where the countries with lower incomes pay a lower price, in the same way they did before the European common market, when price discrimination was the rule, based on commercial objectives [3, 4]. For differential pricing to be possible, it is necessary to prevent re-sale or parallel export and import as well as price referencing between countries. One way to achieve this, which is practiced to some extent for different reasons today, is to negotiate confidential access conditions, which lead to a lower net price. Another model is to change the payment model from a price per pack to a payment scheme price per treated patient, with or without linking to specific outcomes or other parameters in the contract.

It is more complicated to introduce an open and negotiated differentiated price model [2]. Should it just be linked to differences in income levels, or should it take into account efficiency aspects as well? Prices for new medicines should cover both sunk costs for R&D and give provide incentives for development of valuable new medicines, as well as costs for production and distribution. There is an argument for a differentiated pricing model for all countries, not preventing patients' access. Such a two-part tariff is common in many markets, but it is difficult to make agreements at the European level on how this should be applied in practice for new cancer drugs.

Since such a policy could be designed as a win-win for both industry and the health care systems, there are developments in that direction. While costs for production and distribution can rather easily be calculated and agreed on, the major problem is creating proper incentives for research and development. Using historical spending on research and development as a benchmark is neither practical nor relevant, since most drugs that come to the market never cover their costs [5]. It is the few most valuable drugs, with high sales, that pay for development of new drugs. Historical data on R&D also fails to take into account the value society places on new therapies.

Any two-part tariff or other payment system must therefore include some estimate of value. The problem is that value can only be determined from the use of the drug in clinical practice. New performance-based payment models are therefore dependent on data collection in clinical practice, to be used for analysis of value and payment (clinical effectiveness). This is complicated both for the pharmaceutical industry and for the health care system, and disruptive for the traditional model of financing research and development on the price per unit sold. But if successful, it can eliminate the price per pack as a factor for limiting access to cancer drugs between and within countries, at the same time as it creates incentives for use and reward innovations linked to the value of the drug. We will discuss more in detail in a later section the present state of the art in developing new pricing mechanisms.

4.3 Access and value

Recently a number of initiatives have been launched to assist in determining the value of new cancer drugs. This includes the ASCO Value Framework, the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS), the Memorial Sloan Kettering Cancer Center DrugAbacus and the National Comprehensive Cancer Network (NCCN) [6-9]. In all cases, the high price and questionable cost-effectiveness of new cancer drugs have been mentioned as one of the rationales for developing tools to assess the value of new drugs. All except the ESMO-MCBS have been developed in the US, probably due to formal assessment of cost-effectiveness playing a limited role in the US health care setting. However, the precise target audience for this information is unclear; patients, oncologists, payers and/or policy makers.

As can be seen in Table 1, although triggered by the same concern about price and costs, the specific objectives of the scales vary. Whereas the ASCO Value Framework is intended for use by oncologists in discussion with individual patients, ESMO-MCBS intends to give a single measure of the clinical benefit of a new drug for communication of its potential value without specifying the precise target audience for this information; patients, oncologists, payers and/or policy makers. DrugAbacus focus directly on prices, providing an estimate of a price based on how the user values different characteristics of the drug, which indicate that a primary use is for price comparisons and assessment of value for money. The NCCN Evidence Blocks finally graphically illustrates different components of the NCCN Guidelines. Despite the different objectives, they use a similar core set of information to meet them with some minor variations.

From the European perspective, the ESMO-MCBS may be the most relevant scale. In this section we provide a closer analysis of how the ESMO-MCBS relates to decision-making by HTA-bodies and to the uptake of new drugs.

TABLE 1. COMPARISON OF SOME CHARACTERISTICS OF RECENT VALUE FRAMEWORKS IN ONCOLOGY

	ASCO Value Framework [9]	ESMO-MCBS [7]	Sloan Kettering DrugAbacus [6]	NCCN Evidence Blocks [8]
Objective	To assist in facilitating shared decision making with patients about clinical benefits and costs.	To provide unbiased assessments of the magnitude of clinical benefit of anti-cancer interventions.	To allow the user to explore drug prices based on her preferences for different characteristics of the drug and the disease.	To provide a visual representation of five key measures that provide important information about specific recommendations contained within the NCCN guidelines.
Included components	Efficacy (OS, DFS, PFS or RR) Toxicity Palliation of symptoms Treatment free interval	Efficacy (OS, DFS, PFS, RR) Toxicity Quality of life	Efficacy (OS graded by degree of evidence, with PFS treated as OS but with a lower grade of evidence) Toxicity Novelty Development costs Rarity of disease Population burden of disease	Efficacy Safety Quality of evidence Consistency of evidence Affordability
Scoring	0-100 (adjuvant setting) 0-130 (advanced disease)	C – A (curative or adjuvant) 1 – 5 (non-curative)	Suggested price	1 – 5 for each component, no aggregated score.
Evidence base for comparison	Single trial	Single trial	FDA dossier	Systematic review

4.3.1 ESMO-MCBS and HTA

The ESMO-MCBS, like all other similar attempts to assess value, is based on efficacy and toxicity data from clinical trials. When applying ESMO-MCBS, therapies are first divided into curative and non-curative treatments. Within these categories, the therapies are assigned a classification based on pre-defined thresholds for the lower limits of the confidence interval of the reported hazard ratio and the absolute difference in treatment outcome compared to the minimum absolute gain considered beneficial. Different criteria apply to survival, disease free survival and progression free survival, with extra points given if the therapy has reduced toxicity or improves quality-of-life.

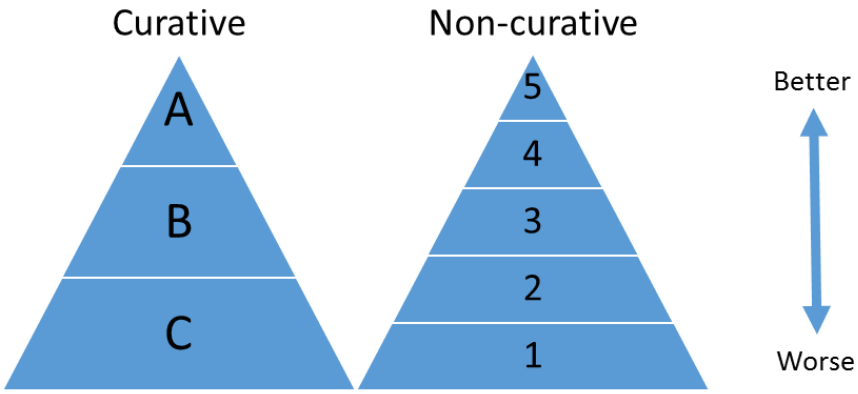
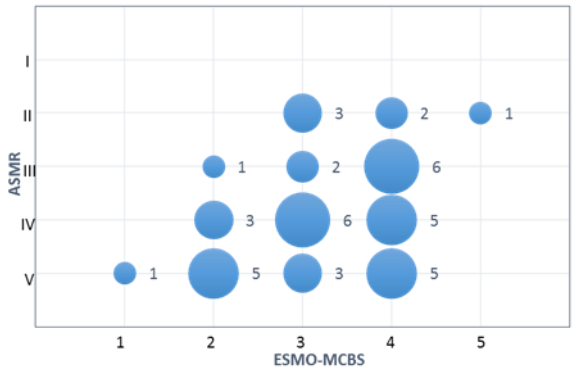


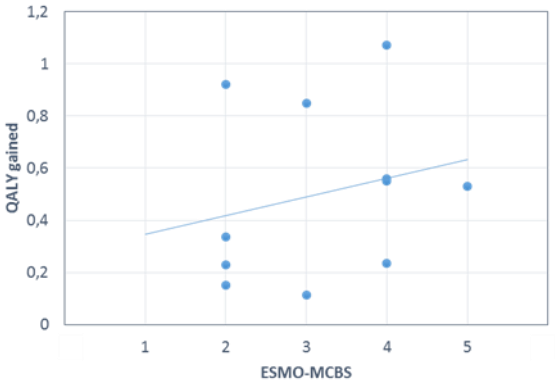
FIGURE 5. CLASSIFICATION ACCORDING TO THE ESMO-MCBS.

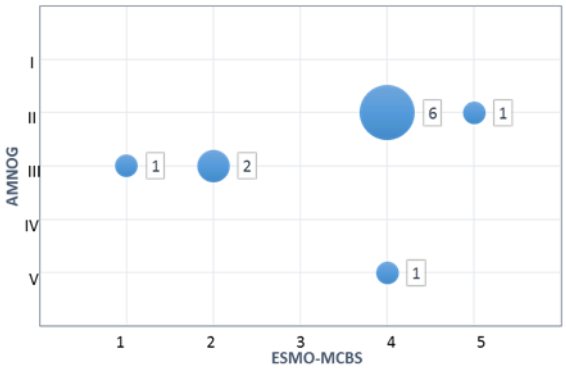
We investigated the correlation, for a selection of drugs based on data availability, between the ESMO-MCBS and the assessments made by three HTA agencies, using different criteria to determine value of drugs, where both an ESMO-MCBS value and a HTA assessment were available. The agencies included in the assessment were:

- The Transparency Committee of the National Authority for Health (HAS, France) measuring improvement in clinical added value (ASMR) [10].
- The Federal Joint Committee (G-BA, Germany), classifying additional clinical benefit in accordance to the AMNOG criteria [11].
- The Dental and Pharmaceutical benefits Board (TLV, Sweden), using Quality Adjusted Life-Years (QALY) gained as the preferred measure of value [12].

The agencies all use estimates of value in the decision process on reimbursement. HAS and G-BA uses it as an input in price negotiations while TLV uses it directly in the calculation of cost-effectiveness ratios to assess whether a drug can be considered cost-effective at a given price or not.







ESMO-MCBS compared to...	ρ	p
ASMR	-0.3779	0.01
QALY	0.2868	0.39
AMNOG	-0.6564	0.03

FIGURE 6. THE RELATIONSHIP BETWEEN ESMO-MCBS AND DECISION MAKING CRITERIA USED BY SELECTED HTA AGENCIES.

As can be seen in Figure 6 there seems to be a reasonable agreement between ESMO-MCBS and the AMNOG scores. Although there is a statistically significant correlation between the scale and ASMR scores overall, there is very little agreement between the two in the middle of the scale. The link between ESMO-MCBS and QALYs as estimated by TLV appears to be very weak. The analysis is hampered by the fact that there were a limited number of AMNOG scores and QALY estimates available for comparison. Many of the drugs were launched prior to the current German system was in place and TLV does not report QALYs in certain cases, for instance if a drug is considered equal to an existing therapy.

4.3.2 ESMO-MCBS and uptake

It is reasonable to assume that drugs being perceived as delivering high value would have a more rapid uptake, all else being equal. Does the concept of value as determined by the ESMO-MCBS scheme correlate with this "value as revealed by the market"? There were 17 drugs launched during the time period under study with an ESMO-MCBS score available from the publication by Cherny and colleagues [7]. As can be seen in Table 2, scores ranged

between 2 and 5 with the majority of drugs having a score of 4.[26] When scoring had been performed for more than one trial the first published one was used below.

TABLE 2. CHARACTERISTICS OF DRUGS INCLUDED IN THE ANALYSIS.

ESMO-MCBS	Drug	Indication	Assumed maximum share of cases[1]	Launch year
2	Cabizatexel	Prostate	25%	2011
	Eribulin	Breast	25%	2011
	Trabectedin	Ovarian	30%	2007
3	Axitinib	Renal	100%	2012
	Lapatinib	Breast	10%	2008
	Panitumumab	Colorectal	50%	2007
4	Afatinib	Lung	10%	2013
	Cetuximab	Colorectal	50%	2004
	Crizotinib	Lung	5%	2012
	Dabrafenib	Melanoma	50%	2013
	Gefitinib	Lung	20%	2009
	Ipilimumab	Melanoma	70%	2011
	Pemetrexed	Lung	40%	2004
	Pertuzumab	Breast	20%	2013
	Temsirolimus	Renal	5%	2007
	Vemurafenib	Melanoma	50%	2012
5	Trastuzumab emtansine	Breast	15%	2013

[1]This is the assumed proportion of cases of the specific cancer type that would be eligible for treatment with the given therapy.

The average EU-wide (plus Norway and Switzerland) sales per case of drugs with each score during the first three years, along with the average sales during the three-year period can be seen in Figure 7. Sales figures (at list prices) were based on data from the IMS MIDAS database. Cases were defined as the number of deaths in the indication for each drug, adjusted for the maximum proportion of these being candidates for treatment (see Table 2). Only one drug received a score of 5 (trastuzumab emtansine), and for this drug sales data was only available for one full year (it was launched late in the covered time period), making it difficult to draw conclusion about this specific group. For the remaining categories there appears to be a pattern with higher sales in group 4 in particular. It should be noted that group 2 and 3 contain only three drugs each.

[26] In addition, there was a drug receiving the classification A (imatinib), indicating use in the adjuvant setting or curative intent. As the size of this market is much larger by nature, this was omitted from the present analysis.

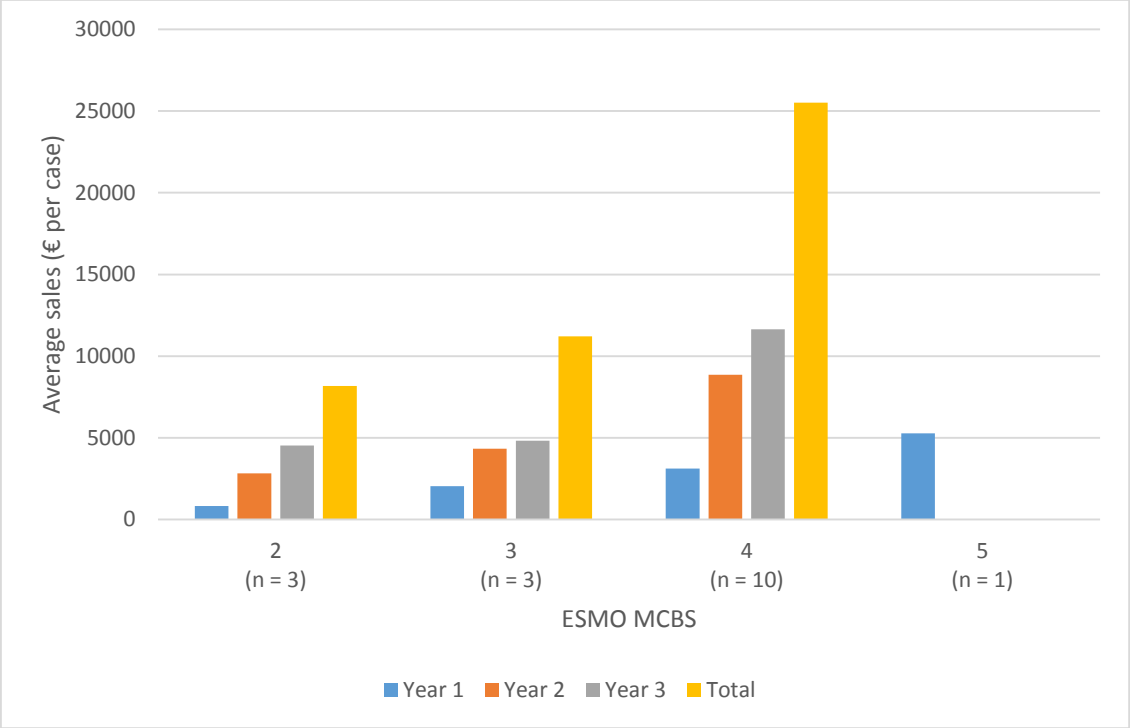


FIGURE 7. AVERAGE SALES PER CASE DURING EACH OF THE FIRST THREE YEARS AND AVERAGES TOTAL SALES DURING ALL THREE YEARS POST-LAUNCH.

To complicate the picture, there are large variations within category 4, as can be seen in Figure 8. In fact, this variation is so large that the observed difference between groups is not statistically significant in spite of the large numeric differences observed.

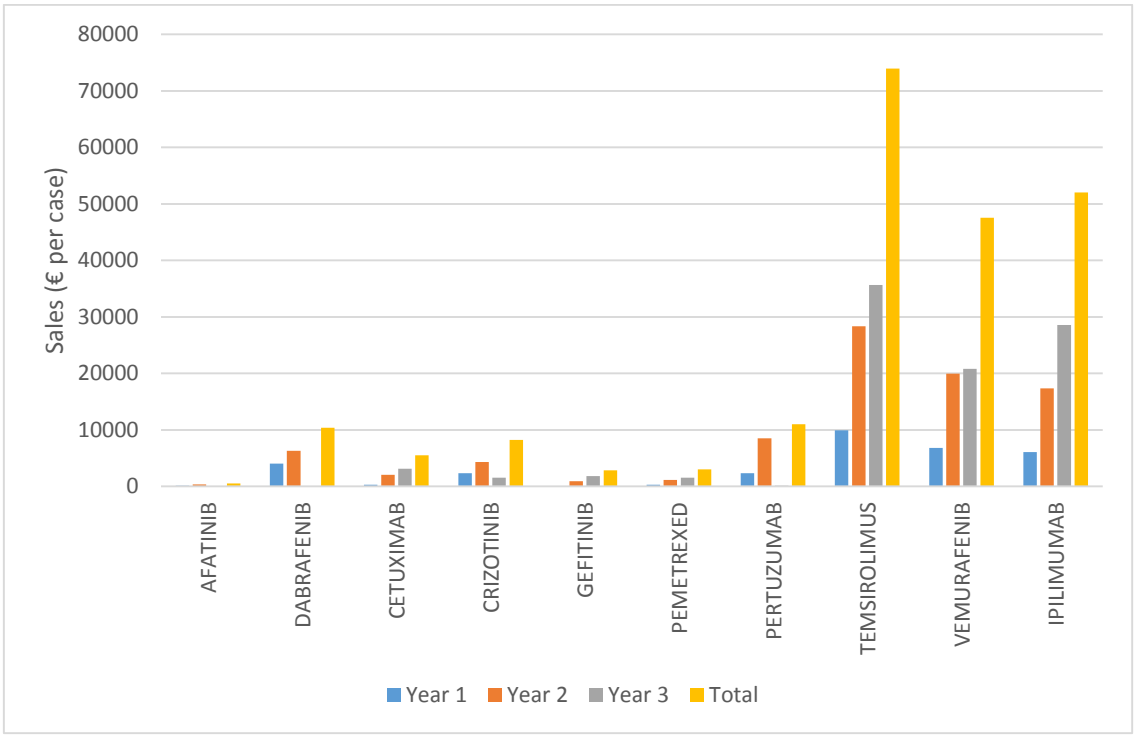


FIGURE 8. SALES PER CASE DURING EACH OF THE FIRST THREE YEARS AND AVERAGES TOTAL SALES DURING ALL THREE YEARS POST-LAUNCH FOR DRUGS WITH AN ESMO-MCBS SCORE OF 4.

4.3.3 Conclusions

The data presented here support the notion that value as defined by ESMO-MCBS and actual uptake is connected, although not statistically significant. ESMO-MCBS also correlates with HTA assessments in France and Germany, in particular with the German model, which have a strong focus on the clinical trial evidence. However, both these analyses indicate a potential shortcoming of the scale as it seems to have difficulties in differentiating between therapies that fall in the middle of the scale, specifically those that receive a score of 3 or 4. Although there is a correlation between results from HTA, the predictive power of the score is low. In France, a drug with a score of 4 is as likely to receive an ASMR of 4 or 5 as it is of being classified as 2 or 3. We can see a similar situation when looking at uptake of drug with a very large variation between drugs given a score 4. There is room for improvement of the scale to better discriminate between drugs.

A common theme for all the value frameworks with the exception of the NCCN Evidence Blocks is that it is unclear how they can or will be adapted to a situation where the evidence base is developing over time. The ASCO Value framework and ESMO-MCBS both are constructed with the analysis of one trial in mind (although it is conceivable that a meta-analysis could be used if trials are similar enough). DrugAbacus is based on the information provided at submission to FDA. The information about the value of a drug however will

evolve as new trials are completed and it remains to be seen how this information can be included in the value assessments.

Value scales may be useful for patients and oncologists looking for differentiation between new cancer drugs in terms of therapeutic value. However, you may assume that oncologists may already have more information than is included in the ranking on the scale. For payers and HTA assessments the validity of the scale, and the additional value in addition to existing classification schemes is still an unanswered question. Ultimately, for payers the endgame is not about value but about value for money, or cost-effectiveness and optimal uptake cannot be judged on value in isolation. If the different scales are to be validated and used in a policy context, the link to cost-effectiveness assessment will be a key issue.

4.4 Access and regulatory decision-making

The European Medicines Agency (EMA) grants marketing authorisation of medicines in the EU after evaluation of safety, efficacy and quality by the Committee for Medicinal Products for Human Use (CHMP). This is done through a centralised procedure where the producer submits an application to the EMA and is granted a single marketing authorisation for all EU member states, as well as for Iceland, Lichtenstein and Norway. The EMA also grants authorisation for new therapeutic indications for already existing medicines. The formal decision of granting marketing authorisation is taken by the European Commission (EC).

The time to marketing authorization in the EU depends on the time it takes the EMA to assess a drug, the time it takes the company behind the submission to answer questions or to come up with additional data or evidence and finally the time between the positive opinion by the EMA and the final decision taken by the ECs.

Certain drugs that are of major interest for public health or which are therapeutic innovations may be subject to an accelerated approval procedure. This has been the case for about 5% of the cancer drugs assessed by the EMA. The time for regulatory review of cancer drugs by EMA is slightly shorter than for other drugs, on average 450 days. The review time is longer at EMA than FDA, which only takes about half the time. The main explanation for the difference is that the FDA evaluates a majority of the cancer drugs using priority review while a standard review was used by the EMA. For a more detailed review of differences between different regulatory agencies see IHE Report 2016:2 [13].

The regulatory review time is not the only variable determining when a new cancer drug is available in Europe or for differences in access between European countries. In fact the centralized procedure for a common European market is an important policy to reduce variation. Other factors to take into account are decisions by the pharmaceutical companies to

apply for market authorisation, and the time it takes for the company to start marketing a new drug after authorisation is granted. The major reason for differences between start of sales is differences in time for pricing and reimbursement processes/decisions (see later section).

However, taking into account the seriousness of cancer diseases, and the lack of effective treatments, options for improvement in order to give patients earlier access has been discussed and developed. "Adaptive pathways" is a new model planning access to new drugs in areas of high unmet medical need [14]. This model is based on early collaboration between companies, regulatory, HTA and reimbursement authorities. Another important feature of the model is the use of real world data as complementary to data from clinical trials to provide evidence on safety and effectiveness.

It is too early to conclude how big a difference the new model will make for access and uptake of cancer drugs. It has the potential to plan access and reduce variations between countries, but the end result will depend on the collaboration with payers, and how funding is organised while information on effectiveness and value in clinical practice is gathered. It is not only a model for regulatory and reimbursement decision-making, but a new model for drug development as well, based on new scientific developments in molecular biology and precision medicine.

4.5 Access, health technology assessment (HTA) and reimbursement decisions

In the first comparator report in 2005 health technology assessment (HTA) was identified as an increasingly important determinant for access [15]. Since HTA often includes an assessment of cost-effectiveness, three important aspects for access were introduced; a measure of relative effectiveness, an outcome measure related to value, and a cost-effectiveness ratio measuring value for money. Health technology assessment is a national policy instrument, and variations in processes and criteria for decision-making between countries could lead to variations in access to new cancer drugs.

