# HEALTH-RELATED QUALITY OF LIFE AND COSTS IN BREAST, PROSTATE AND COLORECTAL CANCER:
# A SPECIAL FOCUS ON COLORECTAL CANCER

**Niilo Färkkilä**

DOCTORAL DISSERTATION

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**Supervised by:**

Professor (emeritus) Harri Sintonen, PhD
Department of Public Health
University of Helsinki

Professor Tiina Saarto MD, PhD
Medical Faculty
University of Helsinki

**Reviewed by:**

Professor (emerita) Kaija Holli, MD, PhD
Medical Faculty
University of Tampere

Professor (emeritus) Hannu Valtonen, PhD
Department of Health and Social Management
University of Eastern Finland

**Official opponent:**

Docent Sirkku Jyrkkiö, MD, PhD
Medical Faculty
University of Turku

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To Ellen and Elsa

## ABSTRACT

**Background and aims**

Cancer is a huge burden to patients, families and to societies in both human and monetary terms. Breast (BC), prostate (PC) and colorectal (CRC) cancer are the three most common cancer types in Finland. Due to improved survival, health-related quality of life (HRQoL) aspects are gaining increasing attention in cancer care. Understanding the cost and HRQoL consequences of different treatment choices is critical to be able to use scarce health-care resources optimally. The aims of this thesis were to evaluate costs and patient-reported HRQoL using three standard instruments (15D, EQ-5D-3L+VAS and EORTC QLQ-C30) in all phases of CRC, to assess HRQoL among end-stage BC, PC and CRC patients, and to assess the direct economic burden of BC, PC and CRC for patients and analyse what are its implications for HRQoL.

**Patients and methods**

A total of 1978 cancer patients from the Helsinki and Uusimaa region having either BC (840), PC (630) or CRC (508) participated in this observational cross-sectional study. Patients were recruited between 2009 and 2011 from different phases of the disease and divided into five mutually exclusive groups according to the stage of their disease: primary treatments; rehabilitation; remission; metastatic disease; and palliative care. Patients completed a questionnaire, which in addition to the HRQoL questionnaires, enquired about demographic factors, health care and informal care resource utilization and work capacity. Furthermore, data on direct medical resource use in both primary and secondary care and productivity costs were obtained from several different registries. Multivariate regression modelling was used to find determinants of deteriorated HRQoL and cost drivers.

**Results**

The HRQoL of CRC patients is fairly good compared to age-, gender- and education-standardized general population except for those under palliative care. The 15D gave highest scores across all states compared to EQ-5D and VAS. Fatigue, pain, age and financial difficulties were strongly associated with impaired HRQoL. The total six-month costs of CRC varied between disease states from €2106 in rehabilitation to €22,200 in the primary treatment state. The costs were highest at the beginning and in the advanced phases of the disease. Most of the CRC-related costs were direct medical costs. Productivity costs were highest in the primary treatment state (40%) and informal care costs highest in the palliative

phase (33%). Outpatient medication was responsible for the major part of patients' out-of-pocket (OOP) payments. High OOP payments were associated with financial difficulties and deteriorated HRQoL.

**Conclusions**

All instruments were applicable for the evaluation of HRQoL of cancer patients in all states of the disease, however the results the different instruments provided varied significantly. Cost of CRC is driven by direct health-care costs in the intense primary care and metastatic phase. Financial difficulties are a substantial burden to some and they have a clear negative impact on patients' HRQoL. Outcomes and costs of the care should be measured routinely in health care to ensure scare resources are used to maximize patients' health.

# TIIVISTELMÄ


**Tutkimuksen tausta ja tavoitteet**

Syöpä on globaalisti valtava haaste: siitä aiheutuu niin potilaille, läheisille kuin yhteiskunnille merkittävää inhimillistä ja taloudellista rasitusta. Rinta-, eturauhas- ja kolorektaalisyöpä ovat kolme yleisintä syöpätyyppiä Suomessa. Syövän parantuneen ennusteen myötä terveyteen liittyvä elämänlaatu on tullut yhä tärkeämmäksi asiaksi syövän hoidossa. Jotta terveydenhuollon rajallisia resursseja voidaan kohdentaa mahdollisimman tehokkaasti, tulee ymmärtää käytettävissä olevien hoitojen kustannus- ja elämänlaatuvaikutukset. Tämän väitöskirjatutkimuksen tavoitteena oli selvittää kolmea yleisesti käytettyä elämänlaatumittaria (15D, EQ-5D-3L+VAS and EORTC QLQ-C30) hyödyntäen kolorektaalisyöpäpotilaiden elämänlaatu ja kustannukset taudin eri vaiheissa diagnoosista palliatiiviseen hoitovaiheeseen saakka, arvioida rinta-, eturauhas- ja kolorektaalisyöpäpotilaiden loppuvaiheen elämänlaatua ja selvittää syöpäpotilaille sairaudesta aiheutuvia kustannuksia ja taloudellisten vaikeuksien vaikutusta.

**Potilaat ja menetelmät**

Kaikkiaan 1978 rinta- (840), eturauhas- (630) ja kolorektaalisyöpäpotilasta Helsingin ja Uudenmaan sairaanhoitopiirin alueelta osallistui tähän havainnoivaan poikkileikkaustutkimukseen vuosina 2009-2011. Potilaat rekrytoitiin taudin eri vaiheista ja jaettiin syövittäin viiteen eri ryhmään: primaarihoidot, kuntoutumisvaihe, remissio, metastaattinen vaihe ja palliatiivinen vaihe. Potilaskyselyssä potilaita selvitettiin elämänlaatukyselyiden lisäksi demografisia taustatietoja, terveydenhuollon ja epävirallisten palveluiden käyttöä ja työkykyä. Lisäksi tietoa potilaiden terveydenhuollon käytöstä saatiin yhdistelemällä erikoissairaanhoidon, perusterveydenhuollon ja KELA:n rekisteritietoja. Monimuuttuja-analyysin avulla pyrittää löytämään elämänlaadun tai kustannusten vaihtelua selittäviä tekijöitä.

**Tulokset**

Kolorektaalisyöpäpotilaiden raportoima terveyteen liittyvä elämänlaatu verrattain oli hyvä verrattuna ikä-, sukupuoli- ja koulutusvakioituun normaali väestöön lukuun ottamatta palliatiivisen vaiheen potilaita. 15D-mittari antoi kaikissa syövissä ja taudin vaiheissa korkeammat arvot kuin EQ-5D tai VAS. Uupumus, kipu, ikä ja taloudelliset vaikeudet olivat selvästi yhteydessä alentuneeseen elämänlaatuun. Syövästä aiheutuneet kustannukset vaihtelivat merkittävästi taudin vaiheen mukaan (€2106 – €22 200). Kuuden kuukauden

jaksolta korkeimmat kustannukset olivat taudin alkuvaiheessa ja ne nousivat jälleen taudin edettyä. Merkittävin osa kustannuksista oli suoria terveydenhuollon kustannuksia. Tuottavuuskustannusten osuus oli merkittävin primaarihoidon vaiheessa (40%). Vastaavasti epävirallisesta hoidosta aiheutuneet kustannukset olivat suurimmat palliatiivisessa hoidon vaiheessa (33%). Avohoidon lääkemenot aiheuttivat potilaiden omavastuutaakasta suurimman osan. Potilaiden maksamat korkeat omavastuut olivat yhteydessä syövästä aiheutuneisiin taloudellisiin vaikeuksiin ja alentuneeseen elämänlaatuun.

**Johtopäätökset**

Kaikki tutkimuksessa käytetyt mittarit toimivat tässä potilas joukossa, vaikkakin niiden antamat tulokset vaihtelivat merkittävästi keskenään. Kolorektaalisyövän kustannukset aiheutuvat enimmäkseen suorista terveydenhuollon kustannuksista ja ne olivat korkeimmat taudin primaarihoitovaiheessa ja taudin edettyä. Syövästä aiheutuneet talousvaikeudet ovat joillekin potilaille merkittäviä ja yhteydessä alentuneeseen elämänlaatuun. Vaikuttavuutta ja kustannuksia tulisi seurata terveydenhuollon arjessa säännönmukaisesti, jotta rajalliset resurssit voidaan kohdentaa mahdollisimman tehokkaasti potilaiden hyvinvoinnin maksimoimiseksi.

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## CONTENTS

## LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

I Färkkilä N, Sintonen H, Saarto T, Järvinen H, Hänninen J, Taari K, Roine RP. Health-related quality of life in colorectal cancer. Colorectal Dis. 2013 May;15(5):e215-22.

II Färkkilä N, Torvinen S, Sintonen H, Saarto T, Järvinen H, Hänninen J, Taari K, Roine RP. Costs of colorectal cancer in different states of the disease. Acta Oncol. 2015 Apr;54(4):454-62.

III Färkkilä N*, Torvinen S*, Roine RP, Sintonen H, Hänninen J, Taari K, Saarto T. Health-related quality of life among breast, prostate, and colorectal cancer patients with end-stage disease. Qual Life Res. 2014 May;23(4):1387-94.

IV Koskinen J*, Färkkilä N*, Roine RP, Saarto T, Taari K, Sintonen H. The association of financial difficulties and out-of-pocket payments with health-related quality of life among breast, prostate and colorectal cancer patients. Acta Oncol. 2019 Jul;58(7):1062-8. *

*Authors share equal contribution.

## ABBREVIATIONS

| | |
|---|---|
| 15D | 15 dimensions quality of life instrument |
| AC | anal cancer |
| AQoL | Assessment of Quality of Life generic HRQoL instrument |
| BC | breast cancer |
| CAPOX | capecitabine and oxaliplatin combination therapy |
| CRC | colorectal cancer |
| CBA | cost−benefit analysis |
| CI | confidence interval |
| CRC | colorectal cancer |
| CUA | cost−utility analysis |
| DALY | disability-adjusted life-year |
| ECOG | Eastern Cooperative Oncology Group performance scale |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer QoL questionnaire for cancer |
| EQ-5D | EuroQol 5 dimensional HRQoL instrument, 3L with 3, 5L with 5 levels each |
| ESMO | European Society for Medical Oncology |
| FACT | Functional Assessment of Cancer Therapy, C = Colorectal cancer, G =general |
| FOLFOX | leucovorin, fluorouracil and oxaliplatin combination therapy |
| GDP | gross domestic product |
| GP | primary care general practitioner |
| HPV | human papilloma virus |
| HRQoL | health-related quality of life |
| HUI | Health Utilities Index, generic HRQoL questionnaire |
| HUS | Helsinki and Uusimaa hospital district |
| ICER | incremental cost-effectiveness ratio |
| KELA | the Social Insurance Institution of Finland |

| | |
|---|---|
| MCID | minimal clinically important difference |
| mCRC | metastatic colorectal cancer |
| MCS | mental health component summary score in SF-36 |
| MeSH | medical subject headings |
| NCCN | National Comprehensive Cancer Network |
| OLS | ordinary least square regression |
| OOP | out-of-pocket |
| OS | overall survival |
| PC | prostate cancer |
| PCS | physical health component summary score in SF-36 |
| PFS | progression-free survival |
| PROM | patient-reported outcome measures |
| QALY | quality-adjusted life year |
| QWB | Quality of Well Being Scale, generic HRQoL instrument |
| RCT | randomized controlled trial |
| SD | standard deviation |
| SF-36 | Short Form, generic HRQoL questionnaire |
| SG | standard gamble |
| TEM | transanal endoscopic microsurgery |
| TME | total mesorectal excision |
| TNM | tumour classification system: tumour (T), nodes (N), and metastases (M) |
| TTO | time trade-off |
| UBQ-C | Utility Based Quality of Life Questionnaire - Cancer |
| VAS | visual analogue scale |
| VIF | variance inflation |
| WHO | World Health Organization |
| XELOX | capecitabine and oxaliplatin combination therapy |

# 1 INTRODUCTION

Cancer is a major global health problem with 18.1 million new cases and 9.6 million deaths annually. The rapidly increasing burden of cancer is due to several factors such as aging, population growth and social and economic development. Colorectal cancer (CRC) is globally the third most common cancer after lung and breast cancer (BC) and second in cancer deaths[1].

Not only due to cancer but also for other reasons health-care systems around the world are struggling with rising costs and limited resources. The need to ensure efficient use of scarce resources has made health economic studies increasingly important. Health economics is a discipline that studies, for example, how scarce resources are allocated in health care, how health should be valued and what defines the demand for and supply of health care. Broadly, the question is about applying economic theories and techniques to the health sector.

Economic evaluation is a treatment-level assessment of health and cost consequences of alternative health-care interventions and it provides important information to health-care decisionmakers on how to use resources optimally. Economic evaluation is a legal prerequisite in most Western countries for new therapies to enter the market and to be accessed by patients. It requires standardized ways to value health gains and to measure resource use and costs associated with alternative treatment options.

Measuring health benefits includes changes both in health-related quality of life (HRQoL) and length of life. Cancer survival rates have risen dramatically during recent decades due to new innovative treatments. As the survival improves, patients live longer with their disease and the HRQoL becomes ever more important. However, there is no gold standard for how to measure HRQoL and many different instruments have been used.

Estimates of the costs associated with cancer care are essential for conducting economic evaluations of interventions or for assessing the burden of disease at the population level.

This thesis studies aspects of the health economics of CRC that are important in clinical practice and essential in the economic evaluation of new interventions for cancer patients. The aim was to assess comprehensively the costs and HRQoL consequences and explore their determinants in different states of CRC. Moreover, as a background, a review of the existing

CRC-related HRQoL and cost literature and a brief introduction to economic evaluation are provided. Also, the financial burden to patients of the three most common cancers is explored, as well as HRQoL among end-stage patients.

# 2 BACKGROUND AND REVIEW OF THE LITERATURE

A cancer is defined as the abnormal growth of cells, which have the ability to spread to other parts of the body. Colorectal cancer originates from the epithelial cells lining the colon or rectum of the gastrointestinal tract.

## 2.1 EPIDEMIOLOGY OF COLORECTAL CANCER

Cancer is a major global health problem, the second leading cause of death and its burden is increasing. Globally, approximately 9.6 million deaths in 2018 were caused by cancer and every sixth death is due to the disease [1]. The economic burden of cancer globally was estimated to be 1.16 trillion USD in 2010 [2].

Measured by the number of new cases per year, the most common cancers globally are: lung (2.09 million cases); breast (BC) (2.09 million cases); colorectal (CRC) (1.80 million cases); prostate (PC) (1.28 million cases); skin cancer (non-melanoma) (1.04 million cases); stomach (1.03 million cases). Leading causes of cancer deaths are lung (1.76 million deaths), colorectal (862,000 deaths), stomach (783,000 deaths), liver (782,000 deaths) and breast (627,000 deaths) cancers[1].

In Finland, the number of new cases of CRC was 3356 in 2017, of which 53% were men. Of the new cases 64 % of the tumours occurred in the colon and 36% in the rectum or rectosigmoid. Colon cancer was more common among women and rectum cancer among men. In Finland the data have been systematically collected since 1953 by the Finnish Cancer Registry. The data show that the number of new cases of CRC has increased substantially during this time period (Figure 1) and this trend continues. The number of new cases has more than doubled during the last 30 years. Roughly half of this growth is explained by population aging and growth[3].

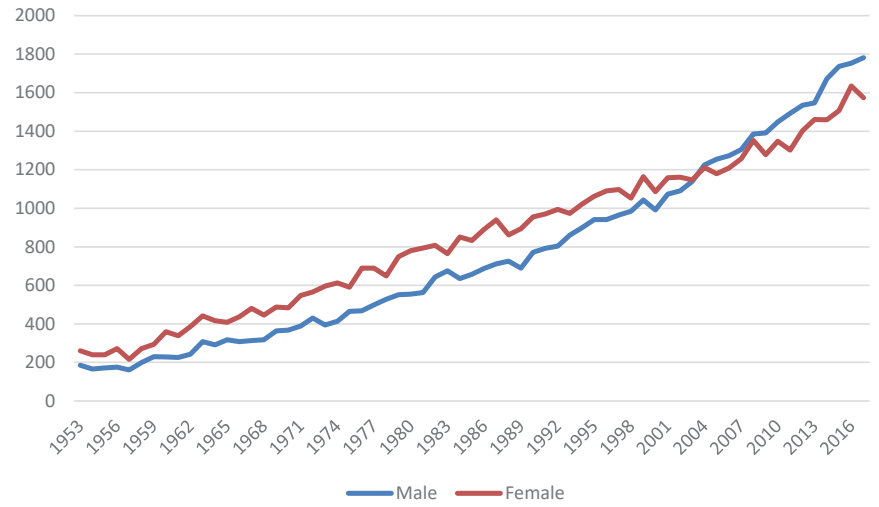



**Figure 1.** Number of new cases of CRC in Finland 1953−2017 [3].

CRC caused 1368 deaths in Finland in 2017 and the number has been heavily increasing as Figure 2 illustrates. However, due to improved diagnostics and treatments the age-standardized mortality rate has been declining since the 1970s.

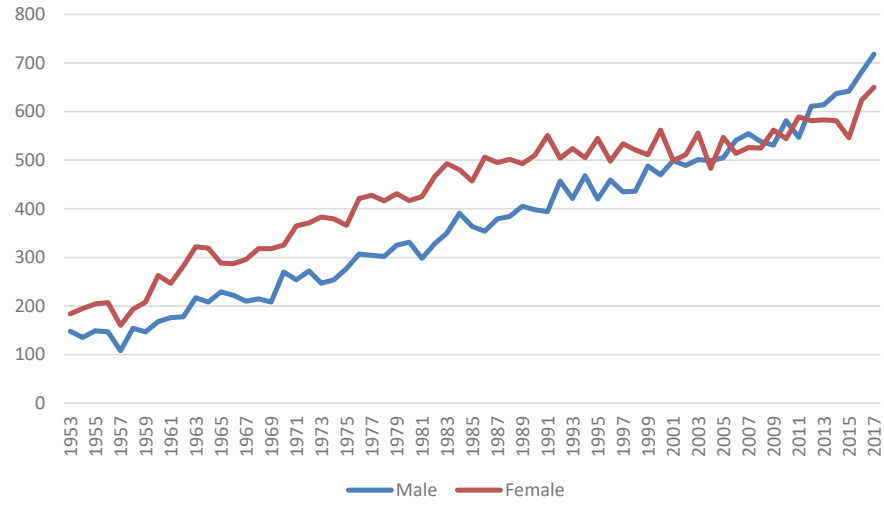



**Figure 2.** Colorectal-cancer mortality in Finland 1953−2017 [3].

The survival after one year from diagnosis is above 80%. Survival rates for females are higher compared to males and for patients with cancer in the rectum or rectosigmoid versus in the colon. Five years from diagnosis, on average 64% of males and 69% of females are alive (Figure 3) [3].

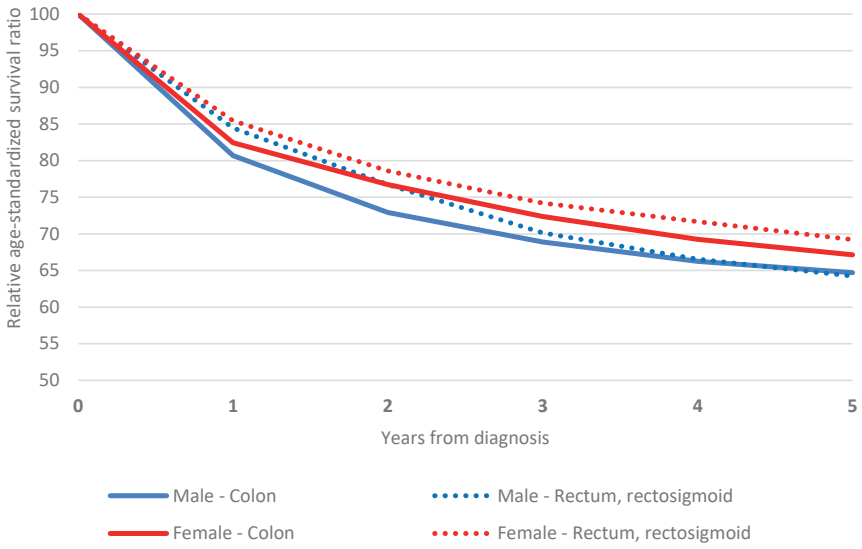



**Figure 3.** Colorectal-cancer 5-year survival ratio in Finland, age-standardized [3].

**Colorectal cancer diagnostics and prognosis**

Typical symptoms of CRC are, for example, a change in bowel habits, diarrhoea, constipation and blood in the stool. Most of the patients are at the time of diagnosis 60−80 years of age. The preoperative diagnosis is based on colonoscopy and histopathologic analysis of the biopsies. Computed tomography scan or magnetic resonance imaging are used to assess the size, location and spread of the cancer. At the time of diagnosis, 20−25% of the cancers are local, i.e., stage I. In 40−45% of the cases the cancer has grown through the colon or rectum, in 15−20% of the cases it has spread to lymph nodes and in 20−30% of the cases distant metastases are present at the time of diagnosis.

The stage at diagnosis is the single most important predictor of survival (Table 1). The classification is based on bowel wall invasion and the presence of lymph node and distant metastases. Several systems for classification have been used: TNM, Dukes, Astler−Coller.

Currently the most common system for staging is TNM classification. Previously the colorectal cancer-specific Dukes system was more often used, but it is no longer recommended for clinical practice. The Astler−Coller system is an adapted version of the Dukes classification. [4, 5]

To improve early diagnostics and thus prognosis, most developed countries have countrywide CRC screening programmes or are preparing such programmes [6]. In 2013 and 2014 almost 50% of the 60−68-year-old Finnish citizens were invited to participate in CRC screening. Based on these results the national CRC screening programme was started in 2019.

