Exercise in patients with cancer

Effects on health-related quality of life, costs, and cost-effectiveness during oncological treatment

Anna-Karin Ax
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Anna-Karin Ax
To my dear family and friends
and my colleagues in cancer care

Once through the forest
   Alone I went;
   To seek for nothing
   My thoughts were bent.

   I saw i’ the shadow
   A flower stand there;
   As stars it glisten’d,
   As eyes ’twas fair.

   I sough to pluck it,—
   It gently said:
   “Shall I be gather’d
   Only to fade?”

   With all its roots
   I dug it with care,
   And took it home
   To my garden fair.

   In silent corner
   Soon it was set;
   There grows it ever,
   There blooms it yet.

Found by Johann Wolfgang von Goethe (1749-1832)
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Exercise in patients with cancer
In my profession as an oncology nurse, I have experienced positive development in cancer care, with new oncological treatments resulting in improved survival. However, being diagnosed with cancer is often a challenging experience for patients, resulting in psychological distress, in addition to short and long-term side effects of treatment. This can result in poorer health-related quality of life, which can limit participation in life activities and delay patients’ return to work.

Over the last decade, I have experienced that a larger number of the patients that I have met have been more interested in how to maintain a healthy lifestyle during and after oncological treatment and are asking for advice on physical activity and exercise. However, previously there has been lack of exercise recommendations on which patients could be advised. This resulted in patients receiving no advice or conflicting advice about exercise from healthcare professionals. At that time (2014), I had the opportunity to join the research team in the Physical Exercise and Cancer (Phys-Can) project to study exercise in patients with cancer during (neo)adjuvant oncological treatment. I have been involved in the study from the early planning and coordination phases until follow up.

The following narrative briefly illustrates the path of a person who is diagnosed with cancer and describes her transition to a patient with cancer, the role of the cancer nurse, and their participation in the exercise intervention on which this thesis is based on. ‘Anna’ is 40 years old. She is in the midst of life, works as a teacher, and has a family, including a husband and two pre-school children. After a routine mammography screening, an examination for suspected breast cancer begins. In cancer care, an interdisciplinary rehabilitation care team provided by a range of healthcare professionals works with Anna. The members of the team take different approaches in assessing Anna’s needs and addressing necessary interventions during the cancer care process. Anna is assigned a contact nurse who helps her navigate the process and provides information and support to Anna and her family. After a few weeks, Anna receives information from a physician that she has been diagnosed with breast cancer, turning the lives of Anna and her family upside down. Anna is worried and has many thoughts. How will I feel? Will I be well again? How will our family cope? Will I see my children grow up? Anna is not just a person anymore; she is now also a ‘patient with breast cancer’. She is on sick leave and will start her treatment by undergoing surgery. After the surgery, Anna will be referred to a physiotherapist to assess post-surgery
Anna was invited to participate in the study at her first visit to the department of oncology.

Anna and her husband first met up with an oncologist and received information about her treatments in the department of oncology. The oncologist explains the recommended treatment plan for Anna; she should start with chemotherapy. The treatment will reduce the risk of recurrence but will have many side effects, including fatigue, alopecia, nausea...the list is long. Anna will need to prolong her sick leave. There is a lot of information for Anna and her husband to process. Anna asks “How will I feel during the treatment? My everyday life, will I be able to cope with being a mom and wife during this time? What can I do to feel better during the treatment?” After the visit, Anna meets her contact nurse and receives an individual care plan and more information of the chemotherapy treatment, routines, side effects, prevention of side effects and self-care. Anna and her family are also referred to a social worker for support. Anna is also informed that there is a study with exercise that she can participate in during the treatment. Participation is voluntary, but the exercise might help her to feel better during the treatment. Anna accepts and meets up with me to find out more about the study.

Anna receives information on the Phys-Can study and on benefits of exercise during treatment. Phys-Can is an exercise study of homebased endurance training and supervised resistance training in peer-groups. She will be randomised to low-to-moderate or high intensity exercise, with or without extra behaviour support. If she is willing to participate, she must also perform fitness tests and report via questionnaires to evaluate the effect of the exercise. Anna is interested but needs more time to decide, she has received so much information today and just wants to start her treatment. The next day, Anna has decided that she will participate in Phys-Can, she is motivated to begin to exercise again after being diagnosed with cancer. She meets up with me and signs up for the study. She performs a cardio fitness test and fills in questionnaires. I inform her that she is randomised to the exercise on low-to-moderate intensity, and she gets an invitation to the gym.

Besides the study preparations in Phys-Can, Anna also attends the policlinic ward to receive her first chemotherapy treatment. Anxious as to
how she will feel afterwards but also keen on beginning treatment. Anna meets her contact nurse again and feels better knowing that the nurse will care for her and follow her during her cancer trajectory. Anna receives a total of six treatments every third week. She has better days when she does daily activities and participates in social life, but also worse days with side effects such as fatigue, nausea, and pain. In connection with the treatments, Anna’s contact nurse assesses Anna’s functional status and her experience of side effects, adjusts her medications, and proposes interventions and self-care strategies accordingly.

Anna finds it is motivating to take part in the Phys-Can intervention and to exercise with a coach. She also finds it supportive to be in a healthy environment together with others who are in the same situation. The exercise is good for her physical and psychological wellbeing and helps her structure her days during sick leave. However, Anna also has days when she is not feeling well enough for exercise due to side effects, must visit the hospital, or has other activities that need to be done.

Over the course of the study, I have sent out questionnaires to Anna so she can report in. Anna has now completed follow-up in Phys-Can, including six measurements, starting from baseline up to five years after completion of the exercise intervention.

Anna-Karin Ax
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ABSTRACT

Background: Short and long-term side effects of oncological treatment negatively affect daily living and health-related quality of life (HRQoL) in patients with cancer. Exercise during treatment is beneficial for HRQoL, however evidence as to what exercise intensity is most optimal for improving HRQoL and cost-effectiveness is lacking. Cost-effectiveness is important information for decisionmakers when implementing healthcare interventions, such as exercise programmes.

Aim: The overall aim of this thesis was to study functioning in daily life, HRQoL, costs, and cost-effectiveness of an exercise intervention of different exercise intensities in patients with cancer receiving oncological treatment.

Method: Study I was qualitative and explored how individuals with cancer receiving curative treatment and participating in an exercise intervention experienced their functioning in daily life. Semi-structured individual interviews (n =21) were performed and analysed with thematic analysis. Studies II–IV were quantitative and used data from a randomised controlled trial (RCT) of high-intensity (HI) and low-to-moderate-intensity (LMI) exercise of combined resistance and endurance training with or without self-regulatory behaviour change support. The RCT was preceded by a descriptive longitudinal study with usual care (UC). Participants were diagnosed with breast, prostate, or colon cancer and received (neo)adjuvant oncological treatment. Study II evaluated the effects on HRQoL of exercising at HI (n =288) and LMI (n =289) versus UC (n =89) up to 18 months after start of oncological treatment, using the EORTC QLQ-C30 questionnaire. Data were analysed using descriptive and multivariate statistics. Study III evaluated resource utilisation and societal costs of the exercise intervention in the RCT (n =534) versus UC (n =85), and of HI (n =269) versus LMI (n =265) exercise 18 months after start of oncological treatment. Societal costs included costs of healthcare resource utilisation (healthcare visits, hospitalisation, prescribed medication), productivity loss (disability pensions and sick leave), and the exercise intervention. Study IV evaluated the cost-effectiveness of the exercise intensities in the RCT (HI: n =99 and LMI: n =90) at 1-year follow-up post intervention. Cost data were retrieved from Study III and health outcome were collected using the EQ-5D-5L questionnaire and calculated for quality-adjusted life-years. Cost-effectiveness was evaluated as the incremental cost-effectiveness ratio (ICER).
Results: Participants experienced impairments from oncological treatment but strove to maintain function in daily life. The exercise programme improved physical and psychological wellbeing during treatment (Study I). There were no significant differences in HRQoL between exercise intensities up to 1 year after the exercise intervention. The exercise groups scored significant better HRQoL compared to UC over time (Study II). There was no significant difference in mean societal costs between the exercise intervention and UC, nor between the exercise intensities (Study III). There was no significant difference in cost or in effect between the exercise intensities. Although the mean ICER indicated that HI was cost-effective compared to LMI, the uncertainty was large (Study IV).

Conclusion: Participating in an exercise programme during oncological treatment was a positive and supportive experience that contributed to increase physical and psychological wellbeing. Exercise of HI and LMI during oncological treatment had similar effect on HRQoL and societal costs. In addition, the exercise group had beneficial effects on HRQoL and no significant difference in societal costs compared to UC, meaning the exercise programme did not save or add societal cost. Thus, based on cost-effectiveness we suggest decisionmakers and clinicians implement exercise programmes including both HI and LMI in cancer care and recommend exercise regardless of intensity according to the patient’s preferences to improve or to maintain aspects of HRQoL during oncological treatment.

Keywords: Cancer, Exercise, Health-Related Quality of Life, Cost-Analysis
SVENSK SAMMANFATTNING

Antalet personer som insjuknar i cancer i Sverige ökar eftersom befolkningen växer och vi blir allt äldre. Samtidigt har överlevnaden av cancer ökat betydligt på senare år tack vare att sjukdomen upptäcks i tidigare skede samt att behandlingarna har blivit mer effektiva. Många som drabbas av cancer får behandling som ger biverkningar som kan försämrar hälsa och livskvalitet. Träning under cancerbehandlingen har positiva effekter på hälsorelaterad livskvalitet och skulle kunna minska vårdkonsumtion samt sjukskrivning. Det är dock oklart om träningsintensitet har betydelse för den hälsorelaterade livskvaliteten samt för samhällsekonomiska kostnader för cancer. Det övergripande syftet med avhandlingen var att studera funktion i dagligt liv, hälsorelaterad livskvalitet samt kostnader och kostnadseffektivitet av träning med olika intensitet under pågående cancerbehandling.


I studie I intervjuades 21 deltagare från träningsstudien med syfte att studera upplevelser om funktion i dagligt liv under cancerbehandling. Studie II utvärderade hur träning på olika intensitet, och i jämförelse med rutinvård påverkade hälsorelaterad livskvalitet. Studie III utvärderade samhällsekonomiska resurser och kostnader för cancer, såsom sjukhusvård, sjukskrivning och träning, för deltagarna som var med i träningsstudien, och i jämförelse med gruppen som inte erbjöds träning. Studie IV utvärderade kostnadseffektiviteten av träning på hög intensitet jämfört med låg/måttlig intensitet under cancerbehandling.

Resultatet visade att deltagarna i träningsstudien upplevde fysisk och mental trötthet som påverkade dagliga aktiviteter, men de kunde fortsätta med dem genom anpassning. Träningen upplevdes positiv och förbättrade välbefinnandet. Det var också viktigt att träffa andra deltagare i träningsgruppen och utbyta erfarenheter med varandra. Efter avslutad träningsperiod skattade deltagarna som träände med hög intensitet högre smärta jämfört med gruppen som träände med låg/måttlig intensitet. Det
fanns inga andra skillnader i hälsorelaterad livskvalitet mellan olika träningsintensitet. Gruppen som var med i träningsprogrammet rapporterade bättre hälsorelaterad livskvalitet jämfört med gruppen som inte erbjöds träning. Det fanns inga skillnader i samhällesekonomiska kostnader, inklusive sjukvård, sjukskrivningar och träning, mellan gruppen som var med i träningsprogrammet och med gruppen som inte erbjöds träning. Träningsintensitet hade ingen betydelse för kostnadseffektivitet; samhällesekonomiska kostnader eller effekt på hälsan mätt i kvalitetsjusterade levnadsår.

Sammanfattningsvis visar resultaten att träningsintensitet inte har någon stor betydelse för hälsan, livskvaliteten eller samhälleliga kostnader under cancerbehandling. Baserat på kostnadseffektivitet så kan beslutsfattare och vårdpersonal införa träningsprogram med både hög och låg/måttlig intensitet till cancervården, och rekommendera patienter med cancer att träna, oavsett intensitet, under sin behandling för att förbättra sin hälsa och livskvalitet.
LIST OF PAPERS

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ABBREVIATIONS

BCS  Behaviour change support
CEA  Cost-effectiveness analysis
EORTC QLQ-C30  European Organisation for Research Treatment in Cancer Quality of Life—Cancer 30
EQ-5D-5L  EuroQoL-5 Dimension 5 Level Questionnaire
HI  High intensity
HRQoL  Health-related quality of life
HRR  Heart rate reserve
ICER  Incremental cost-effectiveness ratio
LMI  Low-to-moderate intensity
PAP  Physical activity on prescription
Phys-Can  Physical activity and Cancer
QoL  Quality of life
QALY  Quality-adjusted life-year
RCT  Randomised controlled trial
RM  Repetition maximum
UC  Usual care
WHO  World Health Organization
INTRODUCTION

The incidence and prevalence of cancer is increasing worldwide and has a significant impact on public health (1, 2). Positive development in cancer care and new oncological treatments have resulted in improved survival. However, the psychological distress of being diagnosed with cancer (3), as well as the side effects of the treatment are challenging, and negatively affect health-related quality of life (HRQoL) in patients (4). This might limit daily activities and delay return to work (5). Moreover, this might lead to increased healthcare utilisation (6) and productivity loss (7), and accordingly, higher costs for society. Therefore, an important task for healthcare professionals is to promote health interventions to prevent or decrease side effects of treatment.

Exercise has positive health effects and is a task that patients can do themselves to improve HRQoL during treatment (8, 9). While research on exercise has increased over the past decade, until recently, patients have not been advised to exercise due to lack of exercise recommendations or have received conflicting advice from healthcare professionals. There is a lack of recommendations as to what exercise intensity can improve health outcomes the most, and no randomised controlled trial (RCT) has directly compared different exercise intensities of combined resistance and endurance training during oncological treatment. Additionally, exercise has not been implemented into cancer care on a larger scale. One reason may be the assumption of additional costs for healthcare. To further optimise exercise recommendations, studies that directly compare the effectiveness of different exercise intensities on HRQoL during oncological treatment are needed. In addition, health economic evaluations are important tools for decisionmakers when prioritising new treatments in healthcare, as these consider both the costs and the health effects (10). Hence, information on costs and cost-effectiveness is important information for decisionmakers and clinicians in the process of implementing exercise into cancer care.

