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LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

Physical activity and breast cancer

Risk, survival and perceived energy

ANNA JOHNSSON
DEPARTMENT OF CLINICAL SCIENCES, LUND | LUND UNIVERSITY

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Anna Johnsson

LUND UNIVERSITY

DOCTORAL DISSERTATION

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Faculty opponent
Patrik Wennberg, Associated Professor
Department of Public Health and Clinical Medicine,
Umeå University, Sweden

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Title and subtitle: Physical activity and breast cancer. Risk, survival and perceived energy

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Methods: Studies I and IV were prospective population-based cohort studies, based on data from 29 524 women included in the Melanoma Inquiry of Southern Sweden (MISS) cohort study 1990-92. In Study I, questions about occupation and established risk factors were used and data were linked to the Swedish Cancer Register and the Cause of Death Register. Study IV included women with breast cancer after the first MISS questionnaire who responded to a post-diagnosis follow-up questionnaire. Questions about physical activity and other risk factors were used and linked to the Swedish Cancer Register, the Cause of Death Register and the Swedish Population Register. Studies II and III were based on self-reported data regarding energy, stress, nausea and pain in 57 women with breast cancer who performed exercise during chemotherapy in the "Phys-Can" (Physical training and Cancer) study. Changes from before to immediately after, and 3 hours after a single exercise session were analysed at different time points during a course of chemotherapy.

Results: Sedentariness was associated with breast cancer risk especially among women younger than 55 years old at diagnosis. After breast cancer diagnosis, energy and nausea improved immediately after a single exercise session performed within the first week after chemotherapy infusion. This was true for both endurance and resistance exercise. Energy level increased after an exercise session throughout the chemotherapy course, and stress was reduced at the beginning of the course. Furthermore, the energy increase was larger when the energy level before the session was lower. Physical activity level after breast cancer diagnosis was associated with survival in a dose-response manner among women at 55 years or older at diagnosis.

In conclusion we have found that avoidance of occupational sedentariness is associated with reduced breast cancer risk in younger women. After diagnosis physical activity is health-enhancing: one single exercise session during chemotherapy improves energy with a higher increase when the level is low before the session, and furthermore, even a rather small dose of physical activity compared to no physical activity is associated with improved survival, especially in older women.

Key words
Breast Cancer, Chemotherapy, Exercise, Perceived energy, Physical activity, Risk, Sedentary behaviour, Survival

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Anna Johnsson

LUND UNIVERSITY

Clinical Sciences, Lund
Division of Cancer Epidemiology and Oncology
Lund University, Lund, Sweden

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Thesis at a glance

	Aims	Participants	Data collection	Main results
I	To elucidate the association between occupational sedentariness and risk of breast cancer, and if there is a difference if the woman is < 55 years old or ≥ 55 years at diagnosis	Women included in the Melanoma Inquiry of Southern Sweden (MISS) cohort study. n=29 524	Occupational history using MISS questionnaire Breast cancer diagnosis using the Swedish Cancer Register and the Cause of Death Register	Occupational sedentariness was associated with breast cancer risk (HR=1.20). In subgroup analysis, the risk increase was seen only among women younger than 55 years old at diagnosis.
II	To describe self-reported energy, stress, nausea and pain immediately after a single exercise session in *the first week* after chemotherapy infusion. Additional aims were to study changes three hours after the session and if the changes were related to reported level before the session, exercise intensity or previous training habits.	Women with breast cancer undergoing chemotherapy included in Phys-Can training study and exercising during the first week after chemotherapy. n=38	Self-reported energy and stress using Stress-Energy Questionnaire-leisure time Self-reported nausea and pain using Visual Analogue Scale	Energy and nausea were improved immediately after both endurance and resistance exercise. Stress was only improved after resistance exercise. Three hours after the session, stress was improved after both endurance and resistance exercise and nausea was improved after resistance exercise. Changes were not related to type of exercise or previous training habits.
III	To describe self-reported energy immediately after a single exercise session at the beginning and at the end of a chemotherapy cycle and *throughout* a chemotherapy course. Additional aims were to study self-reported stress, nausea and pain at the different points *throughout* the chemotherapy course, and changes three hours after the exercise session.	Women with breast cancer undergoing chemotherapy included in Phys-Can training study. n=46	Self-reported energy and stress using Stress-Energy Questionnaire-leisure time Self-reported nausea and pain using Visual Analogue Scale	Energy was increased immediately after an exercise session in three of four measurment periods during the chemotherapy course. Stress was reduced at the beginning of the chemotherapy course. Nausea and pain did not change. Three hours after the exercise session, stress was reduced during the chemotherapy course. Nausea was improved at the beginning of the course.
IV	To elucidate the association between physical activity level post breast cancer diagnosis and survival, and if the association differs between women under or over 55 years at diagnosis.	Women in the MISS cohort study diagnosed with breast cancer and who responded to a post-diagnosis questionnaire n=847	Self-reported physical activity level using MISS questionnaire Mortality using the Swedish Cancer Register, the Swedish Cause of Death Register and the Swedish Population Register	Physical activity was associated with survival in a dose-dependent manner. In subgroup analysis, the association was seen only among women 55 years or older at diagnosis.

List of Papers

This thesis is based on the following Papers, which will be referred to in the text as Studies and roman numerals.

I. Johnsson A, Broberg P, Johnsson A, Tornberg ÅB, Olsson H. Occupational sedentariness and breast cancer risk. *Acta Oncologica* (Stockholm, Sweden). 2016:1-6.

II. Johnsson A, Demmelmaier I, Sjövall K, Wagner P, Olsson H, Tornberg ÅB. A single exercise session improves side-effects of chemotherapy in women with breast cancer: an observational study. *BMC Cancer*. 2019;19:1073.

III. Johnsson A, Sjövall K, Demmelmaier I, Wagner P, Olsson H, Tornberg ÅB. Self-reported energy increases after a single exercise session in women with breast cancer undergoing chemotherapy. *Manuscript*.

IV. Johnsson A, Broberg P, Krüger U, Johnsson A, Tornberg ÅB, Olsson H. Physical activity and survival following breast cancer. *Eur J Cancer Care (Engl).* 2019:e13037.

Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
HR	Hazard Ratio
MET	Metabolic Equivalent
MISS cohort study	the Melanoma Inquiry of Southern Sweden
OR	Odds Ratio
Phys-Can	Physical training and Cancer: A randomised controlled multicentre trial
RR	Risk Ratio
SEQ	Stress-Energy Questionnaire
SEQ-LT	Stress-Energy Questionnaire-Leisure Time
VAS	Visual Analogue Scale
WHO	World Health Organisation

Definitions

Chemotherapy course	A course of treatment, including a number of chemotherapy cycles
Chemotherapy cycle	The time from the start of one round of treatment until the start of the next (1)
Chemotherapy infusion	When the chemotherapy is given intravenously
Exercise	A subcategory of physical activity during leisure time, defined as regularly-performed physical activity with the goal of increasing or maintaining muscular strength and/or cardiorespiratory fitness (2)
Physical activity	Any bodily movement produced by skeletal muscles that results in energy expenditure (2)
Physical activity dose, endurance exercise	Consists of: intensity, duration, and frequency (3)
Physical activity dose, resistance exercise	Consists of: intensity, number of repetitions, number of sets and frequency (3)
Physical inactivity	An insufficient physical activity level to meet physical activity recommendations (4)
Sedentariness/sedentary behaviour	The state of being/any waking behaviour characterised by an energy expenditure ≤1.5 METs while in a sitting, reclining, or lying posture (4)

Abstract

Background: Physical activity and avoidance of sedentariness *do* enhance health in women with breast cancer, and *could* even reduce the risk of developing the disease. One aim of this thesis was to elucidate the association between sedentariness and breast cancer risk in women as a whole, and then separately for those younger than 55 years old and those 55 years or older. Two additional aims were regarding physical activity and its role after diagnosis: to describe the perception of energy, stress, nausea and pain after a single exercise session during chemotherapy, and to elucidate the association between physical activity level and survival in women under 55 years old or 55 years or over at diagnosis.

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Results: Sedentariness was associated with breast cancer risk especially among women younger than 55 years old at diagnosis. After breast cancer diagnosis, energy and nausea improved immediately after a single exercise session performed within the first week after chemotherapy infusion. This was true for both endurance and resistance exercise. Energy level increased after an exercise session throughout the chemotherapy course, and stress was reduced at the beginning of the course. Furthermore, the energy increase was larger when the energy level before the session was lower. Physical activity level after breast cancer diagnosis was associated with survival in a dose-response manner among women at 55 years or older at diagnosis.

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Introduction

Physical activity is a health-enhancing modifiable lifestyle factor and several chronic diseases such as cardiovascular diseases, type 2 diabetes, depression, and various types of cancer can be prevented by increased physical activity. According to health-enhancing guidelines, all healthy adults aged 18-64 years should perform at least 150 minutes of aerobic physical activity at moderate intensity or 75 minutes at high intensity every week. Additionally, muscle-strengthening activities are recommended two days or more every week (3).

Breast cancer is one of the malignancies where the risk has been suggested to be reduced by physical activity. Furthermore, during the last 20 years studies have shown that physical activity is also beneficial after breast cancer diagnosis, as it improves physical function and health-related quality of life, reduces side-effects of treatments, and decreases risk of premature death (5-7). Therefore, exercise could be a valuable part of cancer treatment, and this thesis focuses on avoidance of sedentariness in relation to risk of developing breast cancer, and physical activity in relation to mortality after diagnosis. It also addresses the experience of energy after a single exercise session during chemotherapy.

Physical activity

The definition of physical activity is "any bodily movement produced by skeletal muscles that results in energy expenditure" (2). Physical activity can be categorised by where and when it is performed – for example at work, during transportation, or in leisure time. Exercise is one subcategory of physical activity during leisure time, defined as regularly performed physical activity with the goal of increasing or maintaining muscular strength and/or cardiorespiratory fitness (2). Intensity, duration, frequency, and type of activity are essential factors required when describing the dose and effect of physical activity. The intensity can be described as absolute or relative, where relative intensity reflects the individual capacity, and absolute intensity does not. Both relative and absolute intensities can vary from low to high to very high (vigorous). Response to a single exercise session is not the same as the response to regular exercise. A single exercise session has several effects on the individual such as increased heart rate, altered hormone concentrations and metabolism, while other responses such as increased muscle strength and increased exercise endurance occur after regular training due to physiological adaptation, specific to the type of activity performed (8).

Physical inactivity

Physical inactivity is by consensus defined as: "An insufficient physical activity level to meet present physical activity recommendations" (4). To meet the health-enhancing physical activity recommendations the intensity should be at least moderate (3), which implies that a person could be physically active at low intensity during most of the day and still be classified as physically inactive.

Sedentariness/sedentary behaviour

The most common definition of sedentary behaviour is "any waking behaviour characterized by an energy expenditure ≤1.5 METs while in a sitting, reclining, or lying posture" (4). Just like physical activity, sedentary behaviour can be categorised in subgroups depending on the context, including sitting during transport, at work, and at home during leisure time. It should be noted that sedentary behaviour is not the same as physical inactivity. A person who has a sedentary work might exercise for half an hour every evening and could therefore be classified as both sedentary and physically active (depending on in which domain the assessment is performed) (9).

Measurements of physical activity

Physical activity can be assessed in different ways, either subjectively by self-reported questionnaire, or objectively by a wearable monitor. The assessment enables identification of the dose of physical activity for various health outcomes in the general population and makes it possible to personalise the dose for prescription (10).

In epidemiologic studies the behaviour is often subjectively assessed by a questionnaire or a logbook. Another increasingly-used method is wearable monitors, such as pedometers, heart rate monitors or accelerometers, that provide an objective assessment (10). Questionnaires are relatively easy and convenient for the respondent, and they are cost-effective, but the risk of recall bias or under- or overestimation is a limitation (10).

Pedometers count steps and newer monitors with more complex technology also assess acceleration and are capable of estimating intensity (10). Accelerometers assess duration and frequency of physical activity at various intensities, from no physical activity to vigorous activity (11).

