Sustainable Cancer Care

Enhancing Value and Managing Costs

Cilla Vrinzen

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Table of contents

Chapter 1

General introduction

This General Introduction explains the epidemiology of cancer and sheds light on the costs of healthcare, especially the rising cancer care costs. Moreover, two significant factors contributing to the high and escalating costs of cancer care are highlighted: the coexistence of different diseases alongside cancer and the introduction of more expensive oncological drugs. Additionally, this chapter elaborates on the concept of 'value' within oncological care. Finally, this chapter introduces cancer networks. Cancer networks are a model for cancer care that may fit the challenges of a rising increase in patient costs and create more value by providing personalised and integrated care. This chapter ends with the outline and aim of this thesis.

Cancer Epidemiology

The global infcidence of cancer is expected to increase from 19 million in 2020 to 30 million in 2040.(1) In the Netherlands, cancer incidence has increased from approximately 56,000 in 1989 to 118,000 in 2019 and is expected to reach 156,000 diagnoses in 2032.(2)

Several factors contribute to this increase. First demographic development: as the 'baby boom' generation ages, the number of elderly people increases in absolute terms, and cancer predominantly afflicts the elderly. Elderly people aged 75 or older account for more than a third of cancer incidence.(3) In the Netherlands, there will be an increase in cancer incidence from nearly 40,000 in 2019 to 67,000 in 2032 among people aged 75 or older.(2) Second, lifestyle contributes to an increase in cancer. For instance, obesity, less exercise, smoking, and alcohol consumption all contribute to increased cancer risks, leading to a rise in various cancer types.(2) Thirdly, advancements in screening and diagnostics have led to increased detection of cancer that would have previously remained undetected.(2) Last, life expectancy is increasing. This also leads to more elderly people and, therefore, more cancer diagnoses. Life expectancy is increasing partly because treatment options are improving across healthcare. For example, in the Netherlands, the number of patients dying from cardiovascular disease decreased from more than 49,000 in 2000 to less than 35,000 in 2020.(4) People who previously died from cardiovascular disease or other diseases are living longer and become at risk for cancer. An international comparison shows that cancer incidence in the Netherlands is relatively high.(5) This partly reflects lifestyle-related factors, but better survival from other conditions can also increase these numbers. Besides the growth in incidence, patients with cancer live longer.(6) The percentage of male

patients still alive five years after diagnosis increased from 42% in 1990-1994 to 66% in 2015-2019. For women, the 5-year survival over the same period increased from 56% to 70%.(2) This progress in survival is, among other things, due to improved treatments and diagnostics. Examples of this are the introduction of new systemic treatments (targeted therapies and immunotherapies) or molecular diagnostics and new advanced radiation oncology, which enables precision medicine with more effective treatments. In addition, improved early detection by screening of, for instance, breast, cervical, and colon cancer, detects cancer at a more treatable stage. Even though study results are controversial regarding cost-effectiveness, screening could decrease mortality.(7, 8)

As a result of the increase in incidence and survival rates, there has been a notable increase in the number of cancer survivors. In the Netherlands, the ten-year prevalence of cancer was approximately 292,000 in 2000, representing individuals diagnosed within the previous ten years.(2) In 2019, this ten-year prevalence was higher than 573,000 people and is expected to increase to approximately 780,000 in 2032. It is predicted that in 2032, 1.4 million individuals in the Netherlands will have a history of a cancer diagnosis, reflecting both the increase in cancer diagnosis and the reduced mortality rates.(2)

Costs of care

The costs of healthcare are high and continue to increase.(9) In the Netherlands, the percentage of the gross domestic product spent on collective healthcare costs rose from 6% in 2000 to 10% in 2021 and is expected to increase to 18% in 2060.(10) This is due to a combination of factors, such as an increase in average life expectancy, the entry of new expensive technologies into the market, rising healthcare wages, and policies that accommodate a rise in benefits. In 2020, the Netherlands ranked 5th on the list of European Union countries with the highest share of GDP spent on health, after Germany, France, Sweden and Austria.(11)

In the Netherlands, the direct costs of oncological care were €6.5 billion in 2019, which accounted for 6.7% of total healthcare expenditure.(12) These numbers seem small in comparison to the costs spent on, for example, mental disorders, which was €29 billion in 2019, of which dementia accounted for €10 billion, mainly because of expensive stays in nursing homes.(13) However, cancer is, besides mental disorders, cardiovascular diseases, and oral health, one of the most significant cost groups. In addition, the life span of cancer is (still) relatively short in comparison to most

other chronic diseases, which ultimately leads to lower costs. However, comparing hospital costs in the last year of life, costs are higher for patients with cancer as a cause of death than for patients who die from other diseases.(14)

Costs for cancer care will increase for several reasons. First, the increase in survival from cancer might lead to an increasing need for supportive care, such as physiotherapy and rehabilitation care or nursing home care for elderly people who can no longer continue to live independently after their treatment. Second, because patients with cancer are, on average, older at diagnosis and suffer from comorbidities, care provision is complex. Comorbidities increase treatment costs and pose a challenge for the organisation of care. Last, the increase in more expensive technological developments, most notably new pharmaceuticals, increases healthcare costs. A future projection by the National Institute for Public Health and the Environment (RIVM) predicts that healthcare expenditure on cancer will grow from €5.6 billion in 2015 to €61 billion in 2060.(9) From a predicted average annual real growth of 5.4 per cent, only 0.4 percentage points can be attributed to the demographics of an increasingly ageing population. Most of this is due to medical developments such as new expensive medicines. More than half of the costs of expensive medicine in the Netherlands are in oncological care.(15)

Below, we elaborate on two main cost drivers for oncological care: comorbidity and expensive drugs.

Comorbidity

In addition to the rising incidence of cancer, there is an increasing prevalence of comorbidity.(16) Comorbidity is defined as the coexistence of a disorder in addition to a primary disease of interest. Different factors influence the likelihood of comorbidity. First, the possibility of having multiple chronic conditions increases with age. In the Netherlands, the proportion of patients with comorbidities besides their cancer diagnosis increases from 40% comorbidity in patients up to 60 years to 87% in patients 90 years or older.(16) Also, the number of patients with more than one type of comorbidity increases with age. Of patients up to 60 years old, 14% have two or more concomitant diseases when diagnosed with cancer. This rises to 60% among the patients 90 years or older. Approximately half of the oncological patients above the age of 75 have cardiovascular disease and hypertension.(16) The shift towards an ageing population is a significant driver of co- or multimorbidity. Multi-morbidity is defined as the presence of two or more chronic illnesses. In

addition, medical advancements have led to improved treatments and management strategies for different diseases, enhancing survival rates for many diseases. This also means that individuals are more likely to live with multiple conditions.

Cancer and comorbidities can also be intertwined. Comorbidity can increase the chance of cancer or vice versa. For instance, chronic hepatitis B can increase the chance of liver cancer (17), while neuropathy may result from chemotherapy treatment.(18) In addition, comorbidities can occur that are not related to the cancer diagnosis but may be caused by a shared risk factor. Risk factors such as smoking, alcohol, lack of physical activity and older age are shared between cancer and different common chronic conditions (e.g. diabetes or chronic obstructive pulmonary disease).(19, 20)

Co- and multimorbidity poses complex challenges for patients, healthcare providers, and healthcare systems. Treating individual conditions in isolation might not be effective, as the interactions with other conditions can complicate treatment plans and outcomes. Patients with comorbidities are less likely to receive standard cancer treatments such as surgery, chemotherapy, and radiation therapy, and their chance of completing a course of cancer treatment is lower.(21, 22) Comorbidities affect the outcomes of cancer treatments. Postoperative complications, morbidity and mortality all are higher in patients with comorbidities, while quality of life is lower.(21-24)

Comorbidity management may become more complicated with an increasing sub-specialisation of care in the Netherlands. Due to the centralisation of oncological care, comorbidity management risks increasing fragmentation between healthcare organisations.(25) Patients need personalised treatment plans that address both cancer and possible comorbidity, taking into account potential drug interactions and side effects.

Last, comorbidities increase healthcare utilisation and costs for individuals diagnosed with cancer.(21, 24) The topmost expensive patients in the Netherlands often have multimorbidities. The average number of conditions is 5.5 for the top 1% most costly patients.(26) The cost associated with cancer for people without any comorbidity is lower than costs associated with cancer in patients with a comorbidity.(27)

Given the effect of multiple chronic conditions on patients' survival and quality of life, the potential fragmentation of care, and high healthcare costs, an integrated

approach to healthcare delivery is needed. One way of delivering this integrated care is through oncological networking, in which different organisations collaborate to provide high-quality patient care. We will elaborate on this later in this General Introduction.

Expensive drugs

New developments follow each other rapidly in oncological care, and treatment options for patients are constantly increasing. For a long time, cancer treatments mainly consisted of surgery, radiation therapy, and chemotherapy. Recently, among others, immunotherapies and targeted therapies have been added to that list, which can contribute to more durable clinical outcomes.(28) However, the rapidly increasing number of that kind of medicines, the exceptionally high prices and the increasing use lead to growing pressure on the affordability of healthcare.

In recent years, the use of expensive drugs in cancer treatment has increased from almost 122,000 users in 2017 to over 150,000 users in 2021 in the Netherlands.(29) The average costs per user increased from €7,802 in 2017 to €10,040 in 2021.(30) The expenditure on these drugs is expected to increase by approximately €1 billion between 2021 and 2026 (on average about 7% per year).(31) This increase is mainly due to the introduction of new medicines, particularly for haemato-oncology.(32) This increase is also caused by expanding indications for existing medicines.(31) Allocating an increasing budget to this oncological care might come at the cost of different innovations or regular care for different patients; this is called opportunity costs.

Despite introducing new treatment options, the effect on population-level survival remains uncertain in various patient groups.(33) A report from the Belgium Healthcare Knowledge Centre revealed trends in survival and costs spent on expensive drugs based on observational real-world data for different tumour types.(34) This study stated that half of the tumour types have an increasing trend in survival in combination with an increase in gross drug expenditures. For instance, for stage IV non-small cell lung cancer, 3-year survival significantly improved from 5.6% in 2004 to 15.5% in 2017, although median survival remained constant at 0.5-0.6 years. At the same time, the costs of drugs tripled from around €40 million in 2010 to €120 million in 2017.(34) More recent data from the Netherlands shows that costs for expensive drugs increased from around €170 million in 2018 to €370 million in 2022 for stage IV NSCLC.(15) These costs are probably overestimated

because they do not correct for any discounts. Still, this increase is significant, while the median survival increased from 4.7 months in 2013-2017 to 5.6 months in 2018-2022. The modest increase in real-world survival in patients with metastatic cancer emphasises the need to evaluate the value of (new) treatments critically. Mainly because actual treatment outcomes often differ from those observed in clinical trials, typically involving a younger and fitter patient cohort.(35, 36)

Understanding which patients can benefit from specific medications is essential. With emerging techniques like whole genome sequencing and next genome sequencing, tumours' more complete genetic profiles can increasingly be mapped. As a result of developments in companion diagnostics and targeted therapies, cancer treatment is increasingly becoming a matter of precision medicine.

At this moment, expensive drugs are increasingly hitting willingness to pay (WTP) thresholds. In the Netherlands, the maximum WTP is €80,000 per gain in Quality-Adjusted-Life-Year (QALY).(37) The QALY is a measure of value in which life expectancy and quality of life are merged.(38) However, using such a WTP limit for reimbursement is subject to much public debate because the Ministry of Health can deviate from this threshold. It should also be noted that this threshold was established in 2006 and has not been indexed for inflation since then. As a result of these changes, reimbursement may decline over time. For example, a specific pharmaceutical drug for triple-negative breast cancer was declined for national reimbursement in 2023. This drug could increase survival by 5.4 months. However, it bore extremely high costs with €2.9 million per patient, or between €196,929 and €241,231 per QALY.(39) *Box 1* explains the reimbursement process for expensive drugs in the Netherlands in more detail.

Box 1. Description of reimbursement decision regarding expensive drugs in the Netherlands

The Dutch government decides on the reimbursement provided by the insurance package. The National Healthcare Institute (Zorginstituut Nederland, ZIN) assesses new technologies on (cost-)effectiveness and advises the Minister of Health on the reimbursement and uptake into the insurance benefit package. New drugs with an expected significant budget impact are first placed in the so-called 'reimbursement lock'. A drug is eligible for the 'lock' if the costs for treating a new indication are € 50,000 per patient per year or more; total costs are €10 million per year or more; and treatments with an extension to one or more new indications are placed in the 'lock' if the total expenses exceed € 20 million per year. The ZIN assesses drugs placed in the 'lock' on their necessity, effectiveness, cost-effectiveness, and feasibility. Typically, they use a WTP of 80,000 euros per QALY as a threshold for positive advice. The Ministry of Health makes the final decisions on reimbursement for these drugs and performs price negotiations with pharmaceutical companies. Drugs not placed in the 'lock' and proven to have an added therapeutic effect are immediately admitted for reimbursement.

Value within oncological care

It is argued that current frameworks to evaluate the value of new treatments do not sufficiently considers patient values or societal values. Internationally, different frameworks exist to determine the value of oncological treatments.(40, 41) However, the concept of 'value' seems indefinable. There are no agreements on domains that truly matter, how they should be incorporated into actual decision-making or how much weight should be given to each determinant of 'value'.(40) Existing value frameworks seem inconsistent about the included outcomes, and they often miss (elements from) a societal perspective.(40, 41) Examples of such missing societal values are scientific spillovers or (increased) equity.(42)

In line with this, generic quality-of-life measures used in the QALY do not always seem adequate for mapping "all" values that matter to oncological patients.(42-44) It is known that cancer and its treatment have a tremendous impact on patients' quality of life. Patients experience different physical and emotional consequences caused by their cancer diagnosis or treatment.(45) One common physical consequence is neuropathy, characterised by tingling or numbness in hands or feet due to nerve damage from chemotherapy. More than a third of the patients who have (had) cancer indicate that they suffer from neuropathy.(45) Another example is

the effect cancer and its treatment have on sexual function. About 40% of patients who have (had) cancer experience reduced sexual functioning.(45) A cancer diagnosis and treatment can also affect emotional well-being. Among other things, patients can experience (chronic) fatigue or feelings of anxiety. Three-quarters of the patients who have (had) cancer report fatigue symptoms.(45) In addition, almost half of the patients experience anxiety symptoms. A cancer diagnosis can also have an impact on societal productivity. In a Dutch study, patients with cancer between the ages of 18 and 65 reported that for 18% of the patients, their work situation changed after a cancer diagnosis.(45)

For reimbursement decisions in the Netherlands, generic tools for quality-of-life measurement are preferred over oncology-specific tools. Generic tools enhance the comparability of quality of life across different diseases and thus are in theory useful for fair resource allocation across different healthcare areas. However, these generic tools have a reduced sensitivity to change and cannot capture heterogeneity in more condition-specific patient values.

It seems essential to gain more insights into these challenges regarding reimbursement decisions. This could be done by potentially creating a new value framework and facilitate new decision-making methods, especially in this quickly innovating oncological field. In addition, different strategies for increasing value in oncological care might be beneficial. An example of such a strategy is the re-organisation of oncological care in regional networks, aimed at realising the goals of personalised, integrated and sustainable healthcare.

Oncological networking

The rapid innovations within the oncological field regarding treatment and diagnostics, as well as the increase in incidence and comorbidities, have made oncological care increasingly multidisciplinary and complex.(46) As the complexity of cancer care increases, it is essential to concentrate knowledge, especially for rare cancer types, to ensure the quality of care remains high or increases.

To guarantee a minimum quality level for oncological care in the Netherlands, volume standards were set for oncological care in 2012 by SONCOS (Dutch Multidisciplinary Oncology Foundation, *Stichting Oncologische samenwerking*).(47) This has led to a concentration of specialist care, and many studies have provided evidence that increasing the volume of care improves health outcomes.

(48-50) SONCOS has also set other quality requirements, such as organising multidisciplinary consultations (MDT), maximum waiting times, and participation in (quality) registrations.(47, 51) Since 2012, SONCOS has published new volume standards and quality requirements annually.

However, the concentration of care could further fragment healthcare systems, for example, because knowledge is spread over different organisations. In addition, concentration of care results in an increase in a patient's travel time.(52) However, many patients are willing to travel further for better quality of care, especially for life-threatening diseases.(53) The travel time can nevertheless be a particular problem for the elderly and vulnerable patients with lower incomes.(52, 54)

Cancer care requires collaboration between healthcare professionals with complementary skills, who work together to share the latest data, pool their expertise and exchange information through regular communication streams.(55, 56) Patients should have access to the best possible care suited for that specific patient. They should be referred to or discussed with specialised institutions within a country or even internationally for rare cancers.(57) One approach to accomplish this is an integrated care chain across the boundaries of departments and institutions, for example, in a network context. An example on a European level is the European Reference Network on Rare Adult Solid Cancers (EURACAN). This connects healthcare professionals and centres of expertise to improve healthcare quality for rare adult solid cancers.(57) Examples of networks at a national level are tumour-type networks and so-called comprehensive cancer networks (CCNs).

In 2017, the Netherlands held 75 known tumour-type networks in which a minimum of two hospitals collaborated; and in 2021, this was approximately doubled to 153 known networks.(58) More networks might exist that are not known to us. These tumour-type networks typically originate bottom-up and intend to regulate the care of patients with a specific tumour type. The first oncological networks, such as pancreatic cancer, were created for highly complex low-volume tumours due to volume standards. Volume and quality standards were later established for other tumour types, and hospitals have increasingly collaborated on high-volume tumours such as prostate, breast and colon cancer.(46) There is a significant variation in the organisation and goals of oncological networks.(59) The networks vary, for example, in size and referral patterns. Over the past years, increasing focus has emerged towards developing overarching oncological networks. In CCNs, institutions work together at the board of directors level to facilitate and safeguard the supply, quality and continuity of oncological care in the region across the

different tumour-type networks. In 2023, the Netherlands had five large CCNs divided over different regions.(60)

Several studies have been conducted to test the effectiveness of specific components of networking. Discussing patients in a multidisciplinary team (56, 61) or centralisation of care (62) increases survival, while multidisciplinary care pathways improve the quality of care.(51, 63) However, earlier studies showed variation between tumour-type networks and revealed that they may not yet provide optimal alignment and continuity of care.(64, 65) It is expected that CCNs can contribute to this by enhanced coordination of processes. However, little is known about the overall effectiveness of a CCN on care processes, care outcomes and the exact costs (savings) generated. Demonstrating the (cost-)effectiveness of CCNs and the optimal way of implementation and governance is essential.

Thesis goals and outline

In the changing healthcare landscape, it is essential to keep oncological care sustainable. For this reason, we formulated the research question, 'How can we ensure sustainable and high-value oncological care in the face of rising demand and costs?'. To answer this question, we formulated the following research aims:

1) Explore two significant cost drivers in more depth, particularly comorbidity and expensive drugs
2) Explore the concept of 'value' in oncological care and strategies to maximise value with limited budgets
3) Study an alternative approach for organising care to potentially increase sustainability using Comprehensive Cancer Networks (CCNs)

In Chapter 2 of this thesis, we performed a systematic review and multi-level analysis to explore the exact prevalence and related trends of comorbidity among five common types of cancer: breast, colorectal, lung, skin and prostate cancer. In Chapter 3, we explore how investments in immunotherapy impact real-world survival and costs in a case study of metastatic non-small cell lung cancer. We performed a retrospective cohort study comparing the period before, during and after the introduction of immunotherapy. In Chapter 4, we perform a qualitative study with interviews and a focus group to explore the concept of value regarding new oncological treatments. In addition, we explore how value is incorporated into decision-making procedures at the patient and population levels. In Chapter 5, we

discuss the outcomes and implications of Chapter 4 in more depth using a narrative review in which we provide suggestions to improve value with constrained budgets in oncological care. In Chapter 6, we performed a retrospective study on the impact of four CCNs in the Netherlands on the healthcare costs, survival and healthcare processes for two types of cancer: high-volume cancer (colon) and low-volume cancer (pancreatic). In Chapter 7, we tried to answer our main research question by discussing the main findings of this thesis. In addition, we address limitations and provide recommendations for policy and future research.

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Chapter 2

A Systematic Review and Multilevel Regression Analysis Reveals the Comorbidity Prevalence in Cancer

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Abstract

Comorbidities can have major implications for cancer care, as they might impact the timing of cancer diagnosis, compromise optimal care, affect treatment outcomes, and increase healthcare costs. Thus, it is important to comprehensively evaluate cancer comorbidities and examine trends over time. Here, we performed a systematic literature review on the prevalence and types of comorbidities for the five most common forms of cancer. Observational studies from Organisation for Economic Co-operation and Development countries published between 1990 and 2020 in English or Dutch that used routinely collected data from a representative population were included. The search yielded 3,070 articles, of which 161 were eligible for data analyses. Multilevel analyses were performed to evaluate determinants of variation in comorbidity prevalence and trends over time. The weighted average comorbidity prevalence was 33.4%, and comorbidities were the most common in lung cancer (46.7%) and colorectal cancer (40.0%), followed by prostate cancer (28.5%), melanoma cancer (28.3%), and breast cancer (22.4%). The most common types of comorbidities were hypertension (29.7%), pulmonary diseases (15.9%), and diabetes (13.5%). After adjusting for gender, type of comorbidity index, age, data source (patient records vs. claims), and country, a significant increase in comorbidities of 0.54% per year was observed. Overall, a large and increasing proportion of the oncologic population is dealing with comorbidities, which could be used to inform and adapt treatment options to improve health outcomes and reduce healthcare costs.

Significance

Comorbidities are frequent and increasing in patients with cancer, emphasizing the importance of exploring optimal ways for uniform comorbidity registration and incorporating comorbidity management into cancer care.

Introduction

Worldwide, 10 million patients died of cancer in 2020, whereas another 19 million patients were newly diagnosed with cancer and prevalence is expected to increase (1, 2). In addition, the number of comorbidities increases over time and doctors are more and more faced with patients with cancer managing comorbidities (3, 4). This has major implications for treatment and organization of cancer care and calls for information on prevalence and trends in cancer comorbidities. This information could inform and adapt disease management and care coordination programs to improve health outcomes and manage healthcare costs.

Comorbidity is defined as the coexistence of a disorder in addition to a primary disease of interest. Comorbidities may be a contributing factor in cancer development. For example, chronic hepatitis B increases the chance of development of liver cancer (5). In addition, comorbidities may be causally unrelated to cancer but co-occur, for example, due to shared risk factors. Risk factors of cancer, such as older age, smoking, and lack of physical activity, are shared with other common chronic conditions (e.g., obesity, diabetes, or chronic obstructive pulmonary disease; refs. 6, 7).

There is an increased recognition of the importance of comorbidities, although major challenges remain. First, comorbidities impact cancer diagnosis. Some studies suggest that comorbidities are associated with a delay in cancer diagnosis (8, 9). Contrary, comorbidities that require regular medical visits may increase the chance of identifying cancer in an early stage (9, 10). Second, comorbidities may affect curative treatments, which compromises optimal care (11). Patients with comorbidities are less likely to receive standard cancer treatments such as surgery, chemotherapy, and radiotherapy and their chance of completing a course of cancer treatment is lower (9, 11). Third, comorbidities affect treatment outcomes. Postoperative complications, morbidity, and mortality are higher in patients with comorbidities, whereas quality of life is lower (3, 9, 11, 12). Furthermore, with the increasing subspecialisation of care and surgery, providers often struggle with managing the wide spectrum of comorbidities, potentially negatively impacting outcomes (13). Fourth, comorbidities increase healthcare utilization and costs for individuals diagnosed with cancer (11, 12).

In light of these challenges, it is critical to evaluate the prevalence of different comorbidities in oncologic care to inform and adapt disease management and care coordination programs to improve health outcomes and manage healthcare

costs. However, information on prevalence of cancer comorbidities is limited and fragmented, for example, aimed at specific cancer types (14–16). No large systematic review has been performed to this date. The aim of this systematic review is to infer the evidence about the prevalence of comorbidities among five common types of cancer: breast, colorectal, lung, skin, and prostate cancer. We aim to explore determinants of variation between studies and examine trends in comorbidities prevalence over time.

Materials and Methods

Following a previously written study protocol (17) based on the Centre for Reviews and Dissemination's guidance for under taking reviews in health care (18) and the Cochrane collaboration protocol template (19), an electronic search was carried out in PubMed, EMBASE, Cochrane Library, CINAHL, and Web of Science. The search strategy was tailored to each database (see Supplementary Materials and Methods) and included Medical Subject Headings (MeSH) and text word or text phrase for (i) "neoplasm," (ii) "comorbidities," (iii) "prevalence, index, score, measure, level, number, or scale," and (4) "administrative claim-based or registry data." The search was performed on June 25, 2020.

Inclusion and exclusion criteria are presented in Table 1. We limited our scope to the five most prevalent types of cancer: breast, colorectal, lung, melanoma, and prostate cancer (20).

Titles and abstracts were screened on eligibility by two reviewers (LD and CV) individually. Next, eligibility was assessed on the basis of full texts by the two reviewers individually. Discrepancies were resolved by discussion between the reviewers or, if no consensus was reached, a third reviewer (NS). Article screening was performed in Rayyan (21). All citations were imported into EndNote X8.2 and duplicates were discarded. Studies that used the exact same dataset were labelled as duplicates and discarded from the analysis.

Table 1. Inclusion and exclusion criteria used in the selection process

Inclusion criteria	Exclusion criteria
1. Studies providing data about the prevalence of comorbidities in patients diagnosed with breast, colorectal, lung, melanoma or prostate cancer, including previously diagnosed chronic conditions	Studies not providing data about the prevalence of comorbidities in patients diagnosed with breast, colorectal, lung, melanoma or prostate cancer
2. Routinely collected prevalence data, derived from registries or health insurance claims databases	Incidental data collection or not routinely collected data (e.g. chart- or patient-based prevalence data measured for the purpose of one study)
3. Population studies are representative for a broad oncological population. Selection based on age or insurance type was permitted.	Studies restricted by type of treatment, race, presence of a certain disease or complication, survival or response to a questionnaire
4. Observational studies	Case reports, randomized controlled trials, systematic reviews and meta-analyses
5. Publication between January 1, 1990- June 25, 2020	Published before 1990
6. Published in English or Dutch	Published in other languages than English or Dutch
7. Originating from an OECD-country	Published outside of an OECD-country

Note: The 38 OECD member countries are: Australia, Austria, Belgium, Canada, Chile, Colombia, Costa Rica, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Latvia, Lithuania, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States.

Methodologic quality

The quality of the studies was assessed using Hoy's risk of bias tool for prevalence studies (22). For some questions, modifications were made based on O'Sullivan's (23) adjusted prevalence tool because some questions of Hoy's tool were not relevant to our study or were not applicable to routinely collected prevalence data. The final quality assessment tool and the deviations from Hoy's or O'Sullivan's are presented in the Supplementary Materials and Methods. Three domains assessed external validity and four domains internal validity. For each domain, 1 point could be scored, with the total score ranging from 0 (lowest) to 7 (highest).

Data extraction and synthesis

A standardized extraction form was developed to systematically collect and summarize key data elements from each article and perform quality assessment. This was done individually by two reviewers (LD and CV) using Limesurvey. Answers from both reviewers were compared and differences reported.

The following data were extracted:

Prevalence of comorbidities: This was expressed as percentage of the study population having one or more comorbidities as measured by comorbidities indices [e.g., Charlson comorbidities index (CCI), Elixhauser comorbidity index (ECI)] or count/percentage of co-occurring diseases. The prevalence was extracted directly from the studies or calculated from the available information. Prevalence percentages per type of comorbidities were extracted if reported by the included studies. When the outcomes were presented for different subgroups (tumour types, ages, etc.), multiple observations were entered per study.

Type of comorbidities index: This was categorized as CCI, ECI, Cancer, Care, and Comorbidity (C3) index, and others.

Cancer characteristics: Type of cancer, metastases, and cancer subtype. A distinction was made between studies including metastases only, excluding metastasis, or no distinction. If studies only included a cancer subtype (e.g., rectal cancer as a subtype of colorectal cancer), the subtype was registered.

Study population characteristics: Age, proportion males, ethnicity, socioeconomic characteristics, and country.

Study start and duration characteristics: The start year of the study was defined as the first year of data collection in the included studies. The duration of study inclusion was calculated by the difference between start and end year.

Data source characteristics: Data sources were categorized into claims data, hospital-based routinely collected data, and other or unknown. Hospital-based routinely collected data included data from cancer registries and hospital databases.

Study quality: The sum of quality assessment items where both reviewers scored positive, ranging between 0 and 7, was used as quality indicator. In addition, reporting quality was assessed by checking if percentages of comorbidities add up to 100%.

Data analysis

To evaluate the prevalence of comorbidities in oncologic patients, uncorrected sample means and weighted averages on the percentage of patients having one or more comorbidities were calculated. Averages were weighted by study sample size using a logarithmic transformation. Mean weights were given to studies with missing sample sizes. Specific incidences of common (>10 occurrences) comorbidities were reported.

To test whether a trend in comorbidities over time was present, different multilevel linear regressions were performed: (i) unadjusted model, (ii) model adjusted for tumour type, and (iii) model adjusted for all determinants. Determinants include tumour type, type of comorbidity index, population characteristics, methodologic quality, and data source characteristics. Analyses were performed on individual observations, using multilevel regressions to correct for clustered observations belonging to the same study (24). The study identification number was added as a random intercept. To check the validity of defining study type as a data level, pooled linear regression with clustered SEs was performed.

Additional sensitivity analyses were performed to evaluate the influence of each individual determinant on the prevalence of comorbidity and the trend over time. Collinearity between start year and study duration with the different determinants was checked and defined as a Pearson coefficient above 0.7. Residual errors were plotted to check the normality assumption. IBM SPSS Statistics 25 was used for data cleaning and descriptive statistics; STATA 16 was used for the data analysis.

Data availability

The data generated in this study are publicly available in the Data Archiving and Networked Services (DANS) EASY archive at https:// doi.org/10.17026/dans-zfp-ybfq and are available upon request from the corresponding author.

Results

A total of 3,070 articles remained after deduplication. Title and abstract scrutiny and full-text evaluation led to 163 eligible studies, of which, 2 articles were excluded due to identical data. Details on the selection process are displayed in Fig. 1.

The final set of articles included 161 studies: 47 on breast cancer, 37 on prostate cancer, 30 on colorectal cancer, 37 on lung cancer, 7 on melanoma, and 3 on

multiple cancers. Table 2 presents descriptive statistical analysis; Supplementary Table S1 presents more details on the included studies. The determinant socioeconomic characteristics is not reported and used in the analyses as a result of heterogeneity of measuring and reporting this determinant in the included studies (Supplementary Table S2).

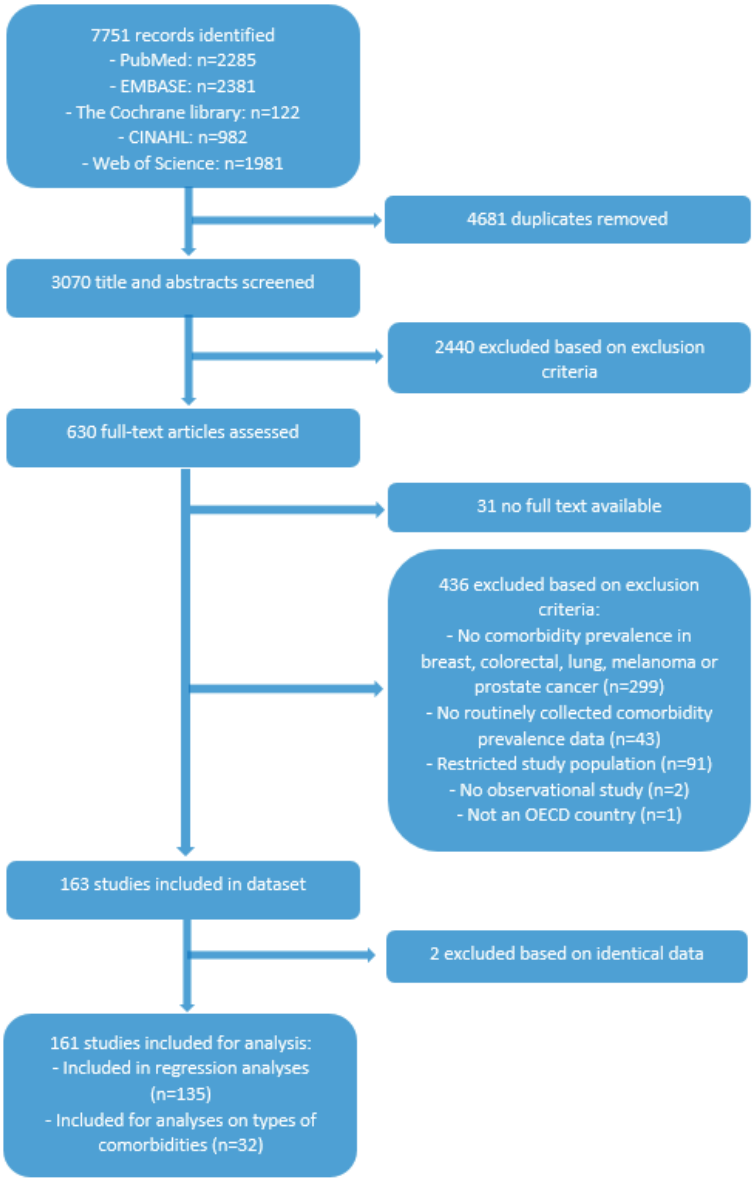

Figure 1. PRISMA-diagram displaying the study selection process.

Twenty-six studies did not report the percentage of one or more comorbidities but reported either percentage of two or more comorbidities or only reported data on types of comorbidities. The 161 studies rendered 243 observations, as some studies reported comorbidity prevalence data for, among others, multiple age groups or tumour types. Figure 2 presents the mean percentage of comorbidities per tumour type. The overall weighted average percentage of patients with one or more comorbidities is 33.4% [95% confidence interval (CI), 31.0–35.8], which is 46.7% (95% CI, 41.6–51.7) for lung cancer, 40.0% (95% CI, 35.4–44.6) for colorectal cancer, 28.5% (95% CI, 24.9–32.2) for prostate cancer, 28.3% (95% CI, 8.5–48.1) for melanoma, and 22.4% (85% CI, 18.8–26.0) for breast cancer.

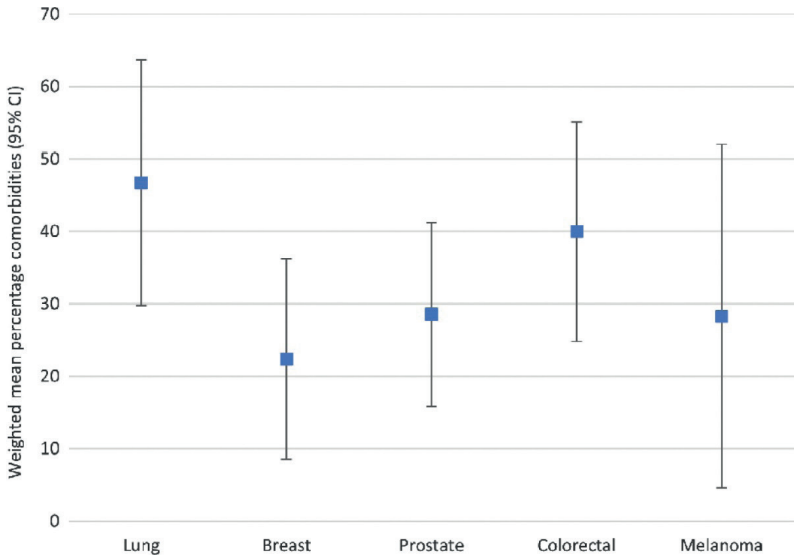

Figure 2. Error plot of the weighted mean percentage of comorbidities for the different tumour types. Averages were weighted by study sample size using a logarithmic transformation. Mean weights were given to studies with missing sample sizes.

Thirty-two studies reported individual types of comorbidities (Table 3). The most common comorbidity was hypertension (29.7%) followed by pulmonary diseases (15.9%) and diabetes (13.5%). For lung, breast, and prostate cancer, these comorbidities were also the most common. For colorectal cancer, the most common comorbidity was hypertension, followed by renal diseases and diabetes. For melanoma, only one study presented comorbidities. The most common comorbidity was diabetes, followed by other malignancies and pulmonary disease. Table 3 presents percentages and confidence intervals of the most common types of comorbidities.

Table 2. Descriptive statistics of 243 observations of comorbidity prevalence derived from 161 studies

	All	Lung	Breast	Prostate
	N	**N**	**N**	**N**
N Studies	161	37	47	37
N observations[b]	243	53	67	56
	N (%)	N (%)	N (%)	N (%)
Age groups[c]				
- Age below 45	146 (60.1)	33 (62.3)	35 (52.2)	32 (57.1)
- Age 45-59	151 (62.1)	34 (64.2)	36 (53.7)	33 (58.9)
- Age 60-69	225 (92.6)	53 (100)	58 (86.6)	50 (89.3)
- Age 70-79	220 (90.5)	53 (100)	58 (86.6)	49 (87.5)
- Age 80 or above	216 (88.9)	53 (100)	59 (88.1)	44 (78.6)
Presence of subtype (yes)	74 (30.5)	27 (50.9)	19 (28.4)	2 (3.6)
Reporting quality check (valid)	187 (77)	45 (84.9)	51 (76.1)	44 (78.6)
Country				
- Australia	9 (3.7)	3 (5.7)	-	-
- Canada	11 (4.5)	2 (3.8)	4 (6)	2 (3.6)
- Denmark	16 (6.6)	4 (7.5)	2 (3)	6 (10.7)
- Finland	1 (0.4)	-	1 (1.5)	-
- France	3 (1.2)	-	1 (1.5)	-
- Germany	1 (0.4)	1 (1.9)	-	-
- Italy	2 (0.8)	1 (1.9)	1 (1.5)	-
- Japan	2 (0.8)	1 (1.9)	-	-
- Netherlands	16 (6.6)	2 (3.8)	-	4 (7.1)
- New Zealand	3 (1.2)	-	3 (4.5)	-
- Norway	6 (2.5)	3 (5.7)	1 (1.5)	1 (1.8)
- Spain	3 (1.2)	-	3 (4.5)	-
- Sweden	17 (7)	2 (3.8)	1 (1.5)	14 (25)
- UK	27 (11.1)	6 (11.3)	13 (19.4)	-
- USA	126 (51.9)	28 (52.8)	37 (55.2)	29 (51.8)
Type of data				
- Hospital-based routinely collected data[d]	147 (60.5)	32 (60.4)	38 (56.7)	36 (64.3)
- Claims data	91 (37.4)	21 (39.6)	26 (38.8)	20 (35.7)
- Other/unknown[e]	5 (2.1)	-	3 (4.5)	-
Metastases				
- No distinction	175 (72)	43 (81.1)	51 (76.1)	31 (55.4)
- Metastases excluded	53 (21.8)	7 (13.2)	12 (17.9)	20 (35.7)
- Only metastases	15 (6.2)	3 (5.7)	4 (6)	5 (8.9)
Type of comorbidities index				
- Charlson comorbidity index	198 (81.5)	42 (79.2)	55 (82.1)	48 (85.7)
- Elixhauser comorbidity index	15 (6.2)	7 (13.2)	3 (4.5)	2 (3.6)

Colorectal	Melanoma	Multiple[a]
N	N	N
30	7	3
54	10	3
N (%)	N (%)	N (%)
37 (68.5)	8 (80)	1 (33.3)
39 (72.2)	8 (80)	1 (33.3)
51 (94.4)	10 (100)	3 (100)
51 (94.4)	7 (70)	2 (66.7)
51 (94.4)	7 (70)	2 (66.7)
21 (38.9)	5 (50)	-
36 (66.7)	8 (80)	3 (100)
6 (11.1)	-	-
3 (5.6)	-	-
2 (3.7)	2 (20)	-
-	-	-
2 (3.7)	-	-
-	-	-
-	-	-
1 (1.9)	-	-
10 (18.5)	-	-
-	-	-
1 (1.9)	-	-
-	-	-
-	-	-
8 (14.8)	-	-
21 (38.9)	8 (80)	3 (100)
36 (66.7)	5 (50)	-
16 (29.6)	5 (50)	3 (100)
2 (3.7)	-	-
40 (74.1)	7 (70)	3 (100)
12 (22.2)	2 (20)	-
2 (3.7)	1 (10)	-
42 (77.8)	8 (80)	3 (100)
3 (5.6)	-	-

Table 2. Continued

	All	Lung	Breast	Prostate
	N	N	N	N
- C3 index	3 (1.2)	-	2 (3)	-
- Other	27 (11.1)	4 (7.5)	7 (10.4)	6 (10.7)
Missing comorbidities percentage	34 (14)	7 (13.2)	8 (11.9)	7 (12.5)
Missing Start year	1 (0.4)	0 (0)	0 (0)	0 (0)
Missing Study duration	1 (0.4)	0 (0)	0 (0)	0 (0)
	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)
Mean % comorbidities	33.6 (31.1-36.0)	46.9 (41.9-51.9)	22.3 (18.6-26.1)	29.1 (25.4-32.9)
Weighted mean % comorbidities[f]	33.4 (31.0-35.8)	46.7 (41.6-51.7)	22.4 (18.8-26.0)	28.5 (24.9-32.2)
Start year	2002.0 (2001.1-2002.9)	2003.1 (2001.2-2004.9)	2002.3 (2000.4-2004.1)	1999.7 (1998.0-2001.4)
Study duration (years)	6.03 (5.59-6.57)	5.38 (4.35-6.40)	5.60 (4.45-6.75)	7.52 (6.31-8.73)
Validity score (0 – 7)	5.81 (5.68-5.94)	6.09 (5.86-6.33)	5.58 (5.38-5.78)	6.02 (5.79-6.24)
Proportion male	0.51 (0.46-0.56)	0.58 (0.54-0.61)	0.02 (-0.01-0.06)	1.00 (1.00-1.00)
Proportion Caucasian	0.82 (0.80 – 0.84)	0.85 (0.83-0.88)	0.80 (0.76-0.85)	0.76 (0.73-0.82)
Study sample size	44569.5 (30287.7 – 58851.2)	62152.2 (14272.7– 10031.7)	48291.8 (11224.0 – 85359.6)	52359.2 (28136.6-76581.7)

[a] The category multiple includes observations that make no distinction between the tumour types and can therefore not be presented within the categories of the individual tumour types

[b] A study can report comorbidities for different subgroups (tumour types, ages, etc.), which we considered as separate observations. Analyses were performed with the individual observations of subgroup comorbidity prevalence.

