Exercise for women receiving adjuvant therapy of breast-cancer: a systematic review

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Abstract

Exercise has become an integral part of breast cancer rehabilitation. A growing body of evidence shows health benefits such as increased physical fitness and reduced fatigue through exercise, not only after breast cancer treatment has finished, but during treatment as well.

The aim of this systematic review was to determine the effectiveness of aerobic and resistance exercise interventions during adjuvant treatment of breast cancer with respect to physical functioning and health-related physical fitness, among other important health outcomes. The findings of controlled trial studies of aerobic, strength, and combined exercise interventions among women undergoing adjuvant treatment of breast cancer were critically evaluated and summarised. The potential harm associated with exercise in this vulnerable period was also examined and discussed. This review was conducted in co-operation with the Cochrane Breast Cancer Group, and followed the rigorous review methodology of the Cochrane Collaboration.

Results indeed indicate that important physical and mental health outcomes, such as health-related physical fitness, fatigue, anxiety, and depression, can be improved through regular exercise training. There is no evidence currently in the literature showing an association of moderate physical exercise training during adjuvant treatment of breast cancer with increased risk of injuries, lymphedema, or other harm. Thus, the results of this systematic review support recommending and encouraging women undergoing adjuvant treatment of breast cancer to exercise.

If the benefits of participation in exercise programmes are to be preserved over the course of cancer survivorship, sustained physical exercise is essential. Exercise adherence thus plays a vital role in maintaining the benefits associated with exercise. The review concludes that understanding the determinants of exercise adherence and the barriers to participation is important. Applying strategies for behaviour change to individual situations can help in developing and maintaining the habits associated with a healthy lifestyle. Besides developing the evidence base through further research, it is recommended that further activities should focus as well on how research findings can be translated in to public health practice.

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List of abbreviations, acronyms and units of measurement

ACSM	American College of Sports Medicine
AET	Aerobic exercise training
ANOVA	Analysis of variance
BDI	Beck Depression Inventory
%BF	Body fat percentage
BMD	Bone mineral density
CACE	Complier-Average Causal Effect
CBCG	Cochrane Breast Cancer Group
CES-D	Center for Epidemiological Studies – Depression Scale
CBCSR	Cochrane Breast Cancer Group Specialised Register
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CONFSCI	Conference Papers Index
CONSORT	CONsolidated Standards of Reporting Trials
DBS	German Federation for Disabled Sports, Deutscher Behindertensportverband
df	Degrees of freedom
DOSB	German Sports Federation, Deutscher Olympischer Sportbund
FACT	Functional Assessment of Cancer Therapy instrument
FACT–An	Functional assessment of cancer therapy – Anemia scale
FACT–B	Functional assessment of cancer therapy – Breast cancer scale
FACT–ES	Functional assessment of cancer therapy – Endocrine symptom scale
FACT–F	Functional assessment of cancer therapy – Fatigue
FACT–G	Functional assessment of cancer therapy – General scale
g	Hedge's g
HR_{max}	Maximum heart rate
$HR_{reserve}$	Heart rate reserve
ICC	Intra-class correlation coefficient
I^2	Degree of inconsistency across studies in meta-analysis
IQR	Interquartile range
LBM	Lean body mass
M	Mean
Min	minutes
12 MWT	12-minute walk test
Mo	months
NA	Negative affects
NCCN	National Comprehensive Cancer Network
NKCA	Natural Killer Cytotoxic Activity
PFS	Piper Fatigue Scale

POMS	Profile of mood states
PA	Positive affects
PANAS	Positive and Negative Affect Schedule
PSQI	Pittsburgh Sleep Quality Index
Q	Cochran's Q
RCT	Randomised controlled trial
RET	Resistance exercise training
RevMan	RevMan Analyses (Computer Programme)
1-RM	One repetition maximum
RPE	Rating of Perceived Exertion
r-PFS	Revised Piper Fatigue Scale
RR	Relative Risk
SAS	Symptom assessment scale
SD	Standard deviation
SD	Self-directed exercise training
$SE_{m_1-m_2}$	Standard error of the difference in means
SF-36	Medical Outcomes Study 36-Item Short Form
SGB IX	Book 9 of the German social code, Sozialgesetzbuch
SIGLE	System for Information on Grey Literature
SMD	Standardised mean difference
SPSS	Statistical Product and Service Solutions
STAI	Spielberger State Anxiety Inventory
SU	Supervised exercise training
TMD	Total mood disturbance
TNM	Tumour node metastasis system
VAS	Visual analogue scale
VO_2max	Maximal oxygen consumption
WHO	World Health Organization
WHOQOL	World Health Organization Quality of Life project
Wk	weeks
WISE	Women International Space Simulation for Exploration
WMD	Weighted mean difference
Yr	years

Executive Summary

Breast cancer remains an important public health problem in Europe and the ageing of the European population will cause cancer incidence data to continue to increase. The principal treatments for breast cancer are surgery, chemotherapy, radiotherapy, and hormonal therapy, and evidence suggests that these are very effective at improving disease-free and overall survival. However, these therapies can compromise women's physical, mental, or social health. Evidence continues to accumulate on the positive impact of exercise on women's physical or mental health and on quality of life improvements during treatment. The literature suggests, however, that many women who exercised prior to being diagnosed with breast cancer do not continue to exercise during their treatment. Over time, prolonged inactivity leads to decreased muscle strength, progressive loss of physical functioning and a decreased ability to perform the activities of daily living. Women, clinicians, and health policy makers need reliable, up-to-date information from controlled trials on the benefits and potential harm from exercise during adjuvant cancer treatment, to make evidence-based decisions about interventions. At present, a diverse range of primary studies exists in the scientific literature regarding the role of exercise during treatment for breast cancer, and this systematic review seeks to summarise this evidence to date.

Methods of the systematic review

This review was conducted in co-operation with the Cochrane Breast Cancer Group, and followed the rigorous review methodology of the Cochrane Collaboration. The research question is: should women undergoing adjuvant treatment of breast cancer be encouraged to exercise? Study identification was based on a comprehensive search strategy with a variety of commonly used electronic databases and manual search methods. Inclusion and exclusion criteria were developed in accordance with the review question, and were defined in terms of the population, interventions, outcomes, and the study designs of interest. Trials were included that reported on women receiving adjuvant treatment (chemotherapy, hormonal therapy, or radiotherapy) for breast cancer. Breast cancer was restricted to stages 0-III, and trials which included women with stage IV breast cancer (i.e., with distant metastasis) were excluded from the review. Trials that included women who had completed adjuvant cancer treatment, or who were being treated for other cancers were excluded. Trials with an intervention consisting of aerobic or resistance exercise were included, but those that examined complex exercise interventions (e.g., a program of exercise and diet, or a program of exercise and behavioural therapy) were excluded. Trials in which exercise interventions were restricted to selected body functions only (e.g., arm mobility) were also excluded. Trials were included that employed at least one of the following outcome measures: physical functioning, health-related physical fitness, symptom experience, biological or physiological outcomes, mental health, health-related quality of life and harm. Both randomised con-

trolled trials and non-randomised controlled trials were eligible for inclusion in the review. No language restrictions were applied. All studies were critically and systematically evaluated with respect to their methodological quality (i.e., design, implementation and analysis), to determine the extent to which the results were reliable. The exercise intervention was evaluated separately regarding its potential to provide an adequate training stimulus. Data from included trials were extracted following a standardised format, and then combined using meta-analysis; this is a statistical procedure that integrates the results of several independent studies to give one overall estimate of intervention effects. A random-effects model was chosen for the meta-analysis since heterogeneity between trials was expected.

In order to answer the research question, whether women receiving adjuvant treatment of breast cancer should be encouraged to exercise, the benefit of exercise has to outweigh the potential harm. This review aimed to evaluate both benefits and harms, and has subsequently required a more complex design, using different search strategies and eligibility criteria for studies of harm to handle different sets of studies for various outcomes. Study designs eligible for assessing potential harm were (randomised) controlled trials to identify well-recognised and easily detectable harmful effects. The study of harm had to be a key trial objective, which means that the harm had to be a major primary or secondary outcome of trials to be included. All studies were eligible that investigated harmful effects in the rehabilitation of breast cancer, either *during* or *after* adjuvant cancer treatment.

Main results

Fifteen studies that had assessed the benefits of aerobic or resistance exercise training (or both) on physical and mental health outcomes in women during adjuvant treatment for early breast cancer were included in the review. The results were based on 1,042 participants from these 15 included studies. These studies were predominantly performed in North America (United States and Canada); only two of these trials, a pilot study followed by a subsequent RCT, were implemented in Europe. Sample sizes across trials ranged from 10 to 242 participants; only recently have large-scale trials of 100 participants or more emerged in the literature, with two of these including more than 200 participants.

With respect to health-related physical fitness, meta-analyses were performed for cardiorespiratory fitness, muscular fitness (strength) and body composition. Exercise was shown to be an effective intervention for improving cardiorespiratory fitness in comparison to usual care (SMD 0.54; 95% CI 0.32 to 0.77), even during breast cancer treatment. This medium effect was based on the results from eight studies with a total of 709 participants. Pooling the data from four studies, with a total of 328 participants, also yielded a medium effect size for a statistically signifi-

cant increase in strength observed in exercising participants, compared to controls (SMD 0.42; 95% CI 0.06 to 0.78). Body composition outcomes, which describe the relative amounts of fat and lean tissue, were pooled from four trials (n=414). Exercise was more effective than usual care in preventing unfavourable changes in body composition (SMD -0.29; 95% CI -0.55 to -0.03)). Self-reported physical functioning was measured in three studies but a meta-analysis for this outcome was not performed due to limited available data. Consequently, this review is unable to make any conclusions about the impact of exercise in self-reported physical functioning. Regarding treatment-related symptoms, a meta-analysis for fatigue was undertaken. Pooling the data from seven studies (n=714) that provided adequate data for fatigue showed that exercise was more effective than usual care in reducing feelings of fatigue (SMD -0.17; 95% CI -0.32 to -0.02), with the SMD indicating a small effect size. Bone health (bone mineral density) was the primary outcome measure in one trial which reported that aerobic exercise preserved lumbar spine bone mineral density better than usual care alone. For mental health outcomes, the effect sizes were small. Pooling the effects of three trials yielded a reduction in cancer-related depression in the exercise groups compared to controls (n=443) (SMD -0.24; 95% CI -0.43 to -0.04). Results for anxiety suggested a small, but non-significant effect of exercise (n=269) (SMD -0.25; 95% CI -0.54 to 0.04) from two studies.

Four studies were included in this review that assessed harm (lymphedema and injuries). Only one of these studies assessed potential harm (i.e., lymphedema) *during* adjuvant treatment of breast cancer. The other three studies examined harm in the post-adjuvant setting. No increases in injury rates, lymphedema or other harm were revealed in the exercise groups compared to non-exercising control groups. Thus, preliminary evidence from exercise intervention studies indicates that there is no increased risk of harm associated with exercise.

Conclusions

Exercise during adjuvant treatment for breast cancer can be regarded as a supportive self-care intervention; exercise results in improved physical fitness and thus the capacity for performing activities of daily life, which may otherwise be impaired due to inactivity during treatment. Furthermore, small improvements in fatigue, depression and anxiety can be observed.

The present available evidence regarding safety of exercise during adjuvant breast cancer treatment is limited. However, safety concerns are highly relevant to exercise promotion in the period of adjuvant cancer treatment because uncertainty about the safety of engaging in exercise may act as a barrier to prescribing exercise despite the growing body of evidence which supports the benefits of moderate intensity exercise during breast cancer treatment. It is also possible that regular exercisers could be discouraged from being physically active during and after breast can-

cer treatment by doctors, other health professionals and their families. Therefore, safety needs to be systematically addressed in future exercise studies.

Since exercise interventions (for sedentary participants) require behaviour change, strategies for behaviour change should underpin these interventions. Theory-based interventions are important in the development and promotion of healthy physical activity habits since theories are a generalised and careful interpreted systematic summary of empirical evidence related to behaviour change and thus, application of theory should improve the likelihood of effectiveness of exercise interventions.

What is known about exercise in cancer patients has been derived largely from research on middle-aged women. Only one study has examined exercise during adjuvant therapy in older breast cancer patients. It is unclear whether older women derive similar benefits from exercise. Possibly, they have lower exercise participation rates and more difficulty adhering to an exercise program. Exercise during adjuvant treatment should be approached from an aging perspective as well.

The included studies provide important guidance to cancer care clinicians as well as those who operate community-based health and fitness programs. Exercise is becoming increasingly recognised as beneficial to cancer patients during treatment. Of necessity, these studies were predominantly conducted as part of academic oncology care programs. Many breast cancer patients, however, approach community-based fitness centres for health promotion training. Finally, existing research findings have to be used to develop evidence-based guidelines or prescriptions for cancer patients. It is recommended that exercise programs for breast cancer patients need to be individualized. However, there is insufficient evidence to allow for the identification of factors that have to be considered in the development of individualized exercise programs. There is a need for an evidence-based set of exercise guidelines to be developed. The exercise rehabilitation programs established in Germany for women who have been treated for breast cancer is an example of how exercise could be offered to breast cancer patients during treatment within a health care context. Germany has embraced the importance of regular exercise in the rehabilitation of cancer patients and may provide a model that could be adopted in other countries.

1 Introduction

Breast cancer is a major public health burden, both in Germany and worldwide. Breast cancer is by far the most common cancer of women, with an estimated 1.15 million new cases worldwide in 2002 (Parkin et al. 2005). Breast cancer incidence and mortality vary considerably by world region. More than half of the cases are in industrialized countries—about 361,000 in Europe and 230,000 in North America 2002 (Parkin et al. 2005). In general, the incidence is high (greater than 80 per 100,000) in developed regions of the world and low (less than 30 per 100,000) in developing regions, although this latter rate is increasing. Variability in mortality rates is much lower (approximately 6-23 per 100,000) because of the more favourable chances of surviving breast cancer in the high-incidence developed regions (Parkin et al. 2005). There was a trend of increasing breast cancer incidence almost everywhere, partly due to increases in risk factors such as decreased childbearing and breast-feeding, increased exogenous hormone exposure, and detrimental dietary and lifestyle changes, such as obesity and reduced physical activity. However, between 2001 and 2004, incidence rates of invasive breast cancer declined more than 8% in the United States, with the greatest drops observed for estrogen receptor-positive tumours among women aged 50 years and over (Ravdin et al. 2007). Patterns of falling incidence reflect a major influence of reductions in hormone therapy use after the early termination of the Women's Health Initiative trial on postmenopausal hormone therapy (Hausauer et al. 2009). Also reductions in the pool of previously unscreened women due to the saturation of mammographic screening programs could have lowered incidence (Hausauer et al. 2009). Breast cancer-related mortality is now decreasing in many high-risk countries due to a combination of intensified early detection efforts and advances in treatment (Parkin and Fernandez 2006).

In Germany, over 57,000 women are currently diagnosed with breast cancer every year. Breast cancer accounts for well over a quarter (27.8%) of all cancers among women. The average age at onset is 63, six years below the average for all cancer sites (Batzler et al. 2008). Overall, breast cancer incidence in Germany has been rising continuously since 1980, while the mortality rate has been falling slightly since the mid-1990s (Batzler et al. 2008) but it remains unclear whether this decrease is due to early diagnosis or improved treatment (Giersiepen et al. 2005).

Being diagnosed with breast cancer usually means undergoing significant and prolonged medical treatments. Although the benefit of current treatments for breast cancer is clear, namely improved survival, treatment-related adverse effects are of considerable importance. In the course of diagnosis and treatment of breast cancer, women are likely to experience situations that cause considerable distress. Not only clinical factors (e.g., type of treatment, presence of pain) and social factors (e.g., availability of support from friends and family) contribute to the distress, but

also role changes may be needed due to the potential inability to continue work and dependency on others; life goals may be disrupted or life plans may need to be modified facing a life-threatening illness. For women, issues related to body image are crucial: body image for women includes feeling feminine and attractive or enjoying the body as a symbol of social expression. Breasts are a symbol of femininity and sexuality, and thus a woman with breast cancer may feel that her body has betrayed her, or the loss of a breast can feel like the end of being female. Women with breast cancer do not only have to cope with changes in physical appearance; often they no longer perceive their body as an intact, properly functioning entity. Breast cancer does not just lead to surgery scars: a loss of feeling in the affected breast may be a further consequence of surgery, radiotherapy can lead to redness and soreness on the affected area and chemotherapy often causes hair loss, weight gain, and premature menopause. Experiencing these types of body changes can be especially challenging for younger women, who may be bothered more by these changes than older women. Breast cancer can result in a subsequent dissatisfaction with appearance, perceived loss of femininity, and body integrity, reluctance to look at oneself naked, and feeling less sexually attractive. A woman dealing with the effects of breast cancer may begin to avoid intimacy, dress alone or in the dark, or even minimise the time that she spends bathing. Such concerns about body image can undermine women as they try to adjust. Altogether, diagnosis and treatment of breast cancer affects women physically as well as psychologically. There is a need for adequate attention to promoting functioning and psychological well-being among women receiving adjuvant treatment of breast cancer.

Medical treatment focuses on beating cancer, but women whose lives are affected by breast cancer have to find how to live with it and what works best for them. Health promotion strategies that place a focus on the restoration of physical, functional, emotional, and social aspects of health can support women to realign. Health promotion strategies become imperative in the face of the widespread use of adjuvant treatment with its increase in time, complexity and dose-intensity, and the steadily decreasing mortality rates from breast cancer, with a five-year survival rate from breast cancer of 79% in Germany (Bertz et al. 2006). In particular, exercise interventions are increasingly prominent in the nursing, medical, and sports science literature that represents a growing body of knowledge, which suggests numerous benefits of regular physical exercise for breast cancer patients. Furthermore, the many health and fitness benefits (e.g., physiological, metabolic, psychological) associated with regular exercise, both in the general population and in clinical populations, support the rationale advanced for exercise interventions in the population of women receiving adjuvant treatment of breast cancer. According to the United States Surgeon General's report on physical activity and health (United States Department of Health and Human Services 1996), people of all ages, both male and female, benefit from regular exer-

cise. The extent and strength of the evidence linking physical activity to many health improvements is impressive: amongst others, physical activity reduces the risk of developing diabetes, hypertension, and colon cancer; it enhances mental health, fosters health-related physical fitness, and helps maintain function and preserve independence in older adults (United States Department of Health and Human Services 1996). It seems plausible that breast cancer patients as well could maintain function and improve the quality of their lives through a practice of moderate physical activity.

The overall question that guided the implementation of this research project was:

Should women, who are undergoing adjuvant treatment of breast cancer, be recommended physical exercise?

A systematic review appeared to provide an adequate methodology for this research project. The Cochrane Breast Cancer Group (CBCG) was approached and provided inputs and peer review for this research project. Accordingly, this systematic review of exercise for women receiving adjuvant therapy of breast cancer was implemented as a Cochrane review, pursuing the respective formal, methodological, and procedural features of a Cochrane review. The first result of the cooperation with the CBCG was that an excerpt of this research project has already been published in the Cochrane Library (Markes et al. 2006).

This systematic review followed three objectives. The primary objective was to assess the effects of a structured exercise training program on the physical functioning and health-related physical fitness in the target group of women, who are undergoing adjuvant treatment of breast cancer. A secondary objective was to determine the effect of exercise training on secondary outcome measures such as treatment-related symptoms, biological and physiological problems, mental health, and health-related quality of life. Given the potential for harmful effects of exercise interventions in this vulnerable target group, a final objective was to identify and assess harm associated with exercise during adjuvant treatment of breast cancer.

2 Setting the context

2.1 Logic model of the review

This systematic review of exercise for women receiving adjuvant treatment of breast cancer started with a logic model in order to guide the review process and to ensure that the review would yield relevant, useful information (Figure 1). Basically, a logic model provides a visual representation of the conceptualisation of the overall topic area; it describes and illustrates expected relationships between pre-intervention conditions, activities and short- and long-term outcomes. Logic models show the program logic and can help review authors understanding how the program works. Logic models are also useful for identifying outcomes that need to be considered in the systematic review and thus can also aid in the design of a strategy for synthesizing data across studies.

The logic model of this review model described the linkage between planned activities and their expected outcomes. The following elements are acknowledged for and further outlined in the following paragraphs:

- Problems that require intervention
- Inputs and resources for a successful exercise program
- Activities that have to be accomplished if access to those resources is given
- Outcomes that can be expected if exercise programs are delivered as planned.

The elements of the logic model also work as a framework for the information regarding the context of the review.

Problems

Being diagnosed with breast cancer usually means undergoing a series of diverse treatments (surgery, radiotherapy, systemic chemotherapy, and hormonal treatment). These treatments often have a persistent deleterious effect on a woman's health status, physical and emotional well-being, and health lifestyle behaviours. Breast cancer rehabilitation programs are often based on psychotherapy or social support. Such interventions do not usually deal with the physical problems faced by women receiving adjuvant treatment of breast cancer, such as fatigue, loss of physical functioning, or weight gain. Exercise is a potential intervention that may both improve health status and boost breast cancer patients' well-being.

Inputs and resources

Implementing an exercise program requires sustainable financing, based on diverse sources of funding and affordable fees. Qualified instructors, together with facilities for exercise that ac-

commodate and encourage participation, are equally important. Social marketing, networking with a varied group of partners and cooperation with health care providers provide a basis for recruiting participants and for delivering exercise programs (implementation of exercise classes). Further, it is essential that certain management skills and resources are committed to the program.

Outputs and activities

Based on these resources, an exercise program providing ongoing training can be established for breast cancer patients. Exercise instructors are faced with the challenge to improve exercise habits through appropriate exercise prescriptions and monitoring. Women receiving adjuvant treatment of breast cancer may require further physical evaluation, i.e., pre-participation stress testing, before starting the exercise program. Furthermore, specific instruction should be given to these women concerning the type, frequency, intensity, and duration of exercise. A variety of safe, effective, and attractive programs – with a range of offerings, including strength and aerobic endurance training, flexibility, and balance elements – can facilitate the development of regular exercise habits. Unfortunately, efforts to help participants adopt an exercise program are often unsuccessful. This is why a variety of methods and tools need to be employed to reach participants – especially those who have been sedentary. Motivation to exercise can be improved and attrition minimised, if program activities are guided through behaviour change strategies to support participation and personal commitment (e.g., pre-activity exercise counselling, individual goal setting sessions, and telephone or mail follow-up of women with repeated absences).

Outcomes

There is a chain of outcomes, since not all outcomes will occur at the same time. Some outcomes must occur before the achievement of other outcomes and program goals. It is expected that the following outcomes will occur over the short-, intermediate, and long-term as a result of the exercise intervention. First, exercise programming, together with exercise counselling and prescription, allows breast cancer patients to change the way they perceive physical activity and exercise during breast cancer treatment. So, as a *short-term health promotion outcome*, breast cancer patients are expected to recognise that exercise is a safe, practical intervention that is effective in combating treatment-related adverse effects and which can increase quality of life and health-related fitness. Exercise self-efficacy, i.e., the belief and conviction that one can successfully exercise, is expected to increase and the intent to regularly exercise should arise. "Health promotion outcomes" such as knowledge about exercise and its benefits or exercise self-efficacy (Nutbeam 2000) are the most immediate outcomes: they represent those personal, social and structural factors that can be modified in order to change intermediate health outcomes. *Intermediate health outcomes* (Nutbeam 2000) are changes in the determinants of health, notably changes in lifestyle

such as exercise patterns. In the long-term regular exercise improves *health outcomes* such as physical functioning, health-related fitness and quality of life. Exercise-induced harms, such as musculoskeletal injuries or cardiovascular complications during exercise, are generally expected to be under control due to appropriate conditioning and the gradual increase in duration and intensity of exercise, together with exercise testing, prior to engaging in a regular exercise program.

Conclusions for evaluating exercise programs

Inputs and outputs on the program level can be evaluated when focusing on structure and processes. Process evaluation, especially, could provide crucial information on participation rates and program implementation (e.g., Were all sessions delivered? Did the program offer exercise options with instruction in proper technique, and provide qualified supervision?). Such information would be crucial because a program can fail either because the intervention was not well suited to the problems or because the intervention was not implemented as planned. However, these questions are not treated in this review because primary studies only dealt with outcome evaluation. The focus of this review is the evaluation of health outcomes.

SITUATION

Women receiving treatment of breast cancer often experience reductions in health-related physical fitness and quality of life. Exercise is an intervention that may improve these problems after diagnosis of breast cancer.

INPUTS	OUTPUTS		OUTCOMES – IMPACT		
	Activities	Participation	Short	Medium	Long-term
	Exercise program		**Health promotion outcomes**	**Intermediate health outcomes**	**Health outcomes**
➢ Organisational commitment of leadership, resources and staff ➢ Networking ➢ Social marketing ➢ Sustainable financing ➢ Qualified/ certified instructors ➢ Facilities for physical activity	➢ Exercise testing ➢ Exercise prescription ➢ Exercise facilitation or exercise counselling ➢ Application of psychological and behavioural theories to effect behaviour change ➢ Addressing exercise barriers and facilitators ➢ Continuous exercise training	➢ Sedentary women receiving adjuvant treatment of breast cancer	Increase in: ➢ Knowledge about exercise during cancer treatment ➢ Attitudes, behavioural intentions: planning participation ➢ Exercise self-efficacy	Increase in: ➢ Initial adoption of exercise ➢ Continued participation or relapse/ resumption ➢ Exercise intensity, frequency and duration of sessions as prescribed	Increase in: ➢ Physical functioning ➢ Health-related fitness ➢ Health-related quality of life ➢ Monitoring safety: No Harm

Figure 1: Logic model for evaluation of exercise interventions

2.2 Breast cancer treatment

The mainstay of breast cancer treatment is surgery with possible adjuvant local and systemic therapy. One important approach for the selection of adjuvant treatment is based on cancer staging. The global standard in cancer staging is the tumour-node-metastasis (TNM) system which represents an attempt to classify malignant tumours based on the major morphological attributes which are thought to influence disease prognosis, namely: size of the primary tumour (T), presence and extent of regional lymph node involvement (N), and presence of distant metastases (M) (Singletary and Connolly 2006). Breast cancer is diagnosed as having progressed to any of four stages: carcinoma in situ (stage 0), early stage breast cancer (stages I, II), locally advanced breast cancer (stage III), and metastatic breast cancer (stage IV).

Depending on the staging and type of the tumour, possibly just a lumpectomy (removal of the lump) or mastectomy (surgical removal of the entire breast) is needed. Although women with lumpectomy do not have overt metastases at the time of staging, they remain at risk of local recurrence and of metastatic spread: undetected micrometastatic deposits of the disease may remain, either locally or at distant sites, that eventually develop into clinically detectable recurrence. These deposits can be treated with local or systemic adjuvant therapies.

Radiotherapy is delivered as an adjuvant local therapy; it is an essential component of breast conserving therapy and is usually given after surgery has been performed. Radiotherapy consists of the use of high powered X-rays that precisely target the area needing treatment. X-rays work by eliminating the microscopic cancer cells that may remain near the area where the tumour was removed, either in the chest wall or in regional lymph nodes. Evidence indicates a significant decrease in local recurrence rates for patients receiving radiotherapy (Poortmans 2007). Radiotherapy administered to the remaining breast tissue is typically delivered over a total duration of 6 weeks.

Systemic treatments include chemotherapy and hormonal therapy. Chemotherapy refers to the use of cytotoxic drugs, which affect either cell division or DNA-synthesis and function. Chemotherapy is designed to eradicate microscopic deposits of cancer cells that may have spread from the primary breast cancer. It has been shown to substantially improve the long-term relapse-free and overall survival in premenopausal and postmenopausal women with both node-positive and node-negative disease (Early Breast Cancer Trialists' Collaborative Group 2005). Combination chemotherapy involves treating a patient with a number of different drugs simultaneously which differ in their mechanism and side effects. There are several different chemotherapy regimens that may be used. Polychemotherapy regimens commonly comprise four to six cycles which are delivered over four to six months. Most chemotherapy is delivered intravenously, although some

agents are administered orally. It may be given on either an inpatient or an outpatient basis depending on the patient, the cancer, the stage of cancer, the type of chemotherapy, and the dosage.

Breast cancer may be endocrine-dependant needing oestrogen for proliferation and is thus expected to be responsive to endocrine treatment. Patients with oestrogen receptor-positive tumours typically receive a hormonal treatment after chemotherapy is completed. The goal of hormonal therapy is to prevent the stimulation of breast cancer cells by oestrogen. Oestrogen deprivation can be achieved either by anti-oestrogens (e.g., tamoxifen) that bind to the oestrogen receptor and thus block the receptors or by suppression of oestrogen synthesis (e.g., aromatase inhibitors). Hormonal therapy for hormone receptor-positive breast cancer is generally delivered over five years.

In sum, cancer treatments such as surgery, radiotherapy, chemotherapy, and hormonal therapy reduce both the risk of relapse and death and are well-established treatments. They are offered to a large proportion of patients (Kuerer et al. 2004, Chia et al. 2005, Early Breast Cancer Trialists' Collaborative Group 2005).

Treatment options depending on diagnosis are summarised in the breast cancer treatment overview (Figure 2).

2.3 Rationale for exercise interventions

During primary treatment of breast cancer, a broad range of treatment-related adverse effects occur which compromise physical health, mental health, social health, and subsequently impact quality of life. In this chapter, it is described how primary treatment of breast cancer interferes with patient-reported and objective health outcomes. Additionally, for each group of health outcomes, the rationale for exercise intervention is depicted.

2.3.1 Health-related physical fitness

Physical fitness has been defined in different ways; however it is generally accepted to define physical fitness as the "ability to carry out daily tasks with vigour and alertness, without undue fatigue, and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies" (United States Department of Health and Human Services 1996). Physical fitness thus includes cardiorespiratory endurance, skeletal muscular endurance, skeletal muscular strength, skeletal muscular power, speed, flexibility, agility, balance, reaction time, and body composition (United States Department of Health and Human Services 1996). Because these attributes differ in their importance to athletic performance as compared to health, a distinction has been made between performance-related fitness and health-related fitness (Caspersen et al. 1985).

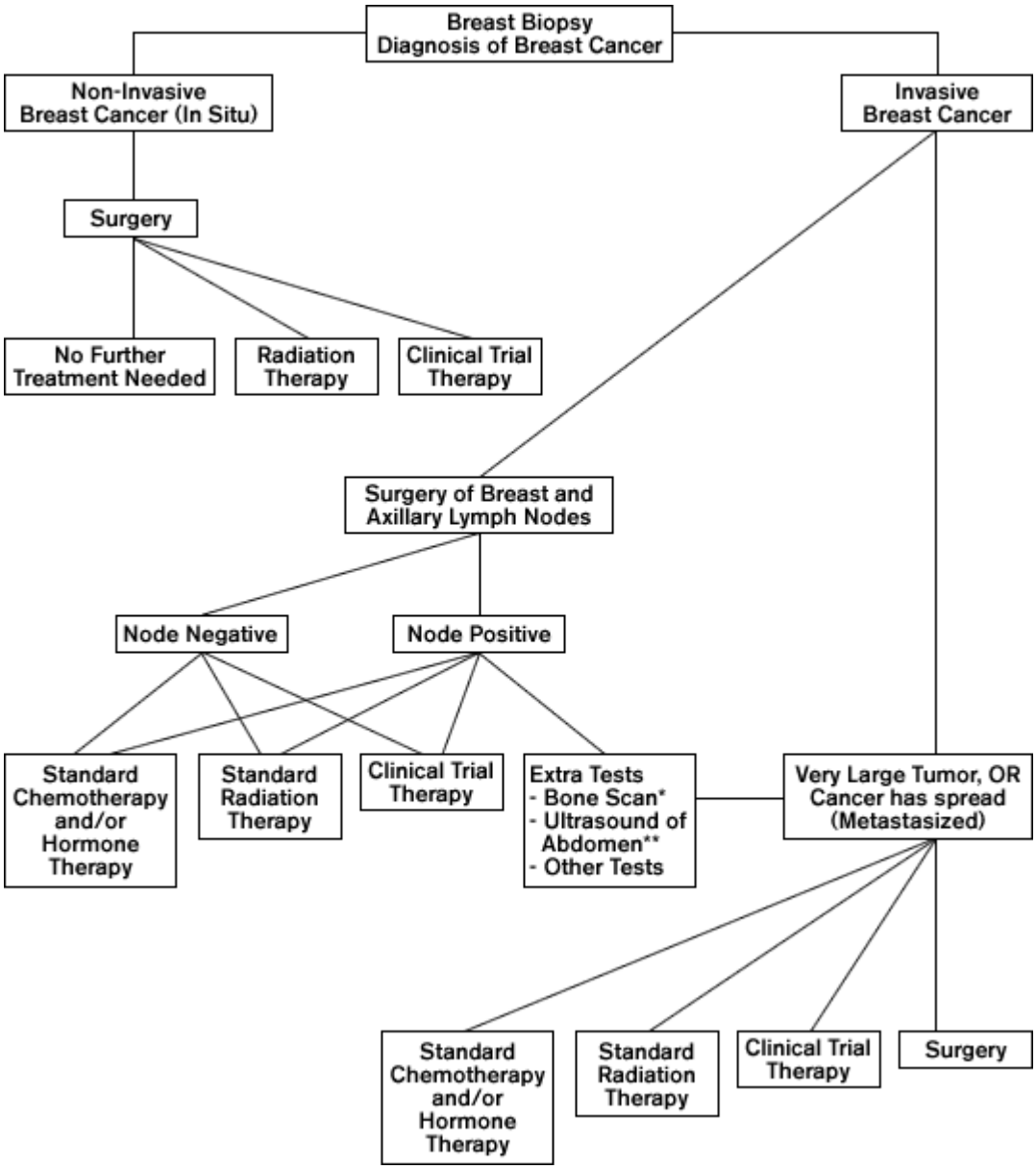

Figure 2: Breast cancer treatment overview

(Alberta Breast Cancer Program 2003)

Health-related fitness includes cardiorespiratory fitness, muscular strength and endurance, body composition, and flexibility. Skill-related components of physical fitness such as balance or coordination are important pre-conditions for safe exercise. Balance for example relates to the "maintenance of equilibrium while stationary or moving" (United States Department of Health and Human Services 1996) and thus is an important skill for preventing falls. Coordination relates to the "ability to use the senses, such as sight and hearing, together with body parts in performing motor tasks smoothly and accurately" (United States Department of Health and Human Services 1996); a lack of coordination could be perceived as a substantial barrier for exercise.

In women receiving adjuvant treatment of breast cancer, physical functioning is particularly important, as the prevalence of physical disability increases with age and can further be enhanced during debilitating treatments. Adequate physical function plays a major role in maintaining participation. Declining physical functioning contributes to the need of assistance in performing basic tasks and may have various social consequences, at its worst permanent incapacity for work or institutionalisation.

There is a progressive relationship between physical fitness, functional performance, and participation in life activities (Rikli and Jones 1997). Participation in life activities (e.g., personal care, shopping, and travelling) requires the ability to perform functions such as walking and stair climbing, that require a certain level of physical fitness (Figure 3). Exercise could improve physical functioning by increasing physical fitness.

