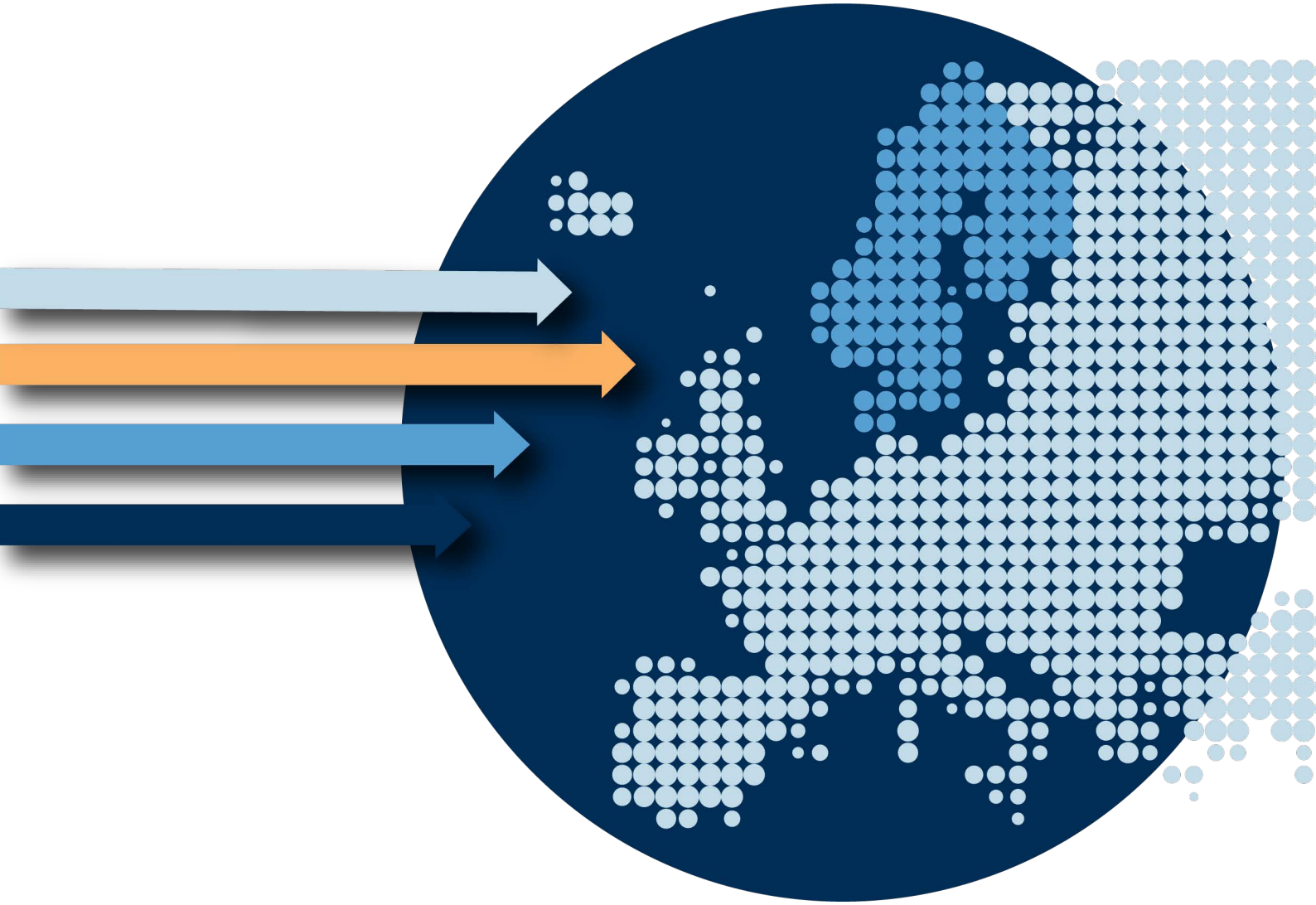
COMPARATOR REPORT ON CANCER IN THE NORDIC COUNTRIES – DISEASE BURDEN, COSTS AND ACCESS TO MEDICINES

SUMMARY



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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 and a shorter summary version (this document).

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 Introduction

Cancer remains a major public health concern, overtaking or posed to overtake cardiovascular disease as the leading cause of death in many western countries. Medical development has also made it into a major target for the development of new medicines, with more than 1,200 candidates in various stages of clinical studies immuno-oncology alone. This rapid development is of course of great potential to patients, but it also poses significant challenges to the health care system. Greater understanding of the system as a whole over time can facilitate the identification and implementation of relevant policies moving forward.

The objective of this project was to provide a comparative overview of the oncology field in the Nordic countries (including Denmark, Finland, Sweden, Norway, and Iceland) over the last 10 years to provide inputs to relevant policy discussions.

This report constitutes a summary of some of the findings from the project. For detailed descriptions of the methods applied, additional in-depth analysis as well as the list of references, please consult the full report (IHE Report 2019:2b).

2 The disease burden and economic burden of cancer in the Nordic countries

2.1 Trends in incidence, mortality and survival

Based on data from NORDCAN (aggregating data from the different cancer registries in the Nordic countries), cancer incidence totaled 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 in their absence, cancer incidence would still have increased by almost 60%.

