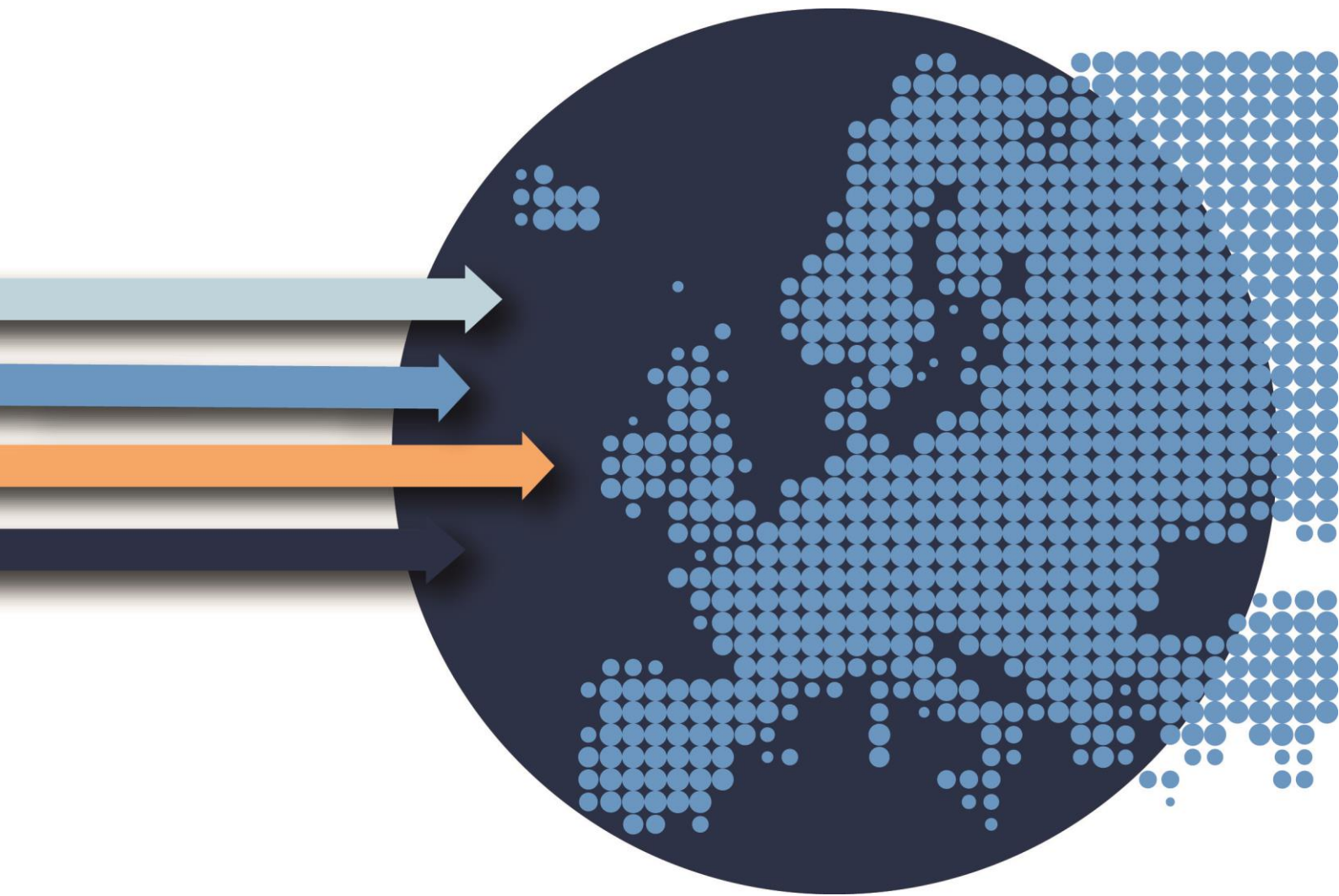


COMPARATOR REPORT ON CANCER IN IRELAND

– DISEASE BURDEN, COSTS AND ACCESS TO MEDICINES



Thomas Hofmarcher
Oskar Ericson
Peter Lindgren



IHE REPORT
2022:4

**COMPARATOR REPORT ON CANCER IN IRELAND
– DISEASE BURDEN, COSTS AND ACCESS TO MEDICINES**

Thomas Hofmarcher
Oskar Ericson
Peter Lindgren

IHE - The Swedish Institute for Health Economics

Please cite this report as:

Hofmarcher, T., Ericson, O., Lindgren, P. Comparator Report on Cancer in Ireland – Disease Burden, Costs and Access to Medicines. IHE Report 2022:4. IHE: Lund, Sweden.

This report was commissioned by IPHA – The Irish Pharmaceutical Healthcare Association and funded with contributions from AbbVie, Amgen, Astellas, Bayer, BMS, Daiichi Sankyo, GSK, Janssen, Merck Serono, MSD, Novartis, Pfizer, Roche, Sanofi, Servier, and Takeda. IPHA and its member organizations had no influence or editorial control over the content of this report, and the views and opinions of the authors are not necessarily those of IPHA nor of its member organizations.

IHE REPORT 2022:4
e-ISSN: 1651-8187
ISSN: 1651-7628

The report can be downloaded from IHE's website.

Foreword

Oncology is one of the most discussed therapeutic areas in public and scientific circles in Europe and also in Ireland. There are several reasons for this. Demographic changes have led to increases in the incidence of cancer. About one in three persons will receive a cancer diagnosis at some point during their lifetime. At the end of 2019, there were nearly 200,000 patients living after a cancer diagnosis in Ireland.

The survival rates of cancer patients have improved over the last decades. The scientific advancements have in some cancer patient groups started to transform cancer from a fatal to a chronic disease. The more than 100 new cancer medicines approved by the European Medicines Agency in the last decade are testimony to oncology being one of the most rapidly developing therapeutic areas. National health systems face the challenge to make these medicines available to patients, while being confronted with higher price tags for new medicines and working with constrained budgets.

This present report focuses on the development in the disease burden of cancer, the economic impact of cancer, outcomes for cancer patients, and patient access to new cancer medicines. It focuses on these four themes for Ireland and how Ireland compares with other European countries. The report is an extension of a report previously published by the Swedish Institute for Health Economics (IHE), IHE Report 2019:7. This previous report presented a European comparison and revealed large differences in spending on cancer care, uptake of new cancer medicines, and outcomes for cancer patients. Some of these differences can be explained by economic factors, but large variations between countries of similar economic status were also observed.

The responsibility for the analysis and conclusions in this report lies solely with the authors.

Lund, April 2022

Peter Lindgren
Managing Director, IHE

Executive summary

Over the past two decades, cancer has become the leading cause of death in Ireland

More than one in four deaths ($\approx 30\%$) in Ireland is due to cancer. This makes cancer now the leading cause of death, ahead of cardiovascular diseases. In many other EU-15 countries, cancer has also replaced cardiovascular diseases as the leading cause of death over the past two decades.

The number of newly diagnosed cancer cases has doubled in Ireland since 1995, driven mostly by demographic changes

Cancer incidence in Ireland doubled from around 12,000 new cases per year in 1995 to around 24,000 new cases per year in 2017–2019, according to the National Cancer Registry Ireland (NCRI). This development was mostly driven by demographic factors – overall population growth and especially population aging, as cancer is an aging-associated disease. Even when taking into account the demographic changes, there was still a remaining increase in incidence of around 20%, which can be attributed to increased exposure to risk factors (e.g., smoking, obesity, alcohol, sun exposure) and increased detection by enhanced screening activities in the Irish population.

Improvements in cancer care are needed to avert at least some of the 15,000 additional yearly new cancer cases and 8,000 additional yearly cancer deaths predicted to occur in Ireland by 2040

Projections by the International Agency for Research on Cancer (IARC) indicate that the annual number of new cancer cases in Ireland might increase by around 15,000 cases, from 27,000 to 42,000 cases between 2020 and 2040 solely due to the expected demographic changes. Similarly, the annual number of cancer deaths might increase by 8,000 deaths, from 10,000 to 18,000 deaths between 2020 and 2040. By continuously improving the quality of cancer care delivered to patients, an increasing number of lives could be saved. Assuming that continuous improvements in the quality of cancer care result in a 1% annual decline in age-specific mortality rates (similar to the development in Ireland in 1995–2019), up to 3,500 lives could be saved in 2040 alone.

Official aggregated data on health spending on cancer are absent in Ireland, but estimates indicate that per capita spending on cancer in Ireland is similar to the EU-15 average

There is a lack of official data to assess the structure of health expenditure on cancer in Ireland. Data from other EU-15 countries indicate that cancer accounts for 4–7% of total health expenditure. Assuming that cancer accounts for 5% of total health expenditure in Ireland (best-guess estimate based on data for the UK), Ireland would have spent the equivalent of €207 per capita on cancer (PPP-adjusted) in 2018. This would be exactly in line with the EU-15 average at €207 per capita, but lower than in France, Germany, Austria, and the Benelux countries.

The indirect costs of cancer have been decreasing in Ireland since 2000 due to better patient outcomes

The indirect costs of cancer equal the productivity loss from premature mortality and from morbidity of patients in working age. In Ireland, the indirect costs of cancer decreased from €177 in 2000 to €132 per capita in 2018. This mirrors the decrease in the EU-15, where the average indirect costs were higher at €137 per capita compared to Ireland's €116 per capita (PPP-adjusted) in 2018. The fact that indirect costs are sizeable even compared to the health expenditure on cancer underlines the economic burden for patients and the importance of applying a societal perspective in the design of policy measures to tackle cancer.

Cancer survival has improved in Ireland, yet if survival rates were on par with the best-performing EU-15 countries, hundreds of deaths could be avoided every year

Survival rates in all major cancer types have improved in Ireland since the 1990s according to the NCRI. The most successful example is multiple myeloma, where the 5-year survival rate increased by 37 percentage points from 27% in 1994–1998 to 64% in 2014–2018. Yet in many cases, Ireland lags behind the cancer survival rates observed in other EU-15 countries. For example, Ireland ranks last in survival rates of breast and ovarian cancer. Hundreds of cancer deaths could be avoided every year if Ireland achieved similar survival rates to the best-performing EU-15 countries.

There is a clear pattern of countries spending more on cancer care achieving higher survival rates, which makes spending in Ireland appear less efficient

Health care systems need to weigh up the opportunity costs from investing in different areas of cancer care against the potential improvements in patient outcomes and survival rates. This will ensure that constrained resources are used in a cost-effective way and provide value-for-money for patients, the Health Service Executive (HSE), and taxpayers. Despite great variation in health spending on cancer between countries with similar survival rates, there is a positive association at the country-level between health expenditure on cancer and cancer survival rates. Ireland is an example where survival rates are comparatively low given the estimated level of health spending on cancer. If there were more specific Irish data on spending on cancer in the future, this relationship would need to be revisited. Nonetheless, the observed disparity should emphasize the need to target cancer expenditure to the treatment of those patients who will get better clinical outcomes – whether that is in quality or length of life. By demonstrating value-for-money with existing spend, the system can be confident in allocating additional funding for continued better outcomes in a greater number of patients.

The last decade has witnessed a distinct increase in new cancer medicines approved by the EMA, yet time to patient access for newly approved medicines in Ireland is almost twice as long as the EU-15 average

Medical oncology entered a new phase in the 21st century, with the introduction of targeted therapy and immunotherapy. On average four new cancer medicines were approved by the European Medicines Agency (EMA) per year in 2004–2011, increasing to around ten new medicines in 2012–2020 and reaching a peak of 17 new medicines in 2021. Of all new cancer medicines approved in 2017–2020, around half (51%) were reimbursed by the HSE at the beginning of 2022. This places Ireland second last among the EU-15 countries, only ahead of Luxembourg, if both full and limited reimbursement through various public schemes is considered. For the reimbursed cancer medicines by the HSE, the average time to the reimbursement decision following EMA approval was almost two years (661 days), equal to the second longest time among the EU-15 countries, only ahead of Portugal. Long times to reimbursement are a result of both the timing of reimbursement applications by pharmaceutical companies and long review times, including price negotiations, by the HSE.

Once reimbursed, the use of modern cancer medicines in Ireland is close to the EU-15 average

The increase in the number of new cancer medicines has led to increased spending on cancer medicines in the last decades. Per-capita spending on all cancer medicines in Ireland more than doubled between 2008 and 2018 from €29 to €64 per capita (inflation-adjusted and including confidential rebates on medicines which are not accounted for in available sales data). Throughout this period, cancer medicines spending in Ireland was below the EU-15 average (€33 in 2008 and €70 in 2018). The uptake of modern cancer medicines measured in volume terms varied by cancer type in Ireland and was close to the EU-15 average in 2018.

The lack of patient access to modern, effective cancer medicines in Ireland leads to a great loss in life years and quality of life of cancer patients

New and effective cancer medicines need to reach patients to confer benefits. While new medicines come at an additional cost, the length of time-to-reimbursement and/or lack of reimbursement (for the time being) also come at a cost. An illustrative analysis of 11 recently EMA-approved treatment-indications shows that time until reimbursement by the HSE together accounted for 2,600 years of potential life lost, of which 1,000 years in working-age patients resulting in an economic loss of €34 million. The full extent of life years lost is far greater when considering all cancer indications. Improved quality of life of patients of all ages and reduced numbers of adverse events are additional benefits of newer treatments. A societal perspective beyond the current health and social care approach to health technology assessment would allow for the consideration of wider implications of new medicines in reimbursement decisions thereby maximizing patient health and returns to society and the taxpayer.

List of abbreviations

ALK – Anaplastic lymphoma kinase	IARC – International Agency for Research on Cancer
AML – Acute myeloid leukemia	ICD-10 – International classification of diseases 10th revision
APC – Annual percent change	NCCP – National Cancer Control Programme
ASR – Aged-standardized rate	NCPE – National Centre for Pharmacoeconomics
ATC – Anatomical therapeutic chemical	NCRI – National Cancer Registry Ireland
CAR-T – Chimeric antigen receptor T	NSCLC – Non-small cell lung cancer
CHMP – Committee for Medicinal Products for Human Use	OECD – Organisation for Economic Co-operation and Development
CSO – Central Statistics Office	OS – Overall survival
EFPIA – European Federation of Pharmaceutical Industries and Associations	PD-1 – Programmed cell death protein 1
EGFR – Epidermal growth factor receptor	PD-L1 – Programmed death-ligand 1
EMA – European Medicines Agency	pp – percentage point
ESMO – European Society for Medical Oncology	PPP – Purchasing power parity
FLT3 – FMS-like tyrosine kinase 3	PSA – Prostate-specific antigen
GDP – Gross domestic product	QALY – Quality-adjusted life year
HER2 – Human epidermal growth factor receptor 2	SWD – Standard weekly dose
HPV – Human papillomavirus	TNBC – Triple-negative breast cancer
HR – Hormone receptor	WHO – World Health Organization
HSE – Health Service Executive	YPLL – Years of potential life lost
HTA – Health technology assessment	

Country abbreviations

EU European Union
EU-15 the 15 member states of the EU in 1995
AT Austria
BE Belgium
DK Denmark
ES Spain
FI Finland
FR France
DE Germany
EL Greece
IE Ireland
IT Italy
LU Luxembourg
NL Netherlands
PT Portugal
SE Sweden
UK United Kingdom

Table of contents

Foreword	3
Executive summary	4
1. Introduction	9
1.1 Purpose and outline of the report	10
2. Disease burden of cancer.....	11
2.1 Burden of disease	11
2.2 Epidemiology of cancer	12
2.2.1 Incidence	13
2.2.2 Mortality.....	17
2.2.3 Future development.....	19
3. Economic burden of cancer.....	22
3.1 Direct costs.....	22
3.2 Indirect costs	27
3.3 Future development.....	29
4. Outcomes of cancer patients	30
4.1 Survival	30
4.2 Potential to improve cancer survival.....	36
4.3 Patient outcomes and health spending.....	37
5. Patient access to cancer medicines.....	40
5.1 Regulatory approval	40
5.2 Reimbursement.....	42
5.3 Uptake	45
5.3.1 Uptake in terms of costs	46
5.3.2 Uptake in terms of volume	48
5.4 Consequences of limited and later access	52
5.5 Current challenges.....	54
6. Conclusion.....	58
References	59
Appendix	65
A.1 Standard weekly dose of medicines	65
A.2 Socio-economic impact of time to reimbursement.....	66
A.2.1 Medicine and indication selection	66
A.2.2 Calculation of the socio-economic impact	67

1. Introduction

In January 2020, we published a report on cancer in Europe investigating the developments in the cancer field over the last decade from an epidemiological, economic, clinical, and patient access perspective (1). The report followed in the footsteps of previous work that used a similar methodology and enabled a description of cancer care since the 1990s (2-5).

Our report emphasized that the management of cancer represents a major challenge for health care systems in Europe. The aging populations across all European countries mean that more and more people are of an age when cancer typically develops. Indeed, the number of cancer cases has been rising for a long time. Between 1990 and 2020, the annual number of new cancer cases (incidence) increased by 87% from 1.4 to 2.5 million cases in the EU-15 countries (6-12); see Figure 1. The annual number of deaths from cancer (mortality) increased by 26% from 0.9 to 1.1 million cases during the same period. The widening gap between incidence and mortality of cancer is a sign of progress. At the individual level, this development is reflected in increasing survival rates of patients. Major advances in diagnosis and medical treatment along with screening programs have been cited as reasons behind this development (13, 14).

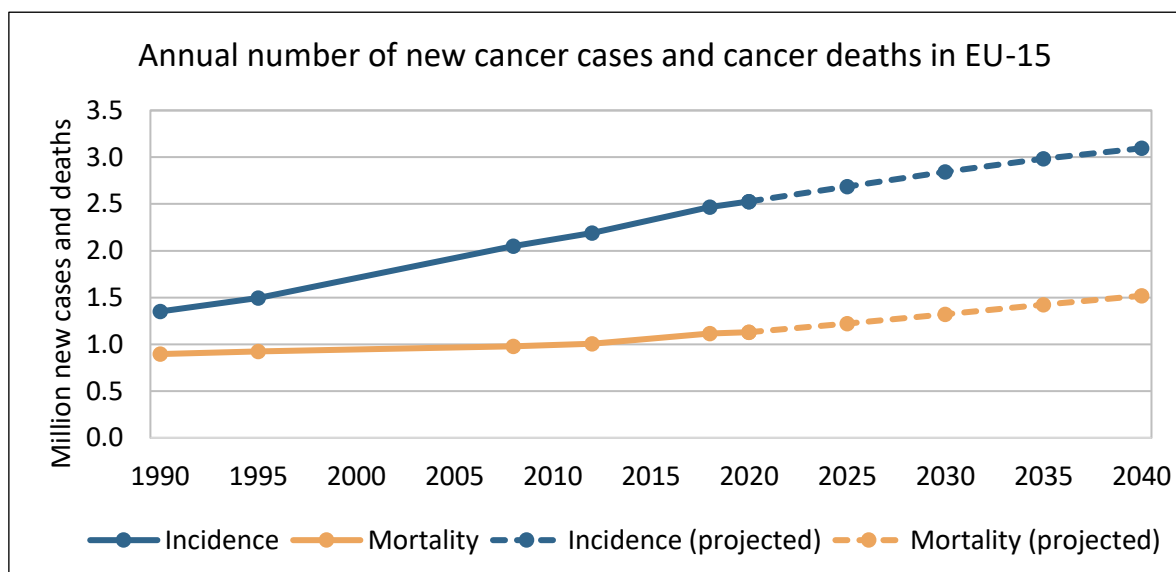


Figure 1: Cancer incidence and mortality (in million cases) in EU-15, 1990–2020 and projection of status quo 2020–2040

Notes: EU-15 are the member states in 1995. Cancer is defined as ICD-10 C00-C97/C44. Source: (6-12).

Europe's Beating Cancer Plan, launched by the European Commission in February 2021, presents an important milestone in the political commitment to put cancer at the top of the health policy agenda (15). It was amongst other reasons launched against the backdrop of alarming projections of the future burden of cancer. Figure 1 projects what would happen in the absence of further improvements in cancer care and prevention. If the status quo remains (with base year 2020), the forecasted demographic development (population aging and minor overall population growth)

would lead to considerably increases in incidence and mortality in Europe. This projection makes it clear that further improvements and investment in all areas of cancer care – prevention, screening, diagnosis, treatment – are needed to meet the demographic challenge and to achieve a lasting turnaround in cancer incidence and mortality.

1.1 Purpose and outline of the report

Our report on cancer in 31 countries in Europe revealed stunning country differences in terms of health spending on cancer care and patient outcomes. The report focused in more detail on patient access to cancer medicines, as this is the most dynamic area of cancer care. In a report focusing on Europe, it is necessary to paint with a broad brush. This may mask important observations at the country level.

This report provides a more concise version of the full European report focusing on Ireland. As a benchmark for Ireland, the report provides key statistics for the set of EU-15 member states as of 1995 (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom). The EU-15 countries were chosen as they are more comparable to Ireland in terms of economic development than the current set of EU countries.¹

In Ireland, the governance of cancer care is shaped by the National Cancer Strategy 2017–2026 developed by the Department of Health (16). The National Cancer Control Programme (NCCP), established as an executive arm of the HSE in 2007, is providing leadership in all areas of cancer control and is responsible for the implementation of nearly all 52 recommendations defined in the National Cancer Strategy 2017–2026. This strategy provides recommendations in all areas of cancer control – prevention, early detection (incl. screening), diagnosis and treatment (incl. optimization of the patient pathway), survivorship. Yet there is surprisingly little focus on cancer medicines, given that Ireland is only ranked in the middle among countries of the Organisation for Economic Co-operation and Development (OECD) for coverage of newer cancer medicines in a recent OECD report (17), and that cancer patients experience financial challenges having to spend on average €158 per month on medicines according to a survey by the Irish Cancer Society (18). Only one of the 52 recommendations explicitly mentions cancer medicines in relation to the aim of improving the model of care for patients receiving oral cancer medicines.

This report consists of four main chapters. Chapter 2 describes the disease burden of cancer. Chapter 3 describes the economic burden of cancer. Chapter 4 describes outcomes of cancer patients. Chapter 5 describes patient access to new cancer medicines as an example of a key area of cancer control.

¹ Averages of the EU-15 countries presented in this report are population weighted (and not the simple average of the individual values from the 15 countries), thus viewing the EU-15 as a single entity.

2. Disease burden of cancer

Cancer is the collective name of a group of over 100 diseases that are characterized by uncontrolled growth and division of cells. The most common types are breast cancer, prostate cancer, colorectal cancer, and lung cancer. Cancer affects people of all ages. However, the risk of getting cancer increases dramatically with age, because the cellular repair mechanisms become less effective as a person grows older and because of an accumulation of and exposure to risks (e.g., smoking, obesity, sun exposure) that increase over a person's lifetime (19).

This chapter describes the burden of cancer in relation to other diseases (section 2.1) and presents key trends in cancer epidemiology (section 2.2).

2.1 Burden of disease

Cancer is in most cases a lethal disease, if left untreated. In 2019, almost 10,000 people died from cancer in Ireland, corresponding to 31% of all deaths; see Table 1. This puts Ireland ahead of the EU-15 average, where 26% of all deaths were due to cancer. However, the number of cancer deaths per 100,000 inhabitants is lower in Ireland (194 cancer deaths) than in the EU-15 (257 cancer deaths). This is partly the result of the younger age composition of the Irish population compared to the EU-15 population (median age of ≈ 38 years vs. ≈ 44 years) and the fact that cancer is an aging-associated disease.

Table 1: Total deaths and deaths by cancer

	Ireland	EU-15
Year	2019	2019
Population (mid-year)	4,9 million	409,9 million
Median age	37.7 years	43.5 years
Total deaths	31,184	4,026,455
Total deaths per 100,000 inhabitants	632	982
Cancer deaths	9,574	1,054,123
Cancer deaths per 100,000 inhabitants	194	257
Proportion of cancer deaths	31%	26%

Notes: Cancer is defined as malignant neoplasms (ICD-10 C00-C97). Source: Eurostat and CSO Ireland (20-22).

The extent of the burden of cancer in relation to other diseases is shown in Figure 2, by comparing the leading the causes of death. According to estimates by the World Health Organization (WHO), cancer was the second leading cause of death in both Ireland and the EU-15 in 2000, representing 24% and 26% of all deaths, respectively. Only cardiovascular diseases caused more deaths than cancer in 2000. From 2000 up to 2019, the proportion of cancer deaths in Ireland increased by five percentage points to 29%, making it the leading cause of death in 2019 by surpassing deaths from

cardiovascular diseases. The proportion of cancer deaths also increased slightly in the EU-15 between 2000 and 2019, but cancer remained the second leading cause of death.