[c] Observations can be classified into multiple age groups (e.g. studies that include ages 60 to 80 are included in age groups 60-69 and 70-79). The observations by age are thus not mutually exclusive.

[d] \This data includes data from cancer registries and hospital databases

[e] The data source is either hospital-based routinely collected data or claims data, however it is unknown which of the two.

[f] Averages were weighted by subgroup sample size using a logarithmic transformati
on. Mean weights were given to studies with missing sample sizes.

Colorectal	Melanoma	Multiple[a]
N	N	N
1 (1.9)	-	-
8 (14.8)	2 (20)	-
10 (18.5)	2 (20)	0 (0)
0 (0)	1 (10)	0 (0)
0 (0)	1 (10)	0 (0)
Mean(95% CI)	Mean(95% CI)	Mean(95% CI)
39.7 (35.0-44.3)	31.3 (10.2-52.4)	38.5 (24.2-52.7)
40.0 (35.4-44.6)	28.3 (8.5-48.1)	39.4 (26.3-52.4)
2002.7 (2000.9-2004.5)	2004.9 (1999.5-2010.3)	1998.7 (1993.5-2003.8)
5.50 (4.47-6.53)	7.00 (4.39-9.61)	6.00 (-0.57 -12.56)
5.63 (5.24-6.02)	5.50 (4.73-6.27)	6.00 (6.00-6.00)
0.52 (0.50-0.53)	0.56 (0.51-0.62)	0.52 (0.51-0.54)
0.81 (0.75-0.88)	0.96 (0.91-1.00)	0.80 (0.70-0.90)
21790.4 (11958.4-31622.3)	22791.6 (-13305.9-58889.2)	117142.3 (-147648.0 –381932.6)

Table 3. Prevalence of types of comorbidities in the included studies

	All		Lung		Breast	
	N[a]	Mean % (95% CI)	N[a]	Mean % (95% CI)	N[a]	Mean % (95% CI)
N Studies	32		8		8	
N observations[b]	65		15		11	
Hypertension	26	**29.68 (23.02-36.35)**	**4**	**37.01 (-8.92 – 82.94)**	**3**	**31.57 (-25.64– 88.78)**
Pulmonary disease (including COPD)	63	**15.85 (12.18-19.53)**	14	**35.64 (26.38-44.90)**	11	**8.12 (6.06-10.17)**
Diabetes	65	**13.47 (11.55-15.39)**	15	**17.55 (13.15-21.95)**	11	**11.52 (6.71-16.33)**
Other Malignancies	32	11.89 (9.47-14.31)	8	16.08 (9.91-22.24)	3	4.95 (1.84-8.06)
Heart failure	47	8.60 (6.92-10.89)	14	12.17 (9.03-15.32)	10	5.08 (2.46-7.70)
Renal disease	41	6.55 (1.68-11.41)	13	5.40 (2.87-7.93)	10	2.20 (1.01-3.39)
Cerebrovascular diseases	36	6.24 (4.90-7.58)	11	7.57 (5.16-9.99)	8	3.95 (1.82-6.08)
Myocardial infarction	31	2.69 (1.95-3.43)	9	4.48 (2.58-6.39)	8	1.37 (0.44-2.30)
Rheuma	31	1.92 (1.47-2.38)	6	2.93 (1.04-4.82)	7	1.80 (0.88-2.73)
Peptic ulcer	36	1.59 (0.91-2.27)	9	1.81 (0.76-2.86)	9	0.75 (0.26-1.23)
Liver disease	34	1.52 (0.64-2.40)	11	2.66 (-0.01 – 5.31)	6	0.33 (0.15-0.50)
Dementia	34	1.17 (0.79-1.55)	11	1.03 (0.68-1.38)	7	1.21 (0.36-2.06)

Note: Bold percentages present the top 3 comorbidities within the tumour type categories

[a] N are number of observations.

[b] A study can report comorbidities for different subgroups (tumour types, ages, etc.), which we considered as separate observations. Analyses were performed with the individual observations of subgroup comorbidity prevalence.

Table 4 presents the multilevel models. In the unadjusted model (model 1), no significant trend in comorbidities was found. This result is unaffected after adjusting for different tumour types (model 2). When adjusting for all determinants (model 3), a significant positive trend is found over time, predicting a yearly increase in comorbidities of 0.54%. These indicate that, ceteris paribus, comorbidity incidence increases by 5.4% per decade. Proportion Caucasians was removed from the model because of the low number of included observations (n ¼ 85). The model is presented in Supplementary Table S3. The robustness check of using a multilevel model is presented in Supplementary Table S4, revealing a comparable yearly

Prostate		Colorectal		Melanoma	
N[a]	Mean % (95% CI)	N[a]	Mean % (95% CI)	N[a]	Mean % (95% CI)
6		9		1	
12		25		2	
4	**41.77 (28.80-54.74)**	**15**	**24.13 (17.91-30.35)**	-	-
12	**7.37 (3.67-11.07)**	24	12.10 (8.09-16.10)	2	**15.95 (14.04-17.86)**
12	**8.90 (4.08-13.71)**	25	**13.39 (10.56-16.21)**	2	**21.95 (11.15-32.75)**
6	4.60 (-0.28 – 9.47)	13	13.3 (10.91-15.70)	2	**18.25 (-3.99 – 40.49)**
8	6.23 (1.14-11.32)	13	8.57 (5.14-11.99)	2	11.00 (-0.04 - 0.26)
7	3.95 (0.01-7.89)	9	**13.98 (-10.86– 38.82)**	2	11.35 (5.63-17.07)
3	4.43 (-2.37 – 11.24)	12	5.77 (3.23-8.32)	2	13.60 (-4.19 – 31.39)
4	1.55 (0.68-2.42)	8	2.33 (1.24-3.43)	2	3.60 (-9.11 – 16.31)
7	1.03 (0.34-1.72)	9	1.75 (1.12-2.37)	2	3.20 (1.92-4.47)
7	1.09 (-0.41 – 2.59)	9	2.62 (0.04-5.19)	2	1.50 (-3.58 – 6.58)
6	0.51 (0.20-0.83)	9	1.22 (0.09-2.34)	2	3.25 (2.61-3.89)
8	0.98 (-0.56 – 2.51)	8	1.52 (0.77-2.27)	-	-

increase in comorbidity prevalence of 0.56% and an R2 of 0.68 when adjusting for all determinants.

Table 4. Multilevel regression models for percentage of comorbidities over time

	Coefficient (SE)	**p-value**
Model 1: unadjusted multilevel model for percentage of comorbidities over time [a]		
Start year	-0.19 (0.24)	0.439
Study duration	-0.28 (0.39)	0.466
Constant	38.74*** (5.92)	0.000
Model 2: multilevel model for percentage of comorbidities over time adjusted for tumour types [b]		
Tumour type		
- Multiple[d]	(baseline)	
- Melanoma	-6.50 (9.70)	0.502
- Prostate	-8.73 (7.16)	0.223
- Lung	13.21 (7.39)	0.074
- Breast	-12.65 (7.34)	0.085
- Colorectal	1.28 (7.39)	0.863
Start year	-0.21 (0.20)	0.304
Study duration	-0.21 (0.33)	0.519
Constant	41.99*** (8.37)	0.000
Model 3: multilevel model for percentage of comorbidities adjusted for all determinants [c]		
Country		
- Australia	(baseline)	
- Canada	-3.25 (4.29)	0.448
- Denmark	18.30*** (5.17)	0.000
- France	0.64 (12.12)	0.958
- Italy	4.60 (11.78)	0.696
- Japan	-18.98 (11.33)	0.094
- Netherlands	31.40*** (5.84)	0.000
- New Zealand	5.61 (8.55)	0.512
- Norway	-1.88 (4.45)	0.673
- Spain	12.94 (10.98)	0.238
- Sweden	16.05** (5.42)	0.003
- UK	5.81 (3.88)	0.134
- USA	11.13** (4.28)	0.009
Data type		
- Hospital-based routinely collected data	(baseline)	
- Claims data	11.62*** (2.58)	0.000
- Other/unknown	9.16 (9.22)	0.320
Tumour type		
- Multiple[d]	(baseline)	
- Breast	3.93 (6.5)	0.545
- Lung	12.96* (5.47)	0.018
- Prostate	-19.64** (6.24)	0.002
- Colorectal	3.87 (5.49)	0.481
- Melanoma	-4.24 (7.03)	0.547

Table 4. Continued

	Coefficient (SE)	p-value
Metastatic		
- No distinction	(baseline)	
- Metastasis only	0.9 (2.02)	0.657
- Metastasis excluded	1.57 (2.64)	0.553
Index category		
- Charlson comorbidity index	(baseline)	
- Elixhauser comorbidity index	14.95*** (2.68)	0.000
- C3 index	18.27*** (5.54)	0.001
- Other	-5.19 (5.85)	0.374
Age group[e]		
- Age below 45	-5.77* (2.41)	0.017
- Age 45-59	-1.83 (2.52)	0.467
- Age 60-69	0.32 (2.54)	0.899
- Age 70-79	5.26 (2.79)	0.059
- Age 80 or above	8.94*** (2.78)	0.001
Presence of subtype		
- No	(baseline)	
- Yes	1.56 (1.98)	0.429
Proportion male	29.43*** (7.37)	0.000
Reporting quality		
- Valid	(baseline)	
- Not valid	4.76 (4.11)	0.247
Validity score	1.75 (1.23)	0.154
Start year	0.54** (0.18)	0.004
Study duration	0.10 (0.31)	0.740
Constant	-26.11* (12.07)	0.030

Note: Significant: *0.05, **0.01, ***0.001.

[a] Observations = 208, Number of groups=140, Log likelihood= -869.06

[b] Observations = 208, Number of groups=140, Log likelihood= -822.30.

[c] Observations = 199, Number of groups=137, Log likelihood= -721.43.

[d] The category multiple includes observations that make no distinction between the tumour types and can therefore not be presented within the categories of the individual tumour types

[e] Observations can be classified into multiple age groups (e.g. studies that include ages 60 to 80 are included in age groups 60-69 and 70-79). The observations by age are thus not mutually exclusive. Therefore dummy variables were entered in the model per category.

The model shows that comorbidities are more prevalent in lung cancer and less prevalent in prostate cancer. Denmark, the Netherlands, Sweden, United Kingdom, and the United States report significantly higher comorbidity incidence. Furthermore, the age group 80 or above, and proportion males display higher comorbidity rates. Finally, the use of claims data and the use of ECI or C3 index is associated with higher comorbidity rates. Cancer characteristics (e.g., time of measurement, metastasis, specific tumours) do not significantly affect comorbidity incidence, nor do we find an effect of study quality. The level of comorbidities is significantly lower for ages below 45. Residuals of the models were normally distributed, and no collinearity was found between the determinants, the start year of the study and the study duration.

Additional sensitivity analysis reveals differences in trends of comorbidity over time for different tumour types (Supplementary Table S5; Supplementary Fig. S1), therefore tumour type is added to every sensitivity analysis. The individual determinants of country, data type, comorbidity index, age, and proportion male affect comorbidity prevalence (Supplementary Table S6). The sensitivity analyses reveal that the switch between a nonsignificant negative time trend in the unadjusted regression to a significant positive trend in the full model is predominantly mediated by type of country, type of data source, and age (Supplementary Table S7).

Discussion

This review sought to infer the evidence on the prevalence of comorbidities among oncologic patients and distinguish differences between the five most common types of cancer: breast, colorectal, lung, skin, and prostate cancer. In addition, we explored determinants of variation between studies and examined trends in prevalence of comorbidities.

We found that the weighted average prevalence of comorbidities in all five cancer types together is 33.4%. Comorbidities seem most common in patients with lung and colorectal cancer, with 46.7% and 40.0%, respectively. This is followed by prostate cancer with 28.5%, melanoma with 28.3%, and breast cancer with 22.4%. However, large variation existed between the data from the different studies. This variation can partly be explained by characteristics of the patient population. However, it can also partly be explained by study characteristics as country, kind of measurement tools, and type of data. After adjusting for all determinants,

a significant increase in comorbidities of 0.54% per year was found. The most common type of comorbidity was hypertension, followed by pulmonary diseases and diabetes.

Previous literature

Previous studies have reported variance in the prevalence of comorbidities for different tumour types. Lee and colleagues performed a systematic review of articles between 1990 and 2009 about the impact of comorbidity on chemotherapy use and outcomes in patients with cancer. They reported a range of 0.4% to 90% of patients with cancer with comorbidities, the highest frequency among patients with lung (35%), breast (20%), or colorectal cancers (20%; ref. 25). A review article by Sarfati and colleagues on the impact of comorbidity on cancer and its treatment stated that some cancers, such as lung, are strongly associated with risk factors (e.g., age and lifestyle) related to other chronic conditions (chronic obstructive pulmonary disease and congestive heart failure; refs. 11, 26). For other cancers, for example, breast and prostate cancer, this association is less strong (11). For instance, obesity in premenopausal women may reduce the risk of breast cancer, whereas the reverse is true for postmenopausal women (27). For prostate cancer, obesity is associated with reduced risk of nonaggressive prostate cancer but increased risk of aggressive prostate cancer (28). A report on the status of cancer from 1975 to 2010 in the United States by Edwards and colleagues is consistent with our findings (26). They reported a comparable prevalence of comorbidities in patients with breast and prostate cancers, higher frequencies in patients with lung cancer and intermediate frequencies for patients with colorectal cancer. Edwards and colleagues additionally reported diabetes, chronic obstructive pulmonary disease, and congestive heart failure as the most common comorbidities for breast, colorectum, lung, and prostate cancer (26). The prevalence is higher in comparison to a population without cancer. Fowler and colleagues found hypertension, COPD, and diabetes as the most common comorbidities for colon and lung cancer (29). Edwards and colleagues used categories from the CCI, which does not include hypertension, whereas Fowler and colleagues added additional comorbidities to the CCI.

Previous studies also supported the increase of comorbidities for specific tumour types over time. Leersum and colleagues found an increase in comorbidities from 47% to 62% over a time period from 1995 to 2010 in patients with colorectal cancer (30). Aarts and colleagues found an increase from 55% to 76% over a time period from 1995 to 2012 for patients with small cell lung cancer (31). Both studies were performed in the Netherlands, and the same comorbidity index and hospital-

based routinely collected data were used during the entire period. These indicate an increase in comorbidity that is not influenced by the type of index, country, or type of data. A different contributing factor of increase in comorbidities is the ageing population, as the prevalence of multimorbidity in the general population increases with age (32, 33).

We found substantial levels of variation between the included studies. Another review from Sarfati found that no gold standard existed for measuring comorbidities in oncologic patients (34). Approaches of measuring comorbidities varied based on the study questions, patient population, and available data. Our study revealed that different study characteristics impacted the prevalence of comorbidities in oncologic patients: type of data, country, and type of comorbidity index did matter.

The finding in our study that the use of claims data results in higher levels of comorbidities is in line with literature. Claims data are constructed for administrative and reimbursement purposes, lack detail on the comorbidities, and are at risk for upcoding and misclassification (35, 36). In addition, the assignment of codes is open to differences in interpretation, which might result in variability in coding practices (36, 37). Full medical records or claims data correcting for upcoding (e.g., by ruling out codes if they appear only once or multiple times but only within a 30-day window) might provide the best insight into the prevalence and burden of comorbidities (35, 38, 39).

Little is known about differences in comorbidities in oncologic patients between countries. Potential differences in prevalence of comorbidities between countries could (partly) be explained by international inconsistencies in the coding and registration of comorbidities (40). Previous studies suggest that the United States has higher rates of multimorbidity and higher healthcare spending in comparison to other countries (41, 42). However, our study showed the highest percentages of comorbidities in the Netherlands, Sweden, and Denmark. One factor that may explain high intercountry variability is differences in registration and claims systems (43). For example, the number of diagnostic-related groups (DRG) differs from over 4,000 in the Netherlands to about 1,000 in Germany, Sweden, and Austria (44). This may result in critical differences in how comorbidities are measured between countries, reducing inter-country comparability. However, this may only explain intercountry differences in claim-based comorbidity assessment.

Strength and limitations

The main strength of this study is that we systematically gathered and summarized the literature on the prevalence of comorbidities. Our review is in line with previous studies; however, it adds knowledge on comorbidity trends for a broad oncologic population, heterogeneity between studies, and determinants that impact comorbidity prevalence. To our knowledge, this is the first study to explore variation between studies regarding the prevalence of comorbidities. Another strength is that our literature search was limited to the five most common types of cancers, whereas our search string in the study protocol was broader. This probably ensures that no studies are missed.

We acknowledge some limitations. First, we limited our inclusion criteria to the use of data from health claims and registries based on ICD codes. This results in the possibility that some diagnoses have been missed or results are overestimated due to upcoding in claims data. On the other hand, the use of administrative data has enabled us to analyse prevalence based on large populations, increasing the generalizability of the results. Second, we use the occurrence of one or more comorbidities as outcome variable, which does not take into account prevalence of multiple comorbidities simultaneously and its increase over time. However, different types of comorbidity indices cannot be compared on this dimension. Third, heterogeneity in the definitions and coding of types of comorbidities in the articles included in our review might affect prevalence and relative importance of specific comorbidities. Fourth, the model adjusting for all determinants (model 3) risks overfitting the data, where too many determinants are added with respect to the number of observations. Because of this risk, caution is needed when interpreting the results, especially of individual determinants. However, a general effect on the main variables of interest can be generated and the sensitivity analyses further explores, and substantiates the main findings. It remains unknown to what extent the remaining unexplained variance relates to heterogeneity in measuring and reporting or other unobserved study characteristics. Finally, the quality assessment form was tailored to the purpose of our review. However, this specific quality assessment form has not been validated.

Implications

With increasing comorbidity prevalence, adjustment of clinical pathways may become increasingly important in the future. This study provides a starting point to benchmark and monitor comorbidity prevalence between countries and within countries, as well as to spur further research into implications of increased comorbidity burden on clinical decision-making. However, we found high

unexplained variation in comorbidity prevalence between studies, potentially due to definition and registration heterogeneity. This emphasizes the importance of a gold standard for definition and registration of comorbidities. Implicitly, a trade-off between accuracy and efficiency may be present: although medical records may be more comprehensive and accurate, it may require additional administrative expenditures to disclose information on comorbidities. Routinely collected data may, therefore, be a less costly alternative to estimate comorbidity prevalence. Two rival indices are commonly used: the ECI and CCI. Although the ECI is argued to match or outperform the CCI, most studies included in this review report the CCI only (45–47). One issue of the CCI is that weights tend to be recalibrated over time, reducing intertemporal comparability. We would argue for an international definition of the ECI as well as a tool to translate the ECI to CCI, so both measures can be reported and applied. The use of standardized registration and measurement tools for comorbidities ensures that differences among countries, trends over time or differences between tumour types can be studied more thoroughly.

Our study contributes to discussions regarding centralizing specialized cancer care, driven by evidence that high volumes improve treatment outcomes (48–50). An increasing comorbidity prevalence may be orthogonal to the trend of increased specialization, as this may require a more generalist approach requiring professional expertise from other departments and organizations. These emphasize the importance to include the high and increasing comorbidity prevalence in debates on centralization of care and the importance to stimulate and facilitate collaborations between different healthcare organizations.

Increasing comorbidity prevalence also affects treatment costs. Although some reimbursement systems adjust for comorbidities, others do not. Reimbursement systems require standardized comorbidity measurement and adequate payment adjustment to counteract perverse incentives such as cherry-picking, adverse selection, and upcoding (44). This is a promising area for future research.

Conclusion

In this systematic review we have gathered and summarized the current literature on the prevalence of comorbidities. We find that as substantial proportion of patients have at least one comorbidity, which comorbidities increase over time, and that large differences in measurement methods, databases used, and reported comorbidities in studies exist.

These findings underline the importance of comorbidities management in cancer care, given that such a large proportion of the oncological population deals with more diseases at once. These high and rising numbers could be included in discussions on optimizing clinical pathways and centralizing specialized oncologic care. However, there is a great extent of variation between reported comorbidities in studies, revealing uniformity in measuring and reporting comorbidities is lacking and needs improvement.

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Supplemental Methods

Search strings

Searchstring PubMEd

(Neoplasms [MeSH] OR Cancer* [tiab] OR Neoplas* [tiab] OR Tumor* [tiab] OR Tumour* [tiab] OR Carcinom* [tiab] OR Melanom* [tiab] OR Malignan* [tiab] OR Lymphoma* [tiab] OR Oncolog* [tiab])

AND

(Comorbidity [MeSH] OR Chronic disease [MeSH] OR Comorbid* [tiab] OR Co-morbid* [tiab] OR Multimorbid* [tiab] OR Multi-morbid* [tiab] OR Chronic disorder* [tiab] OR Concomitant disease* [tiab] OR Chronic disease* [tiab] OR Chronic condition [tiab] OR Chronic conditions [tiab] OR Health condition* [tiab] OR Chronic illness* [tiab] OR Co-occur* [tiab] OR Chronic morbidit* [tiab])

AND

(index [tiab] OR indices [tiab] OR score [tiab] OR scores [tiab] OR scale [tiab] OR scales [tiab] OR Frequency[tiab] OR Frequencies[tiab] OR prevalence estimate* [tiab]

OR (prevalence [tiab] AND (estimate [tiab] OR comorbidit* [tiab] OR co-morbidit* [tiab] OR multimorbidit* [tiab] OR multi-morbidit* [tiab]))

OR ((measure* [tiab] OR level* [tiab] OR number* [tiab]) AND (comorbidit* [tiab] OR co-morbidit* [tiab] OR multimorbidit* [tiab] OR multi-morbidit* [tiab])))

AND

((Administrative [tiab] AND health claim* data [tiab]) OR International Classification of Diseases [MeSH] OR ICD [tiab] OR International Classification of Diseases [tiab] OR Administrative data [tiab] OR claim [tiab] OR claims [tiab] OR Cancer data* [tiab] OR Insurance data* [tiab] OR Cancer registr* [tiab] OR Cancer register* [tiab])
Resultaten: 2.285

Searchstring Embase

(Neoplasm/ OR malignant Neoplasm/ OR (Cancer* OR Neoplas* OR Tumor* OR Tumour* OR Carcinom* OR Melanom* OR Malignan* OR Lymphoma* OR Oncolog*).ti,ab,kw.)

AND

(Comorbidity/ OR Chronic disease/ OR (Comorbid* OR Co-morbid* OR Multimorbid* OR Multi-morbid* OR 'Chronic disorder*' OR 'Concomitant disease*' OR 'Chronic disease*' OR 'Chronic condition*' OR 'Health condition*' OR 'Chronic illness*' OR Co-occur* OR 'Chronic morbidit*').ti,ab,kw.)

AND

((index OR indices OR score OR scores OR scale OR scales OR Frequency OR Frequencies OR 'prevalence estimate*').ti,ab,kw.

OR (prevalence.ti,ab,kw. AND (estimate OR comorbidit* OR co morbidit* OR multimorbidit* OR multi morbidit*).ti,ab,kw.)

OR ((measure* OR level OR number).ti,ab,kw. AND (comorbidit* OR co-morbidit* OR multimorbidit* OR multi-morbidit*).ti,ab,kw.))

AND

((Administrative.ti,ab,kw. AND 'health claim* data'.ti,ab,kw.) OR International Classification of Diseases/ OR (ICD OR 'International Classification of Diseases' OR 'Administrative data' OR claim OR claims OR 'Cancer data*' OR 'Insurance data*' OR 'Cancer registr*' OR 'Cancer register*').ti,ab,kw.)

1 AND 2 AND 3 AND 4 - 6433

Limit 5 to conference abstract - 4052

5 not 6 - 2381

Searchstring CINAHL

((MH "Neoplasms+") OR TI Cancer* OR AB Cancer* OR TI Neoplas* OR AB Neoplas* OR TI Tumor* OR AB Tumor* OR TI Tumour* OR AB Tumour* OR TI Carcinom* OR AB Carcinom* OR TI Melanom* OR AB Melanom* OR TI Malginan* OR AB Malignan* OR TI Lymphoma* OR AB Lymphoma* OR TI Oncolog* OR AB Oncolog*)

AND

((MH "Comorbidity" OR MH "Chronic disease") OR TI Comorbid* OR AB Comorbid* OR TI Co-morbid* OR AB Co-morbid* OR TI Multimorbid* OR AB Multimorbid* OR TI Multi-morbid* OR AB Multi-morbid* OR TI "Chronic disorder*" OR AB "Chronic disorder*" OR TI "Concomitant disease*" OR AB "Concomitant disease*" OR TI "Chronic disease*" OR AB "Chronic disease*" OR TI "Chronic condition" OR AB "Chronic condition" OR TI "Chronic conditions" OR AB "Chronic conditions" OR TI "Health condition*" OR AB "Health condition*" OR TI "Chronic illness*" OR AB "Chronic illness*" OR TI Co-occur* OR AB Co-occur* OR TI "Chronic morbidit*" OR AB "Chronic morbidit*")

AND

((TI Index OR AB Index OR TI Indices OR AB Indices OR TI Score OR AB Score OR TI Scores OR AB Scores OR TI Scale OR AB Scale OR TI Scales OR AB Scales OR TI Frequency OR AB Frequency OR TI Frequencies OR AB Frequencies OR TI "Prevalence estimate*" OR AB "Prevalence estimate*")

OR ((TI Prevalence OR AB Prevalence) AND (TI estimate OR AB estimate OR TI comorbidit* OR AB comorbidit* OR TI Co-morbidit* OR AB Co-morbidit* OR TI Multimorbidit* OR AB Multimorbidit* OR TI Multi-morbidit* OR AB Multi-morbidit*))

OR ((TI Measure* OR AB Measure* OR TI level* OR AB level* OR TI number* OR AB number*) AND (TI comorbidit* OR AB comorbidit*

OR TI Co-morbidit* OR AB Co-morbidit* OR TI Multimorbidit* OR AB Multimorbidit* OR TI Multi-morbidit* OR AB Multi-morbidit*)))

AND

((MH "International Classification of Diseases") OR ((TI Administrative OR AB Administrative) AND (TI "Health claim* data" OR AB "Health claim* data")) OR TI

"International Classification of Diseases" OR AB "International Classification of Diseases" OR TI ICD OR AB ICD OR TI "Administrative data" OR AB "Administrative data" OR TI Claim OR AB Claim OR TI Claims OR AB Claims OR TI "Cancer data*" OR AB "Cancer data*" OR TI "Insurance data*" OR AB "Insurance data*" OR TI "Cancer registr*" OR AB "Cancer registr*" OR TI "Cancer register*" OR AB "Cancer register*")

Results: 982

Searchstring Cochrane

#1	MeSH descriptor: [Neoplasms] explode all trees	77268
#2	(Cancer* OR Neoplas* OR Tumor* OR Tumour* OR Carcinom* OR Melanom* OR Malignan* OR Lymphoma* OR Oncolog*):ti,ab,kw	216255
#3	**#1 OR #2**	**222822**
#4	MeSH descriptor: [Comorbidity] explode all trees	3466
#5	MeSH descriptor: [Chronic Disease] explode all trees	13045
#6	(Comorbid* OR Co-morbid* OR Multimorbid* OR Multi-morbid* OR "Chronic disorder*" OR "Concomitant disease*" OR "Chronic disease*" OR "Chronic condition" OR "Chronic conditions" OR "Health condition*" OR "Chronic illness*" OR Co-occur* OR "Chronic morbidit*"):ti,ab,kw	48030
#7	**#4 OR #5 OR #6**	**48035**
#8	(index OR indices OR score OR scores OR scale OR scales OR Frequency OR Frequencies OR "prevalence estimate*"):ti,ab,kw	565424
#9	(prevalence):ti,ab,kw	41518
#10	(estimate OR comorbidit* OR co-morbidit* OR multimorbidit* OR multi-morbidit*):ti,ab,kw	96954
#11	#9 AND #10	7274
#12	(measure*):ti,ab,kw	422348
#13	(comorbidit* OR co-morbidit* OR multimorbidit* OR multi-morbidit*):ti,ab,kw	18025
#14	#12 AND #13	6279
#15	(level*):ti,ab,kw	331568
#16	#15 AND #13	4617
#17	(number*):ti,ab,kw	189769
#18	#17 AND #13	3510
#19	**#8 OR #11 OR #14 OR #16 OR #18**	**572063**
#20	(administrative):ti,ab,kw	341117
#21	("health claim* data"):ti,ab,kw	6
#22	#20 AND #21	1
#23	MeSH descriptor: [International Classification of Diseases] explode all trees	60
#24	**(ICD OR "International Classification of Diseases" OR "Administrative data" OR claim OR claims OR "Cancer data*" OR "Insurance data*" OR "Cancer registr*" OR "Cancer register*"):ti,ab,kw**	**9854**
#25	#22 OR #23 OR #24	9854
#26	#3 AND #7 AND #19 AND #25	122

Reviews: 1

Trials: 121

Editorials: 0

Searchstring Web of Science

#1	**TS = Neoplasms OR TI =(Cancer* OR Neoplas* OR Tumor* OR Tumour* OR Carcinom* OR Melanom* OR Malignan* OR Lymphoma* OR Oncolog*) OR AB=(Cancer* OR Neoplas* OR Tumor* OR Tumour* OR Carcinom* OR Melanom* OR Malignan* OR Lymphoma* OR Oncolog*)**	3.746.339
#2	**TS = (Comorbidity OR Chronic disease) OR TI = (Comorbid* OR Co-morbid* OR Multimorbid* OR Multi-morbid* OR "Chronic disorder*" OR "Concomitant disease*" OR "Chronic disease*" OR "Chronic condition" OR "Chronic conditions" OR "Health condition*" OR "Chronic illness*" OR Co-occur* OR "Chronic morbidit*") OR AB = (Comorbid* OR Co-morbid* OR Multimorbid* OR Multi-morbid* OR "Chronic disorder*" OR "Concomitant disease*" OR "Chronic disease*" OR "Chronic condition" OR "Chronic conditions" OR "Health condition*" OR "Chronic illness*" OR Co-occur* OR "Chronic morbidit*")**	819.638
#3	TI = (index OR indices OR score OR scores OR scale OR scales OR Frequency OR Frequencies OR "prevalence estimate*""*) OR AB = (index OR indices OR score OR scores OR scale OR scales OR Frequency OR Frequencies OR "prevalence estimate*")	6.215.416
#4	TI = prevalence OR AB=prevalence	641.586
#5	TI = (estimate OR comorbidit* OR co-morbidit* OR multimorbidit* OR multi-morbidit*) OR AB = (estimate OR comorbidit* OR co-morbidit* OR multimorbidit* OR multi-morbidit*)	2.374.972
#6	#4 AND #5	98.788
#7	AB=(comorbidit* OR co-morbidit* OR multimorbidit* OR multi-morbidit*) OR TI=(comorbidit* OR co-morbidit* OR multimorbidit* OR multi-morbidit*)	144.386
#8	TI=(measure*) AND AB=(measure*)	470.063
#9	#7 AND #8	828
#10	TI=(number*) OR AB=(number*)	3.897.898
#11	#7 AND #10	19.519
#12	TI=(level*) AND AB=(level*)	359.320
#13	#7 AND #12	1.450
#14	**#3 OR #6 OR #9 OR #11 OR #13**	**6.291.900**
#15	TS="International Classification of Diseases" OR TI = (ICD OR "International Classification of Diseases" OR "Administrative data" OR claim OR claims OR "Cancer data*" OR "Insurance data*" OR "Cancer registr*" OR "Cancer register*") OR AB = (ICD OR "Administrative data" OR claim OR claims OR "Cancer data*" OR "insurance data*" OR "Cancer registr*" OR "Cancer register*") OR (TI=(administrative AND "health claim* data") OR AB=(administrative AND "health claim* data"))	325.120
#16	#1 AND #2 AND #14 AND #15	1,981

Quality assessment tools

Name of author(s):_____

Year of publication:_____

Name of paper/study:

_____

This tool is designed to assess the risk of bias in population-based prevalence studies. Please read the additional notes for each item when initially using the tool. Note: If there is insufficient information in the article to permit a judgement for a particular item, please answer No (HIGH RISK) for that particular item.

Risk of bias item	Criteria for answers	Additional notes and examples
External Validity		
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. disease stage, type of database?	• Yes (LOW RISK): The study's target population was a close representation of the national population. • No (HIGH RISK): The study's target population was clearly NOT representative of the national population.	The target population refers to the group of people or entities to which the results of the study will be generalised. Examples: • The study was a national registry of people 15 years and over and the sample was drawn from a list that included all individuals in the population aged 15 years and over. The answer is: Yes (LOW RISK). • The study was conducted in one province/city only, and it is not clear if this was representative of the national population. The answer is: No (HIGH RISK). • The study was undertaken in one village/city only and it is clear this was not representative of the national population. The answer is: No (HIGH RISK).
2. Do the inclusion criteria match the target population e.g. age, sex insurance?	• Yes (LOW RISK): The application of the inclusion criteria results in a true or close representation of the target population. • No (HIGH RISK): The inclusion criteria do NOT result in a true or close representation of the target population.	The sampling frame is a list of the sampling units in the target population and the study sample is drawn from this list. Examples: • The sampling frame was a list of almost every individual within the target population. The answer is: Yes (LOW RISK). • The sampling frame was confined to just one particular ethnic group within the overall target population, which comprised many groups. The answer is: No (HIGH RISK).
3. Are all eligible participants included in the study?	• Yes (LOW RISK): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling). • No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	Examples: • All eligible participants are included Yes (LOW RISK) • Part of eligible participant are included No (HIGH RISK)
Internal Validity		

Risk of bias item	Criteria for answers	Additional notes and examples
4. Was an acceptable case definition used in the study?	• Yes (LOW RISK): An acceptable case definition was used. • No (HIGH RISK): An • acceptable case definition was NOT used.	For a study on cancer, the following case definition was used: "The diagnosis of cancer must be given by an physician or pathological proven." The answer is: • The answer is: Yes (LOW RISK). • The answer is: No (HIGH RISK).
5. Was the same mode of data collection used for all subjects?	• Yes (LOW RISK): The same mode of data collection was used for all subjects. • No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	The mode of data collection is the method used for collecting information from the subjects. Examples: • The answer is: Yes (LOW RISK). • The answer is: No (HIGH RISK).
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	• Yes (LOW RISK): the paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of comorbidity). • No (HIGH RISK): the paper dis represent numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	There may be errors in the calculation and/or reporting of the numerator and/or denominator. Examples: • There were no errors in the reporting of the numerator(s) AND denominator(s) for the prevalence of low back pain. The answer is: Yes (LOW RISK) • In reporting the overall prevalence of comorbidities in an oncological population (in both men and women), the authors accidentally used the population of women as the denominator rather than the combined population. The answer is: No (HIGH RISK).
7. Free of other bias?	• Yes (LOW RISK): No other biases are found when examining the paper • No (HIGH RISK): Other biases are found when examining the paper	

Comparison to Hoy's and O'Sullivan's risk of bias tool

Hoy	O'Sullivan	Our tool
External validity		
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	Was the study's target population a close representation of the national population in relation to relevant variables?	Was the study's target population a close representation of the national population in relation to relevant variables, e.g. disease stage, type of database?
2. Was the sampling frame a true or close representation of the target population?	Does the inclusion criteria match the target population of guideline?	Do the inclusion criteria match the target population e.g. age, sex insurance?
3. Was some form of Random selection used to select the sample, OR, was a census undertaken?	Were all eligible participants included in the study?	Are all eligible participants included in the study?
4. Was the likelihood of non-response bias minimal?	Was the likelihood of non-response bias <20?	
Internal validity		
5. Were data collected directly from the subjects (as opposed to a proxy)?		
6. Was an acceptable case definition used in the study?		Was an acceptable case definition used in the study?
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?		
8. Was the same mode of data collection used for all subjects?	Was data extracted/collected in an objective way?	Was the same mode of data collection used for all subjects?
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Was the interval from symptoms to test clinically appropriate for the diagnosis of interest?	
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Did they report extractable measures?	Were the numerator(s) and denominator(s) for the parameter of interest appropriate?
	Other bias?	Free of other bias?

Supplemental data

Table S1 is not printed in this book due to its size. This table and the literature references can be found here:

Table S2. Heterogeneity of measuring and reporting socioeconomic characteristics in different studies

Socioeconomic characteristics	Studies
Area level SES (household income, education levels and unemployment rates)	Beckmann 2016 Beckmann 2014
Area level SES (household income, value housing)	Dik Jansen Ten Berge Van Leersum Van Steenbergen
Occupation	
– blue-collar workers, – farmers, – self-employed, – lower white-collar workers – higher white-collar workers	Berglund, Garmo 2012
– Professional/clerical – manual worker – Housewife – Pensioner – Other – Missing	Capri
SES (education, poverty, income)	Du (but also poverty, income and education separate) Heilbroner
Individual level SES (poverty)	Kong
(education, employment, median household income, poverty, median rent and median housing value)	Parise
Area level SES	Pule Te Marvelde
Continues variable	Singh 2012
Area level (median) income	
– >62999 dollar – 48000-62999 dollar – 38000-47999 dollar – <38000 dollar	Abudu Concors May Duma

Table S2. Continued

Socioeconomic characteristics	Studies
– <30000 dollar – 30000-35999 / 34999 – 36000/35000-45999 – 46000+ – Missing	Cassidy Shi 2016 Shi 2015 Sineshaw Yang, Muralidhar,.. 2017
– less than $27,669, – $27,670–34,464, – $34,465–43,974, – >=$43,974	Osborne
– Quartile 1 – Quartile 2 – Quartile 3 – Quartile 4 – Unknown	Barocas Keating Schonberg Lowrance Du Sinha Williams Yang, Mahal 2017 Lam
– lowest quartile – missing	Farjah
– Highest tertile – Middle tertile – Lowest tertile	Wang
– High – Medium-high – Medium – Medium-low – Low – Missing	Krahn Singh 2010
Personal/family income	
– Low – Intermediate – High	Nilssen
– Lowest – 2nd – 3rd – 4th – Highest	Vehko
– Q1 – Q2 – Q3 – Q4	Tomic
Median household income (continuous variable)	Davidoff 2014 Davidoff 2010
Income deprivation	
– More affluent – More deprived	Di Girolamo

Table S2. Continued

Socioeconomic characteristics	Studies
– Q1 (least deprived) – Q2 – Q3 – Q4 – Q5 (deprived)	Soriano Fowler 2017 Fowler 2020 Lavelle Moller Morgan Pearson Richards Cardwell Jauhari 2020 Jauhari2019 Berglund, Lambe 2012 Busby Seneviratne
Area level poverty	
– high (>18.7%) – moderate (9.7% to 18.7%) – low (<9.7%)	Chow
– less than 6.51% as 'low', – >6.51–12.31% as 'moderate', – >12.31–20.17% as 'high', – >20.17 as 'very high'	Myint
– <8%, – 8%–15%, – 15%–30%, – >30%	Rios
– <5% – 5-9 – 10-14 – 15-19 – >=20	Heck
– lowest (≥20%), – middle low (≥10 and <20%), – middle high (≥5 and<10%), – highest (<5%)	Tannenbaum, Hernandez,.. 2014 Tannenbaum, Koru-Sengul,.. 2014 O'Brien
– first quartile, ≤3.91%; – second quartile, 3.92–7.21%; – third quartile, 7.22–13.08%; – fourth quartile, ≥13.09%	Du
– Lowest tertile – Middle tertile – Highest tertile	Foley
Individual poverty level	
– Yes – No	Unger

Table S2. Continued

Socioeconomic characteristics	Studies
Area level % no high school diploma	
– <7 – 7-12.9 – 13-20.9 – >20.9	Abudu Akensov Barocas
– >=29% – 20-28.9 – 14-19.9 – <14 – Missing	Cassidy Shi 2016 Shi 2015 Duma
– <15%, – 15%–25%, – 35%–35%, – >35%).	Rios
Completed high school	
– low (75.8% to 84.3%) – moderate (84.4$ to 88.0%) – high (88.1% to 91.8%))	Chow
– less than 66.12% as 'very low', – >66.12–75.54% as 'low', – >75.54–85.38% as 'moderate', – >85.38% as 'high'	Myint
– Quartile 1 – Quartile 2 – Quartile 3 – Quartile 4 – Unknown	Keating Schonberg Sinha Williams Yang, Mahal,.. 2017
Education (lower quartile)	Fariah
Area level college education	
– Yes – No	Hoffman Wang
– <16.5% – 16.5-22.4 – 22.4-31.2 >= 31.3	Nambudiri
Level of education	
– 1 = basic/high school (basics); – 2 = primary/lower secondary education (short); – 3 = upper secondary education (medium); – 4 = tertiary education (long); – 5 = unknown	Jespersen

Table S2. Continued

Socioeconomic characteristics	Studies
– low—9 or fewer years mandatory school, – middle—10 to 12 years high school – high—greater than 12 years/ university studies or equivalent	Loeb Nilsson Petterson Tomic Wennstig Willén Vehko Tomic
– low (elementary school) – intermediate (high school) – high (university)	Nilssen Pagano
– elementary school – junior high school – high school – college or higher – missing	Capri
Area level more than 12 years education	
– 18.1%, – 18.1–25.6%, – 25.7–33.2%, >33.2%	Osborne
– first quartile, ≤11.83%; – second quartile, 11.84–19.02%; – third quartile, 19.03–26.90%; – fourth quartile, ≥26.91%	Du
Percentage with some college education were higher or lower than the study sample median	Unger

Table S3. Sensitivity analyses with the addition of proportion Caucasian in model 3

	Coefficient (SE)	**p-value**
Model 3: multi-level model for percentage of comorbidities adjusted for all determinants		
Country		
- Australia	(baseline)	
- UK	-2.60 (11.57)	0.822
- USA	2.99 (9.67)	0.757
Data type		
- Hospital initiated routinely collected data	(baseline)	
- Claims data	15.58*** (2.57)	0.000
Tumour types		
- Multiple[a]	(baseline)	
- Breast	-3.52 (6.12)	0.565
- Lung	10.52* (4.98)	0.035

Table S3. Continued

	Coefficient (SE)	**p-value**
- Prostate	-14.93** (5.57)	0.007
- Colorectal	2.44 (4.89)	0.618
- Melanoma	-9.31 (8.36)	0.265
Metastatic		
- No distinction	(baseline)	
- Metastasis only	1.76 (2.44)	0.469
- Metastasis excluded	1.42 (3.11)	0.647
Index category		
- Charlson comorbidity index	(baseline)	
- Elixhauser comorbidity index	46.92*** (5.49)	0.000
- C3 index	36.49 (28.04)	0.193
- Other	-0.82 (5.71)	0.885
Age groups[b]		
- Age below 45	-6.88 (12.41)	0.579
- Age 45-59	3.91 (13.34)	0.769
- Age 60-69	-1.10 (25.00)	0.965
- Age 70-79	-2.32 (25.8)	0.928
- Age 80 or above	8.09 (22.66)	0.721
Presence subtype		
- No	(baseline)	
- Yes	3.74 (2.69)	0.164
Proportion male	19.52** (7.36)	0.008
Proportion Caucasian	20.66 (14.33)	0.149
Reporting quality		
- Valid	(baseline)	
- Not valid	7.44 (5.54)	0.179
Validity score	-1.15 (2.03)	0.571
Start year	0.49* (0.21)	0.018
Study duration	-0.31 (0.39)	0.427
Constant	-7.38 (28.27)	0.794

Significant: *0.05, **0.01, ***0.001

Observations = 85, N groups=66, Log likelihood= -294.30.