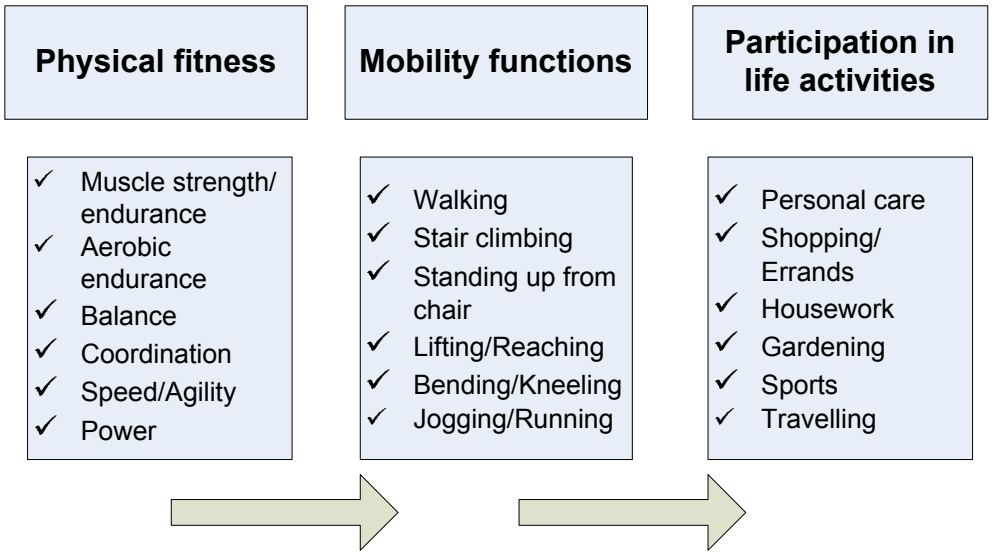

Figure 3: A functional performance framework
(adopted from Rikli and Jones 1997)

Physical functioning can be measured through (1) objective mobility using performance tests such as sit-to-stand-to-sit test, lift-and-reach test; (2) perceived mobility using self-report questionnaires, and (3) participation in life activities using self-report questionnaires as well (Bennett et al. 2006). Performance-based methods measure what the patient *can* do, and self-reports measure what the woman *thinks* she can do (Terwee et al. 2006). While self-report questionnaires have the advantages of being easier to use, less time-consuming, less of a burden to patients, and are not influenced by observer bias, performance-based methods are described as being less influenced by psychological factors such as expectations and beliefs, cognitive impairments, culture, language, and education level (Terwee et al. 2006). Furthermore, it has been suggested that performance-based measures may identify deficits in physical functioning before they can be identified by self-report (Bennett et al. 2006, Terwee et al. 2006).

2.3.1.1 Cardiorespiratory fitness

Cardiorespiratory fitness is a health-related component of physical fitness that relates to the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity (United States Department of Health and Human Services 1996). Cardiorespiratory endurance can be severely impaired as a consequence of breast cancer and its treatment through several pathological mechanisms. To begin with, chemotherapy can damage bone marrow and subsequently impair the production of erythrocytes, so that the resulting anaemia leads to a compromised oxygen saturation of blood (Dimeo 2001). Then cardiotoxic chemotherapeutic agents such as anthracyclines and cyclophosphamide can cause a reduction of cardiac output (Dimeo 2001). There are other functional and anatomic changes due to cancer treatment that may affect oxygen transport and utilisation, such as alterations of the bronchial tree, lung and plasma volume, alveolar surface, pulmonary perfusion, and concentration of oxidative enzymes (Dimeo 2001).

As a consequence of these treatment-related changes, more cardiac and respiratory work is needed to sustain an adequate oxygen supply to the cells during rest and physical activity. However, the oxygen transport systems can be overwhelmed even by normal daily activities such as climbing stairs or housekeeping. Sedentary habits and bed rest aggravate this further with reduced muscle blood flow, red cell volume, capillarization and oxidative enzymes (Convertino et al. 1997) causing a shift away from aerobic metabolism to anaerobic glycolysis. Anaerobic glycolysis is a less effective means of energy production; moreover, anaerobic glycolysis contributes to metabolic acidosis since lactic acid is one of its end products (Dimeo 2001). The combined burden of increased heart rate and respiratory work, shift of aerobic to anaerobic metabolism, and metabolic acidosis can lead to the inability to carry out any intense physical effort.

Evidence suggests that healthy older adults elicit the same 10% to 30% increases in maximum oxygen consumption with prolonged endurance exercise training as young adults (Balady et al. 2000), which may be true for women undergoing adjuvant treatment of breast cancer as well. This increase in maximal oxygen uptake in older adults is a function of training intensity, with light-intensity training eliciting minimal or no changes (Balady et al. 2000).

2.3.1.2 Muscular fitness

Also muscular endurance and strength – the ability of the muscle to continue to perform without fatigue and to exert force (United States Department of Health and Human Services 1996) – can be diminished associated with adjuvant treatment of breast cancer. This decrease is caused by an abnormal accumulation of muscle metabolites, changes in neuromuscular function (National Comprehensive Cancer Network 2007), and an increased release of cytokines as a consequence of tissue necrosis after radiotherapy (Dimeo 2001).

The benefits of resistance training have been well documented: resistance training can enhance strength, muscle mass, and muscle quality (strength relative to muscle mass) (Deschenes and Kraemer 2002, Hunter et al. 2004).

Common recommendations to cancer patients undergoing adjuvant treatment have focused on reduced activity and rest (Dimeo 2001, Pinto and Trunzo 2005) in order to achieve "less discomfort" (Dimeo 2001) through avoiding breathlessness and tachycardia from physical effort. However, sedentary habits and bed rest may further aggravate physiological changes of cancer treatment, resulting in severe atrophy of the peripheral muscle mass and deleterious effects on the cardiovascular system. One bed rest study of 10 days with older adults found a large loss of skeletal muscle, particularly from the lower extremities, that was greater than that observed in young individuals after 28 days (Kortebein et al. 2007). A 2-months bed rest study within the women international space simulation for exploration (WISE) 2005 program showed that prolonged bed rest caused microcirculatory endothelial dysfunction which might participate in cardiovascular deconditioning (Demiot et al. 2007). Thus, a prolonged sedentary lifestyle can precipitate a "disuse syndrome" (Pinto and Trunzo 2005) and further deconditioning (Dimeo 2001) with an increase in both sense of disability and risk of injury (Dimeo 2001, Pinto and Trunzo 2005). Prolonged sedentarism creates a self-perpetuating condition of diminished activity leading to decreased health-related fitness, and vice versa.

2.3.1.3 Body composition

Body composition is a component of physical fitness that relates to the relative amounts of muscle, fat, bone, and other vital parts of the body (United States Department of Health and Human Services 1996). Weight gain and obesity are common occurrences in women diagnosed with breast cancer (Demark-Wahnefried et al. 1997, Rock 1999, Demark-Wahnefried et al. 2001, McInnes and Knobf 2001, Lankester et al. 2002). Significant weight gain occurs in 50% to 96% of women receiving adjuvant chemotherapy for early-stage breast cancer, as indicated by a compilation of study results, and is greater and more prevalent in younger patients (Demark-Wahnefried et al. 2001). Gains in weight usually range from 2 kg to 6 kg during the first year of diagnosis but greater gains can be observed as well (McInnes and Knobf 2001). There is evidence that the majority of the weight gained during breast cancer treatment is composed of body fat; studies that measured changes in body composition, rather than postdiagnosis weight gain only, noted increased body fat in women undergoing adjuvant chemotherapy (Demark-Wahnefried et al. 2001). These alterations can not only lead to declines in physical function but can also predispose women to weight-related chronic illnesses such as diabetes, heart disease, or orthopaedic problems. Moreover, weight gain can have negative impact on psychosocial aspects of quality of

life (McInnes and Knobf 2001). Clinical and epidemiological studies have identified obesity as an important negative prognostic factor for survival after the diagnosis of breast cancer: specifically, increased body weight and waist-to-hip ratio have been associated with greater recurrence and mortality in women with breast cancer (Kumar et al. 2000, Daling et al. 2001, Chlebowski et al. 2002, Barnett et al. 2008).

Causes underlying postdiagnosis weight gain in breast cancer patients are not fully understood, but multiple reasons have been suggested, including being or becoming postmenopausal after diagnosis, decreased physical activity, and increased total caloric intake (McInnes and Knobf 2001). Furthermore, the issue of possible direct effects of adjuvant chemotherapy itself on metabolism has been addressed in an exploratory study (Demark-Wahnefried et al. 1997), in which a transient decrease in resting metabolic rate was observed. Both a potentially decreased resting metabolic rate and reduced physical activity levels postdiagnosis result in a decline in total energy expenditure associated with adjuvant cancer treatment (Irwin et al. 2003). This decline in total energy expenditure justifies an approach to weight control emphasising increased physical activity.

Increased exercise to promote weight loss and maintenance and to restore lean body mass is a strategy whose benefits are fairly well supported by evidence. Exercise can be recognised as an important weight management intervention since exercise can induce a negative energy balance – i.e., where energy expenditure exceeds energy intake – by directly enhancing energy expenditure (the energy cost of the exercise episode) and possibly by affecting resting metabolic rate as well. Because resting metabolic rate and energy expenditure of physical activity account for around 90% of total energy expenditure (Lemmer et al. 2001), any intervention that increases these two components of energy expenditure could be useful in restoring energy balance and preventing weight gain in women receiving adjuvant treatment of breast cancer. Breast cancer patients may benefit from resistance training to restore muscle mass since resistance training in particular has been reported to increase lean body mass, which is associated with an increase in the resting metabolic rate (Lemmer et al. 2001). Putting this together, this suggests that increases in resting metabolic rate and energy expenditure of physical activity could explain the decreases in fat mass that have been reported in response to resistance training (Lemmer et al. 2001). However, current evidence suggests that changes in the resting metabolic rate in response to resistance training may be influenced by sex with resting metabolic rate not being affected in women (Lemmer et al. 2001). Aerobic endurance training is associated with significant metabolic adaptations in skeletal muscles (United States Department of Health and Human Services 1996): besides adaptations that greatly enhance the oxidative capacity of the endurance-trained muscle, the ability of trained

muscles to use fat as an energy source is also improved. This improved capacity to oxidise fat may lead to reductions in fat mass.

2.3.2 Treatment-related symptoms

Women with breast cancer experience a variety of symptoms as a result of their disease or as a result of treatments for their disease. These symptoms are a major problem for the women, as well for their family caregivers, because the management of these symptoms is often the responsibility of the patients themselves (Dodd and Miaskowski 2000). In addition, unrelieved symptoms can have deleterious effects on patient outcomes such as functional status, mood states, and quality of life (Dodd et al. 2001). Symptoms are "subjective perceptions of alterations in normal bodily function and sensation or cognition" (Parker et al. 2005). The cancer symptom experience is complex: individuals undergoing adjuvant treatment of cancer are likely to experience multiple concurrent and related symptoms, i.e., symptoms occur not in isolation but in pairs, groups, or clusters (Dodd et al. 2004). Also interactions between symptoms can be observed: they happen when two or more symptoms coexist, precipitate, or synergize each other, or where they trigger the development of other symptoms (Parker et al. 2005). For example, fatigue and depression have been often documented as examples of concurrent, related symptoms in patients with cancer (Barsevick et al. 2006); likewise with sleep disturbances and pain (Parker et al. 2005). Up to 40 different symptoms may be experienced by breast cancer patients receiving adjuvant chemotherapy (Groenvold et al. 2006). These symptoms include acute consequences of chemotherapy (e.g., nausea, vomiting, loss of appetite, diarrhoea, hair loss, sore mouth), symptoms related to ovarian ablation resulting from chemotherapy (e.g., hot flushes, amenorrhea, vaginal dryness), and symptoms like fatigue, loss of energy or sleep disturbances (Groenvold et al. 2006). Also more specific concerns such as an altered sense of femininity, feelings of decreased attractiveness, and lymphedema (Brady et al. 1997) are important. The experience of a range of symptoms may result in a perceived decrease in quality of life.

2.3.2.1 Cancer-related fatigue

Patients with cancer commonly report a lack of energy during the course of their disease and treatment: fatigue. Fatigue is the symptom that has, by far, the largest impact on limiting function and overall quality of life in breast cancer patients (Arndt et al. 2006). Cancer-related fatigue is defined as a "distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (National Comprehensive Cancer Network 2007). Fatigue is a subjective and multidimensional concept with distinct symptoms concerning physical functioning (e.g., diminished energy

or need to rest), cognitive functioning (diminished concentration or attention), and affective functioning (decreased motivation or interest) (Servaes et al. 2002).

As indicated by the US National Comprehensive Cancer Network (NCCN), fatigue is a nearly universal symptom in patients receiving cytotoxic chemotherapy, radiotherapy, or treatment with biological response modifiers. It is a problem that affects 70% to 100% of cancer patients and has been exacerbated by the increased use of fatigue-inducing multimodal treatments and of dose-dense, dose-intense protocols (National Comprehensive Cancer Network 2007). Months or even years after treatment has ended, people living with cancer report that fatigue is a disruptive symptom (National Comprehensive Cancer Network 2007).

Despite high prevalence, the exact mechanisms involved in the pathophysiology of fatigue are unknown (Winningham 2001, de Jong et al. 2002, Servaes et al. 2002, Tavio et al. 2002, Mock and Olsen 2003, Stasi et al. 2003). Although the relative importance of biological, psychological, and situational factors is usually unclear, these and other factors appear to be important in the pathogenesis. Proposed biological mechanisms include abnormal accumulation of muscle metabolites, production of cytokines, changes in neuromuscular function, and abnormalities in adenosine triphosphate synthesis and anaemia (National Comprehensive Cancer Network 2007) as well as loss of muscle mass (Baracos 2001, Stasi et al. 2003). Psychological factors discussed as contributing to symptoms of fatigue comprise anxiety and depression (Stasi et al. 2003). Finally, situational factors contributing to fatigue include sleep disorders (Stasi et al. 2003) and physical inactivity (Winningham 2001).

Differing definitions and theoretical frameworks within which fatigue is being studied result in differing assessment tools. The Piper Fatigue Scale was among the first multidimensional instruments developed specifically for cancer-related fatigue. It measures the dimensions of subjective fatigue on four scales: behavioural/severity scale (relating to the severity, distress, and degree of disruption in activity of daily living); affective meaning scale (relating to the emotional meaning attributed to fatigue); sensory scale (relating to the physical symptoms of fatigue); and cognitive/mood scale (relating to mental and mood states) (Piper et al. 1989, Piper et al. 1998).

Typically, non-pharmacological interventions and pharmacological therapy are advocated in order to manage cancer-related fatigue: non-pharmacological interventions include education, exercise, rest and sleep, energy conservation and stress reduction (Ahlberg et al. 2003, National Comprehensive Cancer Network 2007), whereas pharmacological therapy comprises psychostimulants, sleep medication, or anaemia treatment as indicated (National Comprehensive Cancer Network 2007).

One promising intervention for combating feelings of low energy and fatigue is regular exercise. However, since mechanisms involved in the pathophysiology of fatigue are unknown, mechanisms potentially contributing to a decrease in feelings of fatigue are also unclear. There may be biological, psychological, and social aspects of a regular exercise experience contributing to improved fatigue status. Neurobiological adaptations that accompany regular exercise (Dishman et al. 2006) may be of importance as well as social interactions that are involved in exercise interventions frequently.

2.3.2.2 Nausea and vomiting

Nausea is a significant problem for most women receiving chemotherapy for breast cancer (Dibble et al. 2003). Nausea is a complex process and can be regarded as a protective reflex against the ingestion of toxins. Cytotoxic antineoplastic agents vary greatly in their potential to induce emesis and in the severity of this symptom (Miller and Kearney 2004).

Besides pharmacological antiemetic therapy, several non-pharmacological interventions have been explored: progressive muscle relaxation, guided imagery, self-hypnosis, biofeedback and cognitive distraction (Markman 2002). Given the complexity of the emetic process, and with only preliminary available evidence showing that benefits can be achieved through exercise, no mechanisms have been proposed yet in the literature for how exercise may affect nausea. However, exercise may induce distraction and thus contribute to relief of nausea symptoms.

2.3.3 Biological and physiological problems

There are substantial short- and long-term biological and physiological problems deriving from adjuvant treatment of breast cancer such as a depression of the immune system, premature menopause with subsequently decreasing bone mineral status, or cardiovascular effects. Short-term problems typically include those effects encountered during the course of treatment that resolve within month of the completion of therapy. By contrast, long-term problems include adverse effects of treatment arising after the conclusion of adjuvant treatment and may have a sustained impact (Partridge et al. 2001).

2.3.3.1 Depression of the immune system

Virtually all chemotherapeutic regimens and radiotreatment can cause myelosupression (Partridge et al. 2001, Shapiro and Recht 2001), a depression of the immune system, often by paralysing the bone marrow and leading to a decrease of white blood cells (neutropenia), red blood cells (anaemia) and platelets (thrombocytopenia).

It has been suggested that enhanced immune system function and reduced susceptibility to cancer may occur with regular moderate exercise, whereas exhaustive exercise and overtraining may

lead to suppressed immune system function (Woods et al. 1999). Based on this working theory, exercise-induced alterations in cancer-related immune system components have received increased research attention: there is evidence that "physical exercise training may improve a number of immune parameters that may be important in cancer defence" (Fairey et al. 2002).

2.3.3.2 Premature menopause and postmenopausal bone loss

Premenopausal women treated with adjuvant chemotherapy frequently develop permanent ovarian failure, or early menopause (Ramaswamy and Shapiro 2003), especially after administration of alkylating agents (e.g., cyclophosphamide, which is a common component in several chemotherapy regimens for breast cancer). The major determinants of ovarian failure are the age at treatment and the total cumulative dose of cyclophosphamide. The overall incidence of ovarian failure related to cyclophosphamide regimens is about 70% (Ramaswamy and Shapiro 2003), with a timeframe between 2 and 16 months to onset of ovarian failure. In chemotherapy-induced ovarian failure, oestrogen levels decline rapidly resulting in oestrogen deficiency-associated bone loss. Aromatase inhibitors (administered for early-stage, oestrogen receptor-positive breast cancer) are likely to increase the risk of osteoporosis in some breast cancer survivors as well (Ramaswamy and Shapiro 2003). Altogether, women with breast cancer are at higher risk for osteoporosis and osteoporotic fractures than other women (Adler 2007, Brown and Guise 2009).

Regular exercise has shown effects on bone density, size, shape, and geometry resulting in substantial improvements in mechanical strength (Wolff et al. 1999, Kelley et al. 2001, Turner and Robling 2005, Hamilton et al. 2009). It has been suggested that gravitational forces and muscle pull related to exercise may affect bone density through the production of strains within the skeleton. These strains are perceived by bone cells as osteogenic resulting in bone formation (Wolff et al. 1999).

2.3.3.3 Cardiovascular injuries

Each chemotherapeutic agent used in breast cancer management is associated with unique acute and long-term cardiac complications (Jones et al. 2007). The majority of complications are transient effects that do not persist after completing chemotherapy which shows the need for action especially in the period *during* cancer treatment. Regarding radiotherapy, it can be said that while modern radiation techniques provide lower cardiac mortality risks than older techniques, cardiopulmonary damage does nonetheless occur (Jones et al. 2007). The direct and indirect effects of adjuvant therapy coupled with an unhealthy lifestyle and the presence of modifiable risk factors all contribute to an elevated risk of future cardiovascular disease especially in middle-aged and elderly women with early breast cancer who are already at risk for cardiovascular disease (Jones et al. 2007). There is the chance that lifestyle modifications, especially exercise interventions, may

mitigate these adverse cardiac effects. At the same time, there is the risk that cardiovascular injuries from adjuvant treatment predispose women to harmful effects of exercise training. These risks have to be evaluated adequately (surveillance for harm).

2.3.4 Mental health

According to the WHO, mental health can be conceptualised as a "state of wellbeing in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community" (World Health Organization 2007). In this positive sense, mental health is the foundation for wellbeing and effective functioning for an individual and for a community.

Identification of emotional distress is a key step in the assessment of mental health problems. Being diagnosed with cancer marks the beginning of a series of difficult but essential life adjustments in response to this challenging life stressor. Frequently, cancer patients develop subsequent mood disturbances such as depression and anxiety. Depressive symptoms can be associated with certain psychiatric disorders (e.g., adjustment disorder, major depressive disorder), or they can be present in the absence of a psychiatric diagnosis. Diagnosis of major depression may be complicated by overlapping effects and interrelationships of psychological distress (anxiety, anger, shock, bereavement), major depressive episode (depressed mood, loss of interest/pleasure, low self-esteem or guilt, suicidal ideation) and symptoms induced by cancer and/or cancer treatment (Somerset et al. 2004).

Besides depression, anxiety is a further concern in the category of emotional distress. Frequently, depression and anxiety coexist in cancer patients. Reactive anxiety, which is related to fear, is by far the most common type of anxiety seen in patients and can be regarded as a normal, however debilitating, reaction to facing the unknown. It includes fear of death, treatment, disability, pain, suffering, and loss or disruption of relationships (Sivesind and Baile 2001).

Several mechanisms have been proposed for how exercise may affect depression: diversion of negative thoughts, mastery of new skills, social contact, positive feedback, and increased sense of self-worth together with physiological effects such as changes in endorphin levels (Lawlor and Hopker 2001). A meta-analysis examining the effectiveness of exercise on general mood (including phenomena such as depression, anxiety, anger, vigour) in the elderly found exercise to be associated with significant improvements in mood in this age group (Arent et al. 2000).

2.3.5 Health-related quality of life

Health-related quality of life plays an important role in helping establish the optimal treatment and care approach for cancer patients: improving the quality of life, not merely the length of life,

is an important parameter of benefit. However, there is only limited information available on the nature and time course of the impact that breast cancer treatment has on health-related quality of life. Quality of life is an important outcome describing the subjective experience of the breast cancer disease and treatment, but there is no consensus on what it really is. Contrary to the vast body of literature relating to happiness, wellbeing and satisfaction, quality of life has been associated with an "astonishing lack of theory" (Bullinger 2002). The World Health Organisation (WHO) has defined *health* as "a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity" (WHO 1948). The WHO's definition of health is widely used and strongly supports the multidimensional aspects of health. This definition has influenced the notion of quality of life as a multidimensional concept. There are several suggestions about how this multidimensional character of the quality of life could be incorporated into its definition. The WHO Quality of Life Assessment group (WHOQOL) defines quality of life as the "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (WHOQOL group 1996). Quality of life refers to a subjective evaluation with a focus upon respondents' *perceived* quality of life, and subsequently quality of life measures assess the value of an intervention based on wellbeing and function rather than based on symptoms, diseases, or conditions. According to Bullinger, health-related quality of life can be viewed as a psychological construct which describes the psychological, social, physical and functional aspects of wellbeing and function from the individual's perspective (Bullinger 2000). Some authors extend the dimensions by further aspects such as spirituality (Bullinger 2002) or financial concerns, job satisfaction, and living conditions (WHOQOL group 1996). The various miscellaneous definitions stress the multidimensionality of the quality of life concept as well as the relevance of respondents' self-report.

There are several valid, reliable questionnaires available to measure a person's health-related quality of life with two basic approaches: first, generic instruments that provide a summary health profile and secondly, disease-specific instruments which focus on specific problems associated with a disease or area of functioning. Currently, one of the most commonly used generic health status instruments is the Medical Outcomes Study 36-Item Short Form (SF-36), a 36-item measure encompassing eight domains: physical functioning, social functioning, mental health, role limitations due to physical problems, role limitations due to emotional problems, vitality, bodily pain, and general health perceptions. The domains and items selected for disease-specific instruments are directly associated with the impairments caused by a specific disease process or its therapeutic interventions. Disease-specific instruments are designed to assess health-related quality of life in patient populations, and so disease-specific instruments are likely to be more reactive than generic instruments to intervention-related changes. A number of such instruments have

been designed for use with cancer populations. Because cancer at different sites may have widely differing effects on health-related quality of life, cancer-specific instruments still represent a rather broad approach. Site-specific instruments are those which attempt to measure the impact on the health-related quality of life for cancer at a particular anatomical site. One example of these instruments is the Functional Assessment of Cancer Therapy (FACT) instrument, which is comprised of a core instrument and subscales. Items are contained within four validated subscales (physical wellbeing, social/family wellbeing, emotional wellbeing, and functional wellbeing).

Despite the extensive use of chemotherapy, the literature investigating the impact of adjuvant chemotherapy on health-related quality of life of breast cancer patients in prospective, longitudinal studies is relatively limited. Many studies either employ a cross-sectional or retrospective design, or lack control groups. Furthermore, a wide range of chemotherapeutic regimens, which may have different toxicity profiles, has been studied. Moreover, most studies have assessed only relatively few variables of health-related quality of life.

Randomised clinical studies were primarily conducted by the large oncological clinical trial groups in North America and Europe. In testing of chemotherapy regimens in breast cancer patients, quality of life has been considered as an outcome parameter. Health-related quality of life during adjuvant chemotherapy for breast cancer shows transient adverse effects during therapy, but it improves after cessation of therapy – either standard therapy (Hürny et al. 1996, Fairclough et al. 1999, de Haes et al. 2003, Land et al. 2004, Martin et al. 2005, Bernhard et al. 2007, Bernhard et al. 2008), dose-intensive therapy (Del Mastro et al. 2002), or high-dose therapy (Macquart-Moulin et al. 2000, Brandberg et al. 2003, Peppercorn et al. 2005). Overall quality of life improves substantially over the first two years (Hürny et al. 1996). For the majority of breast cancer patients, most aspects of health-related quality of life recover without long-term effects after adjuvant chemotherapy has ended – except for vasomotor symptoms and sexual dysfunction (Grimison and Stockler 2007).

Reported changes in quality of life over time have to be treated cautiously since they need not necessarily derive from actual changes in health or symptoms: people with severe chronic illnesses report quality of life equal or superior compared to reports from less severely ill or healthy people, and consistent disparities arise between clinical measures of health and patients' own evaluations (Rapkin and Schwartz 2004). In fact, this paradox is now understood to reflect a psychological adaptation (a "response shift") that occurs in cancer patients as well as in patients with other chronic diseases (Rapkin and Schwartz 2004). The internal standard by which patients appraise their current health state shifts and the same questionnaire items on wellbeing can elicit

fundamentally different answers over time. To the extent that subjective wellbeing reflects psychological adaptation, the connection between subjective quality of life and disease course (or treatment response) weakens (Schwartz and Rapkin 2004).

In light of the observation that quality of life is predominantly disrupted *during* treatment, interventions to sustain quality of life are most needed in this period. Physical exercise is regarded as an intervention with significant potential to influence health-related quality of life in various populations (United States Department of Health and Human Services 1996). The most direct effects are likely to be in the areas of psychological wellbeing (e.g., self-concept, self-esteem, mood, and affect), perceived physical function (e.g., perceived ability to perform activities of daily living), and physical wellbeing (e.g., perceived symptoms and fatigue).

2.3.6 Recurrence and survival

Epidemiological evidence from a recent prospective cohort study of almost 3,000 women suggests that higher levels of physical activity are associated with reduced risks for breast cancer recurrence, breast-cancer-specific mortality, and all-cause of mortality (Holmes et al. 2005).

2.3.7 Prevalence of treatment-related adverse effects

Irrespective of the respective prevalence, there is evidence that a number of health-care professionals do not indicate that patients have certain treatment-related adverse effects – even though those effects are reported by patients. Subsequently, treatment-related adverse effects remain underdiagnosed and managed inadequately (Groenvold et al. 2006).

Prevalence estimates for treatment-related adverse effects are not presented here due to several methodological issues regarding prevalence estimates which have been observed in studies. First, most studies assessing prevalence estimates for treatment-related adverse effects are cross-sectional, and so these studies neglect the time course of the impact of adjuvant cancer treatment. Secondly, no standard has been adopted and a variety of different (self-report) instruments were used across studies. This makes comparison across studies difficult, if not impossible.

Finally, besides the type of adjuvant cancer treatment there are various factors that contribute to the rate of occurrence of treatment-related adverse effects such as age, culture, or co-morbidities, and so studies in different settings will reveal different prevalence estimates for treatment-related adverse effects. Estimates of prevalence are difficult to compare across studies if different time frames are employed, different assessment tools are used, or different inclusion or exclusion criteria are being relied upon.

2.4 The intervention: exercise

Exercise, physical activity, and fitness describe different concepts, where physical activity is the broadest of the three concepts and can be characterised as "any bodily movement, produced by skeletal muscles that results in energy expenditure" (Caspersen et al. 1985). Physical activity can occur in any setting and can be categorised into occupational, household, or recreational physical activity and sports. Exercise is a subset of physical activity and is "planned, structured, repetitive and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective" (Caspersen et al. 1985). Physical fitness refers to a "set of attributes that are either health- or skill-related" (Caspersen et al. 1985) and that can be achieved through exercise. Health-related fitness encompasses cardiorespiratory endurance, muscular endurance, muscular strength, body composition and flexibility (Caspersen et al. 1985).

2.4.1 Exercise patterns in breast cancer patients

Overall, the stress associated with the diagnosis of breast cancer and cancer treatment is known to disrupt health behaviours such as exercise behaviour (Pinto and Trunzo 2005). Many women with breast cancer are reluctant to exercise and may decrease their exercise levels during the period of adjuvant therapy. Several studies have addressed the important questions of whether declines in physical activity are evident during adjuvant therapy and whether observed declines during adjuvant therapy persist beyond treatment completion. These studies suggest that physical activity after treatment completion may remain depressed relative to pre-diagnosis levels.

The evidence regarding exercise patterns in breast cancer patients is predominantly based on cross-sectional and retrospective research. Data from the U. S. National Health Interview Survey with a total of nearly 130,000 adults (Bellizzi et al. 2005) showed that the proportion of cancer survivors who met the recommendations for physical activity level was 29.6%, compared with 36.6% for those without a history of cancer. Courneya and Friedenreich (1997a, 1997b) required retrospective reports from cancer survivors (breast and colorectal cancer) regarding how their physical activity changed after cancer diagnosis and treatment and found decreases in exercise during treatment followed by an increase in exercise after treatment completion. Exercise activity, however, did not return to pre-diagnosis levels. Blanchard et al. (2003) found that 30% of cancer survivors, of whom nearly half were breast cancer survivors reported decreased exercise activity, whereas 15% reported increased activity since diagnosis. Finally, Irwin et al. (2003) compared physical activity levels before and after diagnosis of breast cancer using retrospective reports of pre-diagnosis activity. This showed that physical activity declined by about two hours per week with the greatest decreases in sports-related physical activity in women treated with adjuvant radiotherapy plus chemotherapy. This evidence from cross-sectional or retrospective research

suggests that cancer treatment can be associated with reductions in physical activity. In contrast, one study with a prospective, longitudinal design – while it did indeed find decreased activity levels, relative to the pre-diagnosis baseline– showed that the decreased activity levels seemed to recover quickly and (on average) did not differ from the pre-diagnosis baseline a few months after completion of adjuvant therapy (Andrykowski et al. 2007). But over a third of the sample evidenced a clinically important change in leisure-time exercise over the course of the study: whereas some women reported decreases in leisure-time exercise after diagnosis, other women reported increases in exercise six months after completion of treatment, relative to pre-diagnosis levels. Although the decline in exercise participation during adjuvant therapy was followed by recovery to pre-diagnosis levels in this study, participation in leisure-time exercise activity six months after conclusion of adjuvant therapy was still suboptimal, with only a moderate percentage of participants meeting current guidelines for exercise activity.

In sum, activity levels during adjuvant therapy for breast cancer appear to decline. Even if they recover to pre-diagnosis levels, activity levels among breast cancer survivors seem to be suboptimal and health promotion programs with exercise interventions are required as the following data from health surveillance in Germany indicate: the rate of women who participate in regular physical exercise (weekly exercise activities of two hours or more) declines with age: from 40% of women aged between 20 and 29 years to 22% of women aged between 70 and 79 years (Ruetten et al. 2005). Consequently, even if a decline in exercise participation during adjuvant treatment for breast cancer is followed by recovery to pre-diagnosis levels after the conclusion of treatment, exercise participation may still be suboptimal.

Possibly, the period of adjuvant therapy is the ideal time point for the delivery of health promotion interventions in the cancer diagnosis-rehabilitation continuum. Intervening at the ideal time point would ensure that the women diagnosed with breast cancer are most amenable to both make changes in their behaviour and maintain those changes. It could be assumed that women may be "catapulted in their readiness to alter life-style risk factors by a diagnosis of cancer and its treatment" (Pinto et al. 2000). Receptivity towards health promotion interventions may be high during the period of initial treatment, a period that turned out to be a "teachable moment" (Demark-Wahnefried et al. 2000, Demark Wahnefried et al. 2005). On the other hand, the distress of breast cancer diagnosis and cancer treatment could overwhelm women regarding coping requirements.

2.4.2 Behaviour change theories for program planning

Health promotion interventions based on exercise have the potential to reduce dysfunction and improve long-term health. On the level of personal skills, "health promotion supports personal

and social development through providing information, education for health, and enhancing life skills. By so doing, it increases the options available to people to exercise more control over their own health and over their environments, and to make choices conducive to health" (WHO 1986). Effective health promotion programs can help women to manage their breast cancer experience and reduce further disease risks. Usually, behaviour changes are required in order to achieve success, e.g., previously sedentary women have to adopt a regular exercise program. Health behaviour and health promotion theories can play a crucial role in program planning. They provide tools for developing appropriate interventions and evaluating their success based on findings from various disciplines, such as psychology, sociology, or marketing. These tools are based on an understanding of behaviour and thus allow a program planning to be grounded in more than intuition – but in a grasp of the dynamics of health behaviour and the social/ environmental influences that affect health behaviour. Health behaviour theories suggest how program strategies can be devised that reach the target group and have an impact. Moreover, they help to identify appropriate indicators for monitoring and evaluation. Health behaviour theories can consequently make a major contribution to improving the design of programs and maximising potential effects. There are numerous theories to draw on and no single theory dominates health education and promotion. Some theories focus on individuals as the focus of change (e.g., Health Belief Model). Others examine change within families, institutions, or communities. Some constructs, such as self-efficacy, i.e., the confidence in one's ability to take action and overcome barriers, are central to several theories.

For understanding the determinants of exercise participation, various distinct behaviour change theories have been examined in exercise studies with women undergoing active treatment of breast cancer: the Theory of Planned Behaviour, that assumes that behavioural intentions are the most important determinant of behaviour (Courneya and Friedenreich 1999a, Courneya et al. 2001, Hunt-Shanks et al. 2006); the Transtheoretical model (Stages of Change), whose basic premise is that behaviour change is a process, not an event (Rogers et al. 2007); and finally the Social Cognitive Theory, which identifies self-efficacy, goals, and outcome expectancies as the main factors governing health behaviour change (Rogers et al. 2004, Rogers et al. 2005a, Rogers et al. 2005b).

Using the Transtheoretical Model and the Social Cognitive Theory as examples, the requirements regarding exercise interventions within the framework of a behaviour change theory are highlighted in the following. According to the Transtheoretical Model (Prochaska and DiClemente 1983), changes are processes involving progress through a series of five stages: regarding exercise activity, *precontemplation* is the first stage at which people are not yet considering exercise adoption in the foreseeable future; *contemplation* is the next stage at which people are intending to adopt

exercise in the next six months, being aware of the pros of exercise adoption but also of the cons; *preparation* is the third stage at which people are already intending to start exercise in the immediate future: at this stage, they have a plan of action, such as joining an exercise class or they have already started exercising but not regularly. Following preparation, *action* is the stage in which people have started a regular exercise program within the past six months. In the Transtheoretical Model, action is only one of five stages and can not be regarded as behaviour change. This stage is the stage where vigilance against relapse is critical. *Maintenance*, finally, is the stage in which people are regularly exercising for six months or more. Relapse – the regression from action or maintenance to an earlier stage – tends to be the rule for most health behaviours (Cancer Prevention Research Center). Programs based on the Transtheoretical Model are designed to develop interventions that are matched to the specific needs of the participants and recognise that different individuals will be in different stages of change. Interventions are tailored to the participants' motivational readiness to start exercising, and so participants who are ready for action may receive guidance on exercise adoption such as recommendations regarding specific types of exercise or where to exercise. Such action-oriented recommendations would be regarded as ineffective for those who have no intention of adopting exercise. These individuals might need more detailed information regarding the benefits of exercise benefits or its safety.