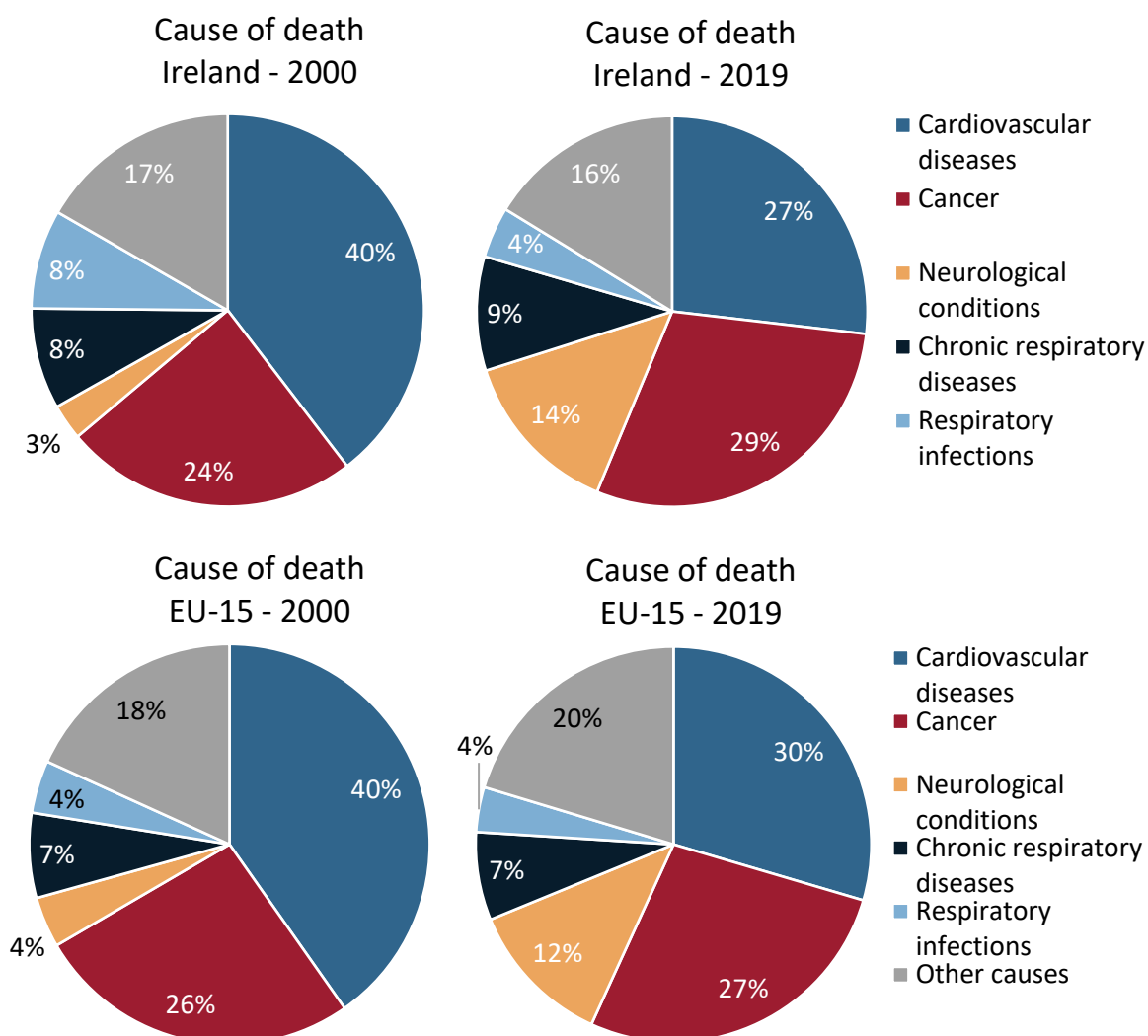


Figure 2: Cause of death 2000-2019, Ireland and EU-15

Notes: Examples of cardiovascular disease are ischemic heart disease and stroke, examples of neurological conditions are Parkinson's disease and Alzheimer's disease, examples of chronic respiratory disease are chronic obstructive pulmonary disease and asthma, and examples of respiratory infections are pneumonia and influenza. Source: WHO (23).

2.2 Epidemiology of cancer

The disease burden of cancer can be characterized by different epidemiological measures, such as incidence and mortality. For this report, information on incidence estimated by IARC and information on mortality collected by the WHO were used for the EU-15 countries. The methods to estimate country-specific incidence by IARC and have changed slightly over time, and care should be taken when interpreting time trends. For Ireland, information on incidence was obtained from the NCRI and information on mortality from the Central Statistics Office (CSO).

2.2.1 Incidence

Cancer incidence refers to the number of new cancer cases diagnosed within a certain year in a specific geographical area. In 1995, the estimated cancer incidence² was 1.5 million in the EU-15, and this number had increased by 65% to 2.5 million until 2018 (7, 9). Ireland also experienced a considerable rise in cancer incidence; see Figure 3. Between 1995 and 2017–2019, cancer incidence doubled (100% increase) from around 12,100 cases (6,300 men and 5,800 women) to 24,100 cases (12,800 men and 11,300 women) (24, 25).

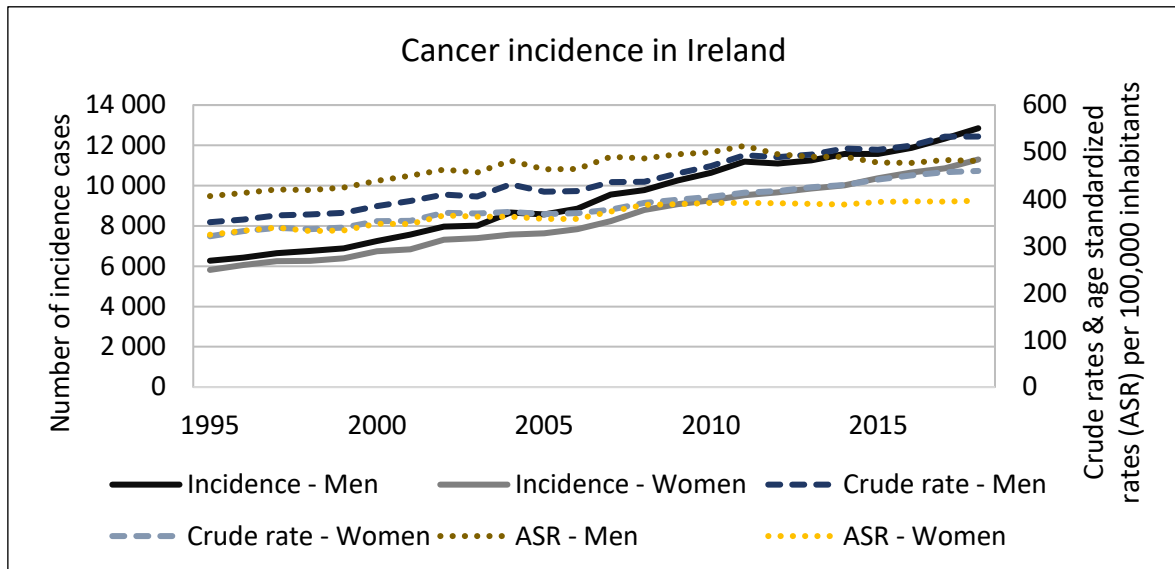


Figure 3: Development of cancer incidence in Ireland, 1995 to 2017–2019

Notes: Cancer is defined as ICD-10 C00-C96/C44. Source: NCRI (24, 25).

The most common cancer types in Ireland and the EU-15 are shown in Figure 4. Four cancer types – prostate cancer, breast cancer, colorectal cancer, lung cancer – account for just more than half of all new cancer cases. Bladder cancer is the fifth most common type in the EU-15, whereas it does not rank in the top 10 in Ireland. Instead, melanoma is the fifth most common type in Ireland.

² All cancer sites except non-melanoma skin cancer (ICD-10 C00-C97/C44).

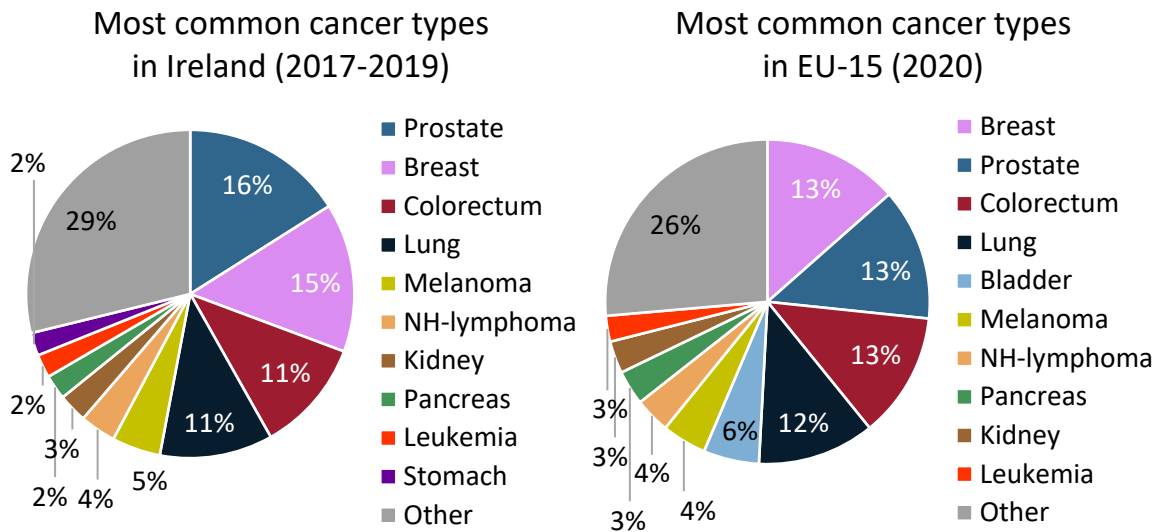


Figure 4: Most common cancer types in Ireland and EU-15

Notes: Cancer is defined as ICD-10 C00-C97/C44. NH = Non-Hodgkin. Source: NCRI and IARC (25, 26).

2.2.1.1 Crude rates and age-standardized rates

To compare countries of different and changing population sizes, a convenient measure is the crude rate. The crude rate expresses the number of new cancer cases per 100,000 inhabitants. As the age structure of the population also influences the number of new cancer cases, age-standardized rates can be estimated. Just as crude rates, they are expressed as new cancer cases per 100,000 inhabitants, but in addition they remove the influence from different and changing age structures.

Figure 3 above shows that while the absolute number of new cancer cases in Ireland doubled (100% increase) between 1995 and 2017–2019, the crude rate increased by 48% from 336 to 496 cases per 100,000 inhabitants during this period. The lower increase in the crude rate than in the total numbers is explained by the substantial growth of the Irish population, which increased by 35% from 3.6 to 4.9 million between 1995 and 2018. Figure 3 also shows that the crude rate of men was higher than of women in Ireland between 1995 and 2017–2019, yet incidence increased continuously in both men (+52%) and women (+43%).

An increase in the number of cancer cases was not just observed in Ireland, but also in all other EU-15 countries with available data; see Figure 5. Among the countries with available data for 1995, Italy had the highest incidence rates with 571 cases per 100,000 inhabitants, whereas Ireland had the lowest incidence rate with 336 cases per 100,000 inhabitants. In all countries, the crude rates increased by between 12% to 55% until 2018, with Ireland ranking close to the top with its 48% increase. In 2018, Italy, Denmark, and Germany recorded close to 650 new cancer cases per 100,000 inhabitants whereas Austria, Ireland, and Luxembourg were the only countries to record just below 500 cases per 100,000 inhabitants.

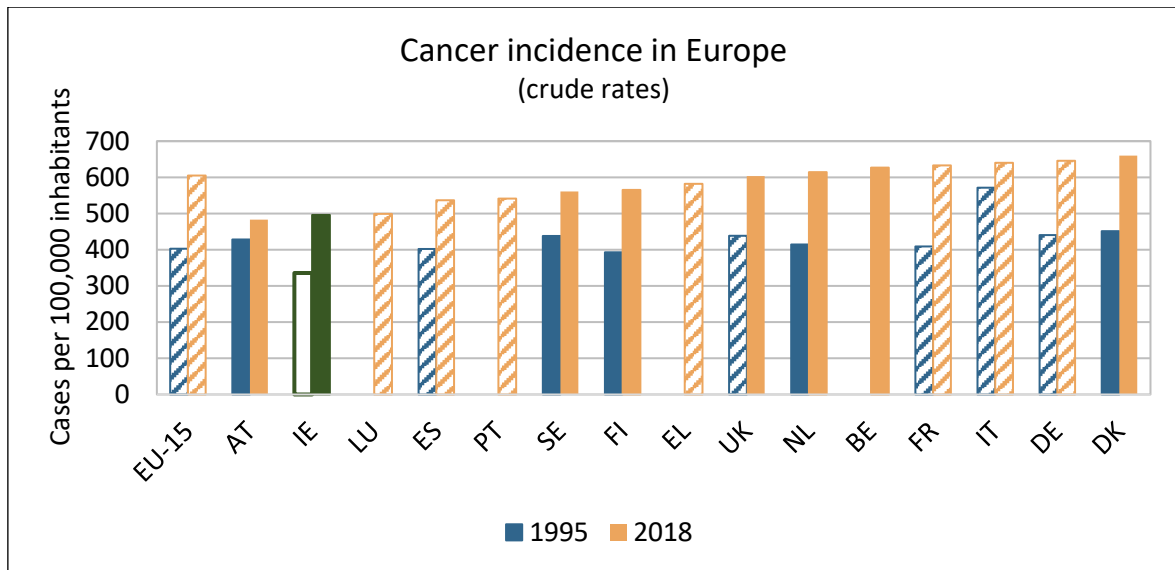


Figure 5: Estimated number of new cancer cases per 100,000 inhabitants (crude rates for both sexes), 1995–2018

Notes: Cancer refers to all cancer sites but non-melanoma skin cancer (ICD-10 C00-C97/C44). Hatched bars indicate that national estimates are based on regional data (DE, ES, FR, IT, PT, UK) or data from neighboring countries (EL, LU). BE, EL, LU, PT are missing in 1995 due to lack of data. For Ireland, the number shown for 2018 refers to the average of the years 2017–2019. Source: IARC and NCRI for Ireland (9, 24, 25, 27, 28).

There are several factors that can help to explain the increase in incidence crude rates in Ireland and the EU-15 between 1995 and 2018 as well as Ireland's comparatively low incidence rates:

- **Population aging:** As the risk of getting cancer increases with a person's age, a growing share of older people in the total population increases the number of new cancer cases. The population share of people aged 65 and older increased from 15% to 20% in the EU-15 and from 11% to 14% in Ireland between 1995 and 2018 (29). The comparatively younger age of the Irish population (median age of 38 years vs. 44 years in the EU-15; see Table 1) contributes to lower levels of cancer in Ireland. Age-standardized incidence rates presented below take into account the effect of an aging population.
- **Risk factors:** Certain lifestyle factors linked to cancer have become more common in Europe in recent decades. This includes obesity (linked to, e.g., colorectal cancer), alcohol consumption (linked to, e.g., liver cancer), and exposure to ultraviolet radiation via sunbathing (linked to, e.g., skin cancer). By contrast, smoking (linked to, e.g., lung cancer) has declined in men and more recently also in women (30). Declining smoking rates do not immediately translate into decreasing cancer incidence, as there are considerable time lags between the exposure to risk factors and the development of cancer.
- **Screening:** Nationwide population-based screening programs for breast cancer, cervical cancer, and (since the beginning of the 2010s) colorectal cancer have been implemented in

many countries and led to the detection of more cases (31, 32). Opportunistic screening for prostate cancer has also become more common and led to the detection of more cases.

- Epidemiological development in other diseases (competing risks of death): People are nowadays surviving previously fatal diseases as a result of improvements in health care and medicine. This is especially true for cardiovascular diseases (33). As more people reach an advanced age, this leaves more people at risk of getting cancer (34).

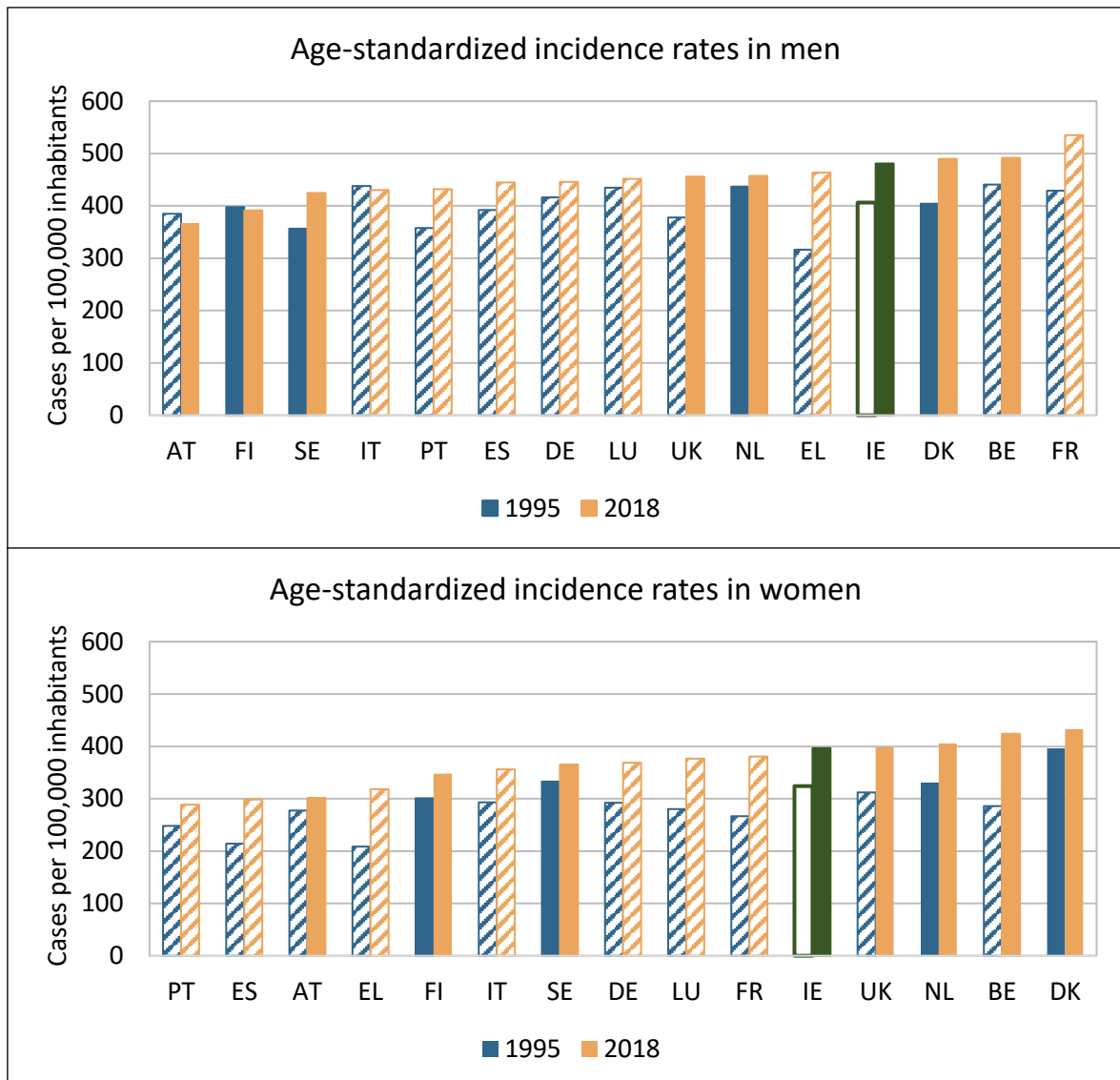


Figure 6: Estimated number of new cancer cases in men and women per 100,000 inhabitants (age-standardized rates), 1995–2018

Notes: Hatched bars indicate that the national estimates are based on regional data (AT, DE, ES, FR, IT, PT, UK) or data from neighboring countries (EL, LU). The age standardization is based on the old European standard. For Ireland, the numbers shown for 2018 refer to the average of the years 2017–2019. Source: IARC and NCRI for Ireland (7, 9, 24, 25).

Age-standardized incidence rates for men and women in the EU-15 are shown in Figure 6. These rates take into account different population sizes and age structures of populations, but do not control for other important factors such as the underlying development of risk factors and

screening. Ireland had the fourth-highest incidence rate in men and the fifth-highest rate in women in 2018. Similar to most other countries, incidence rates in Ireland increased in men (+18%) and women (+22%) between 1995 and 2017–2019. This means that even without the profound impact of demographic factors (population growth and aging) on cancer incidence, the number of new cancer cases would have gone up. The more detailed results in Figure 3 also show that the Irish incidence rate in men steadily increased after 1995, reaching a peak in 2011 and starting to decline slowly afterwards. By contrast, the Irish incidence rate in women increased steadily until 2008 and flattened out afterwards.

2.2.2 Mortality

Cancer mortality refers to the number of deaths caused by cancer in a certain year in a specific geographical area. In 1995, there were 0.93 million cancer deaths³ in the EU-15. This number increased by 13% to 1.05 million cancer deaths in 2018 (21, 35). Ireland also experienced a considerable rise in the total number of cancer deaths; see Figure 7. Between 1995 and 2018, cancer mortality increased by 23% from around 7,500 deaths (4,100 men and 3,400 women) to almost 9,300 deaths (4,900 men and 4,300 women) (21, 35).

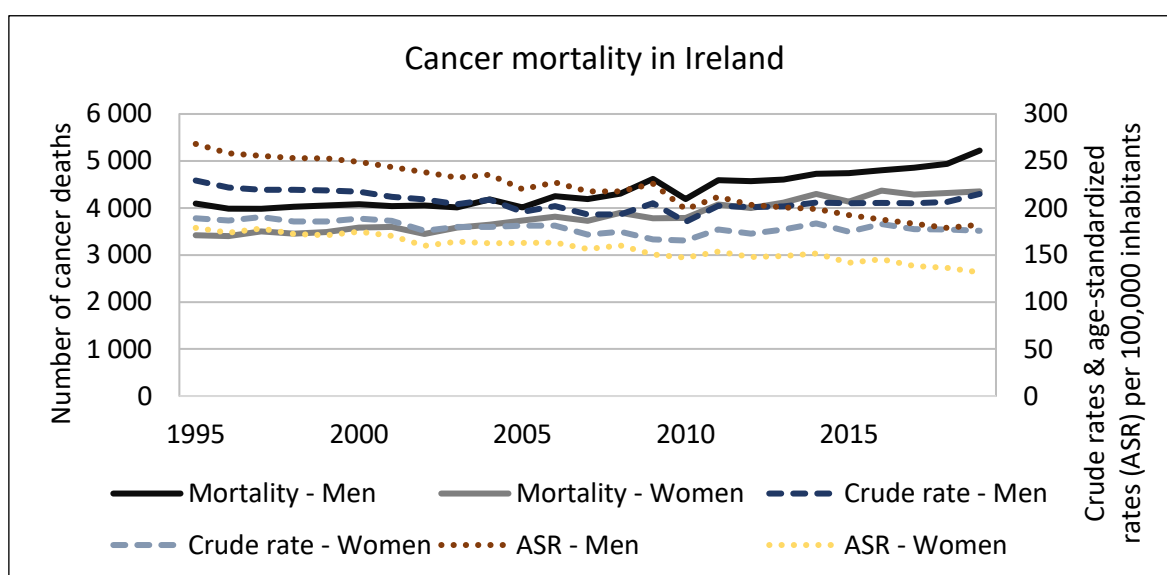


Figure 7: Development of cancer mortality in Ireland, 1995–2019

Notes: Cancer is defined as ICD-10 C00-C97. Age-standardized rates were calculated from age-specific mortality data and population data, applying weights from the old European standard. Source: WHO/IARC for 1995–2010, Eurostat for 2011–2018, CSO Ireland for 2019 (20, 21, 35).

Several factors can help to explain the increase in cancer deaths between 1995 and 2018. Most importantly, the estimated number of new cancer cases increased by 92% in Ireland and by 65% in the EU-15 during this period. More new cancer cases automatically imply more deaths if the rate of curing cancer cases (survival) remains constant. This also means that the factors explaining the

³ All cancer sites (ICD-10 C00-C97).

increase in cancer incidence (the demographic development, the development of risk factors, the introduction of screening programs, and the epidemiological development in other diseases) are important for explaining the increase in cancer mortality. The fact that the increase in the number of cancer deaths was much lower in Ireland (+23%) and the EU-15 (+13%) compared to the simultaneous development in cancer incidence (+92% and +65%, respectively) between 1995 and 2018 is a sign of progress.

2.2.2.1 Crude rates and age-standardized rates

Even though the absolute number of cancer deaths increased (+23%) in Ireland between 1995 and 2018, the crude rate decreased by 9% from 208 to 190 deaths per 100,000 inhabitants during this period. Figure 7 also shows that the crude mortality rate of men was higher than of women in Ireland between 1995 and 2018, similar to the crude incidence rate. The crude mortality rate decreased in men and women in 1995 to 2010 before flattening out afterwards.