This thesis is based on data from the Phys-Can RCT that directly compared high intensity (HI) versus low-to-moderate intensity (LMI) exercise with or without additional behaviour change support (BCS) (11). The primary aim of the Phys-Can was to determine the effects of HI versus LMI exercise with or without additional BCS on cancer-related fatigue in patients undergoing (neo-)adjuvant cancer treatment. The exercise consisted of home-based endurance training and supervised resistance training in group for six months during oncological treatment. The RCT
was preceded by an observational study with usual care (UC). The main results from the RCT showed that HI exercise was slightly more beneficial compared to LMI exercise in terms of muscle strength, cardiorespiratory fitness, and physical fatigue (main outcome) at post-intervention, although the differences in physical fatigue were not considered clinically meaningful. There were no main effects of exercise intensity or additional BCS in overall HRQoL, anxiety, depression, functioning in daily life, or sleep. Adherence to prescribed resistance training was 50.4% and did not differ significantly between the intervention groups. Adherence to endurance training differed significantly between the groups and was higher in the LMI (57.7% with BCS and 51.4% without BCS) compared to the HI group (38.8% with BCS and 41.6% without BCS).
BACKGROUND

Cancer
Cancer includes more than 200 types of diseases characterised by uncontrolled proliferation of cells. The risk of developing cancer increases with age and lifestyle behaviours such as smoking, alcohol consumption, obesity, diet, and physical inactivity (12). In Sweden, more than 68,000 people were diagnosed with cancer in 2021 (13). However, detection of cancer at earlier stages and more effective treatment has resulted in improved survival, and about 75% of individuals diagnosed with cancer are estimated to survive ≥5 years after their cancer diagnosis in Sweden (13). However, prognosis and survival rates differ between cancer diagnoses. Breast cancer is the most common cancer diagnosis in women, with 8619 new cases in 2021. Despite increasing incidence rates in recent decades, mortality rates have decreased, and the 10-year relative survival rate is around 85%. The most common cancer diagnosis in men is prostate cancer, with 10,199 new cases in 2021. The incidence has increased in recent years, but the mortality rate is constant, and the 10-year relative survival rate is around 90%. Colorectal cancer includes colon cancer and rectal cancer, which together are the fourth most-common cancer diagnosis in Sweden. In 2020, 4826 new cases were reported in colon cancer and 2030 new cases in rectal cancer. Colorectal cancer incidence has increased, but mortality has not changed in the past 10 years, and the 10-year relative survival rate is around 60% (14).

Cancer prevalence has increased in recent decades, mainly due to a larger and older population and improved survival (13). This leads to a significant burden on costs for society (15, 16), but also to negative consequences for the individuals, with severe side effects such as fatigue during and after oncological treatment (17).

Cancer treatments and side effects

Cancer treatments
Cancer treatments include surgery and oncological treatments. The most common oncological treatments are chemotherapy, radiotherapy, endocrine therapy, and more recently immunotherapy. Treatment for cancer depends on the tumour profile, location, and stage, the patient’s health and age, and also takes into account the patient’s preferences (18). Curative oncological treatment is aimed at complete remission of the tumour. After primary treatment (surgery, radiotherapy, or
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chemotherapy), adjuvant oncological treatment is given to those who are at risk of disease recurrence. Neoadjuvant oncological treatment is given before primary treatment to shrink the tumour and improve the outcome of the primary treatment and/or reduce the risk of disease recurrence. Palliative oncological treatment does not cure cancer but can prolong life and alleviate symptoms of the disease (19). This thesis focuses on patients receiving neoadjuvant, adjuvant, and curative oncological treatment.

Treatments in breast, prostate and colorectal cancer
Treatments in patients with breast cancer may include (neo)adjuvant chemotherapy (4–5 months) followed by surgery and/or adjuvant radiotherapy (usually up to 15 fractions), and/or adjuvant endocrine therapy for 5–10 years if the tumour is hormone-sensitive. In addition, depending on the tumour profile, monoclonal antibody therapy treatment can be added (18, 20).

Treatments for prostate cancer usually include curative external radiotherapy (up to 39 fractions), with or without interventional radiotherapy, with or without (neo)adjuvant endocrine therapy (21).

Common treatments for colon cancer include surgery followed by six months of adjuvant chemotherapy. For rectal cancer, neoadjuvant radiotherapy (5 fractions) is common, followed by neoadjuvant chemotherapy up to 6 months, followed by surgery with or without adjuvant chemotherapy (22).

Chemotherapy
Chemotherapy treatment aims to stop or reduce proliferation, with mechanisms of action rooted in the DNA of the cancer cells (19). Treatment is repeated in cycles (e.g., every third week) over a longer period of time, often 3–6 months. Chemotherapy can have severe side effects, and the severity depends on treatment-related factors such as type of treatment and dose but may also depend on other factors, such as medical and biological conditions. The most common short-term side effects are fatigue, pain, diarrhoea, nausea and vomiting, constipation, bone marrow depression, hair loss, neurotoxicity, cognitive impairment, and appetite loss. Common long-term side effects are fatigue, neurotoxicity, and cognitive impairments (23, 24).

Radiotherapy
External radiation therapy is a type of treatment that uses ionising radiation to treat cancer, generally in a localised target (25). Interventional radiotherapy (brachytherapy) is a type of radiation therapy that uses
radioactive material to treat cancer (26). The severity of the side effects will vary depending on the dose and the location of the cancer. Most short-term side effects of radiotherapy typically occur a few weeks after treatments begin, and include burning, pain, and dry skin (27). For men with prostate cancer, radiotherapy can cause short term side effects like urinary toxicities, urinary obstruction and urethral stricture; and long-term side effects like rectal and urinary bleeding (28). In patient with breast cancer, radiotherapy can cause late/long-term side effects such as lymphedema, capsular contracture, pain, fibrosis, and limited mobility of the upper limbs (29).

**Endocrine therapy**

Specific hormones can stimulate cancer cell growth, for example, oestrogen and progesterone can stimulate growth in breast cancer (20) and testosterone in prostate cancer (21). Endocrine therapy inhibits the growth of cancer cells by binding to the hormone receptor and reducing the effect of the hormone, or by inhibiting the body’s own hormone production (30). Side effects of endocrine therapy are therefore related to hormone deprivation. Common side effects during treatment include arthralgia, vaginal dryness (in women), flushing, fatigue, headache, sexual dysfunction, cognitive impairment, depression, and gynaecomastia (in men). Late-term side effects that may occur after treatment can include osteoporosis (31, 32).

**Immunotherapy**

Immunotherapy activates the immune system to treat cancer. In this thesis, some participants with breast cancer received monoclonal antibodies, which is a type of immunotherapy. Monoclonal antibodies are targeted cancer therapy, which are designed to interact with specific protein targets to control growth factors or induce apoptosis in the cancer cell (33). Side effects depend on the type of treatment, and may include cardiotoxicity, neuropathy, rash, diarrhoea, and hepatotoxicity.

**Side effects of treatments**

The side effects are associated with a great burden for patients and also lead to additional utilisation of healthcare (6). The severity of toxicity varies depending on the treatment and individual factors, but chemotherapy is associated with high levels of severity. Treatment consequences include both short-term side effects during treatment and long-term side effects that manifest during or shortly after treatment and can persist over longer times and late effects that could occur years after treatment. Furthermore, experience of the side effects is specific to the individual, and the side
effects that affect patients most differ between patients and between treatments. Some side effects are more common and not all side effects affect all patients.

Side effects from oncological treatments have a negative impact on HRQoL and functioning in daily life of patients with cancer (23, 24). As many survive cancer and go on to live with the side effects of the treatment, it is important to optimally manage side effects and help patients find strategies to return to activities and maintain HRQoL. Side effects are mostly manageable, and clinicians can use evidence-based guidelines to manage many side effects with prophylactic and supportive measures, such as antiemetics to prevent nausea (34). However, new interventions need to be addressed to further reduce the side effects of treatments. The idea behind the Phys-Can project, of which this thesis is a part, was to study an intervention that had the potential to reduce side effects of treatments and thereby improve patients’ HRQoL during and after treatment.

Cancer rehabilitation

As cancer incidence and prevalence are increasing (13), many individuals lives with impairments and side effects of oncological treatment, such as cognitive impairments, fatigue, pain, and dyspnoea which affect their HRQoL and functioning in daily life both during and after treatment (4, 35). Therefore, it is important to support patients in cancer rehabilitation. According to the 8 chapter 7 § in the Swedish healthcare act, Swedish healthcare should offer rehabilitation to patients with cancer (36), thus making cancer rehabilitation a public health issue. There is, however, no international consensus as to the definition of cancer rehabilitation. According to the World Health Organization (WHO), ‘rehabilitation’ is defined as “a set of interventions designed to optimise functioning and reduce disability in individuals with health conditions in interaction with their environment” (37). Rehabilitation aims to improve health in individuals’ daily lives by improving functioning and reducing disability. Furthermore, rehabilitation focuses on maintaining the individuals’ ability to participate in education, work, and meaningful roles.

Cancer rehabilitation is provided by an interdisciplinary rehabilitation care team of healthcare professionals, including nurses, physiotherapists, physicians, social workers, occupational therapists, and nutritionists (38). Theses healthcare professionals have different roles in the team, and the collaboration of interdisciplinary healthcare professionals is important to address the myriad of impairments affecting the patient. The team should, together with the patient, assess rehabilitation needs and provide interventions to increase HRQoL. In addition to the efforts of the healthcare in the rehabilitation process, the patient has a responsibility for
Background

Healthy lifestyle behaviours, such as limiting alcohol consumption and tobacco use, being physically active and being at a healthy weight can reduce incidence and mortality from cancer, promote health, and improve quality of life, while also reducing the societal costs of cancer care (40).

The rehabilitation process should start as soon as cancer is suspected and continue before, during, and after treatment to prevent a deterioration in HRQoL and to enable return to normal life after treatment. During oncological treatment, rehabilitation may include support and counselling to increase physical activity, improve nutrition, and return to activity (e.g., school and work), and participation in society (39, 41). Interventions that focus on promoting activity such as exercise could encourage additional positive health behaviours and reduce limitations in activities and participation (42). Furthermore, during and after oncological treatment, patients are often motivated to initiate lifestyle changes to diets and exercise patterns into their survivorship. Thus, it is important that healthcare practitioners have strategies for this, and support patients with evidence-based guidelines (40).

Nursing in cancer care

Nurse-led follow-up has expanded in cancer care, and encompasses care before, during and after oncological treatment (43). Nurses have consistent contact with the patient; from their diagnosis throughout the cancer care trajectory. They play a vital role in cancer rehabilitation and in helping patients adjust to life after their cancer diagnosis (44). Essential components of nursing include educating and providing patients and their families with information, managing side effects of treatment, assessing and supporting maintenance and restoration of functioning, addressing rehabilitation needs and coordinating care (38, 44, 45, 46). In Sweden all patients with cancer should be provided with a contact nurse. The contact nurse should together with the patient establish an individual care plan that comprises rehabilitation (39, 47).

Furthermore, cancer care has shifted over the last decade, and today most treatments occur in outpatient clinics rather than in inpatient care. Hence, it is necessary that patients engage actively in their self-care in order to manage side effects of the treatment. Self-care includes the ability to perform activities to promote health, prevent illness, and to cope with illness oneself or in collaboration with healthcare professionals (48). Therefore, important tasks of cancer nurses include providing self-management and self-care strategies and interventions to patients to improve HRQoL. This includes providing evidence-based recommendations to support self-management and self-care in health promotion and lifestyle behaviours such as exercise (49).
Exercise as rehabilitation for patients with cancer

Exercise is an essential part of self-care in cancer rehabilitation (39). Exercise is a planned, structured, and repetitive physical activity that aims to improve or maintain physical fitness (50). In the past, rest and avoidance of physical activity were recommended during oncological treatment. However, in the late 1980s, Winningham and MacVicaran conducted an exercise study in women with breast cancer undergoing chemotherapy, which showed that endurance training was safe and had positive effects on physical function and nausea (51, 52). Research in exercise was, however, sparse during the following years. A study from the beginning of the twenty-first century showed that only few patients (28%) discussed exercise with their oncologist, while a majority (82%) preferred that the oncologist had initiate such a conversation (53). Also, patients who were recommended exercise by their oncologist were more likely to follow the exercise recommendation during their treatment (54).

Since the 2010s, research into exercise in cancer has increased. Evidence supports that exercise is safe and has beneficial effects and should therefore be an important part of rehabilitation in patients with cancer (9, 41, 55). Today there is strong evidence that exercise—particularly combined resistance and endurance training—can improve HRQoL, physical functioning, anxiety, depressive symptoms, fatigue, and lymphedema. There is moderate evidence that exercise can improve bone health and sleep during and after oncological treatment. Supervised exercise has been shown to be more effective for health-related outcomes than unsupervised exercise (8, 9, 56, 57). Exercise has also been shown to reduce hospitalisation (58, 59, 60), and improve return to work (61, 62, 63), and may therefore reduce costs for society. There is, however, a knowledge gap regarding the optimal exercise intensity for improving cancer-related outcomes such as HRQoL during oncological treatment; and whether the effects are maintained over time (9). A previous systematic review including 56 exercise trials showed that exercise of moderate- or high intensity had greater positive effects on HRQoL compared to low-intensity exercise programmes (8). However, there is a lack of exercise trials that have directly compared different levels of exercise intensities during oncological treatment. Van Wart et al. (63) compared a supervised exercise programme of combined endurance and resistance training at moderate-to-high intensity to a homebased low-intensity walking programme performed during chemotherapy. At post-intervention, the moderate-to-high intensity group had fewer symptoms of obstipation compared to the low-intensity group, but at 6 months follow-up there was no significant difference in HRQoL observed between the groups. Another exercise trial compared combined endurance and resistance training of low-to-moderate versus high intensity, however it was performed after
chemotherapy (64). They found no difference in HRQoL at post-intervention between the intensity groups (64), but greater effects on social and role functioning were found at one-year follow-up in the high intensity group compared to the low-to-moderate group (65). Furthermore, the benefits of combined resistance and endurance training on HRQoL have been proven to be more efficient than endurance or resistance training alone (9), but no study has directly compared combined resistance and endurance training interventions of different intensities during oncological treatment and studied the effects over time. Thus, to improve the prescription of exercise recommendations to optimise HRQoL, well-designed RCTs that directly compare exercise of different intensities have been requested (9).

**Exercise recommendations for patients with cancer**

It is important that nurses—along with other healthcare professionals—inform patients about the benefits of exercise and recommend, motivate, and supports patients with cancer to exercise and to be physically active during their oncological treatment (45). In general, a combination of resistance and endurance training 2–3 times per week at moderate intensity for at least 12 weeks is recommended to improve HRQoL for patients with cancer (9, 55). In 2022, WHO updated their guidelines for physical activity for persons with cancer, which are similar to adults in the general population. Recommendations now include endurance training for at least 150–300 minutes of moderate intensity per week or 75–150 minutes of vigorous intensity; or a combination of the two. In addition, resistance training that involve major muscle groups for at least moderate intensity two times per week or more are recommended (66). The exercise intensity must be appropriate to the patient’s condition. For example, avoiding high-intensity exercise immediately after surgery or recommending low-intensity exercise when symptoms or side effects get worse during moderate-intensity exercise (55). Thus, more detailed exercise prescription is needed regarding which level of exercise intensity can improve cancer-related outcomes the most.