**Table 1.** Classification systems, distribution at diagnosis and five-year relative survival

| Dukes | TNM | Features | Share of new cases | 5-year survival |
|---|---|---|---|---|
| A | I (T1N0M0) | Limited to submucosa | 20–25% | > 90% |
| B | II (T2-3N0M0) | Limited to muscularis propria (T2)<br>Transmural extension (T3) | 40–45% | 60–70% |
| C | III (T1-4N1M0) | Involvement of lymph nodes<br>- C1 ≤3<br>- C2 >3 regional nodes | 15–20% | 35–45% |
| D | IV (T1-4N0-2M1) | Distant metastases present | 20–30% | 0–5% |

**Treatments of colorectal cancer**

Treatment of CRC includes surgery, medication (chemotherapy, targeted therapy and immunotherapy) and radiation based on the stage of the disease. The Comprehensive Cancer Centre Finland (FICAN) has published its first national treatment guidelines for colorectal cancer [7]. The guidelines are mainly similar to the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) consensus guidelines [8-10]. For cancers stage 0-I, surgery is usually the only treatment needed. For stage II disease, where cancer has proliferated through the bowel tissue, in addition to surgery, adjuvant chemotherapy might be needed, based on additional risk factors. At stage III the surgery includes removal of nearby lymph nodes, and adjuvant chemotherapy is recommended: CAPOX (capecitabine and oxaliplatin) or FOLFOX (leucovorin, fluorouracil and oxaliplatin). For patients too frail for surgery, radiation/chemotherapy might be an option. In stage IV the tumour has spread to distant organs, most commonly to the liver followed by the lungs, brain, peritoneum, and distant lymph nodes. In metastatic colorectal cancer (mCRC) the treatment algorithms are mostly based on the tumour's genetic profile, tumour

mutational burden, microsatellite instability, previous treatments and location of the primary tumour [7].

## 2.2 HRQoL IN CRC

Improving health is the main purpose of health care. Thus, the ability to quantify health is an essential requirement for the assessment of the success of health care. In health care, many different measures are used and many of those are not measures of health itself but rather intermediate outcomes (Figure 4) [11].

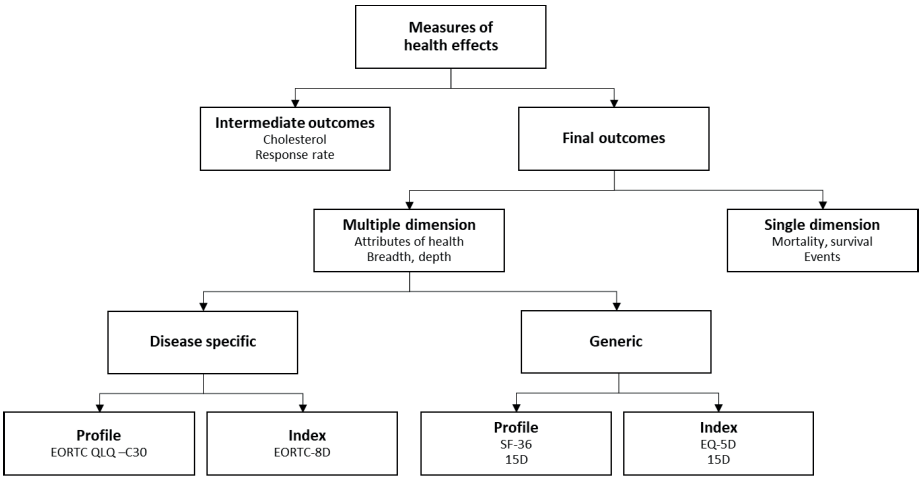



**Figure 4.** Health measures taxonomy (Adapted from Drummond et al. [11]).

Intermediate outcomes, such as cholesterol level, are useful when assessing which treatment option is the most effective but they do not quantify the improvements in health as such. HRQoL is a multidimensional concept that combines the different dimensions of health. The instruments used to measure HRQoL vary in terms of the dimensions included and how they are weighted.

A health effect measure, which could be used widely in health-care decision-making across different diseases, should encompass changes in quality and length of life and be based on valuation of possible health states. The most frequently used measure for health gain is quality-adjusted life-years (QALYs) gained, which was first introduced in 1968 [12].

QALYs gained capture the quantity gains (reduced mortality) and quality gains (reduced morbidity) of health in a single measure. Usually the scale for QALYs varies from 0 (death) to 1 (perfect health). Thus, one QALY is equal to one year lived in perfect health or two years lived with a quality weight of 0.5. Also, a loss of health could be used as a basis in economic evaluations. The most used measure is the disability-adjusted life-year (DALY) [13].

To value the different possible health states, the preferences for them should be measured. The most widely used techniques are rating scales such as the visual analogue scale (VAS) and choice-based methods such as the standard gamble (SG) and the time trade-off (TTO). Many scholars claim that choice-based methods should be used whenever possible. VAS is the simplest method, where subjects rank their health state on a scale from 0 to 100. The SG is based on utility theory [14]. Valuation of a certain health state i is done by offering two alternatives: possible immediate recovery from the health state i to perfect health (probability p) or immediate death (probability 1-p) vs. remaining in the health state i. The preference score is the probability p when the subject is indifferent between the alternatives. TTO was developed for health care by Torrance et al. in 1972 [15]. The method gives comparable results to the SG, but is easier to administer for the subjects [16]. In TTO a subject is offered two alternatives: staying in the health state for time t followed by death vs. being in a perfect health for time x. The preference score is calculated as x/t.

**Instruments used to measure HRQoL**

The HRQoL instruments can be classified into generic instruments and disease-specific instruments (Figure 4). Generic instruments are designed to be applicable in a wide range of different diseases and conditions and are needed when decisions or assessments are made between different diseases. Disease-specific measures are tailored for specific diseases, for example cancer (EORTC QLQ-C30), and thus the dimensions to be included are very relevant in that setting and the instrument may be more sensitive in two respects: it may exhibit more discriminatory power, i.e. be able to detect small differences between individuals or groups, and/or be more responsive to changes, i.e. detect small changes over time. Generic measures could provide a health profile or preference-based single index values. The latter are needed to calculate QALYs. It is impossible to use the SG or the TTO method directly in clinical practice to establish single index values for health states, thus pre-scored multidimensional health state descriptive systems are mainly used. The most often used systems in Finland are the EQ-5D, 15D and SF-6D. Others that are available include the Health

Utilities Index (HUI) [17], the Assessment of Quality of Life (AQoL) [18], the Quality of Well-Being Scale (QWB) [19] and the Rosser-Kind index [20].

*15D*

The 15D is the most used generic instrument in Finland. It consists of 15 dimensions: mobility; vision; hearing; breathing; sleeping; eating; speech; excretion; usual activities; mental function; discomfort and symptoms; depression; distress; vitality; and sexual activity [21]. Each dimension has a range from 1 (no problems) to 5 (extreme problems). In addition to providing a single-index HRQoL score (ranging from 0 to 1), the 15D can also serve as a profile instrument depicting patients' assessment of their HRQoL on each of the 15 dimensions of health. 15D allows imputing up to three missing values per respondent. The minimum clinically important change or difference (MCID) in the 15D score has been estimated to be 0.015 [22].

*EQ-5D*

The EQ-5D is a five-dimensional (mobility, self-care, usual activities, pain/discomfort, and anxiety/ depression) instrument. In the original version each dimension has three levels (EQ-5D-3L, referred to from hereon in as 'EQ-5D'). The EQ-5D was developed in the 1990s by the EuroQol Group. The instrument does not allow calculating the index score if any answer is missing. The minimum score depends on the valuation algorithm used. The commonly used UK time trade-off (TTO) tariff gives the minimum score –0.594 [23]. The MCID for this algorithm is estimated to be 0.08 in cancer [24]. A new five-level version (EQ-5D-5L) was launched in 2011 to improve the ability to detect smaller changes in health and to reduce the evident ceiling effect [25].

The EQ-5D questionnaire also includes a VAS, which is the simplest way to express directly the patient's self-perceived evaluation of his/her health state on a vertical scale from 0 (worst imaginable health state) to 100 (best imaginable health state). For the VAS there is no clearly agreed MCID. It has been estimated to range between 7 and 12 [24].

*SF-6D and SF-36*

The SF (short form)-36 is a 36-item measure which includes eight domains: physical function; role limitations owing to physical problems; bodily pain; general health perception; vitality; social functioning; role limitations owing to emotional problems; and mental health. Its dimensions can be summarized into two summary scores: the physical health component summary score (PCS) and the mental health component summary score (MCS) [26]. SF-36

itself does not allow to convert its results to health state preferences and QALYs so the preference-based SF-6D was developed based partly on the SF-36 questions and was introduced by Brazier et al. in 2002 [27]. To use the SF-6D to get a single index value one must first use the SF-36 or its short version, the SF-12 questionnaire.

*EORTC QLQ-C30*

The EORTC QLQ-C30 is a cancer-specific HRQoL profile instrument developed by The European Organization for Research and Treatment of Cancer. It was developed in the 1980s to unify the measuring of cancer patients' physical, psychological and social functions in clinical trials. The instrument produces a global health status, five functioning scales (physical, role, social, emotional and cognitive functions), three symptom scales (fatigue, nausea/vomiting and pain) and six single-symptom items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) [28]. Although the EORTC QLQ-C30 is one of the most used patient-reported outcome measures (PROMs) in cancer, it cannot be used in health economic analysis. Based on the EORTC QLQ-C30 questionnaire, a preference-based measure EORTC-8D has been developed [29]. It has eight dimensions (physical functioning, role functioning, social functioning, emotional functioning, pain, fatigue and sleep disturbance, nausea, constipation, and diarrhoea) with four or five levels each.

**HRQoL in CRC literature search**

The aim of the literature review was to understand what generic preference-based HRQoL measures have been used in CRC, in which study settings and what the implications have been. The reporting follows the Preferred Reporting Items of Systematic Reviews and Meta-Analyses guidelines (PRISMA) [30].

*Methods*

We used the PubMed database to identify articles about HRQoL and CRC that were published between January 2000 and July 2019 in the English language. We used the medical subject headings (MeSH) search strategy with the subject term “colorectal neoplasms” combined with MeSH major subject term “quality of life”.

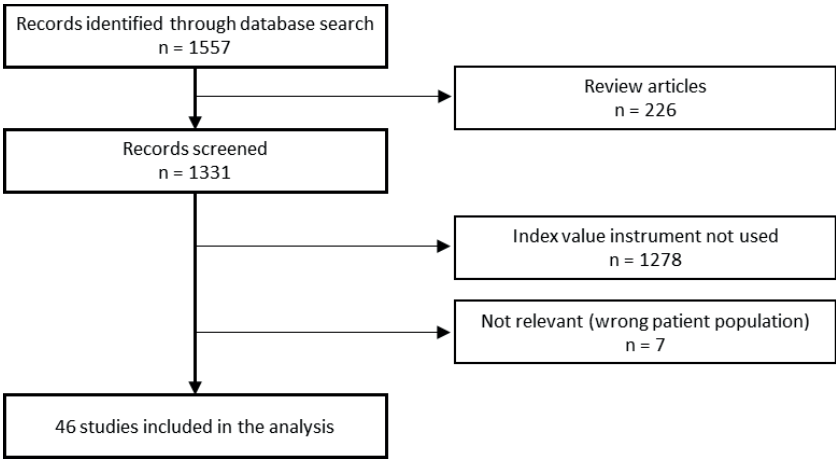



**Figure 5.** Flow diagram of the literature search process of HRQoL articles.

This yielded 1557 studies of which 226 were review articles and thus excluded. Furthermore, congress abstracts were not included. We focused only on single index value instruments such as: 15D, EQ-5D, SF-6D, HUI and AQoL and direct measurements with TTO and SG. Using these criteria 46 papers were selected for closer review (Figure 5).

*Results of the review*

The type of study, country, number of patients, HRQoL instruments used and the stage of patients were recorded (Table 2). Of the 46 publications that were analysed in more depth, 6 were economic evaluations, 16 clinical trials, 14 observational studies and 10 methodologic, mainly mapping, studies. The number of HRQoL in CRC publications increased throughout the study period: 40 studies (87%) were published after 2010, whereas only 6 between 2000 and 2010. Due to the heterogeneous nature of the reviewed studies, a synthesis of the results was not conducted. A majority of the studies (57%) were conducted in Europe.

The most used single value instrument was the EQ-5D, used in 36 studies. SF-6D was used in 10 studies and 15D in two (Studies I and III of this thesis). Time trade-off (TTO) was used in two studies and standard gamble (SG) in one. Other health utility index instruments such as HUI, QWB, Rosser-Kind, and AQoL were not found. In most of the studies, cancer-specific HRQoL instruments were also used, namely the EORTC QLQ-C30 in 15 studies and Functional Assessment of Cancer Therapy – Cancer (FACT-C) in 10 studies.

All the economic evaluations included were cost−utility analyses (CUA) and one also included monetary valuation of the health gain (cost−benefit analysis, CBA). The intervention assessed was in three cases a medicine (bevacizumab, oxaliplatin-based chemotherapy) and in two cases a surgical procedure and in one study a telephone-based follow-up programme. The EQ-5D was used in all the evaluations considering medicines and the SF-6D in the surgery evaluations.

In clinical trials that were included in the review, the EQ-5D was the only single index value instrument used. It was usually combined with the EORTC QLQ-C30 or FACT-C. The intervention studied was in 9 cases out of 16 a surgical procedure and in 7 cases chemotherapy or a biological therapy. All the clinical trial studies were run in Europe except one in the USA. The patient population in the surgery trials were mainly newly diagnosed whereas in the drug trials they were metastatic stage patients. In the observational studies included, the study design was usually cross-sectional and patients' disease stages varied. Patient samples varied from 75 to 6713. Six studies were conducted in Asia.

Mapping is a technique aimed at converting the scores of disease-specific HRQoL measures to single index value, which could then be used in economic evaluations. Of the seven mapping studies reviewed, in four a model to map FACT-C/G values to SF-6D was built and in two of those also to EQ-5D. In two studies EORTC QLQ-C30 values were mapped to EQ-5D. In three studies the reliability and validity of the index value instrument (EQ-5D or SF-6D) was assessed among colorectal patients.

*Conclusions*

There is no gold standard measure but different instruments are used widely. The EQ-5D seems to be the standard single index value instrument used when studying medicines and SF-6D is more often used in the operative settings. In clinical trials and observational studies, a generic instrument is usually combined with a cancer-specific instrument such as EORTC QLQ-C30 or FACT-C.

**Table 2.** Summary of HRQoL publications included

| First author, reference | Country | N | Study setting | HRQoL instruments used | Study population |
|---|---|---|---|---|---|
| **Economic evaluation** | | | | | |
| Carter, 2014 [31] | Australia | 401 | CUA[1] of bevacizumab plus capecitabine | EQ-5D, UBQ-C[2] | mCRC 1st line |
| Cashin, 2018 [32] | Sweden | 48 | CUA of cytoreductive surgery with intraperitoneal chemotherapy vs systemic chemotherapy | SF-36, SF-6D, EORTC QLQ-C30 | mCRC (peritoneal metastases) |
| Franken, 2017 [33] | Netherlands | 492 | CUA of capecitabine and bevacizumab maintenance | EQ-5D | mCRC +2nd line |
| Gordon, 2015 [34] | Australia | 410 | CUA of telephone support, RCT | SF-6D | CRC, various stages |
| Michalopoulos, 2013[35] | Greece | 92 | CUA of laparoscopic vs open surgery | EQ-5D, SF-36, EORTC QLQ-C30 | Local CRC |
| Robles-Zurita, 2018 [36] | Multi-country | 6088 | CUA/CBA[3] of two different oxaliplatin combination | EQ-5D | Local CRC, adjuvant therapy |
| **Clinical trials** | | | | | |
| Antonuzzo, 2015 [37] | Italy | 197 | RCT[4]: Open label bevacizumab plus XELOX | EQ-5D, | Locally advanced or mCRC, 1st line |
| Augestad, 2008 [38] | Norway | 110 | RCT: Compare follow-up strategy after primary surgery: hospital vs primary care until 24 months | EQ-5D, EORTC QLQ-C30 | CRC different stages |
| Bennett, 2011 [39] | Multi-country | 1253 | Combined analysis of 2 phase III panitumumab plus chemotherapy RCTs | EQ-5D | mCRC 1–2 line |
| Brigic, 2017 [40] | UK | 91 | Case control study: HRQoL 2–4 years after colectomy vs healthy controls | EQ-5D | Colon cancer, stage I–III |
| Diouf, 2014 [41] | Multi-country | 620 | Phase III secondary analysis of FOLFOX RCT: prognostic value of HRQoL for OS[5] | EQ-5D | mCRC 1st line |
| Doornebosch, 2007 [42] | Netherlands | 62 | RCT: TEM vs TME[6] vs healthy controls | EQ-5D, EORTC QLQ-C30 | Rectal cancer: primary surgery |
| Gadan, 2017 [43] | Sweden | 98 | Long-term follow-up (12 y) after rectal resection: temporary stoma vs no stoma | EQ-5D | Rectal cancer: resection |
| Haapamäki, 2011 [44] | Sweden | 19 | Follow-up after extended abdominoperineal excision | EQ-5D | Primary or recurrent rectal or anal cancer |

[1] Cost-utility analysis
[2] Utility Based Quality of Life Questionnaire – Cancer.
[3] Cost-benefit analysis
[4] Randomized clinical trial
[5] Overall survival
[6] TEM – transanal endoscopic microsurgery, TME – total mesorectal excision.

| | | | | | |
|---|---|---|---|---|---|
| Janson, 2007 [45] | Sweden | 285 | RCT: Follow-up after laparoscopic vs open surgery | EQ-5D, EORTC QLQ-C30 | Colon cancer, stage I–III |
| Koedam, 2017 [46] | Netherlands | 30 | Follow-up after transanal total mesorectal excision | EQ-5D, EORTC QLQ-C30 | Rectal cancer, primary treatments (I–IV) |
| Odom, 2011 [47] | Multi-country | 463 | Phase III RCT: panitumumab vs best supportive care | EQ-5D, EORTC QLQ-C30 | Chemotherapy-refractory mCRC +3 line |
| Sharma, 2007 [48] | UK | 104 | Follow-up after elective resection | EQ-5D, FACT-C[7] | CRC, primary treatment |
| Siena, 2007 [49] | Multi-country | 463 | Phase III RCT secondary analysis: Association of PFS[8] with HRQoL and OS, panitumumab vs best supportive care | EQ-5D, EORTC QLQ-C30 | mCRC |
| Thaler, 2012 [50] | Austria | 154 | Phase II RCT: skin toxicity and QoL, panitumumab plus FOLFIRI | EQ-5D, EORTC QLQ-C30 | mCRC 1st line |
| Ward, 2014 [51] | USA | 45 | Sub analysis of phase II capecitabine and bevacizumab: follow-up of HRQoL between patients with ECOG 1/2[9] | EQ-5D, FACT-C | Geriatric mCRC |
| Verseveld, 2016 [52] | Netherlands | 24 | Follow-up after transanal minimally invasive surgery | EQ-5D, FIQL[10] | Local (T0–I) rectal cancer |
| **Observational studies** | | | | | |
| Downing, 2019 [53] | UK | 6713 | Cross-sectional survey: HRQoL after curative treatment | EQ-5D-5L, FACT-C | Rectal cancer, primary treatments (I–IV) |
| Escobar, 2015 [54] | Spain | 193 | Cross-sectional survey of 3-year cancer survivors | EQ-5D, EORTC QLQ-C30 | Breast, colorectal or prostate cancer |
| Färkkilä, 2013 [55] | Finland | 508 | Cross-sectional survey of HRQoL | EQ-5D, 15D, EORTC QLQ-C30 | CRC, various stages |
| Färkkilä, 2014 [56] | Finland | 114 | Cross-sectional survey of HRQoL | EQ-5D, 15D, EORTC QLQ-C30 | End-stage mCRC |
| Hornbrook, 2011 [57] | USA | 640 | Cross-sectional survey, analysis of HRQoL determinants | SF-6D, COH-QOL-Ostomy[11] | >5-year survivors of CRC |
| Huang, 2018 [58] | China | 300 | Cross-sectional survey, analysis of HRQoL determinants | EQ-5D-5L | CRC, primary treatments, stage varies |
| Kim, 2012 [59] | Korea | 133 | Cross-sectional survey, assessment of validity and reliability | EQ-5D, SF-36, EORTC QLQ-C30 | CRC, various stages |
| Marcellusi, 2015 [60] | Italy | 465 | Cross-sectional analysis of HPV-induced cancer HRQoL loss | EQ-5D, time trade-off | HPV-related cancers |
| Setiawan, 2018 [61] | Indonesia | 116 | Cross-sectional analysis of HPV-induced cancer HRQoL loss | EQ-5D | HPV-related cancers |

[7] Functional Assessment of Cancer Therapy – Colorectal cancer.
[8] Progression free survival
[9] Eastern Cooperative Oncology Group (ECOG) Performance status.
[10] Faecal Incontinence Quality of Life.
[11] City of Hope Quality of Life-Ostomy.

| | | | | | |
|---|---|---|---|---|---|
| Shiroiwa, 2009 [62] | Japan | 1500 | Direct valuation of 25 CRC health states | TTO, SG | General population |
| Stein, 2014 [63] | Multi-country | 75 | Cross-sectional study, pre- vs post-progression | EQ-5D | mCRC 2nd line+ |
| Wong, 2013 [64] | Hongkong | 160 | Cross-sectional survey, analysis of HRQoL determinants | SF-6D, FACT-C | CRC, various stages |
| Wong, 2014 [65] | Hongkong | 160 | Cross-sectional study, comparison of direct and mapped SF-6D | SF-6D, SF-12, FACT-C | CRC, various stages |
| Wong, 2018 [66] | China | 533 | Cross-sectional survey, HRQoL impact on health service use | SF-6D, FACT-C | CRC, various stages |
| **Mapping and methodologic studies** | | | | | |
| Colwell, 2010 [67] | USA | 391 | Evaluation of reliability, validity and responsiveness of FCSI-9 | EQ-5D, FCSI-9[12] | mCRC |
| Kim, 2014 [68] | Korea | 2211 | Mapping SF-36 to EQ-5D | EQ-5D | Various cancer types |
| Lee, 2013 [69] | Canada | 191 | Validation of SF-36 in postoperative recovery | SF-6D, SF-36 | CRC, primary treatments, stage I–IV |
| Marriott, 2017 [70] | Multi-country | 529 | Mapping EORTC QLQ-C30 to EQ-5D | EQ-5D, EORTC QLQ-C30 | 1L mRC liver-only or liver dominant |
| Teckle, 2013 [71] | Canada | 367 | Mapping FACT-G to EQ-5D and SF-6D | EQ-5D | CRC, breast, lung cancer |
| Teckle, 2011 [72] | Canada | 367 | Mapping FACT-G to EQ-5D and SF-6D | EQ-5D | CRC, breast, lung cancer |
| Wong, 2012 [73] | China | 537 | Mapping FACT-G to SF-6D | SF-6D | CRC different stages |
| Wong, 2014 [74] | China | 333 | Responsiveness of direct and mapped SF-6D values | SF-6D, SF-12, FACT-C | CRC different stages |
| Yang, 2014 [75] | China | 553 | Mapping FACT-C to SF-6D | SF-6D, FACT-C | CRC different stages |

[12] FACT Colorectal Cancer Symptom Index.