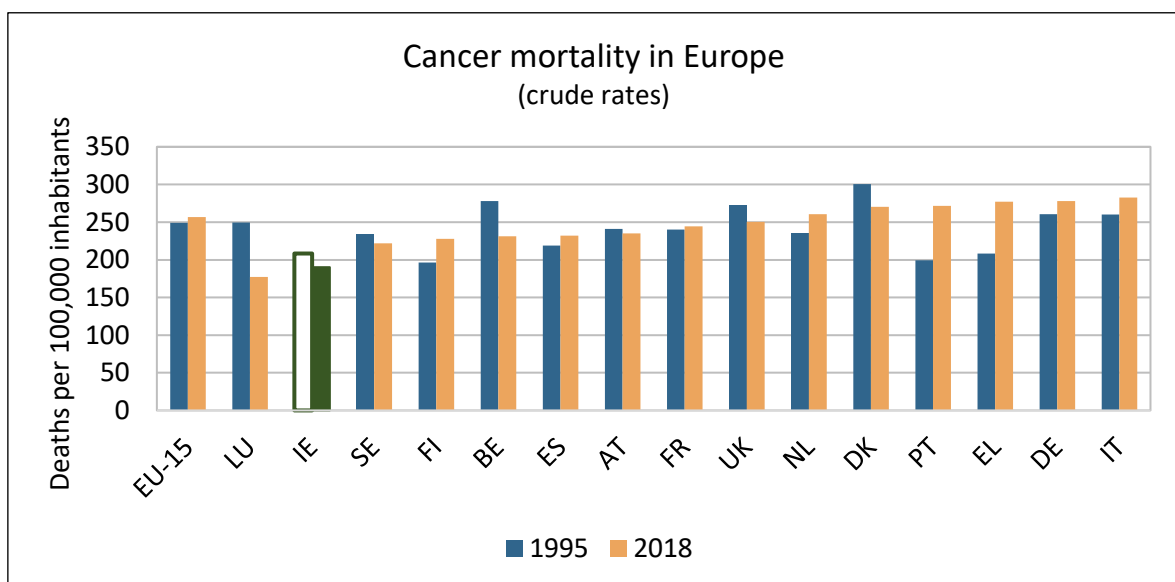


Figure 8: Number of cancer deaths per 100,000 inhabitants (crude rates for both sexes), 1995–2018

Notes: Cancer refers to malignant neoplasms (ICD-10 C00-C97). Source: WHO/IARC and Eurostat (21, 35).

A decrease in the crude mortality rate between 1995 and 2018 was not just observed in Ireland, but also in six other EU-15 countries, whereas the crude rate increased in the remaining countries; see Figure 8. Trends in cancer mortality over time as well as country differences in the size of the mortality rates should not be interpreted in isolation. A high mortality rate of a country does not necessarily indicate something about that country's effectiveness of cancer care, rather it could be a result of the country's high incidence rate. For example, Germany had the second highest incidence rates in 2018 (see Figure 5) and also the second highest mortality rate among the EU-15 in 2018. Ireland had the second lowest incidence rate and also the second lowest mortality rate in 2018.

Age-standardized mortality rates for men and women in the EU-15 are shown in Figure 9. These rates show a clear declining trend in all countries except in Greece between 1995 and 2018. Ireland had the fourth lowest rate in men and the third highest rate in women in 2018, but recorded steady declines in men (-33%) and women (-24%) since 1995; see also Figure 7.

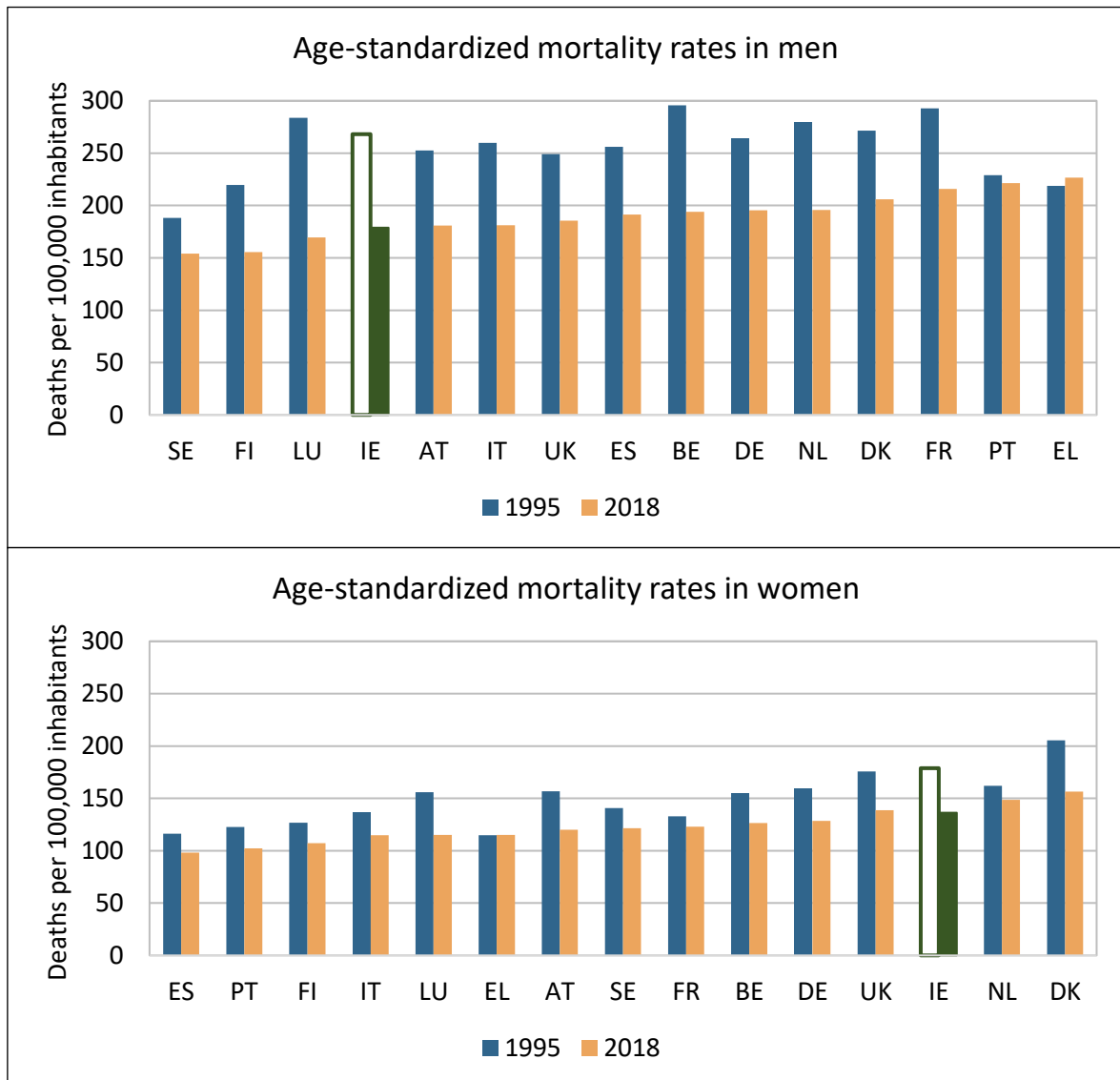


Figure 9: Estimated number of cancer deaths in men and women per 100,000 inhabitants (age-standardized rates), 1995–2018

Notes: The age standardization is based on the old European standard. Source: IARC, and WHO/IARC and Eurostat for Ireland ([7](#), [9](#), [21](#), [35](#)).

2.2.3 Future development

Overall population growth and population aging are key trends for future cancer numbers in Ireland. The biggest challenge ahead is the rising population share of elderly people, who have the highest risk of getting cancer. Future cancer numbers are naturally uncertain, but predictions based on the status quo can provide some insights.

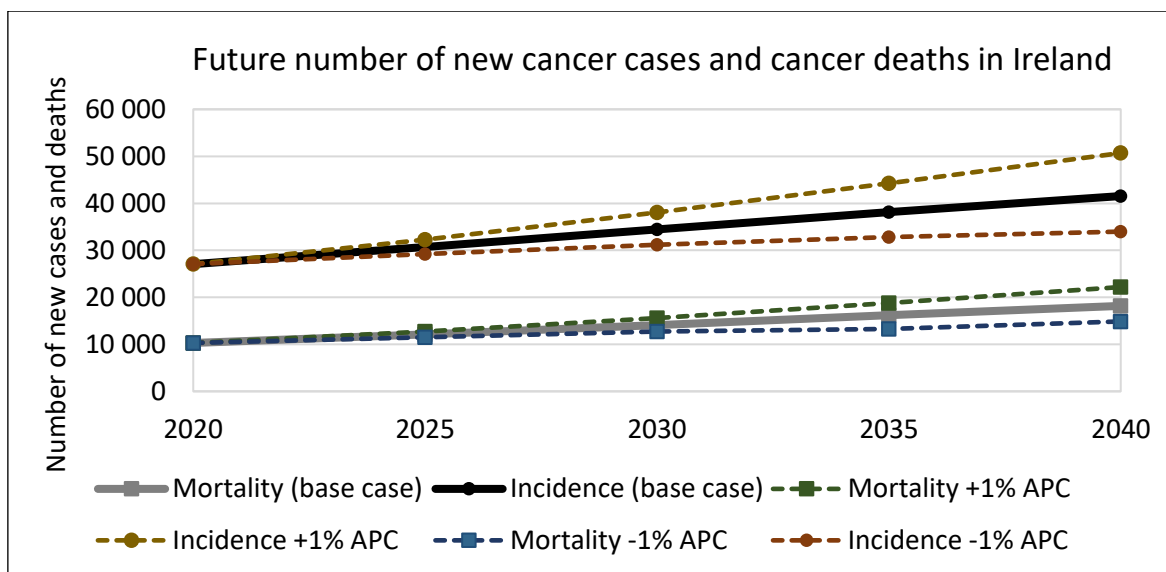


Figure 10: Different scenarios of future cancer incidence and mortality in Ireland, 2020–2040

Notes: Cancer refers to all cancer sites but non-melanoma skin cancer (ICD-10 C00-C97/C44). APC = annual percent change in age-specific rates. Projections in the base case scenario are based on constant age-specific rates and only driven by expected changes in the population composition (base year = 2020). Source: IARC based on population projections by the United Nations (10).

Figure 10 shows different scenarios of future cancer numbers in Ireland until 2040. The base case scenarios for cancer incidence and cancer mortality are based on the current age-specific risk to get cancer and the age-specific risk to die from cancer, respectively. They show what would happen in the absence of changes in risk factors and improvements in cancer care between 2020 and 2040.

- Incidence:** The projections indicate that the annual number of new cancer cases might increase by almost 15,000 cases from 27,000 to 42,000 cases year (from 548 to 757 cases per 100,000 inhabitants) between 2020 and 2040 solely due to the expected demographic changes. As it is difficult to address the demographic changes, it will prove difficult to avert many of the future new cancer cases. Future changes in the prevalence of risk factors will also play a role. Increasing trends in obesity and sun exposure might lead to increased age-specific incidence rates (such as in the “Incidence +1% APC” scenario in Figure 10), whereas declining smoking rates might lead to decreased age-specific incidence rates (such as in the “Incidence -1% APC” scenario in Figure 10) compared to the base case scenario. The “Incidence +1% APC” scenario might be quite likely looking at past trends in Ireland. In fact, the age-standardized incidence rates (i.e., the sum of all age-specific rates) in Ireland shown in Figure 3 increased by 0.7% in men and 0.8% in women on an annual basis between 1995 and 2017–2019.
- Mortality:** The projections indicate that the annual number of cancer deaths might increase by almost 8,000 deaths from 10,000 to 18,000 deaths (from 208 to 331 deaths per 100,000 inhabitants) between 2020 and 2040 solely due to the expected demographic changes. By

continuously improving the quality of cancer care delivered to patients, an increasing number of lives could be saved. Assuming that continuous improvements in the quality of cancer care result in a 1% annual decline in age-specific mortality rates (as shown in the “Mortality -1% APC” scenario in Figure 10), up to 3,500 lives could be saved in 2040 alone compared to the base case scenario. This is not an unrealistic assumption, given past trends in Ireland. In fact, the age-standardized mortality rates (i.e., the sum of all age-specific rates) in Ireland shown in Figure 7 decreased by 1.5% in men and 1.2% in women on an annual basis between 1995 and 2019.

3. Economic burden of cancer

The burden of cancer to society can also be measured in monetary terms. The economic burden of cancer refers to the costs that cancer imposes on society. Costs are here defined more broadly than in an everyday meaning (36). Three types of costs can be distinguished:

- **Direct costs:** These are costs of resource consumption arising from the disease. They include expenditures made for services within the health care system, such as for oncologists, hospital beds, radiation therapy machines, medicines, etc. Formally provided social support services, such as by non-governmental organizations, are also direct costs. The costs of travelling to receive treatment, fees for health care visits, and prescription fees for medicines borne by the patient are also direct costs.
- **Indirect costs:** These are costs of patients' productivity loss arising from the inability to work due to the disease. They consist of the temporary or permanent inability to work in the formal labor market and from premature death of people in working age.
- **Informal care costs:** These costs arise from the time forgone by relatives and friends to provide unpaid care, such as help with transportation to a health care facility and support at home with household chores.

The development of the economic burden partly reflects the development of the disease burden. The growing number of new cancer cases increases the direct costs as more care provision is needed. Yet progress in cancer care might decrease the number of cancer deaths (in patients in working age) and thereby reduce mortality-related indirect costs.

This chapter describes the different parts of the economic burden of cancer, the direct costs (section 3.1) and the indirect costs (section 3.2). Informal care costs are not considered. All costs are expressed in euros (€) in 2018 prices and exchange rates. The results are not adjusted for price differentials between countries (purchasing power parities, PPP), unless otherwise noted.

3.1 Direct costs

The direct costs of cancer are in this report defined as the sum of the costs of all resources used within the health care system. This includes costs for prevention, screening, diagnosis, and treatment. Direct costs include both publicly paid resources, financed by tax money and/or social security contributions, and privately paid resources, including out-of-pocket payments for health care visits and medicines as well as fees for private health insurance. Direct costs of resources outside the health care system could not be included.

The direct costs of cancer were calculated in a top-down manner. The starting point was a country's gross domestic product (GDP) based on data from Eurostat and the GDP-share of total health expenditure⁴ based on data from the OECD and the WHO. These two measures were combined to obtain the total health expenditure. The next step was to find national information on the share of total health expenditure spent on cancer care. In the absence of disease-specific health accounts in most countries, country-specific data on health expenditure on cancer care were gathered from reports and studies from national ministries of health, national statistical offices, research institutes, national cancer societies, peer-reviewed journals, the OECD, and the WHO. National estimates for 11 of the EU-15 countries could be obtained. Ireland was among the countries where no data could be found; see Appendix of the European Comparator Report for more details (1).⁵ For Ireland and the other three countries, data were imputed based on geographical proximity and similarity in GDP per capita. For Ireland, the observed share in the UK was used as a best-guess estimate. In the final step, the share of health expenditure spent on cancer care was used to estimate cancer-specific health expenditure.

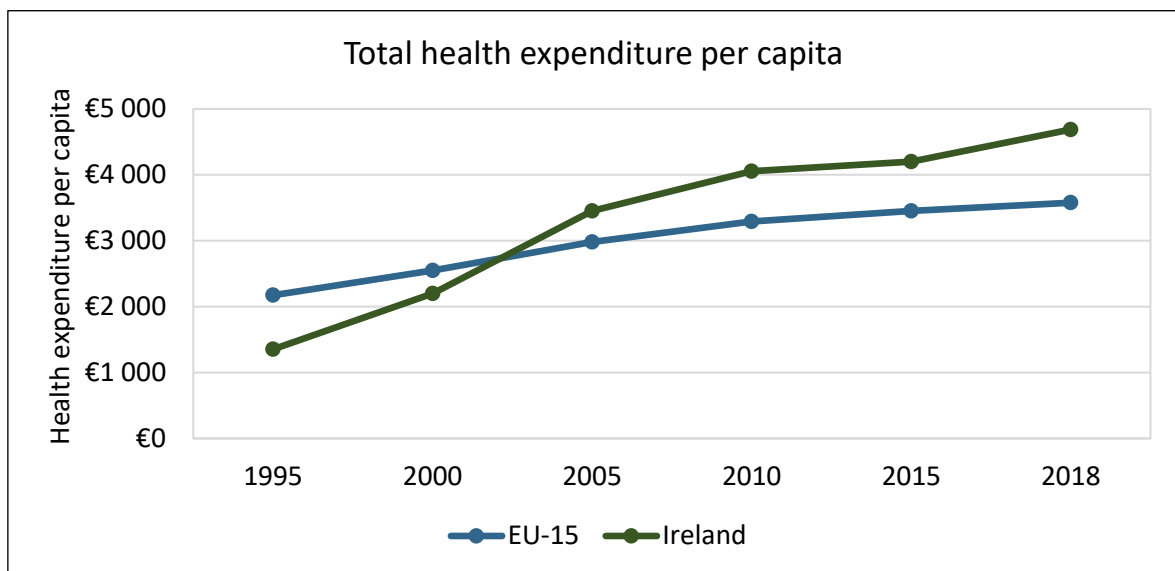


Figure 11: Total health expenditure in Ireland and EU-15 (in €, 2018 prices and exchange rates), 1995–2018

Source: Eurostat, OECD, WHO (38-42).

The total health expenditure in the EU-15 countries amounted to €809 billion in 1995 and increased by 81% to €1,461 billion in 2018 (in 2018 prices and exchange rates). The EU-15 average per-

⁴ Total health expenditure refer to “current health expenditure”, as defined according to OECD’s System of Health Accounts. Current health expenditure include public and private sources. Capital expenditure is not included.

⁵ During the preparation of this report, IHE was in contact with the Department of Health to explore whether there is any information about how much of Ireland’s total health expenditure are spent on cancer. The Department of Health indicated that they do not have such data. Subsequently, IHE contacted the NCCP at the HSE with the same query, but the NCCP did not provide an answer. The budget for the NCCP was €98 million in 2020 and €130 million in 2021 (37).

capita health expenditure increased by 65% from €2,173 to €3,577 per capita during this period; see Figure 11. Total health expenditure in Ireland saw a much greater increase (+367%) over the same period of time, from to €4.9 billion in 1995 and €22.8 billion in 2018. The per-capita health expenditure in Ireland, shown in Figure 11, increased by 247% from €1,353 to €4,688 per capita.

The estimated proportion of the total health expenditure spent on cancer care in Ireland and the EU-15 is shown in Figure 12. As explained above, the proportion of health care expenditure spent on cancer care in Ireland was based on data for the UK and amounted to around 5% between 1995 and 2018. The EU-15 average was slightly higher at around 6% during this period. Figure 12 also includes the maximum range of the national estimates of this proportion of the EU-15 countries, ranging from just below 4% to just above 7%. The fact that the proportion of cancer care spending is only 4–7% of total health expenditure while more than 25% of all deaths are due to cancer in the EU-15 is perhaps surprising. However, even in the United States spending on cancer care has been fairly stable at around 5% of total health expenditure between the 1960s and 2010 ([1](#)).

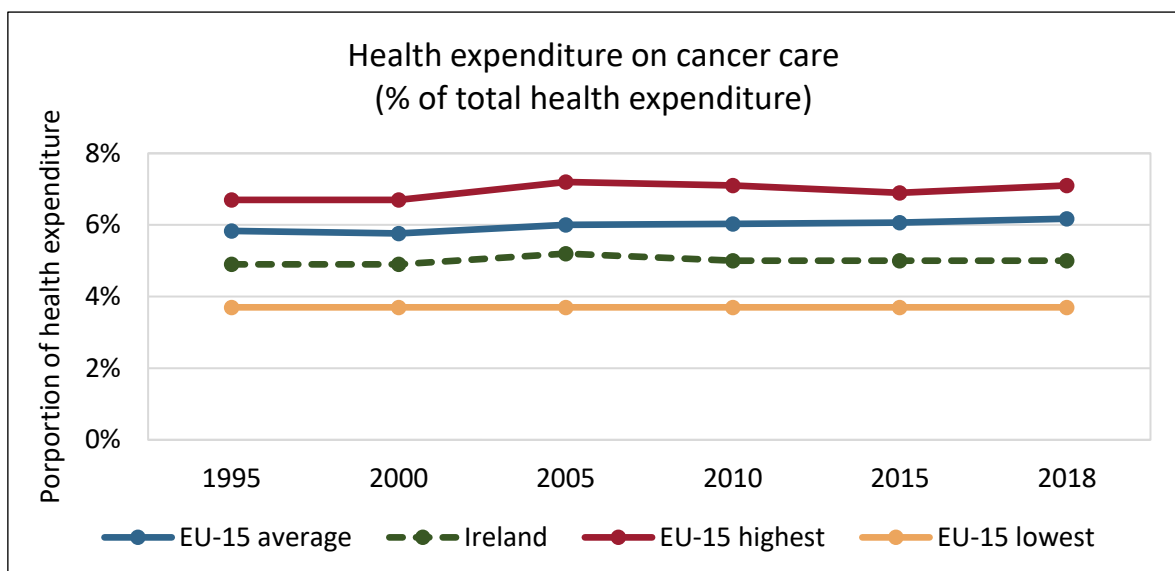


Figure 12: Health expenditure on cancer care (% of total health expenditures), 1995–2018

Notes: The numbers for Ireland are best-guess estimates based on data for the UK. The “EU-15 highest” are Italy in 1995 and 2000, Germany in 2005 and 2010, the Netherlands in 2015, and France in 2018, which had the highest spending proportion in these respective years. The “EU-15 lowest” is Sweden, which had the lowest spending proportion between 1995 and 2018. Source: IHE Comparator Report ([1](#)).

Despite the nearly stable share of the proportion of total health expenditure spent on cancer care, the absolute size of the estimated cancer care expenditure increased between 1995 and 2018 from €239 million to €1,139 million (in 2018 prices and exchange rates). Figure 13 shows that the direct costs of cancer per capita increased by over 250% from €66 to €234 in Ireland (in 2018 prices and exchange rates). Between 2005 and 2015, the direct costs per capita in Ireland were close to the EU-15 average, before slightly surpassing the average of €221 in 2018.

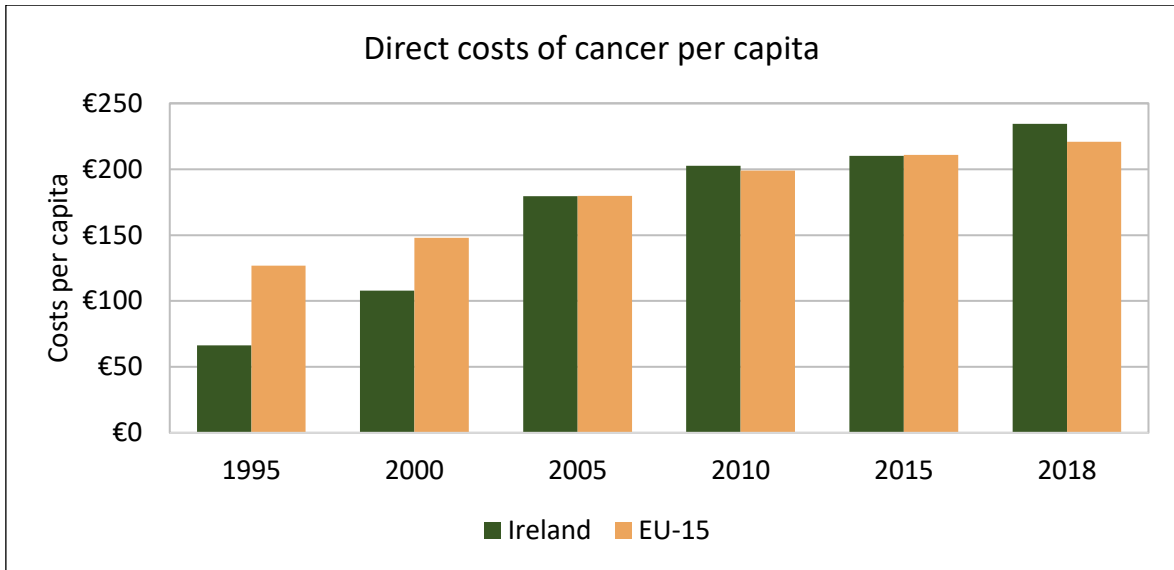


Figure 13: Direct costs of cancer per capita in Ireland and EU-15 (in €, 2018 prices and exchange rates), 1995–2018

Source: own calculations based on IHE Comparator Report (1).

Country-specific estimates of the direct costs of cancer in 2018 are illustrated in Figure 14. The average per capita spending on cancer among the EU-15 countries was €221 (unadjusted for PPP differences) and €207 (PPP-adjusted). The Benelux countries, Germany, Austria, and France spent the most on cancer – between €250 and €300 (PPP-adjusted). Ireland spent €207 (PPP-adjusted), exactly in line with the EU-15 average. Denmark, Italy, the UK, and Sweden spent between €150 and €200 (PPP-adjusted), and the remaining countries spent between €110 to €150 (PPP-adjusted).

