Real world evidence in priority setting and health care planning: an application on the cost of cancer

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List of papers

1. **Bugge, Christoffer**; Sæther, Erik Magnus; Brustugun, Odd & Kristiansen, Ivar Sønbø (2021). Societal cost of cancer in Norway –Results of taking a broader cost perspective. Health Policy. ISSN 0168-8510. doi: 10.1016/j.healthpol.2021.05.008

2. **Bugge, Christoffer**; Brustugun, Odd Terje; Sæther, Erik Magnus & Kristiansen, Ivar Sønbø (2021). Phase- and gender-specific, lifetime, and future costs of cancer: A retrospective population-based registry study. Medicine. ISSN 0025-7974. 100(26), s 1- 8. doi: 10.1097/MD.0000000000026523

3. **Bugge, Christoffer**; Kaasa, Stein; Sæther, Erik Magnus; Melberg, Hans Olav & Kristiansen, Ivar Sønbø. What are determinants of utilisation of pharmaceutical anti-cancer treatment during the last year of life in Norway? a retrospective registry study. BMJ Open 2021;:1–7. doi: bmjopen-2021-050564

4. **Bugge, Christoffer**; Sæther, Erik Magnus & Kristiansen, Ivar Sønbø (2021). Men receive more end-of-life cancer hospital treatment than women: fact or fiction? Acta Oncologica. 60(80). S 984-991 doi: 10.1080/0284186X.2021.1917000

Abbreviations

ATMP	Advanced therapy medicinal products
CBA	Cost-benefit analysis
CBA	Cost-Benefit analysis
CEA	Cost-effectiveness analysis
CI	Confidence interval
CMA	Cost-Minimization analysis
COI	Cost-of-illness
CRN	Cancer Registry of Norway
CUA	Cost-Utility analysis
DALY	Disability adjusted life years
DRG	Diagnosis Related Groups
EMA	European Medicines Agency
EQ-5D	EuroQol Questionnaire
EU	European Union
EUR	Euro
GLM	Generalized linear model
HCA	Human capital approach
HELFO	The Norwegian Health Economics Administration
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IARC	International Agency for Research on Cancer
ICD-10	International Classification of Diseases 10th Revision
ICER	Incremental cost-effectiveness ratio
ICPC-2	International Classification of Primary Care (Second edition)
KUHR	Kontroll og utbetaling av helserefusjoner (claims registry)
LIS	Hospital procurement agency ("Legemiddelinnkjøpssamarbeidet")
MCF	Marginal cost of public funds
NAV	Norwegian Labor and Welfare Administration
NIPH	The Norwegian Institute of Public Health
NOK	Norwegian kroners (Norske kroner)
NoMA	The Norwegian Medicines Agency
NorPD	Norwegian Prescription Database
NPR	Norwegian Patient Registry
OR	Odds ratio
OLS	Ordinary least square
PIN	Personal identification number
QALY	Quality adjusted life year
R&D	Research and development
RCT	Randomized controlled trial
RECORD	Reporting of studies Conducted using Observational Routinely-collected Data
RWE	Real world evidence
SHARE	Survey of Health, Ageing and Retirement in Europe
VAT	Value added tax
VSL	Value of a statistical life
WTP	Willingness-to-pay

English summary

Using cancer as an example, this thesis aims to investigate how real world evidence can support decisions on budgets, reimbursement, and allocation of resources in health care.

In Paper I, we investigated the societal costs of cancer to provide insights into the relative magnitude of the different cost categories. Direct health care costs, indirect costs (production losses) and, intangible costs (value of lost life years) in 2017 were estimated using data from eight different health- and work-related registries in Norway. The costs were estimated over a period of one year with a combination of a top-down and a bottom-up costing approach. The indirect costs (EUR 1,997 million per year) were almost as high as direct costs (EUR 2,154 million), and the value of lost life years and lost quality of life represented the greatest cost related to cancer (EUR 18,200 million). In addition, cancer is associated with other costs which are commonly omitted from cost-of-illness analyses, including informal nursing (EUR 306 million), patient time costs (EUR 85 million), and excess costs of using public funds (EUR 439 million).

In paper II, we explored phase- and gender-specific costs, lifetime costs, and scenarios for future cancer-related costs. Direct medical costs in the initial, continuing, and terminal treatment phases were estimated using nationwide activity data from the Norwegian Patient Registry. Lifetime costs were estimated by combining phase-specific costs and survival models based on data from the Cancer Registry of Norway. For all 13 cancers investigated in the study, monthly costs per patient followed a U-shaped curve: costs decreased with time after diagnosis and increased as death approached. Estimated discounted lifetime costs varied widely across cancers, with multiple myeloma having the highest discounted cost (EUR 89,686) and melanoma of the skin the lowest (EUR 25,363) in 2017. Cancers with an intermediate prognosis (50-70% 5-year relative survival) were associated with higher direct medical costs than those with relatively good or poor prognosis. The scenario analyses indicated that future cancer costs are highly dependent on cancer incidence, changes in death risk, and cancer specific unit costs.

The objective of paper III was to investigate the use of, and predictors for, pharmaceutical anti-cancer treatment towards the end of a patient's life in Norway. The proportions of patients receiving anti-cancer treatment during the last year of life were estimated using individual-level data from the Norwegian Patient Registry and predictors of anti-cancer treatment were estimated with logistic regression. In total, 24 percent of the cancer patients received anti-cancer treatment during the last year of life, while 3 percent were treated during their final month. Patients living in the regions of northern (OR = 0.8) and western (OR = 0.85) Norway had lower odds of receiving anti-cancer treatment end-of-life. Patients with myeloma (OR = 3.0) and breast (OR = 1.4) had higher odds.

In Paper IV, we investigated explanations for the observed differences in cancer costs and resource utilization in paper II. Gender differences in direct medical costs in hospitals, out-patient visits and in-hospital days, and place of death were evaluated using registry data from the Cancer Registry of Norway, the Norwegian Patient Registry, and the Norwegian Cause of Death Registry. Generalized linear models were fitted to adjust terminal care costs for age, region of residence, type of cancer, place of death and use of anti-cancer treatment end-of-life. For the non-gender specific cancers, women aged 0-69 years had an average cost of EUR 26,117 during the last twelve months before death, compared to EUR 29,540 for men, while they were EUR 19,889 and EUR 22,405 for women and men respectively for those aged 70 years or older. A costs difference of 4 percent could not be explained by the covariates included in the regression models.

In summary, evidence from international randomized controlled trials needs to be supplemented with real world evidence to yield a more comprehensive understanding of a treatment or a disease in a local setting.

Sammendrag (Norwegian summary)

Formålet med denne avhandlingen er å undersøke hvordan virkelighetsdata kan benyttes til å understøtte beslutninger knyttet til prioritering, budsjettering og refusjonsspørsmål ved å bruke kreft som et eksempel.

Formålet med Artikkel I var å sammenstille samfunnskostnader forbundet med kreft i Norge og undersøke størrelsesforholdet mellom ulike kostnadskomponenter. Ved hjelp av data fra åtte ulike helse- arbeidsrelaterte registre ble direkte helsetjenestekostnader, indirekte kostnader (produksjonstap) og verdien av tapt livskvalitet og tapte leveår i 2017 estimert. De indirekte kostnadene (1,997 millioner euro) var nesten like store som de direkte kostnadene (2,154 millioner euro), mens verdien av helsetapet (18,200 millioner euro) utgjorde den største kostanden). I tillegg medfører kreft en rekke kostnader som ofte ekskluderes fra kostnadsstudier, herunder uformell pleie (306 millioner euro), pasientenes tidskostnader (85 millioner euro) og skattefinansieringskostnader (439 millioner euro).

I Artikkel II presenteres fase- og kjønnsspesifikke kreftkostnader, livsløpskostnader og senarioer for fremtidige kreftkostnader. Fasespesifikke helsetjenestekostnader ble estimert basert på aktivitetsdata fra Norsk Pasientregister (NPR). Livsløpskostnader ble estimert ved å kombinere fasespesifikke enhetskostnader fra NPR med overlevelsesanalyser basert på data fra Kreftregisteret. For alle 13 kreftformer inkludert i studien var det en reduksjon i månedlig kostnad per pasient i tiden etter diagnose, og en økning i månedene før død. Diskonterte livsløpskostnader var høyest for myelomatose (benmargskreft) (89 686 euro) og lavest for malignt melanom (føflekkreft) (25 363 euro) i 2017. Livsløpskostnadene var høyere for kreftformer med 5-års relativ overlevelse mellom 50 og 70 prosent sammenlignet med kreftformer med svært god eller svært dårlig prognose. Scenarioanalysene viste at fremtidige kostnader i stor grad avhenger av utviklingen i antallet nye krefttilfeller, endringer i overlevelse og kreftspesifikke enhetskostnader.

Formålet med Artikkel III var å undersøke bruk av kreftlegemidler mot livets slutt og forklaringsfaktorer for slik bruk. Andelen pasienter som ble behandlet med kreftlegemidler ble beregnet med data fra Norsk Pasientregister og forklaringsfaktorer for slik bruk siste leveår og levemåned ble estimert med logistisk regresjon. Totalt ble 24 prosent av norske kreftpasienter behandlet med kreftlegemidler i løpet av sitt siste leveår, mens 3 prosent ble behandlet i løpet av de siste fire ukene før død. Pasienter i Helse-Nord (OR = 0,80) og Helse-Vest (OR = 0,85) ble i noe mindre grad behandlet i løpet av livets sluttfase (odds-ratio under 1), mens pasienter med myelomatose (OR = 3,0) og brystkreft (OR = 1,4) hadde stor sannsynlighet for å bli behandlet. Resultatene fra Artikkel III indikerer at andelen som blir behandlet med kreftlegemidler mot livets slutt er lavere i Norge sammenlignet med andre industrialiserte land.

Formålet med Artikkel IV var å undersøke kjønnsforskjeller observert i Artikkel II nærmere. Forskjeller mellom menn og kvinner i ressursbruk, kostnader og dødssted ble analysert med data fra Kreftregisteret, Norsk Pasientregister og Dødsårsaksregisteret. Generaliserte lineære modeller ble tilpasset data for helsetjenestekostnader og estimatene ble justert for alder, pasientens bosted, type kreft, dødssted og bruk av kreftlegemidler siste leveår. Kvinner diagnostisert med en kjønnsnøytral kreftform i aldersgruppen 0-69 hadde en gjennomsnittkostnad på 26,117 euro, mens for menn var kostnaden 29,540 euro. For pasienter 70 år eller eldre var gjennomsnittskostnaden 19,889 euro for kvinner og 22,405 euro for menn. Etter justering av kostnadene gjenstod en kostnadsforskjell på 4 prosent som ikke kunne forklares av variablene inkludert i modellen.

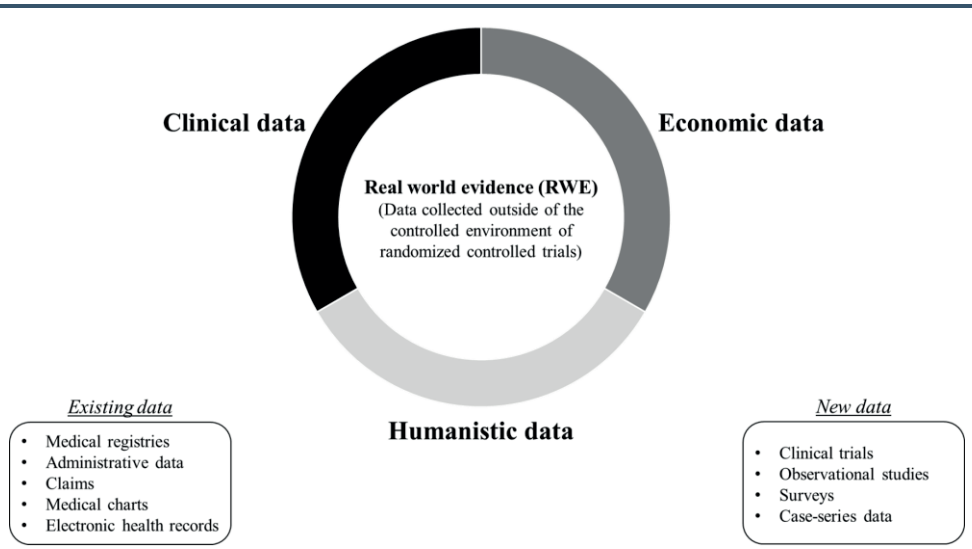
Kombinert med kunnskap fra internasjonale, randomiserte, kontrollerte intervensjonsstudier, kan data fra klinisk praksis, observasjonsstudier og registerdata (såkalt virkelighetsdata) bidra til bedre forståelse av behandling, sykdom og ressursallokering nasjonalt.

1. Introduction

Considering the limited budgets in health care, there is a need for strict priority setting. Thus, information on consequences of introducing new interventions, both in terms of treatment effect and resource use, is required to ensure optimal allocation of budgets. Since the late 1940s, evidence from randomized controlled trials (RCTs) has been used in medical decision making to compare the effects of different treatment options.[1] In modern medicine, however, decision makers rely on other sources of information (so-called real world evidence (RWE)) in order to provide the best possible care. Ideally, evidence from international RCTs should be supplemented with RWE to yield a more comprehensive understanding of a treatment or a disease in a local setting. Using cancer as an example, this thesis highlights how RWE can support decisions on budgets, reimbursement, and allocation of resources in health care.

RWE is evidence collected outside of the controlled environment of RCTs, which may help us understand disease burden, treatment patterns, and patient behavior in settings and populations that are representative of everyday clinical practice.[2] RWE is collected through three main brackets: *clinical* (medical history, survival, adherence, etc.), *economic* (resource utilization and costs), and *humanistic* (e.g., health related quality of life). RWE can be extracted from existing sources of data such as registries or medical charts, or collected through clinical trials, interviews, or surveys (new data).

Figure 1: Real world evidence (RWE) and data sources



Evidence from RCTs is regarded to be the gold standard but is also hampered with methodological challenges. It is based on selective populations which may not be comparable with the heterogeneous population in real world clinical practice. Additionally, longitudinal data are rarely available from RCTs. Today, researchers, governmental bodies, and industry use RWE as a complementary source of information to establish more robust evidence as a basis for making decisions.[2] RWE is used to examine patient populations, treatment pathways in clinical practice, and costs and resources related to different treatments in a local setting.[2] In addition, RWE can be used to inform mathematical simulation models to predict future outcomes of alternative treatment options, instead of waiting until long-term data from RCTs are available. This is especially relevant for cancer, a disease area where rapid medical development is ongoing.

Globally, cancer is the second most frequent cause of death and affects millions of patients and immediate family members.[3] In 2017, cancer surpassed for the first time cardiovascular disease as the leading cause of death in Norway.[4] Over the last decade several new, costly medical innovations have

been introduced to reduce burden on patients and increase survival. This development is expected to continue in the future, and evidence from RCTs may not be sufficient to evaluate all new technologies. Additionally, an aging population creates a greater need for health care services. This is especially the case for cancer, as this group of diseases becomes more prevalent with increasing age. The introduction of new interventions and increased demand for health care services have resulted in debates over resource use and cost control in publicly financed health care systems like Norway.

The covid-19 pandemic and the restrictions introduced to prevent transmission of the SARS-CoV-2 virus have demonstrated the impact of health losses on the national and global economies. The current health crisis has demonstrated that we have a high willingness to pay for health interventions saving lives and supporting the national and global economy. However, both private and public health care systems need to be sustainable in the long term and resources need to be utilized in an efficient way. At the same time, distribution of health care resources should promote equity. Decision makers are required to plan for future financing and organization of the system, as well as continually prioritizing which treatment options should be available to patients. In Norway, the use of economic models has been adapted in priority setting in health care to compare costs and benefits of interventions to assist and guide decision makers. Accurate information about costs is an important prerequisite in priority setting as well as in the planning of future health care services. Inaccurate cost estimates may influence the results of economic analyses, and the consequence may ultimately be that cancer patients are denied lifesaving treatment even when it is cost effective. Additionally, by investigating costs and resource utilization, researchers can identify variation in treatment practice across hospitals, jurisdictions, or patient populations, which is important to improve quality of care.

Norway, as well as the other Nordic countries, is in a unique position when it comes to access to high quality RWE due to their tradition of collecting data through national registries. In a study entitled "*Measuring costs: administrative claims data, clinical trials, and beyond*", Etzion and coworkers (2002) highlight three main challenges with using administrative databases in cost estimation; (1) poor sensitivity of diagnosis codes; (2) lack of direct information about comorbidities and other confounding factors; and (3) lack of representativeness from one data set to other populations.[5] Norway has a public health care system with universal access and virtually all cancer care is performed in public hospitals. Thus, the registries cover all cancer patients, eliminating potential problems with representativeness. Additionally, several of Norway's central health registries include precise information on diagnosis as well as information about comorbidities and other confounding factors. These factors provide a unique foundation for estimating costs to increase the knowledge and understanding of current practice in cancer care.

The overall aim of this thesis is to explore how real world evidence can be used to support priority setting and planning in the health service and to inform decision makers on resource use, treatment practice, and societal consequences of cancer in Norway. The four papers included in this thesis cover knowledge gaps related to the magnitude of different societal costs of cancer (paper I), estimates of lifetime costs for individual cancer sites (paper II), and disparities in end-of-life cancer care (papers III and IV).

This thesis is structured as follows: Chapter 2 provides a general background to medical decision making, priority setting in Norwegian health care, cancer and cancer epidemiology, and real world evidence in decision making. The objectives and research questions are presented in Chapter 3. In Chapter 4 the theoretical framework is presented, including definitions of key cost concepts, the cost-of-illness framework, survival analysis, and a section on how to monetize life years. Chapter 5 presents an overview of materials and methods and a summary of methodological challenges and limitations. The results of papers I-IV are presented in Chapter 6, followed by a discussion in Chapter 7. Chapter 8 summarizes the thesis' conclusions, and references are listed in Chapter 9. Appendices are provided in Chapter 10, followed by full text manuscripts, including supplements, for papers I-IV in Chapter 11.

2. Background

2.1 Medical decision making

A fundamental challenge in every society is how to allocate scarce resources (e.g., people, time, capital, equipment, facilities, land, knowledge) according to individuals' preferences. As society has unlimited wants, while access to resources is limited, allocation of resources to one purpose ultimately implies that less resources can be devoted to other purposes.[6] In economics, the cost of utilizing resources for a specific purpose is referred to as the opportunity cost.[7] The opportunity cost is defined as the economic value of what you must give up in order to choose something else. [7] For society at large, spending more resources on health care displaces resources that could alternatively be spent within other sectors such as transportation, education, environment, or defense. Similarly, spending on one aspect of health care displaces resources that could have been used on other health care measures. Optimal allocation does not only imply making decisions that maximizes the total benefits of the individuals in a society. How benefits are distributed, and other ethical considerations, are also important when allocating resources. Considering these trade-offs is unavoidable, and decision makers need tools to help ensure that resources are allocated in the best possible way.

2.1.1 Economic evaluation

Economic evaluation has played an important role in Norwegian priority setting in health care for several years. This methodological framework is used to support decision makers in the allocation of scarce health care resources and involves a comparative analysis of costs and consequences of alternative courses of action (strategies).[8,9] Economic evaluation is founded on three key economic principles; welfare economics, decision theory and the theory of constrained optimization.[8-10] From welfare economics the value judgment is based on what is known as Pareto improvements and Kaldor-Hicks improvements.[9] Pareto improvement is an economic re-allocation of resources among individuals whereby resources are re-allocated to make at least one individual better off without making any other individual worse off. A Kaldor-Hicks improvement has a less stringent criterion and is usually referred to as "potential Pareto improvements". For a re-allocation to be a Kaldor-Hicks improvement, the individuals that are better off must in principle be able to compensate those who are made worse off, thus leading to a net gain for society. These two principles are grounded on two main assumptions. First, social welfare is made up from the welfare of each individual in a society. Second, individuals are the best judges of their own welfare (consumer sovereignty). For decision makers all Pareto improvements are desirable, while for potential Pareto improvements the distribution of wealth should be considered. The second key principle is that economic evaluation relies on decision theory to inform individual preferences, which involves the probability of outcomes, payoffs associated with these outcomes and expected utility. Expected utility theory is a normative theory on how individuals should make decisions when choices have uncertain outcomes.[9] The implication of the theory is that utility is linear in probability but not in outcomes. The expected utility is calculated by multiplying the value of each outcome under certain circumstances with the probability of that outcome occurring. Finally, economic evaluation relies on constrained optimization, a method where the goal is to maximize desirable outcomes given a set of constrains (typically budgetary or resource constraints).[8]

Methods of economic evaluation in health care

A common goal for analyses in economic evaluation is to inform decision makers on how to allocate health care resources. There are three main methods used in economic evaluation; Cost-Effectiveness analysis (CEA), Cost-Benefit analysis (CBA), and Cost-Minimization analysis (CMA).[9] CEA is used to simultaneously compare outcomes and costs of two or more different interventions. Results are presented as cost per health effect achieved.[9] While costs are measured in monetary units, the health outcomes (or effectiveness) are measured as a single clinical outcome or in natural units such as life

year gained, or avoidance of an event (e.g., hospitalization, case of cancer etc.). A specific variant of CEA is Cost-Utility analysis (CUA) where analysts use quality-adjusted life years (QALYs) to measure health outcomes (see details in Section 0). CEA is the preferred approach within the health care sector. By measuring outcomes in natural units, one avoids the difficulties associated with placing a monetary value on health consequences. Additionally, using clinically relevant outcomes directly reflects the general policy of maximizing health, thus providing relevant information to decision makers in health care. CBA is an alternative to CEA that also simultaneously compare outcomes and costs of two or more different strategies. The main difference is that in a CBA both costs and outcomes are measured in monetary units. CBA is the preferred framework in sectors other than health care and is especially useful to inform resource allocation decisions across sectors. In some cases, the effectiveness or benefits of the interventions that are being investigated are regarded as identical. For such interventions, a CMA can be performed as costs are the only factor that differentiate the alternative choices.[9]

Key guidance documents for economics evaluation

To increase the quality and consistency of priority setting in health care several, several guidance documents for economic evaluation have been published in recent years. In 1996, the Panel on Cost-effectiveness in Health and Medicine published recommendations for conducting economic evaluations to inform priority setting in the US.[10] The recommendations were later updated by the Second Panel on Cost-effectiveness in Health and Medicine.[8] Additionally, Drummond and co-workers have published several additions of the reference book Methods for the Economic Evaluation of Health Care Programmes.[9,11] Most countries have also country-specific guidelines to aid analysts in conducting economic evaluations relevant for national settings. In Norway, the Norwegian Directorate of Health and the Norwegian Medicine Agency have published guidelines for health economic analyses and pharmacoeconomic analyses, respectively.[12,13] The guidelines from the Norwegian Directorate of Health are currently being updated.

Elements in economic evaluation

An economic evaluation follows a series of steps.[9] A first step is to define the problem and state the objectives of the analysis and its perspective. Then, analysts should identify all relevant strategies for the decision problem before analyzing benefits and costs. An economic evaluation should include a sensitivity analysis where the uncertainty is described by investigating how the results are affected by changes in the assumptions. Potential ethical issues should be addressed before results are discussed and key recommendations are presented. The following section briefly presents the main elements included in a CEA/CBA.

Measuring and valuing health outcomes and costs

Depending on the objective of the analysis, analysts must decide which outcomes to evaluate. The time horizon for the analysis should be long enough such that longer perspective will not change the results in terms of outcomes and costs, which in many cases involves using a lifetime perspective. In most economic evaluations health outcomes and costs do not occur in the current year but materialize at different times during the time horizon of the analysis. CEA guidelines recommend that both health outcomes and costs should be discounted to make sure that time preferences are accounted for.[8] However, discounting health outcomes has been criticized because health (unlike wealth) cannot be invested to produce future gains and it has hence been suggested that one should use different discount rates for health outcomes and costs.[8,9,14]

Depending on the type of analysis, health outcomes may be measured in natural units (CEA) or assigned a monetary value (CBA). In order to make economic evaluations comparable across diseases and patient groups, quality adjusted life years (QALYs) are often used as a measure for health outcomes.[8,9] When the outcome of interest have multiple attributes, for example health benefits

include both survival and quality of life, there is need for a generic, composite measurement. QALY is a generic measure that captures both the quality and quantity of life lived.[9] It is analogous to life expectancy except that each year is given an average quality weight (q_i) with a value between 0 and 1, where 1 represents perfect health and 0 represent quality of life equivalent to death. The number of expected QALYs at time t_0 can be calculated using the following formula:

$$QALY = \sum_{i=t_0}^{T} q_i r^{(i-t_0)} \pi_i$$

where π_i is the probability that the individual is alive at each age i in the future and r is the discount rate ($0 \leq r \leq 1$). The QALY term was coined by Weinstein and Stason in 1977 and is based on three key assumptions[15]: (1) Separability (additive independence) of health experience over time, in other words the value of a health state in one period does not depend on health states experienced in other periods, (2) Separability of quality from life years (longevity) for a constant health state, and (3) an egalitarian valuation of outcomes across people (i.e., a QALY is a QALY is a QALY). There are several methods for valuing QALYs, including standard gamble, time tradeoff, person tradeoff and visual analogue scale. For a detailed description of methods for measuring preferences see for example Drummond et. al (2015).[9]

An economic evaluation should include the cost of the intervention being investigated, as well as all costs that might change if the intervention is adapted.[9] This includes future costs induced by the intervention, savings in future health care costs due to disease averted, and possibly changes in future non-health-related consumption. In general, it is recommended that analysts use long-term marginal costs, not average costs.[9] However, in practice average costs are typically used as marginal costs often are unknown. It has been argued that changes in future health care consumption and production during life years gained (e.g.: cost of treating diseases resulting of increased life expectancy) should be included in cost-effectiveness analysis.[16] When adopting a health care perspective, there are few arguments against accounting for future costs. In practice, however, it is rarely done, presumably from convenience or lack of data. It should be noted that inclusion of future costs does not make available budgets greater or smaller, but influences the priority of interventions.[16]

Cost-effectiveness and willingness to pay

A key part of any economic evaluation is to identify which strategies or alternatives that provides "good value for money". Since both outcomes and costs are monetized in CBAs, this is straightforward as analysts can present the net benefit (i.e., total benefits minus the total costs) for each strategy. In CEAs however, presenting the net benefit is not possible as health outcomes is measured in natural units. The predominant metric used in CEAs is therefore the incremental cost-effectiveness ratio (ICER). The ICER is calculated by taking the difference in cost of one strategy (A) compared to the next least costly strategy (B), divided by the difference in health benefit of the two strategies:

$$ICER_A = \frac{Cost_A - Cost_B}{Health\ benefit_A - Health\ benefit_B}$$

New interventions in health care typically have greater effectiveness than its comparators but are more costly (ICER > 0). In these cases, decisions must be based on society's willingness to pay for one unit of health benefit (e.g., life years or QALYs gained). As discussed in section 2.2.2, the willingness to pay threshold in Norway increases with the severity of the disease, but no explicit threshold value has been stated.

Perspective of analysis

The perspective of an economic evaluation determines which costs and benefits that are included in the analysis. Usual perspectives are the societal perspective, where all societal costs and benefits are

included, and the health care perspective, where only consequences for the health care sector are considered. In certain instances, analysts may want to consider a more limited perspective such as a patient perspective or the perspective of a provider. The guidelines form the Second Panel on Cost-effectiveness in Health and Medicine states that CEAs should report a reference case from both a societal and a heath care perspective.[8]

Sensitivity analyses

All economic evaluations should include a section investigating the uncertainty of the analysis.[9] Sensitivity analyses are preformed to determine which values assumed in the analysis that are subject to uncertainty, and how changes in these assumptions influence the results. Sensitivity analyses can be deterministic or probabilistic.[9] In a deterministic sensitivity analysis, one (one-way) or several (multi-way) parameter values are changed through an upper and lower bound before results are reported. In a probabilistic sensitivity analysis, each model parameter is repeatedly drawn from their respective distribution (rather than using point estimates based on mean/median values) and used as model inputs.[17] Each unique set of inputs result in a unique set of model outputs that can be presented as a scatter plot to illustrate the uncertainty in the analysis.

For analyses evaluating interventions over time, uncertainty is also accounted for by the application of a calculation rate when discounting costs and benefits over years (see section 4.1). The recommended discount rate in Norway is four percent, of which two percent is due to time preference and two percent an uncertainty equivalent to account for uncertainty about future costs and benefits.[18]

Mathematical simulation modeling

Clinical trials are pivotal to inform decision makers on the efficacy and safety of new interventions. However, these trials are not able to capture all short- and long-term consequences of adapting a new intervention. In economic evaluation, mathematical simulation modeling (e.g., use of decision-tree models or state-transition models (Markov models)) is used as an alternative way to inform decision makers when data from clinical trials alone are insufficient. These models are based on expected utility theory and provide a systematic approach to decision making under uncertainty. The approach includes synthesizing available evidence from multiple sources such as clinical trials, meta-analyses, population-based registries, and independent studies to better understand how costs and benefits changes with different strategies or choices. Models can be used to extrapolate survival curves for different treatment options beyond the time-horizon of clinical trials and to calculate expected costs of different strategies.

Budget impact analysis

Budget impact analysis is used to describe the financial effects of adopting new technologies in health care.[19] The main goal of the analysis is to assess how financing a new technology will affect payers and their budgets compared to a situation without the new technology. In budget impact analysis it is the expenditures that are of interest, not the economic costs (see description of differences between expenditures and costs in section 4.1). While CEAs aim to evaluate both the costs and the benefits of an intervention, the budget impact analysis describe the financial consequences only. In many health care systems (including Norway), a budget impact analysis is used as a supplement to the CEA and are required for a new technology to be reimbursed.

2.1.2 Equity considerations

As in most other societies, efficiency (i.e., maximizing benefits in society) is not the only criterion used in policymaking in Norway. Equity principles must often be traded against efficiency in priority setting. In economics, the term equity is based on the idea that people should be treated as equals (moral equity).[20] Equity deals with how capital, goods, and access to services are distributed in a society, and involves the issue of whether the distribution is regarded as “fair”. Developing a

consensus of what is regarded as “fair” may be impossible, but when enough people are concerned that the distribution is too inequitable, pressure on those in political power will often result in a change in the distribution of wealth.

In health care, we often distinguish between horizontal and vertical equity.[21] Culyer (1995) defines horizontal equity in health care as “treating the same those who are the same in a relevant respect (such as having the same 'need')” while vertical equity as “treating differently those who are different in relevant respects (such as having different 'need')”[21]. The term equity may also differ according to what measure that are used to describe possible inequality. Equity may deal with outcome (does women survival differ from men?), access to health care (does people with higher education or social status have access to better care?), or in terms of resources used (does one geographic region receive more resources than another?). Another key dimension of the term equity deals with who should be given priority over others. Several empirical studies confirm that many believe that some people should be given priority over others.[22-24] This includes young people (over old people), people looking after young children (compared to those without that responsibility), and those taking care of their own health (those who abstain from smoking, heavy drinking and drug use). In terms of distribution among people depending on age, it has been argued that resources should be distributed in a way where every individual receive sufficient health care to provide them with the opportunity to live for a normal life span in good health (the fair innings argument).[25] In an analysis of the fair innings argument, Allan Williams finds that “intergenerational equity requires greater discrimination against the elderly than would be dictated simply by efficiency objectives”.[26] This works as an example to how equity and efficiency in priority setting may contradict, making it necessary for decision makers to do tradeoffs between these two consideration.

2.2 Priority setting in Norway

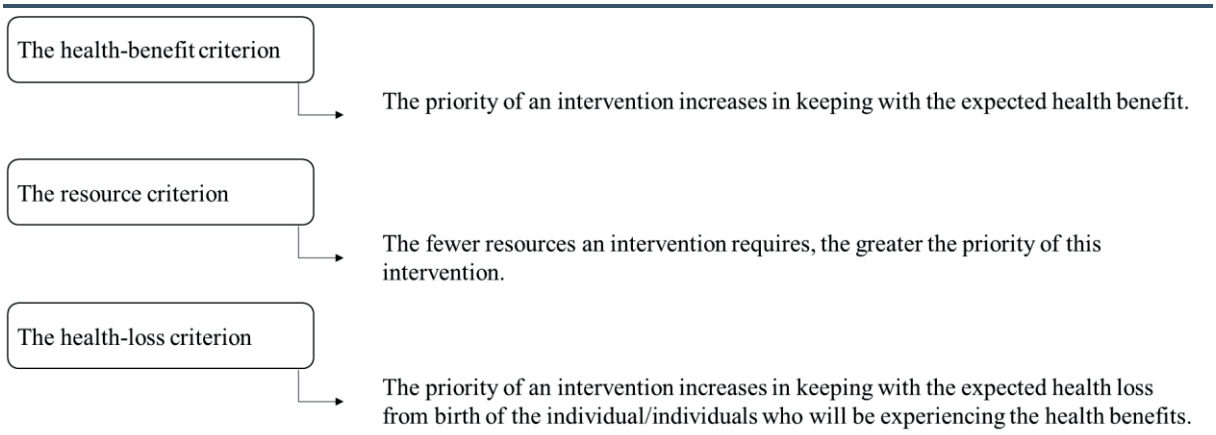
The right to equal access to health care services is a fundamental principle in the Norwegian health care system.[27] Another important principle is to make priorities in a way that maximizes the health benefits in the society.[28] However, as for other publicly financed health care systems, Norway face major challenges in financing future services because of demographic changes and the introduction of new costly medical interventions. This makes priority setting unavoidable. Without a system for priority setting, decision makers run a greater risk of making decisions that are suboptimal or in conflict with the underlying principles of the health care system.

2.2.1 Systematic work with priority setting

Norway has a long tradition of working systematically with priority setting in health care at the national level.[29] The systematic efforts in this space dates back to the 1980s and six government appointed commissions have investigate principles for priority setting in Norwegian health care since that time: Lønning I (1987)[30], Grund (1997)[31], Lønning II (1997)[32], Norheim (2014)[33], Magnussen (2015)[34], and Blankholm (2018)[35]. The first commission (Lønning I), proposed that priority setting should be based on two criteria: the severity of the disease and the efficacy of the new intervention or treatment.[30] A decade later, the Lønning II Commission introduced cost-effectiveness as a third criterion, which also were recommended by the Grund Commission.[31,32] The principles and recommendations of the Lønning Commissions received a widespread acceptance in the national health debate and was approved by the Norwegian parliament in 1999.[36] To this date these principles have formed the foundation for priority setting in Norway.[28] Following a national debate on the public reimbursement of the cancer drug ipilimumab (trade name Yervoy) the Norheim Commission was appointed to evaluate the current criteria for priority setting in Norwegian health care.[37] In the public debate questions regarding how to measure severity, if other criteria than those proposed by Lønning II were used in practice, and the actual willingness to pay threshold were raised. The Norheim Commission presented their report in 2014 and the new framework comprises four general principles for priority setting[33,37]: 1) to pursue the goal of “the greatest number of healthy life years for all, fairly distributed; 2) be based on clear criteria; 3) be open, systematic, and involve user participation; and 4)

be supported by a coherent set of effective instruments. The commission proposed three revised criteria for priority setting: the health-benefit criterion, the resource criterion, and the health-loss criterion (Figure 2). In 2016, these criteria were made official as the Norwegian Ministry of Health published a white paper on priority setting in the Norwegian health care sector.[38]

Figure 2: Criteria for priority setting in Norwegian health care



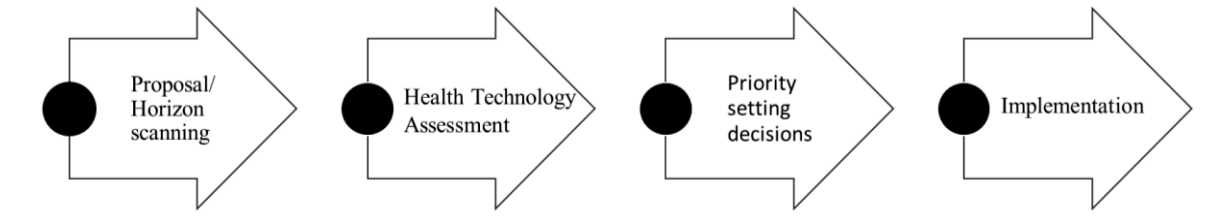
Source: Norwegian Ministry of Health and Care Services (2016)[38]

The criteria presented by the Norheim Commission are in many ways a clarification of the criteria presented by the Lønning II Commission. Although receiving broad overall support in the public, the health-loss criterion was widely debated. This criterion was later assessed by the Magnussen Working Group who recommended that severity should be quantified at group level by measuring the absolute shortfall (i.e., the loss of future healthy life years if the treatment was not available). In 2018, the Blankholm Commission presented the first official principles for priority setting in the municipality health and care services and for publicly funded dental services.[35] The principles proposed by the Blankholm Commission were mainly in line with those for the specialist health care, except that level of physical, psychological, and social coping should be considered when evaluating benefits and absolute shortfall.

2.2.2 Priority setting in practice

The Norwegian health care expenditures amounted to approximately EUR 40 billion in 2018 (1 EUR ≈ 10 NOK), of which 85.5 percent were publicly financed.[39] Public priority setting is thus of great importance for which medical interventions that become available to the general population. In 2013, The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway (commonly referred to as "New methods") was launched.[40] The purpose of the system is to ensure systematic use of Health Technology Assessment (HTA) to inform decision makers in health care. The overall components of the system are presented in Figure 3.

Figure 3: The principal components of The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway



Source: Norwegian Directorate of Health (2019)[40]

Before a new intervention is reimbursed by the public health care system an HTA is conducted by either The Norwegian Medicines Agency (NoMA) (pharmaceuticals) or The Norwegian Institute of Public Health (NIPH) (medical devices). The decision whether to introduce the new intervention or not is made by the Decision Forum, a forum comprised of the chief executive officers of the four regional health authorities. The hospital procurement agency LIS often negotiate with the manufacturer prior to a final decision in Decision Forum. Economic evaluation plays a key part of the HTA and is essential to evaluate the health-benefit criterion and the resource criterion proposed by the Norheim Commission. To account for the worse off and promote equity (the health-loss criterion), cost-effectiveness thresholds are differentiated according to the absolute shortfall. However, thresholds for the willingness to pay have only been introduced informally in Norway and never been examined or approved by Parliament. Because of secret rebates from the manufacturers and the fact that the incremental cost-effectiveness ratio (ICER) is not explicitly stated in the publicly available HTAs, the willingness to pay for a quality adjusted life year (QALY) in Norway is unknown to the public. Based on previous evaluations it is reasonable to believe that the willingness to pay for a QALY ranges from NOK 275,000 (≈ EUR 27,500) up to NOK 1,000,000 (≈ EUR 100,000) depending on the severity of the disease.

Norway has come a long way in developing a system to inform decision makers and in formalizing principles for priority setting. In general, the system and the principles are well accepted in the health care sector and in society in general. However, there are still several practical challenges and issues that are frequently debated. One controversy is related to handling of uncertainty and various assumptions used in the health economic analyses. The choice of input parameters may affect the outcome of a health economic analysis and consequently whether a new intervention receives reimbursement and at what price. Uncertainty with respect to model parameters has led to time consuming processes and heated public debates between governmental agencies and manufacturers. In 2020, the Parliament requested an evaluation of the "New methods"-system, which is expected to be finalized in the fall of 2021. Based on results from the evaluation, the government will make revisions order to improve the system. Other debated issues are transparency of priority setting, decision criteria, and lack of appeal mechanisms.

