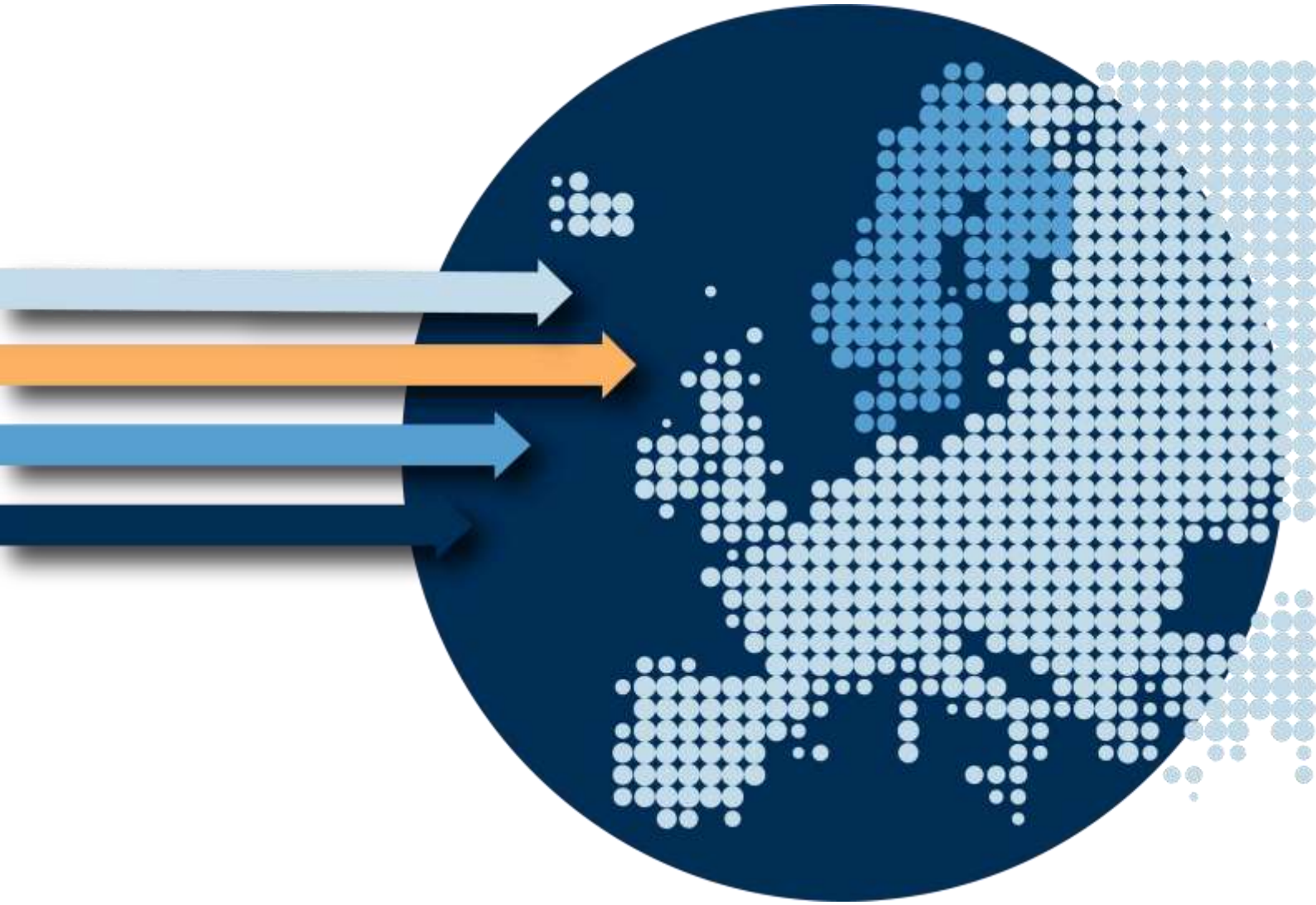
COMPARATOR REPORT ON CANCER IN THE NORDIC COUNTRIES – DISEASE BURDEN, COSTS AND ACCESS TO MEDICINES



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COMPARATOR REPORT ON CANCER IN THE NORDIC COUNTRIES
–DISEASE BURDEN, COSTS AND ACCESS TO MEDICINES

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Foreword

Cancer remains a central topic in the health care debate. With a shifting disease panorama – in part driven by successes in other fields of medicine – and an ageing population the incidence of cancer is increasing throughout the Western world. It is rapidly overtaking cardiovascular disease as the chief contributor to disease burden. At the same time, medical developments have continued apace with improvements in survival in many, but not all, forms of cancer. In some cases, cancer can now be seen as a chronic condition, with introduces new challenges to the health care system.

The present report focuses on the development in the cancer field in the Nordic countries during the last 10 years. It does this by exploring trends in epidemiology, costs, medical developments and use of medicines across and within countries. As can be seen, sometimes differences are larger within a country than between them. The report is divided into two documents: The complete report (this document) and a shorter summary version (IHE Report 2019:2a).

This work was funded by grants from LIF, the trade association for the research-based pharmaceutical industry in Sweden, and from the Bengt Jönsson Foundations for Health Economic Research. Responsibility for the analysis and conclusions lies solely with the authors.

Lund, April 2019

Peter Lindgren
Managing Director, IHE

1. Disease burden and economic burden of cancer in the Nordic countries

1.1 Summary

- More than one in four deaths was due to cancer in the Nordic countries in 2015. In Denmark, cancer was the most common cause of death. Cancer is the disease group causing the greatest disease burden in terms of DALYs (20% in 2015) in the Nordic countries, ahead of cardiovascular diseases.

- Cancer incidence totalled 154,800 new cases in the Nordic countries in 2015. Since 1960, the number of new cases has tripled. Demographic factors (population growth and population aging) have spurred this development. Even if disregarding these factors, cancer incidence would still have increased by almost 60%.

- Cancer mortality totalled 62,000 deaths in the Nordic countries in 2015. Since 1960, the death toll has increased by 75%. In per capita terms, mortality has started to level off since the 1990s in all countries, except Finland. Taking into account all demographic factors, cancer mortality decreased in all Nordic countries except in Norway.

- Since the 1960s, 5-year survival rates for all cancers combined have increased from about 35% to 65% in 2015. Denmark has been trailing behind the other countries but has started to catch up since the 2000s.

- The key factors that have been driving a wedge between the trends in incidence and mortality are advances in medical treatment, as well as in diagnostics and screening. Recent efforts to standardize care processes help to coordinate the efficient use of resources. These factors have also been the drivers behind the steadily increasing survival rates.

- The direct costs of cancer (the total health expenditure spent on cancer care) increased from €2,558 million to €5,514 million in the five Nordic countries between 1995 and 2015 (in 2015 prices). This equals a 116% increase, or a mean annual growth rate of 3.9%.

- Spending on cancer as a share of total health expenditure has remained more or less constant (around 4-5%), despite the increasing number of cancer patients. Even though health care spending on cancer has been increasing continuously in absolute numbers since

1995, the rate of the increase was similar to the overall increase in health expenditure. Total health expenditure increased from around 8% to 10% of GDP between 1995 and 2015.

- Denmark spent the most on cancer care with €138 per capita in 1995 and Finland and Iceland the least with €81. Denmark was surpassed by Norway as the top spending country in 2005. In 2015, Norway spent €285 per capita on cancer care, followed by Denmark with €236 and Sweden with €187. The lowest spending countries were again Finland with €149 and Iceland with €146.

- There have been significant shifts in the composition of the direct costs of cancer. Historically, they have been dominated by inpatient care. During the last decades, inpatient days of cancer patients have been declining in a process of moving treatment to ambulatory care and treatment at home. This pattern reflects a general trend in health care provision, but it was more pronounced in cancer patients in all Nordic countries. Declining expenditure on inpatient care have been substituted with increasing expenditure on ambulatory care and cancer medicines.

- The indirect costs of cancer (productivity loss from premature mortality and from morbidity as well as informal care costs) exceeded the direct costs by far in all Nordic countries in 1995. As opposed to direct costs, many signs point to a decline in indirect costs after 2000. By 2015, indirect costs and direct costs might have been equally large.

- The potential decline in the indirect costs stems mostly from a decrease in productivity loss from premature mortality, which is the largest component of the indirect costs. Due to a decline in mortality among patients of working age, it decreased from €3,796 million to €2,927 million in the five Nordic countries between 1995 and 2015 (in 2015 prices). This equals a 23% decrease, or a mean annual growth rate of -1.3%.

- Evidence from Finland shows that productivity loss from morbidity (based on sickness absence and disability benefits) might have decreased slightly between 2004 and 2014. The extent of informal care is not well documented, and its development is therefore uncertain.

- The economic burden of cancer (the sum of direct costs and indirect costs) is highest in Denmark (partly based on a higher cancer incidence, lower survival, andhigher mortality), closely followed by Norway (partly based on the higher purchasing power). Sweden comes

at a distant third place, followed by Iceland. Finland recorded the lowest economic burden between 1995 and 2015.

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

1.2 Introduction

Cancer is the collective name of a group of over 100 diseases. Common types are breast cancer, prostate cancer, and lung cancer [1]. Cancer represents a major challenge for health care systems around the world. The first chapter in this report analyses two important aspects of cancer in the Nordic countries. The first aspect is epidemiology and disease burden of cancer, i.e., the number of individuals affected and the number of individuals dying of cancer. The second aspect is the economic burden, i.e., the costs that cancer causes in a societal perspective. The aim is to portray the development of these two aspects in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden).

1.3 Epidemiology of cancer

Cancer is a disease that affects people of all ages, although the incidence increases dramatically with age. This is partly because of an accumulation of and exposure to risks that increase over time. These risks include, for instance, tobacco use, alcohol use, unhealthy diet, physical inactivity, but also infection with carcinogenic viruses, such as human papillomavirus (HPV) and hepatitis B virus, or with helicobacter pylori, and air pollution as well as ionizing and ultraviolet radiation. Another important reason an increased risk with age is that the cellular repair mechanisms become less effective as a person grows older, which increases the risk for malignant transformation of cells [1].

The development of two fundamental measures of the disease burden of cancer in the Nordic countries are illustrated in Figure 1. Since 1960, the number of new cancer cases diagnosed every year (incidence) has more than tripled from about 50,000 cases to over 150,000 cases. The number of deaths due to cancer (mortality) has almost doubled from about 35,000 deaths per year to over 62,000 deaths. These developments are not limited to the Nordic countries, but mirror a very similar pattern in other developed countries [2, 3], and to some extent also in developing countries [4].

The distinct developments showed in Figure 1 have not gone unnoticed by policy makers. For many years, various initiatives and calls to action have been put forward. In the US, the Nixon administration declared "The War on Cancer" already in 1971. In Europe, the European Commission's first "Europe Against Cancer" program was adopted in 1987. The WHO has also persistently called for actions and supported countries to reduce premature mortality from cancer. Even though much progress has been achieved in the last few decades, the overall pattern in **Figure 1** makes it clear that a lot still needs to be done, especially in terms of incidence rates.

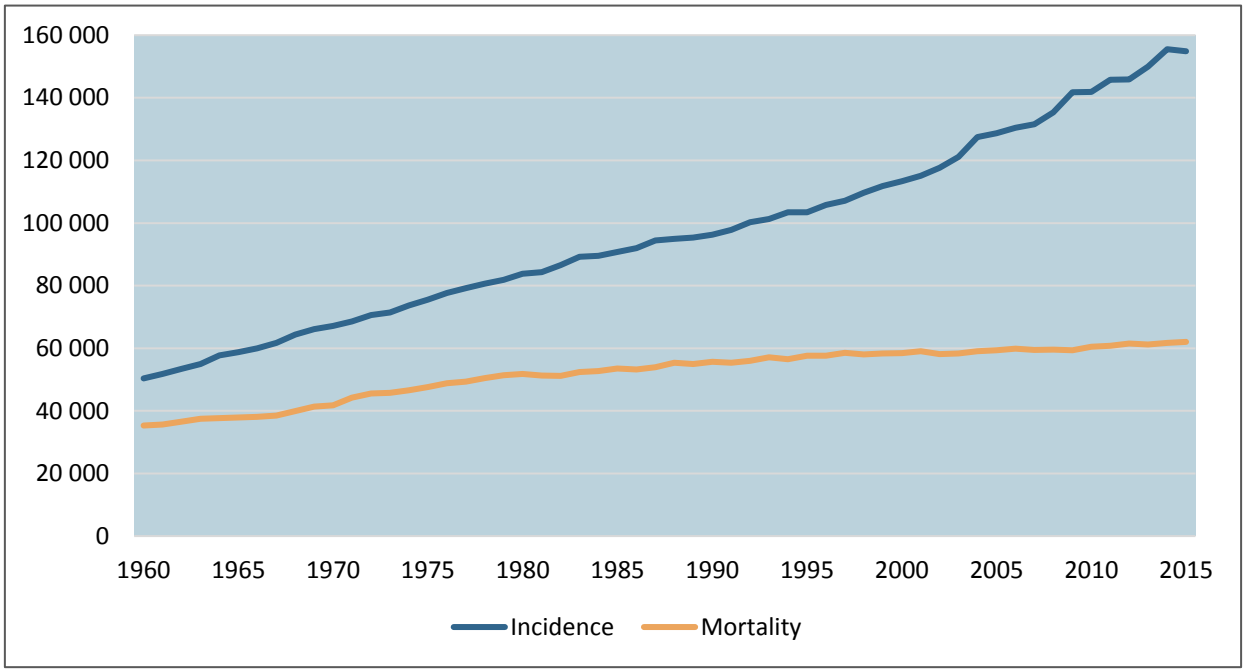

Figure 1: *Number of cancer incidence and mortality cases in the Nordic countries, 1960–2015 [5].*

To understand and analyse the disease burden of cancer in more detail, this section draws heavily on measures such as incidence, mortality, and survival. The data for these measures were primarily collected from NORDCAN[1], which is a database of cancer statistics for the Nordic countries. This database is based on the national cancer registries and the national cause of death registries. It also incorporates some adjustments to ensure comparability of the data between the countries.

1.3.1 Incidence

Cancer incidence refers to the number of diagnosed cases of cancer within a given year in a certain geographical area. In the five Nordic countries as a whole, the incidence[2] was 50,300 cases (24,400

[1] Available from: http://www-dep.iarc.fr/NORDCAN/english/frame.asp

[2] All cancer sites but non-melanoma skin cancer (ICD-10 CXX.X\(C44+C46.0)+D09.0-1+D30.1-9+D35.2-4+D41.1-9+D32-33+D42-43+D44.3-5+D45-46+D47.0-1,3-9). Non-melanoma skin cancer is commonly excluded from incidence data (and also from mortality data in this section of the report) since its registration is often incomplete and inaccurate. The reason for this is that non-melanoma skin cancer is usually non-fatal

men and 25,900 women) in 1960; see Figure 1. Until 1992, this number had doubled to 100,300 cases. After another 21 years, the number had tripled compared to 1960 and reached 150,000 cases in 2013. In 2015, there were 154,800 newly diagnosed cases (81,400 men and 73,400 women).

What explains the almost linear increase in newly diagnosed cases of more than 200% between 1960 and 2015?

- Population growth: The total population in the Nordic countries has grown by 31% from 20.2 to 26.4 million people in this time period [6]. At a constant risk of getting cancer, more people mean more cancer cases. Yet even in terms of cancer cases per capita, the number of newly diagnosed cases has gone up; see the section on crude rates below.

- Population aging: The elderly account for an increasing share of the total population. For example, the share of people aged 60 years and older in the total population has increased from 15% to 25% in this time period [6]. As the risk of getting cancer increases with age (**see Figure 3),** a growing share of older people increases the number of cancer cases. In Appendix 1, age-standardized incidence rates are presented which take into account the effect of population aging. However, even after controlling for population growth and population aging, there is still an increase in incidence of almost 60% between 1960 and 2015 left unexplained.

- Risk factors: Some lifestyle factors such as obesity (linked to, e.g., colorectal cancer and postmenopausal breast cancer), alcohol consumption (linked to, e.g., liver cancer and breast cancer), and exposure to ultraviolet radiation via sunbathing (linked to, e.g., skin cancer) have increased during the last decades in all Nordic countries. Smoking rates (linked to, e.g., lung cancer) have started to decline since the 1970s (the 1990s in Finland) [7]. However, there might be considerable time lags between the onset of exposure to risk factors and the development of cancer. In the case of declining smoking rates, it will take a few decades before this change manifests itself in decreasing lung cancer incidence. In men, lung cancer incidence has stabilized since the 1990s, paralleling a rapid decline in male smoking rates since the 1970s. By contrast, lung cancer incidence in women has been constantly increasing until 2015 as female smoking rates only started to decline in the 1990s.

- Screening: Nationwide population-based screening programs for cervical cancer and breast cancer and to a limited extent also for colorectal cancer have been implemented in recent decades [8, 9]. Unorganized screening for prostate cancer has also become more common. A

and often does not receive the same kind of treatment and is neither treated in the same setting (primary care rather than hospitals) as other cancer types.

higher screening activity might have led to the detection of more cancer cases rather than a true increase in the number of new cases.

- Epidemiological development in other diseases: For instance, the decline in mortality rates from cardiovascular diseases in recent decades entails more people reaching an advanced age. This leaves more people at risk of getting cancer [10].

1.3.1.1 Crude rates

To be able to compare countries of different sizes in a comprehensive way, total numbers of cancer are standardized by the population size. The resulting numbers are called crude rates. Crude rates of cancer incidence are presented in newly diagnosed cases per 100,000 inhabitants. In comparisons of cancer incidence over time, crude rates take into account changes in population size within countries. Crude rates are also the relevant measure to look at for policy makers, as a growing population per se is not a problem, provided that a growing population entails also more taxpayers.

Figure 2 shows crude rates for cancer incidence for all cancers and for both sexes in the Nordic countries. In all countries, incidence rates have more than doubled between 1960 and 2015 from an average of about 250 to 590 diagnosed cases per 100,000 inhabitants. Denmark had the highest incidence rates during the whole period. While Sweden also had almost equally high rates until around 1990, the Danish incidence rates have increased faster than in all other countries in the 2000s. Finland and Norway exhibit an almost perfectly linear increase in incidence rates during the whole period. Iceland recorded the lowest incidence rates throughout the whole period, and it is the only country where incidence rates seem to have stabilized since around 2005.

The fact that Iceland had the lowest incidence rates can be partly explained by the younger age structure[3] of their population. In 1960, 12% of the Icelandic population were 60 years or older, which was only matched by 11% in the Finnish population. In Denmark, Norway, and Sweden the corresponding rates were between 15% and 17%. In 2015, Iceland had still the youngest population with 19% being 60 years or older, compared to 22% in Norway, 25% in Denmark and Sweden, and 27% in Finland [6].

[3] Countries with an older population have, ceteris paribus, more cancer cases to take care of as the risk of getting cancer increases with age.

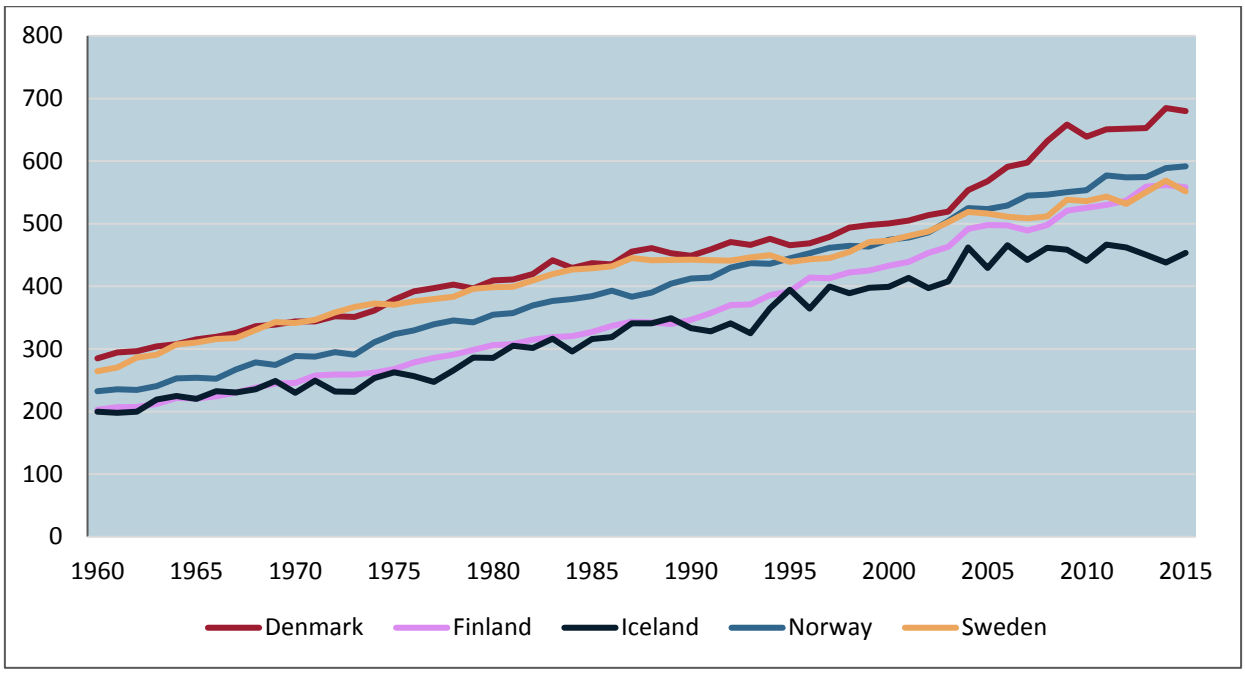

Figure 2: *Cancer incidence per 100,000 inhabitants (crude rates, both sexes), 1960–2015 [5].*

To take into account the influence of different age structures between countries, or within the same country over time, age-standardized rates can be used. Just as crude rates, they are quantified in terms of newly diagnosed cases per 100,000 inhabitants, but in addition, they are standardized according to a pre-defined age distribution. Figures A1 and A2 in Appendix 1 display age-standardized incidence rates separately for men and women. They show that age-standardized incidence rates increased in all countries between 1960 and 2015 (on average by 63% for men and 53% for women). The increases during this period were larger in magnitude (both in absolute and relative terms) for men than for women. However, the rates for men have started to stabilize in Denmark, Norway, and Sweden since the latter half of the 2000s, and in Finland and Iceland they have started to decline since then. The picture is different for women. Female incidence rates continue to increase in all countries except in Denmark, where stable rates have been recorded since around 2008 (but Denmark has also higher rates than the other countries), and in Iceland, where rates have declined since 2011.

1.3.1.2 Incidence by cancer type and age

While the total number of new cancer cases has been increasing, this development was not uniform across all cancer types. In fact, the share of different cancer types has shifted markedly during recent decades – some have become more and others less common in relative terms; see Table 1. In both men and women, the ten most common cancer types accounted for around 70% to 80% of all cases in both 1980 and 2015 in the Nordic countries. The most common cancer type in men was prostate cancer in 1980 accounting for almost every fifth diagnosed case of cancer. In 2015,

prostate cancer accounted for almost every third diagnosed case of cancer. However, it remains unclear to what extent the massive increase in prostate cancer incidence is driven by the detection of latent disease [11]. Breast cancer remained by far the most common cancer type in women, accounting for about every fourth diagnosed case in both 1980 and 2015.

Other noteworthy trends for men are the relative decrease of lung cancer cases between 1980 and 2015. Lung cancer in women exhibits the exact opposite development, as it increased in relative terms, and was in 2015 as frequently diagnosed as in men (9% of all cases). In both men and women, melanoma of skin has seen a rapid increase since 1980 and accounted for 6% of all cases in 2015. Stomach cancer, which was the fifth most common type in 1980 in both men and women, has become much more uncommon since then. Major cancer types associated with female organs (cervix uteri, corpus uteri, ovary) other than breast cancer, have all declined in relative terms between 1980 and 2015.

Table 1: *Top 10 newly diagnosed cancer types in the Nordic countries by sex, 1980 & 2015 [5]*

Men				
1980 (42,391 cases)		2015 (81,453 cases)		Change
1st Prostate	18%	1st Prostate	31%	=
2nd Lung	17%	2nd Colorectal	13%	↑
3rd Colorectal	12%	3rd Lung	9%	↓
4th Bladder	8%	4th Bladder	7%	=
5th Stomach	7%	5th Melanoma of skin	6%	↑
6th Pancreas	4%	6th Non-Hodgkin lymphoma	3%	↑
7th Brain & central nervous system	3%	7th Kidney	3%	↑
8th Kidney	3%	8th Brain & central nervous system	3%	↓
9th Leukemia	3%	9th Lip, oral cavity & pharynx	3%	↑
10th Lip, oral cavity & pharynx	3%	10th Pancreas	3%	↓
Women				
1980 (41,389 cases)		2015 (73,392 cases)		
1st Breast	23%	1st Breast	28%	=
2nd Colorectal	14%	2nd Colorectal	13%	=
3rd Corpus uteri	6%	3rd Lung	9%	↑
4th Ovary	6%	4th Melanoma of skin	6%	↑
5th Stomach	5%	5th Corpus uteri	5%	↓
6th Lung	5%	6th Brain & central nervous system	4%	↑
7th Cervix uteri	4%	7th Ovary	3%	↓
8th Pancreas	4%	8th Non-Hodgkin lymphoma	3%	↑
9th Brain & central nervous system	4%	9th Pancreas	3%	↓
10th Melanoma of skin	3%	10th Bladder	3%	↑

The composition of newly diagnosed cases in all five countries is broadly speaking similar to the Nordic pattern in **Table 1**. Yet there are some exceptions. In Denmark, lung cancer constituted a larger share of about two to four percentage points in both men and women in 1980 and 2015. This is also true in Iceland (except for men in 1980), whereas among men in Finland in 1980 lung cancer was more frequently. In Sweden, prostate cancer constituted a larger share of almost five percentage points and lung cancer an almost equally large lower share in men in 1980 and 2015. Norway is the country that resembles the average Nordic picture the most.

Cancer is an aging-associated disease, yet it affects people in all ages. This is evident in Figure 3, which shows how all newly diagnosed cancer cases in the Nordic countries in 2015 were distributed across different age groups. During childhood, adolescence, and up to the age of 40, cancer is rarely diagnosed. Above the age of 40, cancer becomes increasingly more prevalent. In absolute numbers, most cases are diagnosed between the ages of 65 to 74. Almost two thirds of all cases are diagnosed in people aged 65 or older. In relative numbers, which take into account that there are fewer people at older ages, the incidence rate is highest among people aged 80 to 84. **Figure 3** also draws attention to somewhat different age patterns in men and women. Between the ages of 15 to 54, there are more cases diagnosed in women, whereas the opposite is true at older ages. The reason for this is that common cancer types in women, such as breast cancer and cervical cancer, occur at comparatively younger ages than the most common cancer type in men, prostate cancer.

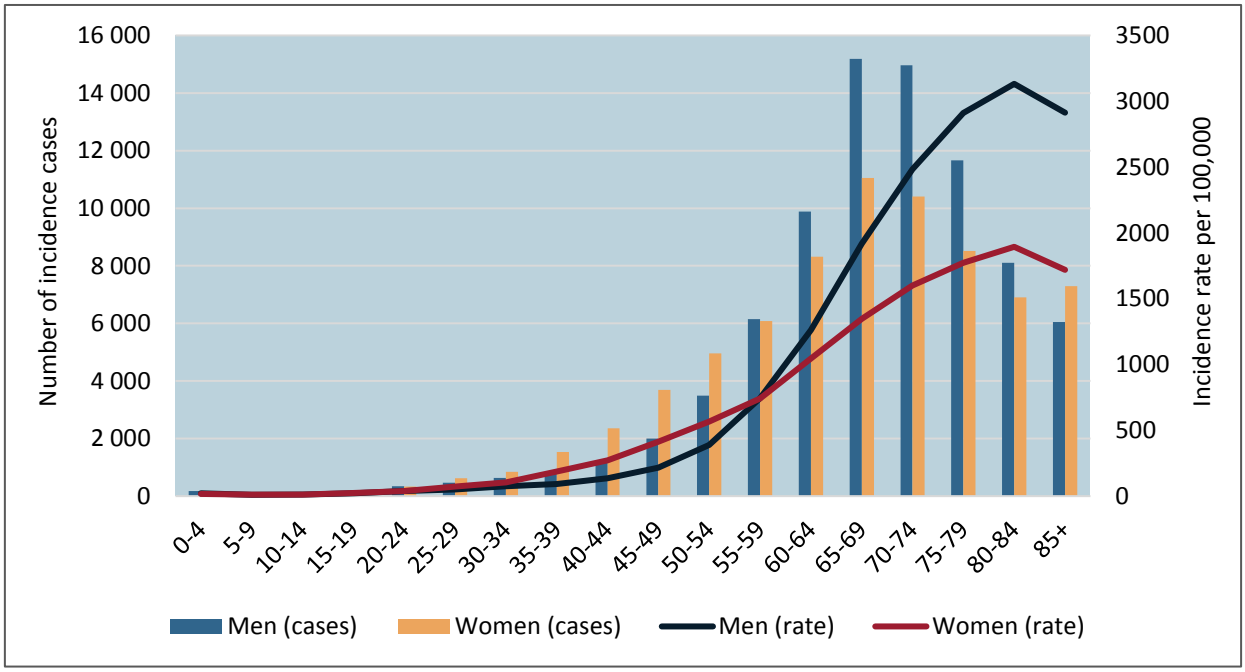

Figure 3: *Cancer incidence and age-specific incidence rates by age group and sex in the Nordic countries, 2015 [5].*

1.3.2 Mortality

Cancer mortality refers to the number of deaths due to cancer within a given year in a certain geographical area. In the five Nordic countries as a whole, the mortality[4] was 35,300 deaths (18,300 men and 17,000 women) in 1960; see **Figure 1**. Until 1984, this number had increased by 50% to 52,700 cases. It increased further every year to reach its peak in 2015 with 62,000 deaths (32,800 men and 29,200 women).

What explains the increase in cancer deaths of more than 75% between 1960 and 2015?

- As shown above, the number of newly diagnosed cases increased during this period. More new cancer cases imply automatically more deaths if the rate of curing cancer cases (survival) remains constant. This means also that the factors explaining the increase in cancer incidence (the demographic development, the development of lifestyle factors, the introduction of screening programs, and the epidemiological development in other diseases) are important for explaining the increase in cancer mortality.

- Population growth: As noted above, the total population in the Nordic countries has grown by 31% during this period. Thus, this factor alone can explain almost half of the increase; see the section on crude rates below.

- Population aging: As noted above, the population in all Nordic countries has become older and a growing number of elderly people gives rise to more cancer cases. In Appendix 1, age-standardized mortality rates are presented which take into account the effect of population aging. They show that mortality rates have slowly started to decrease since around 1980.

- Epidemiological development in other diseases: If the effect of competing causes of death (in particular the decline in deaths from cardiovascular diseases) is taken into account, cancer mortality might have decreased [10].

1.3.2.1 Crude rates

Crude rates for cancer mortality for all cancers and for both sexes in the Nordic countries are shown in **Figure 4**. In all countries, mortality rates were higher in 2015 than in 1960. In all countries combined, the rates increased by 34% from 175 to 235 cases per 100,000 inhabitants. However, the country-specific developments are quite different. In Finland, mortality rates have increased throughout the whole period, with a near stable development between 1985 and 2000. In

[4] All cancer sites but non-melanoma skin cancer (ICD-10 CXX.X\(C44+C46.0)+D09.0-1+D30.1-9+D35.2-4+D41.1-9+D32-33+D42-43+D44.3-5+D45-46+D47.0-1,3-9).

Iceland, mortality rates have been stable since around 1995, and in Sweden they have been stable since around 1985. In Denmark and Norway, mortality rates have increased until around 1995 but afterwards started to decline.

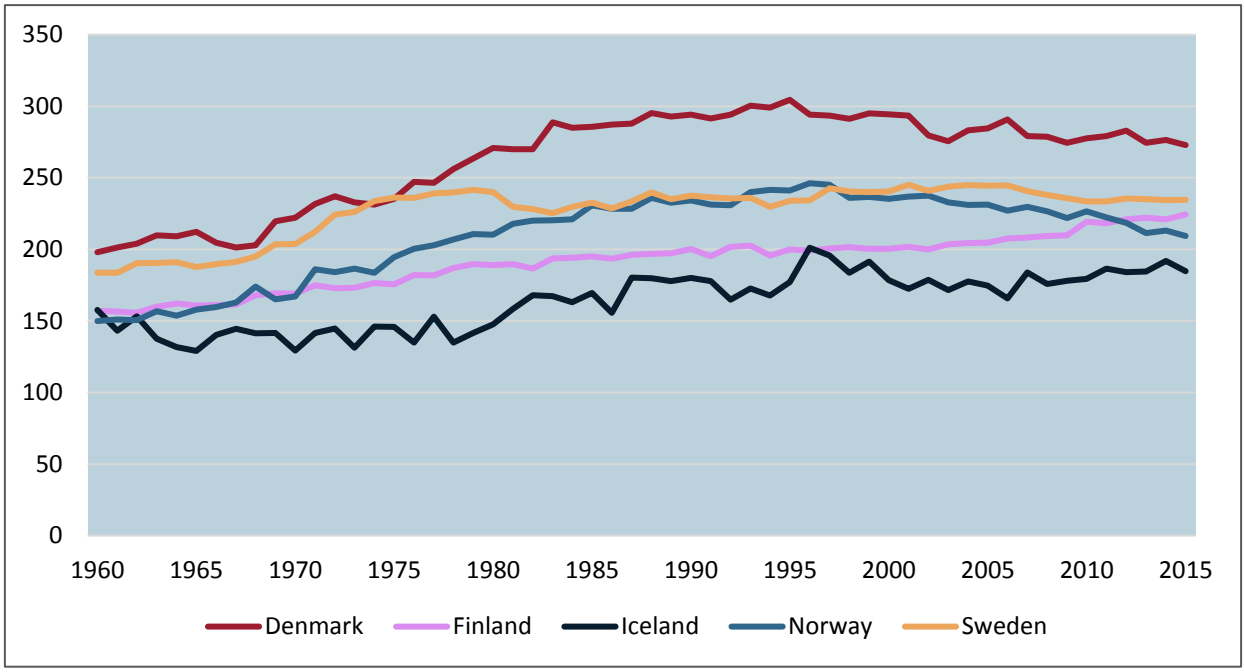

Figure 4: *Cancer mortality per 100,000 inhabitants (crude rates, both sexes), 1960–2015 [5].*

Denmark had the highest mortality rates during the whole period from 1960 to 2015, and Iceland had the lowest rates; see **Figure 4**. This fact is not entirely surprising, since these countries also had the highest and lowest incidence rates during this period. The difference in mortality rates between countries should thus be interpreted carefully. For instance, if two countries are equally successful in curing cancer cases, the country with the higher incidence rate will automatically have a higher mortality rate. Thus, two countries can have different mortality rates, but still be equally good in delivering effective treatment to an individual patient.

Figures A3 and A4 in Appendix 1 display age-standardized mortality rates separately for men and women. They show that once the effect of population aging is taken into account, age-standardized mortality rates decreased in all countries between 1960 and 2015 (on average by -12% for men and -19% for women), except in Norway. Mortality rates in men were highest in Finland in 1960 but decreased more than in other countries and were the lowest rates together with the rates in Iceland and Sweden in 2015. Finland had also the lowest mortality rate in women in 2015 after having had the second highest rate in 1960. In general, mortality rates in men started to decrease around 1980 in Finland, Denmark, Sweden and around 1995 in Iceland and Norway. Mortality rates in women mostly declined until the 1970s, remained stable in most countries in the 1980s and 1990s, and then continued to decline until 2015. It should also be noted that female mortality rates are on average

one third lower than male rates, which is mainly a result of lower incidence rates and partly also of higher survival rates during this period.

1.3.2.2 Mortality by cancer type and age

While the total number of deaths from cancer has been increasing, this development was not uniform across all cancer types. In fact, the share of different cancer types has shifted markedly during recent decades – some have become more and others less common in relative terms; see **Table 2**. In both men and women, the ten most common cancer types accounted for close to 80% of all cancer deaths in both 1980 and 2015 in the Nordic countries. The most common cause of death from cancer in men was lung cancer, accounting for almost every fourth cancer death in 1980 and every fifth cancer death in 2015. In women, breast cancer was the most common cause of death from cancer in 1980 accounting for every sixth cancer death, but in 2015 lung cancer was the most common cause. While deaths due to lung cancer decreased in both relative and absolute terms in men, women experienced an enormous increase. Deaths due to lung cancer were equally frequent in men and women in 2015 (19%).

Other noteworthy trends for men are an increase in prostate cancer mortality, which parallels – to some extent – the increase in incidence. Among women, deaths due to major cancer types associated with female organs (breast, ovary, cervix uteri) have all declined in relative terms between 1980 and 2015. Deaths due to stomach cancer, which was the fourth and third most common type in 1980 in men and women, respectively, have seen a steep fall in absolute and relative terms, mirroring the decrease in incidence. By contrast, mortality due to pancreatic cancer, cancers of the brain and central nervous system, and liver cancer increased in both men and women.

Table 2: *Top 10 fatal cancer types in the Nordic countries by sex, 1980 & 2015 [5]*

Men				
1980 (27,614 cases)		2015 (32,799 cases)		Change
1st Lung	24%	1st Lung	19%	=
2nd Prostate	14%	2nd Prostate	17%	=
3rd Colorectal	12%	3rd Colorectal	12%	=
4th Stomach	9%	4th Pancreas	7%	↑
5th Pancreas	6%	5th Bladder	4%	↑
6th Bladder	4%	6th Liver	4%	↑
7th Leukemia	4%	7th Brain & central nervous system	4%	↑
8th Kidney	3%	8th Stomach	3%	↓
9th Brain & central nervous system	3%	9th Leukemia	3%	↓
10th Non-Hodgkin lymphoma	2%	10th Non-Hodgkin lymphoma	3%	=
Women				
1980 (24,131 cases)		2015 (29,236 cases)		
1st Breast	16%	1st Lung	19%	↑
2nd Colorectal	14%	2nd Breast	14%	↓
3rd Stomach	8%	3rd Colorectal	12%	↓
4th Lung	7%	4th Pancreas	8%	↑
5th Ovary	7%	5th Ovary	6%	=
6th Pancreas	6%	6th Brain & central nervous system	3%	↑
7th Leukemia	4%	7th Leukemia	3%	=
8th Gallbladder	3%	8th Non-Hodgkin lymphoma	3%	↑
9th Cervix uteri	3%	9th Stomach	2%	↓
10th Kidney	3%	10th Liver	2%	↑

The composition of cancer deaths in all five countries deviates not too far from the Nordic pattern in **Table 2**. Notable deviations are observable in Denmark, where lung cancer deaths constitute a higher share of about three to five percentage points in both men and women in 1980 and 2015. This is also true in men in Finland and in women in Iceland. In Sweden, lung cancer deaths constituted a lower share of about five percentage points in men, whereas prostate cancer deaths were more frequently recorded (in 2015). Men and women in Norway and women in Sweden resemble the Nordic picture the most.

Figure 5 shows how all cancer deaths in the Nordic countries were distributed across different age groups in 2015. In absolute numbers, most cancer deaths occur between age 70 and 84. Two thirds of all cancer deaths in both men and women occur at the age of 70 or older. In relative numbers, which take into account that there are fewer people at older ages, mortality rates are highest among people aged 85 or older. Figure 5 illustrates that the sex-specific age pattern differs. As with cancer incidence, more women than men die due to cancer at ages 35 to 54, whereas the opposite is true at younger and older ages.

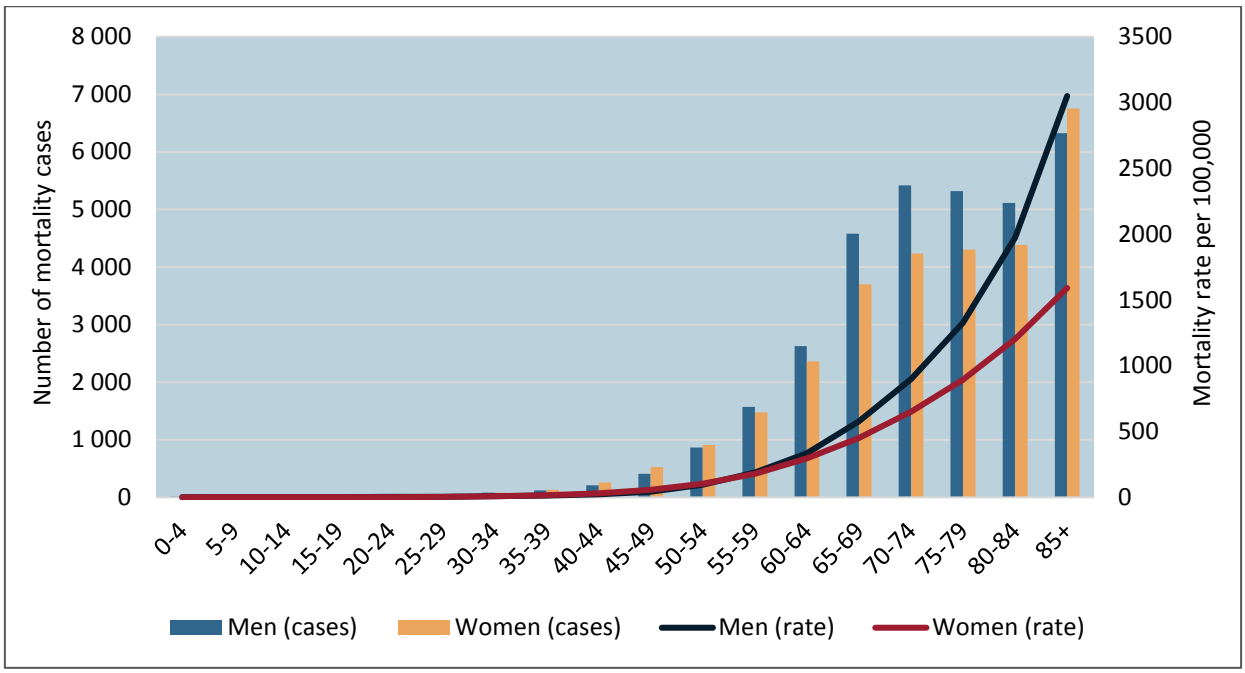

Figure 5: *Cancer mortality and age-specific mortality rates by age group and sex in the Nordic countries, 2015 [5].*

1.3.3 Survival

Survival is the concept that connects the two epidemiological measures of incidence and mortality. It measures the share of people that have been diagnosed with cancer in a certain year and that are still alive after a specified period of time. Survival rates are often measured in terms of 5-year survival rates, i.e., the share of people diagnosed with cancer in year t that is still alive in year t+5. This means that data on the 5-year survival rate of cancer patients diagnosed in 2015 can only be definitely evaluated after 2020, based on what is called "cohort analysis". However, there are other methods available ("period analysis" and "mixed analysis") to be able to obtain a good approximation of the likely result [12, 13].

Two adjustments are usually made to survival rates to receive comparable figures across time and countries. Firstly, relative survival rates rather than absolute survival rates are compared. The relative survival rate is the ratio of two survival rates: the absolute survival rate of cancer patients divided by the expected survival rate of people in the general population with similar age and sex in the same country and calendar year[5] [14]. This adjusts survival rates for the effect of competing causes of death that would otherwise bias comparisons across time and between countries. Thus,

[5] For instance, assume that the observed share of cancer patients that are alive 5 years after their diagnosis is 60%. This is the absolute 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 relative survival rate is then 60%/80% = 75%. Thus, of the 40% (100% – 60%) of cancer patients who died within 5 years after diagnosis, 25% (100% – 75%) can be expected to have died from cancer and the remaining 15% (75% – 60%) from other causes.

relative survival rates indicate the hypothetical situation in which cancer is the only cause of death [12, 15]. Secondly, the age structure of cancer patients differs between countries. Since relative survival rates for most cancer types vary by age (typically they decrease with age), they are adjusted for age at diagnosis [15]. The International Cancer Survival Standard (ICSS) is typically used to this end.

For the Nordic countries, NORDCAN provides 5-year age-standardized (according to ICSS) relative survival rates by sex. Patients with a diagnosis for the years 1966–2015 are included with follow-up for death and emigration until the end of 2016. Survival rates are not available for every calendar year, but in groups of five years. In order to calculate survival rates for men and women combined in this report, the sex-specific survival rates have been weighted according to the sex-specific share of the cancer incidence in the five-year diagnosis periods.

Figure 6 shows the development of the 5-year survival rate of all cancer types for men and women in the Nordic countries. The survival rates have been almost linearly increasing between 1966 and 2015 from about 35% to 65%. Between 1966–1970 and 1981–1985, all countries – except Denmark – converged in terms of survival rates and had a very similar development until 2015, although Sweden was consistently the top-performing country. Denmark achieved much slower improvements until 1996–2000, which widened the gap to the other countries. Since the 2000s, Denmark has been catching up rapidly with the other countries and reached a survival rate of 61% in 2011–2015, but the best-performing country, Sweden, is still quite far ahead with 68%.

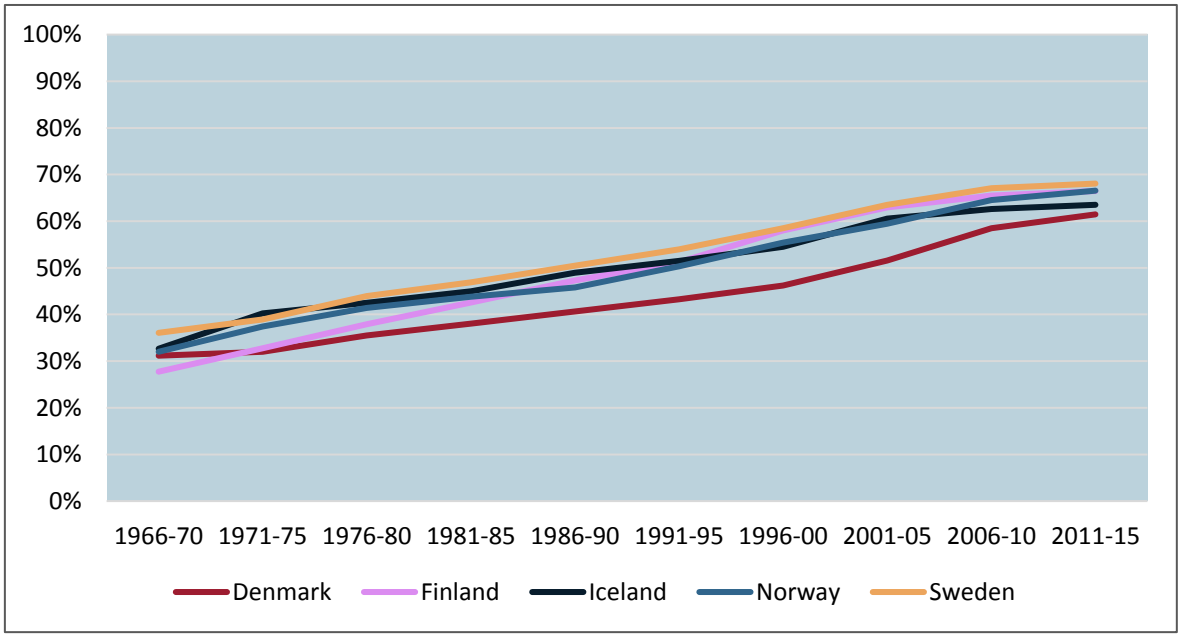

Figure 6: *5-year age-standardized relative survival rates for all cancers in patients aged 0–89 at diagnosis, 1966–2015 [5].*

One potential explanation for why Denmark has had comparatively low survival rates is the different composition of cancer types. Denmark has during the considered time period had distinctly higher crude rates of lung cancer, which is in turn probably related to markedly higher smoking rates in Denmark than in all other Nordic countries up until the early 2010s [7]. Lung cancer has a poor prognosis compared to most other major cancer types, which dragged down the overall survival rates in Denmark. In Figures A5 to A8 in Appendix 1, the country-specific developments in survival rates for lung cancer, colorectal cancer, breast cancer, and prostate cancer are shown. There it is noticeable that Denmark consistently recorded the lowest survival rates for all of these cancer types among the Nordic countries between 1966 and 2015 (except for lung cancer in 2006–2015). This might point to comparatively worse cancer care in Denmark before the 2010s. The other countries have fairly similar survival rates for each cancer type, and over time the survival rates have shown a tendency to converge.

What **Figure 6** does not show are differences in survival rates between men and women. In 1966–1970, the 5-year survival rate in women was on average 38% in the Nordic countries, whereas in men it was only 26%. Since then, there has been a converging trend between the sexes. Since 2001–2005, the survival rates in men slightly exceed those in women in Iceland and Sweden, and since 2006–2010 also in Norway. On average in the Nordic countries, the survival rate was 65% in both men and women in 2011–2015.

1.4 Burden of disease

To understand the extent of the burden of disease of cancer, it is helpful to compare the burden with that of all other diseases. A simple way of doing so, is to consider the number of cancer deaths and all deaths together. In 2015, 237,300 people died in the Nordic countries [16]. 61,400 deaths were due to cancer. This means that more than one in four deaths (25.9%) was caused by cancer. In comparison, deaths due cardiovascular diseases accounted for almost one third (32.2%) of all deaths. The only Nordic country in which the number of cancer deaths exceeded cardiovascular deaths was Denmark (29% vs. 24%).

Figure 7 shows how cancer deaths were distributed across age groups in 2015. Both the number of cancer deaths and all deaths increase throughout most of the age range before falling off after age 90. Cancer deaths peak at ages 70–74 to 80–84 with close to 10,000 deaths in each age group. All deaths combined peak a bit later at age 85–89. When cancer deaths are considered in relative terms of all deaths, it becomes clear that the share of cancer deaths has two peaks. The first one is during childhood (ages 5 to 15) where more than one in four deaths is due to cancer. The second peak occurs between ages 60 to 74, where around 42% to 44% of all deaths are due to cancer.

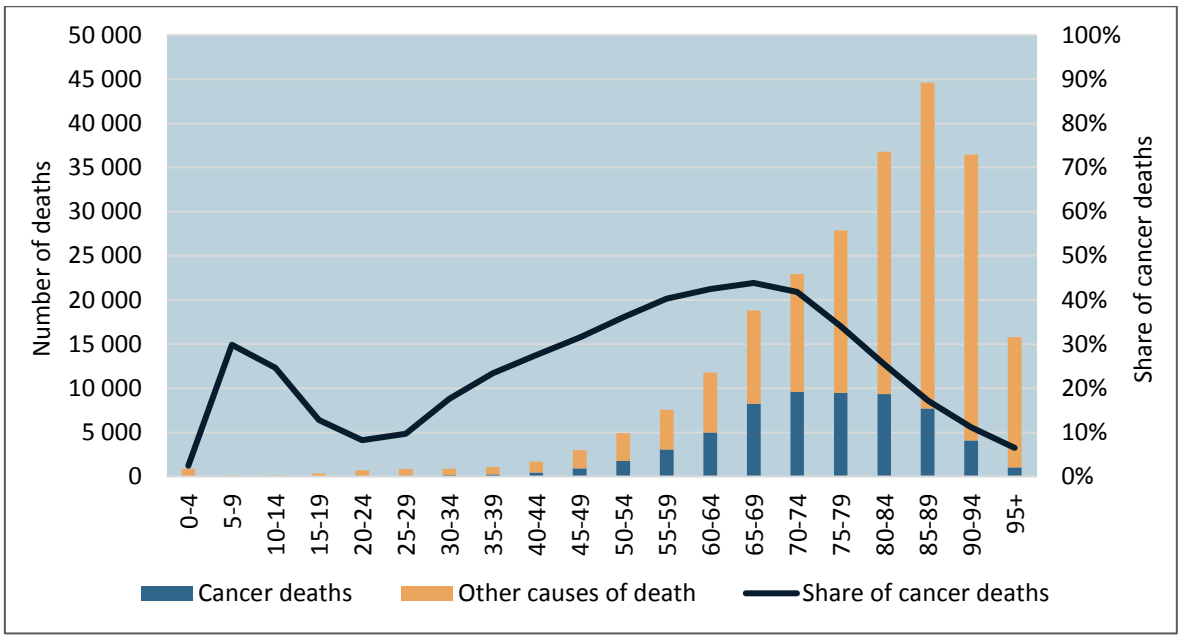

Figure 7: *Number of deaths by cause and share of cancer deaths by age group in the Nordic countries, 2015 [16].*
Note: Cancer is defined as ICD-10 C00-C97 and other causes as all causes of death (A00-Y89) excluding S00-T98 and C00-C97. Deaths refer to all deaths reported in a country.

An important aspect of the burden of disease that a comparison of the number deaths fails to take into account is the burden caused by non-fatal diseases and health conditions. A comprehensive measure of the burden of disease is Disability Adjusted Life Years (DALYs) which was developed by the WHO. DALYs take into account two elements of a disease; the impact on people's lives living with the disease (morbidity) and premature death due to the disease (mortality). Alternative measures are years of potential life lost (YPLL), although this one disregards the morbidity burden, and quality-adjusted life years (QALYs), for which no comparable country-level data across the whole disease spectrum are available.

One DALY represents one year of "healthy" life lost. The sum of all DALYs across a country's population represents the burden of disease in that country. It can be thought of as a measure of the gap between the current health state of the population and an ideal situation in which the entire population lives to an advanced age, free of disease and disability. DALYs for a specific disease or health condition are computed as the sum of two components; Years of Life Lost (YLL) due to premature death caused by the disease or health condition, and Years Lost due to Disability (YLD) for people living with the disease or health condition [17]. Comparable country-level data are available for the years 2000, 2005, 2010, and 2015.

Figure 8 provides an overview of the disease burden measured in DALYs in the Nordic countries for the years 2000 and 2015. Several observations can be made. Firstly, the total disease burden of

all diseases and illnesses decreased in absolute terms from 7.0 million DALYs to 6.8 million DALYs, despite a positive population growth during this period. Secondly, cancer (defined as malignant neoplasms) is the disease group that caused the second greatest burden (19%) after cardiovascular diseases (24%) in 2000. However, in 2015 the disease burden of cancer (20%) exceeded the one of cardiovascular diseases (17%). This pattern can be attributed to substantial decreases in mortality in cardiovascular diseases during this period [18].

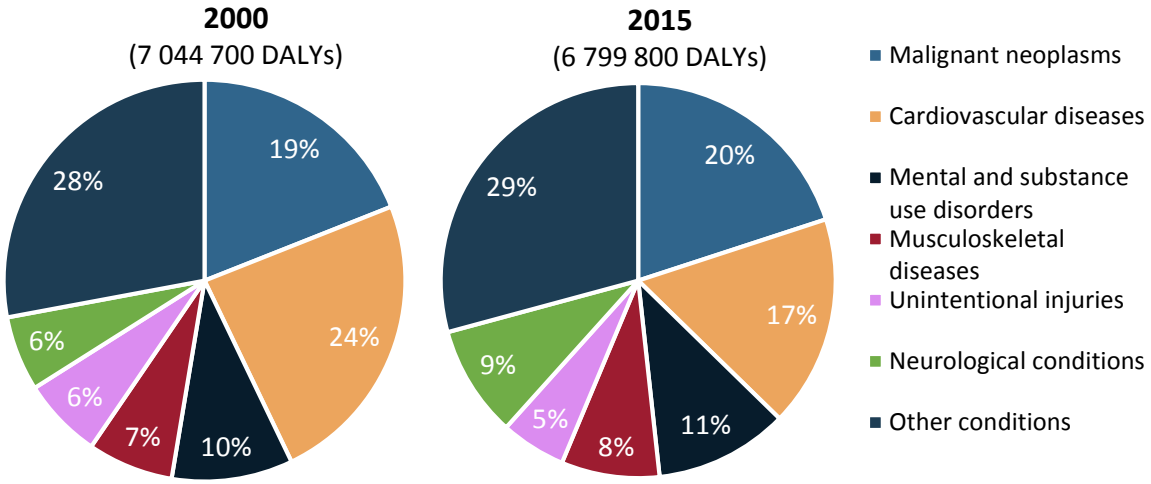

Figure 8: *Disease burden of the largest disease groups in the Nordic countries, 2000 & 2015 [19].*

Table 3 looks at the disease burden of cancer and the ten cancer types causing the greatest disease burden in terms of DALYs. In the bottom row, it can be seen that the total burden of cancer increased slightly between 2000 and 2015, but it decreased in per capita terms. Cancers of the lung, trachea, and bronchus, which are mainly related to smoking, caused the greatest burden and their share increased slightly. Colorectal cancer was in second place and showed no signs of decline, whereas the burden of breast cancer in third place decreased slightly. Since DALYs are composed of a morbidity component (YLD) and a mortality component (YLL), it is possible to take a closer look at the nature of the disease burden. For cancer, the mortality component accounted for 95% of the disease burden and the morbidity component for the remaining 5% in 2000. Especially in cancer types with low survival rates (e.g. pancreatic cancer and lung cancer), the mortality component amounts almost to 100%. By contrast, in cancer types with high survival rates (e.g. prostate cancer and breast cancer), the morbidity component constitutes a larger share of up to 20%.

Table 3: *Disease burden of the top 10 cancer types in the Nordic countries, 2000 & 2015 [19]*

2000					2015				
	Total DALYs ('000)	DALYs/ 1,000 inhab	Share	Share of YLL		Total DALYs ('000)	DALYs/ 1,000 inhab	Share	Share of YLL
1st Trachea, bronchus, lung	244	10	18.2%	99%	1st Trachea, bronchus, lung	263	10	19.4%	99%
2nd Colorectal	164	7	12.3%	95%	2nd Colorectal	165	6	12.2%	94%
3rd Breast	137	6	10.2%	89%	3rd Breast	120	5	8.8%	83%
4th Prostate	108	4	8.1%	89%	4th Prostate	110	4	8.1%	80%
5th Pancreas	78	3	5.8%	99%	5th Pancreas	97	4	7.2%	99%
6th Brain & nervous system	55	2	4.1%	98%	6th Brain & nervous system	59	2	4.3%	97%
7th Stomach	52	2	3.9%	97%	7th Leukemia	45	2	3.3%	94%
8th Leukemia	49	2	3.6%	95%	8th Stomach	41	2	3.0%	97%
9th Non-Hodgkin lymphoma	48	2	3.6%	98%	9th Liver	40	2	3.0%	98%
10th Ovary	44	2	3.3%	96%	10th Malignant skin melanoma	40	1	2.9%	88%
Cancer	1,338	55	100%	95%	Cancer	1,358	51	100%	93%

In **Figure 9**, the disease burden of cancer is compared between the Nordic countries. Among all countries, Denmark has by far had the highest burden in the years 2000 and 2015 with 70 DALYs and 62 DALYs per 1,000 inhabitants, respectively. Iceland has had the lowest cancer disease burden with less than 40 DALYs per 1,000 inhabitants. **Figure 9** also shows that the disease burden of cancer decreased in all countries except in Finland. These results are partly a reflection of higher crude mortality rates in Denmark, lower crude mortality rates in Iceland, and increasing crude mortality rates in Finland in this period.

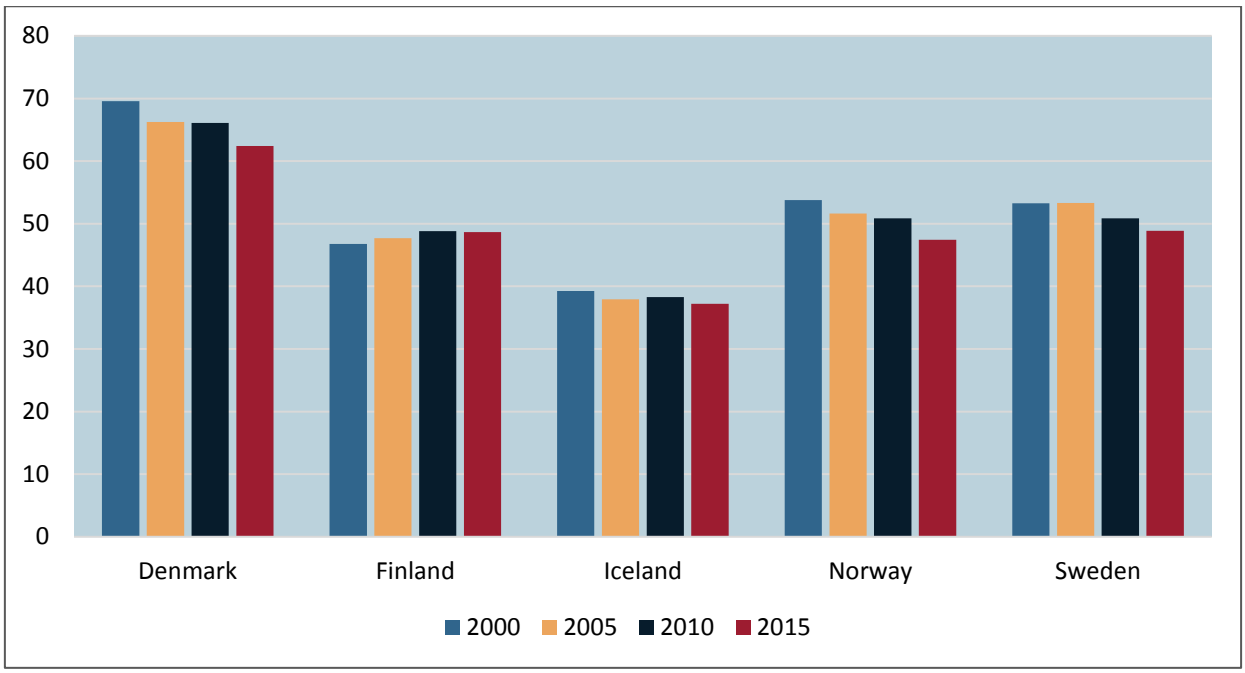

Figure 9: *Estimated DALYs caused by cancer (malignant neoplasms) per 1,000 inhabitants, 2000–2015 [19].*

1.4.1 Explanations for the trends in disease burden

The analysis of cancer incidence and cancer mortality has revealed different trends in their respective development. Measured in absolute numbers, incidence increased by 208% and mortality by 75% in the Nordic countries combined between 1960 and 2015. After taking into account the demographic development (population growth and population aging), the analysis showed that mortality rates decreased on average by 15% over this period (except in Norway), whereas incidence rates still showed an increase of almost 60%. This discrepancy in the development of incidence and mortality is reflected by the simultaneous improvement in survival rates. The cause behind this development has been attributed to "major advances in cancer management" [20, 21].