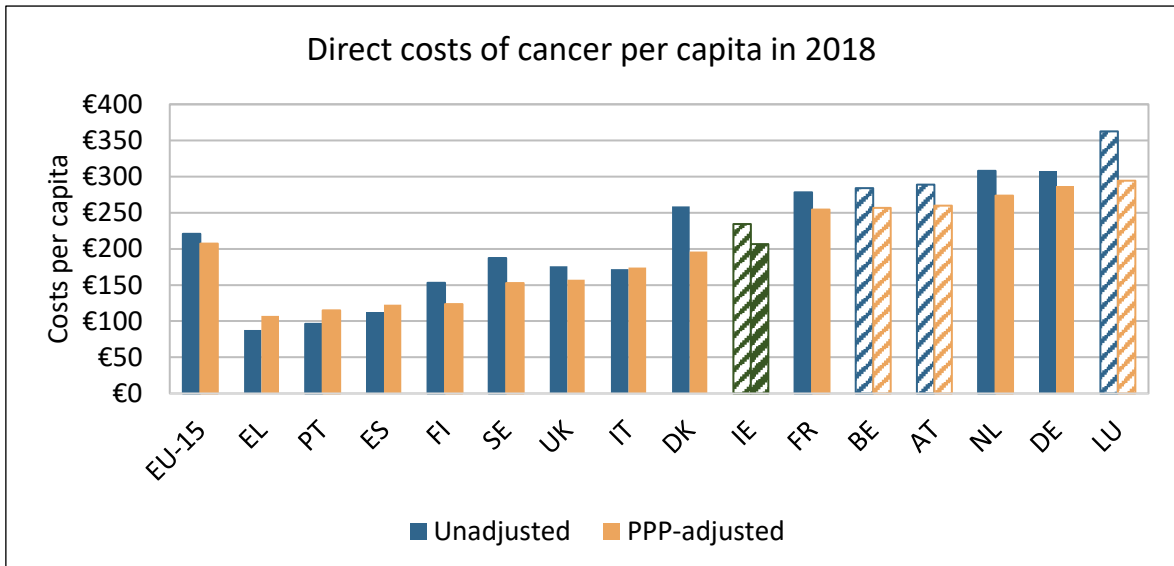


Figure 14: Direct costs of cancer per capita (in €, 2018 prices and exchange rates), 2018

Notes: Hatched bars indicate that the direct costs are more uncertain, as a national estimate of the proportion of health expenditure spent on cancer care was not available and had to be estimated based on data from similar countries. Source: own calculations based on IHE Comparator Report (1).

When comparing the direct costs of cancer between countries, it is important to remember that these costs only represent a single number of the monetary value of all resources used. For the

monetary inputs to yield the highest benefits to patients, the allocation and organization of resources is pivotal (43).

The development of the direct costs (Figure 13) is closely related to the overall development of the total health expenditure (Figure 11). The pattern of increasing direct costs of cancer between 1995 and 2018 is a consequence of increased spending on health care rather than an increased share of health care resources devoted to cancer care (Figure 12). However, there are a range of important factors that can help to explain the overall increase in the direct costs of cancer as well as why the share of health care resources devoted to cancer remained relatively stable:

- **More patients:** As explained in section 2.2.1, the number of new cancer cases has gone up in Ireland (+92%) and the EU-15 (+65%) between 1995 and 2018. The sheer increase in the number of cancer patients increases costs for care.
- **Longer treatment of patients:** As survival has increased (see chapter 4) in recent decades, some patients have required care for a longer time. This affects mostly the costs of long-term care and rehabilitation but also of outpatient care visits for regular medical check-ups for the monitoring of disease progression and of recurrence.
- **Additional prevention and screening services:** Organized screening programs for certain cancer types (e.g., breast, cervical, and colorectal cancer) and vaccination programs against human papillomavirus (HPV) were rolled out in recent decades. The implementation of these measures increases the direct costs in the short and medium run but can in some instances be expected to decrease these costs in the long run.
- **Additional diagnostic services:** The development of personalized/precision medicine entails a growing need for molecular testing. This requires investment in testing laboratories and capacity (44). On the other hand, more targeted treatment holds the potential to reduce exposure to side effects and costs for their treatment.
- **New cancer medicines:** New targeted therapies and immunotherapies have replaced or are given in combination with older and cheaper off-patent chemotherapies. Some new medicines have allowed new patient groups to be treated. Prices for new medicines have also increased. Increases in price and volume have increased total expenditure on medicines (see chapter 5).
- **Shift of the treatment setting from inpatient to outpatient care:** Cancer care has become more effective as new and improved treatment modalities have been introduced. In many cases, these improvements enable shorter hospital stays, entail fewer side effects, and result in quicker recovery and potentially fewer recurrences (45). For example, the introduction of antiemetic medicines in the early 1990s meant that patients no longer had to suffer from

vomiting and nausea due to treatment with cytostatic agents. This enabled more patients to be shifted from expensive inpatient care to cheaper outpatient care treatment.

- Method of medicine administration: There has been a shift from intravenous to oral delivery methods of cancer medicines. As more patients received treatment at home, this decreased the demand for both inpatient and outpatient care.

3.2 Indirect costs

From an economic perspective, it is costly when patients of working age are (i) forced to be on sick leave to receive treatment and recover from the disease, (ii) forced to retire early due permanent incapacity/disability, and/or (iii) die prematurely. An indirect cost to society arises if these patients could have been expected to work in the absence of disease.⁶ Their foregone labor market earnings represent a productivity loss caused by morbidity (i.e., sick leave and early retirement) and premature mortality.

In this report, the indirect costs of cancer were calculated using the human-capital method. This method takes the patient's perspective and counts any hour not worked as an hour lost. The productivity loss from premature mortality was quantified as the lost future earnings that working-age patients (15–64 years) who die would have been expected to generate throughout their working life. Age-specific and sex-specific number of cancer deaths were obtained from the WHO/IARC and Eurostat (21, 35). Potential years of working life lost were calculated and multiplied with sex-specific mean annual earnings and sex-specific employment rates in the age group 15–64 years, based on data from Eurostat (47, 48). Future lost earnings were discounted with a 3.5% annual discount rate, and a zero real growth rate in future earnings was assumed. The estimation of the productivity loss from morbidity is in general more challenging as no detailed international data on disease-specific sick leave and early retirement are available. Previous estimates for EU countries in 2009 were used and converted to 2018 values by adjusting for inflation and changes in exchange rates based on data from Eurostat (39, 40, 49).

The results of the estimation of the indirect costs of cancer are shown in Figure 15. Contrary to the direct costs, the indirect costs decreased in the EU-15 by 17% from €176 to €146 per capita between 1995 and 2018 (in 2018 prices and exchange rates). In Ireland, indirect costs increased between 1995 and 2000 and afterwards decreased until 2010 before flattening out, but nonetheless a 12% decrease from €149 to €132 per capita between 1995 and 2018 was recorded. The decrease

⁶ The fact that individuals' time is a limited resource for which there is an alternative cost is widely accepted in economic theory (46). One hour of lost production thus corresponds to the value of the work that would have been carried out. Transfer payments within the social security system (sick leave benefits, disability benefits, widower's/widow's pensions, etc.) should not be included to avoid double counting of costs.

in the indirect costs was mostly driven by a reduced number of cancer deaths in people of working age during this period. This has decreased the productivity loss from premature mortality.

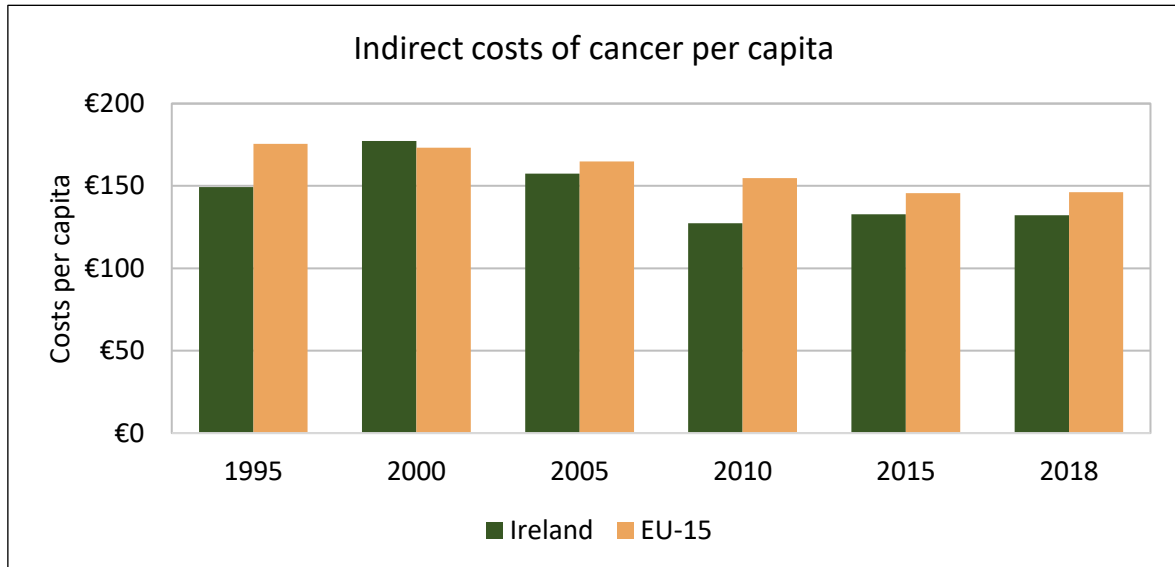


Figure 15: Indirect costs of cancer per capita in Ireland and EU-15 (in €, 2018 prices and exchange rates), 1995–2018

Source: own calculations based on IHE Comparator Report (1).

Country-specific estimates of the indirect costs of cancer in 2018 are illustrated in Figure 16. The average indirect costs of cancer per capita in the EU-15 was €146 (unadjusted for PPP differences) and €137 (PPP-adjusted). Denmark, Belgium, and the Netherlands had the highest indirect costs with just over €200 per capita (PPP-adjusted). The indirect cost of cancer in Ireland amounted to €116 per capita (PPP-adjusted) and were below the EU-15 average. Greece, Italy, and Portugal had the lowest indirect costs of cancer with below €100 per capita (PPP-adjusted), partly driven by a lower valuation of the earnings lost, which in turn is a result of lower general earnings and employment levels in these countries.

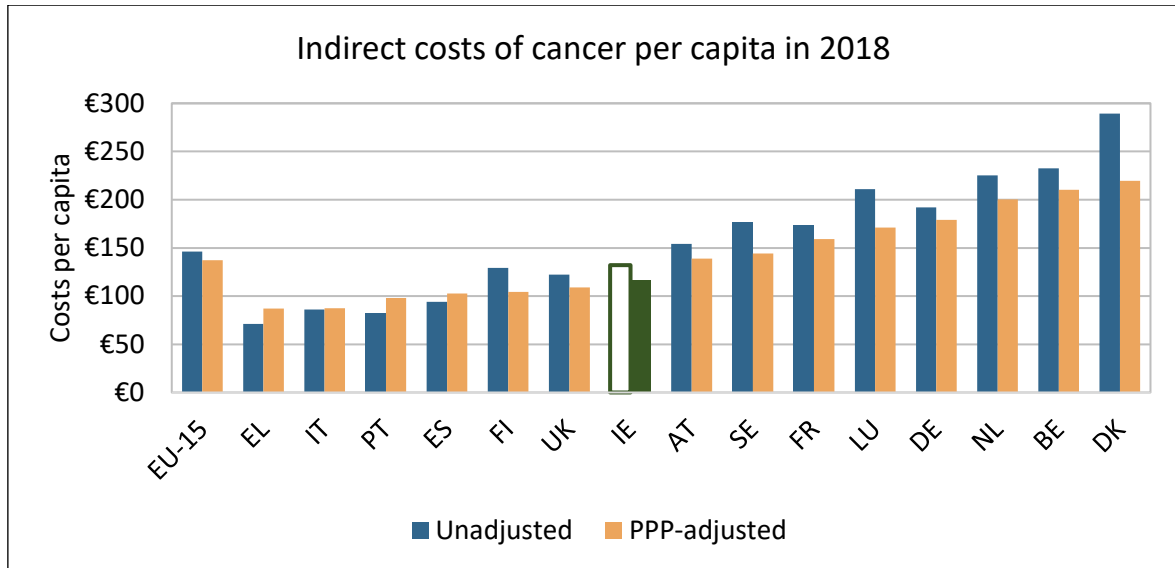


Figure 16: Indirect costs of cancer per capita (in €, 2018 prices and exchange rates), 2018

Source: own calculations based on IHE Comparator Report (1).

3.3 Future development

The future development of the economic burden of cancer in Ireland and the EU-15 is closely linked to the future development of cancer incidence and cancer mortality (see section 2.2.3). The predicted increase in the number of new cancer cases due to the demographic development poses a major challenge for all health care systems. It will require further investment in all areas of cancer care – prevention, early detection, diagnosis and treatment, rehabilitation – as well as an effective and efficient organization to meet this challenge. This will very likely increase the direct costs of cancer.

In the foreseeable future, the introduction of additional organized screening programs, such as for lung cancer, more extensive molecular testing in newly diagnosed patients, as well as the introduction of new cancer medicines at a faster rate than older ones go off patent (see chapter 5) will further increase the direct costs of cancer.

The economic benefits of the advances in cancer care are reflected in the development of the indirect costs. The past decline in the indirect costs shows that the economic benefits from increased health spending on cancer care have mostly fallen outside the health care system. As long as cancer care keeps improving, thereby leading to the avoidance of deaths in working-age people and as well as a reduction of early retirement and temporary sick leaves, the indirect costs of cancer will continue to decrease.

4. Outcomes of cancer patients

There is no definite “cure” for any cancer type. The prime measure of outcomes of cancer patients is therefore survival. Health-related quality of life is an outcome measure that becomes increasingly important as several cancer types start to resemble a chronic disease rather than a strictly lethal disease.

This chapter first describes the survival of cancer patients (section 4.1). It then explores the potential to improve cancer survival in Ireland (section 4.2) and illustrates the relationship between cancer survival and spending on cancer care (section 4.3). Health-related quality of life is not considered, due to a lack of systematic data.

4.1 Survival

Survival is the concept that connects the two epidemiological measures of incidence and mortality. It measures the share of people that have been diagnosed with cancer in a certain year and that are still alive after a certain period of time. Survival is commonly measured as 5-year survival rates, i.e., the share of people diagnosed with cancer in year t that is still alive in year $t+5$. This means that data on the 5-year survival rate of cancer patients diagnosed in 2022 can only be definitely evaluated after 2027, based on what is called “cohort analysis”. However, through alternative methods (“period analysis” and “mixed analysis”) a good approximation of the likely result can be estimated ([50](#), [51](#)).

Two adjustments are routinely made to 5-year survival rates to receive comparable rates across time and countries. Firstly, net (also called “relative”) survival rates rather than gross (“absolute”) survival rates are compared. The net survival rate is the ratio of two survival rates: the gross survival rate of cancer patients divided by the expected survival rate of people in the general population with similar age and sex in the same country and calendar year⁷ ([52](#)). This adjusts survival rates for the effect of competing causes of death (background mortality) that would otherwise bias comparisons across time and countries. Thus, net survival rates indicate the hypothetical situation in which cancer is the only cause of death ([50](#)). Secondly, the age structure of cancer patients differs across time and countries. Since net survival rates for most cancer types vary by age (typically they decrease with age), they are adjusted for age at diagnosis ([53](#)).

⁷ For example, assume that the observed share of cancer patients that are alive 5 years after diagnosis is 60%. This is the gross survival rate. In addition, assume that the 5-year expected survival rate in the general population (with the same age structure, same sex composition and during the same time period) is 80%. The 5-year net survival rate is then $60\%/80\% = 75\%$. Thus, of the 40% ($100\% - 60\%$) of cancer patients who died 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.

Survival rates in Ireland

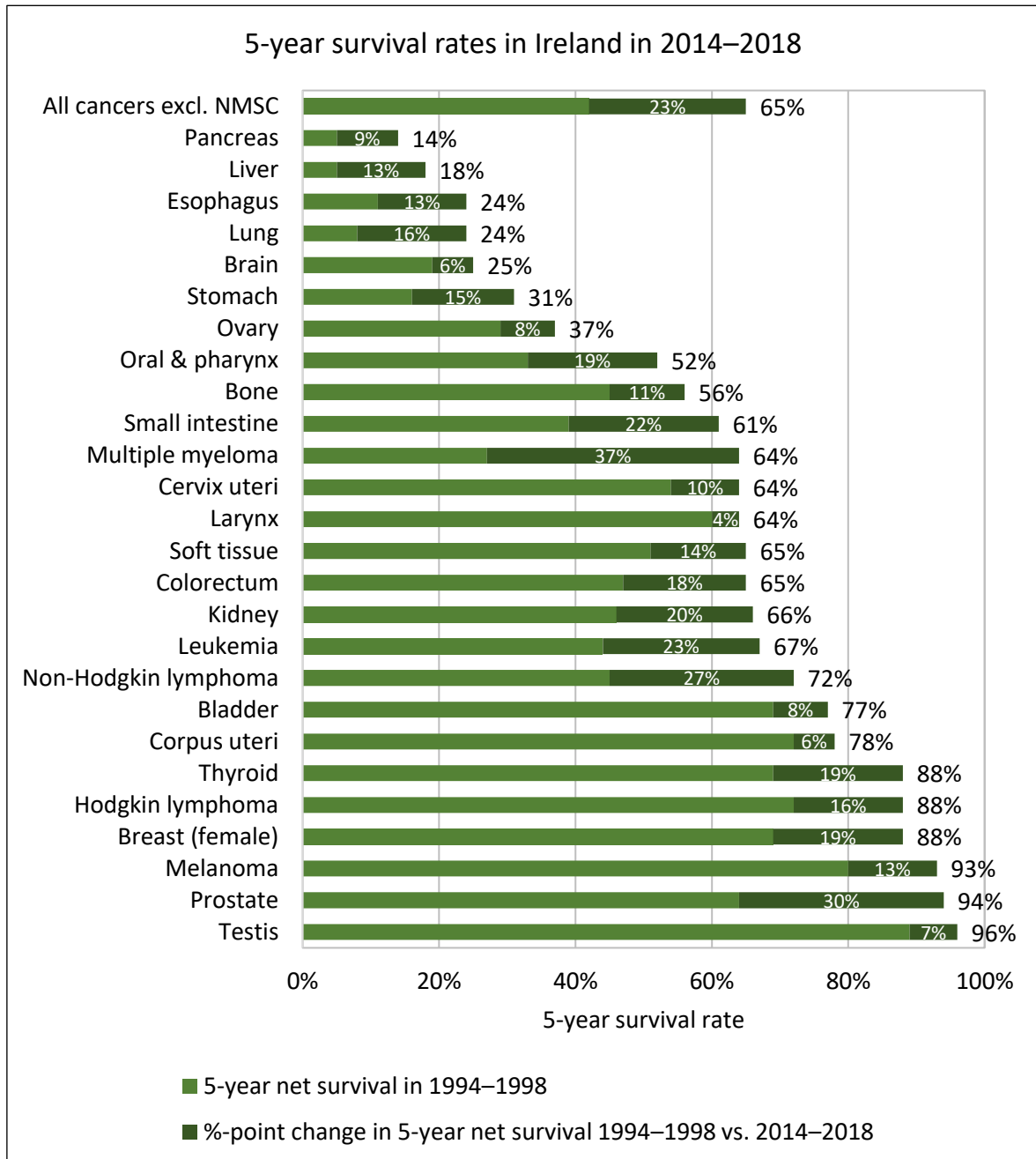


Figure 17: Age-standardized 5-year net survival rates for selected cancer types in Ireland for diagnosis period 2014–2018

Notes: NMSC = non-melanoma skin cancer. Source: NCRI (25).

In Ireland, the NCRI regularly assesses and publishes survival statistics. The latest statistics cover patients diagnosed between 2014–2018 (25). The 5-year age-standardized net survival rate of all cancers (excluding non-melanoma skin cancer) was 65%; see Figure 17. Yet there were huge differences across cancer types, with survival rates ranging from less than 20% for pancreatic cancer and liver cancer to over 90% for melanoma, prostate cancer, and testicular cancer. Figure 17 also shows the change in the survival rates over a 20-year period, between the diagnosis periods 1994–1998 and 2014–2018. For all cancers combined, the 5-year age-standardized net survival rate

increased by 23 percentage points (pp) from 42% to 65%. The smallest improvement over time in absolute terms was achieved for laryngeal cancer (+4 pp from 60% to 64%). The biggest improvements in absolute terms were achieved in three hematologic cancer types – multiple myeloma (+37 pp), leukemia (+23 pp), non-Hodgkin lymphoma (+27 pp) – and in prostate cancer (+30 pp).

Improvements in survival rates are a combination of two factors – early detection and diagnostics plus treatment. Early detection through nationwide organized screening programs is currently being done for three cancer types – breast cancer since 2000 (54), cervical cancer since 2008 (55), colorectal cancer since 2013 (56) – by the HSE in Ireland (57). Non-organized screening for prostate cancer with prostate-specific antigen (PSA) testing is also being done (58). Screening helps to detect asymptomatic cancers as early as possible, thereby increasing the proportion of cancers detected at an early stage (commonly referred to as “downstaging”). Downstaging increases survival rates, because the survival rates of early-stage cancers are higher than of late-stage cancers (59). The increased screening activities in Ireland thus might offer some explanations for the survival improvements seen between 1994–1998 and 2014–2018 in Figure 17 for breast, cervical, colorectal, and prostate cancer.

The treatment of cancer usually involves a combination of surgery to remove the tumor (in solid tumors and non-metastatic stages), radiation therapy, and systemic therapy with cancer medicines. A prerequisite for adequate treatment is diagnosis. Newer diagnostic imaging equipment, such as the introduction of PET-CT scanners in the 2000s, have improved the possibilities of accurate diagnosis by locating and determining the spread of the cancer (60). Better diagnosis helps to improve the accurate application of surgery and radiation therapy (61). In addition, the improved molecular understanding of cancer has spurred the development of molecular diagnostic testing. This type of testing started with the assessment of HER2 status in breast cancer to guide the administration of trastuzumab (EMA approval in 2000) (62). Molecular diagnostic testing has since then become a prerequisite for the administration of most modern cancer medicines, such as targeted therapies and immunotherapies. Based on trends in cancer mortality in the United States during 2000–2009, improved imaging diagnostics and new cancer medicines have been shown to be the main determinants of the observed decline in mortality rates (63).

Improvements in imaging diagnostics as well as surgery and radiation therapy offer no explanations for the observed increase in survival rates in the three hematologic cancer types – multiple myeloma, leukemia, non-Hodgkin lymphoma – in Ireland in Figure 17. The main treatment modality in these three cancer types are cancer medicines and stem cell transplant (64-66).

International comparison of survival rates

International comparisons of cancer survival based on cancer registry data are available through the CONCORD program, a global surveillance program of cancer survival led by the London School of Hygiene & Tropical Medicine. The CONCORD program estimates 5-year age-standardized net survival rates in a comparable way across all countries. The CONCORD-2 program estimated survival rates for ten cancer types diagnosed during 1995–2009 and followed up to December 31, 2009 (53). The CONCORD-3 program extended the analysis to 18 cancer types diagnosed during 2000–2014 and followed up to December 31, 2014 (67). Newer survival data are not available (as of March 2022).

Figure 18 presents 5-year age-standardized net survival rates for seven cancer types for the EU-15 countries with available data, comparing the diagnosis period 1995–1999 (or 2000–2004) to 2010–2014. These cancer types cover the six most commonly diagnosed cancer types in Ireland as well as ovarian cancer (see Figure 4 in section 2.2.1). Similar to the development in Ireland, survival rates for all cancers have generally improved over time in all countries. Looking at the four major cancer types, Ireland ranks in fifth place for prostate cancer and lung cancer, in second-last place for colon cancer (excluding rectal cancer), and in last place for breast cancer. Ireland ranks in the middle of the EU-15 countries for melanoma, in fifth place for lymphoid cancers (which include non-Hodgkin lymphoma and multiple myeloma), and in last place for ovarian cancer. The countries with the highest survival rates vary from cancer type to cancer type, but Belgium, Sweden, Germany, France, and Finland are most often at the top of the ranking.

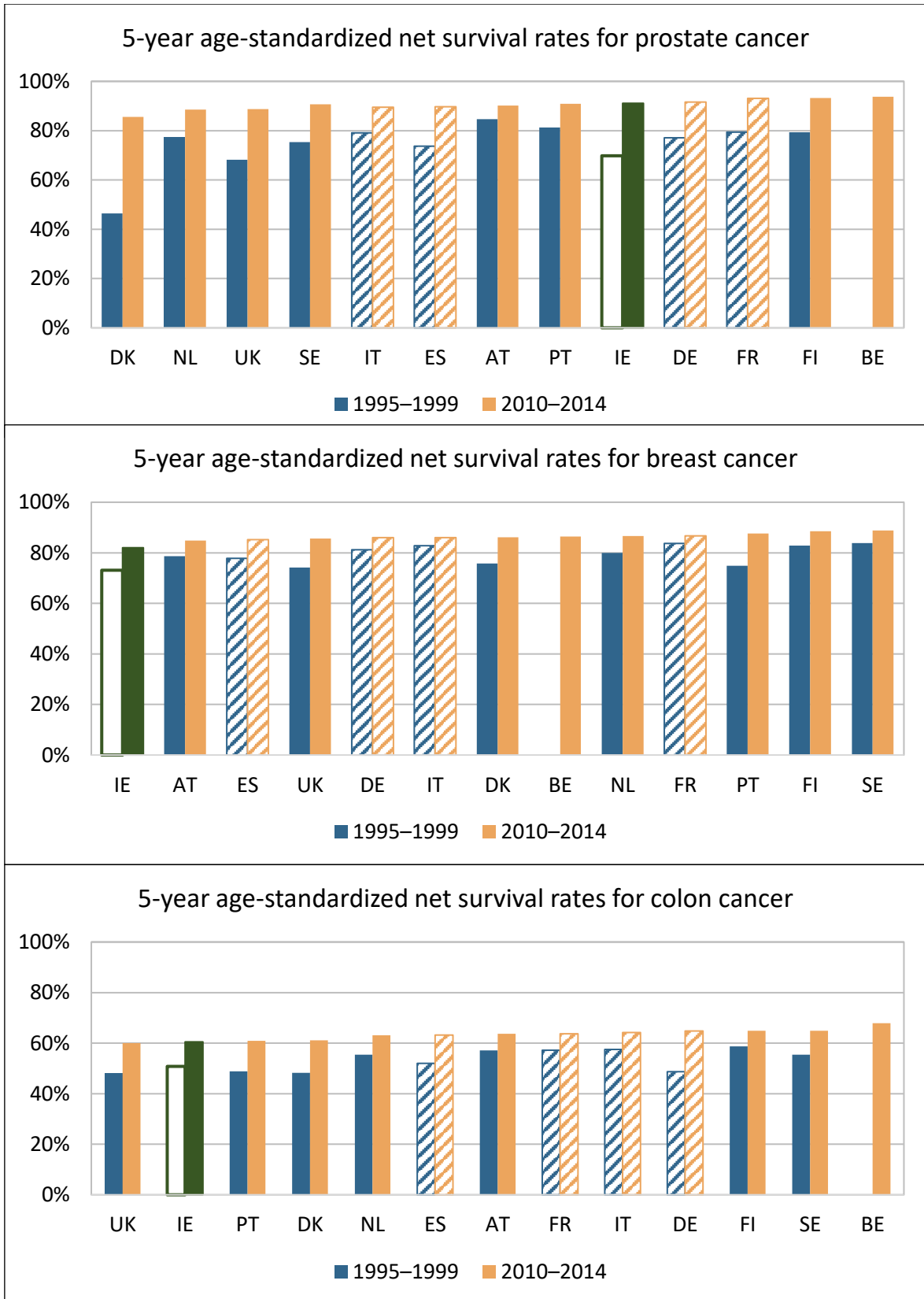


Figure 18: 5-year age-standardized net survival rates for selected cancer types in adult patients (15–99 years), 1995–1999 (or 2000–2004) vs. 2010–2014

Notes: Hatched bars in DE, ES, FR, and IT indicate that national estimates are based on regional data. EL and LU are missing due to lack of data. Source: CONCORD-2/3 (53, 67).