[a] The category multiple includes observations that make no distinction between the tumour types and can therefore not be presented within the categories of the individual tumour types

[b] Age groups are not mutually exclusive. Observations can include multiple categories. Therefore dummy variables were entered in the model per category.

Table S4. Robustness check using a pooled linear regression with clustered standard errors (instead of multi-level model)

	Model 1[a]	**Model 2[b]**	**Model 3[c]**
	Coefficient (SE)	**Coefficient (SE)**	**Coefficient (SE)**
Country			
- Australia			(baseline)
- Canada			2.01 (6.19)
- Denmark			26.39*** (5.32)
- France			9.57 (5.31)
- Italy			11.27*(5.46)
- Japan			-12.87* (6.21)
- Netherlands			39.17*** (4.91)
- New Zealand			9.93 (6.80)
- Norway			3.76 (6.45)
- Spain			23.24*** (4.75)
- Sweden			22.18*** (5.48)
- UK			12.99* (6.09)
- USA			16.02** (5.23)
Data type			
- Hospital initiated routinely collected data			(baseline)
- Claims data			16.11*** (3.71)
- Other/unknown			12.38 (8.98)
Tumour types			
- Multiple[a]		(baseline)	(baseline)
- Breast		-14.56 (4.03)	7.01 (7.06)
- Lung		10.27 (5.36)	7.47 (4.41)
- Prostate		-8.36 (3.90)	-22.17*** (6.70)
- Colorectal		3.12 (4.45)	4.03 (4.30)
- Melanoma		-2.93 (13.56)	-2.38 (9.22)
Metastatic			
- No distinction			(baseline)
- Metastasis only			-0.01 (2.34)
- Metastasis excluded			-1.78 (3.71)
Index category			
- Charlson comorbidity index			(baseline)
- Elixhauser comorbidity index			20.92 (10.75)
- C3 index			20.17*** (5.86)
- Other			-7.98 (6.57)

Table S4. Continued

	Model 1[a]	**Model 2[b]**	**Model 3[c]**
	Coefficient (SE)	**Coefficient (SE)**	**Coefficient (SE)**
Age groups[b]			
- Age below 45			-3.83 (3.38)
- Age 45-59			-1.89 (3.65)
- Age 60-69			-2.39 (2.74)
- Age 70-79			7.23* (3.61)
- Age 80 or above			3.62 (3.90)
Presence subtype			
- No			(baseline)
- Yes			7.02* (3.07)
Proportion male			38.05** (11.82)
Reporting quality			
- Valid			(baseline)
- Not valid			4.84 (4.9)
Validity score			1.10 (1.21)
Start year	-0.31 (0.22)	-0.42 (0.23)	0.56* (0.23)
Study duration	-0.22 (0.32)	-0.22 (0.31)	0.19 (0.29)
Constant	40.32*** (5.11)	45.50*** (5.45)	-31.93** (11.3)
N Observations	208	208	199
R-squared	0.011	0.300	0.684

Significant: *0.05, **0.01, ***0.001

[a] The category multiple includes observations that make no distinction between the tumour types and can therefore not be presented within the categories of the individual tumour types

[b] Age groups are not mutually exclusive. Observations can include multiple categories. Therefore dummy variables were entered in the model per category.

Table S5. Sensitivity analyses with tumour type interactions

	Coefficient (SE)	p-value
Melanoma	-6.32 (60.27)	0.916
Prostate	25.07 (57.74)	0.664
Lung	43.15 (58.07)	0.457
Breast	23.06 (58.03)	0.691
Colorectal	30.66 (58.09)	0.598
Melanoma * Start year	**-0.60 (4.46)**	0.893
Prostate * Start year	**-2.57 (4.37)**	0.556
Lung * Start year	**-2.33 (4.38)**	0.595
Breast * Start year	**-2.67 (4.38)**	0.543
Colorectal * Start year	**-2.3 (4.38)**	0.599
Start year	2.21 (4.37)	0.613
Study duration	-0.22 (0.32)	0.482
Constant	10.58 (57.9)	0.855

Observations = 208, N groups=140, Log likelihood= -818.87.
Multiple and *Multiple * Start year* omitted because of collinearity.

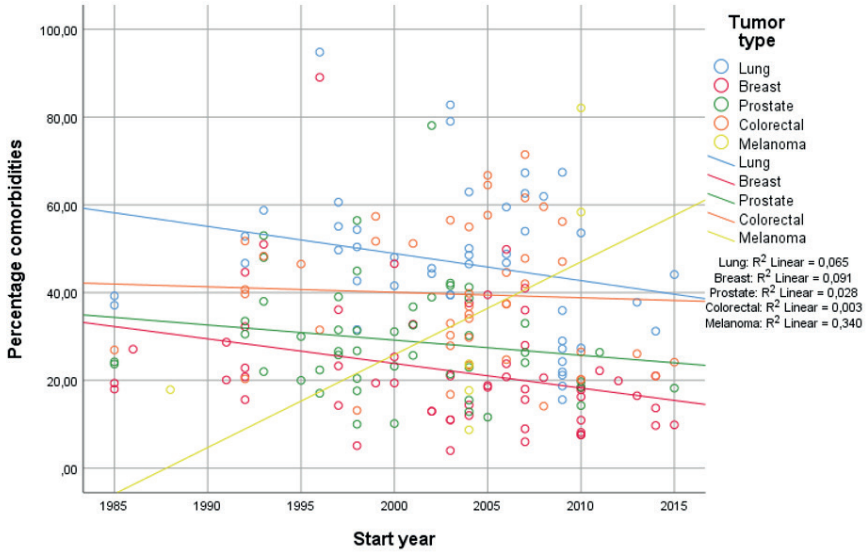

Figure S1. Unweighted percentage of comorbidities over time for different tumour types

Table S6. Sensitivity analysis of the effect of individual determinants on comorbidity prevalence

	Countries	**Data type**	**Metastatic cancer population**	**Comorbidity index type**
	Coefficient (SE)	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**
Tumour type				
- Multiple[a]	(baseline)	(baseline)	(baseline)	(baseline)
- Breast	-11.62 (6.95)	-9.98 (7.16)	-13.20 (7.29)	-14.07* (7.06)
- Lung	14.10* (6.99)	15.85* (7.21)	12.84 (7.34)	12.08 (7.11)
- Prostate	-7.17 (6.80)	-5.62 (7.01)	-9.36 (7.13)	-9.58 (6.90)
- Colorectal	3.01 (7.02)	4.31 (7.23)	0.66 (7.34)	0.01 (7.11)
- Melanoma	-9.81 (8.72)	-6.11 (9.05)	-9.26 (9.30)	-8.90 (8.90)
Country				
- Australia	(baseline)			
- Canada	-4.14 (5.49)			
- Denmark	12.09 (6.23)			
- France	7.56 (10.47)			
- Italy	15.59 (10.84)			
- Japan	-9.21 (13.66)			
- Netherlands	25.43*** (7.09)			
- New Zealand	15.61 (9.36)			
- Norway	-2.06 (6.08)			
- Spain	7.7 (13.47)			
- Sweden	6.2 (6.21)			
- UK	4.84 (5.09)			
- USA	14.6** (5.00)			
Data type				
- Hospital initiated routinely collected data		(baseline)		
- Claims data		8.62*** (2.36)		
- Other/unknown		-7.28 (10.49)		
Metastatic				
- No distinction			(baseline)	
- Metastasis only			0.36 (2.51)	
- Metastasis excluded			3.99 (3.42)	

	Age categories	Presence of subtype	Proportion male	Proportion Caucasian	Reporting quality	Validity score
	Coefficient (SE)	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**
	(baseline)	(baseline)	(baseline)	(baseline)	(baseline)	(baseline)
	-12.20* (6.04)	-13.66 (7.33)	1.32 (8.56)	-11.85 (6.11)	-13.21 (7.32)	-13.14 (7.33)
	13.01* (6.06)	11.22 (7.48)	11.39 (7.33)	13.7* (6.15)	12.79 (7.36)	12.77 (7.37)
	-7.17 (5.79)	-9.38 (7.13)	-24.01** (8.37)	-5.86 (5.47)	-9.30 (7.13)	-9.10 (7.13)
	1.23 (6.07)	-0.51 (7.44)	1.13 (7.33)	2.86 (6.26)	0.62 (7.36)	0.64 (7.38)
	-5.25 (8.38)	-9.92 (9.31)	-10.07 (9.12)	-22.04 (13.34)	-8.96 (9.31)	-9.12 (9.32)

Table S6. Continued

	Countries	Data type	Metastatic cancer population	Comorbidity index type
	Coefficient (SE)	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**
Index category				
- Charlson comorbidity index				(baseline)
- Elixhauser comorbidity index				14.86*** (3.55)
- C3 index				12.94* (6.53)
- Other				3.72 (7.14)
Age groups[b]				
- Age below 45				
- Age 45-59				
- Age 60-69				
- Age 70-79				
- Age 80 or above				
Presence of subtype				
- No				
- Yes				
Proportion male				
Proportion Caucasian				
Reporting quality				
- Valid				
- Not valid				
Validity score				
Constant	24.46** (8.28)	31.56*** (7.09)	37.21*** (7.08)	37.30*** (6.84)
N observations	209	209	209	209
N groups	141	141	141	141
Log Likelihood	-811.79	-819.85	-825.99	-817.52

Significant: *0.05, **0.01, ***0.001

[a] The category multiple includes observations that make no distinction between the tumour types and can therefore not be presented within the categories of the individual tumour types

[b] Age groups are not mutually exclusive. Observations can include multiple categories. Therefore dummy variables were entered in the model per category.

	Age categories	Presence of subtype	Proportion male	Proportion Caucasian	Reporting quality	Validity score
	Coefficient (SE)	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**
	-5.01* (2.50)					
	-3.22 (2.50)					
	2.28 (2.69)					
	5.01 (3.03)					
	10.41*** (3.00)					
		(baseline)				
		2.94 (2.43)				
			30.90*** (9.34)			
				8.91 (17.56)		
					(baseline)	
					4.17 (4.60)	
						-0.57 (1.28)
	25.80*** (7.35)	37.28*** (7.09)	21.44* (8.54)	31.89* (16.07)	37.31*** (7.09)	40.89*** (10.43)
	209	209	200	85	209	209
	141	141	138	66	141	141
	-801.84	-826.00	-788.74	-339.31	-826.31	-826.31

Table S7. Sensitivity analyses of the influence of individual determinants on the prevalence of comorbidity over time

	Countries	**Data type**	**Metastatic cancer population**	**Comorbidity index type**	**Age categories**
	Coefficient (SE)	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**
Tumour type					
- Multiple[a]	(baseline)	(baseline)	(baseline)	(baseline)	(baseline)
- Breast	-11.66 (6.96)	-9.95 (7.16)	-12.96 (7.31)	-13.84* (7.07)	-12.32* (6.00)
- Lung	14.01* (7.00)	15.84* (7.21)	13.20 (7.35)	12.45 (7.11)	12.87* (6.03)
- Prostate	-7.29 (6.81)	-5.66 (7.01)	-9.03 (7.15)	-9.05 (6.91)	-7.21 (5.75)
- Colorectal	2.95 (7.04)	4.25 (7.23)	1.15 (7.36)	0.57 (7.12)	1.04 (6.04)
- Melanoma	-8.46 (9.04)	-5.10 (9.41)	-6.61 (9.66)	-5.94 (9.22)	-3.32 (8.80)
Start year	0.08 (0.20)	0.10 (0.21)	-0.23 (0.20)	-0.25 (0.19)	0.19 (0.21)
Study duration	-0.04 (0.35)	0.15 (0.33)	-0.27 (0.33)	-0.38 (0.31)	0.07 (0.33)
Country					
- Australia	(baseline)				
- Canada	-4.05 (5.50)				
- Denmark	13.05* (6.34)				
- France	7.46 (10.54)				
- Italy	15.70 (10.90)				
- Japan	-9.69 (13.74)				
- Netherlands	25.87*** (7.25)				
- New Zealand	16.43 (9.67)				
- Norway	-2.26 (6.09)				
- Spain	7.26 (13.60)				
- Sweden	7.12 (6.61)				
- UK	4.66 (5.11)				
- USA	15.07** (5.11)				
Data type					
- Hospital initiated routinely collected data		(baseline)			
- Claims data		9.11*** (2.61)			
- Other/unknown		-7.73 (10.71)			
Metastatic					
- No distinction			(baseline)		
- Metastasis only			0.60 (2.51)		
- Metastasis excluded			4.49 (3.47)		

	Presence of subtype	Proportion male	Proportion Caucasian	Reporting quality	Validity score
	Coefficient (SE)	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**
	(baseline)	(baseline)	(baseline)	(baseline)	(baseline)
	-13.47 (7.34)	1.55 (8.57)	-11.98* (6.11)	-12.91 (7.33)	-12.82 (7.36)
	11.33 (7.49)	11.82 (7.35)	13.63* (6.15)	13.13 (7.38)	13.12 (7.39)
	-8.99 (7.16)	-23.48** (8.38)	-5.83 (5.47)	-8.97 (7.16)	-8.76 (7.16)
	-0.16 (7.45)	1.76 (7.36)	2.85 (6.26)	1.08 (7.39)	1.14 (7.41)
	-7.49 (9.66)	-8.03 (9.48)	-21.74 (13.56)	-6.45 (9.68)	-6.47 (9.70)
	-0.27 (0.20)	-0.24 (0.20)	-0.13 (0.31)	-0.19 (0.20)	-0.19 (0.21)
	-0.26 (0.32)	-0.26 (0.32)	0.06 (0.59)	-0.17 (0.33)	-0.20 (0.33)

Table S7. Continued

	Countries	Data type	Metastatic cancer population	Comorbidity index type	Age categories
	Coefficient (SE)	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**
Index category					
- Charlson comorbidity index				(baseline)	
- Elixhauser comorbidity index				15.42*** (3.58)	
- C3 index				13.92* (6.60)	
- Other				3.76 (7.06)	
Age groups[b]					
- Age below 45					-5.31* (2.51)
- Age 45-59					-3.58 (2.53)
- Age 60-69					2.39 (2.68)
- Age 70-79					4.97 (3.01)
- Age 80 or above					10.38*** (2.98)
Presence of subtype					
- No					
- Yes					
Proportion male					
Proportion Caucasian					
Reporting quality					
- Valid					
- Not valid					
Validity score					
Constant	23.04* (9.60)	28.7*** (8.94)	42.46*** (8.34)	43.61*** (8.00)	22.64*** (8.38)
N observations	208	208	208	208	208
N groups	140	140	140	140	140
Log likelihood	= -807.88	-815.97	-821.42	-812.56	-797.43

Significant: *0.05, **0.01, ***0.001

[a] The category multiple includes observations that make no distinction between the tumour types and can therefore not be presented within the categories of the individual tumour types

[b] Age groups are not mutually exclusive. Observations can include multiple categories. Therefore dummy

	Presence of subtype	Proportion male	Proportion Caucasian	Reporting quality	Validity score
	Coefficient (SE)	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**	**Coefficient (SE)**
	(baseline)				
	3.54 (2.47)				
		30.73*** (9.36)			
			8.61 (17.58)		
				(baseline)	
				3.64 (4.63)	
					-0.38 (1.32)
	43.05*** (8.36)	26.84** (9.51)	33.79* (17.22)	41.33*** (8.40)	44.02*** (10.92)
	208	199	85	208	208
	140	137	66	140	140
	-821.30	-784.26	-339.20	-821.99	-822.26

Chapter 3

Healthcare costs and survival in the era of immunotherapy for stage IV non-small cell lung cancer

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Abstract

Purpose: Our study aims to investigate differences in 2-year survival and cost before, during and after the introduction of immunotherapy for patients with stage IV NSCLC.

Methods: We performed a retrospective study in a comprehensive lung cancer network. Patients were 18 years or older, diagnosed with stage IV NSCLC between 2014 and 2020. We used data from the Netherlands Cancer Registry and insurance claims. Three cohorts of patients were compared: pre- (2014-2016), during- (2017-2018) and post-implementation (2019-2020) of immunotherapy. Survival was evaluated with a Kaplan Meier analysis, a weighted Cox regression and a restricted mean survival time analyses. Costs data were collected from a university hospital and imputed for other patients. Log-link gamma regression was used to evaluate cost. Follow-up was 2 years post diagnosis. We calculated the mean cost per life years gained (LYG).

Results: The study included 1,622 patients. Median survival was 154 (95% CI 136-173), 170 (95% CI 138-193) and 212 (95% CI 177-246) days for the pre-, during- and post-implementation cohorts, respectively. The post-cohort had an adjusted hazard ratio of 0.78 (95%-CI 0.68-0.90) in comparison to the pre-cohort. Adjusted mean survival days increased with 74.5 (95% CI 44.8-105.2) days between the pre- and post-cohort. Mean total costs for the pre-, during- and post-cohort were €15,686 (95% CI 14,311-17,062), €33,586 (95% CI 30,747-36,425) and €45,771 (95% CI 42,729-48,812) respectively. Marginal spending was €150,796 per LYG.

Conclusion: Our findings show higher survival rates after implementation of immunotherapy for stage IV NSCLC patients. Concurrently, total costs increased substantially.

Introduction

Over 2 million people were diagnosed with lung cancer globally in 2018, and 1.8 million people died of lung cancer.(1) Being the most common cancer worldwide, lung cancer accounts for 11.9% of all cancer diagnoses and 20.4% of all deaths due to cancer.(2) Of all lung cancer diagnoses, 81% comprises non-small cell lung cancer (NSCLC), with around 20% of patients being diagnosed with stage IV.(3, 4) The relative five-year survival rate of stage IV metastatic NSCLC is only 9%.(5)

For a long time, chemotherapy was the standard of care for metastatic NSCLC, although this treatment reduces a patient's quality of life without a demonstrated effect on improved survival.(6, 7) Recently, however, the introduction of targeted therapies and immunotherapies changed management of metastatic NSCLC. Currently, immunotherapy is recommended for a select group of stage IV NSCLC with no contra-indications, no eligibility for targeted therapy and a WHO performance status of 0 or 1. For this select group, the first line treatment is pembrolizumab, and for second line treatment, pembrolizumab, nivolumab or atezolizumab is recommended. Immunotherapies like nivolumab, pembrolizumab and atezolizumab target the programmed cell death-1 (PD-1) receptor or its ligand PD-L1. Before the full implementation of immunotherapy, limited increases in survival over time were found.(8, 9) However, recent real-world studies show benefit of immunotherapies for metastatic NSCLC.(10, 11) Median survival increased from 6.2 months to 8.9 months after the introduction of first-line immunotherapy for stage IV NSCLC.(11) One-year survival rate increased with 18.8% for females and 19.1% in males between 2010 and 2020.(10)

Due to these innovations in cancer treatment combined with higher incidence, costs of cancer care have continuously increased, making lung cancer one of the most expensive cancer types.(12-16) Especially NSCLC patients with immunotherapy treatments exhibit high costs.(9, 17) While both survival and expenses for lung cancer are increasing, real-world cost-effectiveness is unclear.

In general, insights in trends of real-world healthcare costs in relation to health gains are lacking and long-term follow up studies for introduced expensive drugs are underrepresented for NSCLC. In the context of increasing healthcare costs within constrained budgets, it is crucial to provide insight into how health gains relate to the investments that are made. Therefore, our study has the following two aims. First, to explore real-world survival before, during and after the introduction

of immunotherapy for patients with metastatic NSCLC. Second, to explore real-world cost and cost-effectiveness for this patient group.

Method

Study design and setting

We performed a retrospective cohort study based on real-world survival and cost data. This study was performed in a comprehensive lung cancer network with four affiliated hospitals. This network included one university hospital and three affiliated general hospitals. To study the impact of immunotherapy on survival and costs we compared three cohorts. The pre-implementation cohort, comprising patients before the introduction of immunotherapy in the region (2014-2016); the during-implementation cohort, consisting of patients in the period that immunotherapy was being implemented (2017-2018); the post-implementation cohort, consisting of patients diagnosed in the period in which immunotherapy was fully implemented (2019-2020). Due to the impact of COVID-19 on cancer diagnosis and treatment in 2020, 2019 is considered the most representative year for the post-implementation period.(18, 19)

Participants

All patients aged 18 or above diagnosed with stage IV NSCLC between 2014 to 2020 in one of the four hospitals of the comprehensive lung cancer network were included in the study. Patients with missing survival status were excluded.

Survival data

Patient-level data from the Netherlands Cancer Registry (NCR) was obtained. The NCR collects data based on notification by the national pathology archive (PALGA) and specially trained data managers gather cancer patient data from medical records in all Dutch hospitals.

The data included patient-, disease- and treatment-characteristics. Patient characteristics included age and gender. Disease characteristics included year of diagnosis, localization of metastasis, histology, and date of death. Treatment characteristics included types of first-line treatments.

Costs data

For the patients from the university hospital, additional data on healthcare insurance claims was gathered from the date of diagnosis until 2 years post

diagnosis. The claims data included diagnosis treatment combinations (DTC's) and add-on claims for intensive care (IC) hospitalizations and expensive medications. The DTC data included nationally defined DTC codes and names, start and end dates, related specialism, and related diagnoses. The IC add-on data included each IC hospitalization and date. The add-on medication included the date of registration, medication names, unit volume and quantity. Diagnosis indications were present from 2017. Before 2017, the related DTC diagnoses were used as a proxy for medication indication. The assumption was made that add-on medication with a DTC related to a NSCLC were given for a NSCLC indication.

To calculate total costs, yearly national average prices for the DTC's and yearly national maximum prices for IC days based on data from the Netherlands Healthcare Authority (NZa) were used.(20, 21) By means of expert opinion, DTCs were categorized into three groups: related to, not related to, and potentially related to the NSCLC diagnosis. In 1.2% of the DTCs, no national average price for the DTC was available for a specific year. In case of missing average prices, data from the nearest year or, if not available, hospital list prices were used.(22) For expensive add-on medications, average market prices set at June 2023 were used.(23) All costs were indexed to EURO 2023 using formal price adjustments by the Dutch Healthcare authority.(24)

Analyses

Descriptive data on patient and diseases characteristics were evaluated per incidence year and cohort. Differences between the cohorts were tested with an Analysis of Variance (ANOVA) test for continuous variables and with a Chi-squared test for categorical variables. Median survival was evaluated using Kaplan Meier survival curves for the three cohorts. To account for the violation of the non-proportional hazard assumption (tested with the Schoenfeld test) and to adjust for case-mix differences, a weighted Cox regression was performed to compare mortality hazards between the cohorts. To calculate life years gained (LYG), mean survival days were evaluated with a restricted mean survival time (RMST) with a cut-off at two-year follow-up and adjusted for confounding.(25)

NSCLC-specific utilization in the university hospital, combined with mean national prices, was used to calculate mean costs per patient. Costs for patients from the general hospitals were imputed with multiple imputation by means of a random forest separately for patients with and without immunotherapy. After multiple imputation, mean costs were calculated. Mean costs were evaluated with a log-link gamma regression model adjusted for confounding.

Different sensitivity analyses were performed. First, a different multiple imputation method (predictive mean matching) for the costs from the general hospitals was used. Second, results were adjusted for general hospital effects. Third, costs that were categorized as potentially related to NSCLC were included. Last, different levels of medication discounts of 20% and 40% were applied to correct for potential discounts not incorporated in publicly available data on mean prices. as average market prices may not fully incorporate all discounts. All analysis were performed with R (version 4.3.2).

Results

A total of 1,622 patients with stage IV NSCLC were included in the study. Figure 1 presents the patient selection and the availability of cost data. Four patients were excluded based on missing survival status. The university hospital had 863 patients, of which 78 had no patient number available, and 31 had no cost data available. Patient numbers were missing in the NCR if the university hospital was not the main treatment hospital. It was assumed that no costs were available for patients if the DTC started in 2014.

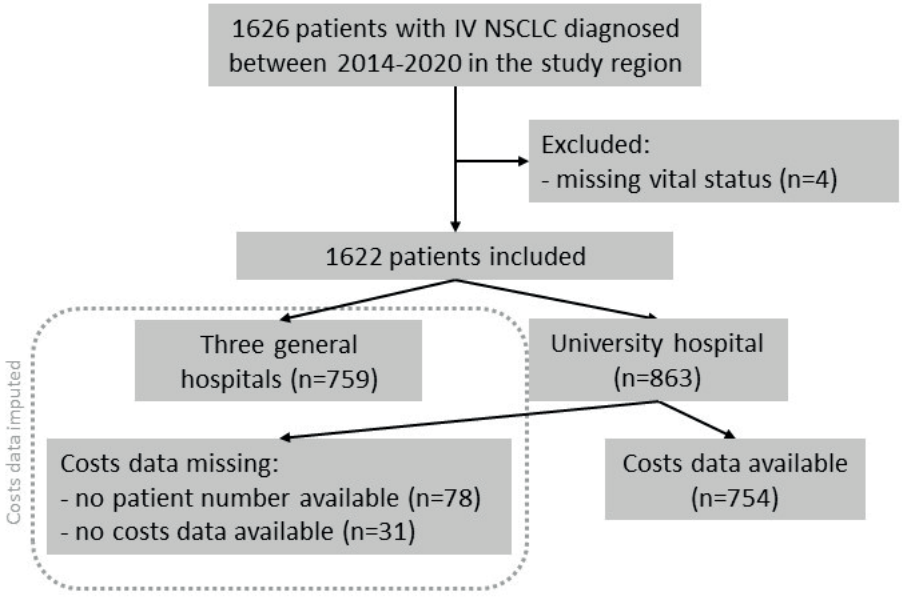

Figure 1. This flow diagram presents the patient selection. The dotted line presents the patients that had no cost data available. For these patients, costs were imputed.

Table 1 presents descriptives of the included patients per incidence year and cohort. For the pre-, during- and post-implementation cohort, the mean age at diagnosis was 66.6 (95% CI 65.9-67.4), 67.8 (95% CI 67.1-68.8) and 68.1 (95% CI 67.2-68.9) respectively. The percentage of males were 59, 54 and 55 respectively. Most patients had adenocarcinoma with 66%, 59% and 66%, respectively. Brain metastasis occurred in 18%, 17% and 18% respectively. Two-year survival was 11.7%, 16.8% and 21.5% respectively. Immunotherapy was a first line treatment in 0.5%, 14.3% and 37.1% of patients, respectively. The majority of patients were administered pembrolizumab (85%), see appendix Table S1.

Survival analyses

The Kaplan Meier survival curve (figure 2) reveals a significant unadjusted difference in median survival times of 154 (95% CI 136-173) days in the pre-implementation cohort, 170 (95% CI 138-193) days in the during-implementation cohort and 212 (95% CI 177-246) days in the post-implementation cohort. The global Schoenfeld residuals were significant with a p-value of 0.02.

Table 2 presents the weighted Cox regression, accounting for non-proportional hazards. During the introduction of immunotherapies, the adjusted hazard ratio decreased to 0.87 (95%-CI 0.76-1.00) and further to 0.78 (95%-CI 0.68-0.90) after the introduction of immunotherapy. Appendix Table S2 presents the model results.

To calculate LYG between the cohorts, mean survival days were evaluated with a restricted mean survival time analyses. The analyses showed a mean increase of 42.1 (95% CI 12.7-71.4) days and 74.5 (95% CI 44.8-105.2) days for the during- and post-implementation cohort respectively, compared to the pre-implementation cohort. Appendix Table S3 presents the model results.

Table 1. Descriptives of patients in the three cohorts and per year of diagnosis

	Pre-implementation cohort			
	2014 (n=190)	**2015 (n=234)**	**2016 (n=225)**	**Total cohort (n=649)**
Academic hospital (%)	47.4	47.9	40.0	45.0*
Immunotherapy[a] (%)	1.1	0.0	0.4	0.5*
Age (mean, 95%-CI)	67.1 (65.8-68.4)	66.4 (65.0-67.8)	66.5 (65.2-67.8)	66.6* (65.9-67.4)
Male gender (%)	60.0	59.0	58.2	59.0
Histology (%)-				
Adenocarcinoma	62.1	70.5	63.1	65.5
- Squamous cell carcinoma	15.3	14.5	17.8	15.9
- Other	22.6	15.0	19.1	18.6
Metastasis in the brain (%)	20.5	17.5	17.3	18.3
2-year survival (%)	11.1	12.8	11.1	11.7*

[a] Immunotherapy as first line treatment as registered in the NCR. This misses patients who received immunotherapy as second-line or third-line treatment.

* Significantly different between the three cohorts with p<0.05

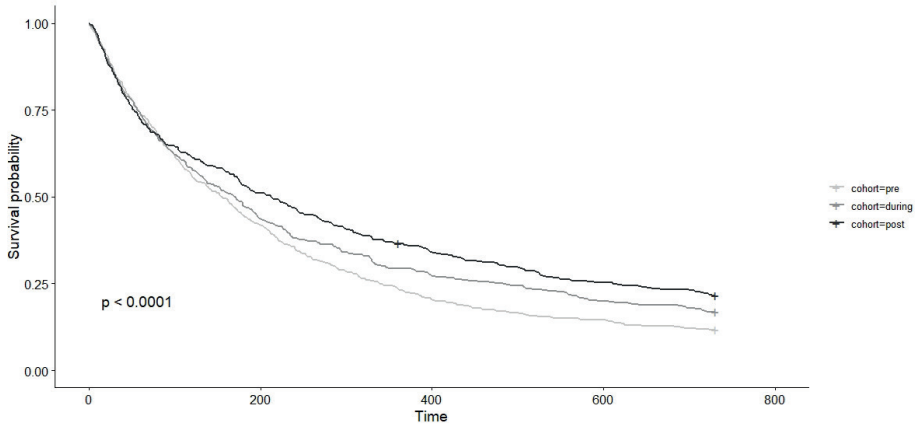

Figure 2. Unadjusted Kaplan Meier survival curve for the pre-, during- and post-implementation cohort

Table 2. Weighted Cox regression unadjusted for confounding and adjusted for confounding

	Unadjusted, HR (95%-CI)	**Adjusted*, HR (95%-CI)**
Pre-implementation	(baseline)	(baseline)
Implementation	0.92 (0.80-1.05)	0.87 (0.76-1.00)
Post-implementation	0.81 (0.70-0.93)	0.78 (0.68-0.90)

* Adjusted for age at time of diagnosis, gender and histology

During-implementation cohort			Post-implementation cohort		
2017 (n=245)	**2018 (n=230)**	**Total cohort (n=475)**	**2019 (n=248)**	**2020 (n=250)**	**Total cohort (n=498)**
45.3	60.9	52.8*	69.8	58.8	64.3*
6.9	22.2	14.3*	33.9	40.4	37.1*
68.1 (66.9-69.4)	67.7 (66.6-68.6)	67.8* (67.1-68.8)	68.8 (67.6-70.1)	67.3 (66.1-68.5)	68.1* (67.2-68.9)
55.1	53.5	54.3	58.5	52.0	55.2
60.0	58.3	59.2	69.8	62.8	66.3
19.2	17.8	18.5	13.7	13.6	13.7
20.8	23.9	22.3	16.5	23.6	20.1
17.1	17.0	17.1	16.5	19.6	18.1
14.3	19.6	16.8*	25.0	18.0	21.5*

For one patient we changed time till death from 0 to 1 day. 0 days is not possible in weighted Cox regression.

Cost analyses

Table 3 presents the mean costs after multiple imputation. Mean total costs were €15,686 (95% CI 14,311-17,062), €33,586 (95% CI 30,747-36,425) and €45,771 (95% CI 42,729-48,812) in the pre-, during- and post-implementation cohort respectively. Unadjusted mean total costs increased by €17,900 (95% CI 12,502-23,298) and €30,085 (95% CI 23,124-37,045) for the during- and post-implementation cohort compared to the pre-implementation cohort. Of this increase, 62% is directly due to immunotherapy costs, 19.4% due to add-on claims for different drugs, 17.1% is due to increases in DTC costs, and 1.1% due to add-on claims for IC.

After adjusting for age, gender, and histology, mean total costs increased by €21,089 (95% CI 15,305-26,873) and €30,779 (95% CI 23,781-37,776) in the during- and post-implementation cohort, respectively. Combining the estimated marginal cost increases with estimated life days gained implies a marginal cost-effectiveness of €182,838 and €150,796 per LYG respectively. Appendix Table S4 presents the output of the log-link gamma models. Appendix Table S5 presents the mean costs for patients from the academic hospital. Appendix Table S6 presents cost data after imputation with predictive mean matching.

Table 3. Mean costs (95%CI) in Euro per patient for the entire patient population after multiple imputation

	Pre-implementation			
	2014	**2015**	**2016**	**Total cohort**
DTC[1]	8,651 (8,123-9,180)	9,697 (9,079-10,316)	9,793 (9,180-10,405)	9,424 (8,832-10,017)
IC costs	187 (126-248)	287 (210-364)	335 (255-416)	274 (198-351)
Medication[1]				
- All	5,012 (4,039-59,85)	7,901 (6,600-9,203)	4,821 (3,928-5,714)	5,988 (4,882-7,093)
- Immunotherapy alone	538 (305-770)	349 (188-510)	491 (323-658)	453 (257-650)
Total costs	13,850 (12,627-15,072)	17,886 (16,302-19,470)	14,949 (13,741-16,158)	15,686 (14,311-17,062)

DTC = diagnosis treatment combination. IC = intensive care. [1]Only related to non-small cell lung cancer

After adjusting for hospital or including costs potentially related to the NSCLC diagnosis did not affect the results (Appendix Table S3, S4, S7 and S8). Including a discount of 20% and 40% for add-on medication costs per LYG were lowered to €125,614 and €100,769 respectively (Appendix Table S8 -S10).

Discussion

This study aimed to explore real-world survival and cost after the introduction of immunotherapy for patients with metastatic NSCLC. We found an HR of 0.78 after the introduction of immunotherapy, indicating a decreased two-year mortality risk of 22%. We found an increased survival of 74.5 days in comparison to the period before immunotherapy was implemented. During that period, total costs per patient increased by €30,779, implying a cost-effectiveness of €150,796 per LYG. Applying discounts of 20% and 40% to immunotherapy medications lowered cost effectiveness to €125,614per LYG and €100,769per LYG, respectively. Costs of immunotherapy utilization and survival slightly declined in 2020 compared to 2019, possibly due to COVID-19 and adjustments to immunotherapy dosages or intervals. However, this rendered a similar marginal cost-effectiveness ratio in 2020, reinforcing the assumption that costs and survival are causally related in this patient group. About 60% of the cost increase is due to add-on claims for immunotherapy drugs, mainly pembrolizumab. Interestingly, a significant percentage of the cost increases is due to higher utilization and increases in regular DTC costs,

During – implementation			Post-implementation		
2017	**2018**	**Total cohort**	**2019**	**2020**	**Total cohort**
11,515 (10,801-12,228)	13,406 (12,711-14,100)	12,430 (11,725-13,136)	15,152 (14,314-15,991)	14,012 (13,243-14,782)	14,580 (13,776-15,384)
596 (450-743)	530 (414-646)	564 (429-699)	967 (685-1,249)	260 (176-344)	612 (402-822)
16,527 (14,163-18,891)	24,921 (22,329-27,513)	20,592 (18,104-23,080)	33,497 (30,750-36,244)	27,684 (25,361-30,007)	30,579 (28,033-33,125)
5,888 (4,596-7,181)	12,688 (11,055-14,320)	9,181 (7,705-10,656)	19,587 (17,649-21,526)	18,844 (16,988-20,701)	19,214 (17,317-21,111)
28,638 (25,905-31,371)	38,857 (35,933-41,780)	33,586 (30,747-36,425)	49,616 (46,313-52,919)	41,957 (39,207-44,706)	45,771 (42,729-48,812)

including add-on claims for different drugs, likely related to the administration of immunotherapy or the effects of immunotherapy. This stipulates the need to assess total costs -including treatment administration costs- when evaluating the effects of immunotherapy.

Comparison to previous literature

The results question the added value of new expensive cancer drugs. A study evaluating FDA cancer drug approvals revealed that, between 2003-2021, 124 drugs were approved in the US for a total of 374 different indications.(26) However, the authors found that cancer drugs only modestly extend patient life with an increase in overall survival by 2.8 months (IQR 1.97-4.60). In the KEYNOTE-024 trial of pembrolizumab, the hazard rate for pembrolizumab in comparison to chemotherapy was 0.60 (95% CI .041-0.89) in patients with at PDL1 expression on at least 50% of the tumour cells.(27) Pembrolizumab also resulted in fewer adverse events. Subsequent studies on the cost-effectiveness of immunotherapy for metastatic NSCLC found that pembrolizumab, nivolumab or bevacizumab are cost-effective, but study outcomes varied.(28-30) This could be explained by methodological differences.(31)

However, patients included in clinical trials differ from patients in the real world. For example, immunotherapy is likely more cost-effective in a subpopulation with higher PDL1 expression.(28, 29) Off-label prescriptions or broadening immunotherapy indications could reduce cost-effectiveness. This stipulates

the need for real-world cost-effectiveness analysis after implementation of immunotherapy into clinical practice. A study by *Cramer-van der Welle et al* compared outcomes of the KEYNOTE-024 to real-world patients, finding survival of 15.8 (95% CI 9.4-22.1) months for real-world patients, compared to 30.0 (95% CI 18.3-NR) months for trial patients.(32) While progression-free survival was similar (HR of 1.08, 95% CI 0.75–1.55), overall survival was significantly shorter (HR of 1.55, 95% CI 1.07–2.25). This is in line with our results, demonstrating lower survival gains in the actual population than implied by immunotherapy clinical trials. A previous real-world data study by *Danesi et al* found comparable results to our study, with an increased median survival of 2.7 months after the introduction of first-line immunotherapy for stage IV NSCLC.(11)

Implications

It could be questioned whether the significant cost increase for patients with stage IV NSCLC, driven by the introduction of immunotherapy, is cost-effective. Although the Netherlands has no official cost-effectiveness threshold in terms of LYG, the reference value for a quality adjusted life year (QALY) of €80,000 in the Netherlands is unlikely to be met in this patient population. Although potential quality of life gains are not taken into account in this study, a LYG likely translates to significantly less than one QALY in this population, which means that the cost per QALY is expected to be higher than €150,000 per QALY. However, this does not include the significant price discounts on medication Notwithstanding the discounts, it does imply significant opportunity costs; i.e. health costs could have been spent more efficiently elsewhere. For example, *Van Baal et al.* estimated opportunity costs of €30,000 per LYG in cardiovascular disease.(33) Although spending may currently not be cost effective, this could change when patents expire. The drug patent of nivolumab expires in 2026 and pembrolizumab in 2028. This is expected to significantly reduce the prices of immunotherapy and, thus, increase cost-effectiveness.

Additionally, several measures could improve cost-effectiveness. First, previous studies show that immunotherapy is not effective for every patient.(34, 35) Further research could explore predictors for patients that benefit most from immunotherapy. In addition, developing biomarkers can help identify patients in which immunotherapy is ineffective in an early stage, and treatment can be stopped accordingly.(36, 37) This could not only reduce healthcare costs but also increase quality of life. Second, more research on adjusting drug doses and treatment duration could improve treatment outcomes while potentially lowering spending. Treatment dose, duration and intervals are often beyond the likely minimum

effective regime and could possibly be adapted. However, dose alterations and treatment intervals are sparsely evaluated in the clinical development of immunotherapy.(38, 39) Prospective studies are ongoing to both optimize dosing and validate well-established and novel biomarkers.(40)

Strengths and limitations

The main strength of our study is the use of real-world data, showing actual effects on costs and survival in real-world patient populations after immunotherapy is implemented in clinical practice. Additionally, looking at a comprehensive lung cancer network in a region in the Netherlands ensures that the population is minimally influenced by the concentration of care in single hospitals and changes in referral patterns during the study period.