Viewed holistically, cancer management refers to all the actions that are taken in the cancer patient pathway. It encompasses primary prevention, screening, diagnostics, and treatment with curative and palliative intent [22]. Although it is impossible to pin down the exact contribution of each one of these components to the observed development in the Nordic countries, the following conclusions can be drawn:

- Primary prevention: This includes a wide range of measures such as efforts to decrease smoking rates and alcohol consumption, promote healthier dietary habits and physical activity, and reduce air pollution as well as exposure to ionizing and ultraviolet radiation. In addition, this includes the implementation of comprehensive vaccination programs. Vaccinations

against the hepatitis B virus infection can prevent liver cancer. Vaccination programs against human papillomavirus (HPV) for girls/women can prevent HPV-related cancers of the cervix, vagina, and vulva and for boys/men HPV-related penile cancer, as well as HPV-related anal cancer and neck and oropharyngeal cancers in both men and women. Since all of these measures aim at preventing cancer from occurring in the first place, they only influence the level of cancer incidence, but cannot help to explain the diverging trends in incidence and mortality.

- Screening (secondary prevention): The roll-out of population-based screening programs for cervical cancer and breast cancer in the 1990s and 2000s in the Nordic countries might have led to the detection of a larger share of cancer cases at an early stage [23-25]. Since the curability at an early stage is higher than at an advanced stage, screening programs can improve survival rates and moderate the increase in deaths from these cancer types even in the absence of changes in the effectiveness of actual treatment.[6] To give an example, the introduction of the population-based screening program for colorectal cancer in March 2014 in Denmark led to 20%-jump in newly diagnosed cases of colorectal cancer between 2013 and 2014. Since this has probably also increased the share of early detected cases, the overall survival rate for colorectal cancer can be expected to increase. Furthermore, mass screening has – especially for prostate cancer – led to the detection of latent disease that would never have become symptomatic [26]. This phenomenon has inflated incidence but since the disease is latent, mortality from it is very low. Thus, screening is a component of cancer management that can explain part of the diverging trends in incidence and mortality. However, it is important to remember that established screening methods are only available for a handful of (rather common) cancer types. It should also be noted that the steady increase in survival rates since the 1960s for all cancers combined, but also for breast cancer and colorectal cancer, set in long before the now established screening methods were implemented.

- Diagnostics: The aim of diagnostics is to locate the cancer, to determine its spread, and to examine its nature. During the last decades, the introduction of computed tomography (CT) scanners, magnetic resonance imaging (MRI) scanners, and positron emission tomography-computed tomography (PET-CT) scanners has improved the possibilities of accurate diagnostics. Since the investment costs for such medical equipment is high, availability of and access to it differs between and within countries and might explain some country-level

[6] For instance, assume that a country has an incidence rate of 500 cases per 100,000 inhabitants. Further, assume that if screening efforts are low, 50% of the newly diagnosed cases are cured and 50% die, whereas with high screening efforts 60% are cured and 40% die. A country with low screening efforts will have a mortality rate of 250 cases per 100,000 inhabitants. A country with high screening efforts will have a mortality rate of only 200 cases per 100,000 inhabitants, but not because it was more successful in treating each and every cancer case but rather because it had fewer advanced cases to treat.

differences. In addition, molecular prognostic/predictive testing, for instance to examine HER2 status in breast cancer, has become more common. As is the case with screening, improved diagnostics provides better preconditions for successful medical treatment, but it alone does not yield any benefit except knowledge on the nature of the cancer. In this sense, better diagnostics has certainly contributed to more effective medical treatment and thus can explain some part of the diverging trend between incidence and mortality. Based on mortality data from the United States during 2000-2009, it has been shown that better diagnostics explains indeed some of the observed decline [27].

- Treatment: Usually cancer is initially treated with surgery or radiation therapy with curative intent and sometimes preceded by neoadjuvant therapy. Afterwards it is treated with adjuvant systemic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, and molecularly targeted therapy). Radiation therapy, systemic therapy, and to some extent surgery are also extensively used in palliative care. The availability of radiation therapy machines and the availability of effective cancer medicines for systemic therapy have been improving during the last decades. New therapy modalities such as molecularly targeted therapy and immunotherapy have been developed and are being increasingly used (see the chapter on uptake of cancer medicines in this report). For instance, for the US it has been shown that the introduction of novel cancer medicines explains some of the observed decline in cancer mortality in 2000–2009 [27]. A Dutch study also presented evidence on the connection between the introduction of novel cancer medicines and declining cancer mortality in the Netherlands in 1960–2008 [28]. As noted above, screening and diagnostics can only unfold their positive effects on cancer mortality if they are accompanied by appropriate medical treatment. Nonetheless, advances in medical treatment have improved survival rates in their own right. This can be assessed by looking at stage-specific survival rates, in order to separate the influence of screening and diagnostics from medical treatment. For breast, colorectal, lung, and ovarian cancer different studies focusing on wealthier European countries (including Denmark, Norway, and Sweden) have shown that stage at diagnosis explains some of the differences in survival rates between countries. Yet they also showed that differences persist even when stage-specific survival rates are compared [29-32]. This suggests that better medical treatment can explain part of the improvements in survival and the diverging trends in incidence and mortality.

Cancer management in the Nordic countries has also undergone some notable organizational changes during the last decade. Denmark was the first country to introduce standardized care processes for some cancer types (called “kræftpakker” or “pakkeforløb for kræft”) in 2007. These standardized care processes span over the whole patient pathway from diagnostics to treatment and follow-up as well as rehabilitation and palliative care. They are supposed to ensure that all patients

receive high-quality care regardless of where in the country they live [33]. It is noteworthy that the introduction of these processes coincides with the time when Denmark started to close the gap in survival rates to the other countries in 2006–2015. Norway introduced standardized care processes for some cancer types in 2014, and Sweden introduced the first processes in 2015. However, the Swedish standardized care processes ("standardiserade vårdförlopp") are not as broad as the Danish ones, as they mainly focus on diagnostics and treatment. Compared to Denmark, where raising of the quality level of care was a central aim, in Sweden the reduction of waiting times was a relatively more important aim [34].

1.5 Economic burden of cancer

The economic burden of cancer is composed of two parts. Direct costs comprise expenditure related to primary prevention, screening, diagnosis, and treatment, rehabilitation, and palliative care, which are borne by the health care system. In addition, formally provided social support services are part of the direct costs. Indirect costs comprise productivity loss from reduced ability to work in the labour market and from premature death of people of working age. Informal care such as help with transportation and support at home provided by family members and friends are also part of the indirect costs.

The development of the economic burden over time is partly a reflection of the development of the disease burden. For instance, a rising number of diagnosed cancer cases increases expenditure on diagnostics and treatment, whereas a declining number of cancer deaths (in patients in working age) reduces mortality-induced productivity loss. Progress in cancer care, such as the introduction of new imaging techniques for diagnosis, new treatment modalities, or additional screening programs, also affects the development of the economic burden, since technological innovations typically come at a higher cost and/or expand the share of patients benefiting from them.

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

The aim of this section is to determine the economic burden of cancer in the Nordic countries and to describe the development between 1995 and 2015.

1.5.1 Direct costs

The treatment of cancer patients is a resource-intensive task. Medical equipment, such as CT, MRI and PET-CT scanners, is used to locate the cancer, and radiation therapy machines are used to treat the cancer. Surgeons, radiologists, and oncologists – assisted by nurses – perform surgery on the tumours, radiation therapy and/or systemic therapy (chemotherapy, hormonal therapy, immunotherapy, and molecularly targeted therapy), after pathologists have examined the nature of the cancer. Modern cancer care also includes psychosocial care and rehabilitation. Primary prevention measures, such as HPV vaccinations, but also public campaigns to promote a healthy lifestyle, and screening programs are additional cornerstones of cancer care. Thus, many different resources within the health care system and partly outside of it are allocated to cancer care. The sum of these resources constitutes the direct costs of cancer [35]. Note also that both publicly paid resources (taxpayers' money and/or social security contributions spent on the health care system) and privately paid resources (mostly out-of-pocket payments for health care visits and medicines, but also private health insurance) are part of the expenditure on cancer care.

It is important to keep in mind that the direct costs of cancer only present a single number of all resources devoted to fight the disease. More resources do not necessarily imply better cancer care. In order for the monetary input to yield the highest benefits to patients, the allocation of the resources and the organization of cancer care are critical [36].

1.5.1.1 Methodology

The method to estimate the direct costs of cancer in the Nordic countries is the same as in the previous comparator reports [2, 37-39]. The starting point is the total expenditure on health in a country.[7] The key issue is to determine how much of the health expenditure is spent on cancer care. The use of this top-down approach is in line with the idea of disease-specific health accounts proposed by the OECD [43]. The main argument for this top-down approach (instead of a resource used-based bottom-up approach) is that it provides the best guarantee against both underestimations and overestimations. It is also an approach where data from different types of studies can be used for the estimation of the share of cancer-specific health expenditure. It is neither dependent on a pre-determined definition of which types of health expenditure to include.

Based on this approach, cancer-specific health expenditure presents a subset[8] of the total health expenditure. The calculation of the total health expenditure is carried out by the national statistical

[7] In the actual calculation, we start with a country's gross domestic product (GDP; measured in euros or national currencies) obtained by Eurostat [40, 41], and multiply it with the share of current expenditure on health of GDP obtained from the OECD [42], to receive the total expenditure on health.
[8] Cancers causes also direct costs that fall beyond the remit of the health care system. Cancer patients are increasingly treated outside hospitals in ambulatory care, which creates a need for social support services.

offices according to the System of Health Accounts (SHA), a common framework developed by the WHO and the OECD. According to the latest version of the SHA, the headline indicator is called "current expenditure on health" and refers to the final consumption of health goods and services [44]. In this section, this indicator is used to define "total health expenditure". Current expenditure on health include services of curative care, services of rehabilitative care, services of long-term nursing care, ancillary services to health care, medical goods dispensed to outpatients, services of prevention and public health, health administration and health insurance, and expenditure on services not allocated by function. Note that expenditure from both public sources and private sources are included. Despite this common framework, the OECD cautions that the comparability of the data is imperfect, since some different practices regarding the classification of long-term care as either health expenditure or social expenditure have not been completely resolved [45].

Even though the SHA framework enables a breakdown of health expenditure by functions (services of curative care, etc.), financing agents (public or private sources), and providers (hospitals, etc.), it does not enable a breakdown by disease. Indeed, none of the five Nordic countries provides disease-specific health expenditure data. This means that the key factor for the calculation of the direct costs of cancer, the cancer-specific share of health expenditure, has to be obtained from other sources. In line with the previous Comparator reports, we reviewed reports and studies from national ministries of health, national statistical offices, research institutes, national cancer societies, and peer-reviewed journals.

In Appendix 1, we provide a description of all identified studies that assessed the direct costs of cancer for each country. Most of these studies are cancer-specific cost-of-illness studies. The completeness in terms of including all relevant sources of costs varies. Several studies left out expenditure on primary prevention and long-term care, resulting in an underestimation of the true costs. We tried to classify all relevant cost categories in these studies in a common manner, resulting in a re-classification or exclusion of certain categories in some studies. **Table 4** summarizes the total costs based on these studies and the calculated shares of cancer-specific health expenditure.

These are often not classified as health care costs, and thus the magnitude of these costs may be difficult to assess. This is also the case for private expenses for goods and services consumed as a consequence of the cancer.

Table 4: *Estimates of the health expenditure on cancer and total health expenditure (in millions of national currencies; current prices)*

	2004	2007	2010	2011	2012	2013	2014
Health expenditure on cancer and share of total health expenditure							
Denmark (DKK)		5,989	9,069				
		(3.7%) [46]	(4.8%) [47]				
Finland (EUR)	506	640.8					775
	(4.1%) [48]	(4.4%) [46]					(4.0%) [48]
Iceland (ISK)		4,573					
		(3.8%) [46]					
Norway (NOK)		6,782		11,137	10,943	11,914	12,456
		(3.6%) [46]		(4.5%) [49]	(4.2%) [49]	(4.3%) [49]	(4.2%) [49]
Sweden (SEK)	16,455	11,523				15,537	
	(5.7%) [50]	(3.4%) [46]				(3.7%) [51]	
Total health expenditure and share of GDP, [42]							
Denmark (DKK)	135,652	162,150	187,126	187,509	194,074	201,522	208,262
	(9.0%)	(9.3%)	(10.3%)	(10.2%)	(10.2%)	(10.2%)	(10.2%)
Finland (EUR)	12,347	14,602	16,593	17,618	18,563	19,479	20,421
	(7.8%)	(7.8%)	(8.9%)	(8.9%)	(9.3%)	(9.5%)	(9.5%)
Iceland (ISK)	91,907	118,962	142,721	145,033	150,933	171,677	186,528
	(9.5%)	(8.7%)	(8.8%)	(8.5%)	(8.4%)	(8.5%)	(8.5%)
Norway (NOK)	157,283	189,209	230,785	245,444	260,181	293,507	315,207
	(8.8%)	(8.0%)	(8.9%)	(8.8%)	(8.8%)	(8.9%)	(9.3%)
Sweden (SEK)	290,837	334,084	374,897	390,485	403,051	438,614	462,326
	(10.4%)	(10.1%)	(10.7%)	(10.7%)	(10.9%)	(11.1%)	(11.1%)

Note: See Appendix 1 for a description of all studies and the underlying calculations. The Danish cancer estimate for 2010 is based on resource use data from 2009 to 2014. The total health expenditure in Sweden for the years 1995–2010 are calculated based on the new definition implemented in 2011, applying the annual growth rates in health expenditure (based on the old definition) in 1995–2010 to the 2011 value (and assuming a 4.16% growth rate between 2010 and 2011 based on old data from Eurostat [52]).

Another methodological challenge is the use of different definitions of cancer in the reviewed studies. Some studies focused only on malignant neoplasms (ICD-10 C00-C97), while others used a broader definition (ICD-10 C00-D48), which includes in situ neoplasms (D00-D09), benign neoplasms (D10-D36), and neoplasms of uncertain or unknown behaviour (D37-D48). In this section, cancer is equated with neoplasms. We use this broader definition of cancer in order to be more consistent with the definition used in the previous section on the disease burden as well as the section on indirect costs below. Since some studies only focused on malignant neoplasms, the direct costs in this section are likely underestimated. The magnitude of this issue can be illustrated

on the basis of data from Germany and the Netherlands. Of all health expenditure spent on neoplasms (C00-D48) in Germany in 2008, 85.6% were spent on malignant neoplasm (C00-C97), 9.1% on benign neoplasms (D10-D36) and the remaining 5.4% on in situ neoplasms (D00-D09) as well as neoplasms of uncertain or unknown behaviour (D37-D48) [53]. In the Netherlands in 2011, 11.1% were spent on benign neoplasms but it is not specified how much was spent on other non-malignant neoplasms [54].[9]

Among the reviewed studies, only two (one for Finland and one for Norway) provide information on the development of the health expenditure spent on cancer over time. This constitutes a challenge for a valid calculation of the development between 1995 and 2015. As shown in a previous comparator report [2], in European countries (Germany, the Netherlands, the UK) for which consistent estimates of the development are available, the national shares of cancer-specific health expenditure remained mostly stable or increased slightly during the 2000s and the beginning of the 2010s. This is similar to the information shown in Table 4 for Finland, where the share was 4.1% in 2004 and 4.0% in 2014, and for Norway, where the share fluctuated around 4.3% in 2011–2014. A stable pattern in the cancer-specific share for a much longer period has been observed in the United States. There, the share has been close to 5% between 1963 and 1995 [55]. In 2010, the cost of cancer care was estimated to be $124.57 billion [56], and total health expenditure amounted to $2,555.4 billion [57], which equals a share of 4.9%. Thus, the cancer-specific share was virtually identical in 1995 and 2010 in the US, but, just as in the Nordic countries, the total health expenditure as a share of GDP increased during this period (see Table A1 in Appendix 1).

Given these results, the use of cancer-specific shares from a single year (2007 for Iceland, 2010 for Denmark, 2013 for Sweden), and its application for the whole period from 1995 to 2015, should yield a valid approximation of the real costs. If there were a slight upward trend in the share during this period, the national estimates of the direct costs for the years preceding (succeeding) the year that the original estimate refers to, would be slightly overestimated (underestimated). In the case of Finland and Norway, with multiple estimates from the same source, the cancer-specific share that was closest to the year in question was used (e.g., the Finnish estimate for 2004 was applied to the years 1995, 2000, and 2005, while the estimate for 2014 was applied to the years 2010 and 2015).

The direct costs are calculated in national currencies and in euros (€) to facilitate a comparison between the countries. As the estimates cover the period from 1995 to 2015, the effects of a general increase in prices (inflation) and of fluctuating exchange rates have to be taken into account. During this period, inflation was similar in all countries except in Iceland, which experienced

[9] One way to address this issue of differing definitions of cancer is to adjust the ones based on malignant neoplasms with a constant factor. Against the backdrop of the German and Dutch studies, it seems reasonable to assume that expenditure on non-malignant neoplasms (ICD-10 D00-D48) constitute approximately 15% of all expenditure on cancer.

distinctly higher inflation rates. The exchange rates were relatively stable in Norway and Sweden (Denmark has its currency closely pegged to the euro), whereas the exchange rate in Iceland went through the roof during the financial crisis of 2007–2008 and the following economic crisis (see Figure A9 in Appendix 2).

1.5.1.2 Results

The development of the direct costs of cancer in terms health expenditure devoted to cancer care is shown in **Table 5**. In all countries, the total costs have increased by a factor 2 to 3 between 1995 and 2015, after adjusting for inflation. The per capita expenditure also increased steadily throughout this period. Over the whole period, per capita expenditure increased by about 80% (corresponding to an average annual real growth rate of about 3%) in all countries, except in Norway which saw expenditure increase by 147% (a 4.6% annual growth rate). This pattern of increasing direct costs of cancer is an immediate consequence of increased spending on health care as a whole, rather than an increased share of health care resources devoted to cancer care. By construction of the direct costs of cancer in this report, they reflect the development of the overall health expenditure one-to-one in Denmark, Iceland, and Sweden, and to a lesser extent also in Norway and Finland (see **Table 4**). A description of the underlying development of the total health expenditure is provided in Table A1 in Appendix 1.

Table 5: *Direct costs of cancer in the Nordic countries, 1995–2015*

	1995	2000	2005	2010	2015	Total change	Annual change
Total health expenditure spent on cancer (in millions of national currency), 2015 prices							
Denmark (DKK)	5,400	6,660	8,142	9,545	9,997	85%	3.1%
Finland (EUR)	414	497	656	731	817	97%	3.5%
Iceland (ISK)	3,182	5,058	6,550	6,317	7,088	123%	4.1%
Norway (NOK)	4,503	6,785	8,975	11,191	13,239	194%	5.5%
Sweden (SEK)	8,374	10,270	12,840	14,385	17,106	104%	3.6%
Total health expenditure spent on cancer per capita (in national currency), 2015 prices							
Denmark (DKK)	1,033	1,248	1,503	1,721	1,760	70%	2.7%
Finland (EUR)	81	96	125	136	149	84%	3.1%
Iceland (ISK)	11,900	17,988	22,135	19,865	21,427	80%	3.0%
Norway (NOK)	1,033	1,511	1,941	2,289	2,550	147%	4.6%
Sweden (SEK)	949	1,158	1,422	1,534	1,746	84%	3.1%

Note: The 1995 estimates are only adjusted for inflation between 1996 and 2015 due to lack of a harmonized inflation measure before 1996 [52]. The annual growth rate is calculated assuming a constant growth rate.

The development of the direct costs of cancer in the Nordic countries as a whole is shown in **Figure 10**. Measured in current prices, total health expenditure spent on cancer amounted to €1,917

million in 1995 and almost tripled to €5,514 million in 2015. Adjusting for inflation and applying constant exchange rates, the expenditure amounted to €2,558 million in 1995, and then doubled until 2015 in real terms.

These results can be compared to the ones obtained in a previous Comparator report [2], which looked at the development between 1995 and 2014 in a larger set of European countries. In the previous report, the sum of the direct costs (in current prices) in the Nordic countries was estimated to be €2,227 million in 1995 (16% higher than in this report), and €5,191 million (12% higher) in 2010. The reasons for this discrepancy can be mainly explained by the use of more accurate information on the direct costs of cancer in all countries except in Iceland. This resulted in higher estimates for Norway and Denmark but lower ones for Finland and Sweden. Revisions of underlying data on health expenditure is another though less important explanation.

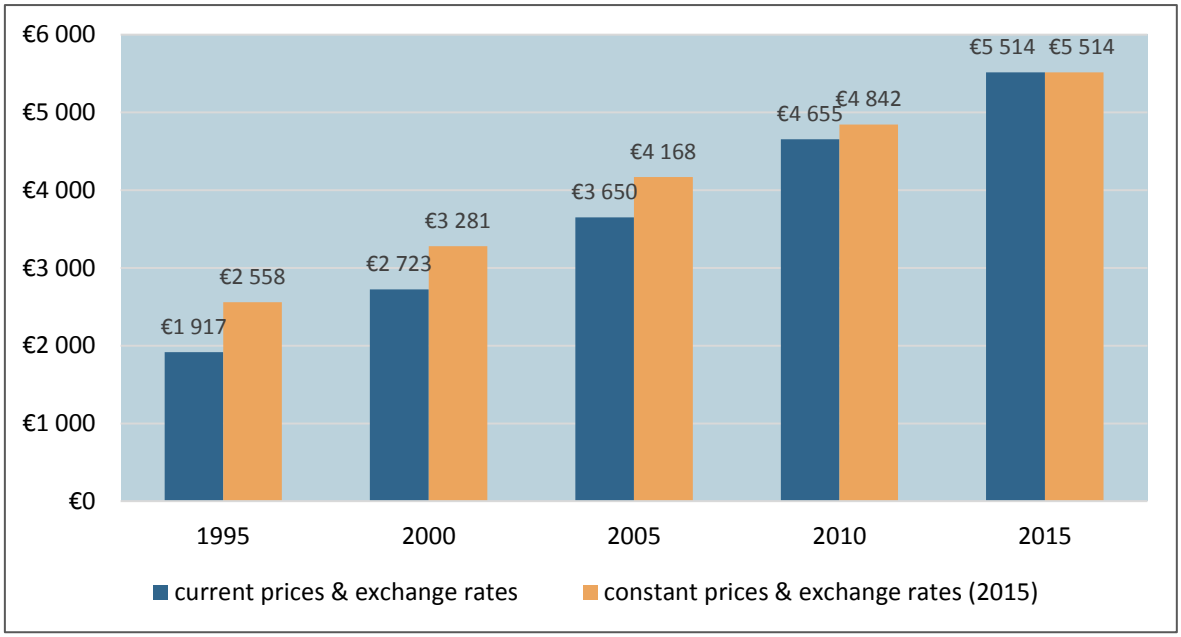

Figure 10: *Direct costs of cancer in the Nordic countries (in million €), 1995–2015. Note: The adjustment for inflation is based on country-specific inflation rates. The 1995 estimates are only adjusted for inflation between 1996 and 2015 due to lack of a harmonized inflation measure before 1996 [58].*

To better compare the level of the direct costs of cancer across the Nordic countries, **Figure 11** shows the per capita expenditure measured in euros at constant prices and constant exchange rates. In 1995, Denmark spent the most on cancer care per capita with almost €140, whereas Finland and Iceland spent just over €80. Finland, Norway, and Sweden exhibited a rather linear growth in expenditure between 1995 and 2015. Denmark followed this pattern until 2010, after which the costs remained nearly unchanged until 2015. Iceland exhibited a different pattern. Whereas the costs increased in line with the other countries before 2005, after 2005 costs fell in real terms until 2010 and then increased again but remained below the peak in 2005. This is most likely a result of

the economic crisis during which Iceland saw its economic activity halt abruptly and was forced to cut back on health care spending.

In 2015, Norway spent clearly the most on cancer care (close to €290), whereas Finland and Iceland spent the least (just below €150); see **Figure 11**. Thus, there is an almost twofold difference between the highest and lowest spending Nordic country. However, this does not mean that Norway spends twice as many resources on cancer as Finland and Iceland. Norway has a higher purchasing power than any other Nordic country. One day spent at a hospital or one doctor's appointment is more expensive there than in the other countries (mainly due to higher salaries of health care staff). Finland on the other hand has the lowest purchasing power among the Nordic countries.

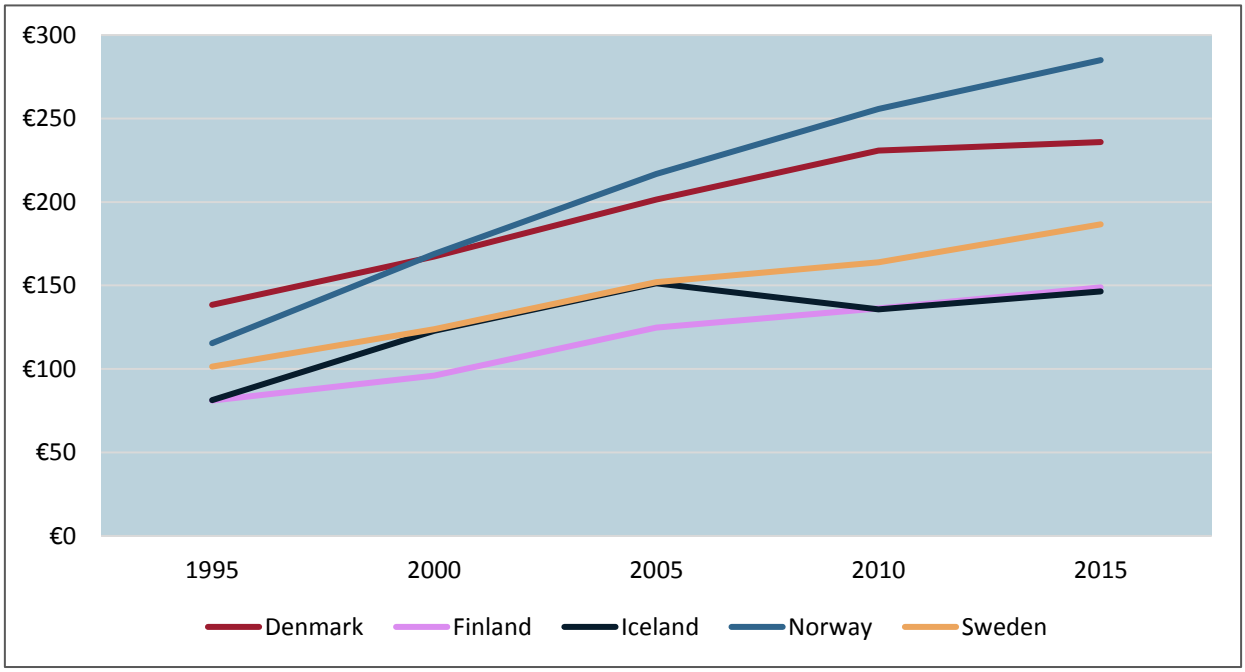

Figure 11: *Direct costs of cancer per capita (in €, 2015 prices and exchange rates), 1995–2015.*
Note: The 1995 estimates are only adjusted for inflation between 1996 and 2015 due to lack of a harmonized inflation measure before 1996 [58].

Apart from differences in purchasing power, the differences in the level of expenditure on cancer in Figure 11 should be interpreted against the backdrop of the disease burden. It seems plausible that countries with a higher disease burden are forced to spend more, given that they have a larger number of patients to take care of. In Figure 2, the development of newly diagnosed cases of cancer showed that the numbers (in terms of crude rates) were highest in Denmark followed by Norway, and they were lowest in Iceland. This pattern is thus somewhat similar to the one in **Figure 11**.

Even though the overall development of the increasing direct costs of cancer is mechanically related to the development of the total health expenditure in this report, a range of factors can help to explain this increase. Some of these factors also help to understand why the share of cancer-specific health expenditure might have exhibited a stable pattern. These factors have also implications for the future development: **Table 5**.

- As shown in **Table 5** and **Figure 10**, the total directs costs in the Nordic countries increased by 116% (from €2.6 to €5.5 billion) between 1995 and 2015. The continuous increase in costs during this period resembles the increase in cancer incidence. Between 1995 and 2015, the number of newly diagnosed cases increased by 55% in the Nordic countries (from 107,385 to 166,103 cases of all cancer sites including non-melanoma skin cancer). Thus, the sheer increase in the number of cancer patients seems to be one important explanatory factor of the observed increase in the direct costs of cancer. As cancer incidence, in crude terms, is still on the rise due to the demographic development and an increasing prevalence of some risk factors, the total direct costs will probably continue to increase in the future.

- Related to earlier detection, improved diagnostics, new cancer medicines, as well as other improved treatment modalities, cancer care has become more effective. Improved care enables shorter hospital stays, entails fewer side effects, and results in quicker recovery and potentially fewer recurrences [59]. This should lower the direct costs of cancer by decreasing the demand for some medical services, especially inpatient care; see the next section.

- There is an ongoing shift from intravenous to oral delivery methods of cancer medicines. As more patients can receive treatment at home, this could potentially decrease the demand for inpatient care and ambulatory care.

- New cancer therapies, such as targeted cancer therapy and immunotherapy, come at a higher price, which has led to substantial increases in expenditure on medicines in recent decades; see the chapter on uptake of cancer medicines in this report. New therapies also allow new patient groups to be treated. This increases the direct costs and is likely to continue to do so in the foreseeable future.

- Since survival has been increasing (see **Figure 6**), patients require care for a longer time. This might mostly affect the costs of long-term care and rehabilitation but also of ambulatory care, as the number of regular medical check-ups for the monitoring of disease progression and of recurrence will increase.

- More resources have been spent on both screening (e.g. population-based breast cancer screening programs were rolled out during this period; cervical cancer screening programs had

been mostly rolled out before) and primary prevention (e.g. HPV vaccination programs for girls were rolled out in the 2010s). They will be further extended to cover more cancer types (e.g., Denmark introduced population-based screening for colorectal cancer in 2014 and Norway is planning to do so in 2019; possibly screening for lung cancer will be introduced) and to cover boys in the case of HPV vaccination programs. These measures increase the direct costs in the short and medium run, but are supposed to decrease them in the long run.

1.5.1.3 Composition of the direct costs

An important aspect of the analysis of the direct costs of cancer is the development of the underlying types of direct costs. This kind of information is vital for policy makers to set the right priorities and implement cost-effective measures to decrease the disease burden.

As an example, **Figure 12** shows the distribution of the total direct costs of cancer across different cost categories in Sweden in 2013. Inpatient care is by far the largest cost category and accounts for almost half of all costs. This includes costs for surgery, but also part of the costs for diagnostics, radiation therapy, and costs for medical staff. Specialized outpatient care (ambulatory care at hospitals) is the second largest cost category accounting for over one fourth of all costs. This includes costs for diagnostics, radiation therapy, and medical staff. Cancer medicines represent the third largest cost category. The costs for palliative care, nursing and other care services account for eight percent of all costs. Four percent of the costs are spent on screening services (only cervical and breast cancer screening is included). Cancer patients are usually not treated in primary care in Sweden, which explains the small share of this cost category. In sum, inpatient and ambulatory care constitute the lion's share of the direct costs of cancer. This also true for other European countries [2].

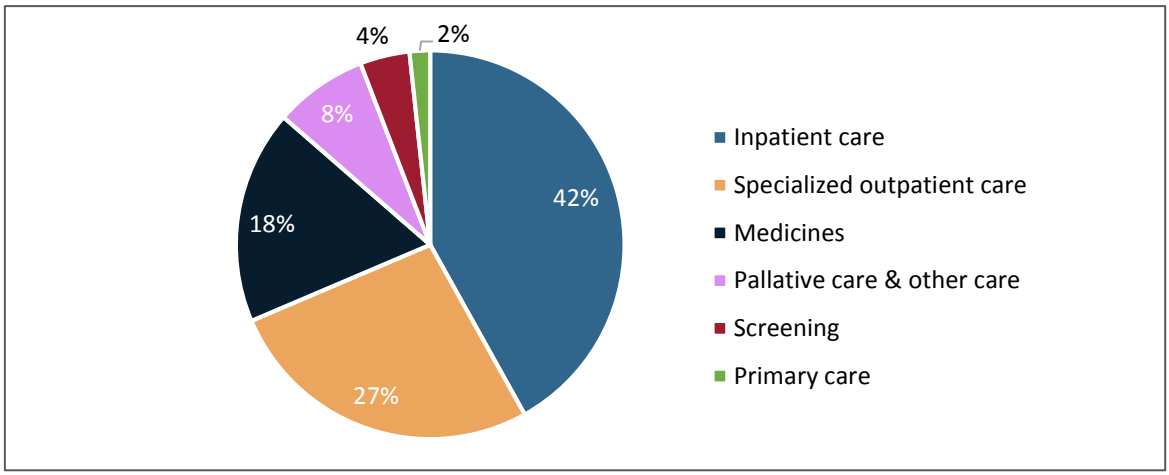

Figure 12: *Composition of the direct costs of cancer in Sweden, 2013 [51].*

The shares of the different cost categories of the total direct costs in **Figure 12** are not set in stone. Changes in the organization of cancer care affect these shares. Even though inpatient care still accounted for the largest share, there is evidence that this share might be declining. **Figure 13** shows the development of the number of bed days, i.e., overnight stays of hospitalized patients, and the number of day cases, i.e., patients who are formally admitted to the hospital but then discharged on the same day, between 2000 and 2016 in the Nordic countries. Both the development in cancer patients (top figures) and the general development in all patients (bottom figures) are portrayed. This provides insights into whether the development in cancer patients simply reflects a general shift in the organization of health care (e.g., from inpatient care to ambulatory care) in a country, or whether there is a disconnection between the overall trend and the specific trend in cancer patients. Note that comparable data for visits in ambulatory care (i.e., outpatient visits) are not available.

Between 2000 and 2016 there was clear downward trend in the number of bed days (standardized by population size) and a simultaneous upward or constant trend in the number of day cases (standardized by population size) in all Nordic countries; see **Figure 13**. This pattern was observable in both cancer patients and on the overall level. In all Nordic countries but Iceland, the number of bed days among cancer patients has essentially halved between 2000 and 2016. This represented a stronger decrease than on the overall level. The development in the number of day cases was more similar among cancer patients and the overall level. Taken together, this means that despite an increasing number of cancer patients in this period, inpatients days in cancer patients have decreased at large. Shorter hospital stays in the form of more day cases are one manifestation of this development, but the largest chunk of patients has most likely been shifted to ambulatory care.

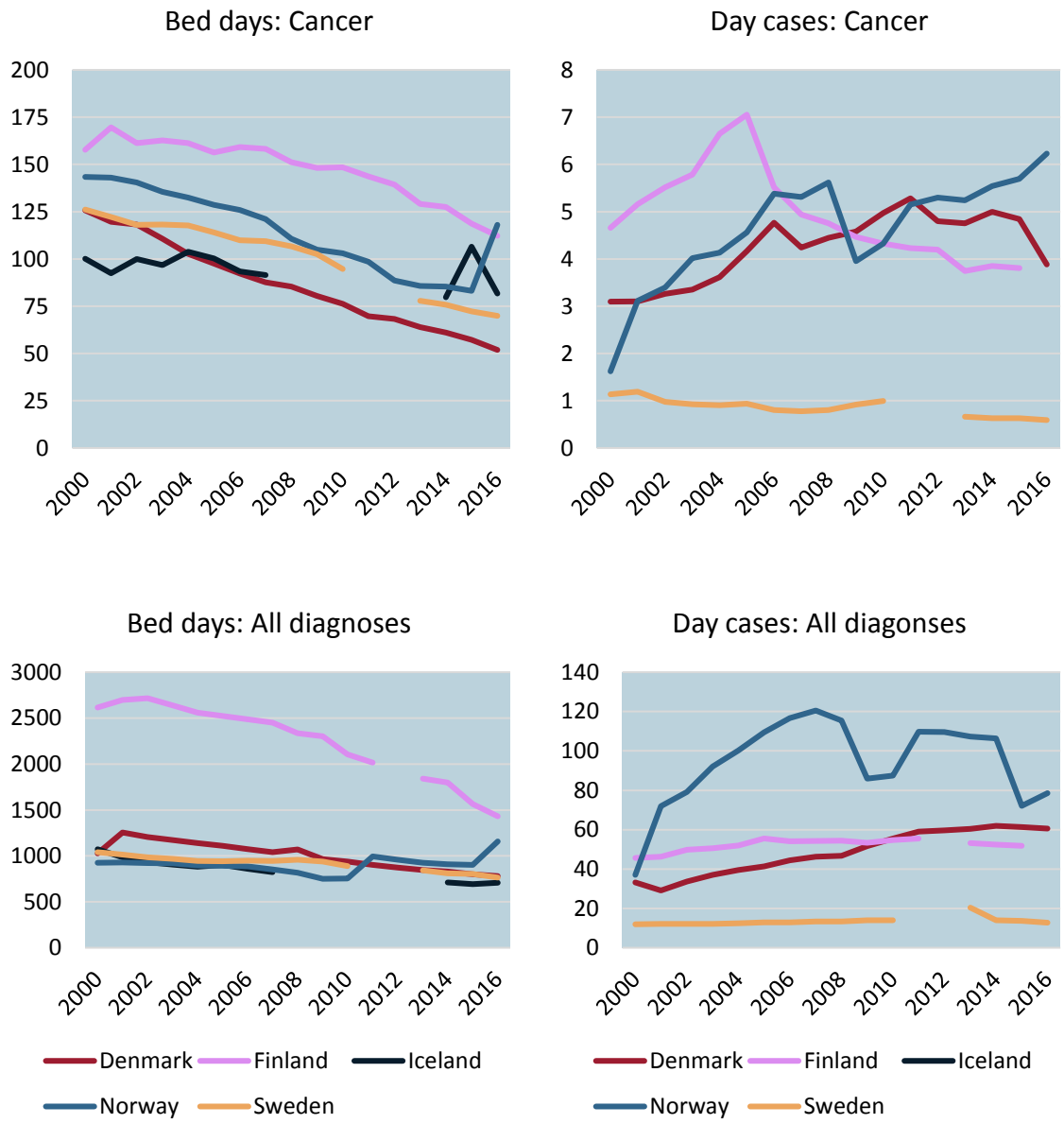

Figure 13: *Bed days spent in hospital per 1,000 inhabitants (left figures) and number of day cases in hospital per 1,000 inhabitants (right figures), 2000–2016 [6, 59, 60]. Notes: "All diagnoses" refers to ICD-10 A00-Z99\V00-Y98+Z38 and "cancer" to ICD-10 C00-D48. There are some breaks in the time series based on changes in the definitions used, which explains for instance the sharp increase in Norway from 2015 to 2016.*

A shifting trend in the composition of the direct costs of cancer solely based on the number of inpatient days should however be interpreted with some caution. A reduction in the number of inpatient days does not automatically imply a decrease in costs of inpatient care, since the cost per inpatient day may have increased. Nonetheless, fewer inpatient days of cancer patients free up hospital beds for other patients.

The shift in the composition of the direct costs in the Nordic countries can be illustrated by the development in Finland. **Figure 14** shows the composition of the direct costs for the years 2004 and 2014 during which the total costs increased from €506 to €775 million (in nominal prices) [48]. Inpatient care was by far the largest cost component in 2004, but its contribution was almost cut in half until 2014. By 2014, ambulatory care provided at hospitals was the largest cost component. In addition, the share of outpatient medications has almost doubled. Other cost categories grew mostly in line with the overall increase in the direct costs.

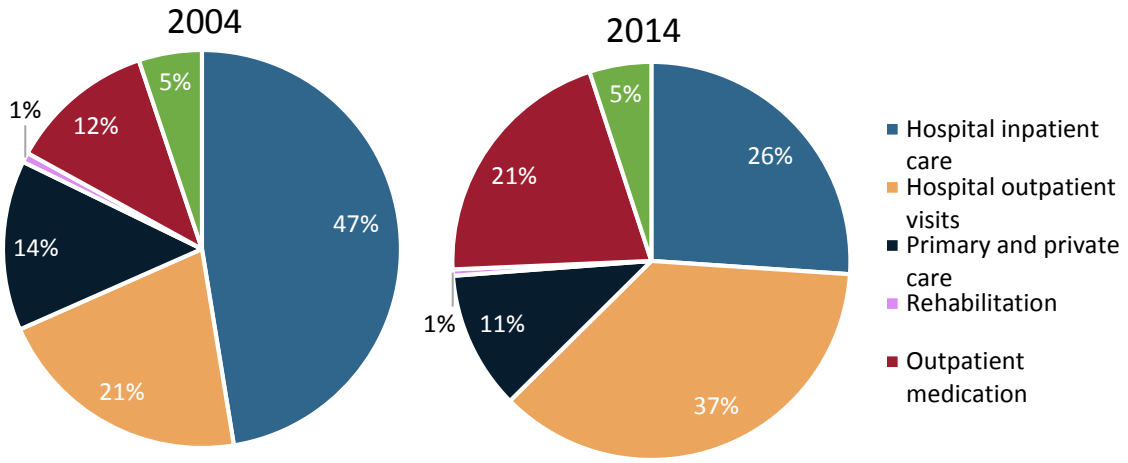

Figure 14: *Composition of the direct costs of cancer in Finland, 2004 & 2014 [48].*

The Finnish development is not unique. Three major trends in the direct costs of cancer have characterized the last two decades [62]. First, the total direct costs have increased, partly driven by the increasing disease burden but also more intensive care and increased overall spending on health (see the previous section). Second, cancer care is shifting more and more from an inpatient setting to an outpatient setting. Inpatient days, which are comparatively expensive, are being partly substituted with outpatient visits, which are comparatively cheaper. This has been made possible through the development of new treatment modalities. Newer cancer medicines with different side effects can more easily be administered in outpatient care (as an intravenous infusion). Oral delivery of cancer medicines has also become more common, which entails more patients receiving treatment at home. Third, the costs for cancer medicines have increased driven by the aforementioned increases in price and use of cancer medicines.

1.5.2 Indirect costs

The indirect costs of cancer are composed of two types of costs. The first type is called productivity loss. Productivity loss due to cancer represents foregone labour market earnings of cancer patients based on three different reasons [35]. First, productivity loss from premature mortality arises from patients who die during working age and who otherwise would have continued to work until

retirement age. Second, productivity loss arises from temporary absence from work (sickness absence) of patients in the labour force who are compelled to take a hiatus from work while receiving treatment and care. Third, productivity loss arises from the permanent discontinuation of work (permanent incapacity/disability) of patients in the labour force who have to quit their job due to the disease and have to retire early. The latter two reasons of productivity loss are usually summarized under the term productivity loss from morbidity.

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

1.5.2.1 Methodology

Even though there is broad agreement on the importance of indirect costs, there is less agreement on the exact methodology to calculate these costs. Two different methodologies are commonly used to calculate the productivity loss; the human-capital method and the friction-cost method. The human-capital method takes the patient's perspective and counts any hour not worked as an hour lost. By contrast, the friction-cost method takes the employer's perspective and counts only those hours not worked as lost until another employee takes over the patient's work [63]. If the human-capital method is used, there is further disagreement about whether public spending on sickness benefits and early retirement/disability benefits should be included in addition to lost labour income, since they only represent so-called transfer payments from the general taxpayer to the cancer patient without altering the use of resources [64]. The choice of the method has an important impact on the size of the indirect costs. If the friction-cost method is used, the estimated costs are typically much smaller than when the human-capital method is used [65, 66].

The assessment of informal care is even more challenging. Even if it were possible to collect data on time inputs from informal caregivers, the valuation or pricing of these time inputs is not obvious; two possibilities are to use minimum wages or mean salary of social care workers. If informal caregivers use their leisure time to provide support (e.g. a retired person supports her spouse) or whether they are compelled to reduce working hours (e.g. a working parent supports his child) has also implications for the value of informal care. It would thus be necessary to know who the informal caregiver is.

In this report, we are forced to limit the analysis of the development of the indirect costs of cancer between 1995 and 2015 to the productivity loss from premature mortality. The main reason for this

restriction is the paucity of consistent data for all Nordic countries on other sources of productivity loss and of informal care. However, as shown in the section on the composition of the indirect costs below, productivity loss from premature mortality represents typically more than half of the indirect costs.

Following the human-capital method, the productivity loss from premature mortality represents the present value of the future earnings that a person who dies could have been expected to receive. Unpaid work such as work at home or volunteering is thus not included in the productivity loss. The first step is to calculate the potential years of working life lost (PYWLL). The working age is assumed to stretch from age 15 to age 64 inclusive. If a death occurs in this age range, it causes a certain number of PYWLL. Information on age-specific cancer deaths in all years and for each country was obtained from NORDCAN [5]. As deaths are grouped into five-year age intervals, all deaths in an age interval are assumed to occur in the middle of that interval. For instance, a death in the age interval 35-39 years is assumed to occur at age 37.5 and result in 27.5 PYWLL (= retirement age of 65 years minus age at death of 37.5 years).[10] The total number of deaths in each age interval is then multiplied with the corresponding PYWLL. Lastly, the PYWLL are summed up over all age intervals. These calculations are carried out separately for men and women as well as for all cancers together and the major cancer types.

Even though PYWLL form the basis of the calculation of productivity loss from premature mortality, there is a general criticism of the approach to count only deaths during working age. While a value is attached to the death of a 15 or 64-year-old person, the death of a 14 or 65-year-old person is disregarded. Moreover, the assumption of a uniform retirement age of 65 years across the Nordic countries and across men and women is imperfect. In Denmark, Finland, and Sweden, the statutory retirement was 65 years and in Iceland and Norway 67 years during most of the considered period (although there are options to retire earlier after certain years of contribution or in exchange of a lower pension), but the effective retirement age has to a greater or lesser extent deviated from the statutory one [67]. As explained above, in the calculations in this report, working age is uniformly defined in each country and all periods. This guarantees a transparent approach and facilitates the interpretation of the results.

In the final step, the PYWLL are combined with annual earnings and adjusted for the employment rate. Sex-specific mean annual earnings from employment for all countries were obtained for the year 2014 [68], and adjusted for inflation to 2015 prices [58], as well as corrected for changes in exchange rates to 2015 levels [69]. Sex-specific employment rates in the age group 15–64 years are applied [70], implicitly assuming a uniform employment rate during the whole age interval. Since

[10] One additional step that is sometimes taken is to correct the PYWLL in each age interval for the general risk of death in each age group to take into account the likelihood of reaching retirement age.

the death of a cancer patient in working age implies the loss of a whole stream of future earnings, the earnings have to be discounted. In line with common practice in health economic evaluation, a 3.5% annual discount rate is applied. A zero real growth rate in future earnings is assumed.

Cancer in this section is defined based on the broadest definition used by NORDCAN, which includes all malignant neoplasms (ICD-10 C00-C97), some in situ neoplasms (D00-D09), some benign neoplasms (D10-D36), and most neoplasms of uncertain or unknown behaviour (D37-D48). As cancer mortality from in situ neoplasms and benign neoplasms is zero (or close to zero), the incomplete inclusion of these types does not impair the comparability with the direct costs of cancer.

1.5.2.2 Results

The development of the total number of PYWLL in the Nordic countries between 1995 and 2015 is shown in **Figure 15**. In 1995, 109,500 PYWLL were lost in me n and women. This number increased slightly until 2000, after which it started to decline. Between 1995 and 2015, the number of PYWLL fell by 27% to 80,300 million PYWLL. This decline occurred despite a growing population in the age range 15-64 years; it increased from 15.5 million people in 1995 by 8.9% to 16.9 million people in 2015 [6]. The reason for the fall in PYWLL is the underlying decrease in cancer mortality. Even though cancer mortality was rather stable in the whole population (see **Figure 1**) between 1995 and 2015, the number of deaths decreased in the age group 15–64 years. This was a result of a shift of deaths towards older ages because of increased survival.

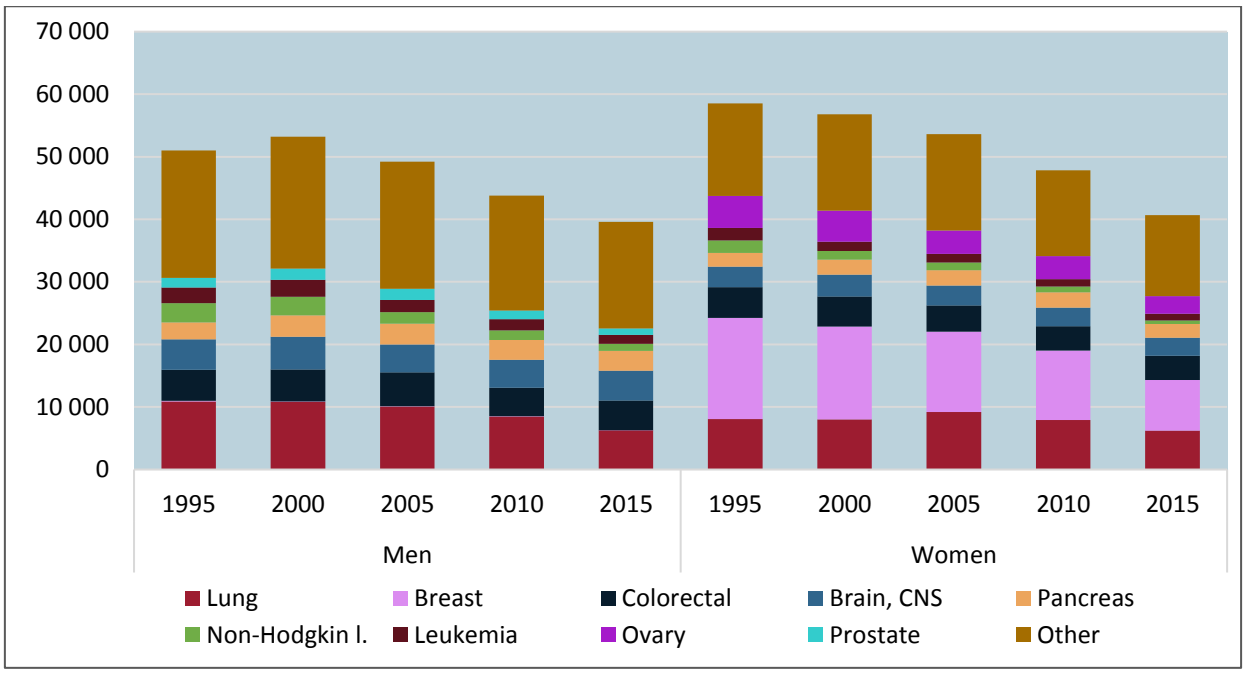

Figure 15: *Potential years of working life lost (PYWLL) due to cancer in the Nordic countries, 1995–2015 [5].*
Note: Cancer is defined as CXX.X+ D09.0-1+D30.1-9+D35.2-4+D41.1-9+D32-33+D42-43+D44.3-5+D45-46+D47.0-1,3-9, lung as C33-34, breast as C50, colorectal as C18-21, brain & central nervous system (CNS) as C70-72+C75.1-3+D32-33+D35.2-4,D42-43,D44.3-5, pancreas as C25, non-Hodgkin lymphoma as C82-86, leukemia as C91-95, ovary as C56,C57.0-4, prostate as C61. Working age stretches from 15 to 64 years inclusive.

Figure 15 also highlights differences in PYWLL between men and women. During the entire period, the number of PYWLL was higher in women than in men, although by 2015 they were almost equally high. This is a reflection of the general pattern that women die of cancer at younger ages than men. This is in turn mostly related to the occurrence of the major cancer types in women (breast cancer) and men (prostate cancer) at different ages. **Figure 15** illustrates this point. While breast cancer caused 28% of all PYWLL in women in 1995, prostate cancer caused only 3% in men in 1995. **Figure 15** also shows that the PYWLL of the nine major cancer types decreased proportionally to the overall trend. One exception is pancreatic cancer, which remained stable. This is related to the lack of improvements in survival in pancreatic cancer during this period.

The overall development in the number of PYWLL on the country level is shown in Figure 16. Finland, Iceland, and Sweden all recorded around 620 PYWLL per 100,000 inhabitants aged 15–64 in 1995. Norway had 680 PYWLL, and Denmark had well over 900 PYWLL as a result of the markedly higher Danish mortality rates; see Figure 4. Until 2015, the population-standardized number of PYWLL decreased in all countries; on average by 33%. The strongest decrease both in absolute and relative terms was observed in Denmark, probably related to the catch-up process of Danish survival rates during this period; see **Figure 6**.

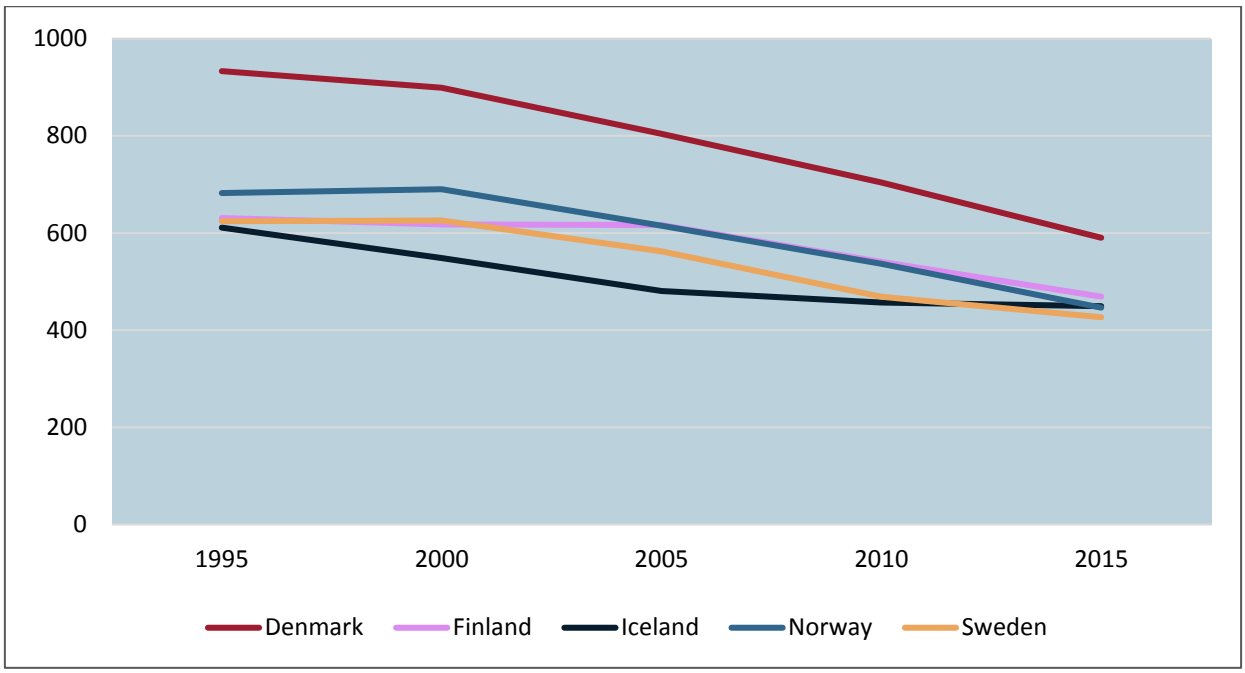

Figure 16: *Potential years of working life lost (PYWLL) due to cancer per 100,000 inhabitants aged 15 to 64, 1995–2015 [5, 6].*
Note: see **Figure 15**.

The development of the productivity loss from premature mortality between 1995 and 2015 in the Nordic countries as a whole is shown in **Figure 17**. The productivity loss amounted to €3,796 million in 1995 and increased by almost €250 million until 2000. Afterwards, it started to decline continuously to €2,927 million in 2015 (all measured in 2015 prices and exchange rates). Over the whole period, the productivity loss declined by 23%. Another observation from Figure 17 is the sex-specific composition of the productivity loss. Throughout the whole period, women's share of the productivity loss is lower than men's share despite their higher number of PYWLL. The two reasons for this pattern are lower earnings and lower employment rates of women than of men in all Nordic countries.

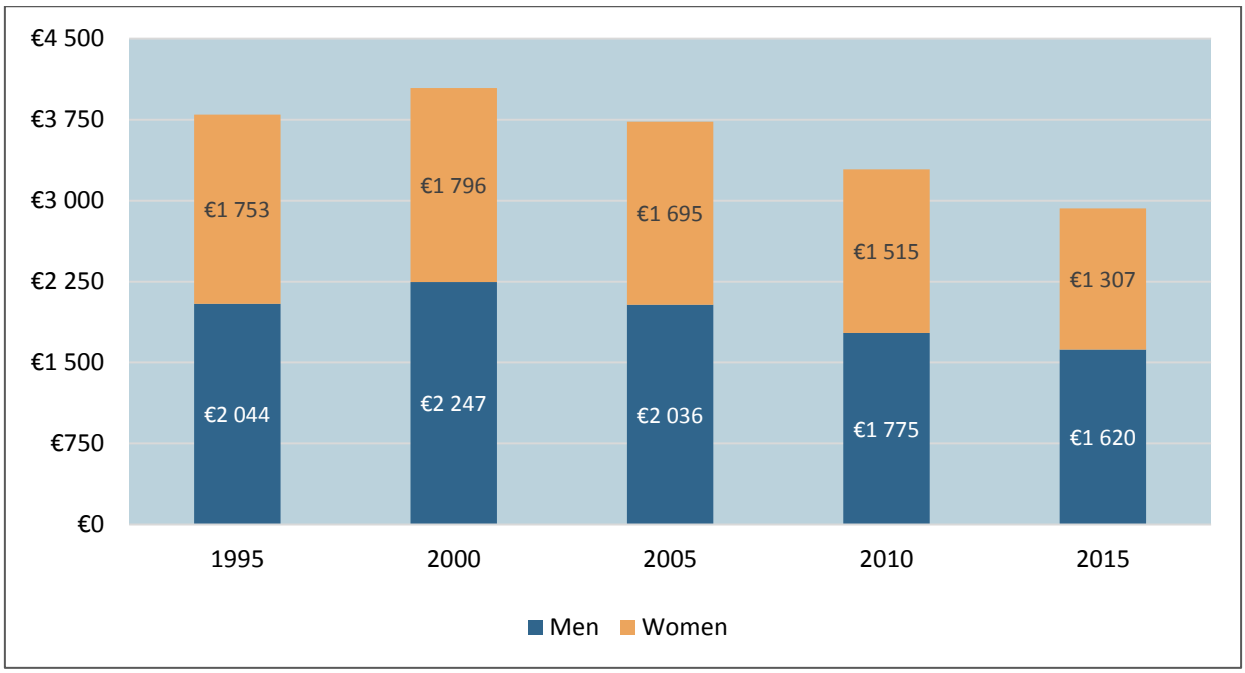

Figure 17: *Productivity loss from premature mortality from cancer in the Nordic countries (in million €; 2015 prices & exchange rates), 1995–2015.*
Note: Earnings in all years are based on 2014 values [68], which have been adjusted for inflation and changes in exchange rates to 2015 levels [58, 69].

To compare the level of the productivity loss from premature mortality across the Nordic countries, **Figure 18** shows the per capita loss measured in euros at 2015 price levels and exchange rates. The overall pattern closely mirrors the development in PYWLL shown in **Figure 16**. In 1995, productivity loss was highest in Denmark with over €250 per capita, and lowest in Finland with €114. Until 2000, productivity loss increased in Norway and remained stable in all other countries. Afterwards, decreases are observable in all countries (in Finland only after 2005). Over the whole period, the strongest decline in both absolute and relative terms was observed in Denmark, and the smallest one in Finland. Yet Finland, together with Sweden, recorded the lowest productivity loss of around €90 per capita in 2015, while in Denmark it was €155.

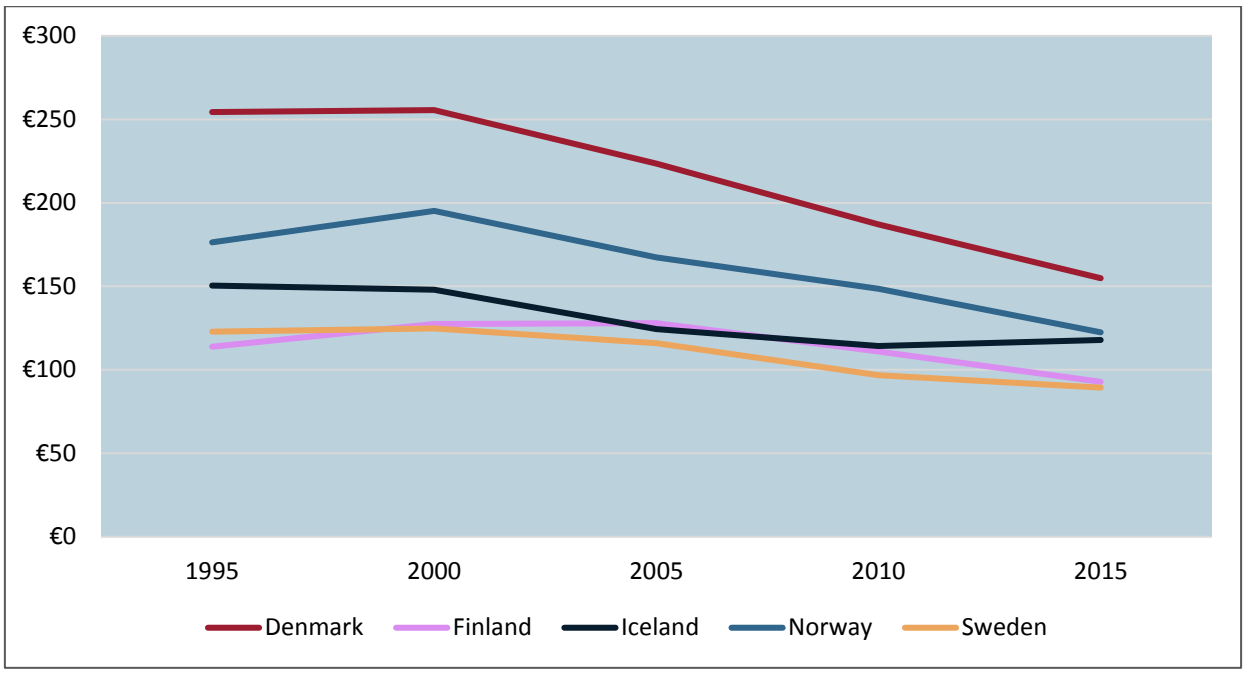

Figure 18: *Productivity loss from premature mortality from cancer per capita (in €, 2015 prices and exchange rates), 1995–2015.*
Note: see **Figure 17**.