2.3 Cancer

Cancer, also known as malignant tumor or malignant neoplasm, is a group of diseases caused by abnormal cell growth.[41] The abnormal cell growth will in most cases create a tumor (or neoplasm) consisting of cells that have undergone an unregulated growth and may spread through the bloodstream to other parts of the body if not treated.[42] For a tumor cell to produce a malignant tumor they must show the six hallmarks of cancer defined by Douglas Hanahan and Robert Weinberg[43]:

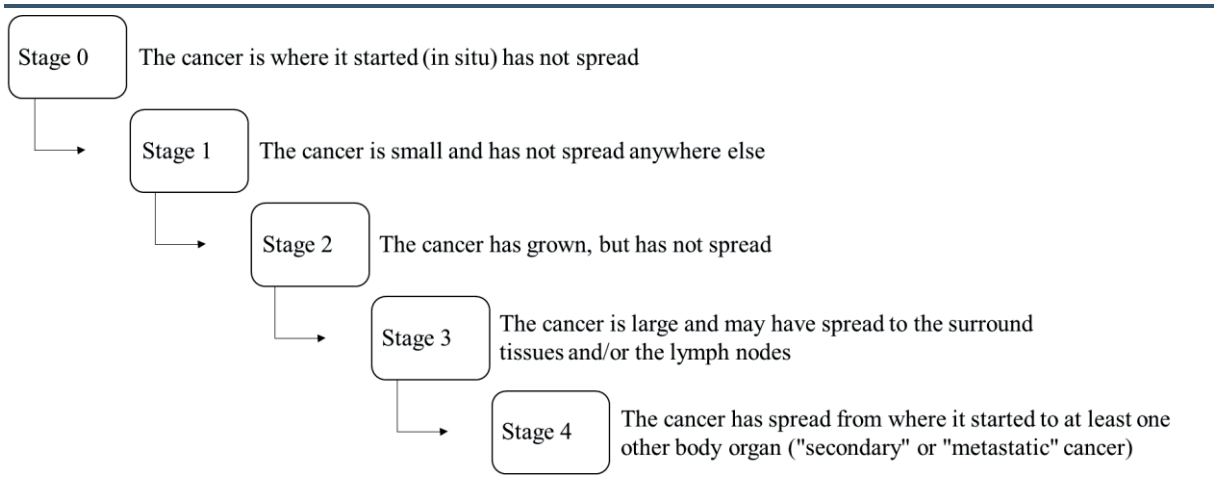
1. Self-sufficiency in growth signals (cell growth/division absent the proper signals)
2. Insensitivity to anti-growth signals (continuous growth/division even when given contrary signals)
3. Evading apoptosis (avoidance of programmed cell death)
4. Limitless replicative potential (limitless number of cell divisions)
5. Sustained angiogenesis (promoting blood vessel construction)
6. Tissue invasion and metastasis

2.3.1 Symptoms, causes, and stages

Cancer can cause several symptoms which may vary across type of cancer. Common signs and symptoms include lumps, weight loss, abnormal bleeding (e.g., blood in the urine), coughing, chest pain and breathlessness, and changes in bowel habits.[44] 90-95 percent of cancer cases are believed to be caused by genetic mutations from lifestyle and environmental factors such as cigarette smoking, alcohol, diet, sun exposure, infections, stress, radiation, and environmental pollutants.[45] Cancer is usually classified into different stages to describe the tumor size and how far it has spread from where

it originated.[46] Different systems of staging cancer are used across different types of cancer, but a common method of staging is presented in Figure 4.[46]

Figure 4: Example of staging system for cancer



Source: NHS (2018)[46]

2.3.2 Diagnosis and treatment

Cancer can be detected through the appearance of symptoms or trough targeted cancer screening (e.g., for breast, cervical or colorectal cancer). However, for the diagnosis to be definitive, a tissue sample needs to be examined by a pathologist.[47] A tumor sample is obtained by performing a biopsy or aspiration before being analyzed and interpreted by a pathologist to determine if it is malignant and possibly the cancer stage (i.e., the degree of metastasis).[47]

Several types of treatment options where the purpose is to cure cancer (curative treatments) exists, including surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, hormone therapy, stem cell transplant, and precision medicine.[48] The preferred treatment option depends on several factors such as type of cancer, cancer stage, and patients' health and preferences. Most patients receive a combination of treatments. The primary curative treatment options have long been surgery, chemotherapy, and radiation therapy, but in recent years immunotherapy has become a common treatment due to the introduction of new biologics.

I addition to treatment intended to cure cancer, patients may receive adjuvant treatment and/or palliative care. Adjuvant treatment is defined as treatment given after the primary treatment with the intention of reducing the risk of the cancer recurring by destroying any remaining cancer cells.[49] Palliative care is given to improve quality of life by preventing or reducing symptoms and side effects of the disease, in addition to relieve related psychological, social, and spiritual problems.[50] Palliative care is often confused with hospice indicating that patients are in their final stage of life, but palliative care does not require that treatment aimed at the cancer is stopped. In fact, early integration of palliative care (in addition to standard oncologic care) has been sowed to result in improvements in quality of life and prolongment of life.[51]

Figure 5: Overview of types of cancer treatments

Primary treatment

Goal: To completely remove the cancer from the body

Common treatments
Surgery: A procedure in which a surgeon removes the tumor from the body
Chemotherapy: A drug treatment targeted to kill cancer cells
Radiation therapy: The use of high doses of radiation to kill cancer cells and shrink tumors
Immunotherapy: A type of biological therapy that helps the immune system to fight cancer cells

Adjuvant treatment

Goal: To remove cancer cells that may remain after primary treatment in order to reduce the chance that the cancer will recur

Common treatments: Chemotherapy, radiation therapy, hormone therapy and immunotherapy

Palliative care

Goal: To help relive side effects of treatment and increase patients' quality of life

Common treatments: Surgery, chemotherapy, radiation therapy and pain management

Source: NIH (2020) and Mayo Clinic (2019)[48,52]

2.3.3 Prevention and screening

As most cancers are related to lifestyle and environmental factors there are several possible prevention measures.[45] Between 30 and 50 percent of cancers are believed to preventable by implementing existing evidence based prevention strategies and avoiding risk factors such as smoking, alcohol use, poor diet, overweight, lack of physical activity, sexually transmitted infections, and air pollution.[42] Additionally, some vaccines have been developed to prevent viruses that can cause cancer. Examples are vaccines for human papillomavirus that can cause cervical cancer and other genital and oropharyngeal cancers and for hepatitis B that can cause liver cancer.[53]

Screening involves activities to detect cancer or precancer before patients have signs or symptoms and efforts are done to help find cancer at an early stage.[54] Screening may include blood or urine tests, physical examination and/or medical imaging.[54] As screening involves several risks (the test can be harmful, false positive, or false negative)[54] and substantial costs, the net benefit of screening in cancer care have been heavily debated.[55,56] Screening is regarded as beneficial in terms of reducing cancer incidence and mortality for some cancers, such as cervical[57] and colorectal cancer[58,59], while it is more controversial for breast cancer[60]. Norway has national screening programs for cervical and breast cancer, while colorectal cancer screening will be introduced in the fall of 2021.

2.3.4 Advanced therapies

During the last few years, several new advanced therapy medicinal products (ATMPs) has been developed. These therapies offer new opportunities for the treatment of various diseases, including cancer, and are especially important for severe and untreatable conditions for which conventional

approaches have proven to be inadequate. The European Medicines Agency (EMA) classifies ATMPs in three categories as presented in Figure 6.[61]

Figure 6: Categories of advanced therapy medicinal products (ATMPs)

Gene therapy medicines

These contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.

Somatic-cell therapy medicines

These contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases.

Tissue-engineered medicines

These contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue.

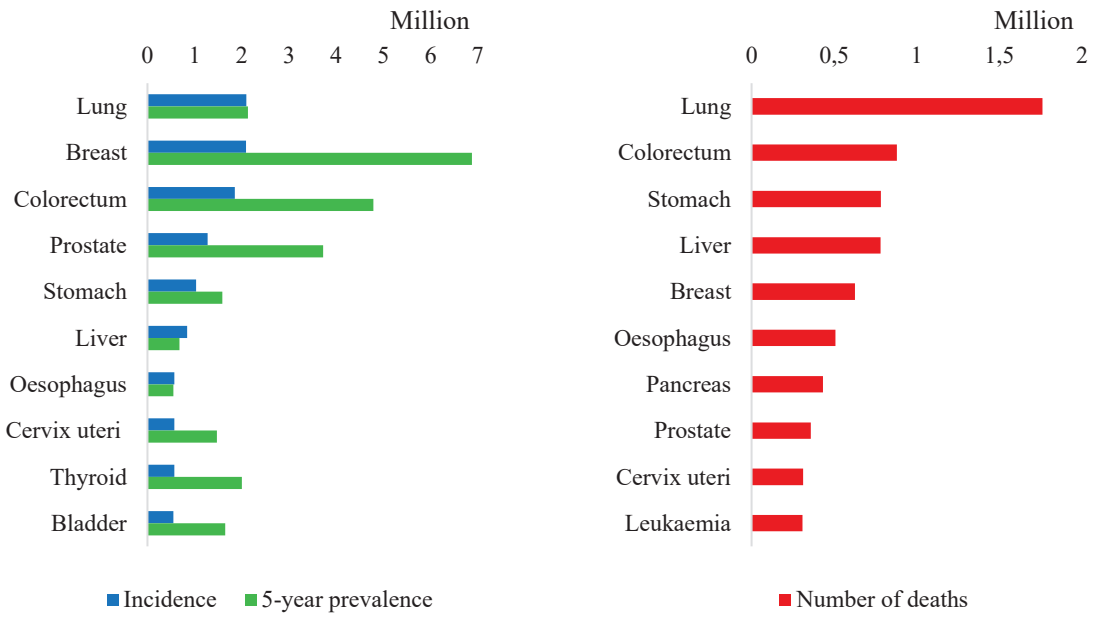
Source: European Medicines Agency[61]

2.3.5 Epidemiology

The International Agency for Research on Cancer (IARC) estimates that the global burden of cancer was 18.1 million new cases and 9.6 million cancer deaths in 2018.[62] The same agency estimate the 1-year and 5-year prevalence (number of people alive within 1 and 5 years of a cancer diagnosis) to be 12.3 and 43.8 million respectively.[63]

Cancer of the lung, breast, and colorectum was responsible for a third of the total number of new cancer cases and cancer deaths worldwide in 2018.[62] The same year, lung cancer caused 1.8 million deaths (18.4% of the total cancer deaths) which can be explained by the poor prognosis and high incidence.[62] Estimated number of new cases, 5-year prevalence, and number of deaths worldwide by cancer site are presented in Figure 7.

Figure 7: Estimated number of new cases, 5-year prevalence and number of deaths worldwide by cancer site 2018, both sexes, all ages



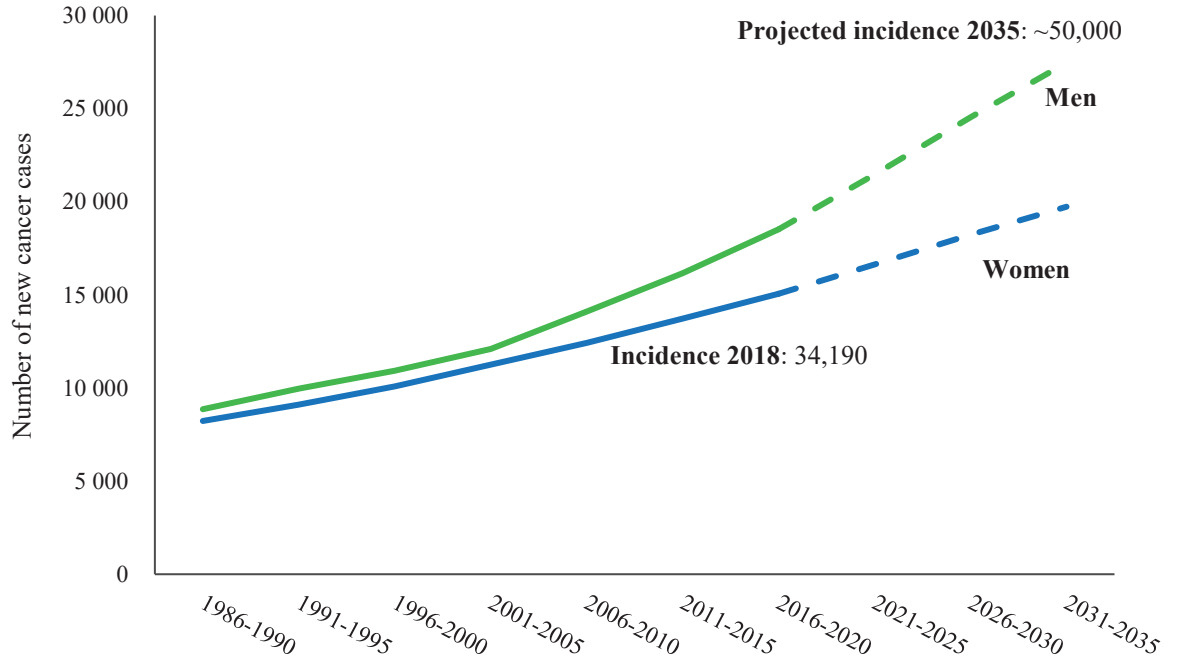
Data source: GLOBOCAN (2018)[63]

2.4 Cancer in Norway

The Cancer Registry of Norway presents detailed statistics on cancer incidence, mortality, survival, and prevalence in Norway.[64] In 2018, 34,190 new cases of cancer were diagnosed in Norway (645 per 100,000 capita) and the number is steadily rising.[64] By the end of 2018 a total of 283,894 patients were alive after being diagnosed with cancer at an earlier point in life (point prevalence by 31.12.2018), representing 5.4% of the Norwegian population.[64] In total, 11,016 patients died from cancer in 2017, accounting for 27.0% of the total deaths that year.[64,65]

Of the 34,190 new cases diagnosed in 2018, 53.6% were among men, while 46.4% were among women. Cancer of prostate, lung, colon, and urinary tract were the most frequent types of cancer in men, whereas breast, colon, lung, and melanoma were most frequent for women. When comparing the period 2014-2018 to 2009-2013 the age adjusted incidence rates for all cancer sites has been stable for men (+0.3%) and increased by 5.6% in women. Projections from NORDCAN[66] indicates that cancer incidence in Norway will increase more than the population growth the coming years, mainly due to the current age distribution of the Norwegian population. NORDCAN estimate the cancer incidence in Norway to be approximately 50,000 in 2035, which represents a growth of 46.2% from 2018 (Figure 8).

Figure 8: Number of new cancer cases in Norway 1986-2016 and projections towards 2035



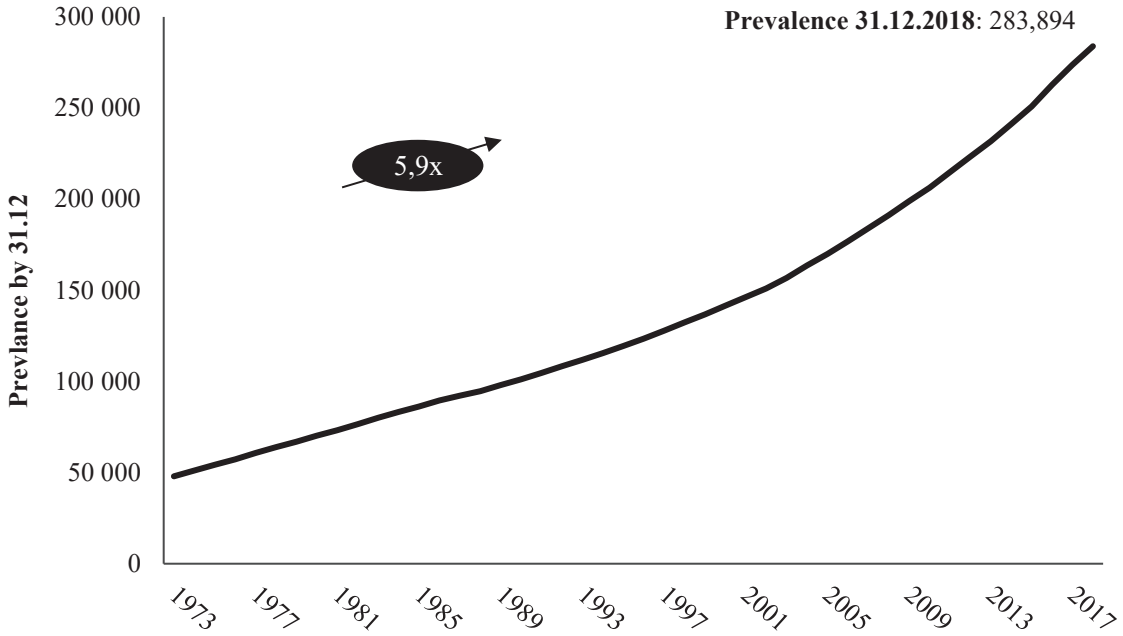
Data source: NORDCAN (2019)[66]

The number of patients alive after being diagnosed with cancer is also increasing steadily (Figure 9). In 1973, approximately 50,000 patients in Norway were alive after being diagnosed with cancer at one point earlier in life, whereas the number was almost six times as high in 2018. In addition, many patients who only have localized disease at the time of diagnosis, later are diagnosed with metastases. This means that cancer increasingly is becoming a chronic disease even among those who cannot be cured.

In Norway, the number of deaths due to cancer is slowly increasing whereas the number of deaths due to cardiovascular illnesses has declined in recent years (Figure 10). In 2017, cancer passed cardiovascular illnesses as the leading cause of death in Norway for the first time. The mortality rate (number of deaths per 100,000 inhabitants per year) has been decreasing for men and constant for women over the past 50 years, whereas the five-year survival rate (those who are alive five years after the time of diagnosis) is rising for both genders. However, the incidence (number of new cases) and the five-year survival rate are affected by diagnostic progress and screening, and these figures must be interpreted carefully.

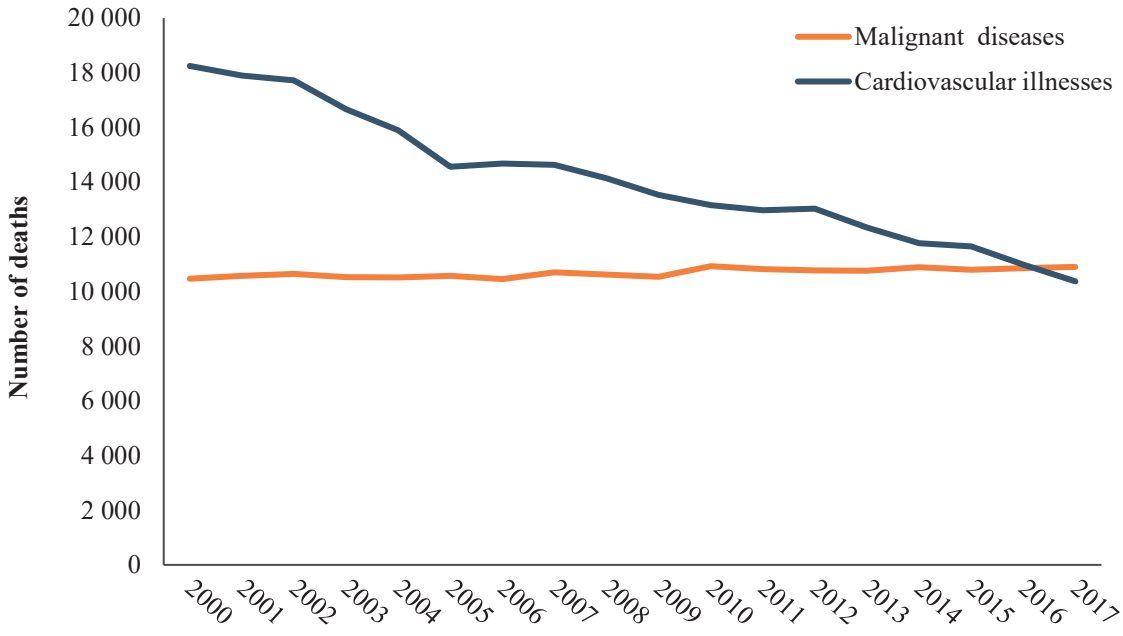
Prostate and breast cancer are the most frequent types of cancer, with 4,848 and 3,596 new cases respectively in 2018. However, lung cancer has the highest mortality and the largest number of life year lost because the patients are relatively young and because many of them die from the disease.

Figure 9: Number people alive after being diagnosed with cancer (point prevalence by 31.12), 1973-2018



Data source: Cancer Registry of Norway (2018)[64]

Figure 10: Number of deaths in Norway caused by malignant diseases (cancer) and cardiovascular illnesses, 2000-2018



Data source: Norwegian Cause of Death Registry (2018)[4]

2.5 Previous studies evaluating the cost of cancer

Cancer poses a major burden worldwide and it is estimated that the disease cluster cause a total of 196.3 lost disability adjusted life years (DALYs) in 2013.[67] Cancer poses a threat to health care systems that have to deal with complex and expensive cancer treatments, to patients and their dependents in terms of pain and suffering, and to society in general because it reduces the workforce's ability to be productive.

Several studies have been published on the cost of cancer, including for the United States, Canada, and Europe.[68-79] Some studies examine cancer as a disease cluster, while other focus on individual cancers. Hofmarcher and coworker recently published a study on the cost of cancer in Europe in 2018.[79] The total cost of cancer in Europa was estimated to EUR 199 billion, ranging from EUR 160 per capita (Romania) to EUR 578 per capita (Switzerland). 103 billion were health care expenditures, 26 billion informal care, and 70 billon production losses from premature mortality and morbidity. In the US approximately USD 87.8 billion was spent on cancer related health care in 2014 and the costs are estimated to rise to USD 157.8 billion (2010 USD) in 2020.[68,69] Researchers have also examined the cost of cancer according to different phases and find that the costs generally follow a 'u-shaped' curve; the resource use is highest in the initial year after diagnosis and in the last year of life, while it is lower in the continuing phase (period between the diagnosis and the last year of life).[72]

Despite having high quality registry data few studies on cancer costs has been published in Norway. Kinge and coworkers examined the economic losses and burden of disease by medical conditions in Norway and found that cancer represented a total economic loss of NOK 26.4 billion in 2013 (≈2.6 billion EUR), of which 16.6 billion were health care expenditures and 9.8 billion were taxed based production losses (18.2 billion using the human capital approach).[73] Additionally, the authors estimated the monetary value of lost life years to be NOK 232.1 billion. In a report evaluating the societal costs of cancer in Norway, the total cost in 2017 was estimated at NOK 210 billion (20.5 billion in health care costs, 26.5 billion in indirect costs, and 165 billion in value of lost life years).[80] The main differences between these two estimates lie in the valuation of lost life years.

Although several studies have been published internationally on the cost of cancer the knowledge is still limited.[81] Especially studies focusing on the broader societal cost of cancer is lacking. Hofmarcher and coworker state in their conclusion that further studies need to document the magnitude of the key components of the total costs. As health- and work-related data sources are improving researchers can use observational research to better understand the impact of disease-, patient- and system-related factors on costs and resource utilization.[82]

2.6 Real world evidence in decision making

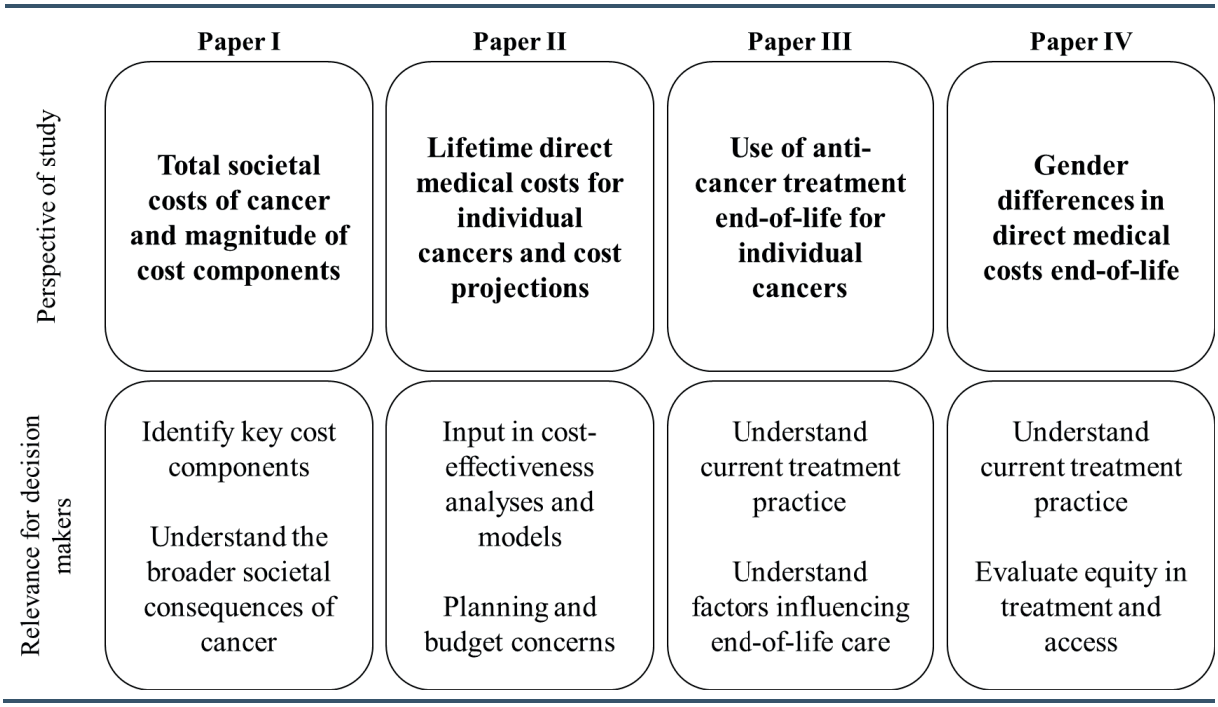
We continually learn more about the biology of cancer and its consequences, which provides better opportunities for prevention and treatment. While radical surgery has long been the only life-extending treatment, radiation therapy and medicines (chemotherapy, immunotherapy, gene therapy, etc.) have yielded noteworthy results for the past 30-40 years for some types of cancer. In recent years we have seen the advent of new medications based on new treatment principles, with greater efficacy than we previously have seen.

For every new treatment principle and every new medicine that is approved for use, several research articles are published concerning their effectiveness. While RCTs are pivotal to establish evidence of clinical effectiveness of new technologies and interventions, they cannot alone be the basis for priority setting. Rather, wider considerations are necessary and trial findings need to be extrapolated in terms of age, sex, geography, time, etc. Economic evaluation is then used in mathematical or numerical models. Here real world evidence can provide information on, among other things, the number of patients, patient characteristics, risk factors, morbidity, mortality, and resource usage.

It is surprising that we know so little about cancer costs in general, and in Norway specifically, as Norway is well known for excellent health registries. Registry data are broader in scope than primary data collection that generally only include a small number of patients in a selected setting, thus giving the opportunity to provide a comprehensive picture of the actual cancer treatment in a cost-effective way. Increased knowledge about the wider burden of cancer, better understanding of different cost components, and detailed analyses of phase specific resource use and health care utilization can help inform economic analyses or evaluate equality and are of interest for different decision makers, such

as clinicians, patient advocates, health care payers, and decision makers in research and education. Making decisions based on insufficient cost estimates and limited understanding of resource use and cost components may ultimately result in cancer patients being denied lifesaving treatment.

Figure 11: Overview of study perspective and relevance for decision makers of papers I-IV



3. Objectives and research questions

Understanding health care utilization and costs, treatment practice, and the wider burden of disease for different patient groups is a prerequisite for optimal resource allocation in health care. A better understanding of these factors is important to ensure efficient and equitable allocation of resources. The general aim of this thesis is to explore how real world evidence can be used to support priority setting and planning in the health service and to inform decision makers on resource use, treatment practice, and societal consequences of cancer in Norway. Specifically, the following research questions are investigated in the four papers included in the thesis:

Paper I

1. What are the total societal costs related to cancer in Norway?
2. How does the magnitude of different cost categories vary across individual cancer types?

Paper II

1. What is the phase-specific cancer costs and lifetime costs of the 13 most frequent individual cancers in Norway?
2. What are the key drivers for future cancer related costs in Norway?

Paper III

1. What proportion of patients receive pharmaceutical anti-cancer treatment during their last year and months of life in Norway?
2. To what extent are treatment decisions influenced by patients' age, gender, type of cancer, or geographic factors?

Paper IV

1. Are cancer related costs in hospital last year of life equal for men and women when adjusted for patient characteristics, type of cancer, place of death and/or use of pharmaceutical anti-cancer treatment?

4. Theoretical foundations

This chapter includes a discussion of different cost concepts, an introduction to the study design known as "cost-of-illness" (COI) and survival analysis, and a discussion of methods used to monetize the value of life years.

4.1 Economic costs, expenditures and resource use

Costs and expenditures are two terms that are often used interchangeably, which is to say that costs are understood as the amount of money that are spent on a product or service acquired.[9] In health care, the term "health care costs" is often used when people are referring to the "health care expenditures", that is the total monetary expenses within the sector. However, in economics, the expenditures merely make up a proportion of the total economic costs. Economists distinguish between two main concepts of costs: opportunity costs and accounting costs. In economic theory costs are regarded as benefits (or utility) foregone, and the term is used to describe the lost benefits of abandoning another possibility or opportunity.[9] When we decide whether to buy a car, go to medical school, or join the military we are giving something up – there will be a forgone opportunity. The opportunity cost is defined as the value of the next best alternative that is foregone when another alternative is chosen.[83] Accounting costs on the other hand, are defined as the monetary outlay for producing or acquiring a certain item or good.

The quantities of productive resources (labor, capital, land etc.) available to society is finite. At the same time society has unlimited wants and needs. Consequently, the use of resources will always represent an opportunity cost, even if no monetary expenditure incurs. This can be illustrated by the following example: For Robinson Crusoe, who makes no monetary payments to anyone, the costs of gathering coconuts can be regarded as his benefit from the sacrificed quantity of fish which he would otherwise have been able to catch with the same amount of time. For many economic costs, the monetary value is often unknown or difficult to estimate because of the absence of a reliable market price. To assign a monetary value to costs where no market prices exists, economists use an imputed valuation based on certain assumptions (a shadow price) to reflect the economic cost.

While accounting costs appear in public accounts and private financial statements, the economic costs (i.e., the opportunity cost) are often not visible as it includes both explicit and implicit costs. Economists also distinguish between costs and transfer of resources. Transfer of resources is not an economic costs, but a shift of control of the use of resources.[84] Examples of transfers are taxes, losses due to forced sale of assets (e.g., loss of property for failure to meet mortgage payments), and stolen property. While a transfer is not a use of resources it may alter the allocation of resources among competing ends.

In accounting and most other business disciplines, costs are usually classified as direct and indirect. In these settings direct costs refers to the resources directly consumed in the production of a particular product or service. For a hospital, direct costs include costs of doctors and nurses, medications, medical supplies etc. Indirect costs on the other hand, are not directly linked to the production of one product or service. The term refers to costs of providing supporting services such as radiology and laboratory services that are centrally supplied by other departments, as well as resources supporting the organization in general (overhead costs), e.g., accounting, security, human resources etc. In the field of health economics the classification of direct and indirect costs is often used differently, where indirect costs refer to the lost production of patient and family members due to illness.[85]

Costs can also be stratified into fixed and variable costs. Fixed costs are costs that stay constant when the output is changed. In health care this might include the cost of building a hospital or investing in research and development (R&D). Even if fewer patients are treated within a certain timeframe, the hospital still has costs related to employee salaries, building maintenance, equipment, and other

overhead. Variable costs on the other hand, are dependent on the output produced. In health care, variable costs include, among other things, health care workers and patient care supplies, diagnostics and therapeutic supplies, and medications. The timeframe of the analyses will impact which costs that are regarded as fixed and which are variable. In the long run, all costs can be thought of as variable costs.

Another important concept in economics is the distinction between average and marginal costs. The average cost (AC) (also referred to as unit cost) is defined as the total cost of all units or goods, divided by the total number of units or goods produced:

$$Average\ cost\ (AC) = \frac{Total\ costs\ (fixed + variable\ costs)}{Number\ of\ units}$$

The marginal cost (MC) is the change in costs of a marginal change in output. In other words, the marginal cost reflects the cost of producing one additional unit of the relevant item or good. The marginal cost can be expressed mathematically as the derivative of the total cost (C) with respect to quantity (Q):

$$Marginal\ cost\ (MC) = \frac{dC}{dQ} = \frac{\Delta C}{\Delta Q} \quad (\Delta = incremental\ change\ of\ one\ unit)$$

The term costs, and which costs that are regarded as relevant, will depend on the perspective of the analysis.[9] In general, economists distinguish between private and societal costs.[86] Private costs are the costs most people think of when talking about costs, i.e., costs paid by a consumer or a company. However, private costs only represent one part of the costs referred to as the societal costs or the "true costs" in economics, which is defined as the sum of private and external costs.[86,87] In addition to the private costs, the societal costs include any other costs incurred by a third party (negative externalities) that arise from the production or consumption of a good or service.[88] When estimating societal costs, analysts must consider the externalities that arise as a result of any given decision.

It follows from rational choice theory that individuals only consider their private costs when making decisions. However, negative externalities may occur when the consumption or production by one individual or entity causes a negative consequence for a third party.[88,89] When deciding whether to drive, use public transportation, or fly to reach a destination, individuals will consider the private costs of each transportation alternative (cost of petrol, ticket prices, travel time etc.). However, the disadvantages or losses (i.e., negative benefits or costs) inflicted on other members of society (e.g., carbon dioxide (CO2) emissions or congestion levels) may not be considered when the individual are evaluating the alternative transportation options. Other examples include manufacturers that produce chemicals and cause pollution or the consumption of alcohol which may increase the demand for police and health care services.

In order to present costs in a common metric, costs are discounted to represent their present value. Discounting is an economic method to compress a stream of future costs (or income) into a single present value amount.[9] By using a discount rate (r), analysts can calculate the present value (PV) of a stream of future values (FV) (also known as cash flow) occurring over time:

$$Present\ value\ (PV) = \frac{FV}{(1+r)^n}$$

where n is the number of periods between the present and the time when the cost occurs. The discount rate (r) represent the rate at which we are willing to trade off present for future benefits (or disbenefits such as costs). There are several arguments for why we prefer having one dollar today rather than receiving one dollar in the future. Resources can be invested to give a positive return; stocks pay dividends and bonds pay interests – making it favorable to have money today compared to having the

same amount in the future. Additionally, inflation diminish the purchasing power over time. There is also the aspect of uncertainty surrounding future income, i.e., the risk that future benefits will never be realized. Some individuals may also prefer consumption today rather than in the future because they are expected to have a higher consumption level in the future due to economic growth. Diminishing marginal utility imply that these individuals would prefer costs to occur in the future as this increases their ability to consume today.[90] Finally, we as individuals are generally impatient and prefer instant enjoyment to waiting for benefits in the future (pure time preference).[91] Although discounting is widely agreed upon, there are evidence of time-inconsistency in discounting preferences.[92] This phenomena is known as hyperbolic discounting and is one of the cornerstones of behavioral economics.[93]

4.2 Cost-of-illness (COI)

Cost-of-illness analysis (COI) is a common approach used in health economics to inform decision makers on the economic consequences of a particular disease or problem.[94,95] The method represents one of the earliest techniques in the field of health economics, and the principal objective of these analyses is to evaluate the economic burden a specific illness impose on society.[96] Specially, COI studies are descriptive studies that aim "*to itemize, value, and sum the costs of a particular problem with the aim of giving an idea of its economic burden*."[97] COI is both conceptually and computationally different from other health economic evaluations such as CEA and CBA. COI serves a different purpose compared with CEA and CBA as the method is descriptive and not analytical. In other words, COI studies does not involve a testable hypothesis, and give no direct guidance to whether a disease or treatment should be given a higher or lower priority.

The methodology of COI was first addressed in detail in a seminal paper by Dorothy P. Rice in the mid-1960s.[94] Years earlier, other authors had estimated cost of individual diseases,[98,99] but Rice set out to extend this framework to all disease categories to establish a standard methodology. In 1978, a task force chaired by Rice was formed to address methodological concerns related to COI estimates in order to promote the use of consistent methodologies.[84] Today, COI is a widely used technique in health economics, and a number of studies from different countries and diseases are being published every year.[95]

When conducting a COI study, analyst face several important methodological decisions, including the choice of costing approach, which cost components to include, and what study perspective and time horizon to use. The choice of method is based on factors such as data availability and study purpose, and differences in the way COI analyses are conducted may lead to variation in COI estimates for a given illness. Decision makers need to be aware of this when interoperation results from COI studies, and to aid non-experts, Larg and Moss (2011) created a guide to critically evaluate such studies. The following sections provides a description of the different methodological aspects of a COI analysis.

4.2.1 Type of costs

A key decision that must be made in all COI studies are what costs to include. Typically, costs are stratified into three main categories: direct, indirect, and intangible costs (Figure 12).[9,85] This section briefly describes the different costs categories, while a more detailed presentation of how costs are monetized is provided in Chapter 5.3

Figure 12: Examples of direct, indirect, and intangible costs for different cost bearers

Cost bearer	Direct costs	Indirect costs	Intangible costs
Health care sector (public and private)	• In-patient care • Out-patient care • Nursing home • Medication • Primary care services • Rehabilitation • Ambulance services • Capital costs and R&D • Prevention programs • Screening	• N/A	• N/A
People with the health condition	• Out of pocket costs • Travel costs • Insurance premiums • Home modifications • Legal fees	• Lost income • Lost leisure	• Reduced quality of life • Pain and suffering
Family and friends	• Damage to property	• Informal nursing and home care	• Reduced quality of life • Pain and suffering
Business/industry/ employers	• Occupational health programs • Insurance premiums	• Lost productivity • Cost of replacing workers	• Reduced employee morale
Society in general	• Infrastructure modifications • Education and training • Community support services	• Production losses due to mortality and morbidity • Deadweight loss of additional taxes	• Lost life years • Lost quality of life (non-fatal health losses)

Direct costs

Direct health care costs can be defined as resource use that can be completely attributed to the disease in question.[100] Direct costs include both health care costs and non-health care costs (or non-medical costs).[85] Direct health care costs are costs in both primary and secondary care related to prevention, diagnostics, treatment, rehabilitation, and terminal care of patients. Direct health care costs outside the health care sector include patient travel costs, legal costs, costs related to modification of patients' homes etc.[85]

Indirect costs

In contrast to direct costs, indirect costs do not entail any direct payments. Even though no payments are made, indirect costs still impact the consumption of resources.[101] In most COI studies, the term indirect cost is used to describe the production losses related to absence of work due to morbidity and mortality.[85] However, indirect costs also stem from patient's foregone leisure time or lost production, informal care costs, and taxation costs (the marginal costs of public funds).

Intangible costs

Intangible costs can be defines as the foregone benefit that have no direct impact on consumption of resources, such as pain and suffering.[101] Health conditions that cause death or reduced quality of life imposes a cost on the patient, their family and friends, and society in general. In addition to what each individual produce, society values the fact that people are alive and in good health. Environmental policies, transportation policies, defense policies, health care policies, etc., involve, among other things, providing good years of life.