## 2.3 COST OF COLORECTAL CANCER

Assessments of colorectal cancer costs are important both to understand the burden of disease on society and to make decisions between different health-care programmes and treatment options to prevent, diagnose and treat the disease.

There is a lot of heterogeneity in the cost studies in health care. One underlying reason is that the cost data are mainly created and used for billing and the availability and structure of the data are defined by the health-care funding structure [76]. An alternative for registry-based data collection is so called 'micro costing', which is not without challenges and is laborious [77].

**Costing principles**

Costing includes two elements: measurement of the quantities of used resources and their valuation (assigning of price or unit cost to the resources). Usually market prices are used for valuation, but theoretically the right price would be the opportunity costs of the used resource. The main categories of costs associated with health care programmes are: costs arising from resource use within the health sector (direct costs), resource use by patients and their families (informal care), resource use by other sectors (direct non-health-care costs), and productivity losses due to inability to work. [11]

*Direct health-care costs*

Direct health-care costs include: intervention costs (practitioners' fees, diagnostic costs, therapy costs etc); service costs (facilities and equipment, hospitalization and clinic fees, and ancillary services); and overheads. The valuation of these is rather straightforward as the market prices are mainly easily available and resource utilization well documented for billing purposes.

*Direct non-health-care costs*

Direct non-health-care costs are a consequence of the consumption of resources outside the health sector, such as transportation to care, social services, household expenditures and informal care.

Informal care is defined as care given by family or friends. Quantification and valuation of informal care is often laborious as the amount of care received is not systematically documented and there is no direct market substitute for pricing. Informal care is rarely

included in economic evaluations, but its share might be substantial, especially in chronic diseases [78]. Informal care is usually unpaid or compensated only partially by government benefits that do not reflect the true value of the service. The alternative methods that could be used for valuation are: the proxy good method; the opportunity cost method; the contingent valuation method; conjoint measurement and valuation of health effects in terms of HRQoL [79]. In the well-being approach, the level of compensation should enable the well-being of the carer to be maintained at the same level as without care [80].

*Productivity costs*

Productivity cost or productivity losses arise due to morbidity and mortality causing patient's or carer's inability to work. Value of lost productive time is borne by the individual, family, society, or the employer. The valuation of productivity losses and to what extent they should be included in economic evaluations are controversial. It is also contentious whether productivity changes should be considered as costs or consequences [11].

The most used evaluation method for productivity losses is the human capital approach where gross earnings including employer costs and benefits is used. This method has been criticized for overestimating the true cost to society as in many cases short-term absences are compensated by other workers. In a case of long-term absence, the employer likely hires someone to replace the absent worker. An alternative method is the so-called friction cost method, where the cost is based on the expenses to the employer of replacing the employee and restoring the production to the initial level [81, 82].

Even when being physically at work, patients with a severe disease like cancer might not be able to fully perform their duties and are more likely to make mistakes. This so called 'presenteeism' is defined as a situation where an employee is not fully functioning in the workplace because of an illness, injury or other condition and this might accrue substantial productivity costs [83].

*Intangible costs*

In early cost-of-illness literature, the willingness to pay to avoid suffering, such as pain and anxiety, was defined as an intangible cost [84]. In economic evaluation where health gains and losses are quantified, intangible costs should not be included to avoid double counting.

**Perspective for the analysis**

The costs included in the analysis vary based on the selected perspective of the study. The perspective defines the budget holder who bears the consequences of the used resources. The most commonly used perspectives are described in the table below (Table 3) [85]. Societal perspective is the broadest, including all resource use.

**Table 3**. The types of costs included in the analysis with a different perspective

| Society | Health system | Payer | Patient |
|---|---|---|---|
| All costs incurred as a whole irrespective of the payer | All costs of health-care providers<br>- Health-care professional salaries<br>- Cost of medication<br>- Equipment<br>- Fixed assets | Costs borne by payer, e.g. municipality, insurance, sick-fund | All costs paid by a patient when seeking care:<br>- Out-of-pocket payments (fees and co-pays)<br>- Costs of transport<br>- Costs of taking time off work |

**Costs in CRC literature search**

The objective of this literature search was to understand what type of cost studies are published, and to summarize the costs related to colorectal cancer care across the disease states.

*Methods*

We used the PubMed electronic database to identify articles about costs and CRC that were published between January 2000 and June 2019 in the English language. We used the Medical subject headings (MeSH) search strategy with the subject term "colorectal neoplasms" combined with MeSH major subject terms "costs and cost analysis". This yielded 365 studies of which 177 were review articles, letters, editorials or congress abstracts and thus excluded. We focused only on CRC care and thus prevention and screening studies were not included. Also, studies focusing on assessing the cost implication of a specific treatment option or its cost-effectiveness were excluded. Using these criteria, 28 papers for closer review were selected (Figure 6).

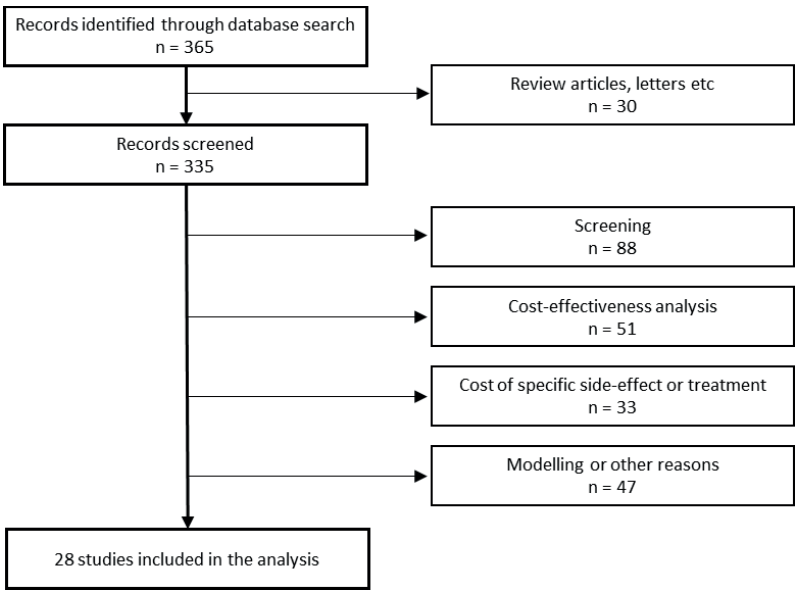



**Figure 6.** Flow diagram of the literature search process of CRC cost articles.

*Results of the review*

A majority of the literature of CRC-related costs was focused on screening or analysing the cost-effectiveness of a specific treatment. In our review we focused on patient level cost analysis of the disease states (Table 4). Of 28 studies, 12 were conducted in the USA where cost data are easily available from health insurance registries. All US studies were conducted from the health insurance perspective. Seven studies utilized the Surveillance, Epidemiology, and End Results database which is linked to Medicare. This health insurance programme is for people who are older than 65. In studies utilizing US health insurance data, the sample size is big, ranging from 598 to 144,130 patients. Twelve studies were conducted in Europe. In these studies, the perspective varied from patient to carers and to society. Four studies were carried out in Asia (China, Malaysia and Jordan).

The most used study setting was the incidence-based observational cohort study after CRC diagnosis (16 studies). The most common follow-up time was one year after diagnosis but it varied from 90 days to lifetime. Six studies were cross-sectional prevalence-based studies. In roughly half of the studies costs were compared to age-matched non-cancer controls, whereas the rest assessed the total costs. Eight studies examined costs to patients and carers through a survey and four of them also assessed the productivity costs due to sick leave and early retirement.

*Conclusions*

The type of the cost studies in CRC is determined mostly by the data available. Health insurance data are easily available especially in the USA and this allows longitudinal costs to be assessed after diagnosis and in the later phases of the disease. In European studies the perspective of the analysis is usually wider than just direct health-care costs to the payer. Patients' perspective, indirect costs or productivity cost are not widely studied and the methodologies used vary.

**Table 4.** Summary of cost studies included

| First author | Country | Patients | Setting | Time frame | Perspective | Cost estimate |
|---|---|---|---|---|---|---|
| Alefan, 2017 [86] | Jordan | 97 CRC | Cross-sectional prevalence-based assessment of annual costs | 1 year | Hospital | Annual cost per patients based on stage I–IV JD 1159; JD 1835; JD 3132; JD 5147 |
| Azzani,2016 [87], 2017 [88] | Malaysia | 138 CRC | Observational cohort after CRC diagnosis, patient survey | 1 year after diagnosis | Patients | Mean annual cost for patient per stage I–IV $2045; $2434; $2750; $2699 |
| Chastek, 2013 [89] | USA | 598 CRC | Observational cohort after mCRC diagnosis | 4 years follow-up after metastasis | Health insurance | Mean total lifetime cost after metastasis $252 200 |
| Chen, 2018 [90] | USA | 44 266 CRC | Observational cohort after CRC, lung, prostate and breast cancer diagnosis. Impact of different control group. | 1 year after diagnosis | Health insurance Medicare | Mean total cost of the first year after diagnosis $59 496 |
| Emmert, 2013 [91] | Germany | 101 Palliative CRC | Observational cohort after palliative care decision (unresectable metastases) | 2 years, palliative decision to death | Health insurance | Mean annual costs: 1st year €42,361, 2nd year €32,023 |
| Färkkilä, 2015 [92] | Finland | 508 CRC | Cross-sectional prevalence based including all stages | 6 months | Societal | Primary treatments €22 200; 6–12 m after diagnosis €2106; 12–18 m €2812; metastatic disease €20,540; palliative care €21 146 |
| Govaert, 2017 [93] | Netherlands | 4202 CRC | Observational cohort after resections for a T1-3N0-2M0 stage CRC | 90 days | Hospital | RC: €13,366–€20,865 based on surgery technic; CC: €10,474–€15,199 |
| Govaert, 2016 [94] | Netherlands | 9913 CRC | Observational cohort after CRC surgery | 90 days | Hospital | €13,145–€14,237 |
| Govaert, 2016 [95] | Netherlands | 783 CRC | Observational cohort after CRC surgery oldest old vs others | 90 days | Hospital | >85-year-old €13,168, <85-year-old €13,644 |
| Hanly, 2016 [96] | Ireland | 159 CRC | Cross-sectional prevalence-based survey to assess productivity loss via friction cost approach | Lifetime | Societal/pro-ductivity loss | €8543 per patient |
| Hanly, 2013 [97] | Ireland | 154 CRC | Assess OOP[1], time and travel costs of carers | 1 year after diagnosis | Patients | 1st year informal care cost total €29,842 of which 85% time costs, 13% OOP and 2% travel |
| Hanly, 2013 [98] | Ireland | 154 CRC | Observational cohort after CRC diagnosis to assess weekly time and costs of informal care | 1 year after diagnosis | Carers | Weekly time costs: initial phase €295 (hospital-related activities); €630 (domestic-related activities) and in the ongoing care phase €359 |
| Lang, 2009 [99] | USA | 56 838 CRC >65 years old | Observational cohort after CRC diagnosis vs non-cancer controls | Lifetime | Health insurance Medicare | Lifetime excess costs CC: $29,500; RC $26,500 |

[1] Out-of-pocket

| | | | | | | |
|---|---|---|---|---|---|---|
| Mar, 2017 [100] | Spain | 529 CRC | Cross-sectional prevalence-based analysis of CRC patients | N/A | Public payer | Mean initial treatment cost: stage I €8644, stage II €12,765, stage, €13,075. From metastases until death (stage IV) €27,633 |
| Marti, 2016 [101] | UK | 83 CRC | Observational cohort of CRC, BC, PC survivorship after a year from diagnosis, patient-reported utilization of resource | 3 months costs, One year after diagnosis | Societal | €409 per 3 mon, 12−15 mon after diagnosis |
| Ritzwoller, 2018 [102] | USA | 1 614 CRC | Observational cohort after recurrence or de novo diagnosis of stage IV CRC | 1 year after diagnosis | Health insurance | $54,956−$79,809 (<65year-old), $43,726−$59,623 (>65year old) |
| Seal, 2013 [103] | USA | 5 160 CRC <65 years old | Observational cohort after CRC diagnosis, total costs | Lifetime | Health insurance | Annual treatment cost per CRC patient $97 400 |
| Song, 2011 [104] | USA | 6 746 mCRC | Observational cohort after diagnosis of mCRC vs non-cancer controls per treatment phase | Lifetime | Health insurance | Monthly costs of mCRC care $14,585 higher vs non-cancer controls |
| Van Gelder, 2013 [105] | Belgium | 539 CRC | Observational cohort after CRC diagnosis including cost of last year | Lifetime | Health insurance + patient | Cumulative cost for an average follow-up of 3 years: €37,696. Patients' OOP 10% |
| Warren, 2008 [106] | USA | 64 554 CRC > 65 years old | Observational cohort of breast, lung, CRC, or prostate cancer from 2 months before diagnosis | -2 months to 1 year after diagnosis | Health insurance Medicare | Initial care costs 2002: $41,134 |
| Wong, 2012 [107] | China | 401 CRC | Observational cohort after CRC diagnosis | 1 year after diagnosis | Public payer | 1st year direct medical costs range $1,941 to $45,115 based on stage |
| Wright, 2007 [108] | USA | 6 108 CRC >65 years old | Observational cohort after CRC diagnosis, explore drivers behind differences (race etc) | 18 months after diagnosis | Health insurance Medicare | 16-month cost after diagnosis $38,821 (white $38,378, African American $44,199) |
| Wu, 2018 [109] | USA | 1 976 AC | Observational cohort after AC diagnosis. direct costs vs non-cancer controls | 2 years after diagnosis | Health insurance, direct costs | 1st 2-year mean cost per AC patient $127,531 |
| Yabroff, 2009 [110] | USA | 76 821 CRC >65 years old | Cross-sectional prevalence-based analysis of annual CRC costs per patient comparing different registries | Annual cost | Health insurance Medicare | Annual cost $12,231−$18,359 per prevalent patient |
| Yabroff, 2009 [111] | USA | 116 430 CRC >65 years old | Observational cohort after CRC diagnosis vs non-cancer controls | 5 year after diagnosis | Health insurance Medicare | 1st year after diagnosis $32,648, mean 5-year costs $37,227 |
| Yabroff, 2008 [112] | USA | 144 130 CRC >65 years old | Costs of all cancers in different phases of the disease | 5 year after diagnosis | Health insurance Medicare | Annual Men: Initial $29,609, Continuing $2254, Last year $36,483<br>Women: $29,930, $1595, $33,610 |
| Ó Céilleachair, 2014 [113] | Ireland | 497 CRC | Cross-sectional survey of recently diagnosed CRC patients to assess OOP burden | 1 year after diagnosis | Patient | Mean OOP payments during 1st year €, 589 |

## 2.4 ECONOMIC EVALUATION

Economic evaluation is needed to systematically identify, measure and value the inputs and outputs of alternative policies and interventions that should improve health. Each decision to choose one intervention over another will have effects both on health, but also on health-care resources. Health-care resources are limited and the true cost of used resources is the benefit from the best alternative choice that was lost (opportunity cost). The purpose of economic evaluations is to help make informed decisions of resource use to maximize health benefits. The evidence of alternative courses of action, which is mainly available from clinical trials, provides the key data for this Economic evaluation is a complement to clinical evaluation as it provides a framework with which to combine clinical evidence of alternative interventions with cost data to maximize value to society [11, 114, 115].

**Evaluation types**

The type of the study should be selected based on what is evaluated and what is the valuation of the consequences (Table 5). The four different types of evaluation studies are: cost analysis; cost-effectiveness analysis; cost−utility analysis, and cost−benefit analysis.

**Table 5.** Economic evaluation types (adapted from Drummond et al. 2015 [11])

| Type of evaluation | Measurement/ valuation of costs | Identification of consequences | Measurement/valuation of consequences |
|---|---|---|---|
| Cost analysis or cost minimization analysis | Money | None or same between alternatives | None |
| Cost-effectiveness analysis | Money | Same single effect for both alternatives but achieved to different degrees | Natural units (e.g. life-years gained, progression-free survival, blood pressure) |
| Cost-utility analysis | Money | Single or multiple effects, not necessarily same in both alternatives | QALYs (healthy years) |
| Cost-benefit analysis | Money | Single or multiple effects, not necessarily same in both alternatives | Money |

Cost analysis is the simplest analysis and should be used if the outcome is shown to be similar in the compared alternatives. Cost-effectiveness analysis could be the right method, when resource allocation decisions are made within one therapeutic area, e.g. progression-free survival (PFS) in certain cancer types. Cost-utility analysis incorporates the quantity and quality of incremental survival. This is needed when decisions around resource allocation are made between different disease areas in health care, and are thus usually based on the

payer's requirement for health technology assessment. In cost−benefit analysis the health gain is valued in money as well. A positive decision should be taken if the monetary value of benefits is higher than that of costs.

**Decision-analytic modelling**

At the time when new treatment options become available, i.e. after marketing authorization approval, a limited amount of evidence is available. Usually the evidence is from randomized clinical trials (RCTs) where the patient population is highly selected, treatment procedure does not match with local procedures, follow-up period is short, or comparators used might not be relevant. Also, in the RCTs the focus is on efficacy – how the treatment works under ideal conditions with selected patients – rather than effectiveness – how the treatment works in everyday clinical practice. Hence, RCTs seldom offer sufficient basis for economic evaluation and decision-making. Decision-analytic modelling provides a decision-making framework under conditions of uncertainty and it allows us to:

- Combine results from different studies
- Quantify and manage uncertainty
- Link intermediate clinical endpoints to final outcomes
- Synthetize head-to-head comparisons where relevant trials do not exist
- Extrapolate beyond the results of trial
- Localize results into different clinical practice

In practice, a health economic model defines statistical relationships between disease states and describes the range of possible disease prognoses and the impact of alternative treatment options. Two commonly used models are decision trees and state transition models [116].

A typical cancer model structure is presented in Figure 7. Each circle corresponds to a disease state associated with certain costs and HRQoL. Arrows present the possible transitions from one health state to another. Each arrow is associated with a probability. When comparing different treatment options, utility values and costs in each state differ as do the probabilities of moving between states. This allows the calculation of incremental costs and effectiveness between the alternatives.

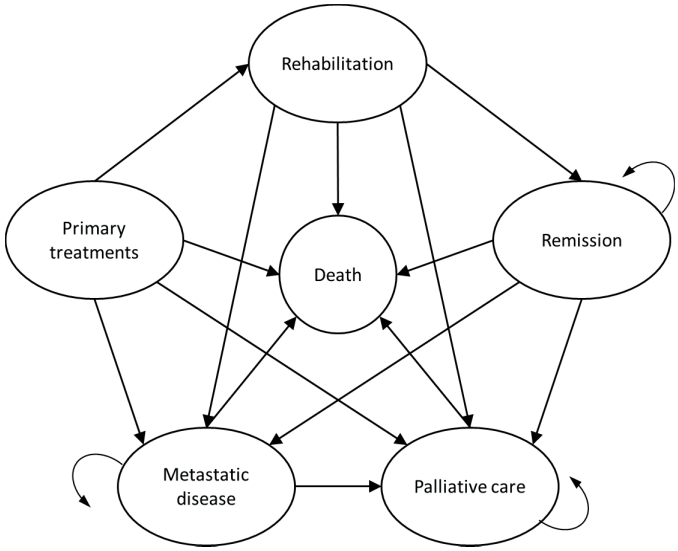



**Figure 7.** Example of health economic model structure used in cancer.

In cancer, the primary outcome measures for the economic evaluation are usually quality-adjusted life-years (QALYs) gained, disease-free survival and total survival. From this, the incremental cost-effectiveness ratios (ICER) can be derived by dividing the incremental costs of treatment A compared to treatment B by the incremental effectiveness (e.g. QALYs gained).

$$\text{Incremental cost-effectiveness ratio (ICER)} = \frac{\Delta\text{Cost}}{\Delta\text{Effectiveness}} = \frac{\text{Cost}_A - \text{Costs}_B}{\text{Effectiveness}_A - \text{Effectiveness}_B}$$

Incremental analysis of costs and health effects is often presented in a cost-effectiveness plane (Figure 8), where the horizontal axis represents the difference in health (usually QALY) and the vertical axis cost the difference between the compared alternatives.