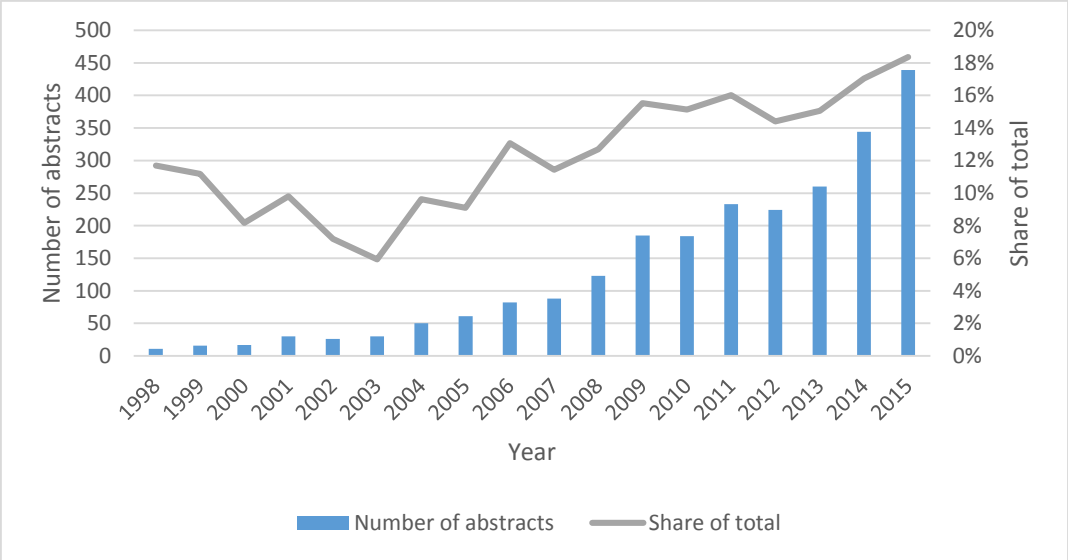


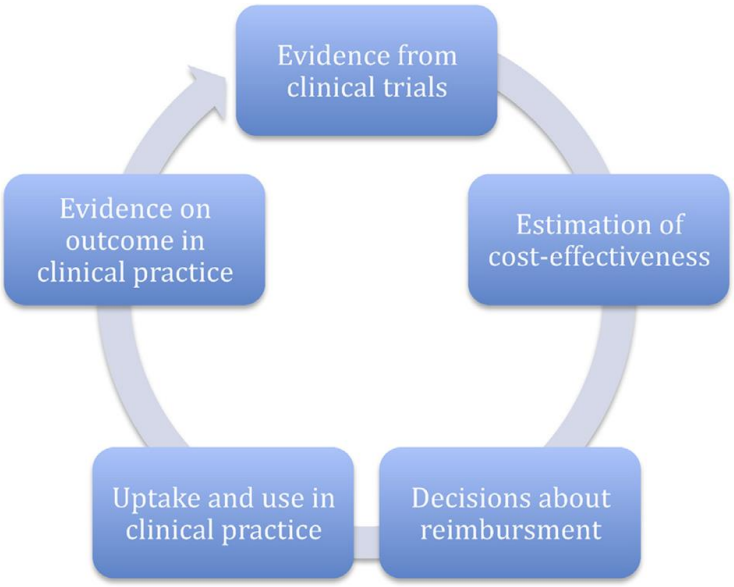
FIGURE 9. ABSTRACTS IN THE FIELD OF ONCOLOGY PRESENTED AT THE ISPOR ANNUAL EUROPEAN CONFERENCE [16].

While the number of studies on value and value for money of new treatment options in cancer continuous to increase, it has become clear that there are a number of obstacles for undertaking HTA studies early in the development of new cancer drugs. While the methodology of health technology assessment, including calculations of cost-effectiveness, is applicable in principle also to oncology, the implementation in practice has its specific problems and consequences. Most of them are linked to the specific need to do the assessment early in the development, with limited data on outcome in clinical practice [17].

One example is estimates of gains in overall survival. Health technology assessments and cost-effectiveness studies need estimates of gains in mean survival, whereas trials are powered to study differences in progression-free or overall median survival. New cancer drugs that have an opportunity for a long survival for some patients, the difference between median and mean survival can be considerable. Immuno-oncology drugs for treatment of malign melanoma are an example [18]. The design of clinical trials also makes it difficult to predict long-term survival as results are often submitted to regulatory agencies with still a large fraction of patients being alive [19]. The increasing use of combination therapies is another complication, which has to be considered..

A practical example of the issues involved is the introduction of new targeted therapies for metastatic renal cell cancer [20]. Economic evaluations and coverage decisions are based on uncertain data, and thus the impact on outcome in clinical practice is uncertain. It is therefore necessary to collect data on actual use to make it possible to study the effects on outcome in clinical practice (clinical effectiveness). Since outcome depends on a number of factors, individual patient data are a necessary requirement for revealing impact on outcome.

Assessment of value and cost-effectiveness is thus not a once only assessment at launch, but a process that should cover for the life cycle of the drugs and its different uses.



While value and cost-effectiveness must be evaluated in life cycle perspective (see figure above), there is still a need to make decisions about reimbursement and use when the drug is granted market authorisation It is thus necessary to think early about evidence generation for value assessment and take this into decisions on the development process. Early HTA advice and relative effectiveness assessments have been introduced as methods to make sure that these aspects are considered in the early development, and that relevant information for assessment of patient benefit and value is provided for payers at time of launch [21].

Early HTA and joint HTA/regulatory advice are important new policy instruments and adaptive pathways model may also provide relevant data for HTA and payer decisions in close collaboration with regulators [22].

Follow-up studies of value and cost-effectiveness are important as guide for future decisions. Data from such follow up studies are also important for management of uncertainty in decisions about funding for early access.

4.6 Access, price and payments for new cancer medicines

Pricing of new cancer drugs has developed as a hot topic for all stakeholders in cancer care, not only payers and policy makers, but also patients, clinicians and the general public. Taking into account the importance of cancer care from both an individual and public interest, this is not surprising. But it is also important to understand that public discussion of prices has a long history. In a study of articles on drug prices in New York Times and Wall Street Journal from 1985 – 2015, it is revealed that media coverage of high drug prices is nothing new [23]. The introduction of Tagamet in 1977 and Zantac in 1983 for treatment of ulcer disease, both at one time the world's largest-selling prescription drug, triggered a similar discussion about increasing drug prices as we now see for cancer drugs [24].

High prices can be addressed by voluntary price reduction from the industry, the introduction of mechanisms for improving price competition, or direct price controls. In a European context, mechanisms for price negotiations as well as direct price controls have been introduced since long in most countries. Present discussions focus on changes in the regulatory framework, and potential collaboration between countries, including joint action at the EU level.

Price controls control prices, but not total expenditures on cancer care and do not include considerations about use and value. Price controls originate from a market where the patient pays for the drug, and is reimbursed for part or whole of this payment. This is not an adequate description of the present market for cancer drugs in Europe where cancer medicines are fully paid for by the health care system in most cases. The decision about public payment takes into account both price and quantity, and is more adequately described as a public expenditure decision. Public expenditure decisions are budget decisions, where financing and opportunity cost of alternative spending must be considered. Funding of new cancer drugs can thus be seen as integrated with funding of other resources for cancer care.

The key factor for access is thus the budget decisions for cancer care made in health care systems, and this stresses the importance of the analysis of expenditures for cancer provided in the first chapter of this report. However, there are still specific mechanisms for allocating resources to new cancer drugs in all health care systems, and we will first review the development of cancer drug prices, and discuss policy issues related to pricing. We will end the section with a short discussion of the development of new payment mechanisms for cancer drugs.

4.6.1 Price comparisons – theory and practice

Prices are seldom interesting by themselves; they need to be compared. The easiest way is to compare the price for the same unit of a drug between different jurisdictions or over time. In

this latter case the choice of unit is less of a concern. When the prices of two different drugs are compared, they must be converted to a common and comparable unit, which may be a defined dose, a defined period of time or a defined treatment. When prices of groups are compared, there are additional problems of defining the appropriate index, since this will affect the result and its interpretation.

Practical problems relate very much to the availability of comparable data over time and between countries. Prices may be reported at the producer or consumer level, can include or exclude taxes, and may be distorted by unofficial rebates or other agreements. Price comparisons over time must state if they are made in current or fixed price level, and international price comparisons are influenced by choice of exchange rates. Thus all price comparisons must be carefully evaluated, and conclusions should be critically reviewed. Ideally all price comparisons should have a clearly stated question, and a critical discussion of the result.

Howard et al assessed the trends in the launch prices for 58 anticancer drugs approved between 1995 and 2013 in the United States [25]. The sample of drugs was selected on the basis that the primary intended outcome was improved survival. Price was defined as the total costs for an episode of treatment, and the unit compared was the number of life years gained by the treatment. Needless to say, there is a range of issues involved in both the estimate of the total cost of an episode of treatment and the resulting gain in life expectancy. Cost is estimated as the monthly cost, multiplied with the number of treatment months. It is not a measure of the total treatment cost, which depend on the need for complementary resources and to what extent it substitutes for other resources, for example the need for hospitalisation.

The study has two important results. The first is that there is a positive correlation between price and outcome. The average drug cost is 63 000 USD and the average gain in survival is 0.46 years, and drugs with higher estimated survival has a higher price (correlation +0.9). This result has been shown before for other studies of launch prices, both in the US and in a regulated market like Sweden [26, 27]. This indicates an overall correspondence between price and therapeutic value, but the variation in price between drugs with the same outcome can be great. This may to some extent be explained by a number of other factors that may enter the pricing decision; potential savings within or outside health care, differences in side effects, size of the population treated, price of competitors etc.

The second result is that over time launch price increase with 12 per cent annually over the study period. Unless there are other quality aspects not measured by the gain in life expectancy, the conclusion is that launch prices has increased over time. The authors discuss several explanations for this increase, which mainly relate to the function of the US pharmaceutical market, which may only in part be relevant for Europe.

What parts of the results for US are then relevant for Europe? For this we need more detailed information on similar studies based on European prices, usage of the drugs, and market conditions. So far most studies have focused on simple price comparisons for individual drugs between countries. However, a study on drugs approved by TLV in Sweden reveals a similar link between price per treatment and expected QALY gains and also an increasing price per treatment over time however with the latter effect disappearing when taking QALY gains into considerations (see figures 10 and 11 below). The study is hampered by the fact that it includes a rather small set of drugs since TLV doesn't review all drugs and do not systematically publish QALY estimates as part of their decisions [28]. An analysis incorporating more data from a European setting would be merited.

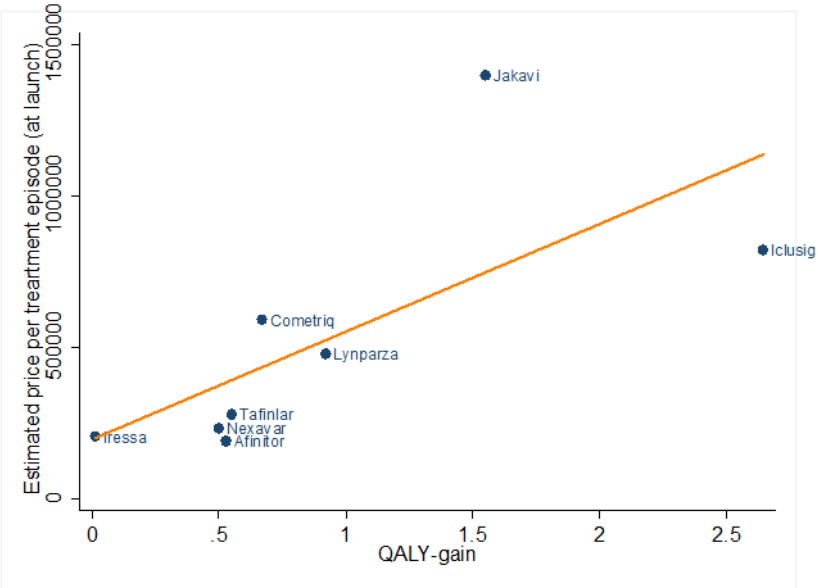


FIGURE 10. PRICE PER TREATMENT EPISODE IN RELATION TO QALY GAINED FOR ONCOLOGY MEDICINES IN SWEDEN [28]

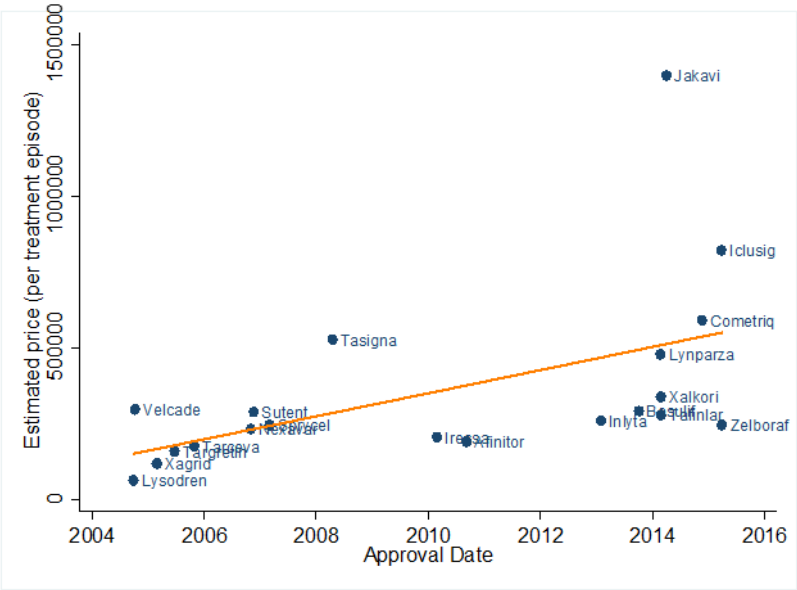


FIGURE 11. PRICE PER TREATMENT EPISODE OVER TIME FOR ONCOLOGY MEDICINES IN SWEDEN [28]

A recent example is a price comparison of official list prices per unit at ex-factory price level for 31 original cancer drugs between 16 European countries, Australia and New Zealand. The study has no other stated objective than to compare list prices. The study found differences in prices, but no systematic analysis was performed [29]. As we have discussed elsewhere in this report, list prices provide only limited information, as negotiated payment models with confidential discounts are often in place.

In a similar study, which took into account discounts collected through a survey, thus providing information about the list price and the actual price van Harten et al found differences in both list price and actual price between countries for nine different drugs [30]. However, the interpretation is not obvious and in a comment to the study it was pointed out that the prices used for Belgium was not correct [31]. As a background for discussing access, we have nevertheless re-analysed the data, and the analysis is presented in the figure below. Although based on a very small sample of drugs in each country (n = 9) and being based on a limited number of surveys, the figure illustrates the relatively poor ability for pharmaceutical companies to differentiate prices based on affordability due to external reference pricing and parallel trade, although there is a tendency for larger rebates in (some) poorer countries.

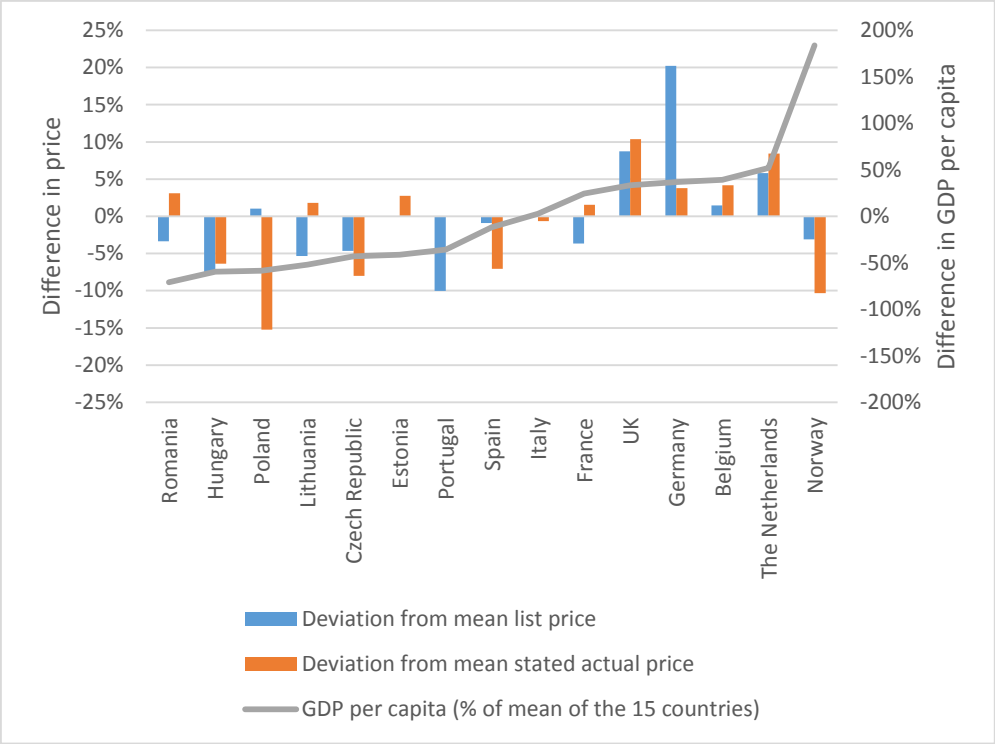


FIGURE 12. DIFFERENCE FROM MEAN PRICE FOR A BASKET OF NINE DRUGS

Source: Adapted from van Harten et al [30]. No list prices presented for Estonia in the original source. List prices for Italy omitted as they include a large mandatory discount. No stated actual prices available for Portugal.

4.6.2 Market access agreements

Market access agreements can be seen both as a response to the uncertainty around effectiveness of new and potentially valuable cancer drugs, and as a response to demand for lower and more differentiated prices. A simple agreement on an undisclosed discount can both be seen as a correction for the uncertainty about projected effectiveness, and as an adjustment of the price (price discrimination) to improve cost-effectiveness and or affordability to gain a positive reimbursement decision in a specific market.

We reviewed the trends in market access agreement with special focus on cancer drugs in a recently published report, noting the difference between risk-based and performance based types of agreements [13]. The common features of risk-sharing schemes are that there is either persistent discount or discount applied at the onset or maintenance phase of the treatment; (1) there is a cap for amount of reimbursed product, (2) there are strict criteria for treatment eligibility under an approved indication along with criteria for response, non-response and treatment discontinuation, and (3) there is often free provision of the drug in some circumstances. Pure risk sharing agreements, aimed at controlling costs, have the advantage that the need for collection of data is minimal. Outcome based agreement demands collection of data on outcomes, which is often difficult to get to work in practice. This is exemplified by

the experiences from Italy, which account for most of the outcome based agreements, while financial risk sharing agreements dominate in the UK.

Ferrario and Kanavos undertook a systematic review of managed entry agreements in Belgium, England, the Netherlands and Sweden [32]. This review conforms that England uses mainly discounts and free doses to influence prices while the Netherlands and Sweden have focused more on addressing uncertainties through coverage with evidence development. An important observation is that market access agreements even for the same drug are very differently designed in different countries, adapting to local health care governance.

We see market access agreements as part of a trend towards more sophisticated strategies from public payers to commission health care from private providers. These strategies involves selecting of providers that meet the specific requirements, a combination of procurement and accreditation of providers dependent on the type of services commissioned, and new payment models that fee for service and fixed budget has been replaced by activity based bundled payments, combined with bonus payments and fines related to positive and negative outcomes specified in the contract. These contracts include collecting and reporting of data for follow up and payment. While this has been developed for commissioning of services, the general knowledge about how to handle these types of contracts can be transferred to designing new contracts for medicines as well. We can also see a development, where medicines are often used in combination with diagnostics, and several medicines may be used in the same treatment process, which makes commissioning of drugs more like a service commission than a single product commissioning. Cancer is the obvious field for application of this new approach to buying and paying for new medicines.

While there is a build-up of competence in the health care systems for more sophisticated form of contracting, there is an expectation of leadership from industry since agreements must be adjusted to the specific technology as well as country specifics. There is no simple formula, but it may be useful to identify model contracts that may be used to in the process. EFPIA has taken an initiative to provide more clarity and uniformity of MAA in order to assist local affiliates to go into discussions about the design of such agreements. In particular the need for appropriate data collection to support the agreement and the importance of trust, confidentiality, simplicity, and clear definitions and agreement on goals.

4.7 Concluding remarks

Access is a critical component of universal health coverage. The 28 Member States of the European Union (EU) have a clear mandate to ensure equitable access to health services for everyone living in their countries. This does not mean making everything available to everyone at all times. Rather, it means addressing unmet need for health care by ensuring that

the resources required to deliver relevant, appropriate and cost-effective health services are as closely matched to need as possible [33].

This report aims at providing information about access to innovative treatments for cancer. While unmet needs can be precisely defined, for example the mortality and number of life years lost due to cancer, it is more difficult to define what is appropriate and cost-effective cancer care when the precise effectiveness of the new treatments are not established. However, uncertainty about patient outcomes is not an argument against systematic studies on how new cancer drugs are introduced and how their use is related to unmet need.

Access is multi-dimensional and studies of access need a multidisciplinary approach. Economic factors play an important role for access, also in health care systems with universal health coverage. While patient co-payments plays a very minor role in European health care systems where cancer care is fully covered, other mechanisms for resource allocation to care of patients with cancer plays an increasingly important role.

The importance of economic factors in allocation of resources for innovative cancer medicines reveals the impact of the differences in income level and thus health care expenditures in different European countries. The existence of a common market for pharmaceuticals in combination with great variations in ability to pay for new medicines creates unequal access between patients living in different countries. While our report shows improvements in outcomes of cancer care in all countries over the last decades, the differences in access to new medicines persists.

There is a growing awareness of the problems for access by the traditional method of financing pharmaceutical innovation by a single price per unit used of the drug, which is the same in all countries, for all indications and independent of the quantity used. Policies are also developed to mitigate this problem, but still there is a long way to an alternative payment system, which give proper incentives for both future development of effective and valuable medicines, and for health care systems to use available medicines in an efficient and equitable way.

While low per capita income and health care spending account is an important factor for variations in access, there are large variations, which cannot be explained by economic factors. This indicates that there are great opportunities to improve access and outcome by a more evidence based and cost-effective spending within cancer care. The available data do not allow us to give precise advice on the sources for these differences and which policies that can improve the situation. There is not a single explanatory factor or an easy solution to the problem. What is clear is that better data, linking resource use and outcomes to individual patients, is needed for development of evidence based polices.

Our update of the 2005 report also reveals the somewhat surprising fact that the share of health care expenditures devoted to cancer has not increased over the last ten years, and available data indicate that the share has been stable for an even longer time. The increasing cost for new cancer medicines has thus been assimilation within a growth rate similar to overall health care expenditures. A shift towards more ambulatory treatments, and a reduction in hospitalizations, may explain this, but the detail of this transformation has still not been presented. For this we need appropriate accounting data on spending on different cost items for different types of cancer. The transformation towards ambulatory care also call for more data on how this has affected resource use in support services outside the health care sector, and for informal care.

With continuous scientific developments and introduction of new treatments there will be a strong pressure to increase the share of health care spending for cancer. To make this possible, it is very important to have a transparent accounting how the resources are spent, and subsequent analysis that they are spent in a cost-effective way. When that is the case, it is easier to advocate for increasing resources, based on careful analysis how they should be spent, and with follow up studies to verify that the spending gives good value for money. Such studies will also provide important information for future drug development, to make it directed to those areas where the value of innovation is greatest for patients and health care systems.