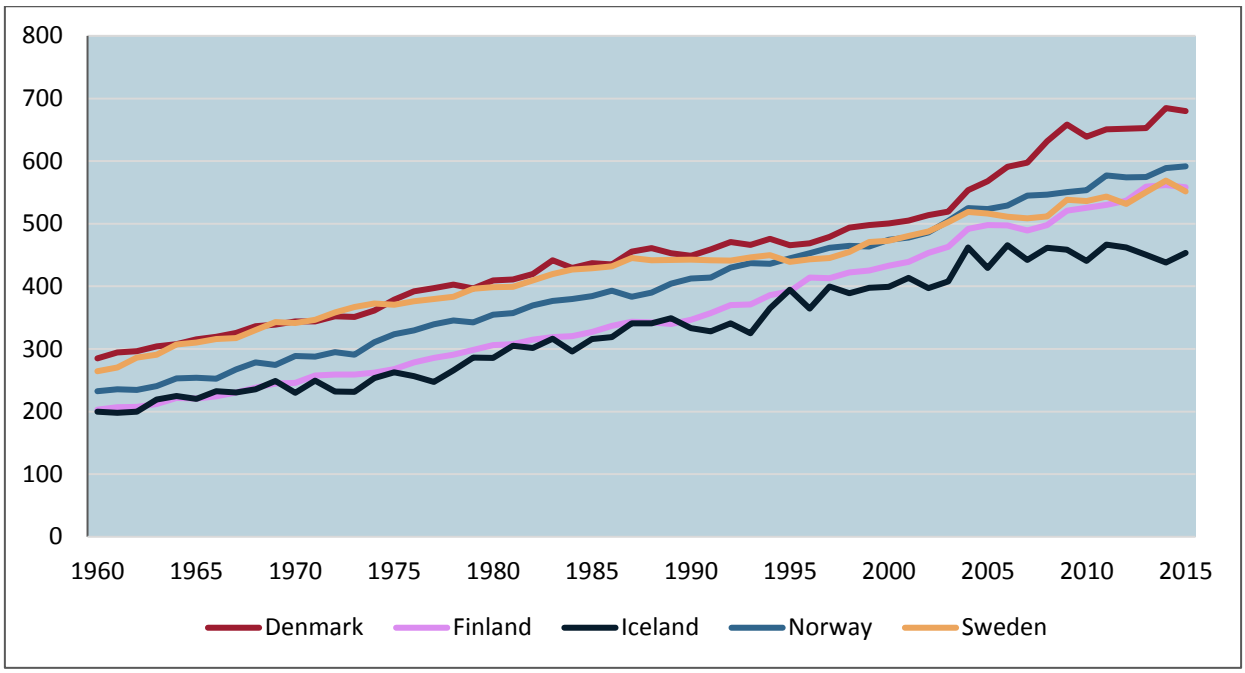


Figure 1: *Cancer incidence per 100,000 inhabitants (crude rates, both sexes), 1960–2015 (source: NORDCAN).*

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 that caused the greatest disease burden in terms of disability adjusted life years (DALYs, 20% in 2015) in the Nordic countries, ahead of cardiovascular diseases.

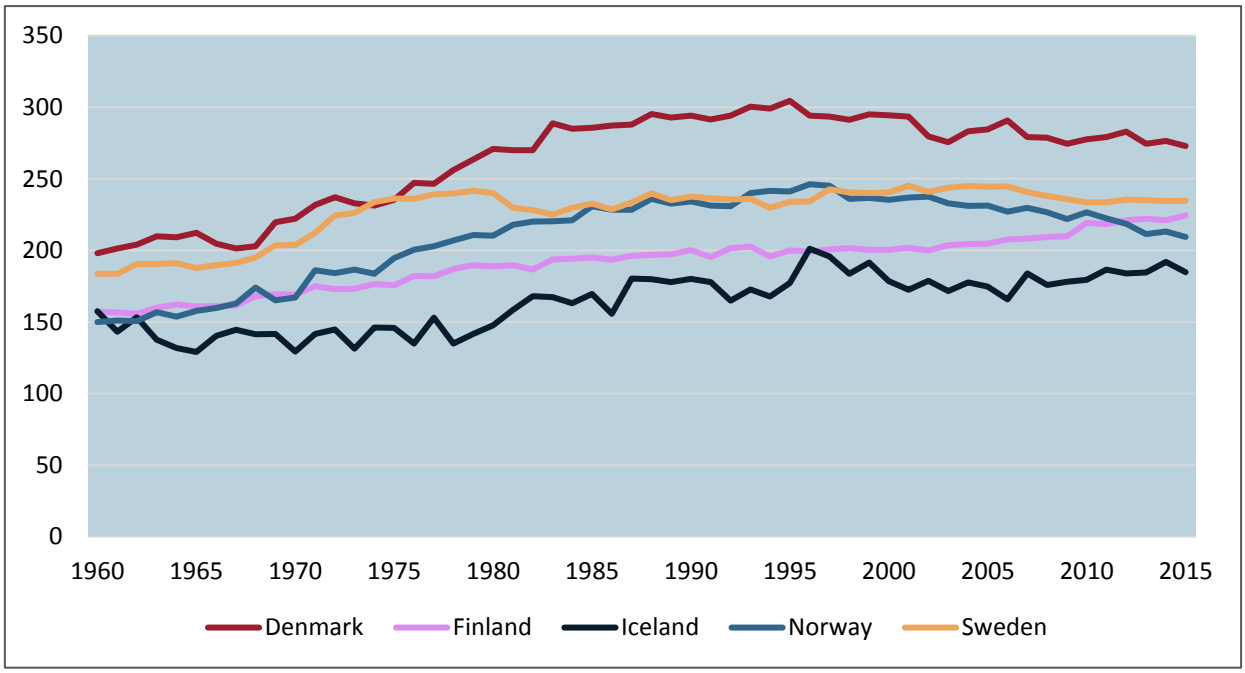


Figure 2: *Cancer mortality per 100,000 inhabitants (crude rates, both sexes), 1960–2015 (source: NORDCAN).*

Since the 1960s, 5-year survival rates for all cancers combined have increased from about 35% to 65% until 2015. Denmark has been trailing behind the other countries but has started to catch up since the late 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. These factors have also been the drivers behind the steadily increasing survival rates.