A heart rate monitor is another direct objective tool, which can be used to assess physical activity levels based on the linear relationship between heart rate and energy expenditure. For moderate to vigorous physical activity, this relationship is strong, but the agreement is weaker at the lowest intensities (12).

Physical activity, sedentary behaviour, and health

The National Board of Health and Welfare in Sweden introduced physical activity recommendations for the promotion of health in the 1970s (13). Since then the guidelines have been developed based on new knowledge, and from 2011 they have also contained recommendations regarding reduced sedentary behaviour (3).

Unfortunately, not all people are as physically active as recommended, for a variety of reasons, and recently researchers have focused not only on moderate and high intensity but also on low intensity physical activity and its association with health and premature mortality. It has been shown that the risk of premature mortality decreases if sitting time is replaced by low intensity physical activity, especially among less physically-active individuals (14). Furthermore, an inverse dose-dependent association has been shown between low intensity physical activity and mortality, regardless of whether the amount of moderate to vigorous physical activity is according to the health-enhancing guidelines or not (15). The physical activity dose consists of intensity, duration and frequency of the activity, and every one of the components may alter the dose. The health benefit is suggested to be greatest when physical activity dose is increased from very low to a little bit higher (Fig. 1). Sedentariness has also been associated with an increased risk of disease and illness, including several types of cancer, regardless of physical activity level (16, 17).

All these benefits are effects after regularly-performed exercise. Moreover, one single exercise session has been shown to improve stress, perceived energy and fatigue in the general population, possibly with some variation in regular exercisers or non-exercisers (18-20).

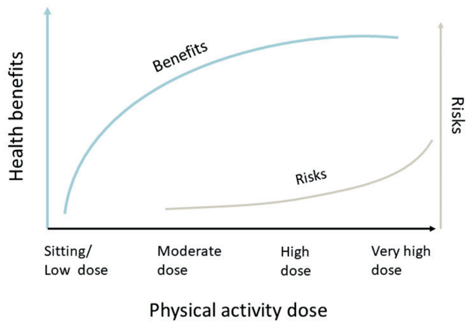

Figure 1. The blue curve represents the dose-response relationship between physical activity dose and health benefits and the grey curve represents the relationship between physical activity dose and risks (musculoskeletal or cardiovascular) (© Yrkesföreningar för Fysisk Aktivitet (YFA) 2016).

Breast cancer

Breast cancer is the most common malignancy in women, and around 10% of Swedish females are affected during their lifetime. In 2016, 7 558 women were diagnosed, and the prevalence was 108 579 (21). Survival has increased from about 50% in 1960 to over 80% in recent years (22)(Fig. 2).

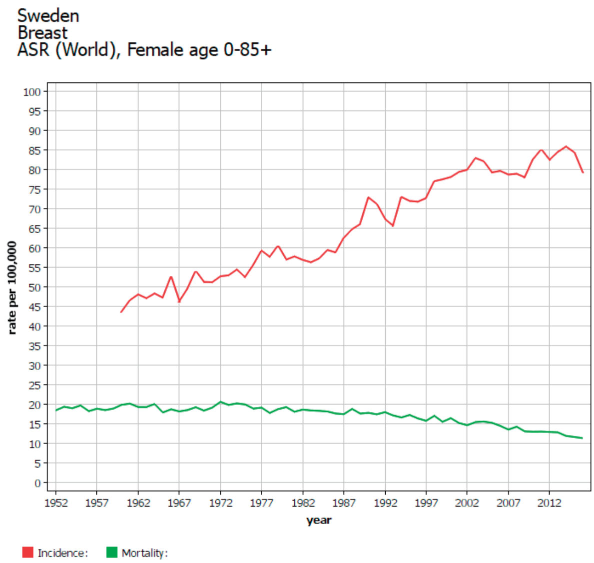

Figure 2. Breast cancer incidence and mortality in Sweden in the last 70 years. Age specific rate (ASR) with the world standard population as reference. Incidence has increased while mortality has declined. Graph from Nordcan (23).

Risk factors

There are several known risk factors for developing breast cancer. The strongest risk factors are female sex and high age. In some cases, hereditary factors can be identified (24, 25). Germline mutations in the most important breast cancer genes BRCA1 and BRCA2 account for 2-5% of all breast cancers (26).

Hormonal risk factors include early menarche, late menopause, high age at first childbirth or exogenous hormone intake (oral contraceptives, hormone replacement therapy) (22). High levels of sex hormones are involved in breast cancer development, and since adipose tissue is the main source of oestrogen production in postmenopausal women obesity is a risk factor for them. In premenopausal women, however, obesity confers a lower risk of breast cancer, but the mechanism for this is unclear (24, 25, 27, 28).

Breast cancer incidence is correlated with several lifestyle factors such as high fat intake, high alcohol consumption, lack of physical activity and sedentariness. Living a healthy life – less tobacco smoking, lower alcohol consumption, less sedentary behaviour, less overweight and more physical activity – lowers the risk of breast cancer by about 25% (HR 0.77, 95% CI 0.72-0.82)(29, 30).

Treatment

For early breast cancer surgery is usually the primary treatment. Depending on tumour stage and characteristics and the patients' health status, surgery is often accompanied by radiotherapy and/or systemic treatments, such as chemotherapy, endocrine treatments, and targeted agents. Systemic therapy can be given before (neoadjuvant) or after (adjuvant) surgery. Treatment guidelines are issued and updated regularly by the Swedish Breast Cancer Group (22). Briefly, most patients with oestrogen receptor (ER) positive tumours receive endocrine treatment for five years, usually tamoxifen and/or an aromatase inhibitor. The selection of patients for adjuvant chemotherapy is mainly based on tumour size, lymph node metastases, expression of ER and human epidermal growth factor receptor 2 (HER2). The most commonly-used adjuvant schedule today is sequential treatment with an anthracycline doublet (epirubicin and cyclophosphamide) 3 cycles administered intravenously (iv) every 3 weeks followed by a taxane (docetaxel), 3 cycles iv every 3 weeks. Thus, the total chemotherapy treatment time is typically 18 weeks. Moreover, patients with an HER2 positive tumour are usually offered treatment with trastuzumab for one year (22).

For treatment of metastatic breast cancer, all of the above-mentioned drugs may be used in individualised sequences, based on age, performance status, tumour burden and symptoms, and ER and HER2 status. In addition, several other cytostatic agents are being utilised in the metastatic setting. More recently newer targeted drugs as well as immune therapy have shown promising efficacy (22).

Treatment-related side-effects

Treatment-related side-effects could be a burden for the patients and may even cause dose-reduction or interrupted treatment. As chemotherapy is an important part of the treatment, it is of interest to reduce the side-effects. One of the most common patient-reported symptoms is fatigue, reported by 25-99% of patients (31). Other common side-effects are cytopenia, nausea, musculoskeletal pain, peripheral neuropathy and neurocognitive dysfunction (32, 33). Overall, side-effects usually increase towards the end of the chemotherapy course (31), and can cause considerable distress (34, 35).

Side-effect focused on in this thesis

Cancer-related fatigue is defined by the US National Comprehensive Cancer Network as *"a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Compared with the fatigue experienced by healthy individuals, cancer-related fatigue is more severe, more distressing, and less likely to be relieved by rest"*(36).

Cancer-related fatigue can for some patients occur before treatment onset, but it then usually increases when undergoing treatment such as radiotherapy, chemotherapy, or hormonal treatment. Most patients experience cancer-related fatigue during active treatment, with 30-60% of them reporting moderate to severe cancer-related fatigue (37). Fatigue typically improves after completed treatment, but in some individuals it may remain for several years. Patients with breast cancer have reported cancer-related fatigue as one of the most severe and distressing symptoms, and one that has substantial consequences for their quality of life. Even though it is very common, the mechanisms are not really known. Proposed mechanisms include physiological factors such as reduced energy metabolism, proinflammatory cytokines, skeletal muscle wasting, and hypothalamic-pituitary-adrenal axis dysregulation (36-38). When patients and nurses describe fatigue, the word *energy* is often used, as low energy or lack of energy (39).

Stress is a widely-used term and can refer to an individual's subjective response to a stressor or the reaction with increased psychological, physiological, and behavioural preparedness (40). A subclass of stress is distress, which is a reflection of the individual's perceived inability to cope with a stressor (41). Due to the side-effects of chemotherapy, up to 90% of women with breast cancer report some level of distress (34, 35).

The adjuvant chemotherapy for breast cancer commonly includes anthracycline plus cyclophosphamide-based regimens, which are associated with a high risk of nausea. Despite effective antiemetics, more than half of patients reported nausea during the first six days after their first chemotherapy cycle of anthracycline plus cyclophosphamide. Some patients report nausea and vomiting as their most feared side-effects of chemotherapy (42).

Myalgia and arthralgia are symptoms during chemotherapy reported by around 40-70% of patients with breast cancer (32, 43). Other types of pain during chemotherapy are hand-foot syndrome, oral mucositis, headache, and peripheral neuropathy (44).

Prognosis

In Sweden, the relative 10-year survival in women diagnosed with breast cancer is 80%. Prognostic factors include tumour size, nodal status, histological subtype, age and menopausal status (22). Furthermore, lifestyle factors such as physical activity, sedentariness, diet, body weight, alcohol consumption and smoking also have an impact on survival after diagnosis of breast cancer (29).

Physical activity and breast cancer

Physical activity as prevention

Physical activity has been found to be associated with risk of breast cancer in epidemiological research, with a risk reduction of 9-21% when comparing the highest and lowest levels of physical activity. However, whether the association applies to both pre- and postmenopausal breast cancer is still not entirely clear (45, 46).

The World Cancer Research Fund, Continuous update project evaluated physical activity level and breast cancer risk in pre- and postmenopausal women in a meta-analysis of 35 studies (46). For *pre*menopausal women, vigorous physical activity was required for a significant risk reduction (highest versus lowest level, RR=0.79, 95% CI 0.69-0.91). There were no statistically-significant associations between the other intensities and domains of physical activity and breast cancer risk. Inverse associations were on the contrary shown between physical activity and *post*menopausal breast cancer risk in different intensities and domains: vigorous activity (RR=0.90, 95% CI 0.85-

0.95), total activity (RR=0.86, 95% CI 0.78-0.94), recreational activity (RR=0.88, 95% CI 0.82-0.94) and occupational activity (RR=0.90, 95% CI 0.85-0.96) (46). In another recent meta-analysis including 38 cohort studies, the highest versus lowest category of physical activity (intensity not defined) was associated with lower risk of both *pre*menopausal (RR=0.83, 95% CI 0.79-0.87) and *post*menopausal breast cancer (RR=0.91, 95% CI 0.85-0.97) (45). This discrepancy indicates that more research is needed especially regarding the differences in menopausal status.

Sedentary behaviour is another lifestyle factor that has been found to be associated with increased risk of breast cancer, but this finding has not always been shown consistently. One meta-analysis including 13 case-control and cohort studies did not show any association between sitting time and risk of breast cancer (47). Another meta-analysis, including 21 case-control and cohort studies, did show an association between sedentary behaviour and breast cancer risk (OR=1.08, 95% CI 1.04-1.13), with no differences when analysed according to menopausal status (48). In a third meta-analysis including three cohort studies, total sitting time was associated with breast cancer risk (RR=1.17, 95% CI 1.03-1.33) (49) and the meta-analysis World Cancer Research Fund, Continuous update project showed an association between the highest versus lowest level of total sitting time with postmenopausal breast cancer risk (RR=1.20, 95% CI 1.00-1.44) (46). Two of these reports performed subgroup analysis with sedentary time in different domains, and one found an association between occupational sitting time and breast cancer risk (OR=1.10) (48), whereas the other did not (46). Thus, according to previous literature, sedentariness is suggested to increase breast cancer risk by 0 and 17% - a wide range that could be narrowed with further study.

Regular physical activity and side-effects of chemotherapy in breast cancer care

Physical activity is an important part of cancer care and rehabilitation. The evidence is convincing regarding physical activity after a cancer diagnosis and during anti-cancer treatment. Regular exercise is a safe and feasible therapy that improves many treatment-related symptoms, lowers the risk of other chronic diseases and is suggested to increase survival (7, 50-52). The optimal intensity, duration, frequency and type are still incompletely known, but patients with cancer should, as everyone else, be as physically active as possible and avoid prolonged sitting. To be as physically active as the health-enhancing guidelines recommend is preferable, and a higher level might be more beneficial. Research has shown that women with breast cancer are less physically active than women from the general population (53), and encouraging them to become more physically active is therefore an important issue. The side-effects from the anti-cancer treatment are a barrier to physical activity among these patients (54).