Spending on new cancer medicines has not been a threat to the financial stability of health care systems so far, and should not been seen as a threat for the future either. New cancer medicines are an opportunity for health care systems to improve survival, quality of life and quality of care for patients with cancer. But new medicines will only provide value if they are used appropriately in clinical practice. Thus access for patients as defined above: “addressing unmet need for health care by ensuring that the resources required to deliver relevant, appropriate and cost-effective health services are as closely matched to need as possible” should be on the top of the health policy agenda.

4.8 References chapter 4

1. Lundqvist, A., E. Andersson, and K. Steen Carlsson, Kostnader för cancer i Sverige idag och år 2040 [Cost of cancer in Sweden today and 2040]. IHE rapport, 2016 (forthcoming). IHE: Lund.
2. Vogler, S., et al., Study on enhanced cross-country coordination in the area of pharmaceutical product pricing. Final report. . 2015, European Commission.
3. Pharmaceutical Pricing Policies in a Global Market. OECD Health Policy Studies. 2008: OECD.
4. Ganslandt, M. and K.E. Maskus, Parallel Imports and the Pricing of Pharmaceutical Products: Evidence from the European Union. Working Paper No. 622. 2004, The Research Institute of Industrial Economics: Stockholm.
5. Grabowski, H., J. Vernon, and J.A. DiMasi, Returns on research and development for 1990s new drug introductions. Pharmacoeconomics, 2002. 20 Suppl 3: p. 11-29.
6. DrugAbacus. 2016.
7. Cherny, N.I., et al., A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol, 2015. 26(8): p. 1547-73.
8. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology with NCCN Evidence Blocks. 2016; Available from: http://www.nccn.org/evidenceblocks/.
9. Schnipper, L.E., et al., American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options. J Clin Oncol, 2015. 33(23): p. 2563-77.
10. HAS, Haute Autorité de Santé. 2015.
11. G-BA, Gemeinsamer Bundesausschuss. 2015.
12. TLV, Tandvårds– och läkemedelsförmånsverket. . 2015.
13. Jönsson , B., Persson, U., Wilking, N., Innovative treatments for cancer in Europe - value, cost and access. IHE Report 2016:2, IHE: Lund.
14. Eurpean Medicines Agency. Adaptive Pathways. 2016; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp.
15. Wilking, N. and B. Jönsson, A pan-European comparison regarding patient access to cancer drugs. 2005, Karolinska Institutet in collaboration with Stockholm School of Economics: Stockholm.
16. ISPOR, International Society for Pharmacoeconomics and Outcomes Research Sceintific Presentations Database. 2016.
17. Jönsson, B., Technology assessment for new oncology drugs. Clin Cancer Res, 2013. 19(1): p. 6-11.
18. Davies, A., et al., The Ends Justify the Mean: Outcome Measures for Estimating the Value of New Cancer Therapies Health Outcomes Research in Medicine, 2012. 3(1): p. e25-e36.
19. Jonsson, L., et al., Analyzing overall survival in randomized controlled trials with crossover and implications for economic evaluation. Value Health, 2014. 17(6): p. 707-13.
20. Jönsson, B., S. Ramsey, and N. Wilking, Cost effectiveness in practice and its effect on clinical outcomes. Journal of Cancer Policy, 2014. 2: p. 12-21.
21. eunethta. SEED (Shaping European Early Dialogues for health technologies). 2016; Available from: http://www.eunethta.eu/seed.
22. European Medicines Agency, Best Practice guidance for Pilot EMA HTA Parallel Scientific. 2014.
23. Leopold, C., J.D. Chambers, and A.K. Wagner, Thirty Years of Media Coverage on High Drug Prices in the United States-A Never-Ending Story or a Time for Change? Value Health, 2016. 19(1): p. 14-6.
24. Berndt, E.R., et al., The Roles of Marketing, Product Quality, and Price Competition in the Growth and Composition of the U.S. Antiulcer Drug Industry in The Economics of New Goods, T.F. Bresnahan and R.J. Gordon, Editors. 1996, University of Chicago Press: Chicago, IL, USA.
25. Howard, D., Bach, PB, Berndt, ER, Conti, RM,, Pricing in the Market for Anticancer Drugs. Journal of Economic Perspectives, 2015. 29(1): p. 139-162.

26. Ekelund, M. and B. Persson, Pharmaceutical Pricing in a Regulated Market. The Review of Economics and Statistics, 2003. 85(2): p. 298-306.

27. Lu, J.Z. and W.S. Comanor, Strategic Pricing of New Pharmaceuticals. Review of Economics and Statistics 1998. 80(1): p. 108-18.

28. Macheridis, K., New anticancer drugs in Sweden. A study on the relationship between the launch price and the effectiveness, as well as trends in cost, effectiveness and launch price of new anticancer drugs approved by the Swedish Dental and Pharmaceutical Benefits Agency to the pharmaceutical reimbursement system 2004 – 2015., in School of Economics and Management. Department of Economics. 2015, Lund University: Lund.

29. Vogler, S., A. Vitry, and Z.U. Babar, Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study. Lancet Oncol, 2016. 17(1): p. 39-47.

30. van Harten, W.H., et al., Actual costs of cancer drugs in 15 European countries. Lancet Oncol, 2016. 17(1): p. 18-20.

31. Block, M.d., The difficulty of comparing drug prices between countries. Lancet Oncology, 2016. 17: p. e125.

32. Ferrario, A. and P. Kanavos, Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. Soc Sci Med, 2015. 124: p. 39-47.

33. Expert panel on effective ways of investing in health (EXPH), Access to health services in the European Union. 2015, European commission DG Health & Food Safety,: Brussels, Belgium.

A Appendix

The references in the Appendix refer to chapter 1.

A.1 Age-standardized incidence rates

Comparisons of cancer incidence between different countries, or the same country over time, need to take into account different population sizes to be meaningful. The obvious approach to do so is to use so-called crude rates, which present incidence figures per 100,000 inhabitants. Moreover, the age structure of the population is an important determinant for the number of new cancer cases, as shown in Figure 1. In a comparison of two countries of equal size, one with a relatively young population and the other with a relatively old population, it would not be surprising to find that there are more new cases in the latter country. To take into account different age structures between countries, it is common to compare so-called age-standardized rates, which present incidence figures per 100,000 inhabitants that are standardized with a pre-defined age distribution.

Screening is an additional issue that needs to be kept in mind when interpreting comparisons of cancer incidence over time and between countries. Established cancer screening methods are nowadays available for breast cancer (mammography), prostate cancer (prostate-specific antigen (PSA) testing), cervical cancer (smear test, HPV test), and colorectal cancer (fecal immunochemical test (FIT), guaiac fecal occult blood test (gFOBT), and colonoscopy). As shown above, these cancer types are also found among the most common types. Thus, at least theoretically, countries with more comprehensive screening activities might record higher incidence rates than other countries. In the same manner, an increase in incidence rates over time might reflect higher screening activities leading to the detection of more cancer cases rather than a true increase in the number of new cases. This issue remains unresolved if crude rates or age-standardized rates are used.

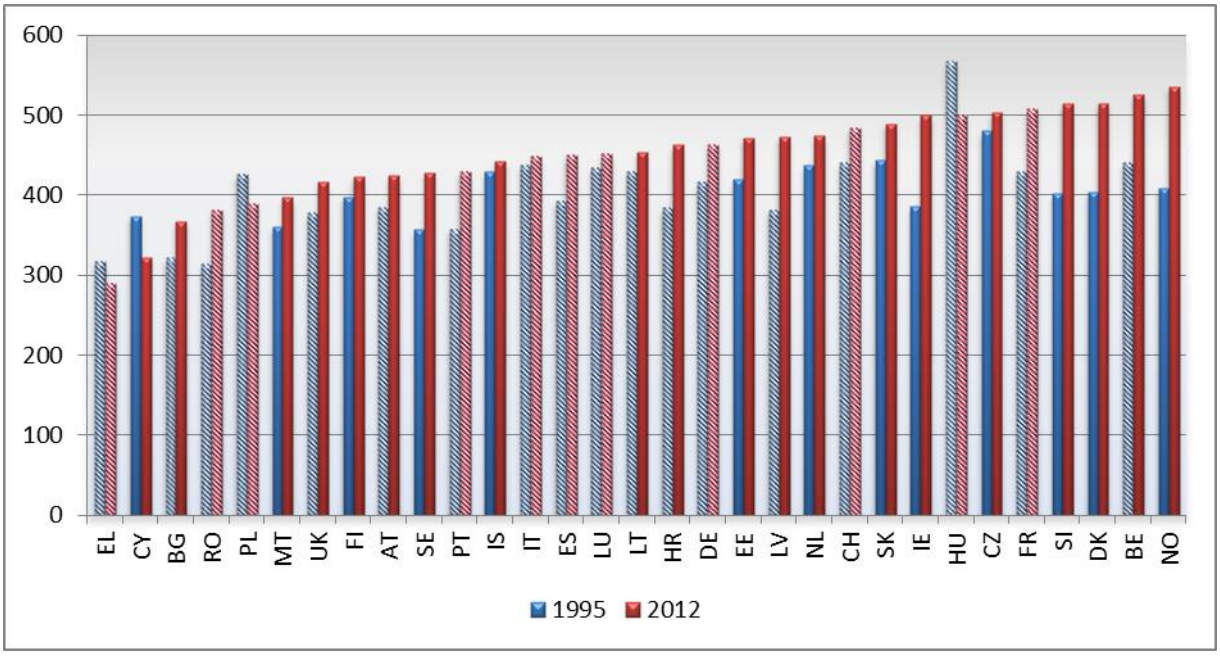


FIGURE A1: ESTIMATED NUMBER OF CANCER INCIDENCE CASES IN MEN PER 100,000 INHABITANTS (AGE-STANDARDIZED RATES), 1995–2012 [3, 4]

Notes: Hatched bars indicate that national estimates are based on regional data or based on neighboring countries.
1995 estimates include all cancers combined, excluding non-melanoma skin cancer (ICD-9 140-172, 174-208).
2012 estimates include all cancers combined, excluding non-melanoma skin cancer (ICD-10 C00-C97/C44).
1995 estimate for Cyprus is from 2006 [79].

Age-standardized incidence rates for all cancers combined (excluding non-melanoma skin cancer[27]) in men are shown in **Figure A1** for all countries. In 1995 the three highest incidence rates were recorded in Hungary, the Czech Republic, and Slovakia, and the three lowest rates in Romania, Greece, and Bulgaria. In 2012 Norway, Belgium, and Denmark recorded the highest incidence rates, and Greece, Cyprus, and Bulgaria the lowest ones. Looking at the development over time, it is evident that incidence rates increased in all but four countries, Cyprus, Greece, Hungary, and Poland (yet the data quality is not ideal in all of these four countries). Thus, even if the upward effect of a growing and aging population in Europe on the number of newly diagnosed cases is neutralized, male incidence rates have by and large increased between 1995 and 2012.

Age-standardized incidence rates for all cancers combined in women are shown in **Figure A2** for all countries. Female incidence rates are markedly lower than male rates in all countries and both years. In 1995 the three highest incidence rates were recorded in Denmark, Iceland, and Hungary, and the three lowest rates in Greece, Spain, and Romania. In 2012 Denmark, the Netherlands, and Belgium recorded the highest incidence rates, and Greece, Romania, and

[27] Non-melanoma skin cancer (ICD-10 C44) is commonly excluded from incidence data (and sometimes also from mortality data, as in parts of section 1.1.2 in this report) since its registration is often incomplete and inaccurate. The reason for this is that non-melanoma skin cancer is usually non-fatal and often does not receive the same kind of treatment and is neither treated in the same setting (primary care rather than hospitals) as other cancer types.

Portugal the lowest ones. Regarding the development over time, the same picture as for male incidence rates emerges. Incidence rates increased in all but two countries, Greece and Hungary (yet again, the data quality is not ideal in these two countries), between 1995 and 2012.

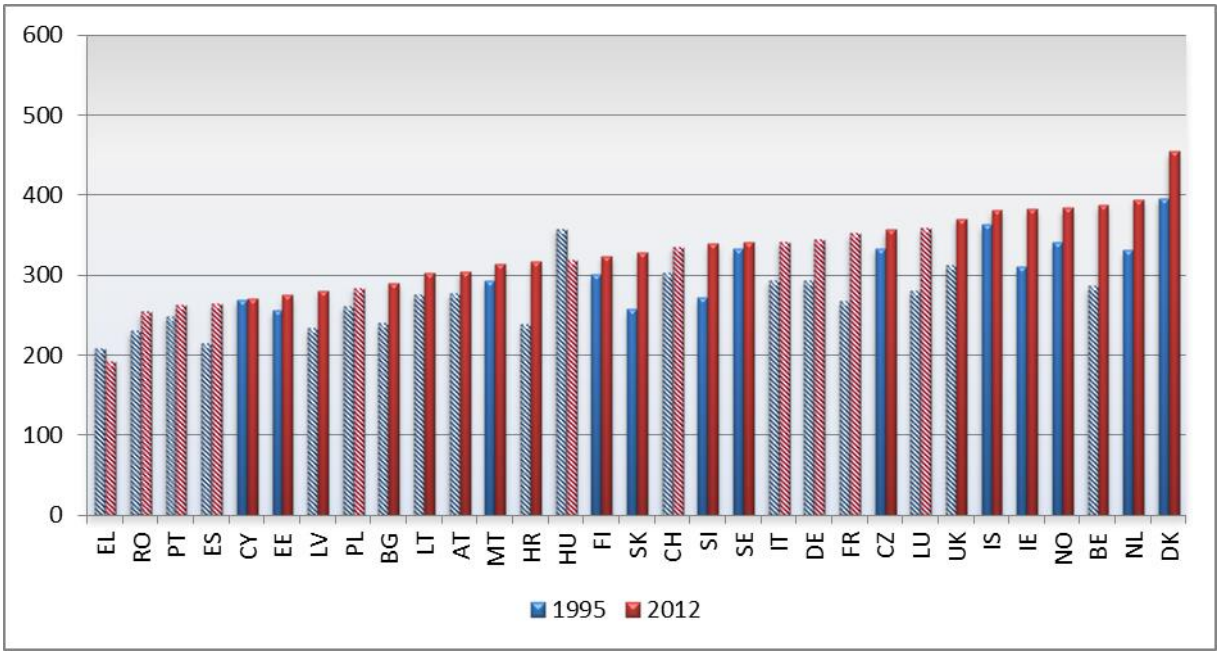


FIGURE A2: ESTIMATED NUMBER OF CANCER INCIDENCE CASES IN WOMEN PER 100,000 INHABITANTS (AGE-STANDARDIZED RATES), 1995–2012 [3, 4]

Notes: see Figure A1

Regarding trends in age-standardized incidence rates for major cancer types during the 1990s and 2000s, the following patterns have been observed. Tobacco-related cancers (lung, laryngeal, oral cavity and pharyngeal, esophageal) are most common in Central and Eastern Europe, Southern Europe, and the Baltic states. Whereas the high incidence rates in men have been falling across Europe, the lower rates in women have been increasing, resulting in a gradual convergence of the rates [80]. Incidence rates in four other major cancer types (prostate, postmenopausal breast, corpus uteri, colorectum) were lower in Eastern European countries, but started to move towards the higher rates in Northern and Western European countries, where incidence rates started to level off in some countries in the second-half of the 2000s. Incidence rates in stomach cancer have been decreasing in all countries [81].

A.2 Age-standardized mortality rates

As with incidence figures, mortality figures are generally presented and compared in the form of age-standardized rates or crude rates. Their interpretation is also subject to certain issues:

- The level of mortality rates across countries: If two countries are equally successful in curing cancer cases, i.e. curing the same share of new cases, then the country with the higher incidence rate will also have a higher mortality rate. So two countries can have different levels of mortality rates, but still be equally good in delivering effective treatment. For instance, let's assume that in two countries in a certain year half of all newly diagnosed cases are cured and the other half dies. Then, if the first (second) country has an incidence rate of 500 (400) cases per 100,000 inhabitants, the mortality rate in the first (second) country will be 250 (200) cases per 100,000 inhabitants, even though both countries cured the same share of cases.
- The development of mortality rates over time in a country: If a country is equally successful in curing cancer cases in every year, then an increase in the incidence rate will automatically lead to an increase in the mortality rate. For instance, let's assume that every year half of all newly diagnosed cases are cured and the other half dies. Then, if the incidence rate increases by 10 percent from 500 to 550 cases per 100,000 inhabitants from one year to the other, the mortality rate will also increase by 10 percent from 250 to 275 cases per 100,000 inhabitants.
- Screening: If greater screening efforts in a country lead to a larger share of cancer cases being detected at an early stage, the chances of curability will increase (since such cases have a higher success rate of being cured) and thereby mortality rates will decrease. Thus, a decrease in mortality rates might not only stem from cancer treatment having become more effective, but rather from a higher share of cancer cases that are "easier" to treat. For instance, let's assume that a country has an incidence rate of 500 cases per 100,000 inhabitants. Further assume that if screening efforts are low, half of the newly diagnosed cases are cured and the other half dies, whereas with high screening efforts 60 percent are cured and 40 percent die. Then, a country with low screening efforts will have a mortality rate of 250 cases per 100,000 inhabitants. A country with high screening efforts will have a mortality rate of only 200 cases per 100,000 inhabitants, but not because it was more successful in treating each and every cancer case but rather because it had fewer advanced cases to treat.

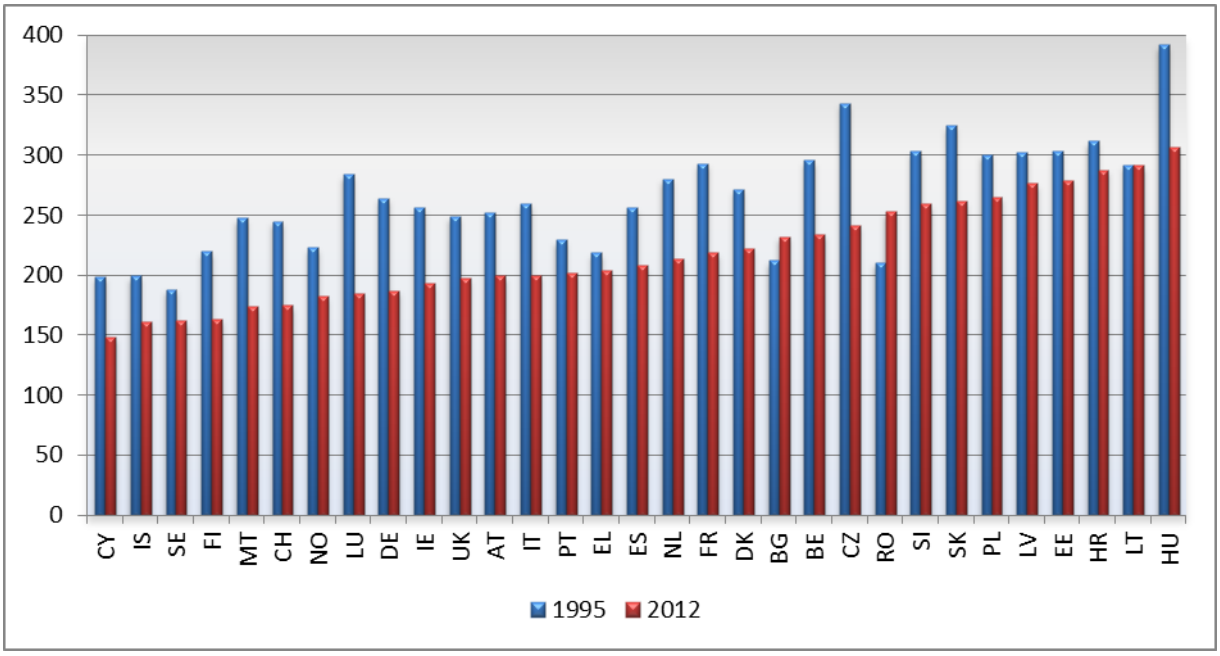


FIGURE A3: ESTIMATED NUMBER OF CANCER MORTALITY CASES IN MEN PER 100,000 INHABITANTS (AGE-STANDARDIZED RATES), 1995–2012 [3, 4]

Notes: see Figure A1

Age-standardized mortality rates for all cancers combined in men are shown in **Figure A3** for all countries. In 1995 the three highest mortality rates were recorded in Hungary, the Czech Republic, and Slovakia, and the three lowest rates in Sweden, Cyprus, and Iceland. In 2012 Hungary, Lithuania, and Croatia recorded the highest mortality rates, and Cyprus, Iceland, and Sweden the lowest ones. Looking at the development over time, it is evident that mortality rates decreased in all but two countries, Bulgaria and Romania, and remained stable in Lithuania. Thus, if the effect of a growing and aging population in Europe is neutralized, male mortality rates have by and large decreased between 1995 and 2012.

Age-standardized mortality rates for all cancers combined in women are shown in **Figure A4** for all countries. Female mortality rates are only around half as high as those of males in most countries and both years, which is partly a consequence of lower incidence rates. In 1995 the three highest mortality rates were recorded in Denmark, Hungary, and the Czech Republic, and the three lowest rates in Greece, Cyprus, and Spain. In 2012 Denmark, Hungary, and the Netherlands recorded the highest mortality rates, and Cyprus, Spain, and Portugal the lowest ones. Regarding the development over time, the same picture as for male mortality rates emerges. Mortality rates decreased in all but two countries, Bulgaria and Romania, and remained stable in Croatia and Latvia between 1995 and 2012.

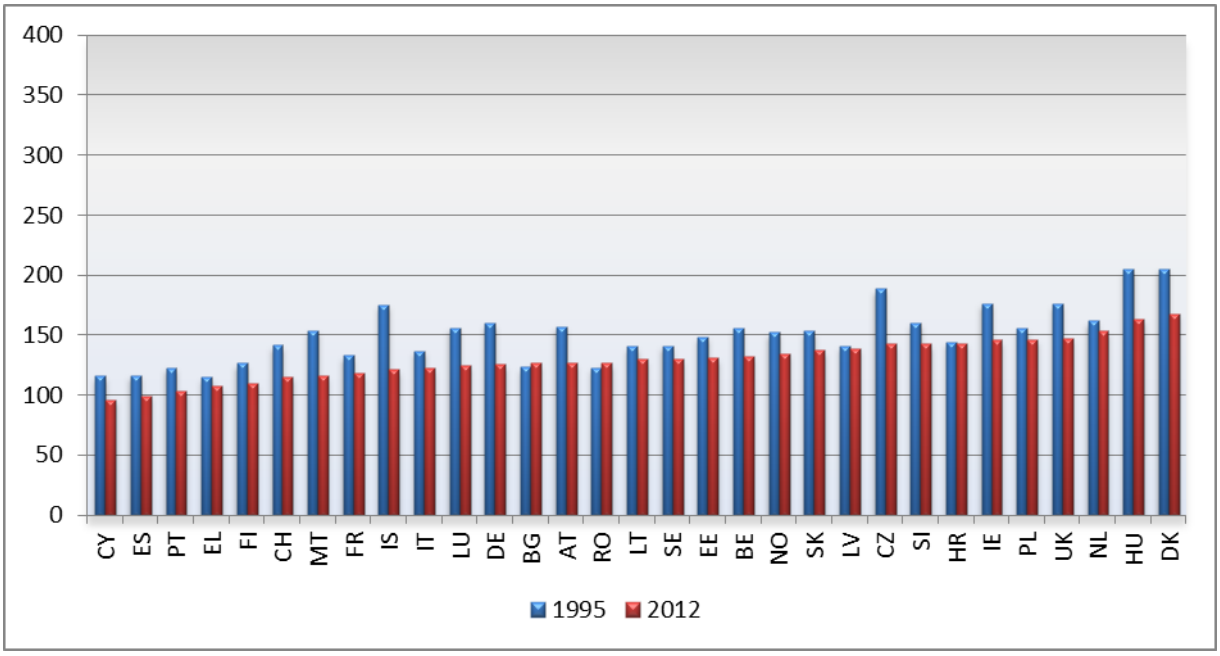


FIGURE A4: ESTIMATED NUMBER OF CANCER MORTALITY CASES IN WOMEN PER 100,000 INHABITANTS (AGE-STANDARDIZED RATES), 1995–2012 [3, 4]

Notes: see Figure A1

Regarding trends in age-standardized mortality rates for major cancer types during the 1990s and 2000s, the following patterns have been observed. Lung cancer mortality rates in men have been decreasing, especially in Northern and Western Europe, whereas in women rates have been increasing [82]. Mixed trends were observed for prostate cancer mortality, but wealthier countries seemed more likely to record decreases [9]. Breast cancer mortality rates decreased in most countries, but in some Eastern European they were increasing [83]. Colorectal cancer mortality rates have also been trending downwards across Europe, particularly in women, although this trend is more recent in Eastern European countries [84]. Corpus uteri mortality rates have, with a few exceptions, been declining [85]. Steep falls in stomach cancer mortality rates have been observed across all countries [86].