1.5.2.3 Composition of the indirect costs

Even though the development of all components of the indirect costs of cancer over time cannot be computed in this report due to data limitations, there is some information available for certain Nordic countries. At least three studies have calculated the indirect costs of cancer in a comprehensive manner by including all three relevant categories. **Figure 19** summarizes the distribution of the cost categories in these studies. The emerging pattern is rather similar in all Nordic countries and years investigated. Productivity loss from premature mortality (calculated based on the human-capital method in all studies) is by far the largest cost category and accounts for more than half of all costs. Productivity loss from morbidity (due to sickness absence and disability benefits in all studies) and costs of informal care each account for about one fifth of the indirect costs. Note however that the productivity loss from morbidity in the estimates for 2009 and 2012 are based on the friction-cost method and the estimate for 2013 on the human-capital method, which limits comparability.[11]

[11] The fact that the share of productivity loss from morbidity is larger in Sweden in 2012 than in 2013 is surprising, as the former is calculated based on the friction-cost method and the latter based on the human-capital method. This is potentially indicative of inadequate use of data in the two European studies estimating the costs for the years 2009 and 2012.

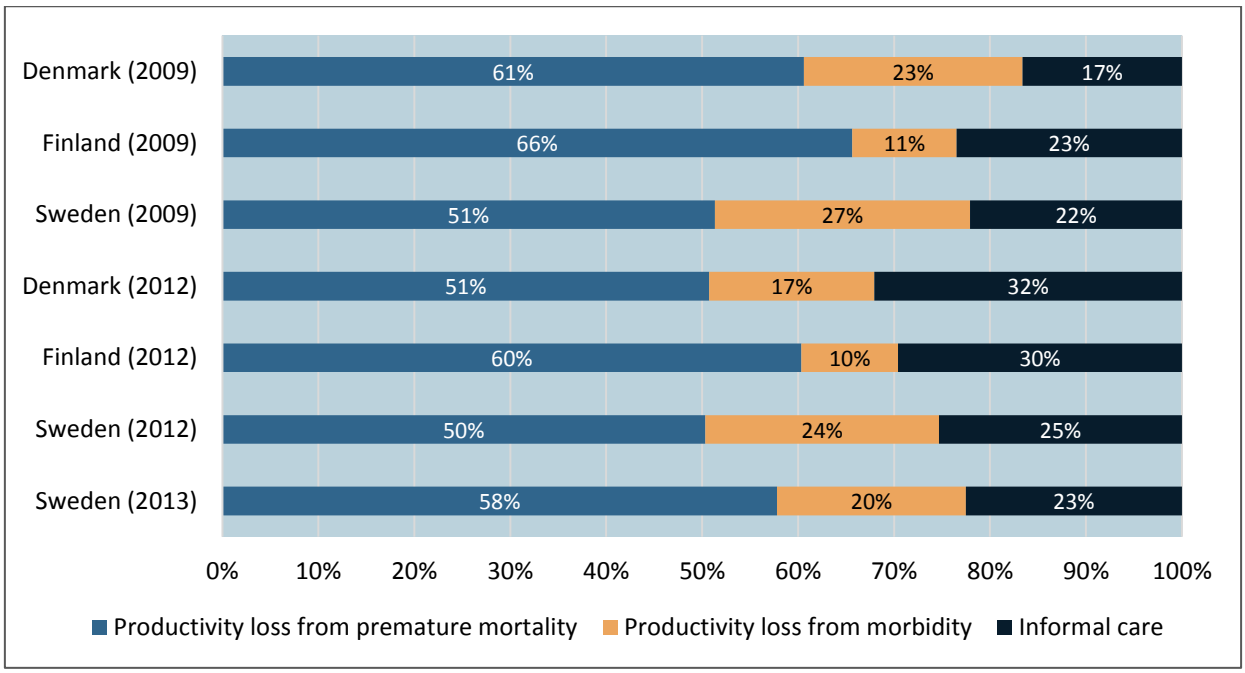

Figure 19: *Composition of the indirect costs of cancer in selected countries in 2009 [71], 2012 [72], and 2013 [51].*
Note: The productivity loss from premature mortality is calculated based on the human-capital method, yet varying definitions of working age and adjustments in the calculation of PYWLL are used. Productivity loss from morbidity is calculated based on the friction-cost method in the estimates for 2009 and 2012, and on the human-capital method in the estimate for 2013.

In the previous section, the development of the productivity loss from premature mortality between 1995 and 2015 was illustrated. The development of the two other cost categories in the Nordic countries is more uncertain. In fact, there seems to be no study that has investigated the development of informal care. By contrast, there is one study for Finland which estimated the productivity loss from morbidity between 2004 and 2014 [48]. It found that expenditure on disability pensions decreased from €80 million to €76 million (in current prices) over this period. Expenditure on sickness benefits increased from €46 million to €58 million. In sum, there was a slight increase in productivity loss from morbidity from €126 to €134 million, but once adjusted for inflation [58], this turns into a 13% decrease from €154 to €134 million (measured in 2014 prices). This happened in spite of an increase in the number of newly diagnosed cases in Finland during this period. Increasing survival rates but also improved quality of life which allows patients to return to work to a greater extent might explain these results.

Based on the results above, the following conclusions about the past and potential future development of the indirect costs of cancer can be drawn:

- While cancer incidence in people of working age (15 to 64 years) has increased by 47%, cancer mortality has decreased by 16% in this age group in the Nordic countries as a whole between 1995 and 2015 [5]. This means that more patients live for longer with the disease. This development is reflected in the reduction of the number of PYWLL from 109,500 to 80,300. As a result, the productivity loss from premature mortality has declined. This trend will continue as long as survival rates in people of working age keep increasing.

- The exact development of productivity loss from morbidity is a bit more uncertain. The sheer increase in cancer incidence in people of working age probably pushed up the expenditure on sickness benefits (as was the case in Finland). Shorter spells of sickness absence due to quicker recovery and fewer side effects of newer treatment modalities might however have moderated this increase. If newer and more effective treatments increase the chances of patients to return to work, this could explain why expenditure on disability pensions did not increase (at least in Finland). Even though cancer incidence is expected to increase further, productivity loss from morbidity might remain stable in the foreseeable future if the treatment of cancer keeps improving.

- Due to a lack of reliable data, the development of informal care is difficult to judge. On the one hand, increased treatment of patients in an ambulatory setting might raise the need of family members and friends to take the cancer patient repeatedly to the hospital. Yet the increase of orally administered cancer medicines enables more patients to receive treatment at home. On the other hand, if increased length of survival entails a prolonged state of being in poor health for some patients, they require (informal) support for a longer time. The fact that the overall number of cancer patients increase also points to potential increases in the need and costs of informal care.

1.5.3 Total costs

Direct costs and indirect costs of cancer represent the economic burden of cancer (the total costs). Thus, the economic burden extends beyond the remit of the health care system. Once a societal perspective is applied, indirect costs arise in addition to direct costs. Ignoring these substantial costs can lead to suboptimal policy decisions from a societal perspective [73].

The economic burden of cancer in the Nordic countries as a whole is summarized in **Figure 20** (total figures) and **Figure 21** (per capita figures). In 1995, the direct costs amounted to €2,558 million (€108 per capita) and were clearly exceeded by the indirect costs solely composed of productivity loss from premature mortality with €3,796 million (or €160). Adding productivity loss from morbidity and informal care costs to the indirect costs would possibly double the size of the indirect costs, which would then dwarf the size of the direct costs. However, in the years until

2015, direct costs and indirect costs developed in opposite ways. Direct costs grew almost linearly and amounted to €5,514 million (€208 per capita) at the end of the period, whereas indirect costs increased until 2000 and then declined to €2,927 million (€111) in 2015. Given that the excluded components of indirect costs are typically smaller than the productivity loss from premature mortality (see **Figure 19**), indirect costs and direct costs might have been equally large in 2015.

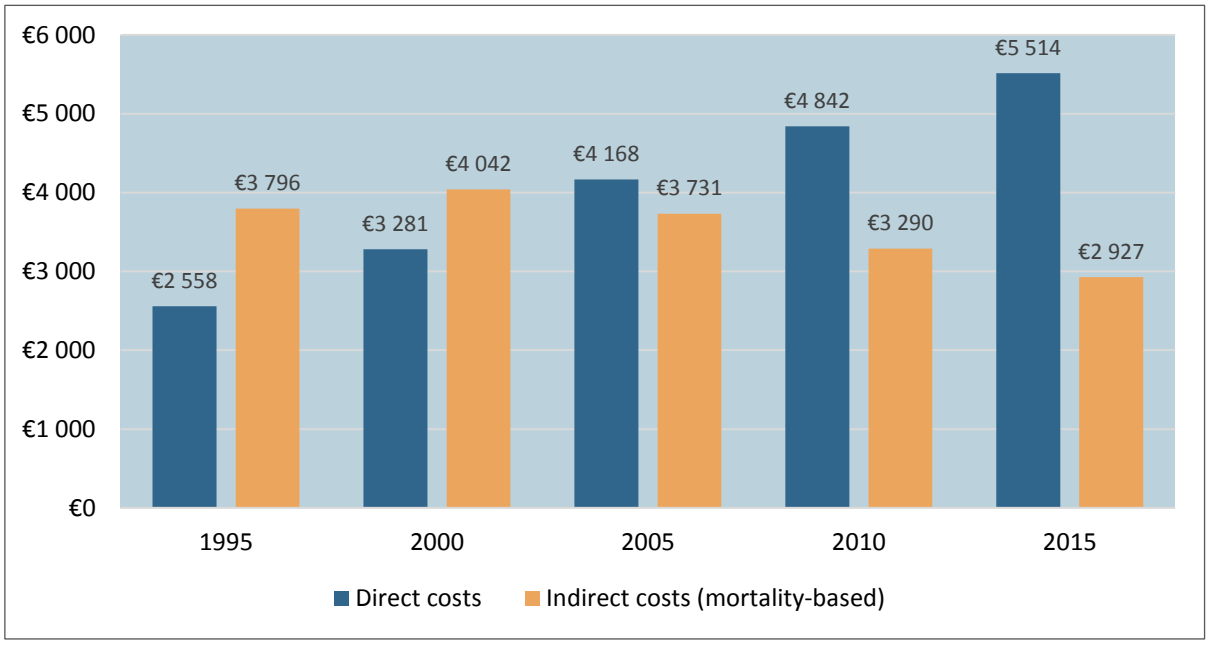

Figure 20: *Economic burden of cancer in the Nordic countries (in million €; 2015 prices & exchange rates), 1995–2015.*

Note: The indirect costs encompass only productivity loss from premature mortality during working age. Cancer includes also some non-malignant neoplasms. See **Figure 10** *and* **Figure 17** *for details on the calculations.*

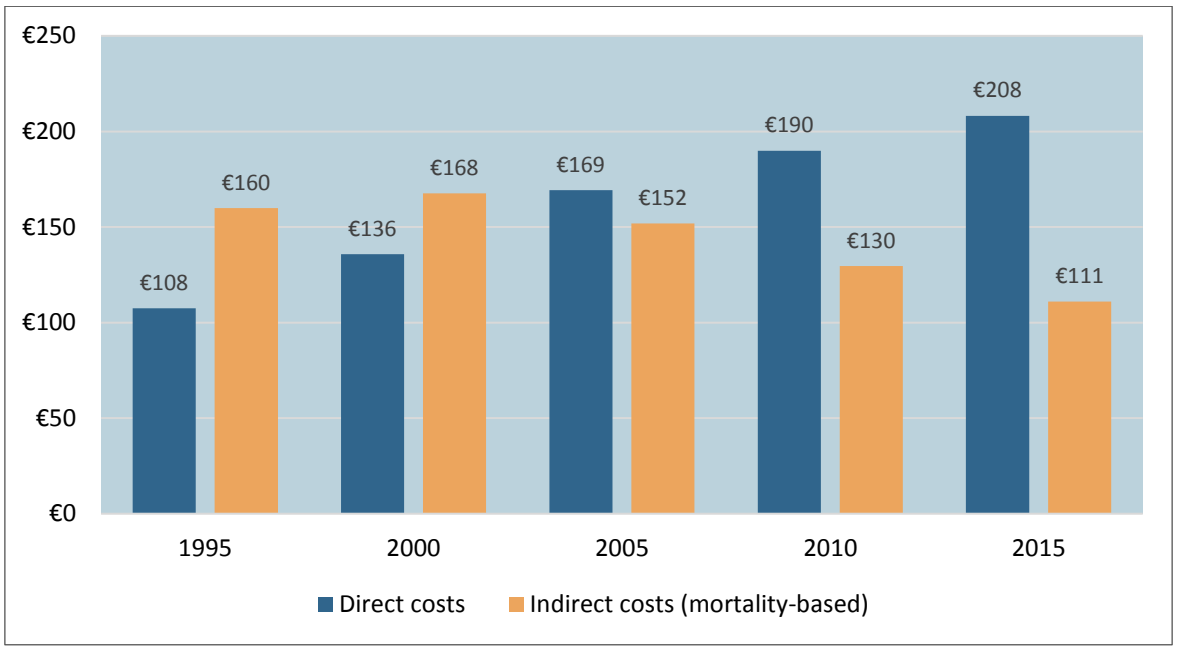

Figure 21: *Economic burden of cancer in the Nordic countries per capita (in €; 2015 prices & exchange rates), 1995–2015.*
Note: see **Figure 20**.

Figure 22 summarizes the economic burden in the five Nordic countries separately. It is evident that all countries experienced a similar pattern between 1995 and 2015. The increase in direct costs was paralleled by a decrease (at least since 2000) in productivity loss from premature mortality. However, there are some striking differences in the level of the economic burden between the countries. The burden is much higher in Denmark (partly related to higher cancer incidence, lower survival rates, and resulting higher mortality) and Norway (partly related to higher purchasing power) than in the other countries. Sweden comes at a distant third place, followed by Iceland. Finland recorded the lowest economic burden throughout the entire period (partly related to having one of the lowest incidences of cancer, one of the highest survival rates, as well as lower purchasing power).

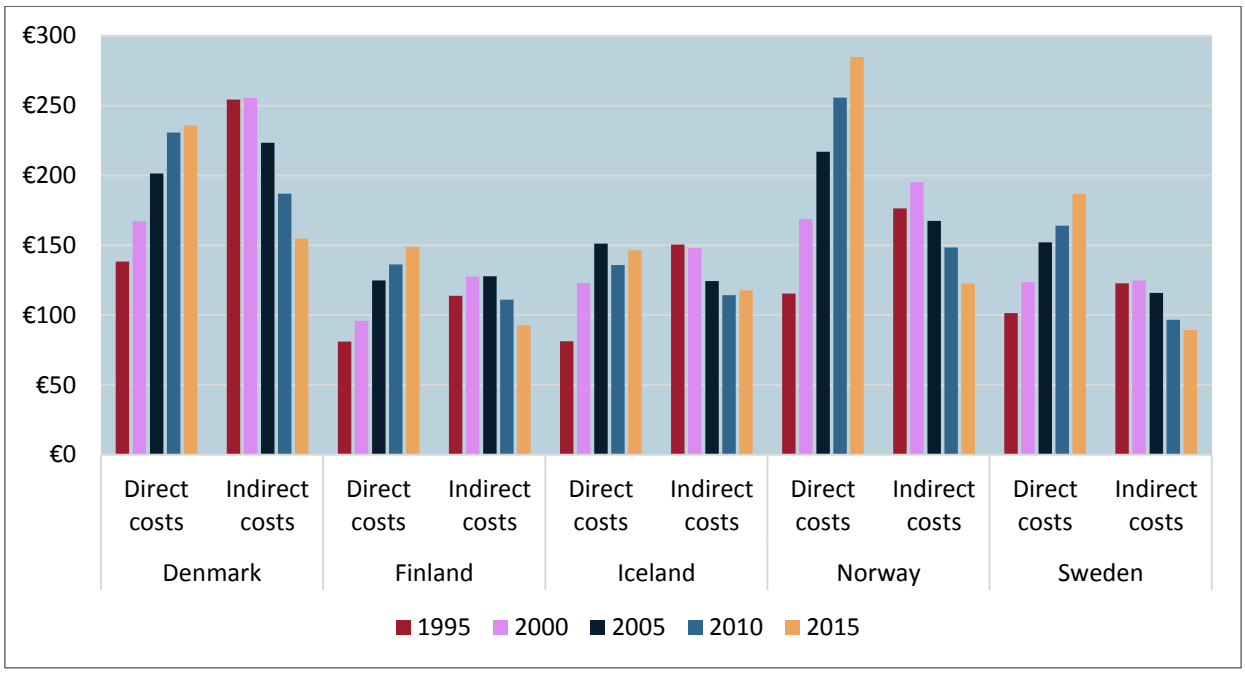

Figure 22: *Economic burden of cancer per capita (in €; 2015 prices & exchange rates), 1995–2015.*
Note: see **Figure 20**.

The results of the economic burden highlight that a focus on the costs of cancer that are borne by the health care system is too narrow. Only considering direct costs, there was an increase of 116% in total costs (94% in per capita) between 1995 and 2015 in the Nordic countries, corresponding to a mean annual growth rate of 3.9% (3.4%). This might seem like a high price to pay. But it should be kept in mind that (1) the increase in costs was paralleled by a 55% (39% in per capita) increase in newly diagnosed patients, and (2) limited evidence shows that health expenditure on cancer grew mostly in line with the overall spending on health care. In particular, the results show that the payoffs from the increased investment in cancer care fell mostly outside the health care system, as witnessed by the 23% reduction (31% in per capita) in productivity loss from premature mortality, corresponding to a mean annual growth rate of -1.3% (-1.8%). Most importantly, patients benefited greatly. While health care spending on cancer increased, a simultaneous increase in the 5-year survival rate from about 55% to 65% was achieved.

1.6 Conclusions

The aim of this chapter was to explore the development of the two key aspects of the burden of cancer (the disease burden and the economic burden) in the Nordic countries over the recent decades. Below, the findings are summarized and some forward-looking conclusions provided based on past trends.

A comparison of cancer with other diseases shows that the disease burden of cancer is high. More than one in four deaths was due to cancer in the Nordic countries in 2015. In Denmark, cancer was the most common cause of death; in the other countries, it was the second most common cause. Measured in DALYs, cancer was the disease group that caused the second greatest burden (19%) after cardiovascular diseases (24%) in the Nordic countries in 2000. In 2015, the disease burden of cancer (20%) exceeded the burden of cardiovascular diseases (17%) owing to significant advances in reducing mortality in cardiovascular diseases.

50,300 cases of cancer were diagnosed in the five Nordic countries in 1960. This number grew steadily in the following decades. In 2015, it had reached 154,800 cases, meaning that cancer incidence had more than tripled over a period of 55 years. Overall population growth during this period explains part of this increase. A more fundamental demographic factor behind this development is population aging. Yet even after taking into account these demographic changes, a marked increase of almost 60% remains in all five countries. An increase in some risk factors related to lifestyle, such as obesity, as well as more extensive screening activities (since the 1990s) offer additional explanations. The positive development in other major diseases, such as cardiovascular diseases, entails more people reaching an advanced age at which the risk of getting cancer is higher. These factors together with the demographic changes will probably make it difficult to achieve a turnaround in the increasing trend of cancer incidence in the near future. A stronger focus on effective primary prevention measures, such as HPV vaccinations for girls and boys, could help to mitigate the expected increase.

Cancer mortality has increased much less between 1960 and 2015 in the Nordic countries. In 1960, there were 35,300 cancer deaths and in 2015, there were 62,000 deaths, corresponding to a 75% increase over a period of 55 years. In per capita terms, mortality has been stable since around 1985 in Sweden and since 1995 also in Iceland. In Denmark and Norway, it has declined after 1995, while in Finland it has kept increasing. After taking into account population aging, cancer mortality has decreased in all Nordic countries except in Norway by on average 15% between 1960 and 2015.

This discrepancy in magnitude of the overall increase in cancer incidence and cancer mortality is reflected by the simultaneous improvement in survival rates. The 5-year survival rates have been almost linearly increasing since 1966 from about 35% to 65% until 2015. Between 1966–1970 and 1981–1985, all countries except Denmark converged in terms of survival rates and had a very similar development until 2015. Denmark was trailing behind the other countries, but started to catch up during the late 2000s.

The cause behind this positive development in survival rates has been attributed to “major advances in cancer management” [20, 21]. The central factors that drove a wedge between the trends in

incidence and mortality are advances in diagnostics and medical treatment. The continued introduction of new and more effective technologies and treatment modalities will reinforce this development. The establishment of standardized care processes (mainly based on the Danish experience) is important to coordinate the use of all resources along the patient pathway. Since the roll-outs of population-based screening programs (for cervical cancer and for breast cancer) in the 1990s, they too contribute in a positive way by detecting more cases at an early stage. The roll-outs of colorectal cancer screening programs (in Denmark since 2014, in parts of Sweden, planned in Norway and discussed in the other countries) will support this development.

The advances in cancer care could not have been achieved without adequate investment into prevention, diagnostics, treatment, and rehabilitation. The total health expenditure spent on cancer care (direct costs of cancer) increased from €2,558 million to €5,514 million in the Nordic countries between 1995 and 2015 (in 2015 prices). This equals a 116% increase, or a mean annual growth rate of 3.9%. In comparison, cancer incidence increased by 55% during this period.

Denmark spent the most on cancer care per capita with €138 in 1995, followed by Norway with €115, Sweden with €101, and Finland and Iceland with €81 each (measured in 2015 prices). Denmark was surpassed by Norway as the top spending country in 2005. In 2015, Norway spent €285 per capita on cancer care, followed by Denmark with €236 and Sweden with €187. The lowest spending countries were again Finland with €149 and Iceland with €146.

Even though health care spending on cancer has been increasing continuously in absolute numbers since 1995, limited evidence from the Nordic countries shows that the rate of the increase was in line with the increase in total health expenditure. Spending on cancer as a share of total health expenditure has remained more or less constant (around 4-5%). This pattern has also been observed in other European countries and in the US. However, total health expenditure increased from around 8% to 10% of GDP between 1995 and 2015. The provision of disease-specific health expenditure data by the national statistical authorities should be a priority for all Nordic countries in order to provide unambiguous evidence on the development of health care costs of all disease groups.

There have been significant shifts in the composition of the direct costs of cancer in recent decades. Historically, direct costs have been dominated by expenditure on inpatient care (irrespective of whether expenditure on cancer medicines administered during the inpatient stay are included or not), accounting for more than half of all costs. During the last decades (at least since 2000), inpatient days of cancer patients have been declining in a process of moving treatment to ambulatory care and treatment at home. This pattern reflects a general trend in health care provision, but it was more pronounced in cancer patients in all Nordic countries.

The shift from an inpatient setting to an outpatient setting means that inpatient days, which are comparatively expensive, are being partly substituted with (repeated) outpatient visits, which are comparatively cheaper. This shift was made possible through the development of new treatment modalities, which can be administered more easily. It also means that the direct costs of cancer are increasingly composed of expenditure on ambulatory care and cancer medicines.

The indirect costs of cancer (composed of productivity loss from premature mortality and from morbidity as well as informal care costs) exceeded the direct costs by far in all Nordic countries in 1995. As opposed to direct costs, many signs point to a decline in indirect costs after 2000. By 2015, indirect costs and direct costs might have been equally large.

The potential decline in the indirect costs stems mostly from a decrease in productivity loss from premature mortality, which is the largest component of indirect costs. As a result of a decline in mortality among patients of working age, it decreased from €3,796 million to €2,927 million in the Nordic countries between 1995 and 2015 (in 2015 prices). This equals a 23% decrease, or a mean annual growth rate of -1.3%. Furthermore, evidence from Finland shows that productivity loss from morbidity (based on sickness absence and disability benefits) might have decreased slightly between 2004 and 2014. More effective treatments, leading to shorter spells of sickness absence due to quicker recovery and fewer side effects, might have given more patients the chance to return to work rather than to retire early. The extent of informal care is not well documented, as it is difficult to study.

The indirect costs must not be forgotten when assessing the economic burden of cancer to society. However, the availability of adequate data to evaluate the size and the development of the indirect costs remains a major challenge. The lack of data is especially serious given that authorities that are responsible for health technology assessment (HTA) in the Nordic countries apply a societal perspective. The inability to estimate indirect cost properly can lead to suboptimal decisions in the design of policy measures to prevent, detect, and treat cancer from a societal perspective.

The economic burden of cancer (the sum of direct costs and indirect costs) is highest in Denmark (partly due to higher cancer incidence, lower survival rates, and higher mortality), closely followed by Norway (partly a result of higher purchasing power). Sweden comes at a distant third place, followed by Iceland. Finland recorded the lowest economic burden between 1995 and 2015 (partly a result of having one of the lowest cancer incidence, one of the highest survival rates, as well as lower purchasing power).

The future development of the economic burden of cancer in the Nordic countries is closely linked to the future development of the disease burden, as the sheer increase in the number of patients

presents a challenge for all health care systems. Further investment in all areas of cancer care – prevention, diagnostics, treatment, rehabilitation – as well as an efficient organization are required to meet this challenge.

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2 Medical review

2.1 Summary

- Cancer treatment today is characterized by a multimodal therapy approach including surgery, radiotherapy and an increasing number of anti-tumour drugs. Optimal care of cancer patients requires multidisciplinary teams; surgeons, radiotherapists, medical oncologists, diagnostic radiologists, pathologists, specialized nurses and psychosocial support.

- Most anti-tumour drugs are introduced in patients with late stage- or metastatic disease. This may lead to improvements in survival, but the magnitude of that effect is seldom known when the drug is first introduced, as surrogate end-points are often used. Effects in late stage disease may translate to increased cure rates in conjunction with surgery or with a curative intent as first-line treatment.

- Anti-tumour drugs are generally cell toxic (kill all rapid growing cells, not only cancer cells), and have often severe side effects. The progress in molecular medicine has led to the development of new agents that target cancer specific cell mechanisms, and generally with less and different toxicity profile. Although, chemotherapy drugs are still the backbone of most drug combinations.

- There has also been an introduction of an increasing number of compounds with a focus on improving the quality of life for patients – supportive drugs.

- Improved diagnostic methods and screening programs have facilitated early detection of tumours, which has led to improved cure rates in some cancer forms.

- The decreased toxicity of new agents, the trend towards oral agents, and the use of supportive drugs have resulted in an increased number of day-care treatments or treatments taken at home.

- It is already possible to predict if a patient is likely to respond to some of the treatments by different molecular markers, and gene/protein expression analyses of tumours will likely improve accuracy in the treatment offered to individual patients.

- New diagnostic tools with functional imaging are increasingly used to evaluate effects of therapy.

- The latest development in cancer treatment is activating the body's own immune system to attack the tumour. This treatment approach has shown important effects in malignant skin melanoma, and has rapidly become standard of care and is studied a number of other tumour types.

2.2 Understanding the biology of cancer cells

The development of invasive cancer is a process with many steps, with an accumulation of genetic changes occurring over a long time period (5-20 years). There are extremely many genetic changes in cells in our body every day, but they are stopped by the cells own protection systems. The requirement for a cell to change into a cancer cell is a combination of many events happening at the same time [1].

Intense research has increased knowledge about the human cell and its molecular mechanisms, and medical oncology entered a new phase in the 21st century with new drugs targeting different molecular markers. The progress in molecular medicine has led to increased understanding of cancer evolution and cancer cells characterization and defects in DNA repair mechanisms. Furthermore, increased knowledge of cancer biology has reduced use of highly cell-toxic treatments (targeting all fast dividing cells) and increased use of agents, targeting specific proteins/pathways in the cell [1].

Today, the main areas of drug mechanisms of action in oncology:

1. Targeting of the cell cycle and apoptosis, DNA replication/transcription and repair
2. Inhibition of hormones, growth factors and cell signalling pathways
3. Inhibition of angiogenesis
4. Immunotherapy

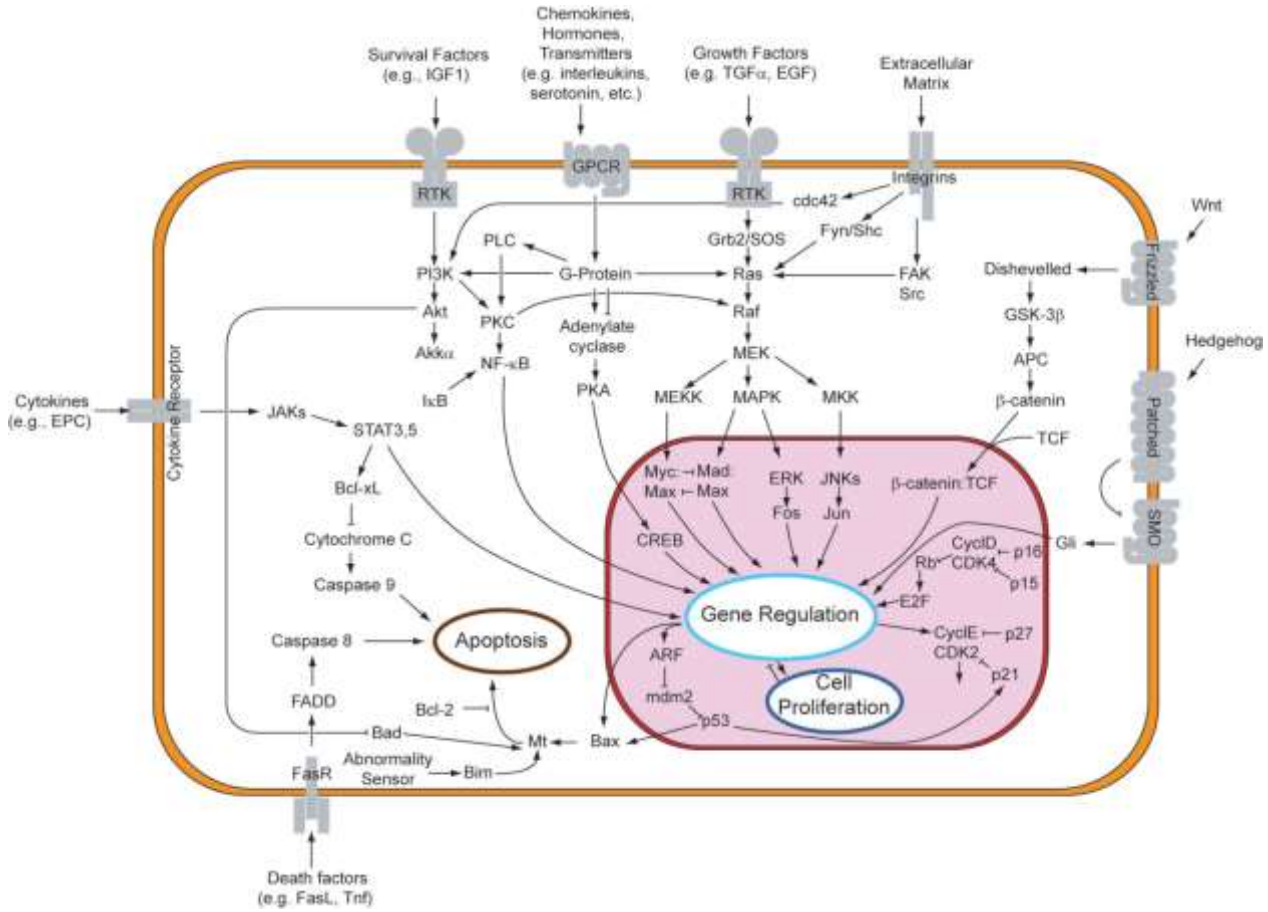

Figure 23: *Simplistic cell signalling pathways [1].*

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

Most chemotherapeutic agents act by inhibiting DNA replication. Although, the mechanisms of action of some older chemotherapeutic agents still remain unclear.

Alkylating agents were the first in use (binding to the DNA strand) already after the second world war. This drug is still in use in many solid cancer forms as breast cancer, and ovarian carcinoma, as well as in haematological malignancies.

In 1984, it was shown that anthracyclines, one of the most effective class of compounds in conventional chemotherapy at the time, worked by inhibiting topoisomerase activity (DNA strand binding). This discovery started the work of finding other agents with similar mechanisms of action. In the 1990-ies, the topoisomerase inhibitors irinotecan and topotecan were introduced with significant clinical impact in – for instance – colorectal cancer (CRC) [2].

During the 1990-ies the role of microtubules (mitotic spindle) in cell division, proliferation and chemotaxis made way for several new agents; taxans (paclitaxel and docetaxel), and vinca alkaloids (vinblastine, vincristine, and vinorelbine), both derived from plant toxins. Since their introduction in the 1990ies, these agents have increased the survival in a variety of cancers as breast cancer, ovarian cancer, and lung cancer [3].

Antimetabolite agents are also important drugs (inhibition of RNA/DNA synthesis), e.g. gemcitabine in pancreatic and lung cancer, and pemetrexed in lung cancer. Capecitabine is an antimetabolite in an oral formulation, with a wide range of indications in mainly solid tumours, making it possible to take the treatment at home [4, 5].

The major challenge with chemotherapy drugs is the side effects. As they target all fast dividing cells, e.g. intestine, hair, bone marrow, they can cause severe unwanted symptoms. This is one of the reasons why the focus is to develop drugs targeting only cancer cells.

2.4 Targeting hormones, growth factors, and cell signalling pathways

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

The endocrine drugs were the first treatments with a molecular target. They interfere with the production of hormones or block the relevant receptor and has become cornerstones in the treatment of both breast- and prostate cancer.

Tamoxifen, acting by blocking oestrogen receptor stimulation in cells, was the first hormonal drug to be widely used in breast cancer. Since its introduction in the 1970-ies, tamoxifen has proved valuable in the treatment of metastatic breast cancer, as well as for adjuvant treatment after surgery, tamoxifen decreases the risk of relapse with 50%, and provide a long-term effect on survival. The efficacy and relatively low toxicity of tamoxifen has led to the development of a new class of hormonal agents for the treatment of hormone sensitive breast cancer; aromatase inhibitors, blocking the non-ovarian oestrogen synthesis, are used in post-menopausal women (e.g. anastrozole, letrozole and exemestane). Other agents as selective estrogen receptor modulator, SERM provide valuable therapeutic options for metastatic breast cancer patients. In premenopausal women blocking of ovarian function is important. This can be achieved by radiotherapy or medical treatments. Gonadotrophin releasing hormone analogues (downregulating hypothalamic stimulation of pituitary glands), GnRH (e.g. goserelin, leuprolide), are used to achieve chemical castration [6-12].

In prostate cancer, anti-androgens (e.g. flutamide, bicalutamide and nilutamide) are alternatives to testicular ablation. Additionally, gonadotrophin releasing hormone analogues (downregulating hypothalamic stimulation of pituitary glands), GnRH (e.g. goserelin, leuprolide), are used to achieve chemical castration. The latest development in prostate cancer includes drugs that block the intra-tumoral synthesis of androgens in patients with hormone refractory disease. These drugs, abiraterone and enzalutamid, approved in patients progressing on first line chemotherapy (docetaxel) and in patients developing hormone refractory disease [13-15].

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

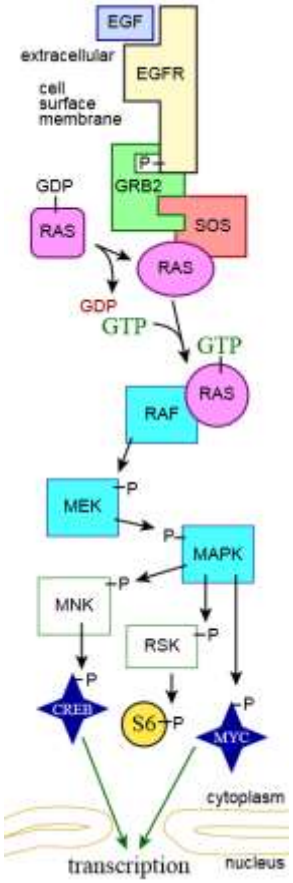

Figure 24: *EGFR signal transduction pathway.*

There are two main groups of agents that have demonstrated efficacy in interfering with growth factor signalling; monoclonal antibodies, and small molecules blocking the receptor and/or tyrosine kinases, the first step in most signal transductions. Cetuximab, a monoclonal antibody developed against EGFR, has demonstrated efficacy in metastatic Colo-Rectal-Cancer, CRC by increasing time to disease progression. In combination with radiotherapy, cetuximab has also demonstrated efficacy in patients with advanced head and neck tumours. The EGFR targeting drug erlotinib has demonstrated efficacy and increased survival as monotherapy in NSCLC, and gefitinib has demonstrated efficacy in a subset of patients with the same disease. Panitumumab is also a monoclonal antibody directed against EGFR, although the effect is only seen in a subpopulation of patients with a non-mutated version of the oncogene KRAS, wild type, wKRAS. Cetuximab has the same restricted indication in CRC [16-18].

B-raf is a protein kinase in the MAP kinase/ERKs signalling pathway, which affects cell division, differentiation, and secretion. B-raf is mutated in around 50% of metastatic melanoma patients. B-raf is the target for the inhibitors vemurafenib and dabrafenib. Response rates are very high (50-80%). Treatment with the monoclonal antibody trastuzumab directed against HER2 led to marked prolonged survival in metastatic breast cancer. Adjuvant treatment with trastuzumab results in an approximately 50% reduction in recurrence rates in patients with HER2-positive breast cancer. The dual HER2 blockade with trastuzumab and pertuzumab has been shown to be superior to trastuzumab alone has become standard of care. Trastuzumab – emtansine, T-DM1 (monoclonal antibody linked with a strong cytotoxic agent) is used for the treatment of metastatic breast cancer. Lapatinib, a small molecule interaction with both HER2 and EGFR (HER1) is also in clinical use in some metastatic breast cancer patients [19-23].

Chronic myeloid leukaemia (CML) was the first malignant disease, for which a characteristic genetic abnormality was described, the Philadelphia chromosome. In the 1980ies, the genetic alteration was identified as the BCR-ABL fusion gene and the protein it encodes was established as the cause of activation of CML. Imatinib, an agent inhibiting BCR-ABL activity, results in complete responses in 80% of patients. Unfortunately, resistance to imatinib is common, but sensitivity to imatinib can be restored (14 of the 15 resistance mechanisms described). For patients with tumours resistant to imatinib there are new therapeutic options (BCR-ABL inhibition) including dasatinib and nilotinib. These drugs are also approved as first line treatment. Imatinib inhibits another cell enzyme, C-KIT, which is mutated in 95% of patients with gastrointestinal stromal tumours (GIST). Treatment with imatinib results in long-lasting tumour regression and has been an enormous step forward, since GIST does not respond to other treatments [24-30].

The agents that inhibit growth factors and their signal transduction pathways represent a new class of anti-tumour agents and their place in the clinical setting continues to evolve. In some cases, like GIST and renal cell cancer (RCC), for which there are no active chemotherapy alternatives, they

are first-line options. In other tumour forms research is ongoing. Data support the concept of combining growth factors with radiotherapy and chemotherapy and combining agents inhibiting different pathways (e.g. bevacizumab [targeting VEGF] in combination with erlotinib [targeting EGFR] in both renal and non-small-cell lung cancer). However, the additive value of combining drug therapies that target the same pathway or sequential use of these drug therapies is uncertain. Although, in breast cancer the use of dual HER2 blockade (targeting different sites of HER2) with trastuzumab and pertuzumab is now standard of care [21, 31, 32].

Another key challenge with growth factors, as with conventional chemotherapy, is to predict responders. The clinical trials and initial introduction of gefitinib illustrate the complexity of clinical trials in different patient populations, the value of continued follow-up, and the potential of today's biological research. The first studies of gefitinib in lung cancer indicated high response rates in the Japanese population that subsequently were not consistently seen in other patient populations. Further analyses indicated that certain subgroups (non-smokers, female patients with tumours of particular histological characteristics) were more likely to respond to treatment. Genetic analysis identified mutations in EGFR in lung cancer patients correlating to response to gefitinib [31, 34].

Other drugs are vemurafenib and later dabrafenib introduced in BRAF mutated malignant metastatic skin melanomas, with 50-80% tumour regression and 20% progression free at 3-years follow-up [19, 35].

Table 6: *Monoclonal antibodies for use in oncology (SEP 2018)*

Generic name	Trade Name	Indication
Alemtuzumab	Campath/MabCampath	CLL
Bevacizumab	Avastin	CRC
Brentuximab vedotin	Adcetris	Hodgkin lymphoma
		Anaplastic large cell Lymphoma
Blinatumumab	Blincyto	Acute Lymphatic Leukemia
Cetuximab	Erbitux	CRC
Denosumab	Xgeva	Giant cell tumor of the bone
Demileukin	Ontak	Skin Lymphoma
		Bone event prevention in cancer
Gemtuzumab	Mylotarg	AML
Ibritumomab tiuxetan	Zevalin	Non-Hodgkin's lymphoma
Ipilimumab	Yervoy	Malignant Melanoma
Obinutuzumab	Gazyva	CLL
Ofatumumab	Arzerra	CLL
Panitumumab	Vectibix	CRC (KRAS wild type)
Panitumumab	Vectibix	CRC
Pembrolizumab	Keytruda	Malignant Melanoma
Pertuzumab	Perjeta	Breast Cancer

Ramucirumab	Cyramza	Gastric cancer or Gastroesophageal junction (GEJ) adenocarcinoma
Rituximab	MabThera	NHL
Dinutuximab	Unituxin	Neuroblastoma
Tositumomab	Bexxar	Non-Hodgkin's lymphoma
Trastuzumab	Herceptin	Breast cancer
Trastuzumab-emtansine	Kadcyla	Breast cancer

2.5 Inhibiting angiogenesis

The development of new blood vessels, angiogenesis, is an important normal physiological function, especially during pregnancy, growth, inflammation and wound healing. The regulation of angiogenesis is complex, with stimulating and inhibiting factors that are kept in balance under normal conditions. Tumours will not grow beyond 1-2 mm without the development of blood vessels. In addition, autopsies have shown that many elderly patients have small, early-stage cancers (such as of the thyroid gland, breast and prostate). The point at which the tumour starts producing pro-angiogenic factors (angiogenic switch) is believed to be one of the most important steps in transforming these dormant tumours into rapidly growing tumours with metastatic potential [45].

Several growth factors are involved in angiogenesis but VEGF has been identified as the most important. Both monoclonal antibodies targeting VEGF receptor and tyrosine kinase inhibitors targeting the VEGF pathway have been developed. Bevacizumab, a monoclonal antibody against VEGF, has increased survival rates in patients with metastatic CRC and lung cancer. Preliminary data indicated an effect in breast cancer, and the drug was approved both in the US and in the EU for metastatic breast cancer. The US approval was later withdrawn, as progression free survival could not be translated into improved overall survival and the risk benefit balance [37, 38].

In renal cancer bevacizumab has extended the period of stable disease. Recent studies have also shown efficacy of bevacizumab in ovarian and cervical carcinoma. Bevacizumab represents an important breakthrough in cancer therapy as it is the first agent in this new class of drugs showing efficacy in a range of tumours. Two agents sorafenib and sunitinib malate, inhibiting tyrosine kinase in the VEGF pathway, have demonstrated efficacy in a variety of tumours, as metastatic CRC and GIST. Furthermore, continuous low-dose chemotherapy (rather than the conventional high-dose intermittent dosing) has effect on tumour angiogenesis [39-43].

As with other new classes of drugs, the place for anti-angiogenesis treatment in the management of cancer is evolving. The ability to predict responders to treatments is an interesting question. Initial studies, using anti-angiogenesis treatment combined with conventional chemotherapy have led to varied results, mostly indicating an additive value of such combination.

In the 1970s, the hybridoma technique enabled mass production of antibodies with a single binding site. The first clinical trials were conducted using murine antibodies (from mice) targeting tumour cell surface structures (antigens). Unfortunately, the results did not meet the expectations, largely because of low target specificity of the antibodies. The development of antibodies with major parts of the molecule of human origin and only the binding fraction being murine (humanised antibody) has overcome these problems. The high specificity and, in general, low toxicity of the monoclonal antibodies makes them attractive therapeutic options [44].

2.6 Immunotherapy

The stimulation of immune system responses has long been a promising approach of cancer therapy. Although, immunotherapeutic drugs provided very limited clinical effect. In years 2010-2011 a revolution in the treatment of metastatic malignant skin melanoma was seen with the approval of the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibitor ipilimumab. The CTLA-4 receptor inhibitors block the natural immunological response to tumours. The drug induces durable responses and long-term overall survival. A large pooled overall survival analysis of >1800 ipilimumab-treated patients showed a plateau in the overall survival curve at ~3 years, with follow-up to 10 years. Median overall survival values and 1-year overall survival are consistent with phase 3 trials in real-world observational studies. These data have established ipilimumab as a standard of care for melanoma. Another new aspect of treatment with immuno-oncology agents is the novel adverse event profile as compared with targeted therapies. Ipilimumab may induce certain severe immune related side effects like colitis and pituitary dysfunction. Still, ipilimumab represents the first breakthrough in the now very rapidly expanding area of immuno-oncology [45].

In 2015 a new class of drugs blocking Programmed cell death protein 1/ Programmed cell death protein ligand 1 (PD -1, PD-L1) was approved (PD-1: pembrolizumab, nivolumab, PD-L1: atezolizumab, avelumab, aurvalumab). The PD-1 inhibitors activate the immune system to attack tumours. PD-1 drugs are approved in the EU for melanoma and NSCLC adenocarcinoma, as well as for renal cancer, and urothelial carcinoma [46].

An important benefit of using an immuno-oncology approach to treatment is that these agents target the immune system and not the cancer, and therefore have the potential of adaptable and durable control across a variety of tumour types. The downside with the immune regulating agents is the side-effect panorama. They are difficult to foresee, as the reactions related to the immune system may be very variable. The side-effects may also be severe. Combinations could have even more difficult side-effects [47, 48].

2.7 Companion diagnostics

Receptors and genes or proteins can be determined with different diagnostic tests, thereby making testing of patients an important step in eligibility for treatment. The proportion of patients with a positive status is for BRAF 50% in metastatic melanoma, for EGFR 10-35% (depending on ethnicity) in NSCLC, for wKRAS 50% in CRC, and for HER2 15% in breast cancer. No other patient is expected to respond to therapy. The importance of companion diagnostics can be illustrated by HER2 positive breast cancer and trastuzumab treatment. In an interesting comparison between treating only patients with HER2 positive breast cancer with trastuzumab versus treating an unselected patient population, 23,586 breast cancer patients would have been required to detect similar survival differences in the studies instead of the 469 patients included in the pivotal studies. There are some important aspects related to use of companion diagnostics for selection of patients for a certain treatment. The technical aspects relate to sensitivity and specificity of methodologies and cut-off levels. The methods may change over time as knowledge increases, and cut-off levels may change. Other aspects are tumour heterogeneity and retesting of recurrences [49-52].

With the expanding treatment possibilities, the aspects of companion diagnostics will become even more important. A drug without a test may not be used (risk of over treatment). A test without a drug must provide prognostic information.

2.8 Orphan drugs

As the number of treatment possibilities will increase, the number of patients in need of treatment will be reduced. Thus, many indications in oncology have rare disease status. The term is defined as generally meaning fewer than 1 in 2,000 people. Below is a list of orphan drugs in oncology.

There are some important aspects in relation to the approval of orphan drugs:

- The required number of patients in clinical studies
- Only Phase II data required
- Short follow-up

Table 7: *Non-targeted orphan drugs in oncology (SEP 2018)*

Generic name	Trade Name	Indication
6-mercaptopurine monohydrate	Xaluprine (previously Mercaptopurine)	ALL in adults, adolescents and children
Azacitidine	Vidaza	Intermediate-2 and high-risk myelodysplastic syndromes (MDS), acute myeloid leukaemia (AML)
Decitabine	Dacogen	AML

histamine dihydrochloride	Ceplene	AML
Lenalidomide	Revlimid	MM, MDS
Mifamurtide	Mepact	Children, adolescents and young adults osteosarcoma
Nelarabine	Atriance	T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL)
Olaparib	Lynparza	BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer
Pomalidomide	Imnovid (previously Pomalidomide Celgene)	MM
Thalidomide	Thalidomide Celgene (previously Thalidomide Pharmion)	MM
Trabectedin	Yondelis	Advanced soft-tissue sarcoma, ovarian cancer.

Table 8: *Targeted drugs in oncology (SEP 2018)*

Generic name	Trade name	Drug class	Target	Orphan drug status
Afatinib	Gilotrif	Small molecule	EGFR (HER1), HER2	
Aldesleukin	Proleukin	Cytokine	IL2	
Alemtuzumab	Campath	Antibody	CD52	
Axitinib	Inlyta	Small molecule	KIT, PDGFRβ, VEGFR1/2/3	
Belinostat	Beleodaq	Small molecule	HDAC	
Bevacizumab	Avastin	Antibody	VEGF	
Bortezomid	Velcade	Small molecule	Proteasome	
Bosutinib	Bosulif	Small molecule	ABL	Yes
Brentuximab vedotin	Adcetris	Antibody	CD30	Yes
Cabozantinib	Cometriq	Small molecule	FLT3, KIT, MET, RET, VEGFR2	Yes
Carfilzomib	Kyprolis	Small molecule	Proteasome	
Ceritinib	Zykadia	Small molecule	ALK	
Cetuximab	Erbitux	Antibody	EGFR	
Crizotinib	Xalkori	Small molecule	ALK, MET	
Dabrafenib	Tafinlar	Small molecule	BRAF	
Dasatinib	Sprycel	Small molecule	ABL	Yes
Denosumab	Xgeva	Antibody	RANKL	
Dinutuximab	Unituxin	Antibody	Glyco lipid GD2	Yes
Erlotinib	Tarceva	Small molecule	EGFR (HER1)	
Everolimus		Small molecule	mTOR	
Gefitinib	Iressa	Small molecule	EGFR (HER1)	
Ibritumomab tiuxetan	Zevalin	Antibody	CD20	
Ibrutinib	Imbruvica	Small molecule	BTK	Yes
Idelalisib	Zydelig	Small molecule	PI3K	
Imatinib	Glivec	small molecular drug	bcr-abl, ckit	
Ipilimumab	Yervoy	Antibody	CTLA-4	
Lapatinib	Tykerb, Tyverb	Small molecule	HER2, EGFR (HER1)	
Nilotinib	Tasigna	Small molecule	ABL	Yes

Generic name	Trade name	Drug class	Target	Orphan drug status
Lenvatinib	Lenvima	Small molecule	Multiple kinase inhibitor	Yes
Obinutuzumab	Gazyva	Antibody	CD20	Yes
Ofatumumab	Arzerra, HuMax-CD20	Antibody	CD20	Yes
Olaparib	Lynparza	Small Molecule	PARP inhibitor	Yes
Panitumumab	Vectibix	Antibody	EGFR	
Pazopanib		Small molecule drug	VEGFR, PDGFR	
Pembrolizumab	Keytruda	Antibody	PD-1	
Pertuzumab	Perjeta	Antibody	HER2	
Ponatinib	Iclusig	Small molecule	ABL, FGFR1-3, FLT3, VEGFR2	Yes
Ramucirumab	Cyramza	Antibody	VEGFR2	Yes
Regorafenib	Stivarga	Small molecule	KIT, PDGFRβ, RAF, RET, VEGFR1/2/3	
Rituximab	Rituxan, Mabthera	Antibody	CD20	
Romidepsin	Istodax	HDAC inhibition	HDAC	
Sipuleucel-T	Provenge	Immunostim	Immune system	
Sorafenib	Nexavar	small molecular drug	VEGFR, PDGFR	Yes
Sunitinib	Sutent	Small molecule	VEGFR, PDGFR	
Temsirolimus	Torisel	Small molecule	mTOR	Yes
Tositumomab	Bexxar	Antibody	CD20	
Trametinib	Mekinist	Small molecule	MEK	
Trastuzumab	Herceptin	Antibody	HER2	
Vandetanib	Caprelsa	Small molecule	EGFR (HER1), RET, VEGFR2	
Vemurafenib	Zelboraf	Small molecule	BRAF	
Vismodegib	Erivedge	Small molecule	PTCH	
Vorinostat	Zolinza	HDAC inhibition	HDAC	
Ziv-aflibercept	Zaltrap	Antibody	PIGF, VEGFA/	

2.9 Survival analyses

Many studies in oncology focus on short term follow-up and therefore use surrogate end-points as recurrence-free survival (RFS) or progression-free survival (PFS). In some cases, this may be useful, but in many other instances these measures do not translate to overall survival. Thus, it is important to start follow-up studies directly after drug approval.

The main end-point for any/all clinical studies is survival (overall survival, OS). In oncology, this is – of course – extremely important. As OS takes many years to achieve in a clinical study, progression free survival (PFS) is often used as a surrogate end-point for OS. Actually, the FDA in the US has accepted PFS in some instances (REF). Many of the new drugs aim at small and targeted populations, which makes the end-point OS even more difficult to achieve.

The use of PFS is controversial, as the date of death is exact, but the date of progression is subject to measurement error and other forms of bias, and the timing of measurements may result in an

artifactual difference in progression dates in clinical trials [80]. This was already discussed after the Vietnam war, and was called the McNamara fallacy, named after secretary of state at that time, Robert McNamara. The McNamara fallacy is regarded as a measurement of whatever can be easily measured and disregard which can't be easily measured or presume that what can't be measured easily really isn't important or doesn't exist [81].

If PFS is used as the only measurement of efficacy, and the OS isn't improved, patients may be treated in vain at the cost of severe side-effects, forgetting what is most important to patients; quality of life and survival (the McNamara fallacy principle).

2.10 Advances in diagnostic techniques

Radiology has come to play a key role in oncology, not only as a diagnostic tool but also as a method of evaluating efficacy of treatment by measuring progression or regression of tumours and metastatic lesions. The introduction of new radiological methods in the 1980ies and 1990ies; Computerized Tomographic Scanning (CT) and Magnetic Resonance Imaging (MRI) have greatly improved the diagnostic accuracy. Ultrasound is useful for screening purposes and bone scintigraphy provides an overall picture of bone. Currently, Positron Emission Tomography (PET) in combination with CT (PET/CT) is introduced in clinical practice with the advantage of being more sensitive in differentiating between viable and non-viable tumour tissue. Radiological techniques, with the ability to accurately separate responders from non-responders after only a brief treatment time or perhaps even before onset of treatment (tracers, probes etc.) will be important measures in decreasing the number of patients receiving treatment with no benefit. We foresee an increased usage of these in the near future [53].

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

Less than 2% of human diseases are caused by aberrations in one gene (monogenic), the rest are caused by multiple gene aberrations or by changes in the proteins they encode. The deciphering of the entire human proteome (HUPO.org) is underway and will undoubtedly shed new light on disease mechanisms and reveal possible targets for intervention. Already, the individual protein

patterns of different tumour types are being mapped and have demonstrated that patients with a specific type of cancer have certain protein patterns present in blood [55-57].

2.11 Advances in supportive drug treatment

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

The fatigue cancer patients suffer is often multifactorial: It may be related to side effects of treatment or psychological stress. Many tumours also secrete substances (cytokines) that may cause fatigue. However, fatigue is primarily caused by anaemia. Traditionally, anaemia has been treated with blood transfusions, but drugs currently in use (e.g. epoetin alpha, epoetin beta, erythropoetin) increase the production of red blood cells reducing the need of blood transfusions. In addition, chemotherapy is often associated with bone marrow depression causing anaemia, neutropenia and thrombocytopenia which may delay/reduce consecutive doses of treatment. The development of erythropoietin, G-CSF (filgrastim, pegfilgrastim), broad spectrum antibiotics and platelet transfusion techniques has decreased morbidity and mortality and has also enabled intensified treatment schedules, increasing cure rates. There are also several agents that prevent nausea (e.g. ondansetron, granisetron). Bisphosphonates (e.g. pamidronat, zoledronic acid), and RANKL (denosumab), reduce the risk of skeletal events (fractures) as well as providing relief of pain caused by skeletal metastases. Actually, the bisphosphonates are also used in the primary breast cancer setting as adjuvant treatment for the prevention of skeletal metastases [59-61].

2.12 Advances towards curing cancer

Although cancer is a common disease, affecting roughly every third person during their lifetime, approximately 50-60% of patients diagnosed with cancer will be ‘cured’ or will die from other causes. Progress in medical treatment of cancer has been made in almost every area. In most tumours, stepwise and relatively modest improvements have over time resulted in impressive increases in the proportion of patients considered cured. For instance, the overall breast cancer mortality in the USA and the UK was reduced by 25% from the 1980ies to the year 2000. This progress is to some extent the result of screening programs, enabling earlier detection of the disease, but it is also a true reduction in mortality due to important improvements in adjuvant treatment. Anthracycline based poly-chemotherapy reduces the annual breast cancer death rate by about 38% for women younger than 50 years and by about 20% for those in the age of 50-69 years. Additional use of 5 years tamoxifen treatment in oestrogen receptor sensitive disease results in a

reduction of the annual breast cancer death rate by 31%. This may be prolonged to 10 years in high-risk patients. Improved chemotherapeutic regimens have increased survival further and recently, adjuvant treatment with the monoclonal antibody trastuzumab in patients with HER2-positive disease has shown a 50% decreased relapse risk and a 33% reduced mortality risk. In CRC adjuvant chemotherapy have reduced mortality with 20-30% and chemotherapy in the metastatic setting has four-folded average survival, from 5 to 20 months. In other diseases like aggressive Non-Hodgkin's Lymphoma (NHL), the combination of CHOP (cyclophosphamide/hydroxydaunorubicin/oncovin/predisone or prednisolone) and rituximab results in a five-year survival rate of 58% in patients over 60 years of age and a 2-year overall survival of 95% in patients under 61 years of age. In recent publications by Gondos, Brenner and Pulte significant improvements in the outcome of NHL, CML and multiple myeloma (MM) was described based on the SEER (the Surveillance, Epidemiology, and End Result) database in the US [62-65, 3].

These publications represent epidemiological support for the value of innovative drugs in oncology and haematology. Similar support for treatment effects at a population level has been reported by von Plessen and co-workers. They reported a significant improvement in the outcome for patients with advanced NSCLC in Norway, linked to the introduction of palliative chemotherapy [66].

In other areas of oncology, such as testicular cancer and Hodgkin's disease, the changes in cure rates have been sudden and dramatic. With the introduction of the MOPP regimen (nitrogen mustard, vincristine, procarbazine and prednisone) in 1967, cure rates of over 50% were obtained in patients with advanced Hodgkin's disease. This was a milestone in medical oncology, proving the ability of cure even in advanced stages of the disease. Since then, even higher cure rates (90%) have been obtained using new combinations of chemotherapy. In testicular cancer, the prognosis has turned from one of the worst to one of the best among the oncological diagnoses. The introduction of cisplatin in the 1970ies was an immediate breakthrough in the treatment of testicular cancer. The addition of chemotherapy agents to surgery and local radiotherapy has further increased cure rates in patients with testicular cancer disease to approximately 90-95% [67-70].

However, it is important to note that breast cancer is a much more common disease; the number of patients cured of breast cancer far exceeds the number of patients cured of testicular cancer and Hodgkin's disease put together.

2.13 Advances towards the prevention of cancer

Epidemiological research has shown that cancer risk is associated with various external and lifestyle factors such as smoking, alcohol consumption, obesity, exercise habits and exposure to certain viruses. For example, it has been known for more than 50 years that smoking increases the

risk of developing many cancers, especially lung cancer. Very little has been done in order to change smoking habits, which has resulted in the global epidemic of lung cancer we see. The strong relationship between hormone exposure and breast cancer was the rationale for the first chemoprevention trials with tamoxifen in women with an increased genetic risk of breast cancer. The women were found to benefit from treatment with tamoxifen (50% risk reduction) [56]. In the 1990-ies, in the USA the FDA approved the use of tamoxifen as a preventive agent in high-risk patients. Also, raloxifene (Selective Estrogen Receptor Modulator, SERM) has proved as efficient as tamoxifen; with less side effects. Several breast cancer prevention studies with aromatase inhibitors have also been performed. Other agents that have potential preventive effect are non-steroidal anti-inflammatory drugs in CRC, finasteride in prostate cancer and recently statins in breast cancer. The first vaccines against human papilloma virus (HPV) -the cause of the vast majority of cervical cancers –were introduced in 2005. There are also studies on potential preventive effect of metformin [71-78].

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

2.14 Clinical effectiveness

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

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

Tumor heterogeneity is a key challenge when treatments are entering clinical practice as the methods of investigating tumors in clinical practice may differ from those in clinical trials. Tumor development from primary tumor to recurrence may include selection of clones that may be treatment related. This is rarely discovered in clinical trials and large cohorts may be required [79].

Co-morbidities may affect proposed treatments and outcome of treatments, and the sequence and combinations of treatments differ from the strict programs of clinical trials. Side-effects resulting in dose reductions will also reduce the amount of drug reaching the target [38, 80].

Anti-tumor treatment guidelines are based on results from clinical studies. The adherence to guidelines and outcome of compliance is rarely evaluated. Many oncology drugs are approved on the surrogate end-point progression free survival (PFS), although there is little support of this translating to overall survival benefit.

To be able to establish the true value of cancer treatments, it is essential to collect survival data from clinical practice.

Clinical efficacy represents the results from clinical studies and shows that the drugs works under controlled conditions in homogenous patient populations. Patients included in clinical trials are usually younger and healthier compared to the general patient population.

Contrary, clinical effectiveness are effects in clinical practice, and shows that a drug improves outcome in a general patient population [82].

As clinical efficacy not always can be translated to clinical effectiveness, it is important to follow-up the results from clinical studies, collecting data from the general patient population, and systematically analyze the collected data. Also, as surrogate end-points (PFS) are often used in clinical studies, it is even more important to continue to collect data in clinical practice to be able to analyze outcome. The data can also be used for other purposes; e.g. quality assurance and quality control [83].