Our study had limitations as well. First, survival data was cut-off at 2-years post diagnosis which results in an underestimation of the survival benefits. Healthcare costs are also underestimated because only the costs 2 years post diagnosis are included. Since longer follow-up increases both survival and costs, net effects on cost-effectiveness are uncertain. Furthermore, costs may be underestimated, as claims data do not include drug costs from clinical trials, costs of care that are not covered by DTC claims and costs for comorbidities. Also, using mean national prices could have underestimated costs at the university hospital, which are generally higher than average. Moreover, survival could have been overestimated in this patient population if survival for diseases other than cancer increased over time. This effect implies that our estimates of cost effectiveness may be interpreted as optimistic. Second, we did not have national data available on costs and survival. However, national trends of NSCLC patients are comparable to the studied population.(16, 41) Third, no data on comorbidities,, smoking and targetable mutations was available over the entire study period. Last, cost data was only available from one hospital. Although our imputation method, in which patients with or without first-line immunotherapy are separately imputed, and sensitivity analyses are robust, we cannot exclude the possibility that utilization patterns in the university hospital differ from general hospitals, given patient characteristics.

Conclusion

Our findings show an increased survival in the patient population of stage IV NSCLC patients after implementation of immunotherapy. However, these survival benefits come with substantial cost increases in this population, due to increased costs of immunotherapy treatment as well as increased spending on regular care. We estimate a real-world cost-effectiveness ratio of €150,796 in this patient group.

Different strategies are needed to manage these costs without compromising patient outcomes.

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Appendix

Table S1. Overview of immunotherapies received by patients based on two different datasets: the Netherlands Cancer Registry and claims data from a university hospital. It is possible for patients to have received multiple immunotherapies.

	Based on the NCR data[a]		**Based on available cost data[b]**
	All patients with immunotherapy (n=256)	**Patients from the university hospital with immunotherapy (n=223)**	**Patients from university hospital with immunotherapy for which cost data is available (n=210)**
Pembrolizumab, n(%)	242 (94.5)	210 (94.2)	179 (85.2)
Nivolumab, n(%)	5 (2.0)	5 (2.2)	17 (8.1)
Durvalumab, n(%)	5 (2.0)	5 (2.2)	4 (1.9)
Ipilimumab, n(%)	4 (1.6)	4 (1.8)	0 (0)
Olaratumab, n(%)	1 (0.3)	1 (0.4)	0 (0)
Bevacizumab, n(%)	2 (0.8)	1 (0.4)	6 (2.9)
Atezolizumab, n(%)	0 (0)	0 (0)	11 (5.2)

[a] The NCR data only includes first line treatment and misses patients that receive immunotherapy as a second line or third line treatment

[b] The cost data misses patients that receive immunotherapy without insurance claims (e.g. drug trials)

Table S2. Three different weighted cox regression models: 1) not adjusted for confounders, 2) adjusted for age, gender and histology, and 3) a sensitivity analyses adjusting for hospital effects.

	Model: Not Adjusted for confounders	**Model: adjusted for age**	**Model: adjusted for gender**	**Model: adjusted for histology**	**Model: adjusted for age, gender and histology**
Cohort					
- Pre	(baseline)	(baseline)	(baseline)	(baseline)	(baseline)
- During	0.92 (0.80-1.05)	0.89 (0.78-1.03)	0.92 (0.80-1.05)	0.89 (0.77-1.02)	0.87 (0.76-1.00)
- Post	0.81 (0.70-0.93)	0.79 (0.69-0.91)	0.81 (0.70-0.93)	0.80 (0.69-0.92)	0.78 (0.68-0.90)
Age		1.02 (1.02-1.03)			1.02 (1.01-1.03)
Gender					
- Female			(baseline)		(baseline)
- Male			1.11 (0.99-1.25)		1.04 (0.92-1.17)
Histology					
- Other				(baseline)	(baseline)
- Squamous cell carcinoma				0.79 (0.66-0.96)	0.75 (0.63-0.91)
- Adenocarcinoma				0.64 (0.56-0.75)	0.65 (0.56-0.76)

For one patient we changed time till death from 0 to 1 day. 0 days is not possible in weighted cox regression.

Table S3. Five different right-censored regression models: 1) not adjusted for confounders, 2) adjusted for age, 3) adjusted for gender, 4) adjusted for histology, and 5) adjusted for age, gender and histology. The last two columns present the sensitivity analyses adjusting for hospital effects.

	Model: Not Adjusted for confounders	**Model: adjusted for age**	**Model: adjusted for gender**	**Model: adjusted for histology**	**Model: adjusted for age, gender and histology**	**Sensitivity analysis: adjusted for general hospital effects**	**Sensitivity analysis: adjusted for age, gender, histology and general hospital effects**
Cohort							
- Pre	(baseline)	(baseline)	(baseline)	(baseline)	(baseline)	*(baseline)*	*(baseline)*
- During	42.2 (6.4-78.0)	47.8 (12.4-83.3)	40.5 (4.7-76.3)	47.7 (12.2-83.2)	51.1 (16.3-86.7)	*43.3 (8.9-77.8)*	*52.2 (17.1-87.4)*
- Post	85.0 (49.6-120.4)	91.4 (56.3-126.6)	83.6 (48.2-119.0)	84.8 (49.7-119.9)	90.3 (55.5-125.2)	*82.7 (47.0-118.5)*	*88.3 (53.5-123.1)*
Age		-4.4 (-5.9- -3.0)			-4.1 (-5.6- -2.6)		-3.94 (-5.5 - -2.4)
Gender							
- Female			(baseline)		(baseline)		(baseline)
- Male			-34.5 (-64.2- -4.8)		17.0 (-12.7-46.6)		17.4 (-12.2 – 47.0)
Histology							
- Other				(baseline)	(baseline)		(baseline)
- Squamous cell carcinoma				30.1 (-18.6-78.7)	40.3 (-8.0-88.6)		40.0 (-8.3 – 88.2)
- Adenocarcinoma				99.2 (62.0-136.4)	95.4 (58.6-132.2)		95.0 (58.1-131.8)
Hospital							
- University hospital[1]						(baseline)	(baseline)
- General hospital 1						-45.0 (-87.4 - -2.6)	-36.7 (-78.4 – 4.9)
- General hospital 2						-47.8 (-85.6 - -10.0)	-41.3 (-78.4 - -4.2)
- General hospital 3						-52.1 (-100.5 - -3.7)	-41.1 (-88.7 – 6.4)

[1] Due to the position of the university hospital as tertiary referral center, the university hospital was used as baseline. This implies that the comparator includes patients that directly visited the university hospital or were referred to the university hospital from outside the cancer network. No correction for secondary referral was included, because this is part of the treatment effect.

Table S4. Five different log-link gamma regression models presenting the log-cost increases: 1) not adjusted for confounders, 2) adjusted for age, 3) adjusted for gender, 4) adjusted for histology, and 5) adjusted for age, gender and histology. The last two columns present the sensitivity analyses adjusting for hospital effects.

	Model: Not Adjusted for confounders	**Model: adjusted for age**	**Model: adjusted for gender**	**Model: adjusted for histology**	**Model: adjusted for age, gender and histology**	**Sensitivity analysis: adjusted for general hospital effects**	**Sensitivity analysis: adjusted for age, gender, histology and general hospital effects**
Intercept	9.66 (0.08)*	11.38 (0.36)*	9.28 (0.16)*	9.22(0.12)*	10.589 (0.415)*	*9.94 (0.10)**	*11.19 (0.43)**
Cohort							
- Pre	(baseline)	(baseline)	(baseline)		(baseline)		*(baseline)*
- During	0.76 (0.12)*	0.81 (0.13)*	0.77 (0.11)*	0.83 (0.12)*	0.87 (0.12)*	*0.74 (0.12)**	*0.79 (0.13)**
- Post	1.07 (0.11)*	1.08 (0.12)*	1.08 (0.11)*	1.10 (0.11)*	1.11 (0.11)*	*1.02 (0.11)**	*1.05 (0.12)**
Age		-0.03 (0.01)*			-0.02(0.01)*		*-0.02 (0.01)**
Gender							
- Female			(baseline)		(baseline)		*(baseline)*
- Male			0.26 (0.10)*		0.15 (0.10)		*0.21 (0.11)*
Histology							[2]
- Other				(baseline)	(baseline)		
- Squamous cell carcinoma				-0.09 (0.15)	-0.02 (0.15)		
- Adenocarcinoma				0.60 (0.11)*	0.59 (0.12)*		
Hospital							
- University hospital[1]						*(baseline)*	*(baseline)*
- General hospital 1						*-0.46 (0.14)**	*-0.42 (0.14)**
- General hospital 2						*-0.35 (0.12)**	*-0.31 (0.12)**
- General hospital 3						*-0.25 (0.14)*	*-0.25 (0.15)*

[1] Due to the position of the university hospital as tertiary referral center, the university hospital was used as baseline. This implies that the comparator includes patients that directly visited the university hospital or were referred to the university hospital from outside the cancer network. No correction for secondary referral was included, because this is part of the treatment effect.

[2] Histology was removed from this model because of multicollinearity

Table S5. Costs of patients from the university hospital for whom the cost data is available

	Pre-implementation cohort				During – implementation cohort			Post-implementation cohort		
	2014	**2015**	**2016**	**Total cohort**	**2017**	**2018**	**Total cohort**	**2019**	**2020**	**Total cohort**
DTC[1]	8090 (7390-8791)	9781 (8811-10752)	11856 (10796-12915)	9961 (9025-10897)	14448 (13208-15688)	16736 (15679-17792)	15699 (14555-16842)	19308 (17961-20655)	17364 (16176-18552)	18529 (17244-19814)
IC costs	148 (84-212)	483 (335-630)	570 (433-707)	416 (290-542)	1053 (772-1334)	688 (527-849)	853 (630-1077)	1317 (820-1815)	177 (102-252)	860 (471-1250)
Expensive medication[1]										
- All	1928 (1548-2309)	6472 (5026-7917)	3354 (2745-3963)	4201 (3196-5205)	22397 (18370-26423)	35025 (30795-39255)	29300 (25146-33455)	45961 (41531-50391)	37178 (33729-40627)	42441 (38371-46511)
- Immunotherapy alone	0 (0-0)	343 (110-577)	845 (534-1155)	405 (176-634)	10578 (8005-13150)	19989 (17147-22832)	15723 (12985-18461)	27867 (24645-31089)	24888 (22011-27766)	26673 (23589-29758)
Total costs	10166 (9236-11096)	16735 (14721-18750)	15780 (14273-17286)	14577 (12961-16193)	37897 (33171-42624)	52449 (47744-57153)	45852 (41120-50584)	66586 (61295-71877)	54719 (50607-58831)	61830 (56968-66693)

Table S6. Sensitivity analysis with the costs of the entire study population after imputation with predictive mean matching

	Pre-implementation				During – implementation			Post-implementation		
	2014	**2015**	**2016**	**Total cohort**	**2017**	**2018**	**Total cohort**	**2019**	**2020**	**Total cohort**
DTC[1]	8616 (8013-9218)	9341 (8738-9944)	9422 (8801-10042)	9157 (8547-9766)	11683 (10936-12430)	14312 (13541-15082)	12956 (12195-13717)	15635 (14785-16486)	14452 (13647-15256)	15041 (14213-15869)
IC costs	336 (245-426)	463 (354-573)	540 (420-660)	452 (341-564)	881 (704-1058)	697 (571-823)	792 (636-948)	1102 (816-1389)	561 (432-691)	831 (607-1055)
Expensive medication[1]										
- All	4829 (3972-5686)	9078 (7643-10513)	6013 (4971-7055)	6772 (5593-7950)	17496 (15239-19754)	25049 (22564-27534)	21154 (18777-23531)	34881 (32152-37610)	27714 (25540-29889)	31283 (28812-33754)
- Immunotherapy alone	838 (485-1191)	585 (384-787)	761 (550-972)	720 (441-1000)	6330 (5016-7644)	13196 (11558-14834)	9655 (8166-11143)	19957 (18012-21902)	19562 (17686-21438)	19759 (17849-21668)
Total costs	13687 (12496-14879)	18522 (16842-20202)	15888 (14558-17219)	16194 (14748-17639)	29875 (27234-32516)	39337 (36521-42153)	34457 (31721-37192)	51097 (47811-54382)	42071 (39481-44660)	46565 (43602-49529)

Table S7. Sensitivity analyses with the costs of the entire study population including DTC potentially related to NSCLC

	Pre-implementation				During – implementation			Post-implementation		
	2014	**2015**	**2016**	**Total cohort**	**2017**	**2018**	**Total cohort**	**2019**	**2020**	**Total cohort**
DTC[1]	8813 (8270-9356)	10084 (9454-10714)	10190 (9558-10823)	9749 (9141-10356)	11726 (10995-12456)	14305 (13520-15090)	12974 (12215-13734)	15582 (14733-16432)	14435 (13619-15252)	15006 (14173-15839)
IC costs										
Expensive medication[1]										
- All										
- Immunotherapy alone										
Total costs	14012 (12788-15235)	18272 (16681-19863)	15347 (14124-16569)	16011 (14626-17395)	28849 (26115-31584)	39756 (36816-42696)	34130 (31281-36980)	50046 (46739-53353)	42379 (39607-45151)	46197 (43143-49251)

Table S8. Sensitivity analyses with the costs of the entire study population with a medication discount of 20%

	Pre-implementation				During – implementation			Post-implementation		
	2014	**2015**	**2016**	**Total cohort**	**2017**	**2018**	**Total cohort**	**2019**	**2020**	**Total cohort**
DTC[1]										
IC costs										
Expensive medication[1]										
- All	4009 (3231-4788)	6321 (5280-7362)	3857 (3143-4571)	4790 (3906-5675)	13222 (11330-15113)	19937 (17863-22010)	16473 (14483-18464)	26797 (24600-28995)	22148 (20289-24006)	24463 (22426-26500)
- Immunotherapy alone	430 (244-616)	279 (150-408)	393 (259-526)	363 (206-520)	4711 (3677-5745)	10150 (8844-11456)	7345 (6164-8525)	15670 (14119-17221)	15075 (13590-16561)	15372 (13854-16889)
Total costs	12847 (11798-13897)	16305 (14958-17653)	13985 (12927-15043)	14489 (13309-15668)	25333 (23055-27611)	33873 (31451-36295)	29468 (27109-31826)	42916 (40146-45687)	36420 (34116-38723)	39655 (37105-42205)

Table S9. Sensitivity analyses with the costs of the entire study population with a medication discount of 40%

	Pre-implementation				During – implementation			Post-implementation		
	2014	**2015**	**2016**	**Total cohort**	**2017**	**2018**	**Total cohort**	**2019**	**2020**	**Total cohort**
DTC[1]										
IC costs										
Expensive medication[1]										
- All	3007 (2423-3591)	4741 (3960-5522)	2893 (2357-3429)	3593 (2929-4256)	9916 (8498-11335)	14953 (13397-16508)	12355 (10862-13848)	20098 (18450-21746)	16611 (15217-18004)	18347 (16820-19875)
- Immunotherapy alone	323 (183-462)	209 (113-306)	294 (194-395)	272 (154-390)	3533 (2758-4308)	7613 (6633-8592)	5508 (4623-6394)	11752 (10589-12916)	11307 (10193-12420)	11529 (10390-12667)
Total costs	11845 (10960-12730)	14725 (13604-15847)	13021 (12103-13938)	13291 (12297-14285)	22027 (20196-23859)	28888 (26959-30818)	25349 (23462-27237)	36217 (33970-38464)	30883 (29017-32749)	33539 (31472-35607)

Table S10. For the three different sensitivity analysis, mean difference in total costs in Euro's from the during- and post-implementation cohort in comparisons with the pre-implementation cohort

	Unadjusted mean difference (95% CI)		**Adjusted mean difference (95% CI)***	
	During	**Post**	**During**	**Post**
Including DTC potentially related to NSCLC	18120 (12692-23547)	30186 (23233-37140)	21175 (15370-26981)	30615 (23647-37582)
20% discount of expensive medication	14979 (10482-19477)	25166 (19449-30884)	17609 (12805-22413)	25639 (19896-31382)
40% discount of expensive medication	12058 (8419-15698)	20248 (15708-24788)	14171 (10298-18043)	20568 (16009-25127)

* Adjusted for age, gender and histology

Chapter 4

Cancer treatments touch a wide range of values that count for patients and other stakeholders: what are the implications for decision-making?

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Abstract

Background: Cancer rates and expenditures are increasing, resulting in debates on the exact value of this care. Perspectives on what exactly constitutes worthwhile values differ. This study aims to explore all values–elements regarding new oncological treatments for patients with cancer and all stakeholders involved and to assess their implications in different decision-making procedures.

Method: Thirty-one individual in-depth interviews were conducted with different stakeholders to identify values within oncology. A focus group with seven experts was performed to explore its possible implications in decision-making procedures.

Results: The overarching themes of values identified were impact on daily life and future, costs for patients and loved ones, quality of life, impact on loved ones, societal impact and quality of treatments. The expert panel revealed that the extended exploration of values that matter to patients is deemed useful in patient-level decision-making, information provision, patient empowerment and support during and after treatment. For national reimbursement decisions, implications for the broad range of values seems less clear.

Conclusion: Clinical values are not the only ones that matter to oncological patients and the stakeholders in the field. We found a much broader range of values. Proper recognition of values that count might add to patient-level decision-making, but implications for reimbursement decisions are less clear. The results could be useful to guide clinicians and policymakers when it comes to decision-making in oncology. Making more explicit which values counts for whom guarantees a more systematic approach to decision-making on all levels.

Introduction

The worldwide cancer rate is expected to increase from 19 million in 2020 to 30 million in 2040.(1) Costs of cancer care are high and continue to rise. In Europe, costs have almost doubled from €52 billion in 1995 to €103 billion in 2018.(2)

Over the years, patient-centred care has gained increasing interest in which the needs and desires of individual patients drive the force behind healthcare decisions and quality measurements.(3-6) For payors and policymakers, it is challenging to provide optimal healthcare needs for individual patients while managing budgets. Decision-making on reimbursement and resource allocation is often aided by using Health Technology Assessment (HTA).(7,8) However, HTA frameworks do not always reflect all values that count for patients and other stakeholders, therefore, various different value frameworks have been published in recent years (9-12), for instance, by the American Society of Clinical Oncology (ASCO)(13) and European Society for Medical Oncology (ESMO)(9). Previous studies compared such oncological value frameworks and revealed some inconsistencies, which mainly derived from the differences in perspective.(14-17) Additionally, it is argued that they do not take the unique aspects of the evolving therapeutic landscape with targeted therapy, immunotherapy and more precision medicine into consideration, which has led to increasing uncertainty about the true value of new treatments.(18,19)

The International Society for Pharmaceutical Outcomes Research (ISPOR) Value Assessment Frameworks Special Task Force emphasised gaps in value assessment in general as elements from a societal perspective are missing, for example, equity.(20,21) It is also argued that the commonly used quality of life (QoL) outcome measures do not always seem adequate for mapping all aspects of the social domain (22); they contain a subset of relevant outcomes.(21-25) Over the years, different disease-specific QoL measurement tools have been developed.(26)

What exactly constitutes value to whom in the context of cancer treatments, limited financial budgets and patient-centred care is still not clear and varies between different stakeholders. The aim of this study is therefore to explore values–elements regarding new oncological treatments and to assess their implications in decision-making procedures to inform the oncological field and generate the maximum value with fixed national budgets.

Method

Study design

We conducted semi-structured interviews to explore values regarding new oncological treatments from different stakeholder perspectives. Values are defined as elements that warrant consideration in treatment assessment and decision-making procedures. In addition, a focus group with an expert panel was performed to discuss the usefulness and potential implications of the values that were found in the interviews in different decision-making procedures. The study was reported based on recommendations in the consolidated criteria for reporting qualitative studies (COREQ) checklist.(27)

Study setting

This study was performed in the Netherlands. See Box 1 for a description of the Dutch healthcare system, and see Kroneman et al. for a more extended description.(28)

Box 1. Description of the Dutch Healthcare system

The Dutch government pursues three main goals for the healthcare system: quality (effective, safe and patient-centred), accessibility and affordability. The *Netherlands Ministry of Health* (*MOH*) supervises healthcare and is responsible for access, quality and cost in the health system, has overall responsibility for setting priorities and can introduce legislation. The *National Healthcare Institute* (*Zorginstituut Nederland*, *ZIN*) assesses new technologies on (cost-)effectiveness and advises the minister on the reimbursement and uptake into the insurance benefit package. Drugs below a certain cost threshold (e.g. budget impact of less than €10 million per year) that are proven to have an added therapeutic effect are immediately admitted into the benefits package. Above certain price thresholds, the ZIN assesses new drugs based on necessity, effectiveness, cost-effectiveness, and feasibility. The health minister makes the final decisions for these drugs above certain cost thresholds and performs price negotiations with pharmaceutical companies. In recent years, the movement towards patient-centred care is stimulated by the government and different professionals.

All residents in the Netherlands are obliged to have a basic health insurance package and pay a minimum of 385 euros on statutory deductible premiums annually. People with lower incomes often receive a care allowance to reduce financial difficulties. In addition, patients can choose complementary insurance, for example extra cover for physical therapy.

Study population

To identify values within oncology, 12 stakeholder groups were defined for interviews: patients, partners of patients, oncologists, oncological nurses, occupational doctors, general practitioners, insurance advisors, the National Healthcare Institute (ZIN), Netherlands Comprehensive Cancer Centre, the Ministry of Health (MOH), Health insurance companies and dedicated oncological care networks. From each group, participants for the interviews were purposively sampled to ensure a minimum of two interviews. We approached 41 potential participants by email through our investigator network, stakeholder websites and snowball sampling.

To discuss the usefulness and potential implications of the values in decision-making procedures, an expert panel was purposively sampled with experts on quality of life, ethics, HTA, and spokesmen of patients, ZIN, health insurance companies, and healthcare professionals. Eleven experts were approached.

Stakeholder selection was based on screening of Dutch policy documents and literature and consultation with experts. The interviews and expert panel meetings were performed by video calls, and informed consent was obtained from all study participants.

Data collection

For the interviews, we drafted a topic guide (Appendix A) on overarching themes found in a literature search (Appendix B). These themes were societal impact, quality of life, impact on daily life, family burden, costs and quality of care. We applied an iterative approach in which, depending on the stakeholder and after reflections, slight adjustments or more emphasis on specific topics were made during the interviews. One trained researcher (CV) conducted the interviews.

The topic guide of the expert focus group (Appendix C) was constructed based on findings from the interviews and contained questions regarding the desire and current use of values in decision-making procedures, within which context it was desirable and with which methods values could be best measured. The expert panel was moderated by an experienced researcher (RH) and planned for 60 minutes.

Data processing and analysis

Interviews and the focus group with the expert panel were audio-recorded and transcribed verbatim. The transcripts were thematically analysed. Codes were assigned to relevant text passages and codes referring to the same underlying

concept were divided into subcategories and themes. Twelve transcripts, one from each stakeholder group, were coded by two trained researchers individually (CV and ES). After comparing transcripts, the researchers reached a consensus on the codes, subcategories and themes. The remaining transcripts were assessed by one researcher (CV) and discussed with the second researcher (ES) until a consensus was reached. All generated themes and subcategories are reported and listed indiscriminatory in the results. Atlas.ti (version 8) was used for data processing and analyses.

Results

For the interviews, 41 stakeholders were approached, of which 32 participated in 31 separate interviews (Table 1), with at least two interviews per stakeholder group. Of the non-participators, one declined based on time constraints, six did not respond to email contact, and two believed not to be the right person for this study. The interviews lasted between 20 and 64 minutes.

For the focus group, seven experts participated: an expert on health-related quality of life, ethics, health technology assessment and a spokesman of a patient organisation, the ZIN, a health insurance company and an oncologist. Of the non-participators, one was not available on the date of the expert panel, and three did not feel able to contribute.

Interviews stakeholders

The themes generated from the interviews were impact on daily life and future, costs for patients and loved ones, quality of life, impact on loved ones, societal impact and quality of treatments. The themes and subcategories generated from the interviews are presented in Table 2. Quotes from the interviews are presented in Table 3.

Impact on daily life and future of patients

The interviewees mentioned several values that can be impacted by a cancer diagnosis or its treatment in daily or future life. Participants mentioned the ability to continue daily activities like sports, hobbies, doing one's own groceries or being independent. It was mentioned that patients can participate less in society and in activities such as working, volunteering, caring for children and being an informal caregiver. Participants stated that the importance of reintegration or continuing work can differ per patient. Different participants mentioned the inability to make

future plans and life choices. In addition, participants stated that mortgages are more difficult to get for (former) patients as they pay higher premiums or are rejected for life insurance, which they need to get a mortgage.

Table 1. Overview of stakeholders interviewed

Stakeholder	**N**
Patient (association)	
- *Ex-patient*	2
- *Patient association*	1
Partner of patient	2
Oncologists	4
Oncological nurse	2
Occupational / company doctor	
- *Company doctor*	1
- *Oncological occupational physician*	1
General practitioner	3
Insurance advisor	
- *Intermediary insurance advisor (for life insurance)*	2*
- *Re-insurance** advisor for life insurance companies*	1
- *Employee Insurance Agency Netherlands (UWV)*	1
National Healthcare Institute (Zorginstituut, ZIN)	2
Netherlands comprehensive cancer organisation	2
Ministry of Health (MOH)	2
Health insurance companies	2
Oncological care networks	
- *Primary care network*	1
- *Secondary care network*	2
- *Chain management*	1
Total	32

* 1 interview with 2 participants

** Insurance companies can re-insure themselves for high-risk clients

Costs for patients and loved ones

The interviewees mentioned values regarding costs for patients and loved ones. A few participants stated that some additional healthcare or complementary care needs to be (partly) paid for by the patients themselves. Another cost aspect mentioned in the interviews was the deductible premium for the health insurance which is statutory in the Netherlands, even after treatments, because of a long-term need for additional care. However, it was also stated that these problems differ per patient as it depends on a patient's personal financial situation.

Additional indirect costs for patients that were mentioned were loss of work and income. This problem also concerns partners as their ability to work might be affected as well (partly) because of caring for children, accompanying patients to the hospital or delivering informal care. Additionally, costs for reintegration after patients have lost their job or for those who are self-employed. Additional costs are spent on higher premiums for life insurance or disability insurance in case of self-employment. Other examples are travel costs for patients and family members, house renovations, new wardrobes after weight loss or gain, wigs and sometimes prosthetics or specialised bras and swimwear.

Quality of life

The interviewees mentioned values regarding the quality of life. Quality of life values is sub-divided into physical, psychological, social and spiritual. It was mentioned that patients might be in need of support or companionship for these domains.

First, a cancer diagnosis can result in many physical consequences. It was mentioned that consequences differ depending on the treatment or tumour type. For instance, early menopause and infertility are common for patients with gynaecological cancers. For colon cancer, bowel dysfunction and stomas are common.

Second, participants stated that the psychological consequences can be quite severe. An often-mentioned psychological effect is fear of death. Also, even after being cured, there is fear of recurrence or suffering from damage caused by cancer treatments. It was mentioned that some of the psychological impacts occur after the passage of a certain time interval, that is when treatments are already completed. Psychological consequences might result in higher healthcare costs. Conflicting opinions existed about the value of hope. Hope can benefit a patient's quality of life but can also interfere with acceptance of the situation. In addition, different participants emphasised to focus more on positivity, fighting spirit and empowerment of patients instead of negative psychological consequences.

Third, participants state that social needs can be negatively influenced, for instance, by not attending social gatherings or not being energetic when a patient does attend a gathering. Additionally, the effect of these cancer treatments can affect patients' relationships.

Last, some spiritual aspects of quality of life were mentioned. Patients can find support in religion or existential questioning about the meaning of life.

Impact on loved ones

The interviewees mentioned values regarding the impact on loved ones like psychological impact, workability, the positive or negative impact on relationships, social activities or the impact on future plans. Loved ones are often informal caregivers to patients. This entails being attentive to patients, driving patients to the hospitals and also providing care for patients at home. In addition, they can experience a change in mentality during the course of the disease. Loved ones might feel the need for support and companionship.

Societal impact

Interviewees mentioned values regarding societal impact. The most frequently mentioned was the loss of productivity and lack of ability to return to work. These costs are borne by the patient (by not receiving wages), the employer and by society. In addition, costs are made on benefits and allowances paid to people losing their job or that are working less. Patients often have a certain capacity to work during the illness, which is not always utilised. One participant mentioned the possibility of increased healthcare costs because of lower work productivity as it can affect a patient's psychological well-being.

Other societal impacts mentioned were the loss of informal caregivers because the oncological patient cannot care for another family member or indirect healthcare costs on long-term effects like heart diseases as a result of chemotherapy.

Participants often mention the importance of societal balancing of resource allocation as premium money paid on health insurance by society must be handled with caution and the most value for money should be created. Additional values that were mentioned to take into consideration were the prevalence of the disease, the development of new knowledge, innovation, freedom of choice for patients, access to care, equality, the necessity of a new drug and implementation feasibility.

Quality of treatments

The interviewees mentioned values regarding the quality of treatments. It was often mentioned that patients should always get the best possible care and treatments should comply with the established medical sciences and practice. Besides survival or extending life, quality of life outcomes were deemed important. In addition, oncological treatments can cause serious long-term health problems, like heart failure or other cancers. It was mentioned that side effects and ease of use of treatments should be proportional to the benefit. The ease of use includes, among others, the possibility and choice for care at home or the need for problems with transportation. Finally, it was mentioned that therapy compliance should be optimised.

Table 2. Themes and subcategories from the interviews

Impact on daily life and future of patients
Daily functioning
Time investment
Impact on future plans and choices
Ability to:
- work
- do voluntary work
- perform hobbies
- perform household chores
- participate/contribute to society
- be an informal caregiver
- receive a mortgage
- sport
- care for children
- be independent/self-sufficient
Costs for patients and loved ones
Costs:
- Reintegration
- Disability insurance premiums
- Additional care
- Statutory deductible premium
- New wardrobe
- Medical devices
- Prosthesis, swimwear, bra
- Wigs

Table 2. Continued

- Home renovation
- Childcare
- Life insurance premiums
- Travel expenses for patients/relatives
- Loss of income
- Additional patient costs
- Family costs
Quality of life – physical
Physical functioning:
- Weakened immune system
- Amputation
- Physical capacity
- Osteoporosis
- Bowel functioning
- Dry mucous membranes
- Eating disabilities
- Hearing damage
- Weight changes
- Joint pain
- Hair loss
- Cardiovascular diseases
- Neuropathy
- Edema
- Infertility
- Pain
- Sexual functioning
- Muscle strength
- Loss of speech
- Stoma
- Change in taste
- Fatigue
- Early menopause
- Skin irritation
- Fever
- Body integrity
- Physical fitness
- Scarring issues
- Nausea

Table 2. Continued

Quality of life – psychological
(Long-term) Emotional functioning:
- Acceptance
- Fear
- Fear of recurrence
- Anger
- Cognition and concentration
- Confrontation
- Loss of control
- Depression
- Dealing with dying
- Loneliness
- Frustration
- Behavioral changes
- Feeling good
- Hope
- Childlessness
- Feeling like a burden
- Misunderstanding by others
- Worry about future health
- Preserving positive attitude
- PTSD
- Sadness
- Anxiousness
- Change in attitude
- Moving on
- Trust in body
- Self Confidence
- Worry for loved ones
- Need for companionship
Quality of life – social
Social functioning
Relationship with (grand)children
Relationship with partner
Relationship with friends/family
Quality of life – spiritual
Religion
Existential questioning

Table 2. Continued

Impact on loved ones
Impact on loved ones:
- Informal care
- Acceptance
- Workability
- Positive attitude
- Psychological impact
- Sexual relation
- Social functioning
- Future perspective
- Being involved
- Change in mentality
- Relationship with partner
Societal impact
Societal costs:
- Workability
- Volunteering workability
- (In)direct healthcare costs
- Costs for employers
- Ability to provide informal care
- Payment benefits
Equality
Societal balancing
Cost-effectiveness
Necessity
Implementation feasibility
Accessibility of care
Prevalence of disease
Freedom of choice
Innovation
Knowledge development
Quality of treatment
Quality of care:
- Effectiveness
- Long term health
- Survival
- Prognosis/progression
- Patient-centred

Table 2. Continued

- Ease of use
- Side effects
- Complications
- Safety
Therapy compliance
Best possible care

Table 3. Quotes from the interviews

Impact on daily life and future
"He was ill for a year, and then he was still at the company, and then it was about leasing a car. You have to do that for 4 or 5 years. Can we? And should we do that?" (Partner of patient)"Well, of course, you look at people as a whole and their participation in society, so it's not only the cost but whether people can go back to their old work what they did before their illness? Can they still do that in the same way, or are there many limitations to that? Do they feel they participate sufficiently in society? Doing sports or interacting with others in their social environment, are there limitations to that?" (General practitioner)
Patient costs
"People lose their jobs and therefore get into financial difficulties, but if you still need physiotherapy for medical complaints and you have to pay for those first 20 treatments yourself and you do not have that money.. It also means that these financial problems actually hinder your recovery. And the same applies to psychological counselling because that also costs money and that is often not insured or only very limited." (Oncological nurse)"Statutory deductible premium recur every year. So, if you already had treatments in the hospital in 2019.. And in 2020 you still have other complaints.. Then you have to pay again every year." (Health insurance company) "Loss of income because people can no longer work or have to look for other work. Is also a loss for the patient but also for society.." (Oncologist)
Quality of life – physical
"Your physical condition can be permanently diminished, for example. Or you can move worse due to radiotherapy that you have had. So you will permanently have complaints about it. Or you will become infertile, maybe." (Health insurance company)"Also physical limitations. If you entered menopause early as a result of the treatment, you will also have all kinds of physical limitations if you are unlucky, which you also have to learn to deal with. Or if you have a very tight scar as a result of an operation that you feel continuously or that causes you to have a limitation of movement, then you may be able to do something about it with a treatment, but it may also be something you have to deal with for the rest of your life." (Oncological nurse)
Quality of life – psychological
"But also that you can sometimes psychologically change a bit because of medicines. You can become a bit unstable or have a different attitude. These are useful things to consider and at least tell patients." (Oncological nurse)"You can remember endless sick beds in which people have gone to extremes and always have hope for just that marginal improvement, and in the end, the last months were agony. You often notice that patients, of course, see the next therapy as a last straw to postpone death a bit, and you do not want to take that straw away from them, while often you know in the back of your mind what a difficult road it will be with many side effects." (General practitioner)
Quality of life – social

Table 3. Continued

"You see a lot of divorces, certainly with breast cancer. For example, because the partner does not grow along or, indeed, that things go wrong in the area of sex and intimacy. But also, the people themselves change. The person changes, and not everyone in the family can change accordingly." (Primary care network)"Direct relationships of the patient can also suffer a lot of damage from a major event and treatment." (Oncologist)
Quality of life – spiritual
"Religion is also part of that, but also: how do you contribute to meaning in your life." .. "I often see this reflected in the quality of life questionnaires; that there are some essential questions in it, like spirituality. This is often not included in the psychological outcome measures such as emotions, fear and fear of recurrence. You can collect it within this, but I think it deserves attention. That meaning and people's existential questions are simply very important."(Oncologist)
Impact on loved ones
"Of course, it is also a lot for their husband or wife. If your partner has cancer and then important decisions have to be made. Of course you also have to go to the hospital and taxi often, so to speak. It takes you time too. How do you arrange that with your work? And perhaps with the care of children. How do you go about all that? It really has consequences for the whole family too." (Health insurance company)"It is not at all that it affects us every day; it is of course, always somewhere in the back of your mind and indeed, it is always comes back with major decisions." (Partner of patient)
Societal impact
"In addition to survival, all other clinical outcomes that you see in the study are also taken into account, and quality of life is always included; at least, there is always an attempt to take that into account. And in addition, a number of societal ones are also included in cost-effectiveness analyses, such as productivity losses, the difference with quality losses." … "And, for example, informal care and informal care costs are also included."(National healthcare institute)"What we need to do is to be careful with health insurance deductible premiums. It's not just about sick people; it's also about young students who have nothing at all and have to pay deductibles. So you have to make sure that deductible premiums don't rise and get the most value with the money you have." (Healthcare insurance company)
Quality of treatment
"When we talk about new medicines, it's always about what to expect from them. Can you live longer? Maybe you can heal? The first question is actually always: can I heal by it? Do I have a chance that I can heal by it? That has more impact than living one or two or three months longer. Does it offer a chance of survival, that has a lot of impact. If it offers no chance of survival but extension of life, then you would like to know with what qualities."(Secondary care network)"Survival alone has, of course, long been an outcome of oncological care. It is a bit of a catch-all term, but quality is really very important. Not because it is a luxury concept but also because poor quality of life also entails high costs. People who are left with health damage from treatments who continue to seek help for that. Both with somatically oriented doctors and with other care providers, such as: physiotherapy, psychology."… "Survival is certainly not only important." (Oncologist)

Focus group with an expert panel

For patient-level decision-making, the extended exploration of values was deemed useful to ensure the inclusion of all values that count for patients in decision-making that are important for a specific patient. However, the usefulness of many values also depends on the situation of the patient, and different aspects are important in different phases of the disease (i.e., palliative or curative), phase of treatment (i.e., when you start treatment or when you have a recurrence) and age of patients. It was mentioned that not all values are always relevant regarding choices of treatments (or not treating). The values were mentioned to be important to discuss with patients regarding long-term effects and long-term quality of life, for general information provision and empowerment of patients. In addition, the extended list of values was mentioned to be of importance in discussions on a patient's life after treatment or after cancer. It was mentioned that patient values are currently already being investigated to some extent during the treatment process, for instance, by means of questionnaires.

For reimbursement decisions, the use of the extended exploration of values was less clear. It was mentioned that the Netherlands has a mechanism of decision-making using the QALY framework which is already incorporated many values. Other values are also considered, like the ease of use, although participants questioned whether national solidarity stretches as far as to reimburse treatments from national budgets due to them being specifically easier to use. Regarding the measurement methods of values, the expert panel mentioned that some values have established methods, while others do not.

Potential disadvantages of incorporating the extended exploration of values for reimbursement decisions were mentioned: (1) Risking an increase of the sustainability dilemma as more therapies might be reimbursed, (2) the uncertainty of how the value of, for example, hope is proportional to benefits regarding survival and (3) the desire to use generic values that are applicable to all diseases instead of specific diseases.

Table 4. Quotes from the expert panel regarding decision-making procedures

Coverage and reimbursement decision-making
"So I find it difficult, as you increase the list of values, that you allow more in the insurance package. Because then the sustainability dilemma will actually become even bigger" (ZIN)
"A value framework should in essence, be generic, because only a value framework for oncology will not help us to keep healthcare sustainable." (HTA expert)
"If you have all that information. How do you include that in a decision-making process? In other words. How are you going to weigh it? And what belongs in which decision-making process? It is not a question of the possibilities, but more a question of willingness. ".. "We already have a working mechanism for what we think should be taken into account and how. The National Healthcare Insitute has methods for that." (HTA expert)
Patient-level decision-making
"We do this in our hospital at the moment with every evaluation of the therapy, so when they have had a CT scan to see if things are going well or not. Then, we discuss again with these patients what their values are and what they find important."… "The moment you are progressive, and you have to make a choice for treating again, it is important to discuss with those patients whether a treatment will be useful." (Oncologist)
"What is that life with and after cancer? What is quality of life? And on which aspects? And who gives me control over that? And what do I need from both the healthcare professional and myself?".. "What do I need from society to ensure that I can still take out a mortgage? Or can participate? Or can continue to work? Or whatever. So there are a lot of questions that I think always belong in the treatment room but are more difficult to weigh at the population level." (Patient association)

Conclusion and Discussion

Our findings reveal a broad range of values that matter to patients and involved stakeholders regarding new oncological treatments and decision-making in oncological care. They can be categorised in (1) impact on daily life and future, (2) costs for patients and loved ones, (3) quality of life (physical, psychological, social and spiritual), (4) impact on loved ones, (5) societal impact and (6) quality of treatment.

Experts revealed the exploration of values was useful in patient-level decision-making. Not all values are always relevant to include in treatment choices, however, they can also be used for patient information and empowerment and support during and after treatment of cancer. The use of the extended exploration of values for reimbursement decisions was less clear.

Previous literature

Previous studies support the broad range of values that are relevant within oncology, going beyond existing value frameworks.

Our results suggest that decision-making at the patient-level should contain many values and patient preferences. Shared decision-making (SDM) between physicians and patients can increase incorporation of patient preferences in treatment decisions, however, different studies reveal that SDM is not yet fully implemented and used to its full potential.(31-33)

Our results also suggest that not all values found in our study are included in reimbursement decisions. A review of US Value Frameworks by the ISPOR Value Special Task Force supports our findings as they state it is difficult for frameworks to represent values for all decision contexts.(34) They mention that reimbursement decisions should be focused on efficiently allocating resources to maximise population health- and patient-level decisions should include patients' values and preferences, within the larger constraints imposed by decisions on national levels.

Different studies found differences across countries regarding reimbursement decisions.(7,35,36) A study by Angelis et al. examined differences in eight European countries regarding the assessment of the value of new medicines in the context of reimbursement decisions.(7) Most countries implement a type of economic evaluation in addition to the assessment of clinical benefit. The preferred health gain measure usually is the QALY. Additional values beyond the QALY concept are captured to a different extent between countries, explaining some of the heterogeneity in reimbursement decisions. Ease of use, nature of the treatment, public health benefit, social productivity, place in therapeutic strategy and ethical considerations are criteria considered in some countries (either implicitly or explicitly) and not considered in others.

Comparison to existing value frameworks

Different frameworks exist for evaluating the value of health interventions. These frameworks can be generic or oncology specific and can inform reimbursement or patient-level decisions. The added value of our findings to these existing frameworks is discussed below.

In the United States, the Institute for Clinical and Economic Review (ICER) has been evaluating the clinical and economic values of health interventions to aid reimbursement decisions.(37) Their value framework incorporates long-term value and short-term affordability. Long-term value includes incremental cost-effectiveness and provides the possibility of incorporating additional other benefits or disadvantages and contextual considerations through deliberative processes. Short-term affordability includes budget impact.