In sum, the consideration of age-standardized rates suggests that cancer mortality is decreasing, if the effects of a growing total population and population aging are taken into account. However, age-standardized rates are a summary measure that could conceal different trends among different age groups, in particular since the occurrence of certain cancer types is related to age. Therefore, **Figure A5 and A6** look at how mortality crude rates for both sexes changed in two different age groups. Effectively this implies considering so-called age-specific rates[28]. The two age groups encompass people aged 40 to 64 years and 65 years and older. Cancer cases below the age of 40 are disregarded in this analysis, because there are

[28] Age-specific rates are presented in terms of cases per 100,000 inhabitants in a specific age group. This means that they take into account changes in the population size in the respective age interval and thus are less affected by population aging than crude rates.

quite few of them (see Figure 1) and 40 to 64 year olds are a more homogenous group than 0 to 64 year olds. The cutoff line between the two considered groups is drawn at age 65, because it represents the legal retirement age in many countries. As is discussed in section 1.5 on indirect costs, cancer deaths prior to retirement age are responsible for huge indirect costs in the form of productivity loss.

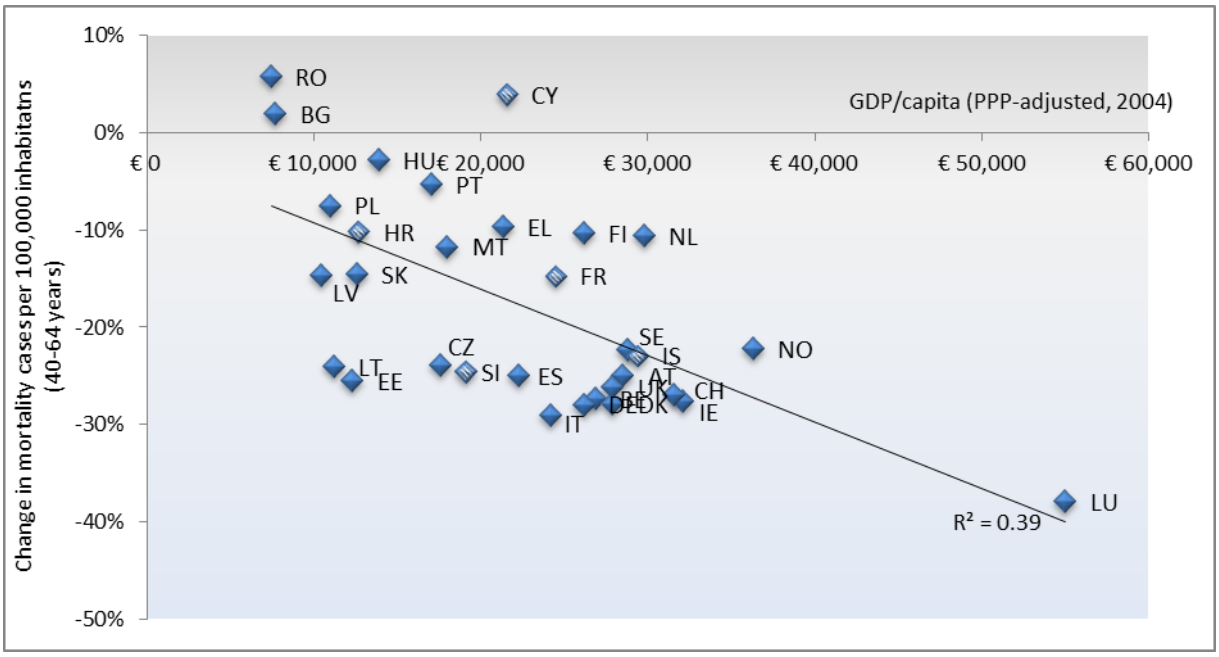


FIGURE A5: ESTIMATED CHANGE IN THE NUMBER OF CANCER MORTALITY CASES PER 100,000 INHABITANTS (BOTH SEXES) BETWEEN 1995–2012 IN THE AGE GROUP 40 TO 64 YEARS (Y-AXIS) AND PPP-ADJUSTED GDP PER CAPITA IN 2004 IN € (X-AXIS), [11, 12]

Notes: see Figure 7.
For Croatia, mortality cases in 1995 were standardized with population estimates from 2001.

Figure A5 plots the relative change of age-specific mortality rates in the age group 40 to 64 years between 1995 and 2012 against the PPP-adjusted GDP per capita in 2004. Similar to the findings from age-standardized rates, only Romania, Bulgaria, and Cyprus recorded an increase in mortality rates. In Europe as a whole the mortality rate decreased by 20 percent in this age group. The trend line in **Figure A5** suggests that there was a tendency that wealthier countries experienced larger decreases. Yet this tendency is not that strong, since, e.g. countries like Lithuania and Estonia recorded a 25 percent decrease just as Austria and the UK did even though GDP per capita was 2.5 times higher in the latter two countries.

Figure A6 provides the same information as **Figure A5** but for the age group 65 years and older. Even in this case there is a tendency that mortality decreased more in wealthier countries. However, the key difference is that there are now several countries (in addition to Romania and Bulgaria) that experienced increases of around 10 to 20 percent. In Europe as a whole the mortality rate decreased by 7 percent in this age group, which is distinctly lower than the 20 percent decrease in the age group 40 to 64 years. A possible explanation for this

might be that elderly patients are more difficult to treat due to frailty and/or concomitant diseases.

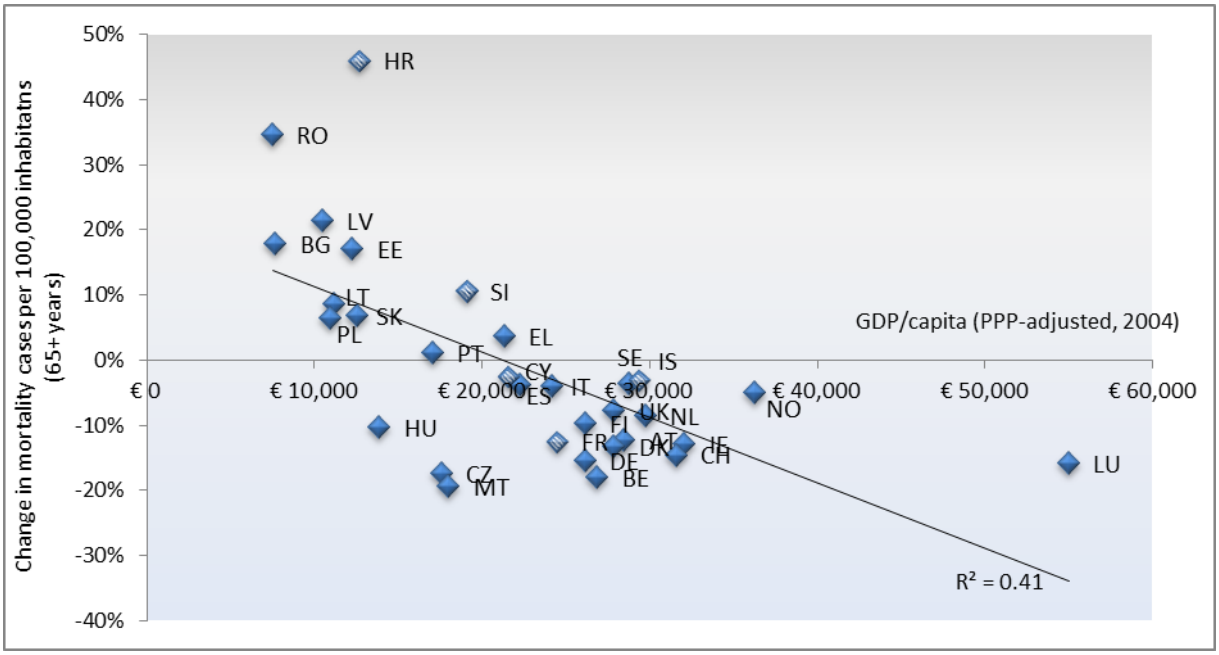


FIGURE A6: ESTIMATED CHANGE IN THE NUMBER OF CANCER MORTALITY CASES PER 100,000 INHABITANTS (CRUDE RATES FOR BOTH SEXES) BETWEEN 1995–2012 IN THE AGE GROUP 65+ YEARS (Y-AXIS) AND PPP-ADJUSTED GDP PER CAPITA IN 2004 IN € (X-AXIS), [11, 12]

Notes: see Figure A5

A.3 Survival rates

In order to get an idea of the long-term trend and also the more recent trend in cancer survival rates, **Figure A7** presents 5-year relative survival rates for three Nordic countries and separately for men and women. Considering first the development in all cancer types combined, it becomes clear that survival rates have been steadily increasing since 1964 up until 2013. At least in Finland, Norway, and Sweden survival rates started to converge since the 1980s and by the end of the 2000s were very similar. It becomes also clear that survival rates in men had been lower than in women in the last century. But even here a clear converging trend between the genders is noticeable and by the end of the 2000s the rates had become very similar. The left-hand side diagram in **Figure A7** shows the development in chronic myeloid leukemia (CML) between 1979 and 2013. It illustrates the general fact that the development of survival in specific cancer types does not perfectly follow the development in all cancer types. From 1979 until the beginning of the 1990s no improvements in the survival rate of CML were recorded, but in the following 20 years survival rates doubled or even tripled.

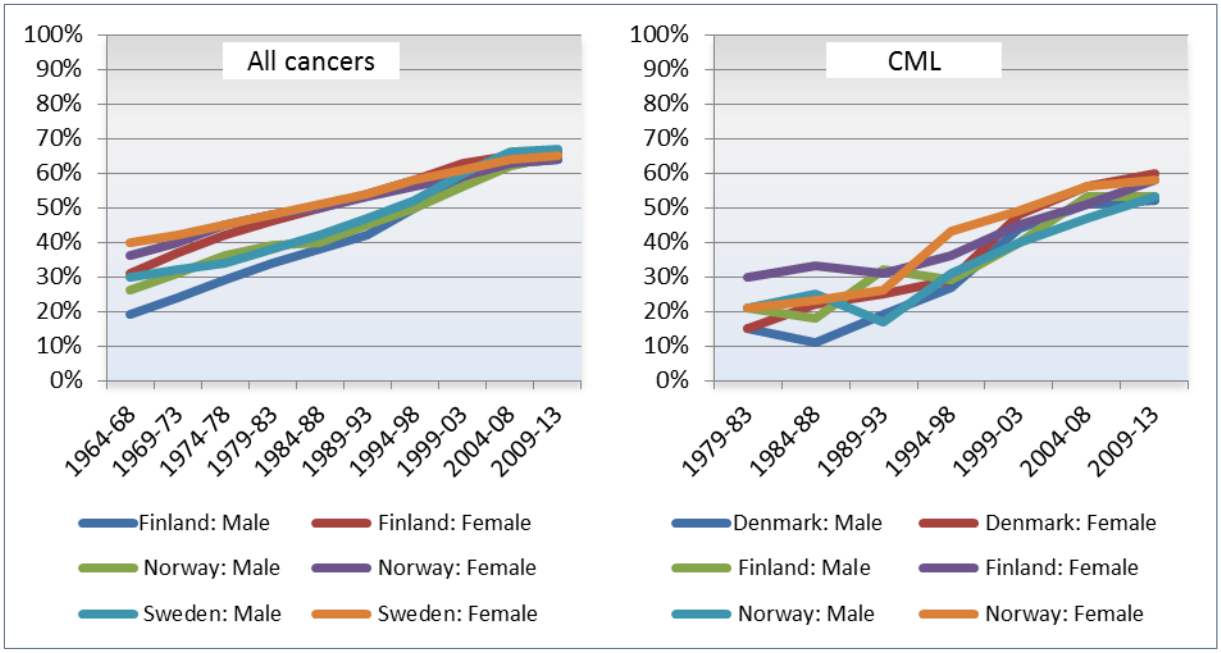


FIGURE A7: 5-YEAR AGE-ADJUSTED RELATIVE SURVIVAL RATES FOR ALL CANCERS AND CML IN PATIENTS AGED ≥15 YEARS, 1964–2013 [87]

Notes: CML = chronic myeloid leukemia

The 5-year relative survival rate for lung cancer is very low compared to most other cancer types. For cancer cases diagnosed between 2000 and 2007 the rates varied from 6 percent in Bulgaria to 16 percent in Austria; see **Figure A8**. Even though this means that there was a great amount of variation between countries, this should not distract attention from the fact that the overall level of survival rates is very low. Also the development over time shows a gloomy picture. Between 1990–1994 and 2000–2007 most countries recorded only minor improvements of around two percentage points, except for Poland which doubled its survival rate. In some countries such as the UK or France survival rates remained unchanged and in Belgium, Portugal, and Spain they even declined. In general, survival rates in lung cancer are closely related to stage of disease and access to surgery with a curative intent. In a previous report on lung cancer, operable stages (I and II) were found in approximately the same proportion in Sweden and in the UK. The share of patients undergoing surgery with a curative intent was twice as high in Sweden as in the UK though [88].

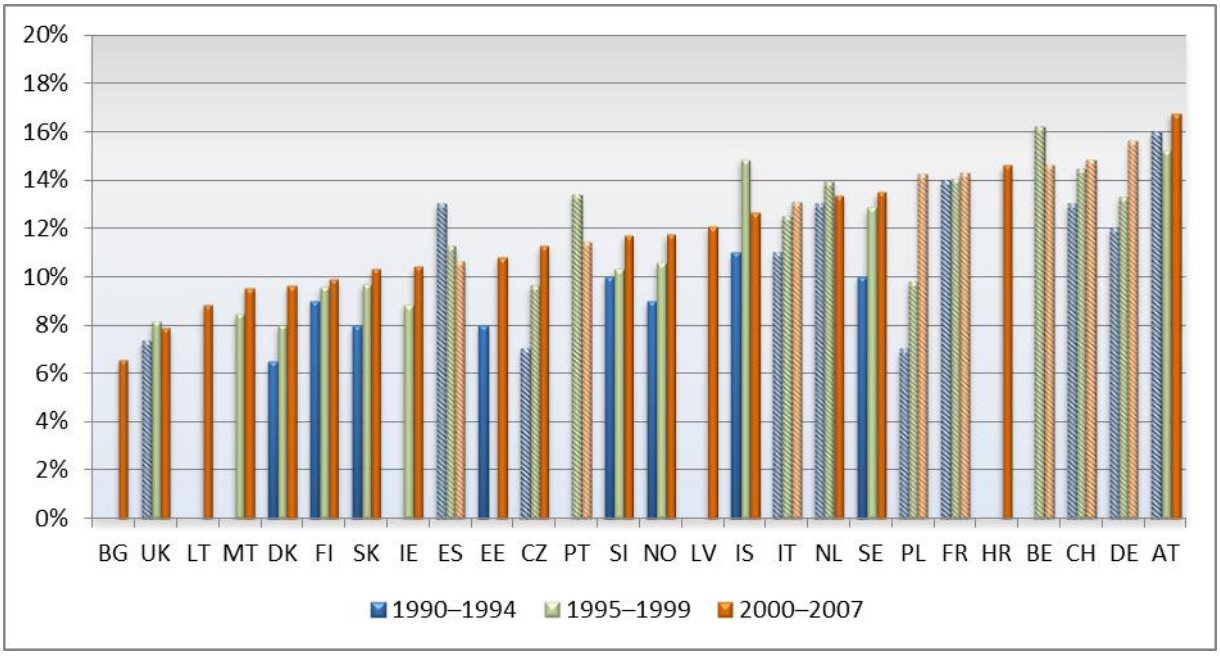


FIGURE A8: 5-YEAR AGE-ADJUSTED RELATIVE SURVIVAL RATES FOR LUNG CANCER IN PATIENTS AGED ≥15 YEARS, 1990–2007 [15, 27]

Notes: see **Figure 8**

The 5-year relative survival rate for colorectal cancer is just above 50 percent, which is about the same as the survival rate for all cancer types combined. For cancer cases diagnosed between 2000 and 2007 the rates varied from 40 percent in Latvia to 64 percent in Iceland; see **Figure A9**. Between 1990–1994 and 2000–2007 survival prospects for colorectal cancer patients improved in all countries. There was a clear catch-up process taking place in the Eastern European countries (see Poland, Czech Republic, Slovenia) which got closer to the levels in the Western European countries. Differences among Western European countries have also become smaller. The only outliers among the wealthier countries are the UK, Ireland, and Denmark, which had distinctly lower survival rates. France had an unusual development, as it had the highest survival rate among all countries in 1990–1994 but stagnated in the following decade. It is noteworthy that the presented survival rates cover the last years before several countries started to roll out population-based screening programs for colorectal cancer. This means also that the improvements achieved during this period stem from better treatment and not from early detection of cancers due to mass screening.

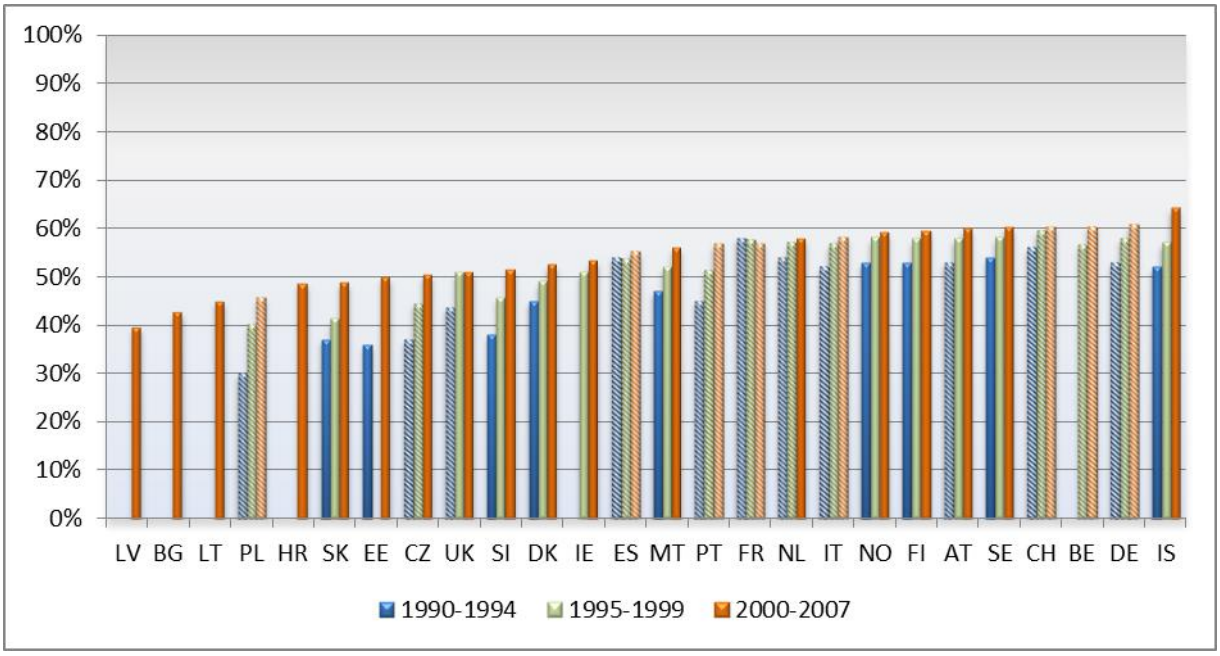


FIGURE A9: 5-YEAR AGE-ADJUSTED RELATIVE SURVIVAL RATES FOR COLORECTAL CANCER IN PATIENTS AGED ≥15 YEARS, 1990–2007 [15, 27]

Notes: see Figure 8

The 5-year relative survival rate for breast cancer is around 80 percent. For cancer cases diagnosed between 2000 and 2007 the rates varied from 70 percent in Lithuania and Latvia to 88 percent in Finland, France, and Iceland; see **Figure A10**. Compared to lung, colorectal and prostate cancer, the relative gap between the best-performing and worst-performing country is much smaller for breast cancer. This might be related to the fact that since breast cancer is the most common cancer type in women, even poorer countries direct their economic resources primarily on this cancer type and invest not only in medical treatment but also in screening activities. Between 1990–1994 and 2000–2007 survival prospects for breast cancer patients improved in all countries, even though they stagnated in Poland between 1995–1999 and 2000–2007. In absolute terms the improvements were greatest in Eastern European countries, but they have not yet reached the levels of Western European countries.