**Health-related quality of life**

One important goal in cancer rehabilitation is to maintain HRQoL during and after treatment. Consequently, nurses in cancer care are focusing on health promotion and maintenance of functioning (46). Thus, one important concept in this thesis is HRQoL. WHO defines 'health' as “a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity” (48) and ‘quality of life’ (QoL) as ‘individuals’ perceptions of their position in life in the context of the culture
and value systems in which they live and in relation to their goals, expectations, standards, and concerns” (67). However, there is no consensus on the QoL definition, and QoL and HRQoL are often used interchangeably. QoL is a broader concept and covers all aspects of life. HRQoL focus on health status and assesses the impact of illness and treatment on QoL. Most definitions of HRQoL includes domains of emotional, physical, psychological, and social functioning, as well as symptoms of the disease and/or treatment (46, 68). Functioning is a dynamic interaction between health-related domains: body functions, body structures, activities, and participation (69). In this thesis, functioning in daily life refers to the ability to perform household, leisure, and work activities, as well as participate in community activities and social engagement. While QoL is influenced by many factors which may not be responsive to nursing action, such as age, cultural aspects, and diagnosis, HRQoL is influenced by factors that could be improved by nursing, like providing information, managing side effects, and delivering interventions (46).

**Impact on HRQoL of cancer and side effects of treatment**

Cancer and treatment-related side effects can have a negative impact on HRQoL and functioning in daily life (70, 71), and lead to psychological distress (3). Compared to the general population, patients with cancer reported poorer HRQoL (4), and more limitations in daily activities, leisure activities, and participation in social life (72, 73). Moreover, a meta-analysis showed a wide range of depression symptoms in patients with breast cancer, from 9.4% to 66.1%, which was higher than in the general female population. Symptoms of anxiety ranged from 17.9% to 33.3%, which were similar to or lower than in the rates in the general female population (Maass et al., 2015). In any case, a review article showed that QoL in patients with breast cancer has improved over the last few years, and explanations for this might be effective interventions such as exercise (74).

Fatigue is one of the most common and distressing side effects of oncological treatment and is reported in 30%–60% of patients in all cancer diagnoses and can persist for years after treatment (75, 76). After treatment, long-term symptoms of fatigue could negatively affect one’s ability to perform activities in daily life; at home, socially, and at work (77). Furthermore, treatment-related side effects such as hot flushes, diarrhoea, rash, and alopecia, body image after surgery, disturbances to one’s sex life, unmet needs and social support, lymphedema, menopausal symptoms, and depression may worsen HRQoL in patients with breast cancer (74). In patients with prostate cancer, side effects such as impaired urinary, sexual,
Background

and bowel function may worsen HRQoL (78). Treatments, including surgery in patient with colorectal cancer, can worsen HRQoL because side effects negatively impact urinary, sexual, bowel, and cognitive function, and include symptoms such as peripheral neuropathy, depression, and anxiety (79).

The HRQoL in patients with cancer can also be impacted by other factors. Comorbidities and lifestyle behaviour such as obesity and inactivity were associated with poorer HRQoL (80). Younger patients and those from lower socioeconomic backgrounds often experienced poorer HRQoL and more distress compared to older patients and patients from higher socioeconomic backgrounds (5, 74, 80). Furthermore, women reported poorer psychosocial outcomes compared to men, while men reported poorer general health compared to women. Patients with colorectal cancer reported poorer HRQoL than patients with prostate and breast cancer due to limitations in activities and health (4).

Longer time elapsed since treatment is associated with better HRQoL (80). A review of HRQoL in cancer survivorship found that most patients experienced HRQoL-related issues such as acute symptoms of nausea/vomiting, appetite loss, constipation, and diarrhoea up to six months after they had completed treatment, and that most treatment related symptoms were resolved one year after completion of treatment. However, stabilising HRQoL and improvements in physical, role-based, and social functioning, as well as a reduction in fatigue were first seen one year after treatment (81).

Health economic evaluation

Healthcare utilisation and productivity loss of oncological treatment

The cost of oncological treatment and care are escalating. The side effects of cancer and its treatment are associated with increased healthcare utilisation and productivity loss, and therefore pose a significant financial burden for society and for the patient with cancer (82, 83, 84). In Sweden, the societal costs of cancer were estimated to be 36 billion SEK in 2013, the largest part of which consists of productivity loss (15.9 billion SEK). The societal costs of cancer are estimated to increase to 70 billion by the year 2040 (16). The societal perspective denotes all costs sustained by society by a disease and consists of costs of healthcare and productivity loss. ‘Productivity loss’ refers to time absent from paid work, but might also include unpaid productivity such as household tasks and volunteering (10).

Symptoms of breast cancer treatment—such as fatigue or limited upper body function—are associated with increased healthcare utilisation,
Exercise in patients with cancer

resulting in higher healthcare costs (6). Furthermore, poor HRQoL (including symptoms such as fatigue, pain, depression, and cognitive impairments) can negatively impact work ability and return to work (7, 61), thus adding additional costs associated with productivity loss for society. Also, arm morbidity with reduced upper limb function and/or lymphedema can have negative impacts on the work ability of patients with breast cancer (85). A significant number of patients are diagnosed with cancer in working age. However, side effects of cancer can persist after diagnosis. A review showed that 73% of patients had return to work within two years after cancer diagnosis (7). A Swedish cohort study among women with breast cancer showed that 71% had some sickness absence the first year after diagnosis, and 40% were absent the second year after diagnosis (86). Therefore, it is important to find interventions to improve return to work after oncological treatment. However, there is a lack of evidence of effective interventions to support return to work (87).

Priority setting in the healthcare

Despite the proven benefits of exercise, it has not yet been widely implemented in the rehabilitation of patients with cancer in Sweden. One challenge is that exercise interventions are associated with additional use of resources such as funding to support staff with expertise in exercise and to purchase exercise equipment (88). In Sweden, healthcare is tax-financed. As resources are scarce, prioritisation is necessary to allocate resources as fairly and effectively as possible in healthcare. The prioritisation process is guided by an ethical platform consisting of three principles: 1. the human dignity principle; 2. the needs and solidarity principle; and 3. the cost-effectiveness principle. The principle of human dignity states that all human beings have equal rights and equal worth. However, further prioritising is required to decide who should be cared for first. The needs and solidarity principle states that resources are allocated to the patients who need them most. Needs are based on the severity and duration of the health problem and the potential health improvement that would be achieved through medical intervention. The cost-effectiveness principle states that the healthcare system should use available resources as effectively as possible. The cost-effectiveness principle is, however, subordinate to the other two principles, which means that serious illness and fundamental deterioration in quality of life have priority over minor conditions, even if the care of serious conditions is associated with a higher price (36).

Cost-effectiveness

Health economic evaluations can provide decisionmakers with helpful information in the prioritisation process. A cost-effectiveness analysis
(CEA), which considers both the cost, and the health outcomes of alternative interventions, can be an important tool in the implementation of new interventions (such as exercise) in healthcare. From a societal perspective, CEA includes all costs, regardless of who pays—both costs related to healthcare services and costs that affect the wider economy, such as productivity loss. Quality-adjusted life years (QALY), a generic measure of health outcome that combines health state values with the time spent in that state, is recommended to use as a health outcome metric in a CEA (89). The incremental cost-effectiveness ratio (ICER) provides the ratio of incremental costs per unit of health outcome, and provides insight into which alternative intervention is most cost-effective (10). The ICER is estimated by \( \frac{\text{cost } A - \text{cost } B}{\text{effect } A - \text{effect } B} \).

**Cost-effectiveness of exercise interventions in cancer care**

Exercise interventions in cancer survivors can be considered cost effective compared to usual care, mainly since exercise might reduce healthcare utilisation and result in health benefits (6, 90, 91, 92). However, differences in cost calculations, health outcomes, prescriptions of exercise, and cancer diagnoses across studies make it difficult to draw firm conclusions as to the cost-effectiveness of exercise. Hence, more studies are needed to confirm these findings. Furthermore, it is unclear whether exercise intensity is important when it comes to cost-effectiveness. A systematic review indicated that high intensity has the potential to be cost-effective compared to usual care (92). One RCT comparing moderate-to-high intensity and low intensity exercise during oncological treatment showed that moderate-high intensity exercise was cost-effective compared to usual care (93). Another RCT of high intensity and low-to-moderate intensity carried out after chemotherapy showed that high intensity exercise was considered cost effective compared to low-to-moderate intensity (65). No previous study has evaluated the cost-effectiveness of an exercise programme that directly compares different exercise intensities of combined endurance and resistance training during oncological treatment. Therefore, requests have been made to evaluate the cost-effectiveness of an RCT comparing different exercise intensities during oncological treatment, so as to provide decisionmakers with information.
Rationale
Although oncological treatments improve survival rates in patients with cancer, they are associated with severe side effects that can negatively impact HRQoL. The side effects also lead to increased consumption of healthcare resources and productivity loss, and therefore higher costs for society.

Important tasks in nursing include managing side effects and providing and coordinating cancer rehabilitation; including promoting healthy lifestyle behaviours such as exercise to maintain functioning and improve HRQoL for patients during their oncological treatment.

Exercise as a part of cancer rehabilitation during oncological treatment has positive effects on health and can improve HRQoL by reducing side effects such as fatigue, pain, and anxiety/depression. However, it is unclear if the effect of exercise on HRQoL is maintained over time. Supervised exercise has been proven to be more beneficial than unsupervised, and combined resistance and endurance training have been proven to be more beneficial than resistance or endurance training alone in improving HRQoL. Additionally, exercise might be beneficial in reducing sick leave and healthcare visits, however, more studies are needed to confirm this. Furthermore, evidence is lacking on which prescription of exercise intensity is most optimal to improve cancer-related outcomes such as HRQoL and the cost-effectiveness. Therefore, exercise trials that directly compare different exercise intensities of combined resistance and endurance training during oncological treatment are required.

Despite the evidence of the positive effect of exercise on cancer-related outcomes, exercise has not yet been implemented into cancer care. One reason might be that supervised exercise is associated with additional resource use. As healthcare resources are limited, the cost-effectiveness—or the effects on health gained in relation to their costs of alternative interventions—is important information in the decision-making process when implementing new interventions such as exercise to cancer care.
The overall aim of this thesis was to study functioning in daily life, HRQoL, costs and cost-effectiveness of an exercise intervention with different exercise intensities in patients with cancer receiving oncological treatment.

The specific aims of each study are:

Study I: To explore how individuals with cancer receiving curative treatment and participating in an exercise intervention experienced their functioning in daily life.

Study II: To evaluate the effect of HI versus LMI exercise on HRQoL up to 18 months after commencement of oncological treatment in patients with breast, colorectal or prostate cancer. In addition, to conduct a comparison with UC.

Study III: To evaluate the long-term resource utilisation and societal costs of an exercise intervention during (neo)adjuvant oncological treatment in a RCT versus UC, and to compare HI with LMI exercise in the RCT.

Study IV: To evaluate the long-term cost-effectiveness of an exercise programme of HI or LMI during (neo)adjuvant oncological treatment.
METHOD

Methodological overview of Studies I–IV

In this thesis, four studies are included with a variation of qualitative (Study I) and quantitative (Study II–IV) methods (94). An overview of the studies included in the thesis is shown in Table 1.

Table 1. Overview of the design, methods, and analysis in the four studies included in the thesis.

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
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</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Qualitative Interview study</td>
<td>Quantitative Longitudinal multicentre RCT and longitudinal descriptive study</td>
<td>Quantitative Longitudinal multicentre RCT and longitudinal descriptive study</td>
<td>Quantitative Longitudinal multicentre RCT</td>
</tr>
<tr>
<td><strong>Sample</strong></td>
<td>n =16 women with BRC, n =2 women with CRC and n =3 men with PRC from the RCT</td>
<td>Participants with BRC, CRC, or PRC. RCT (n =577) and observational study (n =89)</td>
<td>Participants with BRC, CRC, or PRC. RCT (n =534) and observational study (n =85)</td>
<td>Participants with BRC, CRC, or PRC from the RCT (n =189)</td>
</tr>
<tr>
<td><strong>Data collection</strong></td>
<td>Semi-structured individual interviews at completion of interventions</td>
<td>EORTC-QLQ-C30, QLQ-PR25, BR23, CR29. Collected at baseline, 3-month, 6-month and 18-month follow-up</td>
<td>Resource utilisation and associated costs of healthcare, productivity loss, and exercise at 18-month follow-up</td>
<td>Cost measures from Study III, mortality, EQ-5D-5L collected at baseline, post-intervention and 1-year follow-up</td>
</tr>
<tr>
<td><strong>Data analysis</strong></td>
<td>Thematic analysis</td>
<td>Descriptive statistics and linear mixed model</td>
<td>Descriptive statistics and cost-analysis</td>
<td>Descriptive statistics, cost-effectiveness analysis and ICER</td>
</tr>
</tbody>
</table>

n: number; BRC: breast cancer; PRC: prostate cancer; CRC: colorectal cancer.
Setting

The Phys-Can project
The four studies included in this thesis are part of the multi-centre Physical training and Cancer (Phys-Can) project. The Phys-Can project consists of a RCT (NCT02473003, www.clinicaltrials.gov) preceded by a observational study (95).

The observational study (Studies II–III)
The observational study (hereafter referred to as UC) was a longitudinal descriptive study that preceded the RCT and can be used as a comparison to the RCT. Participants received UC, and the study aimed to describe how cancer and oncological treatment are related to HRQoL, mental well-being, physical fitness, and activity over time. The inclusion/exclusion criteria and follow-up protocols were the similar to the RCT. Enrolment of participants to the observational study began in September 2014 and ended in March 2015, and included 102 participants (95).

The RCT (Studies I–IV)
The RCT used a 2x2 factorial design of LMI and HI exercise with or without additional BCS during oncological treatment, with long-term follow-up. The main outcome was to study the effects of LMI and HI physical exercise with or without BCS on fatigue. Secondary outcomes included HRQoL, cost-effectiveness, chemotherapy treatment completion rates, disease outcomes, adverse events (95). RCT enrolment started in March 2015, directly after the observational study, and ended in April 2018. A total of 577 participants were randomised to HI (n =288) and LMI (n =289). This thesis focuses on the differences between the exercise intensities. Since additional BCS did not improve health outcomes at post-intervention, the BCS factor was not included in the analysis.

Inclusion and exclusion criteria in Phys-Can
The Phys-Can project was carried out at three university hospitals in Sweden. Persons ≥18 years of age diagnosed with breast, colorectal, or prostate cancer scheduled for neoadjuvant chemotherapy (breast cancer) or endocrine treatment (prostate cancer), and/or adjuvant chemotherapy (breast and colorectal cancer), adjuvant radiotherapy (breast cancer), and/or adjuvant endocrine treatment (breast and prostate cancer) or curative radiotherapy with or without additional endocrine treatment (prostate cancer). Exclusion criteria were stage IIIb–IV breast cancer, inability to perform basic activities of daily living, cognitive disorders,
severe psychiatric disease, or other disabling conditions that might contraindicate high-intensity exercise (e.g., severe heart failure, severe chronic obstructive pulmonary disease, or orthopaedic conditions), treatment of an additional malignancy, BMI <18.5 kg/m², or pregnancy. Inclusion and exclusion criteria were assessed by a cancer specialist (oncologist or surgeon) at a planned visit before starting oncological treatment. Eligible participants were informed about the study by project staff in the Phys-Can, and written informed consent was obtained from all participants. After baseline measurements, participants were randomised (computer-generated) and stratified in blocks of eight by cancer diagnosis and study site to one of four conditions: 1) HI, 2) HI with BCS, 3) LMI, and 4) LMI with BCS. Participants were followed over time and performed assessment of patient reported outcomes, VO₂ max testing, blood samples, etc. (95).