Exercise reduces cancer-related fatigue in patients with breast cancer, both during and after treatment (55, 56). During treatment, the effects of supervised exercise seem to be superior to non-supervised exercise, and the effect is larger in patients with more fatigue at baseline (55, 57). Lower maximal oxygen uptake has been observed in patients with breast cancer undergoing chemotherapy (58) and the maximal oxygen uptake is suggested to be linked to cancer-related fatigue (59, 60). In a meta-analysis, Björke et al. evaluated which exercise intensity, duration, frequency and type optimise maximal oxygen uptake during anti-cancer treatment (61). They found that the effect was more dependent on exercise session duration, weekly duration and volume than by intensity and frequency (61). Regarding cancer-related fatigue and physical activity, one meta-analysis found that endurance exercise and high adherence to the interventions had a large effect, while intensity did not influence the effect (55). Another meta-analysis showed that supervised intervention and a duration ≤ 12 weeks showed larger effects than unsupervised and longer duration, without any influence of intensity (56). All these findings indicate that supervision and volume of physical activity are the most important components in fatigue reduction.

Musculoskeletal pain is a commonly-reported side-effect during adjuvant chemotherapy in women with breast cancer (44, 62). Arthralgia and myalgia have been reported by up to 72% of patients after taxane-based chemotherapy (62). In order to prevent neutropenia, some patients receive granulocyte colony-stimulating factors, which might cause bone pain (63). Exercise, especially programmes including both resistance and endurance training, might reduce pain intensity in patients with cancer (64, 65).

The impact of exercise on treatment-related nausea is unclear, but there might be a positive effect or at least no worsening of the symptoms (64, 66).

Immediate effects of one single exercise session

To the best of our knowledge this is a rather poorly researched area. One study including 18 inpatients undergoing radiotherapy and/or chemotherapy for various types of cancer, assessed cancer-related fatigue immediately after an exercise session and showed reduced fatigue after the session compared with before (67). Other studies have showed effects on cognitive function after treadmill walking (68) and decreased state anxiety after a session with ergometer cycling among women with breast cancer (69).

Physical activity and survival

Several studies have shown that physical activity both before and after breast cancer diagnosis may lead to increased survival. Most of the evidence is based on observational cohort or case-control studies, but two exploratory survival analysis studies following randomised controlled exercise trials have also evaluated survival after breast cancer diagnosis (70, 71). The two exploratory studies with a median follow-up of 7.4 and 8.3 years, concluded that exercise interventions during and beyond treatment is promising and have a potential to improve survival (70, 71).

In meta-analyses, high levels of physical activity performed *before* breast cancer diagnosis have been suggested to reduce breast cancer specific mortality by 14-27%, and all-cause mortality by 16-27% (72, 73). Physical activity performed *after* diagnosis seems to be even more important. Physical activity can cause a reduction in breast cancer specific mortality of 14-45%, and a reduction for all-cause mortality of 26-50% (72-75). Physical activity level and survival have been proposed to be associated in a dose-response-related manner (76).

One meta-analysis including 24 studies showed that physical activity, both before and after diagnosis, at moderate intensity and a high volume was associated with improved survival. Lower volume or another intensity were less beneficial. Furthermore, patients who decreased their physical activity after diagnosis had the worst prognosis (73). Another meta-analysis, including 10 studies, showed an association between decreased mortality and high level of recreational physical activity (moderate or moderate-to-vigorous intensity) after diagnosis (74). In a third meta-analysis, of 22 cohort studies, Lahart et al. found an association between high physical activity level and reduced breast cancer specific and all-cause mortality (72).

In subgroup analyses divided by menopausal status (2 meta-analyses, including in total 4 studies), the associations between physical activity level after diagnosis and survival were inconsistent (72, 75). Zhong et al. did not find any association between physical activity level and survival in women with *pre*menopausal breast cancer (75), while Lahart et al. found association between high physical activity level and reduced breast cancer specific mortality (HR 0.55) (72). Regarding *post*menopausal breast cancer, both meta-analyses showed an association between high level of physical activity and breast cancer specific mortality (HR 0.70 - 0.75), and all-cause mortality (HR 0.44-0.66) (72, 75). According to the World Cancer Research Fund Continuous update project, *post*menopausal women who participate in physical activity reduce their risk for total mortality, but *pre*menopausal women do not (77). Due to the small number of studies conducted with subgroup analysis according to menopausal status, more studies are needed to strengthen the evidence.

Regarding associations between sedentary behaviour and mortality after a cancer diagnosis, data are limited. A meta-analysis including patients with various type of cancers suggested that time spent being sedentary was related to increased mortality (HR=1.16) (16). In another meta-analysis it was suggested that the association between sedentary behaviour and premature mortality can be modified by physical activity (78).

Proposed mechanisms

The mechanisms by which physical activity affects breast cancer risk and survival are complex and not exactly known. Physical activity leads to decreased visceral fat mass, induction of anti-inflammatory cytokines, and reduction of low-grade inflammation (79). Other suggested mechanisms are improvement in insulin resistance, decreased level of circulating oestrogen, decreased C-reactive protein levels, and improved immune function. All these factors are also associated with development and progression of breast cancer (79, 80). An explanation for the difference in the association between pre- and postmenopausal breast cancer and physical activity level might be that the oestrogen is generated in fat cells, especially in postmenopausal women (81).

A high blood flow through the tumour enhances the effect of radiotherapy, chemotherapy and immunotherapies, and physical activity might increase perfusion, thereby improving the anti-cancer treatment. Physical activity may also help treatment by attenuating side-effects, thereby improving tolerance to treatment (7, 79).

Adjuvant breast cancer therapy, both radiotherapy and chemotherapy, is associated with cardiovascular toxicity that may lead to development of chronic cardiovascular disease. Just like in a healthy population, physical activity seems to have a protective effect on the cardiovascular system of patients undergoing adjuvant anti-cancer therapy (82). In an epidemiological study by Jones et al., the incidence of cardiovascular events was 23% lower in women with breast cancer who met the health-enhancing physical activity guidelines compared with those who did not meet the guidelines (83).

Regarding the effect of physical activity on cancer-related fatigue, various mechanisms have been suggested. Regular exercise improves muscle strength and cardiovascular capacity, which have been shown to reduce cancer-related fatigue (59). Reduced systemic inflammation has also been suggested to contribute to improvement of cancer-related fatigue (7). Another contributing mechanism might be the release of the stress hormones epinephrine, norepinephrine and cortisol immediately after one single exercise session, which could also help reduce fatigue (84).

Rationale

Physical activity has become a popular and important health-enhancing lifestyle factor for many individuals, and more and more accepted in oncological settings after a cancer diagnosis. Recently, the term *Exercise as medicine* has found a place in oncology, even though physical activity and exercise are still not an obvious part of cancer care and cancer rehabilitation for all patients.

Increased knowledge regarding physical activity post diagnosis might be valuable for both care-givers and patients and might facilitate implementation of physical activity as a part in the treatment for patients with cancer. One step to that goal could be to increase knowledge of the survival benefits after breast cancer diagnosis, and, maybe even more important for some individuals, knowledge about the immediate response to a single exercise session.

As a physiotherapist in oncology you meet a lot of patients at various disease stages and with various types of cancer. It is all these meetings that aroused my interest in learning more about the effects of physical activity and sedentariness, especially after a cancer diagnosis. Patients I met gave me the idea to examine the immediate experience of exercise during chemotherapy. They enjoyed sharing their good experiences of the exercise they performed, and I was curious if all patients had the same enjoyable feeling, or if those who did not say anything were quiet because they didn't have positive experiences to share, and instead became more tired and exhausted.

Aims

Overall aim

The overall aim of this thesis was to increase the knowledge regarding physical activity, sedentariness and exercise in relation to breast cancer.

Specific aims

Study I	To elucidate the association between occupational sedentariness and breast cancer risk in pre- and postmenopausal (< 55 and ≥ 55 years old) women.
Study II	To describe self-reported perception of energy, stress, nausea and pain immediately after an exercise session in the *first week* after chemotherapy infusion.
Study III	To describe self-reported perception of energy, stress, nausea and pain after an exercise session at different time points *throughout* a course of chemotherapy.
Study IV	To elucidate the association between physical activity level after breast cancer diagnosis and survival in women with pre- and postmenopausal breast cancer (diagnosed < 55 and ≥ 55 years old).

Methods

The study design, measurements methods, statistical analyses, results and manuscript-writing have been discussed and established in the research group containing of supervisor, co-supervisors and co-authors and all of us have contributed in the research process.

Study design

All four studies included in this thesis have an observational design. Studies I and IV are based on material from a large prospective cohort, the Melanoma Inquiry of Southern Sweden (MISS) and Studies II and III are based on a subset of participants from a randomised controlled trial, the Physical Training and Cancer study (Phys-Can). An overview of the studies is presented in Table 1.

Table 1. Overview of study designs, settings, study populations, outcomes, measurements and statistical analyses.

	Study I	Study II	Study III	Study IV
Design	Prospective population-based cohort study	Descriptive observational study	Descriptive observational study	Prospective population-based cohort study
Setting	General population	Exercise sessions	Exercise sessions	General population
Study population, inclusion criteria	Women included in the MISS cohort	Women with breast cancer undergoing chemotherapy, training in the Phys-Can study, in Lund between October 2016 and April 2018	Women with breast cancer undergoing chemotherapy, training in the Phys-Can study, in Lund between October 2016 and April 2018	Women with breast cancer after inclusion in the MISS cohort
Criteria for including in analysis	The entire cohort	Participants who performed at least one exercise session in the first week after chemotherapy	Participants who performed exercise sessions in chemotherapy cycle 2 and/or cycle 5	Women diagnosed with breast cancer and who responded to a post-diagnosis questionnaire
Sample size, total and in subgroup analyses*	Total, n= 29 524 < 55 years, n= 19 908, ≥ 55 years, n=21 526	Total, n=38 endurance exercise, n=26 resistance exercise, n=31	Total, n=46 Chemotherapy cycle 2, n=43 Chemotherapy cycle 5, n=30	Total, n=847 < 55 years, n= 279 ≥ 55 years, n=568
Main outcomes	Breast cancer diagnosis	Changes in energy, stress, nausea and pain	Changes in energy	Survival
Measurements/ Data sources	Study-specific questionnaire, Swedish Cancer Register and Cause of Death Register	SEQ-LT and VAS	SEQ-LT and VAS	Study-specific questionnaire, Swedish Cancer Register, Cause of Death Register and Swedish Population Register
Statistically analyses	Descriptive statistics, Cox regression	Descriptive statistics, paired sample t-test and multiple linear regression	Descriptive statistics, paired sample t-test and linear regression	Descriptive statistics, Cox regression

*One individual might be represented in more than one subgroup, see flowcharts (Fig. 3-6).
MISS = Melanoma Inquiry of Southern Sweden
Phys-Can = Physical Training and Cancer study
SEQ-LT = Stress-Energy Questionnaire at Leisure-Time
VAS = Visual Analogue Scale

Study populations, procedures and measurements

Study I

The population in Study I consisted of the entire cohort of women included in the MISS cohort study 1990-92 (Fig. 3).