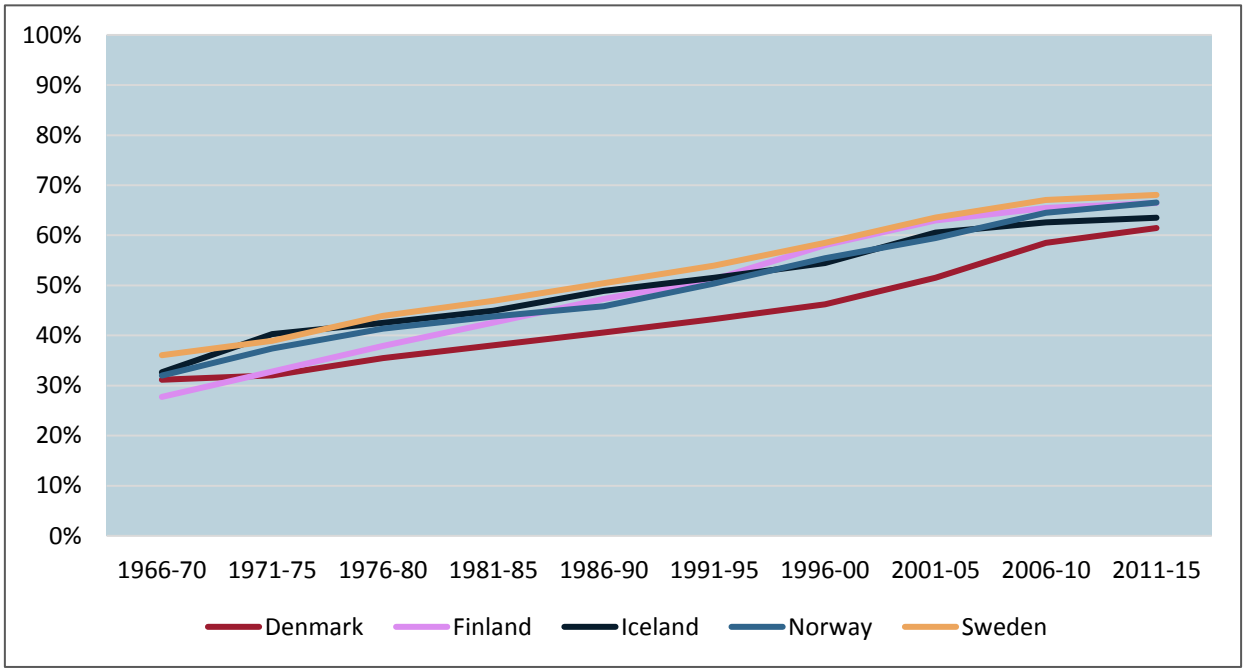


Figure 3: *5-year age-standardized relative survival rates for all cancers in patients aged 0–89 at diagnosis, 1966–2015(source: NORDCAN).*

2.2 The economic burden of cancer

There are multiple components to the cost of cancer: Direct costs are linked to resources consumed due to the disease such as hospital care, test or medicines. Indirect costs are due to production losses caused by the disease e.g. due to sick leave or early mortality. Direct costs were calculated by estimating the share of total health care costs (based on official statistics) made up by cancer costs based on data from the literature. Even though health care spending on cancer has been increasing continuously since 1995, limited evidence shows that the rate of the increase was similar to the overall increase in expenditure on health care. The share of health expenditure spent on cancer remained thus more or less constant, despite the increasing number of cancer patients.

Denmark spent the most on cancer care with €138 per capita (year 2015 prices) 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 expenditures on 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 expenditures on inpatient care have been substituted with increasing expenditures on ambulatory care and cancer medicines.

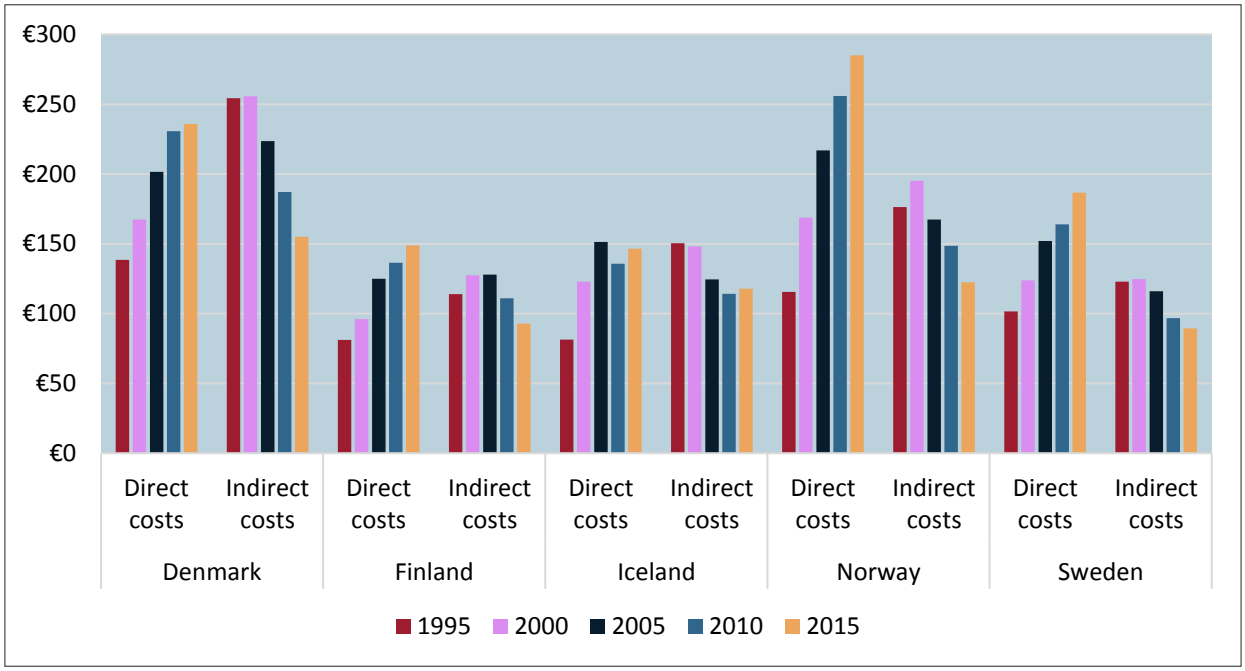


Figure 4: *Economic burden of cancer per capita (in €; 2015 prices & exchange rates), 1995–2015.*

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. Indirect costs due to mortality were estimated by calculating the number of potential years of work loss due to cancer combining this with data on earnings. In contrast to direct costs (see figure above), the indirect costs due to mortality has decreased over time. The exact development of productivity loss from morbidity is more uncertain. 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 sheer increase in cancer incidence in people of working age probably pushed up the expenditures 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 returning to work, this could explain why expenditures 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.