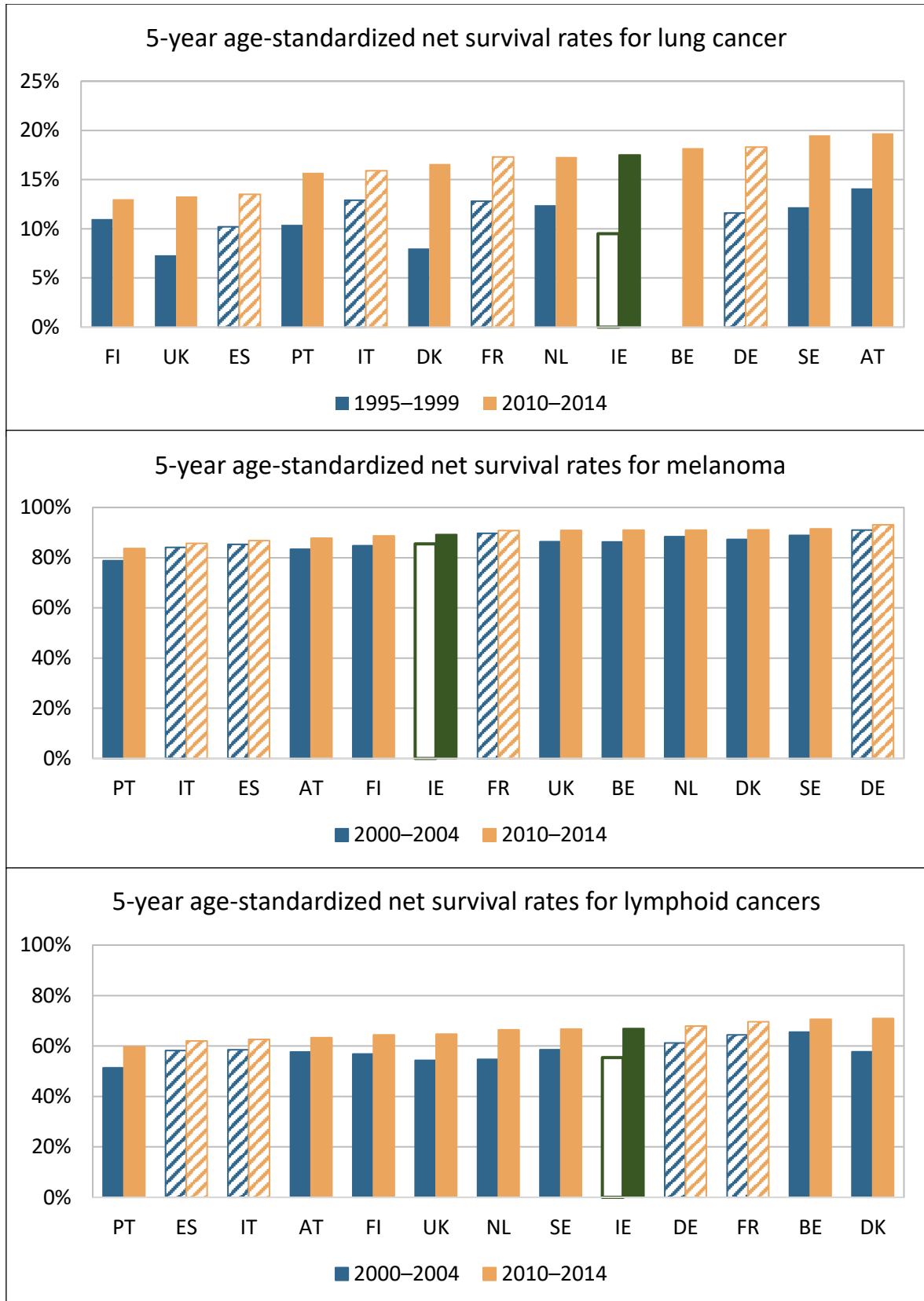


Figure 18 (continued): 5-year age-standardized net survival rates for selected cancer types in adult patients (15–99 years), 1995–1999 (or 2000–2004) vs. 2010–2014

Notes: Hatched bars in DE, ES, FR, and IT indicate that national estimates are based on regional data. EL and LU are missing due to lack of data. Source: CONCORD-2/3 (53, 67).

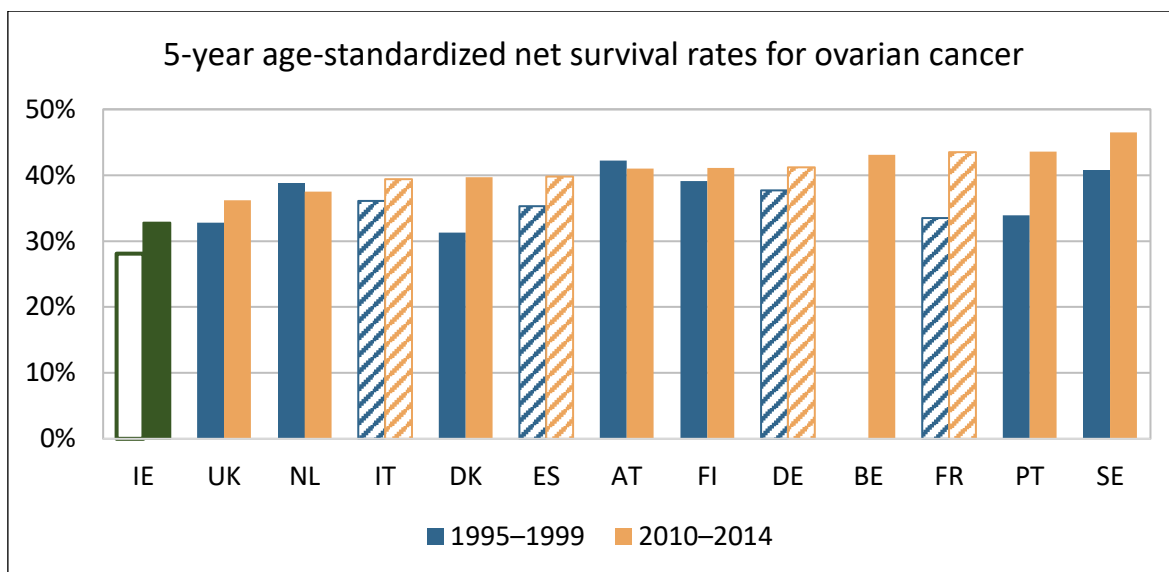


Figure 18 (continued): 5-year age-standardized net survival rates for selected cancer types in adult patients (15–99 years), 1995–1999 (or 2000–2004) vs. 2010–2014

Notes: Hatched bars in DE, ES, FR, and IT indicate that national estimates are based on regional data. EL and LU are missing due to lack of data. Source: CONCORD-2/3 (53, 67).

4.2 Potential to improve cancer survival

The previous section showed that Ireland ranked mostly in the middle or at the lower end of the survival rates distribution across different cancer types in the EU-15. There is thus room to improve survival rates and thereby save additional lives of cancer patients in Ireland.

Figure 19 illustrates the annual number of newly diagnosed cancer patients who are expected to still be alive at least five years after diagnosis (cancer survivors) in Ireland. The light green area shows the number of survivors using the survival rate observed for patients diagnosed in 1995–1999 (2000–2004 for melanoma) for different cancer types (53). The dark green area shows the additional number of survivors from improved survival rates for patients diagnosed in 2010–2014 (67). The red area indicates the number of additional survivors if Ireland had had a survival rate equal to the highest survival rate among the EU-15 countries. If cancer care in Ireland had been as good as the best-performing country in the EU-15 in achieving high survival rates, more than 600 lives could have been saved per year across the six cancer types shown in Figure 19.

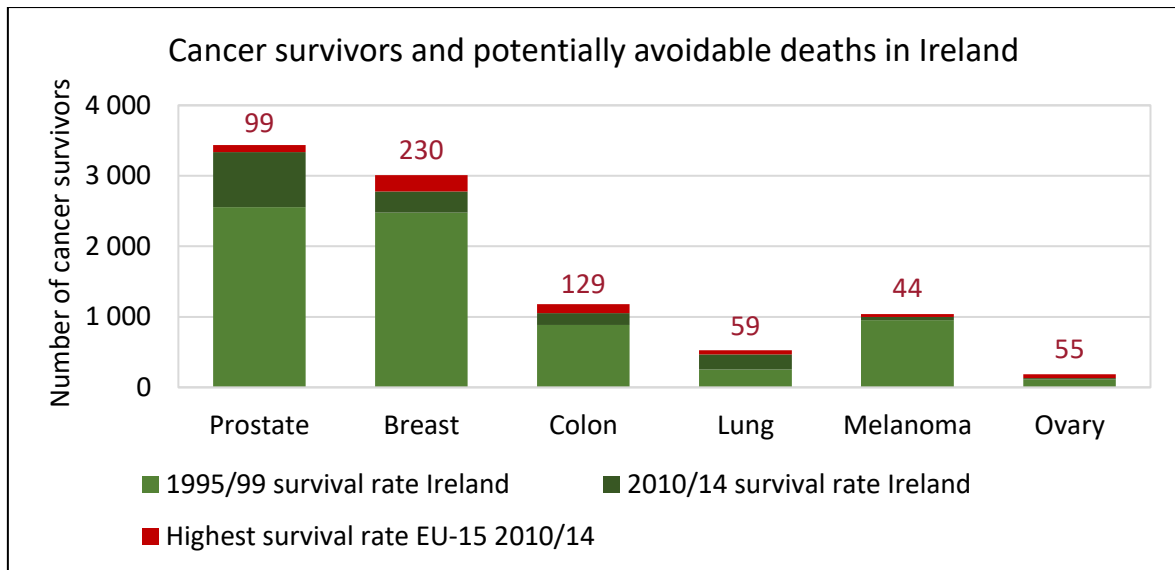


Figure 19: Estimated annual cancer survivors and avoidable deaths in selected cancer types in Ireland

Source: Own calculations based on incidence data for the year 2017 from the NCRI and survival data from CONCORD-2/3 (24, 53, 67). See Figure 18 for the country with the “highest” survival rate for each cancer type.

4.3 Patient outcomes and health spending

The results from sections 4.1 and 4.2 beg the question why many countries achieve higher survival rates than Ireland. A crude way to answer this question is to look how health care inputs relate to health care outcomes. Health care systems need to weigh the costs from investing in different areas of cancer care against the potential improvements in patient outcomes. This ensures that constrained resources are used in a cost-effective way and provide value-for-money for patients and taxpayers.

Figure 20 shows a simple way of relating health care inputs, in the form of health expenditure spent on cancer care per capita (see section 3.1 on direct costs), to cancer patient outcomes, defined as 5-year age-standardized net survival rates (see section 4.1). The total amount of health expenditure per capita spent on cancer is arguably a crude measure of inputs, but it defines the basic limits for the activities of the health care system to produce health. Note that cancer-specific health expenditures refer to the year 2010 and survival to the period 2010–2014 in Figure 20. Each dot represents a country, and each graph contains an (unweighted) trend line.

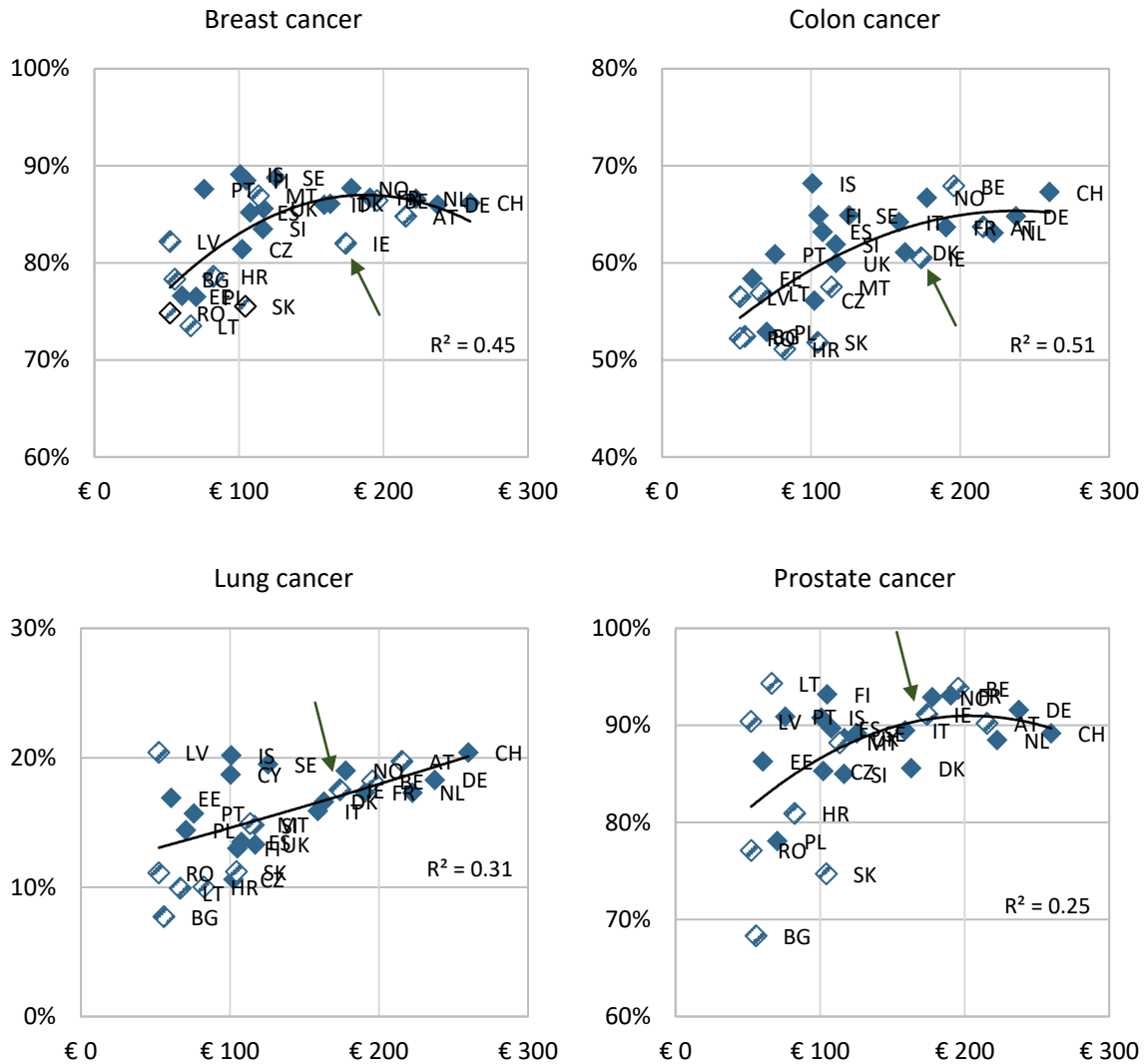


Figure 20: Cancer expenditure (in € per capita, PPP-adjusted) in 2010 and 5-year age-standardized net survival (in %) in 2010–2014

Notes: Hatched dots indicate that the national estimate for cancer expenditure is based on data from similar countries. Cancer expenditure refer to total expenditure on cancer care and not cancer type-specific expenditure. The sample includes the EU-27 countries (except Greece, Hungary, and Luxembourg due to lack of survival data), Iceland, Norway, Switzerland, and the UK. Source: CONCORD-3 for survival rates (67), and own calculations for cancer care expenditure (see section 3.1).

Two important observations can be made from Figure 20. First, adequate spending on cancer seems to be a prerequisite for achieving high survival rates.⁸ The upward sloping trend lines in all four graphs, representing the four largest cancer types, indicate that countries with lower spending tend to record lower survival rates and countries with higher spending tend to record higher survival rates. Second, the relationship between spending on cancer and survival rates might be non-linear (concave shape of the trend lines). This indicates that each additional euro spent on cancer care

⁸ Note that the associations in Figure 20 does not to be fully causal. The positive relationship could potentially also be driven by some third factor (e.g., the level of education in a country) that is related to both the amount of cancer-specific health expenditure and survival.

improves survival rates, but the improvements for every additional euro spent might become smaller the more euros that have already been spent.

Figure 20 also shows great variation in spending on cancer care between countries that achieve similar survival rates. This sort of variation indicates inefficiencies in cancer care, although it is a rather crude way of inferring inefficiencies. The location of Ireland is marked by a green arrow in Figure 20. Ireland is either on the trend line (lung cancer and prostate cancer) or below the trend line (breast cancer and colon cancer). Therefore, Ireland appears to be a country where survival rates are comparatively low given the estimated level of health spending on cancer. If there would be more specific Irish data on spending on cancer in the future, this relationship would need to be revisited. Nonetheless, this observation might motivate a reconsideration of the current allocation of cancer care expenditure into areas with evidence-based added clinical benefits. There seems to be room to improve patient outcomes with existing resources and thereby increase the added value for each additional euro spent in Ireland.

5. Patient access to cancer medicines

Cancer medicines are an integral part of modern cancer care and are essential for improving patient outcomes (63, 68, 69). Chemotherapy and hormone therapy were first introduced in the 1940s–1970s and still today constitute a standard-of-care treatment modality during the treatment course of many cancer types (70). Chemotherapy can cause toxic side effects, as it may damage normal healthy cells alongside malignant cells in the body (71). Targeted therapy medicines, introduced toward the end of the 1990s, use a different mode of action and act on specific molecules that are involved in the growth and survival of cancer cells (2). They have now become one of the main treatment options for some tumors. During the 2010s, immunotherapy medicines, such as checkpoint inhibitor therapies and more recently CAR-T cell therapies that help the body’s immune system to recognize and attack cancer cells, have been added to the therapeutic arsenal (1).

Full patient access to cancer medicines is attained when every patient that may benefit from a certain medicine receives it. For new cancer medicines to reach patients in Ireland, three hurdles have to be overcome. This chapter describes these three hurdles – regulatory approval (section 5.1), reimbursement (section 5.2), and uptake (section 5.3). It then illustrates the consequences of limited and later patient access to newer cancer medicines (section 5.4) and concludes with a description of current challenges for health technology assessment (HTA) and potential solutions (section 5.5).

5.1 Regulatory approval

The first hurdle for patient access to new cancer medicines is marketing authorization by the EMA. The EMA evaluates the safety, quality, and efficacy of new medicines before granting marketing authorization (regulatory approval). The EMA has been responsible for the scientific evaluation of centralized marketing authorization applications of medicines since 1995. Since 2004, all new cancer medicines must follow this centralized procedure to receive marketing authorization throughout the EU from the European Commission (72). After overcoming this hurdle, a new medicine can be sold in the private sector. Very few (wealthy) patients are able to access newly approved cancer medicines through their private health insurance or afford to pay for them out-of-pocket due to high medicine prices upon launch. Instead, most patients have to wait until national reimbursement to access them. In Ireland, cancer patients with a private insurance with the largest insurer, VHI Healthcare, might be able to access some cancer medicines before national reimbursement by the HSE. Yet until 2019, there were no differences in the availability of cancer medicines between VHI Healthcare and the HSE (73).

Between 1995 and 2021, 151 new cancer medicines⁹ were granted centralized marketing authorization by the EMA. There has been a marked increase in the number of approved medicines over time; see Figure 21. Three distinct periods are noticeable. Between 1995 and 2000, on average one new cancer medicine was approved per year. Between 2001 and 2011, the average annual number was close to four. Around ten new medicines were approved per year between 2012 and 2020. 2021 has been an exceptional year with 17 approvals of new cancer medicines.

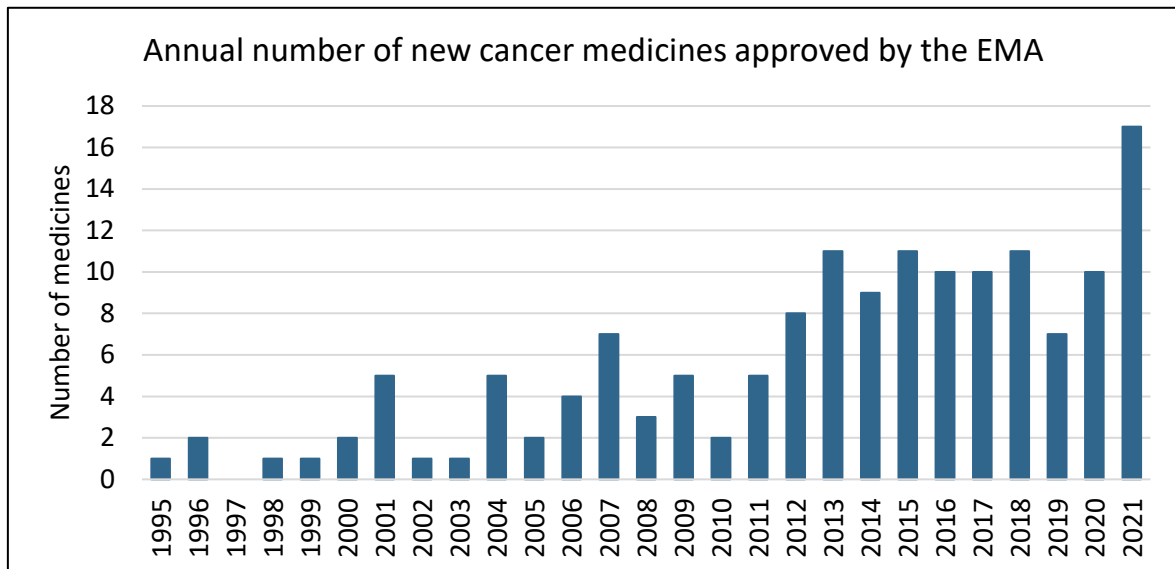


Figure 21: Annual number of new cancer medicines approved by the EMA, 1995–2021

Source: own calculations based on information from the EMA (74).

The initial approval of cancer medicines usually only covers one indication in a specific cancer type. Over time many cancer medicines extend their indication coverage, e.g., use in an earlier line of treatment, use in an earlier disease stage, use in a different cancer type. These extensions of the therapeutic indication also require approval by the EMA. Figure 22 shows that the number of recommended indication extensions of existing cancer medicines was around 20 between 2019 and 2021. The combined number of new cancer medicines and indication extensions of existing cancer medicines reached 41 in 2021. A large proportion of the indication extensions is driven by immuno-oncology checkpoint inhibitor therapies that were originally approved in 2015–2017.

⁹ This includes medicines used in cancer patients in the groups L01, L02, and L04 in the Anatomical Therapeutic Chemical (ATC) classification system. Medicines with identical active substances have only been included at their first instance of marketing authorization.