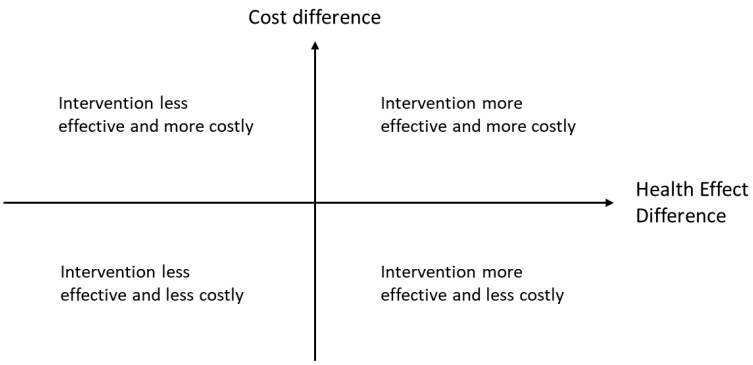


**Figure 8.** Cost-effectiveness plane.

Most of the interventions analysed end up in the upper-right corner: more health with more costs. Then it is not logically clear which alternative should be selected. Therefore, the ICER between the alternatives must be calculated and the maximum ICER threshold for an alternative to be considered cost-effective and acceptable be decided. This threshold represents society's maximum willingness to pay for a unit of effectiveness, e.g. for a QALY gained, and this varies between countries and diseases. In Finland, the ICER threshold is not defined. The World Health Organization (WHO) recommends a threshold range of 1−3 times the gross domestic product (GDP) per capita. In the case of the upper-left and bottom-right corner the decision is clear: one alternative dominates over the other, i.e. is 'better' both in terms of effectiveness and costs.

*Time horizon of the analysis*

In economic evaluations the time horizon is the duration over which health effects and costs are calculated. The time horizon should be the period in which the cost and health consequences might differ between the compared interventions. In the case of cancer, the time horizon is usually lifetime. [117]

*Discounting*

In many cases the costs and consequences of interventions occur at different times. Benefits received today are valued more than those in the future. The reason for this is a phenomenon called 'time preference'. To take this into account in economic evaluation, future health consequences and costs should be discounted [11]. The used discount rate might have a substantial impact on the outcomes of economic evaluations. The controversies around discounting are mainly about the discount rate, should the same rate be applied both to costs and health effects and whether the rate should be constant over time. In most countries, the discount rates are equal for costs and effects and vary between 1.5 and 5%[118].

*Choice of the comparator*

Economic evaluation always involves a comparative analysis of at least two interventions. The choice of comparator is critical as it defines against which alternative the incremental health benefits and costs should be evaluated. The comparator should be the second best alternative and it was thus usually the standard of care used before the new option became

available. Alternative comparators to be considered might be the least costly option and the 'do nothing' scenario [119, 120].

*Sensitivity analysis to manage uncertainty*

One of the benefits of the systematic decision framework that economic evaluation offers is that it helps to handle and manage the uncertainty. All analyses contain uncertainty, which may arise from the random variability between patients (stochastic uncertainty, first-order uncertainty), the uncertainty in estimation of the parameters (second-order uncertainty), heterogeneity between patients, and from the structural uncertainty of the decision model [121].

There are many options for conducting a sensitivity analysis. The decision on what kind of sensitivity analysis to use should be made based on what type of uncertainty should be managed. In *one-way sensitivity* analysis each variable is varied at a time, other things equal, to assess the impact on end-result. In *multi-way analysis* several variables are varied at the same time. In *threshold analysis* one parameter is varied until the tipping point where the outcome measure reaches the predefined threshold (e.g. ICER threshold). Probabilistic sensitivity analysis is the most sophisticated approach to analysing stochastic uncertainty. Here probability distributions of key input parameters are used to produce a distribution of outputs [121].

It has been assessed that in the economic evaluations the parameter uncertainty associated with HRQoL estimates had the biggest impact on results, followed by cost estimates and use of different discount rates [122].

# 3 AIMS OF THE STUDY

Cancer is becoming more and more common as people live longer and new treatment options improve survival rates. However, there is still a substantial unmet need and thus a remarkable share of research and development investments are focused on developing new cancer therapies. Patients' HRQoL is important when making treatment choice decisions, especially in cancer where some therapies might offer limited survival benefit with even a negative impact on HRQoL due to adverse effects. New drug discoveries are expensive and thus it becomes even more important in the future to have a rigid health technology assessment in place to allocate scarce resources optimally. The main aim of this series of studies was to evaluate HRQoL and costs associated with CRC and to generate crucial real-world data to be used in cost-effectiveness analyses. In addition, BC, PC, and CRC patients' financial burden and its HRQoL implications was explored and late-stage BC, PC and CRC patients' HRQoL assessed.

The specific aims were:

1. To assess the HRQoL among various disease states of CRC in a real-world setting using three standard instruments – 15D, EQ-5D and EORTC QLQ-C30 − and to explore clinical and demographic factors associated with HRQoL in CRC (Study I).

2. To explore all resource use and costs, including direct health-care costs, productivity costs and costs of informal care, in different disease states of CRC (Study II).

3. To evaluate end-stage breast (BC), prostate (PC) and CRC patients' HRQoL and to compare three different instruments – 15D, EQ-5D and EORTC QLQ-C30 – in this population and explore factors related to poor HRQoL (Study III).

4. To assess the direct economic burden on BC, PC and CRC patients due to out-of-pocket (OOP) expenditure and to explore how it is associated with decreased HRQoL measured by the 15D. Furthermore, the factors that explain financial difficulties were analysed (Study IV).

# 4 PATIENTS AND METHODS

The study is based on a survey and registry study of 1978 breast, prostate and colorectal patients conducted in the Hospital District of Helsinki and Uusimaa (HUS) between October 2009 and February 2011. Hospital District of Helsinki and Uusimaa covers almost 30% of the Finnish population.

## 4.1 PATIENT ENROLMENT

All patients aged 18 and above, diagnosed with primary or recurrent BC, PC or CRC after 2005 in HUS were eligible for the study. Patient recruitment was designed to achieve a balanced sample of patients from different disease states and cancers. The goal was to include 1000 BC patients, 500 PC patients and 500 CRC patients. The predefined disease states were:

- *Primary treatments* (local disease, 0–6 months after diagnosis),
- *Rehabilitation* (local disease, 6–18 months after diagnosis),
- *Remission* (local disease, more than 18 months after diagnosis),
- *Metastatic disease* (patients having metastases and having received oncological treatment) and
- *Palliative care* (metastatic disease and patients receiving only non-oncological treatment)

The disease states were decided based on clinical relevance and applicability in health economic modelling.

Patients were identified when visiting hospital or from hospital patient records based on the time of diagnosis. Patients were recruited by mailing a consent letter and a questionnaire (Appendix 1). Patients in primary treatments and in a palliative care state were recruited by a research nurse when visiting the hospital or the Terhokoti hospice. Patients who did not respond to the original invitation received one reminder. Patients returned the consent form and the questionnaire to the clinic or via mail in a prepaid envelope.

## 4.2 STUDY POPULATION

The inclusion criteria were met/fulfilled by 1978 patients and these were included in the analysis. Of the population, 840 had BC, 630 PC and 508 CRC (Table 6). Patients' age ranged

from 26 to 96 with a mean of 66 years, and the time from diagnosis varied from 1 week to 24 years with the mean time being 3 years.

The data set is extensive and unique and it is utilized in five other doctoral thesis studies. Table 6 shows which part of the data set is utilized in each article of this thesis.

**Table 6.** Characteristics of the study population, n (%)

| | Breast | Prostate | Colorectal | Total |
|---|---|---|---|---|
| Respondents | 840 (42) | 630 (32) | 508 (26) | 1978 (100) |
| Response rate | | | | |
| Female, % | 835 (99) | 0 (0) | 238 (47) | 1073 (54) |
| Age, mean (SD) | 62 (11) | 69 (8) | 68 (11) | 66 (11) |
| **Disease state** | | | | |
| Primary treatment | 118 (14) | 47 (7) | 61 (12) | 226 (11) |
| Rehabilitation | 150 (18) | 158 (25) | 79 (16) | 387 (20) |
| Remission | 382 (45) | 317 (50) | 217 (43) | 916 (46) |
| Metastatic disease | 176 (21) | 89 (14) | 110 (22) | 375 (19) |
| Palliative care | 14 (2) | 19 (3) | 41[1] (8) | 74 (4) |
| **Other background factors** | | | | |
| Higher education | 483 (58) | 308 (55) | 279 (55) | 1070 (57) |
| White collar | 431 (52) | 309 (56) | 251 (50) | 991 (53) |
| Married/cohabiting | 520 (63) | 457 (82) | 334 (67) | 1311 (70) |
| Employed | 325 (39) | 102 (18) | 115 (23) | 542 (29) |
| Unemployed | 20 (2) | 12 (2) | 7 (1) | 39 (2) |
| Retired | 454 (55) | 432 (78) | 365 (73) | 1251 (66) |

Studies I, II, n = 508
Study III, n = 114
Study IV, n = 1978

## 4.3 MEASURING HRQOL

The HRQoL data were collected through a broad self-administered questionnaire (Appendix 1) utilizing the cancer-specific EORTC QLQ-C30 instrument and two generic, single index measures, the 15D and the EQ-5D including a visual analogue scale (VAS). For the 15D we used the Finnish valuation algorithm for HRQoL scores and profiles. For the EQ-5D the UK time trade-off (TTO) tariff was used. These instruments were selected as they are widely

[1] The definition of palliative care varied between studies. In Studies I, II and IV the patients who had metastatic disease and who were no longer receiving oncological treatments were included. In Study III the patients who died within the following six months after they responded to the questionnaire were also included.

used among cancer patients in Finland and thus allow comparison with previous and future results.

The patient questionnaire also included questions about their socio-demographic situation and health-care resource use. This is a cross-sectional study by design, so patients answered the questionnaire only once. Within the five disease states the patients' date of answering was not defined.

In Study I, the CRC patients' HRQoL measured by the 15D and EQ-5D was compared to that of an age-, gender- and education-standardized sample of the general Finnish population. The population reference values were available from the Finnish Health 2000 Health Examination Survey [123].

### 4.4 COSTS AND RESOURCE USE

Cost and resource data are comprehensive and they were collected from several registries (Table 7) and complemented by the patient survey (Appendix I). Costs were calculated for a six-month period based on the patient's disease state. A six-month period was selected as it reflects the natural phases of the disease and therapies used.

**Table 7. Data sources used**

| Cost and resource use | Data source: |
|---|---|
| Primary care resource use | Data from home municipality: Helsinki, Espoo, Vantaa Terhokoti, Hospice<br>Patient survey (last 3 months) |
| Private health-care use | Patient survey (last 3 months),<br>The Social Insurance Institution of Finland |
| Unit costs primary and private health care | National Institute for Health and Welfare, THL [124] |
| Secondary care resource use and costs | Helsinki University hospital patient records: Ecomed |
| Outpatient medication and unit costs | The Social Insurance Institution of Finland |
| Rehabilitation | The Social Insurance Institution of Finland |
| Travelling and costs | The Social Insurance Institution of Finland |
| Days absent from work | Patient survey (last 3 months),<br>The Social Insurance Institution of Finland |
| Sick allowance | The Social Insurance Institution of Finland |
| Disability pension | Patient survey (last 3 months),<br>The Social Insurance Institution of Finland |
| Informal care use | Patient survey (last 3 months) |
| Informal care costs | Shadow price for a practical nurse [125]. |

**Health-care costs**

Resource use and costs in secondary health care by hospitals were obtained from the Ecomed® patient administration system (Datawell Ltd., Finland), which covers all the costs of treatment for individual patients given in the hospital and is categorized according to resource type.

Primary health-care resource use data were extracted from patients' home municipality. The data were available only from the three biggest cities: Helsinki, Espoo and Vantaa, which represented around 80% of the total study population. The data covered primary care general practioner (GP) and nurse visits, home hospice care, and primary care hospitalization. For the 20% of the patients for whom primary health-care data were missing, the missing values were imputed using propensity score matching, which allowed the calculation of the total costs. We used average unit costs from Helsinki, Espoo and Vantaa to calculate the primary care costs. Resource use and cost data were also available from the Terhokoti hospice. Mean unit costs for primary care visits and treatments were available from the National Institute for Health and Welfare, THL [124].

The Social Insurance Institution of Finland (KELA) provides universal social security coverage. It provides family benefits, health insurance, rehabilitation, basic unemployment security, basic social assistance, housing benefits, financial aid for students, disability benefits and basic pensions. Data for retail medicine reimbursements and usage, travel reimbursement, sick allowance, disability pensions, private health-care utilization and costs, and rehabilitation use and costs were available from KELA's health insurance registry.

Additional data on resource use and background information were gathered from patients with a self-administered questionnaire about:

- Occupational health care by type of service
- Private health-care providers
- Cancer-related retail medicine purchases, including prescription-free products
- Socio-economic status

**Productivity loss**

Productivity losses were estimated based on data collected from the patient survey. Productivity losses arise from early retirement due to cancer and sick leave due to cancer. For patients who are working, we also asked how they assessed their ability to work.

However, reduced work capacity was not included in the assessment. Regarding sick leave, data were also available from The Social Insurance Institution of Finland (KELA) and they were used to validate the days absent from work.

The productivity loss valuation was done using the common human capital approach where the margin of production of the individual is valued by his or her pre-tax salary [82]. The loss was then calculated by multiplying the number of days absent from work by the average daily labour cost, including the employer's social security payments of, on average, 38.6% in addition to the pre-tax salary. The pre-tax salary was established from earnings-based sick allowance available from KELA.

**Informal care**

In the survey, the amount of support and care given outside of the health-care system due to CRC was assessed based on patients' own estimates of the last three months. Patients were asked to estimate the average amount of care and support from family and friends per week. This was then multiplied by two to calculate the total hours per a six-month period. We set a maximum of 16 hours per day as a limit. For imputing the missing values, we used the propensity score matching method.

The proxy good method was used to value the informal care [126]. This is based on the shadow price of a market substitute, in this case a practical nurse. The mean pre-tax hourly salary for them was €13.63 in 2010 [127]. The total labour cost also includes 38.6% of social security payments for employers, which resulted in the final cost of €18.89 per hour, which was then used to multiply the hours used**.**

**Out-of-pocket payments**

In Study IV we assessed all the costs that are paid by the patient. These out-of-pocket (OOP) payments consisted of patient co-pays and fees. In Finland these are regulated by law so we were able to calculate the OOP payments based on total resource use per category. Patients incur co-pays when they use private health-care services, travel to health care, participate in rehabilitation, or buy reimbursed retail medicines. This cost and co-pay information was available from KELA.

Fees are due to the use of public health-care services: primary and secondary health-care visits, hospitalization and hospice care. This information was available from the hospital and primary care records and was supplemented with data from the patient questionnaire.

Finnish law sets a maximum annual OOP ceiling for retail medicines (€672.10), travelling co-pays (€157.25) and health-care services (€633.00). Costs related to informal care and non-medical treatments were not included in the study.

**Incremental cost assessment**

In Study II we included only the cost caused by CRC. The incremental share of CRC costs regarding outpatient medication, the use of private health-care services, travelling, and days absent from work was estimated using two population control samples (n=1016) matched for age, place of residence and sex, and excluding individuals with a cancer diagnosis. The sample was extracted from the KELA register . The resource use in secondary health care was limited to CRC-related visits based on diagnosis code and clinical expertise. In primary health care the incremental part of health-care costs was assessed based on the patient questionnaire and patient registry data from municipalities.

In Study IV, all costs accrued within the previous six-month period were included as the aim was to assess BC, PC and CRC patients' total economic burden.

### 4.5 STATISTICAL ANALYSIS

The descriptive statistics for continuous variables are reported as means, standard errors and ranges. These were cross-tabulated based on patients' background characteristics and disease state. The 95% confidence intervals were also calculated.

In Studies I and III we imputed missing 15D responses if no more than three values were missing by using linear regression. The HRQoL scores from all instruments and EORTC symptom and functional scales as well as the dimensions of 15D were reported graphically by disease state or cancer. In both studies a linear multivariate model using ordinary least square (OLS) was built to understand the factors associated with the 15D, EQ-5D, and VAS scores. We ran the analysis as a stepwise selection using standardized coefficients. The fit of the regression models used was assessed based on adjusted $R^2$. We examined the amount of collinearity using the statistical factor of tolerance and variance inflation (VIF). In Study I the analysis was done in two steps: the first model included as potential predictors clinical and general background factors, and in the second phase we added EORTC QLQ-C30 symptom variables. In Study III all cancer types were pooled together and the regression model included as explanatory variables (in addition to general background variables): time from diagnosis; time from metastasis; time to death; hospice care; appearance of brain,

bone, liver or lung metastases; and oncological treatments given within the last 3 months; as well as EORTC QLQ-C30 symptoms.

In Study I the mean HRQoL scores from 15D and EQ-5D were compared to those of the control population using Student's independent samples t-test. The control population was standardized based on age, gender and education.

In Study II we analysed, by using log linear multivariate analysis, how different background factors, such as cohabiting, age, gender, education level, and tumour site and HRQoL score, measured by the 15D, are associated with total cost. The distribution of cost variables was heavily skewed to the right, so a natural logarithm transformation was performed for the total cost variable. In the analysis, we used the fixed-model method with four different models per disease state (primary treatment state; remission and rehabilitation; metastatic disease; palliative care).

In Study IV we calculated the components of out-of-pocket (OOP) payments and grouped the patients into four categories based on their assessment of the severity of financial difficulties (financial difficulties 0−3). We compared the HRQoL scores from 15D and EQ-5D from groups 1 to 3 to group 0 with no financial difficulties using Student's t-test. To analyse how sociodemographic and cancer-related variables are associated with financial difficulties and HRQoL, we built a path model with two endogenous variables (financial difficulties and HRQoL). In the model, the exogenous explanatory variables were age, high education, employment status, marital status, type of work, total direct health-care costs, OOP payments, and the disease states for three cancer types, and comorbidity. The path coefficients (standardized beta coefficients) were estimated by two stepwise linear regression models (for financial difficulties and for 15D score). We calculated the indirect effect of an explanatory variable on the 15D score by multiplying the direct effects of each variable by the direct effect of financial difficulties on the 15D score.

The analyses were performed with the SPSS 21 software (SPSS Inc., Chicago, IL, USA). All p-values calculated were two-tailed and if less than 0.05 were considered statistically significant.

### 4.6 ETHICAL CONSIDERATIONS

The study did not affect the normal routines of care, but as patients participated in the study by answering the questionnaire, an approval from the Ethics Committee of Helsinki University Central Hospital was obtained (registration number 111/13/03/02/09). Patients were asked to give their written informed consent before inclusion. An approval from all register holders (Social Insurance Institution, home municipalities, Statistics of Finland) was also requested before access to data was granted. The trial has been registered in the Helsinki and Uusimaa Hospital District Register (www.hus.fi) with trial number 233895.

# 5 RESULTS

Altogether 1978 breast cancer (840), prostate (630), and colorectal cancer (508) patients satisfied the inclusion criteria and participated in this cross-sectional study as summarized in Table 1. Studies I and II focus only on CRC patients across all disease states and in Studies III and IV also breast and prostate cancer patients were included. A majority of the patients (77%) had local disease, 19% had metastatic disease and only 4% were in the palliative care phase. PC patients were on average oldest (69 years) and BC patients youngest (62 years). In general, participants were well educated: 57% had a higher education defined as at least high school completed; 53% were white collar workers, but two-thirds were already retired; 70% were married or co-habiting.

**Drop-out analysis**

In total, 3278 patients were approached of whom 2032 responded. The total response rate was 62%. Only age is available from those that did not respond. The mean age (66) did not differ statistically significantly between the groups.

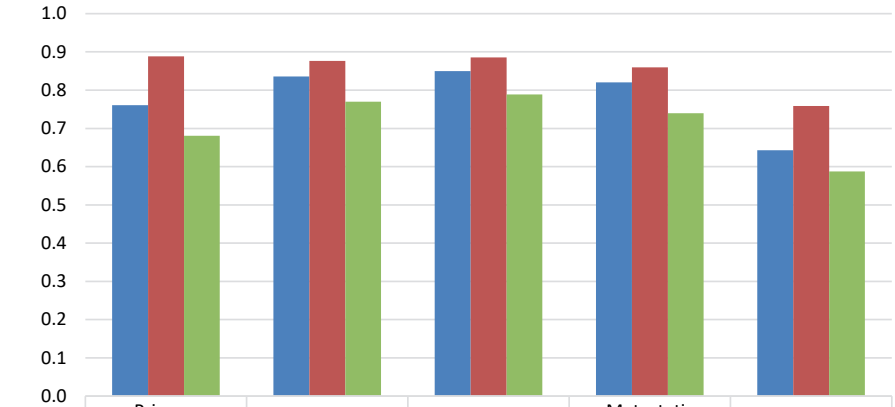
The patient survey questionnaire was extensive (10 pages and 66 questions, see Appendix I) and 386 patients left at least one HRQoL question unanswered. The mean age of those who were not able to complete the questionnaire fully (70 years) was statistically significantly higher than of those who did complete it (65 years).

## 5.1 HRQoL (STUDY I AND III)

Health-related quality of life was assessed using the 15D, EQ-5D-3L ('EQ-5D') and EORTC QLQ-C30 instruments in Studies I and III. Study I focused only on CRC including all disease states and Study III included palliative patients having breast, prostate or colorectal cancer.

**HRQoL in different states of CRC (Study I)**

The HRQoL results varied substantially based on the instrument used: 15D gave the highest scores in all disease states (Figure 9). The mean 15D score among all patients was 0.869 with a range from 0.423 to 1. The mean score by EQ-5D was 0.813, with a range from –0.429 to 1. The mean VAS score, which is a patient's subjective valuation, was 74.6 and the range was from 1 to 100.




| | Primary treatments | Rehabilitation | Remission | Metastatic disease | Palliative care |
|---|---|---|---|---|---|
| EQ-5D | 0.76 | 0.84 | 0.85 | 0.82 | 0.64 |
| 15D | 0.89 | 0.88 | 0.89 | 0.86 | 0.76 |
| VAS | 0.68 | 0.77 | 0.79 | 0.74 | 0.59 |

**Figure 9. HRQoL in different states of CRC measured by 15D, EQ-5D and VAS[1].**

As expected, the mean HRQoL was lowest among palliative care patients measured by all the instruments. According to VAS and EQ-5D, the HRQoL improved after primary treatments, being highest in the remission group.