All of the countries in the Nordic region have population-based registers, and these are important in clinical effectiveness studies for the identification of patients to be included in the analyses. Furthermore, the registers have to include detailed patient data on diagnosis and treatments. If this data is not collected retrospective analyses are required, which has never the same impact as prospectively collected data.

2.15 Summary and conclusions

Cancer treatment today is characterized by multimodal therapy approaches; surgery, radiotherapy and an increasing number of anti-tumour drugs.

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

Improved diagnostic methods have facilitated detection of tumours, and therefore, improving the chance of better cure rates. There is an increased use of diagnostic tools, including functional imaging to evaluate therapy effects.

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

The latest development in oncology includes activating the body's own immune system for the treatment of cancer. Immuno-oncology has rapidly become standard of care in metastatic malignant melanoma and progress is ongoing in a number of other tumour types.

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

2.16 References chapter 2

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3 Uptake of medicines

3.1 Summary

- Spending on cancer medicines has increased during the last 10 years with marked shifts in Denmark and in Norway during 2016 and 2017, where a sharp increase in usage compared to previously low levels. The total spending on cancer medicines in 2017 was 375 million € in Denmark, 315 million € in Finland, 15 million € in Iceland, 319 million € in Norway and 486 million € in Sweden.

- There are differences in the per capita spending on cancer medicines between the Nordic countries (between 44 € and 65 € per inhabitant), however taking incidence into consideration the difference in spending becomes less pronounced.

- Variations within countries are sometimes as large as the difference between countries. Norway has consistently had the least variation in per capita spending between regions while the difference has increased over time in both Sweden and Finland. Denmark has large variations which has been consistent (in relative terms) over the time period of study.

- In Denmark, Sweden and Norway it seems like medicines launched in recent years show less variation than medicines launched earlier

3.2 Data on the use of medicines

The data in this chapter is based on sales statistics provided by different actors in the Nordic countries (AMGROS in Denmark, Pharmarket in Finland, Icelandic Drug Market in Iceland, Pharmastat in Norway and Consise in Sweden). Note that the underlying data has different start years, the first available data for Denmark and Finland is from 2010 and 2009, respectively. For the other Nordic countries, the data collection starts in 2007. It should also be noted that the Western region in Sweden did not report complete data for 2012 (due to the pharmacy reform in Sweden). Furthermore, the data for the South-Eastern region in Sweden for year 2014 is incomplete. This affects all analysis and figures for the country both of these years.

All the prices in the chapter are in expressed in € as fixed, listed prices (2015) **exclusive of VAT**. In Appendix 2 there is a brief discussion and illustration about how this measure affects the prices shown in this report.

This means that the reported costs are overestimated as it has become more common with confidential rebates. This introduces some uncertainty in the comparisons between countries as the magnitude of the discount for a particular drug may vary between countries.[12]

When possible, uptake has been defined as cost per case of the diagnosis for which the drug is indicated with a case be defined by death with the diagnosis as cause. Data on mortality and incidence were extracted from NORDCAN, which is collecting data from the Nordic cancer registries. NORDCAN uses an average for the mortality and incidence in 2011-2015. The national data used in this report is the sum of the regional mortality data for all the regions in each country (except for Iceland). The fact that the dosing of medicines (in mg) vary makes it impossible to express uptake in terms of volume. An alternative would have been to utilize daily defined doses, but unfortunately these are not defined for most new drugs in oncology. Cost per case therefore remains the only option available that allows for aggregation of drugs within a particular cancer form when studying uptake. A complicating factor here is that these figures are sensitive to fluctuation in currency and confidential discounts (as described above) but they provide a clear proxy for volume when studying a single country.

3.3 Use of cancer medicines in the Nordic countries

We will compare the use of cancer drugs between and within countries expressed as cost/capita. However, the incidence and prevalence of cancer may differ between countries and regions, which makes it more relevant to relate use a drugs and costs to a measure of the burden of disease i.e. either cost/ new cancer case or - as most new cancer drugs are introduced in the non-curative, palliative setting - to compare cost/case of cancer mortality. For drugs with a single indication it is possible to relate cost of a certain drugs to mortality in the specific indication/disease, but this is more problematic when a drug or, a class of drugs, have several indications in different tumour types. In such cases, one can relate costs to mortality/per case of primary indication for a drug. One must be aware that this is misleading as drugs may be introduced for different indications at various speed in different countries/regions.

We have in most parts of this document expressed access as cost (in Euro)/case of mortality for the (main) indication, as we believe this best reflects the relevant comparisons in which the drugs are being used.

Spending on cancer medicines has increased during the last years in the Nordics, which can be seen in **Figure 25** where the increase rate of total sales is shown. Except for a minor dip in the increase between 2013 and 2014, total sales per inhabitant has steadily increased over the years. Between

[12] The estimated overall refund in Sweden in 2017 was 29% of total drug sales.

2016 and 2017 sales increased by about 20 percent. It can be noted that the increase in total sales is only slightly higher than the increase in total sales per inhabitant, thus the higher drug costs cannot be explained by a growing population in the Nordic countries.

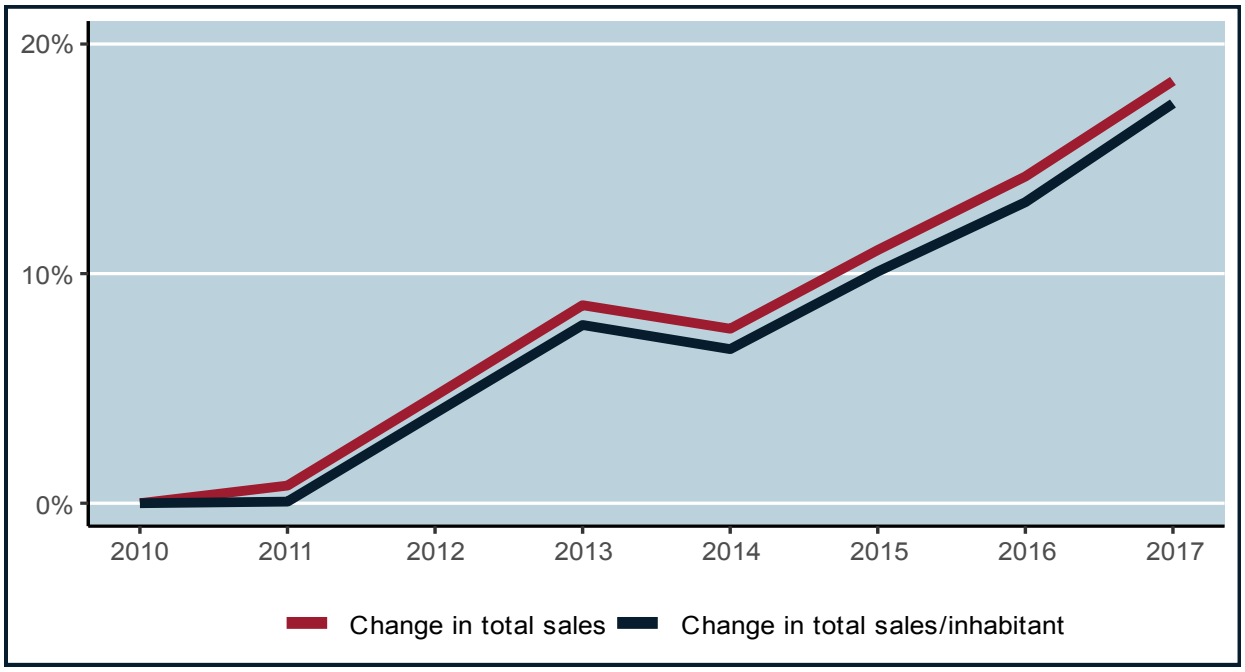

Figure 25: *Increase rate (%) in total sales in the Nordic countries compared to previous year.*
Note: The comparison starts in 2011 since there is not aviable data for all of the Nordic countries before 2010.

There is a marked shift in Denmark, and especially in Norway during 2016 and 2017 (**Figure 26**). The total spending on cancer medicines in 2017 was 375 million € in Denmark, 315 million € in Finland, 15 million € in Iceland, 319 million € in Norway and 486 million € in Sweden. It should be noted that these figures are exclusive of confidential rebates and the actual costs and increases may therefore be somewhat lower.

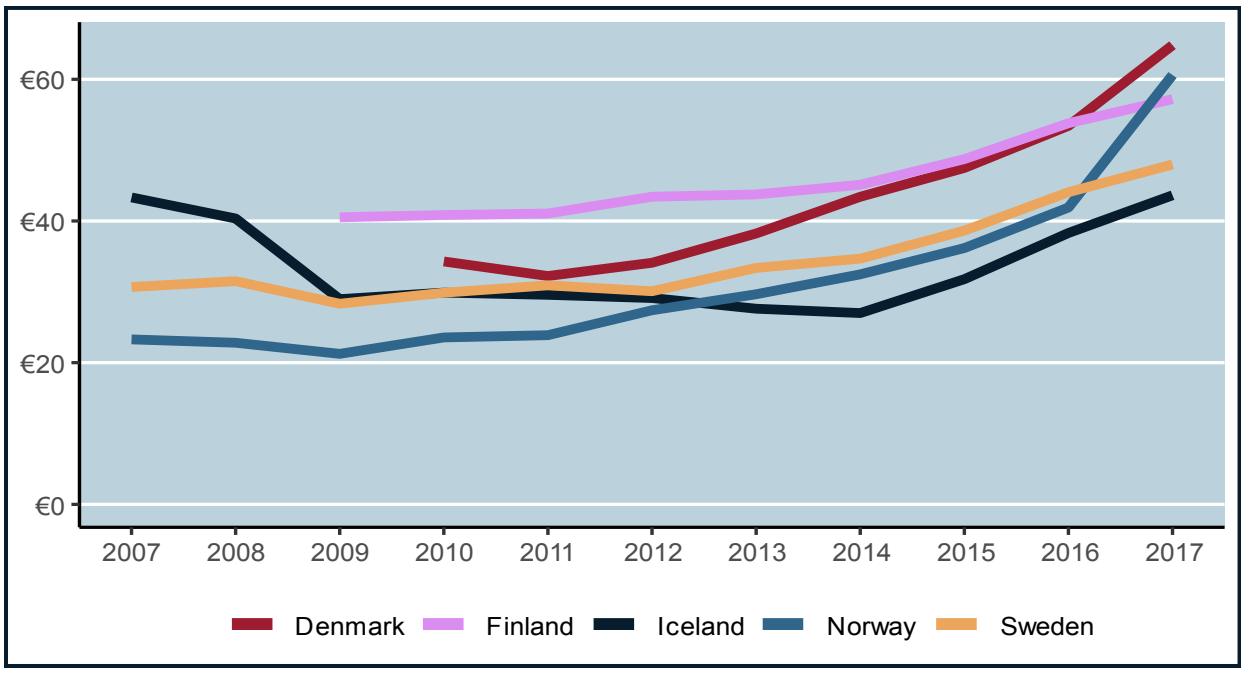

Figure 26: *Euro/inhabitant for all cancer medicines in the Nordic countries.*

Taking incidence of cancer into consideration, we can note that the differences between the countries became smaller in more recent years (**Figure 27**) The difference between the lowest and highest spending country was about 27% in 2017, compared to 49% when considering expenditure per capita.

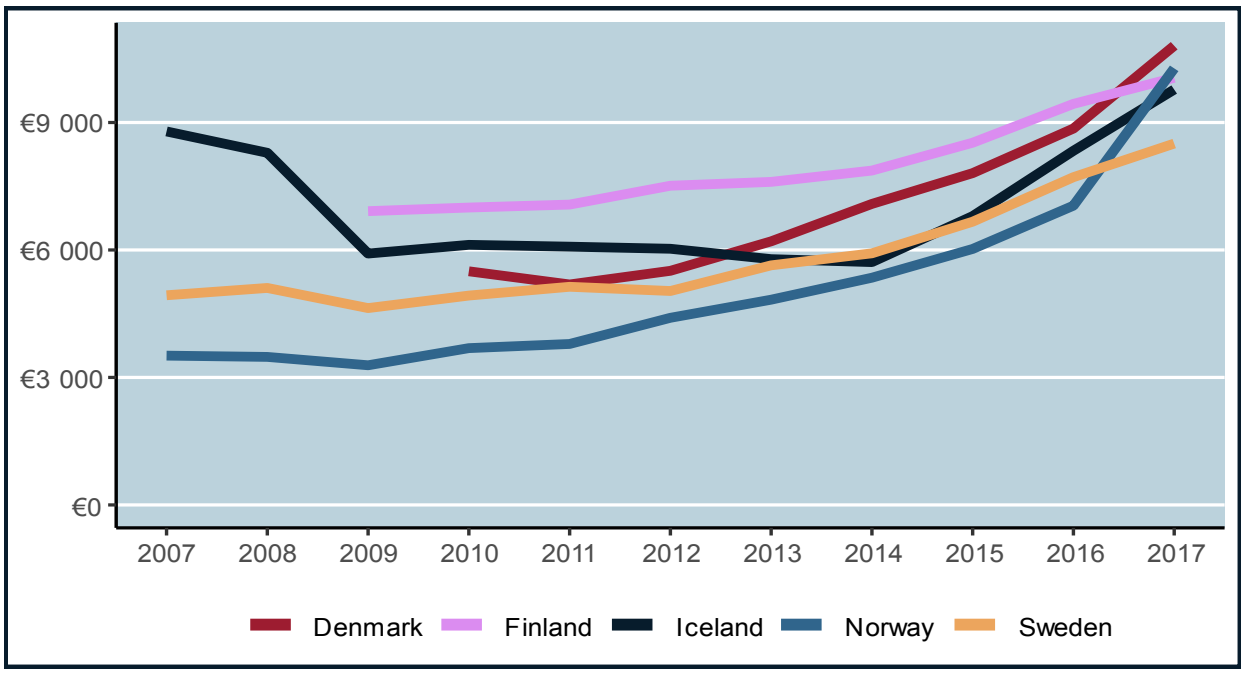

Figure 27: *Euro/new case (incidence) of all cancers in the Nordic countries*.

Expenditure per death has also increased (**Figure 28**), although the order of the countries has shifted which can be explained by variations in the incidence of various cancer types between the countries, e.g. high incidence of lung cancer in Denmark which has high mortality.

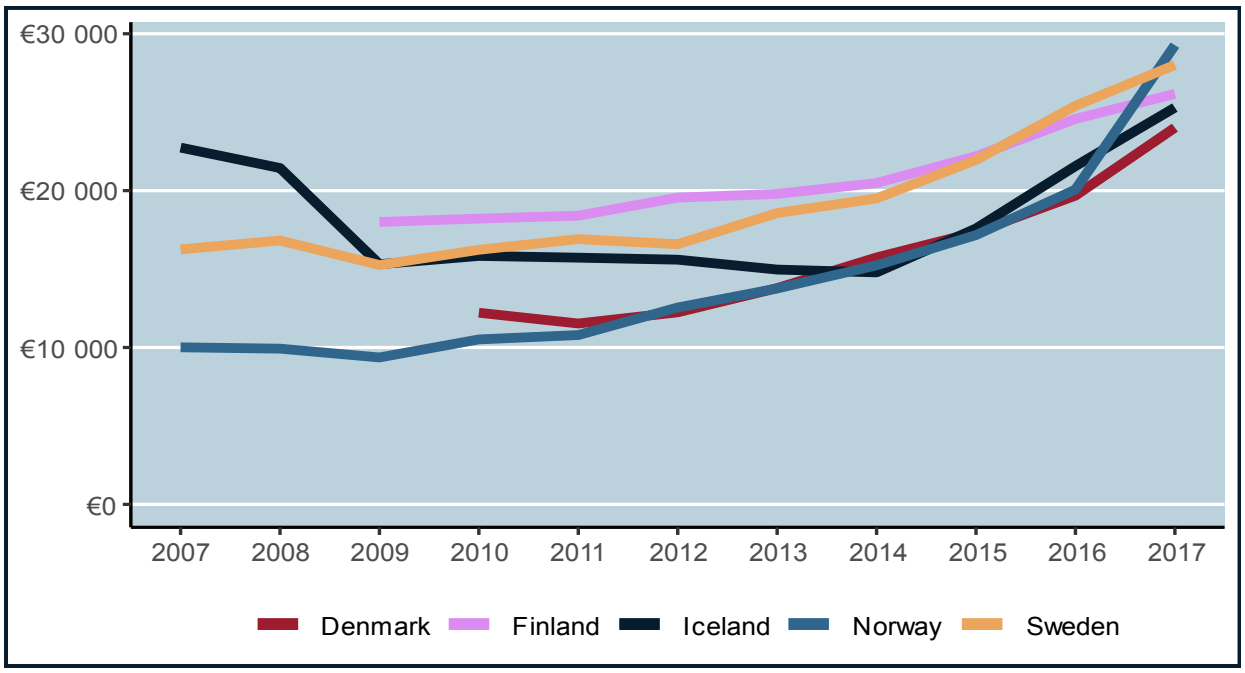

Figure 28: *Euro/case (deaths in diagnosis) in all cancers in the Nordic countries.*

Based on the data on total spending on cancer from chapter 1, we note that the expenditure of medicines has decreased somewhat in Iceland between 2010 and 2015 (the latest year with total health expenditures available). Expenditure of medicines has increased modestly in Finland and Sweden and more sharply in Norway and Denmark (**Table 9**).

Table 9: *Cancer medicine cost as % of total spending on cancer by country 2010 and 2015*

Country	Percentage medical cost 2010	Percentage medical cost 2015
Demark	14.9%	20.2%
Finland	30.0%	32.8%
Iceland	24.8%	22.0%
Norway	8.2%	12.6%
Sweden	18.7%	20.9%

The proportion of costs attributable to new medicines (launched within the last three years) increased in all countries around 2012-2013 but has remained fairly stable since (**Figure 29**). Finland is something of an outlier with higher spending on medicines overall but with a low proportion of spending on newer medicines.

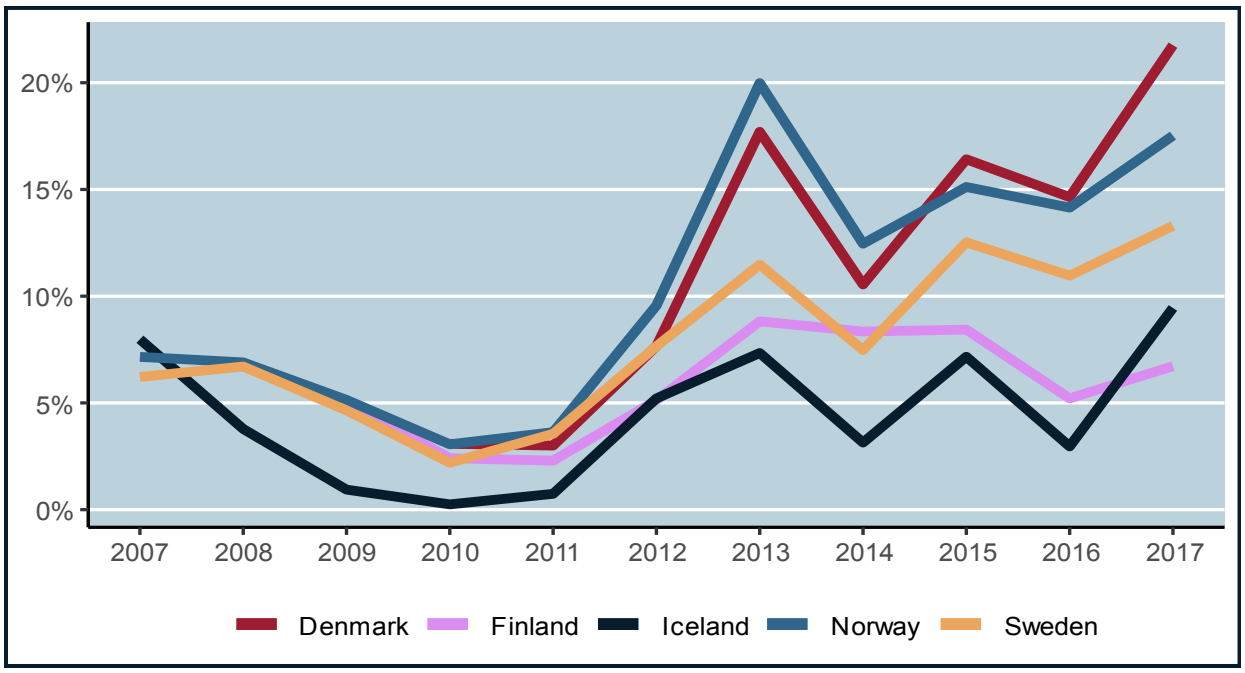

Figure 29: *Share of sales of cancer medicines launched within the last three years in the Nordic countries.*

During 2007-2011 the share of drugs introduced within the last 3 years remained at around 5%. After 2011 this share has gone up to around 20% in Denmark; 15% in Norway; 12-13% in Sweden and 10% in Iceland. In Finland it has remained at 5%, most likely due to slow introduction of immuno-oncology and new drugs like CDK inhibitors.

Table 10 - Table 14 show the most used medicines (in terms of sales value) in 2017 and the earliest available year in our data. Trastuzumab has taken a prominent role over the entire time period, even though it now constitutes a smaller share in relative terms. It can be noted that in all countries a larger proportion of spending was on the 10 biggest sellers earlier compared to the situation in 2017.[13]

[13] Rituximab is used in several indication – we have assumed that 40% of sales are in oncology.

Table 10: *Top 10 cancer medicines in 2010 and 2017 in Denmark*

	Molecule	Share 2010	Molecule	Share 2017
1	Trastuzumab	14.4%	Pembrolizumab	6.9%
2	Bevacizumab	8.9%	Trastuzumab	6.6%
3	Letrozole	7.5%	Bevacizumab	6.2%
4	Imatinib	6.2%	Lenalidomide	5.7%
5	Docetaxel	5.3%	Daratumumab	5.6%
6	Rituximab	4.6%	Enzalutamide	3.9%
7	Cetuximab	4.1%	Abiraterone Acetate	3.4%
8	Goserelin	3.7%	Ibrutinib	3.3%
9	Pemetrexed	3.4%	Rituximab	2.8%
10	Bortezomib	3.2%	Bortezomib	2.4%
	Total	**61.3%**	**Total**	**46.7%**

Note: Total sales of cancer medicines in Denmark 2010 was 191 million euro and 375 million euro in 2017.

Table 11: *Top 10 cancer medicines in 2009 and 2017 in Finland*

	Molecule	Share 2009	Molecule	Share 2017
1	Docetaxel	9.7%	Trastuzumab	8.8%
2	Trastuzumab	8.3%	Bevacizumab	8.0%
3	Bevacizumab	7.4%	Lenalidomide	7.5%
4	Leuprorelin	6.7%	Rituximab	4.9%
5	Imatinib	6.6%	Enzalutamide	4.4%
6	Rituximab	5.1%	Bortezomib	3.9%
7	Sunitinib	3.1%	Leuprorelin	3.4%
8	Bicalutamide	3.0%	Abiraterone Acetate	3.1%
9	Anastrozole	2.8%	Methotrexate	2.9%
10	Capecitabine	2.7%	Pertuzumab	2.8%
	Total	**55.4%**	**Total**	**49.5%**

Note: Total sales of cancer medicines in Finland 2009 was 217 million euro and 315 million euro in 2017.

Table 12: *Top 10 cancer medicines in 2007 and 2017 in Iceland*

	Molecule	Share 2007	Molecule	Share 2017
1	Bicalutamide	13.7%	Trastuzumab	8.7%
2	Trastuzumab	11.1%	Lenalidomide	7.1%
3	Paclitaxel	10.8%	Enzalutamide	7.0%
4	Goserelin	5.8%	Pertuzumab	5.8%
5	Imatinib	5.2%	Pomalidomide	5.7%
6	Docetaxel	4.8%	Bevacizumab	5.2%
7	Rituximab	4.3%	Rituximab	4.3%
8	Letrozole	3.7%	Nivolumab	4.2%
9	Sunitinib	3.6%	Pemetrexed	3.5%
10	Bortezomib	3.0%	Goserelin	3.1%
	Total	**66.1%**	**Total**	**54.5%**

Note: Total sales of cancer medicines in Iceland 2007 was 14 million euro and 15 million euro in 2017.

Table 13: *Top 10 cancer medicines in 2007 and 2017 in Norway*

	Molecule	Share 2007	Molecule	Share 2017
1	Bicalutamide	14.9%	Pembrolizumab	8.8%
2	Trastuzumab	10.0%	Lenalidomide	7.1%
3	Goserelin	7.0%	Enzalutamide	6.2%
4	Docetaxel	7.0%	Trastuzumab	5.4%
5	Imatinib	6.9%	Paclitaxel	4.6%
6	Leuprorelin	4.3%	Nivolumab	4.1%
7	Oxaliplatin	4.2%	Bevacizumab	3.5%
8	Rituximab	4.1%	Rituximab	2.9%
9	Anastrozole	4.0%	Bortezomib	2.9%
10	Temozolomide	3.2%	Imatinib	2.8%
	Total	**65.8%**	**Total**	**48.3%**

Note: Total sales of cancer medicines in Norway 2007 was 109 million euro and 319 million euro in 2017.

Table 14: *Top 10 cancer medicines in 2007 and 2017 in Sweden*

	Molecule	Share 2007	Molecule	Share 2017
1	Trastuzumab	10.4%	Enzalutamide	7.8%
2	Bicalutamide	9.2%	Trastuzumab	7.6%
3	Imatinib	7.3%	Lenalidomide	7.6%
4	Leuprorelin	7.2%	Nivolumab	6.6%
5	Docetaxel	6.3%	Rituximab	4.1%
6	Anastrozole	4.6%	Bortezomib	3.7%
7	Paclitaxel	4.5%	Bevacizumab	3.6%
8	Goserelin	3.3%	Ibrutinib	3.2%
9	Gemcitabine	3.2%	Pertuzumab	2.6%
10	Rituximab	3.1%	Pomalidomide	2.4%
	Total	**59.3%**	**Total**	**49.0%**

Note: Total sales of cancer medicines in Sweden 2007 was 282 million euro and 486 million euro in 2017.

The top 10 selling drugs constituted about 60-65% around 2010 and in 2017 about 50%. This indicates that more competing drugs are on the market. It is interesting to note that there are some marked differences in the top 10 selling drugs in the different countries. This will be further addressed later in the chapter.

3.4 Regional variations in uptake

There are differences on spending between countries, but there are also variations within countries. **Figure 30** - **Figure 33** show the spending on cancer medicines in each region for the countries (except for Iceland, which has too few inhabitants). The thick country line in the figures represents the unweighted average uptake of cancer medicines per inhabitant in the country in order to show the regional deviations from the mean. Thus, the national lines in the following figures do not correspond exactly to the €/inhabitant above.

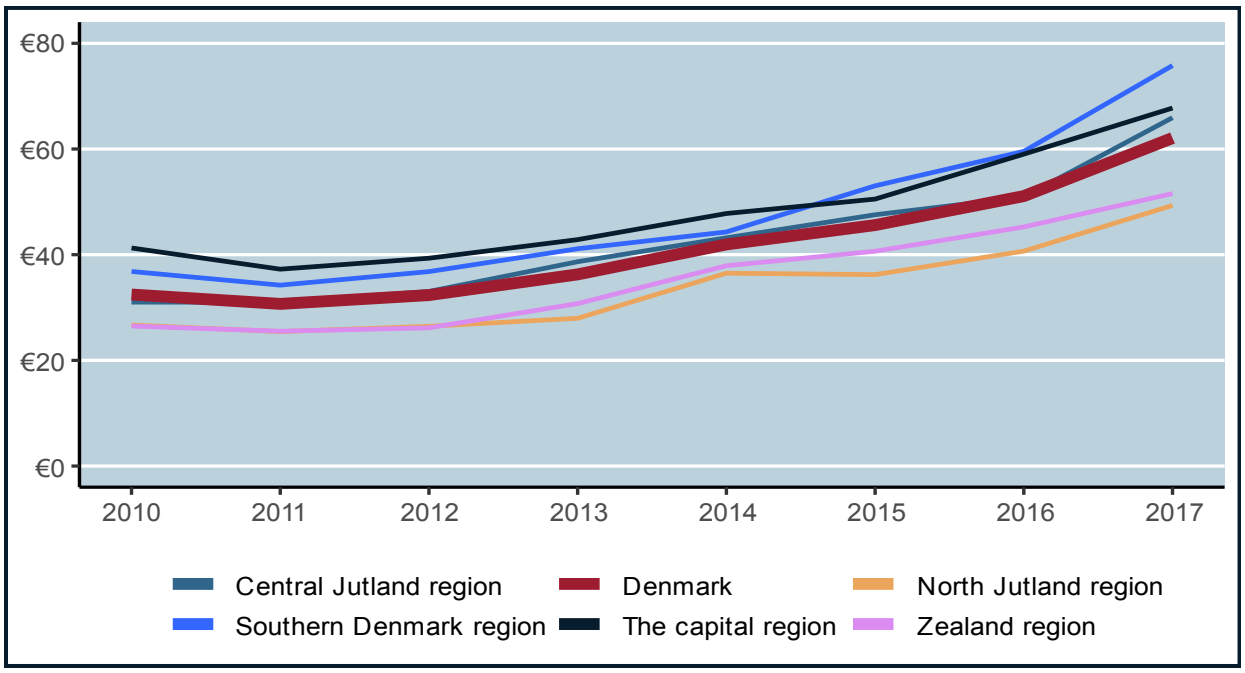

Figure 30: *Euro/inhabitant for all cancer medicines in Denmark.*

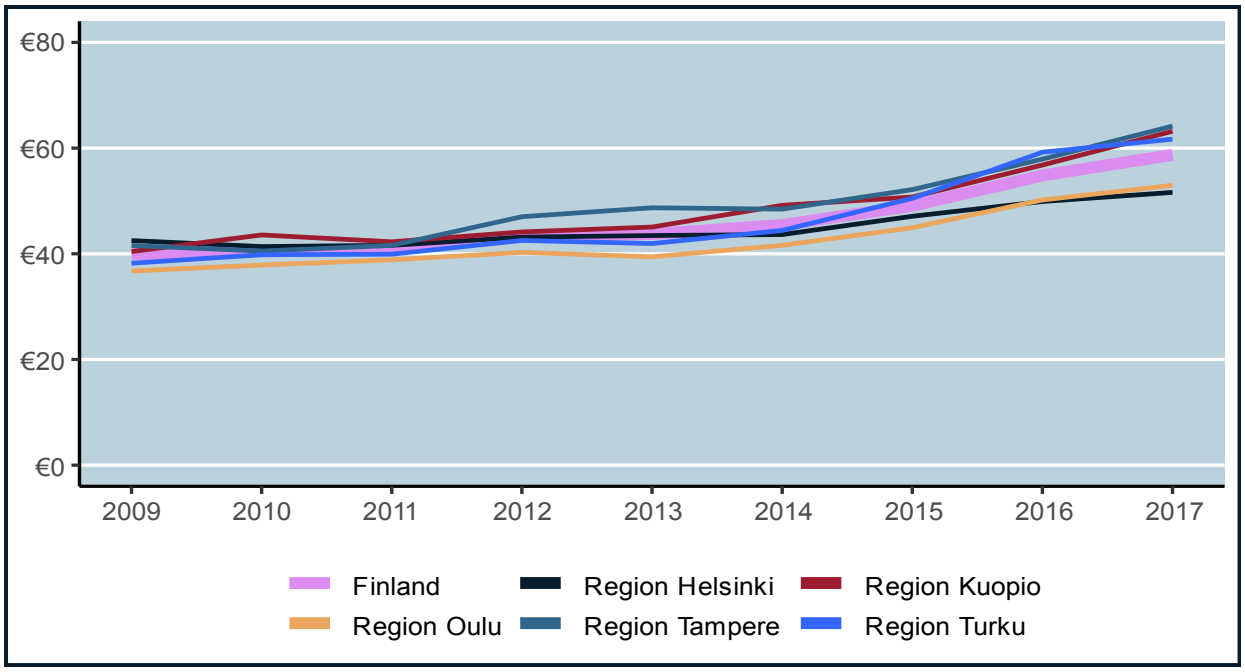

Figure 31: *Euro/inhabitant for all cancer medicines in Finland.*

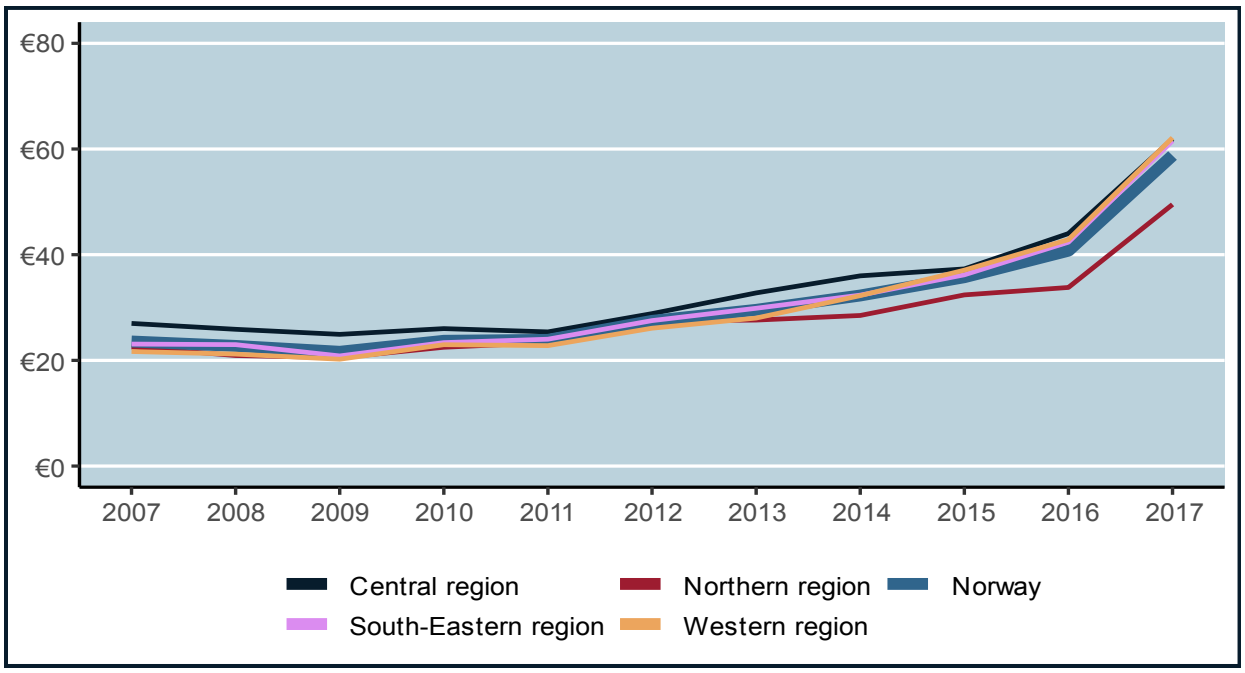

Figure 32: *Euro/inhabitant for all cancer medicines in Norway.*

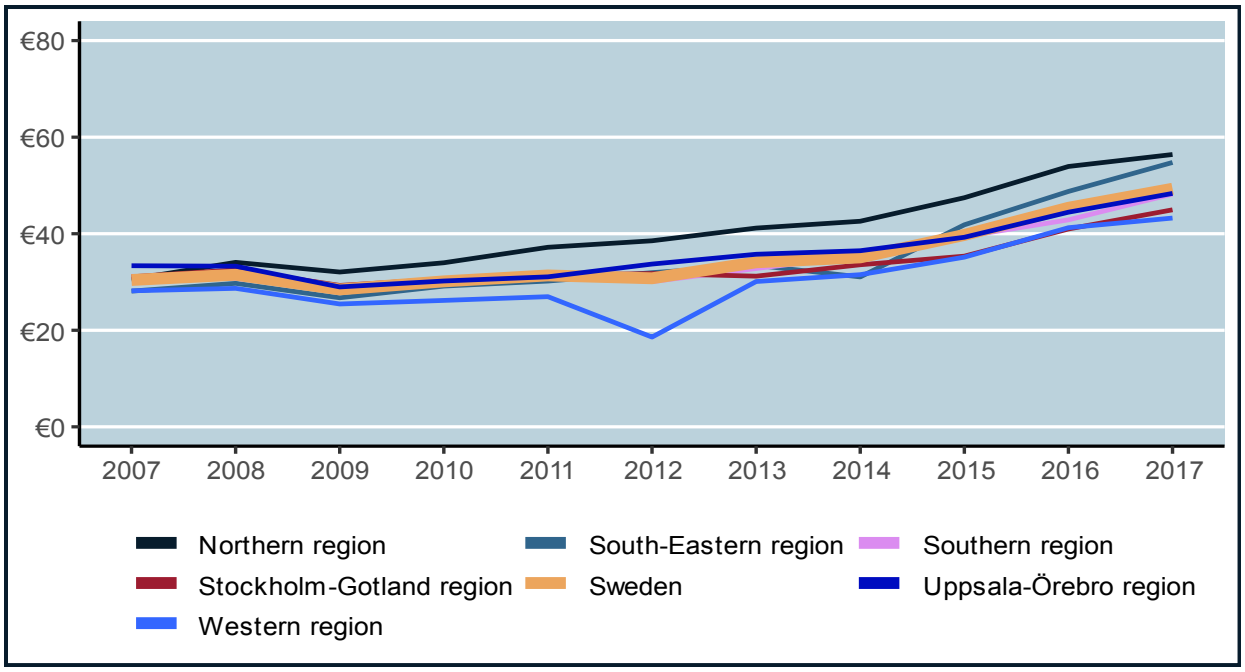

Figure 33: *Euro/inhabitant for all cancer medicines in Sweden.*

In Denmark (**Figure 30**) there is a fairly consistent pattern over the years (in relative terms) with higher spending in the Central Jutland, Southern Denmark, and Capital regions while spending is lower in the Zealand and North Jutland Regions. This picture is complicated by the fact that some regions send patients to other regions for certain cancer forms, and that patients may seek care in other regions on their own.

In Finland (**Figure 31**) there was little regional variation. There are different funding systems, where retails drugs get national funding and hospital drugs local/regional funding. After 2012-2013 some regional divergence can be observed, in particular the Oulu and Helsinki regions are today spending less than the other regions.

Norway (**Figure 32**) stands with comparatively small regional variations. This has been consistent over time, with the possible exception of the Northern region where the spending is lower in recent years.

In Sweden finally (**Figure 33**) spending in the different regions has diverged over time from a situation with relatively small difference in the initial years to a larger variation today. The Northern region has consistently had a higher per capita spending than the other regions. The decrease in use in the Western Region in 2012 is due to changes in reporting practices, as mentioned earlier.

To investigate if there is a tendency to more equal access to newer medicines over time, the average difference in use between the region with highest uptake and the region with lowest uptake was plotted for medicines of different launch year in each country (**Figure 34 - Figure 37**). The difference in use was expressed as the percentage difference from the mean: If the region with the highest use spends 50% more than the mean and the region with the lowest use spends 50% less than the mean this would give a net difference of 100%.

The difference between regions decreases with time in all countries, though they remain quite large in Denmark with no apparent plateau. In Finland and Norway there seems to be a convergence point below a 100% difference, while it is slightly higher in Sweden. If this represents a reasonable variation in praxis can be debated. In Denmark, Sweden and Norway it seems like medicines launched in recent years show less variation than medicines launched earlier (they reach the plateau quicker).

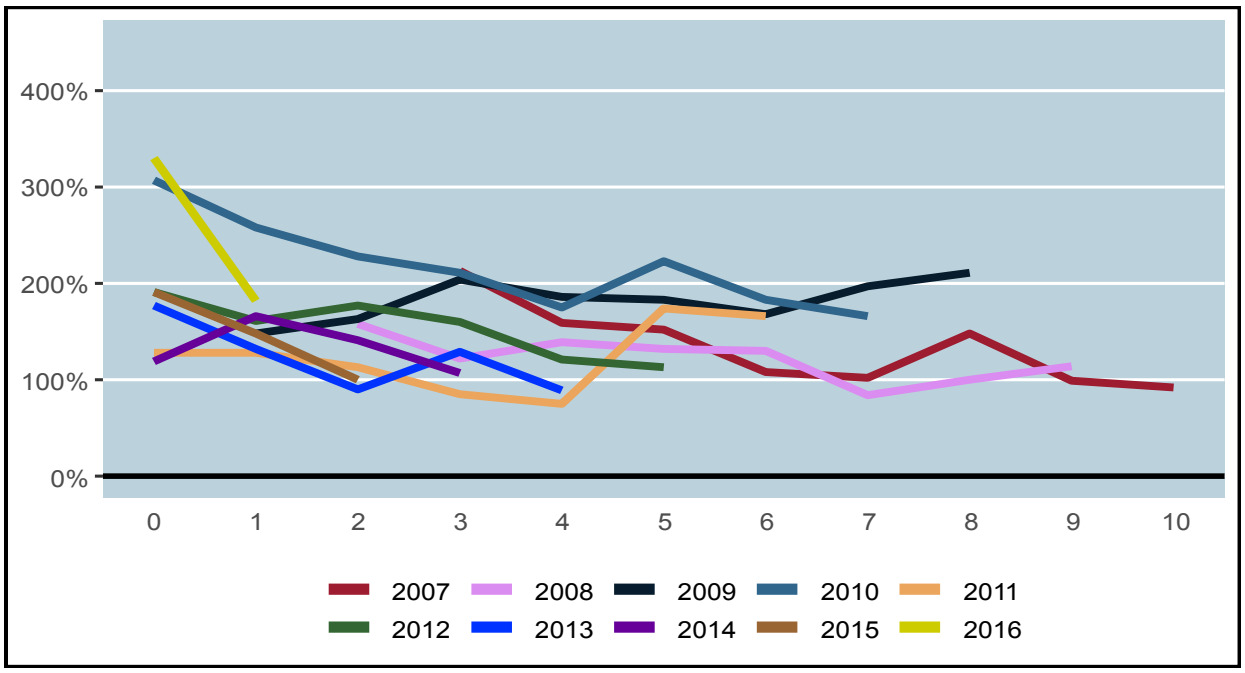

Figure 34: *Difference in use (% from mean) between highest and lowest region by launch year in Denmark.*

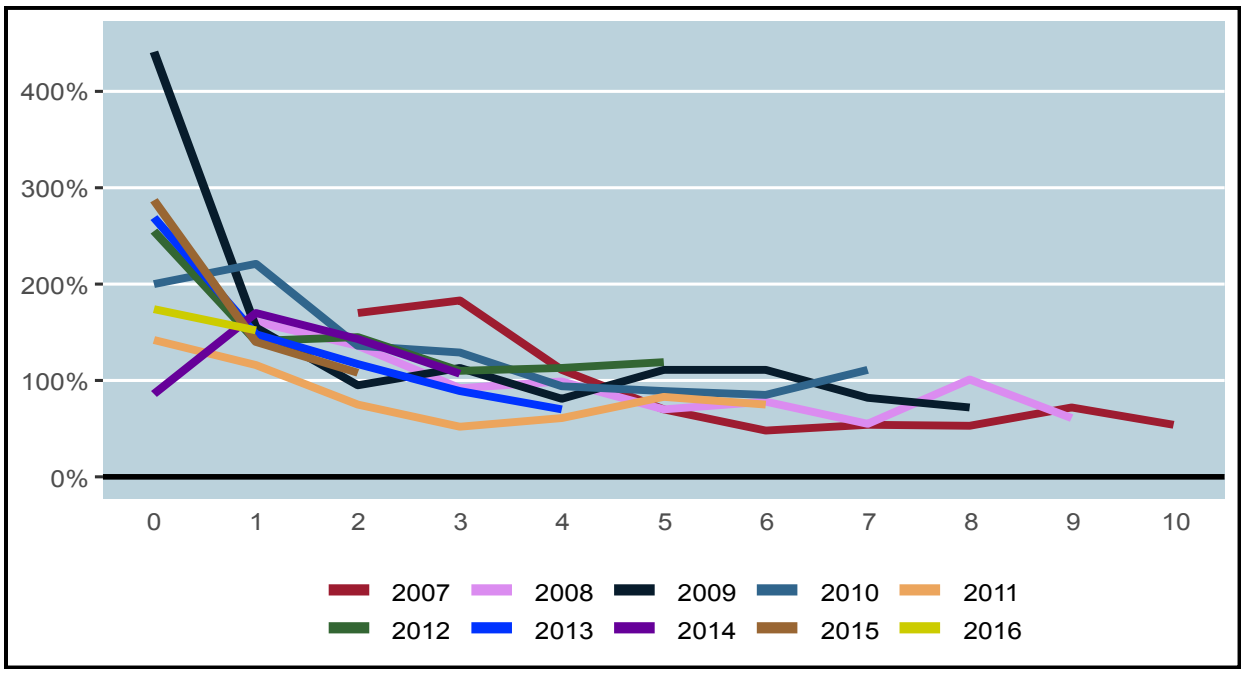

Figure 35: *Difference in use (% from mean) between highest and lowest region by launch year in Finland.*

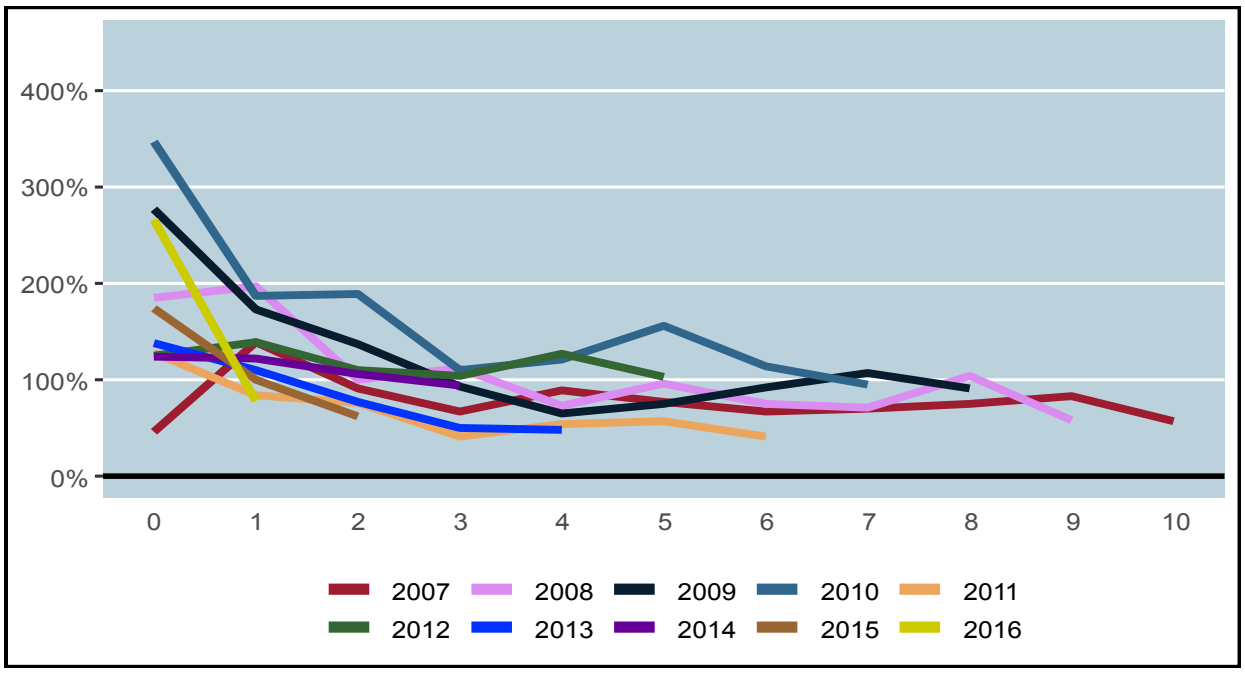

Figure 36: Difference in use (% from mean) between highest and lowest region by launch year in Norway.

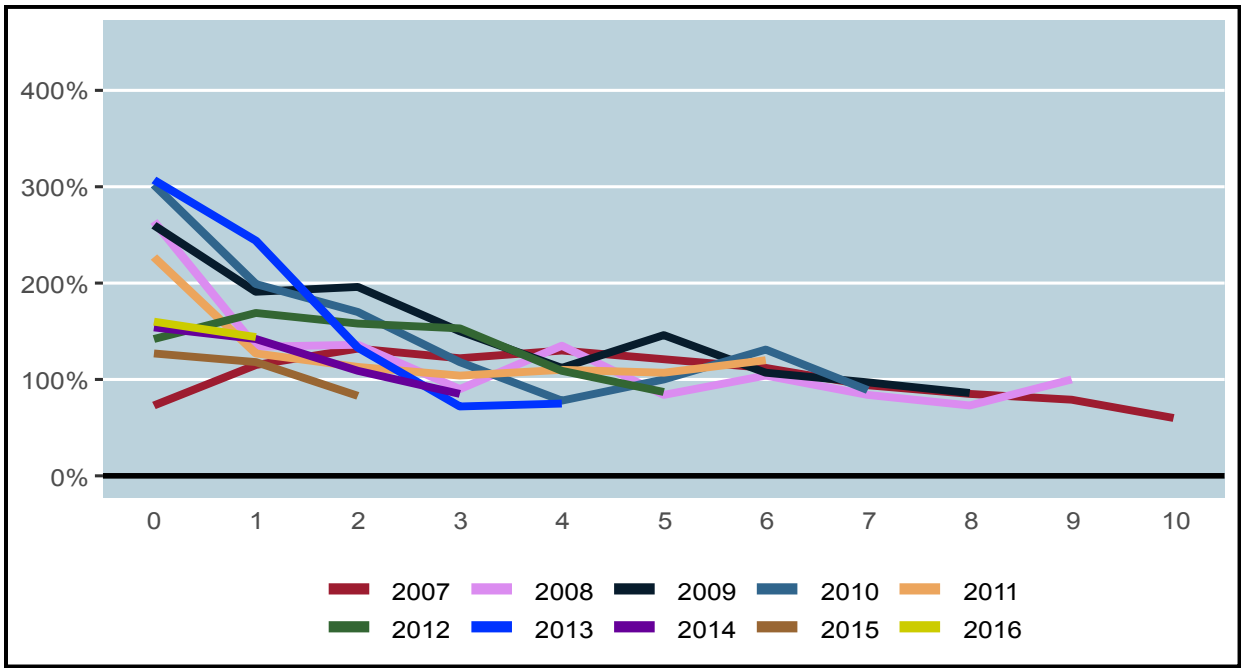

Figure 37: *Difference in use (% from mean) between highest and lowest region by launch year in Sweden.*

3.5 Uptake in specific disease areas

In terms of regional comparisons, we have focused on a comparison between Norway and Sweden to contrast a country with fairly little regional variation (Norway) to one with larger variation in many cases (Sweden).

3.5.1 Breast cancer

In breast cancer we present uptake for the following drugs:

- Trastuzumab (**Figure 38**)
- Pertuzumab (**Figure 39**)
- Trastuzumab emtansine (**Figure 40**)
- All of the drugs above + lapatinib (**Figure 41**)
- CDK-inhibitors (Palbociclib + Ribociclib) (**Figure 42**)
- All of the drugs above (**Figure 43**)

It can be noted that there are large variations between the countries in terms of how large share of sales these drugs constitute (**Figure 46**).

Though uptake was initially slow in Norway, it can be noted that uptake has increased rapidly in recent years. There is significant less variation between regions in Norway compared to Sweden (**Figure 44** and **Figure 45**).

In our first comparator report from 2005 there was a lot of focus on trastuzumab; at that time a relatively new and costly drug for the treatment of metastatic HER2+ breast cancer. The drug was approved in the adjuvant setting in 2006 but still, after more than ten years, there is large variation in the use of trastuzumab (and other HER2+ drugs) over time. The use in Sweden, for example, was initially about 50% higher compared to Norway while Finland and Denmark had a level of use in-between. The use of HER2+ drugs is similar in Sweden and Finland while Norway since 2015 have dramatically increased its use and is catching up with Sweden and Finland. This may partly be related to a delay in approval in Norway compared to Denmark and Sweden for pertuzumab and trastuzumab emtansine.

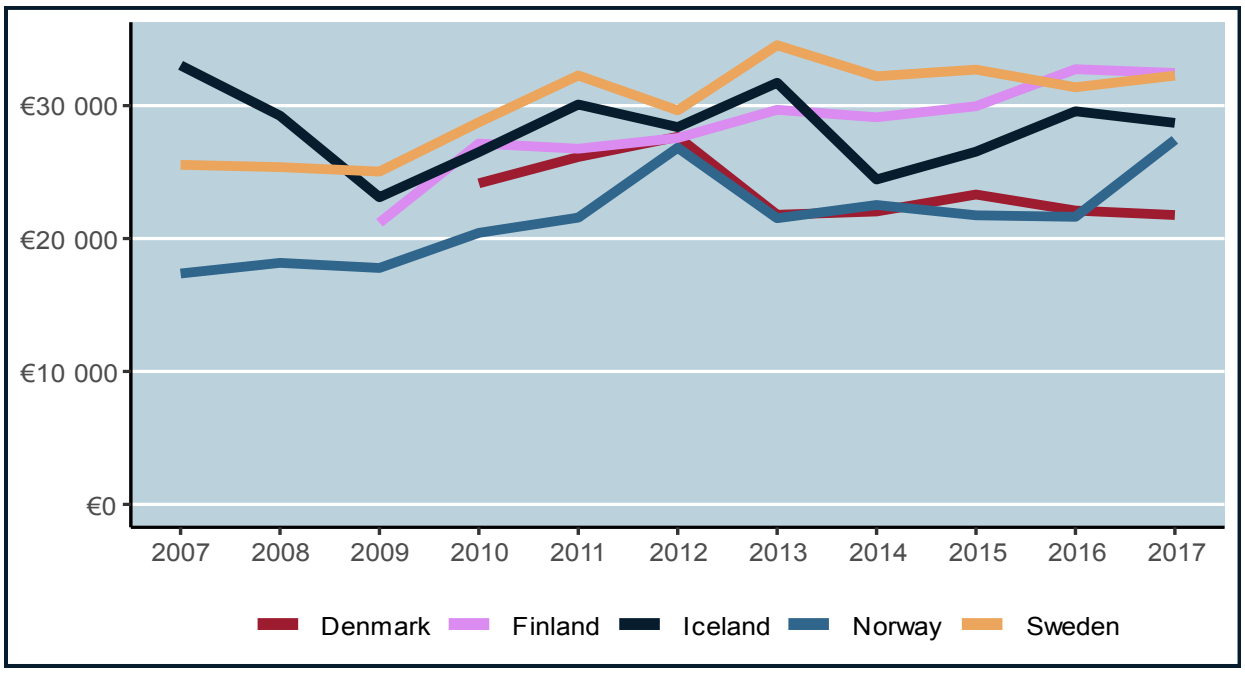

Figure 38: *Euro/case (deaths in diagnosis) in breast cancer for trastuzumab in the Nordic countries.*

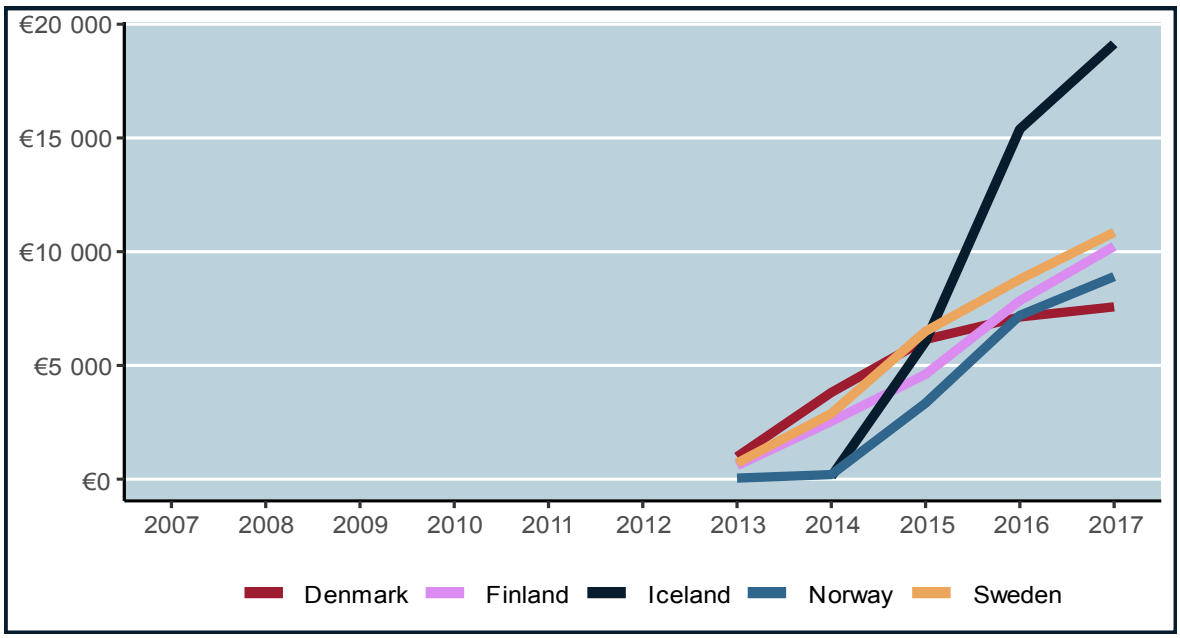

Figure 39: *Euro/case (deaths in diagnosis) in breast cancer for pertuzumab in the Nordic countries.*

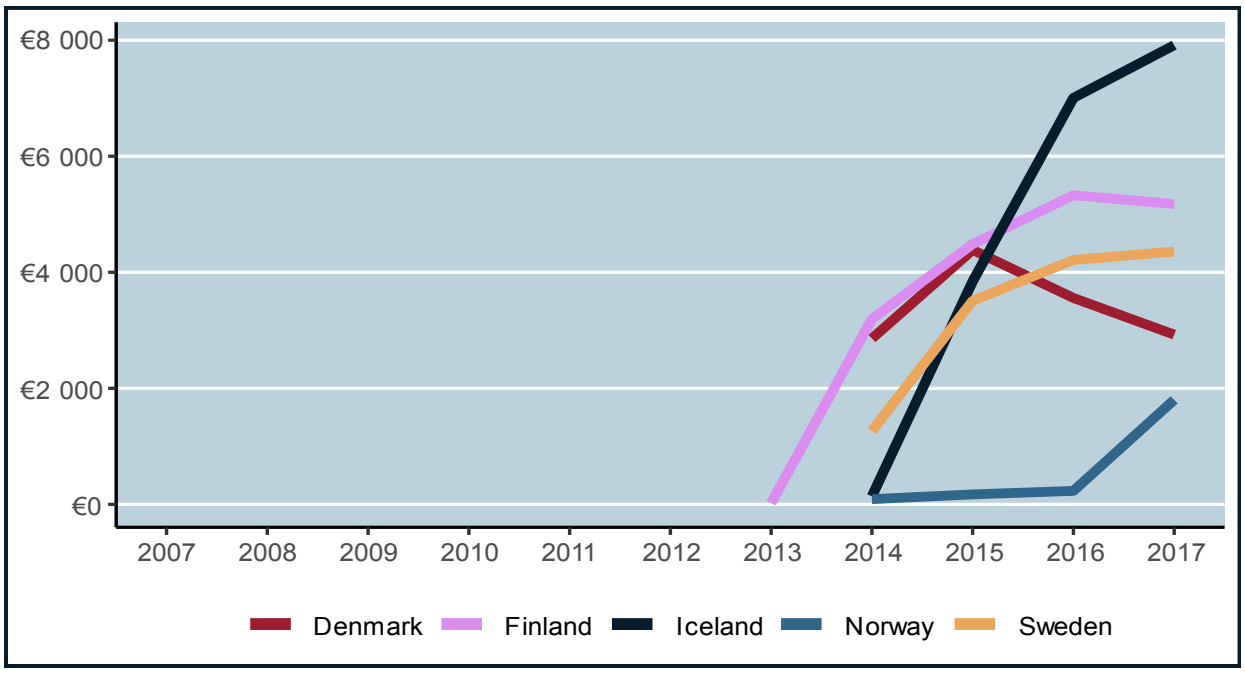

Figure 40: *Euro/case (deaths in diagnosis) in breast cancer for trastuzumab emtanstine in the Nordic countries.*

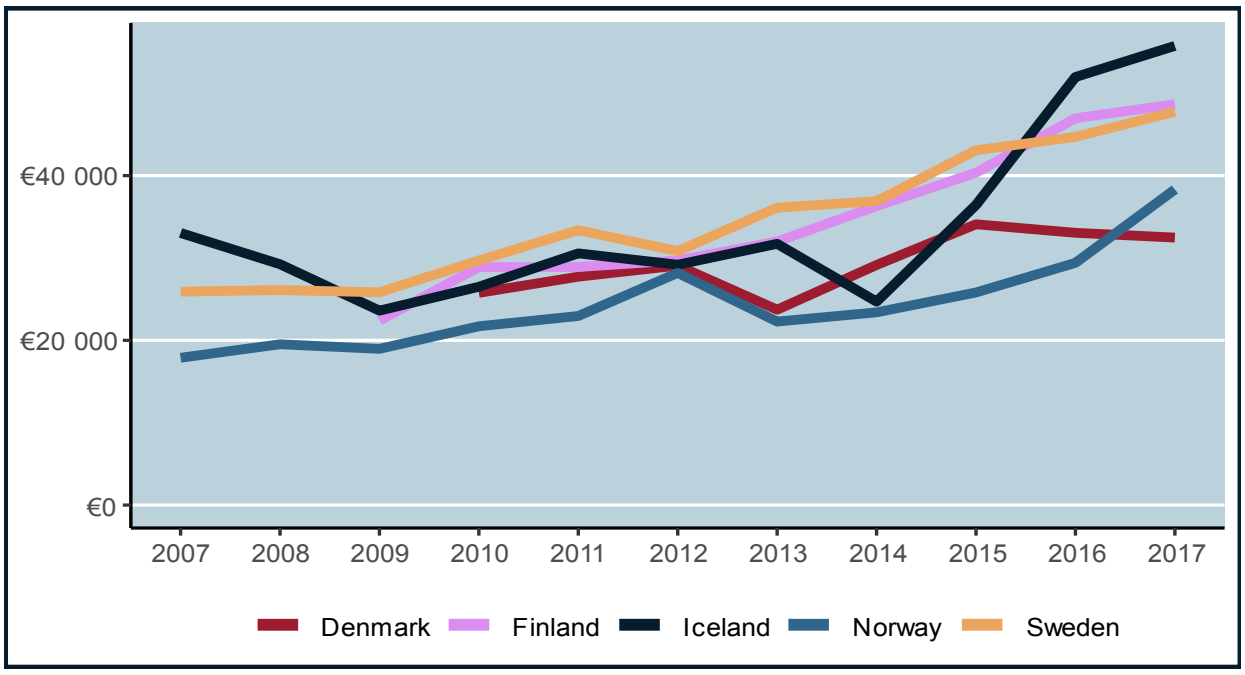

Figure 41: *Euro/case (deaths in diagnosis) in breast cancer for all HER2-drugs in the Nordic countries.*

CDK inhibitors represent a new class of drugs for the treatment of hormonal dependent metastatic breast cancer patients. The first drug, palbociclib was approved in 2016 and we see dramatic differences in access. Norway has by far the most rapid uptake followed by Denmark, while Sweden and especially Finland has a very low uptake. In Sweden this is a reflection of a slow reimbursement process and restrictions in the label introduced by the county councils through the

NT (New Therapies) group. In Sweden it is notable that the uptake in the Stockholm-Gotland region is far higher compared to other health care regions.