4.2.2 Distribution of health care costs

Health care costs are non-negative and seldom normally distributed. However, they tend to be highly asymmetric, and most commonly considered to be right-skewed[102]. A right-skewed distribution imply that most patients have relatively low costs (or zero costs), while some patients are extremely costly. These characteristics influence the choice of econometric model used to estimate costs, and some researchers argue that models beyond linear regression, such as general linear models (GLMs), two-

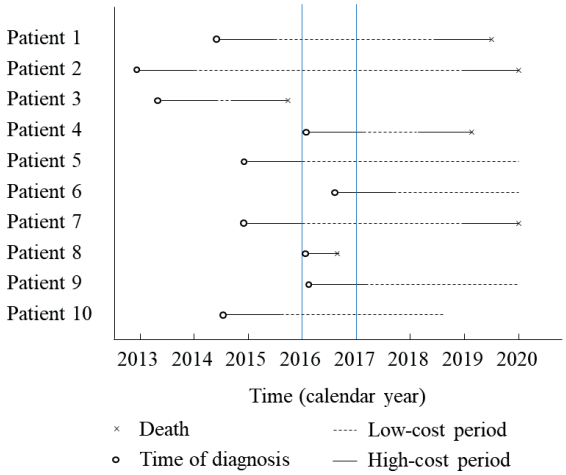
part models, Poisson regressions, negative binominal regressions, and hurdle models, are better suited for modeling health care costs.[103] For a description of most commonly used econometric models for health care costs and their application see book by Partha Deb, Edward C. Norton & Willard G. Manning (2017).[104]

4.2.3 Prevalence vs. incidence approach

COI studies can be described according to the epidemiological data used. They can either be incidence- or prevalence-based.[96] In incidences-based COI studies, life-time costs for new cases are estimated from the time of diagnosis and discounted to represent the present value.[85] The total annual cost is computed by multiplying the number of new cases in a given year with the estimated average life-time cost associated with a new case. A variant of the incidence-based costing approach is to estimate phase-specific costs.[105,106] With this method costs are estimated separately for clinical relevant phases (i.e., initial treatment, continuing care, and terminal care) and survival models are used to determine lifetime costs. The prevalence-based approach involves estimating the cost for all patient with the specific disease for a given time period (usually one calendar year).[107] In prevalence-based COI estimates, costs for patients at different disease stages are included (i.e., newly diagnosed patients, patients who may have been alive with the disease for a long time, and patients who die or get cured within the year). The rationale behind the prevalence-based approach is that costs are assigned to the year in which they are borne; health care costs are assigned to the year they occur, while production losses related to premature death are assigned to the year of death. In contrast, the rationale of the incidence-based approach is that the future stream of costs associated with the disease are assigned to the year in which the stream begins.[96]

Figure 13 illustrates how different patients can contribute to the total cost depending on the costing approach. If incidence-based costs for 2016 were to be calculated, only patients diagnosed in 2016 would be included in the calculation (patient no. 4, 6, 8, and 9). For patient no. 4, 6, and 9, costs occurring in 2016 and the following years would be included. If a prevalence-based costing approach were to be adapted, all patients alive in 2016 would contribute to the estimated costs (all patients except from patient no. 3). However, only costs occurring in 2016 would be included in the estimate.

Figure 13: Difference between incidence and prevalence costs



Incidence costs in 2016: Total cost of patient no. 4, 6, 8, and 9 discounted to 2016-values.
Prevalence costs in 2016: Costs occurring in 2016 for all patients except patient no. 3.
Figure inspired by Yabroff et al. (2011)[108]

Whether analysts choose to adapt an incidence- or prevalence-based approach will in most cases influence the results of the study. In general, the prevalence-based approach result in higher overall costs.[109] This is especially the case for diseases that are treated over a long time period or when annual

treatment costs rise over the course of the disease, as some costs which are discounted with the incidence-based approach are not discounted with the prevalence-based approach. A prevalence-based approach will also provide higher costs estimates when annual costs are declining over time or for diseases with a declining incidence. The reason for the latter is that costs of chronic patients from larger incidence cohorts from earlier years are included in the prevalence-based cost estimates and not in the incidence-based estimate.

Choice of approach (prevalence vs. incidence) will depend on data availability and the purpose of the analysis. The incidence-based approach requires detailed costs data from the time of diagnosis until the patient is cured or dead. However, if these data are not obtainable only a prevalence-based approach is feasible. A prevalence-based approach is particularly useful when results are to be used for cost control, as the method inform decision makers on current resource use for different cost categories. If the purpose of the analysis is to aid decision makers in evaluating prevention policies, an incidence-based approach is appropriate as it provides estimates of potential gains of preventing new cases. An incidence-based study is also more suitable to inform on disease management and as input to CEA or CBA.

4.2.4 Top-down vs. bottom-up estimation

In general, there is two computationally different methods of estimating economic costs; top-down and bottom-up.[85,96,110] The basic idea of top-down costing is to allocate a proportion of a known total cost to the disease under consideration by using various weighting systems or metrics. In bottom-up costing, the costing procedure is stratified into two steps. The first step aims to estimate the quantity of health inputs (i.e., physician contacts, hospitalizations, drug doses etc.). The next step involves assigning a unit cost to each health input used. The total costs are then estimated by multiplying the number of health inputs with their respective unit costs.

Choice of costing method may have a significant impact on the estimate of the total cost.[110,111] Allocating costs with a top-down approach is relatively straightforward and have the advantage that one avoid the risk that the sum of all costs of individual diseases is greater than the "known" total cost (e.g., the health care budget or total health care expenditures). However, the total health care expenditures do not entirely reflect the total economic cost related with a disease, as some cost are not visible in public accounts (e.g., costs inflicted on patients, informal care etc.). Additionally, there is substantial uncertainty related to the weights or metrics for allocation of the total costs. Thus, a top-down method is likely to present a misallocation of costs.[85,96] The key advantage of using a bottom-up approach is that detailed estimation of units and unit prices are more likely to represent the actual resource use related to treatment of a disease. The method also provides the ability to better understand and analyze key cost drivers and how changes in these drives influence total costs. However, a challenge with the bottom-up method is that some cost elements may be overlooked. Costing using a bottom-up approach also require detailed data which may not always be available.

4.2.5 Retrospective vs. prospective

A COI study can either be retrospective or prospective depending on the timing of the initiation of the study and the data collection.[85,96] In retrospective studies, all the relevant events have occurred before the initiation of the study. In these studies, analysts utilize data that are already collected in order to estimate costs. In prospective studies the data are collected after the study starts. At the beginning of the study, analysts define how data are to be collected, before following the patient over time. The key advantage of conducting a retrospective study is that it enables the analyst to use data that are already collected. Utilizing administrative claims data or registry data provides the opportunity to study a large population, to a relatively low cost. Prospective studies on the other hand, are more costly and time-consuming. Prospective studies are especially challenging when the disease that are being investigated have a long duration, or if a large study population is necessary. However, a key advantage with

collecting data after the start of the study is that analysts can design data collection according to the purpose of the study.

4.2.6 Perspective

The perspective of a COI study determines which costs items that are included, and which are not. COI studies can be performed from a variety of perspectives, depending on the objective of the analysis. COI studies can be carried out from the perspective of a society, health care system, patient, third-party payers, government, or business/industry.[85,112] Most studies are performed from a societal perspective, however several important societal costs are often overlooked.[95,101]

4.2.7 Cost of illness studies in decision making

The value of COI studies and their role in decision making have been debated for several years.[81,96,113-115] COI studies do not evaluate the effect or benefit of treatment or prevention, which have made researchers question their value in decision making.[114] The wide variation in estimates for the same diseases have also made researchers question the comparability, accuracy, and validity of COI studies.[116] Critics argue that only a descriptive study of the costs related to a disease have limited value, and that CEA provides a better framework for decision making.[113,114] Some have also gone as far to say that *"COI studies will only confuse, mask and mislead decision-makers*."[113] Rice dissented the claim that these studies are not helpful in priority setting and research activities, and provides historical examples of their usefulness.[117] Rice points to five areas where COI studies can aid decision makers:[117] (1) to define the magnitude of the disease in monetary terms; (2) to help justify intervention programs; (3) to assist in allocation of research funding on specific diseases; (4) to provide a basis for policy and planning relative to prevention and control initiatives; and (5) to provide an economic framework for program evaluation. Others have supported Rice's stance, and argued that COI studies offer valuable information of the amount of scarce resources consumed of illness, useful epidemiological data on morbidity and mortality, and provide information to identify main cost categories.[81,96,115] As COI estimates differs substantially depending on choice of method, researchers are obligated to present their method in detail so that users are able to assess their accuracy and to evaluate the results.[112,118] Most countries have a distinctive health care system, and Norway is no exception. This creates the need for country-specific cost estimates to determine the value of new interventions and methods in health care. COI studies can provide insight on main cost categories, cost differences and variability, and actual treatment practice and how these elements change over time or vary across regions or countries. Country-specific information on costs is necessary to support planning in health care and to ensure proper and systematic assessment of new interventions.

4.3 Survival analysis

Survival analysis is a branch of statistics which includes different statistical procedures to analyze data where the outcome of interest is the time elapsed before a specific event occurs (e.g. death, disease progression, divorce). This type of analysis is commonly used in cancer research to investigate the time from diagnosis to death or the time from complete remission to relapse or progression.[119] The time in survival analysis is defined as the period from the beginning of the observation, such as time of diagnosis or beginning of treatment, to either when the event occurs, the end of the study or end of follow-up.

There are two main reasons why survival analysis may be preferred over other statistical methods. Firstly, the event of interest does not always occur for all individuals. At the end of follow-up some individuals may not have experienced the event, and their true time to event is therefore unknown. This is often referred to a censoring. Secondly, time-to-event data are seldom normally distributed, but are instead skewed. The data typically consists of many early events, and relatively few late ones, which makes survival analysis a more appropriate method than other statistical methods, as it better accommodates for these kinds of distributions.

Survival analysis can be used to investigate several problems, including to describe the survival time of members of a group of patients (using Kaplan-Meier curves, survival functions, hazard functions, and life tables), to compare the survival times of two or more groups (e.g., with a log-rank test) or to describe the effect of quantitative or categorical variables on survival (using Cox proportional hazards regression or parametric survival models).

4.3.1 Censoring

A key challenge in survival analyses is that only a proportion of the individuals have experienced the event of interest, and subsequently, the survival time for a subgroup of the population will be unknown. This phenomenon is commonly referred to as censoring.[120] Censoring may arise for different reasons, including that some patients have not experienced the event by the end of the data period, patients may be lost to follow-up, or some other event has happened that makes further follow-up impossible. This form of censoring is called *right censoring.* Ignoring the survival time of such censored individuals leads to underestimation of the true time to event.[120] In survival analysis censoring is assumed to be uninformative, which means that patients who are lost to follow-up are assumed to have the same survival prospects as those patients who continue to be followed. While we generally encounter right censoring in survival data, patients may also be *left censored* (the event occurred at an unknown time before the individual was included in the study) or *interval censored* (the event occurred between two observations or examinations).

Due to censoring, data needs to be converted to survival data format (Figure 14). When data are collected the time for when patients are included in the study and the follow-up time differs across patients (left panel in Figure 14). Before conducting the analysis, the data must be converted to a format where the survival time is plotted from the time of diagnosis (right panel in Figure 14). As shown in Figure 14, patients 2 and 5 did not experience the event (e.g., death, relapse etc.) during the observation period, and are thus censored after four (patient no. 2) and three (patient no. 5) years. Patient number 4 is also censored after three years due to being lost to follow-up before experiencing the event.

Figure 14: Example of how to convert calendar time data to survival data

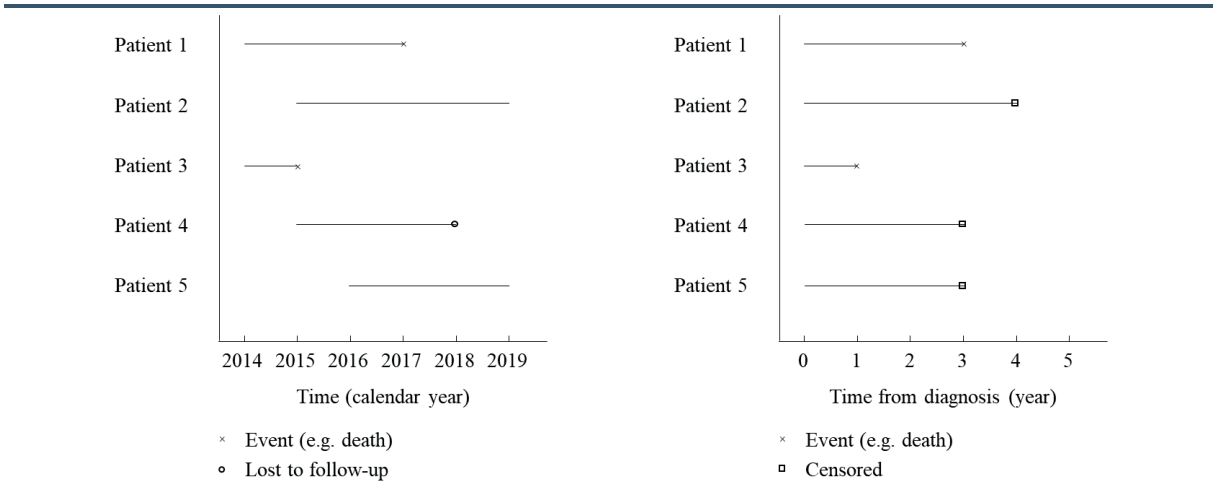


Figure description: Left panel of the figure show the survival time as it is collected in a study or registry (in calendar time). In the right panel, the data are transformed to survival data where each observation starts at the time of diagnosis. Patient 2, 4, and 5 are censored because they did not experience the event by the end of follow-up.

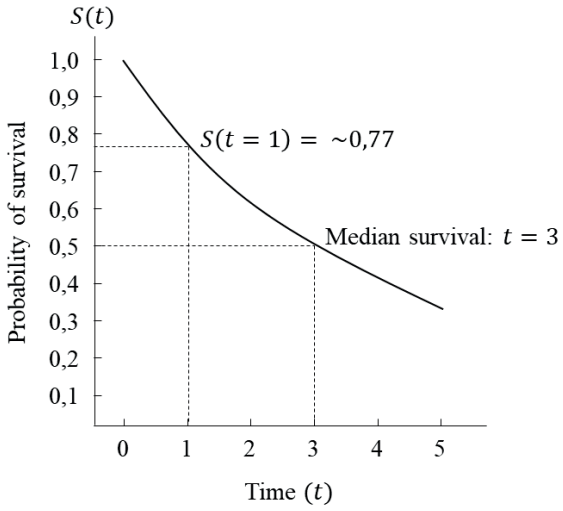
4.3.2 Survival and hazard function

In general, survival data are described in terms of two related functions: (1) the survival function $S(t)$ and (2) the hazard function $h(t)$.[120] The survival function denotes the probability that an individual is alive (or survives until) a single point in time (t) from the beginning of the observation period (e.g.,

time of diagnosis). The survival function is a key element in survival analysis as it describes the probabilities that a patient is still alive at different values of t, which is useful as summary description of the cohort being studied.

The survival function can be graphed as illustrated in Figure 22, with the proportion of patients alive (probability of surviving) on the vertical axis and time (t) on the horizontal axis. At the starting point $(t = 0)$, all patients are alive, and the probability of surviving is equal to 1 $(S(t = 1) = 1.0)$. After one year $(t = 1)$, 77 percent of the patients are alive $(S(t = 1) = 0.77)$. The median survival is the time till 50 percent of the patients have experienced the event, in this case after three years $(t = 3)$. A steep survival curve suggests a poor survival, whereas a relatively flat curve indicates a good survival or prognosis. Note that in this example the survival curve is presented as a smooth curve. However, in many applications, the curve is presented as a stepwise function (see Figure 16).

Figure 15: Illustration of the survival curve $S(t)$



Another important element of survival analysis is the hazard function $(h(t))$, a function directly related to the survival function. The hazard is the probability of an individual that is under observation is experiencing the event at a given time.[120] It is a conditional probability and represents the instantaneous event rate (or death risk) for an individual, given that this individual has not experienced the event previously (i.e., is alive at time t). The hazard is an important element of survival analysis as it gives information to specify mathematical models for survival analysis.

4.3.3 Kaplan-Meier estimator

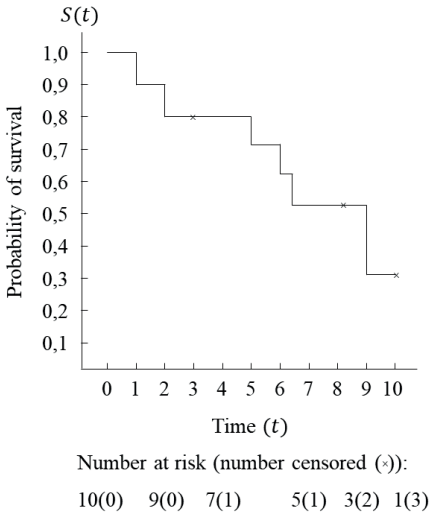
The probability of survival can be estimated using the Kaplan-Meier method, a non-parametric method that uses the observed survival times to estimate the probability of being alive at any given time.[121] The basic idea of the Kaplan-Meier method is that as all events occur independently of each other, the cumulative probability can be estimated by multiplying the probability of surviving from one interval to another. The survival probability at time t $(S(t))$ is estimated from the survival probability at $t - 1$, the number of patients alive just before t (n), and the number of events at time t (d):

$$S(t) = S(t-1)\left(1 - \frac{d}{n}\right)$$

The estimated probability $(S(t))$ changes only at the time of each event. When the Kaplan-Meier survival probability is plotted against time (as showed in Figure 16) the curve is presented as a stepwise function as the probabilities only changes at the time of each event. The Kaplan-Meier

method also enables estimation of confidence intervals. As the data are skewed, with more observations in the early period, the confidence intervals usually become wider when time increases.

Figure 16: Illustration of a Kaplan-Meier survival curve



4.3.4 Log-rank test

It may be of interest to compare the survival of different groups such as men and women or patients receiving a specific treatment and patients not receiving that treatment. The most widely used method for such comparison is the log-rank test. The log-rank test is a nonparametric test used to compare the survival of two or more groups of patients.[122] The null hypothesis for the log-rank test is that there are no differences between the two groups and the test makes no assumption about the survival distribution. The log-rank test is especially appropriate when the data are right skewed and censored (censoring must be non-informative) and is therefore commonly used in survival analysis.

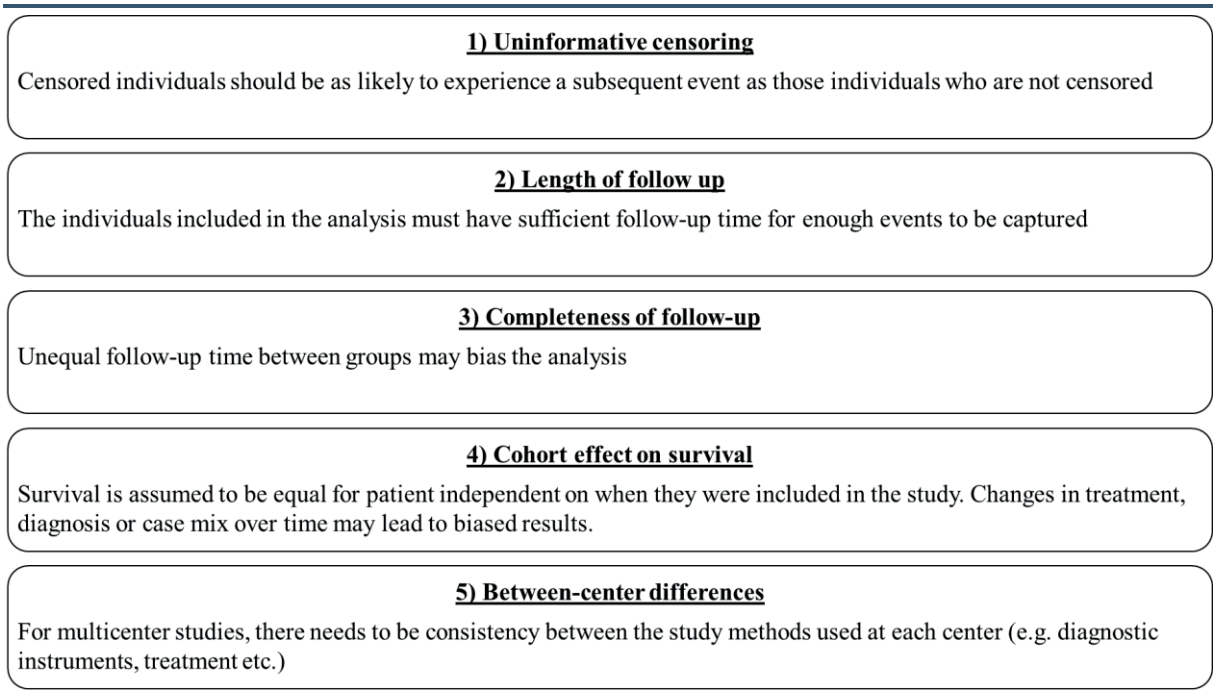
4.3.5 Multivariate regression analysis

Visual assessment of Kaplan-Meier curves and the log-rank test are examples of univariate analysis used to compare the survival for different patient groups. One key limitation of these methods is that they only describe the survival with respect to the factor under investigation, while they ignore the impact of other possible important factors. In survival analysis, it is common that several known factors may affect survival, such as gender, age, cancer stage, etc. Multivariate regression models can assess survival with respect to several factors simultaneously and adjust the survival curves for covariates that are thought to influence the survival. Additionally, such multivariate analysis can also offer an estimate of the effect size for the different covariates. One of the most commonly used methods to investigate the effect of different factors on survival is known as the Cox proportional-hazards model.[123,124] This model assume a proportional hazard (i.e., the hazard ratio for all individuals is assumed to be constant), while this is not necessary for other parametric models based on specific distributions (e.g., Weibull, log-logistic, exponential, Gompertz, and gamma).

4.3.6 Requirements for the analysis of survival data

There are several key assumptions that need to hold for the analysis of survival data. Clark and coworkers (2003)[120] presents five key requirements for survival analysis (Figure 17).

Figure 17: Five requirements for survival analysis



Source: Clark et. al (2003)[120]

4.4 Valuation of life years

While some have argued that it is unethical to express the value of an individual life in monetary terms,[125,126] the competing demand for scarce resources requires that a value be placed on interventions or policies where the goal is to generate more life years in order to make them comparable. The absence of an explicit value will probably result in an implicit valuation on a case by case basis and may lead to inconsistency in priority setting.

When evaluating risk-reward trade-offs people make regarding their health, economists often consider the value of a statistical life (VSL). This value does not reflect what an individual would pay to avoid certain death, but it places a value on changes in the likelihood of death, hence the term statistical life (rather than the value of an actual life). VSL is frequently used by governments to estimate benefits of different policies, especially in public sectors like transportation and environment. VSL differs from the value of a QALY as it does not capture the quality-of-life dimension (see subsection 0), but places a value of reducing the average number of deaths. There is a substantial literature on the VSL and the estimates vary significantly across studies.[127] Several countries, including Norway, operate with an official VSL (30 million 2012-NOK)[128] for all public sectors, while other countries like the US have different values for different government agencies.[129]

Generally, economist adopt two different methods to place a monetary value of a life or a life year. The first one was originally developed by Michael Grossman in 1972 and is known as the human capital approach (HCA).[130,131] The second method was first proposed by Shelling and Mishan and is called the willingness-to-pay (WTP) approach.[132,133]

4.4.1 Human capital approach

In the human capital model, health is viewed as a durable capital stock that yields an output of healthy time.[134] Health is assumed to depreciate with age, and money spent on health is seen as an investment which results in healthy time (output).[134] Investments in health are assumed to contribute to more healthy time, which again results in increased productivity.[9] Because time in good health enables individuals to engage in income-generating activities, good health contributes to the production of

consumable goods and services. HCA is commonly used in COI-analyses to estimate production losses related to an illness, i.e., the societal cost of individuals not being able to engage in production. Selma J. Mushkin suggested that earnings could be used as a measure of labor productivity.[135,136] She argued that an individual's wages reflect their underlying productivity, and thus the wage matches the contribution to production.[135] This approach has been used since the early COI analyses.[94] For morbidity, researchers commonly use average earnings plus social costs (insurance, pensions, welfare funds, etc.) by age and sex to estimate the costs associated with time off work.[84] For mortality (cost of premature death), researchers consider earnings over a lifetime, assuming that the individual, had they not died, would have continued to be productive according to their life expectancy.[96] A problem with this method arises in cases where no market price (e.g., wage) is observable, for instance in the case of homemakers. To deal with this problem economists have used different methods. One could use the opportunity cost of time, where one assumes that the value of production at home must be at least as great as what the individual would have earned in the labor market. Another approach would be to use the replacement cost (cost of buying the services in the market) as a proxy for the value of time spent at home.

Several health economists have criticized the HCA for overestimating production losses due to illness because the model assumes full employment, which in many settings may not be the case.[9,11,137-139] Koopmanschap and van Ineveld argue that while HCA accurately estimates potential lost production, actual losses for society are often smaller.[140] For short term absences, a sick individual's work may be covered by other employees or made up by the sick individual themselves when they return to work. Additionally, some employers have excess capacity in the labor force to cover for short term absenteeism. For long term absences and cases of premature death, work can be covered by someone from the unemployment pool. In 1995, Koopmanschap and co-workers proposed the friction cost method, an approach for estimating indirect costs which considers economic circumstances that limit production losses.[141] With this approach the costs of illness is limited to a short term period called the friction period only including initial disruption and training costs.[141] The length of the friction period depends on the availability of personnel in the labor market and within the firms and the level of unemployment. Even though the method captures some appealing aspects, the friction cost method is rarely used in COI analyses as the method requires extensive data to estimate losses during the friction period.[85,142]

4.4.2 Willingness to pay

In addition to the debate on measurement issues with the HCA, several economists have argued that the method is not grounded in the theoretical foundations of welfare economics.[9,133] Mishan (1971) argued that the valuation method used in the HCA is inconsistent with the value judgment in welfare economics (actual pareto improvement and the Kaldor-Hicks criterion, see subsection 2.1.1) and that the relevant notion of value is what consumers are willing to sacrifice to obtain a particular good.[133] Advocates for this idea argued that focus should be on individuals money-health tradeoffs under uncertainty rather than in situations with decisions regarding certain death.[143] There are in general two different approaches to identify individuals willingness-to-pay (WTP) for a statistical life: revealed preferences and contingent valuation (stated preferences of WTP). The revealed preferences method involves observing actual behavior and is performed by conducting wage-risk studies in which the goal is to examine the relationship between a risk (e.g., a hazardous job) and wage rates (for example see Marin & Psacharopoulos (1982)[144]). With contingent valuation, analysts use surveys with hypothetical questions to identify individuals WTP for different interventions or policies. The purpose is to get participants to state their demand and valuation of non-market goods and benefits (for example see Donaldson & Shackley (1997)[145]).

Even though the WTP method is regarded by economists as the theoretical correct method to value life and health outcomes, it is rarely used in health economic analyses.[85] It often requires analysts to perform extensive surveys or data collection for the particular problem as the valuation likely differ

from the disease or intervention in question.[9] Additionally, empirical studies have given a broad range of estimates of the VSL.[146,147] The HCA is therefore the most common method used in CEA and COI analyses to estimate production gains and losses.

For cost-effectiveness analyses used in priority setting in health care, the budget is in most cases fixed. Therefore, there is need for a threshold of the willingness to pay for a given outcome (e.g. a QALY). This threshold should be based on the opportunity cost (see section 4.1) as this value, at least in principle, reflect what decision makers are giving up if they decide to finance a new intervention or treatment. Claxton and coworkers have developed methods for estimation of this threshold in the UK, and found the threshold to be £12,936 per QALY using 2008 cost and outcome data.[148] This threshold has been adjusted for use in Norway based on exchange rates and the size of the economy.[34] The adjustment resultat in a cost of NOK 275,000 per QALY. Other thresholds have also been recommended, for example 1 to 3 times the gross domestic product (GDP) per capita.[149]

4.4.3 Discounting the value of life years

While discounting of future costs is fairly uncontroversial, the extent to which health benefits should be discounted has raised a lot of debate in the literature.[8,15,150-158] When evaluating vaccination or screening programs, where health benefits occur far into the future, it matters a lot whether the benefits are discounted or not.[159]

One might argue that health cannot be traded over time, hence, it cannot be invested and yield return.[160] However, the reason for discounting health is not that health can be invested and yield a positive return, or that health in the future is less valuable than health today in any absolute utilitarian sense.[15] Rather, at a societal level, one might argue that spending resources on health will transform into more health, and as it is possible to trade health care resources over time, the same should hold for health.[152] The argument is that as health is being valued relative to health care resources, which are discounted, one need to discount future health as well. In other words, saving resources (not spending on health) can ultimately yield more health in the next time period, indicating the logic behind equal discounting of costs and benefits. The main arguments for equal discounting is based on a claim by Weinstein and Stason that different discount rates would led to inconsistencies over time,[15] and the postponement paradox of Keeler and Cretin who demonstrate that the ICER of a given intervention will improve with each year it is postponed if benefits are discounted with a lower rate than costs.[158] However, several researchers have in recent years challenged the arguments put forward by Weinstein and Stason and Keeler and Cretin. It has been argued that the monetary value of health is expected to increase over time, and that unequal discounting is a way to account for health becoming more valuable in economic evaluations.[151,161] Claxton and coworkers[154] point out that several factors are important when deciding on discount rates, including if the objective is to maximize the broader welfare or just health, if the budget is variable or fixed, whether the marginal productivity of health care spending and the value of health are expected to increase over time, and the level of the social time preference rates for health and consumption.

The key recommendation from the Second Panel on Cost-effectiveness in Health and Medicine is that analysts should use a common annual discount rate of three percent for costs and health benefits.[8] In a recently published study, Attema, Brouwer, and Claxton summarize the national guidelines on discounting for 24 countries that use economic evaluations.[157] Their review of national guidelines show that equal discounting is the most common practice. The National Institute for Health and Care Excellence (NICE) in UK changed their guidelines in 2004 and went from discounting costs with 6 percent and effects with 1,5 percent, to equal discounting of 3,5 percent.[157] Four countries currently recommend unequal discounting (The Netherlands, Belgium, Russia, and Poland), while most countries recommend an equal discount rate in the base case, and that the effects of using different discount rates shown in sensitivity analyses.[157]

In addition to influencing the efficiency of resource allocation, choice of discount rate may have equity implications.[157] In cases with a positive discount rate and a very long time horizon, little weight is given to future generations. This challenge is particularly relevant in environmental economics but may also be an issue in health economics. A pragmatic solution to this problem may be to use a discount rate that decreases with time, as recommended by the Norwegian Ministry of Finance (4% during the first 40 years, 3% from 40 to 75 years, 2% after 75 years).[18]

5. Materials and methods

Nationwide health- and work-related registries were used in papers I-IV to evaluate different aspects of the cost and resource utilization related to cancer in Norway. This chapter provides an overview of said registries and their content, followed by a description of the methods used to monetize costs in papers I, II, and IV. The chapter subsequently describe how logistic regression and generalized linear models, block bootstrapping, and survival analysis were used in papers II, III, and IV. Finally, the chapter provides a short summery of important methodological challenges and limitations, as well as ethical considerations.

5.1 Reporting guidelines for observational studies using registry data

The RECORD[162] reporting guidelines was used when developing the manuscripts. RECORD (Reporting of studies Conducted using Observational Routinely-collected Data) is an international collaboration who develops guidelines for studies using routinely-collected health data, such as health administrative data or registry data. For paper III, STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) were used upon request from the editorial board at the journal the paper was submitted to.

5.2 Registry data used in papers I-IV

A registry is a collection of data about individuals on a specific topic. For example, patient registries collect uniform data (clinical and/or other data) for a defined population or for a specific diagnosis or condition. Data registries serves both scientific, clinical, and policy purposes and are commonly used in observational studies to evaluate different outcomes for a population or to map treatment practice.

A key attribute of nationwide registries is that they include the entire population rather than just a sample. The Nordics have a long tradition of systematically collecting data in registries and all Nordic countries have nationwide registries covering virtually the entire population.[163] The Nordic cancer registries coves a combined population of approximately 26 million, are among the oldest population-based registries in the world, and have more than 60 years of complete coverage.[164] Another key attribute of Nordic registries is that all residence have an unique identification number (personal identification number (PIN)), which make it possible to follow individuals over time within each registry and to link different registries. Norway has several general national health registries covering the entire population (e.g., patient registry, cause of death registry, medical birth registry, primary care registry etc.), as well as disease specific registries (cancer registry, cardiovascular disease registry).

5.2.1 Overview of registries

An overview of the registries used in papers I-IV is presented in Table 1. The following section provides a description of each of the data sources. Included variables for all registries are presented in Table 2 in Appendix.

Table 1: Overview of registries used in papers I-IV

Name of registry / data source	Used in paper	Data manager/processor
Cancer Registry of Norway (CRN)	I, II, and IV	Oslo University Hospital
The Norwegian Health Economics Administration's (HELFO) KUHR database	I	The Norwegian Directorate of Health
The Norwegian Patient Registry (NPR)	I-IV	The Norwegian Directorate of Health
The Norwegian Prescription Database (NorPD)	I	Norwegian Institute of Public Health
The Norwegian Cause of Death Registry	I and IV	Norwegian Institute of Public Health
FD-Trygd (Labor market statistics)	I	The Norwegian Labor and Welfare Administration (NAV)
Statistics Norway's Health Accounts	I	Statistics Norway
Statistics Norway's KOSTRA registry	I	Statistics Norway

The Cancer Registry of Norway (CRN)

The Cancer Registry of Norway (CRN) was established in 1951 and is one of the oldest national cancer registries in the world.[165] CRN contains health information about all individuals in Norway who have been diagnosed with cancer. All medical doctors in Norway are required by law to notify CRN of any new cancer case. The data in CRN are collected from several sources, including physicians, hospitals, laboratories, and by linkage with the Norwegian Patient Registry (NPR). The quality of the data in CRN is found to have a high degree of comparability, accuracy, and timeliness, and the completeness is estimated to be close to 100 percent.[166] Key variables included in the registry are time of cancer diagnosis (date/month/year), type of cancer (ICD-10 code), cancer stage at time of diagnosis, patient characteristics (age, gender, place of residence, etc.), and time of death (date/month/year).

The NORDCAN-program[167] presents information on cancer incidence, prevalence, and mortality for the Nordic countries based on data from the national cancer registries and cause of death registries. NORCAN includes a module for short-term (5 years ahead) and long-term (20 years ahead) predicted incidence and mortality. Short-term predictions are based on log-linear models, while long-term predictions are based on age-period-cohort methods.[167]

The Norwegian Health Economics Administration's KUHR database

The KUHR database holds data on patient co-payments and reimbursement claims from practitioners and health institution finances by the central government, including primary physicians, emergency rooms, private practicing specialists, laboratories, and imaging services providers.[168] For each patient contact (episode of care) KUHR collects data on the practitioner (type of practice, speciality, geographic location), the patient (personal identification number, age, gender, diagnosis, place of residence), date and time of contact, type of contact (attendance, telephone service, etc.), patient co-payment, tariff, and reimbursement. Reporting to KUHR is a prerequisite to receive funding for the services provided from the central government and HELFO continuously carry out inspections at physician offices and at private practicing specialist to check the reporting. Thus, both the accuracy and completeness of the KUHR registry are regarded to be good.

The Norwegian Patient Registry (NPR)

The Norwegian Patient Registry (NPR) holds data on all treatment episodes in publicly financed hospitals.[169] Norway provides uniform and public health care services financed by taxation, and the access to health care services is independent of income, societal status, age, etc. As cancer treatment in private hospitals is negligible, NPR covers virtually all cancer related episodes of care. In NPR, each episode (i.e., patient contact) is assigned a diagnostic code (ICD-10 code) and an anonymous, unique

patient identifier. Diagnostic codes in NPR are found to be valid when compared to the Cancer Registry of Norway.[170] In addition to diagnostic codes and patient identifier, the registry holds information, among other things, on patient age, gender, county of residence, time of episode, time of death, type of episode (inpatient, outpatient, or daycare), type of treatment (diagnosis related group (DRG) code), cost weight related to episode, medical and surgical procedure codes, and ATC-codes for infusions of pharmaceuticals.

The Norwegian Prescription Database (NorPD)

The Norwegian Prescription Database (NorPD)[171] holds data on all drugs prescribed (reimbursed or not) and dispensed to patients living outside institutions in Norway. All Norwegian pharmacies are required by law to send electronic data to NorPD and the completeness is regarded to be good.[172] The registry reported missing or incorrect personal IDs on 0,14 percent of the prescriptions in 2019 (information provided by the registry in 2021). Every drug delivery has a reimbursement code, which is equivalent to an ICD-10 code in specialist care and ICPC-2 code in primary care, and a unique patient identifier. Additionally, the registry contain data on patient characteristics (age, gender, place of residence), time of drug redemption, drug cost (pharmacy retail price), package size, number of packages, ATC-code, etc.

The Norwegian Cause of Death Registry

The Norwegian Cause of Death Registry holds information on all deaths in Norway, regardless of whether the deceased are Norwegian citizens, or if the death occur outside of Norway (for Norwegian citizens).[173] The registry dates back to 1951 and causes of death were coded manually until 2005. Cancer related deaths have been compared with records from the Cancer Registry of Norway, and the registry's degree of coverage is regarded to be near-complete.[174] In addition to cause of death, the registry holds information on patient characteristics such as age, gender, and place of residence.

FD-Trygd (Labor market statistics)

The Norwegian Labor and Welfare Administration (NAV) collects labor market statistics for the Norwegian population (FD-Trygd data base).[175] The registry covers most Norwegian cancer patients as private pension schemes and health insurance are not widely used in Norway. A given cancer patient may receive three different types of benefits from NAV. Members of the National Insurance Scheme who are occupationally disabled due to an illness or injury receive sickness benefits to compensate for lost income. Work assessment allowance is given to individuals with reduced work capability (impairment of at least 50%) while they are trying to get back to work. The goal of the scheme is for recipients to be able to find or retain work during the period they receive work assessment allowance. Finally, individuals that are unemployed or temporarily laid-off are eligible to receive unemployment benefits. To obtain one of these benefits the patient must get a medical certificate from a doctor. Sickness payments, work assessment allowance, and disability pensions are registered with a diagnosis, which make us able to identify beneficiaries with cancer as diagnosis and claims related to cancer. While the FD-Trygd data are regarded as reliable in terms of whether a patient receives social benefits or not, the validity of diagnosis (i.e., the medical condition causing need social benefits) in the data base is less certain.[176] However, for diagnoses with a clear biomedical feature such as cancer, it is likely that the diagnoses information in FD-Trygd are more accurate than for more diffuse medical conditions.[176]

Statistics Norway's Health accounts

Statistics Norway's Health Accounts holds data on the total health care expenditures and capital investments in health care infrastructure in Norway.[177] The data are presented in a aggregated form, and include spending by both public and private sources. Expenditures are divided into type of service, provider industry, funding source, and producing sector.

Statistics Norway's KOSTRA registry

Statistics Norway's KOSTRA registry (Municipality-State-Reporting) provides data on municipal and county activities and services. The registry includes expenditures related to nursing and care services provided by municipalities in Norway, including both institutionalized and home care.