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 – are required to meet this challenge.

3 Medical review

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 in the clinical trials on which registration is based. 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. Chemotherapy drugs are however still the backbone of most drug combinations. 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

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. This may contribute to the observed shift in the make-up of direct costs described in the previous chapter.

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. According to a recent review, "since 2011, new immunotherapies have become not only the standard of care for 15 cancer types, but also the front-line treatments for melanoma, lung cancer and kidney cancer, making immunotherapy one of the pillars of cancer therapy".

4 Uptake of medicines

Spending on cancer medicines has increased during the last 10 years and was 375 million € in Denmark, 315 million € in Finland, 15 million in Iceland, 319 million € in Norway and 486 million € in Sweden in 2017. It should be noted that these figures are exclusive of confidential rebates given which has been more common over time.

Data show a fast increase in later years, with marked shifts in Denmark and especially in Norway during 2016 and 2017.

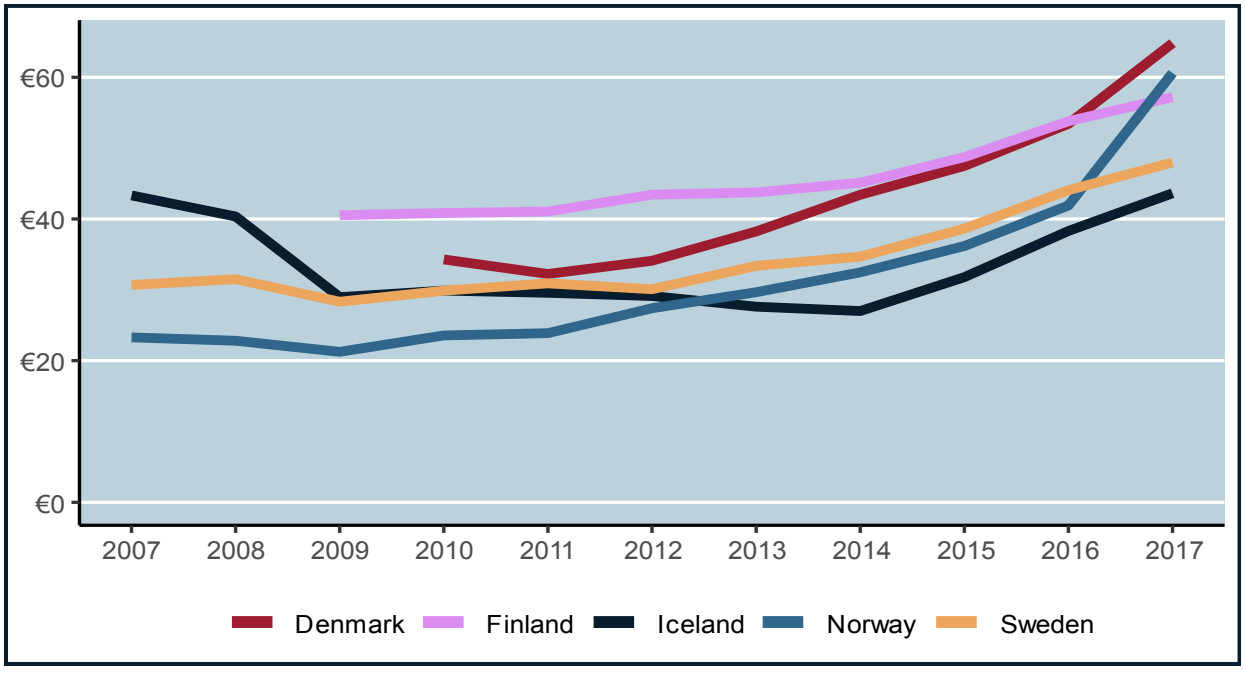


Figure 5: *Euro/inhabitant for all cancer medicines in the Nordic countries (fixed prices and 2015 exchange rates).*

There are differences in the per capita spending on cancer medicines between the Nordic countries (between 44€ and 65€), however taking incidence/mortality into consideration the difference in spending between countries 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 (though overall variation is smaller in Finland). Denmark has large variations which has been consistent (in relative terms) over the time period studied. The picture is complicated somewhat by the fact that the Danish regions sometimes send patients for care in other regions, and patients may also seek care in other regions on their own. There seems to be a tendency for smaller variation for medicines launched in more recent years in Denmark, Sweden and Norway.

4.1 Breast cancer

In breast cancer, there has been significant development in the treatment options for HER2-positive breast cancer in particular, with trastuzumab now having widespread use. In our first comparator report from 2005 a lot of focus was 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 we still now 12-13 years later see 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 their use and is catching up with Sweden and Finland.