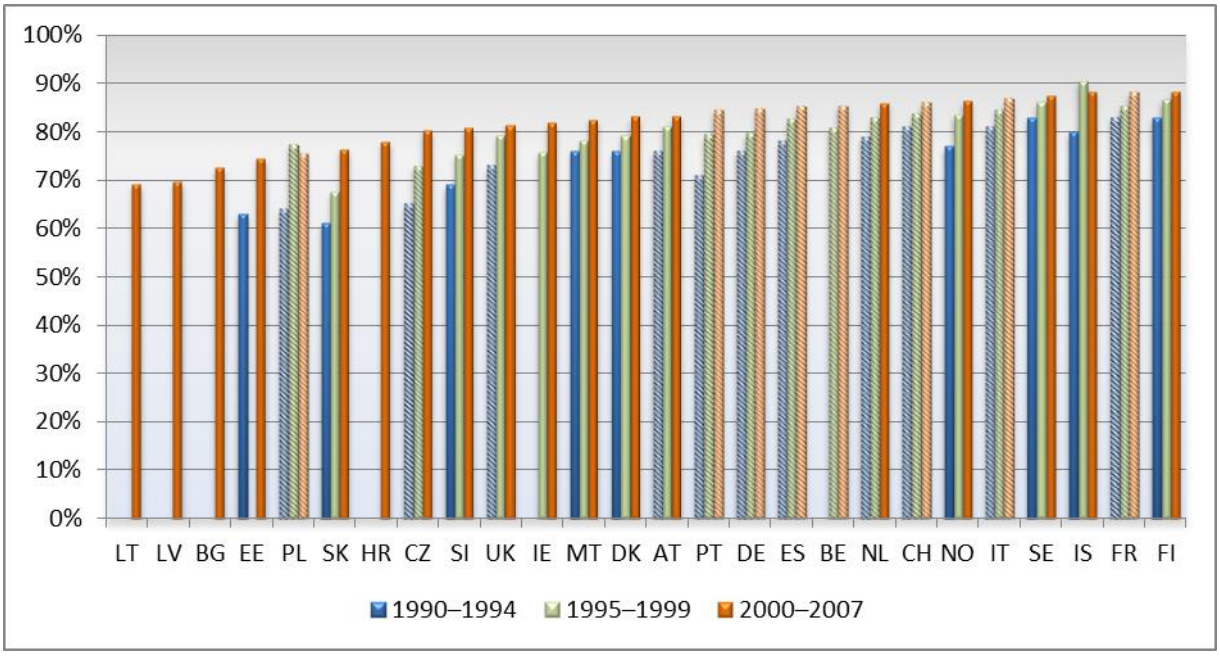


FIGURE A10: 5-YEAR AGE-ADJUSTED RELATIVE SURVIVAL RATES FOR BREAST CANCER IN PATIENTS AGED ≥15 YEARS, 1990–2007 [15, 27]

Notes: see Figure 8

The 5-year relative survival rate for prostate cancer varied considerably between countries. For cancer cases diagnosed between 2000 and 2007 the rates varied from 54 percent in Bulgaria to over 90 percent in France, Belgium, Finland, Germany, and Austria; see **Figure A11**. An explanation for this great variation might be related to screening. Countries with more extensive screening activities might detect more cancer cases at an early stage which have higher chances of being cured, resulting in higher survival rates. Even an increased detection of latent prostate cancer cases can push survival rates upwards since the cancer usually does not become fatal. Between 1990–1994 and 2000–2007 survival prospects for prostate cancer patients improved remarkably in all countries. The biggest improvement was recorded in Malta which jumped from 44 percent to 82 percent, but even Denmark, Slovenia, and Portugal recorded astounding improvements. Despite this development, Eastern European countries are still trailing behind Western European countries, with the exception of Denmark and the UK.

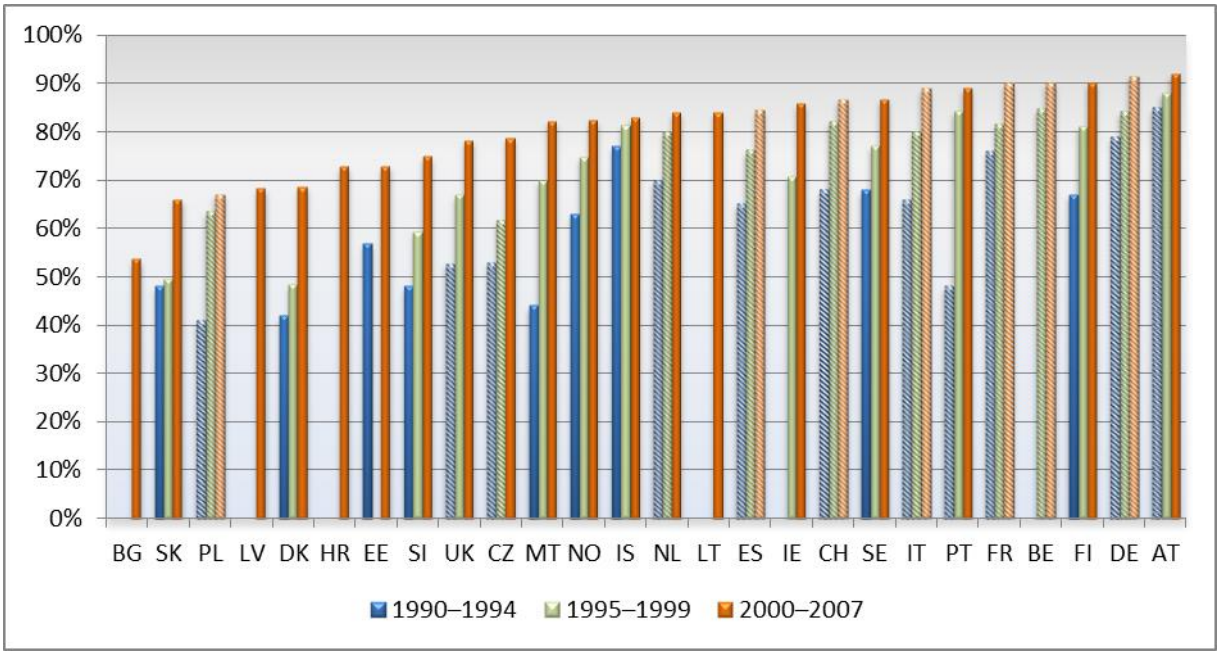


FIGURE A11: 5-YEAR AGE-ADJUSTED RELATIVE SURVIVAL RATES FOR PROSTATE CANCER IN PATIENTS AGED ≥15 YEARS, 1990–2007 [15, 27]

Notes: see Figure 8

Taken together, 5-year relative survival rates for all cancers combined, and for three out of four major cancer types, increased steadily between 1990–1994 and 2000–2007 in all countries. Remarkable increases were recorded for prostate cancer, whereas the improvements for lung cancer were only very marginal. Survival rates in Eastern European countries are lower than in Western European countries, but greater improvements in absolute terms in the East brought it closer to the West. Among the wealthier countries some Nordic countries (Sweden, Iceland, Finland), and the German-speaking countries (Austria, Germany, Switzerland) fared especially well, whereas the Baltic states, Bulgaria, and Poland are the countries with the greatest potential for improvements.

The general trend of increasing relative survival rates during the last decades in Europe has been attributed to advances in cancer care and also to screening [22]. An examination of 5-year survival rates in the United States and Australia has also concluded that the long-run increase in survival is due to improved prevention, screening, or therapy [89]. Country differences in survival rates have been explained by factors such as differences in accessibility to good care, different stage at diagnosis, different diagnostic intensity and screening approaches, differences in cancer biology, variations in socio-economic conditions, different lifestyles and general health [15].

Especially for cancers for which screening methods are available, it is important to keep in mind the way survival rates are affected by them. Increasing screening efforts and more sensitive diagnostic technologies detect more early-stage cancer cases, including cases that

would never have become symptomatic from their cancer [90]. Since survival of early-stage cancer is higher, this can lead to an overall increase of survival rates. To disentangle the influence of screening and medical treatment, stage-specific survival rates can be considered. 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 between countries. However, wide differences among these countries persist even when stage-specific survival rates are compared. This suggests that other factors apart from stage of diagnosis, such as medical treatment, are important for overall survival [91-94].

Even in countries with (population-based) screening programs, actual screening rates have been far from satisfactory in the past [16]. Thus, although screening has the potential to improve survival rates, it can only explain part of the improvement. It is also important to remember that established screening methods are only available for a handful of (admittedly rather common) cancer types. Furthermore, the steady increase in survival in all cancers combined that has been observed in the Nordic countries at least since the 1960s set in long before now common screening methods were discovered and applied. The figures above have also shown that in cancers without screening methods such as CML or colorectal cancer (for which mass screening until 2007 was uncommon in Europe) enormous (for CML) improvements have been achieved. Thus, as described in section 1.1.2, the central factors that can explain this development are advances in diagnostics and medical treatment.

A.4 Economic preconditions and spending on health

Figure A12 contrasts how GDP per capita (between 1995 and 2014) and total health expenditure as a share of GDP (between 1995 and 2013) evolved in a selected number of countries. Based on GDP per capita (at current prices) in 2014, the countries are grouped into three groups; wealthier countries, the so-called “big 5”, and poorer countries. Measured at current prices, i.e., not adjusted for inflation, GDP per capita rose considerably in all countries between 1995 and 2014. It almost doubled in the wealthier countries (e.g. in the Netherlands from €21,000 to €36,000) and even in the big 5 (e.g. in Italy from €15,000 to €26,000). In the poorer countries GDP per capita grew by a factor of 3 to 7 (e.g. in Poland from €3,000 to €11,000), which meant that by 2014 countries like the Czech Republic and Estonia had almost caught up with Portugal and Greece. Since GDP is a measure of economic activity, the rapid economic slowdown in the aftermath of the financial crisis led to a distinct kink in 2009. By 2014 most countries had reached or surpassed pre-crisis levels in GDP per capita.

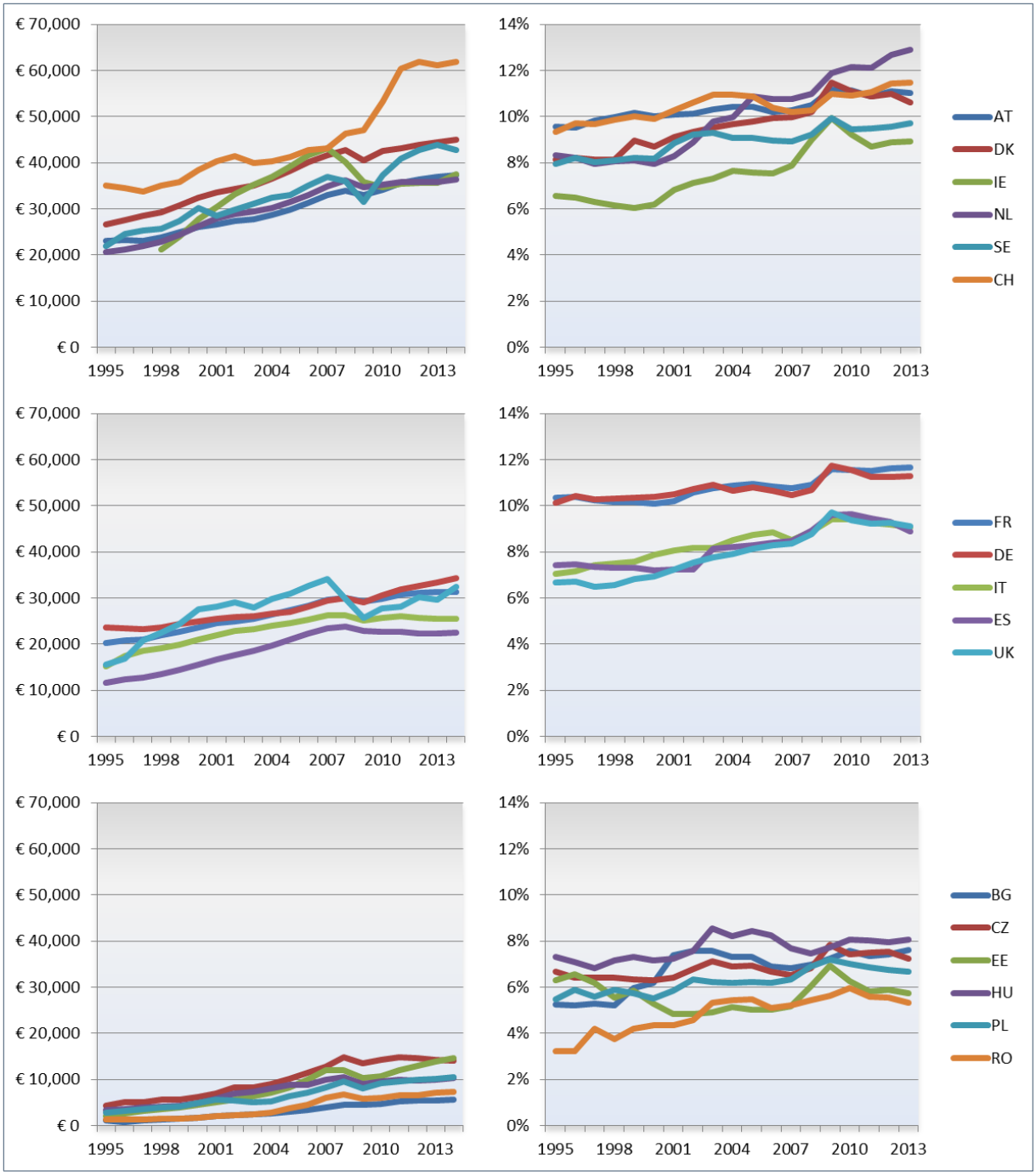


FIGURE A12: GDP PER CAPITA (IN € AT CURRENT PRICES, NOT ADJUSTED FOR PPP) 1995–2014 (LEFT-HAND SIDE FIGURES) AND TOTAL HEALTH EXPENDITURE AS A SHARE OF GDP (IN %) 1995–2013 (RIGHT-HAND SIDE FIGURES) IN SELECTED COUNTRIES, [11, 33, 36]

Notes: GDP data are based on the 1995 European system of national and regional accounts (ESA 95), since data on the share of health expenditure from the WHO are based on these figures. The 2014 values are calculated by applying the nominal growth rate between 2013 and 2014 based on ESA 2010 to the 2013 values.
GDP figures in Ireland and Switzerland are to some extent attenuated due to a high presence of multinational companies; the gross national product (GNP) that strips out this effect is markedly lower.
Note that the development of the share of health expenditure over time should be interpreted with some caution since there are breaks in the time series for some countries.

On the right-hand side of **Figure A12** the share of total health expenditure also shows an increasing pattern between 1995 and 2013 in many countries. This general increase is partly driven by population aging which results in an increasing share of elderly that are in need of health care due to a higher risk of falling ill and contracting diseases like cancer [6]. Between 2008 and 2009 the share of health expenditure increased in all countries (ranging from an increase of 0.2 pp in Malta and Romania to over 1 pp in the Czech Republic, Denmark, Germany, Norway, and Slovakia), since the expenditure for health care could and were not cut to the same extent and as quickly as the overall economic activity. After 2009 this share remained mostly stable or even decreased in most countries.

The share of health expenditure in **Figure A12** differs between countries. In some of the wealthier countries, such as Austria and Switzerland, but also in Germany and France, the share was already high in 1995 with 10 percent and had increased to almost 12 percent in 2013. In the poorer countries the share increased less (mostly by about 1 pp) than in other countries (about 2 pp). In Estonia the share even decreased slightly. In 2013 many of the poorer countries' health expenditure amounted to around 7 percent of GDP, whereas in the wealthier countries and the big 5 they amounted to between 9 and 12 percent.

Since this share is a relative measure, it means that if the share increases over time, growth in health expenditure outpaces general economic growth. Put differently, an increase in GDP per capita together with an increasing share of health expenditure effectively means that health expenditure per capita increased faster than GDP per capita (see e.g. the UK between 1995 and 2007). On the other hand, a decreasing share means that health expenditure per capita either increased slower than GDP per capita (in a time when GDP per capita rises; see e.g. Spain between 1995 and 2002) or decreased faster than GDP per capita (in a time when GDP per capita falls; see e.g. Spain between 2010 and 2013).

In sum, poorer countries' economic performance has improved greatly between 1995 and 2014 and brought them much closer to the wealthier countries, yet large disparities in GDP per capita still persist. Even though the share of health expenditure in the poorer countries increased, it increased even more in wealthier countries. These two factors together imply that per capita spending on health is still considerably lower in the poorer countries. Measured in PPP terms, the differences in GDP per capita as well as health spending per capita are considerably smaller though.

A.5 Methodology for the calculation of the cancer-specific health expenditure as a share of total health expenditure

Austria

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

Belgium

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

Bulgaria

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

Croatia

The share used is the arithmetic average 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 [22]. As a source the OECD cites the OECD Questionnaire on Systems of Cancer Care 2010. In the absence of any other data, 6.3% is used as the best available estimate.

Czech Republic

There are two estimates available. Firstly, in a discussion paper the WHO estimated the share of cancer-related expenditure on total health expenditure to have been 5.5% in 2006 [39]. The WHO's analysis for the Czech Republic was based on data from the OECD. Note that 48% of health expenditure in the disease-specific data for the Czech Republic had initially been unallocated, but in the analysis they were then allocated in the same proportions as the allocated expenditure. Secondly, the OECD reports that cancer (not including benign cancers) accounted for 5.4% of total health expenditure in 2007 [22]. As a source the OECD cites the OECD Questionnaire on Systems of Cancer Care 2010. Taken together, both available estimates seem to be based on OECD data, are almost similar and refer to two consecutive years. Following the principle of providing conservative estimates, the lower estimate of 5.4% is used as the best available estimate.

Denmark

There are two estimates available. Firstly, a comparative study for the Nordic countries estimated that the cancer costs (mainly related to primary diagnosis ICD-10 C00-C97) in Denmark amounted to DKK 5,989 million in 2007 [95]. These costs include expenditure on hospital treatment (comprises inpatient-, day patient- and outpatient activities) (DKK 5,965 million) and prescription drugs (DKK 24 million). Since other relevant expenditure for screening, long-term care and primary care could not be included, the expenditures are underestimated. According to the WHO total health expenditure amounted to DKK 169,311 million in 2007 [33]. Consequently, expenditure on cancer accounted for about 3.5% of total health expenditure. Secondly, the OECD reports that cancer (not including benign cancers) accounted for 4.5% of total health expenditure in 2008 [22]. Yet it is noted that the data refer to costs in hospitals only. As a source the OECD cites the OECD Questionnaire on Systems of Cancer Care 2010. Taken together, both studies provide incomplete estimates of the true costs of cancer. Since costs for prescription drugs seem be very low compared to costs for hospital treatment, both studies provide basically the same information. Compared to expenditure in similar countries both shares of 3.5% and 4.5% seem to be fairly low, but the latter seems to be more realistic. Thus, 4.5% is used as the best available estimate.

Estonia

In a discussion paper the WHO estimated the share of cancer-related expenditure on total health expenditure to have been 9.4% in 2004 [39]. 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 a lower co-payments in Estonia [96]. If all cancer expenditure were exclusively paid for by the Health Insurance Fund, then 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

There are three estimates available. Firstly, the OECD reports that cancer (not including benign cancers) accounted for 4.2% of total health expenditure in 2004 [22]. Yet it is noted

that the data do not include all costs related to drugs. As a source the OECD cites the OECD Questionnaire on Systems of Cancer Care 2010. Secondly, the Cancer Society of Finland estimated that the direct costs of cancer (ICD-10 C00-C97) amounted to €420.1 million in 2004 [97]. These costs include expenditures on inpatient care (€239.8 million), outpatient care (€105.7 million), drugs (€60.2 million), rehabilitation (€4.0 million), and screening (€10.4 million in 2003). According to the WHO total health expenditure amounted to €12,500 million in 2004 [33]. Consequently, expenditures on cancer accounted for about 3.4% of total health expenditure. Thirdly, a comparative study for the Nordic countries estimated that the cancer costs (mainly related to primary diagnosis ICD-10 C00-C97) in Finland amounted to €640.8 million in 2007 [95]. These costs include expenditures on hospital treatment (comprises inpatient-, day patient- and outpatient activities) (€501.6 million), prescription drugs (€109.2 million), and screening programs for breast and cervical cancer (€30 million). Since other relevant expenditures for long-term care and primary care could not be included, the expenditures are underestimated. According to the WHO total health expenditure amounted to €14,464 million in 2007 [33]. Consequently, expenditures on cancer accounted for about 4.4% of total health expenditure.

Taken together, the estimate from the OECD is disregarded as the other two estimates seem to be more comprehensive. A comparison of the cost categories of the estimates for 2004 and 2007 shows that costs increased in all categories, which is in line with the overall development of total health expenditure and the increasing number of cancer patients in Finland. Even though not all relevant costs are included, 4.4% is used as the best available estimate.

France

The National Cancer Institute (INCa) estimated the direct cost of cancer in 2004 [65] (summary table in English in [98]). Direct costs amounted to €11,254 million. 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 total health expenditure used in this report. According to the WHO total health expenditure amounted to €180,224 million in 2004 [33]. Consequently, expenditures on cancer accounted for about 6.2% of total health expenditure. In the absence of any more recent data, 6.2% is used as the best available estimate.

Germany

The Federal Statistical Office (Destatis) provides disease-specific health expenditures based on the WHO International Classification of Disease (ICD-10). The most recent data are from

2008. Expenditures on neoplasms (ICD10 C00-D48) amounted to €18.078 billion [46]. According to the WHO total health expenditure amounted to €264.798 billion in 2008 [33]; note that the figure for total health expenditure stated by Destatis (€254.280 billion) actually refers to current health expenditure. Consequently, expenditures on neoplasms accounted for about 6.8% of total health expenditure. In the absence of any more recent data, 6.8% is used as the best available estimate.

Greece

In its "National Action Plan on Cancer, 2011-2015" the Ministry of Health states the following [99]. "Information 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." In the absence of any other data, 6.5% is used as the best available estimate.

Hungary

There are two estimates available. Firstly, in a discussion paper the WHO estimated the share of cancer-related expenditures on total health expenditure to have been 8.2% in 2006 [39]. The WHO's analysis for Hungary was based on data from the OECD. Note that expenditures in the disease-specific data for Hungary that initially had been unallocated were allocated in the same proportions as the allocated expenditures in the analysis. Secondly, the OECD reports that cancer (including benign cancers) accounted for 7.0% of total health expenditure in 2006 [22]. As a source the OECD cites the OECD Disease Expenditure studies. Taken together, both available estimates seem to be based on OECD data and refer to the same year. Following the principle of providing conservative estimates, the lower estimate of 7.0% is used as the best available estimate.

Iceland

A comparative study for the Nordic countries estimated that the cancer costs (mainly related to primary diagnosis ICD-10 C00-C97) in Iceland amounted to ISK 4,573 million in 2007 [95]. These costs include expenditures on hospital treatment (comprises inpatient-, day patient- and outpatient activities) (ISK 3,867 million), prescription drugs (ISK 228 million), and screening programs for breast and cervical cancer (ISK 479 million). Since other relevant expenditures for long-term care and primary care could not be included, the expenditures are underestimated. According to the WHO total health expenditure amounted to ISK 118,962 million in 2007 [33]. Consequently, expenditures on cancer accounted for about 3.8% of total health expenditure. Compared to the results from similar countries, this estimate is very low. 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 [100]. According to this study, expenditures on cancer amounted to €7.5 billion and total health expenditure to €110 billion, 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 average of the shares in Estonia and Poland.

Lithuania

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

Luxembourg

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

Malta

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

Netherlands

The National Institute for Public Health and the Environment (RIVM) provides a database on cost of illness in line with definitions from the OECD's System of Health Accounts. The most recent data are from 2011. Expenditures on "neoplasms" amounted to €4.099 billion [101]. According to the WHO total health expenditure amounted to €72.458 billion in 2011 [33]; note that the figure for total health expenditure stated by RIVM (€66.757 billion) actually refers to current health expenditure. Consequently, expenditures on neoplasms accounted for about 5.7% of total health expenditure. In the absence of any more recent data, 5.7% is used as the best available estimate.

Norway

A comparative study for the Nordic countries estimated that the cancer costs (mainly related to primary diagnosis ICD-10 C00-C97) in Norway amounted to NOK 6,782 million in 2007 [95]. These costs include expenditures on hospital treatment (comprises inpatient-, day patient- and outpatient activities) (NOK 5,660 million), prescription drugs (NOK 776 million), and screening programs for breast and cervical cancer (NOK 346 million). Since other relevant expenditures for long-term care and primary care could not be included, the expenditures are underestimated. According to the WHO total health expenditure amounted to NOK 201,722 million in 2007 [33]. Consequently, expenditures on cancer accounted for about 3.4% of total health expenditure. Compared to the results from similar countries, this estimate is very low. In the absence of any other data, 3.4% is used as the best available estimate.