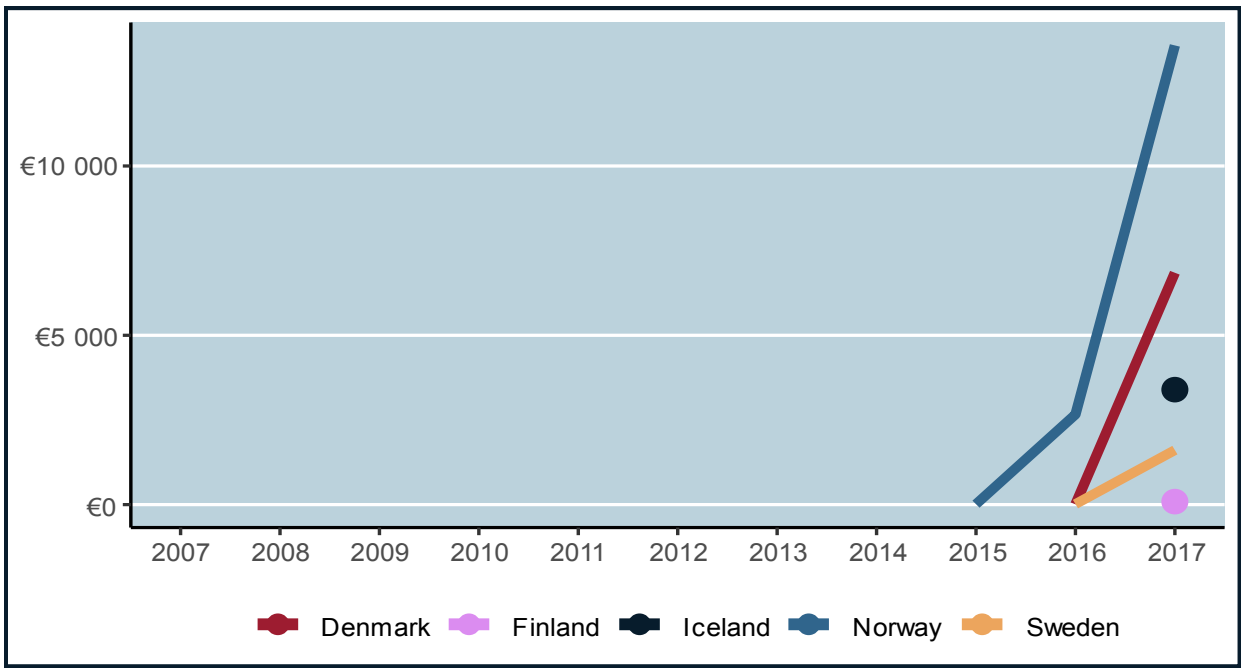

Figure 42: *Euro/case (deaths in diagnosis) in breast cancer for the CDK-inhibitors in the Nordic countries.*

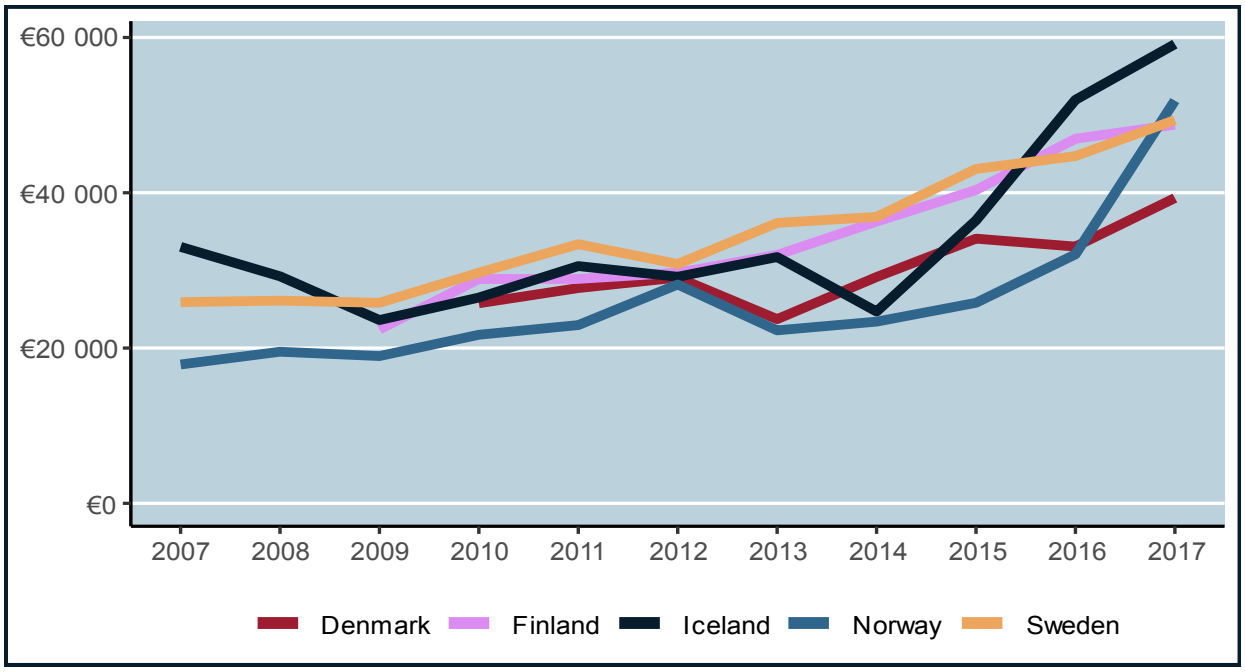

Figure 43: *Euro/case (deaths in diagnosis) in breast cancer for trastuzumab + pertuzumab + trastuzumab emtansine + lapatinib + palbociclib + ribociclib in the Nordic countries.*

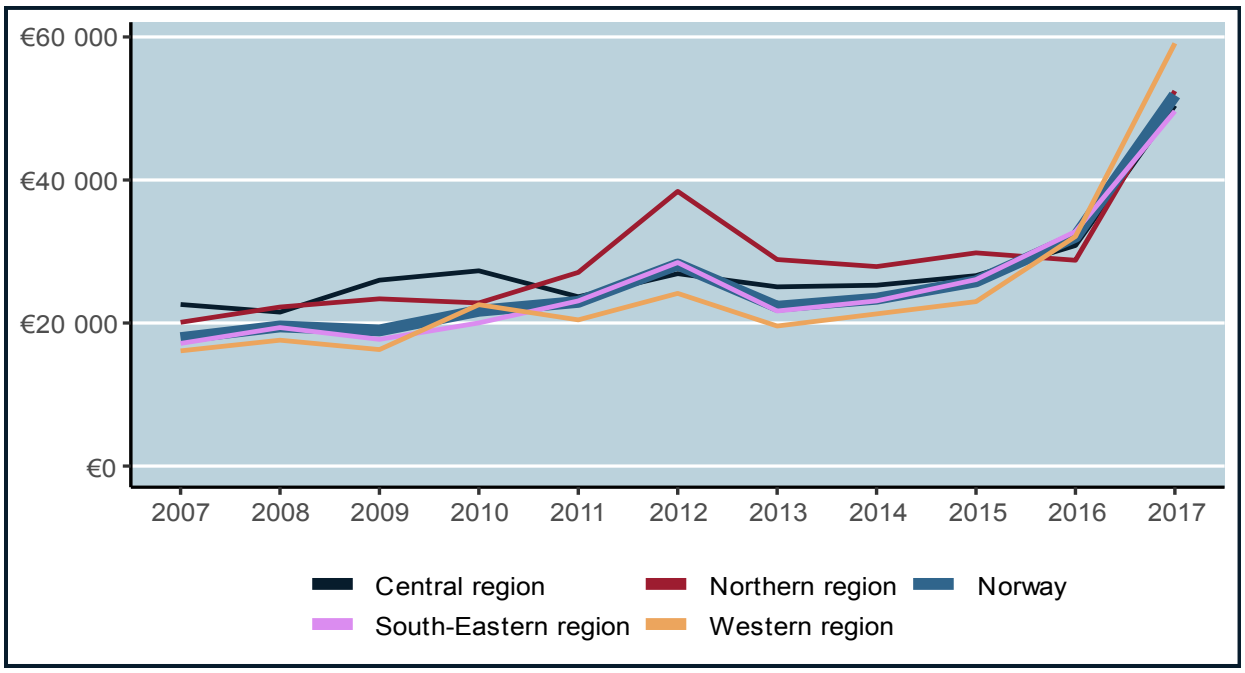

Figure 44: *Euro/case (deaths in diagnosis) in breast cancer for trastuzumab + pertuzumab + trastuzumab emtansine + lapatinib + palbociclib + ribociclib in Norway.*

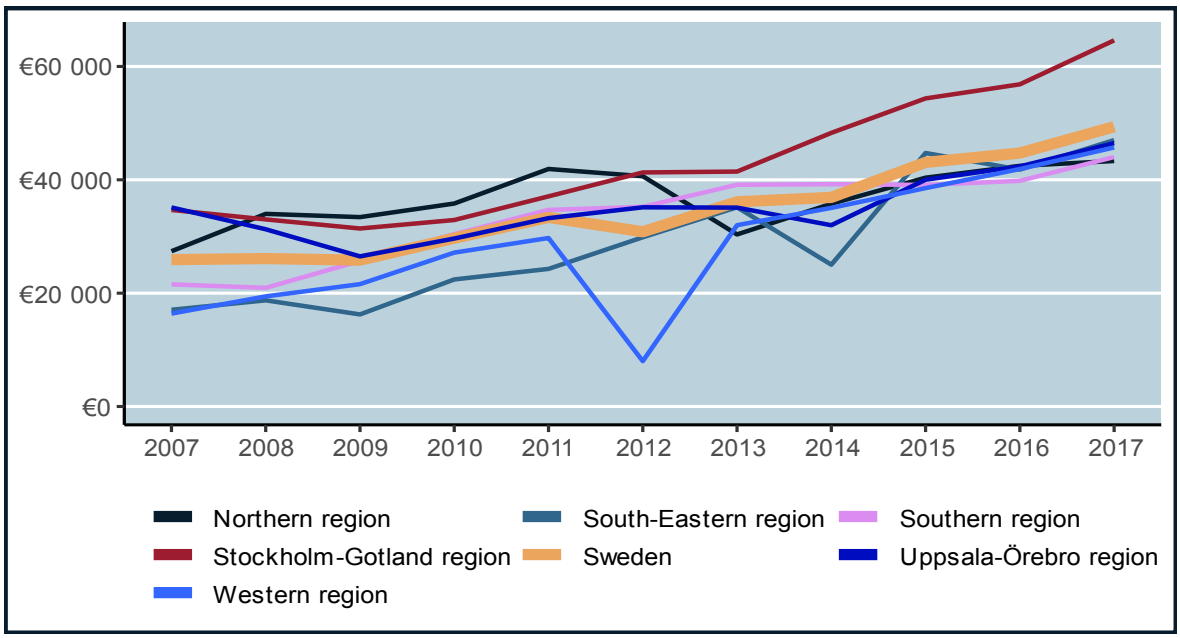

Figure 45: *Euro/case (deaths in diagnosis) in breast cancer for trastuzumab + pertuzumab + trastuzumab emtansine + lapatinib + palbociclib + ribociclib in Sweden. Note: There is incomplete reporting from Western Region in 2012 and South-Eastern region in 2014.*

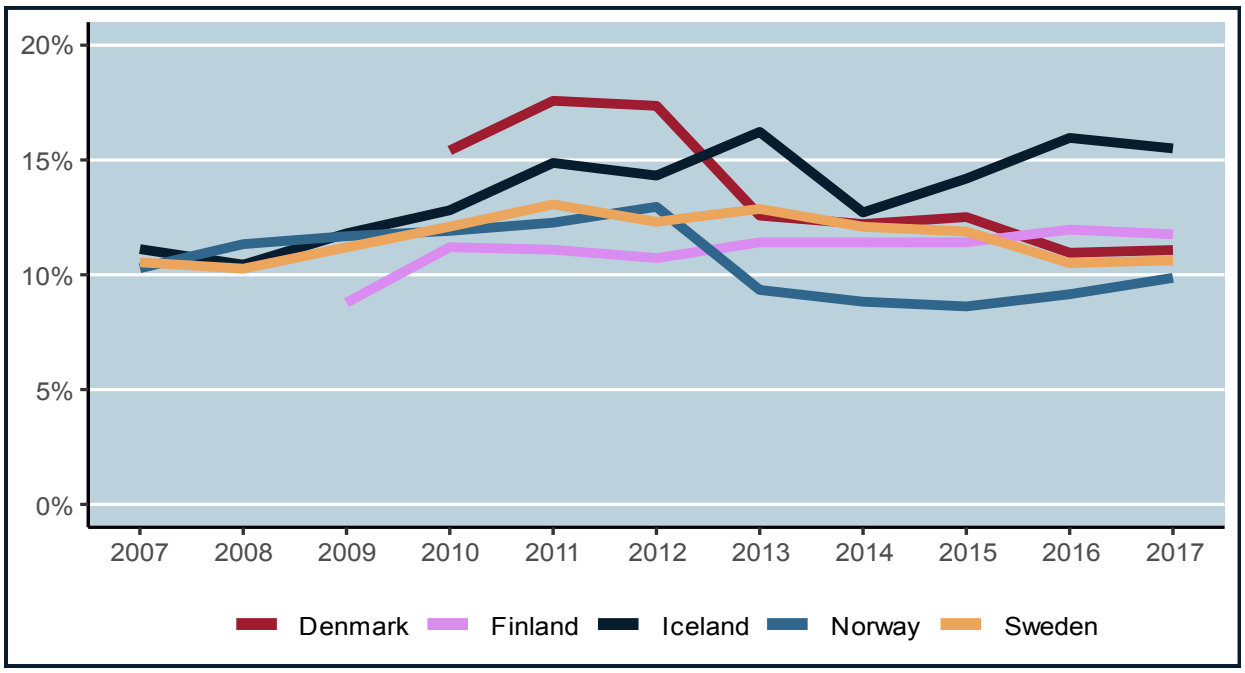

Figure 46: *Share of total cancer drugs sales of breast cancer drugs (trastuzumab + pertuzumab + trastuzumab emtansine + lapatinib + palbociclib + ribociclib) in the Nordic countries.*

3.5.2 Malignant melanoma

In malignant melanoma we present uptake curves for the following drugs:

- Ipilimumab (**Figure 47**)
- Vemurafenib, dabrafenib and trametinib (**Figure 48**)
- Nivolimumab (**Figure 49**)
- Pemrolizumab (**Figure 50**)
- PD-1 (Nivolimumab + Pemrolizumab) (**Figure 51**)
- All of the drugs above (**Figure 52**)

Figure 47 shows ipilimumab has been replaced with PD-1 drugs in 2015-16, but from 2017 has come back in use in combination with PD-1 drugs, though it can be noted that it was barely used in Finland. Finland also has low uptake of the newer drugs.

Regional variation for malignant melanoma drugs in Norway is on par with Sweden (**Figure 53** and **Figure 54**).

The new treatment (immune therapy) of metastatic malignant melanoma represents a revolution in cancer treatment overall. The development of ipilimumab – a CTLA-4 blocking drug – was considered the greatest scientific breakthrough in 2013 and this discovery, together with that of

PD-1 were awarded the Nobel prize in 2018. Still, when approved in 2011, ipilimumab access was very slow and low in the Nordic region with the exception of Denmark (and Iceland in 2012). Over the next 5 years the level of access has varied significantly. In Sweden the drug introduction delayed, partly based on cost, and partly based on the toxicity profile. This resulted in that less than 20% of patients had access to the drug during the first 5 years after approval.[14] More than 20% of patients with metastatic malignant melanoma had a survival of more than 7 years compared to only a few percentages with conventional, non-immunological therapy. We can therefore estimate that about 1,600-1,700 patients in Sweden alone did not receive the therapy that would have given >300 patients a prolonged survival of more than 7-8 years (and potentially cure). Access to ipilimumab was about 40% in Sweden of that in Denmark and around 50% in Norway compared to Denmark. Access in Finland was just over 10% compared to Denmark. Sales for ipilimumab from 2016-2017 show still major differences in access, with Denmark and Iceland on top.

Within Sweden there were large variations in access to ipilimumab, and these differences remain after 2016 as combination therapy with ipilimumab is used in 20-30% of patients in some regions while it is hardly ever used in other regions.

The PD-1 drugs for the treatment of metastatic malignant melanoma was introduced in 2015, a new class of drugs with lower toxicity compared to ipilimumab. The uptake of PD-1 inhibitors is more difficult to assess as these drugs (together with PDL-1 drugs) have several other indications outside of melanoma, including renal, lung and urothelial cancer (with several new indications coming in 2019-2020). Thus, the numbers in **Figure 49 - Figure 55** not only show the uptake of PD-1 in melanoma, but also include sales for the other indications.

For the drugs with an indication in B-RAF mutated metastatic malignant melanoma the situation is somewhat different. We see a more uniform uptake even though Denmark again has the highest uptake followed by Norway and Sweden. Finland has also low level of access for these drugs.

[14] See for example: https://medicinskaccess.se/artiklar/laekemedelsbehandling-av-tarmcancer-ett-lotteri/ (2019-01-18)

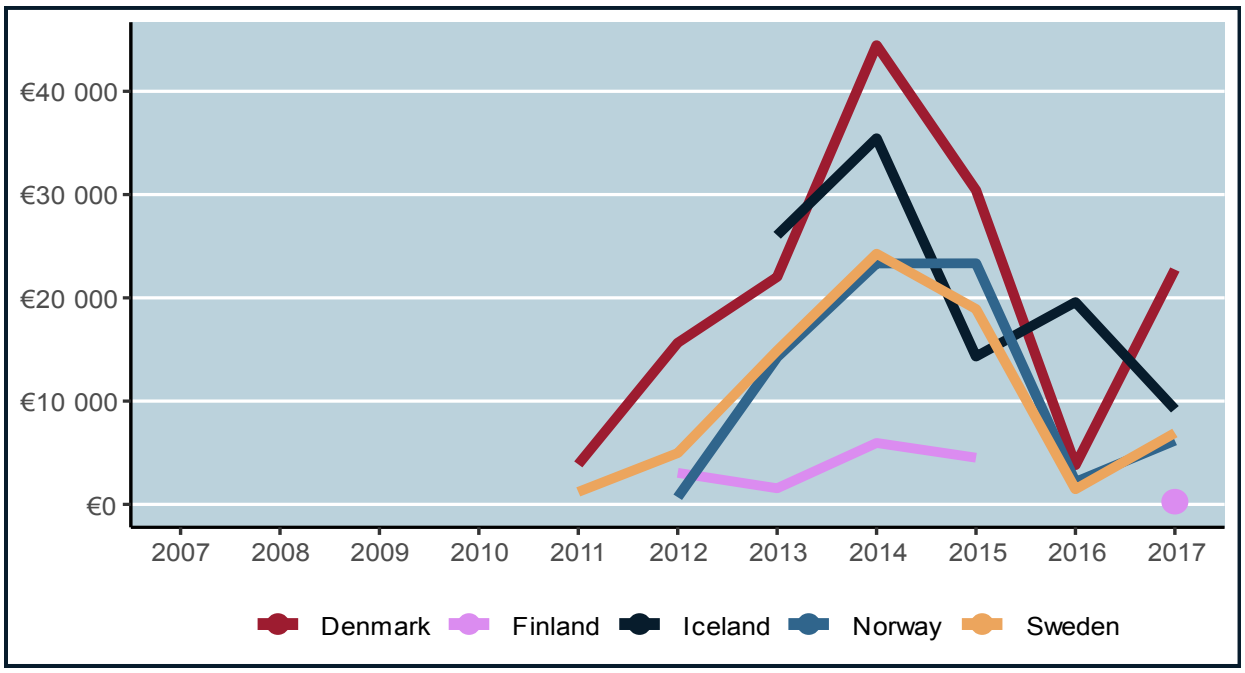

Figure 47: *Euro/case (deaths in diagnosis) in malignant melanoma for ipilimumab in the Nordic countries.*

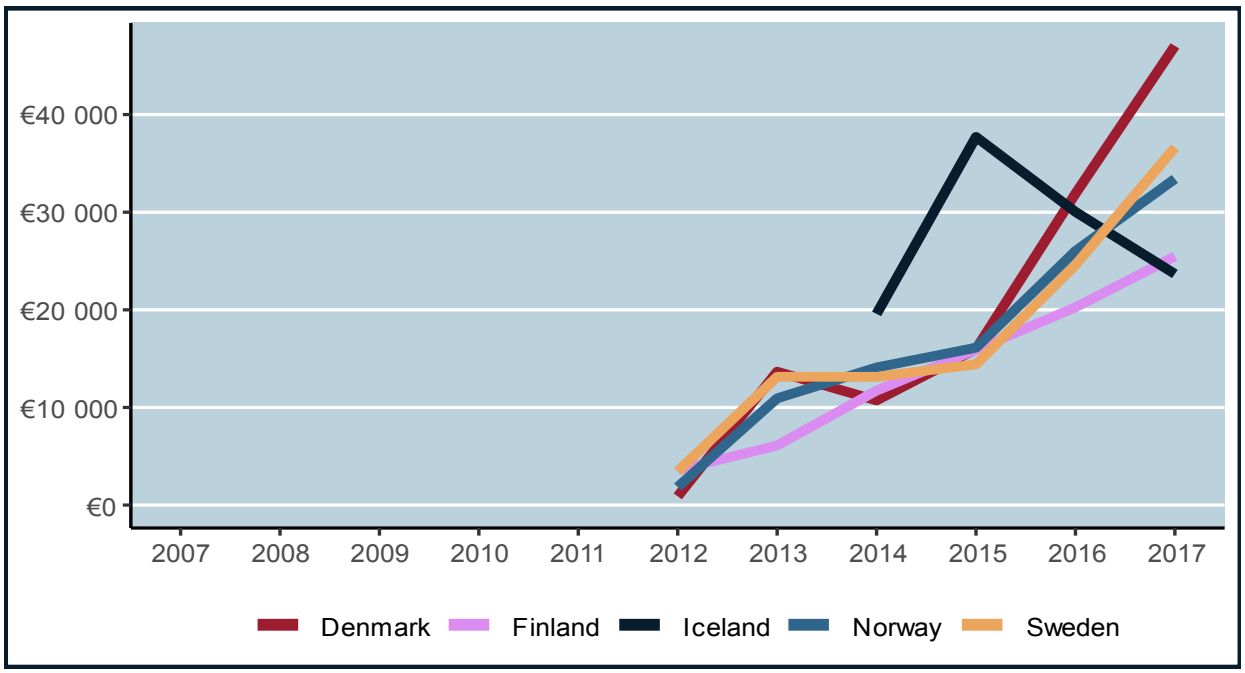

Figure 48: *Euro/case (deaths in diagnosis) in malignant melanoma for vemurafenib + dabrafenib + trametinib in the Nordic countries.*

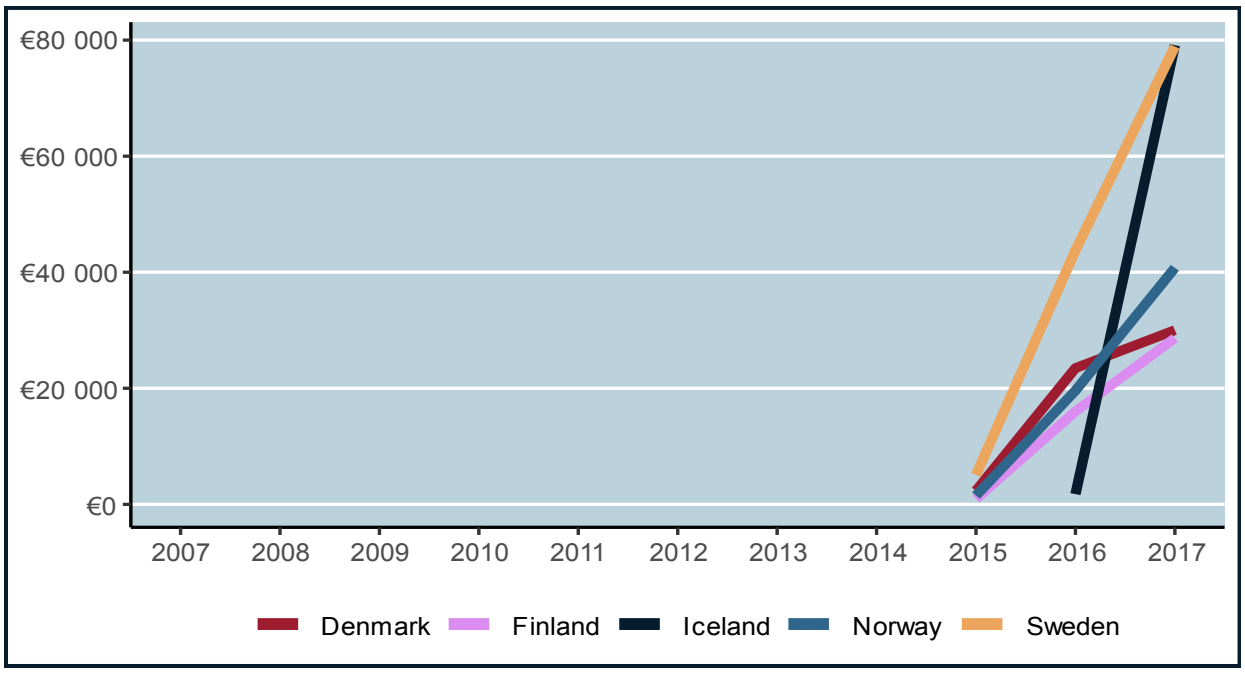

Figure 49: *Euro/case (deaths in diagnosis) in malignant melanoma for nivolumab in the Nordic countries.*

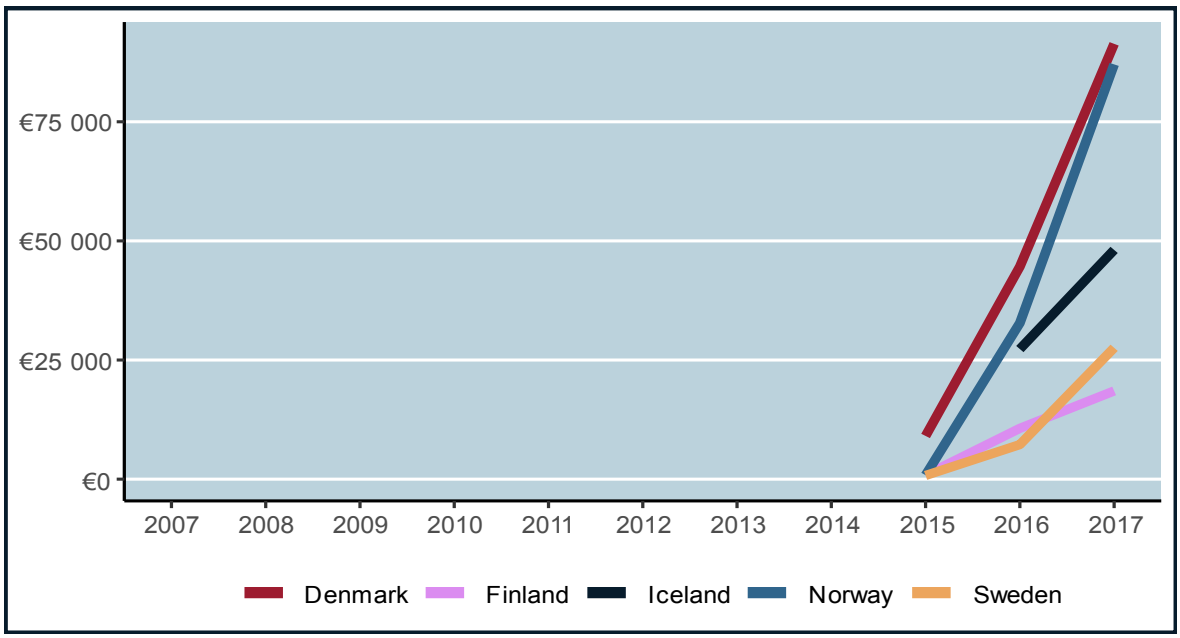

Figure 50: *Euro/case (deaths in diagnosis) in malignant melanoma for pembrolizumab in the Nordic countries.*

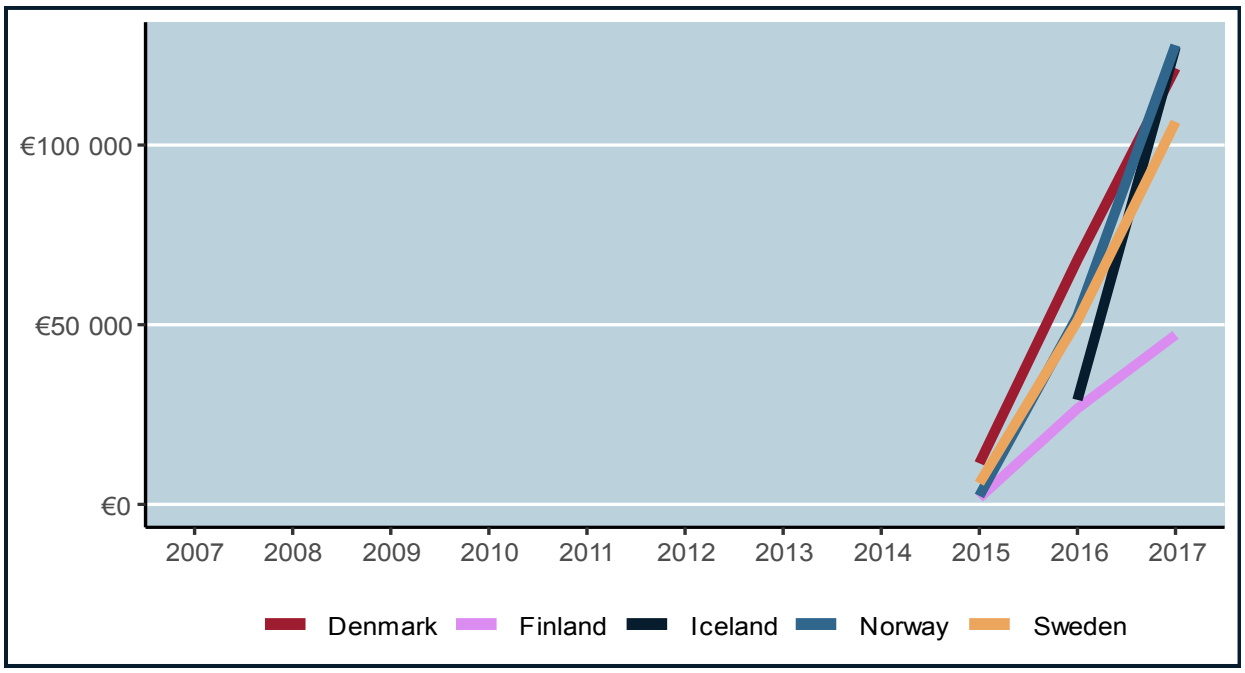

Figure 51: *Euro/case (deaths in diagnosis) in malignant melanoma for PD1-drugs in the Nordic countries.*

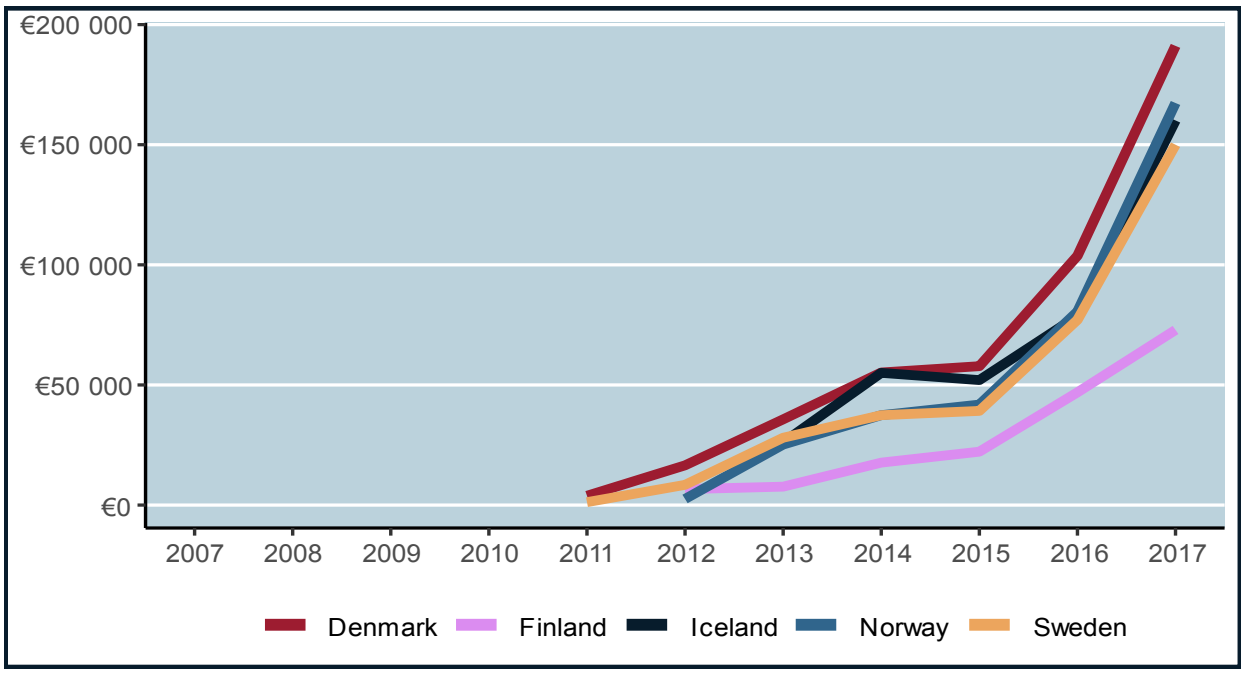

Figure 52: *Euro/case (deaths in diagnosis) in malignant melanoma for ipilimumab + vemurafenib + dabrafenib + trametinib + nivolumab + pembrolizumab in the Nordic countries.*

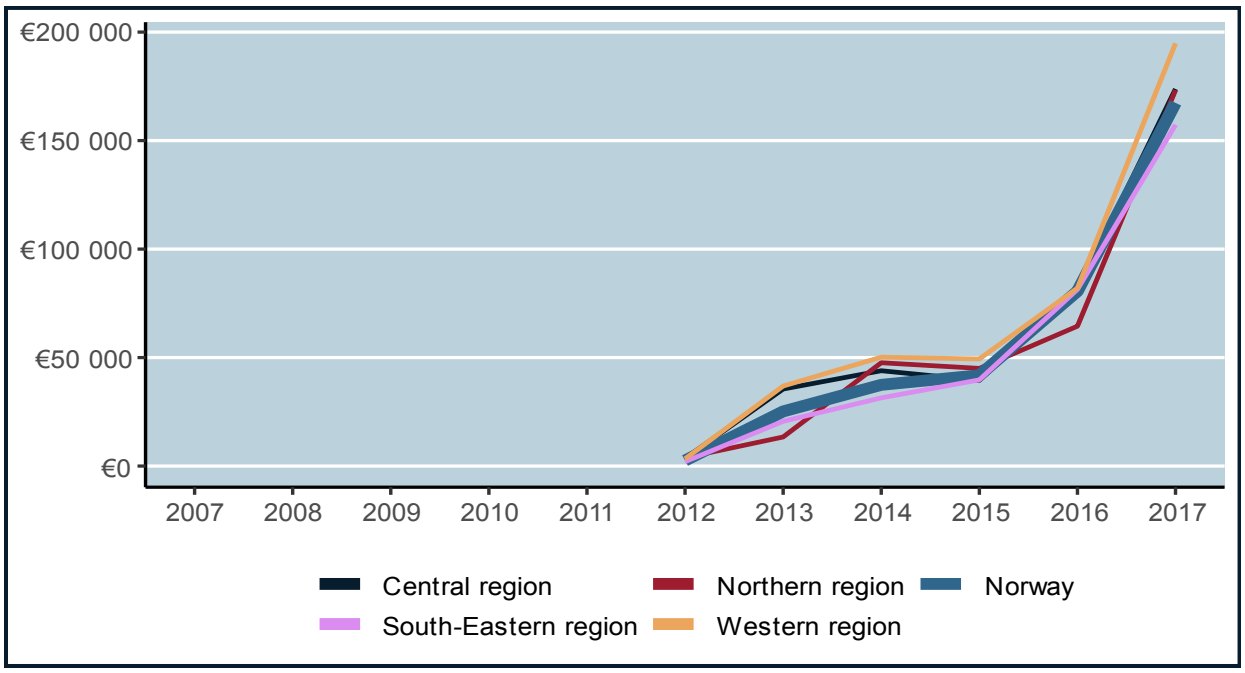

Figure 53: *Euro/case (deaths in diagnosis) in malignant melanoma for ipilimumab + vemurafenib + dabrafenib + trametinib + nivolumab + pembrolizumab in Norway.*

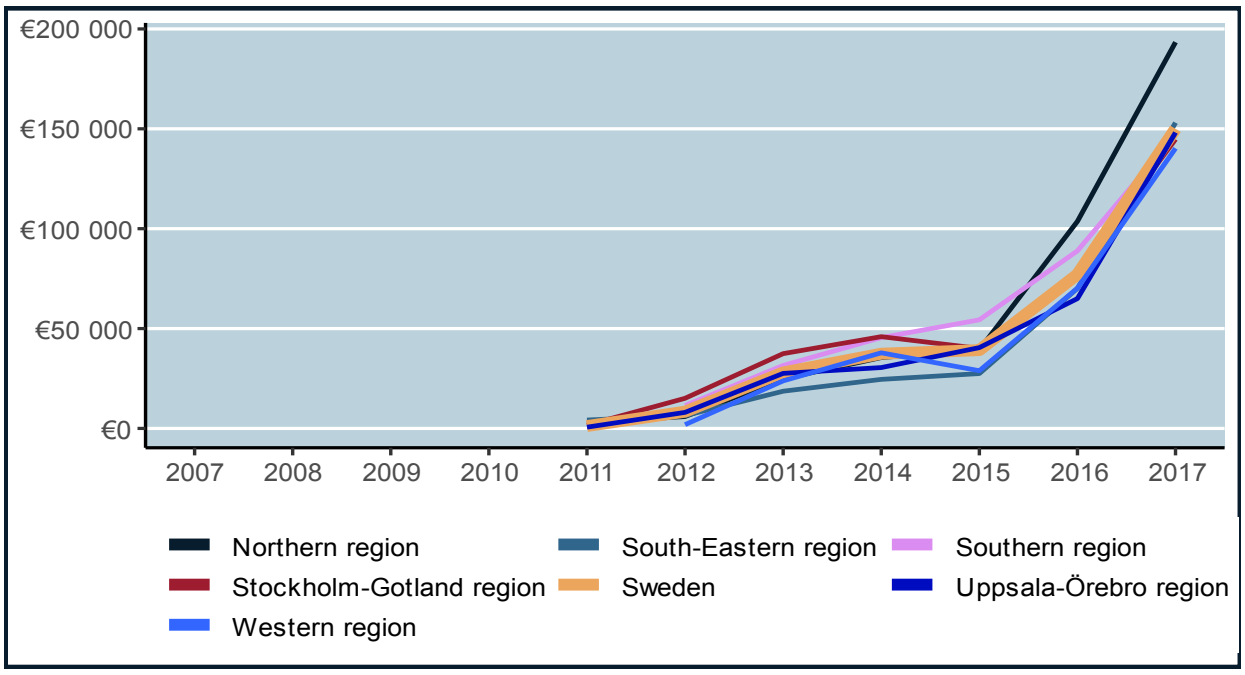

Figure 54: *Euro/case (deaths in diagnosis) in malignant melanoma for ipilimumab + vemurafenib + dabrafenib + trametinib + nivolumab + pembrolizumab in Sweden.*
Note: There is incomplete reporting from Western Region in 2012 and South-Eastern region in 2014.

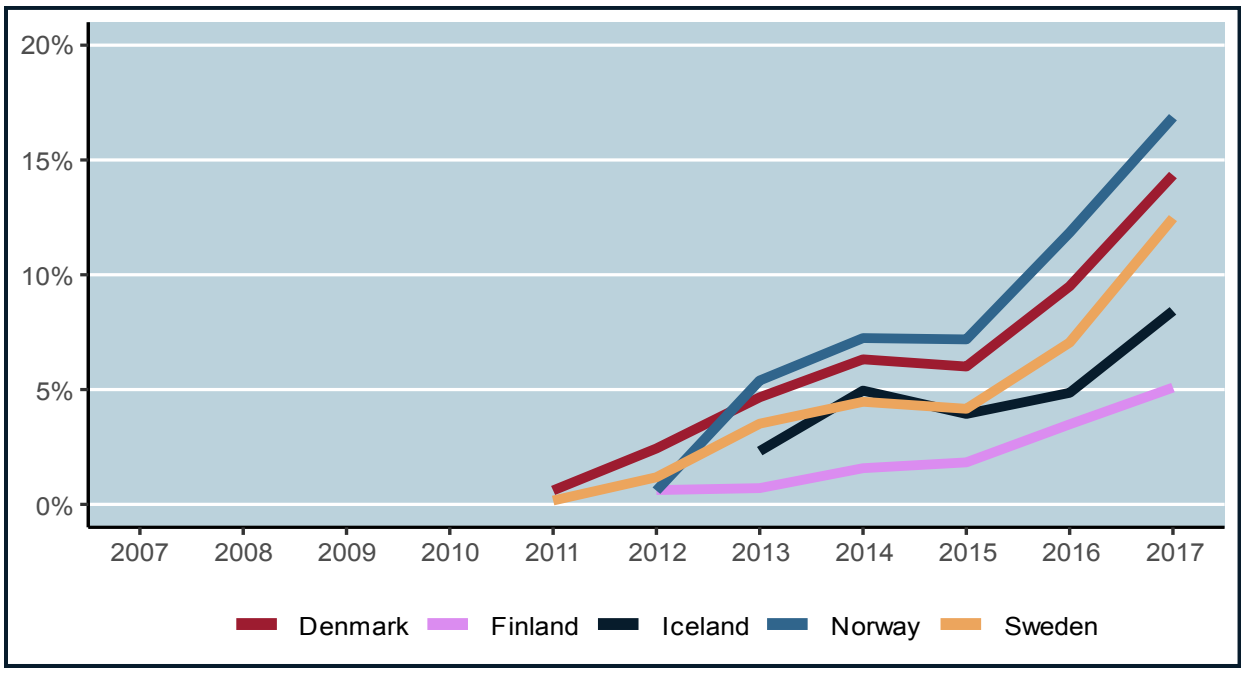

Figure 55: *Share of total cancer drugs sales of melanoma drugs (ipilimumab + vemurafenib + dabrafenib + trametinib + nivolumab + pembrolizumab) in the Nordic countries.*

3.5.3 Multiple Myeloma

In multiple myeloma we present uptake curves for the following drugs[15]:

- Bortezomib (**Figure 56**)
- Lenalidomide, thalidomide and pomalidomide (**Figure 57**)
- Carfilzomib (**Figure 58**)
- Daratumumab (**Figure 59**)
- All of the drugs above (**Figure 60**)

For the older drugs, usage is similar between the countries, although there are drastic differences for the newer drugs. Regional differences (**Figure 61** and **Figure 62**) are fairly consistent with the exception of much lower usage in Northern Norway and higher usage in the Stockholm-Gotland region in Sweden.

Multiple myeloma is a disease where cancer drugs play a significant role. The cost for treatment of the disease has increased dramatically over the last 15 years since the introduction of bortezomib, later followed by thalidomide, lenalinomid and pomolinomid. Most recently carfilzomib and

[15] Since there is no regional data available for the mortality in myeloma from NORDCAN, the regional analysis is based on an approximation of the regional distribution the national cases.

daratumumab have been introduced. The uptake of these two new drugs has been rapid and for daratumumab extremely different, with Denmark having a very rapid and high uptake being >10 times that of the other Nordic countries. Stockholm-Gotland is on a regional Swedish level an out layer with very high sales of myeloma drugs. Overall sales of myeloma drugs represent about 15% of total cancer drug sales in the Nordic countries, while the disease represents about 3% of total cancer mortality.

Daratumumab was partly developed in Denmark leading to high medical knowledge early on. Denmark was also the first Nordic country to recommend mono treatment as well as two combination treatments (September 2016 and June 2017). This most likely explains the high uptake of daratumumab 2016 and 2017 in Denmark. Norway followed in October 2017 with recommendation of mono treatment and one combination treatment. In Finland, Fimea has published two evaluation reports for daratumumab (August 2016 monotherapy and June 2017 combinations), but the uptake of daratumumab started only after the Finnish Myeloma Group published their treatment guideline in November 2017. In Sweden, daratumumab was recommended for mono treatment only in April 2018.

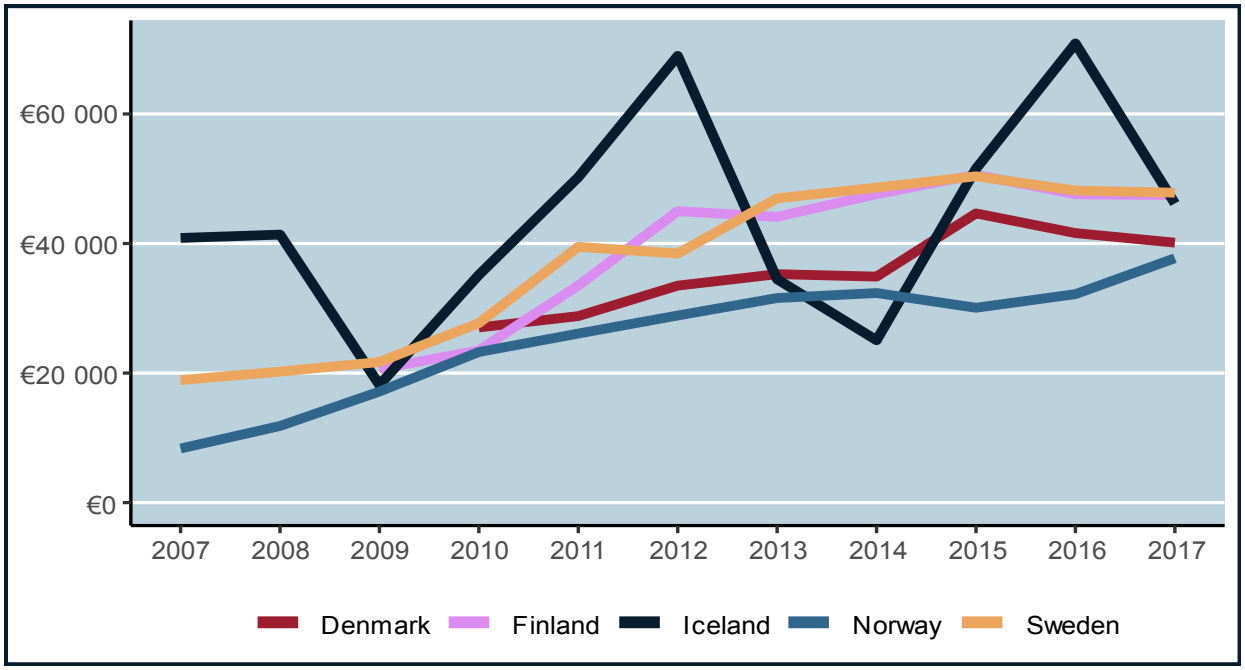

Figure 56: *Euro/case (deaths in diagnosis) in myeloma for bortezomib in the Nordic countries.*

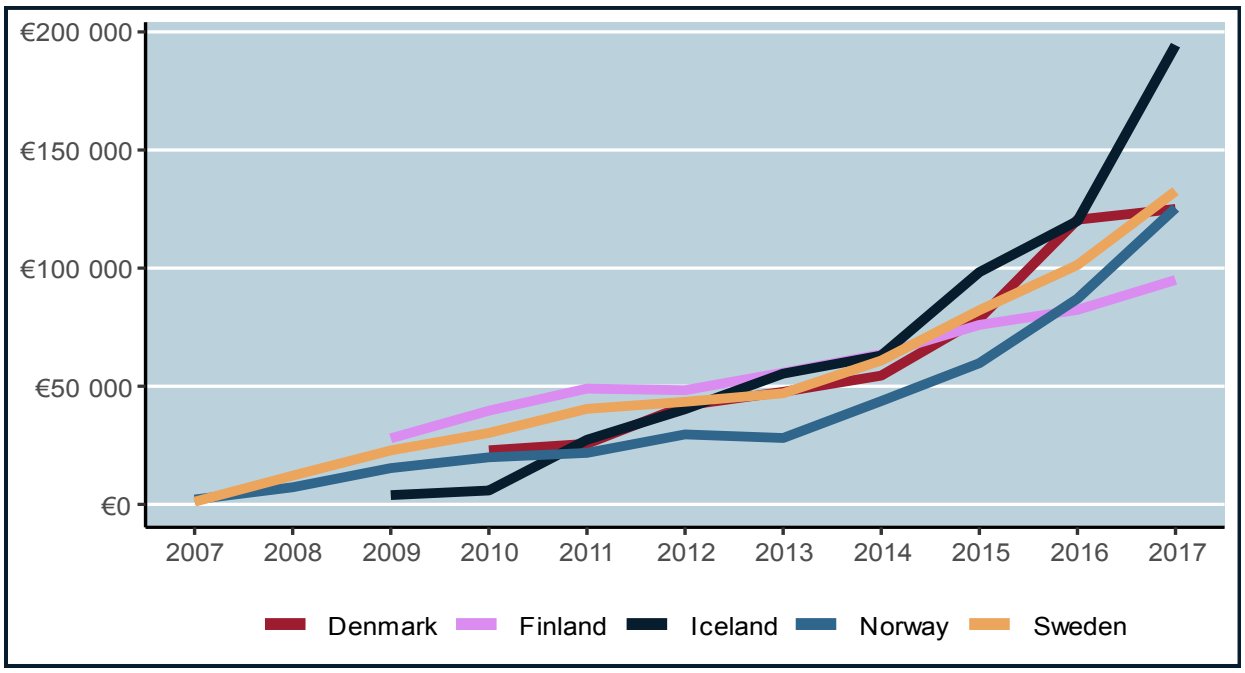

Figure 57: *Euro/case (deaths in diagnosis) in myeloma for lenalidomide + thalidomide + pomalidomide in the Nordic countries.*

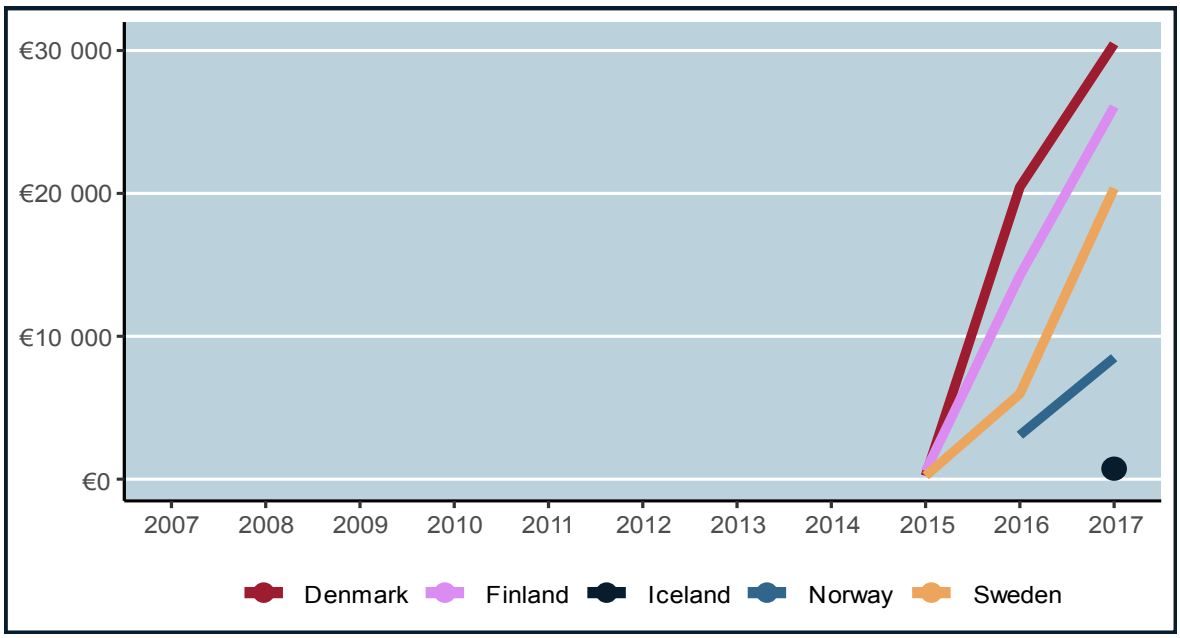

Figure 58: *Euro/case (deaths in diagnosis) in myeloma for carfilzomib in the Nordic countries.*

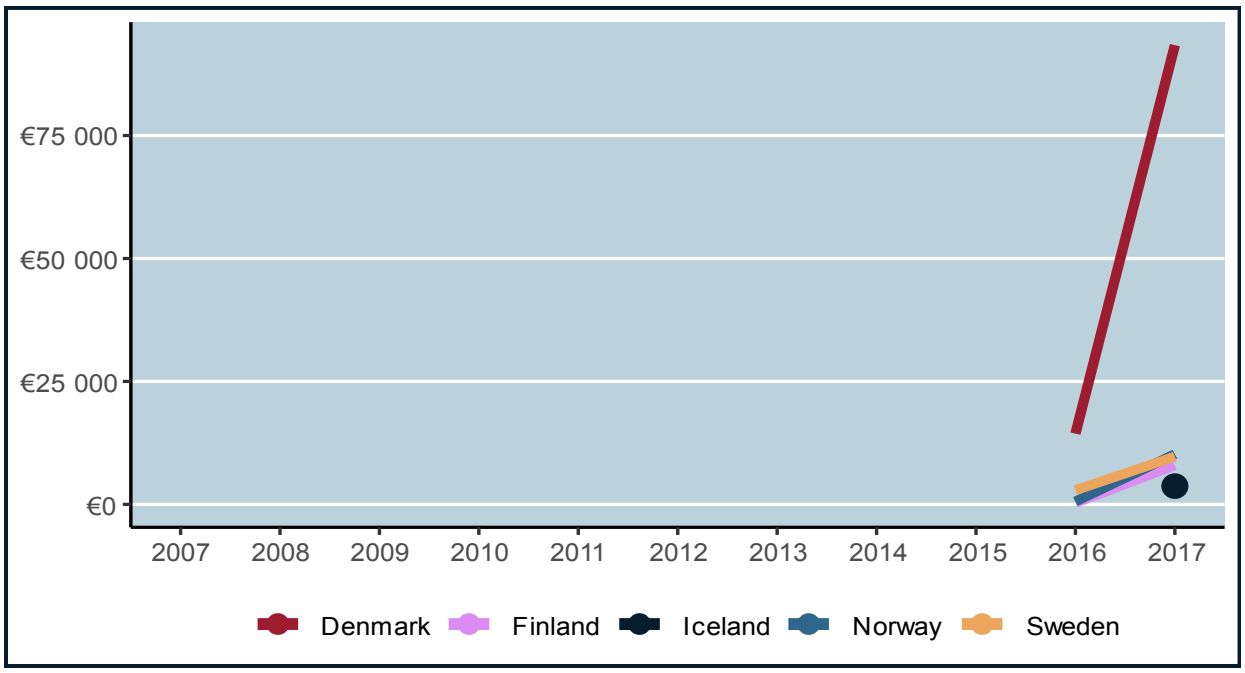

Figure 59: *Euro/case (deaths in diagnosis) in myeloma for daratumumab in the Nordic countries.*

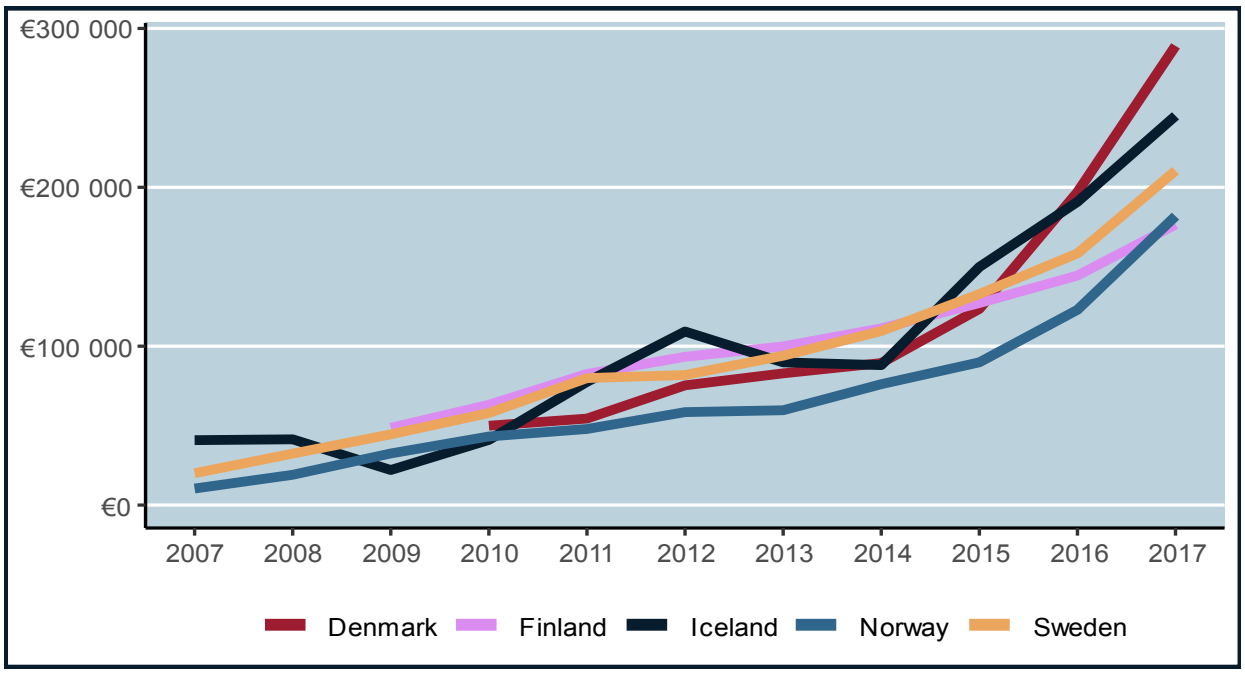

Figure 60: *Euro/case (deaths in diagnosis) in myeloma for bortezomib + lenalidomide + thalidomide + pomalidomide + carfilzomib + daratumumab in the Nordic countries.*

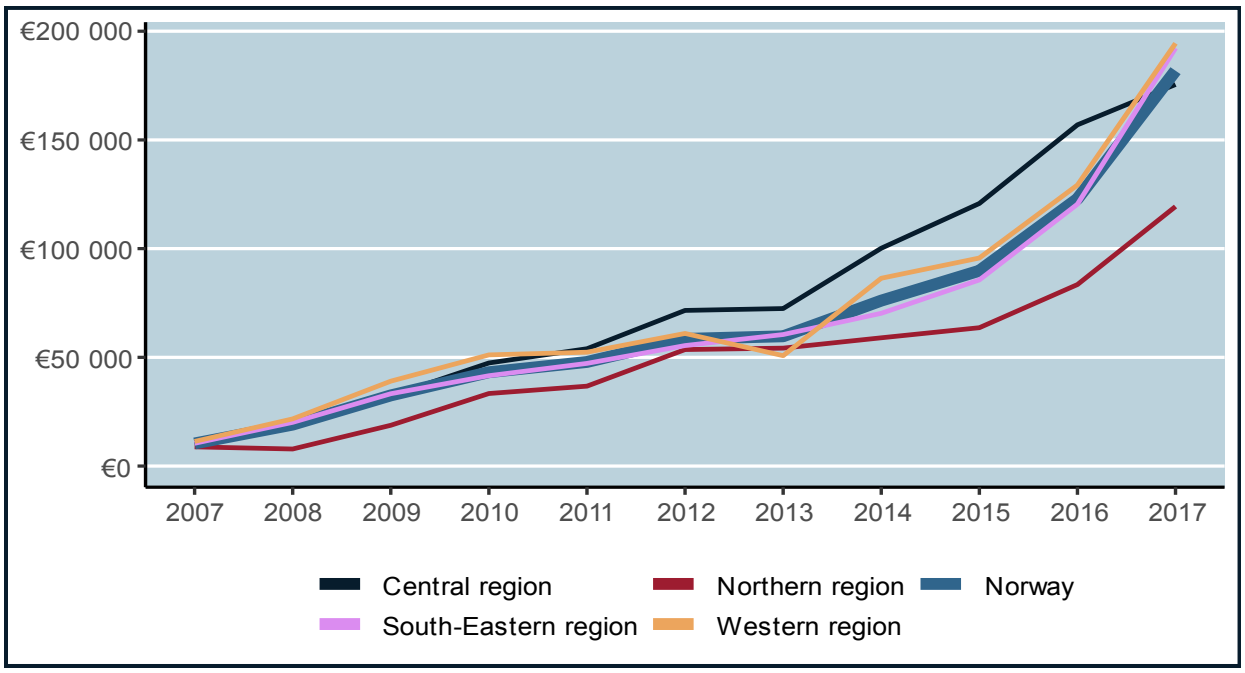

Figure 61: *Euro/case (deaths in diagnosis) in myeloma for bortezomib + lenalidomide + thalidomide + pomalidomide + carfilzomib + daratumumab in Norway.*

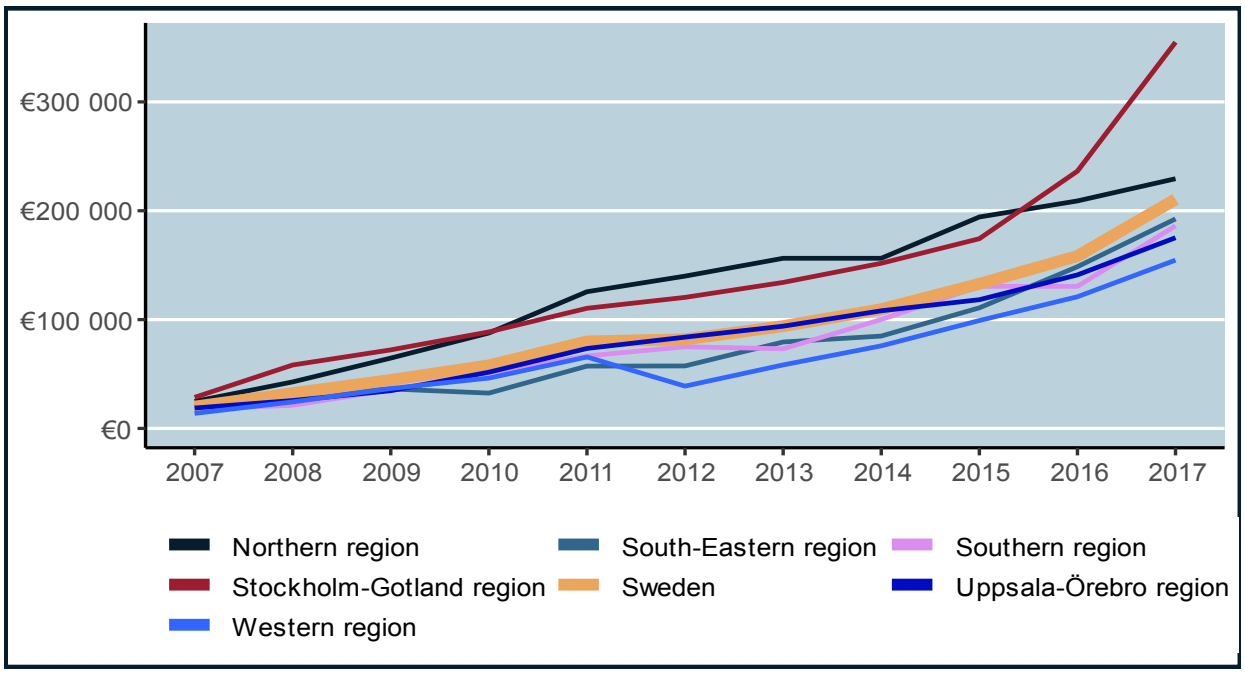

Figure 62: *Euro/case (deaths in diagnosis) in myeloma for bortezomib + lenalidomide + thalidomide + pomalidomide + carfilzomib + daratumumab in Sweden.*
Note: There is incomplete reporting from Western Region in 2012 and South-Eastern region in 2014.