According to the Social Cognitive Theory (Bandura 1997), three main factors affect the likelihood that a person will change health behaviour: self-efficacy, goals, and outcome expectancies. Exercise interventions based on the Social Cognitive Theory often focus on self-efficacy – the confidence in one's ability to take action and overcome barriers. If individuals have a sense of self-efficacy, they can change behaviours even when faced with obstacles. Regarding exercise adoption, the Social Cognitive Theory implies that individuals are not motivated to act, or to persist through challenges if they do not feel that they can have control over their exercise behaviour. Interventions attempt to enhance self-efficacy through techniques such as setting realistic, easily attainable goals, focusing on participants' progress and reinforcing successes.

2.4.3 Exercise adherence

The biggest challenge in encouraging health-related lifestyle change is not the initial change but rather the ability of participants to adhere to a change in the long run. The term adherence refers to the level of participation achieved in a behavioural regimen once the individual has agreed to undertake it (King 1994). Adherence to exercise is a critical concern because the benefits of exercise may not persist when exercise is discontinued (Lennon et al. 2004, Herrero et al. 2007). Regarding exercise adherence, adoption, maintenance, and resumption of exercise are distinguished: for exercise prescriptions to be successful, women must persist and adhere to the recommended

program, i.e., they must initiate and maintain their participation in exercise. Then, adherence to exercise regimens after interventions have ended is a crucial issue. Success in maintaining exercise depends on repeated adoption or resumption of exercise after periods of inactivity (Dishman 1994). There are two components of adherence: attendance at exercise sessions and the exercise intensity achieved when compared with the target intensity as prescribed. Despite the importance of adhering to exercise, exercise adherence appears to be a neglected issue in cancer research. Given that adherence to exercise is a problem in both asymptomatic and diseased populations, with an average dropout rate of 50% (Dishman 1994), it can reasonably be assumed that comparable rates of non-adherence will occur among breast cancer patients. However, better adherence may lead to better outcomes.

Understanding the ways in which individuals sustain healthier long-term lifestyle choices is needed to help cancer patients maintain recommended levels of physical activity. Knowing the key barriers women face when receiving adjuvant treatment for breast cancer may serve as a basis for the development of interventions to assist women in exercising regularly during this difficult time. Several studies have investigated predictors of adherence to exercise in women but these have mainly recruited young healthy women. Predictors of exercise adherence in younger healthy adults may be quite different to those for elderly populations of women with breast cancer. The identification of reliable predictors of exercise adherence will allow healthcare providers to effectively intervene and support sedentary women during the process of changing their patterns of physical activity. Many barriers (real or perceived) exist, which represent obstacles to maintaining regular exercise in this period of cancer treatment. In this respect, the assessment of barriers to supervised exercise in breast cancer patients participating in a randomised controlled trial (Courneya et al. 2008a) showed the importance of disease- and treatment-related barriers: feeling sick, fatigue, chemotherapy day, nausea/vomiting and depression, amongst others, accounted for more than half of the missed sessions among breast cancer patients.

Issues related to gender also appear to be important. A focus-group study (Emslie et al. 2007) of the experiences of women with breast cancer who took part in an exercise trial, suggested that the woman's traditional role as a caregiver and concerns about body image act as potential barriers to physical activity and that a gender-sensitive approach may help overcoming barriers to physical activity, e.g., exercise classes solely for women with breast cancer provided within a supportive group environment. It is clear that addressing barriers, particularly disease- and gender-related barriers, is a critical issue that will impact upon exercise adherence during treatment for breast cancer.

Inactivity, i.e., non-adherence to exercise prescriptions, may actually intensify such treatment-related adverse effects as weight gain, deterioration of lean muscle mass, overall reduction in physical functioning and fatigue, which in turn may subsequently act as further barriers to exercise.

2.4.4 Exercise prescription

According to the American College of Sports Medicine (ACSM), the art of exercise prescription is the "successful integration of exercise science with behavioural techniques that result in long-term program compliance and attainment of the individual's goals" (Balady et al. 2000). Exercise prescription for breast cancer patients must be highly individualised owing to the extreme variability of the effects of cancer and treatment regimens on functional capacity. Furthermore, since cancer is strongly associated with advancing age, other concurrent or prior health problems should be anticipated and taken into account when developing any exercise prescription. For the breast cancer patient, the exercise prescription provides a guideline for safe and effective levels of exercise training, basing the intensity level on exercise testing, the present physical status, and the current phase of treatment. Essential components of a systematic individualised exercise prescription include the appropriate mode(s), intensity, duration, frequency, and progression of exercise.

Regarding exercise intensity, low-fit, sedentary and clinical populations can improve physical fitness with lower intensity, longer duration exercise sessions (Balady et al. 2000). The ability of individuals to undertake exercise successfully at a given absolute intensity is directly related to their relative effort as reflected by heart rate response and perceived exertion. Consequently, the most common method of setting exercise intensity use heart rate and perceived exertion. Public health recommendations for the general population as well as for clinical populations have evolved from emphasizing vigorous activity for cardiorespiratory fitness to including the option of moderate levels of activity for numerous health benefits. Cardiorespiratory fitness gains seem to be similar when exercise occurs in several short sessions (e.g., 10 minutes) as when the same total amount and intensity of exercise occurs in one longer session (e.g., 30 minutes) (Jakicic et al. 1995, United States Department of Health and Human Services 1996). Moreover, for women who might be unable to exercise 30 minutes continuously due to treatment-related side effects, shorter episodes are clearly better than none and, quite significantly, short-bouts of exercise may enhance exercise adherence (Jakicic et al. 1995).

According to the updated recommendation from the American College of Sports Medicine (Haskell et al. 2007), to promote and maintain health adults need moderate-intensity aerobic (endurance) physical activity for a minimum of 30 minutes on five days each week or vigorous-intensity

aerobic physical activity for a minimum of 20 minutes on three days each week. Moderate-intensity aerobic activity is generally equivalent to a brisk walk and noticeably accelerates the heart rate while vigorous-intensity activity causes rapid breathing and a substantial increase in heart rate. Combinations of moderate- and vigorous-intensity activity, for example by walking briskly for 30 minutes twice during the week and then jogging for 20 minutes on two other days, are feasible to meet this recommendation. In addition to endurance physical activity, every adult should perform activities that maintain or increase muscular strength and endurance (i.e., resistance exercise training) a minimum of two days each week. The intensity of resistance exercise training can be adjusted by varying the weight, the number of repetitions, the length of the rest interval between exercises, or the number of sets of exercises completed. Courneya (Courneya et al. 2000) proposed exercise guidelines for early stage cancer patients, to be modified as needed for specific patients. These guidelines recommend walking and cycling as safe and generally well tolerated exercise modes involving large muscle groups, with a recommended frequency of three to five times per week. More deconditioned patients should begin with daily sessions of shorter duration and lower intensity. In general, moderate intensity exercise (50-75% heart rate reserve, rate of perceived exertion 11-14) in sessions of between 20 and 30 minutes duration are recommended, with modifications as needed, including very short exercise bouts (three to five minutes) followed by rest periods. Perceived exertion is based on the physical sensations a person experiences during physical exercise training, including increased heart rate, increased breathing rate, sweating, and muscle fatigue. This is a subjective measure, but exertion rating provides a fairly good means for self-monitoring and adjusting exercise intensity. Perceived exertion ratings between 11 ("light") and 14 ("somewhat hard") on the Borg Scale suggest that exercise is being performed at a light to moderate level of intensity. The Borg Scale ranges from 6 to 20, where 6 mean "no exertion at all" and 20 mean "maximal exertion". With regard to progression, patients should meet frequency and duration goals before they increase exercise intensity, with slower and more gradual progression for deconditioned patients or those who are experiencing severe side effects of treatment. For an exercise program to be successful, participants must be exposed to a therapeutic dose of exercise.

2.4.5 Exercise Testing

Women undergoing adjuvant treatment for breast cancer are generally capable of first completing exercise testing, and then following an exercise prescription based on their functional ability and limitations, regardless of whether disease- or treatment-related (Schwartz 1997). The ACSM recommends pre-participation health screening relative to risk factors (Balady et al. 2000) and thus, the exercise evaluation for breast cancer patients currently receiving adjuvant therapy should consist of a medical examination and exercise testing prior to participation. The objective

of exercise testing is to prescribe a safe and effective exercise level through evaluation of exercise tolerance and aerobic power. Exercise tests for persons with cancer are typically submaximal; submaximal exercise testing is preferred for women receiving adjuvant treatment of breast cancer whose performance may be limited because of fatigue or physical symptoms. Indeed, maximal exercise testing is considered the gold standard for assessing maximal aerobic capacity but only a few individuals reach maximum oxygen consumption, and, furthermore, these tests require participants to exercise to the point of volitional fatigue, so additional monitoring equipment is needed. Predictive and performance tests are the two major categories of submaximal tests. In predictive tests, exercise response to a given workload is used to predict maximal aerobic capacity. Motorised treadmills, stationary cycle ergometers, or weight machines are the most commonly used devices for the assessment of physical fitness. Exercise tests follow standard graded protocols with increments in work rate (e.g., grade, speed of treadmill). Typically, heart rate or oxygen consumption at two or more workloads is measured; results are used to predict maximum oxygen consumption.

Besides predictive exercise testing, performance tests (field tests) are employed that involve measuring the responses to standardised physical activities that are typically encountered in everyday life (Noonan and Dean 2000). Although less precise, submaximal testing provides a reasonably accurate reflection of an individual's fitness: if the heart rate response decreases over a period of exercise training, it is likely that cardiorespiratory fitness has improved, independent of the accuracy with which maximum oxygen consumption is predicted.

2.5 Potential harm associated with exercise

Understanding the potential for harm is important for recommending exercise to women receiving adjuvant treatment of breast cancer. Harms are defined to be all possible adverse consequences of an intervention (Ioannidis et al. 2004); they are the direct opposite of benefits, against which they must be weighed. Since the benefit of an intervention may be outweighed by its harm, a balanced decision requires reliable evidence not only on the benefit, but also on the harm associated with an intervention. Clinical concerns about prescribing exercise to cancer patients are manifold: first, cancer patients may be at an increased risk of musculoskeletal injury from exercise, due to prolonged, reduced levels of overall physical activity, or changes in weight; there is an increased likelihood of pathological bone fractures arising from compromised bone integrity. The risk of musculoskeletal injuries, especially in older exercisers, is substantial. Acute stress from sudden forceful movement, or from repetitive movement, can cause strains, tears, and fractures, with there being a greater risk of injury associated with increased exercise frequency (McTiernan 2004). However, most musculoskeletal injuries related to physical exercise are believed to be

preventable by gradually working up to a desired level of activity and by avoiding excessive amounts of activity (United States Department of Health and Human Services 1996). Second, vigorous exercise has the potential to act as an immunosuppressive, depending upon exercise-type, intensity, duration, and the immune parameters examined. Third, cancer patients may have increased cardiac risks, especially if they receive high or extended doses of cardiotoxic medications (e.g., Adriamycin), or have had their chest exposed to radiation. Moreover, a worsening of side effects such as severe pain and nausea may be triggered by exercising, and fatigue may be exacerbated by physical exercise.

Not least, physical activity is particularly feared as a possible risk factor for arm edema, which is a common complication of breast cancer therapy and can result in substantial functional impairment and psychological morbidity. The risk of arm edema increases when axillary dissection and axillary radiotherapy are used. Lymphedema develops when the lymphatic load exceeds lymphatic transport capacity (Földi et al. 1989). Breast cancer-related arm lymphedema is caused when the axillary lymphatic system is interrupted by axillary lymph node dissection or radiotherapy-induced fibrosis (Johansson et al. 2005), which results in the accumulation of fluid in subcutaneous tissue in the arm. The most commonly applied treatments for arm lymphedema are compression therapy, manual lymph drainage and intermittent pneumatic compressions (Johansson et al. 2005). Although risk factors for lymphedema are poorly characterised, there are fears that physical activity is a possible risk factor (Johansson et al. 2005, Ahmed et al. 2006). In prospective research, however, no form of physical activity has been associated with lymphedema (Ahmed et al. 2006), and guidelines that warn breast cancer patients against vigorous, repetitive or excessive upper body exercise are considered problematic (Ahmed et al. 2006). In contrast to these guidelines, some researchers argue that exercise would act as a treatment modality rather than a causative factor for lymphedema (McKenzie and Kalda 2003, Cheema and Gaul 2006), and subsequently suggest the use of a gradual, progressive upper-body exercise program in the rehabilitation and prevention of lymphedema. McKenzie and Kalda argue that skeletal muscle pump action, which increases lymph flow actions, is stimulated by exercise (McKenzie and Kalda 2003). This argument is further supported by investigations of lymph flow dynamics in healthy people that demonstrate both increased lymph flow rates during exercise and higher lymph clearance rates at rest in trained subjects (Havas et al. 1997). Cheema especially advocates upper-body resistance training, because strong muscles would be more advantageous for "mobilizing stagnant interstitial fluid" (Cheema and Gaul 2006).

In addition, it is important to consider that women receiving adjuvant chemotherapy or radiotherapy may not respond normally to exercise training (Winningham et al. 1986). Due to the increased risks cancer patients face, the following contraindications to exercise for cancer patients

have been given (Winningham et al. 1986): unusual fatigability or muscle weakness, development of irregular pulse, leg pain or cramps, chest pain, acute onset of nausea during exercise, vomiting or severe diarrhoea within previous 24-36 hours, disorientation/confusion, dizziness/blurred vision/faintness, pallor/cyanosis, sudden-onset dyspnoea, decreased heart rate and/ or blood pressure with increased workload and intravenous chemotherapy within previous 24 hours. Finally cancer patients may be unable or unwilling to tolerate exercise in their weakened physical and emotional condition (Courneya et al. 2000). Considering the potentially increased risks, the importance of assessing the harm of exercise interventions in cancer patients is made stronger.

In general, exercise facilitators have the responsibility for not exposing a participant to an unreasonable risk of harm through monitoring, instruction, supervision, or advice. Negligent training, e.g., leaving a participant without instructions about running on the treadmill may constitute an unreasonable risk of harm. Also, allowing or encouraging a participant to bench press more weight than is appropriate without adequate supervision may be seen to be subjecting the participant to an unreasonable risk to her health.

2.6 Previous research

Assessment of previous research indicated that the research question of this review had not been examined yet through a comprehensive systematic review including quantitative synthesis of results.

The protocol of this review was prepared and published in 2004 and at that time there were only narrative, non-quantitative reviews of exercise interventions among cancer patients during and after cancer treatment, which had considered a number of outcomes. Some highlighted specific outcomes and populations, such as weight loss in breast cancer patients (Chlebowski et al. 2002), immune function (Fairey et al. 2002), fatigue (Stricker et al. 2004, Watson and Mock 2004) and quality of life (Courneya and Friedenreich 1999b); others reviewed effects on a variety of physiological and psychosocial outcomes (Friedenreich and Courneya 1996, Courneya 2001, Courneya 2003, Irwin and Ainsworth 2004, Oldervoll et al. 2004, Galvao and Newton 2005, Knols et al. 2005). Narrative reviews of exercise intervention studies have been qualitative; they have noted methodological weaknesses but have been unable to quantify outcomes. For the most part, these reviews included all types of cancer and a range of study designs (i.e., controlled and uncontrolled trials).

Since 2004, a few systematic reviews have emerged that included quantitative analyses (Stevinson et al. 2004, Schmitz et al. 2005, Conn et al. 2006, McNeely et al. 2006). However, all these reviews examined the effectiveness of exercise interventions applying a different scope to the research question, as the following shows:

Schmitz et al. (2005) examined the effectiveness of exercise interventions, either alone or combined with diet modification, during and after cancer treatment across all types of cancers. Effect size estimates were calculated separately for interventions during and after cancer treatment; however, no peculiar data for women undergoing adjuvant treatment of breast cancer were presented. Significant effect sizes were seen in studies, conducted with cancer patients during treatment, showing improvements in cardiorespiratory fitness, physiological outcomes, symptoms and side effects, and for immune parameters. For fatigue as well as for vigour/ vitality quantitative null findings were reported with regard to the period during treatment.

Likewise, Stevinson at al. (2004) examined the effectiveness of exercise interventions during and after cancer treatment across all types of cancers. Meta-analysis on physical function in controlled trials of women with breast cancer (during and after cancer treatment) yielded evidence that exercise improved physical function; but no overall effect of exercise on fatigue could be observed.

Conn et al. (2006) investigated exercise interventions during cancer treatment across all types of cancers. There were significant improvements in physical function, symptoms other than fatigue and body composition. Furthermore, modest improvements were documented for mood, quality of life, and fatigue.

McNeely et al. (2006) examined the sub-group of women with breast cancer and presented effects of exercise interventions during and after cancer treatment jointly. Significant effects were observed of improvements in cardiorespiratory fitness, fatigue, and quality of life.

In sum, previous reviews have presented uniformly affirmative conclusions regarding exercise. However, many of the findings from the early studies were based on small sample sizes and were weak in terms of methodological quality. In recent years, several larger scale experimental studies have complemented previous work.

2.7 Preliminary work: rehabilitation sport in Germany

Exercise opportunities (tailored to the needs of breast cancer survivors who have completed their adjuvant treatment) are already implemented in the communities in Germany: the opportunity for regular exercise participation in rehabilitation sports groups is provided within the organised sports. These rehabilitation sports groups are available to women who have been treated for breast cancer previously *(post-treatment)*; currently these exercise programs are not determined by the needs of women *during* treatment.

Exercise for cancer patients in Germany is counted among rehabilitation sport. Currently, there are more than 600 rehabilitation sports groups for women with breast cancer; 300 alone in

Nordrhein-Westfalen (Landessportbund Nordrhein-Westfalen 2009). In 1991, a training curriculum for exercise facilitators was established and since 1992 exercise for cancer patients has been included in the German Sports Federation guidelines for exercise facilitator training (Große-Waechter et al. 2004). The legal foundations for rehabilitation within organised sports are contained in Book 9 of the German social code, SGB IX (covering rehabilitation and participation of people with disabilities). According to SGB IX, exercise rehabilitation programs are to be provided and funded as supplementary benefits to rehabilitation. Rehabilitation sports groups for breast cancer patients are formally prescribed by the treating physician and led by qualified instructors (Übungsleiter/innen) to ensure competent and skilful guidance and surveillance of classes. However, a physician is always on-hand to counsel participants and the exercise facilitators when required. The cost of participation in these programs is reimbursed to sports clubs by health or retirement insurance funds. Provision of rehabilitation sports groups for women with breast cancer is growing but has not yet achieved full coverage, particularly not in rural areas.

Altogether, Germany has embraced the importance of regular exercise in the rehabilitation of cancer patients. The implementation of exercise opportunities within the national sports federation for this target group seems to be unique. This provides a model of how exercise programs for breast cancer survivors can be offered within a health care context. However, there is still the failure of exercise opportunities for women *during* adjuvant treatment of breast cancer.

3 Methods

The objectives of this piece of work were to assess first, the effects of a structured exercise training program on physical functioning and health-related physical fitness in women receiving adjuvant treatment of breast cancer and secondly, to determine the effect of exercise training on secondary outcome measures such as treatment-related symptoms, biological and physiological problems, mental health, and health-related quality of life. Finally, this review aimed at assessing harm associated with physical exercise during adjuvant treatment of breast cancer.

The scope of application of these objectives was restricted with respect both to the type of cancer (breast cancer) and to the timing of the intervention with regard to cancer treatment (*during* adjuvant treatment). This restriction is for two reasons: First, cancer is a common denominator for a large number of neoplastic diseases, each with a different aetiology, course, and prognosis and a disease pathophysiology that may vary considerably. Similarly, cancer patient groups are clinically heterogeneous in terms of their demographic profile (e.g., age, sex distribution), behavioural profile (e.g., smoking status, alcohol consumption, and obesity), treatment protocols, and symptoms and side effects. Accordingly, summarising the effects of exercise interventions across such disparate groups appeared debateable and problematic. Secondly, cancer patients, who are undergoing adjuvant cancer treatment, are confronted with a number of specific problems. To recap, current cancer treatments are toxic in numerous ways and produce harmful short- and long-term health effects. Clinicians who wish to prescribe exercise for women currently undergoing cancer treatment need to know whether exercise will improve physical and mental health in this period of treatment as well. Clinical advice needs to be based on studies conducted on patients who are at a similar point of the breast cancer experience (pre-treatment, during treatment, post treatment). For example, a study that reports that exercise is useful to combat fatigue among women who have completed treatment will not assist a clinician in deciding whether to prescribe exercise for cancer-related fatigue during adjuvant cancer treatment.

A systematic review was chosen as an appropriate research design in order to answer the research question since several primary studies already exist. The methodology of a systematic review answered the purposes of reducing the quantity of data, of improving precision and reducing bias, and of checking consistency across results and explaining inconsistencies if present.

3.1 The role of systematic reviews in evidence based medicine

There is a body of published medical literature that is often overwhelming; moreover, individual research studies may vary in quality, have conflicting results, or fail to set their findings in the context of previous studies. Systematic reviews, however, identify, appraise, and synthesise research evidence from individual studies. A systematic review can be defined as "a review of the evidence on a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyse data from the studies that are included in the review" (NHS Centre for Reviews and Dissemination 2001). Compared to narrative reviews that use informal, unsystematic and subjective methods to collect and interpret information, and that often summarise information subjectively and in a narrative way, systematic reviews have the advantages of reducing bias, being replicable and of providing a reliable basis for decision making. A systematic review establishes "whether scientific findings are consistent and can be generalised across populations, settings, and treatment variations, or whether findings vary significantly by particular subsets" (Mulrow 1994) and thus conducting a systematic review is central to the practice of evidence based medicine, the "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett et al. 1996).

Nevertheless, systematic reviews are retrospective research, and are thus potentially subject to many of the same biases that affect other retrospective studies (Cook et al. 1995). Therefore, a rigorous review methodology is required. This review was conducted in co-operation with the CBCG and was first published in the Cochrane Database of Systematic Reviews (CDSR) in October 2006 (Markes et al. 2006). Each systematic review conducted under the umbrella of the Cochrane Collaboration follows a quality standard which provides a prescribed format and feedback during the review process from submission of a title, through development and publication of a protocol, to publication of the completed review. Each Cochrane review is prepared within one of the Collaborative Review Groups with a focus on a particular area of health. All these groups have an editorial base where a small team of people supports the production of Cochrane reviews. This review conformed to the formal, methodological, and procedural features of a Cochrane review. Cochrane reviews have the following general features (Higgins and Green 2006):

- Structured format
- Detailed methods section
- Thorough and systematic search strategy
- Quality assessment of included studies using predefined criteria

- Quantitative data synthesis in a meta-analysis if appropriate
- Co-operation with 'consumers' in order to account for issues important to people receiving certain interventions
- Peer review in multi-national editorial teams in order to ensure that a review is applicable in different parts of the world, and a
- Regular update of the review through incorporating results from newly completed or identified clinical trials after publication.

3.2 Execution of the review

The work breakdown structure of the review (Figure 4) describes how the review was executed. All methodological steps are shown here and described in detail within this methods section.

3.2.1 Review protocol

Since systematic reviews are by their nature retrospective, the methods to be used were established and documented in advance. A protocol for the review (see Appendix 1) was published prior to knowledge of the available studies. The aim of this procedure was to promote transparency of methods and processes, to reduce the potential for duplication, and finally to allow for peer review of the planned methods.

3.2.2 Identification of research

The aim of this step was to generate as comprehensive as possible a list of primary studies, both published and unpublished, which are suitable for answering the questions whether exercise contributes to the improvement of physical and mental health and subsequently, whether women, who are undergoing adjuvant treatment of breast cancer, should be offered exercise. A variety of search methods (both computerised and manual) was used to ensure that the search would be as comprehensive and unbiased as possible.

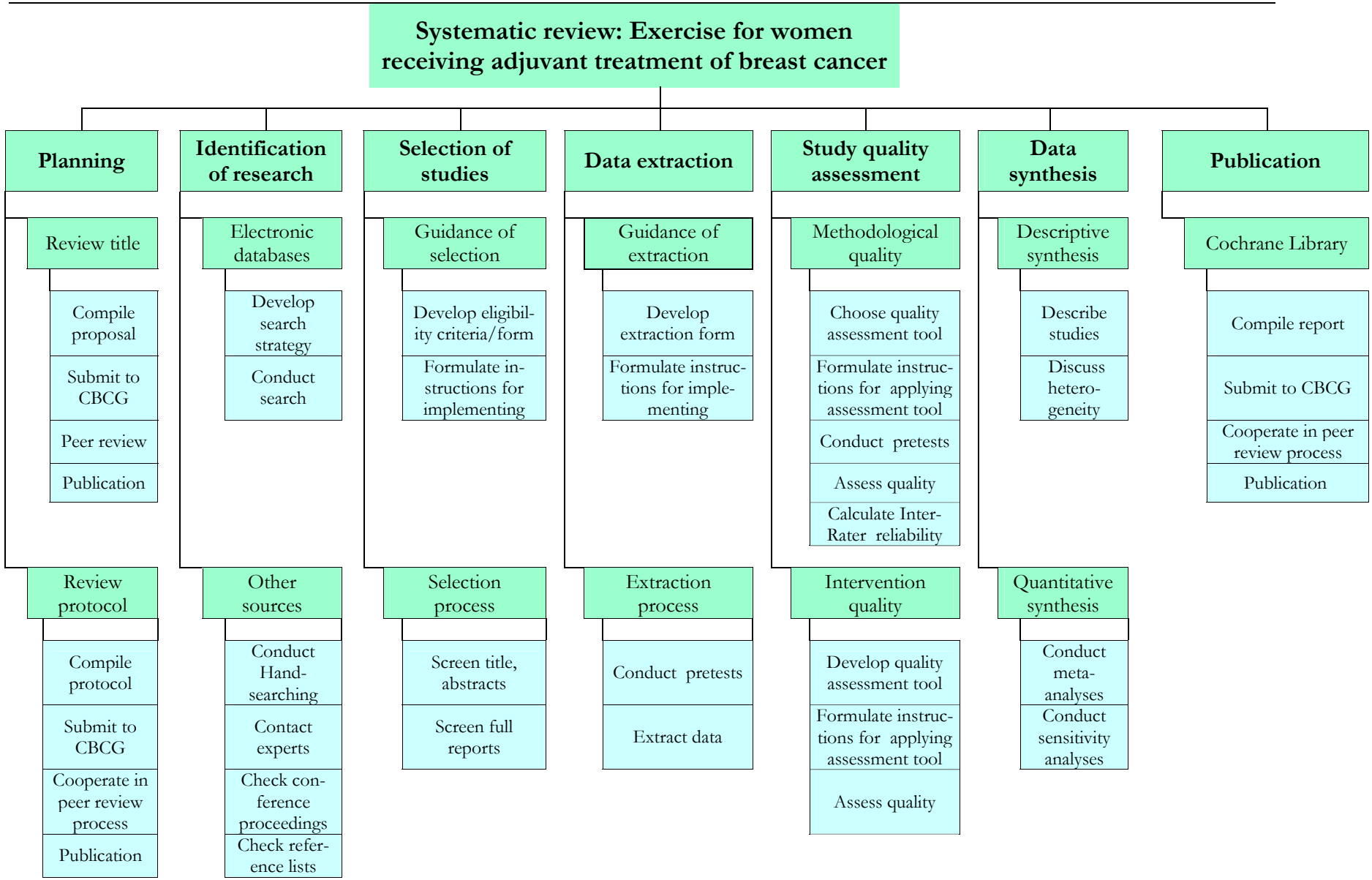

Figure 4: Work breakdown structure

Electronic databases were used as the main source for identifying relevant research. Since ex ante, no single electronic database could be identified as comprehensive in the review topic and because databases also tend to have geographical and language biases, the search strategy included a range of databases:

- **MEDLINE** with records of biomedical literature
- **EMBASE** with records of biomedical literature
- **CINAHL** (Cumulative Index to Nursing and Allied Health Literature) with records of literature on all aspects of nursing and allied health disciplines
- **PsycInfo** with records of research in psychology and related behavioural and social sciences
- **SPORTDiscus** with records of research in sport, health, fitness and sports medicine
- **Cochrane Breast Cancer Specialised Register (CBCSR)** with records of trials in healthcare regarding breast cancer identified through the work of the CBCG.

A separate search strategy was developed for each database. In order to maximise the yield of relevant articles, the search strategies were built to make the literature search sensitive, rather than specific. So, it was expected to retrieve a large proportion of articles, which would not be relevant to the review question. After an initial search for relevant studies, a series of update searches were conducted to identify new studies which appeared after the initial search.

The following structured approach was used in order to develop search terms that could be effectively combined for searching electronic databases: first, the review question was broken down into its facets of population, intervention, and study design. Then, the search terms in each facet which best captured the subject were identified. The group of search terms covering each facet of the review question included textwords (free text) in the title and abstract of studies as well as any available subject indexing terms that were assigned by the database producer. Textwords and their variants were chosen based on relevant studies on the review topic that had already been identified. Information on the subject indexing used by databases was thesaurus-derived. Terms within one facet were joined with the Boolean 'OR' operator; these sets of terms, describing each facet, were then joined together with the 'AND' operator. The search strategy for MEDLINE implemented the standard Cochrane search strategy for randomised controlled trials (RCTs), i.e., the search strategy used for identification of RCTs in Cochrane reviews. Because of the complexity of the question it seemed to be more feasible for most databases to omit the facet describing adjuvant cancer treatment from the search strategy. The periods "during treatment" and "post-treatment" were distinguished later, at the stage of title and abstract checking. The development

of the search strategy was an iterative process and the final strategy was built up from a series of pilot searches.

Reference lists from publications (primary studies and reviews) that were found through database searches were scanned to identify further studies for consideration. These search activities were complemented by handsearching, and by searching grey literature and conference proceedings. Key journals, relevant in the fields of exercise and health promotion in the cancer diagnosis-rehabilitation continuum, were hand-searched to identify articles that might had been missed in database and reference list searches. Hand-searching means that a journal was searched page by page (i.e., by hand), including editorials, letters, etc., to identify reports of randomised controlled trials and controlled clinical trials. Grey literature was searched in the System for Information on Grey Literature (SIGLE), where reports, technical reports, discussion papers or other formats, which are not indexed in the major databases, are indexed. Dissertations and theses were searched for in ProQuest Digital Dissertations, which provides access to American dissertations, and Masters' theses and in DissOnline.de, the information system for German dissertations. Conference proceedings that provide information on research in progress as well as completed research were searched for via relevant specific conferences and Conference Papers Index (CONFSCI), which is a bibliographic database from Cambridge Scientific Abstracts that provides access to international research papers and findings presented at scientific and technical conferences and meetings throughout the world. To further supplement identification of research, eight research registers were searched for ongoing research. Finally, after a thorough and systematic search had been conducted, a list of studies that met the inclusion criteria was sent to experts in the field of exercise interventions in cancer patients. They were requested to check the list for completeness, and to provide information on any ongoing research that could be considered for inclusion in the review. A detailed summary of search activities can be found in Appendix 2.

3.2.3 Search updates within duration of review implementation

The principal search for study identification was conducted in 2004 after the review protocol had been published. This search was updated quarterly during the implementation phase of the review in order to capture newly published reports; the last search for primary studies was conducted in September 2008. MEDLINE and CINAHL turned out to be comprehensive databases in the review topic. Updating searches were conducted in MEDLINE and the Cochrane Breast Cancer Specialised Register; CINAHL was not accessible over the whole review period and subsequently was not searched again after the first basic search.

3.2.4 Selection of studies

Study selection was a multi-stage process that started with the development of study selection criteria. Inclusion and exclusion criteria were developed directly from the review question: Should women, who are undergoing adjuvant treatment of breast cancer, be offered exercise? These criteria were defined in terms of the population, the intervention, the outcomes, and the study designs of interest. Only studies that met the inclusion criteria were included in the review. With regard to the population, trials were included that reported on women receiving adjuvant treatment (chemotherapy, hormonal therapy, or radiotherapy) for breast cancer. Breast cancer was restricted to stages 0-III. If trials had included women with stage IV breast cancer, i.e., with distant metastasis, these trials would have been excluded from this review. Also trials that included women who had already completed adjuvant cancer treatment or were treated for cancers other than breast cancer were excluded. With regard to the intervention, trials with an intervention consisting of aerobic exercise training or resistance exercise training were included. Aerobic exercise training was defined as a training to improve cardiorespiratory endurance and the efficiency of the aerobic-energy producing systems. This type of exercise involves the use of large muscle groups over prolonged periods in activities that are rhythmic and aerobic in nature (e.g., swimming, walking, hiking, cycling, rowing, or endurance games). Resistance training was defined as a training to increase muscle endurance – i.e., the ability of a muscle group to execute repeated contractions over a period of time sufficient to cause muscular fatigue or to maintain a specific percentage of the maximum voluntary contraction for a prolonged period of time. Trials that examined complex exercise interventions – such as a program of exercise training, and diet, or a program of exercise training and behavioural therapy – were excluded. Also, trials with exercise interventions restricted to selected body functions only (e.g., arm mobility) were excluded. With regard to outcome measures, trials were included that employed at least one outcome measure out of the following outcome measurement categories: physical functioning, health-related physical fitness, symptom experience, biological or physiological outcomes, mental health, health-related quality of life, and harm. Study designs that qualified for inclusion into the review were randomised as well as non-randomised controlled trials. No language restrictions were applied**.** Selection criteria are tabulated in Table 1.

Table 1: Inclusion criteria for reviewing benefits of exercise

	Inclusion criteria	Exclusion criteria
Participants	- Women receiving adjuvant treatment of breast cancer - Breast cancer stages I-III	- Adjuvant treatment completed - Cancer other than breast cancer
Intervention	- Aerobic exercise - Resistance exercise - Mixed exercise (aerobic and resistance)	- Exercise as part of a complex intervention - Exercise restricted to local muscular endurance - Stretching or flexibility training
Outcome	- Physical functioning (objective mobility, perceived mobility, participation in life activities) - Physical fitness (cardiorespiratory fitness, muscular strength, muscular endurance, body composition) - Symptom experience - Biological and physiological variables - Mental health (e.g., depression, anxiety) - Health-related quality of life - Harm	- Adherence data only
Study design	- Randomised controlled trials - Non-randomised controlled trials	- Uncontrolled trials - Group assignment based on self-selection

Initially, the selection criteria were applied liberally to the citations generated from computer database searching: reports potentially fulfilling the inclusion criteria of this review were selected based on title and abstract. The titles and abstracts identified as being potentially relevant were provisionally included. Then, full text articles of any possibly relevant reports were retrieved for more detailed evaluation. For the final selection of trials an eligibility form was used. The eligibility form was designed for this review in order to systematically assess eligibility based on the predefined inclusion and exclusion criteria (see Appendix 3). The decision algorithm required the fulfilment of the predefined eligibility criteria (see Table 1). A report was excluded according to the first criterion that it did not fulfil. Study selection was performed independently by two review authors to improve reliability. Disagreements were resolved by consensus; if necessary a third person was consulted to reach a final decision. Figure 5 describes the process flow of the review – from study selection to meta-analysis. These steps are also described in the following sections.