5.2.2 Advantages of using registry data when studying resource use and costs

Information on costs and resource utilization can be collected from multiple sources, including medical records, patient surveys, clinical trials, or administrative registry data. There are several advantages of using registry data to investigate disease related costs and resource utilization. Using registry data are generally the most timely and economical way of assessing resource use related to a disease as data already exist in computer-readable format.[178] In most cases there is no need to contact study participants. Additionally, large, and unbiased study populations have the advantage of providing good statistical power enabling the study of rare outcomes.[163] The bias related to data collection is minimized as data are collected independently.[179] For registries covering the entire population, there is no issues with potential selection bias. Finally, registry data enables researchers to study otherwise unethical or impossible problems, such as the association between pregnancy length and risk of cerebral palsy.[180]

5.2.3 Linking data

Registries in Norway have the desirable attribute that they can be linked to other registries or data sources by using a unique personal identification number (PIN).[181] The PIN was introduced in Norway in 1964 and has contributed to a strong tradition of collecting data on all inhabitants.[163] Linking registries are conducted by the agencies that maintain the registries, or by Statistics Norway. Before data are made available to the researchers, the data are pseudo-anonymized through replacement of the PIN with an arbitrary number that is equal for each individual in all the registries (unique patient identifier). Several laws and regulations limit the access to linked individual patient level data in Norway and the data extraction can be both time- and resource consuming. In some cases, it may take years to get access to linked data. Due to the legal restrictions, we were not able to link data from the different registries within the timeframe of this project.

5.3 Methods for monetizing cost

Several methods can be used to place a monetary value on the economic cost of cancer depending on the cost category, perspective of analysis, and data availability. This section introduces key cost categories and methods used to monetize the economic costs in papers I, II, and IV.

Before identifying and monetizing the different cost categories a clear definition of the disease in question is necessary. In papers I, II, and IV cancer was defined according to the International Classification of Diseases 10th Revision (ICD-10) (see Table 3 and Table 4 in appendix). While ICD-10 codes are used in specialist health care in Norway, primary physicians use the International Classification of Primary Care (Second edition) (ICPC-2) classification system. In addition to ICD-10 codes, ICPC-2 codes were used to identify patients in paper I (Table 3 in appendix).

Once relevant costs in papers I, II, and IV were identified and described, the different cost components were measured and valued using available data and estimates from the literature. I general, costing involves two different elements: measuring the quantities of resources and assigning unit costs for each resource. For some cost categories, like drug costs, a market price is available. For non-market resources (patient time etc.) other methods and proxies can be used to place a value on the economic cost.

Paper I adopted a societal perspective, and reviewed most aspects of societal costs of cancer, including direct health care costs, direct costs outside the health care sector (nonmedical costs), indirect costs

(production losses), and intangible costs (the value of lost life years and lost life quality). In papers II and IV costs were restricted to patient related direct medical costs in hospitals (i.e., only fee for service financed costs, not costs related to R&D, ambulance services and patient transportation, capital costs, etc.).

In papers I, II, and IV relevant cost categories were defined and evaluated in monetary terms. The monetary value was defined as the opportunity cost, or the real economic cost (see section 4.1). As the opportunity costs were not directly identifiable in the raw data, estimates based on tariffs and prices were used as proxies to monetize costs. In cases with cross-subsidizing, tariffs were adjusted to reflect the real economic cost.

The societal cost of cancer can be divided into three main cost categories; direct medical and nonmedical costs, production losses (indirect costs), and fatal and non-fatal health loss (Figure 18). In the following subsections each of these costs are discussed.

Figure 18: Overview of the societal costs of cancer included in papers I, II, and IV

	Type of cost	Cost category	Included in paper
	*Direct medical and non-medical costs (direct costs)*	Health care costs	I, II, and IV
		Patient travel costs	I
	*Production losses (indirect costs)*	Work absenteeism Premature death Informal care Patient time costs Marginal cost of public funds	I
	*Fatal and non-fatal health loss (intangible costs)*	Lost life years and lost quality of life	I

5.3.1 Direct medical and non-medical costs

Health care costs

Generally, cancer related health care costs can be calculated as total direct costs, measuring the value of medical care consumed by cancer patients, or as the additional burden due to cancer.[84] The latter is usually referred to as "net costs" or "attributable costs" and comprises the costs directly attributable to the disease of interest.[84] In a review of methodologies employed in COI studies, Akobundu and coworkers classified four different methodologies used to calculate health care costs.[182] The first method is a total direct cost approach and involves adding all costs related to patient care, regardless of whether the costs is directly related to the disease or not. The second involves only adding costs related to the disease of interest and is sometimes referred to as a attributable costs method.[107] Matched control group and regression analyses methods computes the disease-specific costs as the incremental costs (net costs) between patients with without the disease of interest who are otherwise comparable.[95] Net cost methods are expected to result in lower costs because patients with for instance cancer are expected to use less resources related to health care problems other than cancer (compared with non-cancer patients).[107] Papers I, II, and IV employed an attributable cost approach to estimate the additional burden of cancer.

Papers II and IV employed a bottom-up approach (see subsection 4.2.4) using Diagnosis Related Groups (DRG) weights and a corresponding unit price. In Norway, all treatment episodes in somatic hospitals are assigned a DRG, a primary diagnosis, and possibly one or several secondary diagnoses. All DRGs have a specific cost weight depending on the resource intensity associated with the service delivered. The DRG-system is continuously updated, and the DRG-weights are re-calculated annually based on accounting data from the four regional health authorities. Cost per treatment episode was calculated by multiplying the DRG-weight with the average cost per DRG point. Average cost per DRG point was in 2017 estimated to EUR 5 238 excluding value added tax (VAT) by the Norwegian Directorate of Health.[183] Even though VAT may be a cost for the individual patient or hospital, it is not regarded as an economic cost, but rather a transfer payment from the payer to the central government.[9,84] Hence, VAT were excluded from the analyses. We assumed that episodes with cancer as primary or secondary diagnosis were cancer related when estimating DRG-related costs. Only including episodes with cancer as primary diagnosis resulted in somewhat lower costs (see Table 5 in Appendix). In paper II, costs were discounted with a discount rate of four percent according to guidelines from the Norwegian Ministry of Finance.[128]

Paper I employed a combination of a bottom-up and a top-down approach (see subsection 4.2.4) depending on the data that were available for each cost category. Reimbursement fees and patient co-payments were used to estimate costs associated with primary physicians, emergency rooms, and private practicing specialists using fees from the Norwegian Directorate of Health.[184] Costs in somatic hospitals were estimated in the same way as in papers II and IV (i.e., DRG weights and unit prices). For pharmacy dispensed drugs we used retail price excluding VAT. In paper I, we used data from Statistics Norway's Health Accounts and the Norwegian Directorate of Health to estimate costs in somatic hospitals not included in the DRG cost weights (non-patient related costs such as R&D, ambulance services, and patient transportation, capital costs, etc.). The proportion of these costs attributable to cancer was estimated to ~13%, based on the cancer related DRG-costs relative to the total DRG-costs in somatic hospitals. Costs associated with diagnostics imaging and laboratory services were estimated with data on reimbursement and patient co-payments from all public out-patient clinics and private laboratories from the KUHR database. When patients receive imaging and laboratory services in Norway, a diagnosis is not required to be registered. The proportion of these costs attributable to cancer were assumed to be equal to cancer patients' proportion of out-patient visits each year (ranging from 10.6% in 2014 to 13.1% in 2017). Costs related to screening programs for breast and cervical cancer were collected from the literature.[185,186] Municipality provided nursing home and home nursing services account for approximately 30 percent of the total health care expenditures in Norway.[39] Statistic Norway's KOSTRA-registry holds data on costs in Norwegian municipalities, but lack information about diagnosis. To get an estimate of cancer related costs for municipality provided services we assumed that three percent of the total costs were related to cancer based on a pilot project initiated by the Norwegian Directorate of Health where diagnosis information were collected for three municipalities.[187] Statistics Norway's price index for production of public health services were used to adjust direct health care costs to 2017 EUR.

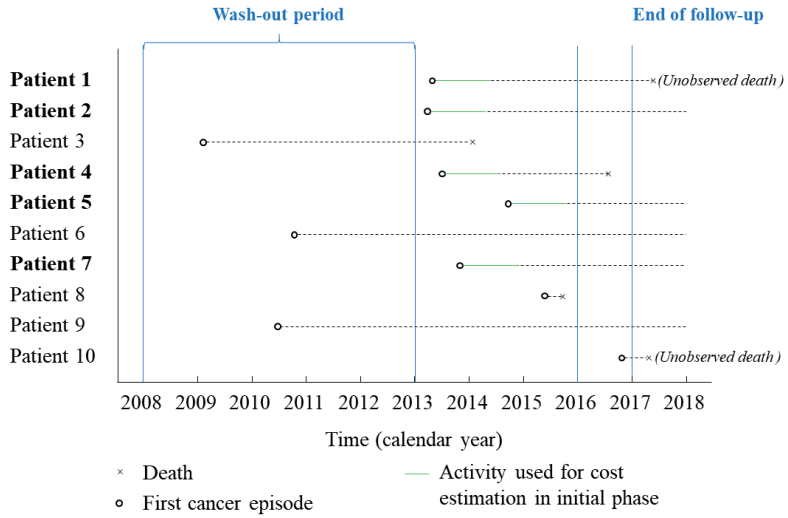
Paper I employed a prevalence-based approach were annual costs were estimated based on the year they were borne.[107] Health care costs in a given year included costs of newly diagnosed patients, patents who may have been alive with cancer for a long time, and patient who died of their cancer during the year (see section 4.2.2 for further description).

In paper II, a phase-specific costing approach were used to estimate direct medical costs in hospitals. Patient care was divided into three distinct phases (initial treatment phase, continuing care, and terminal care) and survival models were applied to monthly costs for each phase to estimate lifetime costs. Average monthly (phase-specific) direct medical costs were estimated using different patient cohorts for each phase (see description below). One key advantage of using this approach to estimate lifetime costs is that the method only requires a few years of cost data, not long-term data from

diagnosis to death for all patients. This makes it possible to use recent cost data, which better reflect current treatment practice.

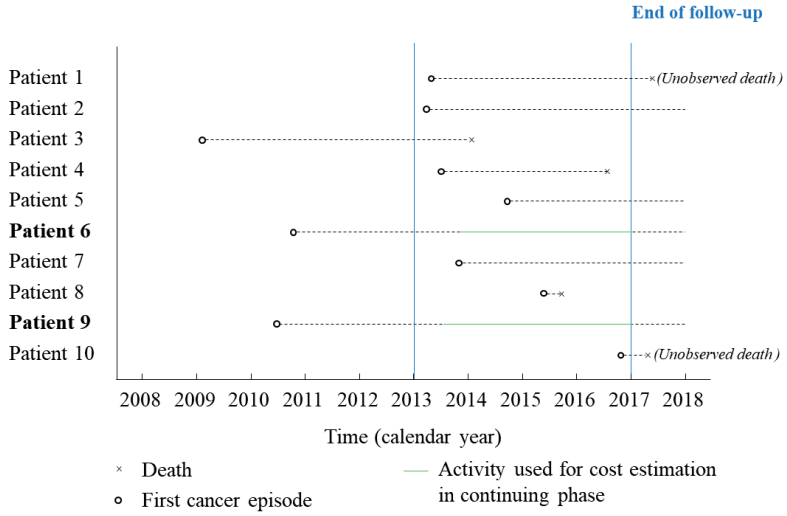
Monthly unit costs in the initial phase were estimated using patients diagnosed with cancer between 2013 and 2016, with at least 12 months follow-up. Patients with no cancer related episodes between 2008 and 2012 were assumed to be newly diagnosed patients. Patients with less than 12 months follow-up were excluded to avoid including costs related to terminal care. Figure 19 illustrate how patients were selected. In this example, patient number 1, 2, 4, 5, and 7 meets the requirements to be included in the calculation. Patient number 3, 6, and 9 were excluded for having a cancer related episode prior to 2013, while patient number 8 and 10 had to short follow-up (< 12 months).

Figure 19: Patients included for estimation of costs in initial phase



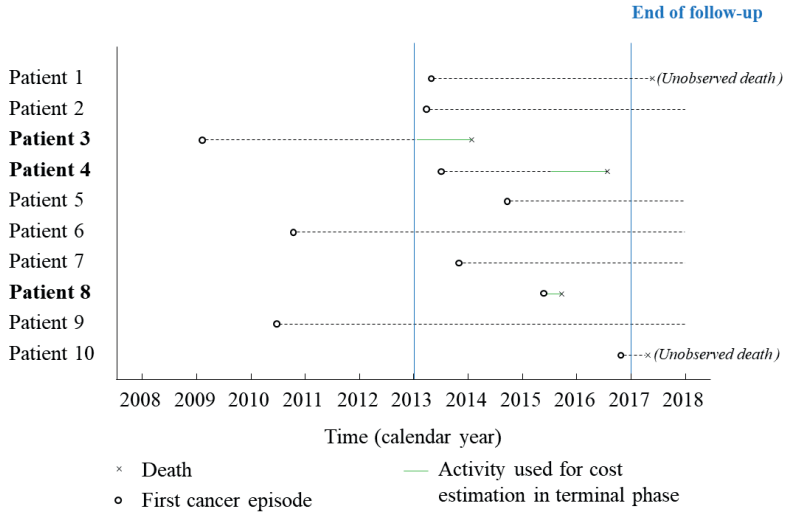
Costs in the continuing phase was estimated by using patients diagnosed with cancer in 2010 (patient no. 6 and 9 in Figure 20). To avoid including costs related to the initial or terminal phase only patients alive by the end of 2017 were included. Activity data from 2013 to 2017 were used to estimate costs because changes in the DRG-weights makes data prior to 2013 unsuitable for estimating costs related to outpatient visits. Additionally, costs occurring in the second and third year after diagnosis (i.e., time of first cancer related episode) were excluded as treatment intensity may be higher in the initial years compared to patients with longer follow-up.

Figure 20: Patients included for estimation of costs in continuing phase



For costs in the terminal care phase, patients deceased between 2013 and 2017 were used to estimate costs (patient no 3, 4, and 8 in Figure 21). Like the continuing phase, costs were estimated based on activity data from 2013 through 2017.

Figure 21: Patients included for estimation of costs in terminal phase



Lifetime costs were estimated by combining monthly unit costs with survival data from the CRN. Lifetime costs were estimated as:

$$Lifetime\ costs\ (t_T) = \sum_{t=1}^{T} \hat{S}(t) C_t$$

where $\hat{S}(t)$ is the probability of being alive in month t and C_t is the cost in month t after diagnosis.[107] Not all patients contributed to costs in all phases. The length of each phase (L) was defined as:

$$L(initial\ phase) = \min(12, t_T - t_0 - L(T)),$$

$$L(contiuing\ phase) = t_T - t_0 - L(T) - L(I),$$

$$L(terminal\ phase) = \min(12, t_T - t_0),$$

where t_0 denotes time of diagnosis and t_T time of death. In other words, a patient surviving for 18 months contributed with 12 months to the terminal phase, and 6 months to the initial phase, while a patient who survived less than one year only contributed to the terminal phase. Similar rules for allocating costs are used in previous studies of cancer costs.[78,105,106,188]

Patient travel costs

Patient travel costs associated with treatment in primary and specialist care and screening were included as a non-medical cost in paper I. Transportation costs were estimated using the number of contacts with primary physicians, emergency rooms, private specialists, and somatic hospitals and unit costs from a study by Moger and Kristiansen.[186] Travel costs related to screening was collected from the literature.[185,186]

5.3.2 Production losses

Production losses are indirect costs inflicted on society when people are away from productive work.[85] There is less than full agreement about which costs that should be considered as production losses (or indirect costs) in the health economics field.[189] Paper I included production losses related to: short-term work absenteeism, long-term disability, premature death, informal care, and work incentives due to taxes (marginal cost of public funds). Paper I employed the HCA to estimate the production losses (see subsection 4.4.1 for a description of the HCA).

Work absenteeism

The societal costs of work absenteeism were estimated using data on sick leave (short term, < 1 year), work assessment allowance (medium-term, < 3 years), and disability pensions (long term) from FD-Trygd (data from the Norwegian Labor and Welfare Administration (NAV)). All Norwegian residents are entitled to welfare payments from the central government if they are diagnosed with cancer and are unable to work. Welfare payments were used as a proxy to estimate the value of lost production due to cancer. Welfare payments per se are not an economic cost, but a transfer of funds from the government to the individual patient. These payments, however, can be used to measure the earnings of individuals diagnosed with cancer. In Norway, work assessment allowance and disability payments make up 66 percent of the recipients' salary and payments were adjusted to reflect the recipients' expected earning in a situation where they did not get diagnosed with cancer. The number of lost workdays forgone due to cancer from FD-Trygd were used to estimate production losses due to sick leave. The value of lost production were estimated using the expected earnings before taxes plus social and overhead costs (40%) according to Norwegian guidelines.[128] Costs of presenteeism (reduced productivity for people still in work) was not included.

Premature death

I addition to work absenteeism cancer causes a production loss because people in working age die earlier than they would have. Costs of premature death were considered over a lifetime rather than a single year. Individuals of working age who die prematurely would have continued to be productive for several years according to their life expectancy. Life tables, gender and age-specific average employment rate and working hours, and real wages (wages before taxes plus social- and overhead costs) from Statistics Norway were used to estimate the production loss. Deaths were assumed to occurred in the middle of each 5-year interval and future costs were discounted with an annual discount rate of four percent according to Norwegian guidelines.[128]

Informal care

Informal care is provided when friends and relatives spend time to take care of sick individuals. For informal care, caregivers (individuals providing the informal care) do not get compensated for the work they do. This does not mean that the resource consumption (caregivers' use of time) is not a cost for society. In a situation without illness, caregivers could have spent this time either doing productive work or as leisure time. In COI analyses, the opportunity cost method is the most frequently used approach to value the cost of informal care.[190] Valuing informal care, however, is challenging. Due to its heterogeneity, the definition, and what is regarded as informal care, may vary. The heterogeneity is related to differences in time spent per week, duration of care (how many weeks), types of tasks provided, and the intensity of care. For some tasks there is a fine line between what is regarded as costs for the individual and what is just people spending time with their loved ones.

In paper I, informal care was defined as the opportunity cost of unpaid care that caregivers forgo to provide care for friends or relatives with cancer. The cost of informal care was valued in monetary terms using estimates from a study by Luengo-Fernandez and co-workers of cancer costs across the European Union.[70] In this study, the authors use data from the Survey of Health, Ageing and Retirement in Europe (SHARE) to estimate the costs of informal care using mean hourly wages for care provided by employed caregivers and hourly minimum wage for retired caregivers.[70,191] The authors assume that only patients severely limited in daily activities or who were terminally ill would receive informal care. Estimates for Norway was not included in the study by Luengo-Fernandez and co-workers. Therefore, estimates from Denmark, Sweden, and Finland were used to get an estimate of costs associated with informal care in Norway. Estimates from the other Nordic countries were adjusted by using population size, purchasing power parity and inflation.

Patient time costs

Patient time costs include time spent traveling to and from physicians, emergency rooms and hospitals, waiting for appointments, and receiving care. Additionally, patients with and without cancer spend time related to screening. The time spent on these activities represents a cost for patients as the time could have been spent on other activities such as work and leisure. For a detailed estimation of patient time costs by cancer site see Yabroff et al. (2007).[192]

In paper I, lost patient time were estimated using the number of contacts with physicians, emergency rooms, private practicing specialists (KUHR data), and somatic hospitals (NPR data) and estimates of time spent per visit. Estimates of patient time associated with travel and care in Norway is not available. As a pragmatic approach, the time spent was estimated to two hours for primary care visits, three hours for specialist visits, and 20 minutes for telephone consultations.

Patient time costs were estimated by multiplying the lost patient time (number of hours) with an hourly value of time. Patients in working age were excluded from the calculation to avoid double counting of costs included in indirect morbidity. Time costs was assumed to be lost leisure and net annual earnings were used to value time costs. Conservative estimates were used when estimating patient time costs, both for time spent on travel and care, and for the value of time, due to limited data. Time costs related to screening activities were collected from the literature.[185,186]

Marginal cost of public funds

The marginal cost of public funds (MCF) is an important concept in public economics.[193] MCF measures the loss inflicted on society related to raising additional revenues to finance government spending.[194] Spending funds collected through taxation imposes an additional cost to a society for two reasons. First, resources are used to administrate and collect taxes, which is not the case for private funds. Secondly, taxes create a welfare loss (economic deadweight loss) because taxes distort the labor supply decisions of workers.[194] The latter reason is believed to be the main societal cost of using

public funds and means that taxes incentivize workers to prioritize leisure (rather than work) more than they would have done in a situation without taxes. MFC is a key component in evaluation of public programs and policies, and the Norwegian Ministry of Finance recommends that the additional costs of public spending should be estimated as 20 percent in cost benefit analyses.[128]

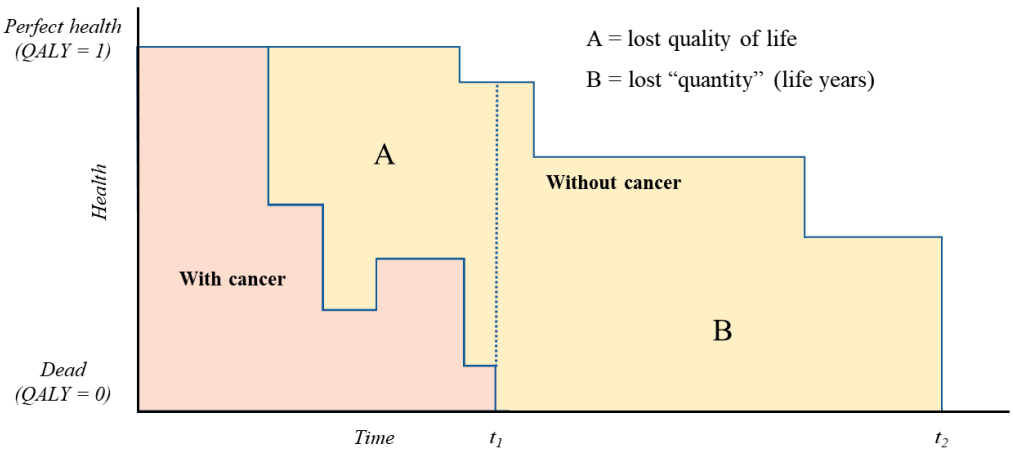
A proportion of the cancer related costs in Norway is covered using public funds. Most of the cancer treatment occur in public hospitals and a substantial proportion of the direct health care costs are therefore publicly financed. Additionally, cancer patients receive welfare payments from the federal government, including sick leave, work assessment allowance, and disability pensions. In paper I, the MCF were estimated as 20 percent of all cancer expenditures covered by public funds according to guidelines from the Norwegian Ministry of Finance.[128]

5.3.3 Fatal and non-fatal health loss

The direct and indirect costs cannot alone fully describe the societal costs related to cancer. In addition to what each individual produce, society values the fact that people are alive and in good health. Environmental policies, transportation policies, defense policies, health care policies, etc., involve, among other things, providing good life years. Fatal and non-fatal health loss (the value of lost life years and lost life quality) represent such a cost and are often defined as an intangible cost: foregone benefits that have no direct impact on the consumption of resources, such as pain and suffering.[101]

A consequence of cancer is that patients may live shorter than expected, and or with reduced life quality. This is illustrated in Figure 22. If a patient were expected to live until time t_1 in the absence of cancer, the cancer related loss would only include the lost quality of life (area A). However, if the patient were expected to live until t_2 (but died at t_1 because of his or her cancer), the number of lost life years would be the difference between t_2 and t_1. As some of the lost life years are not in perfect health, the number of QALYs lost would be equal to $A + B$.

Figure 22: Illustration of lost life years and lost life quality associated with cancer



Data from the Norwegian Cause of Death Registry, combined with the expected remaining QALYs in the general population (age adjusted health state utility values) from the Norwegian Medicines Agency[13] were used to estimate the number of lost QALYs in paper I. The value of lost QALYs were monetized using a value of a QALY of EUR 136,055, consistent with the value used by the Norwegian Directorate of Health.[184,195,196] The value of EUR 136,055 per QALY does not include production losses, hence problems with double counting are avoided. This value is derived from the value of a statistical life (see section 4.3), which again is based on the Norwegian valuation study.[197] The Norwegian valuation study uses a stated preference method with both choice experiments and contingent valuation.[197] Missing access to patient level data with information on costs associated with

lost quality of life (non-fatal health loss) estimates from a burden of disease study conducted by the Norwegian Directorate of Health published in 2019[196] were used to monetize the value of lost quality of life.

5.4 Regression analyses (papers III and IV)

Papers III and IV employed regression models to examine the relationship between an outcome variable and other explanatory variables (covariates).

5.4.1 Logistic regression model (paper III)

In paper III, the outcome of interest was the probability of receiving anti-cancer pharmaceutical treatment towards the end of life. A key objective was to examine the association between the use of anti-cancer treatment and patient related factors such as gender, age, region of residence, and type of cancer diagnosis. As the outcome variable in this case is binary; patients either receive or do not receive anti-cancer treatment, a logistic regression model was used. Logistic regressions model the probability of an event occurring (in this case patient receiving anti-cancer treatment) depending on a series of explanatory variables. The model included one continuous variable (year of death) and four categorical variables (10-year age groups, hospital affiliation (regional health authority), gender, and type of cancer). Additionally, possible interaction between gender, age, health region, and cancer type (in total 36 interactions) were investigated. The models provide odds ratios for patients receiving anti-cancer treatment towards end-of-life (last month and year of life). Odds are a measure of the likelihood of a patient receiving treatment and is defined as the number of patients receiving treatment divided by the number of patients not receiving treatment. Odds ratios are the relationship between the odds of treatment occurring in one group and the odds of it occurring in another group. For example, the odds ratio for women is the odds of a women receiving treatment divided by the odds of a man receiving treatment.

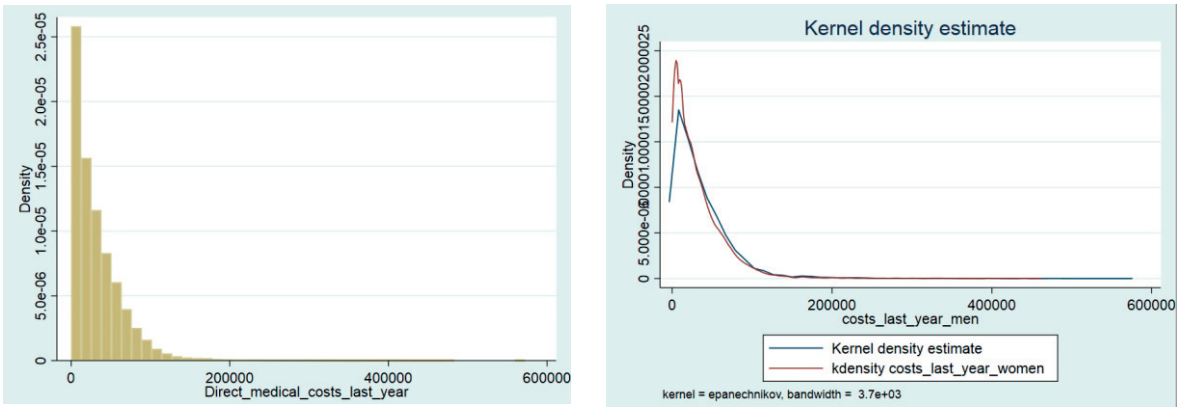
5.4.2 Generalized linear models (GLM) (paper IV)

In paper IV, the outcome of interest was direct medical costs in somatic hospitals during the last twelve months before death. Certain attributes of direct medical costs make traditional ordinary least square (OLS) models unfit for this purpose.[198] The most important of these is the violation of the assumption of normality. In fact, a small proportion of the patients typically have extremely high costs making the distribution right skewed (i.e., not normally distributed, as illustrated in Figure 23). Additionally, the assumption of constant variance (homoscedasticity) is often violated as the variability increases with increasing costs. While the latter can be accounted for using a heteroskedasticity-robust OLS estimator, the first challenge may be handled by transforming the costs to a log scale before using traditional linear regression techniques on the transformed data.[198] However, a drawback to using log-transformed costs is that inference must be done on the log-dollar scale as the retransforming of predictors back the original dollar scale may introduce bias.[199] Generalized linear models (GLM) have been proposed as an alternative method to estimate health care costs.[198] GLM provide a flexible approach to model health care costs that takes into account heteroscedasticity and at the same time retaining the original dollar scale. Instead of transforming costs, GLM represent a reparameterization of the model, thus eliminating issues with retransforming predictors.[198] GLM can also accommodate skewness as distributions based on the gamma or inverse Gaussian distribution can be used to model the underlying distribution. For health care costs, a gamma distribution and a log-link function are commonly used.[200] For a more thorough description of GLM see Blough & Ramsay (2000).[198]

In paper IV, GLMs with gamma distribution and a log-link function were fitted to the cost data. Seven different models were developed by including each explanatory variable sequentially (starting with just gender, then adding cancer type, age, hospital affiliation (regional health authority), place of death, and anti-cancer treatment last month of life). Paper IV reports exponentiated coefficients which

can be interpreted as ratios of x to y. For example, in the simplest model with only gender as a covariate, a ratio of 0.88 for gender (i.e., women = 1) can be interpreted as women having on average 12 percent lower costs than men.

Figure 23: Histogram of the distribution of direct medical costs last year of life (left panel) and kernel density plot for direct medical costs last year of life by gender, EUR



Figures describing the distribution of direct medical costs of patients analyzed in paper IV

5.5 Bootstrapping (paper III)

Paper III employed the bootstrapping method to measure the standard error of the proportion of patients receiving anti-cancer treatment at a given time before death. The method involves using random sampling with replacements to assign a measure of accuracy (bias, variance, confidence intervals etc.) to sample estimates.[201,202] The method was first introduced by Bradley Efron in 1979 and has since then been developed to include a Bayesian extension.[203,204] The basic idea behind the bootstrapping method is that a resample of the data can be used to simulate the variance in the actual sample without knowing the entire population. Estimating the mean weight in the global population can serve as an example of an application. As it is not feasible to weigh the entire global population, we could select a proportion of the population and measure their weight. From this sample we can construct the mean, but we need some idea of the variance of the mean we have computed. One could, of course, simply calculate the variance and standard deviation of weight in the current sample. Alternatively, one can use a simple bootstrap procedure. By randomly selecting observations from our sample (with replacement) we can construct multiple resamples (called bootstrap samples). For each of these bootstrap samples we then compute the mean. By presenting these means in a histogram we have estimates of the shape of the distribution of the sample mean which provides information about how much the mean varies across the samples. One key advantage with this method is its simplicity, and with the recent improvements in computing power analysts can easily construct 1,000 or 10,000 resamples used to derive estimates of standard errors and confidence intervals.

In paper III, the objective was to measure the standard error of the proportion of patients treated with anti-cancer treatment at time t (time before death). In this case, the probability of receiving anti-cancer treatment at time t will depend on the treatment in $t-1$. In other words, if one patient received anti-cancer treatment four weeks before death, we know that the same patient also received treatment within five weeks of death. To reproduce the dependence structure of the observed data in the resampled data blocks of consecutive data defined as each individual patient's treatment course (last year before death) were created. In total, 10,000 resamples of these individual treatment courses were constructed to compute the standard errors. By dividing the data in blocks the time series structure in the original data is preserved within each block of data. This type of bootstrapping is known as block bootstrapping.[205-207]

5.6 Survival analysis (paper II)

As described in section 4.3, the objective of a survival analysis is to evaluate the expected duration of time until one (or more) events happen. In paper II, survival analysis was used to model the probability of a patient surviving after a cancer diagnosis using data from the cancer registry. The survival analysis was conducted to identify how long patients spent in each treatment phase (initial, continuing, and terminal).

Paper II employed the Kaplan-Meier estimator to estimate gender and cancer specific survival curves using data on newly diagnosed patients between 1995 and 2015 (followed until the end of 2018) from the Cancer Registry of Norway (N = 560,265). Patients who emigrated during the observation period (0.3% of the sample) were censored at the time of emigration. Data from 1995 to 2015 were used to estimate long term survival. Expected remaining lifetime for patients diagnosed with cancer in 1995 was lower than for those diagnosed in 2010. From 1995 to 2010, the 5-year relative survival for cancer as a disease group increased from 55.5 percent to 61.5 percent. Changes in survival may lead to biased results (survival bias due to cohort effect in survival, see Figure 17). In paper II, two separate survival models were developed to investigate how changes in survival influence the total lifetime costs and the relative magnitude between costs in different treatment phases. The first model used data from 1995 to 2018, while the second used data from 2010 through 2018 to estimate the survival probability for the first 8 years after diagnosis. The two survival curves from all cancers combined and lung cancer are presented in Figure 24. The probability of survival was higher in the model that utilize updated data for the first eight years.

Figure 24: Survival analysis using 1995-2018 data and updated data (2010-2018) for the first eight years after diagnosis, for all cancers combined and lung cancer

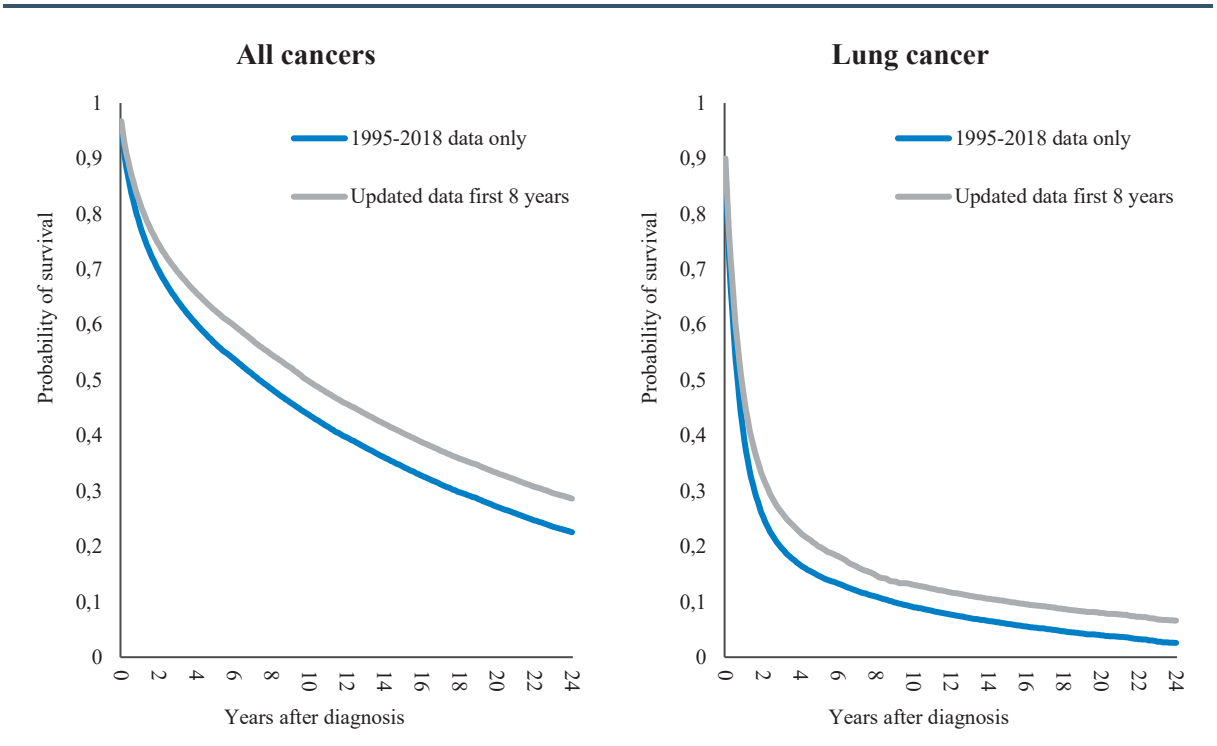
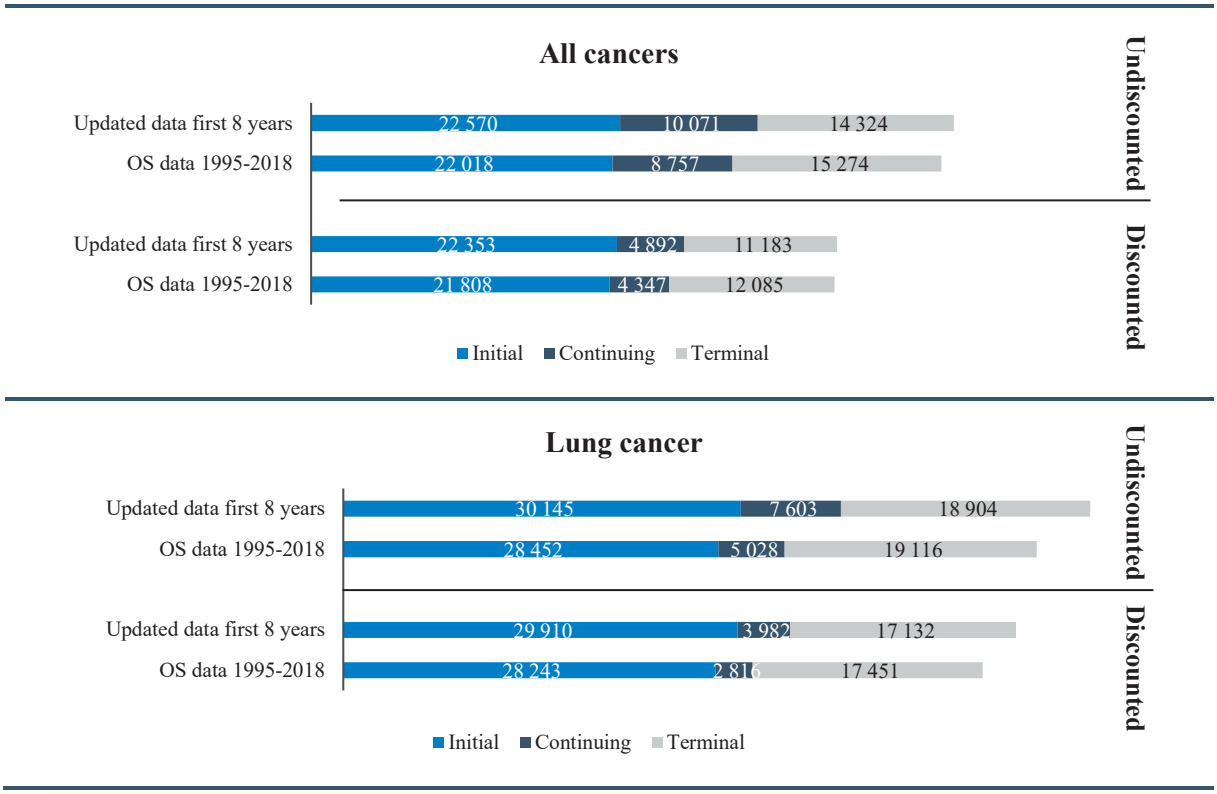


Figure adapted from paper II

Using the survival model with updated data increased the lifetime costs from 38,241 to 38,428 (+0.5%) for all cancers combined (Figure 25). Similarly, for lung cancer costs increased from 48,510 to 51,024 (+5.2%). Costs shifted from the terminal phase to the initial and continuing phase as survival increased.

Figure 25: Changes in direct medical costs per patient (EUR) of using updated survival data (2010-2018 for the first eight years after diagnosis) compared to using survival data from 1995-2018 for all cancers combined and lung cancer, 2017



OS = Overall survival. Figure adapted from paper II

5.7 Methodological challenges and limitations

Limitations were discussed in each individual paper. This section includes a brief discussion of the key methodological challenges and limitations in the four papers included in this thesis.