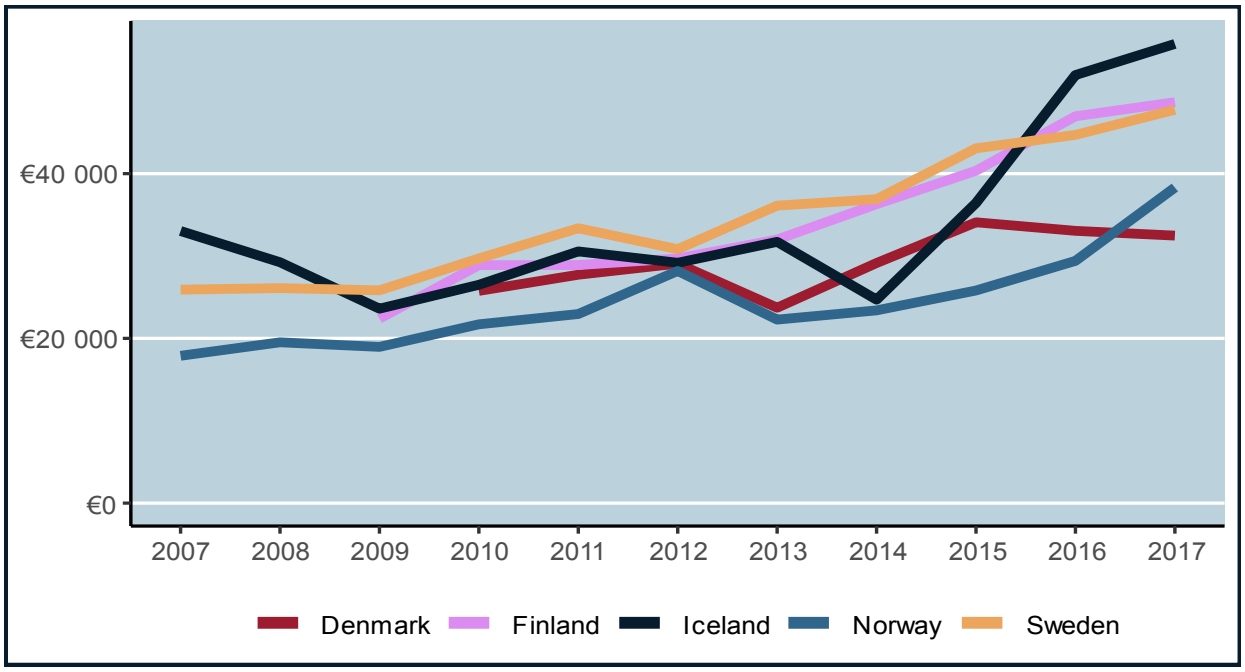


Figure 6: *Euro/case in breast cancer for all HER2-drugs in the Nordic countries.*

In Sweden, the Stockholm-Gotland uses more new breast cancer drugs compare to the other regions where use is more uniform, as can be seen in the figure below.

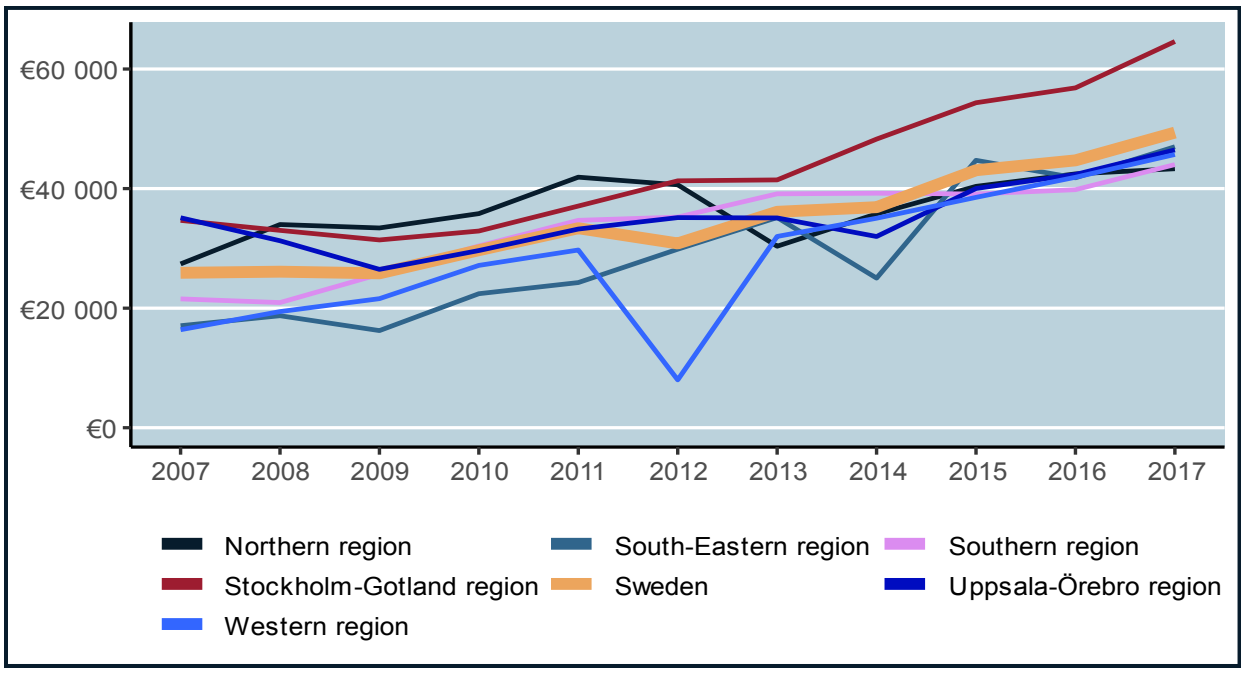


Figure 7: *Euro/case[1] in breast cancer for trastuzumab + pertuzumab + trastuzumab emtansine + lapatinib + palbociclib + ribociclib in Sweden.*

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

4.2 Malignant melanoma

The treatment 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; PDL-1 drugs were awarded the Nobel prize in 2018, Approved in 2011, ipilimumab access was very slow and low in the Nordic region with the exception of Denmark in 2011-12, increased rapidly 2013-15 with the exception of Finland. The use decreased in 2015 with the approval of PD-1 drugs for first line treatment, but in 2016 the combination of ipilimumab with PD-1 was approved and indicated for about 30% of patients with metastatic malignant melanoma. We very large variation in the uptake for ipilimumab, both during the first period (2011-15) when the drug was the only immunotherapy for melanoma but also for 2016-17 when the combination was approved and recommended.

[1] We use death from the diagnosis as the definition of a case throughout.