3.2.5 Data extraction

The aim of data extraction is to produce a data repository out of which the analysis could emerge by means of condensing information from that reported by primary investigators. Because this can be a subjective process and prone to error, several measures were implemented in order to minimise bias at all stages of this process: first, the review protocol already contained a data extraction form which listed the data items to be extracted from each of the primary studies and additionally, a statement of practice for implementing data extraction (see Appendix 4) was developed that included instructions and decision rules about extracting data because this improves accuracy and consistency in data extraction which is extremely important. Finally, data extraction was performed independently by two data extractors to improve reliability. Since published reports did not always provide all the information that needed to be extracted, authors of the respective studies were contacted in such circumstances to provide further information. The data extracted by the review authors were compared and any disagreements were discussed and resolved by consensus among the data extractors. A separate form was used to denote and correct errors or disagreements; thus, a historical record of the decisions and refinements that occurred during the conduct of the review was obtained.

The final data extraction form comprised two rather different parts: one part that contained information about study characteristics, i.e., the study descriptors (see Appendix 4), and the part that contained information about the empirical findings of the study, i.e., effect measure data (see Appendix 4). There is a practical reason for distinguishing between study descriptors and effect size data: study descriptors apply to the entire study and need to be extracted only once for a given study because it is the same for different variables, follow-ups, sample breakdowns, and the like. In contrast, a study can include numerous measured variables that represent different constructs and so data for several distinct effect sizes have to be extracted for each study. Therefore, a complete data extraction per study included one set of data on the study level and as many sets of effect measure data as needed to extract all the relevant quantitative findings that the study reported. A study was regarded as consisting of a set of data collected under a single research plan from a designated sample of respondents. Subsequently, data from multiple written reports of one study were assembled together in the process of data extraction and analysis.

The data extraction form for study descriptors comprised study characteristics such as study methodology, samples, intervention, and setting, all of which representing factors that may influence the nature and magnitude of empirical findings. It was based on open-ended items (as opposed to pre-coded items) to which information relevant to the issue at hand was recorded from the study. These responses were later examined for commonalities and then coded into a man ageable set of categories with the aim of building data files for data synthesis.

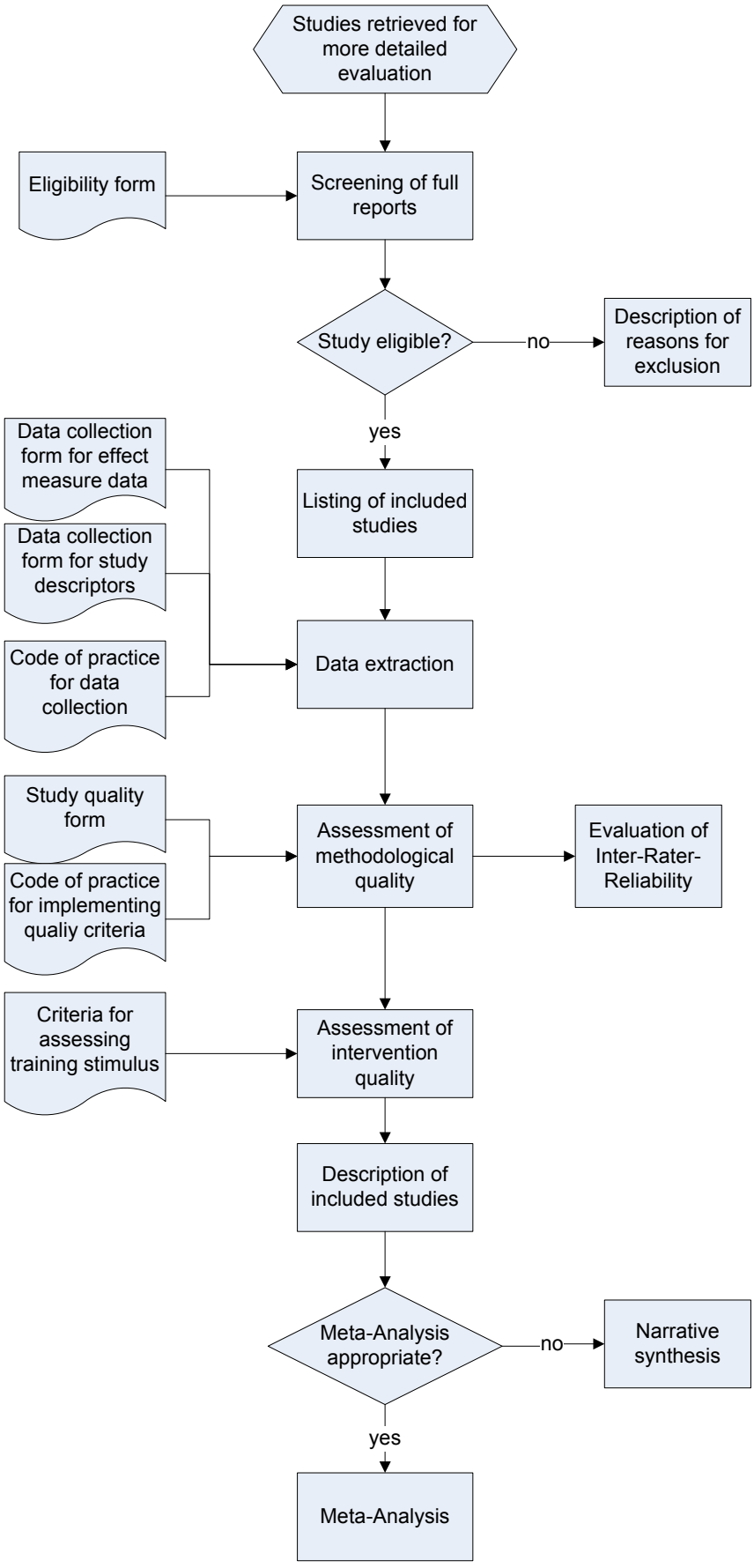

Figure 5: Process flow of review steps

The coding frame comprised methodological, participant, and intervention characteristics needing categorisation. Methodological characteristics included study design (e.g., randomisation) and all information needed for quality assessment. Participant characteristics included age, breast cancer staging, previous physical activity, and type of cancer treatment. Exercise attributes coded included the setting of the intervention, whether a behaviour change theory was applied or not, type of exercise, intensity, frequency per week, and duration per session. With regards to outcome measures, outcome constructs and assessment instruments for each construct were extracted.

Intervention effect data was recorded as a profile of associated information describing the particulars of the statistical findings. As a first step, data on outcomes were extracted in the format in which they were reported; in a second step, data were transformed regarding the requirements of RevMan Analyses, the computer program of the Cochrane Library used for statistical pooling. The following data was extracted from trial reports for analyses: For dichotomous outcomes, the number of events and the number of participants in each group was extracted. For continuous outcomes the mean values of the outcomes, the standard deviations of the outcomes, and the number of participants for whom the outcome had been assessed were extracted in each of the two groups. Further, some supporting information was extracted such as nature of the variable (e.g., construct measured, measurement operationalisation, or presentation of variable as mean change from baseline to final values or as final value) or point in time when a variable was measured and time covered (end of intervention or follow-up).

3.2.6 Study quality assessment

The assessment of trial quality was a crucial part of the process of this systematic review, since the validity of the conclusions of a systematic review depends on the methodological quality of the primary studies included. Assessment of methodological quality of the included trials was guided by the definition of methodological quality as "the likelihood of the trial design to generate unbiased results that are sufficiently precise and allow application in clinical practice" (Verhagen et al. 2001). Components of methodological quality can influence effect estimates in two directions: both underestimation and overestimation of the true effects seem to be possible when study quality is low (Verhagen et al. 2001).

As a quality assessment instrument, a variant of the vanTulder scale was applied (vanTulder et al. 1997): this instrument is based on 17 quality items, which are scored numerically to provide a quantitative estimate of overall study quality. Scores were generated by weighting all items equally. The vanTulder scale is a quality assessment instrument that has already been used in a number of systematic reviews in the field of physiotherapy and therefore appeared to be adequate

for the purposes of this review. This scale includes a set of generic core items with all criteria of the Jadad score (Jadad et al. 1996) and the Delphi List (Verhagen et al. 1998); both instruments were developed according established principles used for creating measurement scales. The items of the scale consist of internal validity criteria, descriptive criteria, and criteria of statistical analysis (Table 2). The internal validity criteria refer to characteristics of primary studies that might be related to selection bias (i.e., systematic differences between comparison groups in prognosis or responsiveness to the intervention), performance bias (i.e., systematic differences in care provided to the participants in the comparison groups apart from the intervention under investigation), attrition bias (i.e., systematic differences between comparison groups arising from withdrawals or exclusions of participants from the study sample), and detection bias (i.e., systematic differences between comparison groups with respect to how outcomes are determined). Accordingly, randomisation and allocation concealment, co-interventions, observer blinding, and intention-to-treat analysis were among those checked in the quality scale. Trials designed to compare exercise interventions to their absence cannot blind neither participants nor exercise facilitators. Therefore, methodological quality regarding blinding was judged solely on blinding assessors who collect outcome data: the aim of blinding assessors is to reduce differential assessment of outcomes. Descriptive criteria of the vanTulder scale refer to external validity: information derived from descriptive criteria (eligibility criteria, similarity of baseline characteristics, and description of intervention, adverse effects, and timing of follow-up measurements) allow assessment of whether effects observed in primary studies may be generalised. Quality forms were used to perform quality assessment (see Appendix 5) and a code of practice for implementing quality criteria was developed in order to allow reliable quality assessment (see Appendix 5).

Each criterion was answered with 'yes', 'no' or 'n/a' (not available); answers were coded with: 'yes' as '+', 'no' as '–' and 'n/a' as '?'. A quality score was calculated for each study by summing positive scores for individual items, resulting in a possible score from 0 to 17. Following vanTulder (vanTulder et al. 1997), moderate quality was defined as fulfilling a score between nine and 12 (50 to 75%) of all methodological quality criteria; high quality was defined as fulfilling at least 13 (> 75%) of all methodological quality criteria.

The process of assessing methodological quality was guided by the intent to distinguish between the quality of the trial and the quality of its report. Following Moher, the quality of a report was regarded as "providing information about the design, conduct, and analysis of the trial" (Moher et al. 1995).

Table 2: Quality criteria assessed with the vanTulder scale

Quality aspect	Quality criteria assessed with the vanTulder scale
Internal validity	
- Selection bias	- Was a method of randomisation performed? - Was the treatment allocation concealed?
- Performance bias	- Were co-interventions either avoided or comparable? - Was adherence acceptable in all groups?
- Attrition bias	- Was the withdrawal/ drop-out rate acceptable and were reasons described? - Did the analysis include intention-to-treat analysis?
- Detection bias	- Was the outcome assessor blinded to the intervention? - Was timing of outcome assessment comparable in both groups? - Were outcome measures relevant?
Description	- Were the eligibility criteria specified? - Were groups similar at baseline? - Were interventions explicitly described? - Were adverse effects described? - Was short-term follow-up measurement performed? - Was long-term follow-up measurement performed?
Statistics	- Was the sample size described for each group at randomisation? - Were point estimates and measures of variability presented for the primary outcome measures?

This distinction between the trial and its report is important to avoid the case where a well reported trial with several biases would receive a high-quality score or where conversely, a well designed and conducted but poorly reported trial would receive a low quality score. Therefore, where it was unclear whether it was the reporting of the trial that was weak or its design and conduct, authors of primary studies were contacted to ask for more detailed information. With over-reporting, on the other hand, the attempt to identify and then subject to quality assessment was made by means of items asking for the details of trial design and conduct: for example, trials were assessed with respect to whether they had performed a method of randomisation, something some "randomised" studies may actually not have done (Verhagen et al. 2001). Methodological quality based on the summary quality score was intended to be used as one criterion in sensitivity analyses by estimating a pooled effect with studies above different methodological cut-off points.

However, scoring systems tend to be subjective and the reliability of this list is unknown, as is the case for most criteria lists. Therefore methodological quality was assessed independently by two

raters in a subset of studies. Disagreements in quality assessments between the two raters were resolved by consensus and, if disagreement persisted, a third person was consulted for a final decision. Inter-rater agreement for the overall methodological quality assessment was measured using the intra-class correlation coefficient (ICC). The ICC is based on the analysis of variance (ANOVA) model. Variance in quality scoring *between* cases (here: primary studies) was distinguished from the variance in quality scoring *within* primary studies that indicates lacking agreement between raters. When differences in quality scores are high between primary studies with simultaneously low variance in quality scores within primary studies, observations are regarded to be reliable. ICC calculation in SPSS (Statistical Product and Service Solutions) was based on the *two-way mixed model* with measures of absolute agreement (Shrout and Fleiss 1979): differences among primary studies and variability among the raters were treated as the two systematic sources of variance; differences among primary studies were treated as a random factor in the ANOVA model, variability among the raters becomes the second factor in the two-way ANOVA model which is treated as a fixed factor, resulting in the two-way mixed model. In the mixed model, inferences are confined to the particular set of raters used in the quality assessment process. The ICC is interpreted as the proportion of total variance accounted for by variation within primary studies. The level of reliability for the ICC was described in this review using the same categories that were suggested by Landis and Koch (1977) for Kappa, as another measure of inter-rater agreement. ICC values of 0.21 to 0.40 were considered as 'fair agreement', values from 0.41 to 0.60 as 'moderate agreement', from 0.61 to 0.80 as 'substantial agreement' and from 0.81 to 1.00 as 'almost perfect agreement'. The ICC was calculated for a sample of included studies solely to assure sufficient reliable quality assessment.

The exercise intervention was evaluated separately regarding its potential to provide any adequate training stimulus. Aspects that were assessed are exercise intensity, exercise frequency, duration of single exercise sessions, and duration of the exercise intervention program. Analysis of the training stimulus roughly followed the ACSM guidelines for exercise prescription for the elderly (Balady et al. 2000), the ACSM references for exercise programming for cancer patients (Schwartz 1997) and the exercise prescription guidelines for early-stage cancer patients and cancer survivors as recommended by Courneya (Courneya et al. 2000). Trials were classified as providing an adequate training stimulus if they met three of four predefined requirements (see Table 3 and Table 4).

The prescribed exercise intensity should be above the minimal level required to induce a "training effect", yet below the metabolic load that evokes abnormal clinical signs or symptoms. For women receiving adjuvant treatment of breast cancer aerobic endurance training of moderate intensity, which is dependent on current fitness level and medical treatments, seems to be feasi-

ble. Guidelines recommend 50% to 75% of maximal oxygen consumption (VO_2max), i.e., the highest rate of oxygen consumption attainable during maximal or exhaustive exercise; or 50% to 75% of heart rate reserve ($HR_{reserve}$), i.e., the difference between the maximum heart rate and resting heart rate; or 60% to 80% of the maximum heart rate (HR_{max}), i.e., the heart rate that a person could achieve during maximal physical exertion; or an rate of perceived exertion (RPE) of 11 to 14 (Courneya et al. 2000). $HR_{reserve}$ is the best guideline if HR_{max} is *estimated* rather than measured. Furthermore, program duration had to be at least six weeks with a frequency of at least three times a week with sessions of at least 20 minutes duration (see Table 3).

Table 3: Criteria for assessing quality of aerobic endurance training

Training stimulus aspect	Quality criteria
Intensity	- 60-80% of maximum heart rate(HR_{max}) or - 50-75% of heart rate reserve($HR_{reserve}$) or - 50-75% of maximum oxygen consumption (VO_2max) - 11-14 rate of perceived exertion (RPE)
Duration per session	20-60 min (continuous bouts of minimum 10 minutes each throughout the day) or exercise to tolerance
Frequency per week	At least three days per week
Program duration	At least six weeks

Regarding resistance training, a minimum of eight to ten separate exercises that train the major muscle groups (arms, shoulders, chest, abdomen, back, hips, and legs) should be performed. Muscular strength as well as muscular endurance is developed by the overload principle, i.e., by increasing the resistance to movement or the frequency or duration of activity to levels above those normally experienced (Balady et al. 2000). The intensity of resistance training can be manipulated by varying the weight, the number of repetitions, the length of the rest interval between exercises, or the number of sets of exercises completed (Balady et al. 2000). The training stimulus of resistance training was regarded as adequate when a minimum of one set, with ten to 15 repetitions of each of these exercises, was performed to the point of volitional fatigue. As with aerobic endurance training, resistance training in primary studies had to be performed on two to three days per week, with program duration of at least six weeks, to be assessed as adequate (see Table 4). Intervention quality forms were used to perform quality assessment (see Appendix 5).

Each criterion was answered with 'yes', 'no' or 'n/a' (not available); answers scored as 'yes' were coded as '+', 'no' as '—' and 'n/a' as '?'. A quality score was then calculated for each study by summing scores for individual items, resulting in a possible score from zero to four. In trials using exercise interventions with both aerobic and resistance modules, the training stimulus was assessed for each module and then the corresponding mean was calculated.

Table 4: Criteria for assessing quality of muscular endurance training

Training stimulus aspect	Quality criteria
Intensity	- 10-15 repetitions to near fatigue or - At least 60% of one Repetition Maximum
Duration per session	At least 1 set
Frequency per week	At least two or three days per week
Program duration	At least six weeks

The next phase following quality assessment and data extraction was to collate and summarise the data that had been extracted from the primary studies. This was accomplished through a descriptive, non-quantitative synthesis that was complemented by the use of meta-analysis. In descriptive synthesis, study characteristics were tabulated to qualitatively assess variation in participants, interventions, and measurement of outcomes across studies. Furthermore, the tabular summaries were used to plan the quantitative synthesis.

3.2.7 Summarising effects across studies

Quantitative synthesis through meta-analysis focuses on the aggregation and comparison of the findings of different research studies. The reason for combining data from individual studies is that these may not be able to estimate effects precisely, because of small sample sizes. By combining the data from these studies, a meta-analysis acquires the statistical power to increase the precision of the estimate of effect. However, the focus lays on magnitude and direction of a relationship, not merely its statistical significance.

The steps involved in meta-analysis are to create an independent set of relevant effect sizes for each construct to be analysed, compute the weighted mean and the confidence interval for the mean, and to test for homogeneity.

3.2.7.1 Creating an independent set of effect sizes

Statistical independence was defined at the study level: if a study presented more than one effect measure for a construct by using different measurement operationalisations (e.g., body composition assessment through weight, body mass index, relative lean body mass, skinfolds), they were not included in the same analysis. In such cases where multiple effect sizes were presented for one outcome, only the effect size that was most comparable with those in other studies was selected for inclusion in the meta-analysis.

The effect measure (treatment effect, estimate of effect) is the statistical representation of the observed relationship between an intervention and an outcome. Outcome assessments across included studies predominantly employed either measurements (e.g., body weight or aerobic

capacity) or assessment scales (e.g., Piper Fatigue Scale or Beck Depression Inventory). These assessment scales actually yield ordinal data, but were analysed as continuous outcomes in the studies included and were subsequently treated as continuous outcomes in meta-analysis as well. This procedure appeared to be adequate because with increasing numbers of categories in assessment scales, ordinary outcomes acquire similar properties to continuous outcomes. Thus, meta-analyses had to deal predominantly with continuous data. For continuous data, the treatment effect is expressed as a difference in means or standardised difference in means. The *unstandardised mean difference* effect size statistic is constructed directly from the differences between the group means; it is applicable when the same operationalisation of a variable of interest, with the same measurement procedures and the same numerical scale, is used in all of the research findings to be meta-analysed. In the Cochrane Database of Systematic reviews, the unstandardised mean difference is termed the *weighted mean difference* (WMD) which is a confusing term since no weighting is involved in calculating the statistical summary of a single trial.

If, however, different measurements or scales are used for assessing the same outcome the *standardised mean difference* (SMD) is used. This effect size statistic applies to research findings that contrast two groups on their respective mean scores on some dependent variable that is not operationalised in the same way across study samples. Under these circumstances, study results are standardised on a uniform scale before they are combined. The standardised mean difference effect size statistic expresses the size of the intervention effect in each study relative to the variability observed in that trial and is calculated according to:

$$\mathbf{SMD} = \frac{m_1 - m_2}{sd_{pooled}}$$

where m_1 is the mean for group 1, m_2 is the mean for group 2, and sd_{pooled} is the pooled standard deviation. By standardising the difference between exercise and control group means on the corresponding pooled standard deviation, intervention effects are represented in terms of standard deviation units irrespective of the original operationalisation and so can be meaningfully combined and compared across studies.

For outcomes with dichotomous data (e.g., onset of lymphedema) the effect measure was generated as a measure of relative effect using the risk ratio (relative risk), i.e., the ratio of the probability of the event occurring in the exercise group versus a non-exercising control group.

3.2.7.2 Meta-analysis

Results from individual studies were statistically combined to provide a weighted average estimate of the overall intervention effect. A weighted average is defined as

$$\text{Weighted average} = \frac{\sum ES_i W_i}{\sum W_{i^d}}$$

Where ES_i is the intervention effect (effect size) estimated in the i^{th} study, W_i is the weight given to the i^{th} study, and the summation is across all studies.

Meta-analysis employs *weighted* analysis for all data-analyses involving effect sizes, because from a statistical perspective effect size values based on larger samples do more precisely estimate the corresponding population value than those based on smaller samples, due to a smaller sampling error in large samples compared to that in small samples. Hence, there is the problem of variable reliability of the information that the effect sizes carry. The way this problem is handled in meta-analysis is to weigh each effect size by a term that represents its precision, so that its contribution to any statistical analysis is proportional to its reliability. Effect sizes based on larger samples are weighted more in statistical analysis than those based on smaller samples because they embody less sampling error. The optimal weights are based on the standard error of the effect size (Hedges and Olkin 1985). Each effect size is weighted by the inverse of its variance (calculated as the square of the standard error).

For computing the mean effect size with the corresponding confidence interval, a random effects model was chosen, since the differences between studies arising from variations in the exercise program, settings etc. whose sources cannot be identified, are expected to be random. The random effects model includes another random component in the statistical model in addition to subject-level sampling error to represent the variation among effect sizes. This means that the weight applied to each effect size represents both subject-level sampling error and the additional random variance component assumed by the model.

Data were analysed using the *RevMan Analyses* statistical package in Review Manager (RevMan 2003). RevMan does accept summary data in only two formats – events and sample size (for dichotomous outcomes), or means and standard deviations (for continuous outcomes). If any studies provide data in another format (such as mean and confidence intervals) it was necessary to manually manipulate the statistical information available in the reports to estimate required statistics for those studies. These estimation procedures can be distinguished into several categories with different degrees of approximation to the required statistics:

- Descriptive data from which means (m) and standard deviations (SD) can be computed (e.g., standard errors or confidence intervals)
- Complete significance tests along with sample sizes (e.g., t-values from a t-test or F-values from a one-way ANOVA)

- Exact p-values for a t-test or a one-way ANOVA, and the sample size for each group, or the total for both, or
- Categorical p-values for a t-test or a one-way ANOVA, and the sample size for each group, or the total for both.

In the meta-analyses conducted within this review, the required statistics were estimated from descriptive data and from significance tests, the approaches with higher levels of approximation. Standard deviations were estimated from the results of significance tests as follows. First, the standard error of the difference in means ($SE_{m_1-m_2}$) was calculated by dividing the difference in means by the *t*-value (the *t*-value in independent t-tests is the ratio of the difference in means to the standard error of the difference in means).

$$\text{Standard error of the difference in means } (SE_{m_1-m_2}) = \frac{m_1 - m_2}{t}$$

The standard deviation was then obtained from the $SE_{m_1-m_2}$ using the following formula:

$$sd = \frac{SE_{m_1-m_2}}{\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$$

This standard deviation was then allocated to both, the exercise and to the control group. This method was also used for test statistics from a one-way F-ratio based on only two groups, where $t^2 = F$. Theoretically it is possible to obtain an estimate of the standard deviation for a specific measure from another study that used that measure with a very similar sample. Nevertheless, within these meta-analyses, no effect size was calculated based on the standard deviation for a particular variable of another study, since samples did not appear to be comparable.

The formulation of the standardised mean difference implemented in RevMan Analyses is Hedges adjusted g, which is very similar to Cohen's d, but includes an adjustment for small sample bias. Further, the version of random effects meta-analysis implemented in RevMan Analyses is that described by DerSimonian and Laird (DerSimonian and Laird 1986). This version incorporates the heterogeneity of effects for obtaining an estimate of the random effects variance component. Weighted individual effect sizes are combined to give a pooled estimate (DerSimonian and Laird Random Effect): each effect size value is multiplied by its respective weight (subject-level sampling error and the additional random variance component), then summed and divided by the sum of weights. The standard error of the pooled intervention effect is used to derive a confidence interval which communicates the precision (or uncertainty) of the summary estimate,

and to derive a p-value which communicates the strength of the evidence against the null hypothesis of no intervention effect. The graphical approach for displaying effect estimates in RevMan Analyses is the forest plot: forest plots for continuous outcomes illustrate (Deeks et al. 2006):

- The raw data (means, standard deviations and sample sizes) for each arm in each study
- Point estimates and confidence intervals for the chosen effect measure, both as blocks and lines and as text
- A meta-analysis using the chosen effect measure (unstandardised mean difference or standardised mean difference) and chosen method (fixed or random effects), both as a diamond and as text
- The total numbers of participants in the experimental and control groups
- Heterogeneity statistics (the chi-squared test and the I^2 statistic)
- A test for overall effect (overall average effect for random effects meta-analyses)
- Percent weights given to each study.

As suggested by Deeks (Deeks et al. 2006), presentation of data as a forest plot (displaying a summary effect of *meta-analysis* , the *grand* mean) was skipped when only a single study was found for a particular outcome. Instead, results of single studies were presented in an additional table.

Trials that contributed to meta-analyses with two exercise groups were incorporated into the meta-analysis with both exercise groups; a control group was allocated to each of them, with a number of participants according to the proportion of participants in the exercise groups.

3.2.7.3 Analysing heterogeneity

The homogeneity of the effect size distribution was analysed to assess the adequacy of the mean effect size for representing the entire distribution, because a mean effect size would not be representative for a distribution with a large variance. In a homogenous distribution the difference of an individual effect size from the population mean arises only by sampling error, whereas in a heterogeneous distribution the variability of the effect sizes is larger than would be expected from sampling error and so each effect size does not estimate a common population mean. Homogeneity testing is based on a comparison of the observed variability in effect size values with an estimate of the variance that would be expected from sampling error alone.

The classical measure of heterogeneity is Cochran's Q, which examines the null hypothesis that all studies are evaluating the same effect. Cochran's Q is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with

the weights being those used in the meta-analysis. Q is distributed as a chi-square statistic with k (number of studies) minus 1 degrees of freedom (df). Q has low power as a comprehensive test of heterogeneity with small numbers of effect sizes, especially if they are based on small subject samples. While a statistically significant result may indicate a problem with heterogeneity, a non-significant result must not be taken as evidence of no heterogeneity.

Higgins (Higgins et al. 2003) developed an alternative approach that quantifies the effect of heterogeneity, providing a measure of the degree of inconsistency in studies' results. The quantity I^2 describes the percentage of total variation across studies, which is due to heterogeneity rather than chance (sampling error). The statistic I^2 is calculated as

$$I^2 = \frac{Q - df}{Q} \times 100\%$$

Where Q is the chi-squared statistic and df is its degree of freedom (Higgins and Thompson 2002, Higgins et al. 2003). I^2 is an intuitive and simple expression of the inconsistency of studies' results. Following Higgins (Higgins et al. 2003), I^2 values of 25% were considered to indicate low heterogeneity, I^2 values of 50% to indicate moderate heterogeneity and I^2 values of 75% to indicate large heterogeneity.

Potential effect modifications due to different populations or exercise intervention characteristics (such as setting or training stimulus) were investigated and discussed descriptively but were not analysed quantitatively using subgroup-analysis or meta-regression since the number of studies was too low. Deeks et al. (2006) advise that for undertaking simple regression analyses at least ten observations (i.e., ten studies in a meta-analysis) should be available for each characteristic modelled, since it is very unlikely that an investigation of heterogeneity would produce useful findings unless the number of studies is substantial. Therefore, possible sources of heterogeneity were investigated and discussed only *descriptively*. As potential explanations for heterogeneity, the exercise dose, adherence, the use of a health promotion theory and the exercise history of participants were examined. Furthermore, sensitivity analyses were employed to investigate heterogeneity, where heterogeneity due to the presence of one outlying trial with results that conflict with the rest of the trials was examined by performing analyses both with and without outlying trials as part of a sensitivity analysis. However, as Deeks et al. (2006) point out, explorations of heterogeneity that are devised after heterogeneity is identified can at best lead to the generation of hypotheses and furthermore, investigations of heterogeneity are of questionable value when there are very few studies.

Reporting biases make positive studies easier to find than those with non-significant results; subsequent over-representation of positive studies in a systematic review may mean that the

respective review is biased toward a positive result. Efforts were made to minimise this by extensive searching. Estimating how big this problem is in this review was not feasible: the method available in RevMan for estimating the problem of publication bias is the funnel plot, which were not performed because the power of this method is limited when it comprises only a few small studies, that is, in those situations when bias is most likely to distort the results of the meta-analyses (Deeks et al. 2006). Furthermore, true heterogeneity in treatment effects may also lead to funnel plot asymmetry and so the option is not available in RevMan Analyses when the random effects model is chosen, which incorporates heterogeneity among trials.

3.3 Methods for the assessment of harm

In order to answer the research question, whether exercise should be offered to women receiving adjuvant treatment of breast cancer, benefits of exercise have to be outweighed with potential harm and thus, the third objective of the review was to answer the research question "what harm is associated with exercise during adjuvant treatment of breast cancer". This means that this review aimed to evaluate both the benefit and harm and subsequently required a more complex design to handle different sets of studies for various outcomes. In fact, using different search strategies and eligibility criteria for studies of harm, compared to studies of benefit, generated a second group of eligible studies. However, compared to the methods for conducting systematic reviews of efficacy, which are well-established, guidance on how systematic reviews of harm should be performed is limited (Golder et al. 2006).

The supplementary search became necessary because there was insufficient evidence regarding the potential harm of exercise interventions during cancer treatment based on information from the studies of benefit. The need for a supplementary search was further underpinned by theoretical reasoning: first, in a (randomised) controlled trial designed to assess aspects of efficacy or effectiveness, this study design may not be able to identify all possible harms caused by exercise because in RCTs, only what was looked for will be seen (Busse et al. 2002). Also, the reporting of RCTs in regard to quality and quantity of harmful effects is currently largely inadequate (Ioannidis et al. 2004).

The following inclusion criteria were applied for reviewing harmful effects of exercise: study designs eligible for assessing potential harm were controlled trials (randomised and non-randomised). This procedure facilitated identification of data on a well-recognised and easily detectable harmful effect. In contrast, it would not allow the identification of information on harmful effects that were new, rare, or long-term. However, this procedure seemed adequate since potential harmful effects of exercise in the context of breast cancer are well-known (e.g., injuries). The study of harm had to be a key trial objective, which means that the harm had to be

one of the major primary or secondary outcomes of trials to be included. This approach ensured that surveillance of harm was active, with structured questionnaires or interviews or predefined laboratory or other diagnostic tests. A preliminary literature search suggested that there would be quite few publications reporting harmful effects of moderate exercise training *during* adjuvant cancer treatment and thus, all studies were eligible that investigated harmful effects in the rehabilitation of breast cancer, either *during* or *after* adjuvant cancer treatment. The rationale behind this is the following: if harm appears to be substantial in breast cancer patients who have completed cancer treatment, then harm is probably to be expected during adjuvant treatment as well. Evidence of no harm however, does not indicate that there is no harm for breast cancer patients under adjuvant treatment as well. For an overview on inclusion criteria see Table 5.

Table 5: Inclusion criteria for reviewing harm associated with exercise

	Inclusion criteria	Exclusion criteria
Participants	- Women with breast cancer - Breast cancer stages I-III	- Cancer other than breast cancer
Intervention	- Aerobic exercise - Resistance exercise - Mixed exercise (aerobic and resistance)	- Stretching or flexibility training
Outcome	- Harm	- Other outcomes only
Study design	- Randomised controlled trials - Non-randomised controlled trials	- Cohort - Case-control - Cross-sectional - Case series

MEDLINE search was conducted with WinSPIRS 5.0 in October 2006 (WinSPIRS is the local access, Windows-based version of – SPIRS – the SilverPlatter Information Retrieval System); October 2006 is the cut-off point for inclusion of trials. The search strategy employed two approaches: first, text words for harms that could already be specified were used, such as lymphedema or injury. This approach is useful for harms under consideration that are already known. The second approach was to use synonyms of harms and related terms (text words). Additionally, references of identified trials were checked for identifying further reports. The search strategy is presented in detail in the Appendix 6. Selection of trials was performed, through title and abstract checking based on the inclusion criteria. For data extraction in selected and finally included studies, a coding form was designed (see Appendix 6), which considered information on the following facets of studies: type of harm assessed, time period of observation, type of exercise, type of study, frequencies or proportions of harms, and statistical tests.

Quality assessment was based on an 8-criteria quality-rating instrument for assessing harm (Chou and Helfand 2005). The following factors were considered: selection of participants, description of population, loss to follow-up, pre-specification and definition of harms, description of ascertainment technique, ascertainment of adverse events, statistical analysis of potential confounders, and duration of follow-up. The quality assessment form for studies of harm can be found in Appendix 6. Each quality criterion was coded with "1" if the study did meet this criterion; otherwise it was coded with "0". The total quality score was calculated by summing up the criteria. The maximum total quality score was eight on a scale from zero to eight: following Chou and Helfand (2005) a quality score of more than six was rated as good, a quality score from four to six as fair and a quality score of less than four as poor quality. Information from primary studies examining harm was synthesised descriptively.

4 Results: Identification and description of studies

Beneficial effects and harmful effects of exercise interventions were reviewed with similar rigour in this systematic review. Therefore, two independent sets of studies were included in this review and are described separately in the following paragraphs. Each included study was assigned one identification label (study-ID) – composed of the name of the first author and the year of publication. This study-ID is used for reporting purposes.

4.1 Studies of benefit

Fifteen studies (as of September 2008) could be identified within the international literature which explored the effects of aerobic or resistance training, or both on physical and mental health outcomes in women during adjuvant treatment of early breast cancer.

The basic search in 2004 resulted in eight studies for inclusion in the review. The process of study selection, starting from initial hits, through potentially relevant studies, and finally to included studies, is illustrated in Figure 6. Through comprehensive searches of bibliographic databases a total of 1688 citations were identified; contact with experts and scanning bibliographies of reviews revealed another 202 studies that deemed potentially relevant. Subsequently, 1890 titles and abstracts were screened. The majority of these citations (n=1858) were excluded because they were not about breast cancer-related health promotion through exercise. These citations included duplicates arising from different databases. Thirty-two study reports were identified as being potentially relevant for inclusion in the review. Full reports were obtained and processed. After screening of the full reports, 23 were excluded from the review. At this stage, the single most important reason for excluding full reports was because the exercise intervention was not concurrent with adjuvant cancer treatment (n=6). One dissertation thesis (Battaglini 2004) that was identified in the basic search had to be excluded temporarily because the author asked for exclusion until publication of his thesis. A total of eight studies were available for inclusion in the review based on the basic search in 2004.

Regular quarterly search updates (overall 17) as well as publication of already identified studies yielded seven more studies to be included in this review. One additional study was identified for potential inclusion based on its abstract only (So et al. 2006); however this study is still awaiting assessment due to language barriers (it is written in Korean) and so is not yet listed in the included studies.