The proportion of patients who obtained a score of 1 indicating full health, varied widely across the instruments: it was 41% for the EQ-5D, compared to 9% for the 15D and 5% for VAS. Such a high percentage in patient groups, where we would not expect scores indicating perfect health, suggests a remarkable ceiling effect, i.e. inability of an instrument to distinguish health states at the better end of the scale. The high ceiling effect reduces the sensitivity of the instrument (discriminatory power) and reduces its ability to capture changes in quality of life over time (responsiveness to change).

**HRQoL comparison to general population**

The EQ-5D and 15D scores were compared to those of age-, gender- and education-standardized scores of the general population. The control group size for the EQ-5D

[1] VAS scores are divided by 100.

measured disease states was on average 4457 and for the 15D 4823. In general, the patients' HRQoL was comparable to that of the general public: only in the palliative state did the scores differ clinically importantly and statistically significantly (Table 8).

**Table 8.** Patients' HRQoL difference from age-, gender- and education-standardized general population[1]

| | Primary treatment Δ | Rehabilitation Δ | Remission Δ | Metastatic disease Δ | Palliative care Δ |
|---|---|---|---|---|---|
| EQ-5D score | -0.033 (0.230) | 0.064 (0.020) | 0.046 (0.002) | -0.005 (0.806) | -0.119 (0.019) |
| 15D score | -0.008 (0.486) | 0.015 (0.203) | 0.008 (0.266) | -0.016 (0.062) | -0.107 (0.000) |

**Symptoms and functionality in different states of CRC**

The 15D dimensions and cancer-specific EORTC QLQ-C30 symptoms and functional scales give a more precise picture of what elements of HRQoL are impacted in different states of the disease.

In the palliative state, all 15D dimension scores were lower compared to earlier disease states. In the metastatic state, usual activity, depression, vitality and sexual activity were impaired (Figure 10).

[1] A negative/positive number indicates that the patients are on average worse off/better off than the general population.

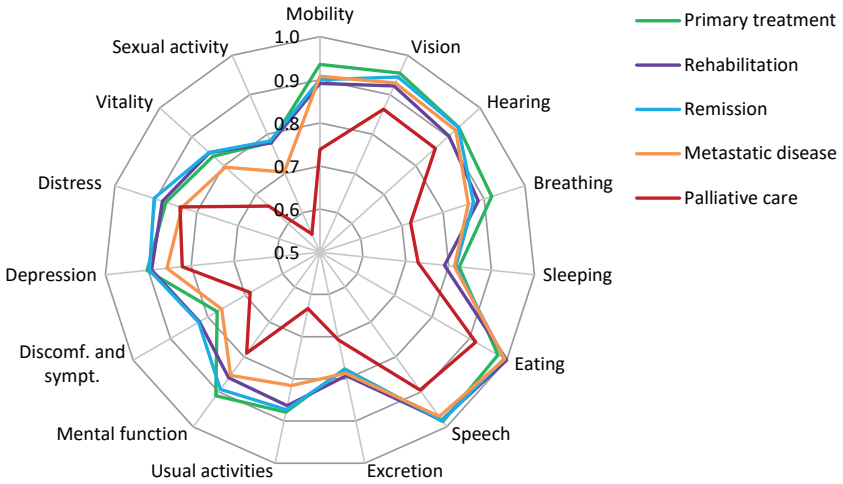



**Figure 10.** The mean 15D profile in different states of CRC.

Role and physical functioning showed largest impairment of EORTC QLQ-C30 functionality scales in the palliative phase. The differences between disease states were moderate in cognitive and emotional functioning (Figure 11).

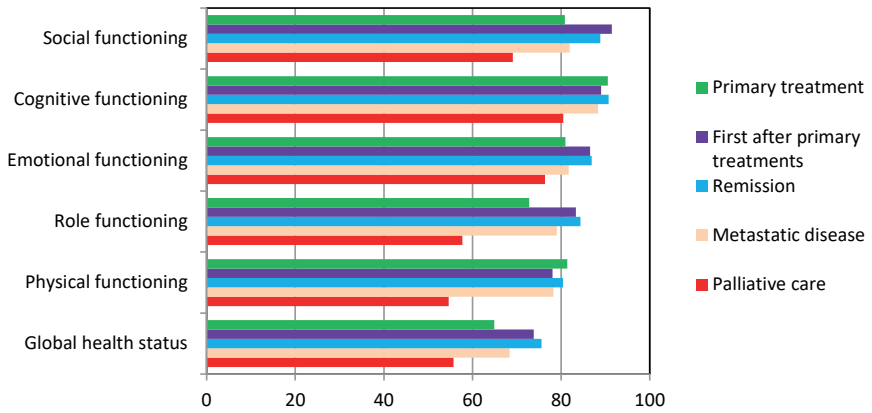



**Figure 11. Mean EORTC QLQ-C30 functionality scale in different states of CRC.**

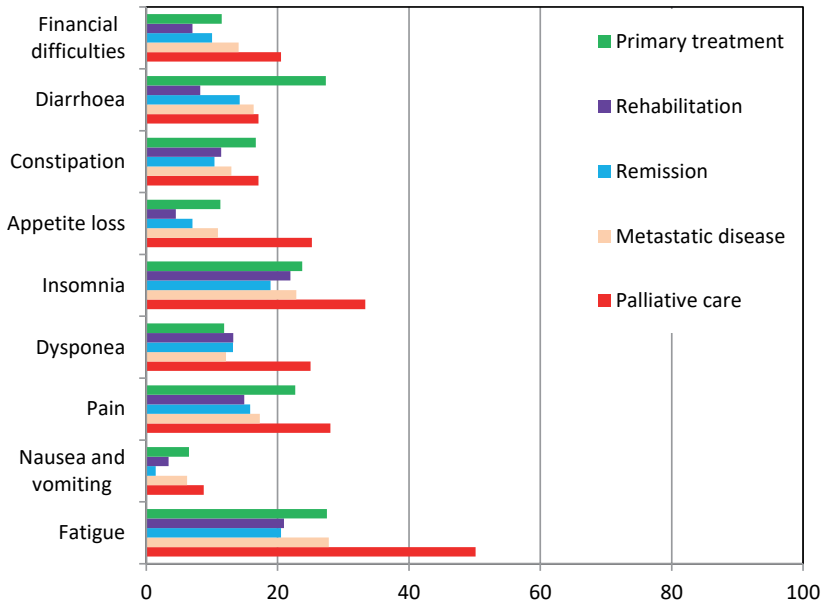



**Figure 12.** Mean EORTC QLQ-C30 symptom scale scores in different states of CRC.

Palliative patients were most symptomatic except that diarrhoea was more prevalent among patients in the primary treatments group. The most frequently reported symptoms were fatigue, pain and insomnia (Figure 12). Among all patients, 24% reported at least some financial difficulties caused by cancer.

**HRQoL of end-stage disease patients (Study III)**

The total number of palliative patients who participated in the study was quite small: 27 breast, 30 prostate, and 57 colorectal cancer patients. To understand better what the HRQoL in late-stage cancer is and what the factors associated with it are, we pooled all the patients to the same analysis. In this study, the end-stage was defined based on two criteria: patients who had metastatic disease and who did not receive oncological treatments any longer, or who died within the six months after they responded to the questionnaire, irrespective of the treatment given.

Closer to death, patients' HRQoL declined as was expected. The differences were greater with the EQ-5D and VAS than when using the 15D (Figure 13A). The utility values also varied substantially between cancer types. Patients with colorectal cancer reported the highest scores whereas breast cancer patients the lowest when using the EQ-5D and VAS. With the

15D the differences were smaller and prostate cancer patients reported the lowest values (Figure 13B).

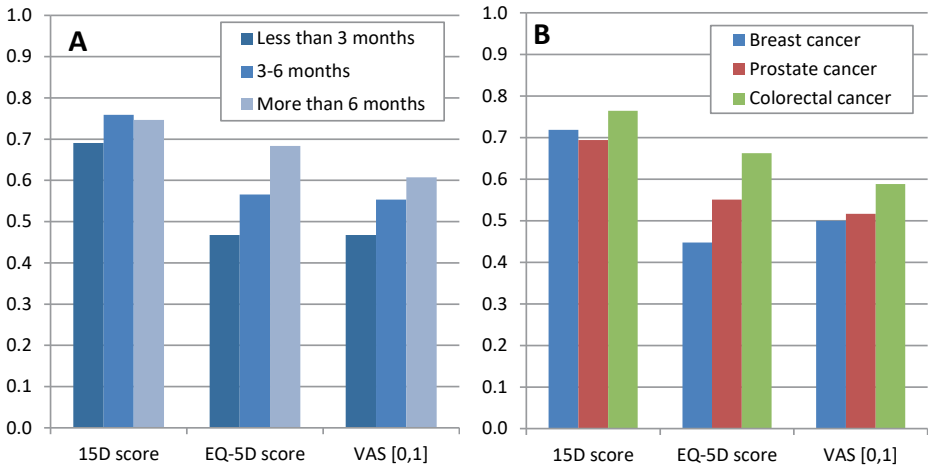



**Figure 13.** End-stage patients' mean HRQoL score by (A) time from response to death and (B) by cancer type.

The most prominent symptoms among end-stage patients were fatigue and pain and their prevalence increased as death became closer. At least some fatigue symptoms were reported by 98% of the patients and pain by 82%. At least some depression was experienced by 64% of the patients. Physical and role functionality were most impacted when time to death became shorter.

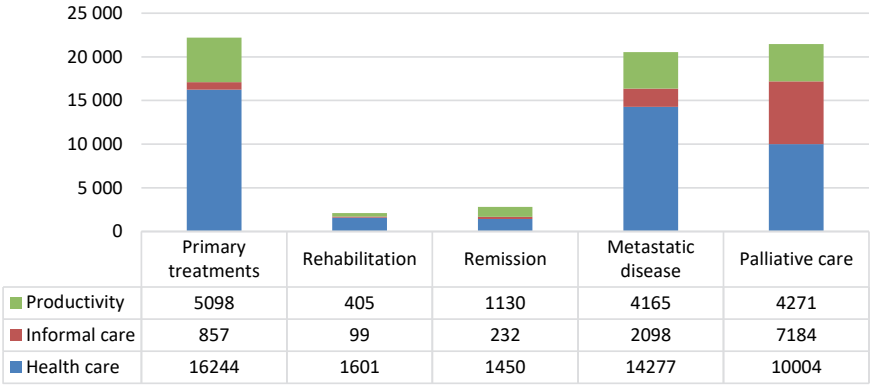
**Factors influencing HRQoL**

In Studies I and III, a multivariate model was built to understand what factors were associated with differences in HRQoL. In colorectal cancer, across all disease states, clinical and socio-economic background factors explained 22−32% of the variance in HRQoL measured by the 15D, EQ-5D and VAS. In the first model, where only background factors were included, the financial difficulties had the most prominent negative impact across all instruments, followed by age. When adding the symptoms from EORTC QLQ-C30 to the model, pain and fatigue had the biggest negative effect on HRQoL. The model explained 52−66% of the variance ($R^2$) based on the instrument used.

Among end-stage patients (III), the multivariate analysis revealed that fatigue was the main driver associated with impaired HRQoL irrespective of the instrument used. Other statistically significant explanatory variables varied based on the instrument used. With the 15D, the time from diagnosis, constipation, female gender and fatigue were negatively associated with HRQoL, and education and nausea and vomiting positively. Pain and fatigue were the only significant factors when the EQ-5D was used. With VAS, financial difficulties, in addition to fatigue, pain, and depression, had a negative impact on HRQoL whereas for the female gender, cohabiting and appetite loss were associated with higher HRQoL. The explanatory power of these models varied between 56 and 79%.

### 5.2 COSTS OF COLORECTAL CANCER IN DIFFERENT STATES (STUDY II)

The mean total costs caused by CRC for a six-month period varied greatly between disease states. They were highest during the primary treatments, followed by palliative care and metastatic disease. Also, the components of costs varied a lot between disease states. Direct health-care costs represented 47−76% of all costs and were highest in the primary treatments state and lowest in the remission state. Informal care made up 33% of the costs in the palliative phase but were less than 10% in the other states. The share of productivity costs ranged from 19 to 40% between states and was highest in the primary treatments phase (Figure 14).

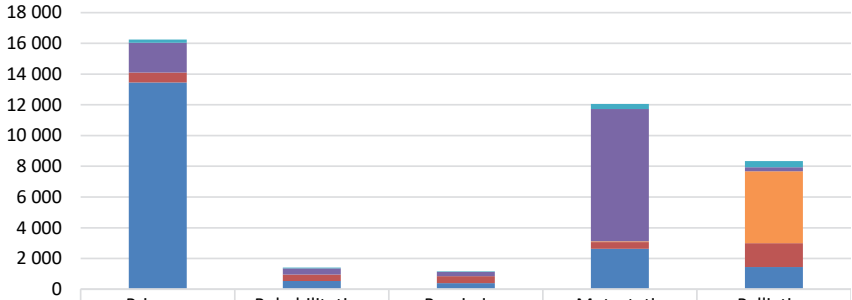



| | Primary treatments | Rehabilitation | Remission | Metastatic disease | Palliative care |
|---|---|---|---|---|---|
| Productivity | 5098 | 405 | 1130 | 4165 | 4271 |
| Informal care | 857 | 99 | 232 | 2098 | 7184 |
| Health care | 16244 | 1601 | 1450 | 14277 | 10004 |

**Figure 14.** Mean costs of CRC by state and type of the cost for a six-month period (€).

**Direct health-care costs**

In the primary treatments phase the direct health-care costs were dominated by inpatient specialist care (83% of total direct costs) whereas in the metastatic phase the medication costs were highest (71%). In the palliative phase hospice care costs were highest (56%). The mean hospice care cost in the palliative phase was €4681 and it varied between patients from €0 to €34,626. Primary care utilization in other states was stable and more modest (€424−640 per patient) than palliative care where the cost per patient was €1567.




| | Primary | Rehabilitation | Remission | Metastatic | Palliative |
|---|---|---|---|---|---|
| Travelling | 206 | 59 | 37 | 335 | 403 |
| Medication | 1944 | 395 | 272 | 8602 | 246 |
| Hospice care | 0 | 0 | 0 | 56 | 4681 |
| Primary care | 640 | 435 | 449 | 424 | 1567 |
| Specialist care | 13454 | 529 | 404 | 2638 | 1436 |

**Figure 15.** Mean direct health-care costs of CRC for a six-month period (€).

**Productivity losses**

Age is naturally the main driver for productivity costs, which were substantial in all disease states. Out of 508 respondents 308 (61%) were above the general retirement age of 65 years in Finland. Twenty-three per cent of all participants were working: 33% in the primary treatments state, 15% in the remission, 25% in the rehabilitation, 24% in the metastatic, and 10% in the palliative care state.

**Table 9.** Mean productivity losses in CRC by disease state for a six-month period (€).

| | Days absent from work | | Productivity loss | | Total (95% CI) |
|---|---|---|---|---|---|
| | Sick leave | Early retirement | Sick leave | Early retirement | |
| Primary treatments | 27 | 9 | 3895 | 1203 | 5098 (2979;7217) |
| Rehabilitation | 1 | 2 | 96 | 310 | 405 (0;1171) |
| Remission | 0 | 8 | 3 | 1127 | 1130 (443;1818) |
| Metastatic disease | 8 | 23 | 1057 | 3108 | 4165 (2568;5762) |
| Palliative care | 0 | 32 | 0 | 4271 | 4271 (20;8522) |

In the primary disease state, the productivity loss was mostly caused by sick leave due to cancer and in the metastatic and palliative care state by early retirement due to cancer. On average, the patients were on sick leave 27 days during primary treatments, 8 days during the metastatic disease and not at all during the other states. Among all respondents 7% were on early retirement due to CRC. This share was highest among metastatic (13%) and palliative (19%) states. (Table 9)

**Informal care**

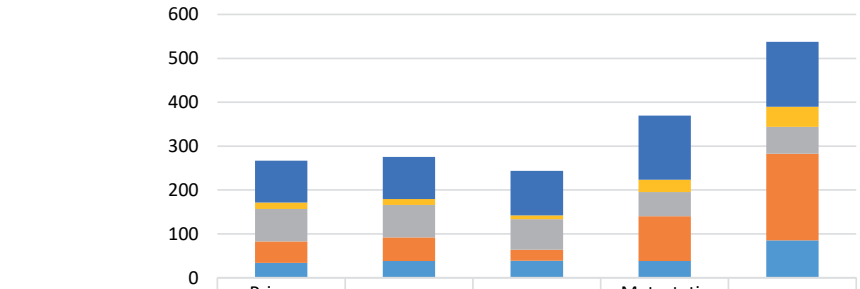
Across all the disease states, 103 patients (20%) reported that they had received at least some informal care from their family or friends during the previous three months. Among those who co-habited, almost half (46%) reported that they had received some help. In the palliative state, 46% of patients were getting informal care whereas in the rehabilitation state this figure was only 4%. The hourly support per patient was 10.2 in the palliative and 4.3 in the metastatic, 1.7 in the primary treatments state and less than 1 in the rehabilitation and remission groups (Table 10).

**Table 10.** Mean informal care costs due to CRC by disease state for a six-month period

| | N | Received informal care (%, share of all patients) | Mean hours of informal care per week | Cost of informal care, € (95% CI) |
|---|---|---|---|---|
| Primary | 61 | 19 (31) | 1.7 | 857 (158;1557) |
| Rehabilitation | 79 | 3 (4) | 0.2 | 99 (0;206) |
| Remission | 217 | 21 (10) | 0.5 | 232 (80;384) |
| Metastatic | 110 | 41 (37) | 4.3 | 2 098 (988;3208) |
| Palliative | 41 | 19 (46) | 10.2 | 7 184 (0;15157) |

## 5.3 COSTS TO PATIENTS (STUDY IV)

The financial burden of cancer is caused by the out-of-pocket (OOP) payments (medicine co-pays, hospital and doctor fees, and travelling costs) and reduction of income due to disability to work. Study IV focuses on OOP payments and patients' own assessment of their financial difficulties. The mean (OOP) payments for a six-month period were €267 in the primary treatments group, €275 in the rehabilitation group, €243 in the remission group, €369 in the metastatic group, and €538 in the palliative care group, respectively. OOP represented 3–8% of the total cost of cancer depending on the disease state. The financial burden caused by OOPs was clearly highest in the palliative state group and was driven by increased use of primary and secondary health care. The co-pays from outpatient medication were the biggest contributor across all disease states (28–42%) followed by private health-care co-pays (11–28%) (Figure 16).




| | Primary treatments | Rehabilitation | Remission | Metastatic disease | Palliative care |
|---|---|---|---|---|---|
| Outpatient medication | 95 | 96 | 101 | 146 | 148 |
| Travelling | 15 | 14 | 9 | 28 | 46 |
| Private | 74 | 74 | 69 | 55 | 61 |
| Secondary health care | 49 | 54 | 25 | 102 | 197 |
| Primary health care | 34 | 38 | 39 | 38 | 85 |

**Figure 16.** Mean out-of-pocket payments in different disease states by category (6-month time, €).

The share of OOP payments from total costs varied from 3 to 10% and was highest in the remission group where total costs and health-care utilization were lowest. The total OOP payments for a six-month period varied from 0 to €2901 per patient.

In the metastatic and palliative disease phases, 17% of the patients were on early retirement due to cancer. This was most common among BC patients (25%). Among patients with local disease, less than 5% were retired due to cancer. Out of those who worked, 83% felt that their ability to work was normal. Among patients with advanced cancer, 63% felt the same.

**Financial difficulties**

Twenty per cent of the patients reported at least some financial difficulties due to their cancer. This varied between disease states and was highest in the palliative group (45%), followed by the metastatic (30%) and primary treatments (22%) groups. In rehabilitation and remission groups, less than 20% had financial difficulties.

Financial difficulties are clearly linked to impaired HRQoL. In the group that reported no financial difficulties by EORTC QLQ-C30, the mean 15D, EQ-5D and VAS scores were 0.896, 0.872 and 79.1, respectively. In the group that reported a lot of financial difficulties, the mean 15D, EQ-5D and VAS scores were 0.714, 0.451 and 49.9, respectively. Compared to the group with no financial difficulties, the differences were statistically significant and clinically important.

A path model was built to assess the direct and indirect effects of financial difficulties on HRQoL (measured by 15D). In the model, age, co-habiting, and higher education had a significant direct negative association with financial difficulties, whereas unemployment, total health-care costs (excluding OOP payments) and OOP payments had a positive association. Age, higher education, total health-care costs (excluding OOP payments) and OOP payments had a direct negative impact on HRQoL, whereas colorectal cancer had a positive association. Financial difficulties had a substantial direct impact on HRQoL: -0.408(Figure 17).