In Europe, the EUnetHTA published an HTA core model to aid reimbursement decisions for which different European countries collaborated.(38) The ontology in this model covers the health problem and current use of technology, description and technical characteristics, safety, clinical effectiveness, costs and economic evaluation, ethical analysis, organisational aspect, patient and social aspects and legal aspects.

The ICER value framework and the HTA core model are extensive frameworks used for the systematic assessment of new treatments for reimbursement decisions, and our study can add to these frameworks by more explicitly using the values that are specific for oncological care in the deliberative processes.

Besides these models, two common oncological value frameworks are the American Society of Clinical Oncology (ASCO) (13) and the European Society for Medical Oncology (ESMO) (9) frameworks. These are used for facilitating shared decision-making by patients and oncologists and could aid reimbursement decisions. The ASCO and ESMO incorporate clinical benefit, toxicity, QoL and improvement of (cancer-related) symptoms beyond QoL. In addition, the ASCO adds treatment-free interval, drug acquisition costs, and patient co-pay, and the ESMO adds daily well-being, response rate, and duration of response.

The value frameworks are used to aid physicians in explaining treatment benefits to patients and facilitate shared decision-making. Our study adds to these cancer-specific value frameworks by presenting explicit values regarding the impact on daily life and future, costs for patients and loved ones, QoL and quality of treatment. In addition, the impact on loved ones and societal impact are (mostly) lacking in these frameworks.

Strengths and limitations

The main strengths of this study are that we included a wide array of various stakeholders in the interviews and that multiple interviews were held per category, thus ensuring the capture of all the relevant perspectives. To our knowledge, this is the first study to explore a wider set of values in oncology.

We acknowledge some limitations. First, possibilities for incorporation of the values found in current decision-making are only explored qualitatively. Case studies on oncological treatments will provide further insights into the true extent of how these values are included in decision-making procedures. Second, our study did not include patients from all tumour types. Different patients with different tumour

types could reveal additional values, mainly for the physical and psychological quality of life. Third, as this study was performed in the Netherlands, the results were mainly generalisable to different countries with comparable healthcare settings (see Box 1 for a description). Finally, the aim of the research was to explore value–elements for the assessment of new treatments. The themes represent those values, however, the subcategories within the main themes went beyond the scope of new treatment assessment based on the explorative and semi-structured design of our interviews. Our approach ensures no mentioned values were missed, and the focus group was used to assess the usefulness of this broad exploration of values. Despite these limitations, an overall idea of the broad range of values and their inclusion in decision-making can be generated.

Conclusion and implications

In conclusion, clinical values are not the only ones that matter to oncological patients and involved stakeholders regarding the evaluation of new treatments and decision-making procedures in oncological care. We found a much broader range of values. The recognition and appreciation of those values might add to patient-level decision-making, but the usefulness for reimbursement decisions is less clear. The values add to existing value frameworks used for both patient-level and reimbursement decisions. In addition, the values might improve patient information, empowerment and support.

The results could be useful to guide clinicians and policymakers when it comes to decision-making in oncology. We recommend exploring a more structural and explicit incorporation of values within oncology in patient-level and reimbursement decision processes. At the patient level, the list of values can inform clinicians on which values to address in SDM, can be used for decision aids and can be used to provide extended patient information. For reimbursement decisions, it would be interesting to explore how the identified values can contribute. More research is needed on making explicit, for different oncological indications, if and how disease-specific values can be systematically inventoried and incorporated to guarantee a more systematic approach to decision-making and the deliberative processes.

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Appendix A: Interview topic guide

Interview questions:

1. In the ideal situation in which there is access to all necessary data, which broad societal values are relevant to incorporate in the evaluation of new therapies?
2. Why these values?

Different categories found in literature are:

- Indirect or lang term costs (also for patients and loved ones)
- Societal costs
- Quality of life
- Impact in daily life
- Impact on loved ones
- Good quality of care

Additional interview questions regarding categories that are not already discussed in the first two questions:

3. Do you recognise [category] as a relevant for society?
4. Why?
5. Which values are relevant for you in this category?
6. Could you think of any more categories that are not mentioned yet?

(the topic guide contained some additional questions concerning a different research question)

Appendix B: Literature study

Method

A scoping review was carried out to identify societal values with oncology and their overarching themes. The final search strategy included keywords (Medical Subject Headings (MeSH-terms)), subject headings and free text terms reflecting the following topic areas: cancer/oncology, biomedical technology assessment and a broader/extended scope regarding value or outcome measures described. The search string contains different terms within the categories: "Cancer" and "Values" and "HTA, cost-effectiveness or societal". The search string is presented in Box S1. The search was performed in PubMed.

Studies were excluded if they were published before the year 1990. After the initial search, duplicates and articles that were published in languages other than English or Dutch were discarded. Studies were included in full-text screening if title abstract screening showed potential for describing values beyond existing value frameworks and basic cost-effectiveness analyses. The studies of *Chandra et al* and *Campolina* present these frameworks and their included values.[14, 40] Articles for which no full text was openly available were excluded for inaccessibility. During full-text screening, studies were excluded if they: (1) were no empirical or (narrative) review study; (2) did not focus on a (partially) cancer-specific population; (3) mentioned no specific value elements; (4) only described value elements already mentioned in existing oncological value frameworks.[14, 40]

Screening of titles and abstracts was done individually by one independent researcher. However, when in doubt, consolations and discussions were held with a second researcher. Two researchers simultaneously worked on screening the full-text articles. In cases of doubt about the in-/ or exclusion of studies, studies were labelled, assessed again by both researchers independently and discussed until a consensus was reached. Grey literature search beyond traditional academic publishing was performed by searching websites of relevant Dutch organisations.

Study characteristics and outcomes were extracted from all included studies. One researcher identified outcomes of broad/societal value with Atlas.ti (version 8). Identified values were categorised in overarching themes.

Box S1. Pubmed search string

("Neoplasms/therapy"[Mesh] OR Oncolog*[tiab] OR cancer [tiab])
AND
("Technology Assessment, Biomedical"[Mesh:NoExp] OR "economics" [Subheading] OR HTA[tiab] OR Health technology assessment*[tiab] OR cost-effect*[tiab] OR cost-analys*[tiab] OR cost-benefit analys*[tiab] OR societal[tiab] OR social[tiab])
AND
((Value*[ti])
OR
((expanding[ti] OR expanded[ti] OR extending [ti] OR extended [ti] OR broader[ti] OR broad[ti] OR future[ti]) AND (HTA[ti] OR Health technology assessment*[ti] OR cost*[ti] OR societal[ti] OR social[ti])))
Filters: from 1990

Results

A total of 900 studies were identified through PubMed search. Two records were excluded manually as duplicates, as these were re-publication done by the same researchers, describing identical results following identical methodology. After TIAB and full-text screening, 19 articles from the primary search remained for final inclusion. Five reports were identified as relevant grey literature, adding up to the total of 24 articles included in this scoping review (Figure S1). An extensive summary of the included studies' characteristics is provided in Table S1.

Table S2 presents all values derived from the articles included in this review. Categorisation of results led to eleven overarching themes: (1) impact on daily life and future, (2) health related outcomes, (3) patient and caregiver costs, (4) family burden, (5) quality of life in general, (6) quality of life – physical, (7) quality of life – psychological, (8) quality of life – social, (9) quality of life – spiritual, (10) societal, and (11) quality of care regarding care/treatment.

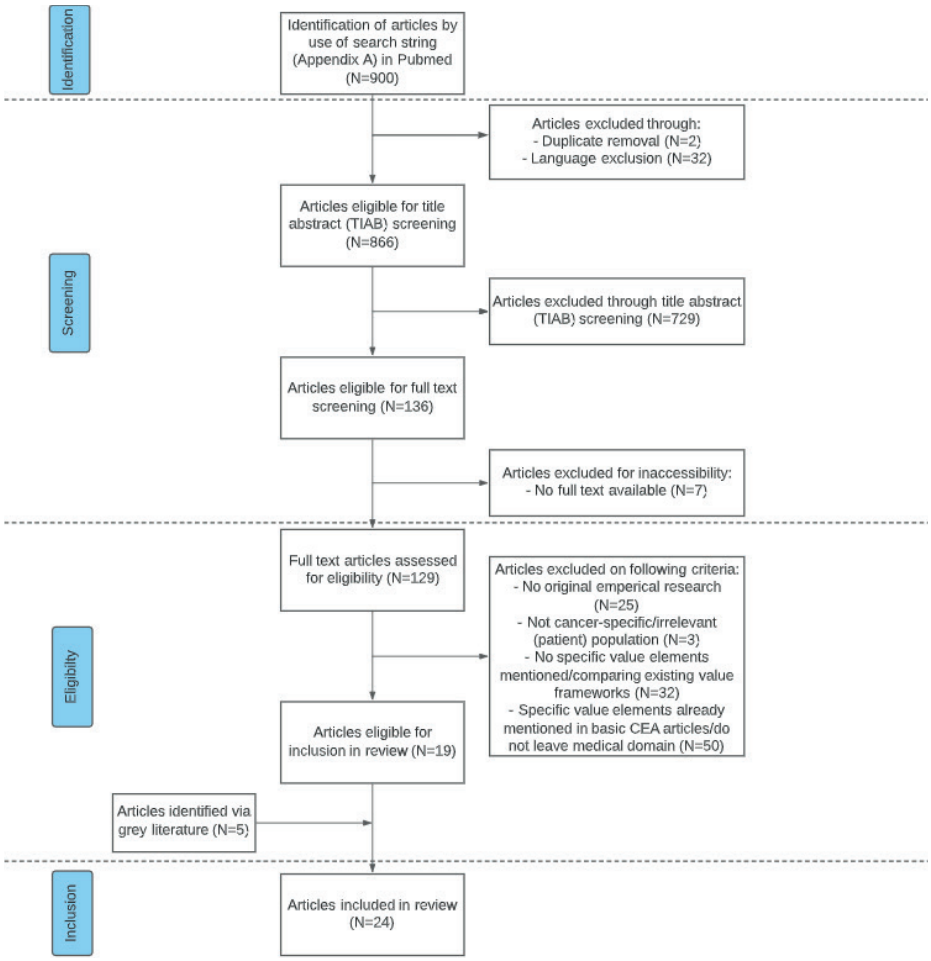

Figure S1. Flowdiagram of study inclusions

Table S1. Characteristics of the included studies

Authors	Year	Country	Study population
Davies[41]	1996	UK	Patients with malignant cerebral glioma and their caregivers
dosReis. [24]	2020	USA	Patient representative members of PAVE Stakeholder Advisory Committee (SAC); patient stakeholder community representatives
Ersek[42]	2018	USA	Metastatic lung cancer patients
Gidwani-Marszowski[43]	2018	USA	Oncologists
Hughes[44]	2019	UK	Studies into hospice patients and/or their caregivers
Jarrett[45]	2013	UK	Cancer survivors
Johnson[46]	2017	Australia	Metastatic cancer patients and family
Kaufman[47]	2019	USA	Immuno-oncology treatment receiving cancer patients
Kim[48]	2012	Worldwide	Caregivers of patients with various cancer types
Konski[49]	2017	USA	Radiation oncology patients
Lakdawalla[25]	2012	USA	Cancer patients
Lorgelly[29]	2020	UK	Cancer patients
Mitchell[50]	2020	USA	Cancer patients
Nardi[51]	2016	USA	NCCN Work Group
Sacristán[52]	2016	Spain	Oncologists, healthcare policy makers, patients, individuals from the general population
Shafrin[53]	2018	Canada	Patients with squamous non-small cell lung cancer (NSCLC)
Teckie[54]	2014	USA	Radiation oncology patients
Tseng[55]	2016	Canada	-
Verdonck-de Leeuw[56]	2012	The Netherlands	Head and neck cancer patients (and caregivers)
Grey literature			
IKNL [57]	2019	The Netherlands	(Ex-)cancer patients
NIVEL[58]	2005	The Netherlands	(Ex-)cancer patients

Goal	Study Type
Exploring perspectives of patients and relatives on the value of radiotherapy	Interview study
Stakeholder-Engaged Derivation of Patient-Informed Value Elements	Mixed-methods
Exploring clinical pathways and patient perspective in the pursuit of value-based oncology care	Review
Exploring oncologists' views on using value to guide cancer treatment decisions	Interview study
Exploring value of patients and family-caregivers regarding hospice care	Systematic review
Reviewing psychological and social problems faced by cancer survivors	Rapid review
Exploring values of patients and their families regarding at the end of life	Interview study
Reviewing the promise of immuno-oncology and the implications for defining the value	Narrative review
Reviewing the value and needs of the caregiver in oncology	Review
Reviewing value in radiation oncology and approaches to weighing benefits vs costs	Narrative review
Exploring how cancer patients value hope and the implications for cost-effectiveness assessments of high-cost cancer therapies	Survey and interview study
Exploring what outcomes patient with cancer value in outcome-based payment schemes	Mixed-methods
Reviewing needs, values, and preferences among adult patients during their cancer treatment and identifying important components of patient-centered cancer care	Systematic review of qualitative studies
Examining the challenges of access, high costs, and defining and demonstrating value at the academic cancer centers.	(Work group) report
Exploring the main factors explaining the relative weight of the attributes that determine the value of oncologic treatments from different perspectives.	Interview study
Exploring the impact of expanding cost-effectiveness analysis for second line nivolumab for patients with squamous non-small cell lung cancer	Cost-effectiveness analysis
Reviewing the meaning of value, the current economic landscape and impediments to achieving value	Narrative review
Reviewing the differences between value-based care and patient-centered care	Narrative review
Exploring the value of quality-of-life questionnaires in head and neck cancer	Review
Exploration of the broad consequences of cancer	Secondary analysis of existing data
Exploring the healthcare and societal situation of people with cancer	Mixed method

Table S1. Continued

Authors	Year	Country	Study population
NIVEL[59]	2010	The Netherlands	(Ex-)cancer patients
NIVEL[60]	2013	The Netherlands	(Ex-)cancer patients
RIVM[61]	2016	The Netherlands	(Ex-)cancer patients

Table S2. Values from literature

Themes	Studies
General health related outcome	DosReis, Ersek, Gidwani-Marszowski, Kaufman, Konski, Lorgelly, Nardi, NIVEL (2013), Teckie, Tseng,
Daily life and future	Davies, DosReis, Ersek, Gidwani-Marszowski, IKNL, Johnson, Kaufman, Mitchell, NIVEL (2005), NIVEL (2010), NIVEL (2013), Lorgelly, RIVM, Sacristan, Shafrin, Tseng
Patient and caregiver costs	DosReis, Ersek, Gidwani-Marszowski, Johnson, Kaufman, Konski, Nardi, Shafrin, Teckie, Tseng, IKNL, NIVEL(2005), NIVEL(2010), NIVEL(2013)
Family burden	Davies, DosReis, Gidwani-Marszowski, Hughes, Jarret, Johnson, Kim, Lorgelly, Mitchell, Tseng, Shafrin, RIVM, Verdonck - de Leeuw
Quality of life in general	Ersek , Gidwani-Marszowski, Kaufman, Konski, Nardi, Sacristan, Jarret, Shafrin, NIVEL (2005)
Quality of life - Physical	Davies, DosReis, Ersek, IKNL, Kaufman, Konski, Lorgelly, Nardi, NIVEL (2005), NIVEL (2010), NIVEL (2013), Sacristan, Shafrin, Teckie, Tseng, Verdonck - de Leeuw
Quality of life - Psychological	Davies, DosReis, Ersek, Gidwani-Marszowski, Hughes, IKNL, Jarret, Johnson, Kaufman, Lakdawalla, Lorgelly, Mitchell, NIVEL (2005), NIVEL (2010), NIVEL (2013), RIVM, Shafrin, Teckie, Tseng, Verdonck - de Leeuw
Quality of life - Social	Davies, DosReis, Hughes, IKNL, Jarret, Johnson, Lorgelly, Jarret, Teckie, Mitchell, NIVEL(2005), NIVEL(2010), NIVEL(2013), RIVM
Quality of life - Spiritual	DosReis, Ersek, Tseng, NIVEL (2013)
Societal	DosReis, Ersek, Gidwani-Marszowski, IKNL, Kaufman, Kim, Konski, Lorgelly, Nardi, NIVEL(2005), NIVEL (2010) RIVM, Sacristan, Shafrin, Teckie, Tseng,
Quality of care	Davies, DosReis, Ersek, Gidwani-Marszowski, IKNL, Johnson, Hughes, Kaufman, Kim, Konski, Lorgelly, Mitchell, Nardi, NIVEL (2005), NIVEL (2010), NIVEL (2013), RIVM, Sacristan, Teckie, Tseng, Verdonck - de Leeuw, Teckie

Goal	Study Type
Exploring the need of support of (ex)cancer patient and the role of the general practitioner	Questionnaire study
Exploration of experienced problems and support need of cancer patients	Questionnaire study
Exploring and informing about cancer, cancer care, cancer patients and society	Narrative review and exploration of different secondary data sources

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Appendix C: Topic guide expert panel

Questions for the focus group with an expert panel:

1. What is the desire for this broad value framework for evaluation and decision-making regarding oncological therapies? Within which context is this desirable? Why?
2. With which methodologies can these values be incorporated into decision-making processes? And how will this look like?
3. What is the current use of these values in evaluations and decision-making processes?

Chapter 5

How to create value with constrained budgets in oncological care? A narrative review

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Abstract

Introduction: As a result of an increasing focus on patient-centred care within oncology and more pressure on the sustainability of healthcare systems, the discussion on what exactly constitutes value re-appears. Policymakers seek to improve patient values; however, funding all values is not sustainable.

Areas covered: We collect available evidence from scientific literature and reflect on the concept of value, the possible incorporation of a wide spectrum of values in reimbursement decisions, and alternative strategies to increase value in oncological care.

Expert opinion: We state that value holds many different aspects. For reimbursement decisions, we argue that it is simply not feasible to incorporate all patient values because of the need for efficient resource allocation. We argue that we should shift the value debate from the individual perspective of patients to creating value for the cancer population at large. The different strategies we address are as follows: (1) shared decision-making; (2) biomarkers and molecular diagnostics; (3) appropriate evaluation, payment and use of drugs; (4) supportive care; (5) cancer prevention and screening; (6) monitoring late effect; (7) concentration of care and oncological networking; and (8) management of comorbidities. Important preconditions to support these strategies are strategic planning, consistent cancer policies and data availability.

Introduction

In recent years, many developments have taken place in oncological care in the field of diagnostics and treatments. Partly because of this and due to the ageing of the population, the number of people living with and after cancer is increasing rapidly.(1) It is expected that the worldwide cancer rate will increase from 19 million in 2020 to 30 million in 2040.(2) Cancer treatments are gradually becoming more successful, resulting in an increase in people who survive.(1) Examples are the cases of metastatic melanoma and haematological cancers. Novel targeted and immunotherapeutic drugs increased median survival for metastatic melanoma patients from 11.8 months in 2013 to 21.1 months in 2018.(3) For haematological malignancies, a study from the Nordic countries (Denmark, Finland, Norway, and Sweden) revealed an increase in 5-year survival from 20% in a cohort from 1971 to 1975 to 50% in a cohort from 2016 to 2020.(4)

Due to increases in survival, patient-centred care is gaining increasing interest. The needs and desires of individual patients are increasingly driving forces behind healthcare decisions and alternative quality measurements that now also include patient experiences.(5-8) However, because of the fast developments within oncology, the costs for oncological care are increasing rapidly. More expensive pharmaceuticals are getting on the market, while post-treatment costs are also increasing. Global costs of oncological medicine rose from 111 billion US dollars in 2017 to 185 billion US dollars in 2021.(9) It is predicted that the costs will rise to 307 billion US dollars in 2026. This does not include the costs of other oncological healthcare spending or costs for comorbidities. Both would add very substantially to the cost burden of oncology.

Within the current era of patient-centred care and the increasing pressures on the sustainability of healthcare systems, the question arises: How do these two relate and what constitutes value in healthcare systems that are under pressure?

In this paper, we reflect on three aspects: (1) the concept of value within oncology, (2) the incorporation of values in reimbursement decisions, and (3) alternative strategies to increase value in oncological care.

The concept of value

We recently explored value-elements regarding new oncological treatments for patients with cancer and all stakeholders involved.(10) We found that clinical values are not the only ones that matter in the oncological field. We found a much broader range of values. Values that have come to the fore regard the impact on the daily life and future of patients, costs for patients and loved ones, oncology-specific quality of life, impact on loved ones, societal impact, and aspects regarding the quality of treatments.(10) Some examples of these values are presented in Table 1.

Besides the values from our previous study, different frameworks already exist for evaluating the value of health interventions. These frameworks can be generic or oncology-specific and can inform reimbursement decisions. Examples of generic frameworks are the framework of the Institute for Clinical and Economic Review (ICER) from the United States (11) or an HTA core model from EUnetHTA from Europe (12). Besides these generic frameworks, two common oncology-specific value frameworks are the frameworks of the American Society of Clinical Oncology (ASCO) (13) and the European Society for Medical Oncology (ESMO) (14). The frameworks do not entirely incorporate all extensive values found in our previous study. Our extensive exploration of values could add to more explicitly using the values that are specific for oncological care in the deliberative processes for the generic frameworks. In addition, these broad values could add to oncology-specific frameworks by presenting explicit values regarding the impact on daily life and future, costs for patients and loved ones, quality of life, and quality of treatment. In addition, the impact on loved ones and societal impact are often underrepresented in oncology-specific frameworks.

A proper recognition of values that count might, in practice, increase the perceived value of oncological care. However, in different contexts, different values are prioritized. Below, we first discuss the incorporation of these values in reimbursement decisions and then discuss different strategies to increase value.

Table 1. Selection of examples of values for oncological patients and other stakeholders. Source: Vrinzen et al (10)

Impact on daily life and future of patients
Impact on future plans and choices
Ability to work
Ability to care for children
Costs for patients and loved ones
Additional care
Travel expenses for patients/relatives
Loss of income
Quality of life
Hair loss
Neuropathy
Infertility
Fear (of recurrence)
Cognition and concentration
Depression
Relationship with (grand)children
Relationship with partner
Relationship with friends/family
Existential questioning
Impact on loved ones
Informal care
Workability
Psychological impact
Societal impact
Workability
(In)direct healthcare costs
Societal balancing
Quality of treatment
Long term health
Survival
Ease of use

Which (patient) values should we include in reimbursement decisions?

Exact definitions of value intensify when healthcare budgets are under pressure. Policymakers seek to provide universal access to high-value health care for all citizens with a limited budget at their disposal. The available resources have to meet the needs of oncological patients, but also of all those with different health conditions. If a substantial and increasing amount of the budget is devoted to oncological care, this reduces the opportunity to invest in care for non-oncological patients. Economists call these the opportunity costs; more recently, displacement (of more valuable treatments) has also been used to describe this phenomenon. An example in the field of oncology is the rise in immunotherapies, which are promising treatments for various types of cancers. These drugs are often very expensive, and reimbursement for these high costs of immunotherapy drugs can come at the expense of other treatments. Therefore, new expensive pharmaceuticals in oncology are increasingly hitting the willingness to pay thresholds of responsible regulatory agencies. For example, in the Netherlands, the new pharmaceutical drug for triple-negative breast cancer was recently declined for national reimbursement. This drug could increase survival by 5.4 months but has extremely high costs (2.9 million per patient) and an incremental cost-effectiveness ratio between 196,929 Euros and 241,231 Euros per Quality-Adjusted-Life-Year (QALY).(15) The QALY is a uniform measure of value in which life years and the health-related quality of life (HRQoL) are merged.(16) In the Netherlands, the maximum willingness to pay threshold is 80,000 euros per QALY.

To ensure fair allocation of resources and maximize population health, it is important to set decision-making procedures with uniform value frameworks to assess healthcare investments over different diseases. Over the past years, the role and limitations of value frameworks in healthcare priority setting and resource allocations have been firmly debated. Different studies emphasize gaps in value assessment for new interventions.(17) For example, aspects such as hope (18) or the reduction in uncertainty by a new intervention are merely never incorporated (17). The use of generic tools for the measure of HRQoL within the QALY is debated.(19) The HRQoL measures do not always seem adequate for mapping out all benefits. They might only contain subsets of the relevant outcomes.(17,20) Generic tools, for example, the EQ-5D, generate utilities that are comparable across different diseases and, therefore, can most sufficiently provide fair resource allocation across different healthcare areas. The downside of these generic tools is the reduced sensitivity to change and the inability to capture heterogeneity in more condition-

specific values between different patient groups. This stimulates the development of more patient-centred and condition-specific health utility tools in which values of the specific patient population are represented, for example, the EORTC QLQ BR-23 tool for breast cancer. However, it could be questioned whether all relevant values could be measured and quantified in a way that the utilities are still comparable over all diseases. In addition, an increased variety of disease-specific tools decreases the ability to compare across studies or populations. Experts desire the use of generic value measures that are applicable to all diseases for efficient resource allocation.(10)

Differences between countries exist in how and which values are considered in decisions on budget allocation. A study by Angelis et al. examined differences in eight European countries regarding the assessment of the value of new medicines in the context of reimbursement decisions.(21) Most countries implement a type of economic evaluation in addition to the assessment of clinical benefit. The preferred health gain measure usually is the QALY. Additional values beyond the QALY concept are captured to a different extent between countries for instance, ease of use, public health benefits, ethical considerations, or social productivity. Often, such values are already either explicitly or implicitly incorporated in reimbursement decisions. Differences in decision-making procedures contribute to the variability in the reimbursement for oncological drugs between countries.(22) Countries with lower rates of reimbursement incorporated cost-effectiveness analyses into reimbursement decisions. The methods and level of negotiations between payers and pharmaceutical companies that are used for cost containment result in these countries for an increase in the number of drug reimbursements.

Because healthcare budgets are under pressure and reimbursement decisions are focused on efficiently allocating resources to maximize value for the entire population, a comprehensive recognition of all individual patient values seems hardly feasible.

Alternative strategies to increase the value of oncological care

Besides reimbursement decisions on expensive drugs, different strategies could contribute to creating value in oncological care. Below we discuss different strategies.

Shared decision-making and information provision

Over the years, patient-centred care and shared decision-making have gained increasing interest. Shared decision-making between physicians and patients increases incorporating patient values in treatment decisions, as well as decision aids and general information provision to patients during and after treatment or cancer.(10) Patients should be well-informed about treatment options, their advantages and disadvantages and decide together with the physician which treatment (or no treatment) fits best. For treatment choices, it is relevant to consider the patient's individual context, values, and priorities. For instance, the patient's desire to maintain physical capabilities (ability to sport or work), psychological well-being, phase of life (e.g. elderly, young parent, or a patient with a child wish), home situation, or education level.(10) Additionally, treatment choices depend on whether patients can still be curatively treated. It should be emphasized that treatment choices also include the option not to treat. A culture shift is needed to emphasize that treating a patient is not always the best option.

Different studies reveal that shared decision-making is not yet fully implemented and used to its full potential.(23-25) What could aid the broader implementation of shared decision-making is as follows: (1) more awareness of the benefits of shared decision-making and incorporating this as a standard in the patient pathway, (2) generating more outcome information based on real-world data to inform and empower patients to make well-informed decisions, and (3) the development and stimulation of tools that systematically address patient values and provide necessary information.

Biomarker and molecular diagnostics

Biomarker testing, including molecular diagnostics, in oncology has received a lot of attention and has become an integral part of cancer treatment. Molecular diagnostics enable precision medicine in which targeted treatment can be applied based on tumour genetics. In addition, prognostic markers can inform treatment selection.(26) For example, a KRAS mutation can predict a lower response to targeted therapies inhibiting the epidermal growth factor receptor (EGFR) in tumour cells.(27,28) A different example is circulating tumour DNA as a prognostic factor for the need for adjuvant chemotherapy to prevent recurrence after tumour resection in stage II colon cancer.(29) Based on biomarkers, clinicians can identify the most effective treatment options for individual patients.

For many tumour types, comprehensive genomic profiling using either Next-Generation Sequencing (NGS) or Whole Genome Sequencing (WGS) is beneficial.(30)

NGS evaluates known genetic alterations, while WGS provides a more comprehensive view of the entire genome, enabling the detection of known and novel genetic alterations, which facilitates research and potentially provides more future-proof genetic information.

The potential treatment benefit in terms of response rate and progression-free survival of comprehensive molecular diagnostics for the individual patient is great.(31) NGS is the most appropriate for patients with metastatic cancer with several identified molecular targets.(31) Additionally, NGS can offer options in patients with rare cancers and help navigate patients to clinical trials. A review by Tan et al. from 2018 found that NGS is effective for the identification of mutation(s) in cancer patients.(32) However, only a few cost-effectiveness studies were found with contradicting results. In addition, WGS could also be cost-effective, but more research is needed.(33,34)

To spread and evolve molecular diagnostics, investments are needed to ensure an appropriate organization in which the high-quality diagnostics form an integral part of patient pathways for specific patient groups. It is of importance to organize access to molecular diagnostics for every eligible patient across a country. In addition, Molecular Multidisciplinary Tumour Boards and tools to support these teams are needed for interdisciplinary discussions to help with the interpretation of molecular results and optimize patient treatment.(35-37)

Appropriate evaluation, payment, and use of drugs

After a positive reimbursement decision for oncological drugs, they may stay monitored after implementation. Drugs that are already on the market and reimbursed should be reevaluated based on real-world data from large national registries to gain insights into the cost-effectiveness of these drugs in a real-world setting. It is known that real-world patient populations differ from the populations in pharmaceutical trials.(38) Besides this, cost calculations are often based on modelling studies and could additionally benefit from re-evaluation based on real-world data.

Comparative cost-effectiveness studies to evaluate different treatment regimens in real-world data could contribute in which different treatments are compared in a routine practice setting.(39) Many countries have existing large cancer registries with rich observational data that can be used for comparative effectiveness studies. These could be used to assess benefits and harms of a treatment in a representative real-world setting.

Alternative payment models should be evaluated and stimulated like value-based pricing and risk-sharing. In value-based pricing models, also referred to as pay-for-performance models, drug prices are set after assessment of a drug's value within the national threshold for cost-effectiveness.(40) Pharmaceutical companies could decide whether or not to market their drugs at that price. Risk-sharing models are agreements between pharmaceutical companies and payers which allow patients access to new drugs in a context of uncertainty of (cost-)effectiveness due to immature evidence. This ensures collection of more evidence on cost-effectiveness and allows prices of drugs to be aligned with their value. These flexible and personalized risk-sharing models seem promising for increasing the sustainability of oncological care.(41) An example of this is the DRUG Access Protocol in the Netherlands, which enables providers access schemes to promising new medicine, which improves access to new drugs and can contribute to the collection of evidence.(42) This is especially relevant for patients with rare cancers in which it is difficult to find enough patients for trials.

To ensure that the value of investments is maximized, it is of great importance to stimulate the appropriate use of expensive drugs after they are accepted for national reimbursement. The rise of precision medicine with molecular diagnostics could stimulate this. Patients who have the indication for a specific drug have been identified, and they could greatly benefit from it. In addition, attention should be paid to reducing 'inappropriate' care.(40) Studies suggest that a great deal of patients can receive inappropriate care at the end of life, which is inconsistent with patient wishes, for instance, the provision of chemotherapy.(43,44) This can result in unnecessary toxicity and side effects, can decrease a patient's quality of life and create unnecessary costs. A substantial portion of costs for oncological care is spent in these last weeks or days of life.

As patient-centred care and the sustainability of oncological care are already widely debated, many different initiatives already exist on maximizing patient value and ensuring efficient healthcare delivery, resulting in an increase in healthcare quality and a reduction of healthcare costs. Initiatives can, for instance, include reduction of expensive medication waste, adjusting drug dosages or adjusting start-and-stop criteria. It is of importance to evaluate these initiatives and stimulate (inter) national spread.

Supportive care

The rapid developments in oncological care, increasing incidence and increasing survival rates are creating more awareness of the need for supportive care for

patients during and after the disease. To prevent and manage the adverse effects of cancer and its treatment, supportive care should be integrated into the care pathway.(45,46) Supportive care needs for patients could, among others, be a psychologist, sexologist, or physiotherapist. Supportive care could, for instance, also include work rehabilitation. A rise in cancer incidence is mainly seen in the older population, however incidence is also rising in the younger population that is still working. More attention should be paid to working and work rehabilitation during and after cancer, for instance, by including an occupational physician in the care pathway.

At the moment, the supportive care needs of patients are not always fully met, which can result in worse HRQoL.(47,48) Clear arrangements should be made on who is addressing the supportive needs of patients in the care pathway and when these are addressed. In addition, arrangements should be set on who refers to supportive care and to what supportive care is referred to. Patients often receive care from multiple care professionals and different care organizations. The continuity of the care pathway (and aftercare) also beyond the medical treatment is important in this aspect. Coordination and communication between the different professionals of this (supportive) care should be organized. It is important that patients are well-informed about possibilities for support during and after the treatments and cancer.

For patients with advanced cancer, advanced care planning (ACP) could additionally contribute to increasing patient-centred care and stimulate the on-time onset of palliative care. ACP enables patients to define and discuss their preferences for future treatment with family and healthcare professionals. There are many different ACP designs, and research is needed on which intervention suits best for different scenarios and what facilitates ACP.(49) For instance, the use of an interdisciplinary group of healthcare professionals or ensuring engagement across the entire illness trajectory could contribute to effective ACP interventions.(50)

Prevention and screening

Screening is a crucial tool for early detection of various types of cancer. It can detect cancers at an early stage before symptoms occur, which increases the likelihood of successful treatment. Several cancer screening programs demonstrate cost-effectiveness. For example, a recent systematic review showed that, for high-risk populations, screening with low-dose computed tomography for lung cancer is cost-effective.(51). In addition, breast cancer screening is proven cost-effective, but risk-adapted screening is more effective than conventional screening.(52,53) The

cost savings by screening, due to early detection of cancer leading to less invasive and more effective treatment, can outweigh the initial screening costs. Screening programs for common cancers with higher incidence rates, such as breast cancer, have a greater impact on public health and cost-effectiveness compared to screening for rare cancers.

Prevention of cancer often includes lifestyle interventions that are aimed at reducing the risk of cancer. This includes promoting healthier lifestyle such as avoiding tobacco and excessive alcohol use, physical activity, or sun protection.(54-56) These interventions can reduce cancer incidence and incidence of other diseases and potentially reduce healthcare costs. For example, interventions for smoking cessation are highly cost-effective, as quitting smoking not only reduces the risk of lung cancer but also lowers the risk of other smoking-related diseases.(57,58)

It should be mentioned that evaluating cost-effectiveness of screening and prevention programs can be challenging because costs and outcomes are projected over large time horizons which introduces a lot of uncertainty. Additionally, discounting future costs and benefits is necessary to account for the large horizons but makes it more complicated the interpret results and impact of the screening. Nevertheless, it is important to research and invest in prevention and screening for different kinds of subpopulations.

Monitoring late effects

Cancer treatment has made significant advancements in recent years in terms of survival rates; however, cancer survivors may experience long-term effects caused by the cancer or the treatments.(59) A cancer diagnosis and cancer treatment can affect patient values regarding daily life and future, costs, quality of life, and impact on loved ones.(10) In addition, treatment for cancer can result in different diseases like secondary cancers or cardiovascular diseases.(60)

As cancer survivorship is becoming a greater aspect of oncology care, understanding and addressing late effects is essential for comprehensive long-term management and emphasizes the need for guidelines. For these (ex-)patients, regular medical checkups are required to monitor overall health and identify any potential long-term effects. Generating risk profiles based on real-world data for (late-)effects of treatment should be stimulated. This could be used to inform patients and as input in shared decision-making. In addition, strategies for monitoring and supporting late effects should be explored. An example of late effects initiatives is the implementation of survivorship care or hospital clinics for patients who

survived cancer (even after many years). A wide variation in support and healthcare needs among cancer survivors suggests a need for survivorship care that is tailored to individual patients.(61) It has shown to be beneficial for patients who desire information about their disease.(62)

Concentration of care and oncological networking

The fast innovation within the oncology field regarding treatment and diagnostics results in more complex care and precision medicine. As the complexity of cancer care increases it is of importance to concentrate knowledge, especially for rare cancer types, to ensure the quality of care remains high or increases. Many studies provide evidence that increasing volumes of care improves health outcomes.(63-65) Concentration of care in specialized institutions increases expertise; however, the importance of collaboration agreements between different hospitals should be emphasized. Patients should have access to the best possible care suited for that specific patient and should be referred to or discussed with specialized institutions within a country or even internationally for rare cancer. For instance, the European Reference Network on Rare Adult Solid Cancers (EURACAN) connects healthcare professionals and centres of expertise to improve access to diagnostics, treatments, and high-quality healthcare for rare adult solid cancer.(66)

Collaboration agreements could be referred to as oncological networking or cancer networks. Several studies have been conducted in which the effectiveness of certain components of an oncological network was tested. Discussing patients in a multidisciplinary team (67,68) or centralization of care (69) increases survival, while multidisciplinary care pathways seem to improve the quality of care (70,71). Although oncological networks seem beneficial for increasing quality of care (72-75), research in oncological networking that may prove this is complicated. There is a large variation in the organization and goals of oncological networks and, in addition, in the indicators and evaluation methods used.(76) The OECI European Cancer Network Quality standard can contribute to establishing principles and standards for evaluating the effectiveness of oncological networks.(76) Demonstrating the (cost-)effectiveness of oncological networking and the optimal way of implementation and governance is important.

Managing comorbidities

The number of comorbidities in oncological patients increases over time by 5% per decade.(77) On average, comorbidity prevalence in oncological patients is 33.4%. This varies for different cancer types, such as lung cancer (46.7%), colorectal cancer (40.0%), prostate (28.5%), melanoma (28.3%), and breast (22.4%).(77) Additionally,

comorbidities increase healthcare costs for oncological patients.(78,79) These high rates of comorbidities have major implications for the treatment and organization of cancer care.

Oncological patients with comorbidities receive different treatments for instance, they are less likely to receive treatment with curative intent and receive less standard cancer treatments such as surgery, chemotherapy, and radiation therapy.(80,81) Additionally, postoperative complications, morbidity, and mortality are higher in patients with comorbidities.(81) In the era of centralization of oncological care, as described above, comorbidity management risks fragmentation between different healthcare organizations. The high comorbidity prevalence should be incorporated in debates on centralization of care. The management of comorbidities requires collaboration between different professionals and healthcare organizations. Patients need personalized treatment plans that address the cancer and comorbidity, additionally taking into account potential drug interactions and side effects. All medications should be reviewed regularly to minimize the risk of adverse effects or drug interactions.

Cancer policies

Nolte et al. studied the link of different cancer policies in a sample of 10 jurisdictions in seven high-income countries for seven cancers from 1995 to 2014.(82) Among other things, the frequency and consistency of cancer plans varied. Some countries have successions of cancer plans that build on each other, while others have isolated plans. Countries that implement cancer control policies with consistent oversight and a clear development plan that builds on previous policies (consistency) appear to be associated with better cancer survival. This reveals that strategic planning is important for patient outcome improvement. Central bodies may play an important role in ensuring the consistency by providing follow-through of cancer plans and using funding to ensure implementation.

In addition, healthcare systems are complex and fragmented systems with makes them resistant to change.(83) Within complex systems, it is expected that incremental steps have little impact and it is more effective to implement multiple of the strategies at ones to increase value in health care.

Data availability

Data availability can be a challenge in (oncological) care. While progress has been made in recent years to improve data collection and data sharing, there are still complications.(84) Data silos can limit the accessibility and sharing of data across

different healthcare organizations. In addition, there may be a lack of standardized data formats across health systems, which results in a decrease in interoperability. Besides this, privacy plays a major role, as it can be restricted to share patient data due to confidentiality and security considerations. These limitations may hinder the improvement of health care at different levels: patients, physicians, and the population.

At patient level, limited data availability may hinder patients' ability to access all their health information. Access to personal health records empowers patients to participate in their care decisions. It can increase understanding of treatment options and an active participation in shared decision-making with healthcare providers.

At physician level, inadequate access to data can hinder assessment of a patient's condition. The availability of comprehensive patient data and full medical history is crucial for accurate clinical decision-making.

At population level, access to comprehensive big datasets is essential for conducting research. This data may, among other things, include electronic health records, genomic sequencing, treatments, outcomes, and costs. For efficient resource allocation and the evaluation of strategies discussed in this paper, it is of importance to perform research with large comprehensive datasets.

It is crucial to stimulate interoperability and secure sharing of data. Efforts like standardized electronic health records, national registries, and privacy-preserving sharing initiatives may all increase data availability.

Conclusion

This paper provides review-based suggestions on what constitutes value in cancer care. Healthcare systems are under pressure due to rising healthcare costs. A wide range of values exist in oncological care. However, the exact definition of value within the context of healthcare policy re-appears when healthcare budgets are under pressure. Ideally, reimbursement decisions should efficiently allocate budget across the entire (not only oncological) population. Different alternatives are suggested to increase value in oncological care.

Expert opinion

What constitutes value in cancer policy depends on the context. Patient-centred care is becoming increasingly important, and individual patient values are increasingly driving forces behind healthcare decisions. However, we have concerns to incorporate all individual patient values in reimbursement decisions regarding expensive oncological drugs. At the moment, existing frameworks and quality-of-life measures used for reimbursement decisions do not entirely incorporate all value-elements relevant for oncological patients. The use of generic value frameworks and measures that are applicable to all diseases is desired for efficient resource allocation. In addition, costs of oncological care are increasing, and healthcare budgets are under pressure. In our opinion, the concept of value in reimbursement decisions is getting more narrow as more expensive drugs are entering the market. We believe that, to efficiently allocate limited resources and keep healthcare sustainable, a more narrow concept of value is valid. Reimbursement decisions should be focused on efficiently allocating resources to maximize value for the entire population (not only the oncological population), and therefore, comprehensive recognition of all individual patient values is unfeasible.

We argue that we should shift the value debate from incorporating 'all' individual patient values of 'all' cancer subpopulations in reimbursement decisions to creating more value by implementing alternative strategies that can contribute to increasing value.