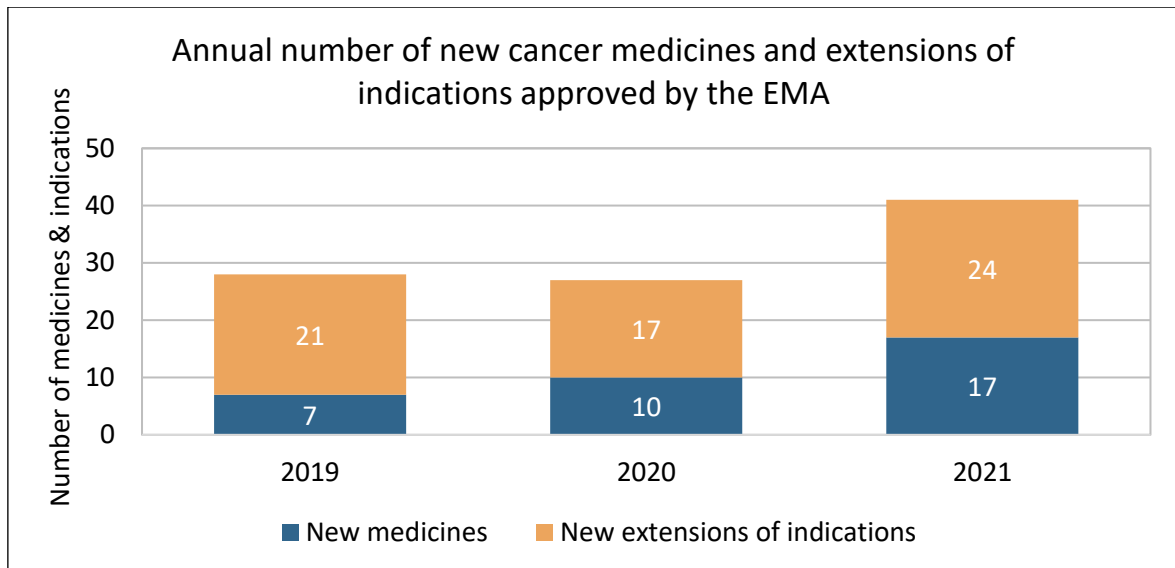


Figure 22: Annual number of new cancer medicines and extensions of indications approved by the EMA, 2019–2021

Notes: “New medicines” refer to the number of new cancer medicines (and not the number of their initial indications, which most often only is one) authorized by the European Commission. “New extensions of indications” refer to extensions of therapeutic indications of existing cancer medicines recommended by the Committee for Medicinal Products for Human Use (CHMP). Extensions of indications of generic cancer medicines were not included. Extensions of indications of cancer medicines given in combination were only counted once here (sometimes they are reported separately for all medicines involved by the CHMP). Source: own calculations based on information from the EMA (74, 75).

5.2 Reimbursement

The second hurdle for patient access to new cancer medicines is pricing and reimbursement by the national/regional health care payer. This requires a reimbursement application by the pharmaceutical company for the EMA-approved indication. In European countries, the pricing and reimbursement decision is often preceded by an assessment of the regional/national HTA body (76). This assessment typically involves an analysis of the additional health benefit as well as costs of a new medicine compared to the current standard of care. A key purpose of HTA in decision making is to establish value for money (cost-effectiveness). Depending on the country, the HTA body either makes the formal reimbursement decision or issues a recommendation for reimbursement to the decision-making body. A positive reimbursement decision means that patients covered by the public health care payer can access the new medicine.

In Ireland, the HSE makes the reimbursement decision for new medicines and new indications of already reimbursed medicines. The pharmaceutical company can file for reimbursement upon receipt of a positive opinion from the CHMP. The National Centre for Pharmacoeconomics (NCPE) is tasked to review all new medicines/indications. It applies a two-step process. All medicines are subjected to a “rapid review” of at most four weeks, which will decide whether a formal HTA is needed. Most new medicines will be subject to a formal HTA. The NCPE assess

efficacy, effectiveness and added therapeutic benefit, cost-effectiveness, and budget impact. The outcome of the HTA is a recommendation to the HSE whether to reimburse the medicine. The HSE considers several additional criteria (e.g., health needs of the public) when making the reimbursement decision (77).¹⁰

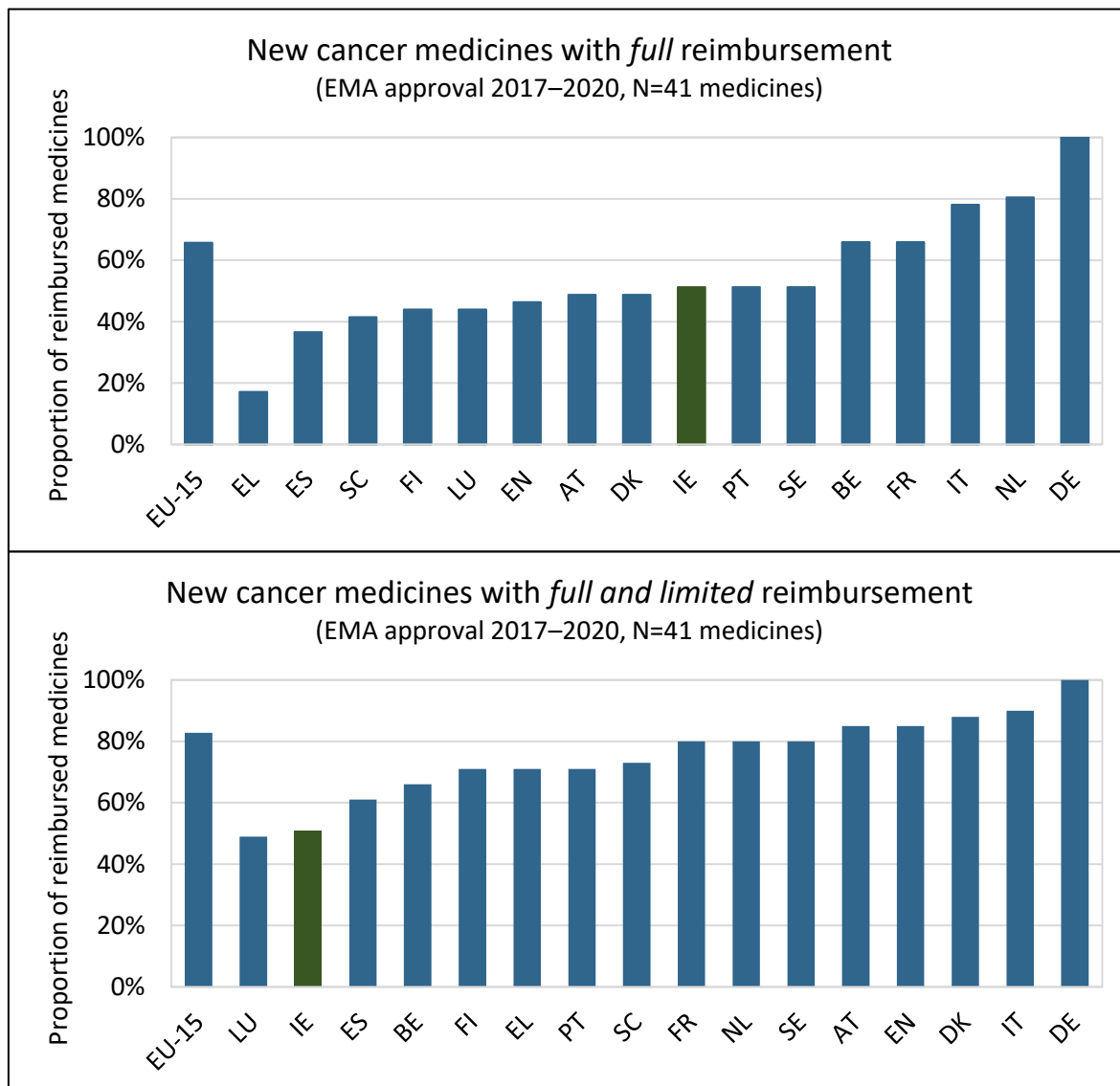


Figure 23: Reimbursement status of new cancer medicines approved by the EMA in 2017–2020 on January 1st, 2022

Notes: Data for UK is missing but available for England (EN) and Scotland (SC). Reimbursement is defined as a medicine being on the public reimbursement list (or having automatic reimbursement by a hospital budget in DK, FI, and SE). Source: IQVIA (79).

The reimbursement status of new cancer medicines in Europe is regularly assessed by IQVIA and EFPIA (European Federation of Pharmaceutical Industries and Associations) through surveys administered to the local pharmaceutical industry associations (79). The reimbursement status of 41

¹⁰ The private health care sector in Ireland has expanded over the past decades and half of the population have private health insurance (78), Yet the availability of cancer medicines in the public sector through the HSE and in the private sector is the same – some differences only emerged for the first time in 2019 (73).

new cancer medicines¹¹ approved by the EMA in 2017–2020 at the beginning of 2022 is shown in Figure 23. Only considering medicines with full reimbursement in the top graph, Germany was the only country among the EU-15 to reimburse all medicines. In Ireland, around half (51% or 21 out of 41 medicines) of the medicines were reimbursed by the HSE, however this is subject to the rate of applications actually made.¹² When both full reimbursement and limited reimbursement¹³ by the public payer is considered in the bottom graph of Figure 23, Ireland ranks second last among the EU-15 countries only ahead of Luxembourg, as no limited reimbursement was indicated for any cancer medicine in Ireland. In other countries with a similar or lower percentage of full reimbursement, limited reimbursement through a named-patient system such as in Greece or special medicine programs such as the Cancer Drugs Fund in England help at least some patients to get access.

The ‘wait time’ between EMA marketing authorization and reimbursement of new cancer medicines in Europe is also regularly assessed by IQVIA and EFPIA (79). Figure 24 shows the average reimbursement time for new cancer medicines approved by the EMA in 2017–2020 which have obtained full or limited reimbursement until January 1st, 2022. Germany had the shortest time with on average 100 days (less than 4 months) for its 41 reimbursed medicines, whereas Portugal had the longest time with 753 days (more than 2 years) among the EU-15 countries. Ireland had the second longest time with on average 661 days (1 year and 10 months) for the 21 reimbursed cancer medicines. It should be noted that in Ireland’s case, the total time to reimbursement is the sum of the time between EMA approval and the reimbursement application by the pharmaceutical company to the HSE, the time it takes for the NCPE to make its assessment, conduct price negotiations and issue its recommendation, and the time it takes for the HSE to reach a decision.

¹¹ Figure 21 shows 38 new cancer medicines for 2017–2020, because four medicines included by IQVIA (79) only contain chemical substances already used in the treatment of cancer before their approval (chlormethine (Ledaga), treosulfan (Trecondi), daunorubicin / cytarabine (Vyxeos liposomal), pertuzumab / trastuzumab (Phesgo)), whereas IQVIA did not include dinutuximab beta (Qarziba).

¹² Information from IPHA (personal communication) shows that 34 out of the 41 cancer medicines had an application with the NCPE in March 2022. The reimbursement rate of NCPE applications is thus 62% (21 reimbursed medicines out of 34 applications). It is interesting to note that pharmaceutical companies with the remaining seven cancer medicines have not (or not yet) chosen to apply for reimbursement to the NCPE, while in a country like Germany the same companies have filed an application at the time of compiling this report.

¹³ Limited reimbursement to specific subpopulations of the approved indication, limited reimbursement on a named patient basis (individual patient basis), limited reimbursement while decision is pending (where system permits), availability through a special program (e.g., managed entry agreements).

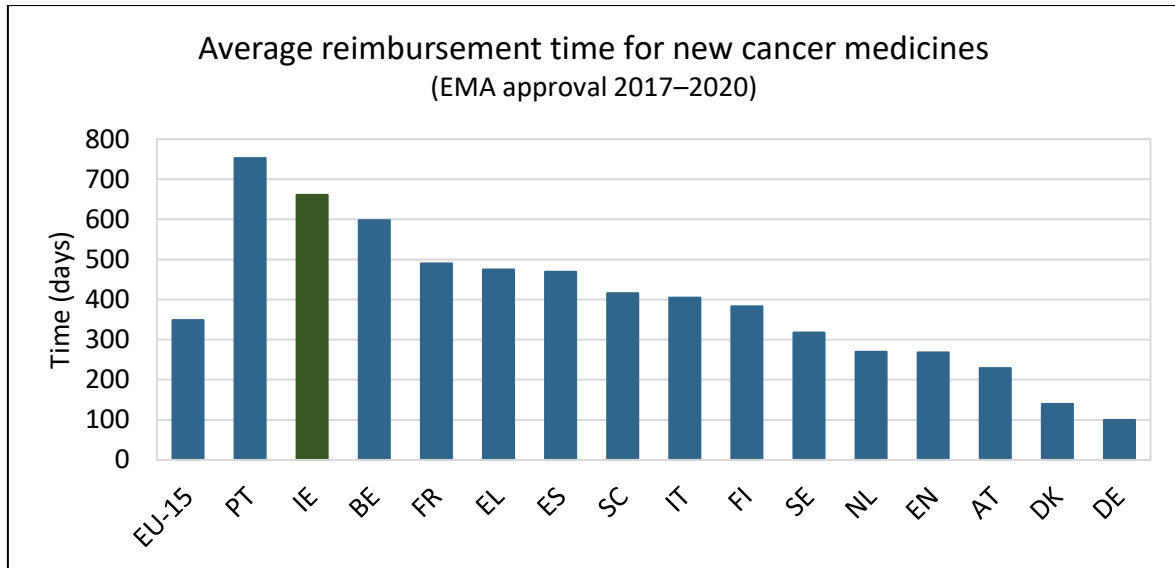


Figure 24: Average reimbursement time for new cancer medicines approved by the EMA in 2017–2020 (cut-off for follow-up: January 1st, 2022)

Notes: Data for LU is not available. Data for UK is missing but available for England (EN) and Scotland (SC). The ‘wait time’ is defined as the time between EMA marketing authorization and the time point when a medicine gains access to the public reimbursement list (except in DK, FI, and SE for some hospital medicines) with full or limited reimbursement. Early access schemes, such as the ATU program in France and the EMAS in the UK, are not included in this analysis. Source: IQVIA (79).

The analysis above shows that patient access to newer cancer medicines is limited and later in Ireland compared to other EU-15 countries. This stands somewhat in contrast with how the access environment is described in the National Cancer Strategy 2017–2026. The strategy notes (p.85) “While overall the current system is working effectively to provide new drugs to patients in Ireland, the approach needs to be kept under on-going review to ensure that the balance between patient care and value for money is optimized against a background of competing needs.” (16). The goal to find the right balance between providing access to new, more effective treatments whilst operating on constrained budgets is shared by all countries. The threshold of what constitutes “value-for-money” (cost-effectiveness) appears more difficult to pass in Ireland for newer cancer medicines.

5.3 Uptake

The third hurdle for patient access to new cancer medicines is uptake. Despite reimbursement, new medicines often take time – months or years – until they are used on a broad scale, as clinical routines need to be adapted and medical staff needs to be trained on how to use the new medicines. Testing infrastructure also needs to be established or extended, as many modern cancer medicines have a companion diagnostic. University hospitals and leading cancer centers may often be early adopters whereas other hospitals are typically slower. High patient co-payments on reimbursed medicines can also restrict the number of patients who can afford to be treated with new medicines.

In this report, uptake in a country was inferred from national sales data of cancer medicines in line with the European Comparator Report (1). Data on sales – in value (€) and volume (milligrams) – were obtained from IQVIA, a global provider of pharmaceutical sales data.¹⁴ They cover the period from 2008 to 2018. Cancer medicines within the ATC groups L01 (antineoplastic agents), L02 (endocrine therapy), and L04 (immunosuppressants) were included.¹⁵ It is important to note that IQVIA sales data measured in value (€) are based on list prices, which often do not represent actual final sales prices, because medicines are granted confidential rebates to payers. These rebates may also vary over time and between countries. Consequently, the use of sales data based on list prices overestimates the cost of cancer medicines. Sales measured in volume (milligrams) do not suffer from this problem (80).

5.3.1 Uptake in terms of costs

The development of cancer medicine sales per capita between 2008 and 2018 in Ireland and the EU-15 is shown in Figure 25. Ireland and the EU-15 had a very similar growth in medicine sales throughout this period, and sales in Ireland were always lower than in the EU-15. Cancer medicines sales (based on list prices) more than doubled between 2008 and 2018, from €29 to €64 per capita in Ireland and from €33 to €70 in the EU-15 (in 2018 prices and exchange rates). In total numbers, cancer medicines sales in Ireland increased from €130 million to €308 million (based on list prices; in 2018 prices and exchange rates), and thus accounted for 27% of the estimated health expenditure on cancer in 2018; see section 3.1. In the EU-15, cancer medicines accounted for 32% of the estimated health expenditure on cancer in 2018.

Country differences in sales of cancer medicines in 2008 and 2018 are illustrated in Figure 26. Sales increased in all countries with complete data. The biggest increases in absolute terms were recorded in Austria (from €46 to €108 per capita) and Germany (from €31 to €92), and the smallest one in France (from €57 to €77). The top spenders in 2018 were Austria, Germany, Belgium, and Denmark with around €90–€110 per capita spent on cancer medicines. France dropped from being the biggest spender in 2008 to fifth place in 2018. Ireland ranked in seventh place in 2018, with similar sales levels as in the Netherlands, Spain, and Finland.

¹⁴ Data come from IQVIA's MIDAS database.

¹⁵ This selection does not cover all medicines used in the treatment of cancer patients. Medicines used for control of pain and side effects of cancer medicines (e.g., antiemetic medicines) are not included. However, many of these medicines have a very low price and are readily available.

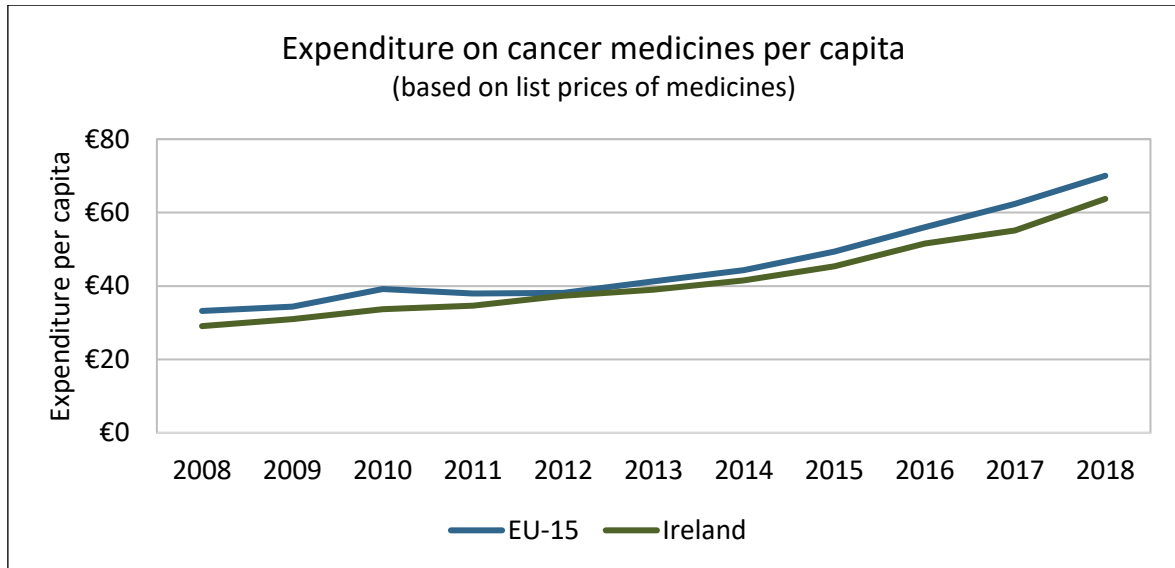


Figure 25: Expenditure on cancer medicines per capita based on list prices of medicines in Ireland and EU-15 (in €, 2018 prices and exchange rates), 2008–2018

Source: own calculations based on sales data from IQVIA.

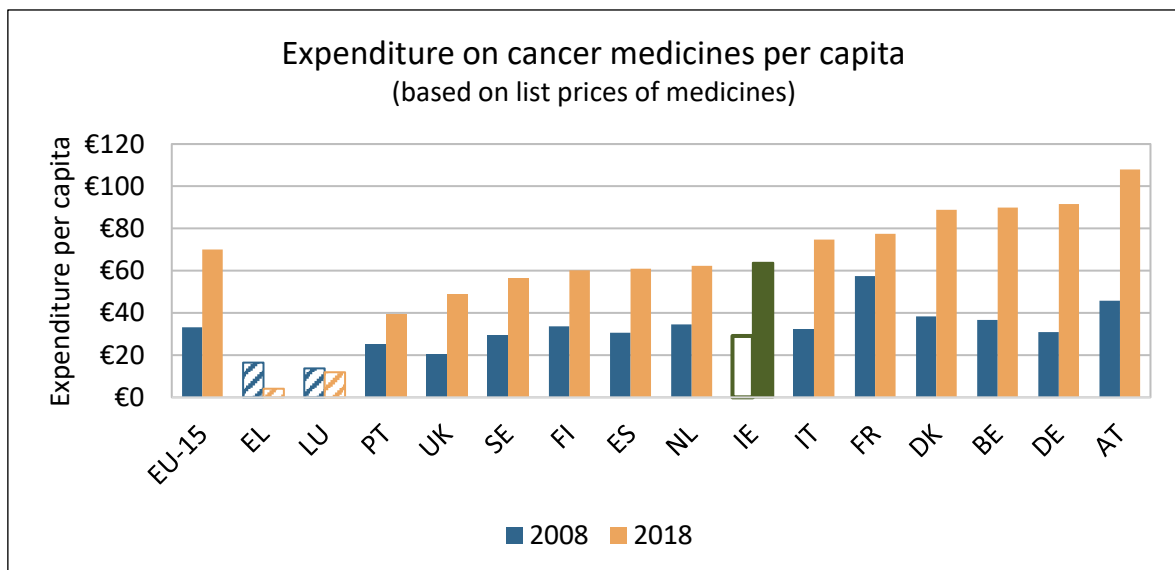


Figure 26: Expenditure on cancer medicines per capita (in €, 2018 prices and exchange rates), 2008 & 2018

Notes: Hatched bars indicate that data for EL and LU only comprise retail sales and lack hospital sales. For PT, the value in 2008 refers to 2010. Source: own calculations based on sales data from IQVIA.

The strong increase in sales of cancer medicines between 2008 and 2018 is a product of many factors relating to prices and volume:¹⁶

- Higher (list) prices of newly introduced medicines (81), i.e., costs per treatment
- Increasing number of cancer patients (see incidence crude rate in section 2.2.1)

¹⁶ The National Cancer Strategy 2017–2026 also cites price increases of newer cancer medicines and increases in the administered volume in its description of the state of medical oncology (16).

- Increasing number of approved cancer medicines and indications (see section 5.1)
- Increasing number of lines of therapy (e.g., two lines of therapy in lung cancer whereas in the past most patients had died after the first line)
- Increasing use of combination therapies, i.e., more than one medicine is administered at the same time and/or older medicines are given in combination with newer medicines rather than being replaced by them
- Increasing use of cancer medicines in an adjuvant setting instead of just in a palliative setting
- Introduction of cancer medicines for previously untreated patient groups (e.g., metastatic castration-resistant prostate cancer)

5.3.2 Uptake in terms of volume

To eliminate the problem of varying medicine prices, rebates, and exchange rates between countries and over time, this section considers medicine volume sold. A limitation of this approach is that medicines would need to be compared one-by-one, because the dose of the active ingredient (milligrams) of medicines varies. However, an aggregation of different medicines used in a certain cancer type is possible by calculating the dose required per patient and per time period. For the analysis in this section, a measure called the standard weekly dose (SWD) per patient was calculated for a selected number of medicines (see Table A1 in Appendix A.1). Annual sales in milligrams were divided by the SWD for every medicine to get the number of weekly doses sold. The weekly doses sold were then summed up across cancer medicines and divided by the number of cancer patients. Cancer patients were defined as the number of deaths from a certain cancer type, as most modern cancer medicines are still used in the palliative setting. The resulting measure of uptake is the number of standard weekly doses sold per cancer patient.

The following medicines used in the treatment of the five most common cancer types in Ireland as well as in multiple myeloma (the cancer type with the highest improvement in survival in Ireland, see section 4.1) and ovarian cancer and a separate category for immunotherapies were used to illustrate the uptake of newer cancer medicines:¹⁷

- Prostate cancer: abiraterone acetate (EMA approval 2011), enzalutamide (2013)

¹⁷ Some of the medicines listed for a specific cancer type might also have approved indications in other cancer types, e.g., bevacizumab and cetuximab. IQVIA sales data do not contain a split by indication and thus do not take into account varying reimbursement of indications across countries.

- Breast cancer: palbociclib (2016), pertuzumab (2013), ribociclib (2017), trastuzumab (2000), trastuzumab emtansine (2013)
- Colorectal cancer: bevacizumab (2005), cetuximab (2004), panitumumab (2007)
- Lung cancer: afatinib (2013), crizotinib (2012), erlotinib (2005), gefitinib (2009), osimertinib (2016), pemetrexed (2004)
- Melanoma: cobimetinib (2015), dabrafenib (2013), trametinib (20), vemurafenib (2012)
- Multiple myeloma: bortezomib (2004), carfilzomib (2015), daratumumab (2016), lenalidomide (2007), pomalidomide (2013)
- Ovarian cancer: niraparib (2017), olaparib (2014)
- Immunotherapy: atezolizumab (2017), ipilimumab (2011), nivolumab (2015), pembrolizumab (2015)

The volume of modern cancer medicines sold per patient in different cancer types for the EU-15 countries with available data in 2018 is shown in Figure 27. Ireland ranked above the EU-15 average in prostate cancer, breast cancer, and multiple myeloma, and close the average in colorectal cancer. Ireland's use of modern medicines was below the EU-15 average for lung cancer, melanoma, ovarian cancer, and for immunotherapies. In sum, the use of modern cancer medicines in Ireland seemed to be fairly close to the EU-15 average. The countries with the highest use of modern cancer medicines varied from cancer type to cancer type, but Austria, France, Belgium had persistently high use. Countries with a persistently low use of modern cancer medicines were Portugal and the UK.