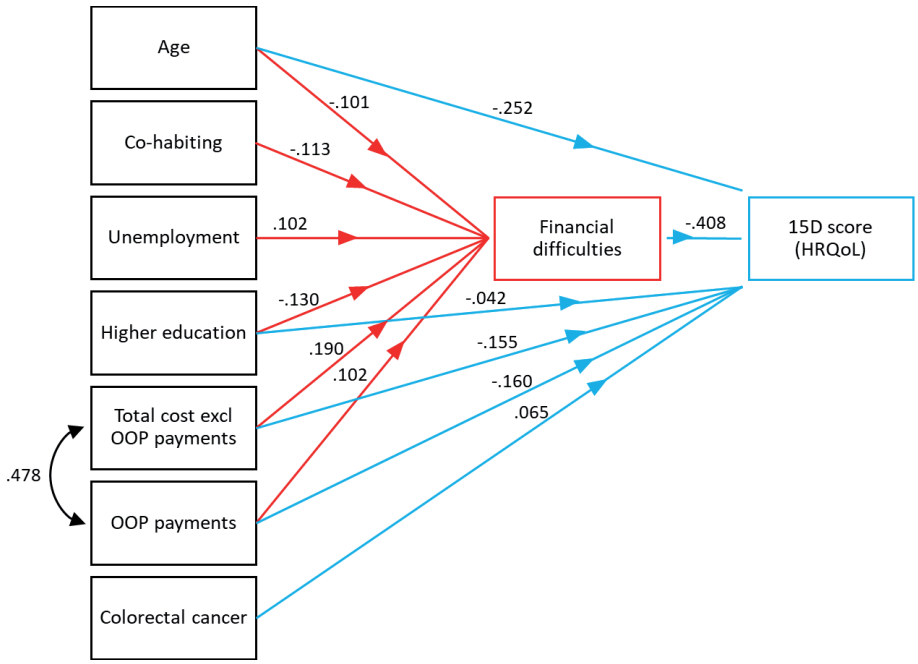



**Figure 17.** HRQoL – financial difficulties path model.[1]

[1] Model presents the direct and indirect effects of socio-economic and clinical factors on financial difficulties and HRQoL (15D score) and the total effect of financial difficulties on the 15D score. Red lines present the association of a single explanatory variable with financial difficulties and blue lines the association with the 15D score. Standardized coefficients from linear regression models were used.

# 6 DISCUSSION

Understanding current costs and HRQoL implications of a disease provides an essential basis for making decisions to introduce new treatment options. Health economics provides tools to analyse how health-care resources are used and how scarce resources should be allocated to maximize health. This study aimed to: assess HRQoL in different states of CRC and define its determinants; evaluate end-stage cancer patients' HRQoL; explore what resource use and costs are associated with CRC in different states of the disease; and to establish what is the financial burden of cancer to patients and what are its HRQoL implications.

Cancer, especially CRC incidence and mortality continues to rise and the burden to society and to patients is substantial. CRC survival rates have improved massively during the past decades due to better treatment options and improved and earlier diagnostics [3]. Still, a significant unmet need for better treatment options remains. At the same time the cost of developing new therapies continues to rise driven by ever more targeted mechanisms and smaller patient groups. The estimated cost of developing a new prescription medicine until marketing approval is $2.6 billion [128]. The substantial challenges between limited health-care budgets, increasing demand and ever more sophisticated but more expensive treatment options highlight the importance of this thesis.

## 6.1 MAIN RESULTS

**HRQoL in different states of the disease (Study I)**

In Study I, the HRQoL among CRC patients was comprehensively assessed using two generic (the 15D and EQ-5D) and one cancer-specific instrument (EORTC QLQ-C30) in all states across the disease from diagnosis until palliative care. The study provides valuable information on patients' HRQoL as it is based on real-life data and helps to identify factors that might have a negative impact on it.

As expected, the HRQoL was lowest among patients in palliative care but the differences in other states were relatively small. The mean utility scores measured by the 15D varied from 0.889 in the primary treatments group to 0.758 in the palliative care group (0.716–0.808). For EQ-5D the scores ranged from 0.850 in the remission group to 0.643 in the palliative care group. Among patients with local disease the HRQoL was comparable with that of a sample of age-, gender- and education-standardized general population controls after the primary

treatments phase. The study showed that the used instruments are applicable in this patient group but also revealed that different instruments provide very different HRQoL results and are not interchangeable. The 15D provided in all states the highest values, whereas patients' own VAS ratings were lowest.

The ceiling effect was substantial with the EQ-5D, as 41% of the patients obtained the score of full health. The multivariate analysis revealed that pain, fatigue and financial difficulties are clear determinants of poor HRQoL.

To our knowledge this is the first study in Finland to examine CRC patients' HRQoL across all disease states using generic instruments. The results are comparable to a Finnish national-level health survey where the mean score for a cancer patient was 0.855 measured by the 15D and 0.741 by the EQ-5D [129]. Compared to Finnish PC and BC patients' HRQoL, CRC patients reported lower scores at the beginning of the disease and higher in the advanced states [130, 131]. In a Japanese study the utility score for non-stoma long-term CRC survivor was 0.865 by the EQ-5D and 0.842 among patients with a stoma [12]. In a European study, conducted in the UK and Netherlands, the EQ-5D scores for pre-progression CRC patients were 0.741 and 0.731 for post-progression – clearly lower than in our study [63]. The most used HRQoL instrument among CRC studies is the EORTC QLQ-C30 [132].

**Resource use and costs of CRC (Study III)**

Study III showed that direct health-care costs represent a majority of costs. Most of the patients were retired (65%) and thus the productivity costs were moderate: 23% on average across the different states. Informal care costs were substantial in the palliative phase of the disease, where 76% of the patients received support.

The costs were calculated for five cross-sectional six-month periods. During the first six months, resource use is most intense and the costs are highest, driven by surgery and hospitalization. However, the most expensive phase is the metastatic phase which usually lasts longer. The median overall survival after metastases are diagnosed is estimated to be almost 30 months [133]. Thus, the metastatic phase lasts roughly five-times longer than the primary treatments phase and the costs are substantially higher. Longitudinal costs follow a U-shaped curve where the lowest costs are after the intense primary care phase.

The direct health-care costs were on average €16,244 in the primary treatments state, €1601 in the rehabilitation state, €1450 in the remission state, €14,277 in the metastatic state and

€10,004 in the palliative phase, respectively. A majority of the identified CRC cost research focuses on initial treatments after diagnosis with one-year follow-up. The mean cost estimates in US studies varied from $32,648 to $59,496 [106, 111, 134] and are clearly higher than what we estimated. The cost estimates in the studies conducted in Europe were comparable to our study. In a Dutch study the mean 90-day costs after CRC diagnosis varied from €13,366 to €20,865 based on the surgical technique used [93]. A study conducted in Spain estimated that the mean cost of initial treatments was €8644 for stage I, €12,675 for stage II and €13,034 for stage III, respectively [100]. In a German study, the mean costs of palliative care were, for the first year €42,361, and for the second €32,023 [91]. Cost data distribution is usually heavily skewed, which means that a small proportion of the patients is causing a substantial share of the costs. The duration of the palliative phase differs between cancer types and the definition of palliative care varies between countries [135]. All this makes the cost comparison difficult.

Torkki et al. estimated that the annual prevalence-based cost of all cancers in Finland was €927 million in 2014, which represents 4.5% of total health-care expenditure, and aligns with earlier European estimates of 3−6% of total health-care expenditure [136, 137]. In Finland the highest costs arise from BC, PC and CRC, which in 2014 were €367 million and of which CRC contributed €89 million [138]. Laudicella et al. have estimated that the direct health-care cost per CRC is the highest among the sites listing the most common cancers [139]. CRC-related costs are expected to continue to grow, driven mostly by an increased number of new patients [140]. At the same time the real cost per patient is decreasing [138].

**HRQoL among end-stage cancer patients (Study III)**

In Study III, we analysed the HRQoL of 114 end-stage BC, PC and CRC patients using three different instruments (15D, EQ-5D+VAS, EORTC QLQ-C30). The HRQoL was deteriorating and symptom burden increased as death was approaching. The most prevalent symptoms, as expected based on earlier studies, were fatigue, pain and insomnia [141]. In the multivariate analysis the association between impaired HRQoL and fatigue was most prominent with both VAS and the 15D. BC patients reported the lowest utility values and their symptom burden measured by the EORTC QLQ-C30 was highest whereas CRC patients' HRQoL was the highest.

All instruments used in this study are applicable in these patient groups. Altogether 21% of the respondents were not able to complete the HRQoL questionnaires fully. Problems with reporting were most common with EORTC QLQ-C30: 19% did not complete the

questionnaire. The results that the single index instruments produced varied substantially. The 15D provided highest values and the VAS gave the lowest. The problem with EQ-5D is that it cannot produce values between 0.88 and 1 and the ceiling effect is substantial. In this study, among end-stage cancer patients 13% obtained the score of full health with the EQ-5D. The EQ-5D can also have negative values (worse than death) in contrast to the 15D and VAS.

In the palliative care setting, generic single index value measures are not commonly used and thus reference values from similar patient populations are not available. The nature of palliative care requires more focus on patients' own experience and, due to the short duration of the phase, cost-effectiveness analysis is not fully applicable in this setting [142]. However, symptoms and HRQoL might be useful for predicting survival in the terminal setting [143, 144]. To our knowledge, this is the first study to assess end-stage cancer patients' HRQoL with generic instruments in Finland. As resource allocation decisions are more and more based on QALYs and palliative care is competing with alternative uses of the same resources, this study provides valuable information for decision-makers.

**Patients' economic burden of cancer (Study IV)**

Study IV revealed the remarkable negative impact of financial difficulties on BC, PC and CRC patients' HRQoL. Twenty per cent of the patients reported at least some financial difficulties due to their disease. The mean OOP payments for a six-month period varied from €243 in the remission state to €538 in the palliative care phase. Those who were unemployed, men, or lived alone were more likely to report health-related financial difficulties.

In Finland the common perception is that health care is universally available, and costs carried by patients are small and do not restrict access to care. The direct financial burden for patients consists of hospital and doctor fees and medicine and travelling co-pays. In this study we did not assess the productivity loss to patients due to disability to work. Maximum co-pays and fees are regulated but the annual total ceiling of €1555 (medicine co-pay, travelling co-pay, hospital and primary care fees in 2019) might be challenging for many. The OOP payments in Finland in 2010 were $660 per capita, clearly above the OECD average of $521 [145].

In Europe, a small number of studies on OOP payments are available. In an Irish study, Ó Céilleachair et al. estimated that the OOP payment costs for patients during the first year after CRC diagnosis was €1589, which is above our estimates [146]. However, there is

growing evidence that cancer patients in many other countries are also at a risk of financial difficulty and the impact it is having on patients' HRQoL and care might be substantial [147]. This so-called financial toxicity is more common in countries like the US, where treatment costs are enormous and social security limited. Financial hardship causes stress and anxiety and is estimated to be the strongest independent predictor of deteriorated HRQoL among cancer survivors [148].

The true costs of cancer to patients and the importance of financial difficulties might be underestimated in clinical practice [148, 149]. This study showed that financial stress is a prevalent issue in Finland among cancer patients, especially those with advanced disease, and needs more focus and support.

## 6.2 LIMITATIONS OF THE STUDY

Some limitations of this thesis require consideration. The most evident limitation is the cross-sectional design. The advantage of a cross-sectional design is that it is much faster to collect the data from all stages of the disease compared to observational follow-up of a cohort. However, the cross-sectional data set does not allow the analysis of causal relationships between observed association of explanatory and independent variables. The design did not allow the analysis of how patients' HRQoL or resource use develops over time.

In the cross-sectional cost study (II), the costs were calculated for a six-month period only. This does not reveal the true costs of each state of the disease as the number of patients entering into each state and the duration of the state vary. This is most evident in the metastatic phase.

The response rate was rather low − 62% − but comparable to other observational cross-sectional surveys among cancer patients, where the response rate has varied between 34% and 79% [53, 57, 150-152]. Only age was available from non-respondents, which made a thorough drop-out analysis impossible. However, it is likely that patients in poor health may have been more likely to leave the extensive questionnaire unanswered. This risk is most evident among late-stage patients. Patients in the palliative care phase were mostly recruited from the hospice or when visiting at the palliative unit and not all patients were capable of completing the survey. Therefore, the HRQoL estimates might be skewed towards the upper end of the scale and the true HRQoL burden might be greater.

Although the total sample was comprehensive (n=1978), the number of patients in each disease-specific state was small. This was especially an issue among palliative care patients where the total sample size was only 74. Also, in the metastatic phase the number of available options and lines of treatment makes the data relatively sparse and thus challenging to utilize in modelling. Patients were recruited only from the Helsinki University Hospital region, which may limit the generalizability of the results as the treatment patterns and patient characteristics may not be representative for the whole of Finland.

The choice of the statistical method for multivariate analysis is not straightforward and our decision to use traditional OLS could be seen as a limitation. There is an ongoing debate about what is the appropriate method for HRQoL scores where distributions are heavily skewed due to the ceiling effect [129, 153-156]. The OLS assumes normal distribution and thus produces biased estimates when data is censored. The study is explorative by nature and thus the exact quantification of the coefficients was not seen as a priority, rather the priority was to find drivers where to focus more on clinical setting to support patients' HRQoL. Statistically more sophisticated models that take into account the censored nature we could have used are Tobit, which is a maximum-likelihood method, and quantile regression method such as CLAD (censored least absolute deviations) regression [129, 153]. The bias is highest with EQ-5D due to the fact that the large share of patients with full health was substantial. Implications and future studies

The studies in this thesis provide much needed local information to be used in economic evaluations of new interventions in the treatment and prevention of CRC. This has been the first study to assess costs and HRQoL comprehensively across all disease states in Finland. The results help to detect determinants of poor HRQoL and reasons behind high costs.

Improved survival means that patients are living longer with their disease and the relevance of mortality measures declines as clinical endpoints and patient-reported outcomes become more important. As the patients' willingness to influence their treatment will also most likely increase, it is increasingly important to understand patients' preferences, drivers of HRQoL and costs of possible treatment pathways. This allows health-care providers to tailor different patient support programmes based on patients' individual needs and to prepare and manage the costs. Outcomes of care and costs should be measured routinely in health care and the data should be easily available to be utilized by all stakeholders in the health ecosystem. The results in this study showed that among patients with local disease, HRQoL

recovers well after primary treatments and is comparable to that of the general public. Based on this, the effectiveness of currently used treatments seems to be high.

There is no common agreement on which HRQoL instrument should be used, which seems to be one of the main barriers to using patient-reported outcomes more widely in clinical trials and practice. Both generic single index measures (the 15D and EQ-5D) used here were applicable in this patient group. However, the 15D provided more data on symptoms and functionality and the statistical properties were predictable. The choice of the instrument might have significant impact on the results of an economic evaluation. As was seen from the results, the mean utility differences were smallest when using the 15D compared to EQ-5D or VAS. In practice, that would mean that when the 15D is used instead of the EQ-5D the QALYs gained would be less as the utility differences between health states are smaller. This could mean that when using the 15D the ICERs are higher compared to EQ-5D and would then reduce the likelihood of implementing the new intervention to clinical practice.

It is known that 15D compresses the utilities versus other commonly used multiattribute utility instruments across other disease areas as well [129, 157-160]. Richardson et al. compared the sensitivity and validity in their article and found that the 15D was the most sensitive instrument among cancer patients measured by the correlations with EORTC QLQ-C30 in comparison to all other widely used generic utility instruments (EQ-5D-5L, HUI3, QWB, SF-6D, AQoL-8D) [161].

Of those who participated in the study, 99% completed the 15D questionnaire fully, 94% the EQ-5D, 95% VAS, and 86% the EORT QLQ-C30, respectively. When selecting the generic instrument for cancer patients the number of questions does not seem to be a hurdle for patients. In addition, the 15D allows the utility value to be calculated even when, at maximum, three answers are missing. Based on this study and earlier research, 15D seems to be the best option to be used routinely in cancer care. To understand cancer-specific symptoms, also disease-specific measures such as the EORTC QLQ-C30 is useful. However, both costs and HRQoL are currently measured in various ways and the comparison between interventions and countries remains challenging.

The articles in this thesis have been cited so far approximately 140 times in scientific articles. A majority of these citations are for studies I and III, which clearly shows the interest in and importance of focusing more on the HRQoL aspects of care.

# 7 CONCLUSIONS

- The three most common cancers, breast, prostate and colorectal, represent a considerable economic burden for society, and they lead to impaired HRQoL and premature deaths. This study generated crucial real-world data to be used in cost-effectiveness analysis.

- The HRQoL results depend heavily on the instrument used. HRQoL among colorectal cancer patients is surprisingly good compared to that of the general population across all disease states except for during the palliative state; this indicates the high level of care. The main determinants of impaired HRQoL were pain, fatigue and financial difficulties.

- The costs of colorectal cancer after the diagnosis are high and mostly driven by the cost of surgery. Costs tend to rise again if the disease progresses. A majority of the costs are direct health-care costs. The share of informal care is substantial, especially in the palliative care state. The costs of colorectal cancer are likely to increase in the near future due to ageing, increasing incidence rates, improved survival, and rising treatment costs.

- 15D, EQ-5D, VAS and EORTC QLQ-C30 are applicable instruments among end-stage cancer patients and provide valuable insights into patients' HRQoL. Fatigue is the most significant deteriorating factor of HRQoL. The 15D produced the highest mean utility values in this patient group.

- The economic burden caused by cancer-related OOP payments is high for many, which leads to financial difficulties. Financial difficulties have a substantial negative impact on patients' HRQoL.

# 8 REFERENCES


1. Ferlay, J., et al., *Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods.* Int J Cancer, 2019. 144(8): p. 1941-1953.
2. Editors: Stewart BW, W.C., *World Cancer Report 2014*. 2014, Lyon: International Agency for Research on Cancer.
3. *Finnish Cancer Registry*. 2019: https://tilastot.syoparekisteri.fi/syovat.
4. Hoff, M.B., W.W. Chang, and K.M. Mak, *Effect of estrogen on cell proliferation in colonic mucosa of the mouse.* Virchows Arch B Cell Pathol Incl Mol Pathol, 1981. 35(3): p. 263-73.
5. Santos, G.F., et al., *Estrogen-induced post-transcriptional modulation of c-myc proto-oncogene expression in human breast cancer cells.* J Biol Chem, 1988. 263(20): p. 9565-8.
6. Navarro, M., et al., *Colorectal cancer population screening programs worldwide in 2016: An update.* World J Gastroenterol, 2017. 23(20): p. 3632-3642.
7. Marja Hyöty, A.L., Heidi Nurmi, Ari Ristimäki, Raija Ristamäki ja Ritja Savolainen, *Kolorektaalisyövän kansalliset hoitosuositukset*. 2019, Duodecim.
8. *NCCN Clinical Practice Guidelines for Treating of Colon Cancer*. 2019.
9. Van Cutsem, E., et al., *ESMO consensus guidelines for the management of patients with metastatic colorectal cancer.* Annals of Oncology, 2016. 27(8): p. 1386-1422.
10. *NCCN Clinical Practice Guidelines for Treating of Rectal Cancer*. 2019.
11. Drummond, M.F., et al., *Methods for the economic evaluation of health care programmes*. 2015: Oxford university press.
12. Klarman, H.E., J.O.S. Francis, and G.D. Rosenthal, *Cost Effectiveness Analysis Applied to the Treatment of Chronic Renal Disease.* Medical Care, 1968. 6(1): p. 48-54.
13. Tan-Torres Edejer, T., et al., *Making choices in health: WHO guide to cost-effectiveness analysis.* 2003.
14. Von Neumann, J. and O. Morgenstern, *Theory of games and economic behavior, 2nd rev.* 1947.
15. Torrance, G.W., W.H. Thomas, and D.L. Sackett, *A utility maximization model for evaluation of health care programs.* Health services research, 1972. 7(2): p. 118.
16. Torrance, G.W., *Social preferences for health states: an empirical evaluation of three measurement techniques.* Socio-economic planning sciences, 1976. 10(3): p. 129-136.
17. Furlong, W.J., et al., *The Health Utilities Index (HUI®) system for assessing health-related quality of life in clinical studies.* Annals of medicine, 2001. 33(5): p. 375-384.
18. Hawthorne, G., J. Richardson, and R. Osborne, *The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life.* Quality of Life Research, 1999. 8(3): p. 209-224.

19. Kaplan, R.M., J.W. Bush, and C.C. Berry, *Health status: types of validity and the index of well-being.* Health services research, 1976. 11(4): p. 478.

20. Rosser, R. and P. Kind, *A scale of valuations of states of illness: is there a social consensus?* International journal of epidemiology, 1978. 7(4): p. 347-358.

21. Sintonen, H., *The 15D instrument of health-related quality of life: properties and applications.* Annals of Medicine, 2009. 33(5): p. 328-336.

22. Alanne, S., et al., *Estimating the minimum important change in the 15D scores.* Quality of Life Research, 2015. 24(3): p. 599-606.

23. Group, T.E., *EuroQol--a new facility for the measurement of health-related quality of life.* Health Policy, 1990. 16(3): p. 199-208.

24. Pickard, A.S., M. Neary, and D. Cella, *Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer.* Health and Quality of Life Outcomes, 2007. 5(1): p. 70.

25. Herdman, M., et al., *Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L).* Quality of life research, 2011. 20(10): p. 1727-1736.

26. Ware, J., M. Kosinski, and S. Keller, *SF-36 physical and mental health summary scales.* A user's manual, 2001: p. 1994.

27. Brazier, J., J. Roberts, and M. Deverill, *The estimation of a preference-based measure of health from the SF-36.* Journal of health economics, 2002. 21(2): p. 271-292.

28. Aaronson, N., et al., *The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology.* J Natl. Cancer Inst, 1993. 85(5): p. 365-376.

29. Rowen, D., et al., *Deriving a preference-based measure for cancer using the EORTC QLQ-C30.* Value Health, 2011. 14(5): p. 721-31.

30. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* BMJ, 2009. 339: p. b2535.

31. Carter, H.E., et al., *The cost effectiveness of bevacizumab when added to capecitabine, with or without mitomycin-C, in first line treatment of metastatic colorectal cancer: results from the Australasian phase III MAX study.* Eur J Cancer, 2014. 50(3): p. 535-43.

32. Cashin, P.H., et al., *Quality of life and cost effectiveness in a randomized trial of patients with colorectal cancer and peritoneal metastases.* Eur J Surg Oncol, 2018. 44(7): p. 983-990.

33. Franken, M.D., et al., *Cost-effectiveness of capecitabine and bevacizumab maintenance treatment after first-line induction treatment in metastatic colorectal cancer.* Eur J Cancer, 2017. 75: p. 204-212.