We believe that cancer policy should shift focus to different strategies that can increase value for the entire oncological population as a whole. These strategies should be (1) greater implementation of shared decision-making in which patients are well-informed about treatment options and a patient's individual context, values are priorities are considered; (2) studying, developing, and organizing biomarker testing and molecular diagnostics for the most promising subpopulations; (3) exploring and incorporating appropriate evaluation, payment, and use of expensive cancer drugs that already have a (temporary) positive reimbursement decision; (4) further development of management of supportive care needs during and after cancer treatments to increasingly meet the patients unmet needs; (5) research and implementation of effective strategies for cancer prevention and screening for different subpopulations; (6) developing and studying the monitoring and management of late adverse effects of cancer and its treatment; (7) stimulating and study optimal ways to concentrate oncological care and organize oncological networking to increase the accessibility and quality of care; and (8) developing effective management strategies for comorbidities in

oncological patients with personal treatment plans and collaborations across different healthcare professionals and organizations.

In our opinion, preconditions exist to increase value across the oncological populations. This includes strategic planning with multiple strategies simultaneously and the implementation of consistent cancer policies. Cancer policies should be implemented with consistent oversight and a clear development plan and build on previous policies. Central bodies should ensure the consistency by providing follow-through of cancer plans and using funding to ensure implementation.

In addition, we believe it is crucial to improve data availability. To overcome the limitations regarding data accessibility and data sharing, interoperability, and secure sharing of data should be stimulated. Initiatives like standardized electronic health records, national registries, and privacy-preserving data-sharing may all increase data availability.

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Chapter 6

Comprehensive Cancer Networks in the Netherlands: how do they affect quality and costs of care for patients with colon- or pancreatic-cancer?

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Abstract

Background: Concentration of care and collaborations between hospitals increasingly re-organizes oncological care into Comprehensive Cancer Networks (CCNs), aiming to improve care outcomes and reduce costs. This study evaluates four CCNs on two-year oncological costs, two-year mortality rate, and care processes (referrals and double diagnostic activities) for patients with colon- or pancreatic cancer.

Method: We performed a retrospective cohort study based on claims data in the Netherlands. All patients with colon- or pancreatic cancer claims between January 2013 and June 2021 were included. Data included patient characteristics, health insurance claims and healthcare activities. All costs were indexed to EURO 2023. We performed propensity score matching per CCN and applied regression models with a difference-in-difference design, adjusting for non-linear trends before the start of a CCN.

Results: We included 92,309 patients with colon cancer and 25,630 patients with pancreatic cancer. For colon cancer, one CCN showed a significant decrease in two-year oncological costs (-€1,899). One CCN showed a significant decrease in referrals (-3.6%), and one showed a significant increase (4.4%). No significant effect on two-year mortality and double diagnostics activities was found. For pancreatic cancer, one CCN showed a significant decrease in two-year oncological costs (-€3,747), and one CCN showed a significant increase in double diagnostic activities (8.6%). No significant effect on referrals and two-year mortality were found.

Conclusion: CCNs do not consistently reduce costs or impact referral patterns or double diagnostics. No impact on mortality was found. Additional insights into determinants of CCN success are required before broad implementation is warranted.

Introduction

Rapid advancements in the field of oncology, particularly in treatment and diagnostics, significantly increased survival.(1) However, these advancements do also increase the complexity and multidisciplinary nature of oncological care. As a result, the need to centralize care and knowledge becomes crucial to ensure and potentially enhance the quality of care, especially for rare cancer types.(2) However, centralization could result in increased travel times for patients and, as a consequence, reducing accessibility to care.(3, 4) This can particularly be a problem for elderly and vulnerable patients.(4, 5)

To address these issues, a new approach to care organization is required, one that facilitates concentration of care where needed, collaboration of experts and organizations, pooling expertise and exchanging information.(6) An approach for accessible, patient-centred, and sustainable care is the Comprehensive Cancer Network (CCN). CCNs comprise healthcare organizations that have common governance and pursue common goals through, among other things, tumour management groups, multidisciplinary team discussions (MTDs), uniform cancer pathways, quality standards and systems for information exchange.(7, 8)

CCNs could provide a benefit for both high-volume and low-volume cancers through these different components. Colon cancer is an example of a high-volume cancer. Worldwide, colorectal cancer is the third most common cancer type, with approximately 10% of all cases.(9) In 2020, there were more than 1.9 million new cases worldwide. Colon cancer accounts for around 70% of colorectal cancers.(10) Pancreatic cancer is an example of a low-volume cancer. It is the eleventh most common cancer worldwide, with 458,918 new cases in 2018.(11) Especially for low-volume cancers, CCNs could also be beneficial by concentrating care and providing access to specialized care and knowledge by means of referrals.

A number of studies evaluate specific components of a CCN. For example, previous work found that selective referrals of complex cancer patients to high-volume hospitals improves health outcomes.(12-14) In addition, multidisciplinary team discussions have the potential to increase survival, mainly for advanced stages of disease.(15) However, multidisciplinary diagnostic workup that could be a result of concentration of care might lead to repeated diagnostic activities.(16) Little is known about the overall impact of CCNs on care outcomes and costs on a systems level. This study aims to evaluate the effect of CCNs on costs, survival and care

processes (referrals and double diagnostic activities) for patients with high-volume cancers (colon cancer) and low-volume cancers (pancreatic cancer).

Method

Study design and population

We performed a case-control retrospective cohort study based on claims data in the Netherlands. A background on the Dutch healthcare system is given elsewhere.(17) All Dutch patients who had a reimbursed claim for colon- or pancreatic cancer in the period from January 2013 to June 2021 were included. Diagnostic treatment combination (DTC) with specific speciality and diagnosis codes were used to identify colon- or pancreatic cancer diagnoses (see Appendix Table S1). Exclusion criteria were age below 18, a previous claim for colon or pancreatic cancer in 2012, and DTCs for (potentially) benign tumours only. Patients with a rectum cancer DTC were excluded. Our outcome measures were two-year oncological costs, two-year mortality, referrals, and double diagnostic activities.

Intervention

CCNs are a contractual agreement between the Boards of Directors of participating general hospitals and an academic hospital. Collaboration includes medical specialists, physician assistants, nursing specialists, nurses and others. Such an agreement includes the governance structure concerning overarching tasks that are important for the functioning and development of the CCN. Additionally, it includes collaboration agreements on, among other things, quality standards, data exchange, accountability, referrals of patients to concentrated care, agreements on MTDs.(7, 18) In 2021, four CCNs were active in the Netherlands.(18) The hospitals participating in these CCNs and the start dates were collected from their websites using internet searches. The regions without a formal CCN in 2021 were treated as a control group.

Data and variables

Claims data were gathered from Vektis, a national claims database with health claims from health insurance companies of all Dutch insured patients. The claims data included reimbursement prices as well as patient characteristics e.g. age, gender and time of death. Socio-economic status (SES) is determined with data from Dutch Social Planning Agency on the basis of the postal code of the patient in 2016. If no postal code was available in 2016, nearby years were used. The SES was categorized into three equal groups: low, middle and high. A fourth category included patients

of which the SES was unknown. Mortality was defined as deceased within two years after the opening of the first colon- or pancreatic cancer DTC.

We only used DTC data on solid tumours. Appendix Table S2 presents specialism and diagnosis codes used to identify solid tumours. The DTC data included care product (claim code), specialism codes, diagnosis codes, start date and reimbursement prices. We used median prices of the DTC care product in the corresponding year as DTC costs. At the start of the study, some prices of 2023 were still unknown. We imputed these with prices from earlier years. We defined metastasis as patients with either a DTC specifically for metastatic treatment or palliative care, or with a non-colorectal or non-pancreatic solid tumour within 3 months post opening of the first DTC. Referrals were defined if oncological DTCs occurred in a different hospital within six months of the first colon- or pancreatic-cancer DTC. Additional costs included costs for intensive care (IC) or expensive drugs (add-ons). Before 2017, diagnosis codes for expensive drugs were missing, and add-ons were included if commonly used in oncological indications (over 50% of add-ons corresponded to oncological indications). From June 2014 onwards, DTCs included care activities (e.g. diagnostic activities). Double diagnostics were defined as an identical diagnostic activity within four weeks between the primary and referral hospital. All costs were indexed to EURO 2023 using claim price adjustments by the Dutch Healthcare authority.(19) Two-year oncological costs were defined as the costs of oncological DTCs, add-on oncological drugs and IC within two years after the opening of the first colon- or pancreatic-cancer DTC.

Data analysis

We performed regression models with a difference-in-difference (DiD) design to evaluate the two-year oncological costs, two-year mortality, referrals and double diagnostics.(20) A DiD is a controlled before-and-after analyses in which the outcomes before and after the start of a CCN were compared to the before and after of controls without a CCN. For the controls, we performed propensity score matching per CCN with the patients from the control group with a 1:1 ratio and with replacement.(21, 22) Nearest neighbour matching was used with age, gender, SES, and metastasis and with a calliper of 0.2. Exact matching was used for the start of the first colon- or pancreatic-cancer DTCs in quarters of a year. A standardized mean difference of <0.1 was taken as an acceptable difference.(23) We used a linear regression model for costs and linear probability models for other outcomes, with robust standard errors to correct for heteroskedasticity. Statistical significance was defined as a p-value below 0.05. The DiD design assumes linear trends before the start of an intervention.(20) This assumption was tested with a joined F-test on the

pre-intervention quarters with an interaction term between time of first DTC in quarters and intervention group.(24) If the assumption was violated, the model was corrected for linear growth and cut off two years post-CCN start date.

Results

A total of 92,309 patients with colon cancer and 25,630 patients with pancreatic cancer were included. The mean age was 69.1 (95%-CI 9.0-69.1) and 68.5 (95%-CI 68.4-68.6) for colon and pancreatic cancer, respectively. The percentage of males was 49.7 and 52.5, respectively. Percentages with a high SES were 28.9 and 28.6, with a middle SES were 41.2 and 41.1, and with a low SES were 29.5 and 29.9, respectively. Percentage of metastasis was 19.1 and 38.4, respectively. Table 1 presents the descriptives of the patients per CCN and the control group. The results of the propensity score matching are presented in Appendix Tables S3 and S4.

Table 1. Descriptives of each CCN and the control group for the colon and pancreatic cancer populations

Colon cancer[1]	**CCN A (n=8,737)**	**CCN B (n=9,243)**	**CCN C (n=11,007)**	**CCN D (n=18,656)**	**Control (n=44,307)**
Age, mean (95% CI)	69.0 (68.8-69.3)	69.0 (68.7-69.2)	69.8 (69.6-70.0)	69.3 (69.1-69.5)	68.8 (68.7-69.0)
Male, %	48.7	48.9	50.2	50.6	49.6
SES, %					
Low	12.9	11.9	37.3	28.6	34.8
Middle	41.0	36.2	44.0	45.9	39.7
High	45.6	51.4	18.2	25.2	25.2
Unknown	0.5	0.5	0.5	0.3	0.3
Metastasis, %	18.4	20.7	19.8	19.3	18.7
Pancreatic cancer[2]	**CCN A (n=2,525)**	**CCN B (n=2,590)**	**CCN C (n=2,890)**	**CCN D (n=5,415)**	**Control (n=12,204)**
Age, mean (95% CI)	68.6 (68.2-69.1)	68.7 (68.3-69.1)	69.1 (68.7-69.5)	68.3 (68.0-68.6)	68.4 (68.2-68.6)
Male, %	52.7	52.2	52.8	52.8	52.3
SES, %					
Low	13.5	13.9	37.5	29.5	35.1
Middle	41.4	35.6	44.5	45.5	39.4
High	44.6	50.2	17.7	24.5	25.1
Unknown	0.5	0.4	0.4	0.5	0.3
Metastasis, %	32.4	40.5	41.2	35.1	40.1

[1] 359 colon cancer patients had missing hospital codes and were not appointed to a CCN or control group [2] 6 pancreatic cancer patients had unknown hospital codes and were not appointed to a CCN or control group

Mean two-year costs per CCN are presented in Figure 1 for colon cancer and Figure 2 for pancreatic cancer. For clarity, costs were smoothed; quartile data can be found in appendix figures S1-S2. For colon cancer, a decrease in mean two-year oncological costs was visible in all regions, with CCN C showing a significantly larger decrease than the control group. All CCNs started with higher costs than the control group. For pancreatic cancer, costs stayed relatively stable over time, with CCN A showing a significant larger decrease than the control group. This control group slightly increased over time. Two CCNs (CCN B and CCN D) showed a non-significant decrease, and CCN C showed a non-significant increase.

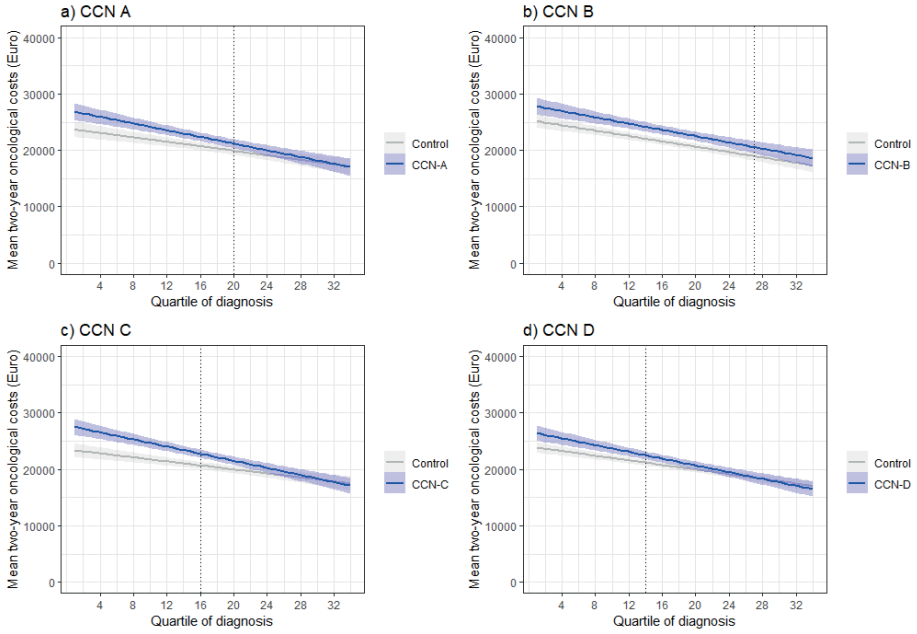

Figure 1. The smoothed mean two-year oncological costs in Euro for colon cancer with a) for CCN A, b) for CCN B, c) for CCN C and d) for CCN D

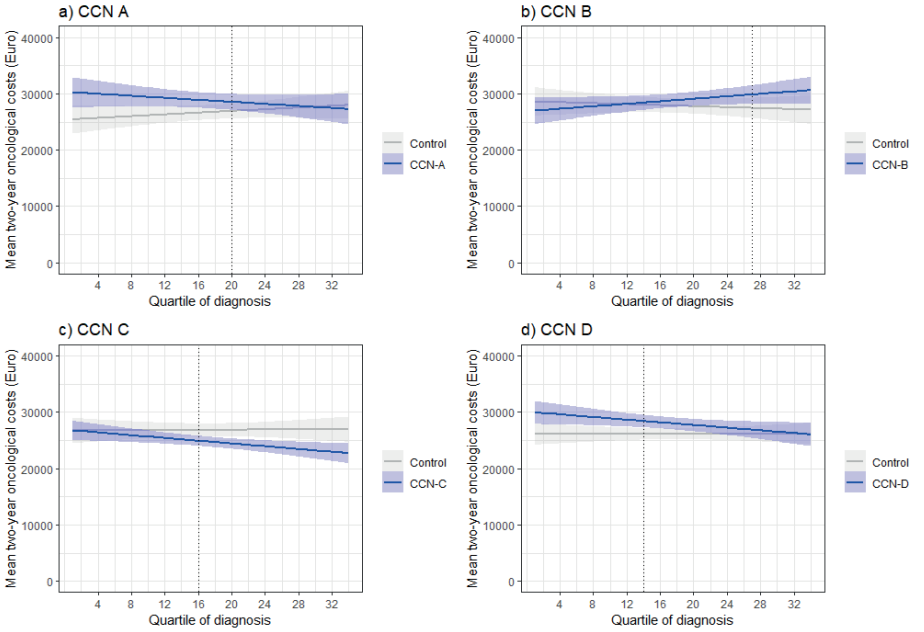

Figure 2. The smoothed mean two-year oncological costs in Euro for pancreatic cancer with a) for CCN A, b) for CCN B, c) for CCN C and d) for CCN D

The results from the DiD models are presented in Table 2. For colon cancer, lower two-year oncological costs were found for all CCNS but only significantly in CCN C (-€1,899). Referral rates showed mixed findings. CCN D showed a significant decrease in referrals of 3.6%, while CCN A showed a significant increase of 4.4%. Non-significant mixed effects on two-year mortality or double diagnostics were found. For pancreatic cancer, three CCNs showed reduced two-year oncological costs, but only for CCN A, the reduction was significant (-€3,747). Noticeably, all CCNs showed an increase in double diagnostics, but this was significant only for CCN A (+8.2%). Non-significant mixed findings on referrals and two-year mortality were found.

Appendix Figures S3-S14 present detailed data for two-year oncological costs, percentage two-year mortality, percentage referrals and percentage double diagnostic activities. For colon cancer, a decline in two-year mortality was visible in all CCNs and control group. There were no statistical differences. Two CCNs (CCN A and CCN B) and the control group showed an increase in referrals, of which the increase in CCN A was significant. For CCN C and CCN D, a significant decrease in referrals was visible, of which CCN D was significant. For all regions, a slight increase

in double diagnostic activities was visible, which was not significantly different. For pancreatic cancer, two-year mortality was relatively stable over time for all regions. Three CCNs (CCN A, CCN B and CCN D) and the control group showed a slight increase in referrals over time. CCN C showed a decrease in referrals over time. All regions show an increase in double diagnostic activities over time. The increase in CCN A is significantly larger than the control group.

Appendix Table S5 presents the analysis uncorrected for linear growth trends as sensitivity analysis. For colon cancer, referrals in CCN A changed from a non-significant reduction to a significant increase of 4.4% after correction. Referrals from CCN C changed from a significant 3.5% decrease to a non-significant increase. For colon and pancreatic cancer, the effect of CCN D on two-year oncological costs changed from a significant decrease of €1,715 and €2,755, respectively, to a non-significant decrease.

Table 2. Results of the difference-in-difference models for each CCN for colon and pancreatic cancer

Colon cancer	**CCN A**		**CCN B**		**CCN C**		**CCN D**	
	result	***p*-value**	**result**	***p*-value**	**result**	***p*-value**	**result**	***p*-value**
Mean two-year costs (€)	-1,347	0.13	-946	0.34	-1,899 *	0.01	-1,580[1]	0.26
% Two-year mortality	-0.4	0.74	-2.6	0.08	0.2	0.86	-0.2	0.86
% Referrals	4.4[1] *	0.03	1.1	0.32	-0.4[1]	0.85	-3.6 *	0.00
% Double diagnostics	0.2	0.30	-0.2	0.48	0.2	0.30	-0.2	0.19
Pancreatic cancer	**CCN A**		**CCN B**		**CCN C**		**CCN D**	
	result	***p*-value**	**result**	***p*-value**	**result**	***p*-value**	**result**	***p*-value**
Mean two-year costs (€)	-3,747*	0.04	2,463	0.20	-2,454	0.11	-2,103[1]	0.44
% Two-year mortality	1.9	0.45	-2.1	0.46	2.5	0.30	-1.6	0.39
% Referrals	-2.4	0.38	0.8	0.81	-4.0	0.12	3.4	0.08
% Double diagnostics	8.2 *	0.00	1.0[1]	0.67	0.6	0.59	1.1	0.23

* Significant with a p-value of 0.05

[1] Model corrected for linear trend

Discussion

This retrospective cohort study aimed to explore the effect of CCNs on oncological costs, survival rates and care processes for patients with a high-volume cancer (colon cancer) and a low-volume cancer (pancreatic cancer). In theory, CCNs reduce mortality and costs through enhanced coordination of processes such as referral or reduction in double diagnostics. CCNs are complex interventions that vary among different regions, and each CCN may have different structures, governance, and processes, which can influence their effectiveness. Therefore, we analysed each CCN separately in order to find common patterns. However, no consistent effects of CCNs on referral rates, double diagnostics, mortality or costs were found in this study.

For colon cancer, one CCN demonstrated a significant larger reduction in two-year oncological costs. It is important to note that costs were substantially higher before the start of this CCN in comparison to the control group. The CCN's significant cost reduction was not accompanied by a significant reduction in referrals. Another CCN showed a significant decrease in referrals but a non-significant reduction in costs, casting doubt on the causal mechanism of cost savings through referral reductions. A different CCN significantly reduced pancreatic cancer costs. Again, costs were substantially higher before the start of this CCN in comparison to the control group. An increase in referrals was expected. However, no significant effects were found. Furthermore, this CCN significantly increased double diagnostics activities. This also casts doubts on the causal mechanisms through with cost reductions were obtained in this CCN. While some, but not all, CCNs obtained cost savings, the causal mechanism through which these savings were obtained remains unclear.

The strength of this study is that it analyses the overall effects of multiple CCNs on a macro-level, contrary to most studies that focus on specific components of a CCN.(25) In the US, hospital networks were not associated with better surgical outcomes or reduced insurance costs.(26) A study evaluating pre- and post-periods of hospitals in a network demonstrated a reduction in annual surgical volume for smaller affiliated hospitals in a network for common surgeries, like colectomy. (27) In addition, they found a reduction in complications and mortality for smaller affiliated hospitals but an increase in complications and mortality for the primary tertiary referral centres for colectomy, likely due to a change in the patient population. Finally, they found no effect on costs. This could explain why, even if networks change referral patterns, this may not affect overall mortality or costs.

Methodological challenges in evaluating CCNs include the retrospective non-randomized design in which confounding differences occur between the control and intervention groups. In addition, the retrospective design and pre- and post-analyses of the intervention make it vulnerable to changes over time that are not related to the intervention. Our study addresses these challenges through propensity score matching and DiD models. Propensity score matching corrects for case-mix with known confounders. The DiD models correct for national changes by comparing differences in pre- and post-intervention periods between the intervention and control group. Our study additionally addresses the challenge of cost effects being influenced by price negotiation and agreements between hospitals and health insurance companies by using median cost prices for DTCs. However, some limitations remain. Confounding differences between hospitals and patient demographics across the different CCNs and the control group may persist, even after propensity score matching. Additionally, the start of a CCN may not be clearly delineated in time, with anticipatory effects and startup effects distorting the boundary between before and after. Furthermore, regions with CCNs do not have clear regional boundaries regarding collaborations between hospitals. Smaller networks or collaborations exist between hospitals within the CCN, as well as with hospitals in the control group or a different CCN. These are often bottom-up tumour-specific networks which consist of partnerships intended to regulate the care of patients with a specific tumour type. CCNs are based on oncological regions and are across these tumour-type networks. Different types of networks complicate collaboration between institutions and additionally complicate the assessment of the true impact of CCNs. In addition, within CCNs, financial arrangements for referrals can be made between hospitals where no DTC is opened in the referring hospitals. This could result in referrals missing in the data. Furthermore, spillovers between CCNs and control groups may be present, complicating isolating the effect of a CCN. For example, a national movement to establish volume norms starting in 2011 stimulated the concentration of pancreatic cancer surgery in expert centres.(28) As all regions have expert centra, concentration may be expected in all regions. Indeed, a slight increase in referrals for pancreatic patients over time was noted in almost all CCNs and the control region. These national trends complicate isolating the additional effect of CCNs. Furthermore, claims data are not the golden standard for identifying patients with pancreatic or colon cancer. Matching this data with, for instance, a cancer registry could have improved the identification of cancer patients and add more disease-specific data to improve case-mix correction. However, if misidentification rates are similar in CCNs and control regions, data limitations would have limited effects on outcomes. Additional care processes that could mediate outcomes, besides referrals and diagnostic activities, were not evaluated due to lack of data.

Last, a two-year cut-off post-CCN formation after a linear growth trend correction may underestimate CCN effects due to a limited time frame. For example, in CCN D, a linear trend correction due to violation of the common trend assumption was required, which resulted in a loss of significance.

Although limited evidence on benefits of CCNs was found, some variation in outcomes was observed. Future research could aim to disentangle the causal drivers of variations in outcomes and potential mechanisms to improve outcomes of CCNs. For example, qualitative research could focus on the mechanisms behind CCNs and how these different mechanisms affect costs, health outcomes and healthcare processes. Exploring underlying dynamics within CCNs will be crucial in understanding their true impact. Further analysis of specific components of CCNs, such as the governance structures or information exchange systems, could help identify best practices and areas for improvement. Future evaluations of CCNs could explore sub-populations for which CCNs are expected to be most impactful. For instance, CCNs may be especially impactful for low-volume surgical pancreatic cancer patients or patients with advanced cancer.

In conclusion, this study analysed effects of CCNs on costs, survival and care processes for both a high-volume and a low-volume cancer. Our study finds no consistent evidence that CCNs affect these outcomes. The observed effects may be influenced by time frame of evaluating CCNs and various regional and underlying factors. While CCNs hold promise for improving cancer care, more research is needed to understand their underlying dynamics and to determine the specific conditions or sub-populations for which they are most effective.

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Appendix

Table S1. Medical specialty and DTC's diagnoses descriptions used for the selection of the patient populations

Cancer type	Specialism (Specialism code)	Diagnosis (Diagnosis code)
Cancer of colon	General surgery (0303)	Malign neoplasm Colon (excluding sigmoid/rectum) (0333)
	General surgery (0303)	Peritonitis carcinomatosis of colorectal carcinoma without metastases elsewhere (Hyperthermic Intraperitoneal Chemotherapy, HIPEC) (0347)
	Internal medicine (0313)	Malign colorectal (0927)
	Gastroenterology (0318)	hereditary non-polyposis colorectal carcinoma (HNPCC) (0607)
	Gastroenterology (0318)	Colorectal malignancy (0610)
Cancer of pancreas	General surgery (0303)	Malign neoplasm pancreas / bile duct (0332)
	Internal medicine (0313)	Malignancy pancreas (0964)
	Gastroenterology (0318)	Pancreatic neoplasm (0755)

Table S2. Medical specialty and DTC's diagnosis codes for the selection of oncological DTC's

Cancer type	Specialism code	Diagnosis code
Cancer of bladder	0306	0030
	0306	0084
Cancer of bone & connective tissue	0305	1140
	0313	0841
	0313	0843
	0316	6107
	0361	0104
Cancer of brain & nervous system	0330	9921
	0304	0353
	0308	1101
	0308	1105
	0308	1110
	0308	1115
	0308	1120
	0308	1125
	0308	1130
	0308	1135
	0308	1140

Table S2. Continued

Cancer type	Specialism code	Diagnosis code
	0308	1810
	0308	2101
	0308	2105
	0308	2110
	0308	2115
	0308	2120
	0308	2125
	0308	2130
	0308	3101
	0313	0802
	0316	3505
	0316	6113
	0327	0316
	0330	0201
	0330	0202
	0330	0204
	0330	0211
	0330	0212
	0330	0213
	0330	0221
	0330	0222
	0330	0223
	0330	0231
	0330	0232
	0330	0233
	0330	0241
	0330	0242
	0330	0243
	0330	0251
	0330	0299
	0361	0108
Cancer of breast	0303	0318
	0313	0811
	0361	0105
Cancer of breast, secondary	0304	0221
	0304	0222

Table S2. Continued

Cancer type	Specialism code	Diagnosis code
	0304	0223
	0304	0224
	0304	0225
	0304	0226
	0304	0230
Cancer of bronchus, lung	0303	0313
	0313	0621
	0313	0622
	0322	1303
	0322	1304
	0328	1210
	0328	1220
	0328	1230
	0328	1240
	0328	1250
	0328	1270
	0328	1310
	0328	1340
	0328	1430
	0328	1440
	0328	1460
	0328	1470
	0328	1510
	0328	1530
	0328	1595
	0328	1420
	0361	0103
Cancer of colon	0303	0333
	0303	0347
	0313	0927
	0318	0607
	0318	0610
Cancer of oesophagus	0303	0319
	0313	0904
	0318	0307

Table S2. Continued

Cancer type	Specialism code	Diagnosis code
Cancer of female genital organs	0307	0M13
	0313	0822
	0307	0M14
	0307	0M15
	0307	0M16
	0307	0M99
	0307	0M11
	0307	0M12
	0313	0821
	0313	0823
	0361	0106
Cancer of Head & Neck	0303	0358
	0301	0358
	0302	0019
	0302	0020
	0302	0021
	0302	0040
	0302	0041
	0302	0042
	0302	0060
	0302	0061
	0302	0062
	0302	0063
	0302	0064
	0302	0065
	0302	0066
	0302	0067
	0302	0068
	0302	0069
	0302	0072
	0302	0084
	0303	0306
	0303	0354
	0313	0801
	0361	0101

Table S2. Continued

Cancer type	Specialism code	Diagnosis code
Cancer of kidney & renal pelvis	0306	0025
	0303	0370
	0306	0010
	0306	0016
	0313	0834
	0316	6116
Cancer of liver & bile duct	0303	0367
	0313	0955
	0316	6118
	0318	0712
	0318	0735
	0303	0348
Cancer of male genital organs & prostate	0306	0050
	0306	0060
	0306	0069
	0306	0092
	0313	0831
	0306	0040
	0306	0045
	0306	0048
	0313	0832
	0361	0107
Cancer of other GI organs, peritoneum	0303	0357
	0303	0331
	0318	0810
	0361	0102
	0303	0349
	0313	0979
Cancer of other respiratory & intrathoracic	0322	1305
	0322	1306
	0322	1307
	0303	0314
	0313	0623
	0313	0624
	0313	0629

Table S2. Continued

Cancer type	Specialism code	Diagnosis code
Cancer of other urinary organs	0306	0020
	0306	0070
	0306	0078
	0313	0833
	0313	0839
Cancer of pancreas	0303	0332
	0313	0964
	0318	0755
Cancer of rectum & anus	0303	0334
	0303	0335
Cancer of stomach	0303	0346
	0313	0914
	0318	0407
Cancer of thyroid	0303	0303
	0313	0214
	0313	0291
Cancer, other & unspecified primary	0316	6119
	0303	0352
	0303	0363
	0305	1150
	0305	1199
	0316	6115
	0316	6120
	0307	OM17
	0361	0111
	0313	0899
	0303	0359
	0318	0906
	0335	0211
	0361	0109
	0389	0100
	0308	1145
	0308	1150
	0313	0243
	0313	0263
	0313	0264

Table S2. Continued

Cancer type	Specialism code	Diagnosis code
	0303	0301
Melanoma	0302	0001
	0303	0350
	0313	0842
Secondary malignancies	0303	0360
	0305	1110
	0322	1308
	0330	0203
Other oncological diseases	8418	0513
Pain, due to malignancy	0389	0100
	0324	0715
Radiology (all)[1]	0362	All

[1] From the radiology specialty all diagnosis codes were include because it was not possible to distinguished oncological diagnoses

Table S3. Details of propensity score matching per CCN for colon cancer

	CCN A			CCN B		
	Means intervention (n= 8,737)	**Means Control (n= 8,737)**	**Stand. mean difference**	**Means intervention (n=9,239)**	**Means Control (n=9,239)**	**Stand. mean difference**
Age	69.0	68.9	0.0063	68.9	69.2	-0.0166
Male	0.4868	0.4885	-0.0034	0.4890	0.4904	-0.0028
SES						
• Low	0.1293	0.1293	0.0000	0.1195	0.1195	0.0000
• Middle	0.4100	0.4100	0.0000	0.3624	0.3624	0.0000
• High	0.4558	0.4564	-0.0014	0.5139	0.5137	0.0004
• *Living abroad*	0.0049	0.0042	0.0098	0.0042	0.0044	-0.0032
Metastasis	0.1842	0.1583	0.0667	0.2072	0.2072	0.1996
Distance	0.1996	0.1996	0.0002	0.2211	0.2211	0.0007

Table S4. Details of propensity score matching per CCN for pancreatic cancer

	CCN A			CCN B		
	Means intervention (n= 2,522)	**Means Control (n= 2,522)**	**Stand. mean difference**	**Means intervention (n= 2,586)**	**Means Control (n= 2,586)**	**Stand. mean difference**
Age	68.7	68.6	0.0059	68.7	68.5	0.0192
Male	0.5270	0.5258	0.0024	0.5213	0.5159	0.0108
SES						
• Low	0.1356	0.1356	0.0000	0.1388	0.1388	0.0000
• Middle	0.4144	0.4151	-0.0016	0.3561	0.3565	-0.0008
• High	0.4461	0.4461	0.0000	0.5027	0.5027	0.0000
• *Living abroad*	0.0040	0.0032	0.0111	0.0023	0.0019	0.0062
Metastasis	0.3247	0.3239	0.0017	0.4053	0.3863	0.0386
Distance	0.2087	0.2087	0.0002	0.2184	0.2183	0.0010

CCN C			CCN D		
Means intervention (n=10,981)	**Means Control (n=10,981)**	**Stand. mean difference**	**Means intervention (n=18,652)**	**Means Control (n=18,652)**	**Stand. mean difference**
69.8	70.1	-0.0229	69.3	69.6	-0.0223
0.5018	0.5089	-0.0142	0.5061	0.5102	-0.0081
0.3740	0.3672	0.0141	0.2862	0.2869	-0.0017
0.4411	0.4476	-0.0130	0.4586	0.4567	0.0039
0.1820	0.1824	-0.0012	0.2518	0.2543	-0.0058
0.0029	0.0028	0.0013	0.0034	0.0020	0.0231
0.1975	0.1706	0.0677	0.1932	0.1772	0.0403
0.2031	0.2031	0.0001	0.2997	0.2997	0.0013

CCN C			CCN D		
Means intervention (n= 2,888)	**Means Control (n= 2,888)**	**Stand. mean difference**	**Means intervention (n= 5,394)**	**Means Control (n= 5,394)**	**Stand. Mean difference**
69.1	69.1	0.0029	68.4	68.6	-0.0237
0.5280	0.5374	-0.0187	0.5276	0.5156	0.0241
0.3750	0.3684	0.0136	0.2959	0.2953	0.0012
0.4449	0.4526	-0.0153	0.4566	0.4575	-0.0019
0.1762	0.1756	0.0018	0.2453	0.2449	0.0009
0.0038	0.0035	0.0056	0.0022	0.0022	0.0000
0.4117	0.3979	0.0281	0.3517	0.3534	-0.0035
0.1961	0.1960	0.0018	0.3116	0.3114	0.0042

Table S5. Results of the difference-in-difference models for each CCN for colon and pancreatic cancer without correction for violation of the parallel trend assumption

Colon cancer	**CCN A**		**CCN B**		**CCN C**		**CCN D**	
	result	***p*-value**	**result**	***p*-value**	**result**	***p*-value**	**result**	***p*-value**
Mean two-year costs (€)	-1,347	0.13	-946	0.34	-1,899 *	0.01	-1,715 *	0.00
% two-year Mortality	-0.4	0.74	-2.6	0.08	0.2	0.86	-0.2	0.86
% Referrals	-0.5	0.60	1.1	0.32	-3.5 *	0.00	-3.6 *	0.00
% Double diagnostics	0.2	0.30	-0.2	0.48	0.2	0.30	-0.2	0.19
Pancreatic cancer	**CCN A**		**CCN B**		**CCN C**		**CCN D**	
	result	***p*-value**	**result**	***p*-value**	**result**	***p*-value**	**result**	***p*-value**
Mean two-year costs (€)	-3,747*	0.04	2,463	0.20	-2,454	0.11	-2,755 *	0.02
% two-year Mortality	1.9	0.45	-2.1	0.46	2.5	0.30	-1.6	0.39
% Referrals	-2.4	0.38	0.8	0.81	-4.0	0.12	3.4	0.08
% Double diagnostics	8.2 *	0.00	-2.0	0.19	0.6	0.59	1.1	0.23

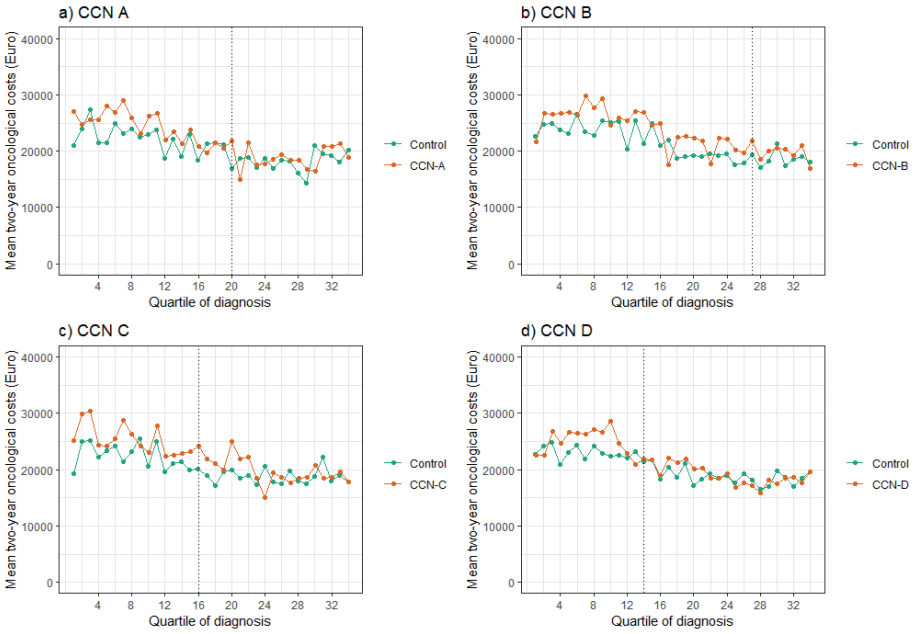

Figure S1. The mean two-year oncological costs in Euro for coloncancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

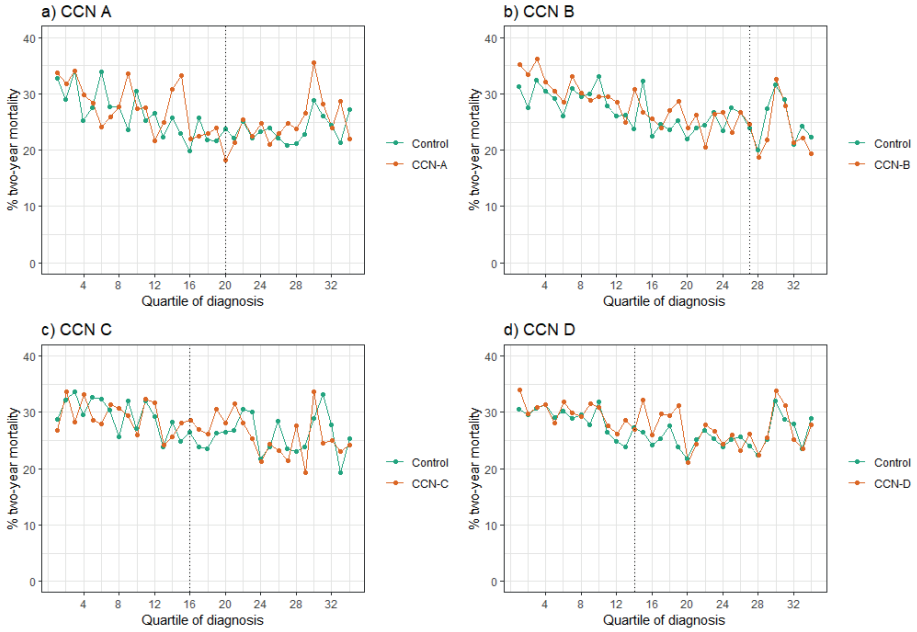

Figure S2. The percentage two-year mortality for coloncancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

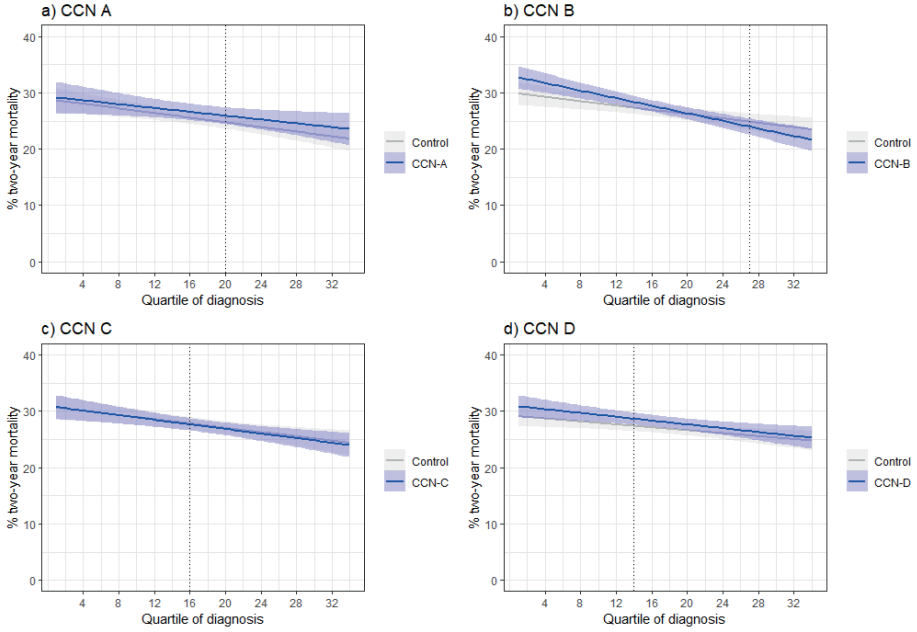

Figure S3. The smoothed percentage two-year mortality for coloncancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