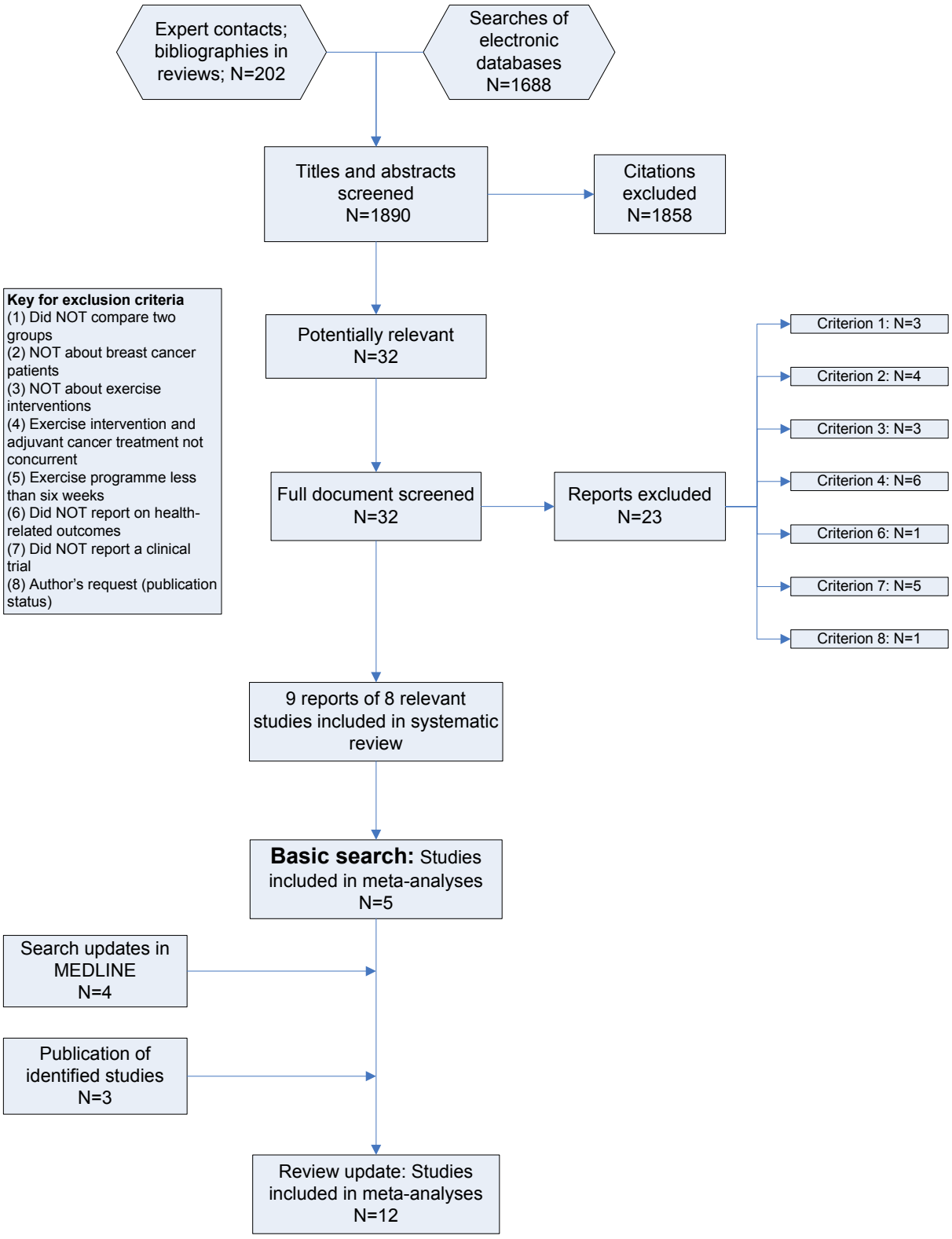

Figure 6: Flow diagram of study selection process

The following 15 studies were included into the review:

Table 6: Reference list of included studies

Study-ID	Reference
1. Battaglini 2007	Battaglini C, Bottaro M, Dennehy C, Barfoot D, Shields E, Kirk D, Hackney A. The effects of resistance training on muscular strength and fatigue levels in breast cancer patients. Rev Bras Med Esporte 12: 139e-144e; 2006. Battaglini C, Bottaro M, Dennehy C, Rae L, Shields E, Kirk D, Hackney A. The effects of an individualized exercise intervention on body composition in breast cancer patients undergoing treatment. Sao Paulo Med J 125: 22-28; 2007.
2. Campbell 2005	Campbell A, Mutrie N, White F, McGuire F, Kearney N. A pilot study of a supervised group exercise programme as a rehabilitation treatment for women with breast cancer receiving adjuvant treatment. Eur J Oncol Nurs 9: 56-63; 2005.
3. Crowley 2003	Crowley, SA. The effect of a structured exercise program on fatigue, strength, endurance, physical self-efficacy, and functional wellness in women with early stage breast cancer. PhD [dissertation]. Ann Arbor: University of Michigan; 2003.
4. Courneya 2007	Courneya KS, Segal RJ, Gelmon K, Reid RD, Mackey JR, Friedenreich CM, Proulx C, Lane K, Ladha AB, Vallance JK, Liu Q, Yasui Y, McKenzie DC. Six-month follow-up of patient-rated outcomes in a randomized controlled trial of exercise training during breast cancer chemotherapy. Cancer Epidemiol Biomarkers Prev 16: 2572-8; 2007. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, Ladha AB, Proulx C, Vallance JK, Lane K, Yasui Y, McKenzie DC. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol 25: 4396-404; 2007.
5. Drouin 2002	Drouin J. Aerobic exercise training effects on physical function, fatigue and mood, immune status, and oxidative stress in subjects undergoing radiation treatment for breast cancer. PhD [dissertation]. Detroit: Wayne State University; 2002.
6. Kim 2006	Kim CJ, Kang DH, Smith BA, Landers KA. Cardiopulmonary responses and adherence to exercise in women newly diagnosed with breast cancer undergoing adjuvant therapy. Cancer Nurs 29: 156-65; 2006.
7. MacVicar 1986	MacVicar M, Winningham M. Response of cancer patients on chemotherapy to a supervised exercise program. Cancer Bull 13: 265-74; 1986.
8. MacVicar 1989	MacVicar MG, Winningham ML, Nickel JL. Effects of aerobic interval training on cancer patients' functional capacity. Nurs Res 38: 348-51; 1989. Winningham ML, MacVicar MG, Bondoc M, Anderson JI, Minton JP. Effect of aerobic exercise on body weight and composition in patients with breast cancer on adjuvant chemotherapy. Oncol Nurs Forum 16: 683-9; 1989.
9. Mock 1997	Mock V, Dow KH, Meares CJ, Grimm PM, Dienemann JA, Haisfield Wolfe ME, Quitasol W, Mitchell S, Chakravarthy A, Gage I. Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. Oncol Nurs Forum 24: 991-1000; 1997.
10. Mock 2005	Mock V, Frangakis C, Davidson NE, Ropka ME, Pickett M, Poniatowski B, Stewart KJ, Cameron L, Zawacki K, Podewils LJ, Cohen G, McCorkle R. Exercise manages fatigue during breast cancer treatment: a randomized controlled trial. Psychooncology 14: 464-77; 2005.

11. Mutrie 2007	Mutrie N, Campbell AM, Whyte F, McConnachie A, Emslie C, Lee L, Kearney N, Walker A, Ritchie D. Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial [online]. BMJ. 334: 517; 2007. Available from: http://www.bmj.com/cgi/reprint/334/7592/517
12. Payne 2008	Payne JK, Held J, Thorpe J, Shaw H. Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. Oncol Nurs Forum 35: 635-42; 2008.
13. Schwartz 2007	Schwartz AL, Winters-Stone K, Gallucci B. Exercise effects on bone mineral density in women with breast cancer receiving adjuvant chemotherapy. Oncol Nurs Forum 34(3): 627-33, 2007.
14. Segal 2001	Segal R, Evans W, Johnson D, Smith J, Colletta S, Gayton J, Woodard S, Wells G, Reid R. Structured exercise improves physical functioning in women with stages I and II breast cancer: results of a randomized controlled trial. J Clin Oncol 19: 657-65; 2001.
15. Winningham 1988	Winningham ML, MacVicar MG. The effect of aerobic exercise on patient reports of nausea. Oncol Nurs Forum 15: 447-50; 1988.

4.1.1 Process of retrieval of included trials in basic search

MEDLINE played a major role in study identification for the review. This is demonstrated through tabulation of initial hits, potentially relevant and finally included studies per database (Table 7). Likewise, from the perspective of the included study, the origin of retrieval shows the importance of MEDLINE for study identification (Table 8). Besides MEDLINE (either searched via WinSPIRS or via PubMed in the internet), CINAHL and the CBCSR were the databases which yielded most studies for final inclusion in the review. Exercise interventions may be regarded as nursing interventions, which is why the CINAHL database with its nursing focus yielded best results. Three studies were identified via MEDLINE (MacVicar 1989, Mock 1997, Segal 2001) and four via CINAHL (Winningham 1988, MacVicar 1989, Mock 1997, Drouin 2002). Two studies were identified exclusively via CINAHL (Winningham 1988, Drouin 2002). ProQuest Digital Dissertations was another important source for identifying relevant studies performed as dissertation research. Two studies were identified this way (Crowley 2003, Battaglini 2004). One problem that emerged with dissertations was that data from dissertations pending publication could not be included in the review. One trial could not be identified via searches in electronic databases but only via reference checking (MacVicar 1986). Via EMBASE, only one trial (Segal 2001) was identified that was also identified by MEDLINE. PsycInfo, SIGLE, CONFSCI and DissOnline.de yielded no studies to include in the review and thus appeared to be of minor importance for the question of the review.

These results substantiate the pragmatic approach to limit search updates to MEDLINE and the Cochrane Breast Cancer Specialised Register: apart from CINAHL which could not be accessed when updating searches, MEDLINE yielded best results. Three dissertation theses and the first

study at all in this topic were not identified via MEDLINE: however, these dissertations did not contribute to meta-analyses in a noteworthy degree due to a small number of participants and fragmentary data availability.

Table 7: Identification of included studies per database in the basic search

Electronic database	Initial hits	No. included at first stage	Unobtainable or not received	No. of trials included at second stage
MEDLINE	596	10	0	3
PubMed (web based)	89	9	0	3
EMBASE	559	3	0	1
CINAHL	79	10	0	4
PsycInfo	89	4	0	0
SPORTDiscus	250	4	0	1
Cochrane Breast Cancer Specialised Register (CBCSR)	14	8	0	3
SIGLE	1	0	0	0
CONFSCI	5	2	0	0
ProQuest Digital Dissertations	6	2	1	2
DissOnline.de	183	0	0	0

Table 8: Origin of reports of included trials in the basic search

	MEDLINE	Pubmed	EMBASE	CINAHL	PsyvInfo	SPORTDiscus	CBCSR	SIGLE	CONFSCI	ProQuest	DissOnline.de	Notes
Battaglini 2007										✓		Thesis
Crowley 2003										✓		Thesis
Drouin 2002				✓								Thesis
MacVicar 1986												
MacVicar 1989	✓	✓		✓			✓					
Mock 1997	✓	✓		✓			✓					
Segal 2001	✓	✓	✓			✓	✓					
Winningham 1988				✓								

4.1.2 Process of retrieval of ongoing trials

Ongoing trials were successfully identified through expert contacts and through clinical trials registers. Table 9 presents how ongoing studies were retrieved for inclusion in this review. In sum, this tabulation indicates that ongoing trials were primarily identified through contact with experts in the field. Clinical trial registers of unpublished and ongoing clinical trial research did not yield as many results as had been expected facing the fact that registration facilitates the dissemination of information among clinicians, researchers, and patients. However, when this re-

view started in 2004, study registration was the exception; only now is it the rule (Laine et al. 2007) and updating searches for ongoing studies in trial registers may yield more results. Tracking of ongoing studies resulted in three studies which had been published during the course of the review and thus could be included in the actual review (Campbell 2005, Courneya 2007, Mutrie 2007). One more study has been wound up in the meantime (Kleine-Tebbe 2006), however data has not been provided despite many queries. Hence the only German study that fulfilled the inclusion criteria for this review could not be included.

Table 9: Origin of ongoing trials

	Experts	Conferences	Trial registers	Notes
Campbell 2005		✓		Published
Chetiyawardana 2004			✓	
Courneya 2005	✓			Published
Kleine-Tebbe 2006	✓			
Mutrie 2005	✓			Published

4.1.3 Characteristics of excluded studies

27 studies were excluded. Reasons for exclusion fell into several categories. The exercise intervention was not concurrent with adjuvant cancer treatment in seven trials; exercise was either part of a complex intervention, or exercise intervention period was too short (less than six weeks), or no exercise intervention at all was implemented in five trials; in five trials the participants were not predominantly breast cancer patients; four trials could not be characterised as controlled trials (they were study protocols or reviews). Four more trials did not compare two groups assigned by the investigator (they compared high exercisers with low exercisers) and one trial did not assess health-related outcome measures. One study (Battaglini 2004) with publication pending was excluded only temporarily. For a detailed description of the reasons for exclusion see Table 10. All unfulfilled exclusion criteria are listed here; however only the first reason according to the inclusion algorithm was counted as reason for exclusion. This table does not only contain clinical studies but also review articles, etc, which were part of the full text retrieval in order to assure decision of exclusion when abstracts were ambiguous. A reference list of excluded studies is presented in Appendix 7.

Table 10: Characteristics of excluded studies

Study-ID	Reason for exclusion
1. Aghili 2007	Participants not predominantly breast cancer patients
2. Battaglini 2004	Transient exclusion due to publication pending (inclusion after publication of dissertation thesis in 2007)

Study-ID	Reason for exclusion
3. Burnham 2002	Exercise not concurrent with adjuvant cancer treatment
4. Courneya 2003a	Participants not predominantly breast cancer patients, exercise as part of a complex intervention
5. Courneya 2003b	Exercise not concurrent with adjuvant cancer treatment
6. Daley 2007	Exercise not concurrent with adjuvant cancer treatment
7. Demark-Wahnefried 2002	No clinical trial, protocol status, exercise as part of a complex intervention
8. Demark-Wahnefried 2003	No clinical trial, design paper
9. Dimeo 1999	Participants not predominantly breast cancer patients, no chemotherapy, radiotherapy or hormonal treatment
10. Fairey 2003	Exercise not concurrent with adjuvant cancer treatment
11. Given 2002	Participants not predominantly breast cancer patients, no exercise intervention
12. Ho 1986	No exercise intervention
13. Hwang 2008	Duration of intervention program less than 6 weeks
14. Latikka 1997	No clinical trial, review
15. McKenzie 2003	Exercise not concurrent with adjuvant cancer treatment
16. Mock 1994	Exercise as part of a complex intervention
17. Mock 2001	Trial does not compare two groups as assigned by investigator
18. Mock 2002	No exercise intervention
19. Mustian 2002	No clinical trial, review
20. Pickett 2002	No health-related outcome measure (adherence study)
21. Pinto 2003	Exercise not concurrent with adjuvant cancer treatment
22. Schneider 2007	Trial does not compare two groups as assigned by investigator
23. Schwartz 1999	Trial does not compare two groups as assigned by investigator
24. Schwartz 2001	Trial does not compare two groups as assigned by investigator
25. Segar 1998	Exercise not concurrent with adjuvant cancer treatment
26. Shaw 2003	No clinical trial, protocol status, exercise as part of a complex intervention
27. Wilkie 2003	Participants not predominantly breast cancer patients, duration of intervention program less than 6 weeks

4.1.4 Characteristics of included studies

The final selection resulted in 15 studies being included in this review. Data extraction tables can be found in Appendix 8. The included studies were predominantly performed in North America (United Sates and Canada); only two studies (a pilot study and a subsequent RCT) were implemented in Europe from one United Kingdom study group. One German study could not be included into the review because results were not provided by the study group. Sample sizes across studies ranged from 10 to 242; just recently, four large-scale trials emerged exceeding 100 participants, two of them even included more than 200 participants. For trial characteristics and outcomes see Table 15.

4.1.4.1 Participants

As specified in the review's inclusion criteria, all studies included women with breast cancer who were undergoing adjuvant cancer treatment. Modes of adjuvant treatment were heterogeneous and varied across the 15 exercise intervention studies. Some studies included women following various treatment regimens and other studies focused either on chemotherapy, radiotherapy, or hormonal therapy, and thus included exclusively women following the respective treatment regimen. Women under various treatments were included in six studies: one study (Segal 2001) included patients on chemotherapy, radiotherapy or hormonal therapy; patients received chemotherapy or radiotherapy in five studies (Battaglini 2007, Campbell 2005, Kim 2006, Mock 2005, Mutrie 2007). Nine studies included exclusively women who received the same mode of adjuvant treatment: just chemotherapy in six studies (Courneya 2007, Crowley 2003, MacVicar 1986, MacVicar 1989, Schwartz 2007, Winningham 1988); radiotherapy in two studies (Drouin 2002, Mock 1997) and hormonal therapy in one study (Payne 2008).

Regarding the pre-intervention lifestyle, three trials explicitly included women who had a sedentary lifestyle before the intervention (Campbell 2005, Mock 2005, Mutrie 2007) and thus might benefit more from a moderate training stimulus than exercisers do and who, on the other hand, might exhibit greater difficulties with adhering to exercise; four trials (Courneya 2007, Crowley 2003, Schwartz 2007, Segal 2001) included sedentary women *and* exercisers. The remaining eight trials did not specify whether participants were sedentary before intervention; several of these studies used sedentary lifestyle as an inclusion criterion without presenting data for exercise history. Subsequently no information regarding sedentarism was available within these studies.

Women included in primary studies were relatively young: mean age was 51 years, with SD=5.1. Only one study (Payne 2008) included exclusively women older than 65 years. Participants were overweight with a mean body mass index of more than 25 in eight of nine trials that reported relevant data (Battaglini 2007, Courneya 2007, Drouin 2002, Kim 2006, MacVicar 1989, Mock

2005, Mutrie 2007, Winningham 1988). Participants were normal weight with a mean body mass index of 24 in only one study (Mock 1997). Study participants were predominantly diagnosed with early breast cancer: five studies included women with breast cancer stages I and/or II (Crowley 2003, MacVicar 1986, MacVicar 1989, Mock 1997, Segal 2001), and seven studies included women with stages 0 to III (Campbell 2005, Courneya 2007, Drouin 2002, Kim 2006, Mock 2005, Mutrie 2007, Schwartz 2007). Only one trial was open for women with metatstatic breast cancer (Winningham 1988). This trial was included although metastatic breast cancer was an exclusion criterion because the proportion of women with metastatic breast cancer was low in the intervention group (13%) and even lower in the control group. No information on disease stage was available for two studies (Battaglini 2007, Payne 2008). Further information on patient characteristics was extracted for each study, e.g., menopausal status or exact type of chemotherapy regimen. However reporting across studies was not consistent at all concerning these patient characteristics: menopausal status, for example, was reported in five trials only.

4.1.4.2 Intervention

Exercise interventions across studies were heterogeneous in several aspects. Three studies compared two exercise intervention groups with one control group; the two interventions varied either in supervision of exercise training (Segal 2001) or in mode of exercise (Courneya 2007, Schwartz 2007).

The exercise interventions were implemented in different settings ranging from community based exercise classes and home-based exercise programs to cancer centre-based exercise programs: interventions in two studies were community based (Campbell 2005, Mutrie 2007) with exercise classes, that were run by specifically trained exercise specialists and took place in several locations. Four studies were centre based, e.g., in fitness centres of Universities or Cancer Centres (Battaglini 2007, Courneya 2007, Kim 2006, Segal 2001), three studies were based in exercise physiology laboratories (MacVicar 1986, MacVicar 1989, Winningham 1988) and a further seven studies implemented a home based intervention (Crowley 2003, Drouin 2002, Mock 1997, Mock 2005, Payne 2008, Schwartz 2007, Segal 2001), where women exercised on their own following their exercise prescriptions. Thus, in seven studies participants' exercise was self-directed and not supervised.

Also mode of exercise differed across studies: studies either tested aerobic exercise interventions, resistance training programs, or applied a combined aerobic-resistance program. Two studies tested two different exercise interventions: an aerobic exercise program and a resistance exercise program (Courneya 2007, Schwartz 2007). Aerobic exercise interventions were implemented in 11 studies using walking, cycle ergometer training, treadmill, or elliptical. Three of these studies

employed interval training with a cycle ergometer (MacVicar 1986, MacVicar 1989, Winningham 1988); the mode of aerobic exercise in home-based interventions was predominantly walking. Four studies (Battaglini 2007, Campbell 2005, Crowley 2003, Mutrie 2007) applied a combined aerobic-resistance program which was implemented as a group exercise program in two of the studies (Campbell 2005, Mutrie 2007). Two studies tested the effects of an isolated resistance training program in a second intervention group (Courneya 2007, Schwartz 2007). Resistance training across studies was either implemented with weight machines or elastic tubing or bands. Besides one study (Drouin 2002) that used a stretching intervention as the comparison arm, studies compared an exercise intervention with no intervention.

Exercise intervention periods in the included studies lasted from six weeks to six months. Exercise interventions were between six and 12 weeks in eight studies (Campbell 2005, Drouin 2001, Kim 2006, MacVicar 1986, MacVicar 1989, Mock 1997, Mutrie 2007, Winningham 1988) and more than 12 weeks in the other seven studies (Battaglini 2007, Courneya 2007, Crowley 2003, Mock 2005, Payne 2008, Schwartz 2007, Segal 2001). The longest intervention period of any trial was 26 weeks (Segal 2001). Studies with shorter intervention periods (six to seven weeks) involved breast cancer patients receiving exclusively radiotherapy, which is of shorter duration than chemotherapy (Drouin 2002, Mock 1997). In one trial (Mock 2005), the exercise intervention was implemented to span the period of time from initiation to cessation of the participant's adjuvant therapy and subsequently participants in the intervention arm of the study had intervention periods of variable length (either six weeks with radiotherapy or three to six months with chemotherapy). In three trials participants exercised less than three times a week (Battaglini 2007, Campbell 2005, Mutrie 2007); in all other trials exercise frequency was three times or more per week.

Two studies only, both studies of the UK study group (Campbell 2005, Mutrie 2007), reported that the intervention was led by a model of behaviour change in order to give women support to change exercise behaviour. Here, the exercise program itself was amended by group discussions after exercise classes. Themes addressed in these discussions were the health benefits from exercise, barriers, goal setting, supportive environments and activity options in the community. Discussions were based on the "Stages of change" approach and were designed to promote independent exercise after the intervention.

Information regarding exercise interventions is tabulated in Table 11. Note that some intervention characteristics number up to more than 15 because of those studies with two intervention groups.

Table 11: Description of interventions and study characteristics

	Intervention or study characteristic	No. of studies
Country	United States	10
	Canada	2
	United Kingdom	2
	Other	1
Year of publication	1986-1990	3
	1991-2000	1
	2001-2005	5
	after 2005	6
Cancer diagnosis	Breast cancer	15
Timing of intervention	During treatment	15
Type of adjuvant cancer treatment	Chemotherapy	6
	Radiotherapy	2
	Chemo- or radiotherapy	5
	Chemo- or radio- or hormonal therapy	1
	Hormonal therapy	1
Exercise history of participants	Sedentary	3
	Sedentary and exercisers	4
	Not specified (or inclusion criterion without assessment)	8
Setting of intervention	Laboratory based	3
	Centre based	4
	Home based	7
	Community based	2
Supervision of exercise	Supervised	9
	Self-directed exercise	7
Theory of behaviour change	Theory based	2
	Not theory based	13
Exercise mode	Aerobic exercise	8
	Aerobic interval exercise	3
	Resistance exercise	2
	Mixed exercise	4
Exercise frequency	Three times or more per week	12
	Less than three times per week	3
Intervention length	Six to 12 weeks – chemotherapy	6
	Six to 12 weeks – radiotherapy	2
	More than 12 weeks	7
Study design	Randomised controlled trial	13
	Non-randomised controlled trial	2
	Two trial arms	10
	Three trial arms	5
	Two intervention groups	3
	Two control groups	2
Nature of control group	No intervention	14
	Stretching exercise	1

4.1.4.3 Outcomes

Exercise interventions are expected to affect several health outcomes, both clinical outcomes and patient-reported health outcomes. Accordingly, multiple outcomes were assessed across exercise studies during adjuvant treatment of breast cancer. Every included study provided information on immediate post-intervention effects. Three studies additionally provided information on sustainability of effects with data on health and/or physical activity outcomes assessed four respectively six months post-intervention (Kim 2006, Courneya 2007, Mutrie 2007).

Exercise interventions tailored to increase aerobic fitness, muscle strength, and other fitness domains can be appropriately measured using physical fitness and physical functioning outcomes. Apart from two studies (Payne 2008, Winningham 1988), all studies assessed physical fitness which is an important determinant of physical functioning. Physical fitness was assessed through either cardiorespiratory or muscular fitness or through body composition. Cardiorespiratory fitness was assessed in all of the 13 studies that assessed physical fitness; six trials additionally measured body composition (Battaglini 2007, Courneya 2007, Drouin 2002, MacVicar 1989, Mutrie 2007, Segal 2001), and five trials measured muscular fitness/ strength (Battaglini 2007, Courneya 2007, Crowley 2003, Drouin 2002, Schwartz 2007).

Assessment of cardiorespiratory fitness across the included studies was typically performed using two major categories of submaximal exercise tests, i.e., predictive and performance tests. Submaximal exercise testing is adequate in people whose performance may be limited because of fatigue or other side-effects of cancer treatment and in cases where maximal exercise testing is contraindicated due to cardiopulmonary, musculoskeletal, and neuromuscular impairments. The predictive submaximal exercise tests applied were the modified Bruce treadmill test (Battaglini 2007, Drouin 2002, Kim 2006), the Cornell treadmill test (Crowley 2003), the modified Canadian aerobic fitness test, a step test (Segal 2001), and one investigator developed a protocol for a bicycle test on a stationary cycle ergometer (MacVicar 1986, MacVicar 1989, Winningham 1988). These (modified) protocols typically involve modest stage-to-stage increments in energy requirements in order to assess cardiorespiratory fitness based on exercise time or peak work rate using predictive equations for maximal oxygen uptake. Courneya 2007 employed a maximal incremental exercise protocol on a treadmill which was not further specified. In five trials a performance test, the 12-minute walk test (12 MWT), was applied (Campbell 2005, Mock 1997, Mock 2005, Mutrie 2006, Schwartz 2007). Performance tests involve measuring the responses to standardised physical activities that are typically encountered in everyday life; in the 12-minute walk test, the total distance covered in 12 minutes is reported.

Assessment of muscular strength was based on submaximal tests as well since maximal strength testing may produce test-induced muscle soreness and muscular injury from muscle strain in previously untrained individuals. In submaximal strength tests, a woman's one repetition maximum (1-RM) lifting capacity is predicted by means of regression equations from the number of repetitions of submaximal weight she could lift. However, only one trial (Battaglini 2007) provided information on how muscular strength assessments were performed, i.e., the submaximal muscle endurance protocol that was used (Kuramoto and Payne 1995); one study (Courneya 2007) employed the eight repetition maximum, i.e., the maximum weight one can lift with eight repetitions. However, again no information was provided concerning the muscle endurance protocol that was used.

Physical fitness measures are important indicators of physiological improvements gained through regular exercise; but effects of improved physical fitness on physical functioning are of even more interest. Physical functioning means the ability to carry out various activities that require physical capability, ranging from basic mobility functions (e.g., climbing stairs) to participation in life activities such as travelling. Physical functioning, the primary outcome of this systematic review, was assessed in three trials only (Crowley 2003, Mock 2005, Segal 2001). In these three trials, physical functioning was measured by perceived mobility only, using the physical functioning scale of the SF-36. Performance tests of objective mobility were not included. Twelve trials thus failed to measure outcomes beyond physical fitness.

Cancer-related fatigue as a symptom of disturbed physical health was measured in ten trials (Battaglini 2007, Campbell 2005, Courneya 2007, Crowley 2003, Drouin 2002, MacVicar 1986, Mock 1997, Mock 2005, Mutrie 2007, Payne 2008) and three trials measured vitality as a related construct (Crowley 2003, MacVicar 1986, Segal 2001). The multifactorial nature of fatigue seemed to be generally acknowledged across studies since multidimensional assessment instruments were employed. Studies predominantly assessed fatigue through either the revised Piper fatigue scale (R-PFS) or the Piper Fatigue Scale (PFS) (Piper et al. 1986, Piper et al. 1989). The original version contains 40 questions and uses a visual analogue scale. The revised PFS incorporates 22 items, which evaluate perception of current fatigue with an 11-point Likert scale. Two studies employed the Functional Assessment of Cancer Therapy (FACT) instrument – either the FACT-Fatigue (FACT-F) consisting of the FACT-General (FACT-G), a core questionnaire, plus 13 fatigue items (the fatigue subscale) or the fatigue subscale only. The fatigue subscale employs a 5-point Likert scale and contains 13 items that attempt to identify the intensity of fatigue experienced during the seven days before questionnaire administration (Cella et al. 1993, Cella 1997, Cella 1998). PFS and FACT fatigue subscale are similar in length and content but differ with respect to evaluation period (i.e., one week versus current).

Two studies assessed sleep disturbances; sleep disturbances are important since alterations in the amount or quality of sleep have been associated with impaired alertness and with impaired cognitive and emotional function and learning. Furthermore, physical health was assessed through bone health, immune conditions and hormonal regulation. A bone mineral density (BMD) test was used to determine bone health (measured density in g/cm^3) in one study (Schwartz 2007). As biological markers for describing immune system conditions, T-cells, natural killer cells, and oxidative stress were examined in one study (Drouin 2002). Cortisol, serotonin, interleukin-6, and bilirubin were used as indicators for hormonal regulation in a further study (Payne 2008).

Besides physical health outcomes, mental health outcomes were assessed across included studies. As mental health outcomes, emotional distress was measured in six studies (Courneya 2007, Drouin 2002, MacVicar 1986, Mock 1997, Mutrie 2007, Payne 2008). Emotional distress refers to unpleasant feelings or emotions and typically comprises aspects of anxiety, depression, and anger. Positive psychological function was assessed in four trials: self-efficacy and self-esteem were measured in one trial, respectively indicating mastery and control (Patient Reported Outcomes Measurement Information System Network 2008). Additionally, positive affects and satisfaction with life were assessed.

One study (Payne 2008) studied a symptom cluster and combined three commonly seen, concurrent symptoms in breast cancer patients (i.e., sleep disturbances, fatigue and depression) into one symptom cluster. They employed a conceptual model which suggested that fatigue, sleep disturbances, and depressive symptoms may result from a dysregulation of hormones. The idea was that aerobic exercise might effect positive changes in involved hormones with subsequent improvements in symptoms from the symptom cluster - supporting the approach of managing these three symptoms simultaneously.

Health-related quality of life was assessed in five studies (Campbell 2005, Courneya 2007, Crowley 2003, Mutrie 2007, Segal 2001). Across these studies, this outcome was assessed with generic quality of life instruments, cancer-specific quality of life instruments, and breast-cancer-specific instruments. These instruments differ in their ability to capture fine changes related to the diagnosis and treatment of breast cancer: the more specific instruments can be expected to better capture breast-cancer-specific experiences compared to such generic instruments as SF-36.

Information on physical activity during the intervention period was presented in six studies (Campbell 2005, Courneya 2007, Crowley 2003, Kim 2006, Mock 2005, Mutrie 2007). Physical activity measures provide an idea of additional physical activity and exercise outside of the study in supervised studies, and of adherence to exercise prescriptions in studies where participants are required to organise their own exercise. Thus, the outcome of physical activity in exercise trials is

closely related to adherence. Results across included studies were formatted either in kcal per week (Mock 2005), minutes of leisure time activity or exercise (Campbell 2005, Crowley 2003, Mutrie 2007) and average weekly frequency of exercise, average duration of exercise per session, and average duration of exercise within prescribed target heart rate range (Kim 2006) or ratio of participants meeting exercise prescription in intensity and duration (Courneya 2007). Studies employed training journals or devices such as heart rate monitors, pedometers, or accelerometers for measuring physical exercise, but predominantly presented participation rates in scheduled exercise sessions (e.g., Drouin 2002, Segal 2001). Only two studies analysed physical activity regarding intensity of prescribed exercise (Courneya 2007, Kim 2006).

According to training principles, effects of exercise training are the result of adaptive processes affecting working muscles and the cardiovascular system that occur during regular training. Physiological adaptations and the subsequent overall increase in fitness levels take place when the magnitude of the training stimulus is greater than normal (overload). Adaptations associated with any training effect are lost within a short period of stopping training (de-training). Thus, long-term exercise adherence is worthwhile and regular physical activity would be an important long-term effect of exercise interventions. Three trials assessed physical activity after four months and six months respectively following intervention (Kim 2006, Courneya 2007, Mutrie 2007).

Two trials (Crowley 2003, Campbell 2005) assessed constructs which are included in health behaviour models: The construct of perceived benefits (assessed in Campbell 2005) comprises beliefs about the positive outcomes associated with the exercise behaviour during adjuvant breast cancer treatment and is included in the Transtheoretical Model (Stages of change). Self-efficacy (assessed in Crowley 2003) is a similar construct and embraces the belief that a person has the ability to complete an action.

Only in one of the included studies was harm a major secondary outcome of the study (Courneya 2007). In this trial, arm volume measurements were performed in order to assess lymphedema. Possible adverse consequences of exercise were reported in nine trials (Battaglini 2007, Campbell 2005, Courneya 2007, Crowley 2003, Drouin 2002, Mock 1997, Mock 2005, Schwartz 2007, Segal 2001). However, it was not clarified how harm-related information was collected – neither concerning the mode of data collection, nor whether surveillance for harm was active or passive. Poor reporting practice for harm-related data was common with vague statements such as "no adverse reactions to taking part in the exercise intervention" (Campbell 2005). Prior evidence of harm was not systematically integrated in the trials. For detailed information on outcome measures see Table 12.

Table 12: Outcomes reported

Outcome category	No. of trials assessing the outcome	Construct assessed	No. of trials assessing the construct
Physical health			
Physical function	3	Physical function (perceived)	3
Physical fitness	13	Cardiorespiratory fitness	13
		Strength	5
		Body composition	6
Symptoms	11	Fatigue	10
		Nausea	1
		Endocrine symptoms	1
		Other symptoms (Pain, skin change, diarrhoea, mouth sores, constipation)	1
Sleep/ wake functions	2	Sleep disturbances	2
Biological markers	3	T-cells, natural killer cells, oxidative stress	1
		Cortisol, serotonin, interleukin-6, bilirubin	1
		Bone mineral density	1
Mental health			
Emotional distress	6	Anxiety	2
		Depression	4
		Mood disturbance	2
		Negative affects	1
Positive psychological function	4	Self-esteem	1
		Self-efficacy	1
		Positive affects	1
		Satisfaction with life	1
Health-related quality of life	5	Generic quality of life:	2
		Cancer-specific quality of life	4
		Cancer-site-specific quality of life	3
Harm	1	Lymphedema	1
Physical activity	6	Physical activity during intervention	6
		Physical activity post-intervention	3

4.1.4.4 Other study characteristics

Small sample size was common among included trials. Only four trials (Courneya 2007, Mock 2005, Mutrie 2007, Segal 2001) had more than 30 participants per group; sample size was based on power calculations in only five trials (Courneya 2007, Mock 1997, Mock 2005, Mutrie 2007, Segal 2001). The median sample size was 42 patients, interquartile range (IQR) 22 to 119. Two trials were controlled clinical trials (CCT) without random allocation of women to intervention and control group (MacVicar 1986, Mock 1997); the other trials were randomised controlled trials.