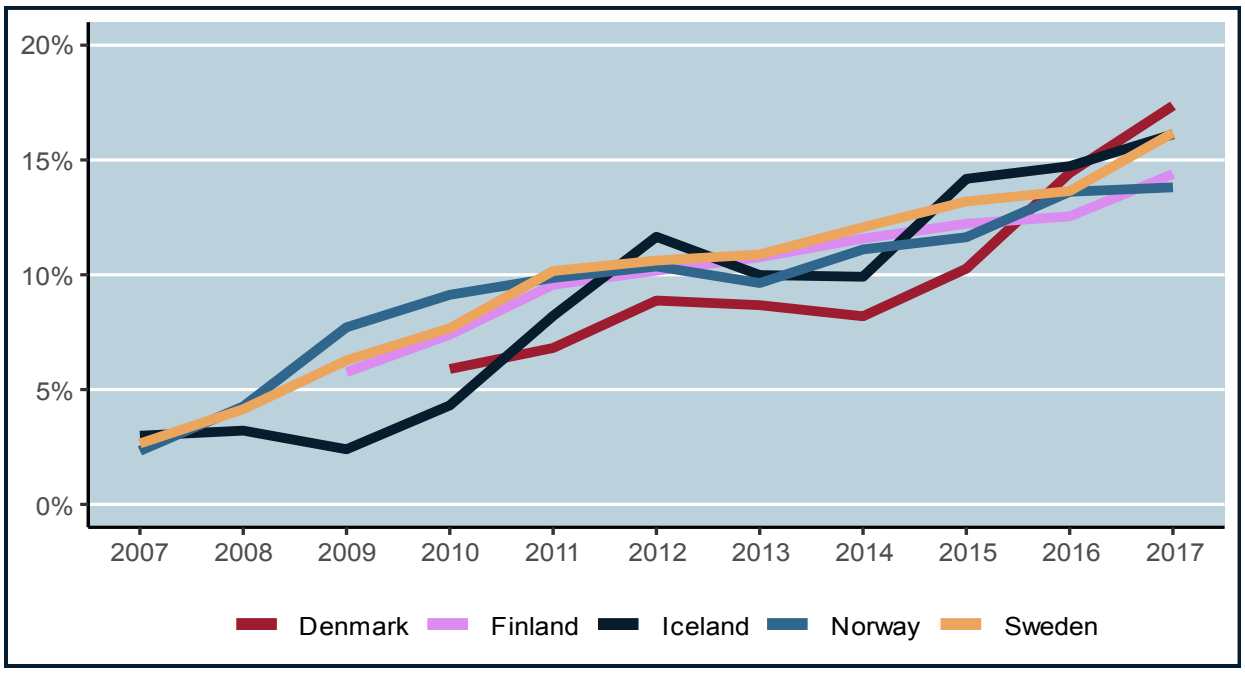

Figure 63: *Share of total cancer drugs sales of myeloma drugs (bortezomib + lenalidomide + thalidomide + pomalidomide + carfilzomib + daratumumab) in the Nordic countries.*

3.5.4 Lung cancer

For lung cancer we present uptake curves for the following drugs

- Erlotinib (**Figure 64**)
- Gefitinib (**Figure 65**)
- Crizotinib (**Figure 66**)
- Osimertinib (**Figure 67**)
- All of the drugs above (**Figure 68**)

In lung cancer we see large variations both between countries and within countries. Over the time period the use of erlotinib varied greatly. There are also large differences in the use of gefitinib, crizotinib and osimertinib. This is not due to substitution between the drugs, as overall variation is also large (**Figure 68**). Regional differences in this field are smaller in Sweden (**Figure 70**) compared to Norway (**Figure 69**). Sweden is on top with 3 times the sales compared to Denmark and Norway and twice the sales compared to Finland. We also note large intra-country variation in the sales both in Norway (contrary to most other cancer drugs) as well as in Sweden.

Please note that we have not included PD-1 or PD-L1 drugs in the lung cancer analysis as we lack information about the extent of use of these drugs in lung cancer. PD-1 and PD-L1 drugs are analyzed in relation to malignant melanoma.

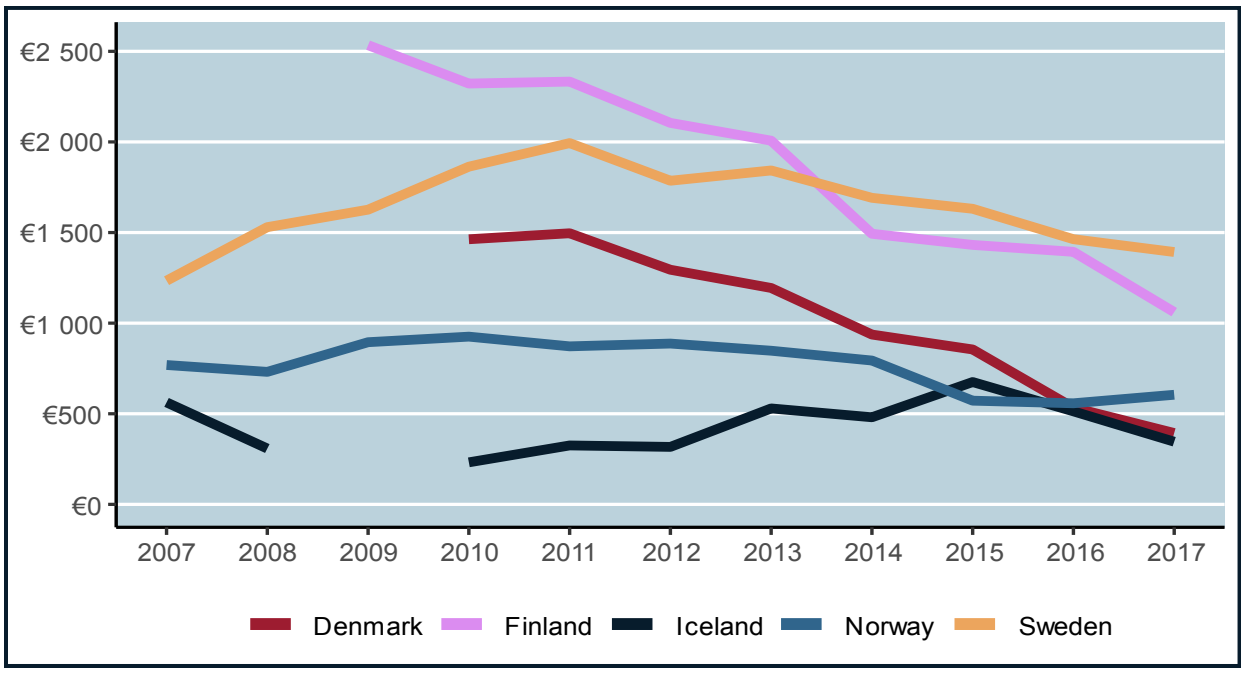

Figure 64: *Euro/case (deaths in diagnosis) in lung cancer for erlotinib in the Nordic countries.*

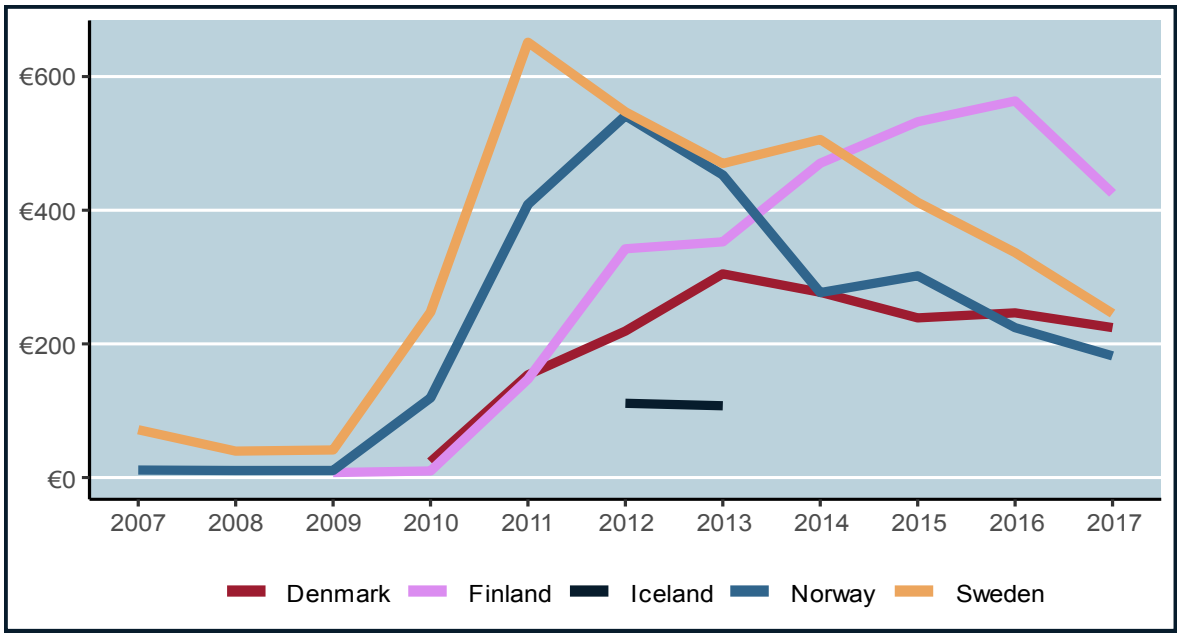

Figure 65: *Euro/case (deaths in diagnosis) in lung cancer for gefitinib in the Nordic countries.*

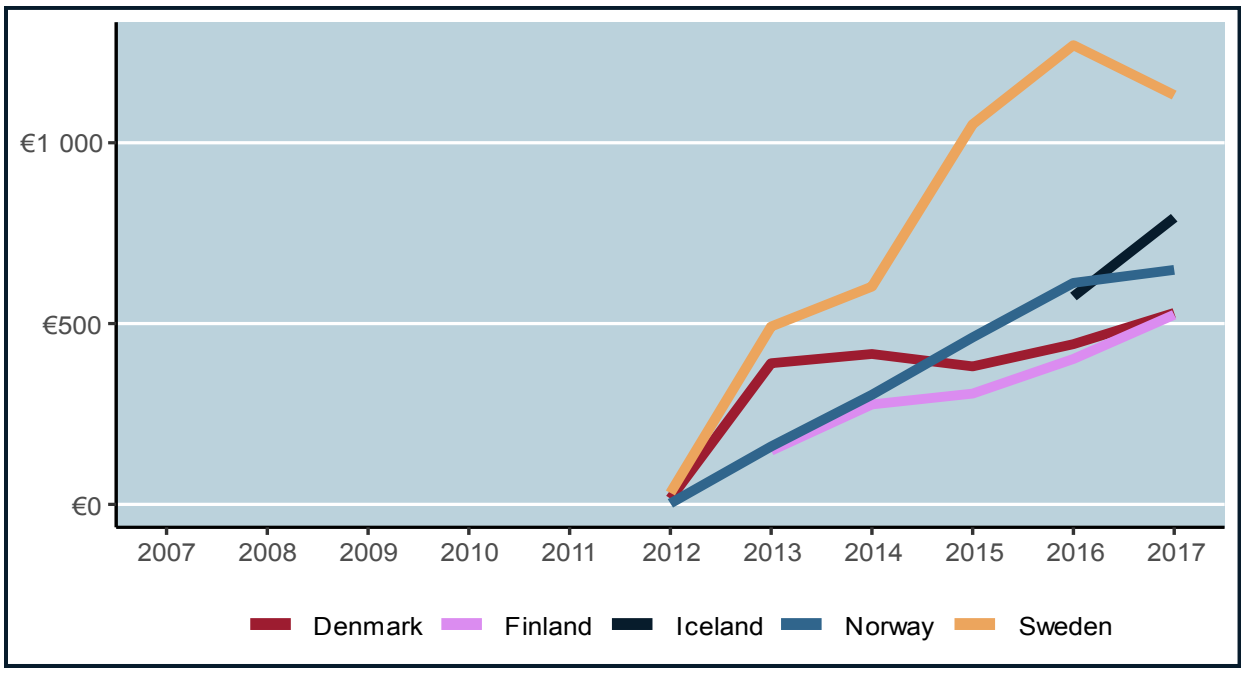

Figure 66: *Euro/case (deaths in diagnosis) in lung cancer for crizotinib in the Nordic countries.*

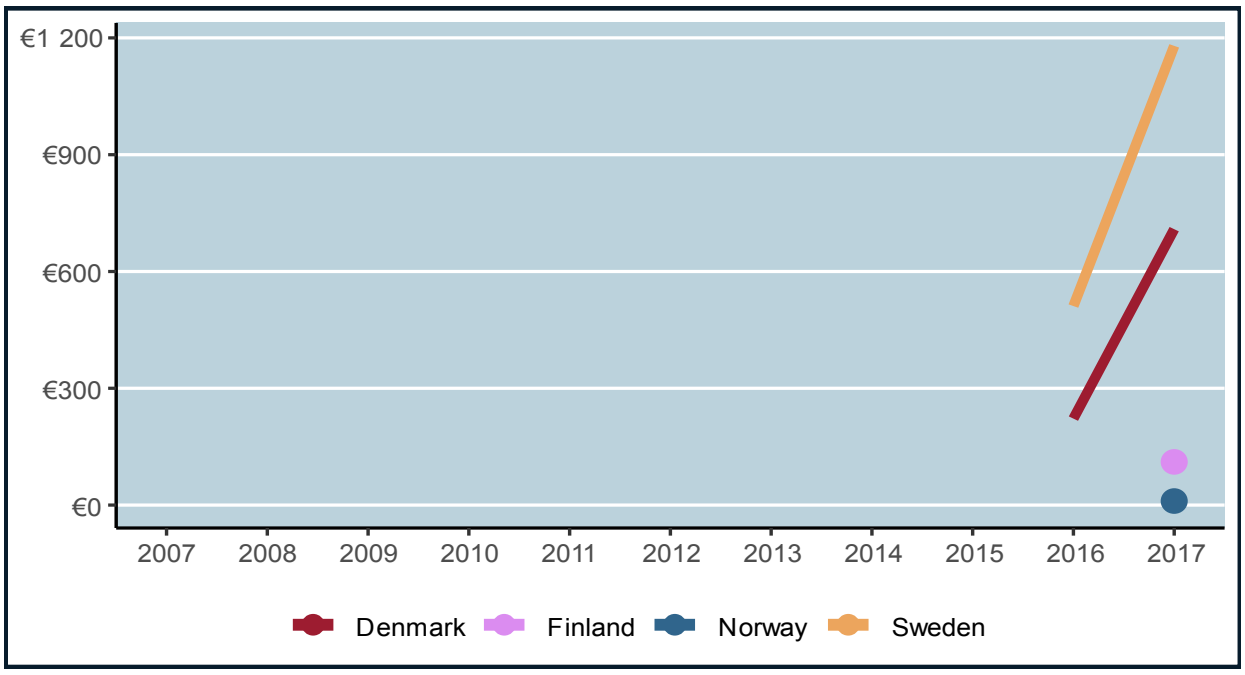

Figure 67: *Euro/case (deaths in diagnosis) in lung cancer for osimertinib in the Nordic countries.*

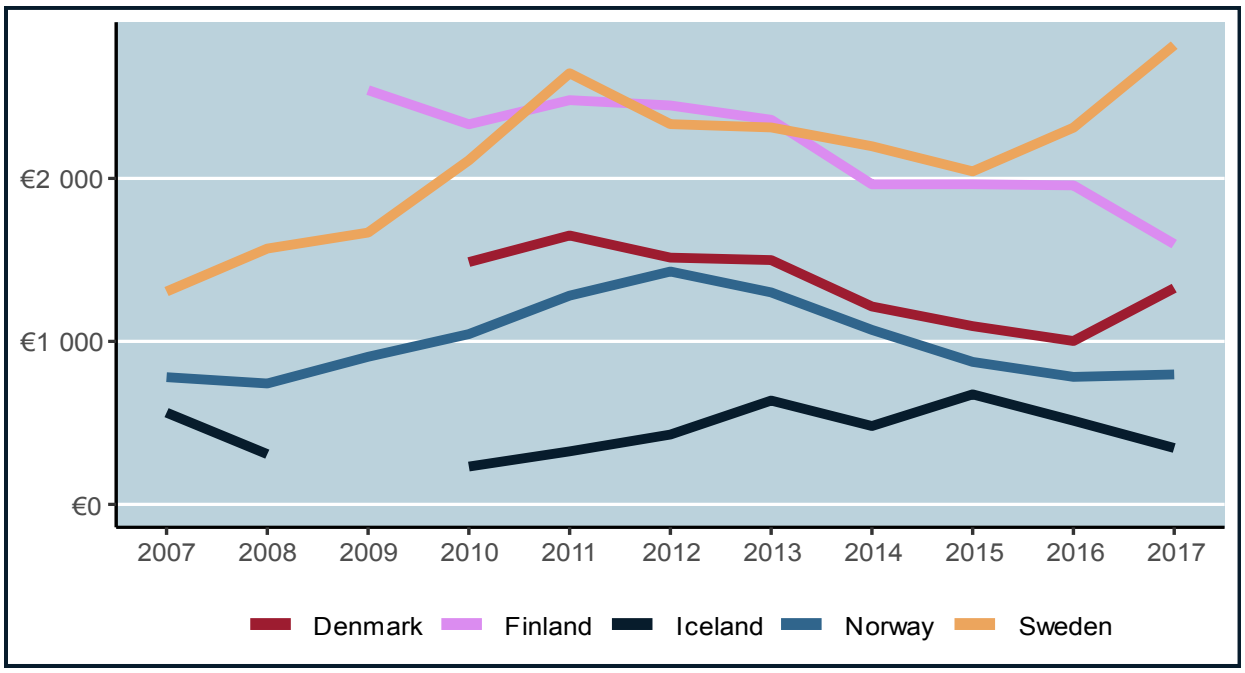

Figure 68: *Euro/case (deaths in diagnosis) in lung cancer for the new drugs in lung cancer in the Nordic countries.*

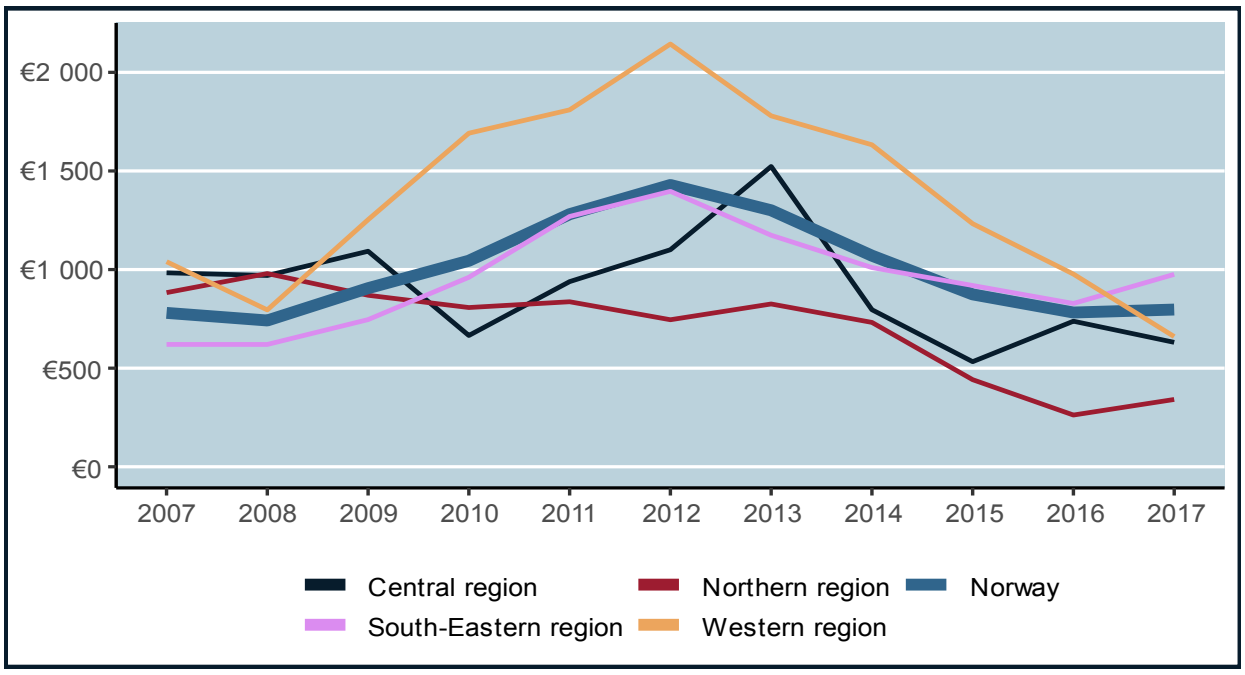

Figure 69: *Euro/case (deaths in diagnosis) in lung cancer for the new drugs in lung cancer in Norway.*

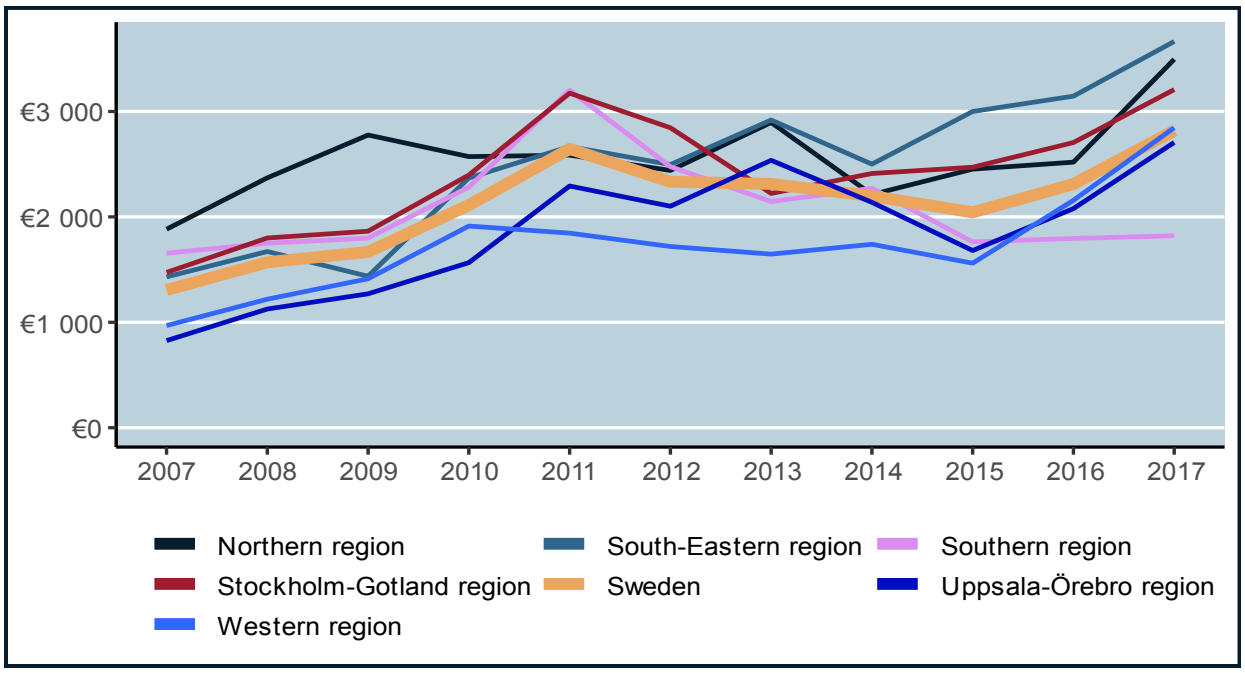

Figure 70: *Euro/case (deaths in diagnosis) in lung cancer for the new drugs in lung cancer in Sweden.*

Note: There is incomplete reporting from Western Region in 2012 and South-Eastern region in 2014.

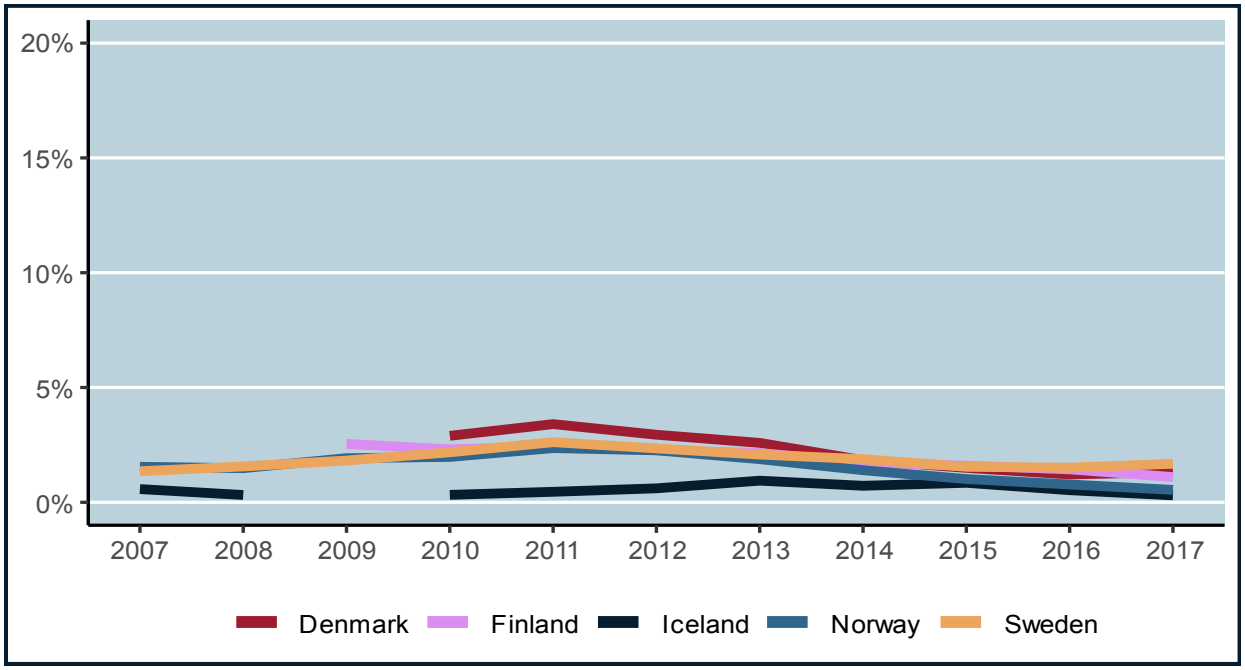

Figure 71: *Share of total cancer drugs sales of the new drugs in lung cancer in the Nordic countries.*

3.5.5 Colorectal cancer

For colorectal cancer we present uptake for the following drugs:

- Bevacizumab (**Figure 72**)
- Cetuximab (**Figure 73**)
- Panitumumab (**Figure 74**)
- All of the drugs above (**Figure 75**)

It is almost 15 years since new monoclonal antibodies (bevacizumab and cetuximab) were introduced for the treatment of metastatic colorectal cancer. Later, panitumumab has been added as a therapeutic option. None of these drugs has showed curative potential in the adjuvant setting. There are very large variations, especially in the use of bevacizumab (which has its main indication in metastatic colorectal cancer but also is approved in renal, lung, ovarian and cervical cancer). The use in Finland is almost 3 times that of Norway and Sweden with Denmark in between. Within country variation is small in Norway, but large in Sweden with South East region at a level 3 times that of the Western region (**Figure 76** and **Figure 77**).

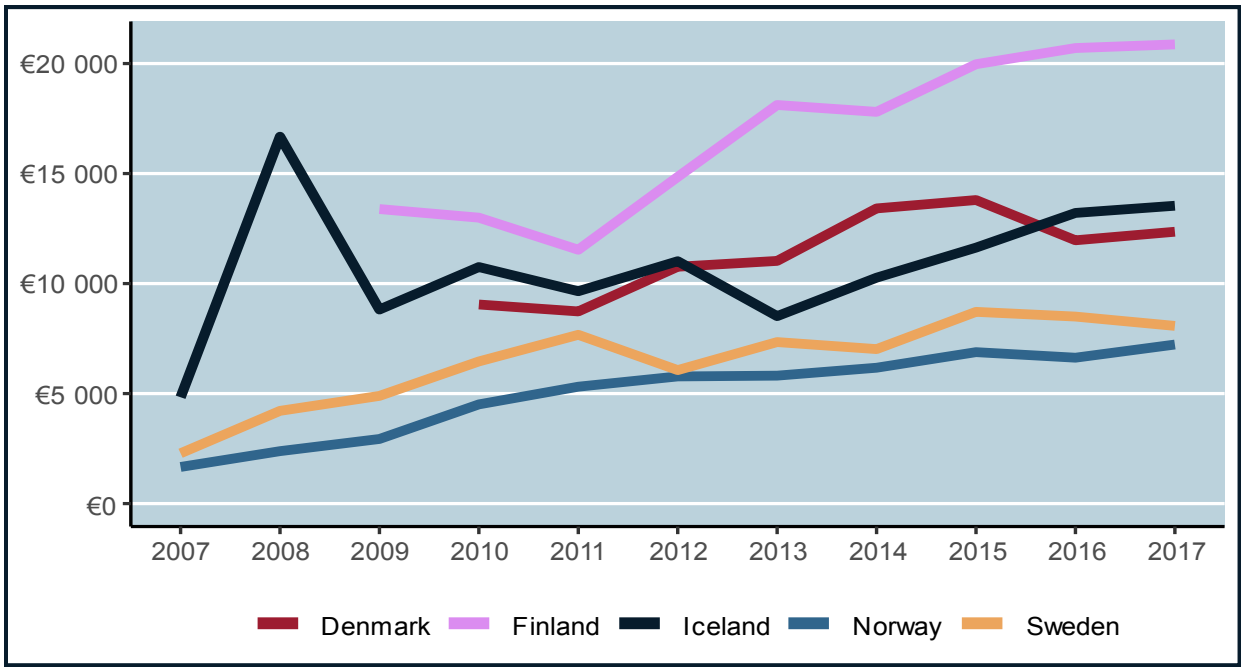

Figure 72: *Euro/case (deaths in diagnosis) in colorectal cancer for bevacizumab in the Nordic countries.*

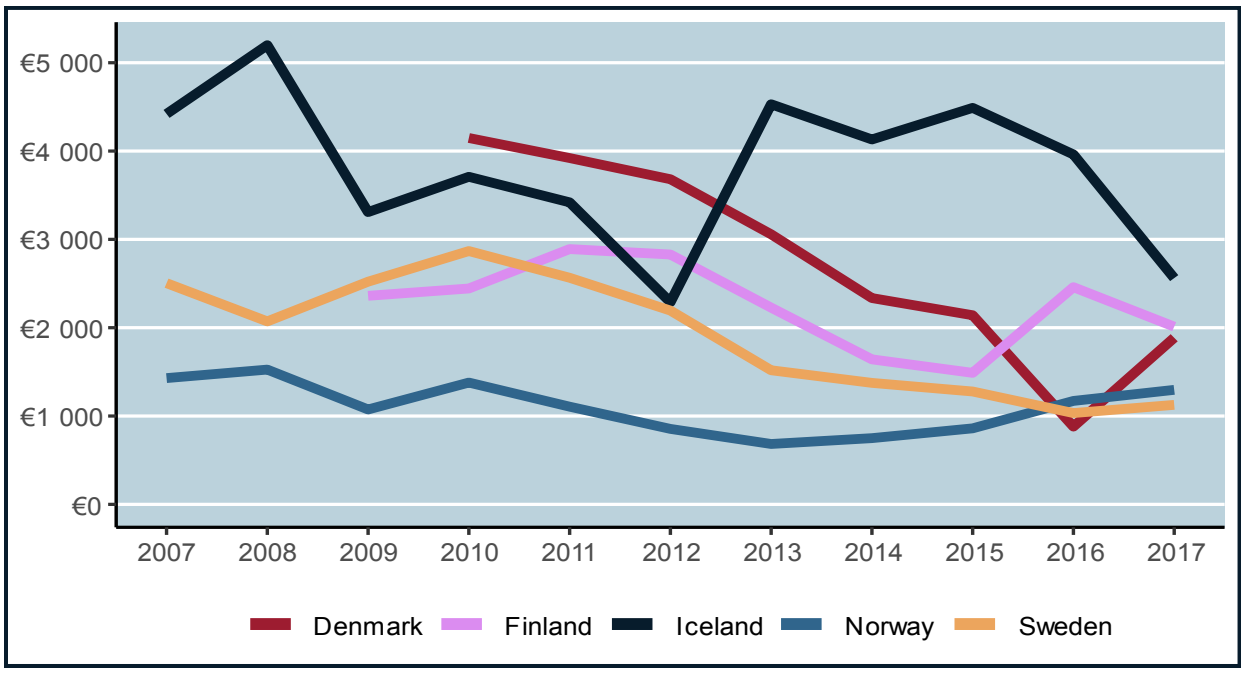

Figure 73: *Euro/case (deaths in diagnosis) in colorectal cancer for cetuximab in the Nordic countries.*

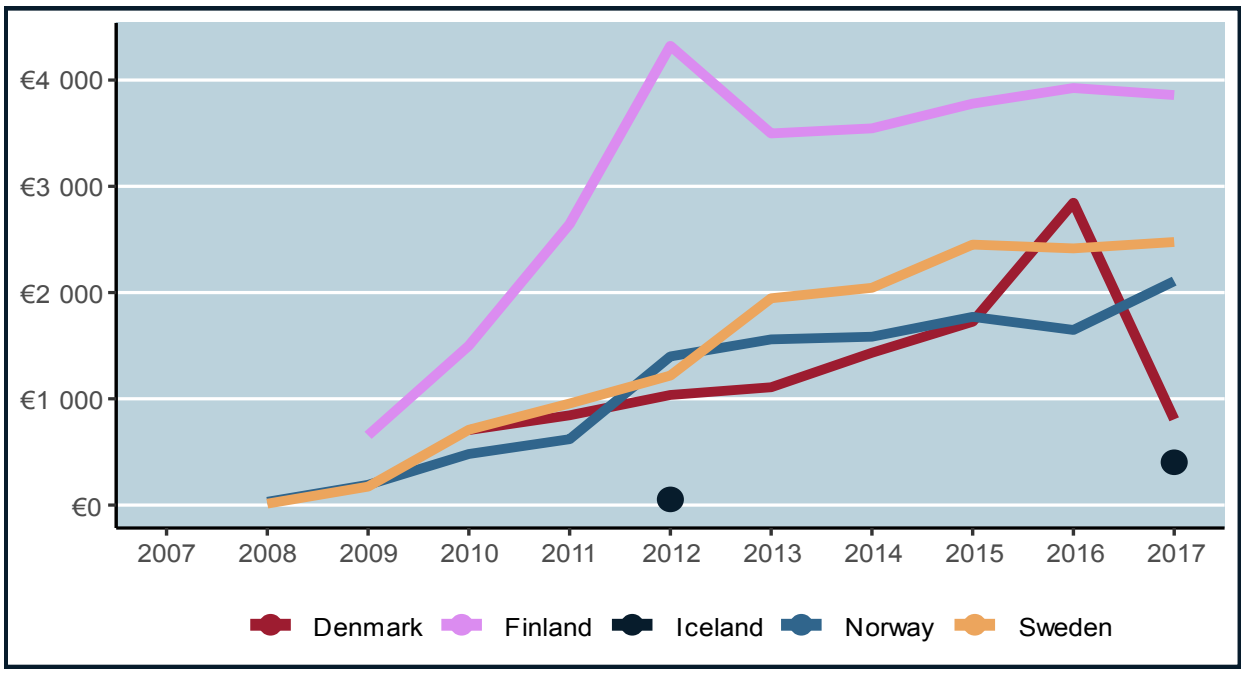

Figure 74: Euro/case (deaths in diagnosis) *in colorectal cancer for panitumumab in the Nordic countries.*

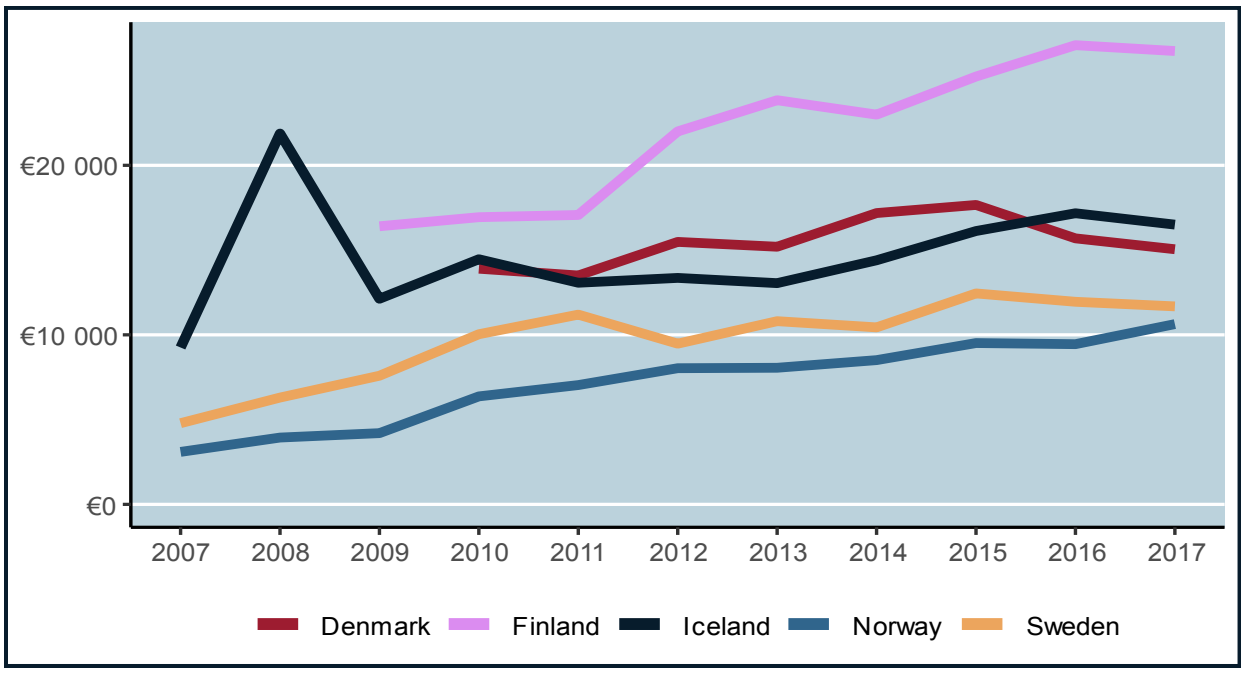

Figure 75: *Euro/case (deaths in diagnosis) in colorectal cancer for the new drugs in colorectal cancer in the Nordic countries.*

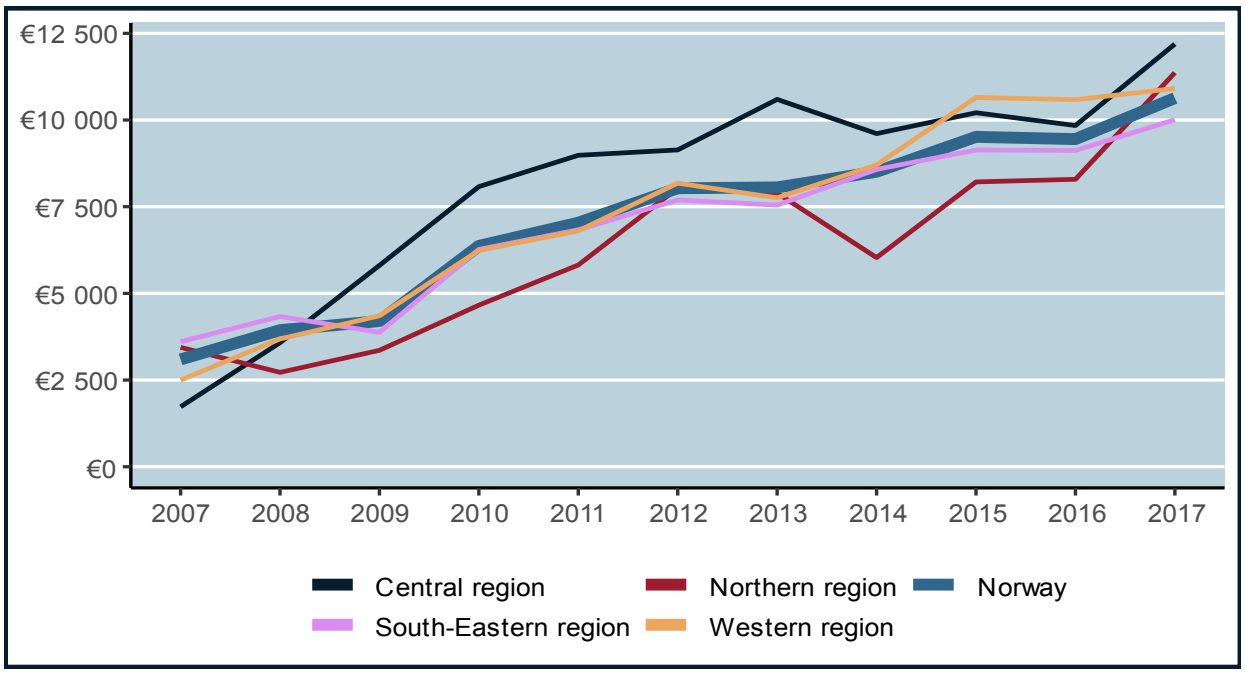

Figure 76: *Euro/case (deaths in diagnosis) in colorectal cancer for the new drugs in colorectal cancer in Norway.*

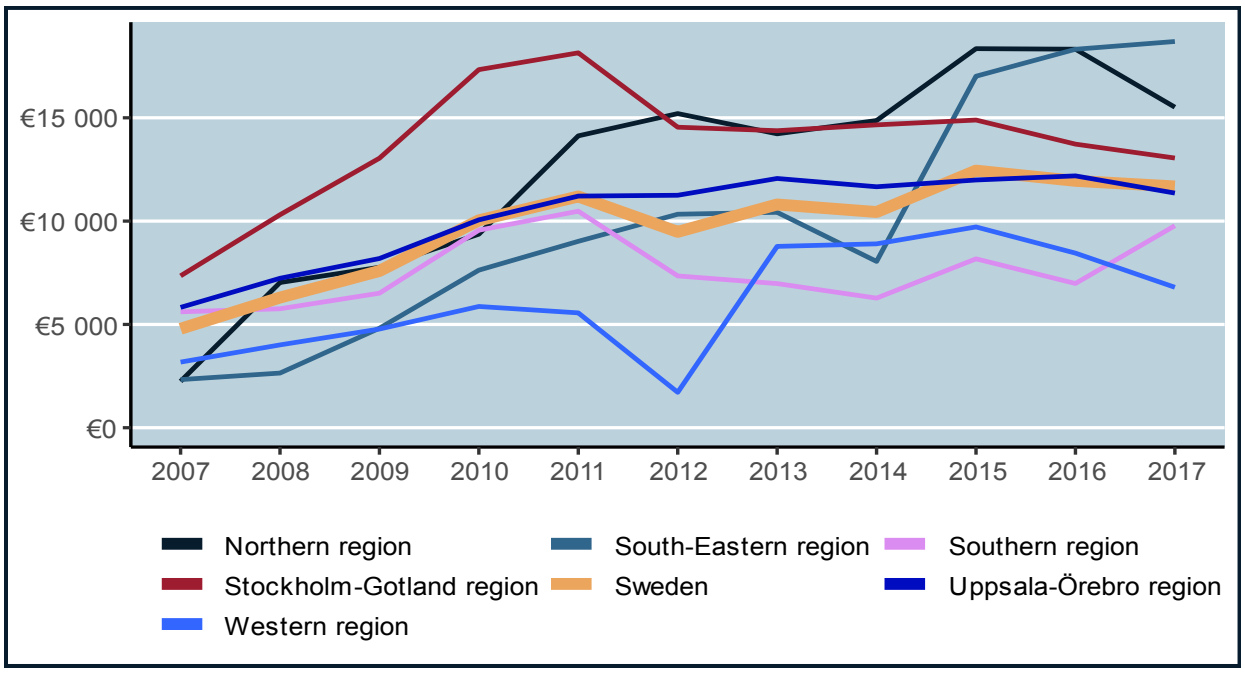

Figure 77: *Euro/case (deaths in diagnosis) in colorectal cancer for the new drugs in colorectal cancer in Sweden.*

Note: There is incomplete reporting from Western Region in 2012 and South-Eastern region in 2014.

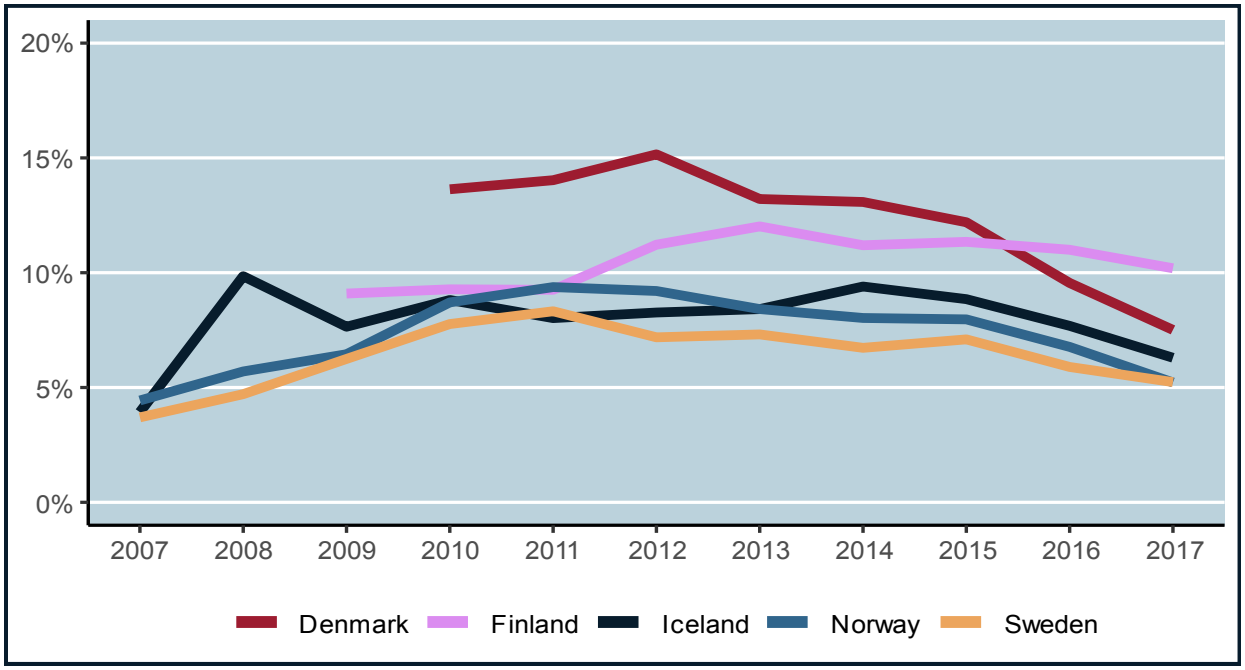

Figure 78: *Share of total cancer drugs sales of the new drugs in colorectal cancer in the Nordic countries.*

3.5.6 Ovarian cancer

In ovarian cancer we present uptake for the following drug:

- Olaparib (**Figure 79**)

The use of olaparib in BRACA mutated ovarian cancer is relatively uniform within the Nordic countries except for a very low uptake in Finland. The uptake of olaparib was the fastest in Sweden, especially in comparison with Finland (**Figure 79**). There are regional differences in both Norway and Sweden (**Figure 80** and **Figure 81**) but given the rarity of this disease this may be at random. The share of total cancer drugs sales of olaparib in the Nordic countries is less than 1 percentage of the total sales.

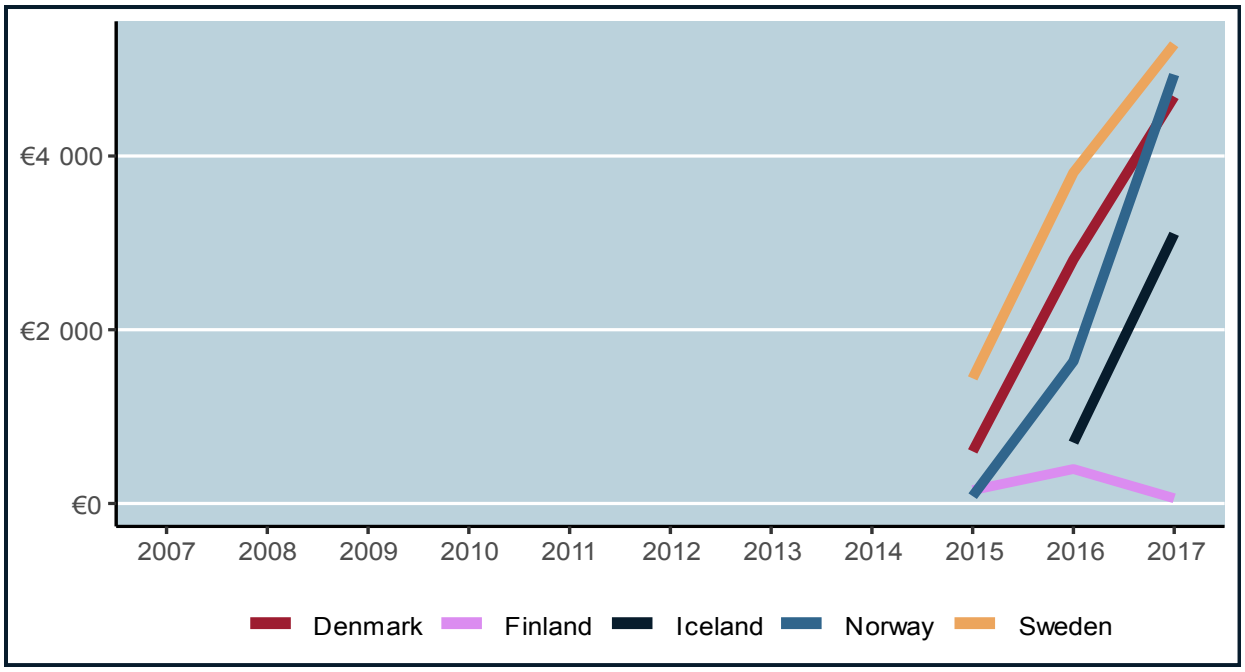

Figure 79: *Euro/case (deaths in diagnosis) in ovarian cancer for olaparib in in the Nordic countries.*

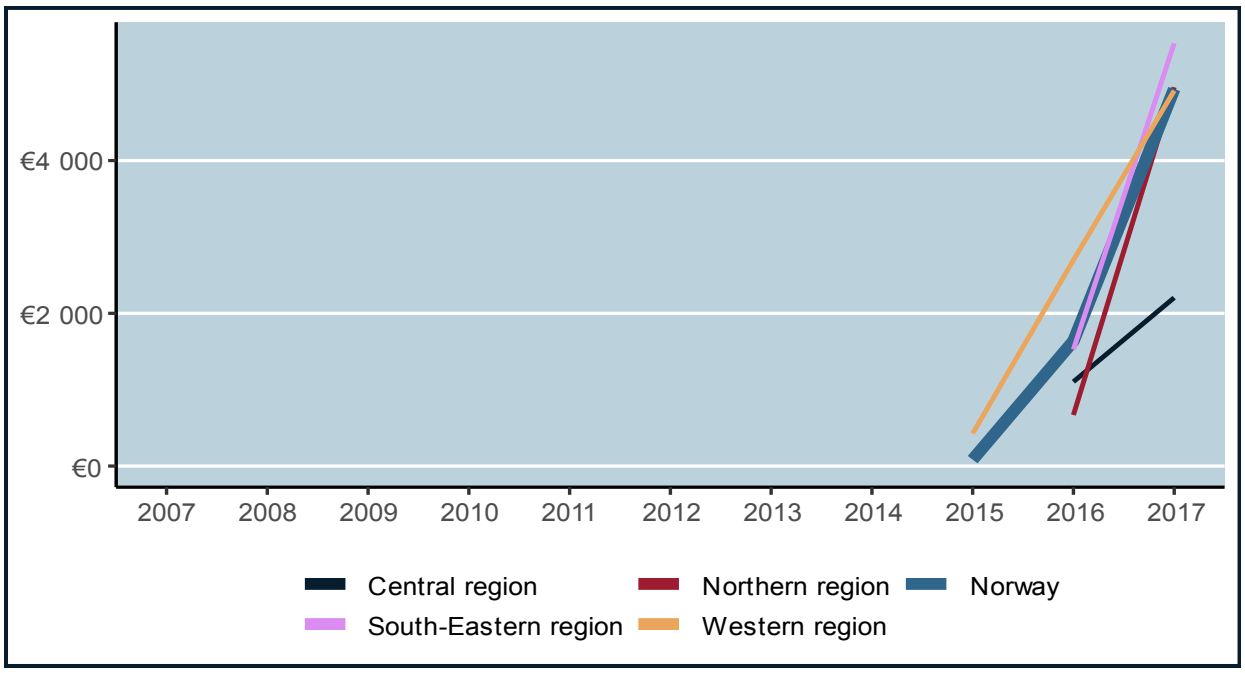

Figure 80: *Euro/case (deaths in diagnosis) in ovarian cancer for olaparib in Norway.*

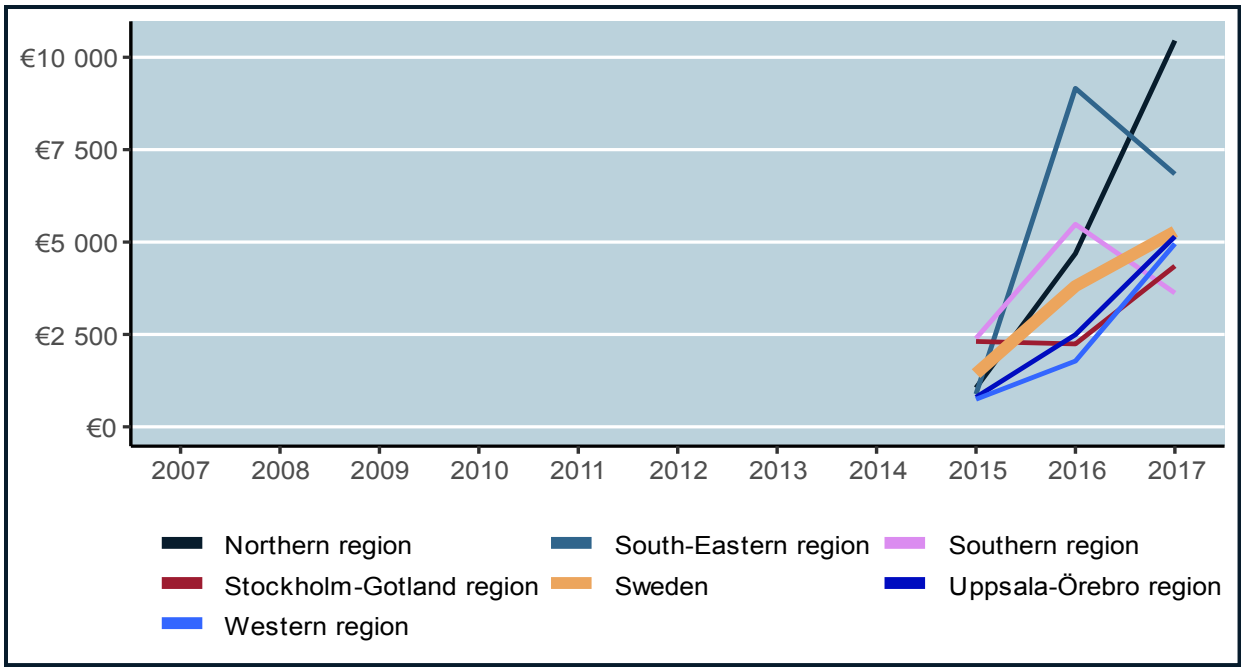

Figure 81: *Euro/case (deaths in diagnosis) in ovarian cancer for olaparib in Sweden.*
Note: There is incomplete reporting from Western Region in 2012 and South-Eastern region in 2014.

3.5.7 Prostate cancer

In prostate cancer we present uptake for the following drugs:

- Abiraterone (**Figure 82**)
- Cabazitaxel (**Figure 83**)
- Enzalutamide (**Figure 84**)
- All of the drugs above (**Figure 85**)

Finland had the most rapid uptake for cabazitaxel. For abiraterone and enzalutamide uptake was more similar between countries. We see a shift from abiraterone to enzalutamide in all countries. There are more marked variations in the uptake of cabazitaxel with an uptake in Denmark and Finland at 5 times the level of Norway.