In spite of its many advantages, the use of registry data in research also carries important limitations. Since data are not collected by the researchers themselves, the data may miss important information, variables may be inaccurate or unfit for the study objective, or data may be less detailed than desired. Different registries sometimes use different coding of variables (classification of diagnosis, age groups etc.) which may present a challenge when combining different data sources. Physicians may also assign the diagnosis code they remember, not the code corresponding to the actual diagnosis, resulting in classification errors. The data quality of registries can be evaluated based on several measures, including (1) comparability; if coding and classification procedures adhere to agreed international guidelines, (2) completeness; to what extent are all relevant subjects included in the registry, (3) validity (accuracy); the degree to which all cases with a given characteristic truly have the supposed attribute, and (4) timeliness; the time from diagnosis to registration and the time from registration to reporting of annual reports.[208,209] Data quality for each registry used in papers I-IV was discussed in section 5.2.

A general methodological challenge in all papers is that none of the registries were linked. Working with unlinked data from several sources poses several challenges as we were not able to follow individuals across different registries. Some registries include complete information about diagnosis, while other lack such information. For example, while the patient registry and the prescription registry include information about diagnosis and costs, these sources do not have information about cancer stage. Working with unlinked data made it impossible to adjust the analyses for relevant clinical information at an individual level. Additionally, the databases with information on resource use and

costs in the nursing and care services and imaging and laboratory services lack information about patient diagnosis. Costs estimates for these categories are therefore imputed with a high degree of uncertainty.

Incomplete observations or missing data due to censoring may be a problem working with registry data. Censoring was discussed in chapter 4.3.1 and involves the condition when a value of a measurement or observation is partially unknown. There is possible information bias related to the quantity (number of patients) and unit costs used for costs estimation. Misclassification of diagnosis may lead to costs being over- or underestimated for either cancer as a disease group or for individual cancers. Several of the registries used have incomplete or incorrect information on diagnosis, and without linking data there is a risk of assigning the wrong cancer diagnosis to patients. Additionally, several proxies were used to estimate the economic costs (opportunity costs), including DRG-weights, reimbursement fees, and payments from societal security schemes. These proxies might not reflect the actual societal costs of the forgone resources, which contributes to uncertainty in the estimates.

There are also potential challenges with selection bias. First, when using the phase specific costing approach in paper II, information on the time of first cancer diagnosis is needed. The cancer registry holds information on the day of first diagnosis, but without linking these data to the patient registry the time of diagnosis cannot be assigned with absolute certainty. Second, in paper II there is potential selection bias due to cohort effects on survival outcomes. Survival was assumed to be equal for patients independent on what year they were diagnosed with cancer. Changes in treatment, diagnostic practice, or case mix over time may lead to biased results. Selection bias due to potential cohort effect in survival was investigated in sensitivity analyses (see chapter 5.6)

Problems related to confounding are relevant for papers III and IV. As discussed in the individual papers, information on several key covariates that may explain the observed relationship between the included covariates and dependent variables (odds of reviving anti-cancer treatment (paper III) or direct health care costs (paper IV)) were lacking.

As discussed above there may be possible systematic errors in the results (bias) which influence internal validity. However, as all papers are based on nationwide data covering the complete Norwegian population, potential sampling bias is avoided, which increases the internal validity. Additionally, Norway has a long tradition of collecting data about their citizens, and hospital and physician funding is based on the reported information (diagnosis, DRGs etc.), which also increases the internal validity. External validity (or generalizability) varies across the different papers. The magnitude of different costs categories and impact of including intangible and indirect costs in COI studies are likely to be relevant for countries with similar health care systems as Norway. Results from paper II indicate a relationship between direct health care costs and five-year relative survival, where cancers with intermediate five-year relative survival tend to have higher costs than those with very poor or very good prognosis. Even if treatment practice and unit costs vary between countries and jurisdictions, there is reason to believe that these findings are relevant to other countries as well.

5.8 Ethical considerations

The included papers in this thesis uses personally identifiable data from the Norwegian Patient Registry. This means that patient identities in theory can be identified through combinations of data items. The Norwegian Data Inspectorate (17/00565-2/CDG) and the Regional Committees for Medical and Health Research Ethics (2017/769/REK) granted approval for the use of data from the Norwegian Patient Registry. Data from other sources were at the time of extraction considered as deidentified data and did not require any approval by law.

Storage and handling of the data was done according to the guidelines from The Norwegian Data Inspectorate, the Regional Committees for Medical and Health Research Ethics, and the individual registries.

6. Results

This chapter provides a short summary of key results in papers I-IV. For a detailed description of the results see each individual paper.

6.1 Paper I

Direct health care costs related to diagnostics and treatment of cancer in Norway in 2017 was in paper I estimated to EUR 2,154 million (EUR 410 per capita), while the direct nonmedical costs (patient travel costs) amounted to EUR 58 million (EUR 11 per capita). The indirect costs totaled EUR 2,827 million (EUR 538 per capita) when costs commonly omitted from COIs were included as indirect costs. Of the total indirect costs, 70.6 percent was production losses due to morbidity and mortality, 10.8 percent informal care, 15.5 percent taxation costs, and 3.0 percent patient time costs. By including costs commonly omitted in COIs (informal care, patient time costs, and taxation costs) indirect costs increased from EUR 1,997 million to EUR 2,827 million (+41.5%). The fatal and non-fatal health loss (value of lost quality adjusted life years) amounted to EUR 18,000 million (EUR 3,420 per capita), of which EUR 15,800 million was the value of lost life years due to premature death (given a value of EUR 136,055 per QALY).

In 2017, health losses represented the greatest societal cost of cancer in Norway and accounted for 78 percent of the total societal costs related to cancer (Figure 26). The indirect costs (production losses) accounted for 12 percent, while direct health care costs represented 9 percent.

Figure 26: Overview of societal costs of cancer in Norway in 2017, million EUR

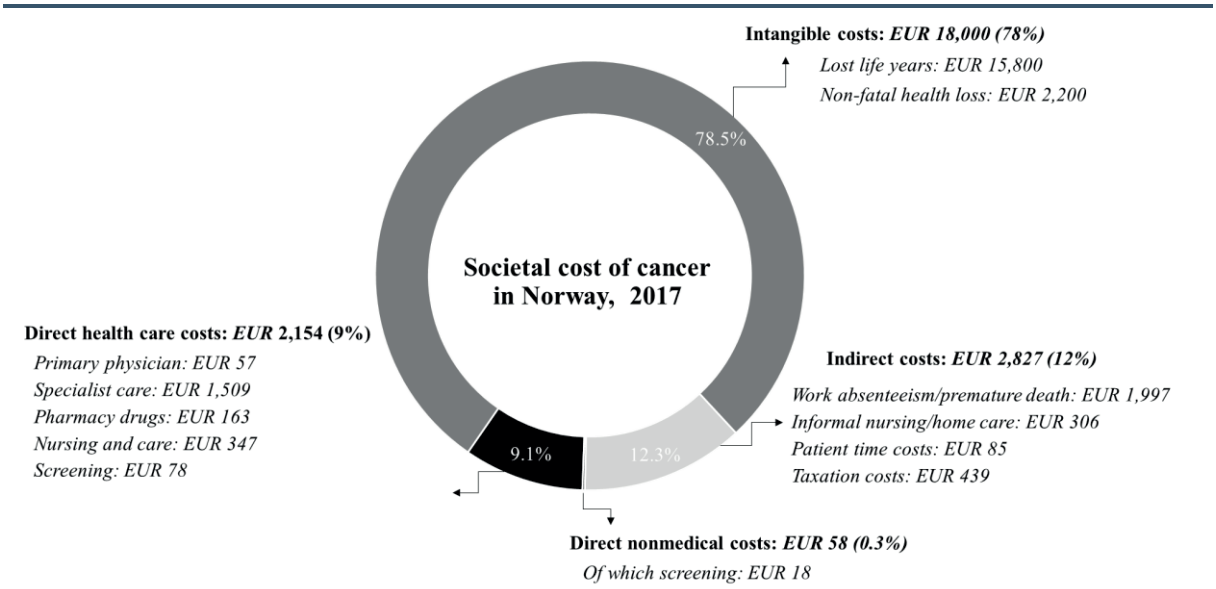
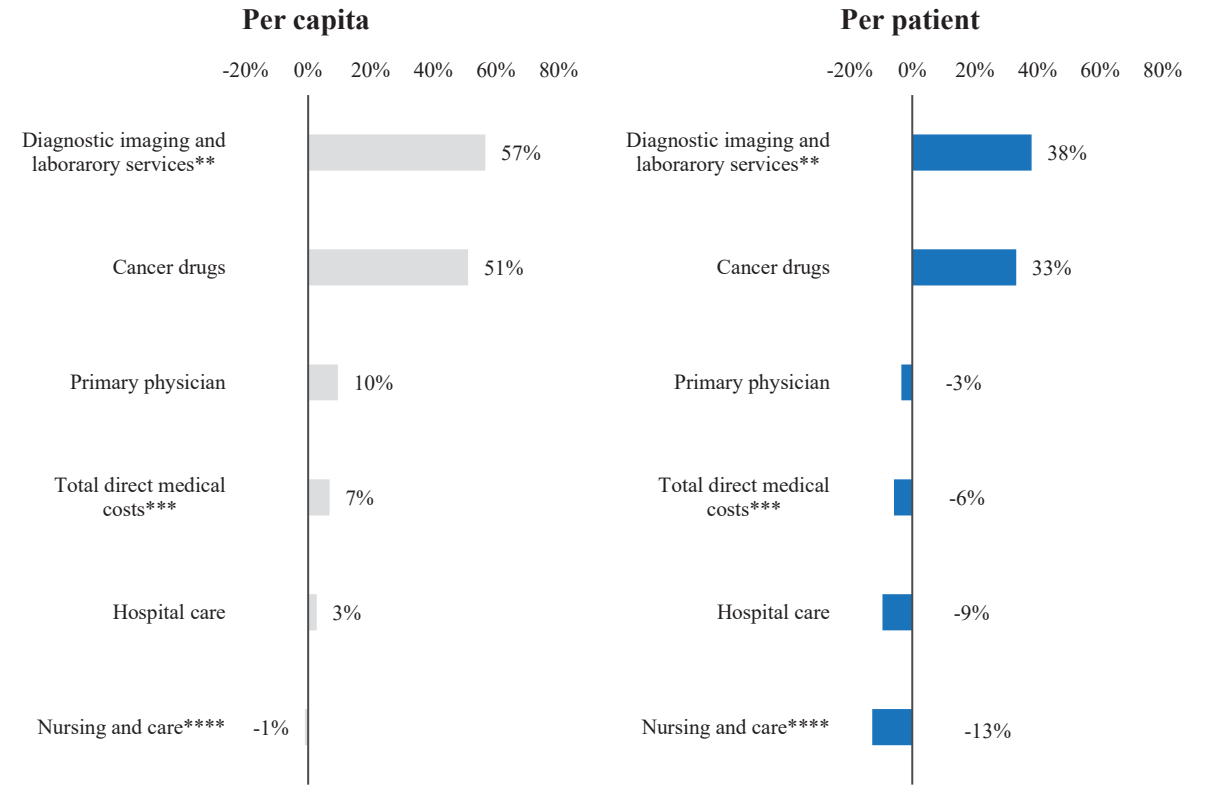


Figure adapted from paper I

Adjusted for inflation, the direct medical costs excluding screening increased by 11 percent during the period 2013-2017 (2.7% annually). The growth was highest for diagnostic imaging and laboratory services (57% per capita and 38% per patient) and cancer drugs (51% per capita and 33% per patient). The increase in costs associated with diagnostic imaging and laboratory services was partly due to increase of utilization, and partly to changes in the reimbursement fees. Per capita, the growth in direct medical costs excluding screening was 7 percent during 2013-2017. When adjusting the costs for the number of cancer patients, the costs decreased with 6 percent. Costs in somatic hospitals, which

accounted for 73 percent of the direct medical costs in 2017, increased with 3 percent per capita (-9% per patient).

Figure 27: Growth in direct medical costs per capita and per patient, 2013-2017*



***Per cancer patient alive 31.12. **Increase in costs partly due to changes in the reimbursement fees. ***Excluding costs related to screening programs. ****Growth based on the total costs of municipality provided nursing and care services. Proportion of cancer related costs are uncertain.**

6.2 Paper II

Monthly unit costs and lifetime costs per patient for 13 individual cancer sites were evaluated in paper II. For all 13 cancer sites, monthly costs per patient followed a U-shaped curve: costs decreased with time after diagnosis and increased as death approached (Table S1, S2, and S3 in paper II). Estimated lifetime costs varied widely across cancers, with multiple myeloma having the highest discounted cost (EUR 89,686) and melanoma of the skin the lowest (EUR 25,363) in 2017 (Table 1 in paper II). The proportion of costs by treatment phase also varied across individual cancers reflecting differences in survival and monthly unit costs. Cancers with a relatively poor prognosis typically had a high proportion of costs in the terminal care phase, while cancers with a good prognosis tended to have a higher proportion in the initial phase. 29 percent of the lifetime costs for multiple myeloma occurred in the continuing phase (compared to 11% for all cancers). Treatment of multiple myeloma involves use of expensive pharmaceutical, and patients are usually treated over a long period of time, which leads to higher costs in this phase.

The results from paper II suggest that there is an association between cancer related lifetime costs and 5-year relative survival for an individual cancer. Cancers with a 5-year relative survival of 50-70 percent (multiple myeloma, mouth/pharynx, and Non-Hodgkin lymphoma) were associated with higher lifetime costs than those with a very poor or very good prognosis. Patients with short life expectancy may not be alive long enough to consume many resources, while expensive treatment may be unnecessary for patients with a relatively good prognosis.

Figure 28: Association between lifetime direct medical costs and 5-year relative survival by cancer and gender

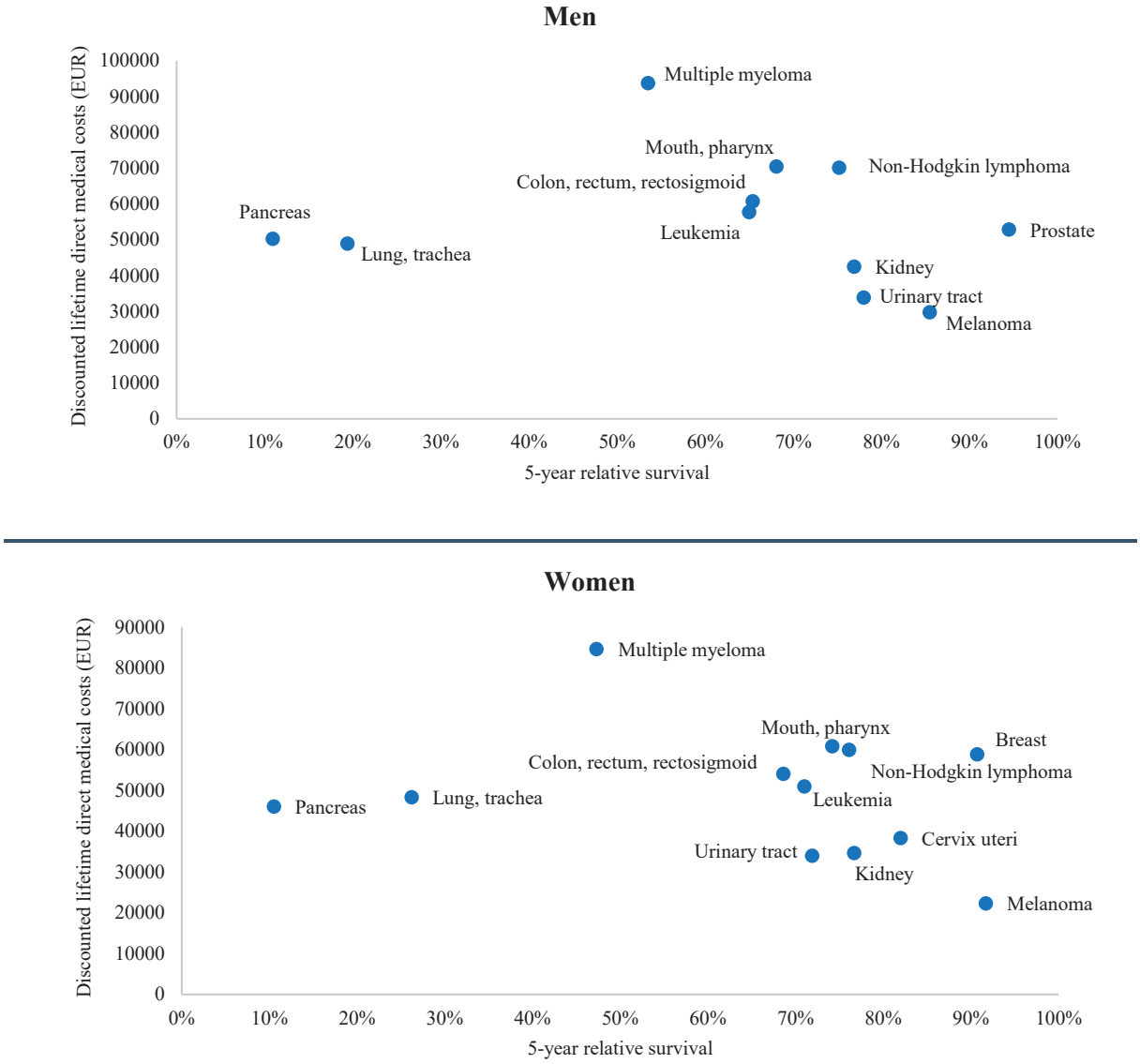


Figure adapted from paper II

6.3 Paper III

Factors that may influence the extent of which patients receive anti-cancer treatment end-of-life were discussed in paper III. Both supply and demand factors may influence end-of-life treatment decisions. Supply factors includes, among other things, department culture, training, experience, marketing, and payment and reimbursement schemes. Examples of demand factors are patient related factors such as age, gender and income, patient preferences, type of cancer, and tumor biology.

Among cancer decedents who received treatment in hospitals during the period 2013-2017 with at least one year follow-up (52,496), 12,604 (24.0%, CI: 23.4-24.6) received anti-cancer treatment during the last year of life. The proportion was highest for pancreatic cancer (60.7%, CI: 58.0-63.5), multiple myeloma (53.0%, CI: 50.2-55.8), and lung cancer (45.7%, CI:44.4-47.1), while kidney cancer (11.7%, CI:9.6-13.7), urinary tract (12.8%, CI:11.6-14.0), and leukemia (14.4%, CI:13.1-15.8) had the lowest

anti-cancer treatment rates during the last year of life (Figure 29). In total 1,691 patients (3.2%. CI: 3.0-3.5) received anti-cancer treatment within the last month of life during 2013-2017. Patients diagnosed with multiple myeloma (12.7%, CI: 10.9-14.5) or breast (6.5%, CI: 5.7-7.3), while urinary tract (1.1%, CI: 0.7-1.5) and kidney cancer (1.4%, CI: 0.7-2.0) were associated with low rates.

Figure 29: Proportion of cancer patients receiving pharmaceutical anti-cancer treatment during last year and month of by cancer type, 2013-2017

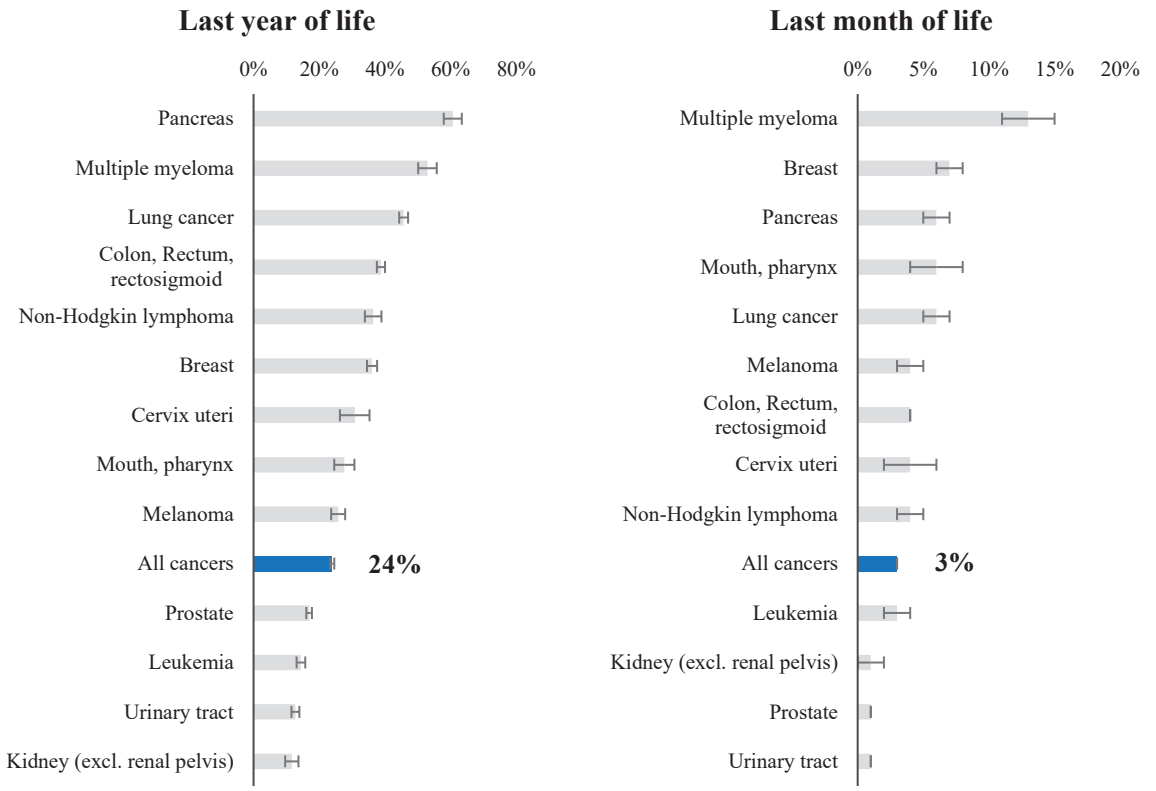


Figure adapted from paper III

Type of cancer was an important predictor for the odds of receiving anti-cancer treatment end-of-life. The odds ratio of patients receiving pharmaceutical anti-cancer treatment during the last month of life is presented in Figure 30. Compared to lung cancer, patients with multiple myeloma (OR = 3.03, CI: 2.48-3.72), breast (OR = 1.36, CI: 1.13-1.63), and pancreatic cancer (OR = 1.21, CI: 0.94-1.54) had higher odds of receiving treatment during the last month of life. Like the results presented in Figure 29 above, kidney (OR = 0.25, CI: 0.15-0.43) and urinary tract (OR = 0.38, CI:0.27-0.53) were associated with a lower probability of receiving treatment last month of life.

Figure 30: Odds ratio (OR) of patients receiving pharmaceutical anti-cancer treatment last month before death from logistic regression analysis in paper III, by cancer type

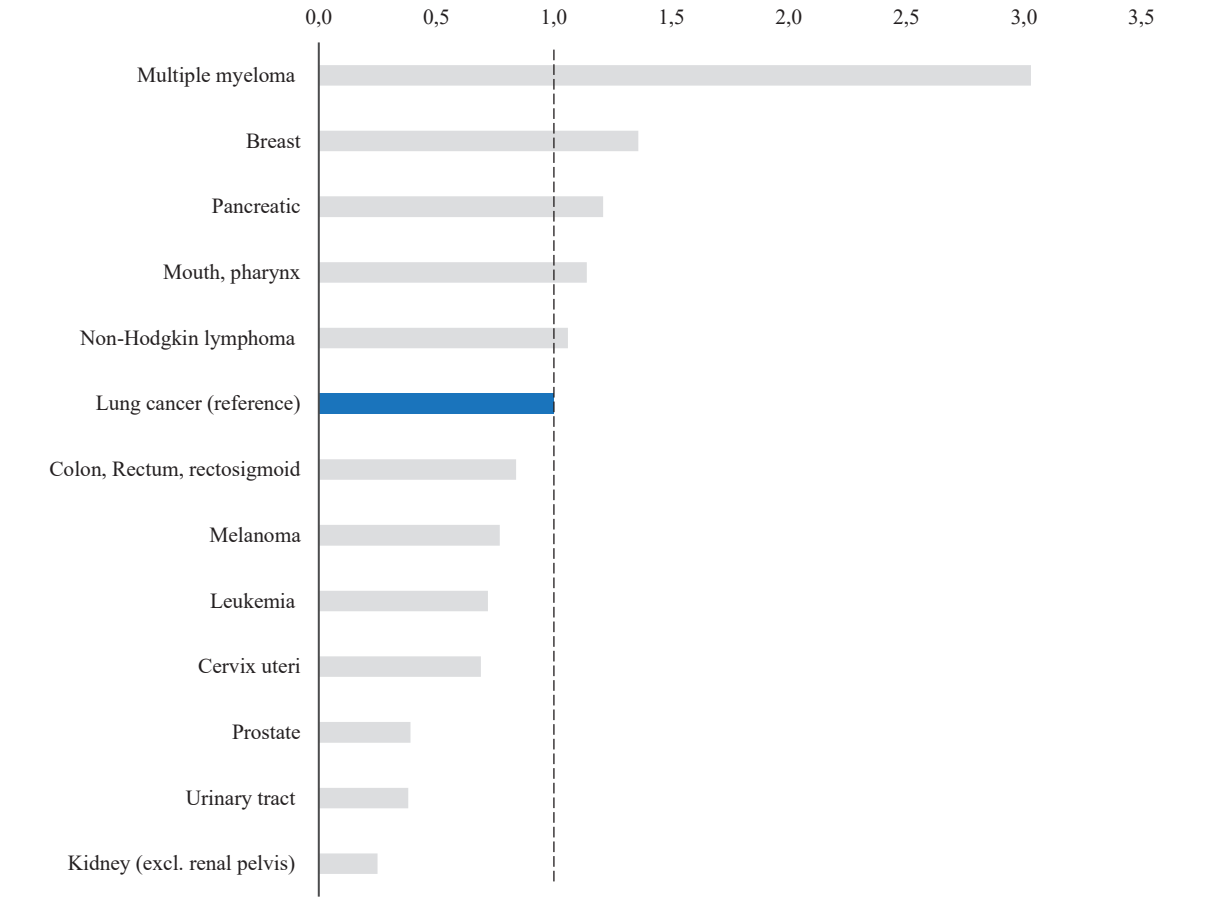


Figure adapted from paper III

6.4 Paper IV

The aim of paper IV was to investigate whether there is a gender difference in terms of cancer care and what the explanations might be. Both differences in resource utilization and direct medical costs last year of life were investigated using data from the Norwegian Patient Registry (NPR). Possible explanations of differences in direct medical costs were analyzed using generalized linear models (GLM).

Except for patients aged 0-69 years diagnosed with pancreatic cancer, lung cancer, or melanoma, women had fewer outpatient visits for all cancer sites (Figure 31). Women aged 0-69 years had more in-patient days for most cancers (all except moth/pharynx, kidney, and multiple myeloma), while those 70 years or older had fewer in-patient days last year of life (all except kidney and urinary tract).

Figure 31: Percentage difference in number of out-patient visits and number of in-patient days among men and women last year of life, by cancer site and age group

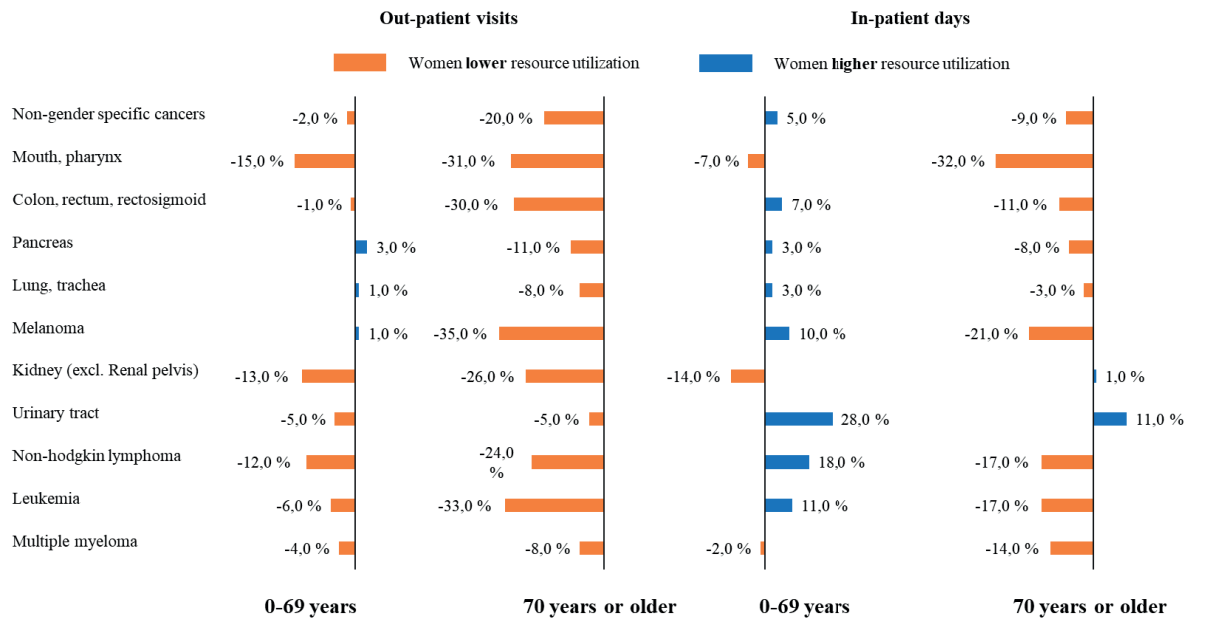
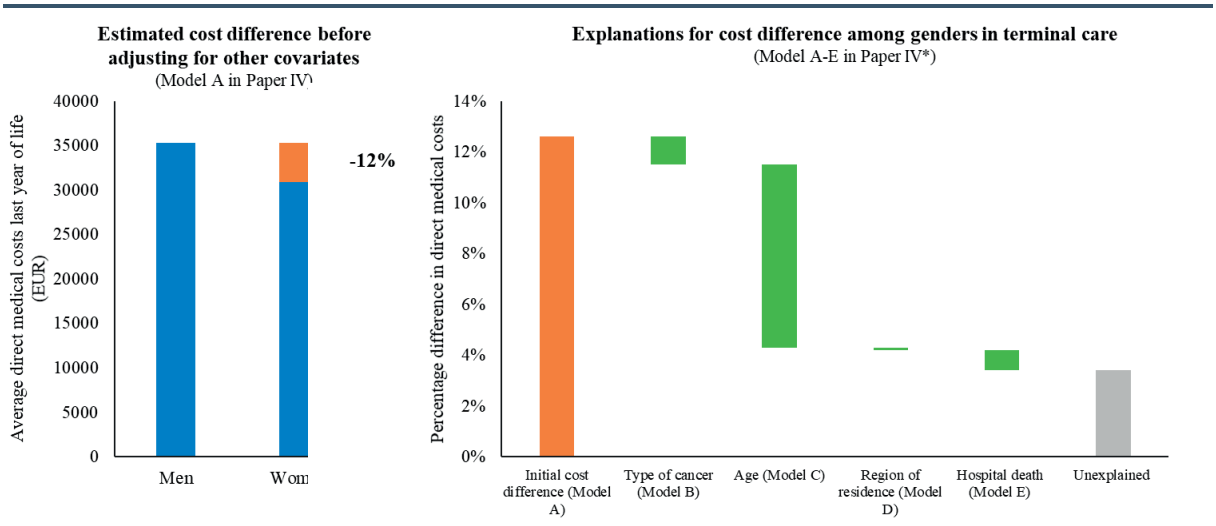


Figure adapted from Table 2 in paper IV

Generalized linear models (GLM) were fitted to the data in paper IV. In the simplest model, only adjusting costs for gender (Model A), the estimate difference in direct medical costs last year of life was 12%. Of this difference, 9 percent could be explained by differences in type of cancer (Model B), 57 percent of differences in age (Model C), 1 percent of differences in region of residence (Model D), and 6 percent of place of death (Model E) (Figure 32). 27 percent of the cost difference (a differences of 4%) was unexplained.

Figure 32: Differences in direct medical costs last year of life before and after adjusting for included covariates



*** Model F (anti-cancer treatment last month) and Model G (proportion with distant metastasis at diagnosis) did not explain any of the differences in costs among genders. Figure adapted from Table 3 in paper IV.**

7. Discussion

The registry-based studies presented in this thesis fill an important knowledge gap related to resource utilization and costs of cancer in Norway. The results highlight important issues in priority setting and how real world evidence can be used to inform decision makers and provide a better basis for decisions in favor of patients, their family, and society in general. The results, methodological challenges, and limitations were discussed in each individual paper and in chapters 5 and 6 of this thesis presentation. This final discussion adopts a broader perspective and explores some important cross-cutting topics related to the papers included in the thesis.

7.1 The value of real world evidence in priority setting and planning

The four papers provide examples of how real world evidence can be used in research and analysis to support decision making in health care. Choices made at different levels in health care involve, at least to some degree, imperfect or unknown information, that is, information that needs to be surmised or deduced based on existing knowledge of the patient and their condition. By reducing the uncertainty in these decisions, we may achieve better outcomes for the benefit of patients and their families, clinicians, and society in general. The use of already collected administrative data is one of several ways of limiting the uncertainty. However, working with such data raises several important questions: How can routinely collected data be used to provide value to society that exceeds the costs of collecting these data and the potential harm of using them?; Can real world evidence be used as an alternative when evidence from randomized clinical trials are insufficient?; What are the main opportunities and challenges going forward? The following discussion aims to shed light on some of these questions.

Calls for better quality in health care, access to new therapies and treatment methods, and more patient-oriented services have never been louder. A digital transformation in health care has long been underway and the role of registries has never been more significant. The number of registries has grown as the health care sector has become more digitized, and increased computer power allows us to analyze large amount of data within few seconds, and to conduct complicated statistical analyses. Increased use of registry data has driven constant improvement of data and procedure quality.[210] Norway has several national health registries covering the entire population, as well as quality registries for specific diseases. These data may provide health care professionals, researchers, analysts, and decision makers with first-hand information about patients with a certain condition, both for individual patients, subgroups, or the entire population. Data can be used to describe the current patient population and treatment, or to track trends over time. As argued by Jansen-van der Weide and coworkers, registries are especially useful to improve the efficiency and quality of clinical trial designed for rare diseases.[211] One key advantage of using registry data is that registries can provide better understanding of who the patients are and how they are treated in a real world setting at a national or local level.[212,213] Information from international RCTs yields valuable knowledge, but this evidence needs to be supplemented with real world evidence to yield a more comprehensive understanding of a treatment or a disease in a local setting. Understanding treatment practice is a prerequisite for improving quality of care and to continually develop services. For example, such information is a key input in simulation models used to evaluate the cost-effectiveness for new pharmaceuticals.[214] Further, registry data enable us to study risk factors and outcomes (for example risk factors for infection after knee arthroplasty as studied by Jämsen and coworkers using data from the Finnish Arthroplasty Register[215]). By tracking patients over time, we can identify risk factors associated with different diseases, which again can be used to improve policy and give advice on behavior. By studying how patients respond to various treatments, we can gain knowledge of the comparative effectiveness in a real world setting.[216] The changes towards more specialized treatment and personalized medicine are forcing us to rethink how treatment effects of new technologies are

documented and evaluated. The introduction of advanced therapies targeting small patient groups may serve as one example. The traditional way of thinking around evidence using comprehensive clinical trials may not be feasible for small patient populations, and ethical issues may make it impossible to compare interventions with a control group over a long period of time. Here, real world evidence can be used to inform models trying to extrapolate outcomes (e.g., survival) or to follow patients over time after a treatment is approved in order to evaluate effectiveness (see for example paper by Moen, Svensson & Steen Carlsson (2017)[217] on how to assess the value of cancer treatments from real world data). Pay for performance schemes (or risk sharing schemes) have been proposed as a solution to ensure early access to advanced therapies where the health benefits are uncertain, and the provider and manufacturer disagree on the price.[218] Examples of such schemes are price-volume agreements, outcome based agreements, or temporary approval conditional on more data being collected.[219] Benefits may include earlier access to new therapies and a paying price closer to the value of the treatment.[220] However, there are associated administrative costs, and there is no consensus on the welfare consequences and the social desirability of such schemes.[220] Real world evidence can also be used for regulatory purposes in evaluation of new methods. For example, the FDA have accepted single group trials with external controls in evaluation of medical devices.[221] A final application of registry data is to evaluate differences in care or resources utilization across groups to ensure equity in health care. Our study on gender differences in end-of-life cancer treatment (Paper IV) serve as one example of such use. Using recorded information on patient age, gender, social status, or region of residence, researchers can investigate subgroups of the population and geographic variation with regards to outcomes or access to treatment.[222,223] Such studies can be used by decision makers to identify areas where improvements must be made to promote equity and quality in health and health care services.

In addition to having several applications, one key advantage of using registry data is that the data are already collected and costs of using the data are limited compared to a situation where we need to collect new evidence.[224] However, the fact that the data are already collected also poses an important limitation of its use. For many registries, data are collected for administrative purposes and the content is not necessarily prepared in a way that is optimal for the questions the analysts want to answer.[225] Additionally, changes in the way data are reported into the registry, or how variables are defined over time, may cause problems when analyzing routinely collected registry data. These challenges, however, are not the most pressing matter in Norway. The complex bureaucracy related to data access and data extraction timelines is one of the main challenges.[163] Some projects are never started because the process of accessing the data is too time consuming. This is especially the case for projects that require linking of different data sources, where limited capacity at several registries delays the process. First, access to registry data in Norway requires an ethical approval and an assessment of privacy considerations according to the general data protection regulation (GDPR). For a project to receive an ethical approval, the potential benefits of the project must exceed the potential costs. Harm may be inflicted on individuals if sensitive personal information is disclosed, or if data are used unethically (e.g., used to evaluate eligibility for insurance coverages). Although measures are implemented to avoid data breaches, there will always be a risk that data end up in the wrong hands. Researchers must therefore justify that the potential benefit to society of their project exceeds the potential costs of them getting access to the data without consent from the patients. The ethical assessment contributes to perhaps the biggest challenge with using registry data in Norway, namely the timeline for the data extraction process. In addition to the ethical approval, researchers must apply to each individual registry individually. The processing time at some Norwegian registries may exceed one year when linking several registries. In recent years, efforts have been made to reduce delivery times, and the health authorities have developed a common platform to apply for access to data.[226] Nevertheless, processing times are considerable, and far more projects could have benefited from access to registry data if waiting times were shorter. An additional concern are the recent signals from the government that researchers will have to pay even more to access these data in the future.

Several times in recent years, Norwegian health data have been highlighted as an important resource for the post-oil future of the Norwegian economy (the "new oil").[227] There seems to be full agreement that the value of these data is significant, but at the same time access is currently perceived as limited. Developing more well-functioning processes to ensure rapid access to health care data in Norway will contribute to researchers being able to utilize the value that lies in the data already collected in a greater extent than what we do today. The new platform for access to data[226] is expected to take several years to be completed and well-functioning. In the meantime, there are several solutions that should be considered. Research institutions could be granted access to data without going through the entire application process as a part of a licensing agreement. A solution where analysts can analyze individual patient level data without seeing the individual patient identifying information are also feasible. Statistics Norway already has a solution like this, however, today it does not include information on diagnosis which makes it far less valuable in health care research. The fact that Norway has detailed data covering all inhabitants and the opportunity to link different registries using individual social security numbers is an important competitive advantage in research and management of health care. A final pressing matter involves data on areas in the health care sector where the information is limited today. Accounting for approximately 30 percent of the health care budget, it is surprising that we know so little about patients in municipality-provided nursing and care services. While pharmaceuticals are subject to strict priority setting with economic evaluation and price negotiations, many new technologies and measures in the municipality-provided services are implemented without any form for analysis of costs and benefits. To enable these methods to be critically reviewed before approval, data on this part of the health care service is needed.