Poland

The National Health Fund (NFZ), responsible for financing public health care, spent PLN 6,291,814,043 on cancer care (ICD-10 C00-C97, D00-D09, D37-D48) in 2011 [68]. 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 drugs reimbursed under the list of pharmaceutical refund (i.e. cancer drugs distributed by pharmacies) are not included. In 2010 (and also in 2009) these expenditures amounted to just over PLN 500 million according to the Ministry of Health and the NFZ [67]. Adding these PLN 500 million to the PLN 6,292 million puts the expenditures on cancer in 2011 to about PLN 6,792 million. According to the WHO total health expenditure amounted to PLN 104,997 million in 2011 [33]. Consequently, expenditures on cancer accounted for about 6.5% of total health expenditure. Note that this estimate does not include private payments for cancer care, leading to an underestimation of the true expenditures. Yet co-payments for oncology services and oncology drugs are very small compared with other health care provisions in Poland [102]. Following the principle of providing conservative estimates, 6.5% is used as the best available estimate.

Portugal

A study on the cost of cancer estimated that “direct medical care expenditures” on cancer amounted to €565.03 million in 2006, while “total health cost” amounted to €14,500 million (in 2005), resulting in a share of 3.9% [103]. Note that “direct medical care expenditures” include expenditures on hospitalization, ambulatory care, chemotherapy, radiotherapy,

medical consultations and drugs, but expenditures on, e.g., screening and primary prevention seem to be excluded. This means that the expenditures on cancer are underestimated. In the absence of any other data, 3.9% is used as the best available estimate.

Romania

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

Slovakia

The share used is the arithmetic average of the shares in the Czech Republic and Hungary.

Slovenia

There are two estimates available. Firstly, in a discussion paper the WHO estimated the share of cancer-related expenditures on total health expenditure to have been 6.7% in 2006 [39]. The WHO's analysis for Slovenia was based on personal communication and also on data from the OECD. Note that expenditures in the disease-specific data for Slovenia that initially had been unallocated were allocated in the same proportions as the allocated expenditures in the analysis. Secondly, the OECD reports that cancer (including benign cancers) accounted for 3.4% of total health expenditure in 2008 [22]. As a source the OECD cites the OECD Disease Expenditure studies. Compared to expenditures in similar countries and in view of the survival rates in Slovenia this latter estimate seems to be fairly low, particularly since it even includes benign cancers. Therefore, 6.7% is used as the best available estimate.

Spain

The OECD reports that cancer (not including benign cancers) accounted for 1.9% of total health expenditure in 2003 [22]. As a source the OECD cites the OECD Questionnaire on Systems of Cancer Care 2010. Compared to expenditures in similar countries and in view of the survival rates in Spain this seems to be an exceptionally low estimate. Data on cancer expenditures in two different regions in Spain provide more realistic estimates. The first estimate is for the Canary Islands in 1998, which then encompassed 4 percent of Spain's population. In 1998 the direct costs of cardiovascular disease and cancer were €134.44 and €58.04 million, respectively, representing together 16% of total health expenditure [104]. This implies that cancer accounted for about 4.8% of total health expenditure.

The second estimate is for Catalonia in 2008, which then encompassed 16 percent of Spain's population. The Catalonian Department of Health provides expenditure data broken down by 17 disease categories based on the WHO International Classification of Disease (ICD-9). The governmental health budget for "neoplasms" was estimated to equal €762 million compared

to the total governmental health budget of €8,945 million in 2008, equaling a share of 8.5% [105]. However, governmental expenditures in all of Spain only comprised 68% of total health expenditure in 2008 [106]. Assuming that the same share of governmental expenditures is valid for Catalonia and assuming that no expenditures on cancer arise outside the governmental sphere, the share of cancer expenditures on total health expenditure amounted to about 5.8% (8.5%*68%). Since the latter assumption is probably not entirely true, this estimate represents an underestimation of the true share of cancer expenditures. In absence of any data covering all of Spain, and given the results from similar countries, the estimate for Catalonia seems to be the most realistic one. Thus, 5.8% is used as the best available estimate.

Sweden

There are four estimates available. Firstly, the Swedish Cancer Society estimated that the direct costs of cancer amounted to SEK 16,830 million in 2004 [71]. These costs include expenditures for care (SEK 14,465 million), drugs (SEK 2,005 million), screening programs (SEK 200 million), and primary prevention (SEK 160 million). Note that publicly funded research (SEK 750 million) is not included, since it is not part of the definition of total health expenditure used in this report. However, a retrospective analysis by the National Board of Health and Welfare and the Swedish Association of Local Authorities and Regions on actual sales data showed that drug costs amounted SEK 1,630 million (SEK 1.530 million for cancer drugs and SEK 100 million for antiemetic drugs) in 2004 [70]. This puts the direct costs in 2004 to SEK 16,455 million. According to the WHO total health expenditure amounted to SEK 241,827 million in 2004 [33]. Consequently, expenditures on cancer accounted for about 6.8% of total health expenditure. Secondly, the OECD reports that cancer (including benign cancers) accounted for 3.1% of total health expenditure in 2006 [22]. Yet it is noted that the data refer to costs in hospitals only. As a source the OECD cites the OECD Disease Expenditure studies. Thirdly, a comparative study for the Nordic countries estimated that the cancer costs (mainly related to primary diagnosis ICD-10 C00-C97) in Sweden amounted to SEK 11,523 million in 2007 [95]. These costs include expenditures on hospital treatment (comprises inpatient-, day patient- and outpatient activities) (SEK 8,956 million), prescription drugs (SEK 1,686 million), and screening programs for breast and cervical cancer (SEK 881 million). Since other relevant expenditures for long-term care and primary care could not be included, the expenditures are underestimated. According to the WHO total health expenditure amounted to SEK 278,754 million in 2007 [33]. Consequently, expenditures on cancer accounted for about 4.1% of total health expenditure. Fourthly, a cost-of-illness study estimated the health care cost of cancer (defined as ICD-10 C00-C97) amounted to SEK 15,537 million in 2013 [107]. These costs include expenditures on screening (SEK 642 million), specialized outpatient care (SEK 4,145 million), inpatient care (SEK 6,513 million), cancer drugs (SEK 2,766 million), primary care (SEK 265 million), and palliative care and

other care services (SEK 1,207 million). Expenditures for primary prevention, screening (PSA), other treatment-related drugs (e.g. antiemetic drugs) and patient fees related health care visits were not included leading to an underestimation. According to the WHO total health expenditure amounted to SEK 353,550 million in 2013 [33]. Consequently, expenditures on cancer accounted for about 4.4% of total health expenditure.

Taken together, the estimate from the OECD is disregarded as the other three estimates seem to be more comprehensive. A comparison of the cost categories of the estimates for 2004, 2007, and 2013 shows that "care" costs in 2004 exceed the ones in subsequent years. Such a strong decline in care costs seems unlikely in the face of an increasing number of patients. Due to the more wide-ranging inclusion of relevant costs and given the results from similar countries with comprehensive disease-specific health accounts, 6.8% is used as the best available estimate.

Switzerland

A report commissioned by the Federal Office of Public Health (Bundesamt für Gesundheit) provides disease-specific health expenditures in 2011 [108]. Expenditures on cancer (ICD-10 C00-C97) amounted to CHF 4.005 billion, whereas total health expenditure amounted to CHF 64.6 billion in 2011 in this report (CHF 64.7 billion according to the WHO [33]). Consequently, expenditures on cancer accounted for about 6.2% of total health expenditure. In the absence of any other data, 6.2% is used as the best available estimate.

United Kingdom

The NHS England provides expenditure data broken down by 23 so-called "programme budgeting categories" based on the WHO International Classification of Disease (ICD-10). The most recent data are from 2012/13. The NHS' expenditures on "cancers & tumours" amounted to GBP 5.68 billion, while total expenditures amounted to GBP 94.78 billion [109]. This equals a share of 6.0% for England within the remit of the NHS. However, governmental expenditures only comprised 84% of the total health expenditure in the UK in 2012 [6]. Assuming that this share of governmental expenditures is the same in England and assuming that that all cancer expenditures were exclusively paid for by the NHS, then the share of cancer expenditures on total health expenditure would be about 5.0% (6.0%*84%). Since co-payments for cancer drugs do occur [110], this estimate represents probably an underestimation of the true expenditures. Following the principle of providing conservative estimates, 5.0% represents nonetheless the best available estimate for England. In absence of any data covering all of the UK, the estimate for England of 5.0% is used as the best available estimate.

A.6 Summary tables of the economic burden of cancer

TABLE A1: TOTAL HEALTH EXPENDITURE AND ESTIMATED DIRECT HEALTH COST OF CANCER IN EUROPE (NOT ADJUSTED FOR PPP), 2014

	Total health expenditure			Direct health cost of cancer		
	% of GDP	total (million €)	per capita (€)	% of THE	total (million €)	per capita (€)
Austria	11.0%	35,231	4,125	6.5%*	2,290	268
Belgium	11.2%	43,674	3,914	6.2%*	2,722	244
Bulgaria	7.6%	3,107	427	6.8%*	210	29
Croatia	7.3%	3,116	738	6.9%*	213	51
Cyprus	7.4%	1,182	1,372	6.3%	74	86
Czech Republic	7.2%	10,678	1,015	5.4%	577	55
Denmark	10.6%	27,003	4,789	4.5%	1,215	216
Estonia	5.7%	1,118	840	5.8%	65	49
Finland	9.4%	18,355	3,364	4.4%	808	148
France	11.7%	242,017	3,661	6.2%	15,005	227
Germany	11.3%	319,669	3,869	6.8%	21,737	263
Greece	9.8%	17,601	1,600	6.5%	1,144	104
Hungary	8.0%	8,113	828	7.0%	568	58
Iceland	9.1%	1,106	3,382	3.8%	42	129
Ireland	8.9%	15,419	3,339	5.0%*	771	167
Italy	9.1%	142,435	2,327	6.7%	9,543	156
Latvia	5.7%	1,382	693	6.2%*	85	43
Lithuania	6.2%	2,252	767	6.2%*	138	47
Luxembourg	7.1%	3,391	6,079	6.2%*	211	379
Malta	8.7%	671	1,576	6.5%*	44	102
Netherlands	12.9%	79,076	4,698	5.7%	4,507	268
Norway	9.6%	35,439	6,900	3.4%	1,205	235
Poland	6.7%	27,034	706	6.5%	1,757	46
Portugal	9.7%	16,387	1,572	3.9%	639	61
Romania	5.3%	7,909	395	6.8%*	534	27
Slovakia	8.2%	6,063	1,117	6.2%*	376	69
Slovenia	9.2%	3,357	1,629	6.7%	225	109
Spain	8.9%	91,705	2,007	5.8%	5,319	116
Sweden	9.7%	40,386	4,159	6.8%	2,746	283
Switzerland	11.5%	57,573	7,105	6.2%	3,570	441
United Kingdom	9.1%	191,073	2,953	5.0%	9,554	148
Europe	10.1%†	1,453,522	2,793	6.0%‡	87,895	169

Notes: GDP = gross domestic product, PPP = purchasing power parity, THE = total health expenditure.
THE in 2014 was calculated with GDP data from 2014 and the share of THE on GDP from 2013 [33].
The underlying GDP data are based on ESA 95. The 2014 values are calculated by applying the nominal growth rate between 2013 and 2014 based on ESA 2010 to the 2013 values [11, 34, 36].
Source for THE on cancer: own estimate based on national sources; see Appendix for methodology.
* Estimated share based on data from similar countries; see Appendix for methodology.
† The estimate is calculated as THE of all countries divided by total GDP.
‡ The estimate is calculated as THE on cancer of all countries divided by THE.

TABLE A2: DEVELOPMENT OF THE ECONOMIC BURDEN OF CANCER (IN MILLION €; UNADJUSTED 2014 PRICES), 1995–2014

	1995		2000		2005			2010			2014		
	Direct health cost	Mortality loss	Direct health cost	Mortality loss	Direct health cost	Cancer drugs	Mortality loss	Direct health cost	Cancer drugs	Mortality loss	Direct health cost	Cancer drugs	Mortality loss
Austria	1,474	1,250	1,686	1,202	2,002	221	1,146	2,270	411	1,129	2,290	510	1,110
Belgium	1,308	1,625	1,523	1,594	2,029	257	1,546	2,527	439	1,489	2,722	488	1,437
Bulgaria	87	159	107	141	160	39	160	191	51	146	210	128	151
Croatia	124	247	179	238	217	29	240	275	61	234	213	67	217
Cyprus	32	40	49	41	65	-	36	85	-	48	74	-	43
Czech Republic	271	786	294	723	480	122	633	648	213	535	577	162	487
Denmark	708	1,319	875	1,335	1,070	119	1,191	1,249	225	1,027	1,215	274	949
Estonia	23	92	32	72	47	4	68	60	10	52	65	9	63
Finland	482	596	548	677	711	124	690	780	185	613	808	219	560
France	10,300	7,764	11,501	8,327	13,460	2,091	8,395	14,740	3,232	7,713	15,005	3,322	7,509
Germany	15,356	13,725	16,060	12,471	18,998	1,568	11,243	21,018	3,920	11,542	21,737	4,765	11,607
Greece	927	810	1,006	797	1,453	107	832	1,395	130	810	1,144	45	699
Hungary	562	669	486	716	760	149	674	606	231	580	568	232	602
Iceland	39	33	71	33	84	-	30	39	-	35	42	-	37
Ireland	252	419	432	545	718	97	524	757	153	448	771	191	486
Italy	5,969	5,822	8,513	5,496	10,039	1,207	5,479	10,551	2,123	5,088	9,543	2,456	4,953
Latvia	28	104	55	85	73	4	89	77	7	82	85	14	80
Lithuania	29	137	71	116	103	10	112	130	12	94	138	16	100
Luxembourg	75	78	131	71	171	5	71	206	8	74	211	6	76
Malta	16	24	26	19	35	-	16	38	-	20	44	-	22
Netherlands	1,780	2,405	2,049	2,877	2,801	336	2,844	4,405	579	2,785	4,507	654	2,480
Norway	427	801	665	919	886	77	811	1,075	106	756	1,205	158	716
Poland	787	1,882	914	1,727	1,183	181	1,660	1,732	344	1,702	1,757	430	1,627

Portugal	392	666	628	757	724	256	783	782	256	760	639	227	698
Romania	465	777	418	731	446	60	668	567	265	662	534	275	651
Slovakia	129	278	123	260	206	48	261	380	129	238	376	148	235
Slovenia	176	204	194	187	203	29	185	231	56	181	225	65	175
Spain	2,950	3,247	3,596	3,784	5,097	972	4,192	6,259	1,796	3,731	5,319	1,658	3,443
Sweden	1,369	1,024	1,857	1,043	2,098	188	982	2,320	281	846	2,746	338	861
Switzerland	1,702	1,723	1,936	1,662	2,157	279	1,513	2,791	439	1,503	3,570	563	1,404
United Kingdom	4,478	8,398	7,873	8,210	10,296	874	7,897	9,074	1,695	7,249	9,554	2,366	7,259
Europe	52,716	57,104	63,895	56,857	78,772	9,455	54,969	87,259	17,359	52,170	87,895	19,784	50,737

Notes: Cancer is defined as ICD-10 C00-D48 for direct health cost and ICD-10 C00-C97,B21 for productivity loss due to premature mortality from cancer during working age ("mortality loss").
The adjustment for inflation was carried out with the country-specific inflation rate [35]. The 1995 estimates could only be adjusted for inflation between 1996 (for BG between 1997 and for HR and RO between 1998) and 2014 due to lack of data. For CH the same inflation rate as in AT was assumed for 1996 and 2000.
Cancer drugs: Data on cancer drugs sales in CY, IS, and MT are missing due to lack of data. Data for EE, EL, LV, and LU only comprise retail sales. The value in 2005 for IE is from 2006 and for PT from 2010.
Mortality loss: The 1995 and 2000 estimates for CY are based on mortality data in 2004. The 2005 estimate for PT is based on mortality data in 2007. The 2014 estimates for HR, CZ, FI, DE, HU, LT, LU, NL, NO, PL, PT, ES, SE, CH, and UK are based on mortality data in 2013, for BE, BG, CY, DK, EE, EL, IE, IT, LV, and RO in 2012, for FR in 2011, for SI in 2010, and for IS in 2009 [12][6]. The 1995 estimates for HU and SI are based on employment rates in 1996, for CZ, EE, PL, and RO in 1997, for LV, LT, and SK in 1998, for CY in 1999, for BG and MT in 2000, and HR in 2002. The 2000 estimate for HR is based on employment rates in 2002 [78]. Earnings in all years are from 2010 [77], and have been adjusted for inflation to 2014 prices[35].

TABLE A3: DEVELOPMENT OF THE ECONOMIC BURDEN OF CANCER PER CAPITA (IN €; UNADJUSTED 2014 PRICES), 1995–2014

	1995		2000		2005			2010			2014		
	Direct health cost	Mortality loss	Direct health cost	Mortality loss	Direct health cost	Cancer drugs	Mortality loss	Direct health cost	Cancer drugs	Mortality loss	Direct health cost	Cancer drugs	Mortality loss
Austria	186	157	210	150	243	27	140	271	49	135	268	60	131
Belgium	129	160	148	156	194	25	148	232	41	137	244	44	130
Bulgaria	10	19	13	17	21	5	21	25	7	20	29	18	21
Croatia	26	53	41	53	50	7	56	64	14	54	51	16	51
Cyprus	49	56	70	57	88	-	50	103	-	58	86	-	50
Czech Republic	26	76	29	70	47	12	62	62	20	51	55	15	46
Denmark	135	253	164	251	198	22	220	225	41	186	216	49	170
Estonia	16	63	24	52	35	3	50	44	8	39	49	7	47
Finland	94	117	106	131	136	24	132	145	35	114	148	40	103
France	173	131	189	138	214	33	134	228	50	119	227	50	116
Germany	188	168	195	152	231	19	136	257	48	141	263	59	142
Greece	88	77	92	74	131	10	76	125	12	73	104	4	63
Hungary	55	65	47	70	75	15	67	60	23	58	58	23	61
Iceland	145	122	253	120	282	-	101	122	-	111	129	-	116
Ireland	70	116	114	144	173	23	127	166	34	98	167	41	106
Italy	105	102	149	97	171	21	95	175	36	86	156	40	83
Latvia	11	42	23	36	33	2	40	37	3	39	43	7	39
Lithuania	8	38	20	33	31	3	33	42	4	30	47	6	34
Luxembourg	183	193	299	165	368	12	153	405	15	147	379	10	142
Malta	43	64	65	49	87	-	39	91	-	49	102	-	51
Netherlands	115	156	129	181	172	21	174	265	35	168	268	39	148
Norway	98	184	148	205	192	17	176	220	22	156	235	31	142
Poland	21	49	24	45	31	5	43	45	9	45	46	11	43

Portugal	39	67	62	74	68	24	74	74	24	72	61	22	67
Romania	21	34	18	33	21	3	31	28	13	33	27	14	32
Slovakia	24	52	23	48	38	9	49	70	24	44	69	27	43
Slovenia	89	103	97	94	102	14	93	113	28	88	109	32	85
Spain	75	83	89	94	118	22	97	136	39	80	116	36	74
Sweden	155	116	209	118	232	21	109	247	30	91	283	35	90
Switzerland	240	246	269	232	288	38	204	359	56	193	441	69	175
United Kingdom	77	145	134	140	171	15	131	146	27	116	148	37	114
Europe	107	115	128	114	155	19	108	169	34	101	169	38	98

Notes: see Table A2.
Population figures come from Eurostat [5].

TABLE A4: DEVELOPMENT OF THE ECONOMIC BURDEN OF CANCER (IN MILLION €; UNADJUSTED CURRENT PRICES), 1995–2014

	1995	2000	2005		2010		2014	
	Direct health cost	Direct health cost	Direct health cost	Cancer drugs	Direct health cost	Cancer drugs	Direct health cost	Cancer drugs
Austria	1,066	1,275	1,661	183	2,063	374	2,290	510
Belgium	927	1,148	1,688	214	2,341	407	2,722	488
Bulgaria	35	57	112	28	183	49	210	128
Croatia	79	124	172	23	254	56	213	67
Cyprus	21	36	55	-	80	-	74	-
Czech Republic	160	217	392	100	602	198	577	162
Denmark	509	680	912	102	1,179	213	1,215	274
Estonia	11	19	33	3	53	9	65	9
Finland	346	420	584	102	707	168	808	219
France	7,721	9,001	11,645	1,809	13,874	3,042	15,005	3,322
Germany	11,708	12,770	16,349	1,349	19,607	3,657	21,737	4,765
Greece	562	706	1,212	89	1,370	128	1,144	45
Hungary	179	253	525	103	543	207	568	232
Iceland	17	34	47	-	34	-	42	-
Ireland	174	333	655	88	728	147	771	191
Italy	4,093	6,322	8,415	1,012	9,782	1,968	9,543	2,456
Latvia	13	30	49	3	72	6	85	14
Lithuania	17	48	73	7	120	11	138	16
Luxembourg	49	92	139	4	188	7	211	6
Malta	10	19	29	-	35	-	44	-
Netherlands	1,228	1,530	2,402	288	4,063	534	4,507	654
Norway	305	523	751	66	1,018	100	1,205	158
Poland	361	636	942	144	1,594	317	1,757	430
Portugal	263	462	623	221	732	240	639	227
Romania	61	117	288	39	495	232	534	275
Slovakia	56	75	168	39	348	118	376	148
Slovenia	80	119	164	23	216	53	225	65
Spain	1,903	2,545	4,220	804	5,851	1,679	5,319	1,658
Sweden	1,050	1,492	1,838	165	2,253	273	2,746	338
Switzerland	1,434	1,705	2,084	269	2,807	442	3,570	563
United Kingdom	3,082	5,726	8,044	682	8,117	1,516	9,554	2,366
Europe	37,520	48,515	66,271	7,960	81,308	16,150	87,895	19,784

Notes: see Table A2

TABLE A5: DEVELOPMENT OF THE ECONOMIC BURDEN OF CANCER PER CAPITA (IN €; UNADJUSTED CURRENT PRICES), 1995–2014

	1995	2000	2005		2010		2014	
	Direct health cost	Direct health cost	Direct health cost	Cancer drugs	Direct health cost	Cancer drugs	Direct health cost	Cancer drugs
Austria	134	159	202	22	247	45	268	60
Belgium	92	112	161	20	215	38	244	44
Bulgaria	4	7	14	4	24	7	29	18
Croatia	17	28	40	5	59	13	51	16
Cyprus	32	52	74	-	96	-	86	-
Czech Republic	16	21	38	10	57	19	55	15
Denmark	97	127	168	19	212	38	216	49
Estonia	7	14	24	2	39	7	49	7
Finland	68	81	111	19	132	31	148	40
France	130	148	185	29	214	47	227	50
Germany	143	155	198	16	240	45	263	59
Greece	53	65	109	8	123	11	104	4
Hungary	17	25	52	10	54	21	58	23
Iceland	63	121	159	-	105	-	129	-
Ireland	48	88	158	21	160	32	167	41
Italy	72	111	144	17	162	33	156	40
Latvia	5	13	22	1	34	3	43	7
Lithuania	5	14	22	2	38	3	47	6
Luxembourg	120	211	298	10	371	14	379	10
Malta	27	48	72	-	84	-	102	-
Netherlands	79	96	147	18	244	32	268	39
Norway	70	117	162	14	208	21	235	31
Poland	10	17	25	4	41	8	46	11
Portugal	26	45	59	21	69	23	61	22
Romania	3	5	13	2	24	11	27	14
Slovakia	11	14	31	7	64	22	69	27
Slovenia	40	60	82	12	105	26	109	32
Spain	48	63	97	19	127	36	116	36
Sweden	119	168	203	18	240	29	283	35
Switzerland	203	237	278	36	361	57	441	69
United Kingdom	53	97	134	11	130	24	148	37
Europe	76	97	131	16	158	31	169	38

Notes: see Table A3

A.7 Composition of the direct cost of cancer

In addition to estimating the direct cost of cancer as a whole, different features regarding its composition can be analyzed. Such features cover how the cost is distributed across cancer types and cost categories. At the patient level it can also be explored how the cost varies by disease stage and, for those who do not survive the disease, how it develops from diagnosis to death. This kind of information is important for policy makers to set the right priorities and implement cost-effective measures to decrease the disease burden.