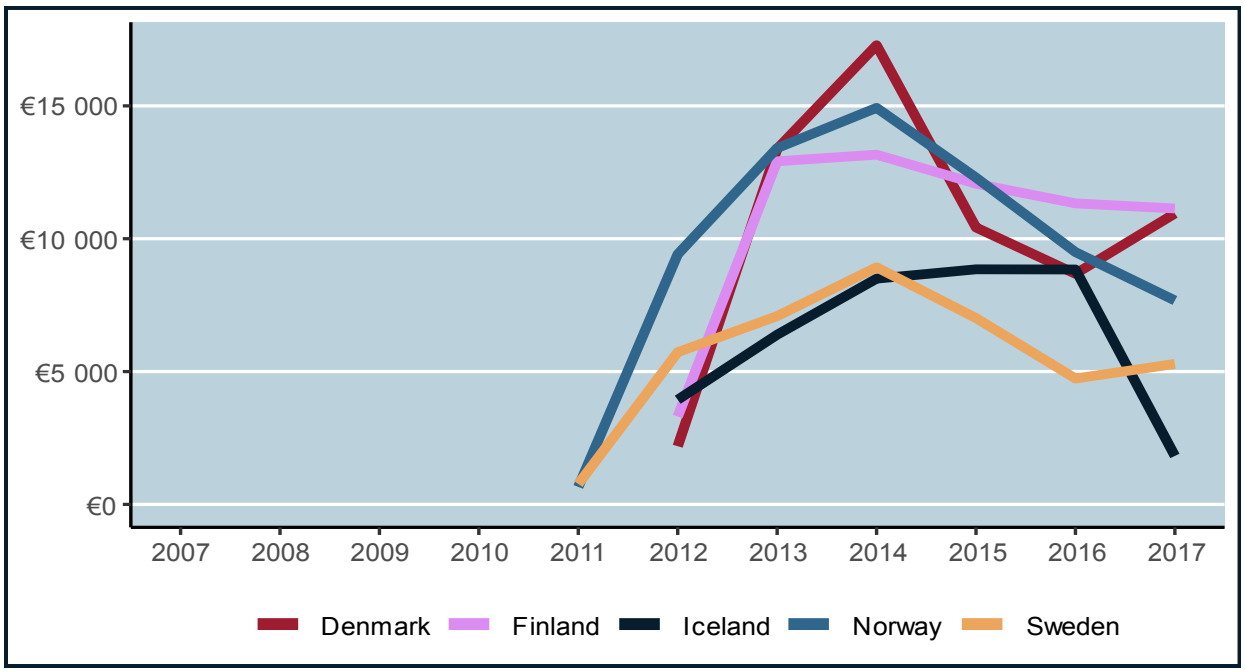

Figure 82: *Euro/case (deaths in diagnosis) in prostate cancer for abiraterone in the Nordic countries.*

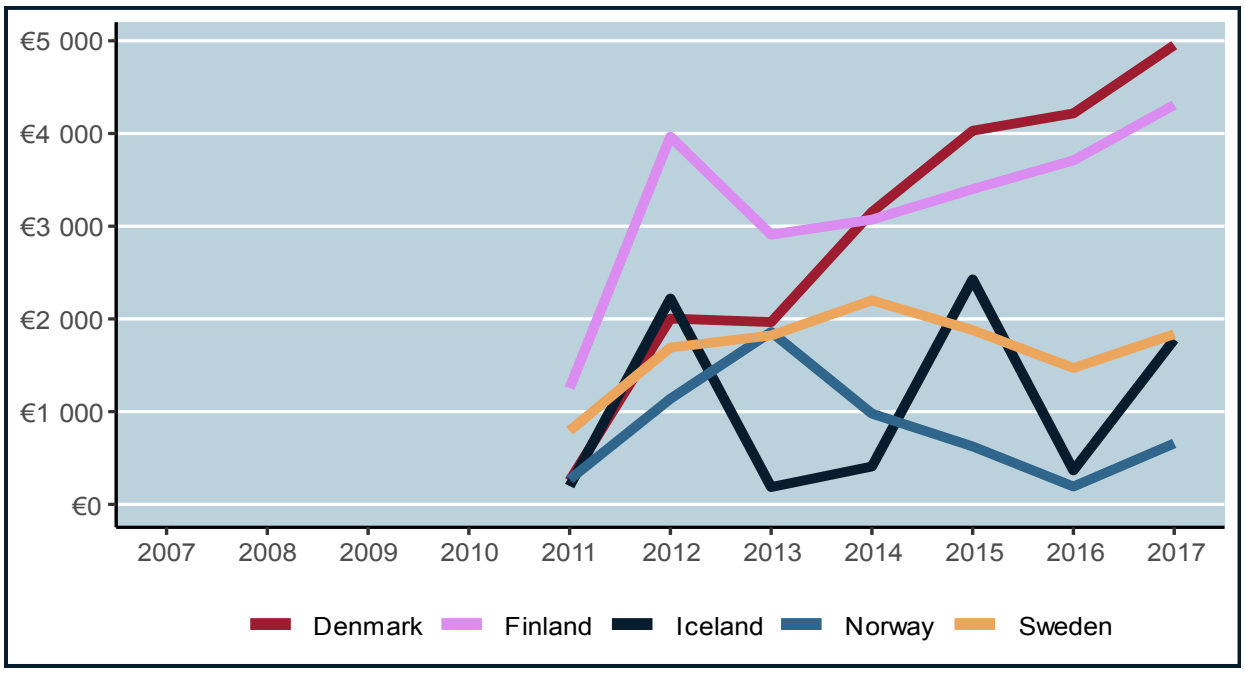

Figure 83: *Euro/case (deaths in diagnosis) in prostate cancer for cabazitaxel in the Nordic countries.*

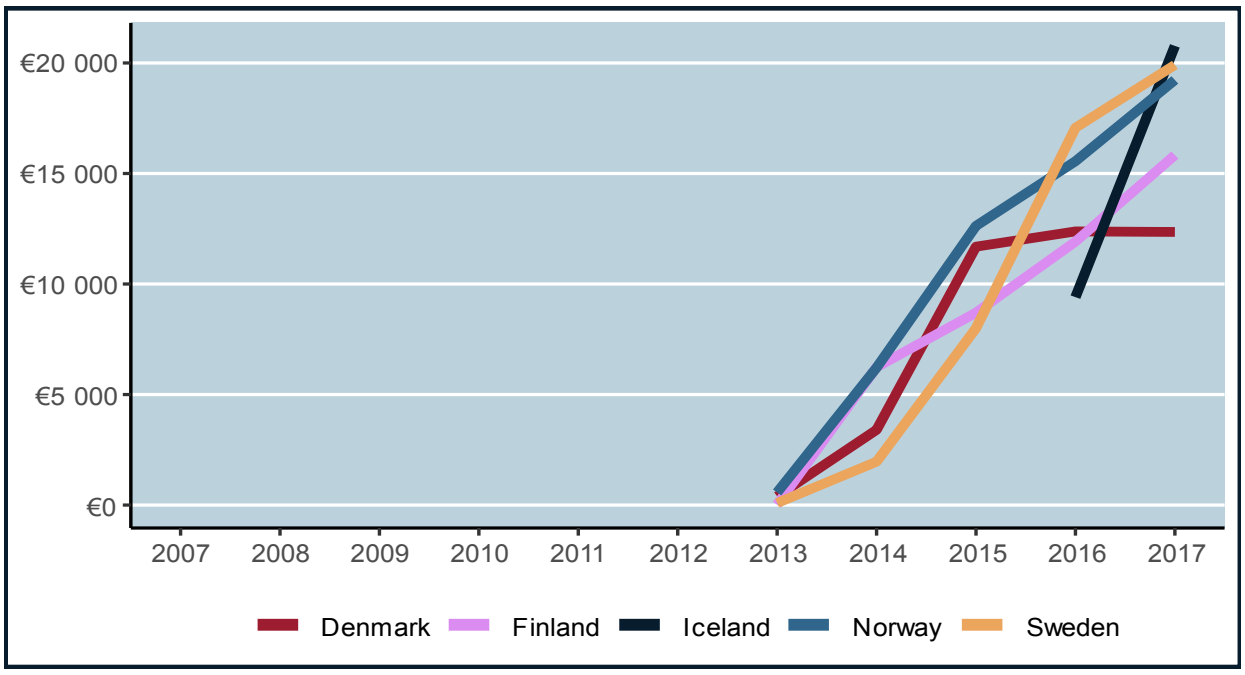

Figure 84: *Euro/case (deaths in diagnosis) in prostate cancer for enzalutamide in the Nordic countries.*

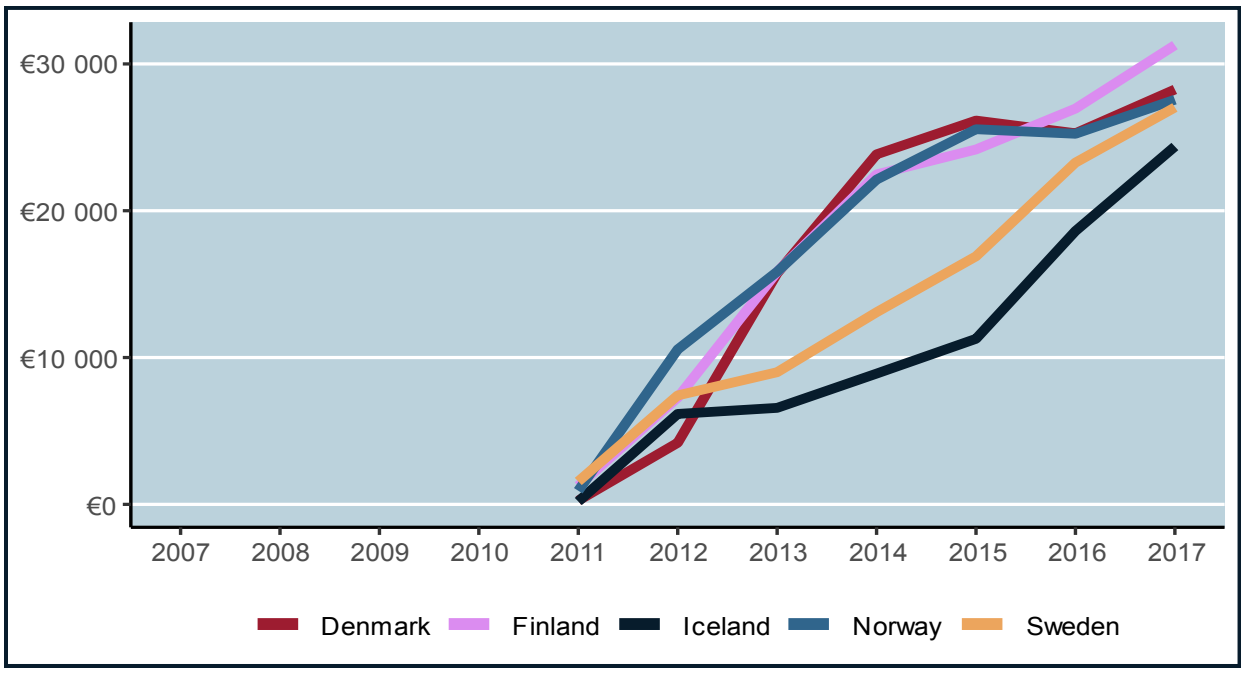

Figure 85: *Euro/case (deaths in diagnosis) in prostate cancer for the new drugs in prostate cancer in the Nordic countries.*

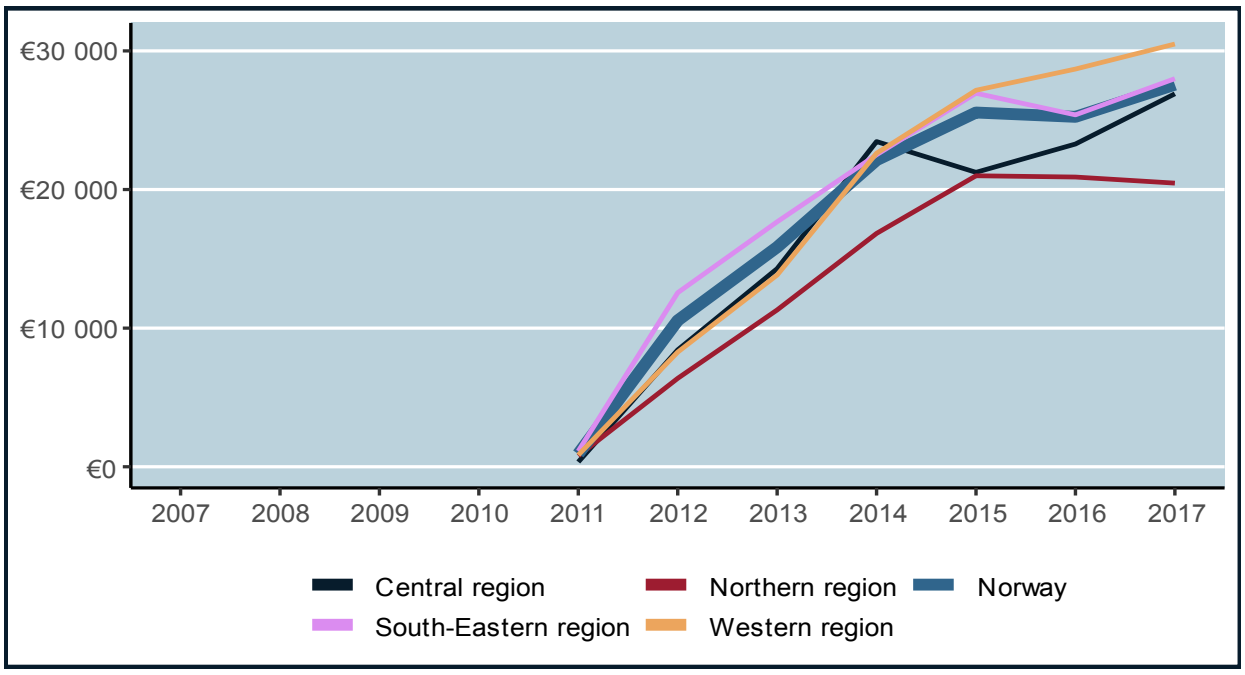

Figure 86: *Euro/case (deaths in diagnosis) in prostate cancer for the new drugs in prostate cancer in Norway.*

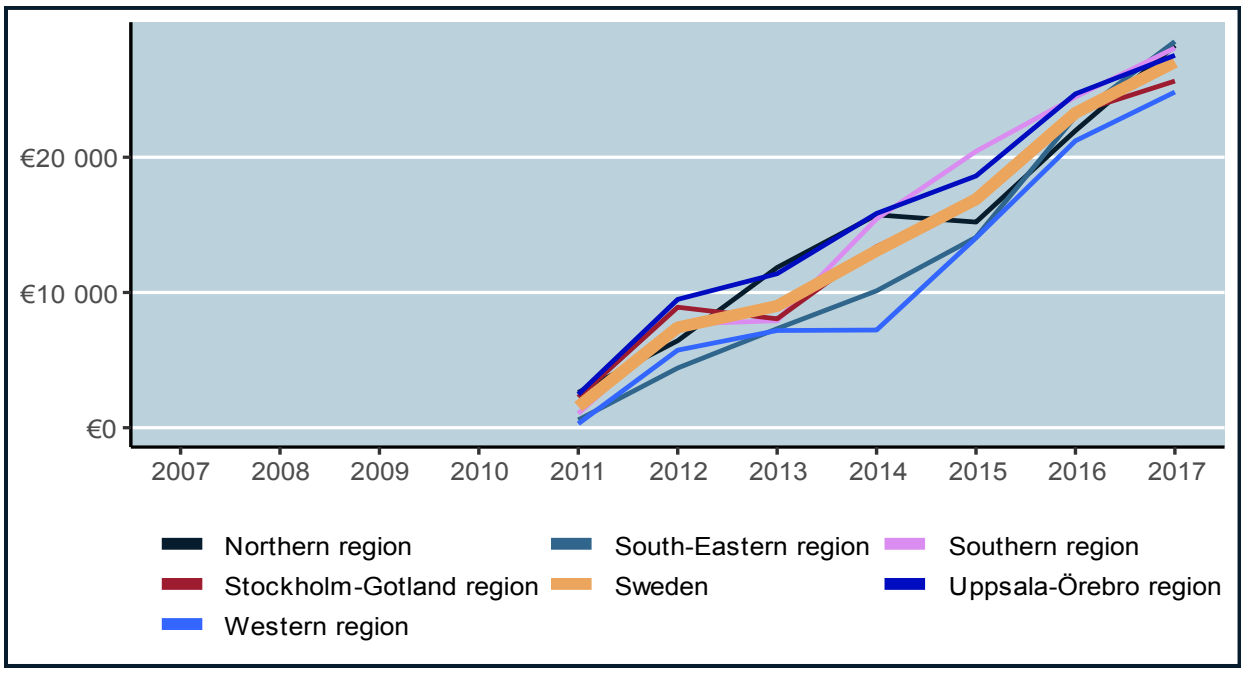

Figure 87: *Euro/case (deaths in diagnosis) in prostate cancer for the new drugs in prostate cancer in Sweden.*

Note: There is incomplete reporting from Western Region in 2012 and South-Eastern region in 2014.

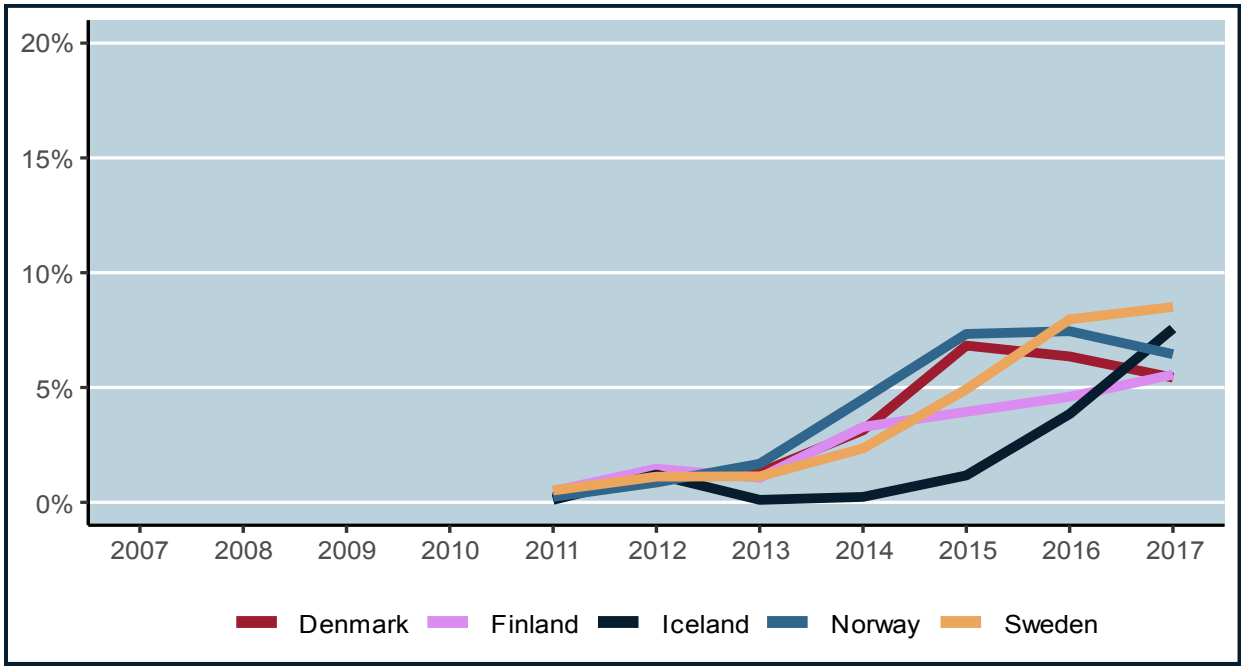

Figure 88: *Share of total cancer drugs sales of the new drugs in prostate cancer.*

3.5.8 Kidney cancer

In kidney cancer uptake curves are included for:

- Axitinib (**Figure 89**)
- Cabozantinib (**Figure 90**)
- Everolimus (**Figure 91**)
- Pazopanib (**Figure 92**)
- Sorafenib (**Figure 93**)
- Sunitinib (**Figure 94**)
- All of the drugs above (**Figure 95**)

There are large variations between the countries for individual drugs, but these become smaller when all the drugs are taken together (**Figure 95**).

There are a number of treatment options in metastatic renal cancer, recently also including immune therapy with PD-1 inhibitors. Please note that we have not included PD-1 or PD-L1 drugs in the lung cancer analysis as we lack information about the extent of use of these drugs in lung cancer. PD-1 and PD-L1 drugs are analyzed in relation to malignant melanoma.

Of special interest is to note that the uptake of cabozantinib in Denmark and Norway is 8-10 times that of Sweden, and even more than that compared to the uptake in Finland. At least in Sweden this represents a delay in the reimbursement process. On a regional lever the Northern region in Norway has a lower uptake of all renal cancer drugs compared to other regions. In Sweden the Stockholm-Gotland region is an out layer with more than twice the use of renal cancer drugs compared to some of the other Swedish regions.

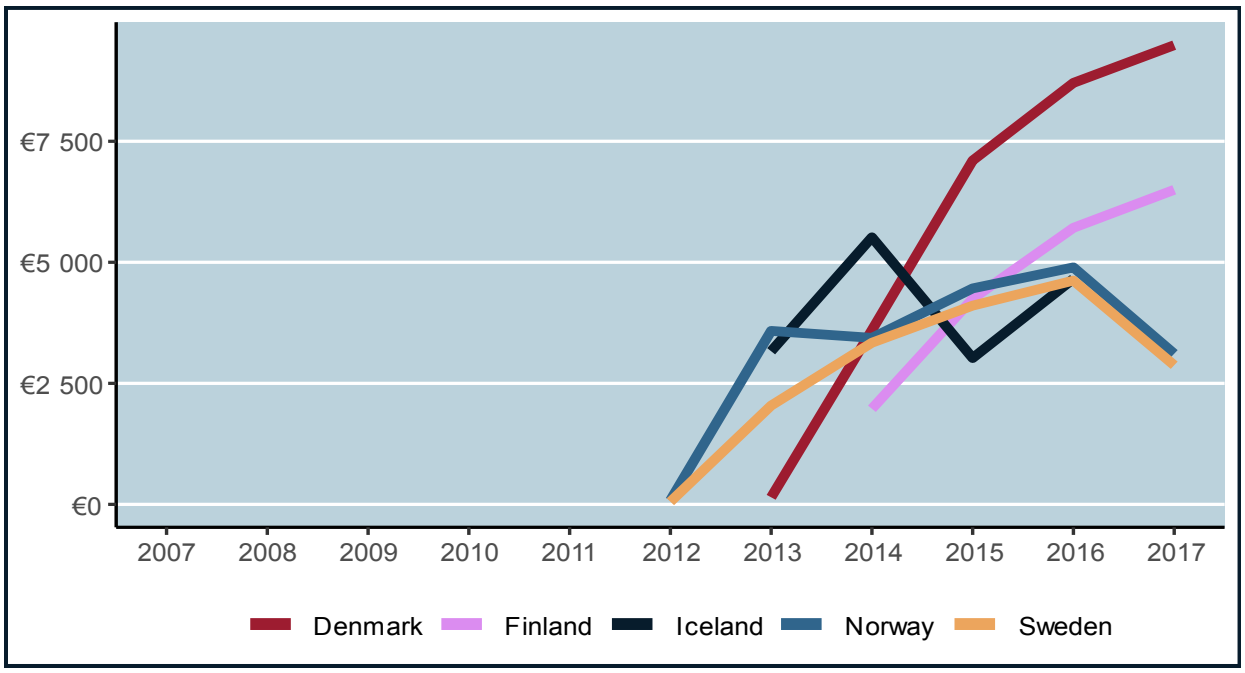

Figure 89: *Euro/case (deaths in diagnosis) in kidney cancer for axitinib in the Nordic countries.*

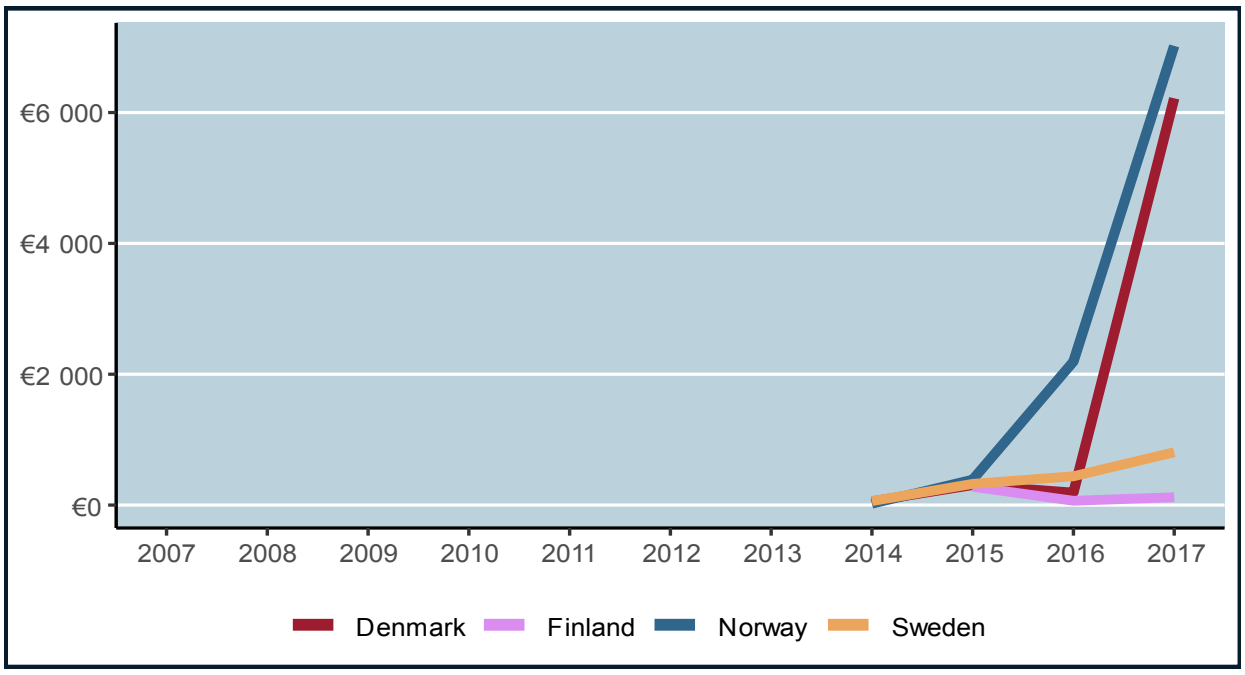

Figure 90: *Euro/case (deaths in diagnosis) in kidney cancer for cabozantinib in the Nordic countries.*

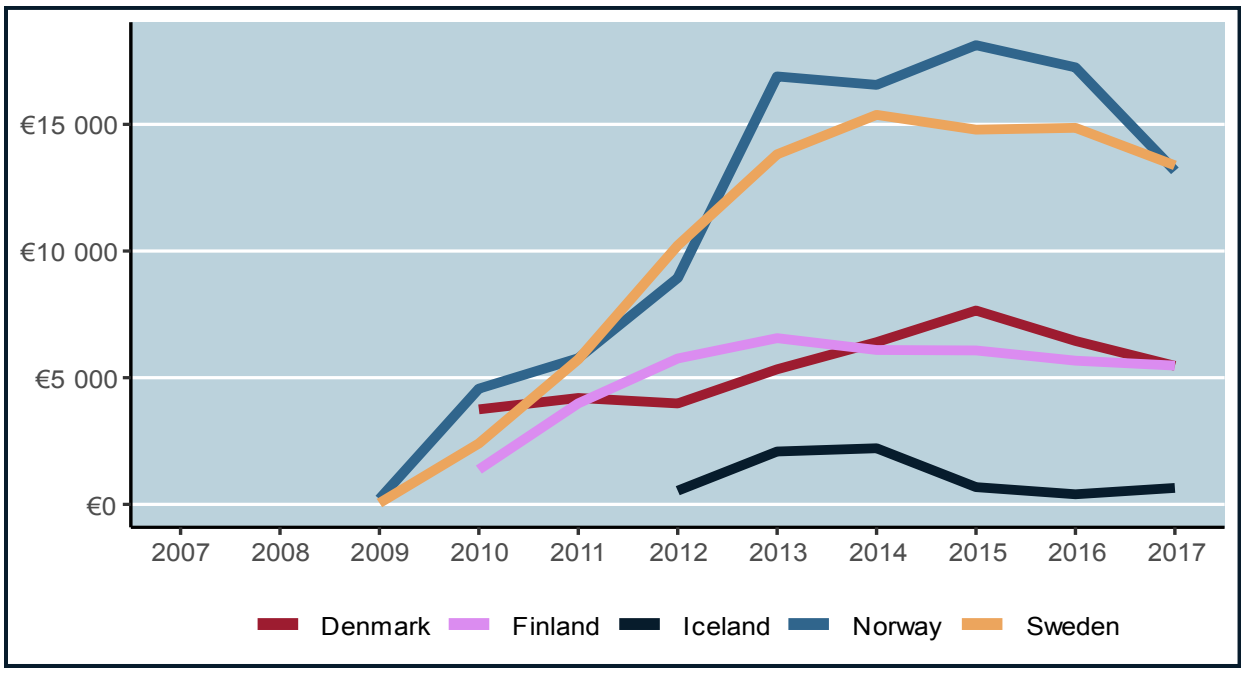

Figure 91: *Euro/case (deaths in diagnosis) in kidney cancer for everolimus in the Nordic countries.*

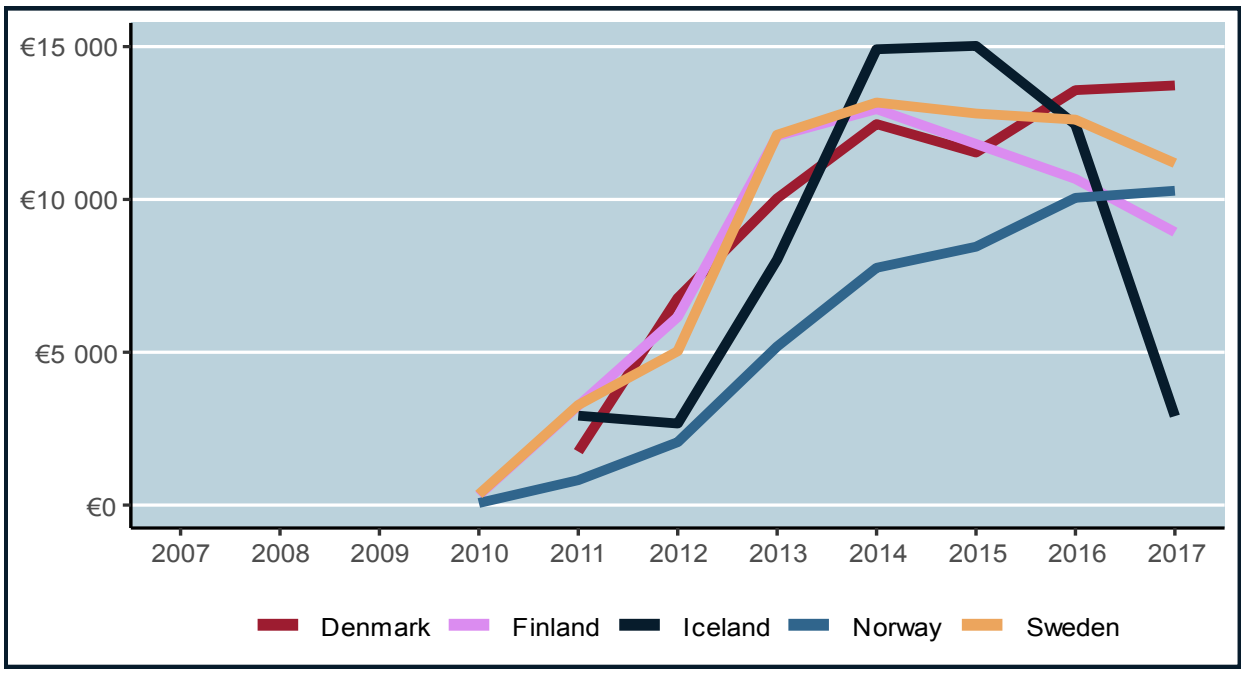

Figure 92: *Euro/case (deaths in diagnosis) in kidney cancer pazopanib in the Nordic countries.*

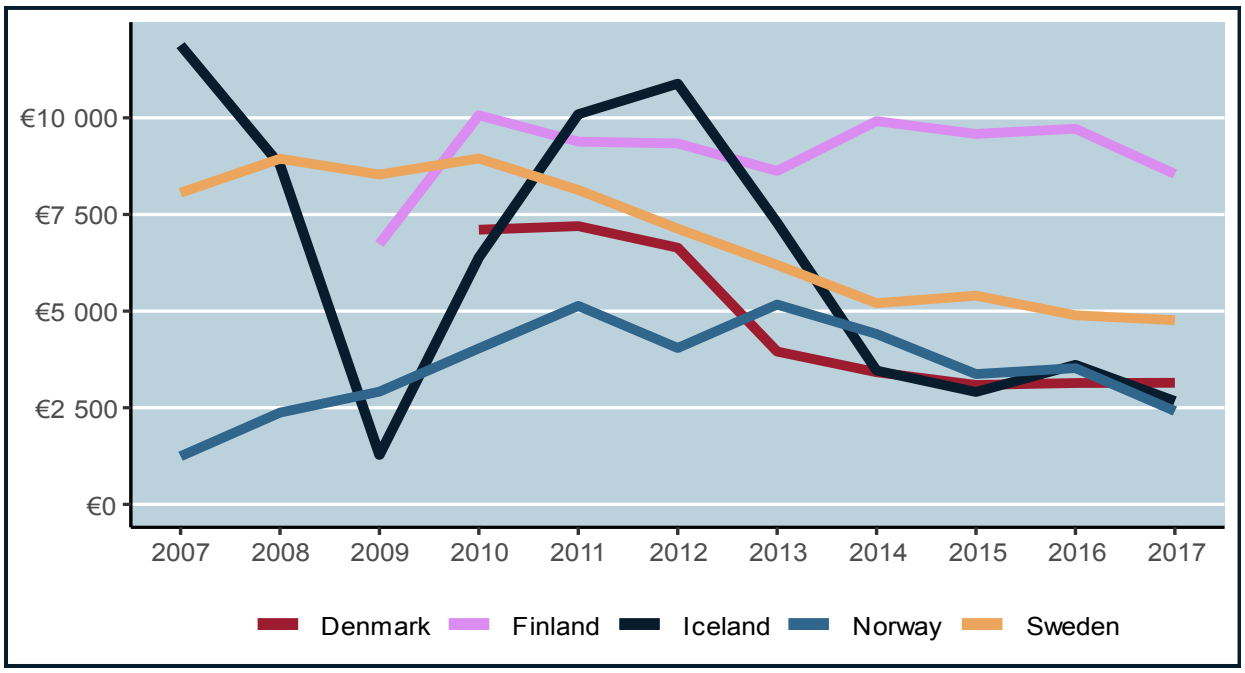

Figure 93: *Euro/case (deaths in diagnosis) in kidney cancer for sorafenib in the Nordic countries.*

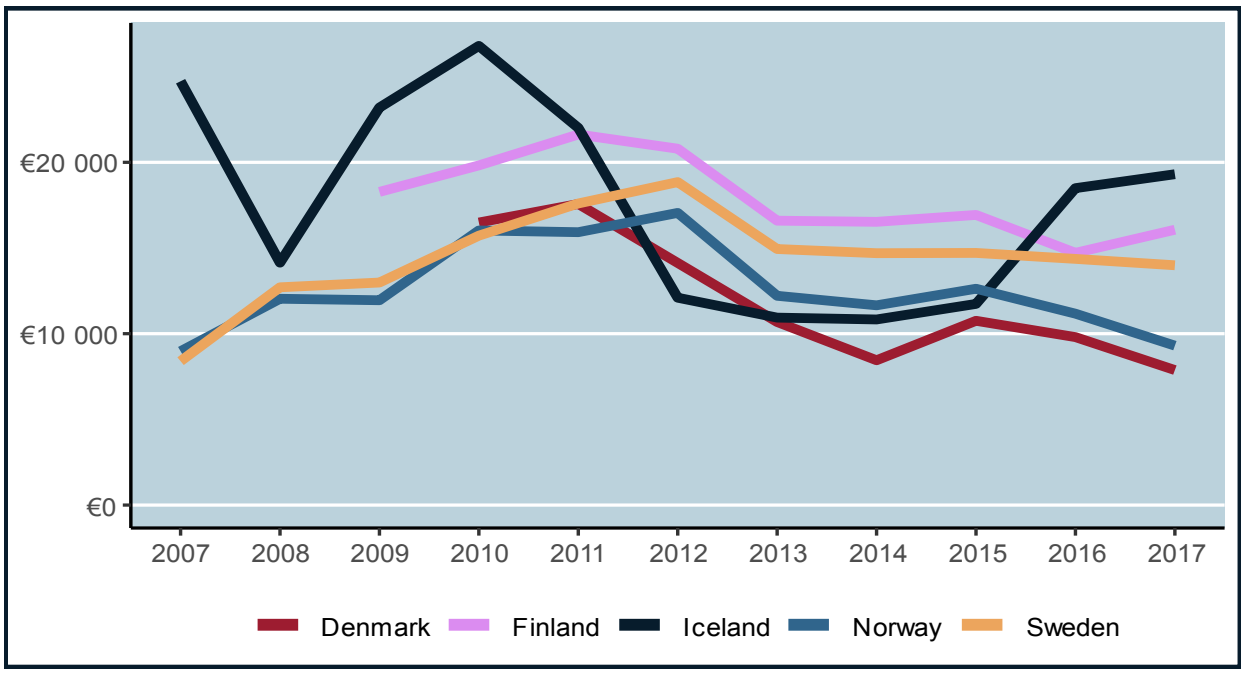

Figure 94: *Euro/case (deaths in diagnosis) in kidney cancer for sunitinib in the Nordic countries.*

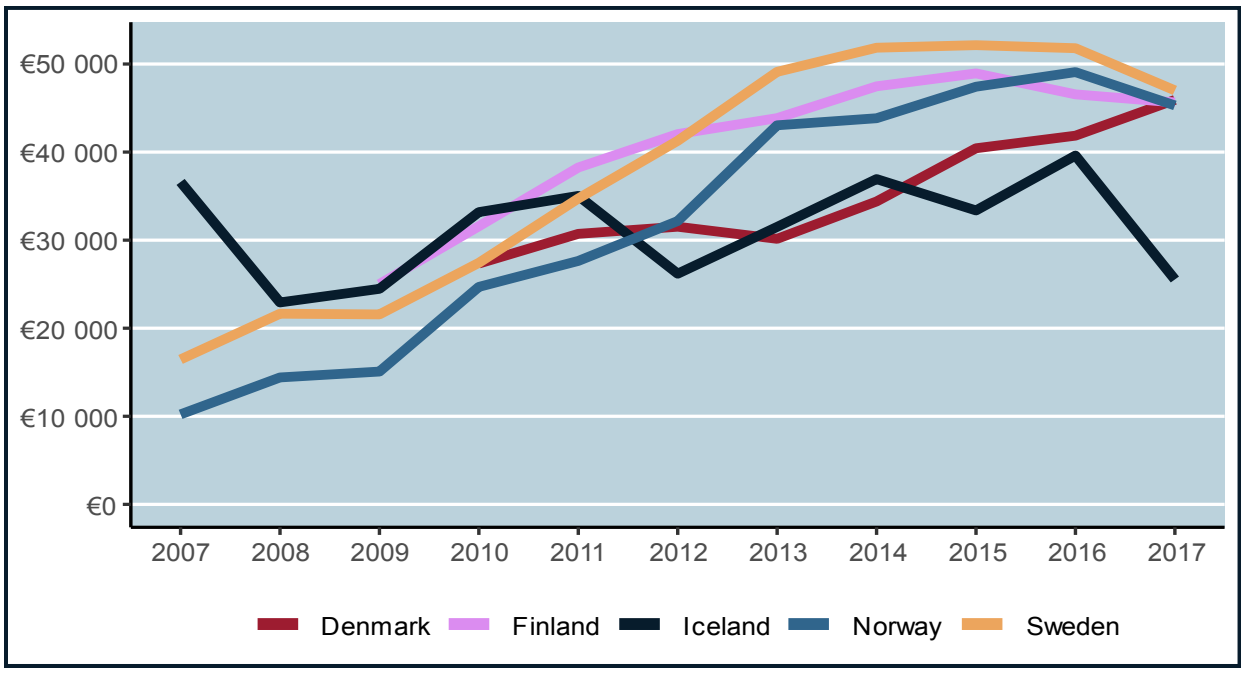

Figure 95: *Euro/case (deaths in diagnosis) in kidney cancer for the new drugs in kidney cancer in the Nordic countries*

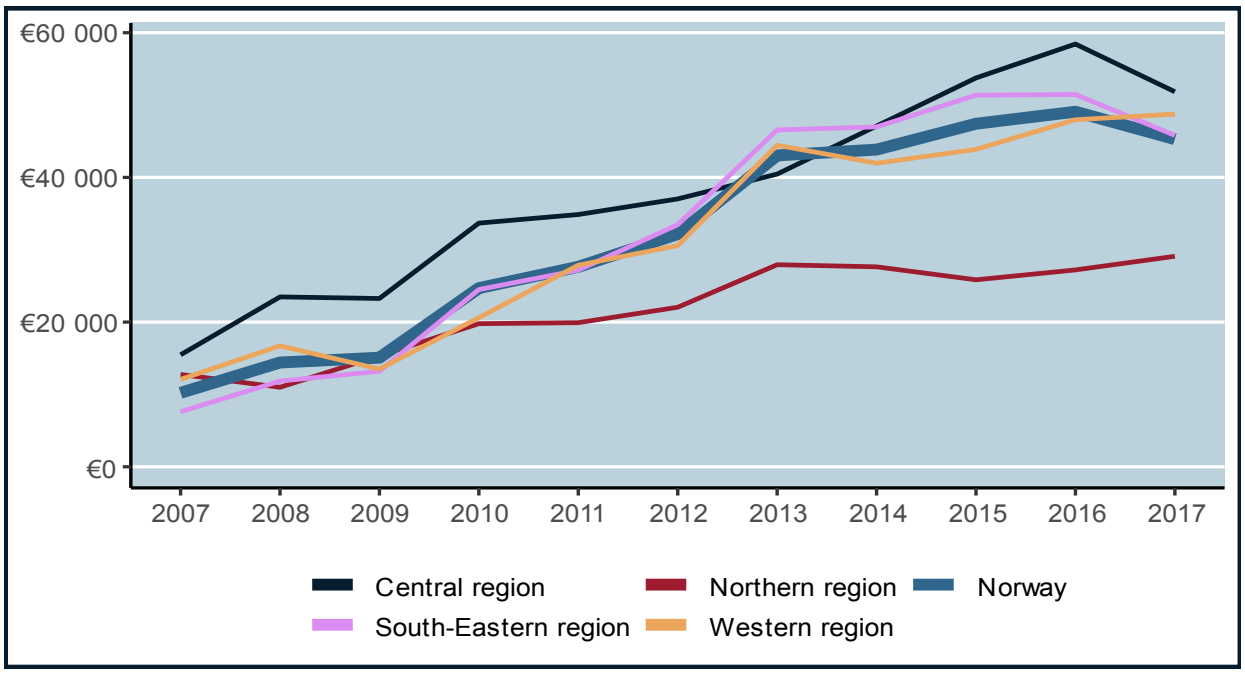

Figure 96: *Euro/case (deaths in diagnosis) in kidney cancer for the new drugs in kidney cancer in Norway.*

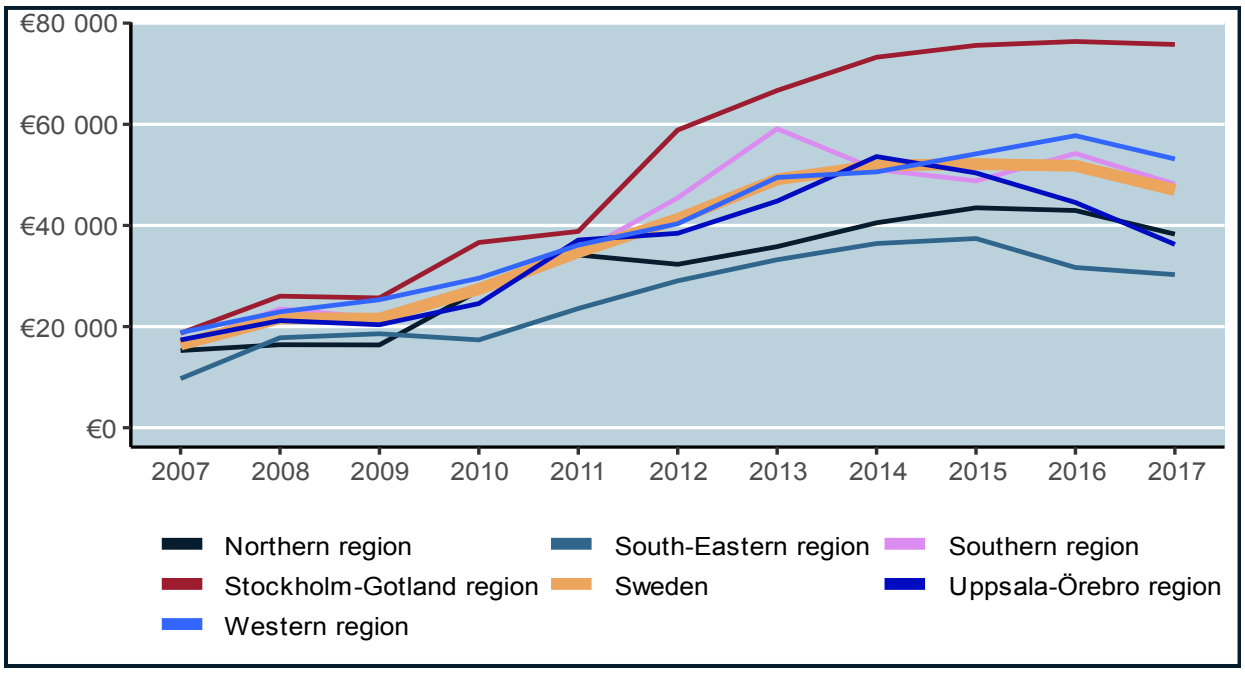

Figure 97: *Euro/case (deaths in diagnosis) in kidney cancer for the new drugs in kidney cancer in Sweden.*

Note: There is incomplete reporting from Western Region in 2012 and South-Eastern region in 2014.

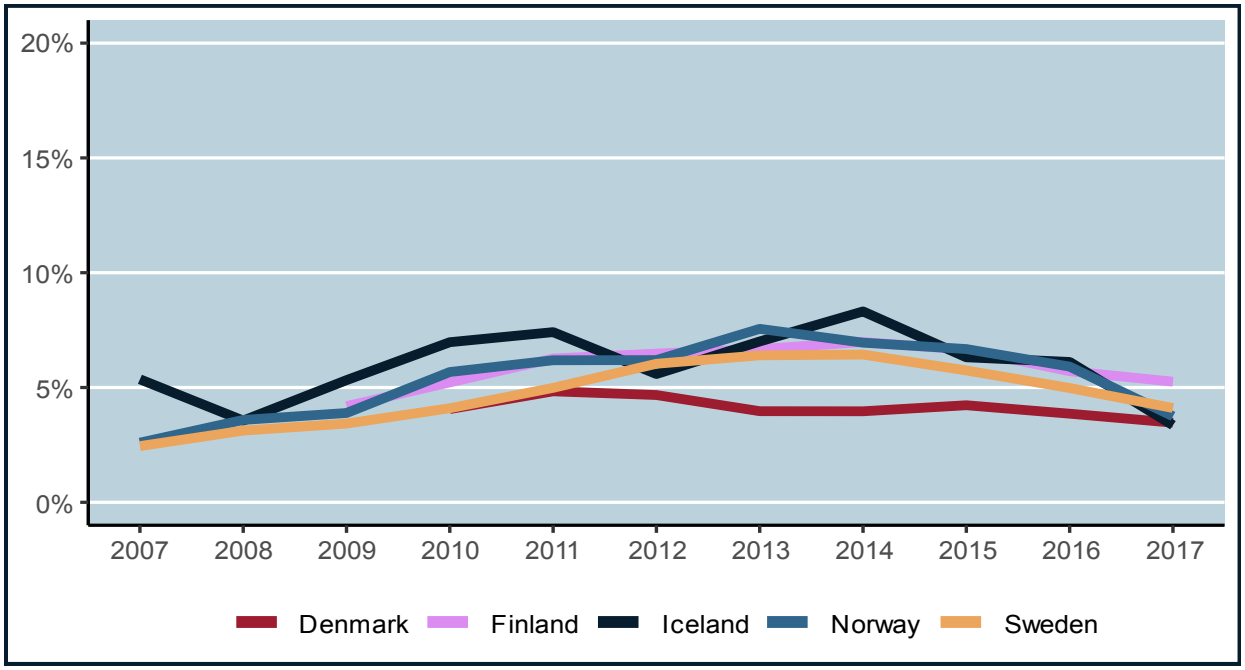

Figure 98: *Share of total cancer drugs sales of the new drugs in kidney cancer in the Nordic countries.*

3.5.9 Outlook Sweden 2018

As we have received data for Sweden for 2018, we will provide an outlook of the development for Sweden in 2018. Unlike the rest of the chapters in this report, all figures here are in Swedish crowns and not in fixed prices (that is, the prices are not adjusted for inflation).

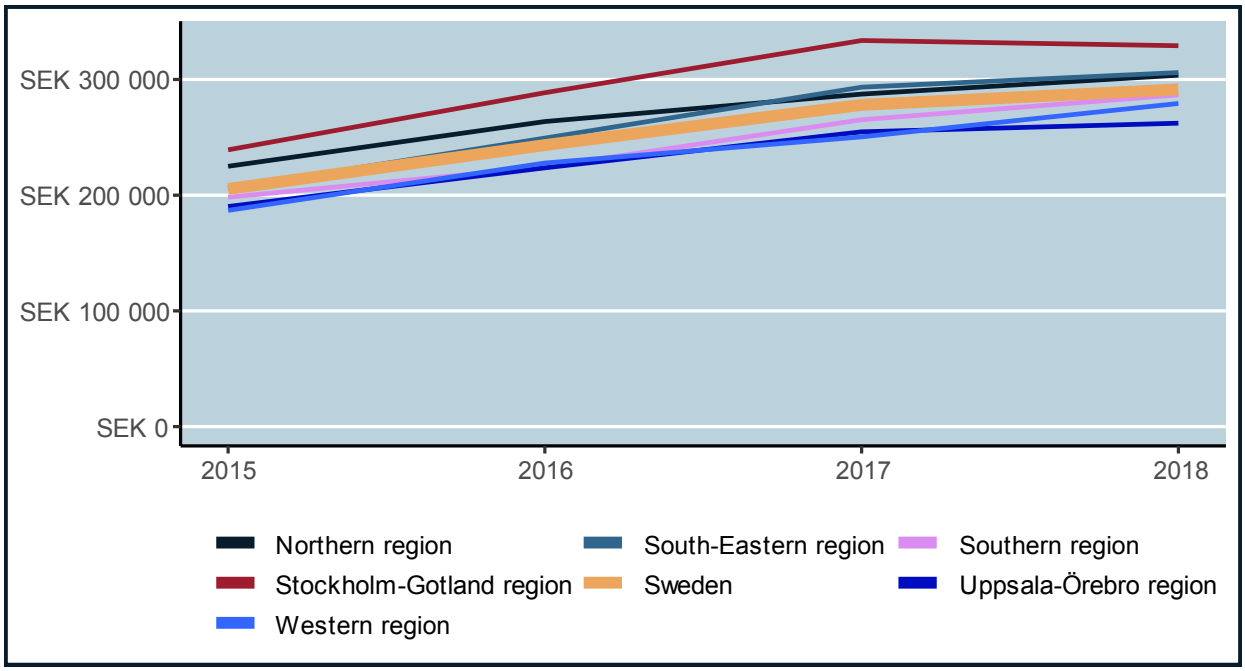

Figure 99: *SEK/mortality in all cancers in the Swedish Health care regions*

Cost of cancer drugs in relation to mortality has increased in 2018 compared to 2017, but at a lower rate than previous years. There is still a difference of about 25% between the region with the highest cost/mortality (Stockholm-Gotland region) and the region with the lowest cost/mortality (Uppsala Örebro).

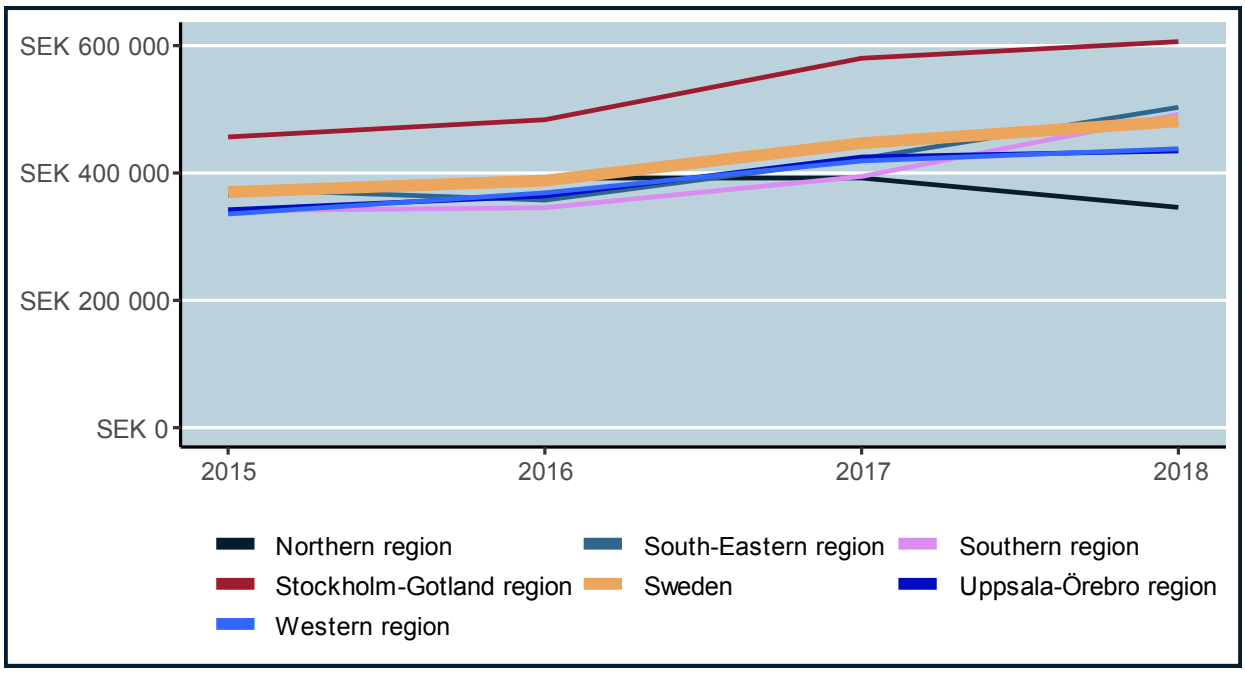

Figure 100: *SEK/mortality in breast cancer in Sweden for trastuzumab + pertuzumab + trastuzumab emtansine + lapatinib + palbociclib + ribociclib.*

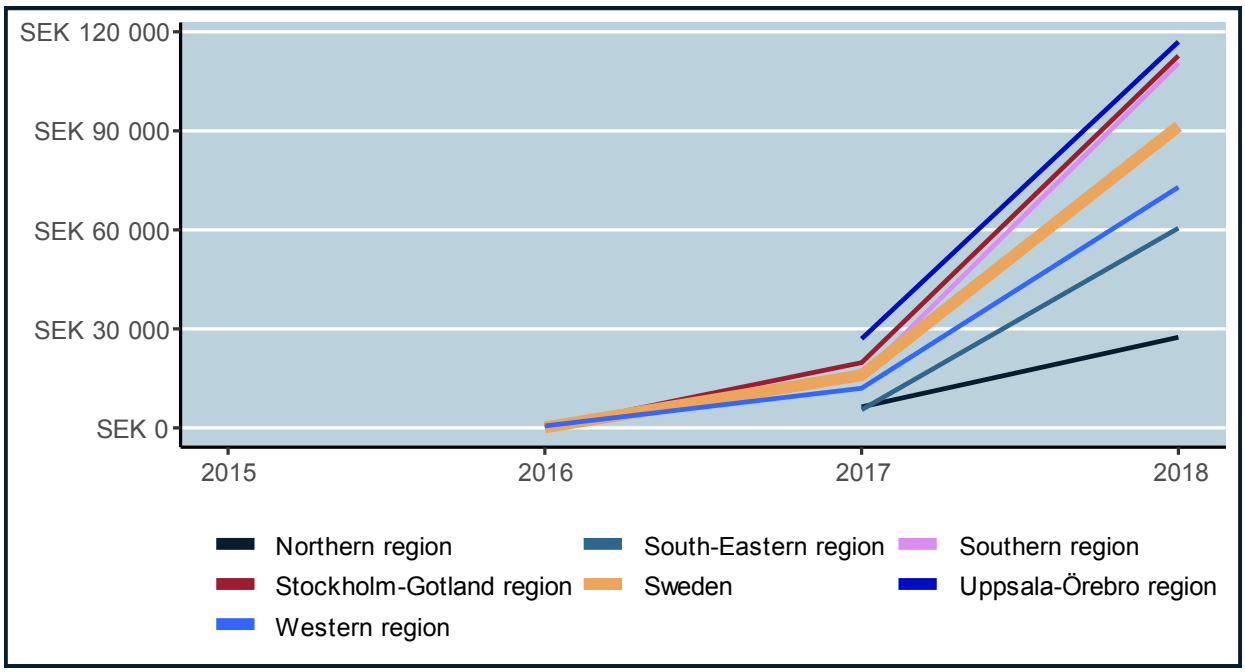

Figure 101: *SEK/mortality in breast cancer for the CDK-inhibitors in Sweden.*

The use of CDK 4/6 inhibitors/ mortality in breast cancer has increased dramatically during 2018. Still, the South Easter region and especially the Northern region have much lower access than other health care regions.

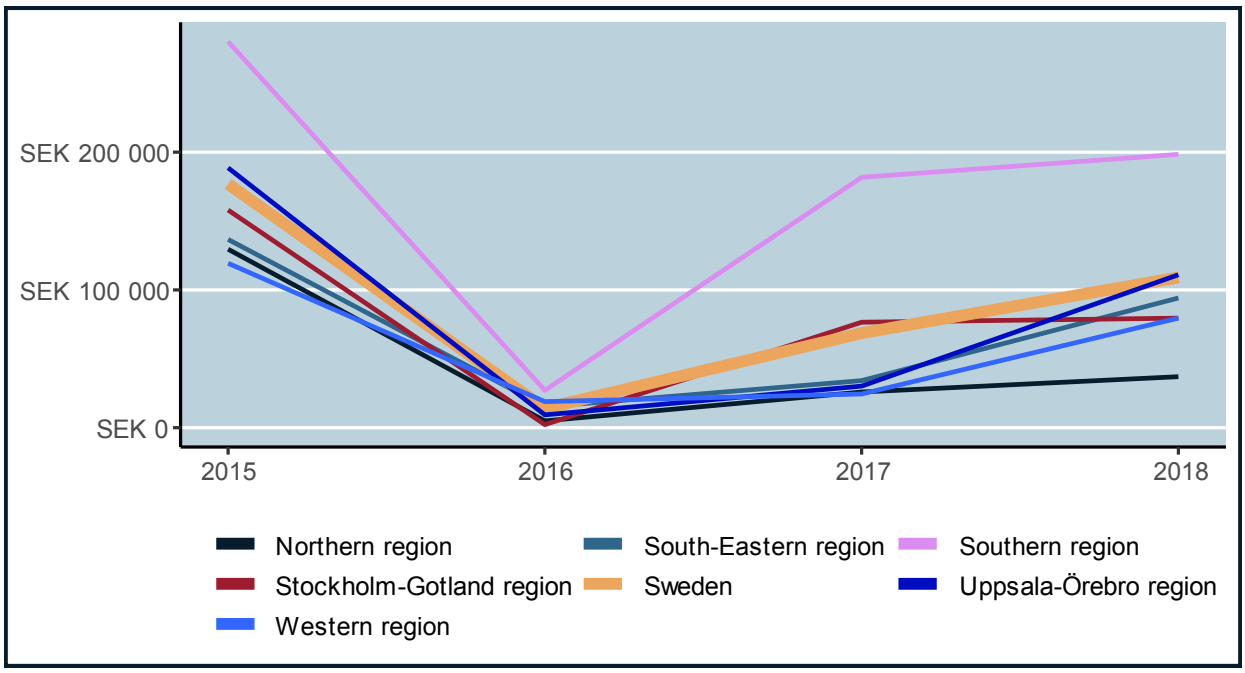

Figure 102: *SEK/mortality in malignant melanoma for ipilimumab in Sweden.*

The use of ipilimumab from 2016 (approval first line use in combination with PD-1 drugs) is still very variable. The use of combination therapy is 6 times more common in the Southern health care region compared with the Northern health care region. The use of combination therapy has increased most (from low levels) in the Uppsala-Örebro region and in the Western health care region.

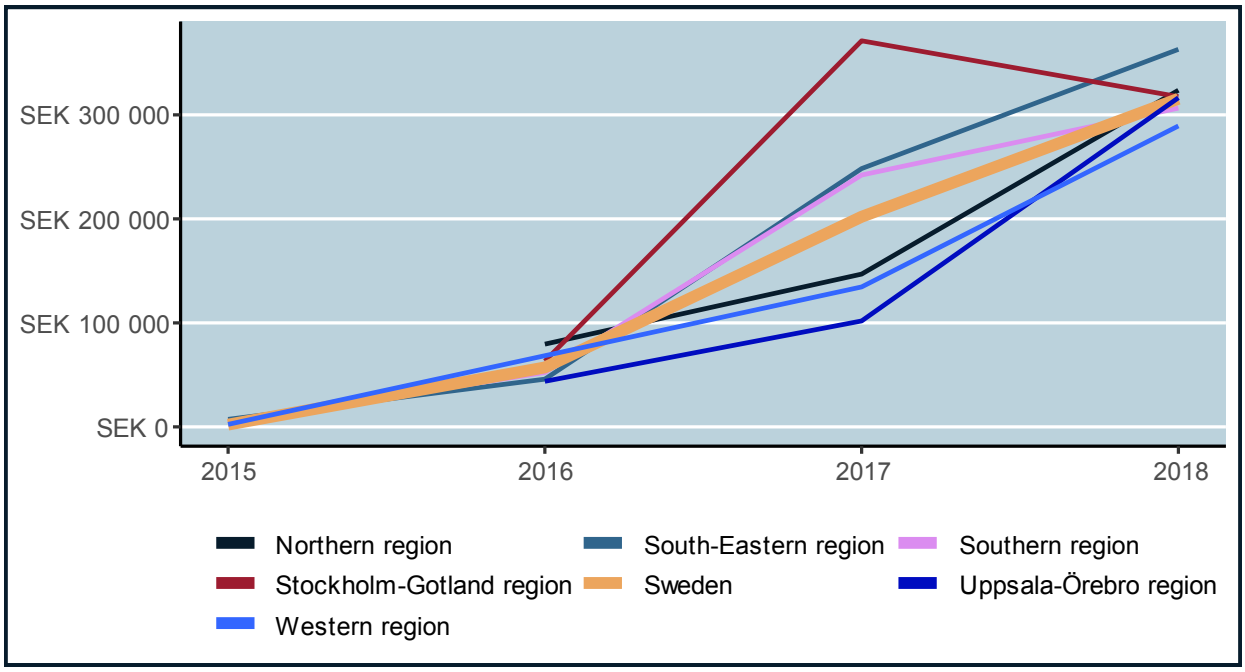

Figure 103: *SEK/mortality in myeloma for carfilzomib in Sweden.*

The use of carfilzomib has increased in 2018, especially in regions with a relatively low use in 2017. The use is now relatively uniform in different health care regions.