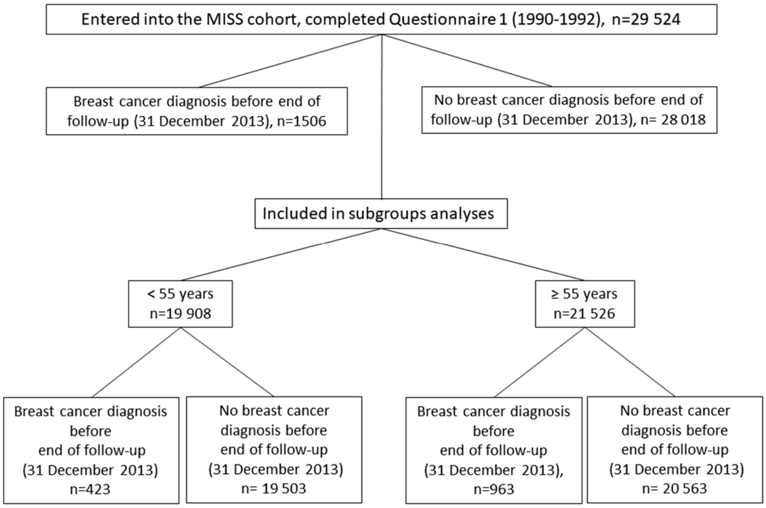

Figure 3. Flowcart for Study I

The MISS-cohort study. In total 40 000 women aged between 25 and 65 years were sent an invitation to participate in the Melanoma Inquiry of Southern Sweden (MISS) in 1990-1992. One thousand women in each one-year group without a history of cancer were randomly selected from the Swedish Population Register. All participants provided written informed consent. Women who participated answered a questionnaire concerning several risk factors for cancer development (questionnaire 1). Between 2000 and 2002 a follow-up questionnaire (questionnaire 2) was sent to the participants and then again between 2010 and 2012 (questionnaire 3). The first questionnaire contained several items regarding educational level, occupational history, hormonal factors, family history of cancer and lifestyle factors such as smoking, alcohol consumption and participation in competitive sports. The follow-up questionnaires were similar but also contained information on weight and height and two additional questions regarding physical activity. An overview of data collected in Studies I and IV is presented in Table 2, see also Appendix 1.

Table 2. Variables collected from MISS questionnaire 1 (Q1), 2 (Q2) and 3 (Q3).

Variables collected from the questionnaires		MISS questionnaire	Used in Study
Age, years	Date of birth	Q1, Q2, Q3	I, IV
Occupation (do/did you have any occupation? If yes: Please fill in all occupations from your first until now)	One to seven occupations were reported	Q1	I
Physical activity (During the last few years, were you physically active if you don't include sports?)	Never / Sometimes / More than one hour every week	Q2, Q3	IV
Exercise (Do you perform any regular exercise?)	No / Yes, walking a few times every week / yes, walking several times every week / yes e.g. cycling, swimming, gymnastics or dancing at least once a week	Q2, Q3	IV
Sports (Did you participate in competitive sports during childhood or adulthood?)	Yes/No Missing value was classified as "No"	Q1, Q2, Q3	I, IV
Education (Years of education)	< 9/ 9-12 / > 12	Q1	I, IV
Family history of breast cancer (in first relatives)	Yes/No Missing value was classified as "No"	Q1, Q2, Q3	I, IV
Age at first childbirth, years	<30 /≥30 Without children: ≥30years	Q1, Q2	I, IV
Age at menarche, years	≤13 / >13	Q1	I
Use of oral contraceptives	Never/Ever	Q1, Q2	I, IV
Use of hormone replacement therapy	Never/Ever	Q1, Q2, Q3	I
Marital status	Unmarried / Married / Divorced / Widow	Q1, Q2	I, IV
Smoking	Never/Ever	Q1, Q2, Q3	I, IV
Alcohol consumption (Centilitre per month, described as standard glasses per month)	≤4 / >4 glasses/month (median)	Q2, Q3	IV
BMI (Based on bodyweight and height (kg/m2))	<25 / 25-29 / >29	Q2	I, IV

Q1 = questionnaire 1, Q2=questionnaire 2, Q3=questionnaire 3

Breast cancer events were identified through Swedish personal identity numbers, linked to the Swedish Cancer Register and Cause of Death Register. The National Board of Health and Welfare (Socialstyrelsen) administers several registers including the Swedish Cancer Register and the Cause of Death Register. Since 1958, it has been obligatory for all health care providers to report new cancer cases to *the Swedish Cancer Register* containing information on tumour site, ICD code, tumour stage (since 2004) and date of diagnosis. The completeness of this register is high, capturing 96% of all cases. *The Swedish Cause of Death Register* consists of date and cause of death from 1961 onwards.

Study II

The study population was women with breast cancer undergoing chemotherapy. They were invited to participate after they started to exercise in the Phys-Can training study and before their second chemotherapy cycle.

Phys-Can is a randomised controlled Swedish multicentre trial where patients newly diagnosed with breast-, colorectal- or prostate cancer were included from 2015 to 2018. The primary aim was to elucidate the effects of low-to-moderate versus high intensity training, with or without behaviour change techniques, on cancer-related fatigue. The training was performed during (neo-) adjuvant cancer treatment. This was done with or without behaviour change techniques, and was performed during adjuvant oncological treatment. The intervention included a combination of home-based endurance training and group-based supervised resistance training at a public gym. The participants exercised for six months, starting their training, preferably, before the start of their oncological treatment. Further information regarding the exercise training intervention is described in the study protocol (85). The populations in Studies II and III were based on a subset of participants training at one of Phys-Can study sites.

Participants in Study II responded to questionnaires regarding energy, stress, nausea and pain just before and just after an exercise session, and once more three hours after the session (Appendix 2).

Energy and stress were assessed using by the Stress-Energy Questionnaire at leisure time (SEQ-LT). The Stress-Energy Questionnaire (SEQ) was developed to describe two components of mood at work: affective stress and energy (86, 87). The scales contain six items to evaluate stress and six items to evaluate energy, ranged from low level to high level of stress and energy. The stress dimension included three positively-loaded items (rested, relaxed and calm) and three negatively-loaded items (stressed, tense and pressured). The energy dimension included three positively-loaded items (active, energetic and focused) and three negatively loaded items (dull, ineffective and passive). All twelve questions have the same response alternatives: "not at all, hardly, somewhat, fairly, much and very much", coded 0-5. The overall question was originally "How do you usually feel at the end of a normal working day?" It has been used in Swedish studies of occupational stress and is a valid tool for assessing stress at work (86).

To assess stress and energy during leisure time the SEQ was modified by using an overall question "How do you usually feel when you are not working?", and renamed SEQ-LT. The psychometric properties when measuring in leisure time have been found to be satisfactory in a population of workers in a service organisation (88).

Nausea and pain were assessed using Visual Analogue Scale (VAS). VAS is a 10-centimetre long line where the respondents make a mark to indicate the level of perceived intensity of the measured outcome. The left end of the line means "not at all", while the right end of the line means "worst possible". VAS is commonly used and well established in both clinical and research settings to measure nausea and pain (89), and is reliable and valid in populations with cancer (90, 91).

To evaluate if the experience was related to type of exercise – endurance or resistance – subgroups were created. One individual could be included in both subgroups if she performed one endurance exercise session and one resistance exercise session in the first week in the chemotherapy cycle (Fig. 4 and 5).

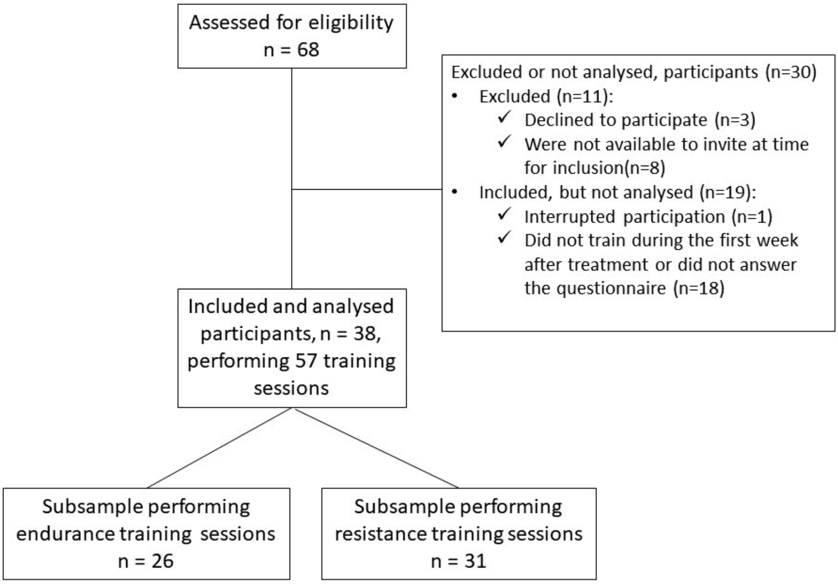

Figure 4. Flowchart Study II

Study III

The study population was based on the same population as study II, and the data collection was made in the same way, but at other time points (Fig. 5).

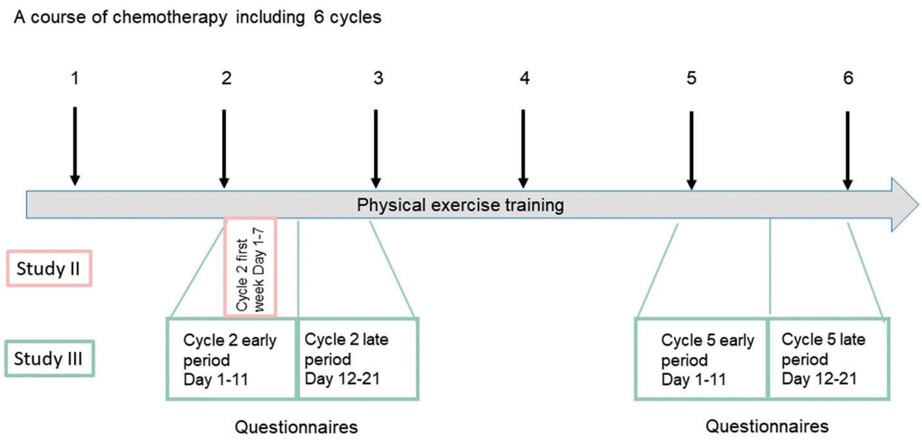

Figure 5. Timeline showing chemotherapy cycles and periods for measurements in Study II and III. One cycle lasted 21 days.

To allow comparison between different time points (periods) subgroups were created. The subgroup in chemotherapy cycle 2 exercised in both the early and the late period in cycle 2, and the subgroup in chemotherapy cycle 5 exercised in both the early and the late period in cycle 5. One individual could be included in both subgroups if they exercised in all four periods (Fig 6).

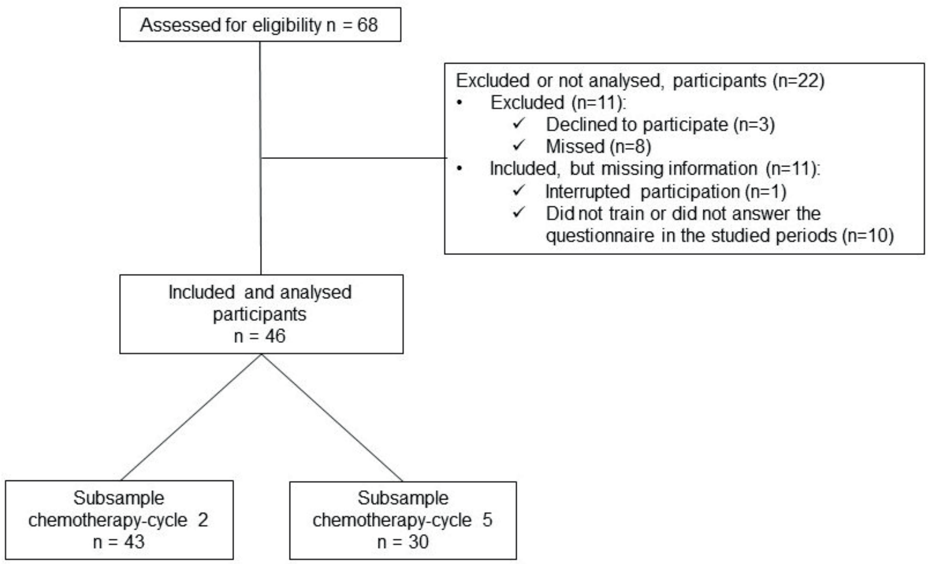

Figure 6. Flowchart Study III

Study IV

The population in Study IV was based on the MISS cohort and consisted of participants diagnosed with breast cancer after inclusion in MISS and who completed a questionnaire (Q2 or Q3) after diagnosis (Fig. 7). Table 2 shows which variables were collected from these patients using the questionnaires. Deaths were identified through Swedish personal identity numbers, linked to the Swedish Population Register and Cause of Death Register.