4.1.4.5 Quality of studies

Methodological quality

On average, the quality of the studies – following the vanTulder quality thresholds described in the methods section – was moderate with a mean quality score of 11.4 (range 7 to 15 points out of 17 possible points). The methodological quality score was associated with year of publication. The mean overall methodological score in the four studies published before 2000 was 8.8 (range 7 to 10 points), compared to a mean of 12.4 (range 10 to 15 points) in the studies published since 2000. Methodological scores attributed to each study are presented in Table 13. Two of these studies (MacVicar 1986 and Mock 1997) were non-randomised controlled trials; but, results from these studies did not appear to deviate from those of randomised controlled trials.

Studies identified during the basic search were critically appraised by two persons in order to explore the reliability of the quality assessment process. The inter-rater reliability was assessed through the intraclass correlation coefficient as described in the methods section. The intraclass correlation coefficient of 0.82 (ICC 0.82, 95% CI – 0.03 to 0.97) for those (nine) studies that were assessed by two quality assessors regarding their methodological quality indicated an almost perfect agreement among the two quality assessors; all disagreements could be resolved by discussion. Based on this result, this process of quality assessment was deemed to be sufficiently reliable and so subsequent quality assessments were performed by only one quality assessor.

Table 14 summarises how many studies there were that met the individual quality criteria. The following methodological issues emerged as problematic: Firstly, lack of observer blinding was common in included studies; only two studies (Crowley 2003, Mutrie 2007) attempted observer blinding, however, the success of blinding activities was not evaluated in those two studies. Secondly, seven studies either did not use adequate methods or failed to describe how they concealed the allocation, i.e., separated the process of randomisation from the recruitment of participants. This is a problem because studies using inadequate allocation concealment are more likely to report significant findings than those using adequate concealment. Moreover, adherence problems were of concern. In deciding if exercise is likely to work for an individual woman, it is necessary to know the effect of the exercise intervention in women who are physically active as prescribed, i.e., who adhered to the exercise intervention. However, participants in the included studies did not adhere to the exercise protocol to the full extent, or withdrew from the exercise intervention for various reasons, e.g., adverse effects of the breast cancer treatment. When exercise during adjuvant treatment of breast cancer is effective but non-adherence is substantial, the analysis following the intention-to-treat principle (i.e., including all eligible participants) underestimates the magnitude of the intervention effect that will occur in adherent participants. On the

other hand, applying the intention-to- treat principle provides an unbiased assessment of the efficacy of the exercise intervention at the level of adherence observed in the study. This level of adherence could be similar to that observed in the community, and the results could inform community-based decisions about the effectiveness of the exercise intervention. Only five studies applied the intention-to- treat principle (or another adequate statistical procedure) to assess the effect of exercise interventions during adjuvant cancer treatment. For example, Mock 2005 applied an innovative, valid statistical analysis and estimated the complier average causal effect (CACE) which maintains randomisation-based properties and addresses non-adherence to the exercise intervention. The other studies predominantly restricted the analysis to women for whom there was complete data on the outcomes involved in the analysis (available case analysis). Estimates from such analysis can be biased, especially if the women who are included in the analysis are systematically different from those who were excluded in terms of one or more key outcomes. Finally, long-term follow ups were considered in the quality score. Long-term follow-ups for physical activity and health outcomes are of relevance because potential adverse effects of adjuvant cancer treatment such as fatigue and weight gain are long-term adverse effects. Long-term follow-ups were performed in three recent, included studies that assessed health and/or physical activity outcomes beyond the period of adjuvant therapy (Courneya 2007, Kim 2006, Mutrie 2007).

Table 13: Quality criteria met by studies

Study-ID	Quality Score	Patient selection				Intervention			Outcome measurement							Statistics		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Battaglini 2007	15	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓
Campbell 2005	13	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓		✓	✓		✓
Courneya 2007	14	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓		✓
Crowley 2003	13	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	
Drouin 2002	12	✓	✓	✓	✓			✓		✓	✓	✓	✓		✓	✓		✓
Kim 2006	11	✓	✓		✓	✓	✓	✓		✓			✓	✓	✓			✓
MacVicar 1986	7	✓				✓				✓		✓	✓		✓	✓		
MacVicar 1989	8	✓			✓		✓	✓		✓			✓		✓	✓		
Mock 1997	10	✓			✓	✓	✓	✓		✓	✓	✓	✓		✓			
Mock 2005	14	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓		✓	✓	✓	✓
Mutrie 2007	13		✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓	✓		✓
Payne 2008	7	✓					✓			✓		✓	✓		✓	✓		
Schwartz 2007	11	✓		✓	✓		✓			✓	✓	✓	✓		✓	✓		✓
Segal 2001	13	✓	✓	✓	✓	✓		✓		✓	✓		✓		✓	✓	✓	✓
Winningham 1988	10	✓			✓	✓	✓			✓		✓	✓		✓	✓	✓	

Table 14: Number of studies meeting individual quality criteria

Quality criterion	No. of studies meeting criterion
Patient selection	
1. Were the eligibility criteria specified?	- 14
2. Was a method of randomisation performed?	- 9
3. Was the treatment allocation concealed?	- 8
4. Were groups similar at baseline?	- 12
Intervention	
5. Were interventions explicitly described?	- 10
6. Were co-interventions either avoided or comparable?	- 12
7. Was adherence acceptable in all groups?	- 8
Outcome measurement	
8. Was the outcome assessor blinded to the intervention?	- 2
9. Were outcome measures relevant?	- 15
10. Were adverse effects described?	- 9
11. Was the drop-out rate acceptable and were reasons described?	- 12
12. Was short-term follow-up measurement performed?	- 15
13. Was long-term follow-up measurement performed?	- 3
14. Was timing of outcome assessment comparable in both groups?	- 15
Statistics	
15. Was the sample size described for each group at randomisation?	- 13
16. Did the analysis include intention-to-treat analysis?	- 5
17. Were point estimates and measures of variability presented for the primary outcome measures?	- 9

Training stimulus

The prescribed training stimulus was adequate in all included studies: all studies provided an exercise prescription that can be supposed to produce the threshold intensity to maintain and achieve improvements in cardiorespiratory and/or muscular fitness in that target group of cancer patients. However, it was difficult to assess whether the actual training stimulus was as prescribed since data on intensity and duration of exercise sessions performed by individuals were not provided. In Appendix 8 intervention quality is tabulated for all included studies.

High quality training studies

Twelve studies that had methodological quality scores of nine points or greater and provided adequate exercise training stimuli were classified as high quality training studies (Battaglini 2007, Campbell 2005, Courneya 2007, Crowley 2003, Drouin 2002, Kim 2006, Mock 1997, Mock 2005, Mutrie 2007, Schwartz 2007, Segal 2001, Winningham 1988). Three studies were not classified as high quality training studies; two of these studies belonged to the pioneer work regarding exercise during adjuvant cancer treatment and were conducted in the eighties (MacVicar 1986, MacVicar 1989), one more study was published in 2008 (Payne 2008) and was the first study to examine breast cancer patients older than 65 years.

Table 15: Characteristics of included studies

Study-ID	Features	Participants	Intervention	Key endpoints
Battaglini 2007 (US)	20 participants; 2 groups; Control: no intervention; Dissertation	Breast cancer patients; Adjuvant treatment: chemotherapy or radiotherapy; Mean age 57 yr (SD 20)	• Mixed aerobic and resistance exercise • 2 x/wk for 15 wk at 40%-60% of predicted exercise capacity; 60 min per session • Supervised	• Strength • Fatigue • Body composition
Campbell 2005 (UK)	22 participants; 2 groups; Control: no intervention; Pilot-study	Breast cancer patients; Adjuvant treatment: chemotherapy or radiotherapy; Mean age 47.5 yr (SD 8)	• Mixed aerobic and resistance exercise • 2 x/wk for 12 wk at 60%-75% of maximum heart rate; 10-20 min per session • Supervised • Community-based exercise classes	• Aerobic fitness • Fatigue • Quality of life
Courneya 2007 (Canada)	242 participants; 3 groups with 2 intervention groups; Control: no intervention; Follow-up 6 mo post-intervention	Breast cancer patients; Adjuvant treatment: chemotherapy; Mean age 49 yr (range 25-78)	• Intervention 1: aerobic exercise (cycle ergometer, treadmill, elliptical), 3 x/wk for 17 wk at 60-80% of aerobic capacity; progressive increase from 15 to 45 min per session; supervised in fitness centre • Intervention 2: resistance exercise (weight machines); 3 x/wk for 17 wk, set with 9 exercises; per session 2 sets of 8-12 repetitions per exercise	• Aerobic fitness • Strength • Body composition • Fatigue • Emotional distress • Quality of life • Lymphedema
Crowley 2003 (US)	22 participants; 2 groups; Control: no intervention; Dissertation	Breast cancer patients; Adjuvant treatment: chemotherapy; Age range 36–58 yr	• Mixed aerobic (walking) and resistance (tubing) exercise. • 3-5 x/wk for 13 wk at 60% of maximum heart rate; for 20-60 min per session • 2-3 sessions resistance exercise • Self-directed • Home-based	• Aerobic fitness • Strength • Fatigue • Quality of life
Drouin 2002 (US)	23 participants; 2 groups; Control: stretching; Dissertation	Breast cancer patients; Adjuvant treatment: radiotherapy; Mean age 50.5 yr (SD 8.2)	• Aerobic exercise (walking) • 3-5 x/wk for 7 wk at 50%-70% of maximum heart rate; for 20-45 min per session • Self-directed • Home-based	• Aerobic fitness • Strength • Body composition • Fatigue • Mood • Biomarker

Study-ID	Features	Participants	Intervention	Key endpoints
Kim 2006 (South Korea)	41 participants; 2 groups; Control: no intervention; Follow-up 16 wk post-intervention	Breast cancer patients; Adjuvant treatment: chemotherapy or radiotherapy; Mean age 50 yr (SD7.6)	• Aerobic exercise (cycling or walking) • 3 x/wk for 8 wk at 60-70% of peak aerobic capacity; for 30 min per session • Supervised • Self-directed aerobic exercise post-intervention	• Aerobic fitness • Physical activity
MacVicar and Winningham 1986 (US)	10 participants; 2 groups; Control: no intervention	Breast cancer patients; Adjuvant treatment: chemotherapy	• Aerobic (interval training on a stationary cycle ergometer) • 3 x/wk for 10 wk at 60%-85% of maximum heart rate; for 20-30 min per session • Supervised	• Aerobic fitness • Mood
MacVicar 1989; Winningham 1989 (US)	45 participants; 3 groups with 2 control groups (no intervention and placebo exercise)	Breast cancer patients; Adjuvant treatment: chemotherapy; Mean age 45 yr	• Aerobic (interval training on a stationary cycle ergometer) • 3 x/wk for 10 wk at 60%-85% of maximum heart rate; for 20-30 min per session • Supervised	• Aerobic fitness • Body composition
Mock 1997 (US)	46 participants; 2 groups; Control: no intervention	Breast cancer patients; Adjuvant treatment: radiotherapy; Mean age 49 yr	• Aerobic exercise (walking) • 4-5 x/wk for 6 wk at 60%-80% of maximum heart rate; for 20-30 min per session • Self-directed • Home-based	• Aerobic fitness • Fatigue • Symptom experience • Emotional distress
Mock 2005 (US)	119 participants; 2 groups; Control: no intervention	Breast cancer patients; Adjuvant treatment: chemotherapy or radiotherapy; Mean age 51.5 yr (SD 9.3)	• Aerobic exercise (walking) • 5-6 x/wk for 6 wk (women receiving radiotherapy) or for 3-6 mo (women receiving chemotherapy) at 50%-70% of maximum heart rate; progressive increase from 15 to 30 min per session • Self-directed • Home-based	• Physical functioning • Aerobic fitness • Fatigue • Physical activity
Mutrie 2007 (UK)	201 participants, 2 groups, Control: no intervention; Follow-up 6 mo post-intervention	Breast cancer patients; Adjuvant treatment: chemotherapy or radiotherapy; Mean age 51.6 yr (SD 9.5)	• Mixed aerobic and resistance exercise • 2 x/wk for 12 wk at 60%-75% of maximum heart rate; for 20 min per session (total session 35-50 min) • Supervised • Community-based exercise classes	• Aerobic fitness • Body composition • Fatigue • Endocrine symptoms • Breast-cancer-specific symptoms • Emotional distress • Quality of life

Study-ID	Features	Participants	Intervention	Key endpoints
Payne 2008 (US)	20 participants, 2 groups, Control: no intervention; Pilot study	Breast cancer patients; Adjuvant treatment: hormonal therapy, Mean age 65 yr (range 56-78)	• Aerobic exercise (walking) • 4 x/wk at moderate intensity for 14 weeks, for 20 min per session • Self-directed • Home-based	• Fatigue • Depressive symptoms • Sleep disturbances • Biomarkers
Schwartz 2007 (US)	72 participants; 3 groups with 2 intervention groups; Control: no intervention	Breast cancer patients; Adjuvant treatment: chemotherapy; Mean age 48 yr	• Intervention 1: aerobic exercise (participants' preferences), 4 x/wk for 6 mo at moderate intensity for 15-30 min per session; self-directed, home based • Intervention 2: resistance exercise (Thera band); 6 mo, 2 sets of 8 exercises (4 upper, 4 lower body); 2 sets of 8-10 repetitions per session	• Aerobic fitness • Strength • Bone mass density
Segal 2001 (Canada)	123 participants; 3 groups with 2 intervention groups; Control: no intervention	Breast cancer patients; Adjuvant treatment: chemotherapy, radiotherapy or hormonal therapy; Mean age 51 yr (SD 8.7)	• Aerobic exercise (walking) • 5 x/wk for 26 wk at 50-60% of peak aerobic capacity; for 20-30 min per session (total session 35-45 min) • Intervention 1: 3 x supervised, 2 x self-directed exercise • Intervention 2: self-directed home-based exercise	• Physical functioning • Aerobic fitness • Body composition • Quality of life
Winningham 1988 (US)	42 participants; 3 groups with 2 control groups (no intervention and placebo exercise)	Breast cancer patients; Adjuvant treatment: chemotherapy; Mean age 46.6 yr	• Aerobic (interval training on a stationary cycle ergometer) • 3 x/wk for 10 wk at 60%-85% of maximum heart rate; for 20-30 min per session • Supervised	• Nausea

4.2 Studies of harm

Through MEDLINE search, 84 citations were identified. All 84 titles and abstracts were screened for inclusion in reviewing harms. Based on title and abstract screening, 76 of these citations were excluded because they were not reports of studies that examined harmful effects of exercise interventions in the context of breast cancer. Eight reports representing seven studies were identified as being potentially relevant for inclusion. Full reports of these seven studies were obtained and screened. Following screening of the full reports, a further four studies were excluded from the review and three studies were included in the review of harmful effects of exercise. A reference list of included and excluded studies is presented in Appendix 9.

The four excluded studies were all excluded for reasons of study design. One study was a series of case reports (Harries 2000) and three studies (Cheema 2006, Johansson 2005, Turner 2004) represented before-and-after studies which, in contrast to studies with an intervention group and a comparison group, were conducted within a single group. Outcomes were measured before and after the exercise intervention. All of these excluded studies dealt with lymphedema comparable to the included studies. It can be expected, therefore, that no qualitative information got lost through the application of inclusion criteria.

The three included studies all examined potential harms of exercise after adjuvant cancer treatment had been completed. No single study could be identified that examined harmful effects of exercise in the time when women were still undergoing adjuvant treatment of breast cancer — besides that of Courneya 2007, one of the included studies of benefit that systematically addressed lymphedema. Methodological quality was assessed as good in two of the included trials (Schmitz 2005, Basen-Engquist 2006) and as fair in one study (McKenzie 2003). All three studies pre-specified and defined those harmful effects that would be assessed: lymphedema and injuries were the only harmful effects that were examined. All three studies used adequate instruments and techniques to ascertain harmful events. Schmitz 2005 was the only study that actively monitored injuries. A standardised survey instrument was used to ask whether participants had experienced injuries during the intervention period. If they responded yes, they were further asked about the type of injury (e.g., heel spur, sprained ankle, shin splints, knee injury, hip injury, pulled/strained muscle, sprained wrist, back problems). Furthermore, participants were asked whether they believed the injury was the result of participation in the study. Other questions on the injury survey were concerned with assessment of the effect of injury on exercise sessions, and an assessment of how the injury was on the day of the injury survey. Ascertainment techniques for lymphedema were the following: measuring and calculating arm volume, measuring arm cir-

cumference, and a validated survey instrument employed by Schmitz 2005 that measured self-report of lymphedema diagnosis, symptoms, and treatment over the last three months.

Studies differed regarding the participants and the interventions examined. McKenzie 2003 included women who already had developed arm lymphedema and examined the effects of an upper-body exercise program (resistance and aerobic training) on secondary lymphedema. Schmitz 2005 evaluated the effects of a resistance training program, which included exercises for the upper and the lower body. Basen-Engquist 2006, finally, examined a lifestyle approach to increasing physical activity, i.e., no detailed exercise prescription was provided but cognitive and behavioural skills were addressed, together with ways to incorporate moderate physical activity into the daily routine. Study characteristics are summarised in Table 16.

Table 16: Characteristics of studies of harm

Study-ID	Methods	Participants	Interventions	Outcomes
Basen-Engquist 2006	RCT, 2 groups, randomisation by minimisation (similar to stratification); Methodological quality score: 7 (score range: 0-8).	60 breast cancer patients, after completion of all treatments for breast cancer, within 7 years of breast cancer diagnosis	**Intervention**: Lifestyle physical activity program (taught women to incorporate short periods of moderate activity into their daily routines); 6 months, 21 sessions **Control**: Standard care	Lymphedema: measured with arm-circumference measurements
McKenzie 2003	RCT, 2 groups; Methodological quality score: 5 (score range: 0-8).	14 breast cancer patients, after completion of all treatments for breast cancer more than 6 months before baseline; with unilateral lymphedema	**Intervention**: Mixed aerobic and resistance exercise; 3 days/week; 8 weeks *Resistance exercise*: 6 exercises, 10 repetitions, 2-3 sets per exercise. *Aerobic exercise* (arm cycle ergometer): 20 minutes **Control**: no intervention	Arm volume: calculated from arm-circumference measurements and measured by water displacement
Schmitz 2005	RCT, 2 groups, partial crossover design, blocked randomisation; stratification for age and body fat; Methodological quality score: 7 (score range: 0-8).	(1) 85 breast cancer patients, after completion of all treatments for breast cancer (except hormonal therapy) 4 to 36 months before baseline; sedentary to moderately physically active; no weight training history; stable body weight over the past year. (2) for lymphedema assessment: analysis of a sub-group of 45 trial participants who had axillary node dissection beyond sentinel node biopsy – a possible risk factor for lymphedema	**Intervention**: Resistance exercise; 60 minutes; 2 days/week; 26 weeks (13 weeks supervised in small groups; 13 weeks self-directed); 9 types of exercise using variable resistance machines and free weights; 8-12 repetitions, 3 sets per exercise. **Control**: no intervention in the first six month; delayed intervention from month 7 to 12.	(1) Injuries: standardised injury reporting based on an injury survey instrument (2) Lymphedema: measured with arm-circumference measurement, self-report of diagnosis, and self-report of symptoms (using a validated survey instrument) Outcomes were assessed 6-month post-intervention in the intervention group.

5 Results: Evidence synthesis

From tabulation of study characteristics, one comparison emerged for quantitative analysis, that is: exercise versus no exercise. The pre-planned comparison of exercise versus other interventions (e.g., psychosocial interventions) was not feasible due to the absence of respective primary studies. Meta-analysis was regarded as appropriate for the comparison of exercise versus no exercise because studies were homogenous enough to be sensibly combined which was a consequence of the rather focused review question and inclusion criteria concerning participants, intervention, and study design. Data are reported in terms of effect size (SMD) and 95% CI. The SMD can serve as a measure of strength of evidence but has limited value as a clinically meaningful measure of intervention effect. In the context of the meta-analysis, the interpretation of an effect as small, medium, or large was based on an operational definition with conventional criteria: an effect size of 0.2 to 0.3 was regarded as a "small" effect, 0.5 to 0.7 a "medium" effect and 0.8 to 1.0 as a "large" effect. Meta-analyses were conducted using final values; change scores were not used in meta-analysis. Effect sizes for outcomes that could not be pooled through meta-analysis are presented in Table 17 and Table 18. Information on health assessment instruments that were used in included studies (e.g., score range, interpretation of score) can be found in Appendix 10. Appendix 11 shows the health assessment instruments and questionnaires that contributed to pooling in meta-analyses for different outcomes.

5.1 Physical health effects

5.1.1 Physical functioning

Self-reported physical functioning was measured in three studies. Meta-analysis for this outcome could not be performed. In one study (Segal 2001), physical functioning improved after exercise training in both the self-directed and supervised exercise groups, whereas in the control group, the physical functioning scale decreased: group comparisons of changes in physical functioning revealed a significant mean difference between the *self-directed* exercise group and the control group in favour of the exercise intervention. The mean difference of changes in physical functioning from baseline to post-intervention between the *supervised* exercise group and the control group did not achieve significance, although it showed a trend in favour of the exercise intervention. However, the authors of this study discussed whether baseline differences in physical functioning (higher physical functioning in the control group) may have accounted for the magnitude and direction of changes in physical functioning observed over the intervention period.

No differences in physical functioning between exercise and control could be observed by Crowley 2003. Mock 2005 reported physical functioning for "high walkers" – participants who exer-

cised on average at least 60 minutes per week in three or mores sessions – compared to "low walkers" who exercised not at all or less than 60 minutes per week (increased in high walkers and decreased in low walkers). No results from analyses following the intention-to-treat principle (i.e., analysing participants in the groups to which they were randomised, without regard to whether they adhered to the allocated exercise intervention) were presented in this study. In summary, there is limited evidence that exercise during adjuvant therapy for breast cancer improves physical functioning. The effect size is presented in Table 17.

5.1.2 Health-related physical fitness

5.1.2.1 Cardiorespiratory fitness

Cardiorespiratory fitness is the health-related component of physical fitness that relates to the supply of oxygen to muscles during sustained physical activity (United States Department of Health and Human Services 1996). Data from eight studies could be pooled in this meta-analysis yielding eleven comparisons (due to three studies with two intervention arms) with a total of 709 participants. The overall pooled effect estimate (SMD 0.54, 95% CI 0.32 to 0.77) indicated that participants in the exercise intervention groups experienced significantly increased cardiorespiratory fitness relative to participants in the control groups (Figure 7). The effect size of 0.54 stands for a medium effect of physical exercise training on cardiorespiratory fitness. Cardiorespiratory fitness was measured in four different units across the studies included in the meta-analysis: first, oxygen uptake data were presented both with dimension mlVO_2/kg/min (Courneya 2007, Drouin 2002, Schwartz 2007, Segal 2001) and with dimension ml VO_2/min (Kim 2006); second, field test data (12-minute walk test) were provided using both walking distances in feet (Mock 1997) and meters (Campbell 2005, Mutrie 2007).

Other studies with cardiorespiratory fitness as an outcome did not provide sufficient data for meta-analysis in cardiorespiratory fitness. One controlled clinical trial (MacVicar 1986), a pilot study, reported only means without standard deviations. In one other trial, data for cardiorespiratory fitness were only presented by level exercise, i.e., high exercisers were compared with low exercisers instead of following group assignment in statistical analysis (Mock 2005). Battaglini 2007 used physical fitness data to explain changes in primary outcomes, i.e., fatigue and lean body mass and provided only means without standard deviations for cardiorespiratory fitness data. Data from the remaining two trials with assessments of cardiorespiratory fitness (Crowley 2003, MacVicar 1989) could not be transformed for meta-analysis requirements.

In a nutshell, exercise was an effective intervention for improving cardiorespiratory fitness relative to usual care even during breast cancer treatment. Preserving cardiorespiratory fitness during

breast cancer treatment is important, because vital aspects of physical functioning require cardio-respiratory fitness.

5.1.2.2 Muscular fitness

Muscular endurance and strength, i.e., the ability of the muscle to continue to perform without fatigue and to exert force (United States Department of Health and Human Services 1996) are important determinants of physical functioning as well. Pooling the effects of four studies – yielding six comparisons due to multiple intervention arms in two studies – with a total of 328 participants yielded a total effect size (SMD 0.42; 95% CI 0.06 to 0.78) that indicated a statistically significant medium increase in strength for participants in the exercise intervention groups compared to a control group (Figure 8). Muscle strength is an important outcome for breast cancer patients because of the assumable impact on health-related quality of life: strength is possibly associated with physical functioning; further, a sense of return to feeling in control of the own bodies (i.e., strength) may translate into feeling greater efficacy in other areas of life and health-related quality of life (Ohira et al. 2006).

There are some inconsistencies in results across studies with moderate statistical heterogeneity (I^2 =50%). Heterogeneity was reduced when only comparisons with interventions based on *resistance* exercise training were included in this meta-analysis of strength (I^2 =0%). Standardised mean difference was 0.67, with 95% confidence interval 0.34 to 1.01 (Figure 9). This effect size indicates that resistance exercise training in particular resulted in improved muscular strength when compared to non-exercising control groups.

Studies assessed changes in muscular strength through the 1-repetition maximum (kg) of one exercise or of several exercises combined. Because various exercises were used across studies to assess muscular strength (e.g., overhead press, bench press, leg extension, or grip strength), the standardised mean difference was used as the effect-size statistic.

5.1.2.3 Body composition

Body composition outcomes – relating to the relative amounts of muscle, fat, bone and other vital parts of the body (United States Department of Health and Human Services 1996) – could be pooled from four trials, yielding five comparisons with a total of 414 participants (Figure 10). Exercise was more effective than usual care on maintaining or decreasing relative body fat and weight (SMD -0.29; 95% CI -0.55 to -0.03). This effect was small but statistically significant. Body composition is a relevant outcome since an increase in body mass index was observed to be associated with a poorer prognosis (Barnett et al. 2008). Across studies body composition was meas-

ured as weight, BMI, lean body mass, fat mass and skinfold thickness. For this meta-analysis BMI and body fat percentage were combined.

5.1.3 Treatment-related symptoms

5.1.3.1 Cancer-related fatigue

Cancer-related fatigue was evaluated in ten studies. Pooling the effects of seven studies yielding nine comparisons due to multiple intervention arms in two studies (see Figure 11) showed that exercise was more effective than normal care on reduction of fatigue (SMD -0.17; 95% CI -0.32 to -0.02). The effect size indicates a small but statistically significant effect. There was no heterogeneity across these studies. Heterogeneity was moderate, with I^2 of 47%, when the study (Battaglini 2007) was included in the meta-analysis (in the course of sensitivity analyses); the resulting effect size was slightly greater with a standardised mean difference, then based on 734 participants, of -0.23, with 95% confidence interval -0.45 to -0.01.

The following assessments instruments for fatigue were employed within these eight studies: first, the revised Piper-Fatigue scale was used in four studies (Battaglini 2007, Campbell 2005, Drouin 2002, Mock 2005); second, the Functional Assessment of Cancer Therapy (FACT) instrument was used in two studies – either the FACT-Fatigue (FACT-F) consisting of the FACT-General (FACT-G), a core questionnaire, plus 13 fatigue items (the Fatigue Subscale) or the Fatigue Subscale only (Mutrie 2007, Courneya 2007); furthermore a visual analogue scale for fatigue was used (Mock 1997); and finally assessments of vitality were made using the vitality scale of the SF-36 in one study (Segal 2001). For statistical pooling in meta-analysis, effect sizes from SF-36 and FACT-F were reversed following the direction of scales (in the fatigue subscale of the FACT instrument, higher scores represent less fatigue). This procedure of combining reversed vitality scores with fatigue scores is supported through substantial evidence supporting the adequacy of the vitality scale of the SF-36 as a valid measure of energy and fatigue (O'Connor 2004).

5.1.3.2 Nausea

Nausea was measured in one trial only (Winningham 1988); the data from this trial show that moderate aerobic exercise may provide relief from the symptom of chemotherapy-associated nausea in some patients. Women in the control and placebo group significantly more frequently experienced worsening or lack of amelioration of nausea: the relative risk (RR) for worsening or lack of amelioration of nausea was 0.57, 95% CI 0.34 to 0.94. Thus, there is limited evidence for an effect of exercise programs on reduction of nausea based on data from one study.

5.1.3.3 Sleep disturbances

Sleep disturbances were examined in two studies (Mock 1997, Payne 2008). Due to methodological limitations in one study (Payne 2008), data were not pooled in meta-analysis. In this study, groups were not similar at baseline; a post-intervention group comparison yielded differences between exercise and control group in favour of the control group, although the Pittsburgh Sleep Quality Index (PSQI) scores for the exercise group decreased significantly over time, indicating improved sleep quality. Sleep disturbances were reduced in Mock 1997, which provided limited evidence for an effect of exercise programs on reduction of sleep disturbances based on data from one study. The effect size is presented in Table 17.

Proper management of the multiple symptoms resulting from cancer and its treatment is important, as symptoms can significantly distress patients and interfere with day-to-day functioning. Furthermore, such symptoms might delay treatment or lead to premature treatment termination (Cleeland 2007, Gapstur 2007). If treatment-related symptoms become so severe that patients abandon important (and sometimes potentially curative) therapies or if they cause treatment delays, they may diminish the chance of long-term remission or cure, and thus can directly affect survival (Cleeland 2007). Residual treatment-related symptoms can also limit vocational activities and inhibit social interaction (Cleeland 2007).

5.1.4 Biological and physiological effects

5.1.4.1 Bone health

Bone health (bone mineral density) was the primary outcome in one trial (Schwartz 2007). At the end of the intervention period, it could be observed that aerobic exercise preserved lumbar spine bone mineral density significantly better compared to usual care. Bone health is a particularly relevant outcome measure for women who have had breast cancer because they are at higher risk for osteoporosis and subsequent osteoporotic fractures than other women (Adler 2007, Brown and Guise 2009). Furthermore, as many women with breast cancer will be long-term survivors, the importance of skeletal health should not be underestimated and thus actively promoted with this population of women.

5.1.4.2 Immune system

The effect of exercise on cell-mediated immunity is of concern since cytotoxic therapies, including radiotherapy and chemotherapy, are discussed to be immunosuppressive. Exercise is associated with physiological changes in the immune system as well: moderate exercise may boost the immune system function, but intense exercise can have the opposite effect.

There is no evidence for an effect of exercise programs on immune functioning during breast cancer treatment based on data from one study (Drouin 2002). No statistically significant differences were observed during radiotherapy for biological markers describing immune system conditions (T-cells, natural killer cells, and oxidative stress). Both the exercise and control group demonstrated significant declines in T-cell counts; since the final T-cell counts were not significantly different between the two groups, this study helped support the safety of performing moderate intensity aerobic exercise alongside radiotherapy of breast cancer. Similarly, exercise was not able to preserve or improve natural killer cytotoxic activity during radiotherapy of breast cancer. However, since final natural killer cytotoxic activity values were not significantly different between exercise and control group following the intervention, aerobic exercise did not appear to impair the immune function. The same was true for oxidative stress. The effect sizes are presented in Table 17.

5.1.4.3 Hormonal regulation

Hormonal regulation was addressed in one study (Payne 2008). The ideas behind addressing hormonal regulation was a conceptual model suggesting that fatigue, sleep disturbances, and depressive symptoms may result from a dysregulation of hormones. The authors hypothesized that exercise interventions may effect positive changes in regulatory hormones, which may suggest a mechanism that contributes to fatigue, sleep disturbances, and depressive symptoms in patients with breast cancer. As biomarkers for hormonal regulation cortisol, serotonin, interleukin -6, and bilirubin were measured.

There is limited evidence for an effect of exercise programs on hormonal regulation during breast cancer treatment based on data from one study (Payne 2008). A significant intervention effect could be observed on serotonin levels: serotonin levels decreased slightly over the intervention period in the exercise group, suggesting that exercise may exert a negative influence on the production of serotonin. Cortisol levels did not demonstrate a significant association with the exercise intervention; however a downward trend in the intervention group did exist. Interleukin-6 levels were not significantly different between groups. A weak (but not significant) intervention effect was seen for bilirubin levels, which may be an important factor related to fatigue. Effect sizes could not be calculated due to insufficient reporting of results in the study.

5.2 Mental health effects

5.2.1 Emotional distress

5.2.1.1 Depression

There were three trials that examined group differences for depression. For assessment of depression, a symptom assessment scale (Mock 1997), the Beck Depression Inventory (Mutrie 2007) and the Center for Epidemiological Studies–Depression Scale (Courneya 2007) were used and combined in meta-analysis. Pooling the effects of these three trials, which had four comparisons due to there being two intervention arms in Courneya 2007, yielded a significant reduction of cancer-related depression in exercise groups when compared to a control group based on a total of 443 participants: SMD -0.24, 95% CI -0.43 to – 0.04 (see Figure 12). There is evidence that exercise is effective in reducing depression during adjuvant cancer treatment.

5.2.1.2 Anxiety

There is limited evidence for positive effects of exercise on anxiety reduction during adjuvant therapy for breast cancer (see Figure 13). The effect size from a meta-analysis with two studies (yielding three comparisons) suggested a small, but not statistically significant, effect of exercise in reducing anxiety: SMD -0.25, 95% CI -0.54 to 0.04.

5.2.1.3 Other outcomes

There is no evidence for the effect of exercise on mood disturbances and negative affects, i.e., the extent to which women felt aversive mood states and general distress. Results from single studies indicated no statistically significant difference between groups. The effect sizes are presented in Table 17.

5.2.2 Positive psychological function

Positive affects, i.e., the extent to which women felt enthusiastic, active, and alert, were increased in the exercise group of one study (Mutrie 2007) compared to participants in the control group. Likewise, exercising participants experienced higher self-esteem than participants in the control group in a further study (Courneya 2007). Self-esteem is an important outcome for breast cancer patients during difficult treatments.

No statistically significant differences between groups were found for satisfaction with life (Campbell 2005), physical self-efficacy and attention performance (Crowley 2003) or for satisfaction with body (Mock 1997).

Thus, there is limited evidence that exercise lifts positive affects and self-esteem during adjuvant therapy for breast cancer, but currently no evidence that exercise enhances other aspects of positive psychological function such as the feeling of mastery and control (self-efficacy).

5.3 Quality of life effects

5.3.1 Cancer- and cancer-site-specific quality of life

Four studies (Campbell 2005, Courneya 2007, Mutrie 2007, Segal 2001) examined effects of exercise on cancer- and cancer-site-specific quality of life. There is evidence suggesting that exercise increases breast-cancer-specific quality of life. Meta-analysis of three studies comprising 416 participants (see Figure 14) found a statistically significant improved cancer-specific quality of life of participants in the exercise intervention groups when compared to non-exercising control groups: the standardised mean difference was 0.23, with 95% confidence interval 0.03 to 0.43. Cancer-specific quality of life was assessed using the Functional Assessment of Cancer Therapy (FACT) instrument – the FACT-Breast (FACT-B) consisting of the FACT-General (FACT-G) and a breast cancer subscale and the FACT-Anemia consisting of the FACT-General (FACT-G) and the anemia subscale.