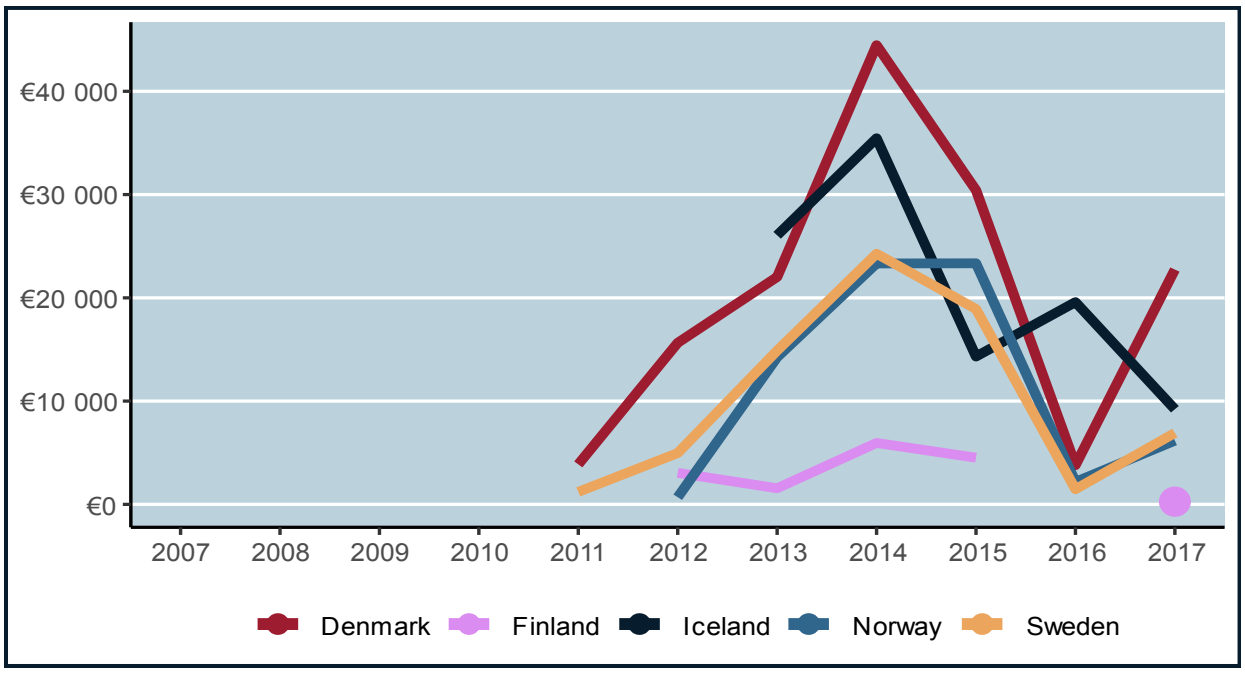


Figure 8: *Euro/case in malignant melanoma for ipilimumab in the Nordic countries.*

For the drugs with an indication in B-RAF mutated metastatic malignant melanoma the situation is somewhat different. (**Figure 9**) We see a more uniform uptake even though Denmark again has the highest uptake followed by Sweden and Norway. Finland has also with these drugs a low level of access.

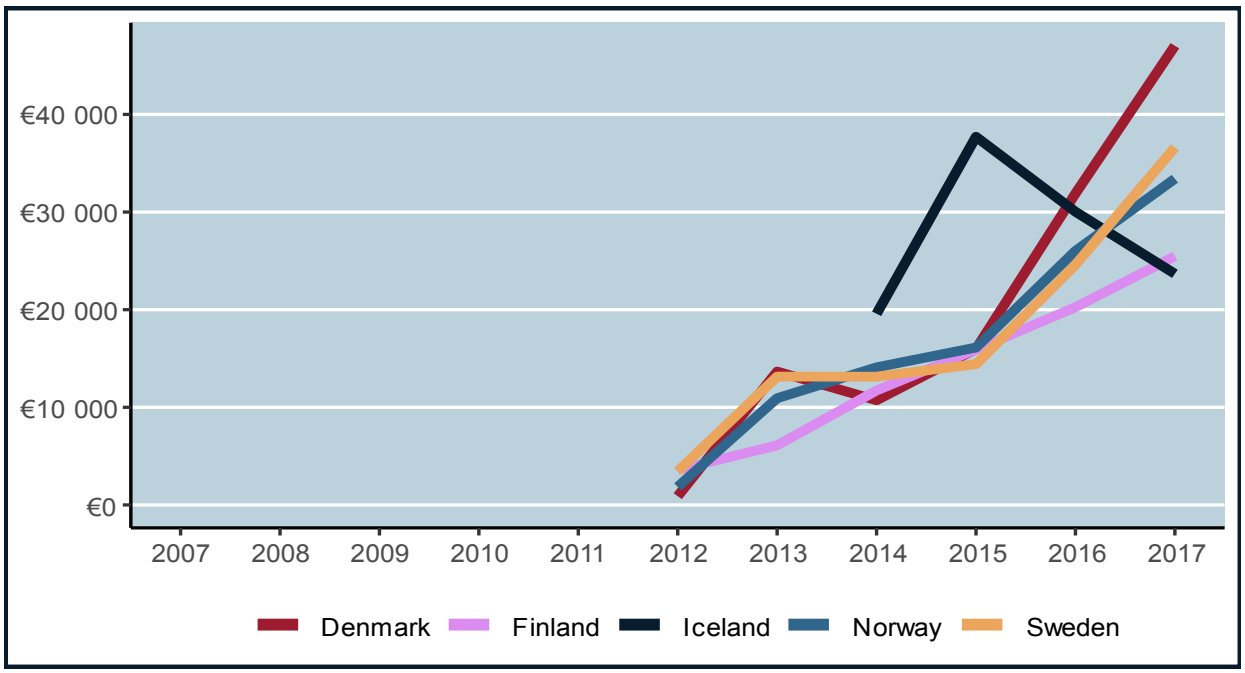


Figure 9: *Euro/case in malignant melanoma for vemurafenib + dabrafenib + trametinib in the Nordic countries.*

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).

4.3 Myeloma

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 introduction of thalidomide, lenalinomid and pomolinomid followed over the next 10 years. Most recently, carfilzomib and daratumumab, has 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 is an outlier when it comes to myeloma drugs in Sweden. For the older drugs, usage is similar between the countries but there are drastic differences for the overall sales of myeloma drugs represent about 15% of total cancer drug sales while the disease represents about 3% of total cancer mortality.