The Swedish Population Register is administered by the Swedish tax agency and contains information such as name, place of birth, emigration details, and death of people living in Sweden. Every registered person has a personal identification number (92).

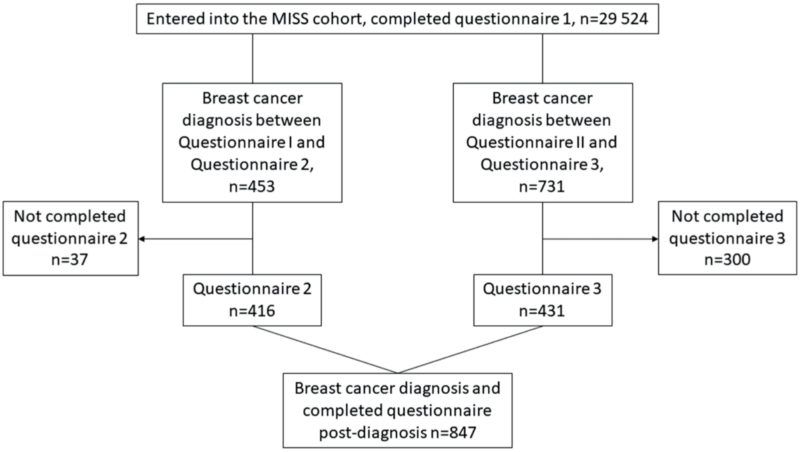

Figure 7. Flowchart Study IV

Data managements and statistical analyses

Risk and survival analyses (Studies I and IV)

To investigate any association between occupational sedentariness and risk of breast cancer (Study I) and between post-diagnosis physical activity level and mortality in women with breast cancer (Study IV) the Hazard Ratio (HR) was estimated by Cox proportional regression. Cox proportional regression is a commonly-used statistical method to estimate risk and mortality in prospective cohort studies. The model gives a time-dependent hazard ratio in one group compared with another. Statistical analysis for Studies I and IV was performed by the statistician and co-supervisor (PB) using the survival package in R.

Association between occupational sedentariness and risk (Study I)

Information about occupational sedentariness was based on data regarding the job-titles in the participants' occupational history, from their first job to their current job at the time of the questionnaire. The reported occupations in questionnaires were classified as sedentary or non-sedentary by two physiotherapists (AJ, main author and ÅBT, co-author). Three different categories were created: (1) only non-sedentary occupations (used as reference group), (2) mixed sedentary/non-sedentary and (3) only sedentary occupations. Examples of the most frequently reported sedentary occupations are administrative work, cashiers, bank tellers, bookkeepers and office cashiers, secretaries and postmasters. To adjust for physical activity, the question "Did you participate in competitive sports during childhood or adulthood?" was used.

The MISS-cohort was linked by personal identity numbers to the Swedish National Cancer register for identification of breast cancer cases and to the Swedish National Cause of death register (31 December 2013).

The hazard ratio for occupational sedentariness and breast cancer risk was estimated in age-adjusted univariate and multivariate models. Analyses were performed for the entire cohort and stratified by age at diagnosis (younger than 55 years old versus 55 years or older). The multivariate model was adjusted for established risk factors. The time from study enrolment to breast cancer diagnosis, death or end of follow-up were calculated.

Self-reported energy, stress, nausea and pain (Studies II and III)

Data were collected by a questionnaire containing SEQ-LT and VAS. Participants responded to the questionnaire just before and just after the exercise session and then again three hours after the session was completed.

To analyse changes from before to after an exercise session in all outcomes (energy, stress, nausea and pain) paired sample t-tests were used. Paired sample t-tests were also used to evaluate differences between the mean changes at different time points. Since both the SEQ-LT score and VAS are ordinal scales, the Wilcoxon signed rank test was performed as a sensitivity analysis in Study II. The results from this analysis were similar, so the results from t-test are presented. In Study II the result is also presented as number of individuals, proportions and as waterfall plots.

Multiple linear regression was performed to investigate the relationship between the self-reported changes in energy and stress and previous training habit, exercise intensity and energy/stress level before the exercise session (Study II). Previous training habits and exercise intensity had no relation to the changes. Therefore, a re-fitted model was performed that included only energy/stress level before the exercise session as an independent variable. In Study III, linear regression was performed with energy/stress before the exercise session as independent variables and the mean changes as the dependent variable. Residual distributions were examined graphically and if they were deemed non-normal the bootstrap standard errors and p-values were used instead of the regular. The analyses were performed using IBM SPSS Statistics version 25.0 (Chicago, IL, USA) by the main author with support from a statistician (PW). Descriptive statistics were calculated to present characteristics of participants in the studies.

Association between physical activity and mortality (Study IV)

Physical activity level was based on three questions regarding physical activity from MISS questionnaire 2 or 3, whichever came first after breast cancer diagnosis. The response alternatives were given points, where "0" implied the smallest amount of physical activity and higher points implied higher physical activity level. The questions were:

1. During the last few years, were you physically active if you don´t include sports?

   Response alternative:

   a) never = 0 points

   b) sometimes = 1 point

   c) more than one hour every week = 2 points

2. Do you perform any regular exercise?

   Response alternative:

   a) no = 0 points

   b) yes, walking a few times every week = 1 point

   c) yes, walking several times every week = 2 points

d) yes, for example cycling, swimming, gymnastics/calisthenics or dancing at least once every week = 3 points

3. Did you participate in competitive sports during childhood or adulthood? Response alternative:

   a) no = 0 points

   b) yes = 1 point

A score was calculated as a sum of the response points of the three questions and could assume a value of 0 to 6, where 0 was the lowest level of physical activity and 6 the highest.

Imputation by Random Forest was used to compute physical activity when one or two questions had missing information from a participant. Around 20% of the participants did not respond to all three questions regarding physical activity. Values were predicted based on data from earlier observations of physical activity, the non-missing values of variables in the score and BMI. The method estimates a model which makes it possible to predict missing data from observed data. Though imputation might be a source of bias, sensitivity analysis was performed without participants with missing data, and that analysis did not change the study results.

The MISS-cohort was linked to the Swedish National Cancer Register for the identification of breast cancer cases, the national Population Register (April, 2016) and to the Swedish National Cause of Death Register for mortality (December, 2013).

Hazard Ratio for post-diagnosis physical activity level and mortality (breast cancer-specific and all-cause) was estimated, with age as an underlying time scale. All analyses were stratified by disease stage at diagnosis. The final model consisted of physical activity level, family history of breast cancer and smoking. Subgroup analyses, divided by age at diagnosis, were performed with physical activity as a continuous variable instead of categorical (score 0-6), due to a small number of events in each score. The trend analysis was conducted using the physical activity score as an ordered factor.

Ethical consideration

Study I and IV were approved by the Regional Ethical Review Board of Lund University approved the studies (LU-34-92, LU 849-05). The women randomly chosen from the Swedish population register were invited to respond to a questionnaire at the study enrolment, the non-responders were sent one reminder. All participating women signed an informed consent.

Study II and III were approved through an amendment to the Phys-Can study by the Regional Ethical Review Board in Uppsala (Dnr 2014/249/3). The eligible women received written and oral information regarding the study and about their right to withdraw from the study at any time. Informed consent was signed before inclusion.

All studies in this thesis include human participants and were performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (93). Data was coded and therefore unidentified during processing and storage. All analyses are performed and presented without possibility to identify individuals.

Study I and IV are observational cohort studies and already collected data is used and therefore not a burden to the participants. However, they have not decided if they want to be part of this research question and it was many years since they signed informed consent. It is not possible to identify any individual and our findings have contributed with information that might be a part of prevention of breast cancer and premature death for women with breast cancer.

Participants who trained within the Phys-Can trial were asked about their willingness to participate in study II and III by the author, for some of them the author was a part of their team of instructors. That might have been a pressure to participate to satisfy the author in the role of instructor. Emphases was placed on that the participation was entirely voluntarily and withdrawal could be chosen at any time without any consequences on the training in Phys-Can or on their treatment at the hospital. Furthermore, the study was initiated from an idea of patients training in the Phys-Can study. There were a few dropouts, but most of the participants told that they were pleased to share what they felt and hoped that it could be beneficial for other patients in the future. The study questionnaire was selected with the ambition to, in addition to collect the required information, also should be easy and convenient to respond to.

Results

We found that occupational sedentariness was associated with breast cancer risk and that physical activity was beneficial as a health-enhancing factor after diagnosis. In addition to the positive association with improved survival, the self-reported energy level increased immediately after a single exercise session performed during chemotherapy.

Occupational sedentariness and breast cancer risk (Study I)

During the study period, with a mean of 19.8 years follow-up, 1506 women were diagnosed with breast cancer. A work history with only sedentary occupations compared with non-sedentary occupations was associated with a higher risk of breast cancer, while a work history with a mix of sedentary and non-sedentary occupation was not. Four hundred and twenty-three women were diagnosed before 55 years old and 1083 at 55 years or older. In analyses stratified by age, the increased risk was only shown in women younger than 55 years at diagnosis (Table 3).

Table 3. Association between occupational sedentariness and breast cancer risk in women at all ages, and in women younger or older than 55 years old. Cox regression, age-adjusted multivariate analyses.

Age at diagnosis	**Occupational sedentariness, HR (95% CI)**		
	No (ref)	Mixed	Yes
All ages [a]	1.0	0.98 (0.86-1.12)	**1.20 (1.05-1.37)**
Younger than 55 years [b]	1.0	1.08 (0.87-1.39)	**1.54 (1.20-1.96)**
55 years or older [c]	1.0	0.96 (0.82-1.13)	1.03 (0.88-1.22)

Results in bold indicate $p < 0.05$.

[a] adjusted for competitive sports, family history of breast cancer, age of birth of first child, age at menarche, use of oral contraceptives, education (years), BMI

[b] adjusted for competitive sports, family history of breast cancer, age of birth of first child, age at menarche, use of oral contraceptives

[c] adjusted for competitive sports, family history of breast cancer, age of birth of first child, age at menarche, use of hormone replacement therapy and BMI

Self-reported energy, stress, nausea, and pain: experience of a single exercise session during chemotherapy. (Studies II and III)

Energy

Energy level increased immediately after exercise in the *first week* after chemotherapy infusion (Study II) and *throughout* the chemotherapy course (cycle 2 and 5), with less increase in the late period in cycle 2 and did, in that period, not reach statistical significance (Study III). The increase was similar independent of type (endurance or resistance) or intensity of exercise (Study II). Energy level before the session was related to the increase, with a lower level before the session relating to a higher increase (Studies II and III). The reported response immediately after did not last at the measurement three hours after the exercise session – energy level three hours after was similar to the level before the session (Fig. 7).

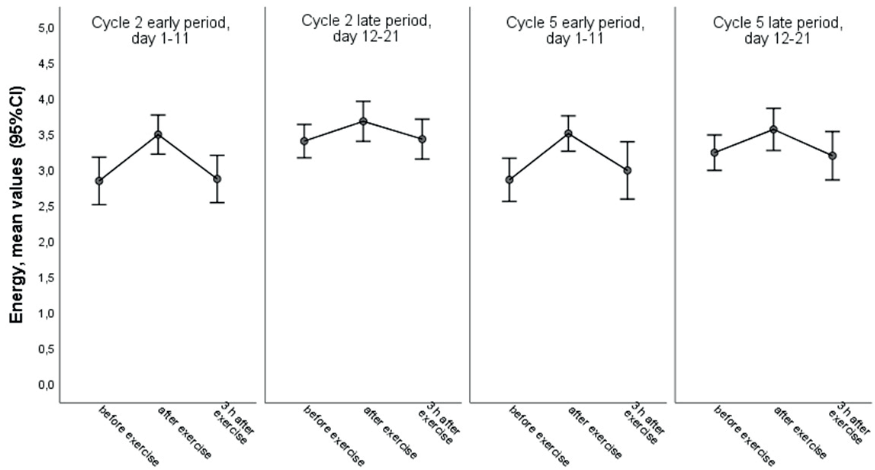

Figure 7. Changes in energy from before to immedately and three hours after the exercise session, during chemotherapy cycle 2 and 5. The changes from before to immediately after are statistically singnificant in C2 early period and in both periods cycle 5.