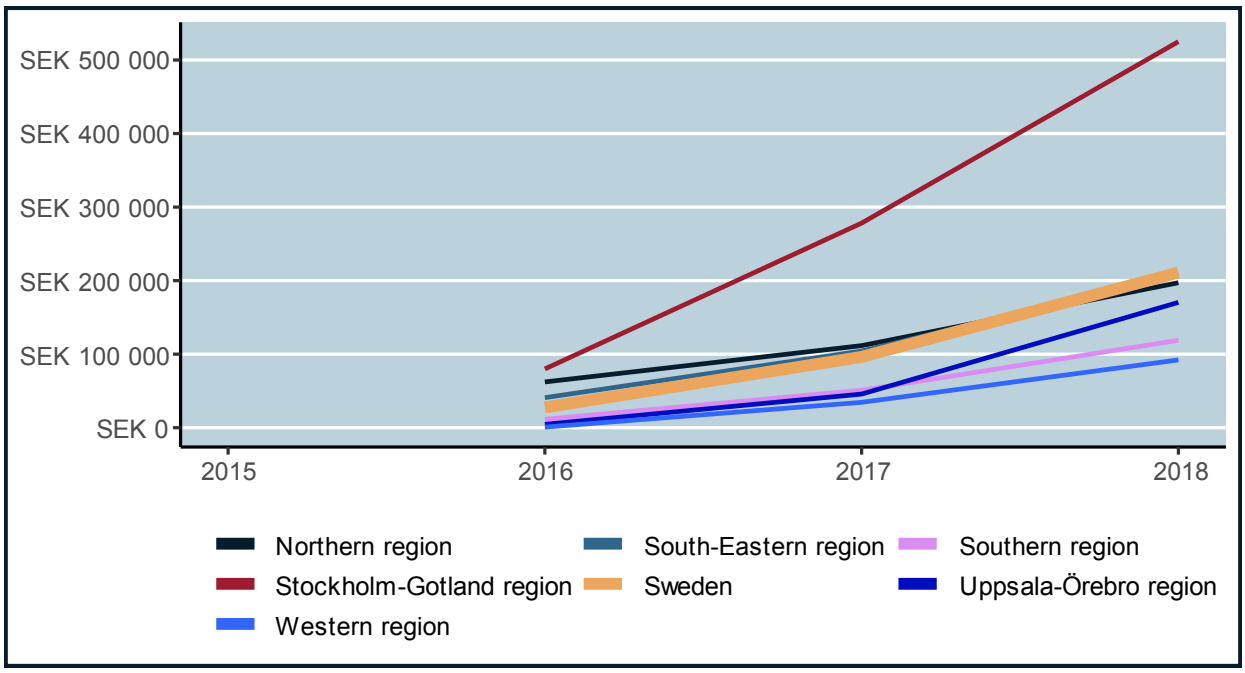

Figure 104: *SEK/mortality in myeloma in Sweden for daratumumab*

The use of daratumumab has roughly doubled in 2018 compared to 2017. The use in Stockholm-Gotland is 5 times that of the Western health care region and more than twice the national average.

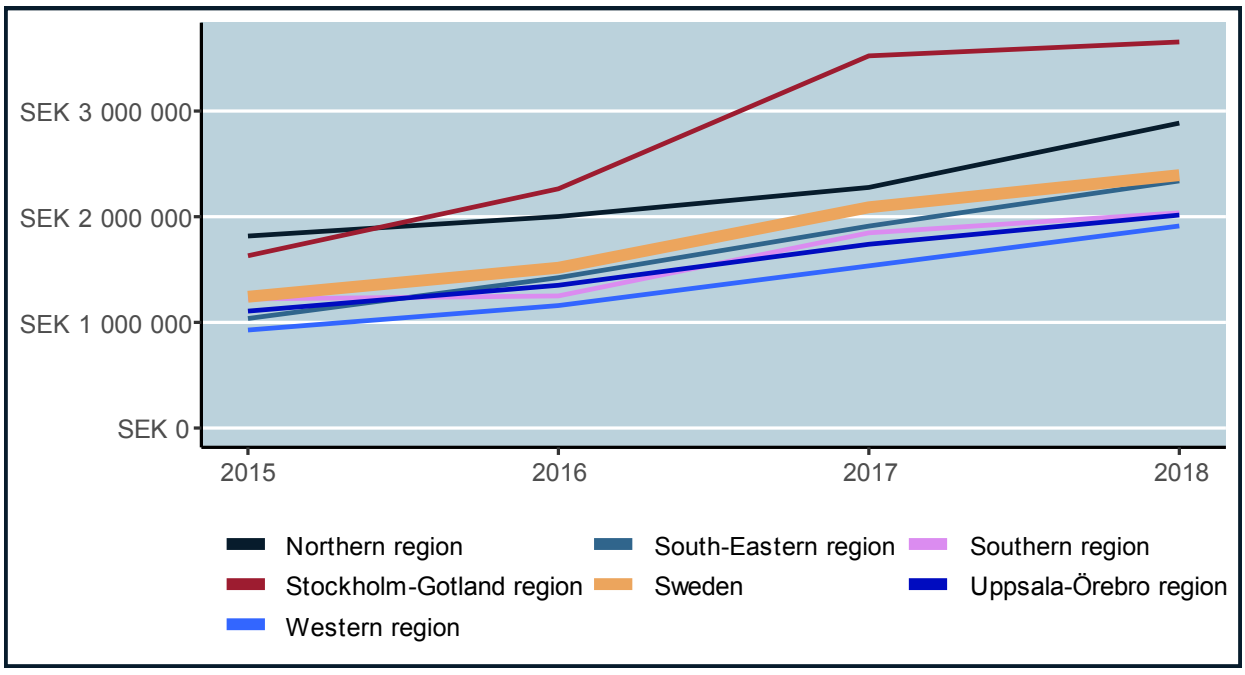

Figure 105: *SEK/mortality in myeloma for bortezomib + lenalidomide + thalidomide + pomalidomide + carfilzomib + daratumumab in Sweden.*

The total use of myeloma drugs has increased with 14% from 2017 to 2018. Stockholm-Gotland is still about 50% over the national level.

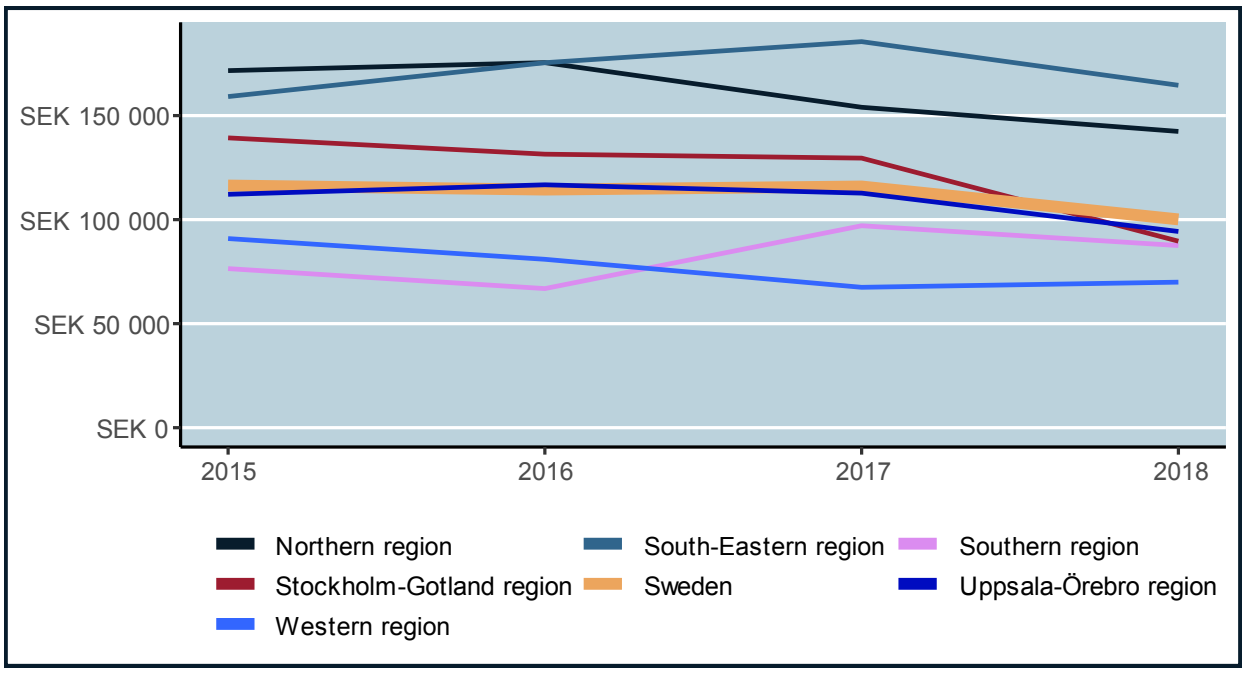

Figure 106: *SEK/mortality in colorectal cancer for the new drugs in colorectal cancer in Sweden.*

For colorectal cancer drugs we see a decrease in all health care regions except for the Western region (lowest over-all use). Still, we see a two-fold variation in the use of these drugs even though they have been on the market for 10-15 years.

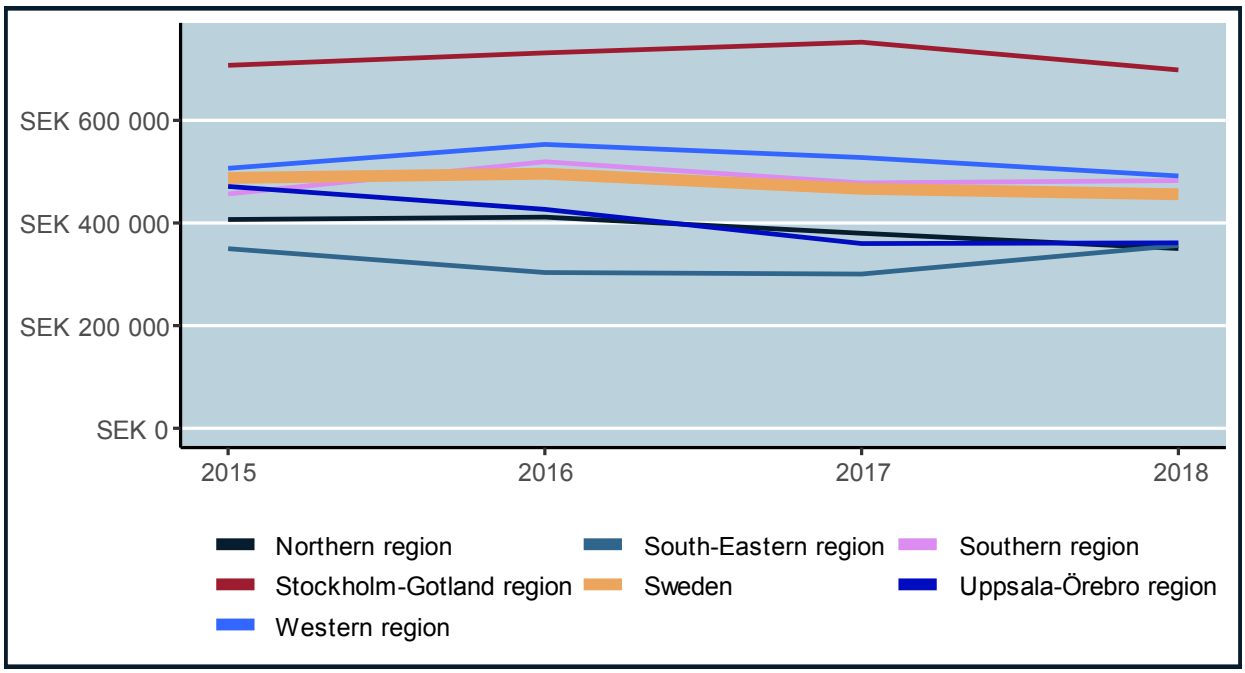

Figure 107: *SEK/mortality in kidney cancer for the new drugs in kidney cancer in Sweden.*

The use of kidney cancer drugs has been stable or even slightly decreased. This decrease most probably relates to the introduction of PD-1; PD-L1 drugs. Note that we have not included PD-1 or PD-L1 drugs in the lung cancer analysis as we lack information about the extent of use of these drugs in lung cancer. PD-1 and PD-L1 drugs are analyzed in relation to malignant melanoma.

There is still a variation of about 50% between the region with highest use (Stockholm-Gotland) and the regions with the lowest use (Uppsala-Örebro, Northern, and South-Eastern region).

4 Concluding remarks

The incidence of cancer in the Nordic countries has continued to increase over the last decades. There are several potential explanations to this, including demographic changes and better detection through screening programs and improved diagnostics. Despite the increase in incidence, mortality in cancer have remained fairly stable over the last 25 years. Partly, the explanation may be cancer with slow progression such as prostate cancer, although a large part is related to improvements in treatment. Five-year survival rates have gradually increased, and the performance of the Nordic health care systems is fairly similar – at the aggregate level – although there may be important differences for the different cancer forms. Historically, the Nordic countries (except for Denmark) have had very good aggregate survival, at the levels of the large European economies (Germany and France), while Denmark was lagging at the same levels as the UK, the worst performer among the big 5. With the improvements that we observe for Denmark in more recent years result in that the Nordic countries as a group are among the top performers in Europe.

The relative unique and population-based registers available – since long – in all the Nordic countries, make studies of incidence and survival very competitive, compared to – for example – the US, where registers only cover a small part of the population. At the same time, these registers could be even better with more patient data and treatment data entered prospectively. This would make way for clinical effectiveness studies on outcome (studies with real-world data), that could be used for different purposes (e.g. guidelines, budget allocations).

The direct costs of cancer have increased over time, largely in pace with the development of the overall health care costs, although the cost share of medicines has increased. At the same time there has been a shift in treatments from in-patient care to out-patient care. However, we may now be at a point where room for further savings from this shift is limited which will pose challenges to health care systems. Also, studies of the most cost-effective treatments will be even more important as the number of treatments available will increase. Thus, information on treatments and outcomes in clinical practice will be required, and data on costs of cancer related to different tumor types and relevant patient characteristics is still lacking. This needs to change in order to get relevant information for the development of policies and budget allocations.

The uptake and use of new medicines vary between the Nordic countries. Among the forms of cancer that was studied in this report it cannot be said that a single country consistently outperforms or underperforms. However, the spending appears to be lower in Finland and there has been a considerable shift to high usage in Norway in recent years in most areas. It can also be observed that there are as large variations in drug usage within and between countries. One of the basic hypotheses we had at the start of this work was that we would observe smaller differences in countries with more centralized procedures and budgets than in decentralized countries. This holds

true (with a few exceptions) as variations between Norwegian regions are fairly small, and Norway is utilizing centralized procurement of drugs, whereas variations are comparably large in Sweden where the local county councils are responsible. Variation between regions in Denmark are often on par with Sweden, indicating that other factors also play a role. The presence of national treatment guidelines has the aim to decrease differences but the adherence to these differs (e.g. colorectal cancer for Sweden), and is not checked for compliance. Regional treatment guidelines seem to be more important, and qualitative studies of this would likely generate some interesting finds.

There are differences between the Nordic countries with respect to the health care structures. In Norway the State has a major role while the regions and the local clinics have a more important role in Sweden. This may explain why the regional differences are much more prominent in Sweden compared with Norway. The complicated Swedish system, with reimbursement decisions made by TLV (Tand- och Läkemedelsförmånsverket; The Dental and Pharmaceutical Benefits Agency) for prescription drugs and recommendations for hospital drugs being made by the SKL (Sveriges kommuner och Landsting; Swedish Association of Local Authorities and Regions) with TLV support (the County councils through its NT; New Therapies group) has had a major impact on access in Sweden. This process has clearly delayed access for drugs like ipilimumab, palbociclib, and daratumumab. The SKL process has also been discussed in a recent governmental report [1] and the recommendation from this report is that the process needs to be fundamentally changed. When examining the Swedish data, we can note that national recommendations seem to play a minor role, both in relation to the introduction of new drugs, but also in limiting use on non-cost-effective drugs already on the market [2].

Another fundamental weakness in the Nordic region, with the population-based registers, is the lack of real-world data on treatments. In Sweden, a national registry for (hospital) cancer drugs has been discussed for over 10 years and a decision was taken already in 2008 by the heads of the oncology clinics; there is still no such complete registry in place. There is now a third version of the registry including about 10 cancer drugs covering less than 30% of the sales. The level of reporting into this registry, based on manual reporting, is still low and the estimation is that it only covers about 15% of the cancer drug use in Sweden. This means that there is a need for a remake of the registry in order to get reasonable quality. One way could be that the state or the health care regions provide a payback for oncology drugs for the first 3-5 years of use if the clinic supplies relevant data to a regional/national registry. This would mean reallocation of drug costs from clinical/hospital level to regional/national level that in turn would provide a database from which data for real-world analyses could be extracted. This information could then form the basis for national recommendations. Another solution could be a national registry similar to that in Norway.

A more fundamental factor for the future is the total structure of cancer research and cancer care in the Nordic countries. The development of Comprehensive Cancer Centers (CCC) was an initiative by OECI; Organization of European Cancer Institutes. To become a CCC there are required quality levels of both cancer research and cancer care. Denmark, Finland and Norway have all CCC structures. A CCC structure present shows investment in the development of cancer research and cancer management and the entire translational process. In Sweden, there are ongoing discussions about establishing CCCs. At present, Stockholm is in the process of becoming an accredited CCC, most likely in 2020.

4.1 References

1. Heinsoo, T. et al (2018), *Tydligare ansvar och regler för läkemedel*, SOU 2018:89.
2. ”Läkemedelsbehandling av tarmcancer – ett lotteri” [accessed: September 24, 2015]; Available from: https://medicinskaccess.se/artiklar/laekemedelsbehandling-av-tarmcancer-ett-lotteri/.

Appendix 1: Additional data for chapter 1

Age-standardized incidence rates

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

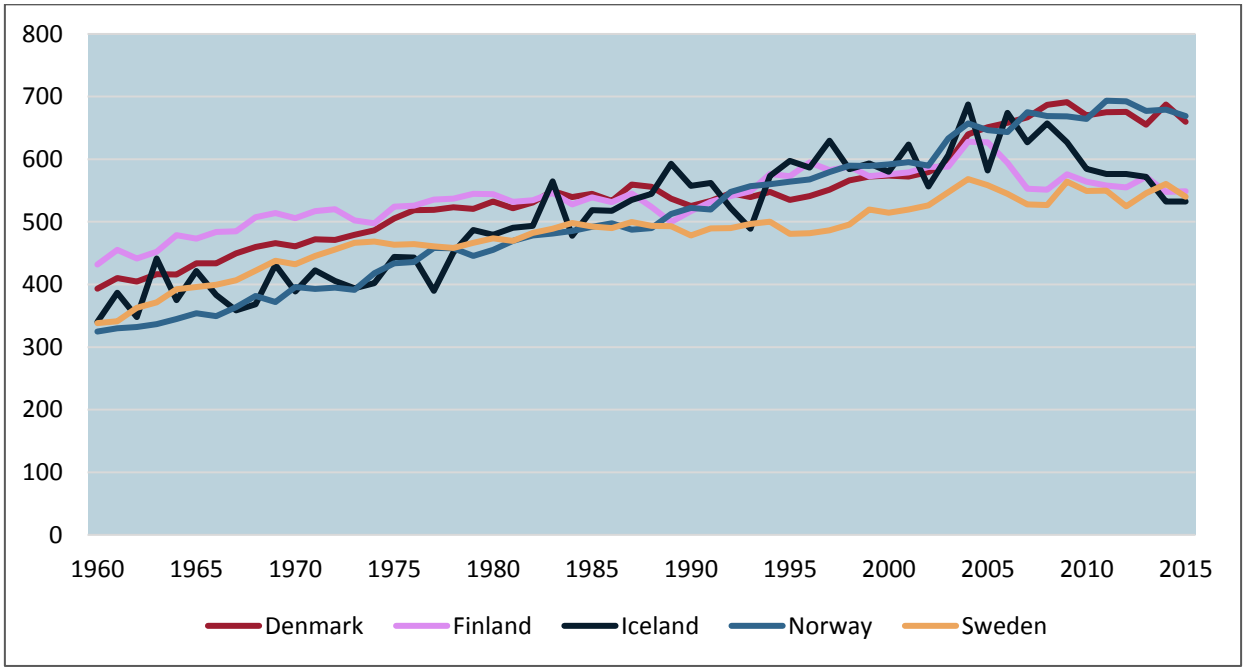

Figure A1: C*ancer incidence in men per 100,000 inhabitants (age-standardized rates (Nordic standard)), 1960-2015 [1]*

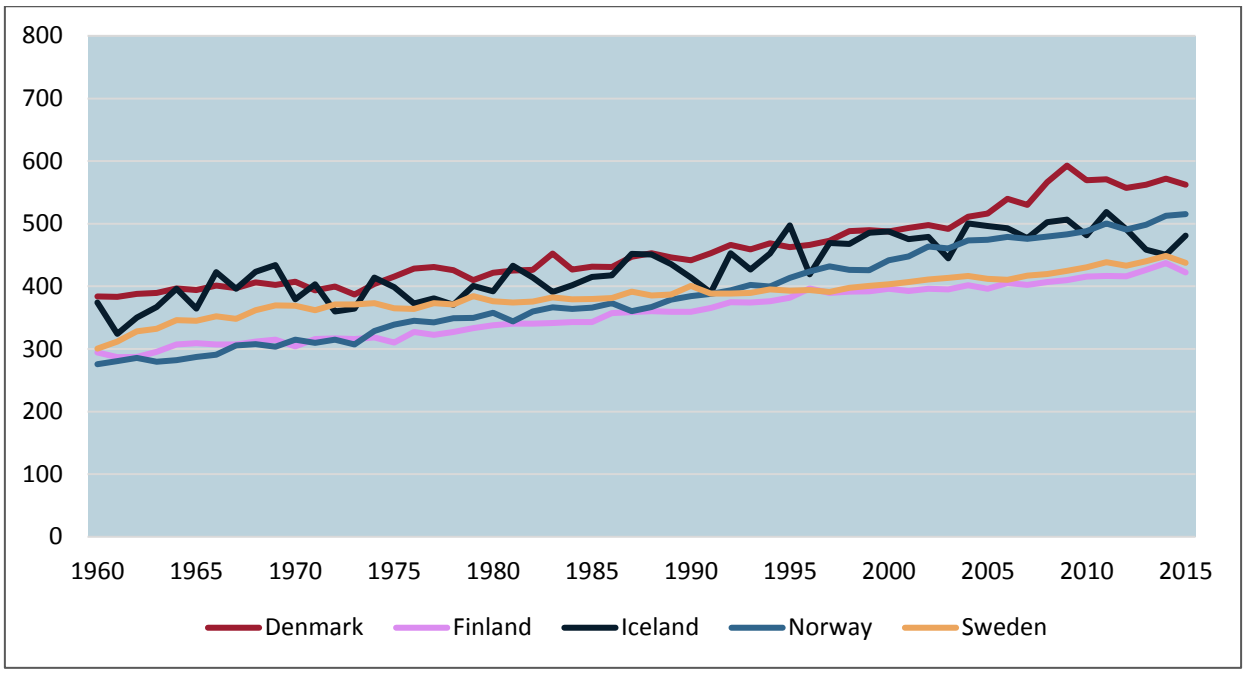

Figure A2: *Cancer incidence in women per 100,000 inhabitants (age-standardized rates (Nordic standard)), 1960-2015 [1]*

Age-standardized mortality rates

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

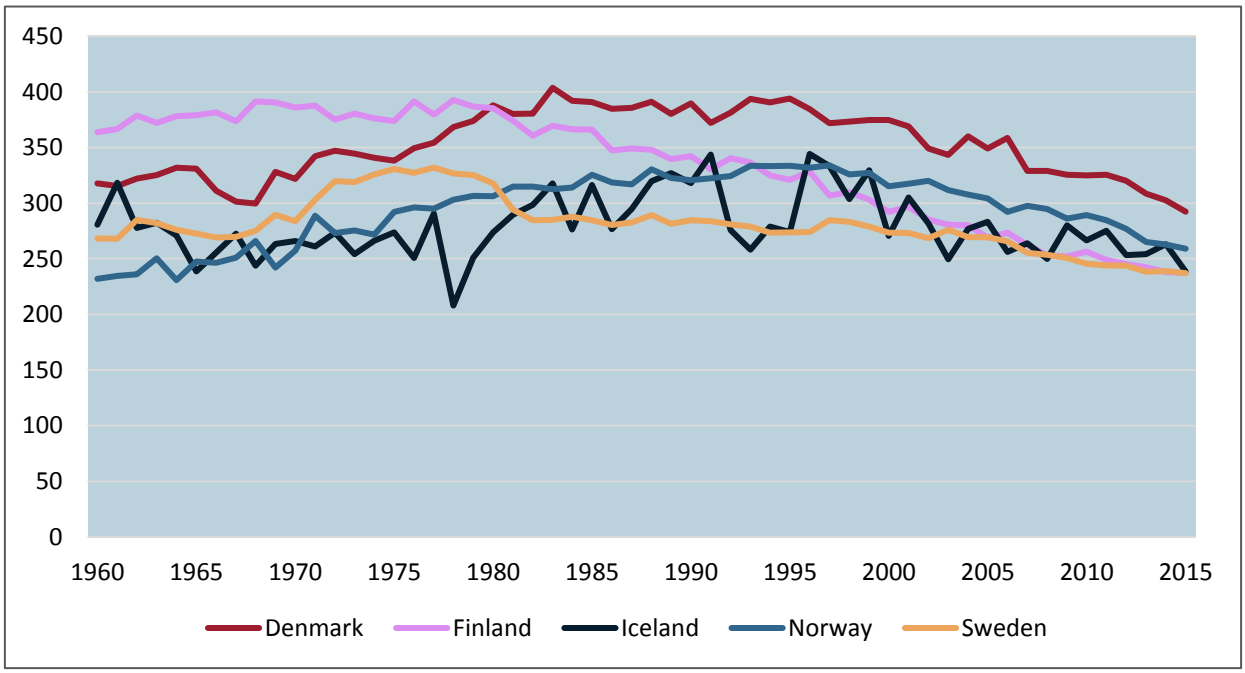

Figure A3: *Cancer mortality in men per 100,000 inhabitants (age-standardized rates (Nordic standard)), 1960-2015 [1]*

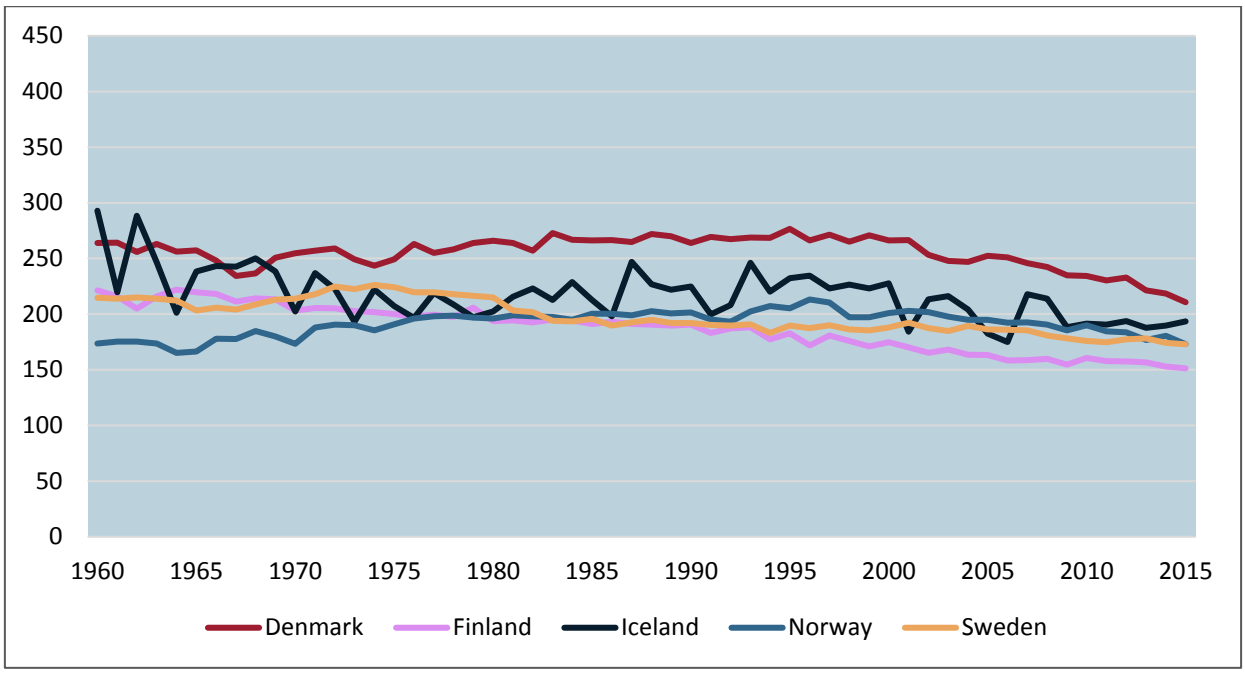

Figure A4: *Cancer mortality in women per 100,000 inhabitants (age-standardized rates (Nordic standard)), 1960-2015 [1]*

Survival rates

Figures A5 to A8 present 5-year age-standardized relative survival rates for the four most common cancer types; lung cancer, colorectal cancer, breast cancer, and prostate cancer. Note that for lung cancer and colorectal cancer, the sex-specific survival rates have been weighted according to the sex-specific share of the cancer-specific incidence in the five-year diagnosis periods.

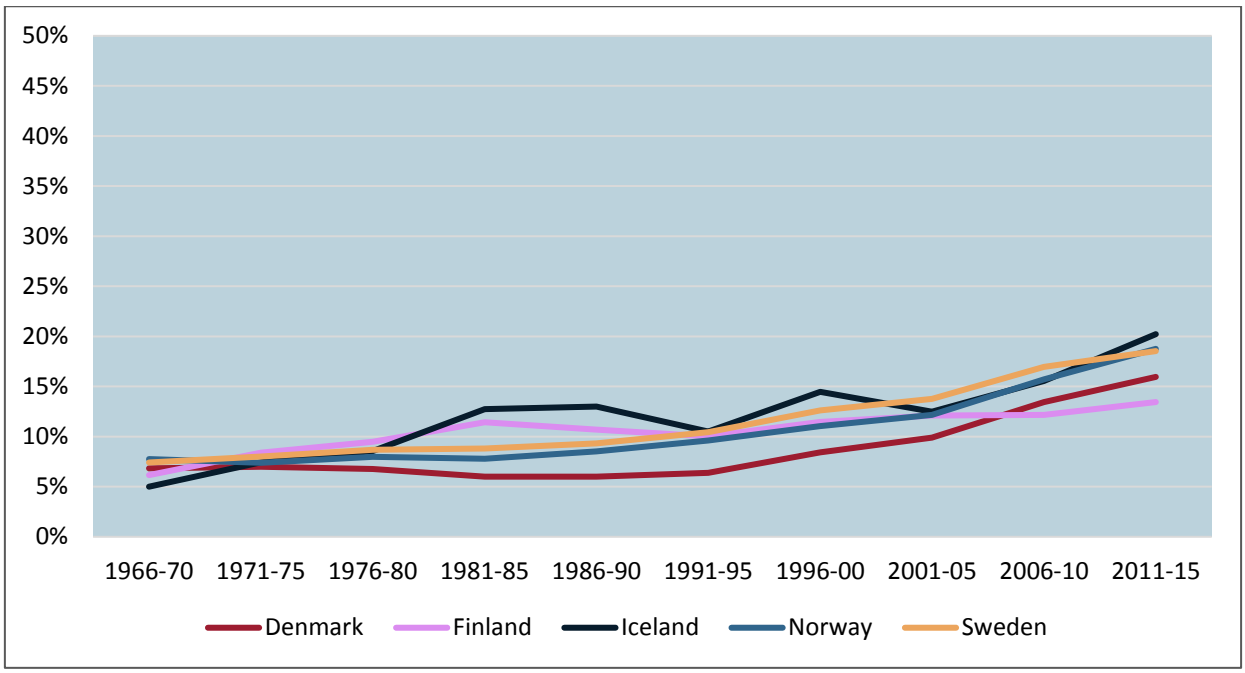

Figure A5: *5-year age-standardized relative survival rates for lung cancer in patients aged 0–89 at diagnosis, 1966–2015 [1]*

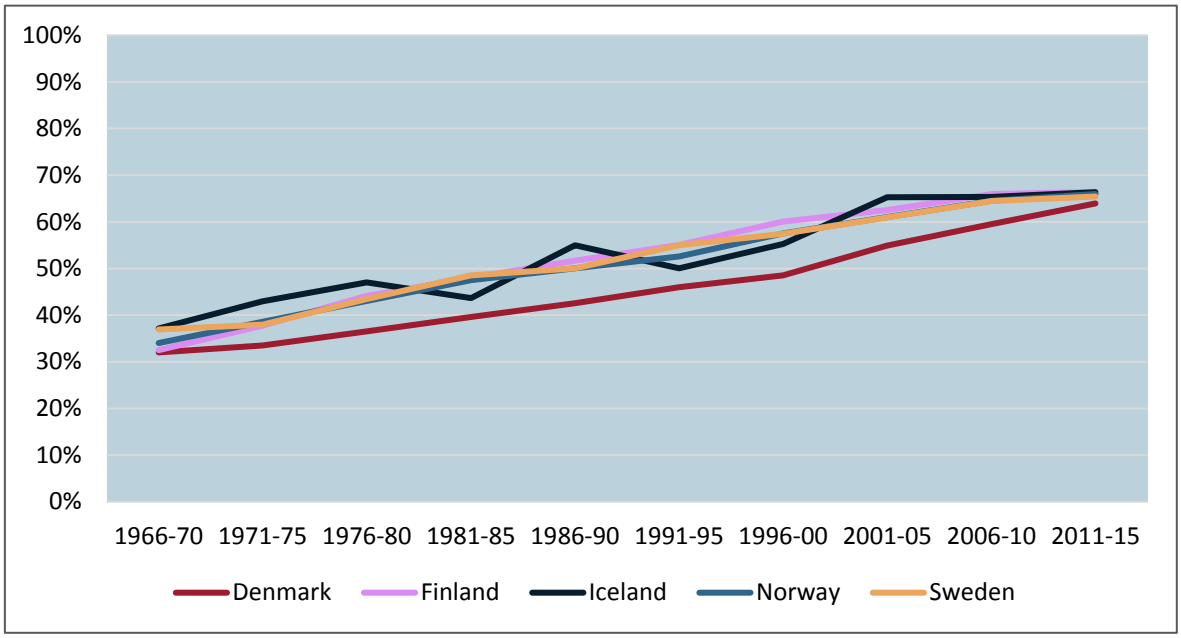

Figure A6: *5-year age-standardized relative survival rates for colorectal cancer in patients aged 0–89 at diagnosis, 1966–2015 [1]*

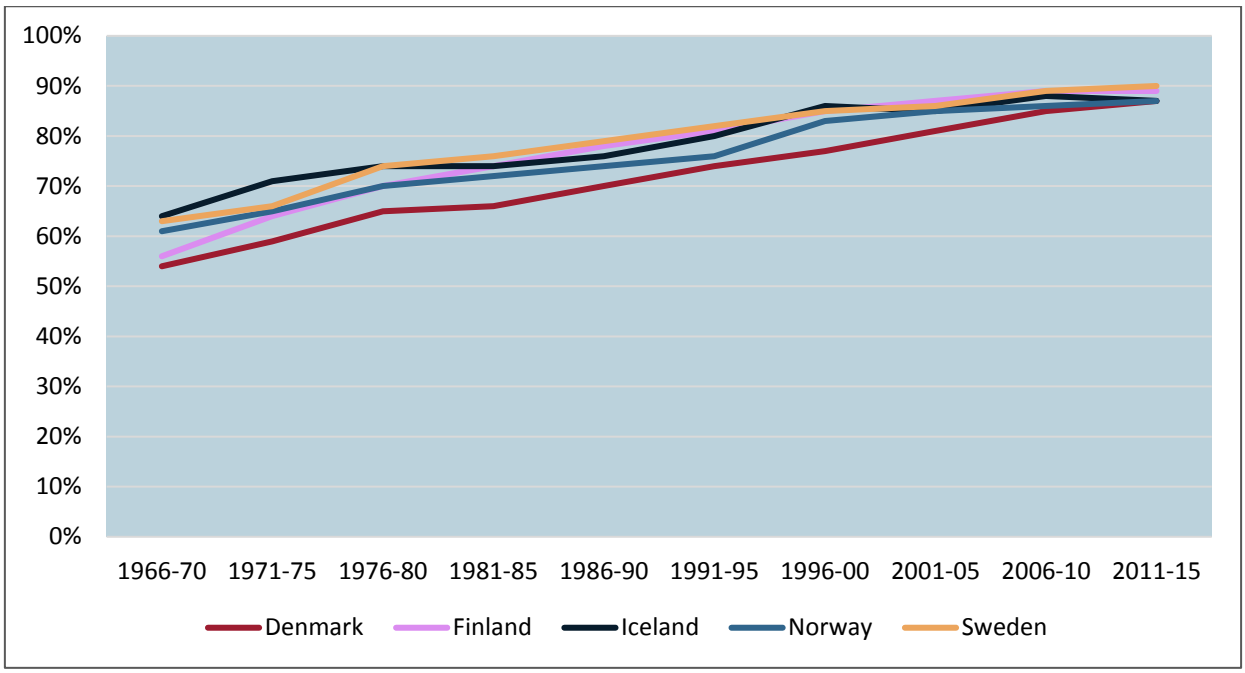

Figure A7: *5-year age-standardized relative survival rates for breast cancer in female patients aged 0–89 at diagnosis, 1966–2015 [1]*

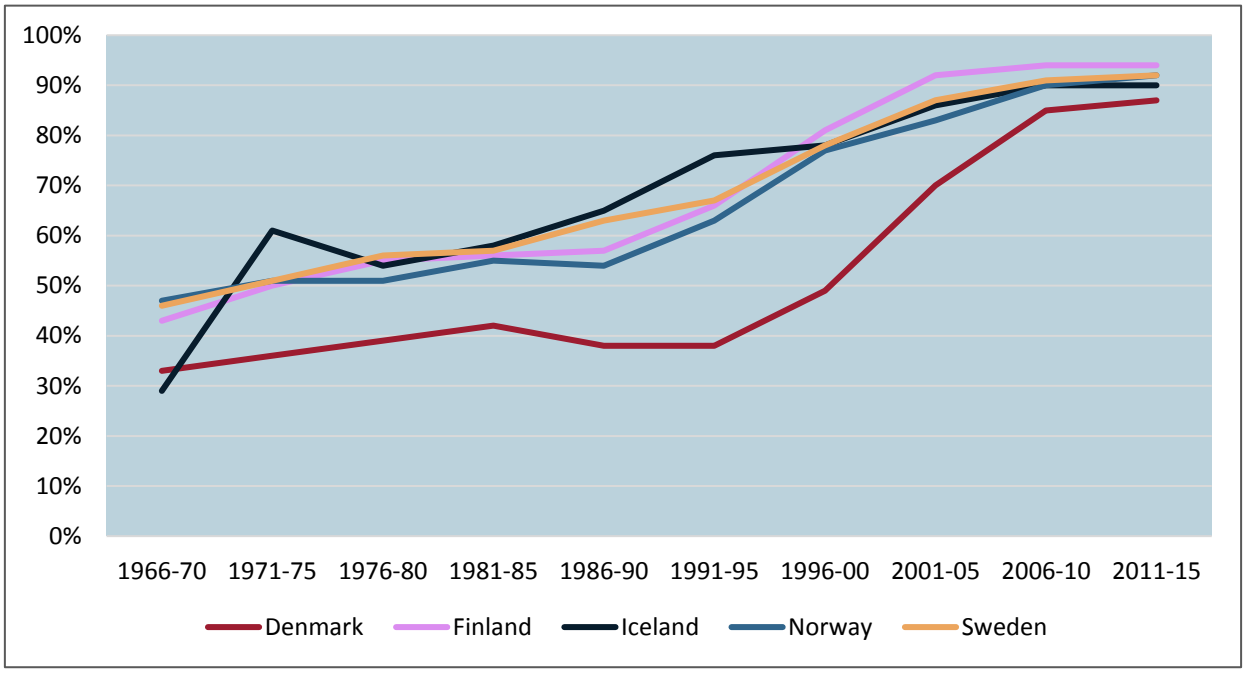

Figure A8: *5-year age-standardized relative survival rates for prostate cancer in male patients aged 0–89 at diagnosis, 1966–2015 [1]*

Cancer-specific health expenditure

Denmark

A report by the Center for Health Economic Research (COHERE) estimates the health expenditure for a cancer patient (ICD-10 C00-D48, though some non-malignant types seem to be excluded) based on matching techniques comparing cancer patients to a healthy control group [2]. Patients diagnosed between 2009–2013 and followed up until 2014 are included and all prices are adjusted to the price level in 2010. The costs included are expenditure on inpatient care and ambulatory care at hospitals (including medicine use) and on primary care for general practitioner (GP) visits. Expenditure on medicines dispensed outside the hospital, primary prevention measures, screening, and long-term care are missing. The additional health expenditure of a cancer patient amount to DKK 259,960 over a five-year period ranging from one year prior to the diagnosis to three years after it. However, the costs of DKK 17,710 in the year prior to the cancer diagnosis can, in line with a cost-of-illness approach, not be assigned to cancer as cancer cannot have been the main diagnosis. This puts the costs per patient to DKK 242,250. According to NORDCAN [1], there were 37,438 cancer patients diagnosed in Denmark in 2010. The total costs thus amount to DKK 9,069.4 million, which puts the share of cancer-specific expenditure on the total health expenditure (DKK 187,126 million in 2010 [3]) to 4.8%.

There are two more estimates available with more relevant cost categories missing and/or unclear methodology. First, a comparative cost-of-illness study for the Nordic countries estimated that the cancer costs (primary diagnosis ICD-10 C00-C97) in Denmark amounted to DKK 5,989 million in 2007 [4]. These costs include expenditure on hospital treatment (inpatient, day patient, and outpatient activities) (DKK 5,965 million) and prescription medicines (DKK 24 million). Expenditure on primary care, primary prevention measures, screening, and long-term care were not included. The share of cancer-specific expenditure on the total health expenditure (DKK 162,150 million in 2007 [3]) thus amounts to 3.7%. Second, the OECD reports that cancer (not including benign cancers) accounted for 4.5% of total health expenditure in 2008 [5]. It is noted that the data refer to costs in hospitals only. As a source the OECD cites the OECD Questionnaire on Systems of Cancer Care 2010.

Finland

A cost-of-illness study covering the period 2004 to 2014 estimated the health expenditure of cancer (ICD-10 C00-C97) to be €506 million in 2004 and €775 million in 2014 [6]. The shares of cancer-specific expenditure on the total health expenditure (€12,347 million in 2004 and €19,479 million in 2014 [3]) thus amount to 4.1% and 4.0%, respectively. The costs include expenditure on inpatient episodes in secondary care (€240 million in 2004 and €202 million in 2014), outpatient

visits in secondary care (€106 and €283), inpatient episodes in primary and private care (€70 and €87), rehabilitation (€4 and €4), outpatient medication (€60 and €160), and screening (€26 and €39). All treatment costs are reported as gross costs; i.e., including both the public expenditure and the patient's co-payment or deductible. Medicines administered in secondary care are included in the respective categories. Expenditure on primary prevention measures and long-term care are missing.

There are three more estimates available with more relevant cost categories missing and/or unclear methodology. First, a report by the Cancer Society of Finland estimates the health expenditure of cancer (ICD-10 C00-C97) to be €420.1 million in 2004 [4]. The included cost categories and estimates are the same as in the Finnish study above, except that the category of inpatient episodes in primary and private care is missing. Second, a comparative cost-of-illness study for the Nordic countries estimated that the cancer costs (primary diagnosis ICD-10 C00-C97) in Finland amounted to €640.8 million in 2007 [4]. These costs include expenditure on hospital treatment (inpatient, day patient, and outpatient activities) (€501.6 million), prescription medicines (€109.2 million), and screening programs for breast and cervical cancer (€30 million). Expenditure on primary care, primary prevention measures, and long-term care were not included. The share of cancer-specific expenditure on the total health expenditure (€14,602 million in 2007 [3]) thus amounts to 4.4%. Third, the OECD reports that cancer (not including benign cancers) accounted for 4.2% of total health expenditure in 2004 [5]. It is noted that the data do not include all costs related to medicines. As a source the OECD cites the OECD Questionnaire on Systems of Cancer Care 2010.

Iceland

A comparative cost-of-illness study for the Nordic countries estimated that the cancer costs (primary diagnosis ICD-10 C00-C97) in Iceland amounted to ISK 4,573 million in 2007[4]. These costs include expenditure on hospital treatment (inpatient, day patient, and outpatient activities) (ISK 3,867 million), prescription medicines (ISK 228 million), and screening programs for breast and cervical cancer (ISK 479 million). Expenditure on primary care, primary prevention measures, and long-term care were not included. The share of cancer-specific expenditure on the total health expenditure (ISK 118,962 million in 2007 [3]) thus amounts to 3.8%. In the absence of any other data, 3.8% is used as the best available estimate.

Norway

A cost-of-illness report covering the period 2011 to 2014 estimated the health expenditure of cancer (ICD-10 C00-D48, though some benign neoplasms seem to be excluded) to be NOK 11,137 million in 2011, NOK 10,943 million in 2012, NOK 11,914 million in 2013, and NOK 12,456

million in 2014 [8]. These costs include expenditure on primary care services, specialized health care (private specialized practitioners, day patient care, inpatient care, polyclinical contacts, polyclinical imaging, polyclinical laboratory services), and medicines (including some non-cancer medicines) dispensed at pharmacies. Expenditure on primary prevention measures, screening, and long-term care were not included in the study. Note that "other costs" among the specialized health care expenditure are excluded, since they are not part of the definition of total health expenditure used in this report. The shares of cancer-specific expenditure on the total health expenditure (NOK 245,440 million in 2011, NOK 260,181 million in 2012, NOK 274,246 million in 2013, NOK 293,507 million in 2014 [3]) thus amount to 4.5%, 4.2%, 4.3%, and 4.2%, respectively.

There is one more estimate available with more relevant cost categories missing. A comparative cost-of-illness study for the Nordic countries estimated that the cancer costs (primary diagnosis ICD-10 C00-C97) in Norway amounted to NOK 6,782 million in 2007 [4]. These costs include expenditure on hospital treatment (inpatient, day patient, and outpatient activities) (NOK 5,660 million), prescription medicines (NOK 776 million), and screening programs for breast and cervical cancer (NOK 346 million). Expenditure on primary care, primary prevention measures, and long-term care were not included. The share of cancer-specific expenditure on the total health expenditure (NOK 189,209 million in 2007 [3]) thus amounts to 3.6%.

Sweden

A cost-of-illness study estimated the health expenditure of cancer (ICD-10 C00-C97) to be SEK 15,537 million in 2013 [9]. The costs include expenditure on inpatient care (SEK 6,513 million), specialized outpatient care (SEK 4,145 million), cancer medicines (SEK 2,766 million), screening (SEK 642 million), primary care (SEK 265 million), and palliative care and other care services (SEK 1,207 million). Expenditure on primary prevention measures, screening (PSA), other treatment-related medicines (e.g. antiemetic medicines) and patient fees related health care visits were not included. The share of cancer-specific expenditure on the total health expenditure (SEK 418,490 million in 2013 [3]) thus amounts to 3.7%.

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

and SEK 100 million for antiemetic medicines) in 2004 [11]. This would reduce the health expenditure in 2004 to SEK 16,455 million. The share of cancer-specific expenditure on the total health expenditure (SEK 290,837 million in 2004 [3]) thus amounts to 5.7%. Second, a comparative cost-of-illness study for the Nordic countries estimated that the cancer costs (primary diagnosis ICD-10 C00-C97) in Sweden amounted to SEK 11,523 million in 2007 [4]. These costs include expenditure on hospital treatment (inpatient, day patient, and outpatient activities) (SEK 8,965 million), prescription medicines (SEK 1,686 million), and screening programs for breast and cervical cancer (SEK 881 million). Expenditure on primary care, primary prevention measures, and long-term care were not included. The share of cancer-specific expenditure on the total health expenditure (SEK 334,084 million in 2007 [3]) thus amounts to 3.4%. Third, the OECD reports that cancer (not including benign cancers) accounted for 3.1% of total health expenditure in 2006 [5]. It is noted that the data refer to costs in hospitals only. As a source the OECD cites the OECD Questionnaire on Systems of Cancer Care 2010.

Total expenditure on health

Table A1: *Total expenditure on health in the Nordic countries [3, 12]*

	1995	2000	2005	2010	2015	Total change	Annual change
Total health expenditure (in millions of national currency), current prices							
Denmark (DKK)	80,541	107,538	144,175	187,126	208,262	159%	4.9%
Finland (EUR)	7,248	9,315	13,148	16,593	20,421	182%	5.3%
Iceland (ISK)	36,227	63,359	96,857	142,721	186,528	415%	8.5%
Norway (NOK)	70,045	116,244	165,734	230,785	315,207	350%	7.8%
Sweden (SEK)	172,370	221,437	302,022	374,897	462,326	159%	4.9%
Total health expenditure (in millions of national currency), 2015 prices							
Denmark (DKK)	112,487	138,759	169,618	198,858	208,262	85%	3.1%
Finland (EUR)	10,099	12,131	15,993	18,269	20,421	102%	3.6%
Iceland (ISK)	83,742	133,107	172,375	166,245	186,528	123%	4.1%
Norway (NOK)	100,065	150,770	199,439	248,691	315,207	215%	5.9%
Sweden (SEK)	226,326	277,560	347,032	388,777	462,326	104%	3.6%
Total health expenditure, in % of GDP							
Denmark	7.8%	8.1%	9.1%	10.3%	10.3%		
Finland	7.4%	6.8%	8.0%	8.9%	9.7%		
Iceland	8.0%	9.0%	9.2%	8.8%	8.3%		
Norway	7.3%	7.7%	8.3%	8.9%	10.1%		
Sweden	9.2%	9.3%	10.4%	10.7%	11.0%		

Note: The 1995 estimates are only adjusted for inflation between 1996 and 2015 due to lack of a harmonized inflation measure before 1996 [12]. The annual growth rate is calculated assuming a constant growth rate. The total health expenditure in Sweden for the years 1995–2010 are calculated based on the new definition implemented in 2011, applying the annual growth rates in health expenditure (based on the old definition) in 1995–2010 to the 2011 value (and assuming a 4.16% growth rate between 2010 and 2011 based on old data from Eurostat [13]).

4.2 References Appendix 1

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Appendix 2: Additional data for chapter 3

Launch year for cancer drugs

Table A2 shows in which year the different cancer drugs has been authorized by EMA. The table consists of the drugs authorized between 2007 and 2017 that are included in the data.

Table A2: *Launch year for cancer drugs between 2007 and 2017*

Substance	Launch year	Substance	Launch year
Trofosfamide	2007	Bosutinib	2013
Lenalidomide	2007	Pomalidomide	2013
Nelarabine	2007	Pertuzumab	2013
Trabectedin	2007	Trastuzumab Emtansine	2013
Panitumumab	2007	Afatinib	2013
5-Aminolevulinic Acid Hydrochloride	2007	Dabrafenib	2013
Nilotinib	2007	Ponatinib	2013
Temsirolimus	2007	Vismodegib	2013
Hydroxycarbamide	2007	Enzalutamide	2013
Lenalidomid	2007	Ramucirumab	2014
Bendamustine	2008	Methyl Aminolevulinate	2014
Azacitidine	2008	Cabozantinib	2014
Lapatinib	2008	Nintedanib	2014
Vinflunine	2009	Olaparib	2014
Catumaxomab	2009	Obinutuzumab	2014
Gefitinib	2009	Trametinib	2014
Everolimus	2009	Ibrutinib	2014
Degarelix	2009	Idelalisib	2014
Ofatumumab	2010	Pembrolizumab	2015
Pazopanib	2010	Blinatumomab	2015
Cabazitaxel	2011	Olaratumab	2015
Pirfenidone	2011	Ceritinib	2015
Tegafur / Gimeracil / Oteracil	2011	Lenvatinib	2015
Ipilimumab	2011	Cobimetinib	2015
Eribulin	2011	Carfilzomib	2015
Abiraterone Acetate	2011	Talimogene Laherparepvec	2015
Pipobroman	2012	Nivolumab	2015
Pixantrone	2012	Panobinostat Lactate Anhydrous	2015
Brentuximab Vedotin	2012	Trifluridine Combinations	2016
Vandetanib	2012	Elotuzumab	2016
Crizotinib	2012	Daratumumab	2016
Axitinib	2012	Palbociclib	2016
Vemurafenib	2012	Osimertinib	2016
Ruxolitinib	2012	Ixazomib	2016
Regorafenib	2012	Venetoclax	2016
Aflibercept	2012	Inotuzumab Ozogamicin	2017
		Avelumab	2017
		Atezolizumab	2017
		Alectinib	2017
		Ribociclib	2017

Price adjustments

The effect of using a fixed price level, € 2015, contains two parts, the adjustment for the exchange rate and the adjustment for the inflation. Both effects are shown in this section in separate figures.

In **Figure A9** the adjustment of the original prices (%) due to the fluctuation in the exchange rate compared to the rate in 2015 is shown.

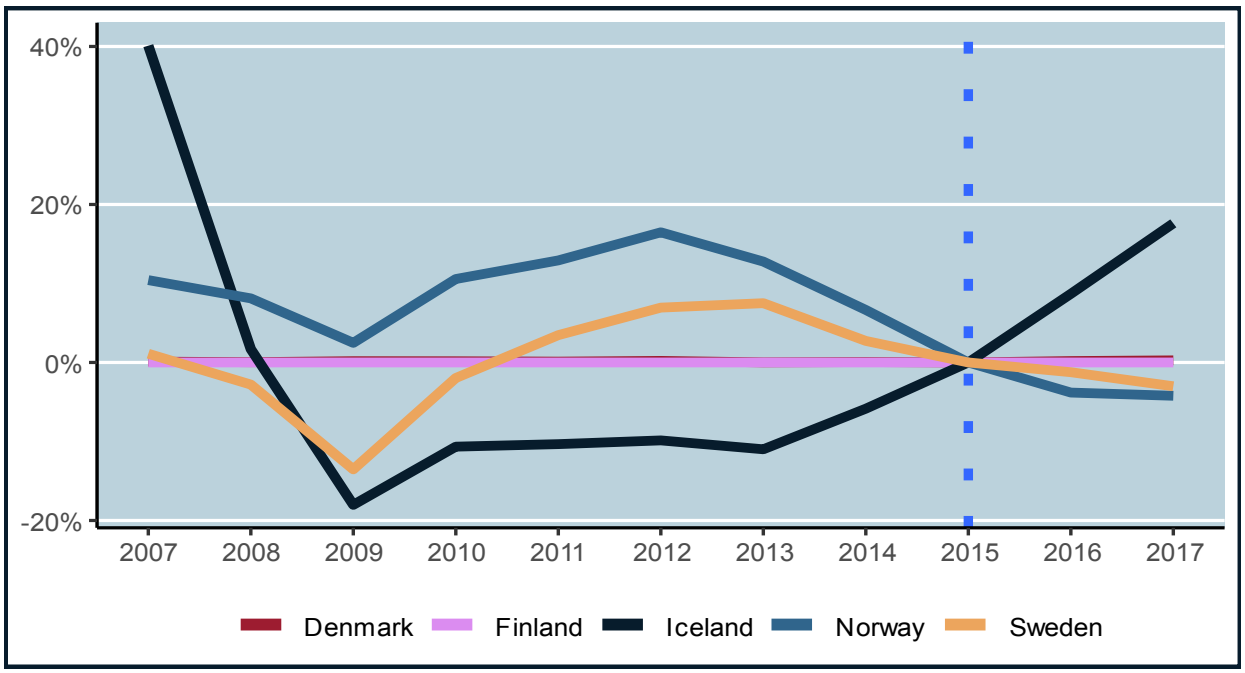


Figure A9: *Adjustment of original prices (%) compared to 2015 due to the exchange rate towards the Euro.*
Note: The exchange rate used in this report is the annual average.

For Finland and Denmark there is no effect on prices from the former factor since Finland has adopted the Euro and Denmark has a fixed exchange rate towards it.

As can be seen in **Figure A9**, both the Swedish and the Norwegian crown increased in value compared to the Euro during the intermediate phase of the financial crises, 2010-2012. After that however, the Euro recovered and has strengthen its value towards the local currencies.

For Iceland, the exchange rate for the Icelandic crown towards the Euro increased by over 60 percent between 2007 and 2008, however it has been more stable since.

In **Figure A10** it is shown how the inflation affects the prices used in this report. Most notably, there was a huge change to the inflation in Iceland during the finical crisis. Apart from Iceland however, the development of the inflation rate has been fairly consistent in the Nordic countries during 2007-2017.

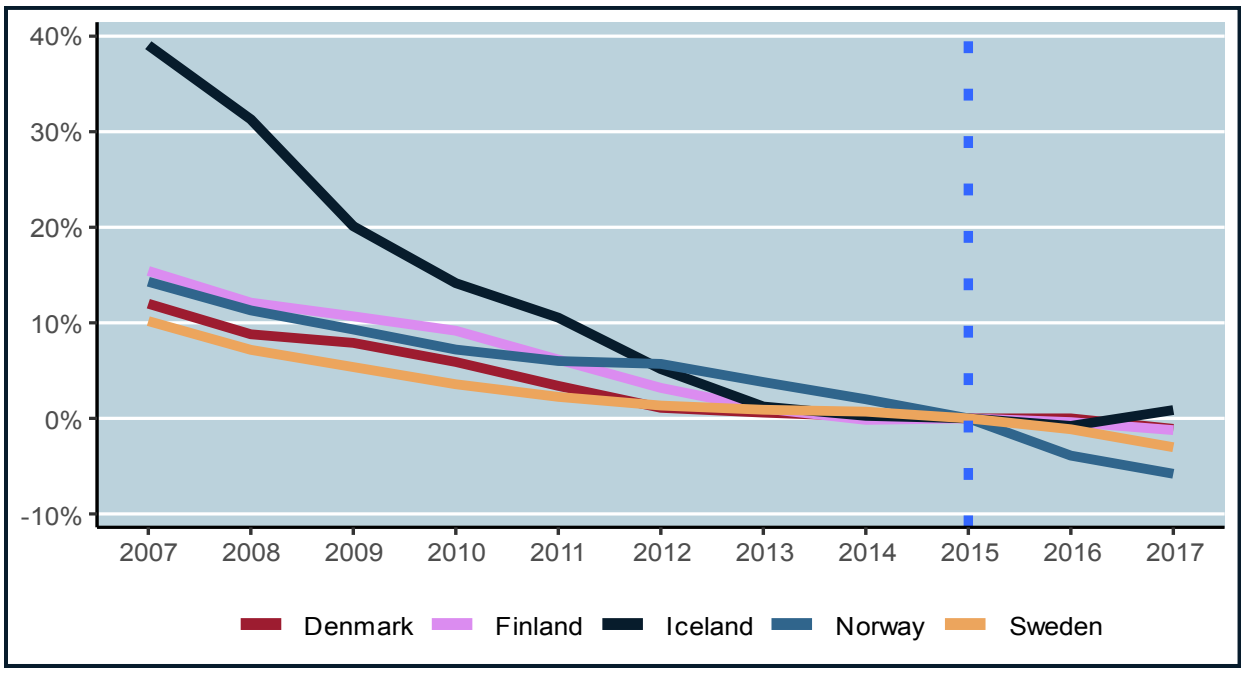
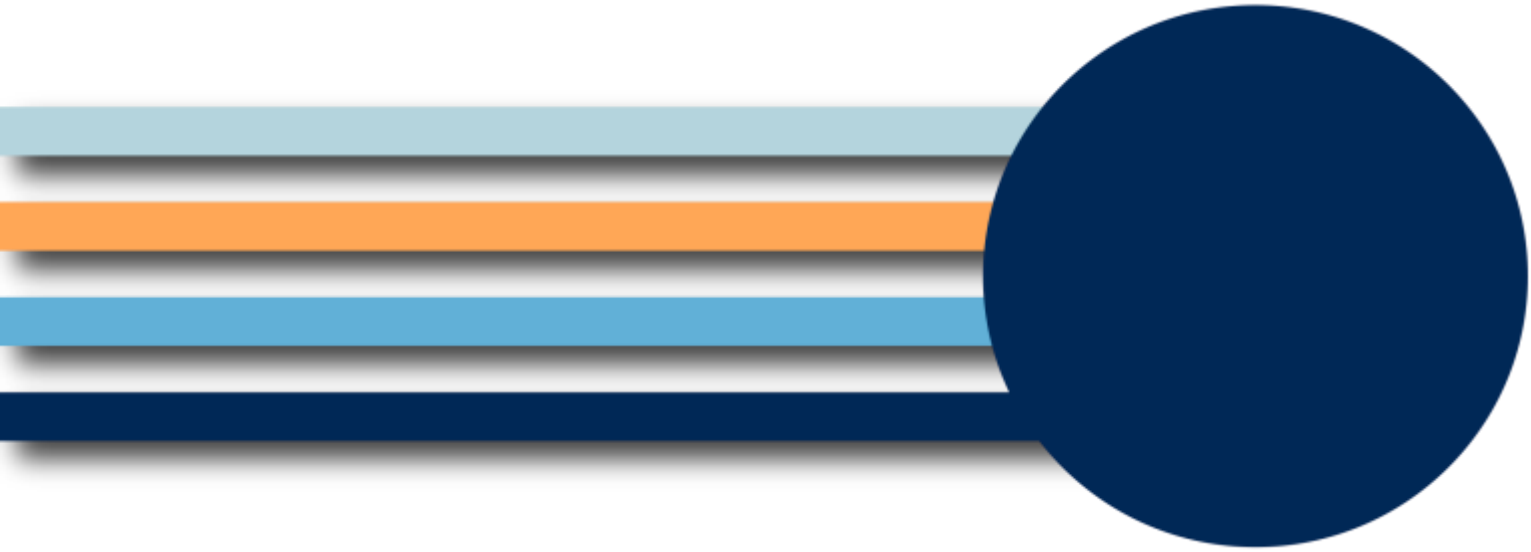


Figure A10: *Adjustment of original prices (%) compared to 2015 due to the inflation.*



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