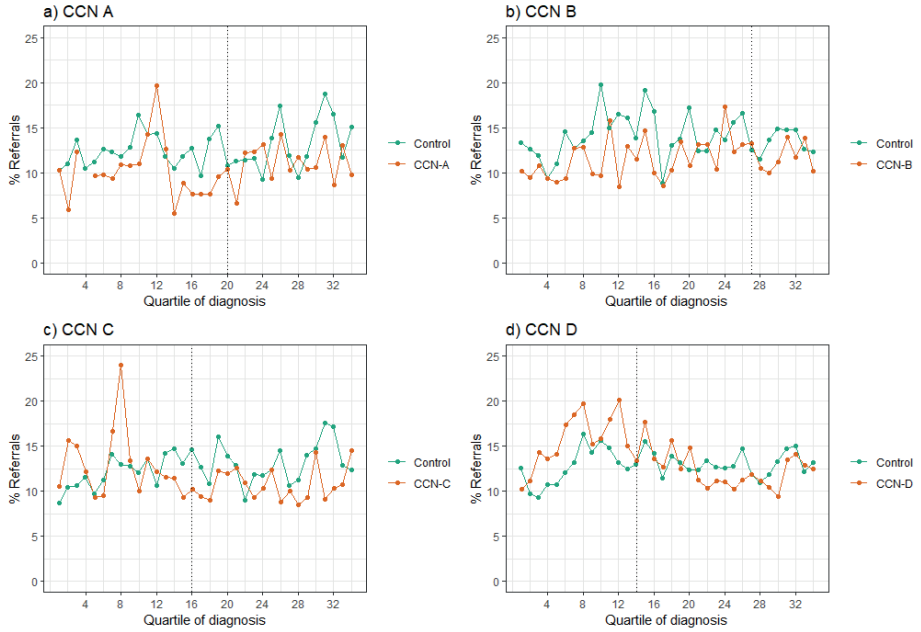

Figure S4. The percentage referrals for coloncancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

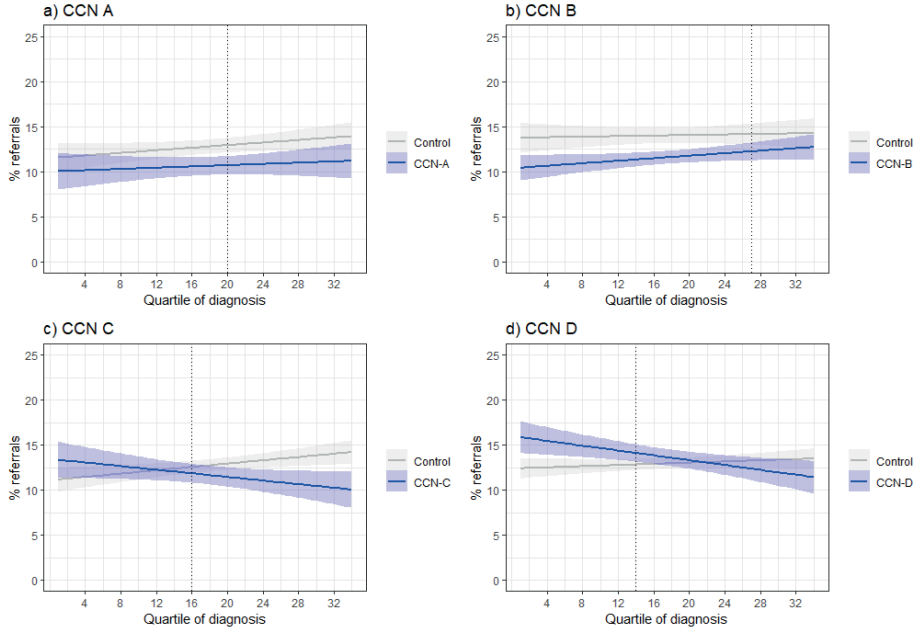

Figure S5. The smoothed percentage referrals for coloncancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

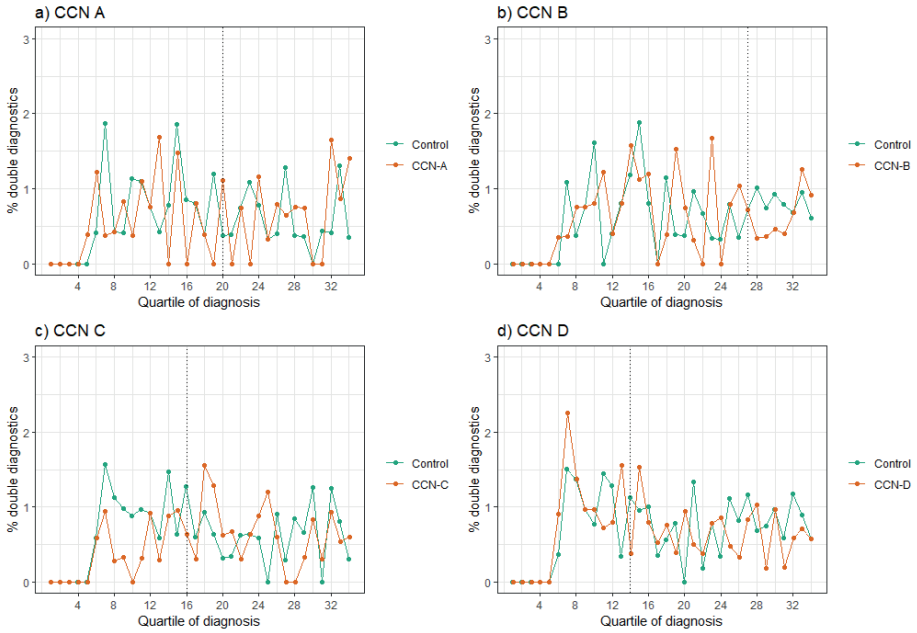

Figure S6. The percentage of double diagnostic activities for coloncancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

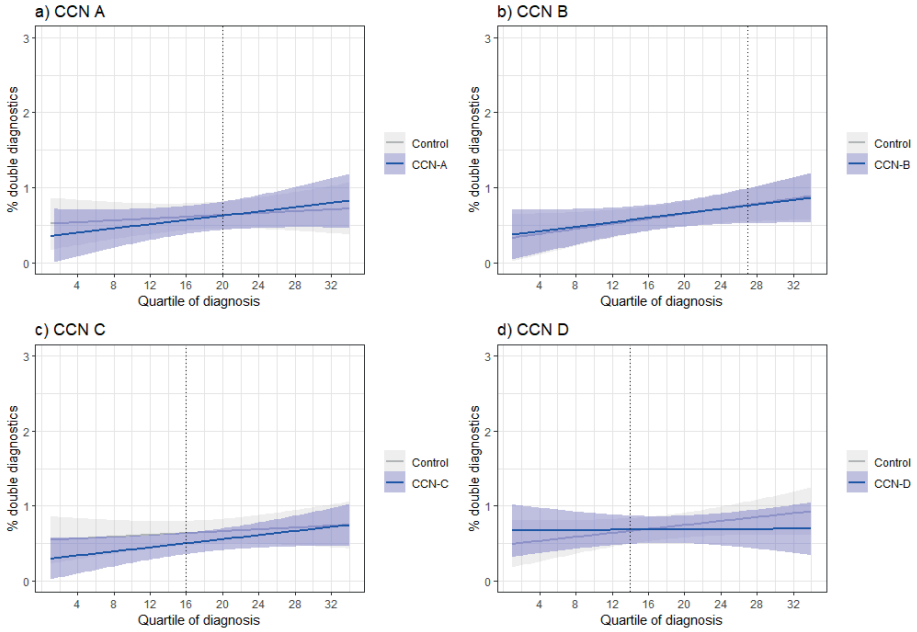

Figure S7. The smoothed percentage of double diagnostic activities for coloncancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

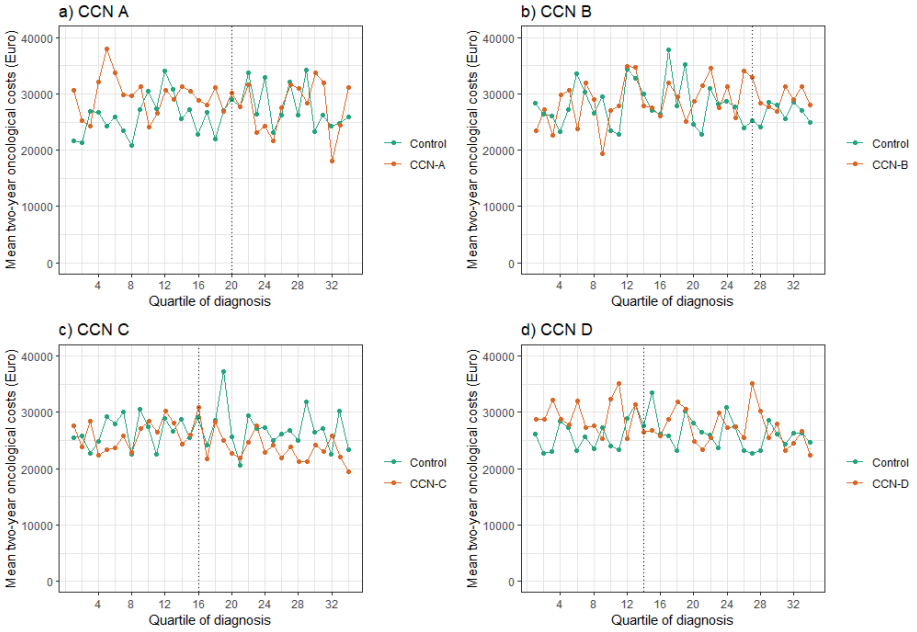

Figure S8. The mean two-year oncological costs in Euro for pancreatic cancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

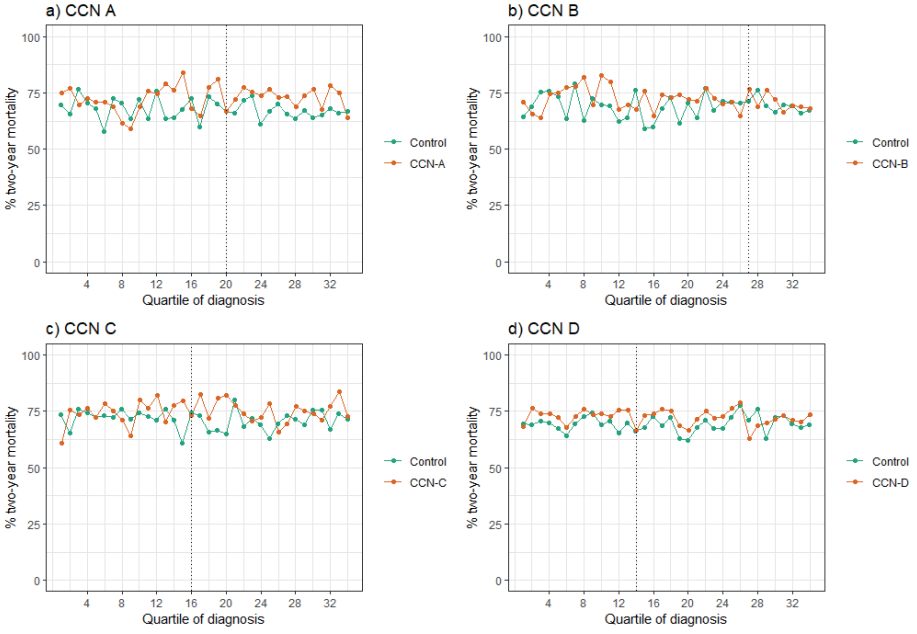

Figure S9. The percentage two-year mortality for pancreatic cancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

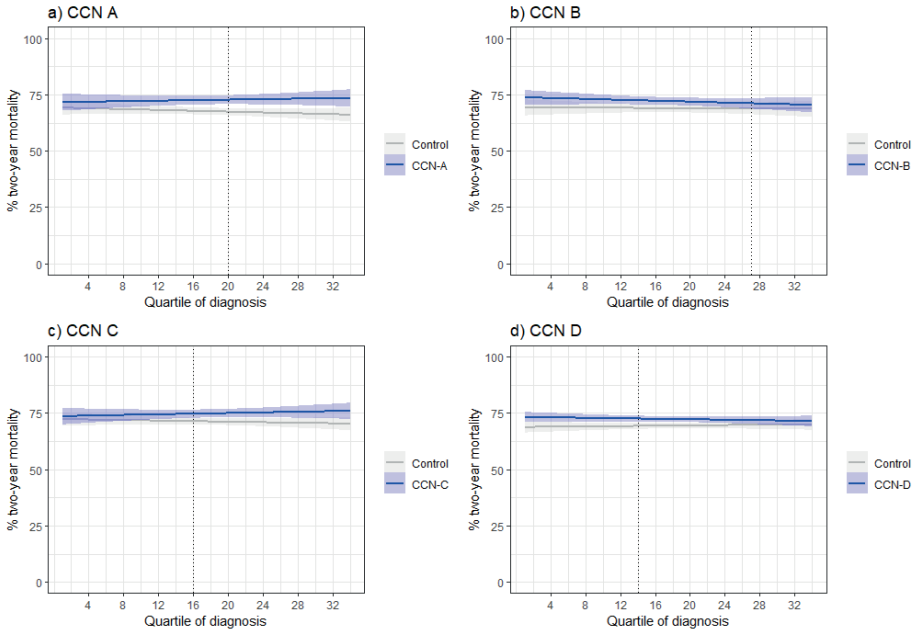

Figure S10. The smoothed percentage two-year mortality for pancreatic cancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

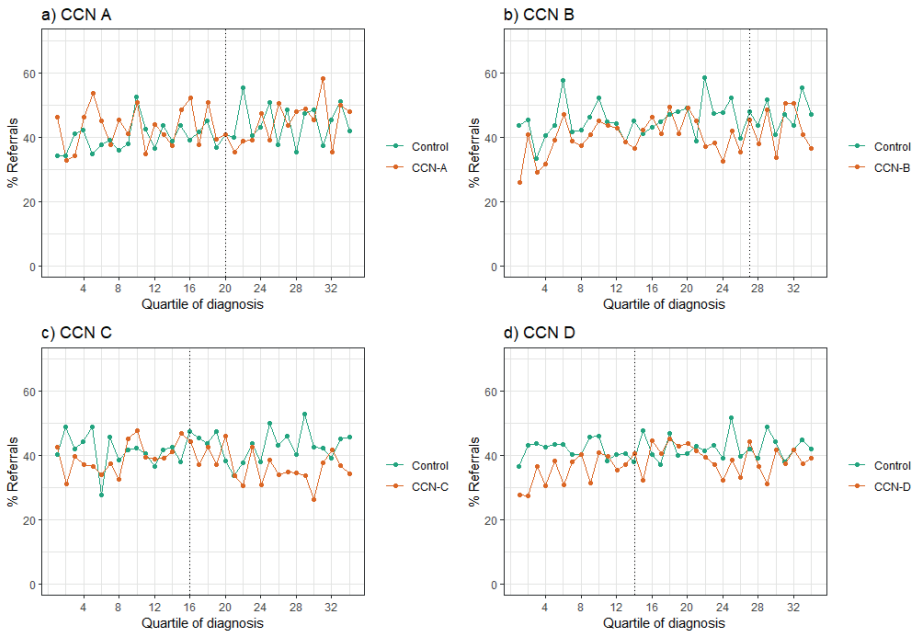

Figure S11. The percentage referrals for pancreatic cancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

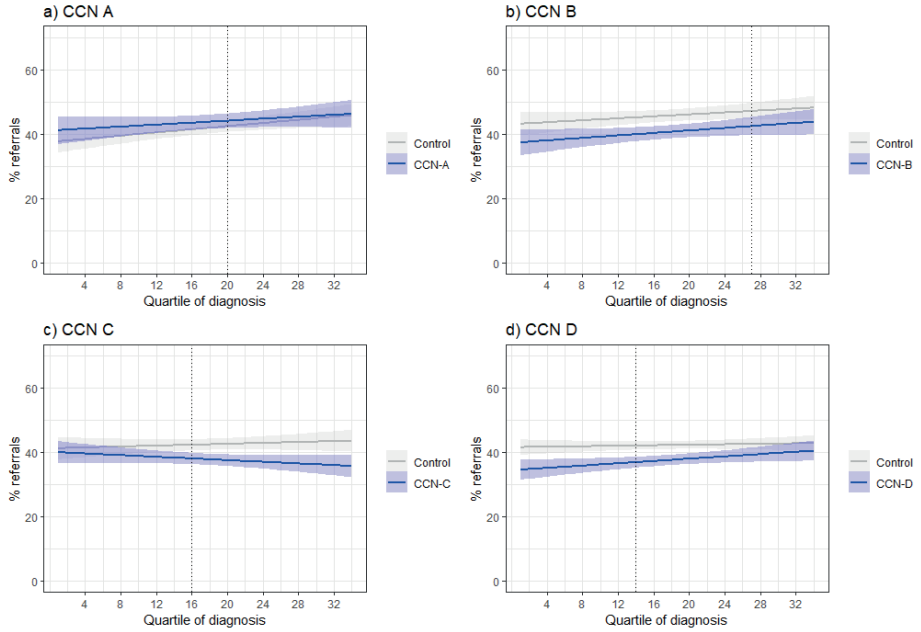

Figure S12. The smoothed percentage referrals for pancreatic cancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

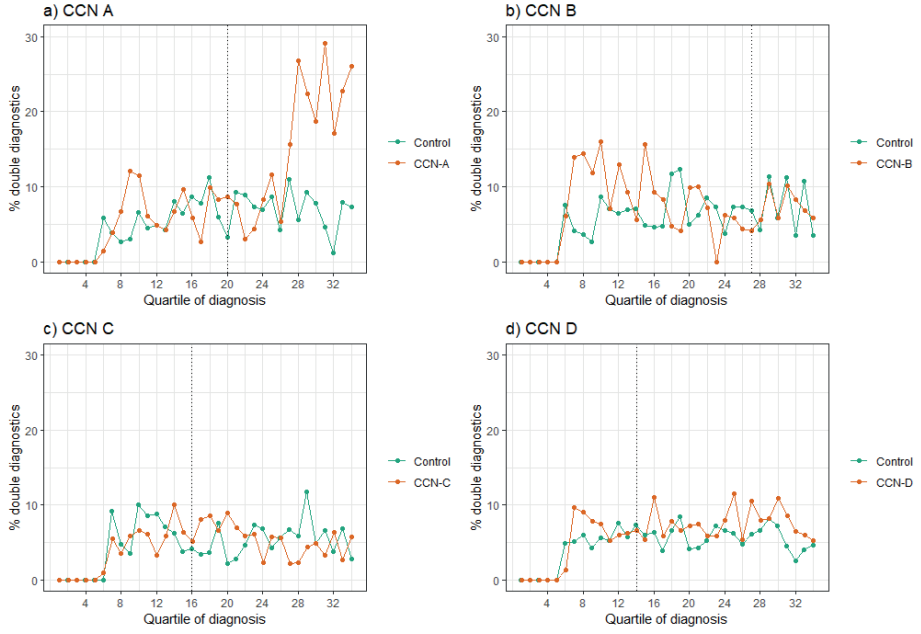

Figure S13. The percentage double diagnostic activities for pancreatic cancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

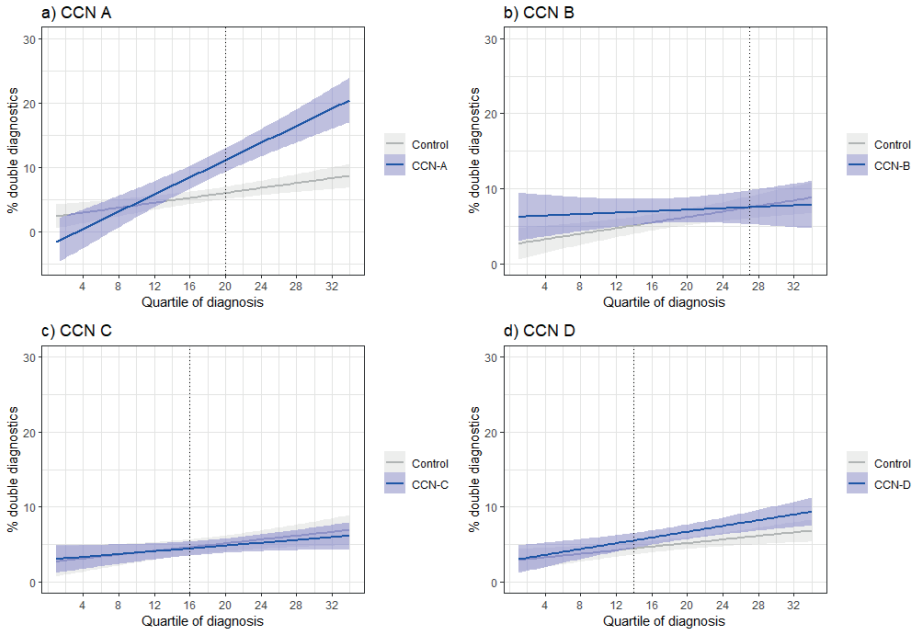

Figure S14. The smoothed percentage double diagnostic activities for pancreatic cancer with a) for CCN A, b) for CCN B, c) for CCN C, and d) for CCN D

Chapter 7

General Discussion

This thesis aimed to answer the question, 'How can we ensure sustainable and high-value oncological care in the face of rising demand and costs?'. We formulated the following research aims:

1) Explore two significant cost drivers in more depth, particularly comorbidity and expensive drugs
2) Explore the concept of 'value' in oncological care and strategies to maximise value with limited budgets
3) Study an alternative approach for organising care to potentially increase sustainability using Comprehensive Cancer Networks (CCNs)

The final chapter of this thesis presents the main findings, a discussion of the main findings, limitations, objectives for future research, recommendations, and overall conclusions.

Main findings

We present the main findings in bullet points per research aim.

Explore two significant cost drivers in more depth, particularly comorbidity and expensive drugs

- A large proportion of the oncological population deals with at least one comorbidity, increasing by 5.4% per decade. The average prevalence of comorbidities in the five most common cancer types together is 33.4%. They are most common in lung cancer (46.7%) and colorectal cancer (40.0%), followed by prostate (28.5%), melanoma (28.3%), and breast (22.4%). The most common types are hypertension (29.7%), pulmonary diseases (15.9%), and diabetes (13.5%).
- For metastatic non-small cell lung cancer, mean survival increased by 74.5 days after the introduction of immunotherapy. Mean healthcare costs per patient increased by €30,779, implying a cost-effectiveness of €150,796 per life year gained. Applying 20% and 40% discounts to immunotherapy medications lowers the cost-effectiveness to €125,614 per LYG and €100,769 per LYG, respectively. These discounts simulate those achieved by negotiations between the Dutch Ministry of Health and pharmaceutical companies.
- About 60% of the cost increase after the introduction of immunotherapy is directly due to claims for these drugs. A significant percentage of the cost

increases is also due to higher utilisation of care and increases in different claims, likely related to the administration or the side effects of immunotherapy.

Explore how we can maximise the value of oncological care with limited budgets

- A broad range of values matters to patients and involved stakeholders regarding new oncological treatments and decision-making in oncological care. These can be categorised in: 1) impact on daily life and future, 2) patient costs, 3) quality of life, 4) impact on loved ones, 5) societal impact, and 6) quality of treatment.
- The recognition and appreciation of the values might add to patient-level decision-making. For reimbursement decisions, it is less desirable to incorporate all patient values because of the need for efficient resource allocation.
- Different strategies can create value on a population level: 1) shared decision-making, 2) biomarkers and molecular diagnostics, 3) appropriate evaluation, payment and use of drugs, 4) address supportive care needs, 5) cancer prevention and screening, 6) monitoring late effects, 7) concentration of care and oncological networking, and 8) management of comorbidities.

Study an alternative approach for organising care to potentially increase sustainability using Comprehensive Cancer Networks (CCNs)

- In theory, CCNs reduce costs through enhanced coordination of processes such as referral or reduction in double diagnostics. In practice, CCNs do not consistently affect referral rates, double diagnostics or costs. One of the four studied CCNs significantly reduced mean two-year oncological costs for one high-volume cancer (colon cancer) with €1,899. A different CCN significantly reduced these costs for a low-volume cancer (pancreatic cancer) by €3,747. The other CCNs have non-significant mixed results.
- For colon cancer, one of the four CCNs significantly decreased referrals, and one significantly increased referrals. For pancreatic cancer, one CCN significantly increased repeated diagnostic activities. The other CCNs have non-significant mixed results for these outcomes.
- All CCNs do not significantly impact mortality.

Discussion of the main findings

We start discussing the main findings by exploring how comorbidity and expensive drugs influence quality of care and healthcare costs. Next, we discuss

what constitutes value in oncological care and how these values are incorporated into decision-making processes. This is followed by a discussion of how we can create value with constrained budgets in oncological care. The section ends with a discussion on if and how CCNs can contribute to creating value and keeping oncological care sustainable.

How do comorbidity and expensive drugs influence healthcare quality and healthcare costs?

In the Netherlands, the direct costs of oncological care were €6.5 billion in 2019, accounting for 6.7% of total healthcare expenditure.(1) Costs for oncological care are expected to further increase due to a combination of factors, such as an increase in cancer incidence. In the Netherlands, cancer incidence is expected to increase from approximately 118,000 in 2019 to 156,000 in 2032.(2) The increasing incidence of cancer has different causes: unhealthy lifestyle, improved cancer detection, and the increase in elderly. Additionally, life expectancy of the general population is increasing. Life expectancy is increasing partly because treatment options are improving across healthcare. For example, the number of patients dying from cardiovascular disease decreased from more than 49,000 in 2000 to less than 35,000 in 2020.(3) People who previously died from cardiovascular disease or other diseases are living longer and become at risk for cancer.

An initial reaction to these numbers could lead to the conclusion that this rising trend in cancer diagnoses is alarming for the fiscal sustainability of care. However, a shift from other diseases to cancer later in life will result in an increase in cancer incidence and a shift in costs, but not necessarily an increase. However, increases in healthcare costs can be caused by other things. Two major cost drivers are comorbidities and technological developments.

Comorbidity prevalence in patients with cancer is high, with an average of 33.4% and increasing by 5.4% per decade (**Chapter 2**). It is known that comorbidities increase healthcare utilisation and costs for individuals diagnosed with cancer (3, 4), and therefore, healthcare costs are likely to increase. For the most frequently reported comorbidity combination (the combination of cancer with a mental health condition in the first year after a cancer diagnosis) holds the highest cost.(5) Cancer in combination with depression has been found to increase overall healthcare costs by 113% in comparison to non-depressed cancer patients.(6) The cost of multiple diseases in combination has shown to be more than the costs of the component diseases individually.(7) A study from France in 2014 showed a per capita cost associated with cancer of €5,115 (95%-CI €4,322 - €5,909).(7) In combination with

heart disease, the costs associated with only the cancer was €5,443 (+€328), and in combination with diabetes, this was €6,240 (+€1,125). This demonstrates the additive costs in the case of disease interaction.

Comorbidities increase treatment costs, but they also challenge the organisation of care.(8, 9) For instance, fast innovations in the oncological field have led to improved health outcomes; however, they have also increased the complexity of care for those who struggle with cancer and comorbidities. This increase in the complexity of care increases the need for care specialisation. In itself, specialisation of oncological care and care concentration improves health outcomes.(10-12) However, a specialist in oncological care may be at risk of decreasing their generalist knowledge that is needed for the treatment of multimorbidity. Furthermore, care for these patients is complex as they often have to rely on several specialists and disciplines. Another significant concern with co- or multimorbidity is polypharmacy, the simultaneous use of multiple medicines by a patient for different conditions. Inappropriate polypharmacy can contribute to adverse reactions and treatment compliance.(13)

To overcome these hurdles, methods are needed to provide optimal holistic care for oncological patients with comorbidities. First, an appropriate clinical assessment of patients is required. Both the Eastern Cooperative Oncology Group (ECOG) Performance Status or World Health Organization (WHO) Performance Status are often used as screening tools in clinical practice to identify patients' performance status. The care of oncological patients should be multidisciplinary, with all medical disciplines involved in diagnosis and treatment. In addition, primary care physicians need detailed information and advice from secondary or tertiary care specialists on likely problems that are caused by cancer and its treatment. The high and rising number of comorbidities (**Chapter 2)**, emphasises the need for improvements in the different care pathways.

Besides comorbidities, the increase in healthcare costs is also affected by expensive technological developments. One example is new expensive drugs. With new drugs entering the market and the expansion of existing drugs to different oncological indications and treatment settings (for example, from advanced disease to (neo-) adjuvant treatment), the costs spent on oncological drugs do increase. A projection by the National Institute for Public Health and the Environment (RIVM) predicts that, without any interference, healthcare expenditure on cancer will grow from €5.6 billion in 2015 to €61 billion in 2060.(14) These numbers do not include costs for comorbidities. From an average annual growth of 5.4%, only 0.4 percentage points can be attributed to the demographics of an increasingly ageing population.

The vast majority of the growth is due to medical developments such as new expensive drugs. Currently, more than half of the costs of expensive drugs in the Netherlands are in oncological care.(15)

Survival gains for different oncological diseases, mainly haematological cancers, have shown immense progress in 5-year survival, with 48% in 2000 to 68% in 2017.(16) Survival gains can be due to organisational changes, improvement in diagnostics and current treatments, and the introduction of effective new drugs. Costs of drugs are the highest for haematological cancers, with a spending of more than €500 million in the Netherlands in 2021.(17) One example is the introduction of expensive tyrosine kinase inhibitors (TKIs) for patients with chronic myeloid leukaemia (CML). TKI substantially improved the life expectancy of CML patients; however, this comes with high costs.(18)

Another expensive cancer type is lung cancer, with a spending of almost €400 million in 2021. This tumour type has increased costs the most, with an increase of nearly €300 million between 2017 and 2021.(17) For lung cancer patients, 5-year survival increased from 13% in 2000 to 25% in 2017. However, for advanced stages of lung cancer, survival gains are still limited, while many expensive drugs are prescribed in this setting.(15) The median survival for metastatic NSCLC increased from 5.1 months in 2014-2016 to 7.0 months in 2019-2020 (**Chapter 3**). When correcting for case-mix, mean survival increased by 74.5 days. When exploring the metastatic NSCLC population in the Dutch Cancer Registry, the 75th percentile of survival has a steeper increase in median survival: median survival was 11 months in 2012 and 19 months in 2021 (see Figure 1).(17) This indicates that the top 25% of patients with the best survival experience even greater survival gains as a result of innovative medicines.

Real-world patients differ from patients included in clinical trials for new drugs. We present two studies that investigate these differences. A study by Westgeest et al compared patients with castration-resistant prostate cancer who participated in a trial in comparison to patients who did not participate.(19) Patients in trials were significantly younger and had fewer comorbidities. This will increasingly be a problem with the ageing population and the increase in the number of comorbidities (**Chapter 2**): the difference between real-world patients and patients in trials will further increase. A study by van der Welle et al. compared the real-world survival of patients with stage IV NSCLC who received immunotherapy to clinical trial data.(20) Progression-free survival times were comparable. However, overall survival was significantly lower for real-world patients.

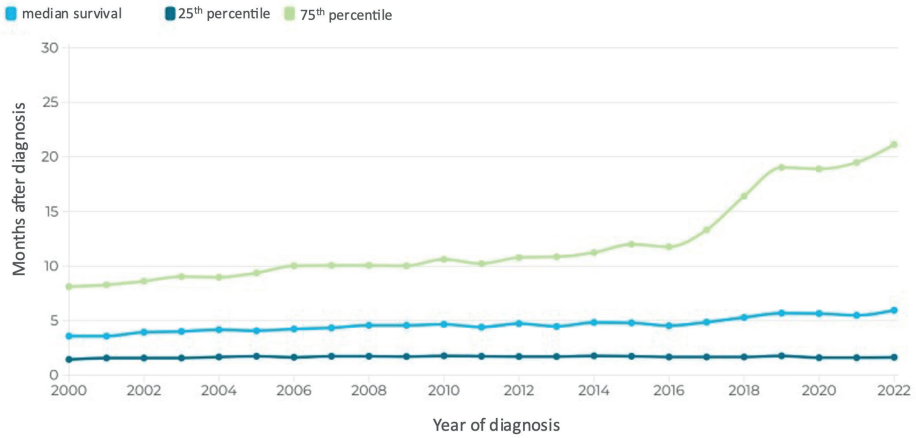

Figure 1. Number of months after diagnosis at which a quarter, half and three-quarters of all patients with metastatic NSCLC died. Source: IKNL (15)

It is essential to increase knowledge of treated patients and gain insights into which patients benefit from which (expensive) drugs. This is important for an individual patient but also for society as this may decrease unnecessary spending on expensive drugs in oncological care. Survival has increased for stage IV NSCLC patients after the implementation of immunotherapy, however, these survival benefits come with substantial cost increases (**Chapter 3**). A cost-effectiveness ratio of around €150,000 per life-year-gained (LYG) is estimated (**Chapter 3**). A study by Pichon-Riviere et al. calculated cost-effectiveness thresholds for 174 countries based on growth in life and health expenditures.(21) They found a cost-effectiveness threshold of $40,998 (€37,692) per LYG for the Netherlands. The €150,000 per LYG spent for stage IV NSCLC far exceeds this threshold. Allocating budget to immunotherapy for NSCLC comes at the cost of different other innovations or treatments that could improve healthcare quality; this is called opportunity costs. For instance, a study by van Baal et al. estimated opportunity costs of €30,000 per LYG in cardiovascular disease.(22)

On the brighter side, different developments might suppress the rise in oncological costs. First, oncological drugs that have been on the market longer lose their patents. Biosimilars can be produced at lower costs and with market competition. Drug prices are expected to decrease from 6.6% to 66% in a few years after patent expiry, depending on the country and the drug.(23) One example of a major cost reduction is lenalidomide, which lost its patent in 2022 and is expected to reduce costs in the Netherlands by €140 million annually.(24) The patent of the most distributed immunotherapy, pembrolizumab, expires in 2030. This could decrease the rising trend in oncological costs. In the Netherlands, 7,300 patients used pembrolizumab

in 2022, which generated total costs of €269 million.(25) Second, the increase in new medicines and the expansion to different oncological indications might, in the long term, increase competition among pharmaceutical companies and potentially lower the rise in costs. Third, an increase in confidential discounts between the Ministry of Health and the pharmaceutical companies is expected because more drugs are feasible for negotiations and the discounts themselves increase annually.(24) Fourth, certain national policies have the potential to decrease costs. In September 2022, healthcare parties in the Netherlands jointly created an integrated healthcare agreement (Integraal Zorg Akkoord, IZA).(26) The IZA formulates various agreements to limit the growth in expenditure on expensive drugs. These are, among others, more emphasis on cost-effectiveness before reimbursement and the possibilities for reassessing medicines after admission to the insurance package. IZA additionally emphasises the benefit of centralising oncological care and networking. Fifth, Artificial Intelligence (AI) can advance diagnostics and drug development and potentially reduce costs.(27) Lastly, *appropriate use* initiatives can potentially decrease costs.(24) Examples or these are:

- Reducing the waste of expensive drugs by re-dispensing unused oral anticancer drugs can save costs.(28)
- Exploring alternative dosages and treatment durations of expensive drugs.(29)
- Adjusting start or stop criteria of expensive drugs. For instance, exploring whether earlier discontinuation of expensive drugs is safe.(30)
- Boosting the effects of expensive drugs. For instance, combining drugs with specific food intake (31, 32), drinks (33), or a different drug (34) can enhance drug exposure, which can reduce the drug dosage needed.
- The use of biomarkers to measure response to expensive drugs.(35, 36)

What constitutes value in oncological care, and how are these values incorporated into decision-making processes?

Internationally, different frameworks exist to evaluate the value of oncological treatments.(37, 38) As we describe in our research report, *Societal Value in Oncology*, 'value' seems indefinable.(39) There are no agreements on domains that truly matter, how they should be incorporated into value-frameworks or how much weight should be given to each.(37) A broad range of values exist in the context of new (expensive) oncological treatments in the Netherlands (**Chapter 4**). These can be categorised in: 1) impact on daily life and future, 2) patient costs, 3) quality of life, 4) impact on loved ones, 5) societal impact, and 6) quality of treatment. These values are not fully incorporated in existing value-frameworks (**Chapter 4**) and existing value-frameworks seem inconsistent about the included attributes.(37, 38, 40)

In addition, a paper by Kaufman et al. illustrates that, especially in the era of immuno-oncology, attributes might be lacking in value-frameworks.(41) Immuno-oncology is different from other therapies and provides new attributes that should be considered in value frameworks. Besides an increased durability of responses, a more manageable side effect profile, and a better overall quality of life, immuno-oncology has the potential for limited treatment durations. These limited treatment durations allow patients to resume routine activities and work.(42)

In comparison to other European countries, the Netherlands already includes a broad range of values, either implicitly or explicitly in formal reimbursement decisions.(43) In the Netherlands, decision-making regarding coverage of expensive oncological treatments is (generally) carried out from a societal perspective by the National Healthcare Institute (*Zorginstituut Nederland*).(44) For example, a distinction is made between costs and benefits within healthcare for patients and families and other sectors. However, this societal perspective is not applied to all new treatments. For example, the National Healthcare Institute only evaluates the cost-effectiveness of treatments in the 'reimbursement lock', which are treatments with a high budget impact (of €10+ million per year or €50.000 per patient per year).(45)

Nevertheless, commonly used quality-of-life outcome measures in reimbursement decisions do not always seem adequate for mapping all benefits and costs; (46) they only contain a subset of outcomes that might be relevant for oncological patients.(40, 46, 47) For example, the Healthcare Institute mainly uses the EuroQol-5 dimensions (EQ-5D) questionnaire. This generic quality-of-life questionnaire can be used for every disease, in theory creating the conditions for fair resource allocation. However, condition-specific questionnaires (like the EORTC QLQ-30 for cancer patients) include more disease-specific values, but these questionnaires are less feasible for resource allocation.

Decision-making at the individual level, in the consultation room, has more opportunities to involve patient preferences (**Chapter 4**). Shared-decision making has gained more attention over the past years to increase patient value; however, this is still not fully implemented. Perceived barriers are, among others, emphasis on medical evidence by physicians, perceived lack of time, and lack of tools.(48, 49) In recent years, tools like the Distress Barometer (in Dutch *Lastmeter*) (50) have been developed to gain insights into the values that matter to a specific patient. In addition, many decision aids have been developed over the years, and patient-reported outcome measures (PROMS) are increasingly used in clinical practice.(51, 52)

Attention to shared decision-making and using these different tools can increase patient values at the individual level. Beyond shared-decision making, these tools can be beneficial to address values and needs for (ex-)cancer patients for supportive care. Supportive care needs for patients (and loved ones) could, among others, be psychological, sexual or work rehabilitation.(39)

How do we create value with constrained budgets in oncological care?

Incorporating all individual patient values in reimbursement decisions is less desirable (**Chapter 4**). In a narrative review (**Chapter 5**), we elaborate on how reimbursement decisions should be focused on efficiently allocating resources to maximise value for the entire population (not only specific oncological subpopulations), and therefore, comprehensive recognition of all individual patient values is unwarranted. In our narrative review, we provide different suggestions for strategies to increase the value of oncological care based on expert opinion and literature. Suggestions in the review include but are not limited to 1) greater implementation of shared decision-making, 2) studying, developing and organising biomarker testing and molecular diagnostics, 3) exploring and incorporating appropriate evaluation, payment and use of expensive cancer drugs, 4) further development of management of supportive care needs during and after cancer treatments, 5) research and implementation of effective strategies for cancer prevention and screening, 6) developing and studying the monitoring and management of late adverse effects of cancer and its treatment, 7) stimulating and study optimal ways to concentrate oncological care and organise oncological networking, and 8) developing effective management strategies for comorbidities.

Furthermore, in our narrative review (**Chapter 5**), we elaborate on how different preconditions exist to increase value with constrained budgets. These include strategic planning, the implementation of consistent cancer policies, the involvement of central bodies for funding and the follow-through of cancer policies. In addition, it is crucial to improve data availability. To overcome the limitations regarding data accessibility and sharing, interoperability and secure data sharing should be stimulated. Initiatives like standardised electronic health records, national registries, and privacy-preserving data-sharing may all increase data availability.

Can CCNs contribute to creating value and keeping oncological care sustainable?

In 2012, volume standards were set by the Society of Oncological Collaboration (Stichting Oncologische Samenwerking, SONCOS) in the Netherlands, leading to a concentration of specialised cancer.(53, 54) In addition, other quality requirements were established, such as the organisation of multidisciplinary meetings, maximum waiting times, and (obligatory) participation in clinical registrations.(54) Since 2012, SONCOS published new volume standards and quality requirements yearly. These movements have contributed towards more partnerships between hospitals.(55) A decade later, in September 2022, healthcare parties in the Netherlands jointly created the IZA. (26) The IZA recognises that significant improvements can be achieved by working more and better together within and between the various healthcare domains. Therefore, the IZA also stimulates the formation of oncological networks.

There are two types of oncological networks in the Netherlands: the tumour-type network and comprehensive cancer networks (CCNs).(56) Tumour-type networks are active everywhere in the Netherlands and often originate bottom-up. A tumour-type network is a partnership of two or more institutions intended to regulate the care of patients with a specific tumour type. The Netherlands had 153 known tumour-type networks in 2021.(57) It is expected that more networks exist; however, these are difficult to identify. In a CCN, institutions work together at the board of directors level to facilitate and safeguard the supply, quality and continuity of oncological care in the region across the tumour-type networks. CCNs include organisations with shared governance and pursue common goals through tumour management groups, multidisciplinary team discussions (MTDs), uniform cancer pathways, quality standards and systems for information exchange.(58) Such a CCN connects multiple tumour-type networks and possibly other regional stakeholders who have a role in oncological care.(59) The term 'Comprehensive' means that all regional care activities of networks are also integrally connected to the organisation of scientific research, training, education and innovation.

The Netherlands is divided into seven oncology regions, as presented in Figure 2. Six of these regions currently have a CCN: West (West-Nederland), South-West (Zuidwest-Nederland), Middle (Midden-Nederland), East (Oost-Nederland), South-East (Zuidoost-Nederland), and North-Holland Flevoland (Noord-Holland Flevoland) (56, 60). The boundaries of the CCNs are diffuse in practice; supra-regional referrals and collaboration always remain possible. Patients are also free to choose which hospital they go to, regardless of which oncology region they are part of.