Stress

After a resistance exercise session in the *first week* after chemotherapy infusion, stress was reduced by -0.4 (p=0.01) units on the 0 to 5 scale. This reduction was not seen after endurance exercise. At three hours after the exercise session, stress was reduced regardless of exercise type (Study II).

Throughout the chemotherapy course stress was reduced in both periods in cycle 2 (early: -0.3, p=0.01; and late: -0.3, p=0.01). In both periods in cycle 5 there was a numeric reduction, but it did not reach statistical significance (early period: -0.2, p=0.09; and late period: -0.2, p=0.06). At three hours after the session, stress level was reduced in all periods through the chemotherapy course (-0.4 to -0.6, p<0.01) (Study III).

Nausea

Nausea decreased in the *first week* after chemotherapy infusion, with a similar decrease independent of type of exercise, endurance or resistance (Study II). In the early period in chemotherapy cycle 2, 53% of the participants reported nausea before the exercise session, and analysis showed an improvement after the session of -0.5 units on VAS 0-10, p=0.02, borderline statistically-significant (Study III). In the other three periods there was a smaller proportion of participants who reported nausea before the exercise session (19%, 10% and 10%).

Pain

In the *first week* after chemotherapy infusion, nine of 26 participants (35%) who performed an endurance exercise session reported pain and nine of 31 participants (29%) who performed a resistance exercise session. Due to the small numbers, analysis was not conducted for this week (Study II). In the four different periods during the chemotherapy course, experienced pain was included in analyses, but no changes were found (p=0.32-0.88). During these periods pain was reported by 17/43 (40%), 11/43 (26%), 11/35 (35%) and 10/35 (32%) participants (Study III).

Physical activity and prognosis

There was an inverse association between post-diagnosis physical activity level and all-cause mortality in a dose-response dependent manner (Fig. 8). Adjustment for duration of breast cancer, family history of breast cancer, smoking and disease stage (strata) were performed in the multivariable model. Between physical activity level and breast cancer specific mortality the association was not statistically significant, even if a numeric risk reduction was observed. Fifty-six (40%) of the deaths during the follow-up was defined as breast cancer specific.

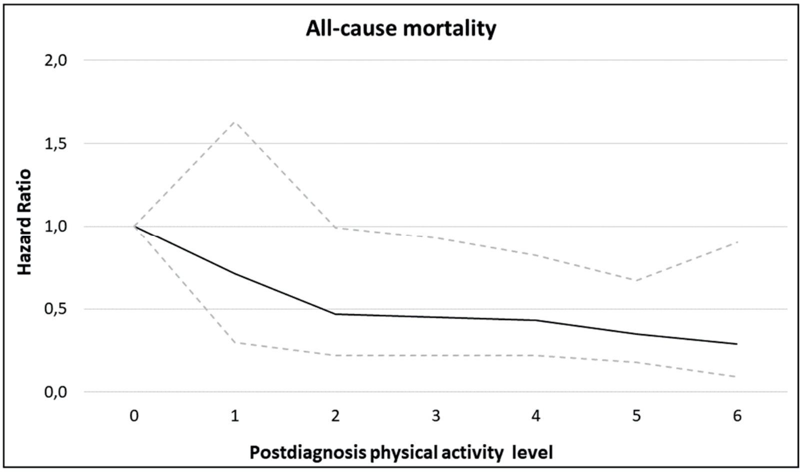

Figure 8. Dose-response physical activity level after breast cancer diagnosis and all-cause mortality. The Cox proportional regression analysis is stratified by desease stage and adjusted for family history of breast cancer and current or former smoking.

Analysis stratified by age, and with physical activity as a continuous variable, showed decreased risk of all-cause mortality only for women 55 years or older at diagnosis, primarily postmenopausal breast cancer (HR=0.78, 95% CI 0.69-0.88). In women younger than 55 years at diagnosis, no association was found (HR=1.08, 95% CI 0.85-1.36). In the multivariable model, adjustment was made for disease stage at diagnosis, family history of breast cancer, and smoking.

General discussion

The aims of this thesis were to elucidate the associations between sedentariness and risk of breast cancer and between physical activity and survival in younger and older women (pre- and postmenopausal breast cancer), and to describe patients' self-reported energy after an exercise session during chemotherapy. This thesis has added knowledge in the field through findings that occupational sedentariness was associated with higher risk of breast cancer, especially in women younger than 55 years old, and that physical activity level after diagnosis was associated with improved survival, especially among women 55 years or older. Moreover, findings regarding improved self-reported energy after a single exercise session have added insight into women's perception of exercising during chemotherapy, which might be an important contribution when to implement exercise in cancer care.

Study I

In Study I we found an association between occupational sedentariness and increased breast cancer risk: women that have a work history of only sedentary occupations have a higher risk of developing breast cancer. Interestingly, women who have a work history with a combination of sedentary occupations and non-sedentary occupations do not have a higher risk than women with only non-sedentary occupations. These findings might indicate that it is never too late to make a change in one's behaviour.

Mechanisms by which sedentariness and breast cancer are linked are unclear, but there are several possible biological mechanisms associated with sedentariness which also are involved in breast cancer development. Such factors include increased intra-abdominal fat, metabolic dysfunction, insulin resistance and elevated levels of Insulin-like Growth Factor 1 (IGF-1), chronic inflammation, and alterations in levels of circulating sex hormones (94, 95). Risk factors for pre- and post-menopausal breast cancer are not exactly the same, due to differences in hormonal conditions. Factors that may be especially significant are high BMI and weight gain, since both are risk factors for postmenopausal breast cancer but not premenopausal (27).

In our study, analysis stratified by age was performed comparing women younger than 55 years with those at 55 years or older. The average age for menopause is 51 years, therefore most of the women younger than 55 years old are pre-, or peri-menopausal and most of the women 55 years or older postmenopausal. Surprisingly, this analysis showed a higher risk only in women younger than 55 years at diagnosis, which is contrary to the results in two meta-analyses of previous studies including subgroup analyses due to menopausal status. One of them, containing cohort studies regarding premenopausal breast cancer, only showed an association between postmenopausal breast cancer risk and time spent sitting (46), whereas the other, containing case-control studies, did not find any differences in the association according to menopausal status (48). Though many studies include mostly women with postmenopausal breast cancer and have not created subgroups by menopausal status, the evidence is still limited.

Meta-analyses with subgroup analyses by domains of sedentary behaviour show inconsistent results: one found an association between occupational sedentariness and breast cancer risk (OR=1.10, 95% CI 1.00-1.20) (49), while another did not (premenopausal women RR=1.14, 95% CI 0.91-1.42; postmenopausal women RR=0.98, 95% CI 0.72-1.35)(46). High levels of physical activity are suggested to compensate for the impact of sedentary behavior on health (78, 96). Therefore, in our study we adjusted for participation in competitive sports, but that did not change the results. However, it might have been different if we had asked more questions regarding physical activity and exercise in the questionnaire.

Studies II and III

In Studies II and III we have added knowledge about exercising during chemotherapy. We found that self-reported energy increased immediately after an exercise session performed during a chemotherapy course. The beneficial finding that lower energy level before an exercise session was correlated to a larger increase afterwards, might make it more conceivable for patients to exercise even when energy is low during chemotherapy.

Energy increased after endurance exercise by 0.4 units and after resistance exercise by 0.7 units on a scale 0-5 with no influence of intensity (Study II). Our findings are in line with a recent study regarding cancer-related fatigue, that study showed an improvement after a single exercise session under guidance of a physical therapist consisting of leg strength and walking training among hospitalised patients with various types of malignancies undergoing radiation and/or chemotherapy (67). We chose to focus on energy as a positive mood, instead of fatigue, though lack of energy is one prominent component in fatigue. It is clinically highly relevant to inform the patient that their energy level will probably increase immediately after exercise, and it might even be more encouraging to talk about increases in energy rather than reductions in fatigue.

Furthermore, other studies have showed beneficial long-term effects of exercise on cancer-related fatigue. Nakano et al. found improved fatigue in a meta-analysis with exercise interventions for patients with cancer irrespective of type of exercise (64) and Björke et al. found that longer duration and higher volume were more important than intensity for improvement of cardiopulmonary fitness in patients exercising during anti-cancer treatment (61).

In the first week after chemotherapy infusion, stress decreased after resistance exercise but not after endurance exercise. Since the resistance exercise session was performed in a group while endurance exercise was not, the stress reduction response might be a combination of the exercise and a group effect and not the exercise per se. Nevertheless, stress was reduced in both periods in cycle 2, and with a numeric reduction in cycle 5, even though these analyses are based on both types of exercise. These results indicate that the exercise itself might affect the level of stress, and not only in combination with a group setting. It is well known that both long-term and short-term exercise reduce stress in populations without cancer (20, 97). Most of the previous studies include endurance exercise, but it seems that resistance exercise has a similar effect (98).

Nausea decreased after both endurance and resistance exercise within the first week after chemotherapy infusion. In the first period of chemotherapy cycle 2, approximately half of the participants reported nausea before the exercise session, in the other periods only a few reported nausea. This distribution was expected since nausea is a common side-effect of treatment with Epirubicin and Cyclophosphamide given in cycle 2. Since $p < 0.01$ was set as the level of statistical significance, due to multiplicity issues, the improvement of -0.5 units on VAS 0-10, $p=0.02$ was not statistically significant. To the best of our knowledge no previous study has examined the immediately effects of one single exercise session on nausea and only a few studies have evaluated the long-term effect. The studies regarding long-term effect concluded that the effects of exercise might be positive or at least do not worsen the symptoms (64, 66).

Pain was reported less than expected, but based on existing data pain did not get worse immediately after an exercise session – although there was no relief either. Since the reasons for not participating in the exercise sessions were unknown it might have been because of pain and the results are therefore a bit uncertain. Long-term exercise has been shown to reduce pain in patients with cancer (64, 65).

Study IV

In Study IV we found an association between post-diagnosis physical activity level and all-cause mortality, especially in women at 55 years or older. Physical activity was divided into seven levels with scores 0 to 6, based on three questions from the MISS questionnaire. Women with the highest physical activity level had a lower risk of all-cause mortality compared with those with the lowest physical activity level (HR=0.29, 95% CI 0.09-0.90). This suggest a larger risk reduction compared with meta-analyses in previous studies (HR 0.50-0.76), but in those studies physical activity level was divided into quartiles or quintiles (72-75). In our study the two levels at the extremes of the spectrum/scale (lowest and highest level) contained a rather small proportion of the participating women (level 0: 5.1% and level 6: 3.5%), who either were entirely physically inactive or physically active at a high level.

In subgroup analyses, divided by age at breast cancer diagnosis (younger than 55 years versus 55 years or older), the association between physical activity and all-cause mortality was seen in the group with older women (most of them postmenopausal), but not in younger. The results in the present study are in line with previous studies that have investigated differences between physical activity level and breast cancer divided by menopausal status. According to the World Cancer Research Fund Continuous update project, physical activity showed a lower risk in total mortality for postmenopausal women but not premenopausal (77), and two previous meta-analyses showed that all-cause mortality is associated with post-diagnosis physical activity level in postmenopausal women but not premenopausal (72, 75).

In our study, the lower mortality was seen even at rather low physical activity levels – those who scored only 2 points (out of 6) had a 50% lower risk of premature mortality than those who did no physical activity (score of 0 out of 6). This shape of the curve is also reported in other studies evaluating physical activity level and mortality in women with breast cancer (75, 99, 100). In a review of a large number of studies regarding health benefits of physical activity, the greatest risk reduction appeared when small volumes of physical activity were compared with very low volumes (101). This indicates that it is *much* better to do a small amount of physical activity than no physical activity at all.