A.7.1 Distribution of the direct cost across cancer types

The distribution of the direct cost of cancer across the major cancer types in Germany, the Netherlands, and the UK is shown in **Figure A13**. These countries are the only ones that provide a breakdown of the direct cost of cancer by cancer type. In these countries five cancer types account for one third to one half of the direct costs. This means also that all other cancer types constitute small shares of the costs. Except in the UK, breast cancer causes the greatest cost followed by colorectal cancer and hematologic cancers, although the latter is a rather broad group of different cancer types. Lung cancer and prostate cancer account also for a considerable share of the direct costs. In Germany and the Netherlands costs are even reported separately for benign neoplasms. This group accounts for around 10 percent of the direct cost of cancer.

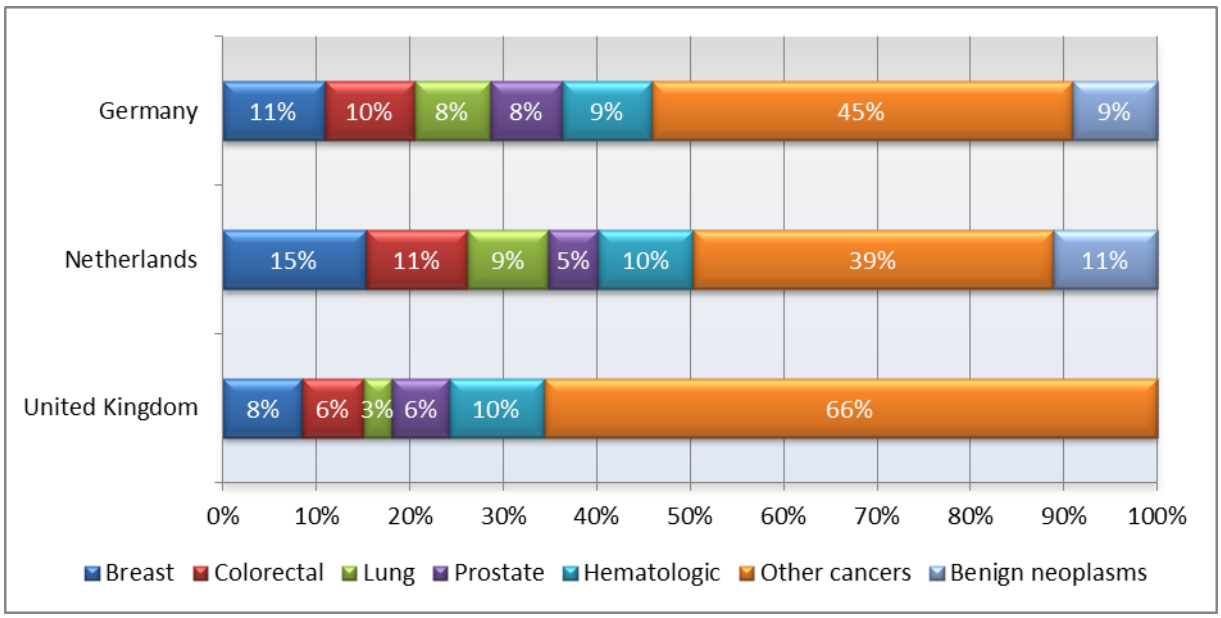


FIGURE A13: DISTRIBUTION OF THE DIRECT COST OF CANCER ACROSS CANCER TYPES IN SELECTED COUNTRIES, [46, 101, 109]

Notes: The estimates refer to year 2008 for Germany, 2011 for the Netherlands, and 2012/13 for the UK. The estimates for the UK cover only England, and the data cover only expenditure paid for by the NHS. In Germany "Breast" refers to ICD-10 C50, "Colorectal" to C18+C20, "Lung" to C33-C34, "Prostate" to C61, "Hematologic" to C81-C96, "Benign neoplasm" to D10-D36, and "Other cancers" to all remaining neoplasms in C00-D48.
In the Netherlands "Breast" refers to Breast cancer, "Colorectal" to Colorectal cancer, "Lung" to Lung cancer, "Prostate" to Prostate cancer, "Hematologic" to Non-Hodgkin's disease and Other lymphoid cancer and leukemia, "Benign neoplasm" to Benign neoplasms of genital organs and Other benign neoplasms, and

"Other cancers" to all remaining neoplasms.
In the UK "Breast" refers to the programme budgeting category Cancers & Tumours (C&T) – Breast, "Colorectal" to C&T - Lower GI, "Lung" to C&T - Lung, "Prostate" to C&T - Urological, "Hematologic" to C&T Haematological, and "Other cancers" to all remaining C&T categories. Note that no separate estimate for "Benign neoplasm" is published.

In general, cancer types with a high incidence (see Table 1) also account for a large share of the direct cost of cancer. In addition the treatability of the cancer types seems to matter. Cancer types for which decent long-term treatment is available and which have a good prognosis, such as breast cancer, take up a larger share of the costs. On the other hand, cancer types which are more difficult to treat and have a poor prognosis, such as lung cancer, take up a smaller share of the costs.

A.7.2 Distribution of the direct cost across cost categories

The distribution of the total direct cost of cancer across different cost categories in six countries is shown in **Figure A14**. The data come from country-specific cost-of-illness studies. The comparability of the shares of cost categories is somewhat limited, since they reflect to some extent how the health care systems are organized. For instance, a certain procedure, such as chemotherapy, might be performed mostly in ambulatory care in one country, whereas in another country a greater share of patients might be treated in inpatient care. Nonetheless several common features can be identified.

Inpatient care is by far the largest cost category and accounts for more than half of all costs. This includes the costs for surgery, but also part of the costs for diagnostics, radiation therapy, and systemic therapy. Ambulatory care (hospital outpatient care) is the second largest cost category accounting for 5 to 33 percent of all costs. In most countries it includes costs for diagnostics, radiation therapy, and systemic therapy. Prescription drugs, i.e. prescribed cancer drugs dispensed at pharmacies, represent the third largest cost category in most countries. However, in some countries their share can be very small, e.g. one percent in Portugal, since cancer drugs are simply not commonly dispensed at pharmacies and instead only administered in an inpatient or ambulatory care setting. Only in Spain primary care costs are reported, but they are modest and account for two percent of all costs. The costs for palliative and hospice care, rehabilitation, and nursing and care services is only reported in Poland and accounts there for six percent of all costs.

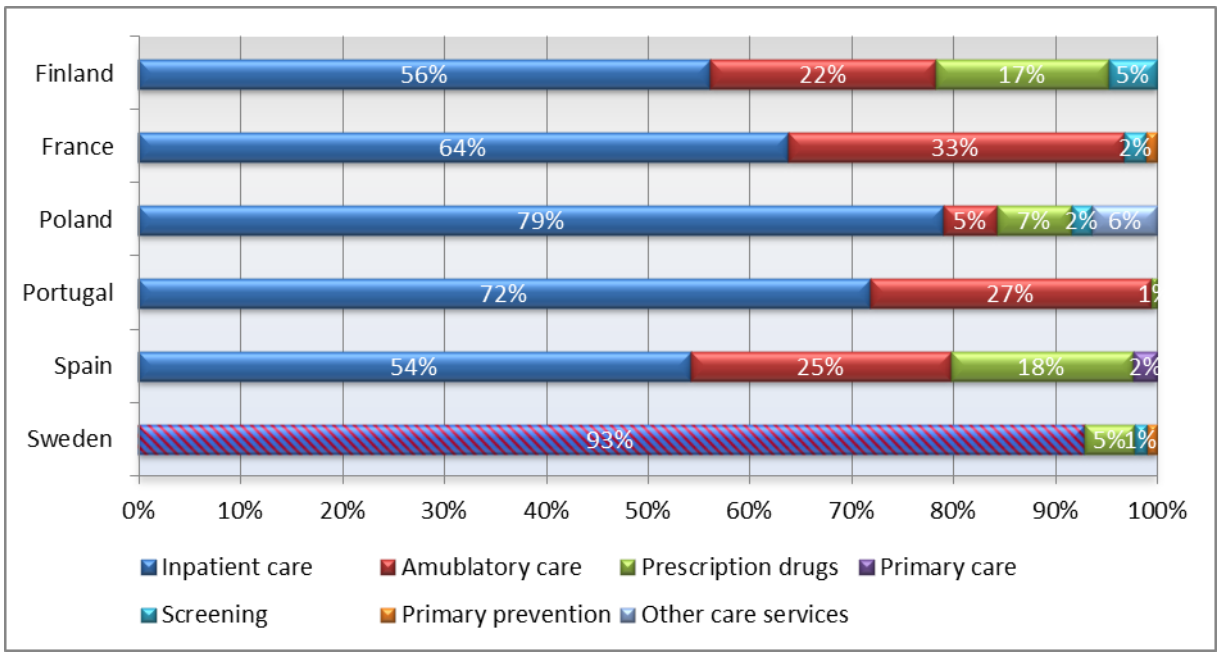


FIGURE A14: DISTRIBUTION OF THE DIRECT COST OF CANCER ACROSS COST CATEGORIES IN SELECTED COUNTRIES, [67, 68, 70, 71, 95, 98, 103, 105]

Notes: The estimates refer to year 2004 in France and Sweden, 2006 in Portugal, 2007 in Finland, 2008 in Spain, and 2011 in Poland.
The estimates for Spain cover only Catalonia.
In Poland and Spain the data cover only public expenditure.
"Inpatient care" includes expenditure on drugs in all countries; in Sweden even expenditure on ambulatory care.
"Ambulatory care" includes expenditure on drugs in France, Portugal, and Spain.
"Screening" includes only screening for breast and cervical cancer in Finland and Poland; in France it includes only screening for breast and colorectal cancer.
"Primary prevention" accounts for 1 percent of the cost in both France and Sweden.
"Other care services" include palliative and hospice care, rehabilitation, nursing and care services, and other services.

Countries differ also in the small share of costs devoted to screening (between one and five percent) and primary prevention (one percent in France and Sweden), but in most countries this information is either incomplete (e.g. does not include PSA testing for prostate cancer) or missing completely. In future years their share might grow as screening programs are rolled out, such as for colorectal cancer and possibly even for lung cancer, as well as new primary preventions are introduced, such as vaccination against HPV.

In sum, the lion share of the direct cost of cancer arises in inpatient and ambulatory care. However, it is not clear from the reviewed studies how much of this cost is spent solely on cancer drugs apart from prescribed cancer drugs. The cost of all cancer drugs will be reviewed below based on new data obtained for this report.

The shares of the different cost categories on the total cost in **Figure A14** are not set in stone. Changes in the organization of cancer care affect these shares. Even though inpatient care nowadays accounts for more than half the total direct cost of cancer, there is some evidence that this share might have been declining in the past. **Figure A15** shows the

development of inpatient days[29], i.e. overnight stays of hospitalized patients, and day cases[30], i.e. patients who do not stay overnight, based on hospital discharge data between 2000 and 2013 in some selected countries. Both the overall development in all diagnoses (dotted lines in **Figure A15**) and the development specifically in cancer patients (solid lines in **Figure A15**) are portrayed. This provides insights into whether the development in cancer patients just 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.

Between 2000 and 2013 there was downward trend in the number of inpatient days (standardized by population size) and a simultaneous upward trend in the number of day cases (standardized by population size) in most countries; see **Figure A15**. This pattern was observable on the overall level in all diagnoses and also in cancer patients. France, the UK, and Spain (after 2004) are examples of this pattern. However, there are some exceptions. In Germany (between 2003 and 2013), Poland, and the Czech Republic inpatient days of cancer patients declined strongly, but remained stable or declined less strongly for all diagnoses. There was no simultaneous increase in day cases in Germany and the Czech Republic. In Cyprus and Slovenia inpatient days as well as day cases remained mostly stable. In Estonia inpatient days increased in cancer patients, but not in all diagnoses, and day cases increased both in cancer patients and overall.

[29] Eurostat defines inpatient days (also denoted as bed days or hospital days) as the days spent from the date of admission in an inpatient institution to the date of discharge (including death). Following a formal admission (hospitalization) a patient has to stay for a minimum of one night or more than 24 hours in the hospital or other institution providing inpatient care [111].
An alternative measure would be average length of stay (ALOS). However, ALOS might decrease if there is a trend towards shorter stays, and it remains silent about whether the shorter stays occur more frequently. By contrast, inpatient days standardized by population size do not suffer from this kind of bias.

[30] Eurostat defines a day case (day treatment) in the following way [112]: "Day care comprises medical and paramedical services (episode of care) delivered to patients who are formally admitted for diagnosis, treatment or other types of health care with the intention of discharging the patient on the same day. An episode of care for a patient who is admitted as a day-care patient and subsequently stays overnight is classified as an overnight stay or other in-patient case."

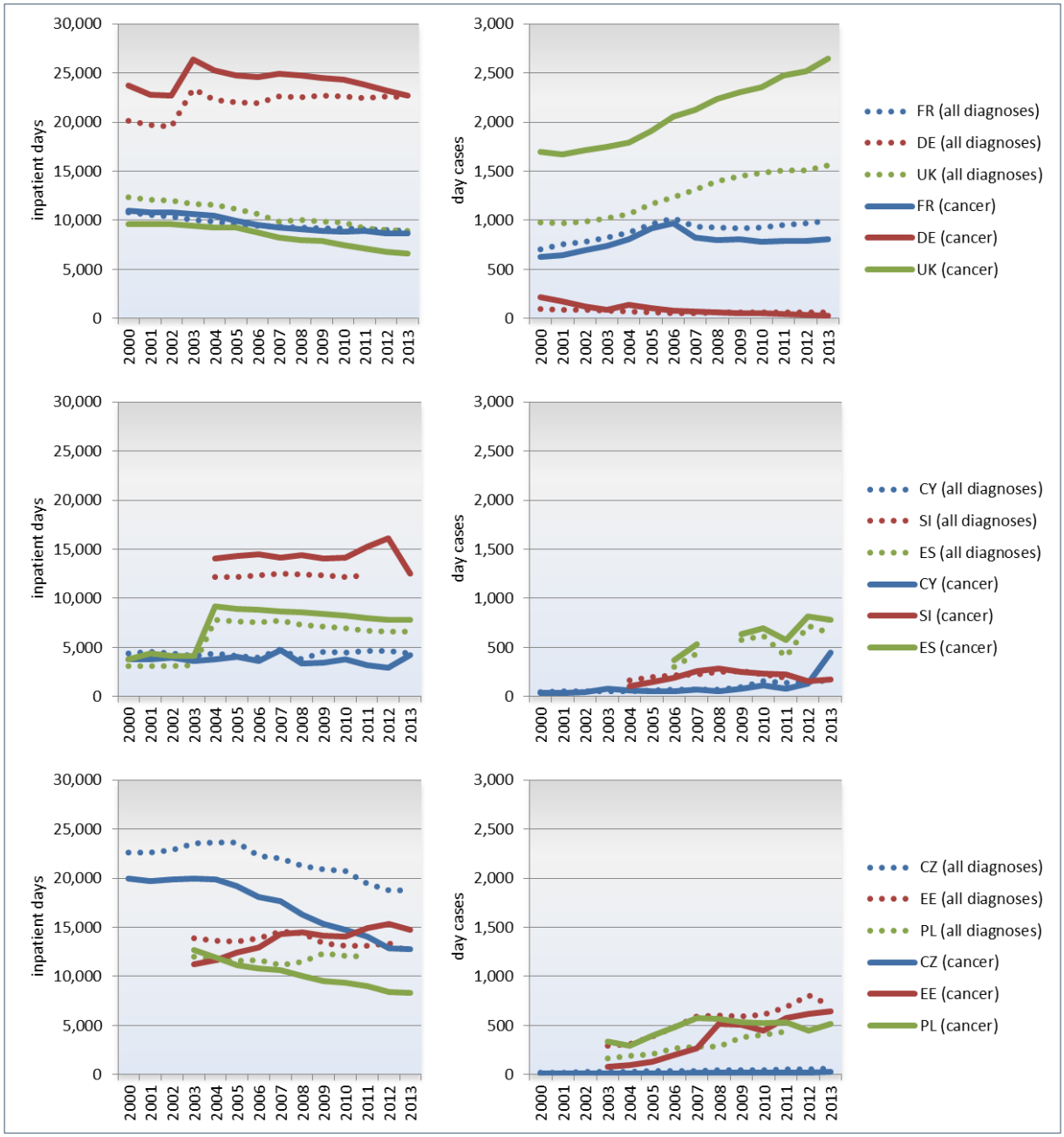


FIGURE A15: INPATIENT DAYS (LEFT-HAND SIDE FIGURES) AND DAY CASES (RIGHT-HAND SIDE FIGURES) PER 10,000 INHABITANTS IN ALL DIAGNOSES AND PER 100,000 INHABITANTS IN CANCER CASES, RESPECTIVELY, IN SELECTED COUNTRIES, 2000–2013 [58, 111, 112]

Notes: "all diagnoses" refers to ICD-10 A00-Z99 excluding V00-Y98 and Z38; "cancer" refers to ICD-10 C00-D48.

Despite the increase in cancer incidence (see section 1.1.1), inpatients days in cancer patients by and large decreased. It seems that inpatient days, which are comparatively expensive, were partly substituted with day cases, which are comparatively cheaper. However, in Table 7 in section 1.3.2 it was shown that the direct cost of cancer as a share of total health expenditure remained mostly stable or only increased slightly during the 2000s. How can these two observations be reconciled? Firstly, the downward trend in inpatient days and the upward trend in day cases were also broadly observable at the overall level in all diagnoses and not just in cancer patients. Thus, in relative terms cancer

patients' share in total inpatient days and day cases remained mostly stable. Secondly, cancer drugs seem to have represented a larger and growing share of the total direct cost of cancer; see section 1.4 for a more detailed discussion.

A.7.2.1 Distribution of the direct cost across cost categories and cancer types

The distribution of the direct cost of cancer across both cancer types and cost categories can also be considered. The LF-2013-study provides estimates for that kind of information for the major cancer types for the EU-27 in 2009 [44]. Note again that several relevant cost categories are missing in this study. However, a contribution is that the costs for cancer drugs do not seem to be included in the costs for inpatient or outpatient care, as in the studies reviewed above.

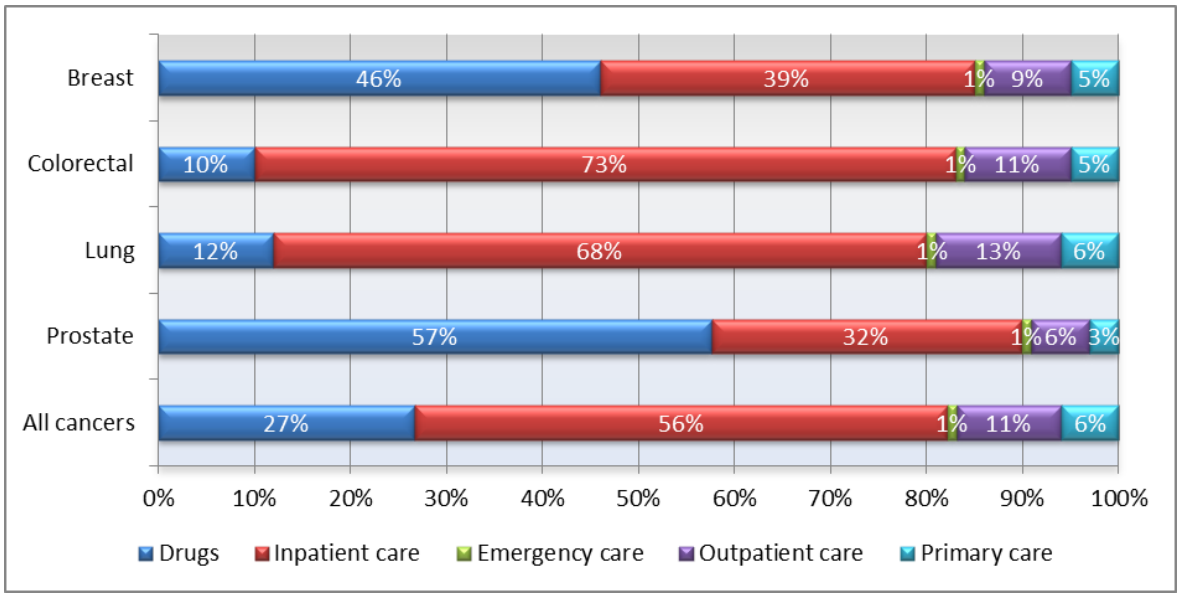


FIGURE A16: DISTRIBUTION OF THE DIRECT COST OF CANCER ACROSS COST CATEGORIES AND CANCER TYPES IN THE EU-27, 2009 [44]

Notes: Cancer refers to ICD-10 C00-C97.
The cost of inpatient care was calculated as the product of cancer type-related days in hospital and day-cases and country-specific unit costs. The cost of outpatient care was calculated as the product of cancer type-related visits to outpatient care and country-specific unit costs. Thus, no costs for cancer drugs seem to be included in these two cost categories.
The cost of cancer drugs is based on both hospital and retail sales and includes drugs with Anatomical Therapeutic Chemical (ATC) Classification System codes L1 and L2.

Figure A16 illustrates that the share of the different cost categories varies considerably between cancer types. In colorectal and lung cancer, inpatient care accounts for more than two thirds of the total cost and the cost of cancer drugs is on a par with the cost of outpatient care. By contrast, cancer drugs are the main cost category in breast and prostate cancer, accounting for around half of the total cost. However, the estimates on the cost cancer drugs in specific cancer types should be regarded with caution since their proportions are only based on real data from Germany and the Netherlands in the LF-2013-study. The authors of the LF-2013-study do not comment on the vast differences of the

share of cancer drugs between cancer types. The explanation is that very large proportions of breast and prostate cancer patients are cured and during this process receive drug treatment. At the same time, patients with these two cancer types who are not cured live usually longer than the average non-curable cancer patient and receive more drug treatment for longer periods.

A.7.3 Distribution of the direct cost across stages of cancer

One important question is whether the cost of cancer at the patient level varies by the stage of the disease at which the cancer is initially diagnosed. In general, cancers can be classified into four stages (or five stages if stage 0, which means cancer in situ, is included); stage I means cancer is localized, stage II means cancer is early locally advanced, stage III means cancer is late locally advanced, and stage IV means cancer is metastasized. As already discussed above, survival rates for individual patients depend crucially on the stage at which the cancer is detected. Thus on top of patient survival, there might be an additional benefit of early detection of cancer if the (life-time) cost of treating such patients is lower than the cost of treating patients with advanced cancers.