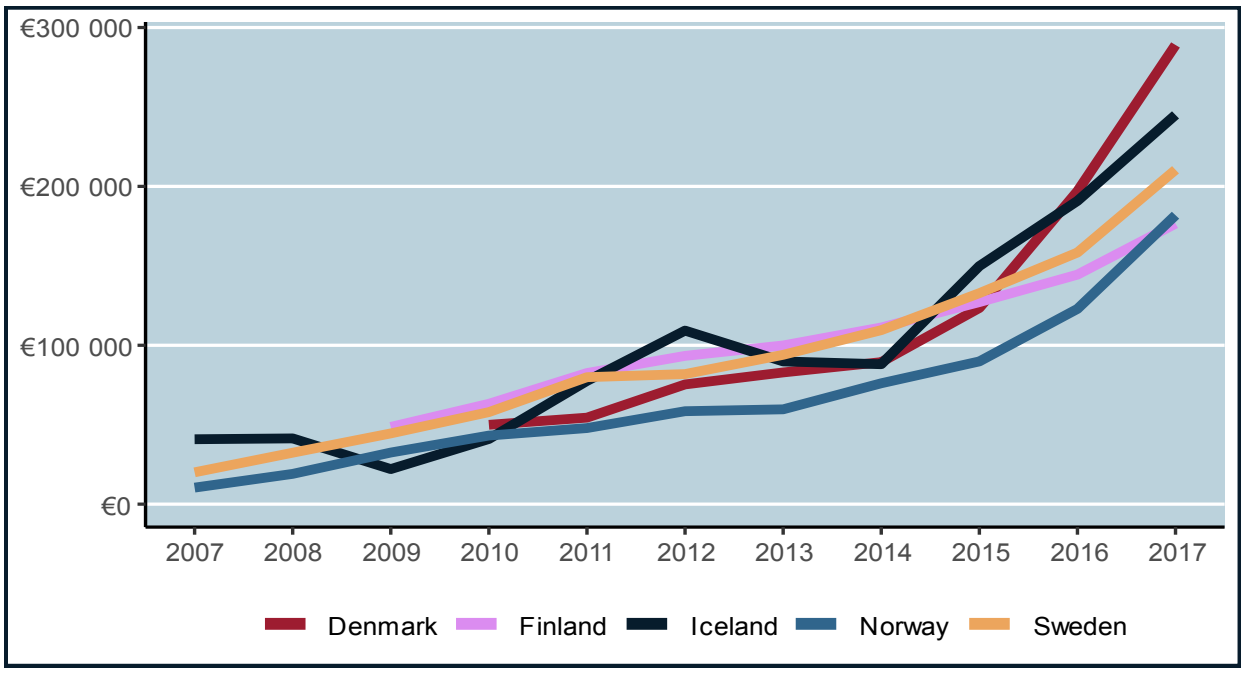


Figure 10: *Euro/case in myeloma for bortezomib + lenalidomide + thalidomide + pomalomide + carfilzomib + daratumumab in the Nordic countries.*

4.4 Other cancer forms

In **lung cancer** (we examined EGFR drugs and drugs for ALK positive disease in this part but did not include PD-1; PD-L1 drugs in the lung cancer analysis) we see large variations both between countries and between regions. Over the time period, use of erlotinib (now declining) 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. Regional differences in this field are smaller in Sweden compared to Norway.

There are also large variations in the sales of new lung cancer drugs. 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 within Sweden with South East region at twice the level of the Southern region.

It is almost 15 years since new monoclonal antibodies (bevacizumab and cetuximab) were introduced in 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 it main indication in metastatic colorectal cancer but also; see medical chapter is approved in renal, lung, ovarian and cervical cancer). We note that 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. In Sweden this is surprising as there are national guidelines for colorectal cancer by the National Board of Health and Welfare as well as by the national county council for the use in ovarian cancer. This fact indicates a failure of implementation of national guidelines on a local level.

The use of olaparib in BRACA-mutated **ovarian cancer** is relatively uniform within the Nordic countries with the exception of a very low uptake in Finland. There are regional differences with both Norway and Sweden, but given the rarity of this disease this may be the play of chance rather than indications of systematic differences.

Prostate cancer is unusual in that we can observe fast uptake in Finland. This is true for cabazitaxel where Finland was the most rapid adopter, but uptake was comparable also for abiraterone and enzalutamide. The access to new hormonal drugs in prostate cancer has been slow but uniform across the Nordic region. We see a similar shift from abirateron 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.

In **kidney cancer** we see large variation between the countries for individual drugs, but these become smaller when they are taken together. There are a number of treatment options in metastatic renal cancer, recently also including immune therapy with PD-1 inhibitors. Of special interest is to note that the uptake of cabozantinib in Denmark and Norway 8-10 times that of Sweden and Finland. At least in Sweden this represents a delay in the reimbursement process introduced by the county councils. On a regional level the Northern region in Norway has a lower uptake of all renal cancer drugs compared to other regions. In Sweden the Stockholm region is an outlier with more than twice the use of renal cancer drugs compared to some other regions.

5 Concluding remarks

The incidence of cancer has been increasing in the Nordic countries over the last decades. There are several potential explanations to this, including demographic changes and better ability to detect cancer through screening programs and regular diagnostics. Despite this increase, mortality rates from cancer have remained fairly stable the last 25 years, potentially even decreased in Denmark. The ability to detect more cases of cancer with slow progression such as some forms of prostate cancer may explain part of this, but improved treatment is likely to contribute to a large part of the explanation for this discrepancy. Five-year survival has gradually improved over time, and the performance of the Nordic health care systems is fairly similar at the aggregate level – although there may be important difference for different forms of cancer. Historically, the Nordic countries with the exception of Denmark has had aggregate survival levels on par with the best of the large European economies (Germany and France), while Denmark was lagging and was more similar to UK, the worst performer among the big 5. With the improvements that we observe for Denmark in more recent years it is now likely that the Nordic countries as a group are among the top performers in Europe.