7.2 Indirect costs in priority setting

The direct health care costs are observable in the cost accounts of health care systems and may explain why they usually get more attention than the other costs categories. Only a proportion of the production loss can be identified in public accounts (through sickness payments and disability pensions in countries with public schemes), while costs of informal care and patients' loss of time potentially affect the national budget indirectly (through lower taxes). This does not mean that the indirect costs are not real economic costs and the magnitude of these can potentially be relevant for policymakers and other stakeholders in their effort to ensure sustainable financing of future health care services.

It is generally agreed that economic evaluation plays an important part in priority setting in health care, but there is no universal agreement on whether indirect costs should be included in cost-effectiveness analysis that are the basis for priority setting. The nature of the events and resource usage that can be classified as indirect costs is also debated.[189] In this discussion indirect costs are considered as the production losses related to a disease or illness. An important choice in priority setting in health care is whether priorities should be made based on a healthcare perspective or a broad societal perspective.[9] If the latter is the case, indirect costs, and benefits (e.g., production gains and losses) should be considered in the analyses. In practice, this means that the benefits of getting sick people back to work, reducing burden on family members (informal care), or reducing patient time costs, should be included when benefits of new technologies are estimated. Here cost-of-illness (COI) analyses with a broad cost perspective will be valuable in identifying relevant costs. Including indirect costs in the analyses may be intuitively appealing, but it also introduces important practical and ethical considerations.

The Second Panel on Cost-Effectiveness in Health and Medicine recommends that a reference case from a societal perspective should be included in economic evaluations.[8] However, a review of the literature from 1976 to 2005 shows that less than one third of the analyses adopted a societal perspective.[228] Even in studies where analysts claim to adopt a societal perspective, potentially important cost elements outside the health care sector are often omitted.[228-230] Additionally, several

national guidelines for priority setting, including the Norwegian guidelines, recommend a more narrow health care perspective.[13] There are at least three concerns with including indirect costs in cost-effectiveness analysis. The first deals with equity considerations. Including indirect costs would implicitly mean priority for individuals in working age.[231] It would imply that younger individuals with potential work capacity would be given priority over older individuals. It may also mean that men are given priority over women, or that immigrants get less priority than ethnic Norwegians. However, this concern can be met by introduction standard wage rates that are independent of factors like gender and ethnicity, similar to the current guidelines for cost-benefit analysis outside the health care sector in Norway.[128] The second concern is technical and deals with challenges of estimating such costs and risk of double counting. The human capital approach has been criticized for overestimating the production losses, as sick individuals can be replaced by the unemployed.[140,141] Including productivity gains may also lead to double counting if the value of improved health used in the analysis already includes the value of increased productivity.[9] The third concern deals with relevance and was first introduced by Gerard and Mooney (1993).[232] They argued that as long as benefits are measured in terms of health gains (e.g., QALYs), the opportunity costs must be defined in terms of health forgone. It then follows that the opportunity cost is determined by the best alternative use of a small increase in the health care budget, not elsewhere in the economy.

The covid-19 pandemic and the restrictions introduced to prevent transmission of the SARS-CoV-2 virus have, in a dramatic way, demonstrated the impact of health losses on the national and global economies. The current health crisis has demonstrated that we have a high willingness to pay for health interventions saving lives and supporting the national and global economy, and that costs outside the health care sector are deemed as relevant in the public debate and in decision making. As noted in paper I, these costs represent a high proportion of the cost of illness. Curing a person who subsequently returns to productive work, or saving a productive person's life, involves benefits to society beyond health gains. It has been argued that since a proportion of the production gain of health care interventions are returned to the society through the tax system, these gains may be relevant in cost-effectiveness analyses and priority setting.[233] Increased taxes (or lower welfare payments) can be used to increase the health care budget to "produce more health". Cervical cancer may serve as an example. Here, work absenteeism costs are high (EUR 73,658 per new case in Norway) and the potential benefits to society outside the health care sector of preventing, or curing cervical cancer are substantial. Migraines may serve as another example, where the production losses are substantial because it affects many people in working age and reduces their ability to be productive.[234] Including indirect cost in cost-effectiveness analyses will for many interventions have a practical implication, and the incremental cost-effectiveness ratio (ICER) may increase or decrease depending on the intervention.[231] In an evaluation of the effect of including indirect costs in cost-effectiveness analyses, Krol and co-workers found that the ICER increased in six and decreased in 30 of the 36 cases they investigated.[231] In six of the cases, the ICER changed from positive to negative (i.e., new treatment became cost-saving). However, although including indirect costs will influence the ICER, it does not mean that more (or less) interventions or methods will be introduced or deemed as cost-effective. In fact, given a fixed budget, including indirect costs in cost-effectiveness analyses will only change the order in which interventions are prioritized. Ultimately, the result will be that interventions that increase people's ability to be productive (typically interventions aimed at people of working age) will get higher priority, at the expense of other interventions.

Economic evaluations are supposed to aid decision makers and, in order to do that, they need to be tailored in a way that make them relevant. There are both advantages and disadvantages to including indirect costs in economic evaluations, and it should be up to decision makers to evaluate whether consequences outside the health care sector are deemed relevant. Decision makers are usually given responsibility only for a specific goal and a budget to maximize that goal.[235] By providing results both based on a health care perspective and a broader societal perspective, economic evaluations can aid decision makers depending on the goal of interest. Whether that is to maximize health, or to maximize

the total welfare in a society. In some cases, decision makers might be forced to take a broader perspective simply because they do not have the luxury of ignoring costs outside the sector of interest. The covid-19 pandemic may serve as an example, where infection control measures have been implemented not entirely based on health gains. By providing a clear and disaggregated overview of costs and effects, decision makers will be able to evaluate which costs and effects should be considered. However, if all effects are reported separately it may place a burden on decision makers, making the analyses less valuable.[236] A way to make it easier would be to present results (such as cost-effectiveness ratios) both in a narrow health care perspective and in a broader societal perspective.

7.3 When to discontinue end-of-life treatment?

Formal health care services have become an important part of end-of-life care in the Nordic countries and the region has a significantly higher use of formal long-term care than countries in the south of Europe.[237] As reported in paper IV, 36 percent of cancer patients died in hospitals in Norway during 2013-2018, while 50 percent died in other health care institutions. The shift of end-of-life care from family-based care to institutions where the main focus has been on curing patients has raised several challenges, including the challenge of when to stop active treatment and prioritize palliative care.

Advances in modern medicine make it easy to forget the inevitable, that in some cases disease progression and death will occur despite aggressive medical management. The advances in technology have increased the number of treatment choices patients face when reaching the final months of life. The result may be that patients continue treatment longer than what is optimal from a patient perspective. As reported in paper III, three percent of Norwegian cancer patients receive anti-cancer treatment during their final month of life. Patients receiving potentially life-prolonging treatment near the end of life is an issue not only in the context of cancer, but also cardiovascular disease where several patients receive cholesterol lowering therapies when they are in their final stage of life.[238]

An obvious starting point when making decisions on end-of-life care is to ask the patient what he or she wants. Discussions between patients, families, and physicians about treatment options, risk, chance of success, and quality of life during and after treatment are not always held and patient preferences are often unknown.[239] Benefits and disbenefits need to be balanced against each other when deciding on whether to initiate, continue, or stop treatment when death approaches. The benefits include measurable variables such as increased life expectancy and quality of life, but also gains associated with hope, faith, and the value of not giving up. The prognosis for a patient with a life-threatening disease, and the potential benefits of treatment, should be estimated according to the best available data. However, these decisions involve uncertainty, and a physician can never be certain about an individual patient's expected remaining lifetime.[240] If the goal is to maximize number of life years it will be optimal to treat a proportion of patients within their final weeks because some patients are expected to survive and benefit from the treatment. In fact, the greater the uncertainty associated with the patient's life expectancy is, the higher the optimal proportion of patients being treated will be. On the other hand, if no uncertainty was involved, and the physician had complete knowledge about expected remaining lifetime and potential benefits, no patients should undergo aggressive treatment close to death.

When making decisions related to end-of-life care, the expected benefits must be seen in context of expected costs. First, treatment may place an additional burden on patients related to adverse events. Medical treatment is often associated with adverse events which may influence patients and their families to engage in meaningful life activities or to prepare for death.[241] Too much aggressive treatment near the end-of-life may also result in reduced life expectancy and quality of life.[51,242,243] Finally, active treatment means use of scarce health care resources, and the challenge is whether to offer this treatment as a part of end-of-life care or to offer it to treat other patients who may benefit from extended life expectancy.

The optimal level of treatment will depend on several factors. Type of disease, available treatment options, uncertainty related to prognosis, and treatment characteristics are all presumably important factors. Patient characteristics such as age and gender will also influence the optimal level of treatment near end-of-life. For patient groups where adverse events are less common, or groups that respond particularly well to treatment, a higher proportion of patients should be treated during their final weeks. However, the optimal time to stop treatment is not only decided by the expected costs and benefits of the treatment. Optimal end-of-life care should start with an honest discussion of disease progression, prognosis, and consequences of treatment between physicians and patients and their family. Patient preferences are vital when deciding on treatment at end-of-life[244] and may explain observed differences in treatment decisions in end-of-life care. One way of supporting the work towards better end-of-life care is to increase awareness about treatment practice today and factors influencing current practice, as done in Paper III.

7.4 Future research

The findings presented in this thesis and the discussion above highlight several areas for future research. Increased knowledge on cancer costs and resource utilization in cancer care may provide better basis for decisions, support health care planning, and improve treatment practice for the benefit of patients. Here, Norwegian (and Nordic) health care registries should be utilized in future research. Three areas seem particularly relevant: to evaluate cancer costs and resource utilization using linked data, to analyzes of changes in cancer costs over time and across countries, and to investigate possible differences in cancer related lifetime costs between genders.

A first step would be to perform several of the analyses presented in papers I-IV using linked data. This will resolve many of the limitations discussed in the four papers, including missing information on cancer stage, cancer diagnosis, and other covariates. Specifically, better estimates of costs in nursing and care services are needed. While introduction of new cancer drugs is subject to strict priority setting, new technologies in municipality-provided care services in Norway are implemented with few or no forms of economic evaluation. Representing approximately 30 percent of the total health care expenditures in Norway[39], nursing and care services should be subject to at least some form of economic analyses. Understanding time trends, variability in care, and key cost drives in this area will be important to improve quality of care. While retrospective studies using registry data can be performed to better understand costs and resource use in the formal nursing and care sector in Norway, new data on informal care must be collected through surveys or interviews. Methods to measure and value informal care have been proposed[245,246], and the importance of measuring the cost and effects of these services has previously been argued.[247]

A second area for future research is to better understand changes in cancer costs over time. Changes in funding responsibilities, reimbursement fees, and reporting of public statistics implies that time trends should be interpreted with caution, however understanding past trends will be important for planning of future care. Comparative analyses of changes in costs across countries will be particularly useful. Future research should aim at exploring how different cancer related cost categories develop over time, identifying key cost drivers, and understanding how costs are expected to change in the future to assist long term planning of cancer care. The increase in cancer drug costs receives much attention in the public debate in Norway. However, drug costs represent a limited proportion of the total health care costs (10% in 2017, see paper I) and there is need for research to understand changes in other important cost categories over time.

Due to lack of information on cancer stage at diagnosis in the Norwegian Patient Registry, the analyses of gender disparities in cancer care in paper IV was restricted to the terminal phase. Researchers should investigate the differences in cost between genders in the initial phase, and how survival and prognosis may influence resource use. In Norway, this will require researchers to link the patient registry and the cancer registry as it will be necessary to adjust cost estimates for cancer stage

at diagnosis. Whether the differences in cancer costs can be explained by observable factors such as cancer stage, age, type of cancer etc. are still unknown, and this will be important to understand before measures are implemented to even out the differences in care.

Several of the above research topics will require linked data. To facilitate this research there is need for accelerated access to linked registry data in Norway. Each year Norway collects a range of health care data for administrative purposes that have great value in research for the benefit of patients and society in general. As discussed earlier, there are several possibilities to ensure access to registry data for research purposes in a cost-efficient way without compromising privacy considerations. While developing a long-term solution for access to health care data, the Norwegian government should explore possibilities to ensure safe and quick access in the short term.

8. Conclusions

Randomized controlled trials (RCTs) have long been the gold standard for answering questions regarding effectiveness in medicine. However, these methods should be supplemented by real world evidence to describe current treatment practice, resource use, and costs.

In priority setting, both costs and effects must be evaluated to ensure optimal resource allocation. Real world evidence, and especially registry data, can play an important part in providing knowledge on treatment practice and costs to support optimal resource allocation and budget planning in a local setting. Such data can also be used to describe variation in resource utilization across hospitals, jurisdictions, or patient populations, and thus stimulate quality improvement initiatives.

As long as privacy considerations are preserved through legislation, costs of utilizing already collected data are minimal. The introduction of new technologies with limited evidence forces us to combine information from several sources to support decisions, and registry data is an important source of information that needs to be utilized. One of the key challenges concerning registry data in Norway is data access, and especially the timelines related to access. Better processes for data access will results in a better basis for decisions and ultimately better patient care.

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10. Appendix

Table 2: Descriptive statistics of registry data from CRN, KUHR, NPR, and NorPD

	Complete sample		Most recent year	
The Cancer Registry of Norway (CRN)	**1953-2015**		**2015**	
	Males	*Females*	*Males*	*Females*
Number of patients	574,494	532,594	18,307	15,978
Age	*Males*	*Females*	*Males*	*Females*
Median age (years)	70	67	69	68
Mean age (years)	67.4	65.2	68.3	66.7
% < 70 years	50.1	44.4	49.5	45.7
Cancer stage at diagnosis	*Males*	*Females*	*Males*	*Females*
Localized (%)	42.3	41.0	43.6	45.2
Regional (%)	16.6	20.6	21.4	20.5
Distant (%)	20.5	18.7	11.7	13.6
Unknown/not applicable (%)	20.6	19.7	23.3	20.8
Cancer diagnosis (number of patients)	*Males*	*Females*	*Males*	*Females*
Mouth, pharynx (C00-14)	15,716	7,102	421	236
Colon, Rectum, rectosigmoid (C18-20)	73,411	74,118	2,287	2,226
Pancreas (C25)	16,449	15,458	435	441
Lung, trachea (C33-34)	60,610	30,539	1,653	1,543
Melanoma (C43)	22,194	24,356	1,119	1,075
Breast (C50)	795	121,899	24	3,705
Cervix uteri (C53 + D05)	-	22,119	-	386
Prostate (C61)	134,510	-	5,138	-
Kidney (excl. renal pelvis) (C64)	15,975	9,972	604	317
Urinary tract (C65-68)	41,224	15,309	1,359	499
Non-Hodgkin lymphoma (C82-86, C96)	16,025	13,521	606	456
Leukemia (C91-95, D45-47)	18,039	14,318	633	535
Multiple myeloma (C90)	8,913	7,383	248	198
Residual group (other cancers)	150,633	176,500	3,780	4,361
The primary care database (KUHR)	**2012-2017**		**2017**	
Number of patients				
Males	177,557		73,640	
Females	195,424		74,396	
Number of episodes				
Primary physician	3,492,003		620,724	
Emergency room	62,229		9,748	
Private practicing specialist	475,575		80,654	
Type of episode				
Consultation with attendance	2,974,344		483,226	
Telephone consultation	833,842		187,869	
No contact service (lab tests etc.)	221,621		40,031	
The Norwegian Patient Registry (NPR)	**2008-2017**		**2017**	
Number of patients				
Male	212,112		66,957	
Female	234,875		72,042	
Age distribution (%)				
0-9	0.4		0.4	
10-19	0.6		0.7	
20-29	3.3		2.6	
30-39	5.4		4.2	
40-49	7.7		7.3	
50-59	13.2		13.5	
60-69	23.9		24.5	
70-79	24.2		29.2	
80-89	17.5		14.8	
90-99	3.9		2.8	
>99	0.0		0.0	
Number of episodes				
Outpatient	6,774,472		829,142	
Inpatient	976,232		96,498	
Daycare	255,580		27,847	
Hospital affiliation (reginal health authority) (% of patients)				
South-Eastern	55.0		55.5	

Western	21.2	20.2
Central	8.5	8.9
Northern	9.1	9.0
Unknown	6.2	6.5
Number of patients by cancer diagnosis		
All cancers (C00-97 + D00-09 + D37-48)	446,987	138,999
Mouth, pharynx (C00-14)	6,332	1,916
Colon, Rectum, rectosigmoid (C18-20)	39,855	10,361
Pancreas (C25)	7,431	1,506
Lung, trachea (C33-34)	28,823	7,176
Melanoma (C43)	18,657	4,611
Breast (C50)	43,041	19,928
Cervix uteri (C53 + D05)	7,640	2,588
Prostate (C61)	56,197	18,131
Kidney (excl. renal pelvis) (C64)	8,157	2,651
Urinary tract (C65-68)	19,278	8,071
Lymphoid/haematopoietic tissue (C82-86, C91-96, D45-47)	34,103	14,822
The Norwegian Prescription Registry (NorPD)	**2009-2016**	**2016**
Number of patients		
Males	119,475	56,210
Females	138,804	79,656
Number of drug deliveries (prescriptions)	15,939,788	2,016,909

Table 3: Diagnosis codes used for inclusion of patients in paper I

	ICD-10 codes	ICPC-2 codes
All cancers	C00-99, D00-09, D37-48	A79, B72, B73, B74, D74, D75, D76, D77, L71, N74, R84, R85, S77, T71, U75, U76, U77, W72, X75, X76, X77, Y77, Y78 or Y79
Mouth, pharynx	C00-14	D77*, R85*
Colon, Rectum, rectosigmoid	C18-20	D75
Pancreas	C25	D76
Lung, trachea	C33-34	R84
Melanoma	C43	S77*
Breast	C50	X76
Cervix uteri	C53, D05	X75
Prostate	C61	Y77
Kidney (excl. renal pelvis)	C64	U75
Urinary tract	C65-68	U76 + U77
Lymphoid/haematopoietic tissue	C82-86, C91-96, D45-47	B72* + B73 + B74

***Only a proportion of the patients were included in the analyses (based on data from CRN)**

Table 4: Diagnosis codes used for inclusion of patients in papers II-IV

	ICD-10 codes
All cancers	C00-97 + D00-09 + D37-48
Mouth, pharynx	C00-14
Colon, Rectum, rectosigmoid	C18-20
Pancreas	C25
Lung, trachea	C33-34
Melanoma	C43
Breast	C50
Cervix uteri	C53 + D05
Prostate	C61
Kidney (excl. renal pelvis)	C64
Urinary tract	C65-68

Non-Hodgkin lymphoma	C82-86, C96
Leukemia	C91-C95, D45-D47
Multiple myeloma	C90

Table 5: Effects of including episodes with cancer as primary and secondary diagnosis compared to primary diagnosis only on number of episodes and patient related costs, for all cancers and by cancer site, 2013-2017

	Episodes with cancer as primary or secondary diagnosis					**Episodes with cancer as primary diagnosis only***				
	Number of episodes (thousands)									
Cancer site	2013	2014	2015	2016	2017	2013	2014	2015	2016	2017
All cancers	828	858	896	904	953	752	785	822	818	851
Mouth, pharynx	19	23	24	21	23	17	22	23	20	21
Colon, Rectum, rectosigmoid	84	86	88	89	92	78	80	81	80	80
Pancreas	15	16	17	16	18	13	15	15	15	16
Lung, trachea	64	69	69	70	72	59	63	64	64	65
Melanoma	17	19	20	20	23	15	17	18	18	19
Breast	156	162	171	164	178	147	154	161	151	161
Cervix uteri	15	19	19	19	18	14	18	18	17	16
Prostate	122	120	131	128	130	111	111	122	118	118
Kidney (excl. renal pelvis)	10	10	10	11	13	8	8	9	9	10
Urinary tract	29	30	31	33	34	24	25	26	27	27
Non-Hodgkin lymphoma	36	37	39	42	42	32	33	35	38	38
Leukemia	46	47	48	50	57	39	41	43	44	51
	Patient related costs in somatic hospitals (DRG-based costs) mill. 2017-EUR, 1 EUR = 9.8 NOK									
Cancer site	2013	2014	2015	2016	2017	2013	2014	2015	2016	2017
All cancers	1,249	1,258	1,262	1,303	1,321	995	1,008	1,023	1,057	1,071
Mouth, pharynx	29	30	32	32	29	25	26	26	28	26
Colon, Rectum, rectosigmoid	180	185	184	185	187	152	156	156	156	159
Pancreas	37	38	39	37	40	31	31	32	31	32
Lung, trachea	127	125	122	124	136	96	94	93	94	106
Melanoma	24	26	33	38	43	21	22	29	34	39
Breast	132	134	131	126	129	116	117	116	109	110
Cervix uteri	16	18	17	19	17	14	16	15	15	14
Prostate	103	96	99	94	93	74	69	73	69	69
Kidney (excl. renal pelvis)	23	25	25	27	27	17	18	18	20	20
Urinary tract	50	50	50	55	52	38	37	38	42	41
Non-Hodgkin lymphoma	60	63	65	72	66	48	50	52	58	52
Leukemia	96	99	98	106	102	70	75	74	81	76

***ICD-10 code Z51 (other treatments including radiotherapy, chemotherapy, palliative care etc.) were assumed to be cancer specific**

Table 6: Overview of included variables in obtained registry data, by registry

Variable name	Description
Cancer registry of Norway (CRN)	
Patient ID (PID)	Unique patient identifier
Project-specific ID (SID)	Unique project-specific ID for each case of cancer (A patient may have several cancer diagnoses)
Year of birth	Year
Gender	Male/female
Patient status	A variable taking one of the following values: 1. Alive and living in Norway 2. Dead 3. Lost to follow-up (migrated)
Patient status date	Month of last follow-up date or death
Time of diagnosis	Month and year of diagnosis
Diagnosis	Diagnostic code (ICD-10)
Cancer stage at diagnosis	Local, regional or distant metastases
Primary physician registry (KUHR)	
Patient ID	Unique patient identifier
Episode ID	Unique episode of care identifier
Date	Year, month, day of episode
Age	10-year age groups
Gender	Male/female
County	Name county where care is provided
Diagnostic code	ICPC-2 (primary care) / ICD-10 (private practicing specialists)
Patient co-payment	Patient co-payment in NOK
Reimbursement	Reimbursement in NOK
Type of contact	Simple contact/attendance, telephone, consultation or home visit
Type of provider	Description of care provider (i.e., family physician, emergency room, specialist etc.)
Norwegian Patient registry (NPR)	
Patient ID	Unique patient identifier
Year	Year of episode
Month	Month of episode
Length of stay	Duration of in-patient treatment (number of days)
Primary diagnosis	Primary diagnostic code (ICD-10)
Supplementary diagnosis	Supplementary diagnostic code (ICD-10)
Age	10-year age groups
Gender	Male/female
County	Name county where patient is resident
Days until death	Number of days from episode of care to death
DRG	Diagnosis Related Group (DRG) code
DRG-weight	Number of DRG-points for the specific episode
Level of care	Out-patient, in-patient or day care
Type of contact	Description of type of episode (i.e., treatment, investigation, control, indirect patient contact, patient administrated drug treatment, training)
Procedure code	Code defining type of procedure
ATC code	ATC code if drug treatment

Kur-ID	Special code for drugs
The Norwegian Prescription Database (NorPD)	
Patient ID	Unique patient identifier
Age	10-year age groups
Gender	Male/female
Health region	Name health region where patient is resident
Year/month of death	Year and month of death
Year/month of drug redemption	Year and month of drug redemption
Reimbursement code	ICD-10 or ICPC-2 code
AUP	Pharmacy retail price incl. VAT for the specific redemption
Package size	Number of defined daily dose (DDD) for the specific redemption (according to WHO definition)
Number of packages	Number of packages
Item name	Drug brand name
ATC code	According to the Anatomical Therapeutic Chemical (ATC) Classification System

Table 7: Definition of pharmaceutical anti-cancer treatment in Paper III and IV (ATC-codes)

Anatomical Therapeutic Chemical code (ATC-code)	**Name**
L04AX04	lenalidomide
L01XC18	pembrolizumab
L01XC02	rituximab
L01XC17	nivolumab
L01XC03	trastuzumab
L02BB04	enzalutamide
L01XC07	bevacizumab
L01XC24	daratumumab
L01XE33	palbociclib
L01XX32	bortezomib
L04AX06	pomalidomide
L01XE27	ibrutinib
L01XE18	ruxolitinib
L01XC13	pertuzumab
L01XE01	imatinib
L02BX03	abiraterone
L01XE10	everolimus
L01XC32	atezolizumab
L01XX45	carfilzomib
L01XE23	dabrafenib
L01BC07	azacitidine
L01XC08	panitumumab
L01XE26	cabozantinib
L01XE04	sunitinib

L01XE06	dasatinib
L01CD01	paclitaxel
L01XE08	nilotinib
L01XC11	ipilimumab
L01XC14	trastuzumab emtansine
L01XC06	cetuximab
L01XE11	pazopanib
L01XX46	olaparib
L01DB01	doxorubicin
L01XE25	trametinib
L01XC12	brentuximab vedotin
L01CD04	cabazitaxel
L01XE42	ribociclib
L01XE16	crizotinib
L01XX35	anagrelide
L01CA04	vinorelbine
L01XE03	erlotinib
L01XE24	ponatinib
L01XX24	pegaspargase
L01XE36	alectinib
L01XE05	sorafenib
L01BC08	decitabine
L01CX01	trabectedin
L01AD01	carmustine
L01XE17	axitinib
L01XX47	idelalisib
L01XC15	obinutuzumab
L01AX03	temozolomide
L01BC06	capecitabine
L01BC02	fluorouracil
L01BC59	trifluridine, combinations
L01XA02	carboplatin
M05BX04	denosumab
L01XX05	hydroxycarbamide
L01XX43	vismodegib
L01XE21	regorafenib
L01XX02	asparaginase
L01AA06	ifosfamide
L01CB01	etoposide
L01XE02	gefitinib
L01BA04	pemetrexed

L01XA03	oxaliplatin
L01XX19	irinotecan
L01DB03	epirubicin
L01BB02	mercaptopurine
L01AA03	melphalan
L01AA01	cyclophosphamide
L01XE28	ceritinib
L01AA07	trofosfamide
L01DC03	mitomycin
L01AA09	bendamustine
L01XE29	lenvatinib
L03AX16	plerixafor
L01CD02	docetaxel
L01BC05	gemcitabine
L01XX52	venetoclax
L01XE14	bosutinib
L01XD03	methyl aminolevulinate
L01XC26	inotuzumab ozogamicin
L01XD04	aminolevulinic acid
L01XE13	afatinib
L01XE15	vemurafenib
L01BB05	fludarabine
L04AX02	thalidomide
L01XE39	midostaurin
L01AC01	thiotepa
L01AB01	busulfan
L01XC19	blinatumomab
L01XX25	bexarotene
L01XX42	panobinostat
L01XX50	ixazomib
L02BA03	fulvestrant
L01AD04	streptozocin
L01BC01	cytarabine
L01XE38	cobimetinib
L01XX27	arsenic trioxide
L01XA01	cisplatin
L01DB06	idarubicin
L01XE35	osimertinib
L01XX01	amsacrine
L01AD02	lomustine
L01CA02	vincristine

L01XB01	procarbazine
L01XC21	ramucirumab
L01XX14	tretinoin
L01BB04	cladribine
L01DC01	bleomycin
L01DB02	daunorubicin
L01DA01	dactinomycin
L02BB03	bicalutamide
L01AX04	dacarbazine
L01XX23	mitotane
L01XX17	topotecan
L01CA05	vinflunine
L01BB06	clofarabine
L01CB02	teniposide
L01XE12	vandetanib
L01XE07	lapatinib
L02AE03	goserelin
L01CA01	vinblastine
L01DB07	mitoxantrone
L02BX02	degarelix
L01AA02	chlorambucil
L01DB11	pixantrone
L01BB03	tioguanine
L01XC05	gemtuzumab ozogamicin
L02BG04	letrozole
L02BG06	exemestane
L01XC10	ofatumumab
L01XE31	nintedanib
L01BC53	tegafur, combinations
L01XC23	elotuzumab
L01CA03	vindesine
L02BA01	tamoxifen
L02AE02	leuprorelin
L02BG03	anastrozole
L01BA03	raltitrexed
L02AB01	megestrol
M05BA06	ibandronic acid
L02BB01	flutamide
S01AX	Other antiinfectives

Table 8: Definition of pharmaceutical anti-cancer treatment in Paper III and IV (in-hospital treatment, DRG-codes)

DRG code	2013	2014	2015	2016	2017
410A	x				
410B	x				
410C	x				
410D	x				
410X		x	x	x	x
856D		x	x	x	x
856F		x	x	x	x
856G		x	x	x	x
856K		x	x	x	x
856M		x	x	x	x
856N		x	x	x	x
856O		x	x	x	x
856R		x	x	x	x
856X		x	x	x	x
856J			x	x	x

Table 9: Definition of pharmaceutical anti-cancer treatment in Paper III and IV (patient-administered treatments, DRG-codes and diagnosis)

Requirements for registration of patient-administered cancer treatment	2013	2014	2015	2016	2017
Z51.10, Z51.11, Z51.12 or Z51.13 as primary diagnosis and cancer (ICD-10 C00-99) as secondary diagnosis Kur-ID for type of treatment (ATC-code)	x				
Cancer (ICD-10 C00-99) as primary diagnosis and Z51.10, Z51.11, Z51.12 or Z51.13 as secondary diagnosis Kur-ID for type of treatment (ATC-code)		x			
Cancer (ICD-10 C00-99) as primary diagnosis and procedure code/special code for issuing H-prescription = WL000. Special code for the drug or ATC code to identify the relevant drug			x	x	
STG system (JS02, NS01, OS01, RS01, XS01)					x

11. Papers I-IV

Paper I

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Societal cost of cancer in Norway –Results of taking a broader cost perspective

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Societal cost

ABSTRACT

Background: The broader cost consequences of diseases may be of interest for a wide range of stakeholders. We aimed to estimate all relevant societal costs of cancer and to provide insight into the relative magnitude of the different cost categories.

Method: We used data from eight different health and work-related registries in Norway. Direct, indirect, and intangible costs (value of lost life years) were estimated over a period of one year with a combination of a top-down and a bottom-up costing approach.

Results: The indirect costs (EUR 1,997 million per year) are almost as high as direct costs (EUR 2,154 million), and the value of lost life years and quality of life represents the greatest cost related to cancer (EUR 18,200 million). In addition, cancer is associated with other costs which are commonly omitted from cost-of-illness analyses, including informal nursing (EUR 306 million), patient time costs (EUR 85 million), and excess costs of using public funds (EUR 439 million). Breast and cervical cancer had relatively high work absenteeism costs, while pancreatic and lung cancer had relatively high production costs due to premature deaths.

Discussion: Direct health care costs represent small proportions of the total societal costs of cancer. Costs commonly omitted in cost-of-illness analyses represent a significant cost and should be measured and valued in these analyses.

1. Introduction

Both private and public health care systems face major challenges in financing future services because of changes in the demographic profile of the population and costly medical innovations. Considering the increasing financial burden of health care there is need for strict priority setting, and thus information about resource use. In priority setting, policymakers use cost-effectiveness analysis, often restricting the costs to those of the health services provided [1]. Having a broader perspective, cost-of-illness analyses (COI) aim "to itemize, value, and sum the costs of a particular problem with the aim of giving an idea of its economic burden." [2]. The economic burden of a disease includes several cost elements, but in practice most COI studies capture the health care expenditures reported in the public accounts and some of the indirect costs, and not all other illness-related costs [3].

Cost of illness are commonly divided into three main categories: direct, indirect and intangible costs [4,5]. Even though the intangible costs (value of lost life years and quality of life), and some of the indirect costs, do not affect the national budget directly, these are real economic costs and the magnitude of these components can potentially be relevant for policymakers and other stakeholders in their effort to ensure sustainable health care. In fact, the Second Panel on Cost-Effectiveness in Health and Medicine recommends that all studies report a reference analysis based on a broader societal perspective [6].

A range of studies explore the cost of cancer in general and of individual cancers [7-12]. A key challenge in such studies is the choice of methodology and type of costs included which may vary

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considerably [13-15]. Most studies focus on direct health care costs and production losses due to morbidity and mortality, and many disregard other relevant societal costs [3,16]. Specifically, intangible costs are often omitted from COI studies even though any society would value prolongation of lives highly [17]. It has been argued that researchers should avoid underestimating the societal cost of diseases [15,17]. Tarricone concludes that in order to provide useful information to political processes and policymakers, COI studies must be able to measure the main cost components and their relative magnitude [18]. Previously published studies on the costs of cancer lack information on the total societal cost, the magnitude of the different cost categories and the relationship between these categories and individual cancer types.

To the best of our knowledge no previous cancer cost studies has included all the relevant societal costs related to cancer. Given the wide variation in COI analyses and the disagreement about their value in policymaking, the primary aim of this study was to provide a comprehensive overview of all cancer related costs and a better understanding of the relative magnitude of different cost categories. As a secondary objective we sought to provide insight on how different cost categories vary across individual cancer types.

2. Method

We used a prevalence-based approach, where the economic burden of cancer was estimated for a period of one year [4]. Cancer was defined according to ICD-10 and ICPC-2 codes (presented as supplementary material) and the diagnosis codes were used to identify cancer patients in the different registries. We evaluate the incremental costs attributable to cancer (including only costs related to cancer), not total direct costs (all costs of cancer patients). Although the latter method is known for being straight forward and relatively simple, it tends to overestimate costs for patients with co-morbid conditions [3].

2.1. Data sources

Norway provides uniform and public health care services, most of them financed by taxation and a national insurance system for all residents, independent of income, social status, age etc. Cancer treatment in private hospitals is still negligible [19], thus the public registries covers virtually all episodes of cancer care.

We used unlinked patient level data from three Norwegian health registries. The Norwegian Health Economics Administration's (Helfo) KUHR database holds data on primary physicians, emergency rooms, and private practicing specialists. The Norwegian Patient Registry (NPR) captures detailed information on all episodes of in-patient and out-patient care in specialist health care [20]. Each episode of care has an ICD-10 code (diagnostic code) and an anonymous, unique patient identifier, which makes us able to follow individual patients over time. The diagnostic codes in NPR have proved valid against the Cancer Registry of Norway [21]. Drug costs were obtained from The Norwegian Prescription Registry (NorPD) which holds data on pharmacy dispensed prescription drugs on public reimbursement. NorPD has a reimbursement code, which is equivalent to an ICD-10 code (specialist care) and ICPC-2 code (primary care) and a unique patient identifier. Descriptive statistics for the three registries and included variables can be found in supplementary material.

We also collected aggregate data from five other registries. Norwegian labour and Welfare Administration (NAV) holds diagnosis-based information on sickness payments and disability pensions. The use of private pension schemes and health insurance is limited in Norway, and the registry therefore covers the majority of Norwegian cancer patients. Total costs related to cancer medicines were obtained from the Norwegian Pharmacy Association. The Norwegian Cause of Death Registry holds information on the number of deaths caused by to cancer. Aggregated data on health care expenditures were obtained from Statistics Norway's Health accounts and KOSTRA (Municipality-State-Reporting), and the Norwegian Directorate of Health.

Due to legal restrictions, we were unable to link data from the different registries.

2.2. Included costs

To get a complete overview of cancer related costs we identified costs as the three categories stated by Drummond and co-workers [5]: direct costs, indirect costs and intangible costs (Table 1). Direct costs were divided into direct health care costs and direct costs outside the health care sector. Additionally, we included costs commonly omitted from COI analyses in a separate group ("other costs") to make our results comparable with previous studies.

2.3. Direct health care costs

Direct costs were estimated as attributable costs by including only costs of cancer related treatment episodes. Cancer related treatment episodes were identified by using the diagnostic codes registered for each patient episode in the individual registries.

We used a combination of a bottom-up and a top-down approach [22] depending on the cost category of interest. We estimated costs associated with primary care physicians, emergency rooms and private practicing specialists using reimbursement fees and patient co-payments, costs in somatic hospitals using Diagnosis-related group (DRG) weights and costs of pharmacy drugs using retail price (ex. VAT). Cancer related treatment episodes in somatic hospitals were identified by the assigned primary and secondary diagnosis at discharge for each treatment episode. For primary physicians, emergency rooms and private practicing specialist we used fees from the Norwegian Directorate of Health [23]. The DRG unit price in somatic hospitals in Norway include all patient-related treatment costs and is based on CPP (cost per patient) [24], a patient-related accounting method using reported accounting figures from the four regional health authorities. Average cost per DRG point in specialist health care (€ 5 238 ex. VAT in 2017) was obtained from a study done by the Norwegian Directorate of Health [25].

We estimated non-patient-related costs (R&D, capital costs, municipality grants etc.) with a top-down approach [22], using aggregate data from Statistics Norway's Health Accounts and the Norwegian Directorate of Health. For out-patient diagnostics imaging and laboratory services we used data from the KUHR database on reimbursement and patient co-payment from all public out-patient clinics and private laboratories. We assumed that the proportion of tests related to cancer was equal to cancer patients' proportion of out-patient visits (ranging from 10.6 to 13.1% each year).

Costs associated with municipality provided nursing home and home nursing services were estimated using data from Statistic Norway's KOSTRA-registry. Three percent of the total costs of these services were assumed to be cancer related based on results from a trial project in three municipalities initiated by the Norwegian Directorate of Health [26].

Norway has screening programs for cervical cancer and breast cancer. Annual direct health care costs related to these programs were collected from previously published studies in Norway [27,28] and adjusted to 2017 Euros. The costs of other health promotion and prevention activities (excluding screening) were excluded due to difficulties in consistent identification and estimation of cancer specific proportions.

Table 1
Included costs.

Cost category	Description	Costs included in this study
Direct health care costs	Direct health care costs are resource use in the health care sector that can be completely attributed to an illness (e.g.: costs of diagnostics, treatment, rehabilitation and terminal care of patients). Costs are usually observable as payments or expenditures.	Primary physician care (Physician visits, emergency room visits) Specialist health care (Private specialists, hospital out-patient care, hospital in-patient care, hospital day treatment, out-patient diagnostics imaging, out-patient laboratory services, in hospital drug use, ambulance services, patient transport, pension costs of health personnel, capital costs (hospital constriction), research and development costs (R&D), purchases from private sector entities) Drugs dispensed at pharmacy (patient-administered cancer drugs, analgesics, painkillers and sleeping medications) Nursing home and home nursing services (home practical assistance, day care centers, home nursing and institutions) Screening (breast and cervical cancer screening programs)
Direct costs outside the health care sector (nonmedical costs)	Direct costs outside the health care sector (nonmedical costs) can be defined as resource use outside the health care sector that can be completely attributed to an illness (e.g.: patient travel costs, legal costs and modification of patients' home). Costs are usually observable as payments or expenditures.	Patient travel costs (Transportation costs inflicted on patients related to getting to screening and treatment in primary and specialist health care)
Indirect costs	Indirect costs are costs which impact consumption of resources, but which do not entail any direct payments. These costs are not directly linkable through payments to the treatment or follow-up of the disease.	Production losses due to mortality and morbidity (the economic loss that reflect the individual's potential contribution to the economy)
Intangible costs	Intangible costs are related to foregone benefits that have no direct impact on the consumption of resources, such as pain and suffering.	Value of lost life years (loss of quality adjusted life years due to premature death) Value of lost quality of life (reduction in life quality for cancer patients)
Other costs	Other costs commonly excluded in COIs.	Informal nursing/home care (costs associated with relatives/friends spending time and resources taking care of patients with cancer) Patient time costs (patients' loss of time due to treatment in primary and specialist health care) Cost of public funds (cost associated with financing care with funds that are collected by taxes)

Although we mainly present 2017 results, all direct health care costs were estimated for the period 2013–2017 and all prices were adjusted to 2017 Euros (EUR) using Statistics Norway's price index for production of public health services.