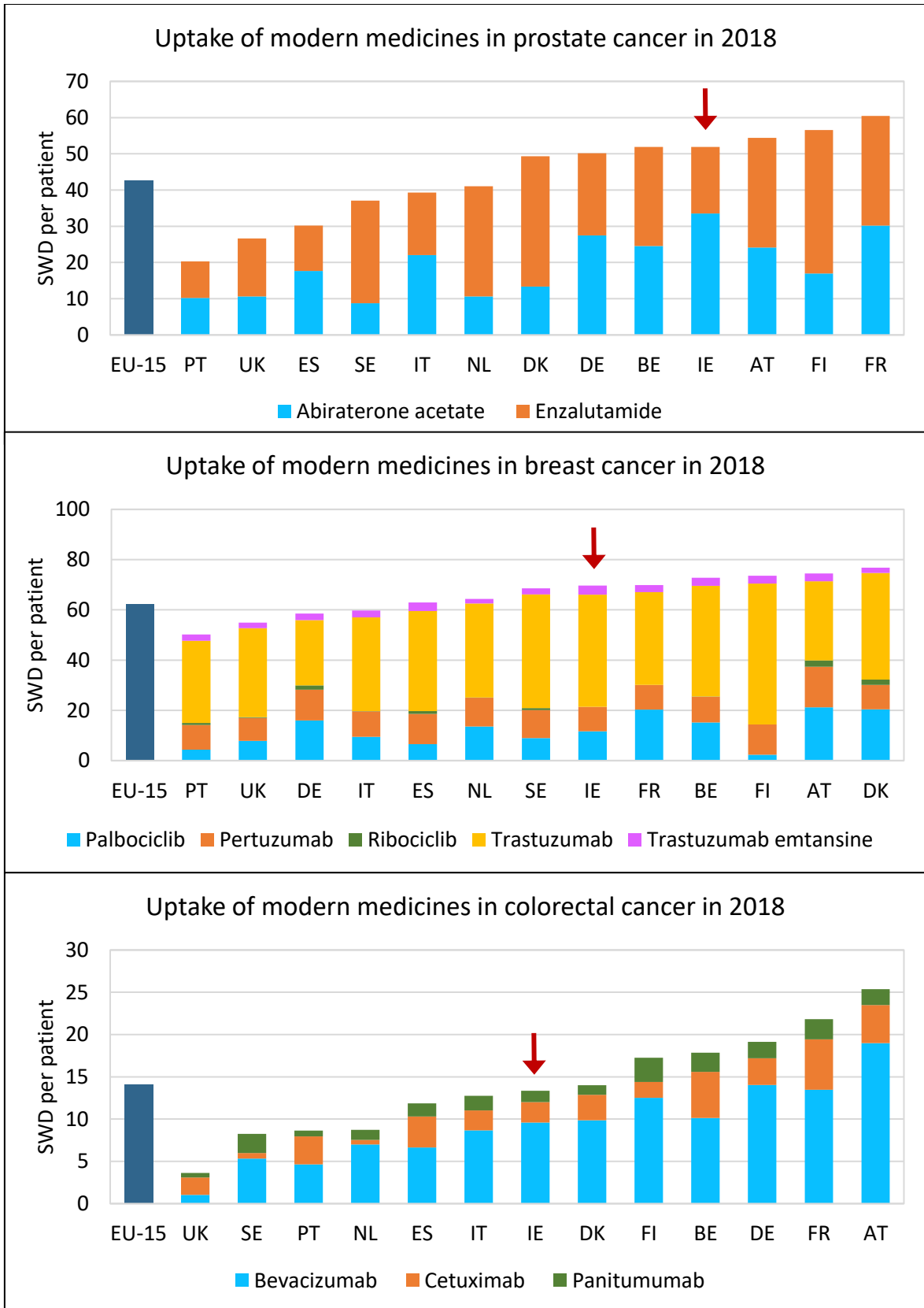


Figure 27: Uptake of modern medicines in selected cancer types expressed as standard weekly doses (SWD) per patient, 2018

Notes: Data is not available for EL and LU. “Patient” is defined as the number of cancer deaths in the respective cancer type and country using data from IARC for 2018 (9).

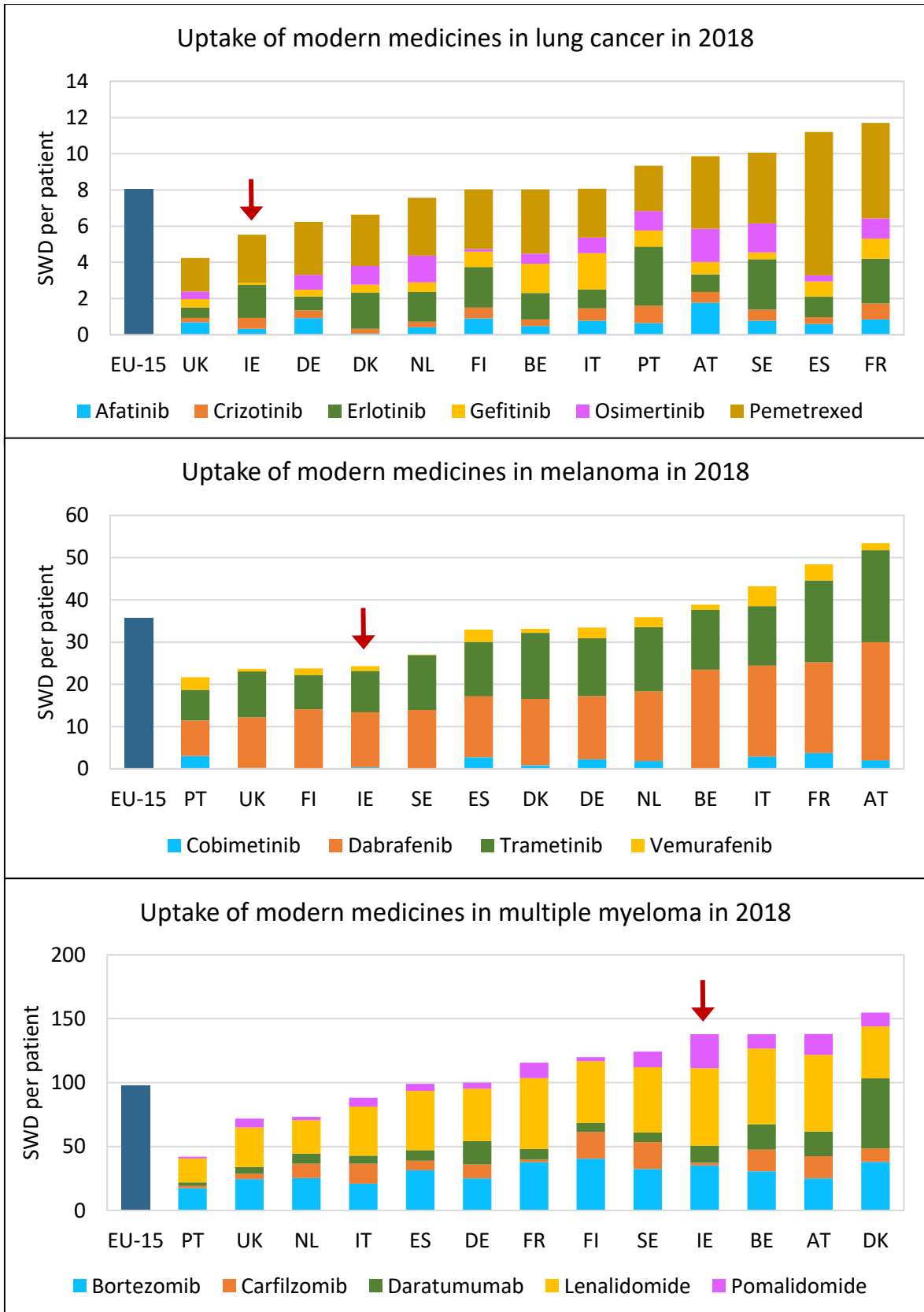


Figure 27 (continued): Uptake of modern medicines in selected cancer types expressed as standard weekly doses (SWD) per patient, 2018

Notes: Data is not available for EL and LU. “Patient” is defined as the number of cancer deaths in the respective cancer type and country using data from IARC for 2018 (9).

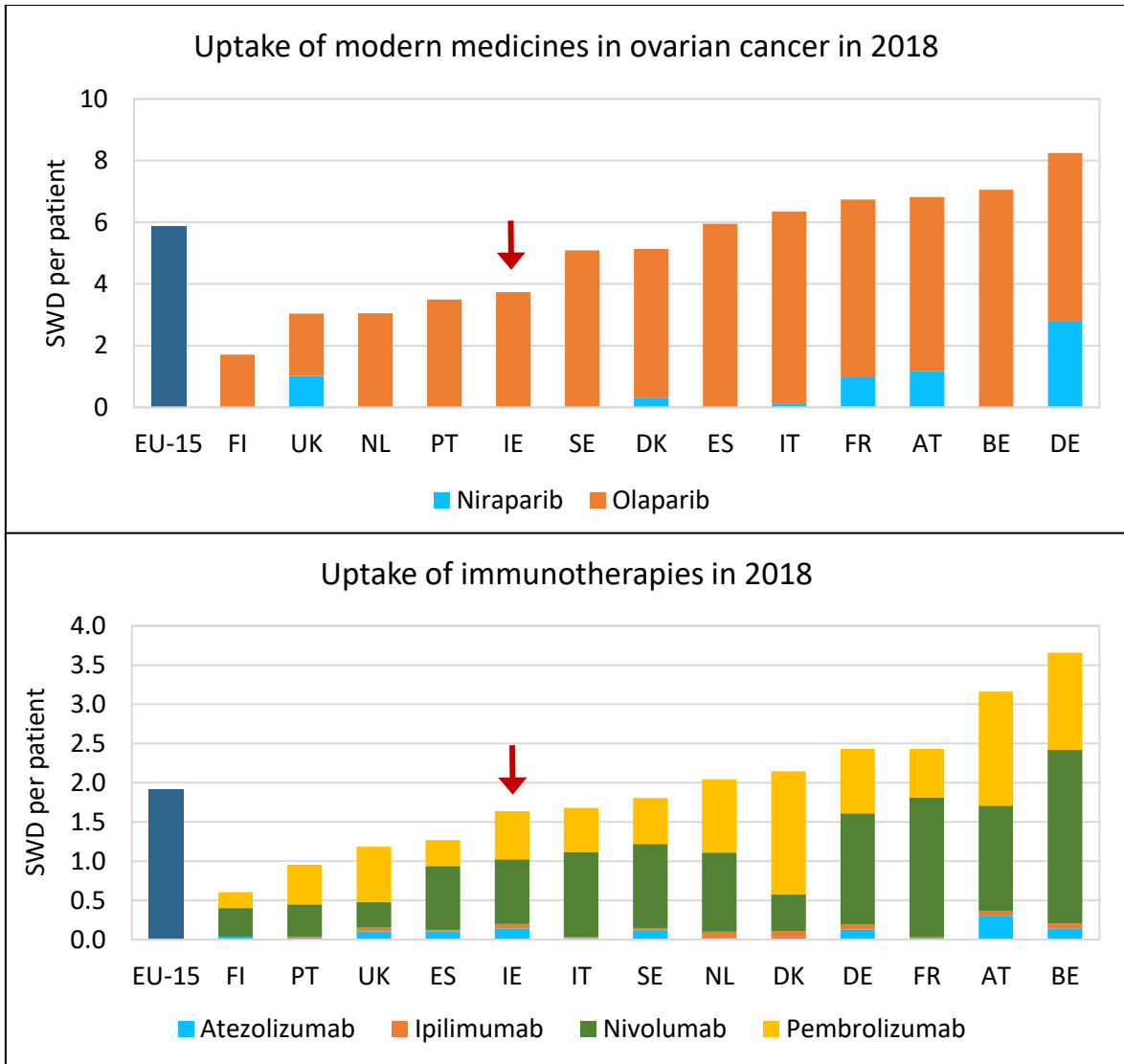


Figure 27 (continued): Uptake of modern medicines in selected cancer types expressed as standard weekly doses (SWD) per patient, 2018

Notes: Data is not available for EL and LU. “Patient” is defined as the number of cancer deaths in the respective cancer type (for “immunotherapies” all cancers except non-melanoma skin cancer were used) and country using data from IARC for 2018 (9).

5.4 Consequences of limited and later access

As described above, patient access to modern cancer medicines in Ireland is limited in comparison with many other EU-15 countries. While modern medicines come at an additional cost, the length of time-to-reimbursement and/or lack of reimbursement (for the time being) also come at a cost. Limited and later reimbursement leads to a loss of life years and quality of life as well as avoidable indirect costs. Two examples are provided below to illustrate these consequences in Ireland.

Example 1: Introduction of immunotherapies (PD-1/PD-L1 checkpoint inhibitors) in Ireland

A recent study assessed the impact of immunotherapies (PD-1/PD-L1 checkpoint inhibitors) in Ireland (82). The study considered health and economic outcomes of PD-1/PD-L1 inhibitors in eight cancers¹⁸ over a five-year period (2020–2024) compared to the standard of care treatments.¹⁹ Health and economic outcomes in two scenarios – with and without immunotherapies – were estimated. The results are shown in Table 2. In general, the use of immunotherapies was estimated to improve all forms of health outcomes (life years, progression-free life years, quality-adjusted life years, adverse events). There was also an increased overall economic impact, equivalent to approximately 0.32% of total health care expenditure. Medicine acquisition costs were estimated to increase but were partially offset by cost reductions associated with adverse events, end-of-life costs, and indirect costs, as patients could work for longer due to the improved health outcomes.

Table 2: Estimated health and economic outcomes of immunotherapies in 2020–2024 compared to the standard of care treatments in Ireland

Outcome measure	Absolute change	Relative change
Life years	+3,194	+27%
Progression-free life years	+2,411	+43%
Quality-adjusted life years (QALYs)	+2,638	+31%
Adverse events	-92	-2%
Economic impact (annual)	Not reported	+0.32% of total health expenditure

Source: Browne et al. (2021) (82).

Example 2: Socio-economic impact of longer time to reimbursement of modern, effective cancer medicines in Ireland

For the purpose of this report, an impact assessment of the possible gains from expedited time until reimbursement by the HSE in Ireland was made. 11 indications approved across six cancer types²⁰ by the EMA between 2015 and 2021 were selected for illustration purposes (see Appendix A.2.1 for the selection criteria). Only indications with a statistically significant gain in median overall survival (OS) were included. According to the approved EMA label, the annual number of eligible patients was calculated for each indication (both for patients of all ages and for working-age patients 15–64 years). The period between approval by the EMA and reimbursement by the HSE was calculated for each indication (see Appendix A.2.2).

¹⁸ Metastatic melanoma, metastatic triple-negative breast cancer, non-small cell lung cancer, head and neck cancer, urothelial cancer, renal cell carcinoma, and adjuvant treatment of melanoma and neo-adjuvant treatment of triple-negative breast cancer.

¹⁹ Standard of care treatment included chemotherapy, immuno-oncology treatments not part of the anti PD-1/PD-L1 class (e.g., ipilimumab), and radiation therapy.

²⁰ Bladder cancer, breast cancer, colorectal cancer, leukemia, lung cancer, and prostate cancer.

The outcome measures of the impact assessment were health effects (years of potential life lost, YPLL) and economic effects (the economic value of productivity loss associated with the YPLL). YPLL were calculated by combining the period between EMA approval and HSE reimbursement with the annual number of eligible patients and the median OS gain per patient. For the subset of YPLL among working-age patients, their economic value was calculated using sex-specific annual earnings and employment probability.

The results of the impact assessment are shown in Table 3. The length of time observed between EMA approval and HSE reimbursement of the 11 included indications affected almost 1,600 patients annually. This ‘wait time’ resulted in 2,600 YPLL. More than 1,000 of these YPLL occurred in working-age patients, which corresponded to an economic loss of €34 million. There are thus great gains to be made from expedited reimbursement of effective cancer medicines by the HSE. Expediting reimbursement would require both faster reimbursement applications by pharmaceutical companies upon CHMP approval and faster HTA by the NCPE and decision-making by the HSE.

Table 3: Socio-economic impact of ‘wait time’ until reimbursement of 11 modern, effective cancer medicine-indications in Ireland

Outcome measure	Result
Annual number of patients affected	1,567
Years of potential life lost (patients of all ages)	2,591
Years of potential life lost (patients aged 15–64 years)	1,049
Economic value of years of potential life lost	€34.1 million

Source: see Appendix A.2 for details.

Since the impact assessment was only based on 11 indications, the full extent of YPLL would be far greater when considering all effective cancer indications. In addition, the impact assessment did not calculate losses in QALYs and their value across all patients (and not just working-age patients). As highlighted by Example 1 in this section, new medicines can affect patient health also in terms of improvements in quality of life and avoidance of treatment-related adverse events.

5.5 Current challenges

A joint evaluation of the costs and benefits of new medical technologies is crucial to guide a cost-effective allocation of scarce health care resources. In Ireland, most new cancer medicines/indications are subject to a formal HTA by the NCPE that includes a clinical evaluation along with an economic evaluation (77). There are several current challenges in the evaluation of new cancer medicines/indications that are shared by the NCPE and other HTA bodies across Europe.

Capacity shortages to perform HTA

As shown in Figure 21, the annual number of cancer medicines approved by the EMA has increased significantly in recent years. The Department of Health has recently acknowledged that this had implications for the NCPE. It noted that “[t]he NCPE’s workload has increased significantly in recent years, from fewer than 10 assessments per year in 2007 to 98 assessments in 2021. In addition, the complexity of individual assessments has increased.” (83). Furthermore, it noted that the NCPE’s capacity has been strengthened by additional funding provided in 2018, which saw staffing increase from 10.5 to 20.5 whole time equivalents (83).

One solution to address the current situation is to re-assess the staffing needs of the NCPE to perform HTA. This would need to consider potential future increases in the number of EMA-approved medicines/indications. Another solution could be to expedite the assessment of “me-too medicines” (also known as “follow-on medicines”). Since me-too medicines are similar to pre-existing medicines in terms of clinical benefits, a full clinical assessment during the HTA might not be needed.²¹

Limited clinical evidence of new medicines

A key challenge for access to new medicines is the trade-off between early access and evidence of value to patients (86). Regulatory approvals of cancer medicines by the EMA naturally have to be based on clinical trial data that involve uncertainty about the effects in clinical practice. The criteria for regulatory approval – safety, quality, and efficacy – are also not the same as the criteria applied for reimbursement – (relative) effectiveness and cost-effectiveness. Some challenges for reimbursement are short follow-up times in clinical trials, use of surrogate endpoints (such as progression-free survival instead of overall survival), use of single-arm clinical trials, and lack of validated quality-of-life measures (87, 88). The misalignment of evidence criteria required by the EMA and HTA bodies can prolong the time to reimbursement.

One solution to allow for faster reimbursement in these circumstances is “coverage with evidence development”. This kind of managed entry agreement means that a new medicine is reimbursed for a limited period of time during which real-world data on its effectiveness are collected in clinical practice (89, 90). This helps to reduce uncertainty of the benefits of a new medicine over time but requires a monitoring system to collect data. The collected data would be used to make a decision about (i) permanent reimbursement, (ii) reimbursement with price adjustment, (iii) withdrawal of reimbursement. Such a system would share the risk between payers and pharmaceutical companies.

²¹ Recent examples of me-too medicines in oncology are CDK4/6 inhibitors for use in breast cancer, ALK inhibitors for use in non-small cell lung cancer, and PD-1/PD-L1 inhibitors (84, 85).

Multi-indication treatments

Many cancer medicines are effective in multiple indications. More than 50% of major cancer medicines marketed in 2014 were approved in multiple indications, and this share was expected to have grown to 75% in 2020 (91). New cancer medicines are often initially approved with a later-line indication in metastatic disease of a certain cancer type. Additional indications are added over time in early-line treatment of metastatic disease, in the adjuvant or neo-adjuvant setting, and in other cancer types (92). The degree of effectiveness may differ across different indications. The application of product-based pricing and reimbursement system with a single price per medicine means that the medicine does not necessarily receive a price in relation to the value it provides in different indications. If the price of a medicine with varying value in multiple indications is set based on the highest-value indication, the price may be too high to be cost effective in lower-value indications. As a result, the treatment will not be reimbursed for these indications and pharmaceutical companies may be discouraged to invest in trialing additional indications (93).

One solution to link the price of a medicine to its value in different indications is to switch from product-based pricing to indication-based pricing (93). Such a change requires data infrastructure to track the use of a medicine in different indications. Another solution is to use a “weighted-average” price (93). This requires the determination of a single product-based price based on an average value of all indications weighted by patient numbers in each indication. Whenever a new indication is to be reimbursed, the weighted-average price needs to be re-assessed and revised upwards or downwards.

Combination treatments

The combination of two or more patent-protected cancer medicines from the same or different pharmaceutical companies has become more common in recent years, especially in the treatment of melanoma, multiple myeloma, and kidney cancer (94). The value of a combination of medicines is often less than the sum of the value of each component as a monotherapy. Adding the monotherapy-based prices of the involved medicines will result in a total price for the combination that exceeds its value. The key issue is how to attribute the value of the combination to its different components. From a legal perspective, competition law might also prevent two companies from discussing and agreeing on a common price strategy for a combination (95).

One solution is to determine the value of a combination and then to define a price that is split in equal parts among the components (i.e., in case of two components, each component gets a 50% share of the total price). Unless the components contribute equally to the joint value, such a solution is unsatisfactory, as one of the components is likely to get less than the “fair” share for the value of the treatment. This creates disincentives for trialing combination treatments. Two other

solutions are indication-based pricing (i.e., different prices of a medicine if used in monotherapy or in combination) or using a “weighted-average” price (i.e., single product-based price based on an average value of all indications weighted by patient numbers in each indication). The latter solutions are the same as for multi-indication treatments, because combination treatments can be viewed as a special case of multi-indication treatments (93).

Cell therapies

August 2018 marked a new era in cancer treatment in Europe with the approval of the first two CAR T-cell therapies (96). These cell-based therapies are entirely different from previous types of cancer medicines because they only require a single treatment administration. In addition, these therapies can be expected to lead to complete remission (i.e., cure) in a certain share of patients and thus create long-lasting positive effects on both patient health, health care costs, and indirect costs. The features of these therapies represent new challenges for the valuation of clinical benefits and payment (97, 98). This includes uncertainty about whether the curative effect really persists over time, the valuation of a curative therapy, and the temporal disconnection between the payment for the one-time treatment and the time during which the value is realized. The latter can lead to an affordability barrier, where a medicine can be cost effective but not possible to pay for under the current payment model.

The first experiences with CAR T-cell therapies in France, Germany, Italy, Spain, and the UK showed that different payment models were used to address their unique features (96). A commonality is that all payment models involved risk sharing between the payer and the pharmaceutical company. France and the UK chose “coverage with evidence development” to make reimbursement conditional on collecting additional data for future reassessments. In Germany, “outcomes-based rebates” were used where the pharmaceutical company grants rebates to the payer based on individual patient outcomes. In Italy and Spain, “outcomes-based staged payments” (annuity payments) were used to split the total payment into two to three installments that are linked to individual patient outcomes.

6. Conclusion

With cancer now being the leading cause of death in Ireland, there is an urgent need to address the growing health and economic burden of the disease. Improvements in cancer care are needed to prevent future cancer cases and to improve the chances to survive of existing cancer patients. Even though Ireland has made great strides in improving survival rates of cancer patients in recent decades, Ireland lags behind the survival rates observed in many other EU-15 countries. Estimations in this report show that hundreds of cancer deaths could be avoided every year if Ireland achieved similar survival rates to the best-performing EU-15 countries.

Just like any health care systems, the Irish systems needs to weigh the costs from investing in different areas of cancer care against the potential improvements in patient outcomes. The analysis in this report showed that there is a positive association between how much countries spend on cancer care and the survival rates they achieve. Ireland is an example where survival rates are comparatively low given the *estimated* level of health spending on cancer. If there were more specific Irish data on spending on cancer in the future, this relationship would need to be revisited. The production of such data ought to be pursued as a priority. Nonetheless, these circumstances should emphasize the need to target cancer expenditure to the treatment of those patients who will get better clinical outcomes. An increased focus on spending on evidence-based interventions in all areas of cancer care should be considered.

The most dynamic area of cancer care in the last decade has been medical oncology. There has been a distinct increase in the annual number of new cancer medicines approved by the EMA in the last decade. The combined number of new cancer medicines and indication extensions of existing medicines reached a peak of 41 in 2021. Patients in Ireland must wait substantially longer until they can access new cancer medicines compared to patients in most other EU-15 countries. Other countries have implemented partial reimbursement schemes that allow at least some patients to gain faster access to new medicines before full reimbursement (e.g., through a special cancer medicine fund or managed entry agreements). Once reimbursed, the use of modern cancer medicines in Ireland is close to the EU-15 average.

The growing number of new cancer medicines and their indication extensions puts a strain on HTA and reimbursement bodies. This is especially true in Ireland, where most new cancer medicines and indications are subject to a formal HTA. Currently, the ‘wait time’ between EMA approval and HSE reimbursement of effective cancer medicines affects thousands of cancer patients and results in many years of potential life lost. Expediting the reimbursement of the subset of new cancer medicines/indications with evidence of high relative clinical benefits could alleviate this situation and improve patient outcomes.