34. Gordon, L.G., et al., *A telephone-delivered multiple health behaviour change intervention for colorectal cancer survivors: making the case for cost-effective healthcare.* Eur J Cancer Care (Engl), 2015. 24(6): p. 854-61.

35. Michalopoulos, N.V., et al., *A cost-utility analysis of laparoscopic vs open treatment of colorectal cancer in a public hospital of the Greek National Health System.* J buon, 2013. 18(1): p. 86-97.

36. Robles-Zurita, J., et al., *SCOT: a comparison of cost-effectiveness from a large randomised phase III trial of two durations of adjuvant Oxaliplatin combination chemotherapy for colorectal cancer.* Br J Cancer, 2018. 119(11): p. 1332-1338.

37. Antonuzzo, L., et al., *Bevacizumab plus XELOX as first-line treatment of metastatic colorectal cancer: The OBELIX study.* World J Gastroenterol, 2015. 21(23): p. 7281-8.

38. Augestad, K.M., et al., *Should the surgeon or the general practitioner (GP) follow up patients after surgery for colon cancer? A randomized controlled trial protocol focusing on quality of life, cost-effectiveness and serious clinical events.* BMC Health Serv Res, 2008. 8: p. 137.

39. Bennett, L., et al., *Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first- or second-line treatment.* Br J Cancer, 2011. 105(10): p. 1495-502.

40. Brigic, A., et al., *A prospective case control study of functional outcomes and related quality of life after colectomy for neoplasia.* Int J Colorectal Dis, 2017. 32(6): p. 777-787.

41. Diouf, M., et al., *Could baseline health-related quality of life (QoL) predict overall survival in metastatic colorectal cancer? The results of the GERCOR OPTIMOX 1 study.* Health Qual Life Outcomes, 2014. 12: p. 69.

42. Doornebosch, P.G., et al., *Quality of life after transanal endoscopic microsurgery and total mesorectal excision in early rectal cancer.* Colorectal Dis, 2007. 9(6): p. 553-8.

43. Gadan, S., et al., *Does a Defunctioning Stoma Impair Anorectal Function After Low Anterior Resection of the Rectum for Cancer? A 12-Year Follow-up of a Randomized Multicenter Trial.* Dis Colon Rectum, 2017. 60(8): p. 800-806.

44. Haapamaki, M.M., et al., *Physical performance and quality of life after extended abdominoperineal excision of rectum and reconstruction of the pelvic floor with gluteus maximus flap.* Dis Colon Rectum, 2011. 54(1): p. 101-6.

45. Janson, M., et al., *Randomized trial of health-related quality of life after open and laparoscopic surgery for colon cancer.* Surg Endosc, 2007. 21(5): p. 747-53.

46. Koedam, T.W., et al., *Transanal total mesorectal excision (TaTME) for rectal cancer: effects on patient-reported quality of life and functional outcome.* Tech Coloproctol, 2017. 21(1): p. 25-33.

47. Odom, D., et al., *Health-related quality of life and colorectal cancer-specific symptoms in patients with chemotherapy-refractory metastatic disease treated with panitumumab.* Int J Colorectal Dis, 2011. 26(2): p. 173-81.

48. Sharma, A., et al., *Predictors of early postoperative quality of life after elective resection for colorectal cancer.* Ann Surg Oncol, 2007. 14(12): p. 3435-42.

49. Siena, S., et al., *Association of progression-free survival with patient-reported outcomes and survival: results from a randomised phase 3 trial of panitumumab.* Br J Cancer, 2007. 97(11): p. 1469-74.

50. Thaler, J., et al., *Skin toxicity and quality of life in patients with metastatic colorectal cancer during first-line panitumumab plus FOLFIRI treatment in a single-arm phase II study.* BMC Cancer, 2012. 12: p. 438.

51. Ward, P., et al., *Physical function and quality of life in frail and/or elderly patients with metastatic colorectal cancer treated with capecitabine and bevacizumab: an exploratory analysis.* J Geriatr Oncol, 2014. 5(4): p. 368-75.

52. Verseveld, M., et al., *Transanal minimally invasive surgery: impact on quality of life and functional outcome.* Surg Endosc, 2016. 30(3): p. 1184-7.

53. Downing, A., et al., *Functional Outcomes and Health-Related Quality of Life After Curative Treatment for Rectal Cancer: A Population-Level Study in England.* Int J Radiat Oncol Biol Phys, 2019. 103(5): p. 1132-1142.

54. Escobar, A., et al., *Cross-cultural adaptation, reliability and validity of the Spanish version of the Quality of Life in Adult Cancer Survivors (QLACS) questionnaire: application in a sample of short-term survivors.* Health Qual Life Outcomes, 2015. 13: p. 182.

55. Farkkila, N., et al., *Health-related quality of life in colorectal cancer.* Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland, 2013. 15(5): p. e215-22.

56. Farkkila, N., et al., *Health-related quality of life among breast, prostate, and colorectal cancer patients with end-stage disease.* Qual Life Res, 2014. 23(4): p. 1387-94.

57. Hornbrook, M.C., et al., *Complications among colorectal cancer survivors: SF-6D preference-weighted quality of life scores.* Med Care, 2011. 49(3): p. 321-6.

58. Huang, W., et al., *Assessing health-related quality of life of patients with colorectal cancer using EQ-5D-5L: a cross-sectional study in Heilongjiang of China.* BMJ Open, 2018. 8(12): p. e022711.

59. Kim, S.H., et al., *Validity and reliability of the EQ-5D for cancer patients in Korea.* Support Care Cancer, 2012. 20(12): p. 3155-60.

60. Marcellusi, A., et al., *Health utilities lost and risk factors associated with HPV-induced diseases in men and women: the HPV Italian collaborative study group.* Clin Ther, 2015. 37(1): p. 156-167.e4.

61. Setiawan, D., et al., *Health-Related Quality of Life of Patients with HPV-Related Cancers in Indonesia.* Value Health Reg Issues, 2018. 15: p. 63-69.

62. Shiroiwa, T., T. Fukuda, and K. Tsutani, *Health utility scores of colorectal cancer based on societal preference in Japan.* Qual Life Res, 2009. 18(8): p. 1095-103.

63. Stein, D., et al., *Assessing health-state utility values in patients with metastatic colorectal cancer: a utility study in the United Kingdom and the Netherlands.* Int J Colorectal Dis, 2014. 29(10): p. 1203-10.

64. Wong, C.K., et al., *Clinical correlates of health preference and generic health-related quality of life in patients with colorectal neoplasms.* PLoS One, 2013. 8(3): p. e58341.

65. Wong, C.K., et al., *Health-related quality of life and risk of colorectal cancer recurrence and All-cause death among advanced stages of colorectal cancer 1-year after diagnosis.* BMC Cancer, 2014. 14: p. 337.

66. Wong, M.Y., et al., *Effects of health-related quality of life on health service utilisation in patients with colorectal neoplasms.* Eur J Cancer Care (Engl), 2018. 27(6): p. e12926.

67. Colwell, H.H., et al., *Psychometric evaluation of the FACT Colorectal Cancer Symptom Index (FCSI-9): reliability, validity, responsiveness, and clinical meaningfulness.* Oncologist, 2010. 15(3): p. 308-16.

68. Kim, S.H., et al., *Deriving a mapping algorithm for converting SF-36 scores to EQ-5D utility score in a Korean population.* Health Qual Life Outcomes, 2014. 12: p. 145.

69. Lee, L., et al., *Valuing postoperative recovery: validation of the SF-6D health-state utility.* J Surg Res, 2013. 184(1): p. 108-14.

70. Marriott, E.R., et al., *Mapping EORTC-QLQ-C30 to EQ-5D-3L in patients with colorectal cancer.* J Med Econ, 2017. 20(2): p. 193-199.

71. Teckle, P., et al., *Mapping the FACT-G cancer-specific quality of life instrument to the EQ-5D and SF-6D.* Health Qual Life Outcomes, 2013. 11: p. 203.

72. Teckle, P., et al., *The ability of cancer-specific and generic preference-based instruments to discriminate across clinical and self-reported measures of cancer severities.* Health Qual Life Outcomes, 2011. 9: p. 106.

73. Wong, C.K., et al., *Mapping the Functional Assessment of Cancer Therapy-general or -Colorectal to SF-6D in Chinese patients with colorectal neoplasm.* Value Health, 2012. 15(3): p. 495-503.

74. Wong, C.K., et al., *Responsiveness was similar between direct and mapped SF-6D in colorectal cancer patients who declined.* J Clin Epidemiol, 2014. 67(2): p. 219-27.

75. Yang, Y., et al., *Improving the mapping of condition-specific health-related quality of life onto SF-6D score.* Qual Life Res, 2014. 23(8): p. 2343-53.

76. Yabroff, K.R., L. Borowski, and J. Lipscomb, *Economic studies in colorectal cancer: challenges in measuring and comparing costs.* J Natl Cancer Inst Monogr, 2013. 2013(46): p. 62-78.

77. Xu, X. *Micro-costing studies in the health and medical literature: protocol for a systematic review.(Report)*. 2014. 3.

78. Weatherly, H., R. Faria, and B. Van den Berg, *Valuing Informal Care for Economic Evaluation*, in *Encyclopedia of Health Economics*, A.J. Culyer, Editor. 2014, Elsevier: San Diego. p. 459-467.

79. Koopmanschap, M.A., et al., *An overview of methods and applications to value informal care in economic evaluations of healthcare.* Pharmacoeconomics, 2008. 26(4): p. 269-80.

80. van den Berg, B., D.G. Fiebig, and J. Hall, *Well-being losses due to care-giving.* J Health Econ, 2014. 35: p. 123-31.

81. Koopmanschap, M.A., et al., *The friction cost method for measuring indirect costs of disease.* J Health Econ, 1995. 14(2): p. 171-89.

82. Liljas, B., *How to calculate indirect costs in economic evaluations.* Pharmacoeconomics, 1998. 13(1 Pt 1): p. 1-7.

83. Schultz, A.B., C.Y. Chen, and D.W. Edington, *The cost and impact of health conditions on presenteeism to employers: a review of the literature.* Pharmacoeconomics, 2009. 27(5): p. 365-78.

84. Rice, D.P., *Estimating the cost of illness.* Am J Public Health Nations Health, 1967. 57(3): p. 424-40.

85. Drummond, M.F.S., Mark J. ; Claxton, Karl; Stoddart; Greg L.; Torrance, George W. , *Methods for the Economic Evaluation of Health Care Programmes* Fourth Edition ed. 2015: Oxford.

86. Alefan, Q., R. Malhees, and N. Mhaidat, *Direct medical cost associated with colorectal cancer in north of Jordan.* Curr Probl Cancer, 2017. 41(5): p. 371-381.

87. Azzani, M., A.C. Roslani, and T.T. Su, *Financial burden of colorectal cancer treatment among patients and their families in a middle-income country.* Support Care Cancer, 2016. 24(10): p. 4423-32.

88. Azzani, M., et al., *Catastrophic Health Expenditure Among Colorectal Cancer Patients and Families: A Case of Malaysia.* Asia Pac J Public Health, 2017. 29(6): p. 485-494.

89. Chastek, B., et al., *Impact of metastatic colorectal cancer stage and number of treatment courses on patient health care costs and utilization.* Postgrad Med, 2013. 125(2): p. 73-82.

90. Chen, A.B., et al., *Estimating Costs of Care Attributable to Cancer: Does the Choice of Comparison Group Matter?* Health Serv Res, 2018. 53 Suppl 1: p. 3227-3244.

91. Emmert, M., et al., *Palliative treatment of colorectal cancer in Germany: cost of care and quality of life.* Eur J Health Econ, 2013. 14(4): p. 629-38.

92. Farkkila, N., et al., *Costs of colorectal cancer in different states of the disease.* Acta Oncologica (Stockholm, Sweden), 2015. 54(4): p. 454-462.

93. Govaert, J.A., et al., *Multicenter Stratified Comparison of Hospital Costs Between Laparoscopic and Open Colorectal Cancer Resections: Influence of Tumor Location and Operative Risk.* Ann Surg, 2017. 266(6): p. 1021-1028.

94. Govaert, J.A., et al., *Nationwide Outcomes Measurement in Colorectal Cancer Surgery: Improving Quality and Reducing Costs.* J Am Coll Surg, 2016. 222(1): p. 19-29.e2.

95. Govaert, J.A., et al., *Hospital costs of colorectal cancer surgery for the oldest old: A Dutch population-based study.* J Surg Oncol, 2016. 114(8): p. 1009-1015.

96. Hanly, P., M. Koopmanschap, and L. Sharp, *Valuing productivity costs in a changing macroeconomic environment: the estimation of colorectal cancer productivity costs using the friction cost approach.* Eur J Health Econ, 2016. 17(5): p. 553-61.

97. Hanly, P., et al., *How much does it cost to care for survivors of colorectal cancer? Caregiver's time, travel and out-of-pocket costs.* Support Care Cancer, 2013. 21(9): p. 2583-92.

98. Hanly, P., et al., *Time costs associated with informal care for colorectal cancer: an investigation of the impact of alternative valuation methods.* Appl Health Econ Health Policy, 2013. 11(3): p. 193-203.

99. Lang, K., et al., *Lifetime and treatment-phase costs associated with colorectal cancer: evidence from SEER-Medicare data.* Clin Gastroenterol Hepatol, 2009. 7(2): p. 198-204.

100. Mar, J., et al., *The cost of colorectal cancer according to the TNM stage.* Cir Esp, 2017. 95(2): p. 89-96.

101. Marti, J., et al., *The economic burden of cancer in the UK: a study of survivors treated with curative intent.* Psychooncology, 2016. 25(1): p. 77-83.

102. Ritzwoller, D.P., et al., *Medical Care Costs for Recurrent versus De Novo Stage IV Cancer by Age at Diagnosis.* Health Serv Res, 2018. 53(6): p. 5106-5128.

103. Seal, B.S., et al., *Medical costs associated with use of systemic therapy in adults with colorectal cancer.* J Manag Care Pharm, 2013. 19(6): p. 461-7.

104. Song, X., et al., *Cost of illness in patients with metastatic colorectal cancer.* J Med Econ, 2011. 14(1): p. 1-9.

105. Van Gelder, M., M. Peeters, and L. Annemans, *Longitudinal economic consequences of colorectal cancer in a university hospital setting.* Acta Clin Belg, 2013. 68(2): p. 97-100.

106. Warren, J.L., et al., *Evaluation of trends in the cost of initial cancer treatment.* J Natl Cancer Inst, 2008. 100(12): p. 888-97.

107. Wong, C.K., et al., *Direct medical costs of care for Chinese patients with colorectal neoplasia: a health care service provider perspective.* J Eval Clin Pract, 2012. 18(6): p. 1203-10.

108. Wright, G.E., et al., *Differences among the elderly in the treatment costs of colorectal cancer: how important is race?* Med Care, 2007. 45(5): p. 420-30.

109. Wu, C.F., et al., *Health Care Costs of Anal Cancer in a Commercially Insured Population in the United States.* J Manag Care Spec Pharm, 2018. 24(11): p. 1156-1164.

110. Yabroff, K.R., et al., *Comparison of approaches for estimating prevalence costs of care for cancer patients: what is the impact of data source?* Med Care, 2009. 47(7 Suppl 1): p. S64-9.

111. Yabroff, K.R., et al., *Comparison of approaches for estimating incidence costs of care for colorectal cancer patients.* Med Care, 2009. 47(7 Suppl 1): p. S56-63.

112. Yabroff, K.R., et al., *Cost of care for elderly cancer patients in the United States.* J Natl Cancer Inst, 2008. 100(9): p. 630-41.

113. Ceilleachair, A.O., et al., *Inter-relationships between the economic and emotional consequences of colorectal cancer for patients and their families: a qualitative study.* BMC Gastroenterol, 2012. 12: p. 62.

114. Husereau, D., et al., *Consolidated health economic evaluation reporting standards (CHEERS) statement.* Cost Effectiveness and Resource Allocation, 2013. 11(1): p. 6.

115. Sintonen, H. and M. Pekurinen, *Terveystaloustiede*. 2 ed. 2006, Porvoo: WSOY.

116. Briggs, A., M. Sculpher, and K. Claxton, *Decision modelling for health economic evaluation*. 2006: OUP Oxford.

117. Kim, D.D., et al., *The influence of time horizon on results of cost-effectiveness analyses.* Expert Rev Pharmacoecon Outcomes Res, 2017. 17(6): p. 615-623.

118. Smith, D.H. and H. Gravelle, *The practice of discounting in economic evaluations of healthcare interventions.* International journal of technology assessment in health care, 2001. 17(2): p. 236-243.

119. Neyt, M. and H. Van Brabandt, *The Importance of the Comparator in Economic Evaluations.* Pharmacoeconomics, 2011. 29(11): p. 913-916.

120. Ziouani, S., D. Granados, and I. Borget, *How To Select The Best Comparator? An International Economic Evaluation Guidelines Comparison.* Value in Health, 2016. 19(7): p. A471-A472.

121. Briggs, A., M. Sculpher, and M. Buxton, *Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis.* Health economics, 1994. 3(2): p. 95-104.

122. Schackman, B.R., et al., *How often do sensitivity analyses for economic parameters change cost-utility analysis conclusions?* Pharmacoeconomics, 2004. 22(5): p. 293-300.

123. Aromaa, A. and S. Koskinen, *Health and functional capacity in Finland. Baseline results of the Health 2000 health examination survey*. 2004.

124. Kapiainen, S.V.A.H., Taru, *Terveyden- ja sosiaalihuollon yksikkökustannukset Suomessa vuonna 2011*, in *THL Raportti*. 2014.

125. Farkkila, N., et al., *Health-related quality of life in colorectal cancer.* Colorectal Dis, 2013. 15(5): p. e215-e222.

126. Hoefman, R.J., E.J. van, and W. Brouwer, *How to Include Informal Care in Economic Evaluations.* Pharmacoeconomics, 2013.

127. *Official statistics of Finland. Structure of earnings 2010.* 2011.

128. DiMasi, J.A., H.G. Grabowski, and R.W. Hansen, *Innovation in the pharmaceutical industry: new estimates of R&D costs.* Journal of health economics, 2016. 47: p. 20-33.

129. Saarni, S.I., et al., *The impact of 29 chronic conditions on health-related quality of life: a general population survey in Finland using 15D and EQ-5D.* Quality of life Research, 2006. 15(8): p. 1403-1414.

130. Rautalin, M., et al., *Health-related quality of life in different states of breast cancer–comparing different instruments.* Acta Oncologica, 2018. 57(5): p. 622-628.

131. Torvinen, S., et al., *Health-related quality of life in prostate cancer.* Acta Oncologica (Stockholm, Sweden), 2013. 52(6): p. 1094-1101.

132. Jansen, L., et al., *Quality of life among long-term (⩾ 5 years) colorectal cancer survivors–systematic review.* European Journal of Cancer, 2010. 46(16): p. 2879-2888.

133. Kopetz, S., et al., *Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2009. 27(22): p. 3677-3683.

134. Lang, L., *Colorectal cancer treatment costs vary widely.* Gastroenterology, 2009. 136(1): p. 6-7.

135. Haltia, O., et al., *The indirect costs of palliative care in end-stage cancer: A real-life longitudinal register-and questionnaire-based study.* Palliative medicine, 2018. 32(2): p. 493-499.

136. Luengo-Fernandez, R., et al., *Economic burden of cancer across the European Union: a population-based cost analysis.* The lancet oncology, 2013. 14(12): p. 1165-1174.

137. Torkki, P., et al., *Cancer costs and outcomes in the Finnish population 2004–2014.* Acta Oncologica, 2018. 57(2): p. 297-303.

138. Torkki, P., et al., *Cancer costs and outcomes for common cancer sites in the Finnish population between 2009–2014.* Acta Oncologica, 2018. 57(7): p. 983-988.

139. Laudicella, M., et al., *Cost of care for cancer patients in England: evidence from population-based patient-level data.* British journal of cancer, 2016. 114(11): p. 1286.

140. Kriza, C., et al., *Cost of illness in colorectal cancer: an international review.* Pharmacoeconomics, 2013. 31(7): p. 577-588.

141. Teunissen, S.C., et al., *Symptom prevalence in patients with incurable cancer: a systematic review.* Journal of pain and symptom management, 2007. 34(1): p. 94-104.

142. Yang, Y.T. and M.M. Mahon, *Palliative care for the terminally ill in America: the consideration of QALYs, costs, and ethical issues.* Medicine, Health Care and Philosophy, 2012. 15(4): p. 411-416.

143. Park, S.M., et al., *EuroQol and survival prediction in terminal cancer patients: a multicenter prospective study in hospice-palliative care units.* Supportive Care in Cancer, 2006. 14(4): p. 329-333.

144. Vigano, A., et al., *Quality of life and survival prediction in terminal cancer patients: a multicenter study.* Cancer, 2004. 101(5): p. 1090-1098.

145. OECD, *Health spending (indicator). doi: 10.1787/8643de7e-en* 2019.

146. A, O.C., et al., *Counting the cost of cancer: out-of-pocket payments made by colorectal cancer survivors.* Support Care Cancer, 2017. 25(9): p. 2733-2741.

147. Altice, C.K., et al., *Financial hardships experienced by cancer survivors: a systematic review.* JNCI: Journal of the National Cancer Institute, 2017. 109(2).

148. Henrikson, N.B., et al., *Communication with physicians about health care costs: Survey of an insured population.* The Permanente journal, 2017. 21.

149. Stump, T.K., et al., *Cost concerns of patients with cancer.* Journal of oncology practice, 2013. 9(5): p. 251-257.

150. Demark-Wahnefried, W., et al., *Physical function and associations with diet and exercise: Results of a cross-sectional survey among elders with breast or prostate cancer.* International Journal of Behavioral Nutrition and Physical Activity, 2004. 1(1): p. 16.