Methodological considerations

Strengths and limitations

Studies I and IV are based on data from a cohort with a large number of participants aged from 25 to 65 years old at enrolment, randomly selected from the Swedish population register. The age distribution enabled subgroup analyses divided by women younger than 55 years (most of them pre- or perimenopausal) and 55 years old or older (primarily postmenopausal) to make distinctions between pre- and postmenopausal breast cancer. The high response rate (74%) and long follow-up regarding risk of breast cancer (mean 19.8 years) and mortality after a breast cancer diagnosis (mean 8.7 years) are other advantages in addition to the prospective design. Though the questionnaires consist of questions regarding several risk factors, such as hormonal factors, education, smoking and BMI, it allowed us to include and adjust for them in the analyses. Linkage by the personal identity numbers to the Swedish population register, the Swedish Cancer Register and the Cause of Death Register, provided good control of both breast cancer diagnosis and mortality. Another strength was that we had information about the participants' work history from their first occupation to their current at baseline and not only the occupation at one time point (Study I). We believe that Studies I and IV offer added epidemiological evidence to that already existing on physical activity and sedentariness as risk factors in relation to pre- and postmenopausal breast cancer.

Studies regarding the immediate response of a single exercise session performed during chemotherapy is a rather new area, and Studies II and III were initiated after ideas from patients. It is a strength to focus on knowledge requested by patients, especially since physical activity and exercise should be a part of cancer treatment and rehabilitation, which also makes it clinically important and relevant. To the best of our knowledge Study III is the first to examine perceived energy at different time points during a chemotherapy course, which is meaningful since most side-effects increase toward the end of the chemotherapy course.

A limitation with observational studies is the uncertainty regarding cause and effect and the possible impact of unidentified confounders. Even though we assessed the role of, and adjusted for, several potential confounders, there might be others that we do not know of. Alternative explanations to our findings in Studies I and IV, possible confounders, might include for example, living environment (a city or in countryside) and eating habits (diet). Limitations with self-reported data include the risk that the respondent misunderstood the questions (Studies I-IV), and recall bias (Studies I and IV). In Studies II and III the aim was to study the self-reported perceived energy, stress, nausea and pain after a single exercise session. To assess the effect of a single exercise session, a randomised controlled study (RCT) should be performed, but our question was about the experience, and so an observational design is more suitable. It might have been of interest to investigate if the experienced energy differs between women with breast cancer and healthy women, but that was not the aim either.

Another limitation was that the classification of occupational sedentariness was based on job titles, without information on actual time spent engaging in sedentary behaviour at work (Study I). The results might have been slightly different if we had had data from self-reported sedentary time at work, but those data would probably have been affected by recall bias since some of the occupations were held a long time ago. Job titles are commonly used to identify occupational sedentariness in epidemiological studies (48). In the first MISS questionnaire the question regarding physical activity was about participating in competitive sports and more data such as leisure time physical activity would have been preferable, though time being physically active probably counteracts the unhealthy effects of time being sedentary (78, 96).

The questions regarding physical activity in Study IV are rather general and unspecific, but they do link to 1) Physical activity, 2) Exercise and 3) Sports. The MISS cohort study was initiated 1990 and not originally designed for studies on physical activity. Because of this, it is unfortunately not possible to state exactly what the different scores correspond to in a more absolute way. This research field has changed and progressed a lot, and lately accelerometer-measured data have been used in studies to measure physical activity and sedentary behaviour and their association with mortality (102).

The SEQ-LT was originally developed to measure work-related energy and stress and has then been tested and used for leisure-time, but not in patients with cancer. The low level of stress reported in Studies II and III before exercise may perhaps imply that SEQ-LT measures another kind of stress not relevant to patients with cancer undergoing chemotherapy. However, the fact that stress decreased or did not increase, is most likely an indication of a beneficial effect of exercise on stress, and distress, in patients with breast cancer undergoing chemotherapy.

In addition, all four Studies would have been strengthened with more information regarding potential confounders such as comorbidities, information regarding smoking such as current or former smoker (Studies I and IV) and medication for nausea and pain (Studies II and III).

External validity and generalisability

Studies I and IV. In the MISS study, 40 000 women aged 25 to 64 years old with no history of malignancy were randomly selected from the Swedish population register.

This selection represented 20% of women in the age group who lived in the Southern part of Sweden and should be representative of the whole population. Of these 40 000 invited women, 29 524 (74%) returned the questionnaire and were included in the MISS study. Even if the response rate was rather high there is a risk of selection bias, and we know nothing about the ones not included.

Studies II and III. Before inclusion in Phys-Can, participants were screened by a physician, which means that patients that have comorbidities are not represented in the exercise study and those who were not interested in exercising during their chemotherapy are of course not represented either. Altogether we can only generalise to women with breast cancer without comorbidities that hinder exercise. Patients with cancer who choose to participate in exercise studies might have different characteristics from those who do not – they probably have higher education levels, less fatigue, a higher health-related quality of life, more positive attitudes towards exercise, and more social support (103).

Conclusions

In conclusion, this thesis has increased knowledge regarding the role of physical activity and sedentariness in relation to breast cancer in younger and older women. Furthermore, new knowledge has been created regarding patient-reported immediate perception of a single exercise session during chemotherapy.

Main conclusions

- Occupational sedentariness was associated with risk of developing breast cancer, especially in women younger than 55 years old (Study I).
- Self-reported energy, stress and nausea were improved immediately after an exercise session performed during the *first week* after chemotherapy infusion. Energy and nausea were improved after both endurance and resistance exercise and stress decreased after resistance exercise (Study II).
- Self-reported energy increased immediately after an exercise session when measured at different time points *throughout* a course of chemotherapy, with a larger improvement when energy was lower before the session (Study III).
- Physical activity level after breast cancer diagnosis was inversely associated with mortality, especially in women at 55 years or older at diagnosis (Study IV).

Clinical implications

The findings in thesis should be useful in the implementation of physical activity and exercise in clinical settings and in cancer rehabilitation. Knowledge regarding the perception immediately after a single exercise session can be motivating for patients that are fatigued during chemotherapy. To know that even one single exercise session could improve energy independent of intensity and even more if the energy level is low, could be a good reason for exercise. Furthermore, exercise does not seem to worsen stress, nausea and pain either.

Another important finding is that even a small dose of physical activity seems to be much better than no physical activity at all. Altogether this can be a help for both care givers and patients to manage side-effects such as cancer-related fatigue and may also improve the prognosis.

Future perspectives

Physical activity has been investigated in several studies and most of them conclude how important it is to be physically active and to avoid spending too much time being sedentary. Research is ongoing regarding the right dose of physical activity for the individual, and the right dose to achieve a specific effect. This knowledge could contribute to more individualised prescriptions of physical activity. On the other hand, all this research includes participants who are willing to take part in clinical research. But what about those who don´t participate? How can we reach them?

Further research is warranted regarding implementation of physical activity in clinical oncological settings. Outside of support or exercise groups for patients during anti-cancer treatment, as said before, it is important to find other ways to reach patients who are not in the right physical state or are not willing to perform regular exercise. Finding everyone's reachable level of physical activity is a real challenge that needs to be focused on.

Another interesting area of investigation could be regarding those individuals who do not report more energy (or less stress, nausea and pain) after an exercise session. What is the reason for not perceiving any improvements? Is it personality, timing or something else? Deeper knowledge regarding these non-responders might give a clue about how we can motivate more patients towards enjoyable physical activity. So, in the future we need find ways to support all patients to discover their individual way to be physically active after a cancer diagnosis as a part of cancer care; to boost quality of life, enhance health and even increase survival.

Populärvetenskaplig sammanfattning

Fysisk aktivitet är en hälsofrämjande livsstilsfaktor som minskar risken för flera kroniska sjukdomar såsom hjärt-kärlsjukdomar, diabetes typ 2, depression och vissa typer av cancer. En av cancerformerna där risken minskas är bröstcancer som är den vanligaste cancern hos kvinnor, i Sverige insjuknar ungefär 7 500 kvinnor per år. Bröstcancer kan delas in i olika subgrupper som till viss del styr behandlingen, indelning sker exempelvis baserat på tumörens hormonkänslighet men också baserat på kvinnans menopausalstatus. Den primära behandlingen vid bröstcancer är vanligtvis operation, ibland i kombination med cytostatika och/eller strålbehandling. Biverkningar vid framför allt cytostatikabehandling är oftast besvärande och cancerrelaterad fatigue (trötthet) brukar förvärras mot slutet av behandlingsperioden.

Det finns idag vetenskapligt stöd för att fysisk aktivitet och undvikande av långvarigt stillasittande är faktorer som kan minska risken för bröstcancer. Däremot är kunskapen något bristfällig avseende om dessa samband ser likadana ut för pre- eller postmenopausal bröstcancer, de studier som finns tyder på att det finns skillnad, men de är inte helt samstämmiga. Också efter bröstcancerdiagnos finns det vetenskapligt belägg för att regelbunden fysisk aktivitet och träning är av godo, exempelvis så minskar behandlingsbiverkningar såsom cancerrelaterad fatigue, nedsatt kondition och muskelstyrka, oro och försämrad livskvalitet. Studier har också visat att det finns ett samband mellan fysisk aktivitetsnivå och överlevnad. Trots det är många kvinnor mindre fysiskt aktiva efter att de fått bröstcancer jämfört med före diagnos, en av anledningarna till det är just trötthet och andra behandlingsbiverkningar. Emellertid finns det väldigt lite kunskap om hur biverkningarna upplevs direkt efter ett enstaka träningspass, förbättrad förståelse för det, skulle kunna leda till ökad motivation till träning både under och efter behandlingsperioden.

I det första arbetet studerade vi om yrke med mycket stillasittande var associerat med risken att få bröstcancer och om det skiljde sig åt för bröstcancer som debuterade före 55 års ålder eller efter. Vi använde oss av ett frågeformulär som besvarats av drygt 29 500 sydsvenska kvinnor 1990–92 (MISS-kohorten). Frågeformuläret innehöll bland annat frågor om deras yrken, från första och fram till nuvarande vid formulärets ifyllnad. Kvinnorna delades in i tre grupper beroende på vilka yrken de haft: (1) de som endast haft yrken med mycket stillasittande, (2) de som haft blandade yrken, både stillasittande och icke stillasittande och (3) de som endast haft icke stillasittande yrken. Via cancerregistret inhämtades data avseende vilka som fått bröstcancer efter enkäten och fram till december 2013. Därefter undersöktes sambandet mellan stillasittande arbete och risken att få bröstcancer. Resultatet visade att kvinnor som endast hade haft stillasittande yrken hade en riskökning med 20% jämfört med de som haft en blandning eller endast icke stillasittande yrken. Vid beräkningar med indelning efter ålder hade kvinnor yngre än 55 år en riskökning med 54%, medan de äldre inte hade någon ökad risk (Studie I).

I delarbete II och III undersökte vi hur självrapporterad energi, stress, illamående och smärta förändrades direkt efter ett träningspass under cytostatikabehandling. Studierna var tilläggsstudier till PhysCan träningsstudie. Alla 57 kvinnor som deltog i studie II och III fick cytostatika som tilläggsbehandling till operation. Behandlingen gavs uppdelad på sex behandlingscykler, en cykel bestod av 21 dagar, och behandlingen gavs som intravenösa dropp dag 1 i varje cykel. Deltagarna besvarade enkäter före och efter träningspassen (konditionsträning och styrketräning) som de deltog i via Phys-Can.

I det andra delarbetet undersökte vi upplevelsen av träning som utfördes under den första veckan i en behandlingscykel. Resultatet visade att energi ökade och illamående minskade efter ett träningspass oavsett om det bestod av konditionsträning eller styrketräning. Stress minskade efter styrketräning, men inte efter konditionsträning. Energin ökade mest när den var som lägst före träning medan stressen minskade mest när den var som högst före träning. Smärta rapporterades av så få deltagare att analyser inte var meningsfulla (studie II).

I det tredje delarbetet undersökte vi upplevelsen av träning vid fyra olika mättillfällen under cytostatikabehandlingen för att se om upplevelsen skiljde sig åt beroende på om det var i början eller i slutet av en behandlingscykel alternativt i början eller slutet av hela behandlingsperioden. Resultatet visade att energi ökade vid alla fyra mättillfällena och ökningen var precis som i studie II störst när nivån var som lägst före träning. Stress minskade efter träningen i början av behandlingsperioden, mest när den var som högst före träning. Illamående och smärta förändrades inte vid något av mättillfällena (studie III).