The exercise intervention
The six-month exercise intervention consisted of individually-tailored supervised resistance training and homebased endurance LMI or HI training, with or without BCS, and was initiated at the beginning of oncological treatment. There were separate training groups for each randomisation arm, with 5–10 participants in each group. The exercises were supervised by educated coaches (qualified and experienced physiotherapists or personal trainers).

The resistance training was performed twice a week in a public gym and supervised by educated coaches within the Phys-Can. The programme consisted of exercises performed on machines: seated leg press, chest press, leg extension, seated row, seated leg curl, and seated overhead press using dumbbells (Supplementary Figure 1), along with core exercises including sit-ups, the plank, bird-dog, and pelvic floor exercises (Supplementary Figure 2). Exercise intensity was determined using regular strength testing throughout the intervention with repeated measurements of six and ten repetitions maximum (RM). The content of training sessions is described in Table 2. Participants registered their resistance training in a diary.

For endurance training, the first four sessions were performed in the gym and supervised by coaches. After this, the sessions were home-based and accompanied by a coach. To determine intensity-level based on heart rate reserve, each participant performed a maximal oxygen uptake (VO₂ max) tests prior to the intervention. Each session began with a warm-up of 5–10 minutes. The HI training consisted of interval training twice a week, and the LMI training consisted of 150 minutes a week, detailed in Table 2.
The participants wore a heart rate monitor each session to examine adherence to intensity.

Half of the participants in HI respectively LMI received BCS from educated coaches within Phys-Can. The BCS focused on strategies for adherence to the home-based endurance training using goal setting, short-term action planning, self-monitoring, review of goal setting, behavioural analysis, and long-term coping planning. The BCS was performed face-to-face at the same time as the resistance training at the gym. Long-term coping planning was performed after the exercise period (11).

Table 2. The content of the resistance and the endurance training according to HI and LMI exercise.

<table>
<thead>
<tr>
<th>Content</th>
<th>HI</th>
<th>LMI</th>
</tr>
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<tbody>
<tr>
<td>Resistance training</td>
<td>First weekly session: 3 sets x 6 RM (2 min rest between sets). Last set until failure. Second weekly session: 3 sets x 10 RM (1 min rest between sets). Last set until failure.</td>
<td>First weekly session: 3 sets x 12 repetitions at 50% of 6 RM (2 min between sets) First weekly session: 3 x 20 repetitions at 50% of 10 RM (1 min rest between sets) once a week.</td>
</tr>
<tr>
<td>Endurance training</td>
<td>Interval sessions twice a week. Alternating two min of exercise (e.g., running, cycling, walking uphill) at 80%–90% heart rate reserve with two min of active rest. Participants started with 5 intervals and increased over time with a max of 10 intervals.</td>
<td>150 min a week of continuous-based exercise (e.g., walking, cycling) in bouts of at least 10 min at 40%–50% of heart rate reserve.</td>
</tr>
</tbody>
</table>

HI: high intensity; LMI: Low-to-moderate intensity; RM: repetition maximum; min: minutes.
Method

Participants and procedure

Study I
Individual interviews were conducted with participants from the Phys-Can RCT, with the aim of exploring how individuals with cancer receiving curative treatment and participating in an exercise intervention experienced their functioning in daily life. A convenience sample of 22 participants at one site were invited to participate by their coach at the end of the exercise intervention. A total of 21 participants with breast, prostate and colorectal cancer accepted the invitation and written informed consent was obtained.

Studies II–IV
All available participants in the RCT (Studies II–IV) and the UC group (Studies II–III) were included (Figure 1). In the RCT, 1451 participants were eligible, and 600 participants were included in the study. Of these, 23 patients dropped out of the study before randomisation, and therefore 577 were randomised to HI (n =288) or LMI (n =289) exercise groups. In the observational study, 233 participants were eligible, and 102 participants were included in the study. Of those, 23 participants withdrew the study before baseline measurements, and 89 completed the baseline measurement. In Study III, complete data on resource utilisation and costs were available for n =534 in the RCT (HI: n =269, LMI: n =265) and n =85 for the UC. Data was missing due to participants’ withdrawal of their consent from the study, and data from 10 participants was missing randomly. Study IV included 189 participants from the RCT (HI: n =99 and LMI: n =90). The questionnaire EQ-5D-5L used in the 1-year follow-up was not included in the data collection from the beginning but was added later. Therefore, only about 30% of participants completed the 1-year follow-up. Due to the missing data, we chose to exclude those participants who had not completed 1 year follow-up.
Figure 1. CONSORT flow chart of participants in the Phys-Can Project including the observational study with UC and the RCT.
UC, usual care; HI, high-intensity exercise; LMI, low-to-moderate intensity exercise; BCS behaviour change support. Note: 18 months follow-up in the RCT is 1 year post treatment.
Data collection

Background characteristics—Studies I–IV
Demographic data such as living situation, education, working situation, age and number of comorbidities were self-reported at baseline. Medical background data, including cancer diagnosis, cancer stage, oncological treatment and mortality were collected from medical records and the Swedish National Quality Registers at 18 months follow-up.

Interviews—Study I
The data was collected through face-to-face interviews by the author (AA). The respondent chose the location of the interview, and the interviews took place at the hospital, at the respondents’ home or at a fitness centre. Before the start of each interview, the author introduced herself and the aim of the study, followed by some small talk to get the respondent relaxed. A semi-structured interview guide with an opening prompt to encourage respondents to share experiences was used (Table 3). Probing questions were then asked so that the respondent could explore their experience.

Two pilot interviews were conducted prior to the study’s start. In these pilot interviews, respondents emphasised exercise more than expected, so we added aspects of exercise to the interview guide. We included the pilot interviews in the analysis as they covered the revised interview guide. The interviews were conducted between December 2016 and May 2017 and lasted for a range of 25–73 minutes. All interviews were digitally recorded and transcribed verbatim.

Table 3. Interview guide Study I.

<table>
<thead>
<tr>
<th>Main questions</th>
<th>Probing questions</th>
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<tbody>
<tr>
<td>What was your experience of performing household chores over the past six months?</td>
<td>Differences compared to before illness?</td>
</tr>
<tr>
<td>How have you experienced the opportunity to do what you wanted in your free time?</td>
<td>If difficulties exist, how have they affected you?</td>
</tr>
<tr>
<td>Can you tell me about your social life over the last six months?</td>
<td>What sort of impact do you think it had on you?</td>
</tr>
<tr>
<td>Can you tell me what the relationship with your family has been like?</td>
<td>How did you feel?</td>
</tr>
<tr>
<td>Can you describe any everyday situations where you found that exercise has affected you?</td>
<td>What initiatives did you take to participate in different activities?</td>
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<tr>
<td></td>
<td>How did your health affect your ability?</td>
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<tr>
<td></td>
<td>At home?</td>
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<td></td>
<td>Socially?</td>
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<td>Why?</td>
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</table>
HRQoL—Studies II and IV

In Study II, data was collected at baseline before starting oncological treatment, at 3 months (mid intervention for the RCT), at 6 months (post-intervention for the RCT), and at 18 months (1-year post-intervention for the RCT). In Study IV, data was collected at baseline, at 6 months (post-intervention), and at the 1-year follow-up post-intervention (Figure 2). Participants choose whether to complete the questionnaires online in a web portal or on paper via mail. Reminders were sent up to three times, with one week between every reminder.

Figure 2. Flowchart of the Phys-Can RCT. The UC study had the same follow-up measurements as the RCT. Abbreviations HI: high intensity exercise; LMI: Low-to-moderate intensity exercise; BCS: Behaviour change support.
In Study II, the European Organisation for Research and Treatment of Cancer, Quality of life Questionnaire C30 (EORTC QLQ-C30) for patients with cancer, version 3.0 (Swedish version) (96, 97) was used to measure HRQoL (Table 4). The items have four response categories: not at all, a little, quite a bit, and very much, except; for two items (global health status and QoL), which are rated with responses on a scale from 1 (very bad) to 7 (excellent) (Table 4). The questionnaire are validated and measure disease-specific symptoms and side effects of treatment (98). The items were scaled and scored ranging from 0 to 100, according to the EORTC guidelines (99). A higher score on the global status scale and the functional scales indicates a high degree of health and functioning, while a higher score on the symptomatic scale indicates a high degree of symptom burden.

Table 4. HRQoL-questionnaire with comprising scales used in Study II.

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Global health status/QoL</th>
<th>Functioning scales</th>
<th>Symptom scales</th>
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<tbody>
<tr>
<td>EORTC-QLQ-C30 (30 items)</td>
<td>Global health status/QoL</td>
<td>Physical functioning</td>
<td>Fatigue</td>
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<td></td>
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<td>Role functioning</td>
<td>Nausea and vomiting</td>
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<td>Emotional functioning</td>
<td>Pain</td>
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<td>Cognitive functioning</td>
<td>Dyspnoea</td>
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<td>Social functioning</td>
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<td>Financial difficulties</td>
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</table>

In Study IV, the Swedish version of the generic HRQoL instrument EuroQoL-5 Dimension (EQ-5D) Questionnaire including EQ-5D-5L and EQ-VAS was used to assess participants’ health status (100, 101). The EQ-5D-5L is a standardised non-disease specific instrument, and measures five dimensions of the self-reported health state: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with a five-level severity scale of no, slight, moderate, severe, and extreme/unable to. EQ VAS rated respondents’ overall health on a scale from 0 (worst imaginable health) to 100 (best imaginable health). There is no currently recommended value set for the calculation of the EQ-5D-5L index. Hence we applied the cross walk method, and the responses from EQ-5D-5L were mapped to EQ-5D-3L value set (102), from which a health state index was calculated. The UK value set was used for the crosswalk (103), and the EQ-5D index score ranged from 0 (dead) to 1 (full health). These weights,
Exercise in patients with cancer

varying from 0 to 1, were used to calculate QALY (quality-adjusted life-year) by multiplying the time spent in that health state.

Costs and resource utilisations—Studies III & IV
Costs and resource utilisation were evaluated from a societal perspective and included costs from the exercise interventions (6-months period), healthcare utilisation and productivity loss. Data were collected 6 months before baseline and up to 18 months after baseline for participants in the UC, and up to 1-year follow-up post-intervention for participants in the RCT.

Costs and resource utilisations measures
Costs measured consisted of:

Exercise intervention
- Staff
- Membership card for the fitness centre
- Performance of maximal oxygen uptake (VO2 max) tests
- Equipment (heart rate monitors and exercise diaries)

Intervention costs were estimated using invoices from the Phys-Can study.

Healthcare
- Outpatient visits
- Hospitalisations
- Prescription for medications

Resource utilisations were retrieved from the National Board of Health and Welfare. Each healthcare visit was coded according to the Swedish NordDRG, and valued according to the Swedish NordDRG pricelists (104). Prescribed medications were estimated using market prices (105).

Productivity loss
- Sick leave (the number of workdays lost)
- Disability pension days

Data were retrieved from the Swedish Social Insurance Agency (106). Since the first 14 days of sick leave in Sweden are paid for by the employer, we do not have data on sick leave shorter than 15 calendar days. The value of the productivity loss was estimated using the human capital approach, which measures lost productivity as the length of time absent from work due to illness (10). Lost time is then valued at the market wage. In the present study, general wage for full-time employees from 2019 (107) was used and converted into full-time equivalent days. Cost discounting was not applied, since the total study time was less than two years. Costs have
been converted into Euros, using an exchange rate of SEK 9,963 = 1 Euro as of 29 November 2020 (108).

Data analysis

Qualitative method—Study I
Thematic analyses according to Braun and Clarke were performed to analyse data (109). Thematic analysis provides a flexible method for identifying, analysing, and reporting themes in datasets and can be applied in several epistemological approaches. Themes can be identified in an inductive manner when themes are strongly linked to the data, or in a deductive manner when themes are driven by the researcher’s theoretical question. A semantic approach can be used when the themes are identified close to the data and a latent approach is used to identify underlying ideas and assumptions at an interpretive level. The analysis followed six steps, which are described in Figure 3.
In order to increase trustworthiness, all researchers involved in the analysis process engaged in peer-debriefing, with AA assuming the main responsibility (110). The research team consisted of four oncology nurses and one psychologist. AA had limited experience with qualitative research, but the other members of the research group were experienced in conducting qualitative research. All researchers except MC were involved in the Phys-Can study. AA had met some of the participants during recruitment for the Phys-Can, and two in connection with oncological treatment, but had not been their contact nurse.
Quantitative methods—Studies II–IV
Statistical analyses were performed in IBM SPSS statistics 25 and 28. Data were analysed according to the intention-to-treat principle. A level of $p \leq 0.05$ was considered statistically significant for all analyses. The sample size in Phys-Can was determined to detect the factorial effects of the main outcome of fatigue on the Multi dimension Fatigue Inventory MFI Physical Fatigue subscale (11), not reported in this study. A power calculation demonstrated that 600 participants (150 per experimental arm) were required to detect main effects with 80% power at an alpha level of 0.05.

**Background characteristics—Studies II–IV**
Descriptive statistics were used to present background characteristics of the participants as means and standard deviations or frequencies and percentages. Background characteristics of the groups were compared using Chi² tests for categorical data and ANOVA or independent-sample t-tests for continuous data.

**Study II**
Linear mixed models were used to estimate longitudinal changes in each HRQoL outcome within and between groups. This method is appropriate when longitudinal data are available and the outcome is influenced by a certain factor; e.g., effects of an intervention and by characteristics that are thought to vary within participants. Linear mixed models account for the correlations between repeated measurements in each participant and generally include both fixed effects (a parameter that is assumed not to vary between participants) and random effects (parameters that vary between participants) (Detry & Ma, 2016). In this study, the data for all HRQoL outcomes used in the models were assumed to be normally distributed, but we used robust covariances to allow for violations of the model’s assumptions. Time was considered categorical, and an interaction term between time and group was included in all models. The baseline measurement of each HRQoL outcome, age, education, study site, cancer diagnosis, and treatment were incorporated as potential confounders or auxiliary variables. Pairwise comparisons between groups were made using estimated marginal means calculated from the model.

Clinically meaningful changes over time (111) and clinically relevant differences between groups (112) were interpreted using evidence-based guidelines for the EORTC QLQ-C30. The change score over time or difference in score between groups refer to an improvement or deterioration in each scale as trivial (unlikely to have a clinically relevance) small (subtle but nevertheless clinically relevant), medium (likely to be
clinically relevant but to a lesser extent), or large (unequivocal clinical relevance).