The direct costs of cancer have increased over time, largely in pace with the development of health care costs overall. This has occurred at the same time as the cost of medicines have increased, indicating that so far, the cost of medicines has been offset by more efficient use of other health care resources such as e.g. making it possible to shift care from the inpatient setting to outpatient care. We may now however be at a point where the room for such gains is limited which will pose a challenge to the health care system. Data on the cost of cancer, for example related to different tumor types and other relevant patient characteristics are still lacking. This needs to be changed in order to get relevant information for 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 the other even though spending in general appears to be lower in Finland and there has been a considerable shift in Norway in recent years.

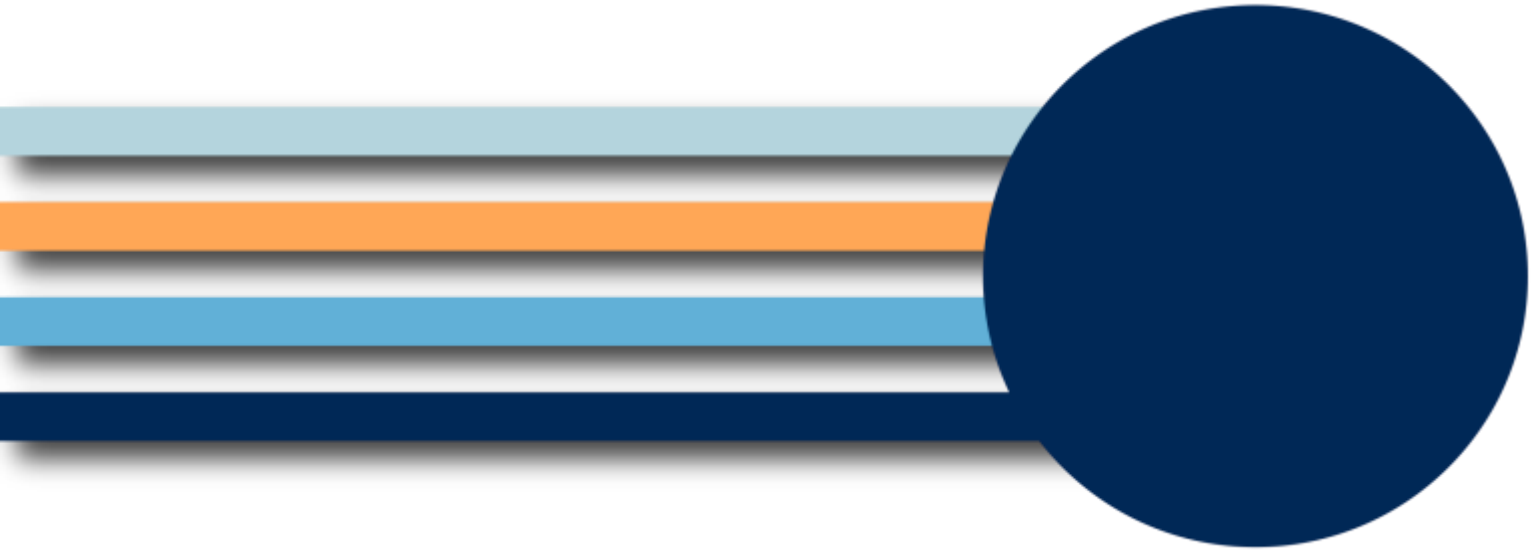
It can also be observed that in some cases there are as large variations within countries as between them. A basic hypothesis we had at the start of this work was that we would observe smaller differences in countries with more centralized procedures and budgets than in decentralized countries. This holds true up to a point – with a few exceptions variations between Norwegian regions are fairly small, Norway utilizing centralized procurement of drugs whereas variations are comparably large in Sweden where the county councils are responsible. Variation between regions in Denmark are often on par with the Swedish ones though, indicating that other factors also play a large role. The presence of national treatment guidelines can play a role – but the adherence to these

may also differ (as in the case for colorectal cancer for Sweden). Regional cultures seem to be important, and qualitative studies of this would likely generate some interesting finds.

There are differences in between the Nordic countries with respect to the health care structures. In Norway the state plays a major role while the regions and the local clinics have a more prominent role in Sweden. This may explain that the regional differences are much more prominent in Sweden compared with Norway. The complicated Swedish system, with reimbursement decisions made by TLV for prescription drugs and recommendations for hospital drugs being made by the SKL 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, daratumumab. The SKL process has also been discussed in a recent governmental report and the recommendation from this report is that the process needs a fundamental change. What we can note when examining the Swedish data is that national recommendations seem to play a minor role, both in relation to introduction of new drugs, but also in limiting use of non-cost-effective drugs already on the market.

Another fundamental weakness, especially in Sweden, is the lack of data on Real World Evidence. Although a national registry for (hospital) cancer drugs has been discussed over 10 years and a decision was taken to establish one already in 2008 by the heads of the oncology clinics in Sweden, there is still no such registry in place. We now have, after > 10 years a third version of the registry. This registry only includes 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 one can estimate that this version of the registry, at present only covers about 15% of the cancer drug use in Sweden. There needs to be an urgent remake of the registry in order to get reasonable quality. One way would be that the state or the region would provide a payback for oncology drugs for the first 3-5 years of use if the clinic supplied relevant data to a regional/national registry. This would mean a reallocation of drug budget from clinical/hospital level to regional/ national level but would provide a database from which RWE 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 critical factor for the future is the structure of cancer care in the Nordic countries. Denmark, Finland and Norway have all established Comprehensive Cancer Centers (CCC) within their countries thus establishing a structure for front line development of cancer care in line with what has been established in most European countries already (there are presently 30 CCC in Europe). In Sweden, there is an ongoing process establishing a CCC in Stockholm. The New Karolinska hospital/ Karolinska Institutet will most likely be established as a formal CCC in 2019-2020.



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