Figure 2. Oncology regions in the Netherlands (56)

In theory, CCNs reduce mortality and costs through enhanced coordination of processes such as referral or reduction in double diagnostics. For high-volume cancers, it is expected that CCNs do either not affect or reduce referral rates, while for low-volume cancers, an increase is expected due to centralisation agreements. As care is better aligned within CCNs, with among other things, uniform cancer pathways and systems for information exchange, it is expected that double diagnostic activity will be reduced. However, in practice, there is no consistent evidence that CCNs affect healthcare costs, referrals and double diagnostic activities (**Chapter 6**). These findings may be influenced by the time frame of evaluating CCNs and various regional and underlying factors. CCNs appear not to influence two-year mortality. This is the case for colon cancer and pancreatic cancer, respectively, a high-volume cancer and a low-volume cancer. However,

CCNs are complex interventions that vary among different regions, and each CCN may have different structures, governance, and processes, which can influence their effectiveness.

Furthermore, regions with CCNs do not have clear regional boundaries regarding collaborations between hospitals. Tumour-type networks exist between hospitals within the CCN, as well as with hospitals outside the CCN. These tumour-type networks complicate the assessment of the true impact of CCNs and the other way around. However, both the CCNs and the tumour-type networks are expected to increase quality of care by, among other things, discussing patients in MTDs (61, 62), concentration of complex cancer care to high-volume hospitals (63-65) or creating multidisciplinary care pathways.(66, 67)

To give an example, 15 tumour-type networks exist for pancreatic cancer in the Netherlands.(68) These networks are formed around pancreatic cancer centres. Pancreatic centres have specialised multidisciplinary teams and perform pancreatic surgery. Non-pancreatic centres do not provide pancreatic surgery but provide diagnostics, chemotherapy and supportive care. Almost half of non-metastatic pancreatic cancer patients receive multicentre treatment.(69) The networks differ in size and organisation. Organisational differences include, among other things, the use of service level agreements (SLAs) for referrals, communication with general practitioners (GPs) or the organisation of MTDs.(68) Room for improvements includes agreements concerning diagnostic workup, use of SLAs, participation of pancreatic-centre clinicians in multidisciplinary teams of non-pancreatic centres and the exchange of patient information. Multicentre workup in pancreatic cancer networks can risk repeated diagnostic activities, a delayed time-to-diagnosis and a delayed time-to-treatment.(70) CCNs can contribute to these challenges and reduce variation between tumour-type networks by setting standards and facilitating, for example, the continuity of oncological care, SLAs, and systems for information exchange. However, top-down networks at regional level, in our case CCNs, are at risk of creating uncertainty and division within existing (tumour-type) networks.(71)

CCNs can have a role in creating value for patients beyond the medical-technical domain. In our research report, *Societal Value in Oncology*, we performed a first exploration of how CCNs can impact patient values.(39) We present different examples of initiatives. First, CCNs can align their approaches to incorporate supportive care and working groups for rehabilitation, psychosocial care, and supportive care. Second, less-equipped hospitals might benefit from networking

with well-equipped hospitals with, for example, rehabilitation doctors, occupational therapists, or physiotherapists. Third, networking might increase the visibility of initiatives, and providers can learn from each other's best practices. Last, if networks involve general practitioners (GPs) in setting up patient pathways and protocols, it can contribute to efficient referrals, information exchange with GPs, and supportive primary care.

Some scepticism towards oncological networking exists because networking for one specific disease does not necessarily increase coordination and continuity of care for comorbidities. Many different networks around different diseases are developing, for instance, ParkinsonNet (72) or DementiaNet (73). This might increase the coordination and continuity of care for a specific disease but does not necessarily resolve fragmentation of care between different diseases, which becomes more problematic as the number of patients with comorbidities increases (**Chapter 2**). This emphasises the need for flexible networks around the patient in addition to or instead of networking for specific diseases.

Limitations

Each study in this thesis has its own methodological strengths and limitations, which are discussed in the corresponding chapters. The overall thesis has multiple strengths. For instance, we shed light on many different aspects concerning the affordability of oncological care: comorbidity, immunotherapy for stage IV NSCLC, value in oncological care and its role in decision-making, and CCNs. We used a wide array of research methods: a systematic and narrative review, data analysis with claims and registry data, interviews, and a focus group. In addition, we studied many different types of cancer in this thesis. We studied comorbidity in the five most common cancers: breast, colorectal, lung, skin, and prostate cancer. We studied the cost and effects of immunotherapy in NSCLC, and we studied the effects of CCNs for colon- and pancreatic cancer. For each study, we had profound reasons for choosing a certain cancer type to best answer our main research question.

However, this thesis also has multiple limitations. First, some aspects are missing in this thesis to be able to fully answer the main question, 'How can we ensure the long-term sustainability of oncological care in the face of rising demand and costs?'. For example, prevention strategies for cancer are missing. Since a large part of cancers are preventable (33% in men and 44% in women (74)) research and implementation of effective cancer prevention and screening strategies is needed.

More aspects that are missing include but are not limited to shortages in the labour market, alternative payment models, and costly innovations in diagnostics, radiotherapy, and expensive drugs beyond immunotherapy for NSCLC.

Second, limiting our studies to the use of data from health claims and cancer registries results in the possibility that some patients have been missed or results are overestimated due to upcoding in claims data. If we had performed prospective studies, we could have included patients with the oncological diagnosis with clear selection criteria. On the other hand, using administrative data has enabled us to analyse large populations, increasing the generalizability of the results.

In line with this, if we used prospective study designs in our quantitative studies, we would have included additional data, for instance quality-of-life data. We thoroughly explored values for patients and involved stakeholders (**Chapter 4**); however, the perspective of the patient is underrepresented in the quantitative studies. It would have been beneficial to explore the impact of immunotherapies for stage IV NSCLC on quality of life (**Chapter 3**). The benefits of immunotherapy could go beyond survival alone. Additionally, this would have enabled us to calculate costs per quality-adjusted-life-year after the introduction of immunotherapy, which can be compared to a nationally set willingness to pay thresholds for expensive drugs. Furthermore, adding quality-of-life data and patient experiences could have given more insights into CCNs' impact on patients (**Chapter 6**). Patient experiences and quality of life data for oncological patients are not systematically gathered and are therefore not useable for retrospective studies.

Last, most of our studies are performed in the Netherlands, making generalizability of this thesis to other countries difficult. Our study on comorbidity prevalence (**Chapter 2**) included studies from all OECD countries, making the results more generalisable. Our study on values and its role in decision-making procedures regarding expensive drugs (**Chapter 4**) is performed in the Netherlands, which makes the results mainly generalisable to countries with comparable healthcare settings and values. However, the conclusion that a broad range of values exists for patients and involved stakeholders is expected to be generalisable. Our study on costs and effects of immunotherapy for stage IV NSCLC is from one region in the Netherlands (**Chapter 3**). Although this patient population is comparable to the Dutch patient population, it might slightly deviate from different countries. Finally, we explored CCNs in a Dutch setting (**Chapter 6**). While CCNs exist in different countries and even at a European level, the governance and context of these CCNs differ from each other nationally and internationally. Additional research is needed

to evaluate specific components and mechanisms to understand the impact of a CCN. The effectiveness of particular components might be generalisable to CCNs in different countries.

Future research

This thesis focuses on two main cost drivers: comorbidity and expensive medicines. For comorbidities, the adaptivity of oncological costs for patients with comorbidities should be further explored. In addition, more research on methods for optimal multidisciplinary and streamlined care for patients with comorbidity is needed. Regarding expensive medicines, we only evaluated immunotherapy in a stage IV NSCLC population. Existing research should continue on exploring the real-world cost-effectiveness of additional expensive diagnostics and treatments over different populations. Examples are whole-genome sequencing, CAR T-cell treatment, proton therapy, MR-Linac, and expensive drugs for (neo-)adjuvant treatment. We recommend to incorporate quality of life in these studies and emphasise the relevance of matching national claims data with cancer registries.

Future research on how to ensure the long-term sustainability of oncological care should not only focus on exploring cost drivers but should also entail research on ways to suppress rising costs. For instance, studies on *appropriate care initiatives* are recommended. Many of such initiatives are already being studied. Here, we recommend continued research on reducing the waste of expensive drugs, exploring alternative dosages and treatment durations, exploring different start and stop criteria, boosting the effect of drugs, and creating biomarkers to evaluate the impact of drugs.

Additionally, more research on incorporating values in decision-making procedures is needed. At a societal level, it should be established whether there is a need to expand further values incorporated in reimbursement decisions in the era of immuno-oncology. If this is the case, more research is needed on making explicit for different (oncological) indications, if and how disease-specific values can be systematically inventoried and incorporated in reimbursement decisions. At the individual level, much research is already being performed on how best to include patient values in decision-making procedures. We recommend this research continues and emphasise research on tools to improve shared decision-making and addressing supportive care needs.

How the organisation of oncological care can contribute to long-term sustainability should additionally be explored in more depth. For example, future research could aim to disentangle the causal drivers of variations between CCNs. In addition, qualitative research could focus on the mechanisms behind CCNs and how these different mechanisms affect costs, health outcomes and healthcare processes. Further analysis of specific components of CCNs, such as the governance structures or information exchange systems, could help identify best practices and areas for improvement. In addition, studies on the impact on the quality of life for patients and patient experience are needed. Beyond CCNs, studies on different forms of networking and their interactions could be performed. For example, tumour-specific networks, primary care networks, or flexible patient-centred networks, which include different specialities within a hospital but also specialists in primary care and even professionals outside the healthcare domain. The latter could be particularly important in the face of a rising comorbidity prevalence.

Recommendations

This thesis results in different recommendations for sustainable and high-value oncological care:

1) Developing effective management strategies for comorbidities in oncological patients with personal treatment plans and collaborations across healthcare professionals and organisations. The management of comorbidities requires collaboration between different professionals, healthcare organisations and disease-specific networks. Patients need personalised treatment plans that address cancer and comorbidity, additionally taking into account potential drug interactions and side effects.
2) Stimulating different methods for suppressing costs for expensive drugs. First, it is essential to gain insights into which patients benefit from which (expensive) drugs. This could be improved by further developing and organising biomarker testing, molecular diagnostics and imaging diagnostic tools. Investments are needed to ensure an appropriate organisation in which high-quality diagnostics are available for every eligible patient. Second, drugs that are already on the market and reimbursed could be re-evaluated based on real-world data from large national registries to gain insights into the cost-effectiveness of these drugs in a real-world setting. Third, further exploration of alternative payment models such as value-based pricing and risk-sharing. Fourth, it should be

explored how AI can advance drug development and diagnostics. Last, it is of great importance to continue promoting initiatives regarding appropriate use of expensive drugs. This includes reducing waste, exploring alternative dosages and intervals, adjusting start- and stop-criteria, and boosting drugs. (Inter)national spread of such initiatives should be stimulated.

3) Continued implementation of shared-decision making is recommended in which patients are well-informed about treatment options and a patient's context, values, and priorities are considered. What could aid the broader implementation of shared decision-making is 1) more awareness of the benefits of shared decision-making and incorporating this as a standard in the patient pathway, 2) generating more outcome information based on real-world data to inform and empower patients to make well-informed decisions, and 3) further development and stimulation of tools that systematically address patient values and provide the necessary information. Besides shared-decision making, continued development of tools or methods for addressing supportive care needs for cancer patients and cancer survivors is also recommended.
4) Evaluating and stimulating optimal ways to concentrate oncological care and organise oncological networking to increase the accessibility and quality of care. CCNs should collaborate with and contribute to challenges from tumour-type networks and reduce variation between them, standardising care protocols and facilitating, for example, the continuity of oncological care, SLAs, and systems for information exchange. For CCNs it is important to identify best practises and areas for improvement. It should be explored how CCNs and tumour-type networks interact and benefit from each other. Collaboration among CCNs is pivotal in which they share experiences and learn from each other. In addition, CCNs should be stimulated to enhance patient value by initiatives such as 1) aligning supportive care and creating interhospital workgroups on for instance paramedic or psychosocial care, 2) share initiatives and good practices, and 3) involving GPs in policy development.
5) Improve data availability to perform real-world studies on costs and effects. It should be stimulated and facilitated to merge claims data to cancer registries. This would facilitate re-evaluation of the cost-effectiveness of expensive drugs after reimbursement decisions and evaluation of other innovations. An example of this is SEER-Medicare database in the US, derived from the linkage between the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program with Medicare claims.(75) In addition, a more systematic collection of quality-of-life or patient satisfaction data is recommended to explore the effects

of new innovations (for instance, expensive drugs of oncological networks) on quality-of-life or patient satisfaction in retrospective studies with real-world data.

Conclusion

This thesis aimed to answer the question, 'How can we ensure sustainable and high-value oncological care in the face of rising demand and costs?'. We explored two important cost drivers (comorbidity and expensive drugs), explored how we can maximise value in oncological care with limited budgets and studied an alternative approach for organising oncological care to potentially increase sustainability.

Comorbidities and expensive drugs are significant cost drivers within oncological care. Comorbidities prevalence is high and will increase over time, while expensive drugs – with the example of immunotherapy for metastatic NSCLC – result in survival benefits but at a substantial increase in costs. We explored the concept of value in oncological care. Incorporating all individual patient values is desirable at patient-level decision-making but less desirable for reimbursement decisions. Instead of incorporating 'all' individual patient values in reimbursement decisions, we suggest alternative strategies that can contribute to increasing value with limited budgets, including but not limited to comorbidities, expensive drugs and oncological networking. Regarding oncological networking at a regional level – defined as CCNs - we found no consistent evidence of contributing to the sustainability of oncological care. Additionally, this thesis provides different recommendations to enhance the long-term sustainability of oncological care. These entail comorbidity management, methods for suppressing expensive drug costs, addressing patient-values in patient-level decision making, stimulating optimal ways for oncological networking, and improving data availability for research. More research is still needed to fully answer our main research question(s).

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Chapter 8

Summary
Dutch Summary (Samenvatting)

Summary

The global incidence of cancer rises due to ageing, lifestyle factors and advancements in screening and diagnostics. In addition, improved treatments and diagnostics have increased cancer survival rates, leading to more long-term survivors. At the same time, costs spent on cancer care are high and rising, driven by factors like the rising incidence and expensive medical advancements. Therefore, this thesis tried to answer the question, 'How can we ensure sustainable and high-value oncological care in the face of rising demand and costs?'. To answer this question, we formulated the following research aims:

1) Explore two significant cost drivers in more depth, particularly comorbidity and expensive drugs
2) Explore the concept of 'value' in oncological care and strategies to maximise value with limited budgets
3) Study an alternative approach for organising care to potentially increase sustainability using Comprehensive Cancer Networks (CCNs)

Comorbidity

Comorbidity is defined as the co-existence of a disorder in addition to a primary disease of interest. These comorbidities can create different challenges in oncological care. They can impact cancer diagnosis and treatment choices, affect treatment outcomes and increase healthcare utilisation and costs. In **Chapter 2,** we performed a systematic review to explore the prevalence and related trends of comorbidity for the five most common types of cancer: breast, colorectal, lung, skin and prostate cancer. In addition, we explored determinants of variation between studies. Our systematic review yielded 161 articles. We found that the weighted average prevalence of comorbidities in all five cancer types together is 33.4%. Comorbidities were the most common in lung cancer (46.7%) and colorectal cancer (40.0%), followed by prostate (28.5%), melanoma (28.3%), and breast (22.4%). Considerable variation existed between the data from the different studies. The characteristics of the patient population could partly explain this variation. However, this could also partly be explained by the study's characteristics, such as country, measurement tools, and data type. After adjusting for all determinants, a significant increase in comorbidities of 0.54% per year was found. The most common types of comorbidities were hypertension (29.7%), pulmonary diseases (15.9%), and diabetes (13.5%).

Our findings underline the importance of comorbidities management in cancer care, given that a large proportion of the oncological population deals with more diseases simultaneously. These high and rising numbers could be included in discussions on optimising clinical pathways and centralising specialised oncological care.

Expensive drugs

Lung cancer is the most common cancer worldwide, accounting for 11.9% of all cancer diagnoses. Of all lung cancer diagnoses, 81% comprises non-small cell lung cancer (NSCLC). Due to the innovations in cancer treatment with the introduction of immunotherapies and targeted therapies combined with higher incidence, the costs of NSCLC have continuously increased. For this reason, **Chapter 3** studies the costs and effectiveness of immunotherapy in patients with stage IV NSCLC. We performed a retrospective study with real-world data from four hospitals as part of a comprehensive lung cancer network. When comparing a cohort of patients before the introduction of immunotherapy (2014-2016) and after the introduction of immunotherapy (2019-2020), adjusted mean survival days increased by 74.5 (95% CI 44.8-105.2) days for patients with stage IV NSCLC. The probability of two-year mortality decreased by 22%.

On the other hand, total costs per patient increased by €30,779, implying a cost-effectiveness of €150,796 per LYG. About 60% of the cost increase is directly due to add-on claims for immunotherapy drugs, mainly pembrolizumab. Interestingly, a significant percentage of the cost increase is due to higher utilisation and increases in different claims, likely related to the administration of immunotherapy or the effects of immunotherapy. In the Netherlands, negotiations on prices of expensive drugs between pharmaceutical companies and the Ministry of Health lead to significant discounts. These discounts are not openly available. Applying discounts of 20% and 40% to immunotherapy medications in our study lowered cost effectiveness to €125,614 per LYG and €100,769 per LYG, respectively**.**

Overall, the survival increased for stage IV NSCLC patients after the implementation of immunotherapy. However, these survival benefits come with substantial cost increases due to increased costs of immunotherapy treatment and regular care. We emphasise that different strategies are needed to manage these costs without compromising patient outcomes. Examples of these are reducing waste, exploring alternative drug dosages or development of more biomarker testing.

'Value' within oncological care

Over the years, the needs and desires of individual patients have increasingly driven the force behind healthcare decisions. It is argued that current value frameworks do not consider the unique aspects of the evolving therapeutic landscape with targeted therapy, immunotherapy and more precision medicine. The aim of **Chapter 4** was to explore all value elements regarding new oncological treatments for patients with cancer and all stakeholders involved and to assess their implications in different decision-making procedures. We performed in-depth interviews and a focus group. Decision-making regarding expensive drugs can occur at various levels. We studied patient-level and reimbursement-level decision-making.

A broad range of values were revealed that matter to patients and involved stakeholders regarding new oncological treatments. They can be categorised into 1) impact on daily life and future, 2) patient costs, 3) quality of life (physical, psychological, social and spiritual), 4) impact on loved ones, 5) societal impact, and 6) quality of treatment. The recognition and appreciation of the values might add to patient-level decision-making, but the usefulness of reimbursement decisions is less clear. The values can also be used to empower patients with information and support during and after cancer treatment.

In **Chapter 5,** we elaborate on these outcomes by means of a narrative review. For reimbursement decisions, we argue that incorporating all patient values is not feasible because of the need for efficient resource allocation. The value debate should shift from incorporating 'all' possible individual patient values in reimbursement decisions to creating more value for the entire oncological population as a whole. The different strategies we address are: 1) shared decision-making, 2) biomarkers and molecular diagnostics, 3) appropriate evaluation, payment and use of drugs, 4) supportive care, 5) cancer prevention and screening, 6) monitoring late effects, 7) concentration of care and oncological networking, and 8) management of comorbidities. Strategic planning, consistent cancer policies, and data availability are essential preconditions to support these strategies.

Comprehensive Cancer Networks

In **Chapter 6**, we further explore one of the strategies addressed in **Chapter 5**: the concentration of care and oncological networking. To do this, we explored the effect of four Comprehensive Oncological Networks (CCN) in the Netherlands on oncological costs, survival rates and care processes for patients with high-volume cancer (colon cancer) and low-volume cancer (pancreatic cancer). A CCN comprises healthcare organisations that have joint governance and pursue common goals

through, among other things, tumour management groups, multidisciplinary team discussions, uniform cancer pathways, quality standards and systems for information exchange. In **Chapter 6**, we performed a retrospective cohort study comparing the pre- and post-implementation outcomes for each CCN to those of a control region. For colon cancer, one CCN demonstrated a significant larger reduction in two-year oncological costs. One CCN showed a significant decrease in referrals but a non-significant reduction in costs, casting some doubt on the causal effect of referral reductions on cost savings. A different CCN showed an increase in referrals and no significant impact on costs. No significant changes were found in mortality rate and double diagnostic activities for colon cancer patients. For pancreatic cancer, one CCN significantly reduced costs. Non-significant mixed effects were found in the other CCNs. One CCN significantly increased double diagnostics activities. No significant effect on referrals and mortality rates was found.

Overall, we found no consistent evidence that CCNs affect costs, survival and care processes. The time frame of evaluating a CCN and various regional and underlying factors may influence the observed effects. While CCNs hold promise for improving cancer care, more research is needed to understand their underlying dynamics and to determine the specific conditions or sub-populations for which they are most effective.

In **Chapter 7**, we tried to answer the research question 'How can we ensure sustainable and high-value oncological care in the face of rising demand and costs?' by discussing findings from the previous chapters. In addition, we address limitations and provide recommendations. We conclude that comorbidities and expensive drugs are indeed significant cost drivers for oncological care. Comorbidities prevalence is high and will increase over time, while expensive drugs – with the example of immunotherapy for metastatic NSCLC – result in survival benefits but at a substantial increase in costs. We explored the concept of value in oncological care and provided strategies to increase the value and sustainability of oncological care, including but not limited to comorbidities and expensive drugs. Regarding oncological networking – defined as CCNs - we found no consistent evidence of contributing to the sustainability of oncological care. Overall, we provide different strategies to enhance the long-term sustainability of oncological care. However, more research is still needed to fully answer our main research question.

Samenvatting

Wereldwijd komen er steeds meer nieuwe patiënten met kanker bij per jaar (incidentie). Dit komt door veroudering van de bevolking, leefstijlfactoren en verbeterde screening en diagnostiek. Daarnaast hebben verbeterde behandelingen de overlevingskansen bij kanker verhoogd, wat leidt tot meer overlevers. Tegelijkertijd zijn de kosten voor kankerzorg hoog en blijven deze stijgen. Dit komt door factoren zoals de toenemende incidentie en dure medische ontwikkelingen. Daarom probeert dit proefschrift de volgende vraag te beantwoorden: 'Hoe kunnen we betaalbare en waardevolle oncologische zorg waarborgen rekening houdend met een stijgende vraag en stijgende kosten?'. Om deze vraag te beantwoorden, hebben we de volgende onderzoeksdoelen geformuleerd:

1) Het verkennen van twee belangrijke kostendrijvers, namelijk comorbiditeit en dure medicijnen
2) Het verkennen van het concept van 'waarden' in de oncologische zorg en strategieën om waarde te maximaliseren met beperkte budgetten
3) Oncologische netwerkzorg bestuderen als een alternatieve wijze van de organisatie van zorg om de duurzaamheid te vergroten

Comorbiditeit

Comorbiditeit wordt gedefinieerd als het gelijktijdig hebben van een andere aandoening naast een primaire ziekte. Deze comorbiditeiten creëren verschillende uitdagingen in de oncologische zorg. Ze kunnen de diagnose en behandelingskeuzes van kanker beïnvloeden, de behandelresultaten beïnvloeden en het zorggebruik en de zorgkosten verhogen. In **Hoofdstuk 2** hebben we een systematisch literatuuronderzoek uitgevoerd om de prevalentie en gerelateerde trends van comorbiditeiten te verkennen voor de vijf meest voorkomende soorten kanker: borst-, darm-, long-, huid- en prostaatkanker. Daarnaast onderzochten we de determinanten van variatie tussen studies. Onze systematische review leverde 161 artikelen op. We ontdekten dat de gewogen gemiddelde prevalentie van comorbiditeiten bij alle vijf kankertypen samen 33,4% is. Comorbiditeiten kwamen het meest voor bij longkanker (46,7%) en darmkanker (40,0%), gevolgd door prostaatkanker (28,5%), huidkanker (28,3%) en borstkanker (22,4%). Er bestond aanzienlijke variatie tussen de gegevens van de verschillende studies. De kenmerken van de patiëntenpopulatie kunnen deze variatie deels verklaren. Dit kan echter ook deels worden verklaard door de kenmerken van de studie, zoals het land, de meetinstrumenten en het type gegevens. Na het corrigeren van alle determinanten werd een significante toename van comorbiditeiten van 0,54% per

jaar gevonden. De meest voorkomende soorten comorbiditeiten waren hypertensie (29,7%), longziekten (15,9%) en diabetes (13,5%).

Onze bevindingen benadrukken het belang van het managen van bijkomende ziekten in de kankerzorg, aangezien veel kankerpatiënten tegelijkertijd met meerdere ziekten te maken hebben. Deze hoge en stijgende aantallen zouden moeten worden meegenomen in discussies over het optimaliseren van behandeltrajecten en het centraliseren van gespecialiseerde kankerzorg.

Dure medicijnen

Longkanker is wereldwijd de meest voorkomende kanker, goed voor 11,9% van alle kankerdiagnoses. Van alle longkankerdiagnoses bestaat 81% uit niet-kleincellige longkanker (NSCLC). Door innovaties in kankerbehandeling met de introductie van immunotherapieën en doelgerichte therapieën in combinatie met een hogere incidentie, zijn de kosten van NSCLC enorm gestegen. Om deze reden bestudeert **Hoofdstuk 3** de kosten en effectiviteit van immunotherapie bij patiënten met uitgezaaide NSCLC. We voerden een retrospectieve studie uit met real-world data van vier ziekenhuizen die deel uitmaken van een longkankernetwerk. Bij het vergelijken van een cohort patiënten van vóór de introductie van immunotherapie (2014-2016) en na de introductie van immunotherapie (2019-2020), nam de gecorrigeerde gemiddelde overleving toe met 74,5 (95% CI 44,8-105,2) dagen voor patiënten met uitgezaaide NSCLC. De kans op overlijden binnen twee jaar na diagnose nam af met 22%.

Aan de andere kant stegen de totale kosten per patiënt met €30.779. Dit impliceert een kosteneffectiviteit van €150.796 per gewonnen levensjaar (LYG). Ongeveer 60% van de kostenstijging is te wijten aan directe declaraties voor immunotherapie, voornamelijk pembrolizumab. Een aanzienlijk percentage van de kostenstijgingen is ook te wijten aan de stijgingen in reguliere DBC-kosten. Dit is waarschijnlijk gerelateerd aan de toediening van immunotherapie of de effecten van immunotherapie. In Nederland leiden onderhandelingen over prijzen van dure medicijnen tussen farmaceutische bedrijven en het Ministerie van Volksgezondheid tot aanzienlijke kortingen. Deze kortingen zijn niet openbaar beschikbaar. Toepassing van kortingen van 20% en 40% op immunotherapie in onze studie verlaagde de kosteneffectiviteit tot respectievelijk €125.614 per LYG en €100.769 per LYG.

Over het algemeen is de overleving voor patiënten met uitgezaaide NSCLC toegenomen na de invoering van immunotherapie. Deze overlevingsvoordelen gaan echter gepaard met aanzienlijke kostenstijgingen vanwege de verhoogde

kosten van immunotherapiebehandeling en reguliere zorg. We benadrukken dat er verschillende strategieën nodig zijn om deze kosten te beheren zonder de uitkomsten voor patiënten te compromitteren. Voorbeelden hiervan zijn: het verminderen van verspilling, het verkennen van alternatieve medicijndoseringen of de ontwikkeling van meer biomarkeronderzoek.

'Waarde' binnen oncologische zorg

Door de jaren heen zijn de behoeften en wensen van individuele patiënten steeds meer de drijvende kracht achter gezondheidszorgbeslissingen. Er wordt gesteld dat de huidige waarde-kaders geen rekening houden met de unieke aspecten van het evoluerende therapeutische landschap met gerichte therapie, immunotherapie en meer precisiegeneeskunde. Het doel van **Hoofdstuk 4** was om alle waarde-elementen met betrekking tot nieuwe oncologische behandelingen voor patiënten met kanker en alle betrokken belanghebbenden te verkennen en hun implicaties in verschillende besluitvormingsprocedures te beoordelen. Besluitvorming over dure medicijnen kan op verschillende niveaus plaatsvinden. We bestudeerden besluitvorming op patiëntniveau en vergoedingsniveau met diepte-interviews en een focusgroep.

Een breed scala aan waarden werd onthuld die van belang zijn voor patiënten en belanghebbenden met betrekking tot nieuwe oncologische behandelingen. Ze kunnen worden gecategoriseerd in 1) impact op dagelijks leven en toekomst, 2) patiëntkosten, 3) kwaliteit van leven (fysiek, psychologisch, sociaal en spiritueel), 4) impact op naasten, 5) maatschappelijke impact, en 6) kwaliteit van behandeling. De erkenning en waardering van deze waarden-elementen kan bijdragen aan besluitvorming op patiëntniveau, maar het nut voor vergoedingsbesluiten is minder duidelijk. De waarden kunnen ook worden gebruikt om patiënten te informeren en te ondersteunen tijdens en na de kankerbehandeling.

In **Hoofdstuk 5** gaan we dieper in op deze uitkomsten door middel van een narratief review. Voor vergoedingsbeslissingen stellen we dat het incorporeren van alle patiëntwaarden niet haalbaar is vanwege de noodzaak van efficiënte toewijzing van middelen. Het waarde-debat moet verschuiven van het opnemen van 'alle' mogelijke individuele patiëntwaarden in vergoedingsbesluiten naar het creëren van meer waarde voor de gehele oncologische populatie als geheel. De verschillende strategieën die we bespreken zijn: 1) gedeelde besluitvorming, 2) biomarkers en moleculaire diagnostiek, 3) geschikte evaluatie, betaling en gebruik van medicijnen, 4) ondersteunende zorg, 5) kankerpreventie en screening, 6) monitoring van late effecten, 7) concentratie van zorg en oncologisch netwerken,

en 8) management van comorbiditeiten. Strategische planning, consistente kankerbeleid en beschikbaarheid van data zijn essentiële voorwaarden om deze strategieën te ondersteunen.

Oncologische netwerkzorg

In **Hoofdstuk 6** verkennen we een van de strategieën die in **Hoofdstuk 5** wordt besproken: de concentratie van zorg en oncologisch netwerken. Hiervoor onderzochten we het effect van vier regionale oncologische netwerken (CCNs) in Nederland op oncologische kosten, overlevingspercentages en zorgprocessen voor patiënten met hoog-volume kanker (darmkanker) en laag-volume kanker (alvleesklierkanker). Een CCN bestaat uit zorgorganisaties die een samenwerking hebben op het niveau van de Raad van Bestuur en gemeenschappelijke doelen nastreven door onder andere tumormanagementgroepen, multidisciplinaire teamdiscussies, uniforme kankertrajecten, kwaliteitsnormen en systemen voor informatie-uitwisseling. In theorie verminderen CCN's de mortaliteit en kosten door verbeterde coördinatie van processen zoals verwijzing of vermindering van dubbele diagnostiek. In **Hoofdstuk 6** voerden we een retrospectieve cohortstudie uit waarbij we de uitkomsten voor- en na-implementatie van CCNs vergeleken met die van een controlegroep.

Voor darmkanker toonde een van de vier CCNs een significant grotere daling van de twee-jaar oncologische kosten. Een ander CCN liet een significante afname van het aantal doorverwijzingen zien, maar een niet-significante daling van de kosten, wat enige twijfel doet rijzen over het causale effect van minder doorverwijzingen op kostenbesparingen. Een ander CCN liet een toename van het aantal doorverwijzingen zien en geen significante impact op de kosten. Er werden geen significante veranderingen gevonden in de sterftecijfers en dubbele diagnostische activiteiten voor darmkankerpatiënten. Voor alvleesklierkanker verlaagde één CCN de kosten significant. Niet-significante gemengde effecten werden gevonden in de andere CCN's. Eén CCN verhoogde de dubbele diagnostische activiteiten significant. Er werd geen significant effect op doorverwijzingen en sterftecijfers gevonden.

Over het geheel genomen vonden we geen consistent bewijs dat CCN's kosten, overleving en zorgprocessen beïnvloeden. De tijdsperiode voor het evalueren van een CCN en verschillende regionale en onderliggende factoren kunnen de waargenomen effecten beïnvloeden. Hoewel CCN's veelbelovend zijn voor het verbeteren van de kankerzorg, is er meer onderzoek nodig om hun onderliggende dynamiek te begrijpen en om de specifieke omstandigheden of subpopulaties te bepalen waarvoor ze het meest effectief zijn.

In **Hoofdstuk 7** proberen we de onderzoeksvraag ''Hoe kunnen we betaalbare en waardevolle oncologische zorg waarborgen rekening houdend met een stijgende vraag en stijgende kosten?' te beantwoorden door de bevindingen uit de voorgaande hoofdstukken te bespreken. Daarnaast behandelen we beperkingen en doen we aanbevelingen. We concluderen dat comorbiditeiten en dure medicijnen inderdaad significante kostenfactoren zijn voor oncologische zorg. De prevalentie van comorbiditeiten is hoog en zal in de loop van de tijd toenemen, terwijl dure medicijnen – met als voorbeeld immunotherapie voor uitgezaaide NSCLC – overlevingsvoordelen opleveren maar tegen aanzienlijke kostenstijgingen. We hebben het concept van waarde in oncologische zorg onderzocht en strategieën aangedragen om de waarde en duurzaamheid van oncologische zorg te vergroten, waaronder maar niet beperkt tot, comorbiditeiten en dure medicijnen. Wat betreft oncologisch netwerkzorg – gedefinieerd als CCN's – vonden we geen consistent bewijs dat het bijdraagt aan de duurzaamheid van oncologische zorg. Over het geheel genomen bieden we verschillende strategieën om de lange termijn duurzaamheid van oncologische zorg te verbeteren. Er is echter meer onderzoek nodig om onze hoofdonderzoeksvraag volledig te beantwoorden.

Addendum

Research Data Management

Ethics & Privacy

All studies in this thesis were conducted in accordance with the Declaration of Helsinki and the guideline of Good Clinical Practice. Approval from the Medical Ethics Review Committee of the Radboudumc (CMO Radboudumc) was obtained for the studies presented in Chapter 3 and Chapter 4 (file number 2021-13025). The studies were exempted from Dutch National Law (Medical Research Involving Human Subjects Act (WMO)). Digital informed consent (IC) was obtained from participants in Chapter 4 to collect and process their data for this research project. No IC was asked for sharing and reuse of the data. The privacy of the participants in these studies was warranted by the use of pseudonymization. Other studies in this thesis were studies on literature (Chapter 2 and Chapter 5) or from existing national claims data (Chapter 6). These did not require approval of the Medical Ethics Review Committee. We did not collect IC for Chapter 3 and Chapter 6 because we made use of existing data from national registries. The data of Chapter 3 and Chapter 6 are pseudonymized by third parties. We do not have identifiable information of the participants from these studies.

Data Collection and storage

For Chapter 4, the ICs and pseudonymization key were stored on a secured network drive that was only accessible to two members of the project who needed access to it because of their role within the project. The ICs and pseudonymization key were stored separately from the research data. Raw and processed data from Chapter 2, Chapter 3, Chapter 4 and Chapter 6 is stored on a Radboudumc IQ Health department server.

Data availability

All manuscripts within this thesis have been published open access (chapter 2, 4, 5) or will be published as such (chapter 3 and 6). Meta data, raw data and SPSS and Stata syntaxes of Chapter 2 are findable and accessible in the Data Archiving and Networked Services (DANS) EASY archive. All DOIs are presented in the table below. In Chapter 4, no IC was asked for reuse and sharing of the data which makes reuse and sharing of the data impossible. Besides the Radboudumc IQ Health department server, this data is archived for 10 years in Data Acquisition Collection (DAC) of the Radboud Data Repository. The data underlying Chapter 3 and Chapter 6 are data from third parties (Netherlands Comprehensive Cancer Organisation (IKNL) and Vektis) and are only usable for the research project for which the data was requested. Reuse and sharing of the data is not possible without permission of the

third parties. Besides the Radboudumc IQ Health department server, the data will be archived for 15 years in DACs after termination of the studies.

Chapter	***DANS-EASY***	***DAC***	***License/Data Use Agreement***
2	*https://doi.org/10.17026/dans-zfp-ybfq*		*CC BY 4.0*
3		*https://doi.org/10.34973/jvav-8q93*	*CC-BY-NC-ND-4.0/ RUMC-RA-DUA-1.0*
4		*https://doi.org/10.34973/5gpj-0246*	*CC-BY-NC-ND-4.0/ RUMC-RA-DUA-1.0*
6		*https://doi.org/10.34973/hnf2-8y32*	*CC-BY-NC-ND-4.0/ RUMC-RA-DUA-1.0*

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Submitted papers

Vrinzen CEJ, Stadhouders N, van den Heuvel M, Atsma F, Hermens RPMG, Merkx MAW, Jeurissen PPT, Bloemendal HJ. Healthcare costs and survival in the era of immunotherapy for stage IV non-small cell lung cancer.

Vrinzen CEJ, Stadhouders N, Bloemendal HJ, Hayen A, Reitsma J, ten Hove M, Jeurissen PPT, Merkx MAW, Hermens RPMG. Comprehensive Cancer Networks in the Netherlands: how do they affect quality and costs of care for patients with colon- or pancreatic-cancer?

About the author

Cilla Vrinzen was born in Roermond on the 3rd of January 1996. After completing her pre-university education, she pursued a Bachelor's degree in Biomedical Sciences at Radboud University in 2014. Following the completion of her Bachelor's, she continued her studies with a Master's degree in Biomedical Sciences at the same university. During her Master's, she specialized in Health Technology Assessment, Consultancy, and Health Systems. To further expand her knowledge, she also took two additional courses at Maastricht University: Economics of Healthcare and Organizing and Managing Patient Flows.

Throughout her Master's program, Cilla completed two internships. The first was a research internship at the Department of Operating Rooms at the Radboudumc, where she explored the potential value of different innovative strategies for the Helicopter Emergency Medical Services. The second was a consultancy internship at VGZ, a health insurance company, where she investigated possibilities of shifting hospital care to homecare.

After graduating Cum Laude, Cilla began her PhD in 2020 at the IQ Health department of the Radboudumc. Her PhD project focused on exploring and improving the affordability and organization of oncological care in the Netherlands. Simultaneously, she joined the Netherlands Comprehensive Cancer Organization (IKNL) as a project assistant, where she assisted in research projects and had the opportunity to be part of establishing the team *Passende Zorg*.

Throughout her PhD, Cilla developed a strong interest in the organization and affordability of healthcare, as well as in data analysis and data science. To further enhance her skills in this area, she completed an additional course in Artificial Intelligence in Healthcare. She plans to apply her knowledge and continue developing her expertise in data science at VGZ.

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*

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*

PhD portfolio of Cilla Vrinzen

Department: **IQ Health**
PhD period: **02/08/2020 – 31/07/2024**
PhD Supervisor(s): **prof. dr. P.P.T. Jeurissen, prof. dr. H.J. Bloemendal, prof. dr. M.A.W. Merkx, prof. dr. R.P.M.G. Hermens**

Training activities	Hours
Courses	
• RIHS - Introduction course for PhD candidates (2020)	15.00
• Introductiecursus Kwalitatief Onderzoek in de Gezondheidszorg (2021)	16.00
• RU - Scientific Writing for PhD candidates (2021)	84.00
• Oncologisch Spectrum 2021. Basis cursus oncologie (2021)	49.00
• Multilevel and Mixed Models Using R Evaluation (2021)	24.00
• Workshops project supervision (2022)	9.00
• RU - Design and Illustration (2022)	26.00
• RU - Projectmanagement voor Promovendi (2022)	45.00
• Radboudumc - Scientific integrity (2022)	20.00
• Career development for PhD candidates & postdocs "The next step in my career" (2023)	20.00
• Survival Analysis in R for Public Health (2023)	11.00
• AI for Health (2024)	110.00
Seminars	
• Domeinsoverstijgende- en regionale samenwerking (2020)	1.00
• Webinar Passende zorg (2021)	1.00
• Naar een houdbaar zorgstelsel. De uitdagingen voor de toekomst: welke keuzes moet Nederland maken? (2022)	2.50
• Kiezen voor houdbare zorg (2022)	1.50
• Oncologiezorgnetwerken in beeld (2022)	1.50
• Oncolytica in the real world (2023)	1.00
• Samenwerken aan de beste oncologische zorg in de regio (2024)	4.00
• Network event research program Value-Based Networked Care - laptop presentation (2024)	3.00

Conferences	
• Van ketenzorg naar netwerkzorg (2020)	8.00
• Zorgen voor zorgpaden in de oncologie (2020)	6.00
• Waardegedreven financiering in Oncologienetwerken (2020)	2.50
• Person-centred care 4 sustainable health systems (2021)	3.00
• NKR Symposium (2021) (2021)	6.50
• VGE congres (2022)	4.00
• Making Healthcare Sustainable (2022)	8.00
• PhD retreat (2022)	16.00
• Partner Event Janssen-Radboud - oral presentation (2022)	4.00
• BUNDLE congres (2022)	8.00
• Cancer research retreat (2022)	14.00
• NKR Symposium (2022) - poster presentatie (2022)	6.50
• Comprehensive Cancer Network Symposium Oost Nederland (2022)	5.00
• Citrienfonds Impactfestival (2022)	5.50
• Zorg onder druk. Barrières voor optimale kwaliteit, toegankelijkheid en betaalbaarheid van zorg begrijpen en beslechten (2022)	6.00
• LolaHESG (2023)	14.00
• Cancer research retreat - oral presentation (2023)	14.00
• IKNL avondsymposium Dure Geneesmiddelen (2023)	4.00
• Cancer research retreat - laptop presentation (2024)	14.00
• Congres Goed Gebruik Geneesmiddelen (2024)	7.50
• EUHEA Conference 2024 - oral presentation (2024)	35.00
Teaching activities	
Supervision of internships / other	
• Supervision master student literature review (2020)	8.00
• Coaching a student internship for 20 weeks (2021)	50.00
• Supervision master student literature review (2022)	8.00
• Coaching a students research proposal (2022)	5.00
• Supervision of 2nd year (bio)medical students research project (2022)	45.00
Total	**752.00**

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IN DEI NOMINE FELICITER

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