Figure A17 shows three stylized cost patterns varying by disease stage. The first pattern indicates that the cost is increasing with stage. In the second pattern the cost is independent of the stage. The third pattern indicates that the cost is decreasing with stage. The findings of the following three patient level studies show that all patterns might occur to some extent. Consequently, there is no conclusive evidence on whether early diagnosis provides the benefit of lower treatment costs (in addition to better survival) compared to later diagnosis. However, the following studies cover only the costs during the first year after diagnosis and thus cannot provide a definite answer on this matter.

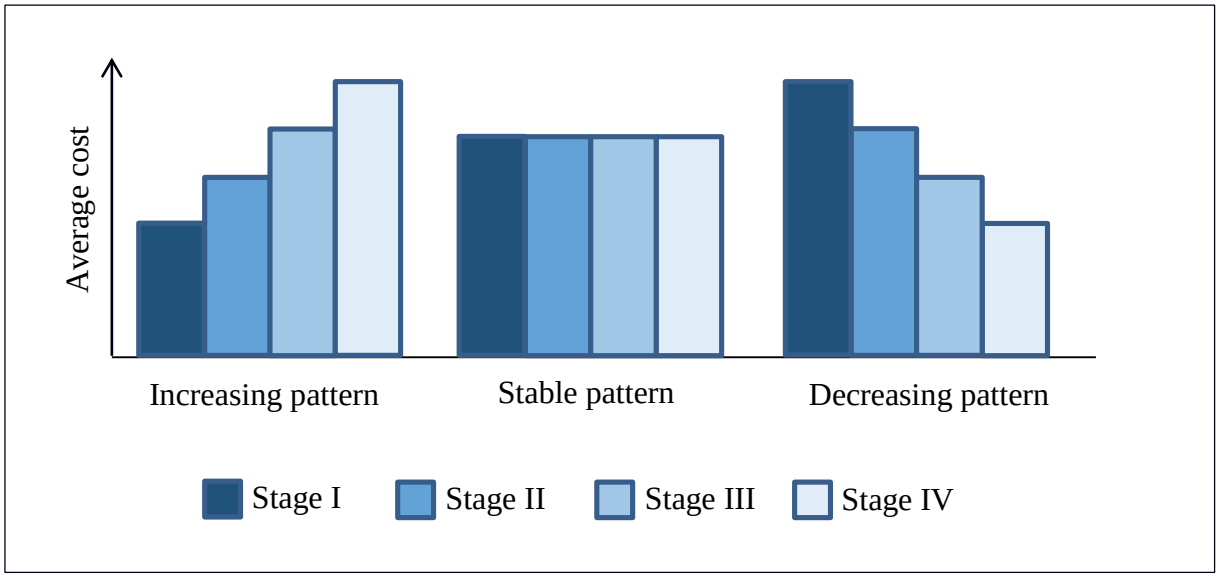


FIGURE A17: SCHEMATIC OF THREE POSSIBLE PATTERNS OF THE AVERAGE COST OF TREATING A PATIENT VARYING BY STAGE OF THE CANCER

Notes: Stage I = cancer is localized, stage II = cancer is early locally advanced, stage III = cancer is late locally advanced, stage IV = cancer is metastasized.

Studies estimating the cost of cancer by disease stage typically focus on a specific cancer type. They use a sample of patients that is followed from the diagnosis (at which the stage of the cancer is determined) over some period of time during which all cancer-related health care costs are recorded.

The first study examined the treatment cost of prostate cancer in the first year after diagnosis in France (1,364 patients), Germany (2,042), Italy (1,831), Spain (2,474), and the UK (2,865) in 2006 [113]. The average costs per patient with stage I and stage II were almost identical in each respective country. The average cost per patient diagnosed with stage III was lower than of stage I and II in all countries (except in Germany where it was similar to stage I and II), and in patients with stage IV the average cost was even lower than in stage III. Thus, a mostly decreasing cost pattern emerged. This pattern is explained by the different types of treatment received after the diagnosis. In stage I and II surgery and radiation therapy were the most common treatments, whereas in stage III surgery was less common but more patients received hormonal therapy. In stage IV surgery was almost not performed at all and also radiation therapy was uncommon, but instead patients received hormonal therapy and chemotherapy. Even though this study pointed towards a decreasing cost pattern, it is important to note that the ability to treat patients can change over time and in turn reverse the cost pattern. For instance, in 2006 treatment of stage IV prostate cancer was difficult, but since then several new drugs, such as abiraterone acetate, radium Ra 223 dichloride and enzalutamide, have been developed that specifically target this group of patients. This may have changed the cost pattern completely due to these drugs' considerable impact on total treatment costs.

The second study examined the direct medical cost of breast cancer in 1,142 patients diagnosed in Lithuania during 2011 [114]. Only costs that arose during 2011 were recorded, resulting in an average follow-up of 6.23 months. The average cost per patient in stage 0 was €2,720, which was higher than in stage I with €2,409 and in stage II with €2,432. The average cost increased for patients diagnosed with stage III cancer to €2,899 and peaked in stage IV with €3,688. Thus, an increasing cost pattern emerged in this study, if stage 0 is disregarded. In all stages the costs of outpatient and inpatient treatment (including surgery and chemotherapy) amounted to around €2,000 to €2,300. Higher costs for prescription drugs were responsible for the higher average cost in stage IV compared to lower stages. By contrast, in Western European countries the treatment cost in stage IV is much higher due to significant higher treatment intensity of HER2-positive breast cancer, in particular adjuvant treatment of advanced HER2-positive breast cancer.

The third study examined the direct cost of colorectal cancer in 2,667 patients diagnosed in Italy during the years 2000 and 2001 [100]. Data on costs were collected during the first year after diagnosis and averaged over the period 2000–2002. The average annualized cost per patient ranged between €8,000–12,500 for patients with stage I and II. In stage III the cost per patient ranged between €9,000–18,000, and increased to €14,000–21,000 in stage IV. Thus, an increasing cost pattern emerged in this study.

A.7.3.1 Distribution of the direct cost from diagnosis to death

The distribution of the direct cost of cancer can also be analyzed at the patient level over the whole disease pathway. In the most basic setting, three clinically relevant phases can be defined and the average costs calculated for each phase. The first phase is the initial phase following the diagnosis of cancer and may be defined as to last up to one year. The second phase is the continuing phase that lies between the initial and the final phase. The third phase is the final phase covering the period of time (at most a year) before death. Note that the initial and the final phase might overlap or even coincide if the patient dies shortly after the diagnosis.

On the overall level the direct cost of cancer is related to the epidemiological disease measures. Costs in the initial phase are related to cancer incidence. Costs in the continuing phase are related to survival, and costs in the final phase are related to cancer mortality.

The result of patient level studies on the development of the cost from diagnosis to death is typically a U-shaped pattern, stylized in **Figure A18**. The cost is highest right after diagnosis when treatment is initiated. After several months of treatment the cost drops since only regular health care visits to follow-up on the treatment are required. A few months before death and especially during the final one or two months the cost surges due to hospitalization, renewed treatment attempts and/or palliative care. Below two country-

specific studies are described that examined the cost from diagnosis to death in colorectal cancer.

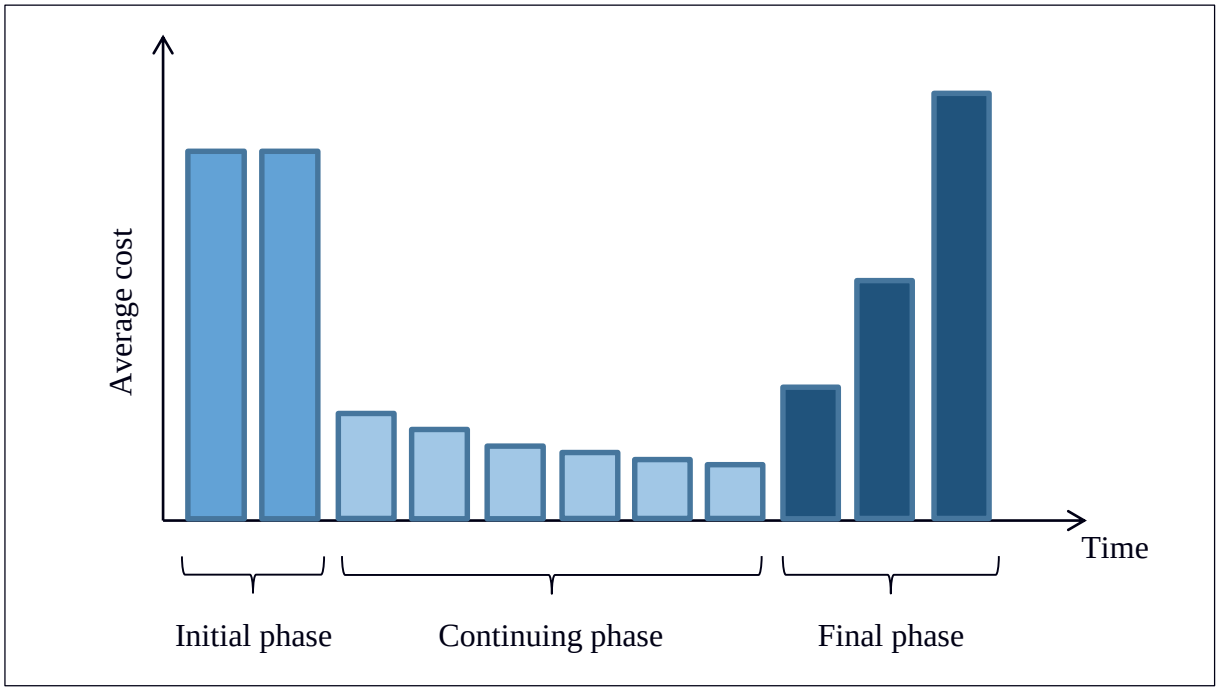


FIGURE A18: SCHEMATIC OF THE COST PATTERN OF A CANCER PATIENT FROM DIAGNOSIS TO DEATH

Notes: The bars represent months. The continuing phase can last for many years or even decades.

The first study followed over 20,000 patients diagnosed with colorectal cancer between 2007 and 2010 in Germany until the end of 2010 [115]. A sample of 110,000 patients with no colorectal cancer was matched to the colorectal cancer patients by age and sex, in order to calculate the incremental treatment cost between these two groups. Three phases of care were defined; initial phase (initial year after diagnosis), intermediate phase, and end-of-life phase (last year before death). The average annualized incremental cost per patient was €26,000 in the initial phase, €2,300 in the intermediate phase, and €51,700 in the end-of-life phase. Thus, compared to the stylized pattern in **Figure A18**, the cost in the final phase in this study was twice as high as the cost in the initial phase.

The second study followed 2,667 patients diagnosed with colorectal cancer in Italy during the years 2000 and 2001 [100]. Three phases of care were defined; initial phase (initial year after diagnosis), continuing phase, and final phase (last year before death). Data on the cost of the initial phase were averaged over the period 2000–2002, for the continuing phase over the period 2001–2006, and for the final phase over the period 2000–2006. The average annualized cost per patient ranged between €10,000–16,000 in the initial phase, between €2,000–3,000 in the continuing phase, and between €14,000–18,000 in the final phase. In addition, the study provided a monthly breakdown of the cost in each phase. The result showed that the cost was not spread out evenly across the phases. Instead, a pattern similar to **Figure A18** emerged. The cost in the initial phase was only exceptionally high

during the initial two months before falling off sharply. In the continuing phase a slight decline throughout the whole phase was observable. In the final phase the cost doubled admittedly between the twelfth month and the second-last month before death, but the massive upsurge in the cost occurred only during the very last month.

The high end-of-life costs in cancer patients have been subject to considerable discussions [116, 117]. The main criticism is that lots of resources are spent on chemotherapy and inpatient care without providing any or only small benefits to patients with very advanced disease and poor prognosis. Instead palliative and hospice care has been suggested as a more inexpensive alternative which can maintain quality of life and achieve equally good results in survival [118, 119].

A.8 Composition of the indirect cost of cancer

The composition of the indirect cost of all cancers and four major cancer types for the EU-27 in 2009 is illustrated in **Figure A19**. In all cancers combined productivity loss due to premature mortality is by far the largest component causing 82 percent of the €52.0 billion in indirect costs. Productivity loss due to morbidity (i.e. sickness absence and early retirement) stood for the remaining 18 percent. The latter component was calculated according to the friction-cost method. If the human-capital method had been used, the productivity loss due to morbidity would have increased from €9.4 billion by around €7 billion, putting its share to 28 percent on the then higher total indirect costs of €59 billion.

The study for Spain described in Table 8 was more consistent and detailed in its approach and used the human-capital method in the calculation of all three sources of productivity loss [69]. It estimated that productivity loss due to (1) premature mortality accounted for 61 percent, (2) sickness absence for 7 percent, (3) early retirement for 32 percent of the total indirect costs.

A comparison of the four different cancer types in **Figure A19** based on the LF-2013-study shows that the composition of the indirect costs varies considerably. In lung cancer productivity loss due to premature mortality accounts for nearly all indirect costs (92 percent). By contrast, in prostate and breast cancer productivity loss due to premature mortality accounts for less than two thirds of the indirect costs. As mentioned before, the overall size of the indirect costs but also their composition in specific cancer types depends crucially on three factors; age at diagnosis, age at death, and survival probability. This explains why the indirect costs of prostate cancer (€1.1 billion) are much smaller than of lung cancer (€10.7 billion).

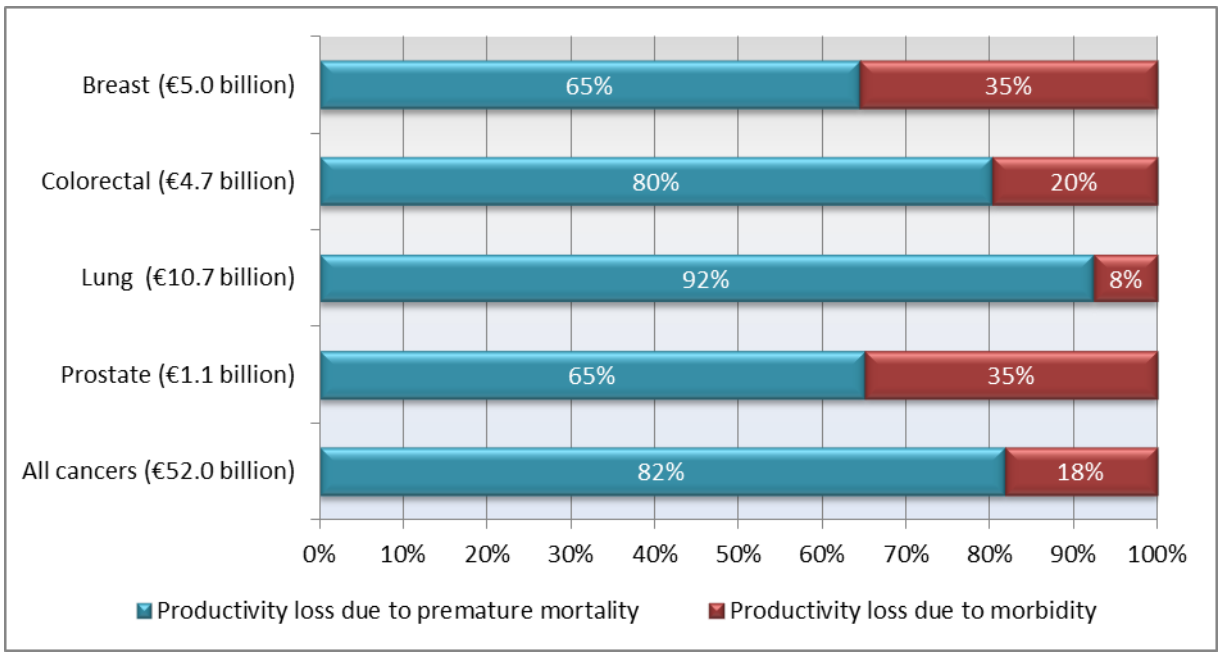


FIGURE A19: DISTRIBUTION OF THE INDIRECT COST OF CANCER ACROSS COST COMPONENTS AND CANCER TYPES IN THE EU-27, 2009 [44]

Notes: Cancer refers to ICD-10 C00-C97.
Productivity loss due to premature mortality was calculated by the human-capital method and productivity loss due to morbidity by the friction-cost method, resulting in an underestimation of the shares of the latter component.

In the studies reviewed above productivity loss due to premature mortality typically accounted for more than half of the indirect costs. If it is calculated according to the human-capital method, its exact size is dependent on a number of parameters, such as starting age of work, age of retirement, employment rate (of men and women), current wage rate/income (of men and women), real growth rate of future wages/income, discount rate of future wages/income, and the definition of cancer. This plenitude of parameters explains why studies calculating the same outcome can end up with widely different estimates.

There are two studies available that calculated the productivity loss due to premature mortality for the EU and its member states in 2008 and 2009 according to the human-capital method [44, 64]. Hanly, et al. (2015) estimated the total loss for the EU-28 (excluding Greece) to €71.3 billion in 2008[31], whereas the estimate in the LF-2013-study was €42.6 billion for the EU-28 (excluding Croatia) in 2009. Even though the estimate for 2009 used a broader definition of cancer (ICD-10 C00-C97 compared to ICD-10 C00-C96/C44) and included deaths in a wider age range (15-79 years compared to 15-64 years), the productivity loss per capita in many member states was almost only half as large as the one for 2008; see **Figure A20**. Hanly, et al. (2015) attributed the difference to the use of age-specific wage rates (as opposed to average wage rates in the LF-2013-study) and an assumption of positive future wage growth (as opposed to zero wage growth in the LF-

[31] Corrected for the inflation rate in the EU-28 between 2008 and 2009 (1.0 percent) [35], the 2008 estimate is even a bit higher; €72.0 billion measured in 2009 prices.

2013-study). A lower employment rate in 2009 compared to 2008, due to the economic crisis, might have also partly contributed to the lower estimates for 2009.

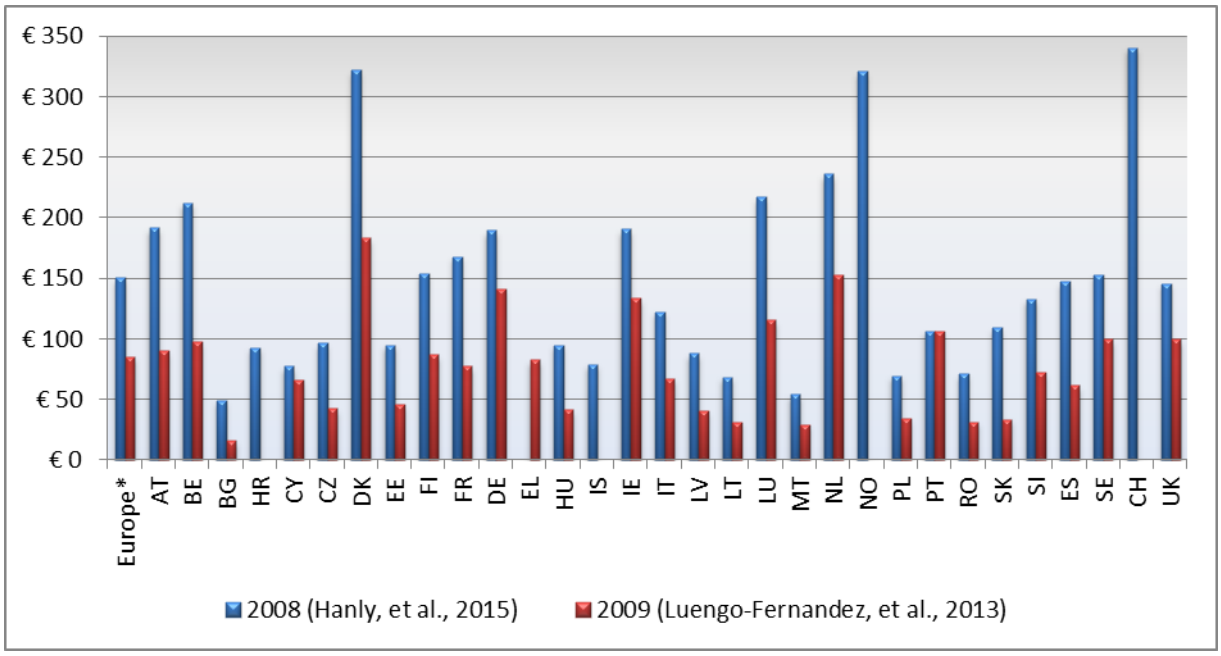
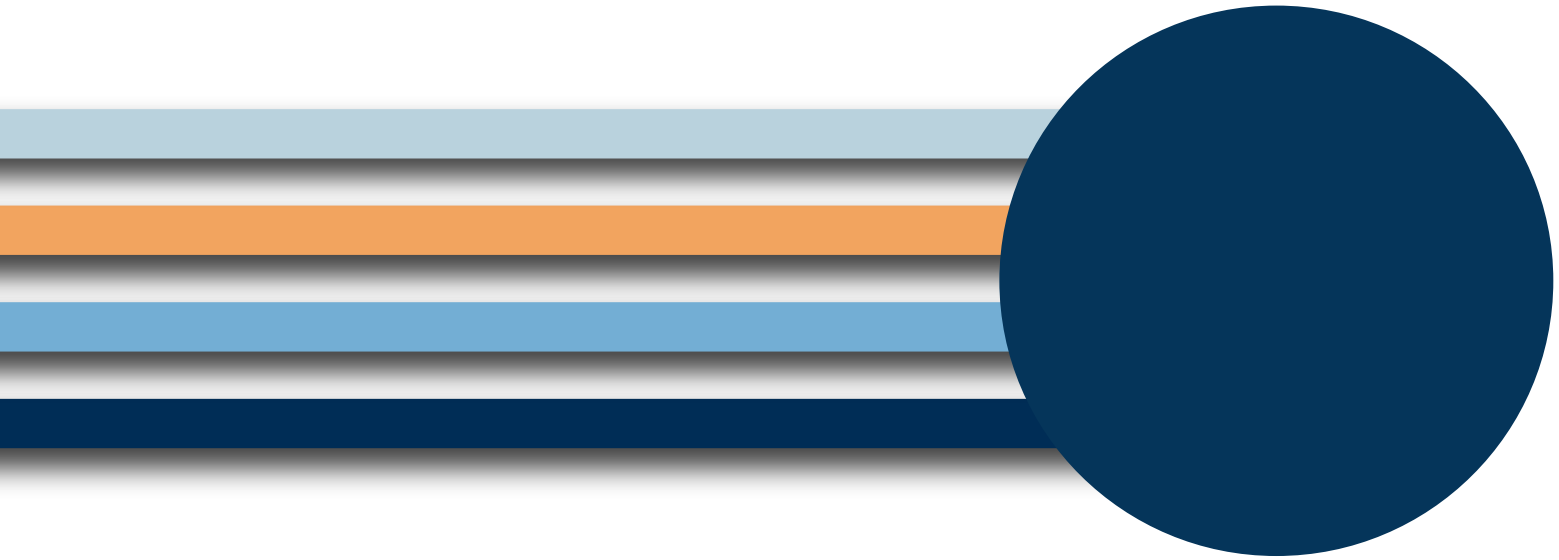


FIGURE A20: TWO ESTIMATES OF THE PRODUCTIVITY LOSS DUE TO PREMATURE MORTALITY FROM CANCER PER CAPITA, [44, 58, 64]

Notes: * Europe does not include Greece in 2008 and Croatia, Iceland, Norway, and Switzerland in 2009. The estimates are not adjusted for inflation between 2008 and 2009.



Institutet för Hälso- och Sjukvårdsekonomi
The Swedish Institute for Health Economics
www.ihe.se