**Study III**

Differences in resource utilisation and total and disaggregated costs between the RCT and UC were estimated using analyses of covariance (ANCOVA). To adjust for possible confounders, measurements 6 months prior to baseline of each outcome and age as covariates, while gender and chemotherapy (yes/no) were included as fixed factors in the model. Differences in resource utilisation and total and disaggregated costs within the RCT (HI versus LMI) were analysed using independent sample t-tests.

**Study IV**

The Last Observation Carry Forward (LOCF) method (113) were used to impute missing values of the EQ-5D-5L value set. The last observed value was put forward, unless there were none, in which case the last value was carried backward. Since we excluded participants that had not completed the 1-year follow-up, we imputed data on the missing observations (2%) at baseline and at post-intervention.

Independent-sample t-tests were used to compare differences between HI and LMI group for QALY, costs, and health status scores. The Mann-Whitney U test was used to compare differences between HI and LMI group in the distribution of EQ-5D-5L dimensions of health at each measurement. ANCOVA was used to analyse differences between groups for EQ VAS (adjusted for baseline measurement). The paired-sample t-test was used to study the difference within each group over time for health status values, and the Wilcoxon matching pairs test for the distribution of the EQ-5D-5L dimensions. Cost effectiveness, evaluated as incremental cost-effectiveness ratios (ICERs), were calculated by dividing the difference in the total costs by the difference in health outcome (QALY) between the groups. We used Microsoft Excel 2016 to estimate the uncertainty around the ICERs from both a societal and a healthcare perspective, using bootstrap intervals (10,000 repetitions), and cost-effectiveness planes were constructed. Sensitivity analyses were performed with all participants, with complete cost measurements (HI: n =269 and LMI: n =265).
Ethical consideration

Ethical approval was obtained from the Swedish Ethical Review Authority in Uppsala Dnr 2014/249/3 (Study I), Dnr 2014/249 (Study II), Dnr 2014/249/5 (Studies III and IV), and the studies were conducted in agreement with the Declaration of Helsinki (114). All participants provided written informed consent. There is always a risk that participants did not dare to decline participation, but they were informed that they could withdraw from the study at any time without explanation or consequences for their future care.

Previous exercise trials have shown positive effects of exercise on HRQoL and fatigue during oncological treatment (115). Since the positive effects of exercise are well documented, the researchers in Phys-Can considered it unethical to assign participants to a control group with usual care in the RCT. Thus, a design including an observational study, which could be used as comparison, was initiated to precede the RCT.

Participation in the RCT could lead to increased physical activity, which would result in positive effects on individuals’ health and well-being. A meta-analysis has shown that it is safe to exercise during oncological treatment, and there is only a small risk of injury, like for the general population (115). To minimise the risk of injury, a physician assessed contraindications for high intensity exercise according to exclusion criteria for each patient. Furthermore, to minimise the risk of injury, participants were regularly monitored by the coaches.

In Study I, participants may have experienced feeling exposed during the interviews. In order to minimise this, the questions were carefully chosen, and participants were informed that they could stop the interviews at any time. The audio recordings and transcripts are kept safe so that only persons in the research team have access to them. The results of the interviews were presented in such a way that the respondents could not be identified.

Participation in the Phys-Can study may have been perceived as an additional burden for the participants with physical tests and the exercise intervention to an already difficult situation. In addition, there was a potential risk that the data collection of questionnaires in Studies II and IV could be perceived as stressful by participants. Consideration was given to limit the number of questions to answer as much as possible to study possible effects of the interventions. Participants were assured of full confidentiality. The data collected in Phys-Can were stored securely at a web portal at Uppsala University. The author received a re-coded data file from the web portal, so the participants could not be identified. Only members of the research group had access to the collected data. Participant and study IDs are kept in a locked, fireproof room.
Exercise in patients with cancer
RESULTS

Background characteristics of participants
Most of the participants in all studies were women with breast cancer and their mean age varied from 58 to 62 years of age. An overview of participants' background characteristics is presented in Table 5 (Study I) and in Table 6 (Studies II–IV).

Table 5. Background characteristics of the participants in Study I.

<table>
<thead>
<tr>
<th>Participants (n)</th>
<th>Exercise group (n)</th>
<th>Age, mean years (min–max)</th>
<th>Female n (%)</th>
<th>Breast cancer (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Surgery, Chemotherapy, Radiotherapy, Endocrine therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Surgery, Chemotherapy, Radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Surgery, Radiotherapy, Endocrine therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Surgery, Endocrine therapy</td>
</tr>
<tr>
<td></td>
<td>Exercise group (n)</td>
<td></td>
<td></td>
<td>Prostate cancer (n)</td>
</tr>
<tr>
<td></td>
<td>High intensity</td>
<td></td>
<td></td>
<td>Radiotherapy</td>
</tr>
<tr>
<td></td>
<td>Low-to-moderate intensity</td>
<td></td>
<td></td>
<td>Radiotherapy, Endocrine therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Colorectal cancer (n)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Surgery and Chemotherapy</td>
</tr>
</tbody>
</table>
Exercise in patients with cancer

Table 6. Major background characteristics of the participants in Studies II–IV.

<table>
<thead>
<tr>
<th></th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HI (n = 288)</td>
<td>LMI (n = 289)</td>
<td>UC (n = 89)</td>
</tr>
<tr>
<td></td>
<td>HI (n = 269)</td>
<td>LMI (n = 265)</td>
<td>UC (n = 85)</td>
</tr>
<tr>
<td></td>
<td>HI (n = 99)</td>
<td>LMI (n = 90)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>58 (12)</td>
<td>58 (11)</td>
<td>59 (12)</td>
</tr>
<tr>
<td>Female</td>
<td>231 (80)</td>
<td>234 (81)</td>
<td>272 (83)</td>
</tr>
<tr>
<td>Living with partner</td>
<td>213 (77)</td>
<td>218 (79)</td>
<td>63 (76)</td>
</tr>
<tr>
<td>University</td>
<td>163 (60)</td>
<td>173 (66)</td>
<td>41 (55)</td>
</tr>
<tr>
<td>Any sick leave</td>
<td>97 (35)</td>
<td>99 (36)</td>
<td>25 (31)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>157 (58)</td>
<td>170 (61)</td>
<td>45 (55)</td>
</tr>
<tr>
<td></td>
<td>147 (58)</td>
<td>155 (60)</td>
<td>38 (52)</td>
</tr>
<tr>
<td></td>
<td>53 (57)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>228 (71)</td>
<td>119 (70)</td>
<td>73 (70)</td>
</tr>
<tr>
<td>Chemo therapy</td>
<td>118 (65)</td>
<td>127 (66)</td>
<td>24 (63)</td>
</tr>
<tr>
<td>Antibody treatment</td>
<td>39 (24)</td>
<td>40 (24)</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Radio therapy</td>
<td>170 (81)</td>
<td>177 (84)</td>
<td>44 (81)</td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td>147 (70)</td>
<td>164 (77)</td>
<td>48 (77)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>49 (57)</td>
<td>48 (53)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Radio-and/or brachy therapy</td>
<td>45 (100)</td>
<td>47 (100)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td>25 (57)</td>
<td>25 (53)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>11 (100)</td>
<td>12 (100)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Chemo therapy</td>
<td>11 (100)</td>
<td>11 (100)</td>
<td>4 (100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Data are mean (SD) or number (%). N vary due to missing data, % is of those with data available.

Abbreviations: HI: High-intensity exercise; LMI: Low-to-moderate-intensity exercise; UC: Usual care.

a. Adjuvant or neoadjuvant Anthracycline-based and/or Taxane-based.
b. Trastuzumab single or combined with Pertuzumab.
c. Breast and/or axilla.
d. Oxaliplatin and/or Capecitabin

Experiences of functioning in daily life during oncological treatment

The interviews, which explored the experience of functioning in daily life in individuals with cancer receiving curative treatment and participating in an exercise intervention, resulted in two themes: "struggling with impairments from side effects of cancer treatment", and "striving to maintain a normal life in a new context", with three sub-themes
respectively (Figure 4). Sub-themes are in bold with quotation marks within the text below.

**Struggling with impairments from side effects of cancer treatment**

Participants described the distress of cancer and the side effects of treatment, that negatively impact their functioning in life activities and participation.

Experiences of fatigue had both physical and mental dimensions. Being “exhausted all the time” limited activities in social life and participation in family life and in work.

“You can’t work all day, or you get tired, and you don’t work more than a certain number of days in a row. The body says, now we’re taking it easy to recover. This message has been very clear.” (P11)

**Impaired cognitive functioning**, such as difficulties with concentration and memory, were described by participants. It was harder to stay focused throughout the day at work and the ability to handle stressful situations and to multitask was reduced. Some experienced that they had forgotten what activities they had been planned with others.
Experiences of “impaired physical functioning” were described, especially after surgery and hence being dependent on help from family and friends with household activities that required heavy lifts or lifting arms over shoulder. Bodily changes after treatment as stoma, urinary urgency and mastectomy could limited social life in public places, but also intimate relations with partners.

**Striving to maintain a normal life in a new context**

Participants expressed that it was important to keep living as normally as possible during and after cancer treatment. Accordingly, they strove to adjust activities and participation to maintain routines. Exercise was an important part of rehabilitation after cancer to maintain functioning.

Participants stated that it was important to maintain physical functioning and health during treatment, and that the “exercise facilitated functioning in daily life.” Being physically active made it easier to perform daily activities that were physical demanding. Furthermore, participants experienced that exercise increased psychological wellbeing and self-esteem, and also helped them structure their day and focus on things other than their cancer.

“I’ve been healthier and stronger, both mentally and physically. I can manage, if I hadn’t exercised like that, I think it would have taken longer for me to get going physically.” (P3)

“...stoma, urinary urgency and mastectomy could limited social life in public places, but also intimate relations with partners.”

“I felt really mushy in the head. I couldn’t concentrate on facts, so I felt that I didn’t need to get it right now, so I filed it away and didn’t even think about it because it felt exhausting.” (P3)
Results

Social life could be restricted during treatment for the participants. The exercise intervention provided a setting for “social and informative support from the exercise group”. Participants emphasised that it was important to meet with others in similar situations to share experiences. Participants also experienced that supervised exercise in group was supportive and motivating.

“It’s also been positive in a social way. We’re a great group and have gotten to know each other. We talk, support, and encourage each other...Yes, it’s important to meet others who understand what you’re going through.” (P1)

Being able to continue with activities was important to maintain a sense of normal life. The prerequisite for this was by “adjusting activities” to their capacity. Sick leave made participation in activities easier as they had time to rest between them. In social life, adjustments were made, such as keeping in contact by email or phone instead of meeting in real life or moving activities to earlier in the day instead of the evening due to fatigue. Importantly, returning to work contributed to being in a social context and in maintaining daily routines after treatment. However, due to fatigue and impaired cognitive function, an adjustment of occupational task or working hours may be necessary to be able to work.

Effect on HRQoL of different exercise intensities during oncological treatment

In Study II, 577 participants were randomly assigned to HI (n =288) and LMI (n =289) in the RCT. In the UC-study, 89 participants were included at baseline. Baseline questionnaires were completed for 97% in HI, 98% in LMI, and 99% in the UC. The response rate was >71% of each follow-up time within all groups of participants remaining in the study. In total, 18% of participants had dropped out at 18 months in HI, 16% in LMI, and 29% in UC. Background characteristics (presented in Table 6) were well-balanced between groups except that a lower proportion of participants with breast cancer received chemotherapy in the UC compared to the RCT (p <0.01).


**HRQoL in HI versus LMI exercise**

HRQoL was compared between the exercise intensities up to 18 months (1-year post intervention). There was statistically significant higher pain in the HI group, mean difference = 4.7 (95% CI 0.9 to 8.5) compared to the LMI group at post-intervention (6 months), however this difference was not clinically relevant. No other difference in HRQoL were found between the groups.

**HRQoL in HI exercise and LMI exercise versus UC**

HRQoL was compared between HI exercise, LMI exercise, and usual care up to 18 months (1-year post intervention for the exercise groups). The exercise groups scored statistically significant better in HRQoL compared to UC (Figure 5). At 3 months, both the HI and LMI groups scored better global health status/QoL and the LMI group scored better emotional functioning than UC. At 6 months, both the HI and LMI groups scored better global health status/QoL, better physical- and role functioning, and less fatigue, and the HI group less dyspnoea than UC. At 18 months, both the HI and LMI groups scored better emotional functioning, and the LMI group scored better global health status/QoL and less fatigue than UC. Additional scales of EORTC-QLQ-C30 for HI, LMI and UC over time are presented in Figure 6.

Clinically meaningful changes were found in groups over time. There were more favourable changes in the exercise groups over time compared to UC (Table 7).
Figure 5. Significant p-values of functioning and symptoms of EORTC QLQ-C30 for high intensity (HI) and low-to-moderate intensity (LMI) exercise versus usual care (UC) over time.

Baseline measurements were scaled to 100, and changes are presented in percentages. A high score for the global health status and functional scale represents a high QoL and a high level of functioning. A high score for the symptom scale/item represents a high level of symptoms/problems. Unscaled observed mean differences between groups are presented within the brackets. Clinically relevant differences were defined as T: trivial (unlikely to have a clinically relevance); S: small (subtle but nevertheless clinically relevant); M: medium (likely to be clinically relevant but to a lesser extent) and N/A: No guidelines applicable (Cocks et al. 2011.) The figure is reprinted and used with permission (Ax, Johansson, Lyth, Nordin, and Börjeson, 2022).
Exercise in patients with cancer

Figure 6. Non-significant p-values of functioning and symptoms of EORTC QLQ-C30 for high intensity (HI) and low-to-moderate intensity (LMI) exercise versus usual care (UC) over time.

Baseline measurements were scaled to 100, and changes are presented in percentages. A high score on the global health status and functional scale represents a high QoL and a high level of functioning. A high score for the symptom scale/item represents a high level of symptoms/problems. Unscaled observed mean differences between groups are presented within the brackets. Clinically relevant differences were defined as T = trivial (unlikely to have a clinically relevance); S: small (subtle but nevertheless clinically relevant); M: medium (likely to be clinically relevant but to a lesser extent) and N/A: No guidelines applicable (Cocks et al. 2011.)
Table 7. Clinically meaningful changes within groups of EORTC QLQ-C30, exercises of high and low-to-moderate intensity, and usual care.