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Denna avhandling har fördjupat kunskapen avseende stillasittande och bröstcancerrisk, samt fysisk aktivitet efter diagnos och överlevnad, och skillnader i dessa samband beroende på ålder vid diagnos. Avhandlingen har också tillfört ny kunskap om upplevd energi, stress, illamående och smärta direkt efter ett träningspass under cytostatikabehandling för bröstcancer. Denna nya kunskap kan gagna patienter genom att ge ökad motivation för fysisk aktivitet och träning även när tröttheten periodvis kan kännas som ett hinder.

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Appendix 1

Onkologiska institutionen
Lunds universitet

Selected questions from

MISS Questionnaire 1 (1990-92)

10. Har Ni annars någon första grads släkting (moder, fader, syster, broder, dotter, son) som har eller har haft annan tumör- eller cancersjukdom?

37 [1] Ja

[0] Nej

Om ja, hur är Ni släkt och vilken sjukdom har släktingen drabbats av?

Släkting ______ Sjukdom ______

YRKE, UTBILDNING M M

15. Har Ni/har Ni haft förvärvsarbete?

44 [0] Nej → Fortsätt till fråga 16

[1] Ja

Ange i tur och ordning Ert/Era arbete/n från skoläldern och framåt.

Namn på företag/ arbetsplats	Egen titel	Anställn.tid år månader	Anställd åren fr o m	t o m
45 YRKE 1				
46 -"- 2				
47 -"- 3				
48 -"- 4				
49 -"- 5				
50 -"- 6				
51 -"- 7				

17. Har Ni sysslat med aktiv tävlingsidrott under uppväxt eller i vuxen ålder?

REGISTRERAS I SLUTET AV PROGRAMMET

118 [0] Nej IDROTTERNA KODAS ENLIGT LISTA

[1] Ja

Om ja, vilken idrott och när?

119 IDROTT 1 120 IDROTT 2 121 IDROTT 3

122 IDROTT 4 123 IDROTT 5

RÖKVANOR

78 34. Hur ser Era rökvanor ut?

[1] Jag har aldrig rökt

[2] Jag röker/har rökt cigaretter

[3] Jag röker/har rökt pipa eller cigarr

Hur mycket dricker Ni per månad?

ANTAL

92 starksprit CL cl

93 vin ______ cl

94 starköl ______ cl

95 folk-mellan öl ______ cl

(dricksglas ungefär 15 cl, ölflaska 33 cl, snapsglas 4 eller 6 cl)

HÖGSTA ANTALET!

HORMONELLA FÖRHÅLLANDEN

LÄGSTA

37. Vid vilken ålder fick Ni er första menstruation? ÅLDER år

LÄGSTA

38. Vid vilken ålder upphörde menstruationerna? ÅLDER år
(Besvaras endast om menstruationen upphört)

98 Upphörde menstruationen spontant? [1] ja [0] nej

99 Upphörde menstruationen efter operation? [1] ja [0] nej

39. Har Ni varit gravid?

0 [0] Nej

[1] Ja

101 Om ja, hur många gånger har Ni varit gravid? ANTAL

102 Hur många barn har Ni fött? ANTAL

103 Vid vilken ålder fick Ni Ert/Era barn? ÅLDER

110

41. Har Ni fått hormonell behandling för övergångsbesvär?

[0] Nej

[1] Ja

LUNDS UNIVERSITET

Jubileumsinstitutionen
Avdelningen för onkologi

Selected questions from

MISS Questionnaire 2 (2000-02)

12. **Har Ni förvärvsarbete?**

90 [0] Nej

[1] Ja, ange Ert nuvarande yrke 91

Namn på företag/arbetsplats Kod

IH 2001

Fysisk aktivitet

13. **Är/var Ni fysiskt aktiv, om Ni ej räknar in utövande av sport/idrott?**

De senaste åren

92 [1] aldrig [2] då och då [3] mer än en timma per vecka

I 18–30 års åldern

93 [1] aldrig [2] då och då [3] mer än en timma per vecka

I barndomen (yngre än 18 år)

94 [1] aldrig [2] då och då [3] mer än en timma per vecka

14. **Bedriver Ni förutom Er dagliga sysselsättning även regelbunden motion?**

95 [1] Nej

[2] Ja, promenad någon gång i veckan

[3] Ja, promenader flera gånger i veckan

[4] Ja, cykling, simning, motionsgymnastik, motionsdans eller dylikt en eller flera gånger i veckan

15. **Har Ni sysslat med aktiv tävlingsidrott under uppväxttiden eller i vuxen ålder?**

96 [0] Nej

[1] Ja, nämn vilken idrott och vilket år.

97 - 101 Kodas

10. **Har Ni någon första grads släkting (far, mor, syster, bror, dotter eller son) som har eller har haft annan tumör- eller cancersjukdom?**

86 [0] Nej

[1] Ja, hur är Ni släkt och vilken sjukdom har släktingen drabbats av?

Släkting 87 Bröst Sjukdom Mor = 1 Syster = 2 Dotter = 3

Släkting 88 Äggstock Sjukdom -"- -"- -"-

Rökvanor

36. Hur ser Era rökvanor ut?

134 [1] Jag har aldrig rökt

[2] Jag röker/har rökt

[3] Jag röker/har rökt pipa eller cigarr

137 Hur mycket dricker Ni per månad?

Folk/mellanöl cl

138 Starköl cl

139 Vin cl

140 Starksprit cl

(Dricksglas ungefär 15 cl, ölflaska 33 cl och snapsglas 4 cl eller 6 cl)

Hormonella förhållanden

39. Vid vilken ålder upphörde menstruationerna? *(Besvaras endast om menstruationen upphört)*

141 Ålder ....

40. Har Ni varit gravid?

144 [0] Nej

[1] Ja

145 Om ja, hur många gånger har Ni varit gravid? ....

146 Hur många barn har Ni fött? ....

47-155 Vid vilken ålder fick Ni Ert/Era barn .... Bo1a1-89 Age child 1

42. Har Ni använt/använder Ni p-piller?

168 [0] Nej

[1] Ja

Under vilka år har Ni använt p-piller och vad hette preparatet?

43. Har Ni fått hormonell behandling för övergångsbesvär?

183 [0] Nej

[1] Ja, under vilka år har Ni fått behandling och vad hette preparatet?

64 Hur lång var Ni vid födelsen .... cm [ ] Vet ej

65 Hur lång var Ni vid 18 års ålder .... cm [ ] Vet ej

66 Hur lång är Ni nu? .... cm

67 Hur mycket vägde Ni vid födelsen .... g [ ] Vet ej

68 Hur mycket vägde Ni vid 18 års ålder .... kg [ ] Vet ej

69 Hur mycket väger Ni nu .... kg

Selected questions from

MISS Questionnaire 3 (2010-12)

MEDICINSKA FAKULTETEN
Lunds universitet

REGION SKÅNE

Fysisk aktivitet

31. Är/var Ni fysiskt aktiv inom Er dagliga sysselsättning, om Ni ej räknar in utövande av sport/idrott?

De senaste åren

☐ Aldrig ☐ Då och då ☐ Mer än en timme per vecka

Vid 18-30 års ålder

☐ Aldrig ☐ Då och då ☐ Mer än en timme per vecka

I barndomen (yngre än 18 år)

☐ Aldrig ☐ Då och då ☐ Mer än en timme per vecka

32. Bedriver Ni förutom Er dagliga sysselsättning även regelbunden motion?

☐ Nej
☐ Ja, promenerar någon gång per vecka
☐ Ja, promenerar flera gånger per vecka
☐ Ja, cykling, simning, gym etc, en eller flera gånger per vecka

33. Har Ni sysslat med aktiv tävlingsidrott under uppväxttiden eller i vuxen ålder?

☐ Nej
☐ Ja, nämn vilken idrott och vilket/vilka år.

|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_| |_|_|_|_|-|_|_|_|_|

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Släkt

3. Har Ni någon förstagradssläkting (fader, moder, syster, bror, dotter eller son) som har eller haft tumör- eller cancersjukdom?

☐ Ja
☐ Nej

Om *ja*, hur är Ni släkt och vilken sjukdom har släktingen drabbats av?

Släkting: Sjukdom:

|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_| |_|_|_|_|_|_|_|_|_|_|_|_|_|

|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_| |_|_|_|_|_|_|_|_|_|_|_|_|_|

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Rökvanor

37. Hur ser Era rökvanor ut?

☐ Har aldrig rökt

☐ Röker

☐ Har rökt tidigare

Alkoholvanor

41. Hur mycket alkohol dricker Ni per månad?
(dricksglas ungefär 15 cl, ölflaska 33 cl, snapsglas 4 eller 6 cl)

Starksprit |__|__|__|__| cl

Vin |__|__|__|__| cl

Starköl |__|__|__|__| cl

Folk-mellanöl |__|__|__|__| cl

Hormonella förhållanden

42. Vid vilken ålder upphörde menstruationerna? *(Besvaras endast om menstruationen upphört.*

Ålder |__|__|

Upphörde menstruationen spontant?

☐ Ja

☐ Nej

Upphörde menstruationen efter operation?

☐ Ja

☐ Nej

44. Har Ni fått hormonell behandling för övergångsbesvär?

☐ Nej

☐ Ja, under vilka år har Ni fått behandling och vad hette preparatet?

Stress-energi formulär

Svara genom att markera rutan under det svarsalternativ som bäst motsvarar hur du känner dig **just nu**. Fyll i snabbt utan att tänka efter alltför mycket.

	Inte alls 0	Knappast alls 1	Något 2	Ganska 3	Mycket 4	Mycket mycket 5
Avslappnad	☐	☐	☐	☐	☐	☐
Aktiv	☐	☐	☐	☐	☐	☐
Spänd	☐	☐	☐	☐	☐	☐
Slö	☐	☐	☐	☐	☐	☐
Stressad	☐	☐	☐	☐	☐	☐
Energisk	☐	☐	☐	☐	☐	☐
Ineffektiv	☐	☐	☐	☐	☐	☐
Avspänd	☐	☐	☐	☐	☐	☐
Skärpt	☐	☐	☐	☐	☐	☐
Pressad	☐	☐	☐	☐	☐	☐
Passiv	☐	☐	☐	☐	☐	☐
Lugn	☐	☐	☐	☐	☐	☐

Frågor om illamående och smärta

Markera på skalan hur det är **just nu**

Illamående:

Inget illamående | Värsta tänkbara illamående

Kräkning

- ☐ Ja
- ☐ Nej

Markera på skalan hur det är **just nu**

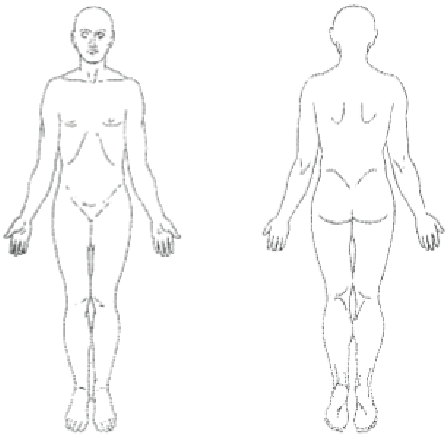
Smärta:

Ingen smärta | Värsta tänkbara smärta

Skugga på figuren de områden av kroppen där Du upplever smärta. Markera med X det område som gör mest ont. Markera även vilken typ av smärta Du besväras av på de olika ställena på kroppen.

Smärtans karaktär är:

M = Molande
T = Tryckande
I = Ilande
P = Pulserande
S = Stickande
H = Huggande
B = Brännande, svidande
D = Domningar
Ö = Övrigt



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Risk, survival and perceived energy

Anna Johnsson has spent most of her working career in oncology, helping patients with cancer in different ways. She started off in the 1980s as a radiotherapy nurse. In the mid 1990s she shifted direction and became a physiotherapist. Since 2000 she has worked at the Cancer Rehabilitation Unit, Department of Oncology at Skåne University Hospital in Lund, where her main focus in recent years has been to study and to promote physical activity in patients with cancer.

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Department of Clinical Sciences, Lund
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