There is no evidence that exercise is effective in increasing cancer-specific quality of life during adjuvant therapy for breast cancer: three studies examined cancer-specific quality of life (Campbell 2005, Mutrie 2007, Segal 2001); meta-analysis could not be performed due to data availability and compatibility (change scores or final values of results). Mutrie 2007 and Segal 2001 found no significant intervention effect for FACT-G.

5.3.2 Generic health-related quality of life

Generic health-related quality of life (assessed via SF-36) was examined by Segal 2001 and Crowley 2003 and no statistically significant differences between groups were found. Thus there is no evidence for the effectiveness of exercise programs for generic health-related quality of life during breast cancer treatment. Quantitative synthesis was not performed because the data for subscales were presented without summary measures.

5.4 Adherence and contamination

Adherence was employed as a descriptive variable in the context of this review: Measuring adherence to exercise is important because a failure of participants to adhere to exercise prescriptions may bias results obtained by research studies, limiting the strength of the empirical evidence generated. In general, exercise adherence can be calculated by comparing actual exercise behav-

iours with the standards determined in the exercise recommendation. Different approaches were used among the included studies to measuring adherence, that is, the level of exercise participation achieved once the woman had agreed to undertake it. First, the ratio of attendance to scheduled exercise sessions was widely used as an index of adherence in trials with supervised and self-directed exercise interventions. Attendance in self-directed, home-based interventions was measured via participant diaries and self-report questionnaires. The ratio of attendance was calculated by dividing the number of sessions attended by the number of scheduled sessions. Second, adherence was operationalised as a dichotomous variable and assessed as the proportion of adherent participants with various cut-points of exercise per week (Mock 1997, Mock 2005).

Adherence to exercise was said to be 70% or more of possible exercise sessions (supervised or self-directed) in seven studies (Battaglini 2007, Campbell 2005, Courneya 2007, Crowley 2003, Drouin 2002, Kim 2006, Segal 2001). Adherence may be of a similar magnitude in one more study (MacVicar 1989), since they let participants repeat missed sessions. In one study (Mutrie 2007), less than 40% (38.8%) of participants attended at least 70% of the possible exercise sessions. The proportion of adherent participants was found to be 86% by Mock 1997 and 72% by Mock 2005 based on cut-points of 90, respectively 60, minutes of exercise per week.

Attendance rates alone do not inform on participants' adherence behaviours *during* exercise sessions; two of these trials additionally employed an evaluation of exercise behaviours during the sessions and reported exercise adherence regarding exercise intensity and duration (Courneya 2007, Kim 2006). The aerobic exercise training group in Courneya 2007 met their prescribed duration 96% of the time, and likewise for intensity 87% of the time. The resistance exercise training group of the same study completed all prescribed nine exercises - two sets each, with eight to 12 repetitions each set at least 95% of the time. Kim 2006 reported an average duration of exercise of 43 minutes, with an average duration of exercise within prescribed target heart rates of 28 minutes.

All but two of the studies (MacVicar 1986, Winningham 1988) monitored physical activity but did not report the data. There was a range of methods used for monitoring physical activity: some trials employed (electronic) devices such as heart rate monitors (e.g., Drouin 2002, Kim 2006); accelerometers (Schwartz 2007) or pedometers (Payne 2008); others used pulse rates or perceived exertion (Mock 1997, Mock 2005).

Exercise levels in non-exercising control groups (contamination) were reported in three trials (Crowley 2003, Courneya 2007, Mock 2005). Whereas Crowley 2003 stated the significant difference in activity levels between the two groups in terms of frequency and duration of exercise, Mock 2005 observed 39% of the control group beginning regular walking during the study, at a

level greater than 45 minutes per week, which was regarded as demonstrating considerable contamination. However, when adopting the underlying cut-point of 45 minutes per week (Mock 2005), contamination can also be observed in the trial of Crowley 2003: participants in the control group walked a mean time of 53 minutes per week. In Courneya 2007, less than 15% of participants in the control group reported regular exercise.

No information on adherence to prescribed exercise was given in four trials (MacVicar 1986, Schwartz 2007, Payne 2008, Winningham 1988).

Attendance rates are difficult to compare due to different exercise stimuli prescribed across studies and due to various cut-points for determining rates of adherent participants. In sum, adherence seemed to be a problem in some, but not all, studies.

One study (Courneya 2007) examined predictors of supervised exercise adherence in breast cancer patients receiving adjuvant chemotherapy. Exercise adherence in that study was good, with an adherence rate of 70%, but was still not optimal. Independent predictors of adherence were location/centre, aerobic fitness, disease stage, and depression. Results suggested that motivational variables were not important predictors of adherence in those breast cancer patients already motivated enough to volunteer for an exercise study. Higher exercise adherence to supervised exercise training during chemotherapy for breast cancer was achieved by women who were "fitter, stronger, thinner, more advanced disease stage, better educated, less depressed, and not smoking" (Courneya et al. 2008b). But most of the variation in exercise adherence remained unexplained (21% was explained in multivariate analyses) indicating that there are other important predictors.

Furthermore, Courneya 2007 prospectively assessed exercise barriers by tracing reasons for each session that any women in the intervention groups missed. By this means they obtained 2,090 reasons for missed exercise sessions. Based on content analysis, exercise barriers were assigned to disease-/treatment-related barriers, life-related barriers, or motivation-related barriers. Disease-/treatment-related barriers, such as fatigue, dizziness, depression, or coincidence with chemotherapy day, accounted for more than half of all missed sessions. Life-related barriers, such as vacation or work issues, accounted for about one-third of missed sessions. Only a small portion of barriers (13%) appeared to be motivation-related (Courneya et al. 2008a).

Table 17: Summary of findings: immediate post-intervention effects

Outcome	No. of studies	No. of participants	Effect size [95% CI]
Physical functioning	1	123	SMD 0.04 [-0.33; 0.42]
Physical fitness			
Cardiorespiratory fitness	8	709	SMD 0.54 [0.32; 0.77]
Strength	4	328	SMD 0.42 [0.06; 0.78]
Body composition	4	414	SMD -0.29 [-0.55; -0.03]
Symptoms			
Fatigue	7	714	SMD -0.17 [-0.32; -0.02]
Nausea	1	42	RR 0.57 [0.34, 0.94]
Endocrine symptoms	1	174	SMD -0.14 [-0.44; 0.16]
Biological markers			
Natural killer cells	1	21	SMD 0.24 [-0.65, 1.12]
T-cells	1	21	SMD 0.63 [-0.27, 1.54]
Oxidative stress	1	15	SMD -0.53 [-1.63, 0.57]
Bone density	1	66	SMD 0.14 [-0.37; 0.65]
Sleep disturbances	1	46	SMD -0.67 [-1.27; -0.08]
Emotional distress			
Anxiety	2	269	SMD -0.25 [-0.54; 0.04]
Depression	3	443	SMD -0.24 [-0.43; -0.04]
Mood disturbance	1	21	SMD -0.69 [-1.60, 0.22]
Negative affects	1	174	SMD -0.30 [-0.60, 0.00]
Positive psychological function			
Self-esteem	1	223	SMD 0.28 [0.00; 0.56]
Positive affects	1	174	SMD 0.44 [0.14, 0.74]
Quality of life			
Cancer-specific	3	416	SMD 0.23 [0.03; 0.43]
Harm			
Lymphedema	1	242	RR 0.85 [0.31; 2.3]

5.5 Forest plots for immediate post-intervention effects

For those outcomes, where combining of results was feasible, the pooled effect sizes are presented in a forest plot. Studies with two intervention groups are included in meta-analyses with both intervention arms using the study-ID plus a code for the exercise intervention in order to distinguish between the two interventions and their contribution the overall pooled effect (AET and RET for aerobic resp. resistance exercise training; and SD and SU for self-directed resp. supervised exercise). More forest plots for immediate post-intervention outcomes (presenting sub-totals only) can be found in Appendix 12

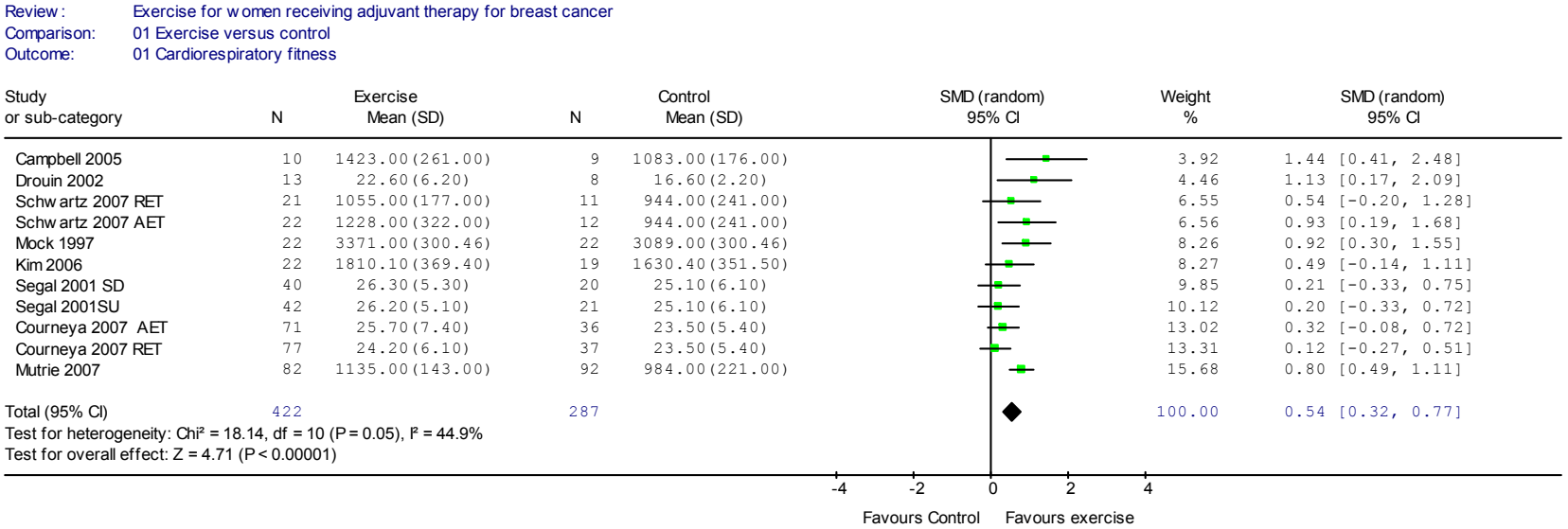

Figure 7: Meta-analysis for cardiorespiratory fitness

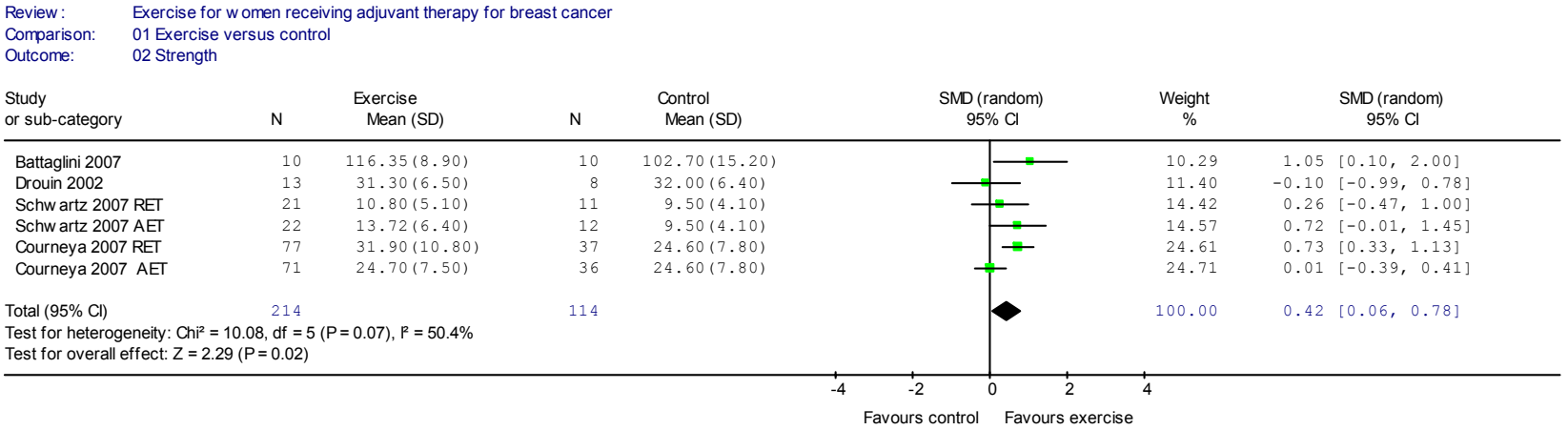

Figure 8: Meta-analysis for strength

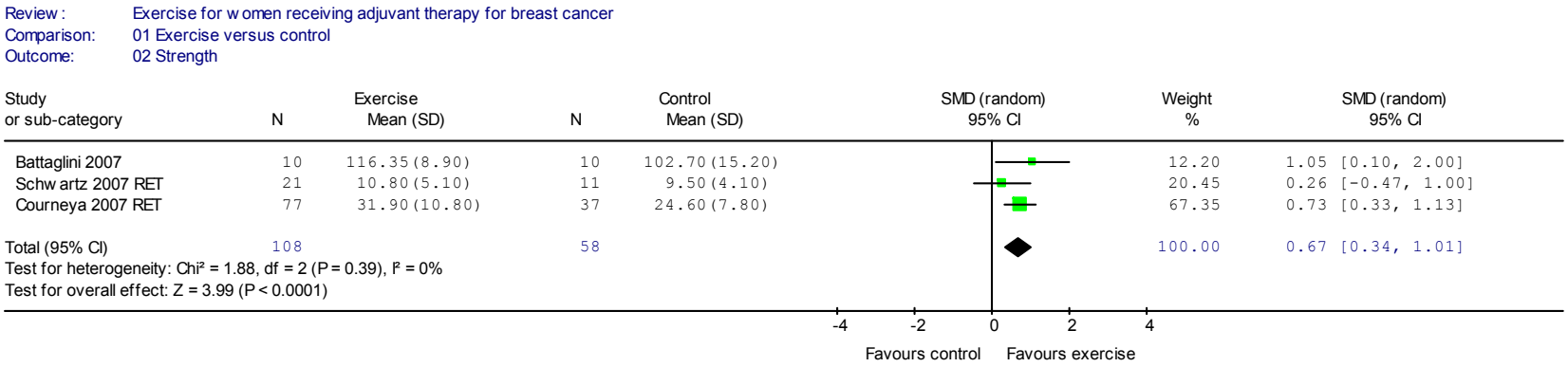

Figure 9: Meta-analysis for strength with resistance exercise training studies

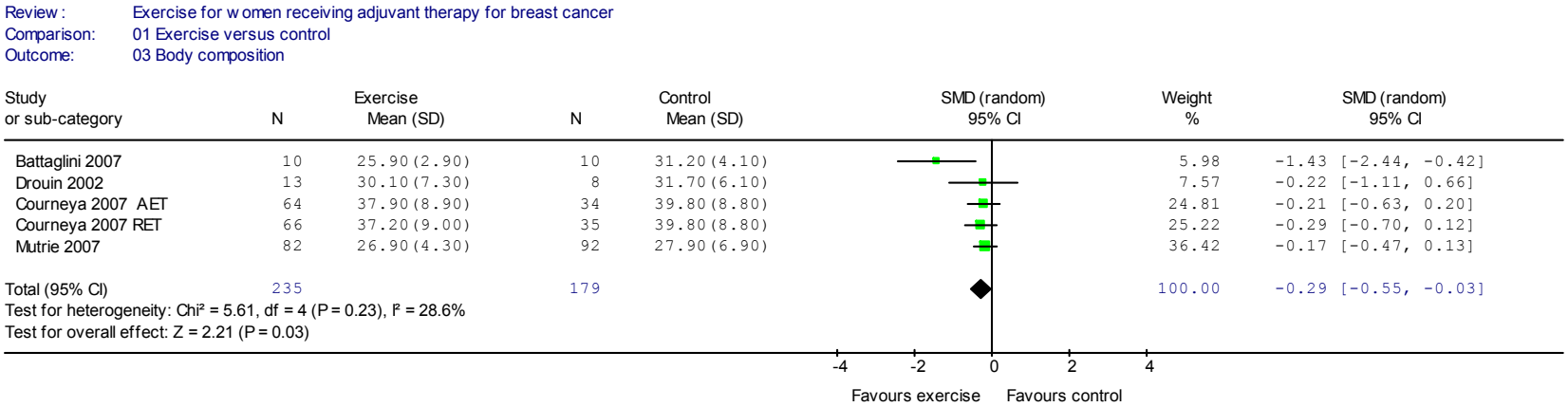

Figure 10: Meta-analysis for body composition

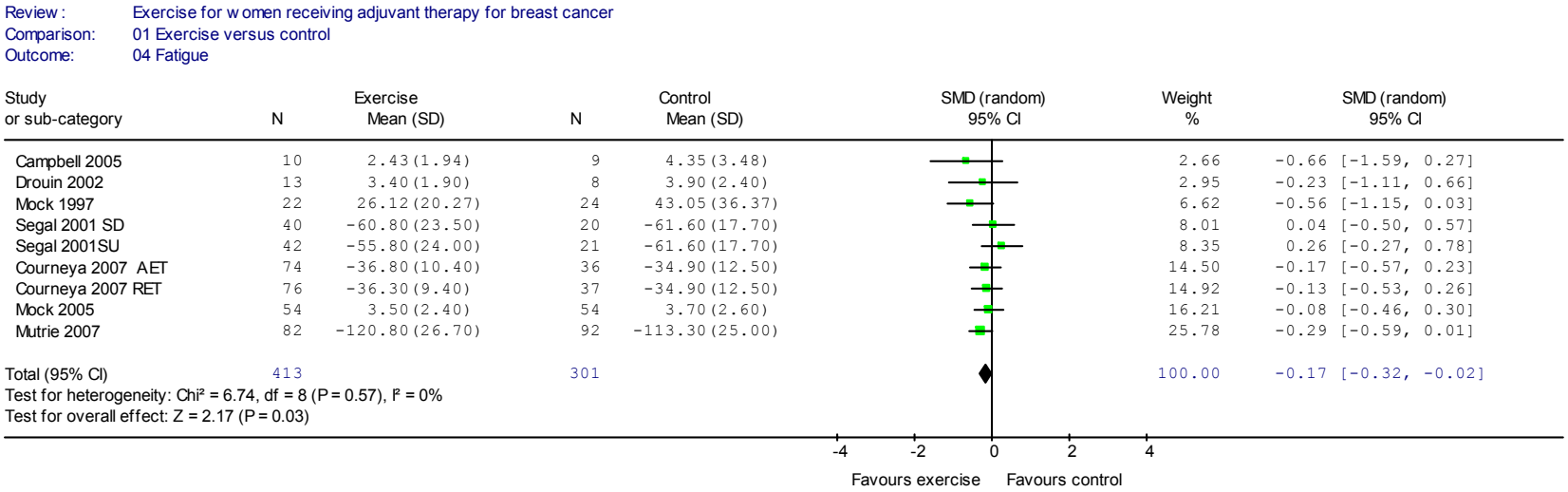

Figure 11: Meta-analysis for cancer-related fatigue

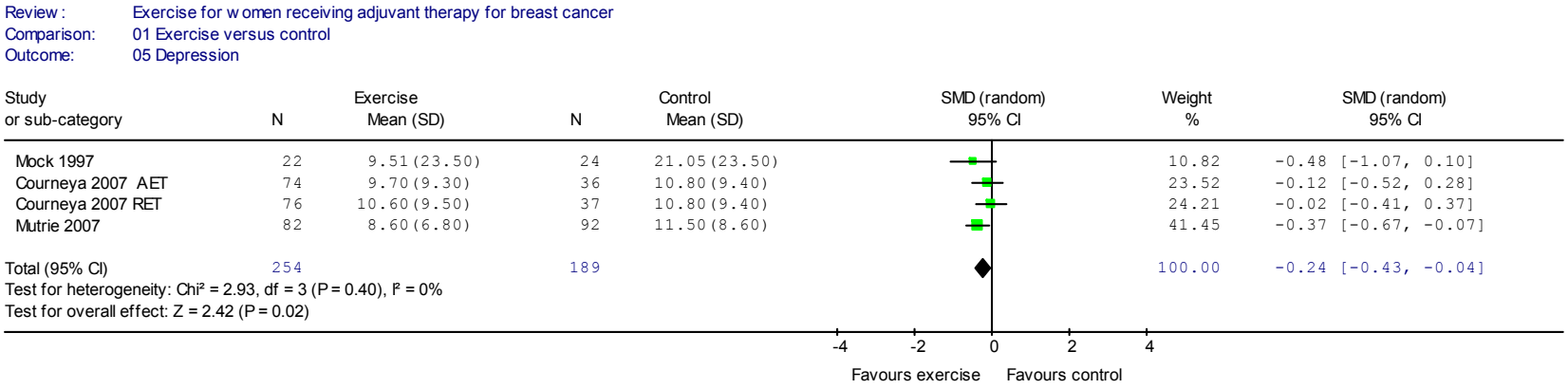

Figure 12: Meta-analysis for cancer-related depression

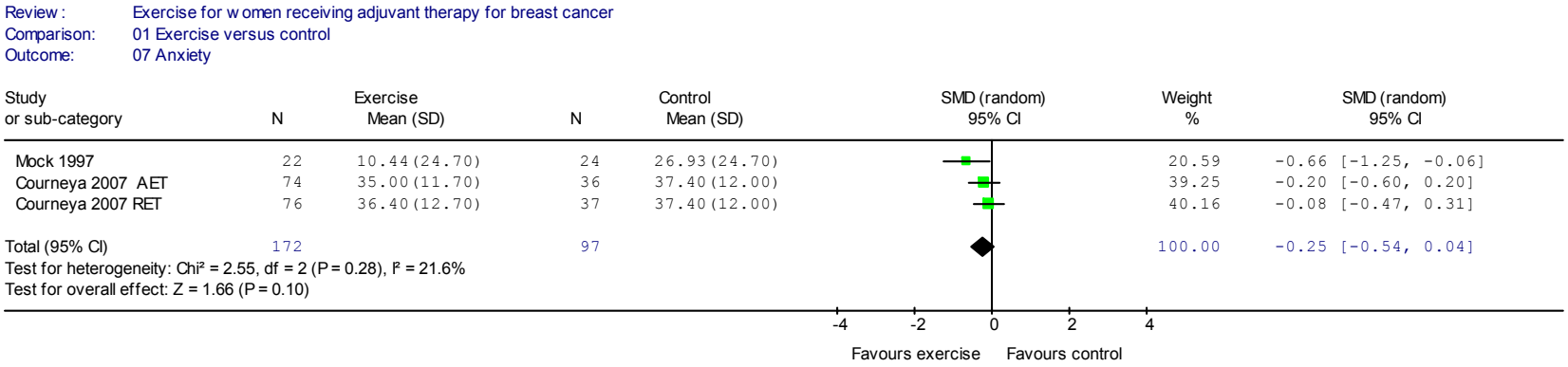

Figure 13: Meta-analysis for anxiety

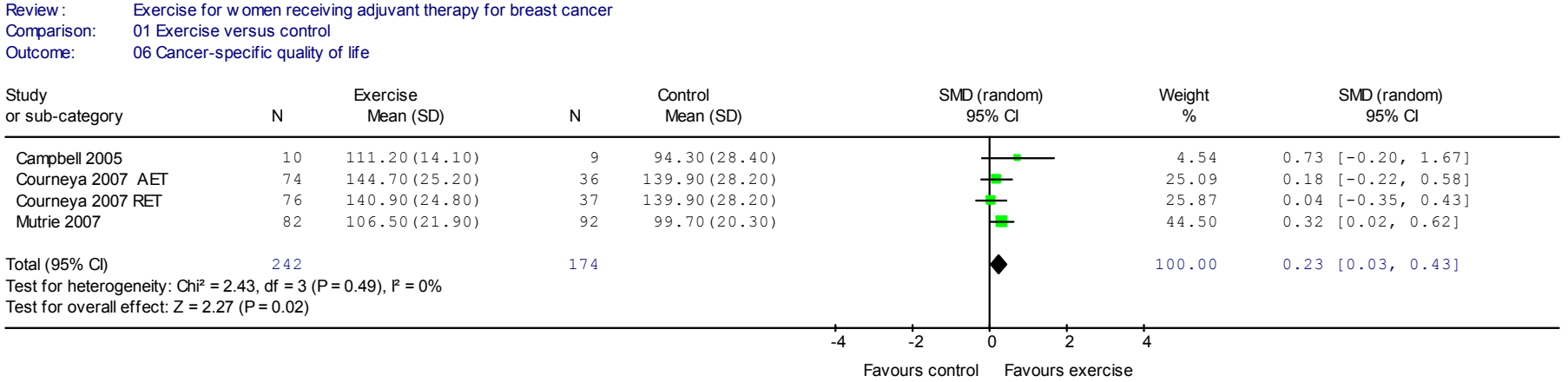

Figure 14: Meta-analysis for cancer-specific quality of life

5.6 Sustainability of effects

Three exercise studies about breast cancer patients receiving adjuvant therapy have reported longer-term follow-up of outcomes, going beyond the immediate post-intervention time point; however, only two of these include health-related outcomes and moreover one study could not be confirmed as assessing post-intervention outcomes after closer examination (Kim 2006). These studies provide an insight into the question of whether any of the benefits of exercise training during breast cancer therapy could be maintained into survivorship (i.e., longer-term effects) or if any new benefits emerged (i.e., late effects). Furthermore, these studies provide information on whether participants continued with exercise after the exercise study and whether such continuation resulted in further improvements in outcomes.

5.6.1 Exercise behaviour

Maintaining exercise beyond the exercise intervention, i.e., long-term adherence to exercise is a critical concern because the benefits of exercise may not persist when exercise is discontinued. There is conflicting evidence regarding long-term exercise maintenance post-intervention. Three studies provided post-intervention data on exercise behaviour or physical activity behaviour. Kim 2006 assessed levels of physical activity four months post-intervention: there were no overall group differences after four months. However, within-group changes indicated significant increases in voluntary exercise, as well as a significant decrease in sedentary activity in the intervention group, indicating positive long-term changes during the post-intervention period. Comparable changes could not be observed in the control group. However, the so-called post-intervention period in this study is the same as the intervention period in other studies included in this review: during the post-intervention period participants were continuously encouraged by a trained exercise physiologist every two weeks to maintain their physical activity at home or in a community setting. This procedure was employed in studies with self-directed home based interventions. The main intervention of Kim 2006 was an on-site aerobic exercise program under direct supervision by trained exercise physiologists in an exercise facility within the School of Nursing. Strictly speaking, Kim 2006 employed a graded exercise intervention of six months, with two months supervised exercise followed by four months of self-directed exercise. Merely, reporting in this study was guided by a deviant terminology regarding exercise intervention and post-intervention period.

This leaves two studies that present data on long-term adherence to exercise and/or physical activity. Mutrie 2007 observed a decrease in the activity levels of the exercise group between the end of the intervention period and the final assessment six months post-intervention. At the six-

month follow-up assessment, there were no differences in physical activity between women who had originally been assigned to the intervention group and those of the control group.

Courneya 2007 categorised participants into those meeting and those not meeting current guidelines for aerobic exercise (150 minutes of moderate-to-vigorous exercise per week) and for resistance exercise (more than two resistance-training sessions per week). They observed that in the aerobic exercise training group, as well as in the resistance-exercise training group, more than 30% of participants reported meeting at least one guideline at the six-month follow-up, and 18% and 29% in the aerobic exercise training group and in the resistance exercise training group, respectively, reported meeting both guidelines.

While data from Courneya 2007 suggest that a supervised exercise training program during adjuvant chemotherapy may be an effective strategy for helping sedentary breast cancer patients' transition towards an active lifestyle, data from Mutrie 2007 show difficulties of maintaining physical activity without classes and supervision.

Pooling of physical activity data (assessed as minutes per week) from Mutrie 2007 and Kim 2006 indicates that participants in the exercise groups demonstrated higher physical activity levels (standardised mean difference 0.25, with 95% confidence interval -0.02 to 0.51). However, it has to be noted, that the participants described by Kim 2006 still received motivational support in the post-intervention period. Results from meta-analysis based on the unstandardised mean difference shows that participants from the intervention group are 73 minutes more physically active compared to participants from the control group (Figure 15).

5.6.2 Long-term intervention effects

Both studies with long-term follow-up of six months (Courneya 2007, Mutrie 2007) reported that immediate post-intervention effects were largely maintained at six-month follow-up. Mutrie 2007 reported long-term intervention effects for cardiorespiratory fitness, endocrine symptoms, depression, and positive affects. Furthermore, they observed a borderline-significant late effect for general quality of life. Results of Courneya 2007 showed a longer-term effect on self-esteem and a late effect on anxiety that emerged in the post-intervention period. The effect sizes are presented in Table 18.

Results could be pooled for three outcomes: fatigue, depression, and cancer-specific quality of life. Meta-analyses for these outcomes indicated a small, and not statistically significant, effect of exercise on reducing fatigue (see Figure 16), a small, statistically significant, effect of exercise on reducing depression (see Figure 17), and a small, not statistically significant, effect on improving cancer-specific quality of life (see Figure 18).

Thus, there is increasing, though limited, evidence for sustained benefits of exercise at six months post-intervention.

5.6.3 Recurrence and survival

There is no evidence that exercise during adjuvant therapy for breast cancer improves recurrence and survival. These long-term outcomes were not examined in the body of studies included in this review.

Table 18: Summary of findings: long-term effects

Outcome	No. of studies	No. of participants	Effect size [95% CI]
Physical fitness			
Cardiorespiratory fitness	1	177	SMD 0.63 [0.33; 0.94]
Body mass index	1	177	WMD 0.00 [-1.47; 1.47]
Symptoms			
Fatigue	2	378	SMD -0.15 [-0.40; 0.10]
Endocrine symptoms	1	177	SMD -0.13 [-0.42; 0.17]
Emotional distress			
Depression	2	378	SMD -0.27 [-0.48; -0.06]
Anxiety	1	201	SMD -0.30 [-0.60; 0.01]
Negative affects	1	177	SMD -0.26 [-0.56; 0.04]
Positive psychological function			
Self-esteem	1	201	SMD 0.24 [-0.06; 0.54]
Positive affects	1	177	SMD 0.4 [0.10; 0.70]
Cancer-specific quality of life	2	378	SMD 0.24 [0.00; 0.49]
Physical activity	2	218	SMD 0.25 [-0.02; 0.51]

5.6.4 Forest plots for long-term intervention outcomes

Results for long-term outcomes are presented in meta-analyses, where combining of results was feasible. To distinguish intervention arms of Courneya 2007, a code for aerobic and resistance exercise was created (AET resp. RET). More forest plots for long-term outcomes can be found in Appendix 12.

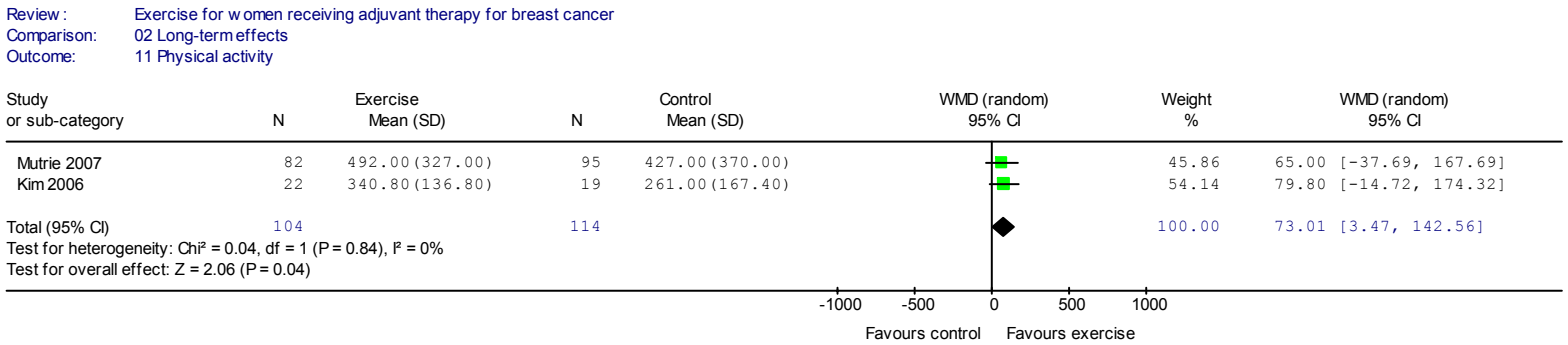

Figure 15: Meta-analysis for physical activity

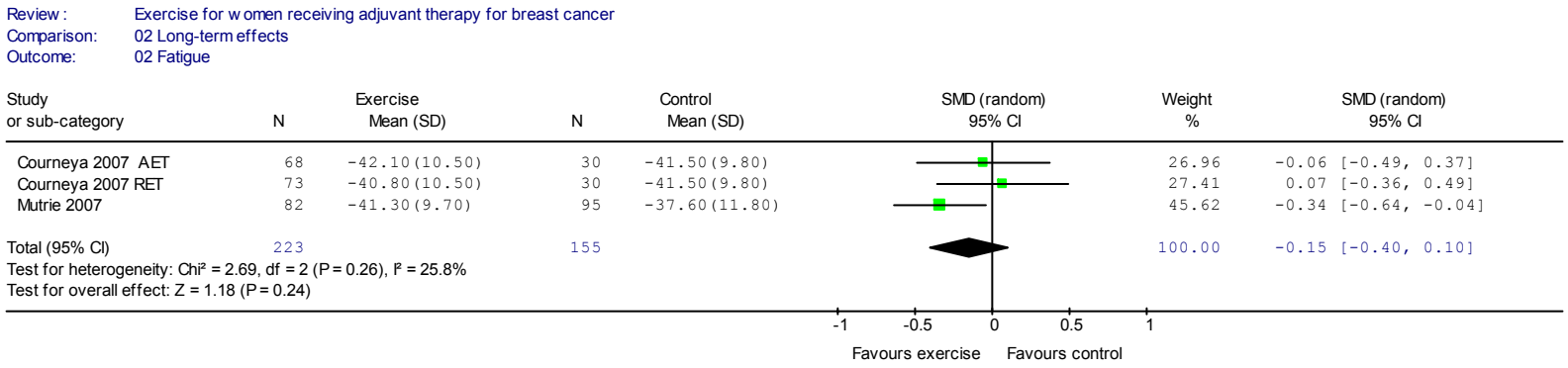

Figure 16: Meta-analysis for long-term effect on fatigue

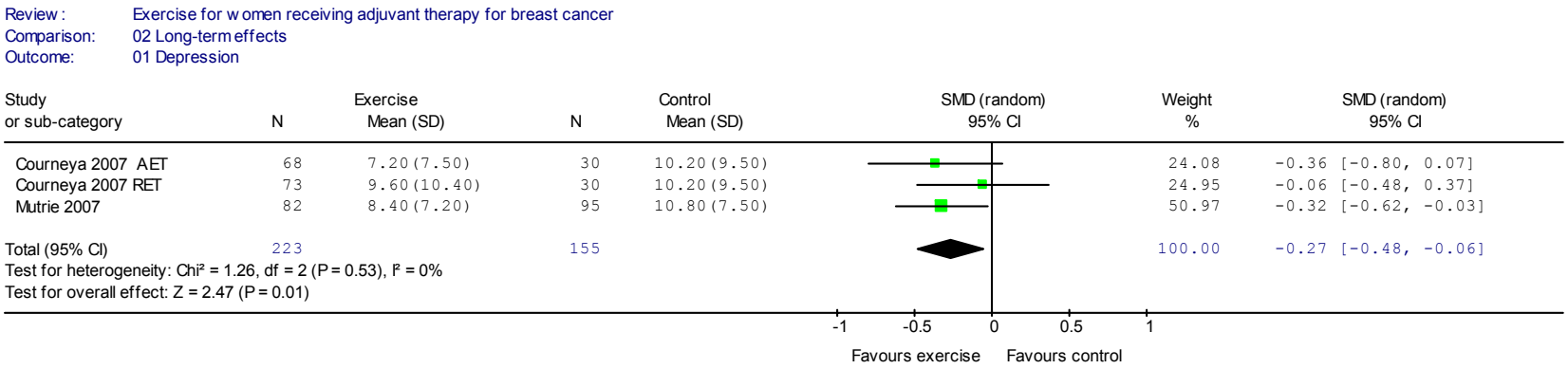

Figure 17: Meta-analysis for long-term effect on depression

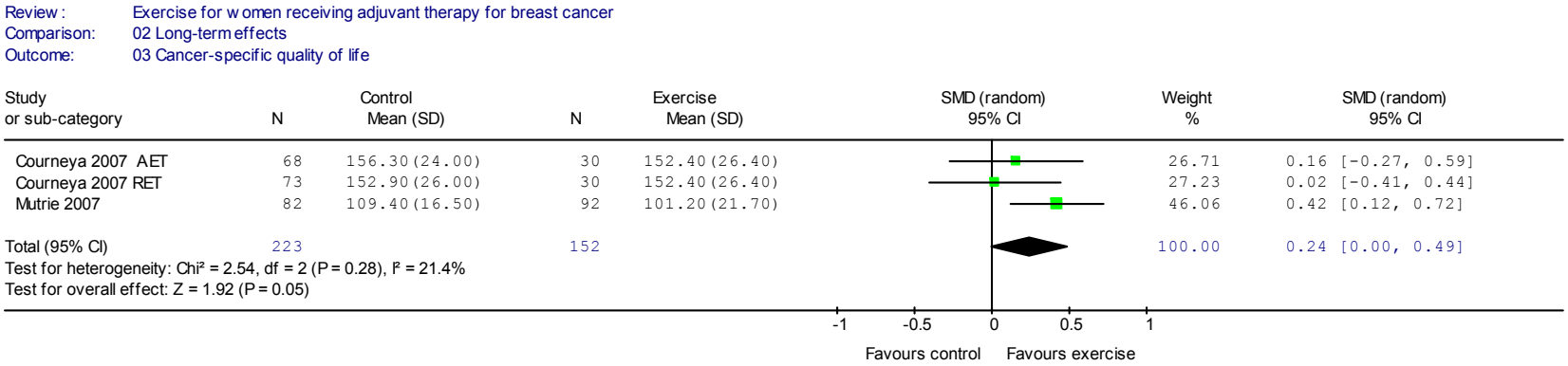

Figure 18: Meta-analysis for long-term effect on cancer-specific quality of life

5.7 Harm from exercise interventions

Adverse effects due to exercise were reported for nine of the studies included in the effectiveness review (Battaglini 2007, Campbell 2005, Courneya 2007, Crowley 2003, Drouin 2002, Mock 1997, Mock 2005, Schwartz 2007, Segal 2001). Harmful effects were observed in three of these studies: Crowley 2003 reported onset of lymphedema in one participant, Drouin 2002 reported shoulder tendonitis and decreases in strength due to overtraining in one participant, and Courneya 2007 reported some mild to moderate harmful effects related to maximal exercise testing in two participants (hypotension, nausea, dizziness, weakness, and mild diarrhoea). Both participants recovered quickly. No harmful effects were observed in the other six studies that reported on harmful effects. However, none of these studies described how relevant information was collected. To summarise, *passive surveillance* (spontaneous reports) of harm across the included studies of benefit has not revealed any increase in injury rates or other adverse events in the exercise groups compared to non-exercising control groups. No single study has performed active surveillance of injuries in exercise interventions studies during adjuvant treatment for breast cancer. One study (Courneya 2007) actively surveyed lymphedema and no increased risk of lymphedema associated with exercise during adjuvant treatment for breast cancer was reported. Quite the contrary, women in the exercise groups less frequently experienced an onset of lymphedema compared to women in the control group (RR 0.85, 95% CI 0.31 to 2.3). Onset of lymphedema (defined as a 200 ml increase in the difference between affected and unaffected arm volumes, using volumetric arm measurement based on water displacement) was a secondary outcome in this study and therefore regularly monitored. The effect size is presented in Table 17.