<table>
<thead>
<tr>
<th></th>
<th>Clinically meaningful changes within group from baseline to 6 months</th>
<th>Clinically meaningful changes within group from baseline to 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global health status/QoL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>+7 Small*</td>
<td>+6 Small*</td>
</tr>
<tr>
<td>LMI</td>
<td>+9 Medium*</td>
<td>+9 Medium*</td>
</tr>
<tr>
<td>UC</td>
<td>–3 Trivial</td>
<td>+1 Trivial</td>
</tr>
<tr>
<td><strong>Physical functioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>+1 Trivial</td>
<td>–1 Trivial</td>
</tr>
<tr>
<td>LMI</td>
<td>+1 Trivial</td>
<td>+1 Trivial</td>
</tr>
<tr>
<td>UC</td>
<td>–3 Trivial</td>
<td>0 Trivial</td>
</tr>
<tr>
<td><strong>Role functioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>+9 Small*</td>
<td>+10 Small*</td>
</tr>
<tr>
<td>LMI</td>
<td>+12 Small*</td>
<td>+11 Small*</td>
</tr>
<tr>
<td>UC</td>
<td>0 Trivial</td>
<td>+10 Small*</td>
</tr>
<tr>
<td><strong>Emotional functioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>+7 Small*</td>
<td>+9 Small*</td>
</tr>
<tr>
<td>LMI</td>
<td>+8 Small*</td>
<td>+10 Medium*</td>
</tr>
<tr>
<td>UC</td>
<td>+5 Trivial*</td>
<td>+1 Trivial</td>
</tr>
<tr>
<td><strong>Cognitive functioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>+2 Trivial</td>
<td>+2 Trivial</td>
</tr>
<tr>
<td>LMI</td>
<td>–1 Trivial</td>
<td>+2 Trivial</td>
</tr>
<tr>
<td>UC</td>
<td>–1 Trivial</td>
<td>–1 Trivial</td>
</tr>
<tr>
<td><strong>Social functioning</strong></td>
<td></td>
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</tr>
<tr>
<td>HI</td>
<td>+2 Trivial</td>
<td>+3 Trivial*</td>
</tr>
<tr>
<td>LMI</td>
<td>+5 Small*</td>
<td>+6 Small*</td>
</tr>
<tr>
<td>UC</td>
<td>–1 Trivial</td>
<td>+3 Trivial</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td></td>
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</tr>
<tr>
<td>HI</td>
<td>–2 Trivial</td>
<td>–1 Trivial</td>
</tr>
<tr>
<td>LMI</td>
<td>–4 Trivial*</td>
<td>–5 Small*</td>
</tr>
<tr>
<td>UC</td>
<td>+9 Small*</td>
<td>+4 Trivial</td>
</tr>
<tr>
<td><strong>Nausea and vomiting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>–1 Trivial</td>
<td>–2 Trivial*</td>
</tr>
<tr>
<td>LMI</td>
<td>–1 Trivial</td>
<td>0 Trivial</td>
</tr>
<tr>
<td>UC</td>
<td>–1 Trivial</td>
<td>1 Trivial</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>+1 Trivial</td>
<td>+3 Trivial</td>
</tr>
<tr>
<td>LMI</td>
<td>–5 Small*</td>
<td>–2 Trivial</td>
</tr>
<tr>
<td>UC</td>
<td>+2 Trivial</td>
<td>+4 Trivial</td>
</tr>
<tr>
<td><strong>Dyspnoea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>–1 Trivial</td>
<td>+1 Trivial</td>
</tr>
<tr>
<td>LMI</td>
<td>+2 Trivial*</td>
<td>+2 Trivial</td>
</tr>
<tr>
<td>UC</td>
<td>+9 Small*</td>
<td>6 Small</td>
</tr>
<tr>
<td><strong>Insomnia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>+2 Trivial</td>
<td>–1 Trivial</td>
</tr>
<tr>
<td>LMI</td>
<td>0 Trivial</td>
<td>–2 Trivial</td>
</tr>
<tr>
<td>UC</td>
<td>+2 Trivial</td>
<td>+5 Trivial</td>
</tr>
<tr>
<td><strong>Appetite loss</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>–5 Small*</td>
<td>–3 Small*</td>
</tr>
<tr>
<td>LMI</td>
<td>–5 Small*</td>
<td>–5 Small*</td>
</tr>
<tr>
<td>UC</td>
<td>–2 Trivial</td>
<td>+1 Trivial</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>+1 Trivial</td>
<td>+1 Trivial</td>
</tr>
<tr>
<td>LMI</td>
<td>+2 Trivial</td>
<td>+2 Trivial</td>
</tr>
<tr>
<td>UC</td>
<td>+2 Trivial</td>
<td>+6 Small</td>
</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>–1 Trivial</td>
<td>–1 Trivial</td>
</tr>
<tr>
<td>LMI</td>
<td>1 Trivial</td>
<td>–1 Trivial</td>
</tr>
<tr>
<td>UC</td>
<td>+3 Trivial</td>
<td>+1 Trivial</td>
</tr>
<tr>
<td><strong>Financial difficulties</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>–1 Trivial</td>
<td>–1 Trivial</td>
</tr>
<tr>
<td>LMI</td>
<td>–2 Trivial</td>
<td>–5 Small*</td>
</tr>
<tr>
<td>UC</td>
<td>0 Trivial</td>
<td>–4 Small</td>
</tr>
</tbody>
</table>
Interpreted as clinically meaningful, as defined by Cocks et al. 2012: Trivial: no/unlikely difference; S: small change of subtle clinical relevance; M: medium change of likely clinical relevance and NA: no available guidelines. *Indicate statistically significant differences from baseline. Bold font indicates clinically meaningful variables. HI: high intensity exercise; LMI: low-to-moderate intensity exercise and UC: usual care.

Costs and cost-effectiveness of exercise during (neo)adjuvant oncological treatment

Resource utilisation and costs in the RCT versus UC

Resource utilisation and associated costs were compared between the exercise intervention and the UC group. At 18 months, participants in the RCT had significant lower rates of disability pension days and associated costs, and pharmacy costs compared to UC. The societal costs were €35,253 per participants in the RCT and €32,338 in UC and did not differ significantly (Table 8).
Table 8. Resource utilisations and costs of RCT versus UC at 18 months.

<table>
<thead>
<tr>
<th>Measures</th>
<th>RCT (n =534)</th>
<th>UC (n =85)</th>
<th>RCT versus UC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted mean (SE)</td>
<td>Adjusted mean (SE)</td>
<td>Adjusted mean difference (95% CI)</td>
</tr>
<tr>
<td><strong>Exercise intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labour and equipment (€)</td>
<td>1693 (0)</td>
<td>0 (0)</td>
<td>1693 (1693 to 1693)*</td>
</tr>
<tr>
<td>Out-of-pocket (travel costs) (€)</td>
<td>928 (0)</td>
<td>0 (0)</td>
<td>928 (928 to 928)*</td>
</tr>
<tr>
<td>Total costs (€)</td>
<td>2622 (0)</td>
<td>0 (0)</td>
<td>2622 (2622 to 2622)*</td>
</tr>
<tr>
<td><strong>Healthcare</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient visits (n)</td>
<td>13.3 (0.5)</td>
<td>15.4 (1.1)</td>
<td>−2.1 (−4.3 to 0.1)</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-days</td>
<td>2.3 (0.3)</td>
<td>1.9 (0.5)</td>
<td>0.4 (−0.7 to 1.5)</td>
</tr>
<tr>
<td>-visits</td>
<td>0.8 (0.1)</td>
<td>0.7 (0.1)</td>
<td>0.1 (0.2 to 0.3)</td>
</tr>
<tr>
<td>Outpatient costs (€)</td>
<td>6840 (252)</td>
<td>7539 (547)</td>
<td>−700 (−1767 to 368)</td>
</tr>
<tr>
<td>Hospitalisation costs(€)</td>
<td>4663 (383)</td>
<td>3687 (818)</td>
<td>976 (−644 to 2,596)</td>
</tr>
<tr>
<td>Pharmacy costs (€)</td>
<td>1040 (50)</td>
<td>1295 (107)</td>
<td>−254 (−466 to −43)*</td>
</tr>
<tr>
<td>Total costs (€)</td>
<td>12,480 (513)</td>
<td>12,066 (1090)</td>
<td>414 (−1746 to 2574)</td>
</tr>
<tr>
<td><strong>Productivity loss</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sick leave (days)</td>
<td>132 (6)</td>
<td>110 (12)</td>
<td>22 (−1 to 45)</td>
</tr>
<tr>
<td>Disability pension (days)</td>
<td>7.2 (1.3)</td>
<td>16.7 (2.7)</td>
<td>9.5 (−15 to −4.2)*</td>
</tr>
<tr>
<td>Sick leave (€)</td>
<td>19,654 (826)</td>
<td>16,376 (1757)</td>
<td>3277 (−201 to 6755)</td>
</tr>
<tr>
<td>Disability pension (€)</td>
<td>1074 (190)</td>
<td>2499 (404)</td>
<td>−1425 (−2230 to −621)*</td>
</tr>
<tr>
<td>Total costs (€)</td>
<td>20,592 (841)</td>
<td>19,216 (1784)</td>
<td>1376 (−2171 to 4923)</td>
</tr>
<tr>
<td><strong>Societal costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total costs (€)</td>
<td>35,253 (1135)</td>
<td>32,338 (2408)</td>
<td>2914 (−1865 to 7694)</td>
</tr>
</tbody>
</table>

RCT, randomised controlled trial with exercise; UC, usual care; n, numbers; SE, standard error of the mean; CI, confidence interval; €, Euro.

*Statistically significant at p ≤0.05.

**Resource utilisation and costs in HI exercise versus LMI exercise**

Resource utilisation and associated costs were also compared between exercise intensities. At 1-year follow-up post-intervention, there were no significant differences in healthcare resource utilisation or days of productivity loss between the groups. There was no significant difference
Exercise in patients with cancer

in societal costs or in any cost category between HI and LMI (Table 9). At the 1-year follow-up, there was no significant difference in societal costs between the intensity groups. In Study III, the mean societal costs were €35,519 in the HI and €33,387 in the LMI group. In Study IV, the mean societal costs were €27,314 per participant in the HI group and €29,788 in the LMI group. Furthermore, there were no significant differences between groups in the cost categories: exercise intervention, healthcare utilisation, and productivity loss (Table 9).
### Results

Table 9. Resource utilisation and costs of HI versus LMI exercise at 1-year follow-up post-intervention.

<table>
<thead>
<tr>
<th>Measures</th>
<th>HI(^{\text{III}}) (n = 269)</th>
<th>LMI(^{\text{III}}) (n = 265)</th>
<th>HI(^{\text{III}}) versus LMI(^{\text{III}})</th>
<th>HI(^{\text{IV}}) (n = 99)</th>
<th>LMI(^{\text{IV}}) (n = 90)</th>
<th>HI(^{\text{IV}}) versus LMI(^{\text{IV}})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise intervention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labour equipment (£)</td>
<td>1693 (0)</td>
<td>1693 (0)</td>
<td>0 (1693 to 1693)</td>
<td>1693 (0)</td>
<td>1693 (0)</td>
<td>0 (1693 to 1693)</td>
</tr>
<tr>
<td>Out-of-pocket (travel) (£)</td>
<td>928 (0)</td>
<td>928 (0)</td>
<td>0 (928 to 928)</td>
<td>928 (0)</td>
<td>928 (0)</td>
<td>0 (928 to 928)</td>
</tr>
<tr>
<td>Total costs (£)</td>
<td>2622 (0)</td>
<td>2622 (0)</td>
<td>0 (2622 to 2622)</td>
<td>2622 (0)</td>
<td>2622 (0)</td>
<td>0 (2622 to 2622)</td>
</tr>
<tr>
<td><strong>Healthcare</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>13.5 (11.0)</td>
<td>13.2 (10.5)</td>
<td>0.3 (-1.6 to 2.1)</td>
<td>11.0 (7.8)</td>
<td>11.6 (8.0)</td>
<td>0.6 (-2.9 to 1.7)</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-days</td>
<td>2.1 (5.8)</td>
<td>1.8 (3.8)</td>
<td>0.3 (-0.6 to 1.1)</td>
<td>1.6 (4.9)</td>
<td>1.5 (2.8)</td>
<td>0.1 (-1.0 to 1.3)</td>
</tr>
<tr>
<td>-visits</td>
<td>0.6 (1.3)</td>
<td>0.6 (1.0)</td>
<td>0 (-0.2 to 0.2)</td>
<td>0.4 (0.8)</td>
<td>0.6 (0.9)</td>
<td>-0.2 (-0.4 to 1)</td>
</tr>
<tr>
<td>Outpatient costs (£)</td>
<td>6,553 (5404)</td>
<td>6,306 (5228)</td>
<td>248 (-657 to 1,173)</td>
<td>544 (3775)</td>
<td>559 (4251)</td>
<td>-154 (-1,006 to 897)</td>
</tr>
<tr>
<td>Hospitalisation costs (£)</td>
<td>3,711 (8794)</td>
<td>3,588 (5944)</td>
<td>122 (-1,156 to 1,400)</td>
<td>2,121 (4655)</td>
<td>3,321 (5740)</td>
<td>-1200 (-2,694 to 294)</td>
</tr>
<tr>
<td>Pharmacy costs</td>
<td>850 (1056)</td>
<td>943 (1140)</td>
<td>-92 (-279 to 194)</td>
<td>923 (1022)</td>
<td>1012 (1270)</td>
<td>-2474 (-10,170 to 5222)</td>
</tr>
<tr>
<td>Total costs (£)</td>
<td>11,114 (11,902)</td>
<td>10,837 (9,096)</td>
<td>277 (-1,525 to 2,080)</td>
<td>8488 (7,137)</td>
<td>9931 (8,607)</td>
<td>-1443 (-3,704 to 818)</td>
</tr>
<tr>
<td><strong>Productivity loss</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sick leave (days)</td>
<td>140 (164)</td>
<td>130 (155)</td>
<td>10 (-17 to 37)</td>
<td>108 (153)</td>
<td>115 (151)</td>
<td>-3.86 (-47.0 to 39.3)</td>
</tr>
<tr>
<td>Disability pension (days)</td>
<td>5.6 (45)</td>
<td>3.3 (25)</td>
<td>2.3 (-3.9 to 8.4)</td>
<td>0 (0)</td>
<td>3.0 (28.8)</td>
<td>-6.1 (-17.8 to 5.4)</td>
</tr>
<tr>
<td>Sick leave (£)</td>
<td>20,946 (24,470)</td>
<td>19,732 (23,141)</td>
<td>1514 (-2,536 to 5,564)</td>
<td>16,205 (22,867)</td>
<td>16,782 (22,017)</td>
<td>-577 (-7,032 to 5,978)</td>
</tr>
<tr>
<td>Disability pension (£)</td>
<td>838 (6665)</td>
<td>497 (3723)</td>
<td>340 (-581 to 1,262)</td>
<td>454 (4309)</td>
<td>454 (-1,308 to 400)</td>
<td>-454 (-1,308 to 400)</td>
</tr>
<tr>
<td>Total costs (£)</td>
<td>21,783 (25,134)</td>
<td>19,929 (23,644)</td>
<td>1854 (-2,295 to 6,004)</td>
<td>16,205 (8,607)</td>
<td>17,236 (22,608)</td>
<td>-1031 (-7,566 to 5,504)</td>
</tr>
<tr>
<td><strong>Societal costs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total costs (£)</td>
<td>35,519 (31,163)</td>
<td>33,387 (28,044)</td>
<td>2,132 (-2,911 to 7,714)</td>
<td>27,314 (28,105)</td>
<td>29,788 (27,517)</td>
<td>-2,474 (-10,170 to 5,243)</td>
</tr>
</tbody>
</table>

HI: high intensity exercise; LMI: low-to-moderate intensity exercise; III refers to Study III; IV refers to Study IV; n: numbers; SD: standard deviation; CI: confidence interval; €: Euro.
Cost-effectiveness of different exercise intensities during oncological treatment

The long-term (1-year post-intervention) cost-effectiveness of the exercise intervention of HI or LMI during (neo)adjuvant oncological treatment was evaluated (Study IV). The societal costs used in the cost-effectiveness are detailed in Table 9 (Study IV).