2.4. Direct costs outside the health care sector

Patients' travel costs were estimated using the number of contacts with primary care physicians, emergency room visits, private practicing specialists, and somatic hospitals from the registers and unit costs from a study by Moger and Kristiansen [28]. The latter was based on location of patients and location of care providers. Travel costs related to screening were collected from the literature [27,28].

2.5. Indirect costs

The economic costs of lost production were estimated using the human capital approach [4]. For work absenteeism we used data on sickness payments and work assessment allowance (short- and medium-term absenteeism) and disability pensions (long-term disability) from NAV as a proxy for the value of lost labour due to cancer. The welfare payments were adjusted up to reflect the wages of the beneficiaries. Social and overhead costs were added according to Norwegian guidelines to reflect the real societal costs of work absenteeism [29]. We estimated lost production due to premature death with an incidence approach, using life table, gender-specific average working hours and employment rate by age group and real wages expenses for 2017 from Statistics Norway. Deaths were assumed to occur in the middle of each 5-year age interval. Future production losses were discounted with an annual rate of 4 percent according to guidelines from the Norwegian Ministry of Finance [29]. Production losses related to screening were collected from the literature [27,28].

2.6. Intangible costs

The number of lost quality adjusted life years (QALYs) due to cancer were estimated using data from the Norwegian Cause of Death Registry and the expected remaining QALYs in the general population from the Norwegian Medicines Agency. To monetize the value of lost life years we applied a value of a QALY of EUR 136 055 which is consistent with the value used and recommended by the Norwegian Directorate of Health [23,30]. This value does not include production losses (hence we avoid double counting) and is derived from the value of a statistical life, which is based on the Norwegian validation study (a study using a stated preference method with both choice experiments and contingent valuation) [31]. Cost associated with lost quality of life (non-fatal health loss) was based on a burden of disease study conducted by the Norwegian Directorate of Health published in 2019 [30].

2.7. Other costs (costs commonly excluded in COIs)

Informal care costs are costs of unpaid care provided by caregivers such as friends and family. In a study of cancer costs across the European Union, Luengo-Fernandez and co-workers estimate the opportunity cost of unpaid care from relatives and friends (informal care) using data from the Survey of Health, Ageing and Retirement in Europe (SHARE) [10,32]. The authors assume that only patients severely limited in daily activities or who were terminally ill would receive informal care. For informal care provided by employed caregivers, mean hourly wage was applied, while hourly minimum wage was used for retired caregivers. To get an estimate for cancer related cost of informal care in Norway we used estimates from Denmark, Finland, and Sweden. For each of the three countries, we adjusted the cost estimates by population size and differences in purchasing power to reflect the Norwegian setting.

Then we used the average cost from the three countries and adjusted for inflation to express costs in 2017-values.

For patient time costs we assumed two hours for primary care visits, three hours for specialist visits, and 20 min for telephone consultations [33]. To avoid double counting of costs included in indirect morbidity costs we excluded patients in working age from the calculation and assumed time costs to be lost leisure, using net annual earnings to calculate the opportunity cost.

For tax financed services (direct costs and cancer related welfare payments), we added the marginal costs of using public funds as 20 percent of all cancer expenditures covered by the public according to guidelines from the Norwegian Ministry of Finance [29].

2.8. Statistical analysis

All analyses were performed using STATA software version 14 (College Station, TX, USA) and Microsoft Excel (2016). We performed one-way sensitivity analyses on key assumptions and costs including price per DRG point, cancer related proportion of nursing and care service expenditures, excluding societal and overhead costs in real wage estimation for production losses, informal care costs, taxation costs, and value of a QALY.

2.9. Ethics

Approval to use data from Norwegian Patient Registry were granted from the Norwegian Data Inspectorate (17/00565–2/CDG) and the Regional Committees for Medical and Health Research Ethics (2017/769/REK).

3. Results

The direct health care costs for diagnostics and treatment of cancer in Norway were estimated to EUR 2154 million (EUR 410 per inhabitant) in 2017 (Table 2). The costs in specialist health care accounted for 70 percent of the direct costs, while only 2.6 percent of the costs were incurred in primary care. Cancer drugs amounted to EUR 225 million, representing 10.4 percent of direct health care costs. Of the costs in somatic hospitals, 55 percent were related to medical DRGs, while 45 percent were related to surgical ones. The direct health care costs increased by 2.7 percent annually adjusted for inflation from 2013 to 2017 (cost per patient decreased by 1.5% annually) (data not shown). Patient travel costs amounted to EUR 58 million in total in 2017, of which 31 percent was related to screening. The total patient co-payments were estimated to EUR 37.5 million, representing 1.7 percent of the direct costs.

The production losses related to morbidity and mortality (short/medium-term absenteeism, long-term disability, and premature death) amounted to EUR 1997 million in 2017 (EUR 380 per inhabitant) (Table 2). 49.8 percent of the males and 53.1 percent of the females diagnosed with cancer in Norway between 2013 and 2017 were of working age (20–69 years) at the time of diagnosis.

Informal care (EUR 306 million), patient time costs (EUR 85 million), and costs of public funds (EUR 439 million) amounted to EUR 830 million in 2017 (EUR 158 per inhabitant).

A total of 5118 women and 5776 men died from cancer in Norway in 2017. This corresponds to 78,358 lost future life years for women and 77,326 for men, equivalent to a total of 116,620 lost QALYs (Table 3). Lung cancer and cancer of colon, rectum and rectosigmoid caused the most lost life years and lost QALYs. The value of the lost QALYs related to premature death corresponds to EUR 15.8 billion in total. In total, 17,888 QALYs were lost due to morbidity [30]. The value of lost quality of life for patients living with cancer were estimated to EUR 2.4 billion based on calculations from the Norwegian Directorate of Health.

In the sensitivity analyses, a 20 percent increase in the DRG unit price corresponded to a 12.3 percent increase in the direct costs (data not shown). Indirect costs were most sensitive to changes in the estimated real wage used in valuating time off work. When societal costs and overhead costs were excluded from the real wage estimation, the total indirect costs decreased from EUR 1997 million to EUR 1426 million (−28.6%) (data not shown). The value used to monetize QALYs had a great impact on the level of the intangible costs. However, this is not a question about uncertainty, but value judgement.

When comparing patient-related hospital costs (out-patient, in-patient and day care) and production losses due to work absenteeism and premature death, the production losses accounted for 61 percent of the costs for all cancers (Fig. 1). The production loss accounted for relatively high proportions for breast cancer (74%), cervical cancer (72%), and pancreatic cancer (68%). As expected, costs related to premature death accounted for a relatively high proportion for cancers with high mortality rates, such as pancreatic cancer (58%) and lung cancer (51%). For breast and cervical cancer, a substantial proportion of the costs (57% and 43% respectively) were related to production losses from work absenteeism. For urinary tract (40%) and prostate cancer (42%) the production loss accounted for a small proportion of the costs.

4. Discussion

For cancer in Norway, direct health care costs (EUR 2154 million) are at about the same level as indirect costs (EUR 1997 million) and represent a relatively small proportion compared the value of lost QALYs (EUR 18,200 million). Costs commonly omitted from COI analyses represent a significant cost (EUR 830 million). The different cost categories vary substantially across individual cancers, and for breast and cervical cancer, costs associated with work absenteeism account for a relatively high proportion of the costs.

To our knowledge, no previous studies have captured so many aspects of cancer costs. Unlike most other COI studies, we include estimates of primary care nursing services, informal care, patient time and travel costs, taxation costs, and the value of lost QALYs (lost life years and lost health related quality of life). Our study is based on a range of cancer specific registry data and covers virtually the entire Norwegian population. By including the entire population, we avoid selection bias. The fact that all citizens of Norway have a unique individual social security number makes us able to follow patients within each registry over time and diagnosis specific data enables us to perform detailed cost analyses (bottom-up costing). Norway also has diagnosis specific data for sickness payments and disability leave, as well as a complete national cause of death registry that dates back to 1951. These data sources provide an excellent foundation for estimating the production losses due to cancer, as well as the number of lost life years.

Still, our study has important limitations. We did not have diagnosis-specific data for primary care nursing services and outpatient imaging and laboratory services, and allocating costs using a top-down approach may lead to misallocated costs [18]. Representing a relatively small proportion of the total costs, however, errors here would likely have little impact on the results. For some costs (out-patient imaging and laboratory services, formal and informal nursing and care services and cost of public funds), we did not have data for individual cancers, which made us unable to compare the direct and indirect costs of different cancer types. Informal care costs were estimated indirectly based on data from other countries and are therefore associated with uncertainty. Another limitation lies in the use of reimbursement fees and DRG-weights for costing as these may not always represent the actual societal costs. Co-morbidities may bias hospital costs as they

Table 2
Direct, indirect and intangible costs (in million EUR) and cost per inhabitant (in EUR) of cancer in Norway in 2017 (1 EUR = 9.8 NOK).

	Total costs (million EUR)	Cost per inhabitant (EUR)
Direct health care costs	2154	410
Primary physician health care	57	11
Specialist health care	1509	287
Of which:		
Specialists practicing privately	12	2
Hospital treatment (out-patient)	356	68
Hospital treatment (in-patient)	928	176
Hospital treatment (day care)	37	7
Out-patient diagnostic imaging	41	8
Out-patient laboratory services	96	18
Non-patient-related costs*	40	8
Medicine costs (dispensed at pharmacy)	163	31
Of which anti-cancer medicines	133	25
Cost of cancer medicines (total)**	225	43
Municipality-provided nursing and care	347	66
Screening	78	15
Direct nonmedical costs	58	11
Patient travel costs treatment and diagnostics	58	11
Of which related to screening	18	3
Indirect costs	1997	380
Of which:		
Short-term absenteeism	296	56
Long-term disability	599	114
Premature death	1102	210
Intangible costs	18,200	3455
Lost QALYs due to mortality	15,800	3000
Lost QALYs due to morbidity	2400	455
Costs commonly omitted from COIs	830	158
Informal nursing/home care	306	58
Patient time costs	85	17
Of which related to screening	45	9
Cost of public funds (taxation costs)	439	83

* Portion of costs not directly related to patient treatment: Not ISF (fee for service) financed such as R&D, treatment aids, municipality grants. **ATC codes: L01, L02AB01, L02AE02, L02AE03, L02B and L03AA. **Costs included in hospital treatment costs and pharmacy dispensed drugs.

Table 3
Number of deaths due to cancer, number of lost life years and number of lost QALYs by type of cancer, 2017.

Type of cancer	Number of deaths	Total number of lost life years	Total number of lost QALYs*	Life years lost per death	QALYs lost per death*	% of lost QALYs*
All cancers	10,894	155,684	116,620	14.3	10.7	100%
Mouth, pharynx	138	2371	1822	17.2	13.2	2%
Colon, Rectum, rectosigmoid	1608	21,822	16,321	13.6	10.1	14%
Pancreas	787	11,437	8533	14.5	10.8	7%
Lung, trachea	2150	31,811	23,840	14.8	11.1	20%
Melanoma	284	4111	3105	14.5	10.9	3%
Breast	594	10,514	7499	17.7	12.6	6%
Cervix uteri	74	1599	1156	21.6	15.6	1%
Prostate	934	8067	6298	8.6	6.7	5%
Kidney (excl. renal pelvis)	253	3765	2894	14.9	11.4	2%
Urinary tract	283	4132	3123	14.6	11.0	3%
Lymphoid/haematopoietic tissue	913	12,547	9439	13.7	10.3	8%
Other cancers	2876	43,508	32,590	15.1	11.3	28%
By age group (all cancers)						
0–17 years	24	1744	1439	72.7	60.0	1%
18–67 years	3496	87,192	66,862	24.9	19.1	57%
67+	7374	66,748	48,318	9.1	6.6	41%

*Numbers do not include QALYs lost due to morbidity.

may cause resource use that is not directly related to cancer although patients have a cancer diagnosis. However, the fact that DRG-weights and DRG-unit price were based on cost per patient (CPP) calculations reduces the uncertainty in the estimates. We use the human capital approach to estimate production losses. This method has been criticized because unemployed individuals may in part replace those away from work because of sickness [34,35]. With an unemployment rate below 4 percent this problem may be limited in Norway. There is a great variation in the value used to monetize lost life years both across and within countries, and the value of a statistical life depends, among other things, on the valuation method used, income level and its application [36-38]

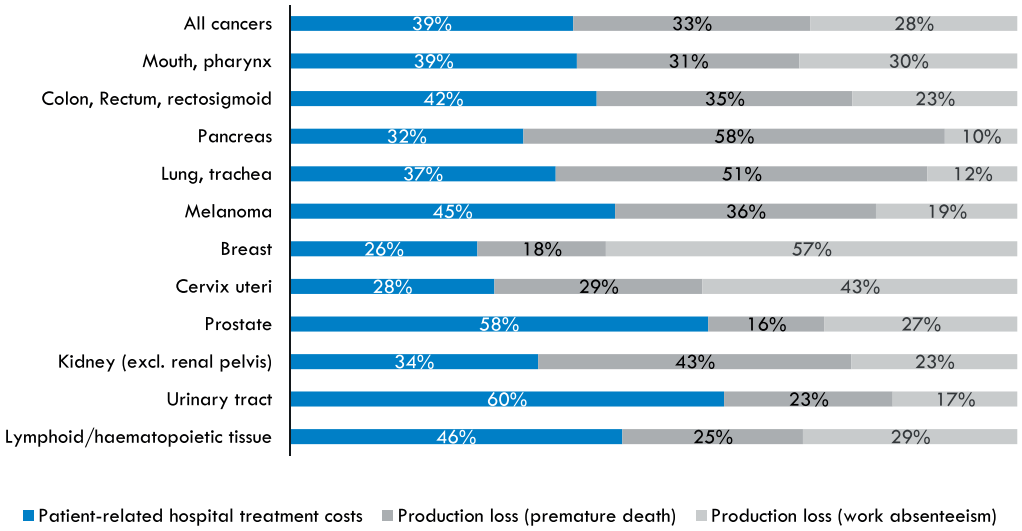

Fig. 1. Comparison of patient-related hospital treatment costs and production loss, by type of cancer, 2017.

Several studies have investigated the economic burden of cancer [7-12], but the evidence on the broader cost of cancer is limited [7-11,17]. Our estimates of the level of direct health care costs (as a proportion of total health care expenditures) and on the relative magnitude between direct health care costs and production losses align well with previous studies in Europe and in Norway [7-10,12]. Kinge and coworkers (2017) estimated the total economic burden of cancer in Norway (excluding intangible costs) at EUR 3550 million (1 EUR = 9.8 NOK) in 2013, of which 1694 million were direct health care costs and 1857 million were production losses [7]. The estimate of direct health care costs does not include costs of home care and nursing care or screening, which explain why it is lower than our estimate of EUR 2154 million. Kinge and coworker's estimate of production losses corresponds well to our estimate of EUR 1997 million. We were not able to find any other estimates of the total societal cost of cancer in the literature and it is unknown how our estimates for Norway compare with other countries.

In practice, many COI studies disregard intangible costs and other relevant societal costs, thus underestimating the burden of illness. The implication on cost estimates of using a wider definition of indirect costs is substantial, and in this study the indirect costs increases from EUR 1997 million to EUR 2827 million (+41.5%) when cost of informal care, patient time costs, and taxation costs were classified as indirect costs. In the COI framework, the term indirect cost usually refers to the production losses from absence of work due to morbidity and mortality [4]. However, indirect costs also stem from relatives and friends who spend time and resources taking care of patients (informal care) or patient's loss of leisure due to the illness. Additionally, the use of funds collected through taxation imposes a production loss to the society because taxes distort the labour supply decisions of workers (which create an economic deadweight loss) [39]. The latter means that taxes incentivize workers to prioritize leisure (rather than work) more than they would have done without taxes, hence creating a production loss in the economy. These costs are relevant when comparing the costs of different diseases or the costs of health care systems with different level of public spending. Finally, intangible costs are related to foregone benefits that have no direct impact on the consumption of resources, such as pain and suffering [16]. The problem with adding intangible costs, which usually are on the benefit side in an economic evaluation, is that it may represent double counting unless estimated as a "pure value of health per se".

The value of COI studies and their legitimate role in policymaking have been debated in the health economics literature [18,40-43]. Critics argue that such studies have limited value in priority setting because they do not provide any insight on the effectiveness related to health care investments [43]. Some researchers also believe that COI studies may mislead policymakers, and lead to the prioritization of interventions directed to diseases which are already costly [40]. In contrast, we argue that better knowledge of the broader societal cost of cancer and including costs usually omitted from COI analyses enrich our understanding of the burden of illness, and that these estimates can be relevant for policy-makers and researchers for several reasons. First, such knowledge can assist policymakers in budgeting, planning and financing of future health care services and research. Second, when adopting a broader societal perspective, COIs can inform later cost-effectiveness analyses and identify cost categories that are relevant for priority setting. Lastly, understanding the composition of societal costs is important when investigating time trends or when conducting comparative analyses of countries or health care systems. For example, jurisdictions where informal care is an important part of the service, informal care costs may explain the lower formal care costs.

Although COI are relevant for policy making, the total societal cost of cancer does not provide direct guidance to the question whether more (or less) resources should be devoted to cancer care in general or to specific cancers. However, when reported in a transparent way, comprehensive COI studies can provide policymakers and other stakeholders with valuable information about the disease of interest. A fundamental decision in COI lies in the choice of which costs to include and how they are classified to make correct and meaningful observations and conclusions. Data availability and purpose of the analyses will presumably be important factors, but we consider that authors as a minimum should state explicitly which types of costs that are included and which are not. To avoid misunderstandings or to mislead policymakers, different costs categories should always be presented separately.

5. Conclusion

While direct health care costs represent a crucial part of cancer costs, other societal costs, and in particular the value of lost QALYs, are greater. This indicates the magnitude of burden of cancer as well as the potential for relief through better treatment.

Disclaimer: Data from the Norwegian Patient Registry has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred.

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Individual contributions

Christoffer Bugge: Data collection, study design, analysis, interpretation of results, preparation of the manuscript, and approval of the manuscript.

Odd Terje Brustugun: Study design, interpretation of results, preparation of the manuscript, and approval of the manuscript.

Erik Magnus Sæther: Data collection, study design, analysis, interpretation of results, preparation of the manuscript, and approval of the manuscript.

Ivar Sønbø Kristiansen: Data collection, study design, interpretation of results, preparation of the manuscript, and approval of the manuscript.

Declaration of Competing Interest

Christoffer Bugge, Erik Magnus Sæther and Ivar Sønbø Kristiansen are affiliated with Oslo Economics and have all completed consultancy assignments for several pharmaceutical companies in recent years.

Odd Terje Brustugun has no conflicts to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.healthpol.2021.05.008.

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Paper II

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Phase- and gender-specific, lifetime, and future costs of cancer

A retrospective population-based registry study

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Abstract

Valid estimates of cancer treatment costs are import for priority setting, but few studies have examined costs of multiple cancers in the same setting.

We performed a retrospective population-based registry study to evaluate phase-specific (initial, continuing, and terminal phase) direct medical costs and lifetime costs for 13 cancers and all cancers combined in Norway. Mean monthly cancer attributable costs were estimated using nationwide activity data from all Norwegian hospitals. Mean lifetime costs were estimated by combining phase-specific monthly costs and survival times from the national cancer registry. Scenarios for future costs were developed from the lifetime costs and the expected number of new cancer cases toward 2034 estimated by NORDCAN.

For all cancers combined, mean discounted per patient direct medical costs were Euros (EUR) 21,808 in the initial 12 months, EUR 4347 in the subsequent continuing phase, and EUR 12,085 in the terminal phase (last 12 months). Lifetime costs were higher for cancers with a 5-year relative survival between 50% and 70% (myeloma: EUR 89,686, mouth/pharynx: EUR 66,619, and non-Hodgkin lymphoma: EUR 65,528). The scenario analyses indicate that future cancer costs are highly dependent on future cancer incidence, changes in death risk, and cancer-specific unit costs.

Gender- and cancer-specific estimates of treatment costs are important for assessing equity of care and to better understand resource consumption associated with different cancers.

Cancers with an intermediate prognosis (50%–70% 5-year relative survival) are associated with higher direct medical costs than those with relatively good or poor prognosis.

Abbreviations: CRN = Cancer Registry of Norway, DRG = diagnosis-related group, EUR = euros, ICD-10 = International Classification of Diseases, Tenth Revision, NPR = Norwegian Patient Registry.

Keywords: cancer costs, cost analysis, cost of illness, lifetime costs, phase-specific costs

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CB, EMS, and ISK have all completed consultancy assignments for several pharmaceutical companies in recent years.

Data from the Norwegian Patient Registry has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred. The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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1. Introduction

The increasing financial pressure on public health care systems entails need for strict priority setting and planning of future health care. Valid estimates of treatment costs are a necessary input in cost-effectiveness analyses used for allocating resources and evaluating new interventions. The medical improvements in cancers care make the demand for accurate and updated costs estimates related to cancer even more important.

Globally, cancer is the second most frequent cause of death, and a major public health challenge that represents a significant economic burden to society.[1,2] The NORDCAN-program presents projections of cancer incidence and mortality based on data from national cancer registries and cause of death registries in all the Nordic countries.[3] NORDCAN projections indicate that the annual average number of new cancer cases in the Nordics will increase from 163,881 in 2012 to 2016 to 230,565 in 2032 to 2036 (+40.7%).[4]

Analysts use different approaches to describe illness-related costs, including incidence, prevalence, and phase-specific approaches.[5–10] Costing by "phase of care" involves dividing care into clinically relevant phases and applying survival probabilities to the cost estimates for each phase.[11] This approach has several appealing aspects as it incorporates the natural history of the disease and corresponding treatment patterns.[6] When combined with survival data, these phase-specific cost estimates can be used to determine lifetime costs for individual cancers.[5,12] Furthermore, when applied to projections of future incidence rates, such lifetime costs enable the estimation of future cost of care. Additionally, a phase-specific approach enables analysts to evaluate how changes in prognosis, and changes in time spent in each phase, influence the costs associated with the disease. Costs can be computed using cancer-related services and treatments (attributable costs) or by matching patients with individuals without cancer (net costs).[11] One key advantage with the former method is that it is fairly straightforward and simple if diagnosis-specific cost data are available, which is the case in Norway.

Several previous studies have presented phase-specific cancer costs.[5,6,12–17] Most studies, however, present lifetime costs for single cancers while few have examined multiple cancers in the same setting (examples of studies covering multiple cancers are Yabroff et al,[5] de Oliveira et al,[6] and Blakely et al[16]). The Nordic countries all have excellent registries capturing virtually all individuals residing in those countries.[18] Having a universal public insurance system, where virtually all cancer patients are treated in public hospitals, provides a foundation for developing precise costs estimates. Additionally, Norway has diagnosis-specific data on hospital treatment and costs at the individual patient level and a national cancer registry which has had a mandatory reporting of new cancer cases since 1953 and is 99% complete.[19]

The primary aim of this study was to estimate phase-specific and lifetime costs for cancer as a disease group and for the 13 most frequent individual cancers. A secondary aim was to develop scenarios of future cost of cancer based on incidence projections from the Nordic NORDCAN-project and estimated lifetime costs.

2. Methods

We performed a retrospective population-based registry study to evaluate phase-specific (initial treatment phase, continuing care, and terminal care) and lifetime cancer costs incurred in hospital (direct medical costs). This was done for 13 individual cancer types (representing 75% of all new cancer cases in Norway in 2017)[20] and all cancers combined (International Classification of Diseases [ICD]-10 codes C00-99, D00-09, D37-48). We included costs of out-patient care, in-patient care, day treatment, and in-hospital drug use. Non-patient-related costs (research and development, capital costs, ambulance services, etc) and out-patient diagnostics imaging and laboratory services were not included due to lack of diagnosis-specific data.

2.1. Data sources

We used data from the Norwegian Patient Registry (NPR)[21] with the following variables for each episode of care (i.e., hospital encounter: out-patient, in-patient or day care visit): unique patient identifier, patient age, gender, and county of residence, time of episode (year/month), main and supplementary diagnosis (ICD-10 code), Diagnosis Related Group (DRG) code and corresponding cost weight, and days until death. In NPR, each episode of care is assigned an ICD-10 main diagnostic code (possibly also a supplementary diagnostic code) that enables us to isolate cancer-specific treatment costs. Norway has a national health care system that provides health care for all residents. Virtually all cancer treatment is provided by publicly financed hospitals.[22] The dataset from NPR encompasses all episodes of care (hospital encounters) for cancer patients during the period 2009 to 2017 with ICD-10 codes C00-99, D00-09, D37-48. In total, the dataset encompassed 7,423,828 episodes for 420,655 patients.

The Cancer Registry of Norway (CRN) holds data on type of cancer diagnosis, time of diagnosis, time of death, patient characteristics (gender and age), and cancer stage in condensed form at the time of diagnosis for all patients diagnosed with cancer in Norway. Notification of cancer cases to CRN is mandatory, and the data are collected from multiple sources, including hospitals, physicians, pathology laboratories, and by linkage with NPR. CRN data proved to be valid with 98.8% overall completeness for the registration period 2001 to 2005.[19] We collected data on patients diagnosed with cancer between 1953 and 2015, in total 1,107,088 patients. Patients were followed to the end of 2018, and the dataset included information on the month of death for all patients who died between January 1, 1953 and December 31, 2018.

Projections of future incidence were obtained from the NORDCAN-program (www.ancr.nu), a database that includes detailed information on cancer incidence, mortality, and prevalence in each of the Nordic countries.[3] At the time of data collection (January 2020) the database included projections of cancer incidence until 2036 (presented as annual average for 5-year periods).

2.2. Patient classification

Patients were classified by tumor site into mutually exclusive cancer diagnosis for those with a diagnosis of cancer of mouth/pharynx, colon/rectum, lung, breast, cervix uteri, prostate, kidney (excl. renal pelvis), or urinary tract or with melanoma of the skin, non-Hodgkin lymphoma, leukemia or multiple myeloma. In cases where patients had multiple cancer diagnoses, diagnosis was assigned based on the most frequently listed diagnosis.[23] Additionally, all cancers (C00-99, D00-09, D37-48) were evaluated together.

2.3. Survival analyses

We used the Kaplan–Meier estimator to estimate gender-specific survival models for each cancer site and all cancers combined. We estimated the probability of a patient surviving each month after diagnosis based on the month of first cancer diagnosis and month of death (or end of follow-up for patient alive by December 31, 2018). Patients who emigrated during the observation period were censored at the time of emigration. All survival analyses were performed on data with patients diagnosed with cancer between 1995 and 2015 (N = 560,265) from the cancer registry. The choice of time period was based on the need for long-term survival and also more recent treatment practice. Additionally, sensitivity analyses were conducted to examine the effects of using more updated data (2010–2018) for the first 8 years after diagnosis.

2.4. Estimation of phase-specific direct medical costs

We used an incidence-based cost approach where time between diagnosis and death were divided into 3 clinically relevant phases; initial treatment phase (primary course of therapy and adjuvant therapy), continuing care (surveillance, active follow-up, and active treatment of metastatic/relapsed disease), and terminal care (including palliative care). Length of each phase was defined as in a study by Yabroff et al[5] with the initial phase defined as the first 12 months after diagnosis, terminal phase as the last 12 months before death and continuing phase as the time in between the initial and terminal phase. To ensure comparability between cancers and with previous research, we employed the same length across all sites similar to previous studies.[5,6]

We used data from NPR to estimate monthly costs by cancer for each phase. We defined costs as the additional cost of care in hospitals due to cancer (direct medical costs) by estimating attributable costs, only including treatment related to the cancer diagnosis based on primary and secondary diagnosis.[24] Costing method followed guidelines from the Norwegian Medicine Agency and the Norwegian Directorate of Health and were performed as in previous studies of cancer costs in Norway.[25,26] We used the DRG weights for each episode of care and a price per DRG point from the Norwegian Directorate of Health of EUR 5238 ex. value added tax (2017 value).[27] This unit price include all patient-related treatment costs associated with each episode of care in hospitals and is based on cost-per-patient calculation of reported accounting figures from the regional health authorities in Norway.[27] There is virtually no patient copayment for cancer patients in Norway, and the DRG cost weights therefore reflect the actual resources consumption (economic cost) related to the patient care. Costs occurring before 2017 were adjusted for inflation to represent 2017 values. For the initial treatment phase and terminal care phase monthly costs were estimated for the first 12 months following diagnosis and the last year of life respectively. For the continuing phase, we estimated an average monthly cost for the entire phase.

We employed different patient cohorts to estimate costs for each phase. To estimate monthly costs in the initial phase we selected patients with no cancer related episodes prior to 2013 in NPR who survived at least 12 months and used activity data from 2013 through 2016. The 2008 to 2012 wash-out period was chosen to ensure that we only included newly diagnosed cancer patients, while 12 months follow-up were used to avoid including costs related to terminal care. Monthly costs in the terminal phase were estimated using decedents between 2013 and 2017 in NPR. For the continuing phase we selected patients diagnosed with cancer in 2010 who were alive by the end of 2017 in NPR. Average monthly costs were estimated by using cost data from 2013 through 2017. The treatment intensity may be higher in the initial seven years as compared with longer follow-up. To adjust for this, we excluded treatment costs in the second and third year after diagnosis when computing costs in the continuing phase.

2.5. Estimation of lifetime costs

By utilizing the phase-specific monthly unit costs from the patient registry and the survival models from the cancer registry we computed lifetime costs as $Lifetime\,costs\,(t_T) = \sum_{t=1}^{T} \hat{S}(t) C_t$ where $\hat{S}(t)$ is the Kaplan–Meier survival estimate at month t (i.e., the probability of being alive in month t) and C_t is the monthly cost in month t after diagnosis.[11]

Lifetime costs were expressed in 2017 Euros using a 4% real (inflation-adjusted) discount rate according to national guidelines.[28]

Patients who died within 24 months of diagnosis did not contribute with costs to all phases. For patients with less than 24 months follow-up we first allocated costs to the terminal phase. If the patient survived more than 12 months (but less than 24), the remainder of the costs were allocated to the initial phase. More precisely, we defined the length (L) of the terminal phase (T) as $L(T) = \min(12, t_T - t_0)$, initial phase ($I$) as $L(I) = \min(12, t_T - t_0 - L[T])$, and continuing phase ($C$) as $L(C) = t_T - t_0 - L(T) - L(I)$, where t_0 denotes time of diagnosis and t_T time of death. This way of allocating costs for patients with short follow-up is consistent with previous studies and was chosen to ensure comparability with previous research.[5,6,15,29]

2.6. Scenarios for costs toward 2034

To compute scenarios for future costs we multiplied lifetime costs per new cancer case with projections of the number of new cases from the NORDCAN-program.[3] NORDCAN reports average yearly incidence in 5-year intervals (until the period 2032–2036 at the time of data collection). As a simplification the predicted incidence were assumed to occur in the middle of the 5-year interval (i.e., 2034). We evaluated the following scenarios: a hypothetical 10% decrease in the death risk per month for cases diagnosed in 2034 (i.e., an increase in the proportion of patients alive each month by 10%); a 3% annual increase in incidence (compared with the 2.4% increase estimated by NORDCAN); and a hypothetical 30% increase in the monthly unit costs in each phase and all phases combined. For all scenarios, costs were presented as 2017 EUR.

2.7. Statistical analyses

All analyses were performed using Microsoft Excel (2016) and STATA software version 14 (College Station, TX).

2.8. Ethical review

Approval to use data from Norwegian Patient Registry was granted by the Norwegian Data Inspectorate (17/00565-2/CDG) and the Regional Committees for Medical and Health Research Ethics (2017/769/REK).

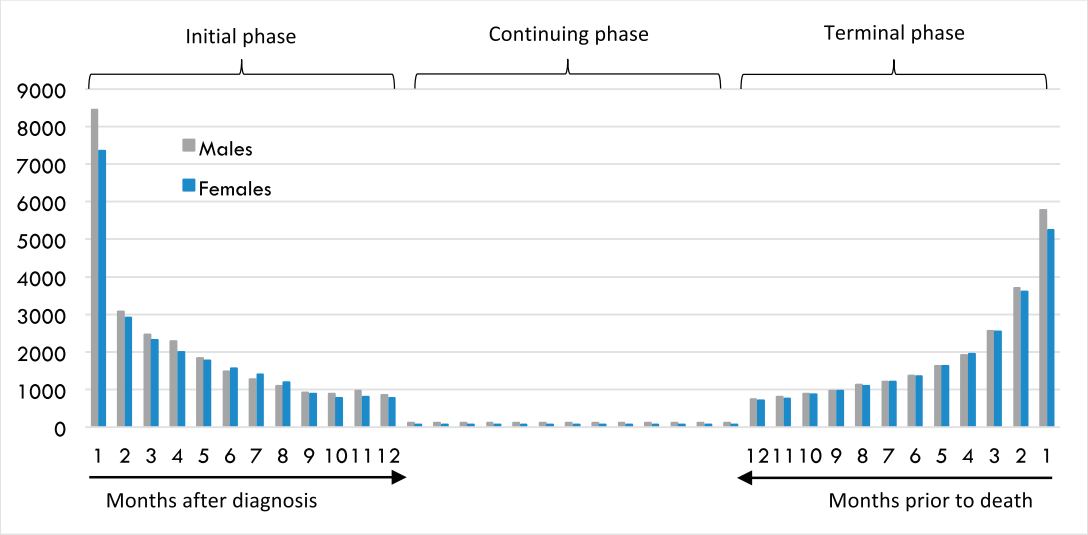

Figure 1. Mean monthly undiscounted direct medical costs in hospitals after diagnosis per patient 2017-EUR (1 EUR = 9.8 NOK).

3. Results

3.1. Monthly phase-specific costs per patient

In general, cost per patient was highest during the first month after diagnosis and the last month before death (Fig. 1). The monthly cost per patient decreased with time after diagnosis and increased as death approached following a U-shaped curve for all 13 cancers (see Table S1, S2, and S3, Supplemental Digital Content 1, http://links.lww.com/MD2/A257 which presents monthly per patient costs by phase, cancer site and gender). For all cancers combined, the mean cost per patient during the first month after diagnosis were EUR 8454 for males and EUR 7362 for females, with mouth/pharynx (EUR 18,128) and cancer of colon, rectum, and rectosigmoid (EUR 16,975) having the highest monthly cost per patient (both genders). During the last month before death the mean monthly cost was EUR 5777 for males and EUR 5240 for females, while the monthly costs in the continuing phase were EUR 111 for males and EUR 75 for females (all cancers combined). Multiple myeloma was associated with particularly high costs in the continuing phase with EUR 968 for males and EUR 913 for females.

3.2. Lifetime and phase-specific costs

Based on the survival models estimated from CRN data the mean durations were 10.2 months for the initial phase (30.9% of the patients lived less than 24 months from diagnosis), 96.9 months for the continuing phase, and 7.7 months for the terminal phase (22.1% died within less than 12 months from diagnosis). Patients with cervical cancer (155.5), breast cancer (148.2 months), melanoma of the skin (147.2 months), and prostate cancer (109.0 months) spent relatively longer time in the continuing phase when compared with other cancers (Table 1).

Estimates of lifetime costs varied widely across cancers, reflecting differences in survival and phase-specific unit costs. Discounted mean lifetime costs for all cancers combined were EUR 40,608 for males and EUR 36,921 for females (48,967 and 45,427 undiscounted). For all patients combined, costs were highest in the initial phase (EUR 21,808), followed by the terminal phase (EUR 12,085), and the continuing care phase (EUR 4347). Cancers with the highest lifetime costs per patient were myeloma (EUR 89,686), mouth/pharynx (EUR 66,619), non-Hodgkin lymphoma (EUR 65,528), and colon cancer (EUR 57,303), while melanoma of the skin (EUR 25,363), urinary tract (EUR 33,839), cervical cancer (EUR 38,294), and kidney cancer (EUR 39,561) were associated with the lowest lifetime costs.

The expected remaining lifetime for a patient diagnosed with cancer in 2010 was higher than for those diagnosed in 1995 (5-year survival of 61.5% and 55.5%, respectively). When data from 2010 through 2018 were used to estimate the probability of surviving for the first 8 years (compared with using data from 1995) the discounted lifetime costs for all cancers combined increased from 38,241 to 38,428 (+0.5%). Costs shifted from the terminal phase to the initial and continuing phase.

3.3. Cost scenarios toward 2034

When the lifetime costs were applied to NORDCAN projections for future incidence (assuming constant unit costs and survival), the yearly mean costs for all cancers combined were estimated at EUR 1911 million in 2034 (Table 2). This represents an annual growth of 2.4% (total growth of 52%) from 2016. The average annual growth in hospital costs was highest for melanoma of the skin (3.2%), kidney (2.9%), pancreatic (2.9%), and prostate cancer (2.9%).

In the scenario with a 10% decrease in the death risk in 2034 (scenario A), the yearly mean costs for all cancers combined were estimated at EUR 2039, corresponding to an increase in the yearly average costs of 130 million EUR (+6.7%) compared with the scenario with constant unit costs and survival. In the scenario with an annual increase in incidence of 3% (compared with 2.4% from NORDCAN) (scenario B) the yearly average cost totaled EUR 2139 (+230 million EUR), while a 30% increase in monthly unit costs (scenario C1) implied a total cost of EUR 2485 (+575 million EUR). Finally, when scenario A and C1 were combined, the total costs was estimated at EUR 2651 (+740 million EUR),

Table 1

Lifetime direct medical costs in hospitals and cost by phase per patient 2017-EUR (1 EUR = 9.8 NOK), 2017.