References

1. Hofmarcher T, Brådvik G, Svedman C, Lindgren P, Jönsson B, Wilking N. *Comparator Report on Cancer in Europe 2019 – Disease Burden, Costs and Access to Medicines*. IHE Report 2019:7. Lund: IHE. 2019.
2. Jönsson B, Hofmarcher T, Lindgren P, Wilking N. *Comparator report on patient access to cancer medicines in Europe revisited*. IHE Report 2016:4. Lund: IHE. 2016.
3. Jönsson B, Wilking N. *A global comparison regarding patient access to cancer drugs*. *Ann Oncol*. 2007;18 Suppl 3:iii1-iii77.
4. 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.
5. Wilking N, Jönsson B, Högberg D, Justo N. *Comparator Report on Patient Access to Cancer Drugs in Europe*. Stockholm: Karolinska Institutet & Stockholm School of Economics & i3 Innovus. 2009.
6. Black RJ, Bray F, Ferlay J, Parkin DM. *Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990*. *Eur J Cancer*. 1997;33(7):1075-107.
7. 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.
8. Dyba T, Randi G, Bray F, Martos C, Giusti F, Nicholson N, et al. *The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers*. *Eur J Cancer*. 2021;157:308-47.
9. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. *Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018*. *Eur J Cancer*. 2018;103:356-87.
10. Ferlay J, Laversanne M, Ervik M, Lam F, Colombet M, Mery L, et al. *Global Cancer Observatory: Cancer Tomorrow*. Available from: <https://gco.iarc.fr/tomorrow/en> [accessed Mar 14, 2022].
11. Ferlay J, Parkin DM, Steliarova-Foucher E. *Estimates of cancer incidence and mortality in Europe in 2008*. *Eur J Cancer*. 2010;46(4):765-81.
12. 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.
13. 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 EURO CARE--5-a population-based study*. *Lancet Oncol*. 2014;15(1):23-34.
14. OECD. *Cancer Care: Assuring Quality to Improve Survival*: OECD Publishing; 2013.
15. European Commission. *Europe's Beating Cancer Plan - Communication from the commission to the European Parliament and the Council*. 2021.
16. Department of Health. *National Cancer Strategy 2017-2026*. 2017.
17. OECD. *Addressing Challenges in Access to Oncology Medicines*. 2020.
18. Irish Cancer Society. *The Real Cost of Cancer*. 2019.
19. World Health Organization. *Cancer*. Available from: <https://www.who.int/health-topics/cancer> [accessed Mar 1, 2022].

20. Central Statistics Office Ireland. Deaths Occurring. Available from: <https://www.cso.ie/en/index.html> [accessed Feb 12, 2022].
21. Eurostat. Causes of death - deaths by country of residence and occurrence [HLTH_CD_ARO]. Available from: <https://ec.europa.eu/eurostat/data/database> [accessed Feb 12, 2022].
22. Eurostat. Population structure indicators at national level [DEMO_PJANIND]. Available from: <https://ec.europa.eu/eurostat/data/database> [accessed Jan 27, 2022].
23. World Health Organization. Global health estimates: Leading causes of death. Available from: <https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death> [accessed Feb 7, 2022].
24. National Cancer Registry Ireland. Incidence statistics. Available from: <https://www.ncri.ie/data/incidence-statistics> [accessed Jan 27, 2022].
25. National Cancer Registry Ireland. *Cancer in Ireland 1994-2019: Annual report of the National Cancer Registry*. Cork, Ireland: NCRI. 2021.
26. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today. Available from: <https://gco.iarc.fr/today> [accessed Mar 9, 2022].
27. ECIS - European Cancer Information System. Incidence and mortality historical data. Available from: <https://ecis.jrc.ec.europa.eu> [accessed Jun 19, 2019].
28. Engholm G, Ferlay J, Christensen N, Hansen HL, Hertzum-Larsen R, Johannesen TB, et al. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 8.0 (20.12.2017). Available from: <http://www-dep.iarc.fr/NORDCAN/english/frame.asp> [accessed Jun 4, 2018].
29. Eurostat. Population on 1 January by age group and sex [DEMO_PJANGROUP]. Available from: <https://ec.europa.eu/eurostat/data/database> [accessed Mar 15, 2022].
30. OECD. OECD Health Statistics 2019. Available from: <http://www.oecd.org/els/health-systems/health-data.htm> [accessed Aug 16, 2019].
31. Ponti A, Anttila A, Ronco G, Senore C, Basu P, Segnan N, et al. Cancer Screening in the European Union (2017) - Report on the implementation of the Council Recommendation on cancer screening. Luxembourg: European Commission; 2017.
32. 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 Recommendation on cancer screening – First Report. Luxembourg: European Commission; 2008.
33. Di Girolamo C, Nusselder WJ, Bopp M, Bronnum-Hansen H, Costa G, Kovacs K, et al. *Progress in reducing inequalities in cardiovascular disease mortality in Europe*. Heart. 2020;106(1):40-9.
34. Honoré BE, Lleras-Muney A. *Bounds in Competing Risks Models and the War on Cancer*. Econometrica. 2006;74(6):1675-98.
35. International Agency for Research on Cancer. WHO Cancer Mortality Database. Available from: <http://www-dep.iarc.fr/WHODb/WHODb.htm> [accessed Jun 19, 2019].
36. Guinness L. *Counting the costs*. In: Guinness L, Wiseman V, editors. Introduction to Health Economics. 2nd ed. Maidenhead, England: Open University Press. 2011.
37. Health Service Executive. *National Service Plan 2021*. 2021.
38. Eurostat. GDP and main components (output, expenditure and income) [nama_10_gdp]. Available from: <https://ec.europa.eu/eurostat/data/database> [accessed Aug 26, 2019].

39. Eurostat. HICP (2015 = 100) - annual data (average index and rate of change) [prc_hicp_aind]. Available from: <https://ec.europa.eu/eurostat/data/database> [accessed Aug 26, 2019].
40. Eurostat. Euro/ECU exchange rates - annual data [ert_bil_eur_a]. Available from: <http://ec.europa.eu/eurostat/data/database> [accessed Aug 13, 2018].
41. OECD. OECD Statistics - Health expenditure and financing. Available from: <https://stats.oecd.org/> [accessed Aug 26, 2019].
42. World Health Organization. Global Health Expenditure Database. Available from: <http://apps.who.int/nha/database> [accessed Feb 11, 2016].
43. 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.
44. Faulkner E, Annemans L, Garrison L, Helfand M, Holtorf AP, Hornberger J, et al. *Challenges in the development and reimbursement of personalized medicine-payer and manufacturer perspectives and implications for health economics and outcomes research: a report of the ISPOR personalized medicine special interest group*. Value Health. 2012;15(8):1162-71.
45. Civan A, Koksall B. *The effect of newer drugs on health spending: do they really increase the costs?* Health Econ. 2010;19(5):581-95.
46. Sculpher MJ. *The role and estimation of productivity costs in economic evaluation*. In: Drummond M, McGuire A, editors. *Economic Evaluation in Health Care: Merging theory with practice*. Oxford, UK: Oxford University Press. 2001.
47. Eurostat. Structure of earnings survey: annual earnings [earn_ses_annual]. Available from: <https://ec.europa.eu/eurostat/data/database> [accessed Aug 6, 2019].
48. Eurostat. Employment rates by sex, age and citizenship (%) [lfsa_ergan]. Available from: <https://ec.europa.eu/eurostat/data/database> [accessed Aug 8, 2019].
49. 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.
50. 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.
51. 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.
52. Henson DE, Ries LA. *The relative survival rate*. Cancer. 1995;76(10):1687-8.
53. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. *Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2)*. Lancet. 2015;385(9972):977-1010.
54. Fitzpatrick PE, Greehy G, Mooney MT, Flanagan F, Larke A, Connors A, et al. *Evolution of the National Breast Screening Programme in Ireland: Two-year interval analysis (2004-2013) of BreastCheck*. J Med Screen. 2018;25(4):191-6.
55. Gallagher F, Gallagher J. *A closer look at cervical smear uptake and results pre- and post-introduction of the national screening programme*. Ir Med J. 2010;103(7):199-200, 2.
56. Sharp L, Tilson L, Whyte S, Ceilleachair AO, Walsh C, Usher C, et al. *Using resource modelling to inform decision making and service planning: the case of colorectal cancer screening in Ireland*. BMC Health Serv Res. 2013;13:105.
57. Health Service Executive. About Cancer Screening - Health Professionals. Available from: <https://www.hse.ie/eng/services/list/5/cancer/profinfo/screening/> [accessed Apr 6, 2022].

58. Health Service Executive. GP Prostate Cancer Guideline. Available from: <https://www.hse.ie/eng/services/list/5/cancer/profinfo/resources/gpreferrals/gp-prostate-referral-form-and-guideline.html> [accessed Apr 6, 2022].
59. World Health Organization. Screening and early detection. Available from: <https://www.euro.who.int/en/health-topics/noncommunicable-diseases/cancer/policy/screening-and-early-detection> [accessed Apr 6, 2022].
60. Kapoor V, McCook BM, Torok FS. *An introduction to PET-CT imaging*. Radiographics. 2004;24(2):523-43.
61. Unterrainer M, Eze C, Ilhan H, Marschner S, Roengvoraphoj O, Schmidt-Hegemann NS, et al. *Recent advances of PET imaging in clinical radiation oncology*. Radiat Oncol. 2020;15(1):88.
62. Cooke T, Reeves J, Lanigan A, Stanton P. *HER2 as a prognostic and predictive marker for breast cancer*. Ann Oncol. 2001;12 Suppl 1:S23-8.
63. Lichtenberg FR. *Has Medical Innovation Reduced Cancer Mortality?* CESifo Economic Studies. 2014;60(1):135-77.
64. American Cancer Society. Treating Multiple Myeloma. Available from: <https://www.cancer.org/cancer/multiple-myeloma/treating.html> [accessed Apr 6, 2022].
65. American Cancer Society. Treating Non-Hodgkin Lymphoma. Available from: <https://www.cancer.org/cancer/non-hodgkin-lymphoma/treating.html> [accessed Apr 6, 2022].
66. American Cancer Society. Types of leukemia. Available from: <https://www.cancer.org/cancer/leukemia.html> [accessed Apr 6, 2022].
67. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, et al. *Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries*. Lancet. 2018;391(10125):1023-75.
68. Hofmarcher T, Jönsson B, Wilking N. *Access to high-quality oncology care across Europe*. IHE Report 2014:2. Lund: IHE. 2014.
69. Lichtenberg FR. *The impact of new drug launches on life-years lost in 2015 from 19 types of cancer in 36 countries*. Journal of Demographic Economics. 2018;84(3):309-54.
70. National Cancer Institute. Milestones in Cancer Research and Discovery. Available from: <https://www.cancer.gov/research/progress/250-years-milestones> [accessed Mar 18, 2022].
71. American Cancer Society. Chemotherapy Side Effects. Available from: <https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/chemotherapy-side-effects.html> [accessed Mar 18, 2022].
72. European Commission. Authorisation procedures - The centralised procedure. Available from: https://ec.europa.eu/health/medicinal-products/legal-framework-governing-medicinal-products-human-use-eu/authorisation-procedures-centralised-procedure_en [accessed Mar 18, 2022].
73. TheJournal.ie. Private cancer patients getting access to drugs that public patients can't get is 'incredibly unfair'. Available from: <https://www.thejournal.ie/private-public-cancer-drugs-vhi-4591865-Apr2019/> [accessed Mar 18, 2022].
74. European Medicines Agency. Download medicine data. Available from: <https://www.ema.europa.eu/en/medicines/download-medicine-data> [accessed Feb 23, 2022].
75. European Medicines Agency. *CHMP: Agendas, minutes and highlights*.

76. Allen N, Pichler F, Wang T, Patel S, Salek S. *Development of archetypes for non-ranking classification and comparison of European National Health Technology Assessment systems*. Health Policy. 2013;113(3):305-12.
77. National Centre for Pharmacoeconomics. Overview of the Drug Reimbursement process. Available from: <https://www.ncpe.ie/submission-process/> [accessed Mar 18, 2022].
78. Mercille J. *Privatization in the Irish hospital sector since 1980*. J Public Health (Oxf). 2018;40(4):863-70.
79. Newton M, Scott K, Troein P. *EFPIA Patients W.A.I.T. Indicator 2021 Survey*. IQVIA. 2022.
80. Wilking N, Hofmarcher T, Wilking U, Jönsson B. *Drug utilization research in the area of cancer drugs*. In: Elseviers M, Wettermark B, Almarsdóttir AB, Andersen M, Benko R, Bennie M, et al., editors. Drug Utilization Research: Methods and Applications: Wiley-Blackwell. 2016. p. 315-27.
81. IQVIA Institute for Human Data Science. *Global Oncology Trends 2019 - Therapeutics, Clinical Development and Health System Implications*. Parsippany: IQVIA. 2019.
82. Browne I, Weadick C, Duffy AG, Doig H, Bradley E, Bell E, et al. *Assessing the impact of anti-PD-1/PD-L1 inhibitors on cancer care health and budget in Ireland*. Journal of Clinical Oncology. 2021;39(15_suppl).
83. Department of Health - Medicinal Products. Written answers - Tuesday, 8 March 2022. Available from: <https://www.kildarestreet.com/wrans/?id=2022-03-08a.1443> [accessed Apr 6, 2022].
84. Laderian B, Fojo T. *CDK4/6 Inhibition as a therapeutic strategy in breast cancer: palbociclib, ribociclib, and abemaciclib*. Semin Oncol. 2017;44(6):395-403.
85. Olivier T, Haslam A, Prasad V. *Anticancer Drugs Approved by the US Food and Drug Administration From 2009 to 2020 According to Their Mechanism of Action*. JAMA Netw Open. 2021;4(12):e2138793.
86. Eichler HG, Bedlington N, Boudes M, Bouvy JC, Broekmans AW, Cerreta F, et al. *Medicines Adaptive Pathways to Patients: Why, When, and How to Engage?* Clin Pharmacol Ther. 2019;105(5):1148-55.
87. Jansen C, Amesz B. *Every day counts – Improving time to patient access to innovative oncology therapies in Europe*. Vintura. 2020.
88. Naci H, Davis C, Savovic J, Higgins JPT, Sterne JAC, Gyawali B, et al. *Design characteristics, risk of bias, and reporting of randomised controlled trials supporting approvals of cancer drugs by European Medicines Agency, 2014-16: cross sectional analysis*. BMJ. 2019;366:15221.
89. Pauwels K, Huys I, Vogler S, Casteels M, Simoens S. *Managed Entry Agreements for Oncology Drugs: Lessons from the European Experience to Inform the Future*. Front Pharmacol. 2017;8:171.
90. Wenzl M, Chapman S. *Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward*. OECD Health Working Papers No 115. Paris: OECD. 2019.
91. IMS Institute for Healthcare Informatics. *Developments in Cancer Treatments, Market Dynamics, Patient Access and Value - Global Oncology Trend Report 2015*. Parsippany: IMS Health. 2015.
92. Rejon-Parrilla JC, Hernandez-Villafuerte K, Shah K, Mestre-Ferrandiz J, Garrison L, Towse A. *The Expanding Value Footprint of Oncology Treatments*. OHE Consulting Report. London: OHE. 2014.

93. Persson U, Norlin JM. *Multi-indication and Combination Pricing and Reimbursement of Pharmaceuticals: Opportunities for Improved Health Care through Faster Uptake of New Innovations*. Appl Health Econ Health Policy. 2018;16(2):157-65.
94. Bayat Mokhtari R, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, et al. *Combination therapy in combating cancer*. Oncotarget. 2017;8(23):38022-43.
95. Latimer NR, Pollard D, Towse A, Henshall C, Sansom L, Ward RL, et al. *Challenges in valuing and paying for combination regimens in oncology: reporting the perspectives of a multi-stakeholder, international workshop*. BMC Health Serv Res. 2021;21(1):412.
96. Jorgensen J, Hanna E, Kefalas P. *Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries*. J Mark Access Health Policy. 2020;8(1):1715536.
97. Aballea S, Thokagevistik K, Velikanova R, Simoens S, Annemans L, Antonanzas F, et al. *Health economic evaluation of gene replacement therapies: methodological issues and recommendations*. J Mark Access Health Policy. 2020;8(1):1822666.
98. PwC. *Pathfinder Study for the Adoption of Cell and Gene Therapies in Ireland*. 2021.
99. Hofmarcher T, Lindgren P, Wilking N. *Diagnosed but not treated: How to improve patient access to advanced NSCLC treatment in Europe* IHE Report 2022:2. Lund: IHE. 2022.

Appendix

A.1 Standard weekly dose of medicines

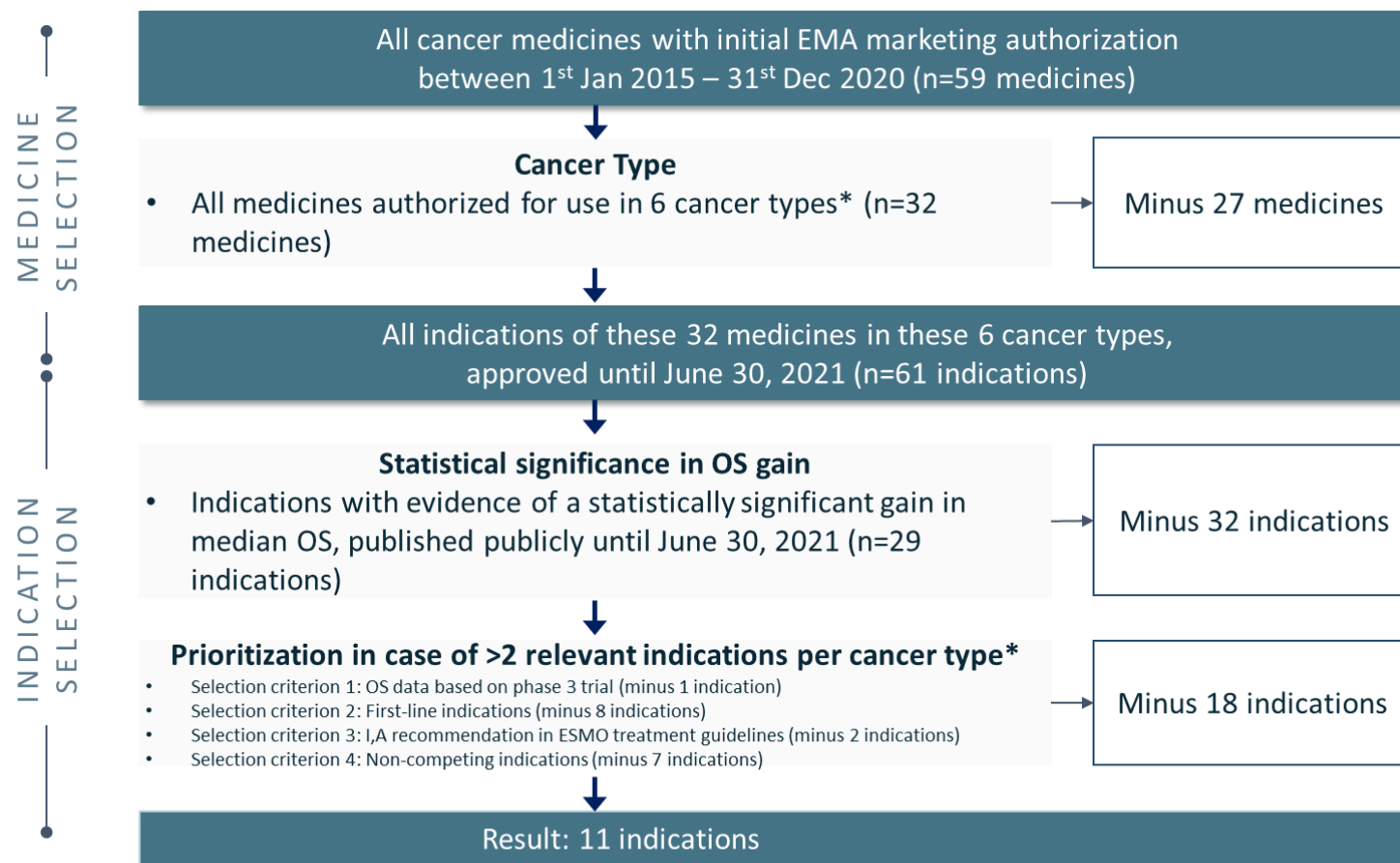
The standard weekly dose (SWD) is based on the recommended dose in milligram (mg) for a standard patient (70–80 kg body weight and body surface 1.7–1.8 m²). Table A1 lists the SWD used for the selected medicines in section 5.3.

Table A1: SWD for selected cancer medicines

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

A.2 Socio-economic impact of time to reimbursement

A.2.1 Medicine and indication selection



* At least 1 indication related to the following 6 cancer types: bladder cancer, breast cancer, colorectal cancer, leukemia (AML), lung cancer, prostate cancer.

A.2.2 Calculation of the socio-economic impact

Table A2: Inputs and results of the calculation of the socio-economic impact of time-to-reimbursement in Ireland

Cancer type	Medicine	Indication	EMA approval	HSE reimbursement	Time to reimbursement (days)	Clinical trial	Median OS gain (months)	Eligible patients – annual	YPLL – all patients	YPLL – patients 15–64y	Economic value of the YPLL
Bladder	Avelumab	1L-maintenance, urothelial, locally advanced/metastatic	21-Jan-2021	None (31-Mar-2022)	(434)	JAVELIN Bladder 100	7.1	138	97	20	€695,981
Bladder	Pembrolizumab	2L, urothelial, locally advanced/ metastatic	24-Aug-2017	1-Feb-2021	1,257	KEYNOTE-045	2.9	60	50	10	€358,237
Breast	Atezolizumab	1L, TNBC, locally advanced/ metastatic, PD-L1≥1%	26-Aug-2019	1-Mar-2022	918	IMpassion130	7.0	91	134	82	€2,185,160
Breast	Ribociclib	1L, HR+/HER2-, locally advanced/ metastatic, pre- or perimenopausal	17-Dec-2018	1-Sep-2020	624	MONALEESA-7	10.7	151	230	230	€6,141,006
Colorectum	Encorafenib	2L, metastatic, BRAFV600E+	2-Jun-2020	None (31-Mar-2022)	(667)	BEACON	3.4	77	40	13	€451,066
Colorectum	Trifluridine / tipiracil	3L, metastatic	25-Apr-2016	None (31-Mar-2022)	(2,166)	RECOURSE	1.8	464	413	140	€4,671,270
Leukemia	Midostaurin	AML, 1L, FLT3+	18-Sep-2017	1-Oct-2021	1,474	RATIFY	49.1	41	669	239	€8,274,991
Leukemia	Venetoclax	AML, 1L, standard-chemo-ineligible	19-May-2021	None (31-Mar-2022)	(316)	VIALE-A	5.1	68	25	9	€307,110
Lung	Osimertinib	1L, NSCLC, locally advanced/ metastatic, EGFR+	7-Jun-2018	1-Oct-2020	847	FLAURA	6.8	143	188	51	€1,693,526
Lung	Pembrolizumab	1L, NSCLC, metastatic, PD-L1≥50%, EGFR/ALK-	27-Jan-2017	1-Apr-2018	429	KEYNOTE-024	15.8	176	273	75	€2,462,277
Prostate	Apalutamide	1L, non-metastatic, castration-resistant, high-risk	14-Jan-2019	1-Aug-2021	930	SPARTAN	14.0	159	472	179	€6,893,254
							SUM	1,567	2,591	1,049	€34,133,879

Notes: OS = overall survival, YPLL = Years of Potential Life Lost, 1L = first line, 2L = second line, 3L = third line, NSCLC = non-small cell lung cancer, TNBC = triple-negative breast cancer, AML = acute myeloid leukemia. Sources: EMA approval dates were sourced from the EMA website. HSE reimbursement dates were sourced from the NCPE website. Data on median OS gain were sourced from the clinical trials. The annual number of eligible patients was calculated in a top-down manner starting from incidence numbers (all cases and sex-specific case in the age range 15–64 years) by broad cancer type (column 1) for the year 2017 from the NCRI (24), and combined with information from epidemiological studies to estimate the patient population specified in the approved EMA label. For the two lung cancer indications, a 53% treatment rate was assumed in addition for the annual number of eligible patients based on finding from previous research for the year 2018 (99). The economic value of one YPLL was calculated based on sex-specific earnings (men €51,861; women €42,166) and employment rates (men: 74.1%; women: 63.3%) for 15–64-year-olds based on data for the year 2018 from Eurostat (47, 48).

The Swedish Institute for Health Economics (IHE) is an independent research institute grounded in health economics. Together with clients from the public, private and civic sectors, we strive to provide evidence for sound decision making. We work in Sweden, rest of Scandinavia and internationally, studying a wide range of issues related to health and health care.

IHE specializes in applied policy analysis and health economic studies, using knowledge drawn from the cutting edge of international developments as well as independent in-house methods development. We have long experience of developing method for health economic evaluations and to conduct analysis of treatment alternatives to support decision making in the health care sector.

IHE constitutes one of the largest and most experienced health economic research groups in the Nordics. IHEs staff consists of experienced academic health economists and highly skilled multidisciplinary specialists in health economics, medical science, statistics and business administration.

In addition to project work, IHE organizes IHE Forum, an annual policy-oriented conference where actors across the health care system meet and discuss current topics. We also arrange open and bespoke courses in health economics to different stakeholders. Moreover, IHE organizes a network of Swedish health economists with annual meetings since 2002.



Informed decision making for health and welfare

The Swedish Institute for Health Economics
Institutet för Hälso- och Sjukvårdsekonomi
www.ihe.se