There was no significant difference reported between the intensity groups on the five single dimensions of health in EQ-5D-5L. The distribution (in percent) of reported levels 1–5 by EQ-5D-5L dimensions of HI and LMI exercise over time are presented in Table 10.
Table 10. The distribution of reported levels 1–5 of health in EQ-5D-5L dimension of HI and LMI exercise at baseline, at post-intervention (6 months) and at 1-year follow-up post-intervention.

<table>
<thead>
<tr>
<th>EQ-5D dimensions</th>
<th>HI (n =99)</th>
<th>LMI (n =90)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post-intervention</td>
</tr>
<tr>
<td>Mobility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>93%</td>
<td>79%</td>
</tr>
<tr>
<td>Level 2</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>Level 3</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Level 4</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Level 5</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Self-care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>91%</td>
<td>95%</td>
</tr>
<tr>
<td>Level 2</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Level 3</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Level 4</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Level 5</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Usual activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>68%</td>
<td>71%</td>
</tr>
<tr>
<td>Level 2</td>
<td>17%</td>
<td>20%</td>
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<tr>
<td>Level 3</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Level 4</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Level 5</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>49%</td>
<td>43%</td>
</tr>
<tr>
<td>Level 2</td>
<td>36%</td>
<td>33%</td>
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<tr>
<td>Level 3</td>
<td>0%</td>
<td>19%</td>
</tr>
<tr>
<td>Level 4</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Level 5</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>38%</td>
<td>47%</td>
</tr>
<tr>
<td>Level 2</td>
<td>41%</td>
<td>43%</td>
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<tr>
<td>Level 3</td>
<td>16%</td>
<td>7%</td>
</tr>
<tr>
<td>Level 4</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Level 5</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Level 1: no problem; Level 2: slight problems; Level 3: moderate problem; level 4: severe problems; Level 5: unable to or extremely problems. HI: high intensity exercise; LMI: low-to-moderate intensity exercise; FU: follow-up.

Based on the results of EQ-5D-5L, a health state index was calculated. There was no difference in health state index between the intensity groups. For EQ-VAS, HI scored better overall health compared with LMI at
baseline (mean diff 6; p = 0.026), no other significant differences were found (Table 11).

Table 11. Impact of exercise intensity on EQ-5D-5L health state index and EQ-VAS.

<table>
<thead>
<tr>
<th></th>
<th>HI (n=99) Mean (SD)</th>
<th>LMI (n=90) Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health state index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.80 (0.15)</td>
<td>0.76 (0.18)</td>
<td>0.052</td>
</tr>
<tr>
<td>Post intervention</td>
<td>0.79 (0.20)</td>
<td>0.80 (0.16)</td>
<td>0.565</td>
</tr>
<tr>
<td>1-year follow-up</td>
<td>0.79 (016)</td>
<td>0.78 (0.19)</td>
<td>0.723</td>
</tr>
<tr>
<td><strong>EQ VAS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>72 (17.3)</td>
<td>66 (18.7)</td>
<td>0.026</td>
</tr>
<tr>
<td>Post intervention</td>
<td>76 (1.4)</td>
<td>77 (1.5)</td>
<td>0.949</td>
</tr>
<tr>
<td>1-year follow-up</td>
<td>75 (1.5)</td>
<td>75 (1.6)</td>
<td>0.966</td>
</tr>
</tbody>
</table>

HI: high intensity; LMI: low-to-moderate intensity.

The QALY was estimated by the value of health state index and time spent in that health state (Figure 7). The mean QALY did not differ significantly between the intensity groups. At 1-year follow-up, mean QALY was 1.190 (SD = 0.223) for HI, and 1.185 (SD = 0.211) for LMI.
The ICER provides a ratio of incremental cost per unit of health outcome in HI exercise versus LMI exercise. The mean ICER was $-516.698$, but there was no significant difference in either total cost or in effects between the intensity groups. Bootstrap analysis showed that the ICER was dominant in 56% of the 10,000 replications. The uncertainty around the ICER for QALY gained from HI versus LMI exercise was considerable and is shown in the cost-effective plane in Figure 8. Furthermore, sensitivity analyses showed no significant difference in costs or in QALYs between intensity groups after including all participants.

Figure 8. Cost-effectiveness plane indicating the uncertainty around the ICER for quality adjusted life year (QALY) gained of HI versus LMI exercise.
Exercise in patients with cancer
DISCUSSION

Result discussion

The overall aim of this thesis was to study functioning in daily life, HRQoL, costs, and cost-effectiveness of an exercise intervention with different exercise intensities in patients with cancer receiving oncological treatment. The most important findings of the studies are: 1) participating in an exercise intervention during oncological treatment was perceived as positive for maintaining physical and psychological functioning and performing activities in daily life; 2) there were no clinically relevant differences in HRQoL outcome between the exercise intensity groups, but the exercise groups reported statistically significant better HRQoL compared with the non-randomised UC-group (discussed in more below); 3) there was no statistically significant difference in societal costs between the exercise intervention and usual care, or between the exercise intensities; and 4) there was no significant difference in cost or effect between the exercise intensities. Although the mean incremental cost-effectiveness ratio indicated that HI was cost-effective compared to LMI, the uncertainty was large.

Experiences of functioning in daily life

The participants experienced challenges in daily life with impaired physical and cognitive functioning during oncological treatment, consistent with previous studies (71, 116). Despite struggling with impairments, participants were resourceful and described that they were able to maintain meaningful daily activities and participate in social life but had to make adjustments according to their capacity. This is in line with another study on women with breast cancer (117).

Many of the participants were on sick leave due to reduced work capacity during treatment, which has given them more time to adjust their activities in daily life and to attend the scheduled exercise groups in PhysCan. Similar to us, a cohort study indicated that it is common to be on sick leave after cancer diagnosis, and about 70% of the women with breast cancer in working age were on sick leave during the first year after diagnosis, with an average of 185 days (86). Therefore, when planning rehabilitation interventions, decisionmakers must take into account that cancer patients may need to be on sick leave to be able participate in their rehabilitation and maintain physical and psychological functioning. Also, it is important that the nurse assess patient’s functioning regularly during
their cancer trajectory and provide support to make changes necessary to adapt to a life with cancer (45). Referral to an occupational therapist in the rehabilitation care team may address needs created by impairments related to cancer; e.g., by helping patients with fatigue to make personalised adjustments and to structure modification and prioritisation of activities (118).

Staying healthy and maintaining physical and psychological functioning during oncological treatment was important for the participants in Study I, and they experienced that the exercise intervention emphasised this. The result is similar to a previous study investigating the role of physical activity on QoL (119). The participants also experienced that the exercise intervention promoted health instead of focusing on cancer, which is consistent to another exercise study (120). Also, exercise is one important self-care intervention that can contribute to a healthy lifestyle in patients (48). Therefore, it is essential that healthcare professionals educate patients about self-care interventions and provide recommendations to increase patients self-care behaviour (121). The nurse and the rest of the rehabilitation care team should recommend and motivate patients to exercise during treatment and inform them about the benefits of exercise, and continuously evaluate improvements in HRQoL (41).

Participants also described that the context for the exercise in PhysCan in group with coaches and others like them was important in sharing experiences and supporting each other in coping with cancer. This result is confirmed by an qualitative review and meta study of physical activity in cancer survivors (122). These findings are valuable information for decisionmakers to consider when they are planning how exercise advice will be delivered.

**Effects of exercise on HRQoL**

When comparing the HI versus LMI exercise groups, the symptom of pain was statistically significantly higher, but not clinically relevant in the HI group at post-intervention. There was no other significant difference in any HRQoL outcome in the EORTC QLQ-C30 or in the EQ-5D-5L questionnaire up to one-year post-intervention. Therefore, exercise intensity does not seem to be vital for HRQoL. Our results are in line with other exercise trials with similar designs (63, 64). van Waart et al. compared a low intensity home-based walking programme with a supervised moderate/high intensity programme of combined resistance and endurance training, but did not control for exercise volume, which limited their ability to draw conclusions about the effect of exercise intensity, per se (63). Kampshoff et al.’s study compared a combined exercise programme of resistance and endurance training of high intensity
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and low/moderate intensity, but the exercise was first performed after oncological treatment (64). The results of both studies point in the same directions as our findings, but they are not directly comparable. Also, previous research has shown that exercise is beneficial for HRQoL compared with usual care (8, 9, 62, 63, 123), which is an indication that exercise of either intensity can be recommended to receive positive effects on HRQoL.

One reason why we did not find significant differences in HRQoL between the exercise intensities might be that both exercise groups were very comprehensive and had a quite demanding prescription. The groups performed the same exercise programme but on different exercise intensities. Furthermore, the context of supervised physical activity in group have shown to be important for social and emotional support in a recent review (122). Thus, another reason to why we did not find differences between groups could be that both exercise intensities performed resistance training in the same context, with support from coaches and social interactions with other group members.

The BCS factor was not included in our analysis. A previous study in the Phys-Can RCT concluded that BCS had no effect on health outcomes post-intervention (11). However, a more recent study in Phys-Can showed that BCS improved the possibility to maintain physical activity at 1-year follow-up (124). Therefore, it’s possible that the BCS component could improve HRQoL over the longer term. This is an interesting idea for future study.

Finally, positive significant differences of HI and LMI exercise on HRQoL were find over the short and long term compared to UC, which confirms previous findings (8, 9, 62, 63, 123). Hence, our findings strengthen the importance of implementing exercise in cancer care.

Cost-effectiveness of exercise in Phys-Can

There was no statistically significant difference in societal costs between the exercise groups in RCT and the UC group, and our result agrees with previous findings by van Waart et al (93). The largest costs were driven by costs of healthcare and productivity loss, compared to smaller costs of the exercise interventions. These findings indicates that the exercise interventions did not add or save any costs, at least not in the short time period evaluated in this study. This is important information for decisionmakers in the implementation process and indicates that employing additional staff to supervise an exercise intervention would not necessarily result in additional costs. Contrary to our results, another exercise trial by May et al. found that societal costs were lower in an exercise intervention for patients with colon cancer compared to usual care
Exercise in patients with cancer

(59). However, in the same exercise intervention, May et al. found higher societal costs for participants with breast cancer compared with usual care, and concluded that exercise was cost-effective only for colon cancer compared to usual care. Also, it is possible that there might have been differences in costs and health effects between cancer diagnoses and treatments in the exercise programme in Phys-Can, but we did not have large enough sample size to perform subgroup analyses.

There was no significant difference in total healthcare costs between the RCT and UC, consistent with the results by van Waart (93). However, the RCT had lower costs of prescribed medication compared to UC, which might be explained by the fact that UC had one participant with high outlying costs. Hospitalisation costs were similar between the RCT and UC in our study, similar to May et al.’s finding of patients with breast cancer. However, Mijwel et al. found lower proportion of hospitalisation rates in their resistance and high-intensity interval training groups compared to usual care in contrast with our results. However, they found no effect of moderate-intensity aerobic and high-intensity interval training compared to usual care, like us. Mijwel et al. have not compared the total number of hospitalisation days and associated costs between groups, so our findings are not entirely comparable (60).

Moreover, the lack of significant difference in costs of productivity loss between the exercise group and UC in Study III is consistent with the study by van Waart et al. (93). However, in contrast to our results, Mijwel et al. found benefits of moderate-intensity aerobic and high-intensity interval training during oncological treatment on return to work compared to usual care. (62). However, they found no effect of resistance and high-intensity interval training on return to work, in line with our results. The results are, however, not directly comparable, as they used self-reported sick leave data reported in percentages and we collected sick leave days from register data (from day 15 on). It might be possible that we have underestimated the effect of exercise on sick leave, as we have missed the data on sick leave for the first 14 days from the health insurance register. To sum up available data so far, exercise is not indicated to improve productivity loss compared to usual care.

In Studies III and IV, we evaluated the societal costs of the exercise intensity groups in the RCT and found no significant differences between the groups, confirming previous findings by Kampshoff et al. (65). There were, however, different mean societal costs between Study III and Study IV, most likely because the study population was not the same in both studies. We could include less patients because we could not include all participants from the RCT in Study IV. There were no significant differences in any cost category; costs of healthcare, loss of productivity, and exercise interventions between the exercise intensities in our study.
This is different compared to Kampshoff et al.’s study showing lower healthcare costs and higher interventions costs in high-intensity exercise compared to low-to-moderate-intensity exercise. Thus, more studies are needed to confirm our results. We found no significant difference on health outcome—QALY—between exercise intensities, which also agrees with the findings of Kampshoff et al. Based on costs and health outcome, our results indicate that decisionmakers and clinicians can recommend exercise programmes of both high intensity and low-to-moderate intensity in cancer care.

Cost-effectiveness, expressed as mean ICER, showed that HI exercise tended to be dominant compared to LMI. However, there were no significant differences found between costs and health outcomes, and therefore there is a large uncertainty in the ICER. Hence, based on cost-effectiveness, we recommend decisionmakers consider implementing both exercise intensities in cancer care. Different from our findings, Kampshoff et al. concluded that high-intensity exercise was cost-effective compared to low-to-moderate exercise mostly due to lower healthcare costs. One important difference between our studies is that Kampshoff et al. performed their exercise intensities after chemotherapy. Therefore, additional exercise trials directly comparing different exercise intensities during oncological treatment are required to confirm our results.

A challenge of the health economic evaluation is that comparisons between other studies can be difficult due to different cancer populations, healthcare systems, payment structures, intervention content and characteristics, and follow-up times.

**Implementation of exercise programmes in cancer care**

Our findings add to previous evidence on the positive effects of exercise compared to usual care in patients with cancer (9), and show that any exercise intensity could be recommended to decisionmakers based on cost-effectiveness. In support of implementation, previous findings showed that exercise was safe, and only few adverse events were reported (125). Hence, it is high time to implement exercise protocols in cancer care and bridge the gap of knowledge between researchers, healthcare, patients, and decisionmakers. However, implementation of exercise in cancer care might be challenging; particularly due to organisational barriers in healthcare (88). A successful implementation of research to clinical practice requires careful planning, with dynamic interactions between evidence, context, and facilitation. Evidence includes research evidence, clinical experience, and patient experience. Context includes culture or leadership and a commitment to evaluation. Facilitation includes the role of facilitator and facilitation strategies to support implementations (126). The clinical nurse leader plays an important role in the implementation of interventions, as
Exercise in patients with cancer

they are highly skilled, competent, and focused on improving patient outcomes and putting evidence into action. In implementation of exercise interventions, the role can include being updated on new research and clinical guidelines, educating healthcare professionals in the interdisciplinary team of the oncology department, and being a resource for creating and maintaining exercise programmes in cancer care (127). Hence, we suggest future research focus on overcoming barriers to implementing exercise in cancer care (88).