	Months in phase			Discounted (EUR)				Undiscounted (EUR)			
	Initial	Cont.	Terminal	Initial	Cont.	Terminal	Total	Initial	Cont.	Terminal	Total
All cancers											
All patients	10.2	96.9	7.7	21,808	4347	12,085	38,241	22,018	8757	15,274	46,049
Males	10.1	87.4	8.2	22,565	4952	13,091	40,608	22,776	9700	16,490	48,967
Females	10.3	106.8	7.3	21,137	3898	11,887	36,921	21,344	8038	16,045	45,427
mouth, pharynx											
All patients	10.6	89.7	8.5	40,303	4892	21,424	66,619	40,581	9616	26,940	77,137
Males	10.5	85.8	8.7	41,681	4807	23,977	70,465	41,960	9390	30,020	81,370
Females	10.7	96.7	8.2	37,838	5095	17,863	60,796	38,114	10,114	23,271	71,499
colon, rectum, rectosigmoid											
All patients	10.2	81.0	8.7	37,070	4960	15,273	57,303	37,388	9503	19,308	66,199
Males	10.2	77.1	8.9	38,277	5656	16,742	60,675	38,617	10,738	21,069	70,424
Females	10.3	84.8	8.6	35,725	4241	14,050	54,016	36,019	8191	18,150	62,359
Pancreas											
All patients	5.0	8.6	5.6	28,663	1294	18,100	48,057	28,865	2370	18,974	50,209
Males	5.0	8.2	5.6	29,464	1809	18,964	50,238	29,672	3201	19,930	52,803
Females	4.9	8.8	5.5	27,828	887	17,324	46,039	28,025	1674	18,210	47,909
lung, trachea											
All patients	7.0	20.6	7.3	28,243	2816	17,451	48,510	28,452	5028	19,116	52,596
Males	6.7	16.4	7.1	28,499	2519	17,921	48,940	28,709	4405	19,428	52,542
Females	7.5	26.8	7.6	28,105	3161	17,059	48,324	28,316	5764	19,218	53,299
melanoma											
All patients	11.5	147.2	6.4	11,260	5057	9045	25,363	11,409	10,832	12,101	34,342
Males	11.4	130.7	7.2	12,512	5805	11,380	29,698	12,678	12,184	14,970	39,832
Females	11.7	162.8	5.6	9913	4301	8091	22,305	10,041	9353	12,325	31,720
breast											
Females	11.7	148.2	7.0	40,775	6537	11,514	58,826	41,188	13,742	19,234	74,163
cervix uteri											
Females	11.3	155.5	5.1	20,002	3223	15,068	38,294	20,138	7158	25,687	52,983
prostate											
Males	11.5	109.0	9.7	40,526	4417	7871	52,815	40,934	8340	10,898	60,172
kidney (excl. renal pelvis)											
All patients	10.2	96.0	8.2	22,691	5175	11,695	39,561	22,822	10,213	15,130	48,165
Males	10.3	93.9	8.4	23,341	6349	12,773	42,464	23,477	12,439	16,532	52,448
Females	10.1	99.4	7.9	21,416	3379	9861	34,655	21,539	6739	13,053	41,331
urinary tract											
All patients	10.7	88.6	9.0	18,516	5699	9624	33,839	18,679	10,843	12,392	41,915
Males	10.8	88.7	9.1	18,420	6086	9317	33,823	18,583	11,514	11,998	42,095
Females	10.3	88.2	8.7	18,782	4822	10,376	33,979	18,942	9319	13,354	41,616
non-Hodgkin lymphoma											
All patients	10.3	104.6	7.4	35,738	12,942	16,848	65,528	36,038	26,290	21,534	83,861
Males	10.3	101.2	7.4	38,015	13,014	19,044	70,073	38,337	26,466	24,040	88,843
Females	10.4	108.8	7.4	32,795	12,796	14,322	59,913	33,065	25,974	18,675	77,714
leukemia											
All patients	10.0	91.0	7.3	30,902	6962	16,845	54,709	31,250	14,065	20,482	65,797
Males	10.1	87.9	7.2	33,416	6257	18,043	57,717	33,803	12,601	22,411	68,815
Females	10.0	94.8	7.4	27,890	7760	15,329	50,978	28,192	15,733	18,502	62,427
multiple myeloma											
All patients	10.0	45.2	9.7	40,045	25,632	24,009	89,686	40,472	42,590	28,653	111,715
Males	10.1	46.7	9.7	42,167	26,908	24,652	93,728	42,603	45,206	29,474	117,283
Females	10.0	43.4	9.8	37,355	24,195	23,063	84,614	37,771	39,628	27,326	104,725

while the combination of scenario A, B, and C1 implied a total cost of EUR 2967 (+1050 million EUR) in 2034.

4. Discussion

Lifetime costs were highest for patients with myeloma (EUR 89,686), mouth/pharynx cancer (EUR 66,619), and non-Hodgkin lymphoma (EUR 65,528), and lowest for melanoma (EUR 25,363), urinary tract (EUR 33,839), and cervical cancer (EUR 38,294). With constant prices, survival, and health care utilization, future cancer costs were estimated to increase by 2.4% annually toward 2034.

Several studies have estimated cancer-specific costs by using a "phase of care" approach," [5,6,12–17] making it a standard method to estimate costs over time.[6] Consistent with similar studies, we found that cancer-related costs followed a U-shaped curve, with most costs occurring in the initial and terminal phases.[5,6,15] Like previous estimates from United States,[5]

Table 2

Scenario analysis: future total direct medical cancer costs under different assumptions, by cancer type in Norway, million 2017-EUR (1 EUR = 9.8 NOK).

		2034* (Annual growth %)								
	2016	Constant unit costs without changes in prognosis†	10% decrease in the death risk per month (A)	3% annual increase in incidence (B)	30% increase monthly unit costs all phases (C1)	30% increase monthly unit costs initial phase (C2)	30% increase monthly unit costs continuing phase (C3)	30% increase monthly unit costs terminal phase (C4)	10% decreased death risk and 30% higher unit costs (A+C1)	10% decreased death risk, 30% higher unit costs and 3% annual increase in incidence (A+B+C1)
All cancers	1255	1911 (2.4%)	2039 (2.7%)	2139 (3.0%)	2485 (3.9%)	2238 (3.3%)	1976 (2.6%)	2092 (2.9%)	2651 (4.2%)	2967 (4.9%)
Mouth, pharynx	42	67 (2.5%)	70 (2.8%)	72 (3.0%)	87 (4.0%)	79 (3.5%)	68 (2.7%)	73 (3.1%)	91 (4.3%)	98 (4.8%)
Colon, rectum, rectosigmoid	249	386 (2.5%)	413 (2.9%)	424 (3.0%)	502 (4.0%)	461 (3.5%)	396 (2.6%)	417 (2.9%)	537 (4.4%)	590 (4.9%)
Pancreas	34	57 (2.9%)	62 (3.4%)	58 (3.0%)	75 (4.4%)	68 (3.9%)	58 (3.0%)	64 (3.5%)	81 (4.9%)	82 (5.0%)
Lung, trachea	149	179 (1.0%)	194 (1.5%)	255 (3.0%)	232 (2.5%)	210 (1.9%)	182 (1.1%)	198 (1.6%)	252 (2.9%)	359 (5.0%)
Melanoma	53	94 (3.2%)	94 (3.3%)	90 (3.0%)	122 (4.8%)	106 (4.0%)	99 (3.6%)	104 (3.8%)	122 (4.8%)	117 (4.5%)
Breast	198	275 (1.8%)	280 (1.9%)	338 (3.0%)	358 (3.3%)	333 (2.9%)	285 (2.0%)	292 (2.2%)	365 (3.4%)	447 (4.6%)
Cervix uteri	13	16 (1.1%)	16 (1.2%)	22 (3.0%)	21 (2.6%)	18 (1.9%)	16 (1.2%)	18 (1.7%)	21 (2.7%)	30 (4.6%)
Prostate	270	452 (2.9%)	463 (3.0%)	461 (3.0%)	588 (4.4%)	556 (4.1%)	463 (3.0%)	472 (3.1%)	602 (4.5%)	613 (4.7%)
Kidney (excl. renal pelvis)	34	57 (2.9%)	61 (3.2%)	59 (3.0%)	75 (4.4%)	67 (3.8%)	60 (3.1%)	62 (3.4%)	79 (4.7%)	81 (4.8%)
Urinary tract	60	90 (2.3%)	95 (2.6%)	101 (3.0%)	117 (3.8%)	104 (3.2%)	94 (2.6%)	97 (2.8%)	123 (4.1%)	139 (4.8%)
Non-Hodgkin lymphoma	67	85 (1.4%)	91 (1.7%)	113 (3.0%)	110 (2.8%)	99 (2.2%)	90 (1.7%)	91 (1.8%)	118 (3.2%)	158 (4.9%)
Leukemia	40	58 (2.2%)	63 (2.6%)	68 (3.0%)	76 (3.7%)	68 (3.0%)	60 (2.4%)	64 (2.7%)	81 (4.1%)	95 (4.9%)
Multiple myeloma	38	58 (2.4%)	63 (2.8%)	66 (3.0%)	76 (3.9%)	66 (3.1%)	63 (2.8%)	63 (2.8%)	82 (4.3%)	92 (5.0%)

* NORCAN reports average yearly incidence for the period 2032 to 2036. As a simplification the predicted incidence was assumed to occur in 2034.

† Assuming changes in the number of new cancer cases as reported by NORDCAN. Lifetime costs per new cancer case assumed to be equal to 2017 numbers (as reported in Table 1).

A, Annual growth in the number of new cases from NORDCAN, 10% decrease in monthly death risk, and no changes in monthly unit costs (costs as reported in Fig. 1).

B, Assuming a 3% increase in the number of new cases (compared with 2.4% reported by NORDCAN). Lifetime costs per new cancer case assumed to be equal to 2017 (as reported in Table 1).

C, Annual growth in the number of new cases from NORDCAN, 30% increase in monthly unit costs (reported in Fig. 1) in all phases (C1), initial phase (C2), continuing phase (C3), and terminal phase (C4) and no changes in death risk (prognosis).

Canada,[6] and New Zealand[16] our results suggest that there is an association between 5-year relative survival and cancer-related lifetime costs. Cancers with very poor prognosis and cancers with a relatively good prognosis tend to have low costs compared with those with a 5-year relative survival of 50% to 70%. Previous research also finds differences in costs between genders and these findings suggest that males may have higher treatment costs than females for the majority of cancer types.[5,6] In our study, estimated lifetime costs were higher for males in 9 out of 10 non-gender-specific cancers. Only urinary tract had higher costs for females (lifetime costs were marginally higher for females), a cancer which males tend to have better survival when compared with females.[30,31] Differences in cancer stage and age at the time of diagnosis and prognosis may explain some or all of the differences in costs. However, even for cancers with almost equal stage distribution at the time of diagnosis (colon, lung, and pancreatic cancer), males had higher lifetime costs when compared with females.

In contrast to other studies, we use gender and cancer-specific lifetime costs to develop scenarios for future treatment costs. Our results suggest that melanoma, kidney, pancreatic, and prostate cancer is expected to have a relatively high growth in coming years, while the growth in lung and cervical cancer costs is expected to be modest. The introduction of new costly treatment options (better overall survival) and screening programs may be of great importance for the future costs of some cancers (e.g., lung cancer).

Our findings may be important for policymakers for several reasons. First, timely gender- and cancer-specific estimates of cancer treatment costs are important for assessing equity of care and to better understand resource consumption associated with different cancers. For example, our results may indicate that cancer-related lifetime costs in Norway are higher for males when compared with females. Additionally, our results suggest a relationship between 5-year relative survival and treatment costs. Second, few studies of lifetime costs in public health care systems in Europe have been published, and current estimates found in the literature need to be updated. Incidence-based cost estimates are particularly relevant when policymakers evaluate different prevention and screening strategies, as lifetime costs give information on the potential resources the health care sector could save by preventing a new cancer case.[32] Third, scenarios for future treatment costs can aid policymakers in planning of future health care and increase understanding of how key factors such as incidence, survival, and unit costs influence the total health care costs. Policymakers must decide whether to increase capacity within all areas of oncology, or if some specialties should be prioritized. Projections of future costs by cancer site are useful for identifying future growth areas and to evaluate possible measures for cost containment.

There are several advantages of using registry data from a national health care system to estimate cancer-related treatment costs. Frist, the data cover the entire Norwegian population as cancer treatment in private hospitals is negligible. Additionally, the use of individual personal identification numbers allows patients to be followed over time after diagnosis. Second, all episodes of care are assigned a diagnostic code which enables us to estimate attributable costs because we know which treatment episodes are related to cancer. Third, DRG-weights and DRG-unit price used to estimate costs include all patient-related costs and are based on cost per patient calculation from reported accounting figures from Norwegian hospitals. This enables us to estimate the actual resource use (economic costs), and we avoid problems that arise when the market price differs from the actual resource use needed to produce the service (e.g., out of pocket payments).

Despite the strength of a large national sample, our study has several limitations. Due to legal restrictions, we were not able to link NPR and CRN data. However, previous studies indicate that the diagnostic codes in NPR are valid when compared with data from CRN and misclassification of patients is unlikely to influence our results.[33] Our data did not allow for a net cost strategy (differences in costs between cancer patients and matched non-cancer patients) due to lack of information about non-cancer patients. Although the attributable cost strategy is fairly straightforward, we may run the risk of underestimating cancer-related costs because some costs are attributed to other diseases (e.g., costs associated with heart problems arising downstream from the cardiotoxicity associated with chemotherapy may not show up in the data as a cancer-related episode if the ICD-10 coding indicates cardiovascular disease).

Cancer stage at the time of diagnosis is presumably of great importance for the treatment intensity and thereby the costs. For melanoma, several patients with local disease undergo relatively simple treatment (surgical excision of the primary melanoma) and are associated with low costs compared with patients with distant metastases, thus contributing to a low average cost. We only included patient-related hospital costs which account for approximately 65% of the direct health care costs in Norway.[34] The remaining 35% include primary care (2.7%), institutional care and home nursing services (16.7%), out-patient diagnostics imaging and laboratory services (6.6%), pharmacy dispensed drugs (7.8%), and other non-patient-related costs in hospitals (research and development , capital costs, ambulance services, etc) (1.9%).[34] We did not have long-term data to estimate costs in the continuing phase, and estimates were based on years 4, 5, 6, and 7 after diagnosis for patients diagnosed in 2010. The treatment intensity may be higher in these years as compared with longer follow-up and costs in the continuing phase may be slightly overestimated. To ensure comparability we employed the same length for all phases. However, for some cancers, the initial treatment phase may extend beyond the first year (e.g., hormonal therapy for breast cancer). Finally, predictions of future costs are by nature associated with much uncertainty. Structural changes over time in technology and medical practice will likely affect future lifetime costs as survival and unit costs change.

In conclusion, cancers with an intermediate prognosis (50%–70% 5-year relative survival) are associated with higher direct medical costs than those with relatively good or poor prognosis. Additionally, our results suggest that costs of treating male patients are higher compared with females. Future research should investigate possible explanations of these differences.

Author contributions

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Paper III

BMJ Open

What are determinants of utilisation of pharmaceutical anticancer treatment during the last year of life in Norway? A retrospective registry study

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ABSTRACT

Objectives The objective of this study was to investigate the use of, and predictors for, pharmaceutical anticancer treatment (PACT) towards the end of a patient's life in a country with a public healthcare system.

Design Retrospective registry study.

Setting Secondary care in Norway.

Participants All Norwegian patients with cancer (International Classification of Diseases tenth revision (ICD-10) codes C00–99, D00–09, D37–48) in contact with a somatic hospital in Norway between 2009 and 2017 (N=420 655). Analyses were performed on a subsample of decedents with follow-back time of more than 1 year (2013–2017, N=52 496).

Interventions N/A.

Primary and secondary outcome measures Proportion of patients receiving PACT during the last year and month of life. We calculated CIs with block bootstrapping, while predictors of PACT were estimated with logistic regression.

Results 24.0% (95% CI 23.4% to 24.6%) of the patients received PACT during the last year of life and 3.2% (95% CI 3.0% to 3.5%) during their final month. The proportion during the last month was highest for multiple myeloma (12.7%) and breast cancer (6.5%) and lowest for urinary tract (1.1%) and prostate and kidney cancer (1.4%). Patients living in northern (OR 0.80, 95% CI 0.68 to 0.94) and western (OR 0.85, 95% CI 0.75 to 0.96) Norway had lower odds of PACT during the last month, while patients with myeloma (OR 3.0, 95% CI 2.5 to 3.7) and breast (OR 1.4, 95% CI 1.1 to 1.6) had higher odds. Kidney cancer (OR 0.25, 95% CI 0.2. to 0.4), urinary tract (OR 0.38, 95% CI 0.3 to 0.5) and prostate cancer (OR 0.4, 95% CI 0.3 to 0.5) were associated with lower probability of receiving PACT within the last month.

Conclusions The proportion of patients receiving PACT in Norway is lower than in several other industrialised countries. Age, type of cancer and area of living are significant determinants of variation in PACT.

Strengths and limitations of this study

- ► Nationwide registry data during a period of 5 years with a range of key covariates.
- ► No selection bias as virtually all patients with cancer in Norway receive medical care in public hospitals.
- ► The data capture both hospital-administered and patient-administered pharmaceutical treatment.
- ► The findings do not allow conclusions about whether patients receive too much or too little treatment.
- ► Lack of information on disease stage, the treating clinician and comorbidities (possible explanatory variables).

INTRODUCTION

A fundamental problem for clinicians who consider prescribing end-of-life pharmaceutical anticancer treatment (PACT) is the assessment of the remaining lifetime of an individual patient and the expected patient benefit from the treatment. Whether oncologists should prescribe PACT near the end of life raises controversial ethical issues concerning the potential prolongation of life, quality of life for patient and their families, and the use of scarce healthcare resources. When such treatment is given near the end of life—the terminal phase, it may offer little potential to prolong life and is sometimes called futile—'serving no useful purpose, completely ineffective.'[1 2] The definition of the terminal phase has varied over time. Initially, terminal phase was defined as the time in which palliative care should be applied instead of active therapies. More recently it has become clear that palliative care should start earlier when active therapies are still in use.[3] In this study, we explore those receiving PACT who are not in the terminal phase according to the first definition.

PACT may be associated with extensive adverse effects, and may impact the patient's ability to engage in meaningful life and prepare for death.[4] It has been suggested that too much PACT in the last month of life may shorten life and, if side effects are not diagnosed and treated, reduce quality of life.[5–7] Still, the treatment requires funds and

may displace beneficial treatment for others. In Norway, health authorities only fund new treatments that are cost-effective according to national guidelines and prioritising processes because budgets are not large enough to cover all treatments even if they are effective.[8]

Previous studies indicate that up to 38% of patients with cancer receive chemotherapy or other life-sustaining treatments during their last month of life.[9] However, end-of-life treatment decisions may differ across countries or within jurisdictions.[9] In some healthcare systems, oncologists have an incentive to prescribe PACT because their remuneration depends on it.[10] Such systems typically also impose a cost on patients in terms of copayments. In contrast, Norway has a public healthcare system in which oncologists have no personal financial incentive to prescribe, but also little disincentive in terms of patient co-payments (Norway has copayment on certain types of treatments, but a low total annual maximum of approximately US$270 in 2020). It is, therefore, unclear which system results in the highest end-of-life PACT rates. The evidence of factors influencing end-of-life care in European countries is also lacking. In a 2014 systematic review of end-of-life studies in cancer care, Langton *et al*[9] found 15 studies that examined quality indicators (including use of chemotherapy) for end-of-life care, of which none were from Europe. More recently, however, such studies have been published for Denmark and France.[11 12] The proportion receiving chemotherapy during the last 14 days of life was 4.2% in Denmark and 11.3% in France.[11 12]

Use of PACT towards the end of life represents a difficult medical decision and an important policy issue for patients and society. One approach to improve the quality in end-of-life care is to gain a better understanding of current patterns of end-of-life treatment at a national level in a public healthcare system where the overall goal is to offer patients equitable access to care. We used comprehensive individual patient-level nationwide data from the Norwegian Patient Registry[13] to answer two research questions: First, what proportion of patients receive PACT during their last year and months of life in Norway? Second, to what extent are treatment decisions influenced by patients' age, gender, type of cancer or geographical factors?

METHODS

We performed a retrospective cohort study using data from the Norwegian Patient Registry (delivered August 2018). Each episode of care (inpatient stay, day care or outpatient visit) in the Norwegian Patient Registry has a main International Classification of Diseases Tenth Revision (ICD-10) diagnostic code, possibly supplementary diagnostic codes, and a unique patient identifier that allows patients to be followed over time. Diagnostic codes in the Norwegian Patient Registry have proved valid when compared with the Cancer Registry of Norway.[14] Each episode of care also had a diagnosis-related groups (DRG) code and an Anatomical Therapeutic Chemical (ATC) code in cases where PACT was administered. Additionally, the dataset encompassed the following variables: unique patient ID, patient age and gender, county of residence (19 counties), year/month of episode, medical and surgical procedure codes, code for infusion of PACT, days until death and level of care (hospital outpatient/day care and inpatient).

We included all episodes of care with ICD-10 codes C00–99, D00–09, D37–48. Norway has a population of approximately 5.4 million, and in 2017, a total of 33 564 new cancer cases were reported and 273 741 Norwegians were alive after having received a cancer diagnosis.[15] Cancer treatment in hospice and private hospitals is negligible, thus, the Norwegian Patient Registry includes virtually all Norwegian patients with cancer. Our dataset encompassed 7 423 828 episodes for 420 655 patients. Our data included all patients with cancer who had been in contact with Norwegian hospitals (outpatient or inpatient) between 2009 and 2017 among whom 128 413 were reported dead by the end of 2017. All analyses were performed on a subset of the data (a 5 year cohort of patients who died during 2013–2017 with at least 1-year follow-back data, N=52 496) as patient administered treatment (oral and subcutaneous) were not identifiable in the registry before 2013 (see figure 1). Patient characteristics for the complete sample for the period 2013–2017 and the subsample used for analyses are presented in online supplemental table S1. The Norwegian Patient Registry has systems for data cleaning and continually check for correctness. We have further checked for correctness and consistency without detecting need for further cleaning.

Classification of cancer diagnosis

Patients with more than one cancer diagnosis were classified into mutually exclusive cancer diagnoses based on their main and supplementary diagnosis (online supplemental table S1). Patients with multiple cancer diagnoses were assigned to a single diagnosis based on their most frequently listed cancer diagnosis type. Classification of cancer diagnosis was based on data from 2009 to 2017.

Pharmaceutical anticancer treatment

PACT included cytostatic agents, cytotoxic agents, targeted therapies and immunotherapies. We classified PACT as intravenous, subcutaneous or oral by means of ATC codes and the DRG system. To calculate the proportion of patient who received PACT 1 year before death, patients with follow-back time less than 1 year from first episode of cancer until death were excluded from the analyses. We ran additional analyses to investigate the effect of limiting our study population to patients with at least 1-year follow-back.

Statistical analysis

For each patient, we registered whether he or she received PACT during the following periods prior to death: 12, 9, 6 and 3 months, and 1, 2, 3, 4, 5, 6, 7 and 8 weeks. Proportion of patients receiving PACT were defined as $\frac{PACT_t}{N}$

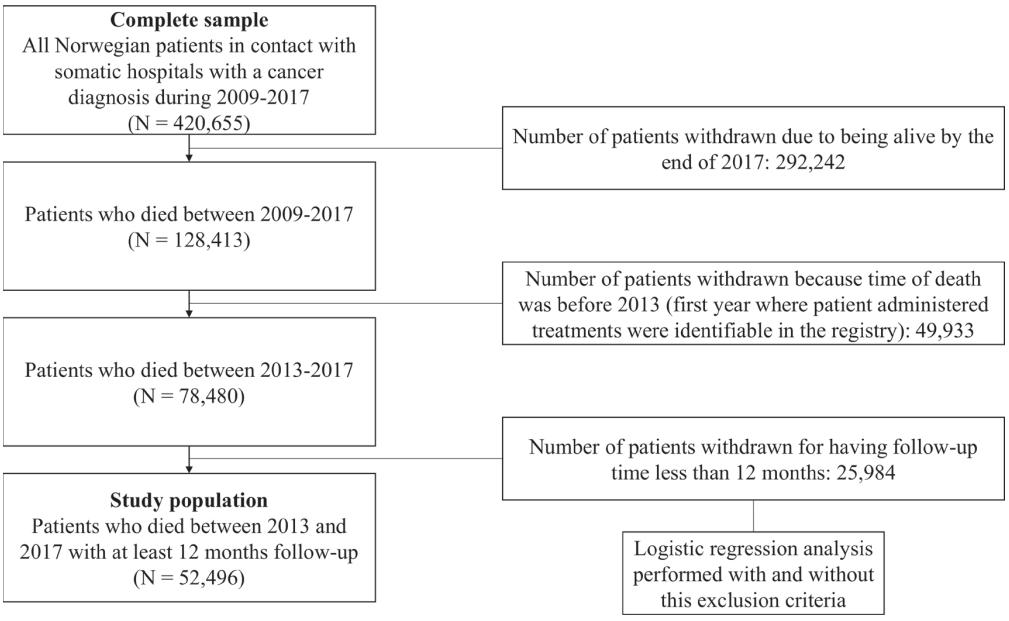

Figure 1 Flow diagram for selection of study population.

where $PACT_t$ is the number of patients who received PACT during time period t (t = *time period prior to death* and N is the number of patients with more than 12 months follow-back time before death. In other words, the numbers present aggregates over time periods, not treatment at a point in time.

We used block bootstrapping to estimate the SE of the proportion of patients who received PACT during time period t.[16] To reproduce the dependence structure of the observed data in the resampled data, we created blocks of consecutive data defined as each individual patient's treatment course (last year before death). We estimated logistic regression models to identify predictors of receiving PACT during the last month of life. The following variables were included in the multivariable regression model: year of death, patient's age at death, region of hospital, gender and type of cancer. The variables were chosen because they were expected to influence the use of PACT and due to availability in the obtained data.

All analyses were performed using STATA software V.14 (StataCorp).

Patient and public involvement

No patient involved.

RESULTS

Use of end-of-life PACT

A total of 301 611 patients with cancer received care in a hospital during the period 2013–2017. Of these patients, 52 496 patients (17.4%) were reported dead by the end of 2017 and had at least 1-year follow-back. Of this group, 12 604 (24.0%, 95% CI 23.4% to 24.6%) received PACT during the last year of life (figure 2). The rates of PACT 1 year prior to death were highest for pancreatic cancer (60.7%, 95% CI 58.0% to 63.5%), multiple myeloma (53.0%, 95% CI 50.2% to 55.8) and lung cancer (45.7%, 95% CI 44.4% to 47.1%). Kidney cancer (11.7%, 95% CI 9.6% to 13.7%), urinary tract (12.8%, 95% CI 11.6% to 14.0%) and leukaemia (14.4%, 95% CI 3.1% to 15.8%) had low PACT rates during last year of life. In total 1691 (3.2%, 95% CI 3.0% to 3.5%) received PACT at least once during the last month before death, and patients with multiple myeloma (12.7%, 95% CI 10.9% to 14.5%), breast (6.5%, 95% CI 5.7% to 7.3%) and mouth/pharynx cancer (6.0%, 95% CI 4.3% to 7.7%) had the highest rates. Among cancers with low PACT rates during the last month before death were urinary tract (1.1%, 95% CI 0.7% to 1.5%), kidney cancer (1.4%, 95% CI 0.7% to 2.0%) and prostate cancer (1.4%, 95% CI 1.1% to 1.6%).

Predictors of variation in treatment decisions

The odds for receiving PACT during the last month of life were highest for patients aged 40–59 years and lowest for those aged 80+ (table 1). Adjusted for the included covariates, patients living in Northern (OR 0.80, 95% CI 0.68 to 0.94) or Western Norway (OR 0.85, 95% CI 0.75 to 0.96) had lower odds of receiving PACT within the last month of life compared with those living in the South-East region. Also, patients diagnosed with multiple myeloma (OR 3.03, 95% CI 2.48 to 3.72) and breast cancer (OR 1.36, 95% CI 1.13 to 1.63) had higher odds of receiving PACT during the last month of life (compared with lung cancer). Kidney cancer (OR 0.25, 95% CI 0.15 to 0.43), urinary tract (OR 0.38, 95% CI 0.27 to 0.53) and prostate cancer (OR 0.39, 95% CI 0.31 to 0.49) had significantly lower odds. There was no clear trend towards higher or lower provision of end-of-life PACT during the

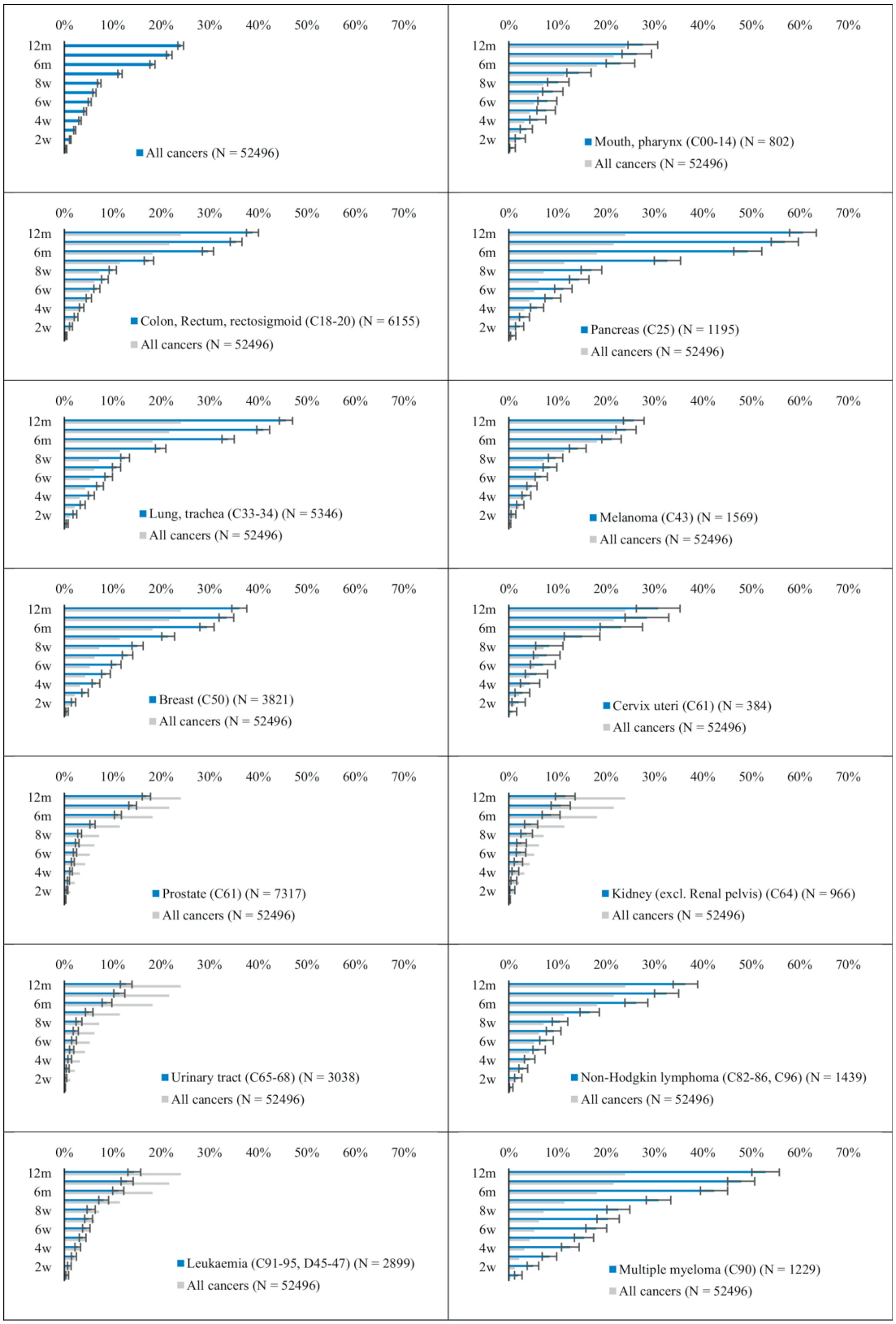

Figure 2 Proportion of patients with cancer receiving pharmaceutical anticancer treatment during last weeks or months of life, 2013–2017.

Table 1 Multivariable logistic regression analysis of the odds that patients received pharmaceutical anticancer treatment last month before death

	OR (95% CI)	P value
Year of death		
Reference: 2013	0.99 (0.96 to 1.03)	0.74
Age		
60–69 years (reference)	1.00	NA
0–9 years	0.85 (0.20 to 3.52)	0.82
10–19 years vs 60–69 years	0.74 (0.23 to 2.38)	0.62
20–29 years vs 60–69 years	0.68 (0.29 to 1.55)	0.36
30–39 years vs 60–69 years	1.08 (0.73 to 1.61)	0.70
40–49 years vs 60–69 years	1.46 (1.19 to 1.78)	<0.001
50–59 years vs 60–69 years	1.33 (1.16 to 1.53)	<0.001
70–79 years vs 60–69 years	0.62 (0.55 to 0.69)	<0.001
80–89 years vs 60–69 years	0.14 (0.12 to 0.17)	<0.001
90–99 years vs 60–69 years	0.03 (0.14 to 0.53)	<0.001
Hospital affiliation (regional health authority)		
South-Eastern (reference)	1.00	NA
Central	1.02 (0.90 to 1.17)	0.74
Western	0.85 (0.75 to 0.96)	0.01
Northern	0.80 (0.68 to 0.94)	0.01
Gender		
Women	0.97 (0.87 to 1.07)	0.52
Type of cancer		
Lung cancer (reference)	1.00	NA
Mouth, pharynx	1.14 (0.84 to 1.55)	0.41
Colon, rectum, rectosigmoid	0.84 (0.71 to 0.99)	0.05
Pancreatic	1.21 (0.94 to 1.54)	0.14
Melanoma	0.77 (0.58 to 1.03)	0.08
Breast	1.36 (1.13 to 1.63)	<0.001
Cervix uteri	0.69 (0.42 to 1.13)	0.14
Prostate	0.39 (0.31 to 0.49)	<0.001
Kidney (excl. renal pelvis)	0.25 (0.15 to 0.43)	<0.001
Urinary tract	0.38 (0.27 to 0.53)	<0.001
Non-Hodgkin's lymphoma	1.06 (0.81 to 1.38)	0.69
Leukaemia	0.72 (0.57 to 0.93)	0.01
Multiple myeloma	3.03 (2.48 to 3.72)	<0.001
Residual group*	0.66 (0.57 to 0.76)	<0.001

Constant: 0.10 (0.08–0.11).
*Residual group includes all cancers not presented above.
NA, not applicable; OR, odds ratio.

observation period and we found no differences between genders.

Additionally, we ran analyses for women and men separately and analyses excluding cancers that only occur for one gender (breast, uterine, prostate), but we were not able to find any differences between genders. Also, we tested for several plausible interactions between gender, age, health region and cancer type. In total, we tested for 36 interactions. Six were borderline significant, but none of the interactions were meaningful (online supplemental table S2). Finally, we investigated the impact of restricting our population to patients with at least a 1-month follow back period (compared with 1 year in our base-case analysis). The predictors were not substantially affected by the change in patient population (online supplemental table S3).

DISCUSSION

One in four Norwegian patients with cancer receive PACT during their last year of life, while 3% are treated within the last month. Patients who are elderly or residents of Northern or Western Norway (regions with a lower population density compared with the south-east region) are less likely to receive PACT during the last month of life. The proportion receiving PACT end-of-life in Norway are relatively low compared with other European countries with similar healthcare systems, indicating that medical culture and patient preference impact choice of treatment end of life.

Previous studies indicate high levels of PACT use near the end of life with rates up to 38% during last month in countries in North America, Asia and Europe.[9 11 17–24] Our findings of generally low PACT rates in Norway align well with results reported previously[23] and the relative low rates found in our neighbouring country Denmark[12] which has a similar healthcare system. Having a public healthcare system, where oncologist have no financial incentive to prescribe, may explain the lower rates in Norway. Additionally, due to strict priority setting for pharmaceuticals, not all new treatment options are available to Norwegian patients. Other factors may also explain the lower rates, such as the role of palliative care teams or culture and attitude towards end-of-life treatment in the clinical environments. Even if the negligible patient copayments in Norway should favour use of PACT, the inhibitive factors dominate the final decisions. Our findings support previous research that factors such as age, tumour site and region of residence influence the level of PACT near death.[11 20 24]

The main strength of our study lies in the use of nationwide registry data for a period of 5 years with a range of key covariates. Almost all patients with cancer in Norway receive medical care in public hospitals, so our data cover virtually the entire Norwegian population (no selection bias). Our data also include a range of covariates allowing adjustment for patient characteristics, year of treatment, type of cancer and patient's place of living. Another strength is that we capture both hospital-administered and patient-administered PACT. In recent years, subcutaneous and oral PACT have become important modalities, making it essential to include these treatments when studying end-of-life care.

However, the study also has several limitations. First, we do not have information on disease stage, the treating clinician, comorbidities or functional status. Complete information of ATC codes was also not available; thus,

classes of PACT were not considered as determinant in the analyses. A key challenge of the study design is that we cannot translate the findings directly into how to change clinical practice. Second, there is some risk of misclassification of diagnosis. We chose patients' most frequent diagnosis but tested alternative algorithms for assigning diagnosis. In 90% of the cases the same cancer diagnosis was assigned regardless of which algorithm had been applied. For legal reasons, our diagnosis data could not be confirmed by linkage to the cancer registry, but diagnostic codes in the Norwegian Patient Registry have proved valid when compared with the Cancer Registry of Norway.[14] Even though some patients may have been assigned an incorrect diagnosis, it is unlikely that this would substantially impact the analysis of predictors. Third, we do not have information on the cause of death and assumed that all patients died from their cancer. We analyse a subsample of descendants between 2013 and 2017 (52 496 patients), which correspond well to the number of cancer deaths in Norway during this period in the cause of death registry (54 204 deaths). Lastly, retrospective studies like this one may create a biased portrait of terminal care because of the way subjects are identified and the time periods that are examined.[25] To address this challenge, we ran additional analyses illustrating that our results only were marginally affected by changes in the study population. Our analyses are not based on any specific definition of terminal phase, because we only have information on the time of death, not the intention of the treatment given.

Clinicians' choice of end-of-life treatment may be influenced by characteristics of the provider (supply factors) and of the patients, their dependents and society in general (demand factors). On the supply side, clinicians may be affected by their department's culture, their training, experience and marketing from the pharmaceutical industry. Additionally, payment systems and reimbursement schemes have been found to influence clinicians' use of PACT.[26] The regional differences found in our study may indicate that department culture and training may influence end-of-life treatment. Also, distance to hospital may play a role as travel distances are less in the south-east region of Norway than others. However, it is not necessarily the case that lower use of PACT during the patient's final months imply better or more appropriate care.

Better knowledge on end-of-life treatment and factors influencing the use of PACT are important in order to ensure optimal treatment to avoid undue suffering among patients and their dependents and unnecessary use of healthcare resources.

CONCLUSION

Use of chemotherapy near end of life is modest in the Norwegian healthcare system with universal access to care and minimal patient copayment. Several other countries with similar systems have higher PACT rates during the last months of life, which indicate that not only financial incentives, but also medical culture and patient preferences may impact choice of treatment. Information on PACT rates may be useful for clinicians in order to achieve optimal end-of-life care.

Contributors CB: Data collection, study design, analysis, interpretation of results, preparation of the manuscript and approval of the manuscript. SK: Study design, interpretation of results, preparation of the manuscript and approval of the manuscript. EMS: Data collection, interpretation of results, preparation of the manuscript and approval of the manuscript. HOM: Interpretation of results, preparation of the manuscript and approval of the manuscript. ISK: Data collection, study design, interpretation of results, preparation of the manuscript and approval of the manuscript.

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Competing interests CB, EMS and ISK are affiliated with Oslo Economics and have all completed consultancy assignments for several pharmaceutical companies in recent years. None of the projects have been related to the work presented in this paper.

Patient consent for publication Not applicable.

Ethics approval The Norwegian Data Inspectorate (17/00565–2/CDG) and the Regional Committees for Medical and Health Research Ethics (2017/769/REK) granted approval for the use of data from the Norwegian Patient Registry.

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