151. Glaser, A.W., et al., *Patient-reported outcomes of cancer survivors in England 1–5 years after diagnosis: a cross-sectional survey.* BMJ Open, 2013. 3(4): p. e002317.

152. Grabsch, B., et al., *Psychological morbidity and quality of life in women with advanced breast cancer: a cross-sectional survey.* Palliative & supportive care, 2006. 4(1): p. 47-56.

153. Austin, P.C., *A comparison of methods for analyzing health-related quality-of-life measures.* Value in Health, 2002. 5(4): p. 329-337.

154. Austin, P.C., *Bayesian extensions of the Tobit model for analyzing measures of health status.* Medical Decision Making, 2002. 22(2): p. 152-162.

155. Austin, P.C., M. Escobar, and J.A. Kopec, *The use of the Tobit model for analyzing measures of health status.* Quality of Life Research, 2000. 9(8): p. 901-910.

156. Clarke, P., A. Gray, and R. Holman, *Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62).* Medical Decision Making, 2002. 22(4): p. 340-349.

157. Kontodimopoulos, N., et al., *Comparing the sensitivity of EQ-5D, SF-6D and 15D utilities to the specific effect of diabetic complications.* The European Journal of Health Economics, 2012. 13(1): p. 111-120.

158. Linde, L., et al., *Health-related quality of life: validity, reliability, and responsiveness of SF-36, EQ-15D, EQ-5D, RAQoL, and HAQ in patients with rheumatoid arthritis.* The Journal of rheumatology, 2008. 35(8): p. 1528-1537.

159. Richardson, J., et al., *Comparing and explaining differences in the magnitude, content, and sensitivity of utilities predicted by the EQ-5D, SF-6D, HUI 3, 15D, QWB, and AQoL-8D multiattribute utility instruments.* Medical Decision Making, 2015. 35(3): p. 276-291.

160. Stavem, K., S.S. Frøland, and K.B. Hellum, *Comparison of preference-based utilities of the 15D, EQ-5D and SF-6D in patients with HIV/AIDS.* Quality of Life Research, 2005. 14(4): p. 971-980.

161. Richardson, J., et al., *Measuring the sensitivity and construct validity of 6 utility instruments in 7 disease areas.* Medical Decision Making, 2016. 36(2): p. 147-159.

# Appendix

## Patient questionnaire

# SUOSTUMUS
# JA
# KYSELYLOMAKKEET

HELSINGIN JA UUDENMAAN SAIRAANHOITOPIIRI

# SUOSTUMUS TUTKIMUKSEEN OSALLISTUMISEEN JA SIINÄ KERÄTTÄVIEN HENKILÖTIETOJEN KÄSITTELYYN

## *Elämänlaatu ja kustannukset rinta-, eturauhas- ja kolorektaalisyöpäpotilailla*

Minua on pyydetty osallistumaan yllä mainittuun tutkimukseen, jossa selvitetään kyselyn avulla syöpäpotilaiden elämänlaatua, kustannuksia ja oirekuvaa. Olen saanut tätä tutkimusta ja sen yhteydessä suoritettavaa tietojen keruuta ja käsittelyä kuvaavan tutkimustiedotteen.

Suostun vapaaehtoisesti osallistumaan yllämainittuun tutkimukseen ja annan suostumukseni tutkimuksen yhteydessä tapahtuvaan tietojen keräämiseen ja niiden käsittelyyn. Voin myöhemmin peruuttaa suostumukseni sen vaikuttamatta mitenkään saamaani hoitoon.

Annan tällä suostumuksella luvan siihen, että oheisilla kyselylomakkeilla kerätyt tiedot saadaan yhdistää muihin minua koskeviin Helsingin ja Uudenmaan sairaanhoitopiirissä oleviin hoitotietoihin sekä Tilastokeskuksen, Terveyden ja hyvinvoinnin laitoksen (THL) ja Kansaneläkelaitoksen (KELA) sekä kotikuntani sairauteni hoitoa koskeviin tietoihin. Ymmärrän, että henkilötunnuksella varustettu tieto tulee vain tutkimusryhmän tietoon ja, että tiedot tallennetaan erityistä salattua potilastunnusta käyttäen, jolloin niistä ei voi päätellä henkilöllisyyttäni.

*Suostumuksen antaja täyttää*

| | |
|---|---|
| Paikka ja aika | Allekirjoitus |
| Henkilötunnus (xxxxxx-xxx) | Sukunimi, Etunimi |
| Osoite | |

**Olkaa ystävällinen ja palauttakaa tämä suostumuslomake yhdessä täytetyn kyselylomakkeen kanssa.**

*Täytetään HUS:ssa*

| | |
|---|---|
| *Paikka ja aika* | *Suostumuksen vastaanottajan allekirjoitus* |
| *Nimenselvennys* | |

# TERVEYTEEN LIITTYVÄN ELÄMÄNLAADUN KYSELYLOMAKE (15D©)

Lukekaa ensin läpi huolellisesti kunkin kysymyksen kaikki vastausvaihtoehdot. Merkitkää sitten rasti (x) sen vaihtoehdon kohdalle, joka parhaiten kuvaa nykyistä terveydentilaanne. On tärkeää, että vastaatte kaikkiin 15 kysymykseen rastittamalla kustakin yhden vaihtoehdon.

**Liikuntakyky**

1 ☐ Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
2 ☐ Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia.
3 ☐ Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja/tai portaissa melkoisin vaikeuksin tai toisen avustamana.
4 ☐ Pystyn kävelemään sisälläkin vain toisen avustamana.
5 ☐ Olen täysin liikuntakyvytön ja vuoteenoma.

**Näkö**

1 ☐ Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).
2 ☐ Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
3 ☐ Näen lukea lehteä ja/tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman).
4 ☐ En näe lukea lehteä enkä TV:n tekstejä ilman silmälaseja tai niiden kanssa, mutta näen kulkea ilman opasta.
5 ☐ En näe kulkea oppaatta eli olen lähes tai täysin sokea.

**Kuulo**

1 ☐ Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojeella tai ilman).
2 ☐ Kuulen normaalia puheääntä pienin vaikeuksin.
3 ☐ Minun on melko vaikea kuulla normaalia puheääntä, keskustelussa on käytettävä normaalia kovempaa puheääntä.
4 ☐ Kuulen kovaakin puheääntä heikosti; olen melkein kuuro.
5 ☐ Olen täysin kuuro.

**Hengitys**

1 ☐ Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia.
2 ☐ Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä.
3 ☐ Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni.
4 ☐ Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa.
5 ☐ Minulla on hengenahdistusta lähes koko ajan, myös levossa.

**Nukkuminen**

1 ☐ Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen.

2 ☐ Minulla on lieviä uniongelmia, esim. nukahtamisvaikeuksia tai satunnaista yöheräilyä.

3 ☐ Minulla on melkoisia uniongelmia, esim. nukun levottomasti tai uni ei tunnu riittävältä.

4 ☐ Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain.

5 ☐ Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä.

**Syöminen**

1 ☐ Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.

2 ☐ Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin).

3 ☐ Tarvitsen hieman toisen apua syömisessä.

4 ☐ En pysty syömään itse lainkaan, vaan minua pitää syöttää.

5 ☐ En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti.

**Puhuminen**

1 ☐ Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti.

2 ☐ Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta.

3 ☐ Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen.

4 ☐ Muilla on vaikeuksia ymmärtää puhettani.

5 ☐ Pystyn ilmaisemaan itseäni vain elein.

**Eritystoiminta**

1 ☐ Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta.

2 ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa.

3 ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli.

4 ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti "vahinkoja" tai peräruiskeiden tai katetroinnin tarvetta.

5 ☐ En hallitse lainkaan virtsaamista ja/tai ulostamista.

**Tavanomaiset toiminnot**

1 ☐ Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot).

2 ☐ Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin.

3 ☐ Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi.

4 ☐ Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin.

5 ☐ En pysty suoriutumaan lainkaan tavanomaisista toiminnoista.

**Henkinen toiminta**

1 ☐ Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin moitteettomasti.

2 ☐ Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai muistini ei toimi täysin moitteettomasti.

3 ☐ Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on jonkin verran muistinmenetystä.

4 ☐ Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on huomattavaa muistinmenetystä.

5 ☐ Olen koko ajan sekaisin ja vailla ajan tai paikan tajua.

**Vaivat ja oireet**

1 ☐ Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.

2 ☐ Minulla on lieviä vaivoja tai oireita, esim. lievää kipua, särkyä, pahoinvointia, kutinaa jne.

3 ☐ Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne.

4 ☐ Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne.

5 ☐ Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne.

**Masentuneisuus**

1 ☐ En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.

2 ☐ Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.

3 ☐ Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.

4 ☐ Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.

5 ☐ Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.

**Ahdistuneisuus**

1 ☐ En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

2 ☐ Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

3 ☐ Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

4 ☐ Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

5 ☐ Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

**Energisyys**

1 ☐ Tunnen itseni terveeksi ja elinvoimaiseksi.

2 ☐ Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi.

3 ☐ Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi.

4 ☐ Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes "loppuun palaneeksi".

5 ☐ Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin "loppuun palaneeksi".

**Sukupuolielämä**

1 ☐ Terveydentilani ei vaikeuta mitenkään sukupuolielämääni.

2 ☐ Terveydentilani vaikeuttaa hieman sukupuolielämääni.

3 ☐ Terveydentilani vaikeuttaa huomattavasti sukupuolielämääni.

4 ☐ Terveydentilani tekee sukupuolielämäni lähes mahdottomaksi.

5 ☐ Terveydentilani tekee sukupuolielämäni mahdottomaksi.

# **EORTC QLQ-C30** (VERSION 3.0)

Selvitämme kyselyssämme joitakin teitä ja terveyttänne koskevia asioita. Pyydämme teitä vastaamaan itse kaikkiin kysymyksiin ympyröimällä parhaiten sopiva numero. Tässä kyselyssä ei ole "oikeita" eikä "vääriä" vastauksia. Pidämme antamanne tiedot ehdottoman luottamuksellisina.

| | **Ei lainkaan** | **Vähän** | **Melko paljon** | **Hyvin paljon** |
|---|---|---|---|---|
| 1. Tuntuvatko rasittavat työt kuten painavan ostoskassin tai matkalaukun kantaminen teistä työläältä? | 1 | 2 | 3 | 4 |
| 2. Tuntuvatko pitkät kävelymatkat työläiltä? | 1 | 2 | 3 | 4 |
| 3. Tuntuvatko lyhyet kävelymatkat kotinne ulkopuolella työläiltä? | 1 | 2 | 3 | 4 |
| 4. Pitääkö teidän pysytellä levolla tai istumassa päivän mittaan? | 1 | 2 | 3 | 4 |
| 5. Tarvitsetteko apua ruokaillessanne, pukeutuessanne, peseytyessänne tai WC:n käytössä? | 1 | 2 | 3 | 4 |

| **Kuluneella viikolla:** | **Ei lainkaan** | **Vähän** | **Melko paljon** | **Hyvin paljon** |
|---|---|---|---|---|
| 6. Oliko teillä vaikeuksia suoriutua työstänne tai muista päivittäisistä toimistanne? | 1 | 2 | 3 | 4 |
| 7. Oliko teillä rajoituksia harrastus- tai muissa vapaa-ajan toiminnoissanne? | 1 | 2 | 3 | 4 |
| 8. Oliko teillä hengenahdistusta? | 1 | 2 | 3 | 4 |
| 9. Oliko kipuja? | 1 | 2 | 3 | 4 |
| 10. Tunsitteko levontarvetta? | 1 | 2 | 3 | 4 |
| 11. Oliko unettomuutta? | 1 | 2 | 3 | 4 |
| 12. Tunsitteko heikotusta? | 1 | 2 | 3 | 4 |
| 13. Oliko ruokahaluttomuutta? | 1 | 2 | 3 | 4 |
| 14. Oliko pahoinvointia? | 1 | 2 | 3 | 4 |
| 15. Oksensitteko? | 1 | 2 | 3 | 4 |

| Kuluneella viikolla: | Ei lainkaan | Vähän | Melko paljon | Hyvin paljon |
|---|---|---|---|---|
| 16. Oliko ummetusta? | 1 | 2 | 3 | 4 |
| 17. Oliko ripulia? | 1 | 2 | 3 | 4 |
| 18. Olitteko väsynyt? | 1 | 2 | 3 | 4 |
| 19. Häiritsikö kipu päivittäisiä toimianne? | 1 | 2 | 3 | 4 |
| 20. Oliko teillä keskittymisvaikeuksia esim. sanomalehteä lukiessanne tai televisiota katsellessanne? | 1 | 2 | 3 | 4 |
| 21. Olitteko jännittynyt? | 1 | 2 | 3 | 4 |
| 22. Olitteko huolestunut? | 1 | 2 | 3 | 4 |
| 23. Olitteko ärtynyt? | 1 | 2 | 3 | 4 |
| 24. Olitteko masentunut? | 1 | 2 | 3 | 4 |
| 25. Oliko teidän vaikea muistaa asioita? | 1 | 2 | 3 | 4 |
| 26. Häiritsikö hoito tai fyysinen kuntonne perhe-elämäänne? | 1 | 2 | 3 | 4 |
| 27. Häiritsikö hoito tai fyysinen kuntonne sosiaalista kanssakäymistä? | 1 | 2 | 3 | 4 |
| 28. Aiheuttaako fyysinen kuntonne tai hoito taloudellisia vaikeuksia? | 1 | 2 | 3 | 4 |

**Vastatkaa seuraaviin kysymyksiin ympyröimällä numerosarjasta 1-7 teihin parhaiten sopiva vaihtoehto**

29. Millainen yleinen terveydentilanne oli kuluneella viikolla?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Erittäin huono | | | | | | Erinomainen |

30. Millainen yleinen elämänne laatu oli kuluneella viikolla?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Erittäin huono | | | | | | Erinomainen |

# TERVEYSKYSELY EQ-5D

Olkaa hyvä ja merkitkää rastilla (x), yksi rasti kunkin alla olevan ryhmän kohdalle, mikä väitteistä kuvaa parhaiten terveydentilaanne tänään:

**Liikkuminen**

- ☐ Minulla ei ole vaikeuksia kävelemisessä
- ☐ Minulla on jonkin verran vaikeuksia kävelemisessä
- ☐ Olen vuoteenomana

**Itsestään huolehtiminen**

- ☐ Minulla ei ole vaikeuksia huolehtia itsestäni
- ☐ Minulla on jonkin verran vaikeuksia peseytyä tai pukeutua itse
- ☐ En kykene peseytymään tai pukeutumaan itse

**Tavanomaiset toiminnot** *(esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot)*

- ☐ Minulla ei ole vaikeuksia suorittaa tavanomaisia toimintojani
- ☐ Minulla on jonkin verran vaikeuksia suorittaa tavanomaisia toimintojani
- ☐ En kykene suorittamaan tavanomaisia toimintojani

**Kivut/vaivat**

- ☐ Minulla ei ole kipuja tai vaivoja
- ☐ Minulla on kohtalaisia kipuja tai vaivoja
- ☐ Minulla on ankaria kipuja tai vaivoja

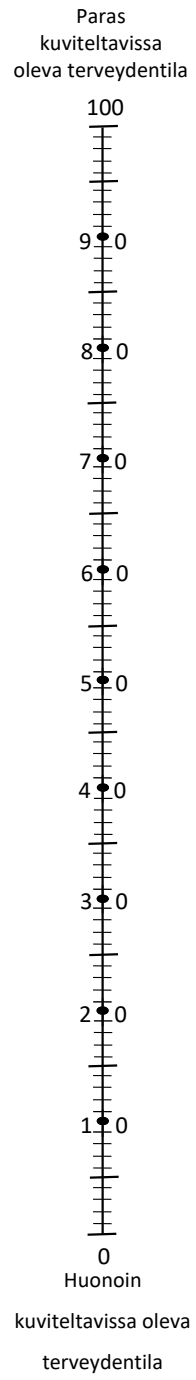
**Ahdistuneisuus/Masennus**

- ☐ En ole ahdistunut tai masentunut
- ☐ Olen melko ahdistunut tai masentunut
- ☐ Olen erittäin ahdistunut tai masentunut

Auttaaksemme ihmisiä sanomaan, kuinka hyvä tai huono jokin terveydentila on, olemme piirtäneet lämpömittaria muistuttavan asteikon. Parasta terveydentilaa, jonka voitte kuvitella, merkitään siinä 100:lla ja huonointa 0:lla.

Haluaisimme Teidän osoittavan tällä asteikolla, miten hyvä tai huono Teidän terveytenne on mielestänne tänään. Olkaa hyvä ja tehkää tämä vetämällä alla olevasta laatikosta viiva siihen kohtaan asteikolle, joka osoittaa, miten hyvä tai huono terveydentilanne on tänään.

**Terveydentilani tänään**



# TAUSTAKYSYMYKSET JA RESURSSIEN KÄYTTÖ

On tärkeää, että vastaatte **kaikkiin** 25 kysymykseen rastittamalla tai numeroin.

## TAUSTATIEDOT

**1 Sukupuoli**
- ☐ Nainen
- ☐ Mies

**2 Siviilisääty**
- ☐ Naimaton
- ☐ Naimisissa
- ☐ Avoliitossa
- ☐ Leski

**3 Mikä on koulutuksenne (korkein loppuun suoritettu koulutus)?**
- ☐ Kansakoulu tai vähemmän
- ☐ Keskikoulu tai peruskoulu
- ☐ Ammattikoulu
- ☐ Lukio
- ☐ Opisto- tai ammattikorkeakoulutasoinen koulutus
- ☐ Yliopisto tai korkeakoulu

**4 Mikä kuvaa parhaiten tämänhetkistä toimintaanne. Oletteko?**
- ☐ Kokopäivätöissä
- ☐ Osapäivätöissä
- ☐ Vanhuuseläkkeellä
- ☐ Työkyvyttömyyseläkkeellä syövän takia
- ☐ Työkyvyttömyyseläkkeellä tai varhaiseläkkeellä muun syyn vuoksi
- ☐ Työtön
- ☐ Olen poissa työelämästä muun syyn takia

**5 Missä ammattiasemassa olette tai olette viimeksi ollut työelämässä?**
- ☐ Työntekijä
- ☐ Alempi toimihenkilö
- ☐ Ylempi toimihenkilö
- ☐ Yrittäjä
- ☐ Muu
- ☐ En ole ollut työelämässä

**6 Mikäli olette töissä, miten arvioisitte nykyisen työkykynne?**
- ☐ Täysin työkykyinen
- ☐ Osittain työkyvytön
- ☐ Täysin työkyvytön

**7 Mikäli olette työelämässä, kuinka monta päivää olette olleet poissa töistä viimeisen kolmen kuukauden (3 kk) aikana syövästänne johtuen?**

____ päivää viimeisen 3 kk aikana

## TERVEYSPALVELUIDEN KÄYTTÖ

**Kuinka usein olette käynyt viimeisen kolmen kuukauden aikana seuraavissa terveydenhoidon yksiköissä syöpänne vuoksi?**

**8 Lääkärillä terveyskeskuksessa**

____ kertaa viimeisen 3 kk aikana

**9 Terveydenhoitajan/sairaanhoitajan vastaanotolla terveyskeskuksessa**

____ kertaa viimeisen 3 kk aikana

**10 Työpaikan työterveyslääkärillä**

____ kertaa viimeisen 3 kk aikana

**11 Työpaikan työterveyshoitajalla**

____ kertaa viimeisen 3 kk aikana

**12 Yksityisellä erikoislääkärillä**

____ kertaa viimeisen 3 kk aikana

**13 Erikoislääkärillä sairaalan poliklinikalla**

____ kertaa viimeisen 3 kk aikana

**14 Erilliskäynti laboratoriossa tai röntgentutkimuksissa**

____ kertaa viimeisen 3 kk aikana

**15 Kuinka monta kertaa olette viimeisen kolmen kuukauden aikana ollut syöpänne vuoksi yhteydessä puhelimitse sairaanhoitajaan tai lääkäriin?**

____ kertaa viimeisen 3 kk aikana

**16 Kuinka monta kertaa olette viimeisen kolmen kuukauden aikana tavannut kotonanne syöpänne vuoksi kotisairaanhoitajan tai terveydenhoitajan?**

____ kertaa viimeisen 3 kk aikana

**17 Kuinka monta kertaa viimeisen kolmen kuukauden aikana luonanne kotona on käynyt teitä hoitamassa/auttamassa kodinhoitaja tai kotiavustaja syöpänne vuoksi?**

____ kertaa viimeisen 3 kk aikana

**18 Miten paljon olette saanut hoitoa ja apua perheeltänne tai ystäviltänne syöpänne vuoksi keskimäärin viikossa viimeisen kolmen kuukauden aikana?**

Keskimäärin ____ tuntia/viikossa viimeisen 3 kk aikana

**Kuinka monta kertaa ja vuorokautta (vrk) olette ollut viimeisen kolmen kuukauden aikana syöpänne vuoksi hoidossa seuraavissa paikoissa?**

**19 Terveyskeskuksen vuodeosastolla**

____ kertaa yhteensä ____ vrk viimeisen
3 kk aikana

**20 Keskus- tai yliopistosairaalassa**

____ kertaa yhteensä ____ vrk viimeisen
3 kk aikana

**21 Muussa yleissairaalassa (aluesairaalassa)**

____ kertaa yhteensä ____ vrk viimeisen 3 kk aikana

**22 Yksityisessä sairaalassa**

____ kertaa yhteensä ____ vrk viimeisen 3 kk aikana

**23 Kuntoutuslaitoksessa**

____ kertaa yhteensä ____ vrk viimeisen 3 kk aikana

**24 Kunnallis-/vanhainkodissa,**

____ kertaa yhteensä ____ vrk viimeisen 3 kk aikana

## LÄÄKEMENOT

**25 Arvio, kuinka paljon olette käyttäneet rahaa lääkkeisiin viimeisen kolmen kuukauden (3 kk) aikana?**

_____ € viimeisen 3 kk aikana

**Kiitos vaivannäöstänne.**