There was higher adherence to endurance training in LMI compared to HI, but similar adherence to the resistance training in the Phys-Can RCT (11). This might be one reason why no significant differences in results were found between the exercise intensity groups. In any case, it is unclear whether the difference in adherence to the exercise between the intensity groups was due to lack of motivation, not being able to tolerate exercise on a high intensity level, or another reason. Thus, an important finding of this thesis to consider when implementing exercise in cancer care is that patients should be advised to exercise on both LMI and HI, according to their own preferences, as they would still be able to gain health benefits.

Public health strategies focus on the population, and the greatest health gains will be made when small changes reach a larger population (128). Thus, from a public health perspective, it is important to promote exercise recommendations that most patients can adhere to. Tolerance of exercise intensity during oncology treatment may vary over time due to individual experience of side effects. Some patients are only able to perform exercise on low intensity levels during treatment, while some are able to tolerate exercise at higher intensities (55). Therefore, research is requested to understand how different oncological treatments interact with exercise (9).

The nurse who accompanies the patient throughout the cancer trajectory plays a crucial role in providing patient-centred care through individualised exercise programmes during treatment and refers the patient to another member of the healthcare team; namely physiotherapists when needed.

Engaging in physical activities require motivational efforts (129), especially for patients with cancer as they are less likely to engage in physical activities than the general population (130). In the Phys-Can RCT, resistance training was supervised, and participants were guided and motivated to exercise by their coaches (11). The participants in Study I described positive experiences of exercising in this context. Previous evidence shows that supervised exercise had larger effect on health-related outcomes such as HRQoL and physical function than unsupervised exercise for patients with cancer (9, 131). Therefore, it’s possible that the context in Phys-Can has increased participants’ motivation to exercise and thereby increased their health outcomes. Therefore, with support from
previous findings, decisionmakers can be advised to implement supervised exercise programmes in cancer care.

Furthermore, prescribing exercise during the cancer trajectory may prevent the onset of side effects and cancer related impairments (132). In Sweden, physical activity on prescription (PAP) is a method that has been shown to be useful for increasing physical activity in patients with insufficient level of physical activity (133, 134). Registered healthcare professionals prescribe PAP, and the advice is based on diagnosis-specific and evidence-based recommendations for physical activity. The patient receives a written prescription, which is followed up by their healthcare team. The healthcare team collaborates with the local gym or wellness centre. Thus, PAP may be a useful tool for counselling patients with cancer about physical activity, but there is no evidence specific for patients with cancer and research is required.

Methodological considerations
This thesis included a mix of qualitative and quantitative data to explore the specific aims in the four studies. The strengths and limitations of the methods are discussed in this section.

External validity
In quantitative research, generalisability is the extent to which the results might be valid for other settings and populations. The multicentre RCT Phys-Can, with 577 randomised participants, is one of the largest exercise trials so far. Although the intention was to include a variation of participants with breast, colorectal, and prostate cancer, the majority (80%) of participants were diagnosed with breast cancer. Reasons for this were that there were fewer eligible participants with colorectal cancer than expected and that they declined to participate to a higher degree than participants with breast cancer. Also, it is possible that not all eligible participants were invited to the study. All participants were deemed suitable (or not) regarding inclusion/exclusion criteria by a physician. Due to exclusion criteria of comorbidities, the population in Phys-Can was likely to be healthier compared to the general cancer population. Patients with comorbidities and long-standing conditions are, however, less likely to participate in cancer research in general (135). Also, a majority of the participants in Phys-Can were women with higher levels of education. Furthermore, only 29% of eligible patients consented to participate. Participants in the RCT had a larger proportion of women diagnosed with breast cancer, scheduled to undergo chemotherapy treatment, and with a university education compared to the decliners (136). Hence, the generalisability of the result in this thesis may be limited to patients with...
breast cancer undergoing (neo)adjuvant treatment who are motivated to exercise. However, since much evidence shows the benefit of exercise in other cancer diagnoses, the outcome of this work is likely applicable to most patient populations receiving oncology treatment with curative intentions.

In qualitative research, transferability is the extent to which the findings are transferable to other contexts or settings (137). In Study I, participants were recruited by convenience sampling included from one study site, with the aim of including participants who represented all cancer diagnoses, oncological treatments, and exercise intensities that were included in the Phys-Can RCT. A convenience sample might, however, reduce the study’s credibility, and the sample may not be representative of the population in Phys-Can. Further, the participants volunteered to participate in an exercise intervention. Thus, they might be more positive about exercise compared to those who have not chosen to participate in an exercise intervention. Hence it is unclear whether the results may be transferred to other cancer populations.

**Internal validity**

Strengths of this study were the design of a RCT with a longitudinal data collection. The RCT directly compared two exercise intensities with similar exercise types and volumes and followed a strict standardised protocol. Furthermore, both the exercise being delivered by the instructors as well as the exercise being performed by the participants were closely monitored to ensure the accuracy of the exercise. Phys-Can was designed to answer the research question “what exercise intensity is best” and therefore we did not include a randomised control group with usual care. Also, other studies before ours had problems with patients dropping out of the control arm (63). Therefore, we chose to include the observational study with UC as a comparison to the RCT, but the non-randomised UC group had had a much smaller sample size than the groups in the RCT. However, the UC group was almost similar in background characteristics, except for participants with breast cancer, who received chemotherapy to a greater extent in the RCT. Thus, we adjusted for possible confounders in our statistical analysis in Studies II–III when including UC to reduce the risk of bias.

The use of validated instruments that have shown good validity in Studies II and IV, and with few missing data (Study II) over longer periods of time was a strength. However, as described in the methods section, the power calculation in the Phys-Can RCT was determined according to the main outcome of fatigue. Thus, the results in Study II, based on exploratory analysis with multiple HRQoL subscale endpoints, along with other secondary outcomes of costs and Effects in studies III–IV may not be
Discussion

powered appropriately to draw conclusions. However, our results are in the same directions as the findings of similar studies (63, 64, 65, 93).

In Studies III–IV, reliable measures of health resource utilisation and productivity loss were collected from a national registry, reducing the risk of missing data. However, not including utilisation of community care and primary care were limitations in data collection. Furthermore, we did not have data on sick-leave shorter than 15 days, and possible costs of participants’ informal caregiving, unpaid productivity, or reduced productivity at work were not included in the analyses. Therefore, the costs of productivity loss might be underestimated. However, since this study is an RCT, the randomisation assumes that the underestimation is equal across groups. Productivity losses have been estimated using the human capital approach. The approach has been criticised as it may overestimate values of lost productivity. Another method, the friction costs approach, estimates productivity loss by assuming that society incurs losses only during the time it takes to replace a worker (friction time) (138). In the event of longer period of absence from work, the friction time approach assumes that an unemployed worker can take over. However, the friction cost approach requires detailed data on levels of unemployment and efficiency of replacement workers, which is constantly changing and often unknown.

The EQ-5D-5L questionnaire was not included in the follow-up measurements for the UC group. Thus, we were not able to include this group in the cost-effectiveness analysis. Furthermore, in Study IV, the EQ-5D-5L questionnaire was added later to the 1-year follow-up in RCT. As large proportions of the participants were missing EQ-5D-5L questionnaire at 1 year post intervention and missing at random, we considered the proportion of missing data too large to use imputation and chose to exclude the participants who had not completed 1-year follow-up. (139). For those values missing at 0 and 6 months (only 2%) we chose to use the LOCF imputation method. This method is commonly used in clinical trials; however, the method is criticised, as there is a risk of introducing bias and interfering with the treatment effect (140). As the missing values remain constant after drop-out, there is a risk of not detecting whether participants get worse over time and thus underestimating the effect. We might have underestimated the effect of the exercise interventions; however, the results were similar when we did not include the missing values in the analysis. As a result, only a third of the participants from the RCT were included in Study IV, and this has decreased the study’s statistical power. A lower statistical power increases the risk of making a type II error when interpreting the results; the risk that we have concluded that there is no difference between the intensity groups when there actually is. Background characteristics of the participants were similar between HI and LMI in
Study IV. However, the participants that were included in Study IV were older, there were larger proportions of retired participants and men with prostate cancer, together with lower proportions of participants on sick leave and women with breast cancer receiving chemotherapy compared to the excluded participants with missing data at 1-year follow-up; which might have biased the results.

When measuring HRQoL in longitudinal studies, there is a risk of bias due to response shift, with adaption of side effects of treatment over time, (141). However, the HRQoL instrument used in Studies II and IV have acceptable psychometric properties, even taking this into account.

All statistical analysis were performed as intention-to-treat analyses. Hence, the adherence to the exercise prescription was not considered in the analyses. However, a previous study within Phys-Can has shown that adherence to the prescribed resistance training was, on average, 50.4% with no significant differences between the intervention groups, and adherence to the prescribed endurance training ranged between 38.8%-57.7% with significantly higher adherence to LMI than to HI (11). Furthermore, this thesis only focused on exercise intensities and not BSC. As a recent published study in Phys-Can showed that additional BSC improved physical activity maintenance at 1-year post-intervention (124), it is likely that additional BCS increase positive effects on health over the long-term.

In Study I, the information provided by the participants was rich and repetitive, so we decided that the sample size of 21 participants was sufficient. To increase credibility, triangulations and peer debriefing were performed within the research group (137). Experienced qualitative researchers within the group were an advantage during the data analysis process. The reflexivity recognises that the researcher’s experience might influence the research process, as the researchers are using themselves as instruments in qualitative research (142). ‘Reflexivity’ describes the researcher’s position in relation to the study objects, data collection, and analysis. In Study I, a majority of the researchers were involved in Phys-Can, and this might have influenced the interpretation of data. Also, since AA was involved in Phys-Can, the participants might feel that they couldn’t express negative experiences of the intervention during the interviews. However, one researcher had not been involved in the planning or implementation of the intervention.
CONCLUSIONS

In conclusion, the findings in this thesis showed that participating in an exercise programme during oncological treatment was a positive and supportive experience that contributed to increased physical and psychological wellbeing. The findings contribute new knowledge that combined resistance and endurance training of LMI and HI had similar effects on HRQoL, costs of healthcare utilisation, and productivity loss. In addition, the findings confirm that exercise has beneficial effects on HRQoL compared to UC. Furthermore, the exercise interventions did not save or add societal costs compared to UC. Thus, the key message of this thesis is to promote exercise programmes in cancer care, independent of exercise intensity. The findings suggest that patients with cancer should be recommended exercise regardless of intensity by the cancer rehabilitation care team to improve or to maintain aspects of HRQoL during oncological treatment. Decisionmakers should prioritise implementation of exercise programmes of both HI and LMI in cancer care into the healthcare budget.

Clinical implications

Maintaining activity and functioning is an essential part in the care of patients with cancer. Exercise has positive effects on HRQoL, including managing symptom of treatments. Thus, nurses, in cooperation with the cancer rehabilitation care team, should:

- Assess patient’s functioning and include exercise in the rehabilitation plan from the start.
- Motivate and encourage patients to exercise during their oncological treatment.
- Refer to an exercise programme and a physiotherapist when needed.

It is necessary that all healthcare professionals in the cancer rehabilitation care team have knowledge about the evidence of the exercise recommendation and give the same information to the patients to avoid contradictory advice.

Patients with cancer can be recommended to exercise on both low-to-moderate or high intensity according to their own preferences to gain positive effects on health. The exercise can be performed on a combination of resistance training twice a week and endurance training of 150 min on low-to-moderate intensity or 75 minutes on high intensity or a combination
per week. It is important to communicate within the clinical setting about what exercise programme should be suggested to the patients with cancer. In addition, the findings of this thesis suggest that supervised exercise programmes on different levels of exercise intensity should be a part of the rehabilitation and need to be implemented in cancer care to facilitate exercise for the patients. As resources are limited in healthcare, exercise is suggested to be performed within clinical settings or in public gyms, and to be supervised by physiotherapists or personal trainers with relevant education in cancer care.

**Future research**

Evidence of beneficial effects of exercise during curative/(neo)adjuvant oncological treatment is sufficient to start the implementation process of exercise as cancer rehabilitation. However, this thesis has provided further research questions that need to be addressed:

- To further precise exercise prescriptions according to cancer type, timing of treatment, and/or types of treatment.
- To investigate the most appropriate strategy in the implementation process of exercise into clinical practice in cancer care.
- To perform health economic evaluations of exercise in clinical practice.
- To perform exercise interventions in cancer populations with advanced cancer stages regarding safety and effects to further improve exercise recommendations.
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REFERENCES


Exercise in patients with cancer

Survivors of Rectal Cancer. The Permanente journal. 2017;21


References


Exercise in patients with cancer


71. Fleischer A, Howell D. The experience of breast cancer survivors’ participation in important activities during and after treatments. British


80. Han X, Robinson LA, Jensen RE, Smith TG, Yabroff KR. Factors Associated With Health-Related Quality of Life Among Cancer Survivors in the United States. JNCI Cancer Spectr. 2021;5(1).


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References


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References


**Supplementary Material**

**Supplementary Figur 1. Resistance training in Phys-Can**

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<thead>
<tr>
<th>Övning</th>
<th>Illustration</th>
<th>Träningsfokus</th>
<th>Övningsdata</th>
<th>Kommentar</th>
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<tr>
<td>2. Bröstpressa</td>
<td><img src="image2.png" alt="Illustration" /></td>
<td>Sitt med anpassade stolar och fels att två grep om handtagen. Armlikorna ska vara i höjden med händerna. Pressa hårt tills amma är på en och för dem långvarigt tillsamman mot kläderna.</td>
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<tr>
<td>4. Bonport</td>
<td><img src="image4.png" alt="Illustration" /></td>
<td>Se till att ha bra stöd från kroppen och att med kroppsträning i sträck. Sitt ben på på fotbladen och kontrollera till startpositionen och upprepa.</td>
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<tr>
<td>5. Ställande ärkruit</td>
<td><img src="image5.png" alt="Illustration" /></td>
<td>Se till att ha bra stöd från kroppen och försvare axelkroppen med hjälp av handtagen. Pressa omkring dyran. Börja tränar när dyran är på en och denna kontrollerar till startpositionen.</td>
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Träning för bälte, rygg och bäckenbotten

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<td>Ställ dig upp med bena breda och axelbreddväld mellan fötterna. Täcka</td>
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<td>2. Bäckenbotten-</td>
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<td>på ryggen. Vika några sekunder och gör sitt hopp.</td>
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<td>över ryggen. Vika några sekunder och gör sitt hopp.</td>
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<td>4. Arm och benytt</td>
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<td>Sätta på alla foter utan att &quot;hänga&quot; i skulder, först med ena foten utan</td>
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<td>att tåla rörelsen. Röra bena upp och ned över ryggen.</td>
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Supplementary Figure 2. Core exercises in Phys-Can.
Papers

The papers associated with this thesis have been removed for copyright reasons. For more details about these see:

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