The included studies of harm all performed *active surveillance*. Lymphedema and injuries were evaluated in the included studies. The three included studies (see Table 19) yielded evidence of no increased risk of lymphedema due to exercise. Active injury surveillance in exercise studies *after* adjuvant treatment for breast cancer indicated that weight training is well tolerated, with rates of minor injuries comparable to those observed in the general population. However, results relating to harm were evaluated after adjuvant cancer treatment had been completed. Vulnerability may be increased during adjuvant treatment.

Table 19: Summary of findings: harm

Study-ID, n	Lymphedema	Injury (%)
McKenzie 2003 n=14 with lymphedema	No group differences in changes of arm volume	n/a
Schmitz 2005 n=85 for injury assessment n=45 for lymphedema assessment	**Arm circumference increase** of ≥ 2cm: Control: 1/22 (4.4%); Intervention: 0/23 (0%). **Self-reported incidence**: Control: 2/16 (12.5%); Intervention: 2/16 (12.5%). **Increase in symptoms**: Control: 3/22 (13.6%); Intervention: 0/23 (0%).	**Intervention**: 6 months: 10.5%, 12 months: 22.5% **Control** after delayed intervention: 6 months: 20%
Basen-Engquist 2006 n=60	No group differences in numbers of arm circumference increase of ≥ 2cm	n/a

5.8 Perception of exercise during breast cancer treatment

Besides the effects of the exercise intervention, experiences of participants are of interest as well. One attendant focus-group study (Emslie et al. 2007) explored the perceptions of women exercising in community-based groups established solely for women during their breast cancer treatment. They found that classes helped them to adopt exercise or return to exercise. With regards to the expert instruction in these groups, the women especially valued not having to explain their problems to the instructor, and at the same time they could rebuild confidence in their ability to participate in exercise in spite of feeling vulnerable. Women appreciated that through expert instruction constant adjustment of pace and exercise to the composition of the group was made possible. Then, with regards to the group context, the women emphasised how important it was for them to exercise among women in similar circumstances; they valued the empathy, solidarity, and acceptance they received from others, the friendships that evolved, the information-gathering function of the group, and the freedom in choosing to share experiences. Finally, the exercise focus in classes was seen as "upbeat, enjoyable and fun" (Emslie et al. 2007), giving them a chance to forget about cancer for a while. Participants commonly complained that exercise classes stopped abruptly at the end of the intervention of the supervised group exercise trial they had taken part in (Emslie et al. 2007).

6 Discussion

6.1 Summary of main results

Physical exercise appears to be an intervention that effectively improves health-related physical fitness even in the period of breast cancer treatment. There is evidence for a medium effect of exercise on cardiorespiratory fitness, strength, and body composition. Moreover, exercise offered a small benefit against fatigue, anxiety and depression compared to no exercise. Evidence for quality-of-life outcomes is limited; cancer-site-specific quality of life was better in exercisers than in non-exercisers. Similar effects could not be observed for generic or cancer-specific quality of life; generic or cancer-specific measures may be too broad for capturing changes in breast-cancer-specific health outcomes.

For the purposes of forming an impression of the magnitude of effects, the effect size statistic can be translated into a more intuitively understandable unit: e.g., for cardiorespiratory fitness, a medium effect from physical exercise training could be established. The effect size of 0.54 means that the average exercise group scored 0.54 standard deviation units higher on cardiorespiratory fitness after exercise intervention compared to the average control group. In order to provide a frame of reference and to put this effect size in some interpretable context, it can be translated into walked distance (12 minutes) as a more intuitively comprehensible metric following a method suggested by Lipsey and Wilson (2001). To do this, the overall mean and standard deviation on the measure of interest (i.e., walked distance) for the control groups has to be generated through pooling the results from multiple studies. With this information, an overall mean for the intervention groups can be calculated on that same metric: it is the control group mean plus the product of the effect size and the standard deviation value for the metric of interest (Lipsey and Wilson 2001). So, for the control groups a mean of 977 meters walking distance was calculated, together with a standard deviation of 208 meters, which – multiplying 0.54, the effect size for cardiorespiratory fitness, by 201 meters – gives the equivalent of 112 meters Thus, with the control group's mean of 977 meters, the average exercise group at post-intervention achieved 1089 meters, within these 12 minutes of test duration.

The potential harm of exercise during breast cancer treatment has generally been disregarded in the literature. Where harm has been recorded, it has been spontaneously reported by participants, rather than systematically assessed by active surveillance (where participants are asked about the occurrence of specific harms in structured questionnaires or interviews, or predefined diagnostic tests are performed at pre-specified time intervals). Passive surveillance of harm across the studies included in the review did not reveal any increase either in injury rates or for other harms in the exercise groups, when compared to non-exercising control groups. No single study per-

formed active surveillance of injuries occurring in exercise interventions *during* adjuvant treatment for breast cancer. Of some relevance here however, is that active injury surveillance undertaken in exercise studies *after* adjuvant treatment for breast cancer has indicated that weight training is well tolerated, with rates of minor injuries comparable to those observed in the general population. Active surveillance of lymphedema both during (one study) and after adjuvant treatment (two studies) did not produce evidence of any increased risk associated with exercise during adjuvant treatment for breast cancer. In summary, the present available evidence regarding safety of exercise during adjuvant breast cancer treatment is limited.

Primary studies have examined exercise interventions over very broad ranges of exercise volume: frequencies ranged from two to six times per week; duration from 15 to 60 minutes, intensity from low to moderate with heart-rate ranges between 50 to 85 percent of maximum heart rate. Within these broad ranges, there is little empirical data to give recommendations regarding exercise volume. The available evidence does not allow the determining of the relationship between the exercise volume and either the changes in health-related physical fitness and other physical or mental health outcomes. Furthermore, there is insufficient evidence to determine whether aerobic exercise, resistance exercise, or mixed exercise is the most appropriate type of exercise for women receiving adjuvant treatment of breast cancer. Finally, evidence is insufficient regarding the individualisation of exercise prescriptions: treatment-related symptoms may require that prescriptions need to be individualised; however, factors that must be considered in the development of individualised exercise programs still have to be identified systematically as well as subsequent adjustments of the exercise program.

Regarding long-term post-intervention effects of exercise, evidence is preliminary only. There was a trend of benefits being maintained over time. However, differences between exercise and control groups decreased compared to the immediate post-intervention time. Fitness outcomes require attendance of participants and were examined in only one study at six-month follow up. Pooling was feasible for patient-reported outcomes such as fatigue and depression. Pooling results from two studies still indicated a small benefit from exercise. However, the pivotal question is whether women do continue their regular exercise program after the end of exercise intervention. Maintenance of physical activity, however, appears to be a problem and particularly presents a challenge for formerly sedentary women.

In sum, to answer the overall guiding review questions: yes, women should be offered exercise in the period of adjuvant therapy for breast cancer. Exercise can be expected to provide benefits for health-related physical fitness. There is modest evidence that benefits can also be expected for other physical health outcomes such as alleviation of fatigue symptoms, and for mental health

outcomes like anxiety and depression. The possibility of harm due to exercise in this sensitive period could not be ruled out, since this problem has not been systematically examined in primary studies. There is limited relevant evidence from studies of benefit, but it does not indicate any gateway for harm through exercise. Nevertheless, providing such evidence is necessary because, in the absence of such evidence, patients and physicians may avoid physical exercise training.

6.2 Applicability and overall completeness of evidence

One concern about the applicability of the results is the age of patients. Compared to the mean age of 63 years at the time of breast cancer diagnosis in Germany (Batzler et al. 2008), the women included in the primary studies of this review were relatively young, with a mean age of 50 years - due to the restrictive inclusion criteria. Thus, evidence about exercise in women receiving adjuvant treatment of breast cancer has been derived largely from research on middle-aged women. If we try to apply these results in the context of older breast cancer patients, several problems emerge: Do older breast cancer patients derive similar benefits from exercise? Are older breast cancer patients more vulnerable to injury? Are exercise participation rates and adherence to an exercise program comparable? Are determinants of exercise motivation and behaviour comparable? One recent pilot study (Payne 2008) did focus on older women. Participants had a mean age of 65 years, compared with the mean age of 50 years across the other studies. However, results from this small study are only preliminary and thus older women remain an understudied patient population.

One further problem regarding applicability are recruitment rates which vary considerably across studies: for example, Mutrie 2007 approached 1,114 women and included 203 (18%) of them, while Mock 1997 approached 65 women and 50 (77%) of these agreed to participate. Given the range of reported recruitment rates, it can be assumed that studies were subject to selection bias, and so participants might differ from the target population with respect to relevant characteristics. For example, it is possible that consenting women in the control groups may have had more disposition to increase exercise or activity than those declining to participate, simply as a function of their general activity levels and motivation. Thus, it is difficult to assess the generalisability of the results to the wider population.

The evidence of this review is not complete: harm appears to be disregarded in the literature on exercise intervention studies during treatment. This gap in the evidence appears all the more important in light of the finding that none of the reviewed studies have explored the appropriateness, effectiveness, or safety of exercise in an older breast cancer population. Given the known functional decline in older cancer survivors, going along with loss of skeletal muscle mass (sarco-

penia), loss of flexibility, muscle weakness, and decreased bone density, which can be further exacerbated by breast cancer disease and treatment, an increased risk of exercise-related traumatic or overuse injuries has to be taken into account. Previously sedentary middle-aged and older women who are treated with cardiotoxic drugs may be at increased risk of an adverse cardiovascular event occurring during or following an acute bout of physical exercise and thus, cardiovascular risks of exercise during cancer treatment should not be ignored. Sudden cardiac death and acute myocardial infarction are serious complications of exercise in adults, and pre-participation stress testing often does not reveal any abnormality in patients who subsequently suffer an acute cardiac event (Thompson 2001). A commensurate statement regarding cardiovascular risks is overdue because virtually all adjuvant therapies for breast cancer are associated with unique and varying degrees of cardiovascular injuries (Jones et al. 2007), and as women progress through the selected treatment regimens, they will be subjected to a series of cardiovascular insults.

Problems of applicability and the lack of evidence of harm may deter oncologists from recommending exercise to women with breast cancer, although the evidence – as presented in this review – suggests that exercise training may enhance health-related physical fitness, may alleviate debilitating symptoms such as fatigue, and may improve such mental health outcomes as anxiety and depression. Oncologists' attitudes from a Canadian national survey indicate that there is already consensus that exercise is beneficial (62%), important (56%) and safe (63%) for patients with cancer during treatment (Jones et al. 2005). However, despite these positive attitudes, only 28% of oncologists had recommended exercise to their patients in the last month. Similarly, a national survey in the United Kingdom showed that most clinicians (56%) did not routinely discuss physical activity with their patients (Daley et al. 2008). Evidence of the relationship, if any, between level of exercise and increased harm from exercise, may contribute to further development of the field of exercise interventions applied to breast cancer patients.

6.3 Strengths and limitations of included studies

Since the earliest exercise intervention studies during adjuvant therapy for breast cancer, the field of exercise interventions has grown impressively and the methodological rigour has improved within this time as well. The amount of evidence is based on 15 controlled studies that could be included in this review. Recent studies more often, though not always, had larger sample sizes (with nearly 100 participants per group), and were based on power calculations. Adequate sample size is important, since benefits of exercise interventions may be relatively small. Therefore, the number of participants included should be great enough to allow the detection of small differences between groups. Also reporting has improved, with nearly complete reporting according to CONSORT (CONsolidated Standards of Reporting Trials) guidelines in some recent studies.

Key methodological limitations of the included studies were observer blinding, concealment of intervention allocation, and missing intention-to-treat analysis. Moreover, there were some inconsistencies between results, and for several results wide confidence intervals were observed.

A wide range of outcome constructs was assessed across the studies, which made it difficult to combine outcomes in meta-analysis. For example, emotional distress was assessed by means of, among other indicators, mood, anxiety, depression, and negative affects; then body composition was evaluated via weight, body mass index, subcutaneous fat, and lean body mass. Within this broad range of outcome measures, each outcome was assessed through several different assessment instruments. Moreover, data reporting in early trials was very poor and did not provide estimates of effect size that could be pooled.

6.3.1 Inconsistencies of effects across studies

Variation in the effects of exercise interventions could be observed for several outcomes. In the sections below, some factors are discussed that may have affected heterogeneity. First, the percentage of total variation across studies that was due to heterogeneity rather than chance was 45% for cardiorespiratory fitness. Heterogeneity was 40% when the study arms with resistance exercise training were excluded from meta-analysis in a sensitivity analysis, and it was further reduced to barely 20% when Segal 2001 was excluded. The resulting standardised mean difference based on 440 participants was 0.73, with the 95% confidence interval of 0.48 to 0.97. Heterogeneity in the meta-analysis for cardiorespiratory fitness might be explained based on specificity as a core exercise training principle. The principle of specificity states that training effects derived from an exercise intervention are specific to the exercise performed and muscles involved (Balady et al. 2000). To improve cardiorespiratory fitness, predominantly aerobic exercise training is required, and the effects from resistance exercise training programs can be expected to be relatively small. Furthermore, in one study (Segal 2001), a non-specific exercise test was employed as an assessment instrument for cardiorespiratory fitness: cardiorespiratory fitness was assessed through a step test, but women had trained in walking. It might be expected that effects assessed on a stepping ergometer would be lower compared to those assessed on a treadmill. Furthermore, compared to other studies, the training stimulus was relative low in the Segal study. This low training stimulus becomes even more important in light of the observation that baseline cardiorespiratory fitness of women in this study was relatively high compared to the fitness level of women in other studies: oxygen uptake in two studies (Drouin 2002, Crowley 2003) was below the 10th percentile rank for a 50-59 year-old female and, as such, these participants demonstrated markedly low cardiorespiratory fitness (Balady et al. 2000). In contrast, oxygen uptake of participants in the Segal trial was around the 30th percentile rank for a 50-59 year-old female. Higher

fitness levels require higher training stimuli to yield effects. The remaining heterogeneity can be explained with clinical heterogeneity (various adjuvant treatment regimens) and differences in the exercise interventions regarding frequency, program duration besides intensity.

Second, variability in results between studies was 50% in the meta-analysis for strength. As for the meta-analysis for cardiorespiratory fitness, heterogeneity can be attributed to neglect of the principle of specificity: across included studies, strength was measured not only after resistance exercise training but also after aerobic exercise training. Typically, only resistance training is designed to increase strength, power, and muscle endurance. Since effects of exercise training tend to be specific, walking as an aerobic exercise for the lower body could not be expected to change strength in the upper body. Heterogeneity resolved when only resistance exercise training studies were pooled.

Furthermore, there was moderate heterogeneity of 47% in the meta-analysis for fatigue, which could be resolved after exclusion of Battaglini 2007 from sensitivity analysis. One explanatory approach for this heterogeneity is given in Battaglini's operating schedule for fatigue assessments: fatigue assessments were scheduled with some temporal distance to the cancer treatment cycles: this assessment procedure avoided the highest levels of fatigue in the first days post-treatment. It can be suspected that differences between groups do not become obvious before recovery from acute treatment. No information regarding similar procedures was available from the other studies.

However, sensitivity analyses across outcomes indicated that Battaglini's dissertation thesis, involving around 20 participants, systematically contributed to heterogeneity in various outcomes; results from this study suggest greater effects from exercise than other studies. However, since predominant inconsistencies could be explained and resolved through sensitivity analyses, inconsistencies of studies' results in meta-analyses do not reduce the confidence of results.

6.3.2 Replicability of the intervention and mediational pathways

Basically, exercise interventions in included studies were atheoretical. Theory-based interventions are preferable because these interventions allow for results that are replicable and generalisable. The intervention (package) has to be successful at helping sedentary individuals initiate and maintain a moderate-intensity exercise regimen. The planning of reasonable and effective exercise-promotion activities calls for knowledge of the natural fluctuations of exercise in women receiving adjuvant treatment of breast cancer: determinants of planning for participation, initial adoption of exercise, continued participation, or maintenance, and overall periodicity of participation (e.g., relapse, resumption, and seasonal variations) have to be characterised and targeted in order

to influence exercise patterns. Primary studies included in this review lacked a compelling conceptual basis for exercise promotion and behaviour change: apart from two trials (Campbell 2005, Mutrie 2007), interventions were restricted to the delivery of an adequate training stimulus. These interventions, that focus on exercise dosage only, neglect the complexity of exercise behaviour as a psychological, behavioural and social phenomenon.

The exercise studies of this review failed to include an assessment of program integrity, i.e., the degree to which the exercise interventions were implemented as intended. Integrity information is particular important in the context of exercise interventions during adjuvant cancer treatment, since this context stands for dynamic and complex conditions that present numerous obstacles to complete intervention delivery. Apart from two studies, only the prescribed training stimulus was available with details for intensity, time, frequency and program period. Because integrity data, an important source for information about the feasibility of exercise interventions in real-life settings, are lacking, it remains difficult to determine whether the intervention has the potential to be implemented as planned.

The training stimulus can be severely compromised by a lack of participants' adherence to the exercise intervention. For sedentary individuals, a change in personal health behaviour is required in order to take up regular exercise. Thus, any exercise intervention can additionally be evaluated according to the degree of behavioural change achieved in the intervention group. Adherence problems do not only affect participation in exercise sessions and frequency of sessions, but also affect the training intensity and duration achieved during each exercise session; insufficient exercise intensity or duration may compromise the training stimulus as a whole. However, these two facets of the training stimulus were poorly evaluated and reported in the included studies.

Besides adherence, the extent of exercise in the control group (contamination) is a further critical component in exercise studies, and was described as a problem in a few trials. However, exercise contamination was rarely reported and often only when the exercise program was home based. This reporting practice indicates that contamination was not systematically investigated across trials. Accordingly, it can not be determined based on available data whether small or non-significant results are simply due to failure of implementation or are due to failure of the exercise program.

The individual's level of fitness is an important factor to consider before determining the level of exercise intensity. According to ACSM (Balady et al. 2000), deconditioned individuals may demonstrate increases in their cardiorespiratory fitness from exercise intensities at the lower end of the intensity continuum, whereas fitter individuals need to work at the higher end of the intensity continuum to improve fitness. The initial fitness level was considered in only a few studies, which

were studies that limited participation to sedentary individuals; however, definitions of sedentary varied.

Replicability of interventions across studies of atheoretical exercise interventions is compromised. Theory-based interventions allow for results that are replicable and generalisable, and furthermore provide guidance in the development of the intervention and the mechanisms of change. There was one study that additionally performed a predictor analysis of exercise adherence (Courneya 2007); the predictor analysis was guided by the theory of planned behaviour, a social cognitive model of human behaviour that proposes that intention is the most important determinant of behaviour. However, results were not translated into intervention characteristics for future studies. Moreover, important details of intervention components are not available: no discussion guides, class outlines and materials, or motivational strategies for telephone counselling and other details of the intervention are given.

6.4 Potential biases in the review process

The basic search in 2004 was the most comprehensive one. Updating searches were less comprehensive and based only on MEDLINE and the Cochrane Central Register of Controlled Trials, as already explained in detail. The practice of basing updates only on searches of these two registers means in particular that no further unpublished trials, or those that are difficult to locate could be identified. However, trials that are difficult to locate are often of low quality (Egger et al. 2003). This tendency, of difficult to locate trials to be of low quality, "raises the worrying possibility that rather than preventing bias through extensive literature searches, bias could be introduced by including trials of low methodological quality" (Egger et al. 2003). Additionally, in spite of comprehensive attempts to identify all relevant studies, predominantly English language studies were retrieved for inclusion in this review, with one German trial awaiting assessment after its publication. This may reflect a language bias, where authors, whose native language is not English, are more likely to publish RCTs in an English-language journal if the results were statistically significant. The policy taken in the registration of trials may provide an interesting basis for addressing publication bias in the future (Antes 2004).

The meta-analyses were performed using final values instead of change scores. However, it is possible for baseline imbalances to occur between intervention groups for one or more variables in a randomised controlled trial. Hence, statistically significant intervention effects may be due to the baseline imbalances between intervention and control groups, rather than as a result of the exercise intervention. There is the possibility, that effects from participating in an exercise program may be in fact smaller and not statistically significant.

The assessment of training stimulus was based on two scores, one for aerobic and one for resistance exercise. For exercise interventions with both aerobic and resistance modules, applicability of these two single scores (developed for assessing training stimulus of aerobic or resistance interventions only) may lead to the underestimation of the size of the total training stimulus. However, for all included trials an adequate training stimulus was determined.

Finally, critical appraisal of more than half of the included studies was performed by one reviewer only. However, inter-rater reliability of the first charge of included studies indicated almost perfect agreement between the two reviewers. Thus, results from critical appraisal can be expected to be still reliable.

6.5 Agreements with other reviews

Findings of this review are supported from results of other reviews: exercise was found to be beneficial for cancer patients with any cancers during cancer treatment (Conn et al. 2006), as well as for cancer survivors with various cancers in the post-adjuvant setting (Stevinson et al. 2004, Schmitz et al. 2005, Conn et al. 2006, McNeely et al. 2006). Effects in the post-adjuvant setting seem to be larger when compared to effects of exercise during treatment (Stevinson et al. 2004, Schmitz et al. 2005). Finally, exercise was found to be beneficial for individuals with cancer-related fatigue, both during and post cancer, in one Cochrane review (Cramp and Daniel 2008). Benefits resulting from exercise included physical and mental health outcomes, and quality of life. There is no evidence for harm in the other reviews that examined exercise in the continuum of cancer experiences, regardless of focus.

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7 Conclusions and forecast

7.1 Implications for research

There is a need for ongoing research, involving studies with adequate statistical power to further develop the evidence base.

Achieving a consensus of researchers on outcome measures for exercise studies involving breast cancer patients receiving adjuvant treatment is needed in order to assist interpretation and comparison of results across various interventions. Given the known functional decline, especially in older women receiving adjuvant treatment of cancer, physical functioning becomes an important outcome. Following the model of Bennett et al. (2006) for examining physical functioning in cancer survivors, physical functioning assessments may include objective measures of mobility such as balance, standing, reaching, and climbing stairs as well as self-reports of mobility and lifestyle activities such as self-care, daily living, and occupational activities. Besides health-related outcomes, the potential for harm should be assessed and reported as well. Reporting standards for harm (Ioannidis et al. 2004) should help to inform both practitioners and the public on the potential harm of exercise interventions during adjuvant cancer treatment. The long-term follow up of exercise interventions requires attention, because some health problems linked to adjuvant cancer treatment are either long-term, such as fatigue or deconditioning, or may be related to recurrence and mortality, such as weight gain. Future research will need to improve understanding of the ways in which individuals can sustain long-term lifestyle choices.

Regarding the exercise intervention, attention should be concentrated to tailoring type (e.g., aerobic or resistance training), dosage (i.e., frequency, intensity, and duration), progression, and context (e.g., centre-based, community-based, or home-based, with either individual or group format) of exercise prescription to the specific needs of patients.

As described above, the actual training stimulus may substantially deviate from the assigned exercise regimen. If participants allocated to the exercise group do not exercise (non-adherence), and at the same time participants allocated to the control group do exercise (contamination), the originally intended trial groups are degenerated into groups with participants who exercise and those who do not, and moreover in unknown proportions. If those groups are analysed as 'randomised', effects may be underestimated. In efficacy trials, investigators need to ensure adherence to the intervention to determine whether exercise interventions in this population work. Inclusion of sedentary participants only may be a way to deal with contamination issues: sedentary women can be expected not to start their own exercise program in the period of adjuvant cancer treatment. In effectiveness trials, both adherence and contamination should be reported as

an outcome measure because poor adherence can render an efficacious intervention as ineffective.

Finally, further development of the field of exercise intervention will require more attention to identifying more cost-effective ways to expose patients to the exercise prescription: outside University or cancer centres – inside the communities.

7.2 Implications for practice

The benefit of any exercise intervention is determined not only by its efficacy, but also by the extent to which it is appropriately adopted and implemented in the community. The exercise rehabilitation programs established in Germany for women who have been treated for breast cancer provide a model of how exercise could be offered to breast cancer patients *during* treatment within a health care context. This model of regular exercise in the rehabilitation of women with breast cancer could be adopted in other countries. Currently, more than 600 rehabilitation sports groups, providing exercise classes for women who have been treated for breast cancer, exist in Germany within the framework of organised sports. A particular strength of these groups is that they are local, thus allowing participation in structured exercise programs in the vicinity of participants' homes, a model which could easily be adapted for women undergoing treatment for breast cancer.

Currently, being treated for breast cancer is widely regarded as a contraindication for participating in existing rehabilitation sports groups. However, evidence indicates that there is no increased risk of injury or lymphedema even during adjuvant cancer treatment, neither in home-based, self-organised interventions nor in clinical settings, or community-based interventions. Where rehabilitation sports groups for breast cancer survivors are accessible, women who are still being treated for breast cancer should be offered the opportunity to practise sport within one of these groups. Exercise classes during adjuvant treatment should focus on maintaining exercise levels among previously active women, and increasing exercise levels among inactive women.

7.2.1 Setting up exercise classes

There are some organisational pre-conditions that have to be ensured: first, there needs to be a qualified group exercise instructor, to conduct the group exercise sessions for the target group of women with breast cancer and a physician has to be enlisted to supervise the exercise classes. Pre-activity participation screening by treating physicians and medical clearance are mandatory before women can participate in the exercise program. Exercise facilities and sports equipment such as balls, thera-bands or step boards are usually provided by the sports club. Venues should be accessible by public transport and preferably barrier-free. An additional room for socializing

and informal exchange after exercise sessions would be an asset. Not least, recruitment and retention of participants is crucial to the success of rehabilitation sports programs. In contrast to exercise programming for post-cardiac rehabilitation, recommending exercise to women diagnosed with breast cancer is still made reluctantly by physicians. The idea of regular exercise as a beneficial behaviour during breast cancer treatment has to be "sold" to treating physicians, to sports clubs, and not least to women. Methods of social marketing may contribute to overcome recruitment problems. Further, partnerships could be cultivated with physicians in breast centres/ rehabilitation facilities and with self-help initiatives to facilitate access to breast cancer patients.

One focus in the conduct of exercise classes is on helping sedentary individuals to initiate and maintain a moderate-intensity exercise regimen. Conducive to this is a well-balanced exercise program meeting the needs of participants. Women with low levels of fitness might need instruction and programs where they can experience enjoyment in movement and success in a positive, non-competitive environment. This creates a challenge for exercise instructors to come up with an interesting variety of movement combination, music, and teaching formations. Varied teaching formations, other than front-facing formation, such as using circles, lines, and partner groupings, also facilitate social interaction. Emotional and social components contribute to the success of the exercise program and when programs meet exercise needs but fail to facilitate social and emotional aspects, they may stagnate. For enjoyment, aerobic or resistance exercise, flexibility, or balance exercises may be embedded in traditional and non-traditional movement games that encourage physical activity. Performing movement to music may encourage feeling at ease and experimenting with new movement activities. Safety is another important aspect of the exercise program: monitoring exercise intensity does not only assure that the targeted training dosage is achieved but also gives important feedback on how women are responding to the exercise class. Using a variety of techniques to monitor exercise intensity increases the safety of the program, e.g., taking exercise pulse and recovery pulse rates in conjunction with rates of perceived exertion.

The art of exercise prescription is the "successful integration of exercise science with behavioural techniques that result in long-term program compliance" (Balady et al. 2000): Especially for groups of sedentary women, in addition to the pure exercise stimulus, a behaviour change approach is essential in order to motivate them to keep exercising. They not only need to feel that they can carry out physical exercise (i.e., physical exercise self-efficacy), but they also need to feel that they are fully responsible for initiating and maintaining exercise. Besides disease- and treatment-related barriers, one cause for non-adherence to exercise prescriptions is motivational in nature. Motivation is a critical variable in producing maintained change, especially with respect to the post-treatment period, when disease- and treatment-related barriers can be expected to be less

relevant. The exercise instructor is challenged here to gain a clearer understanding of how to facilitate motivation in the context of exercise behaviour.

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9 Appendices

9.1 Appendix 1 – Protocol

BACKGROUND

Breast cancer detection and management have undergone dramatic changes over the past three decades. Women are increasingly diagnosed with early stage disease leaving them with treatment choices ranging from breast conserving options to mastectomy (Newman 2003). With the majority of breast cancers diagnosed at an early stage, treatment is focused on cure and the prevention of relapse due to micrometastatic disease. Because systemic adjuvant therapy effectively prevents or delays some relapses and deaths in early-stage disease, this treatment approach has become standard practice throughout most of the Western world (Hudis 2003). The mainstay of care is local therapy, consisting of surgery (with or without radiotherapy), along with systemic adjuvant therapy, which includes chemotherapy (cytotoxic agents), hormonal therapy or a combination of these treatments.

Besides these major advances in managing early and locally advanced breast cancer, patients still have to deal with severe side effects and psychological distress during adjuvant therapy and this has a substantial impact on their quality of life.

- Side effects of radiotherapy can be distinguished in common short-term side effects such as fatigue and skin erythema and in long-term side effects, including lymphedema, cardiac and pulmonary toxicities and brachial plexopathy (Truong 2004).
- Chemotherapy is associated with short-term side effects such as emesis, nausea, stomatitis, alopecia, myelosuppression, thromboembolism, myalgias, neuropathy and fatigue. Long-term side effects are premature menopause, weight gain, fatigue, cardiac dysfunction, and cognitive dysfunction (Partridge 2001).
- Patients receiving radiotherapy or chemotherapy furthermore report anxiety and depression prior to, during and after therapy due to treatment side effects (Spiegel 1997).
- Adjuvant hormonal therapy produces symptoms secondary to oestrogen withdrawal, such as hot flushes, bone demineralization and psychosexual effects (Rutqvist 2004).

Although research is producing increasingly hopeful insights into the causes and cures for cancer, efforts to manage the side effects of adjuvant therapy have not kept pace (Patrick 2003). Exercise interventions may be effective in managing some of these side effects such as fatigue, weight gain, emotional distress, nausea/vomiting and premature menopause. The rationale for exercise interventions is described in the following paragraphs:

Cancer-related fatigue is defined by the National Comprehensive Cancer Network as a "persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning" (NCCN 2003). Fatigue results in substantial physical, psychosocial, cognitive and socioeconomic consequences (Holley 2000). Acute and chronic radiotherapy-related fatigue oc-

curs in up to 80% and 30% of patients respectively (Jereczek-Fossa 2001). During and after adjuvant chemotherapy prevalence of fatigue is high and fluctuating (de Jong 2002) with a frequency of 60 to 90% (Feyer 2001). Fatigue is also associated with factors such as depression, impaired quality of sleep or pain (de Jong 2002). The rationale supporting exercise interventions for cancer-related fatigue is based on the proposition that the combined effects of toxic treatment and a decreased level of activity during treatment cause a reduction in the capacity for physical performance. Patients must therefore use greater effort and expend more energy to perform daily activities leading to fatigue (NCCN 2003). Physical exercise training programmes may increase functional capacity leading to reduced effort and decreased fatigue.

Weight gain is also common among breast cancer patients receiving adjuvant chemotherapy with gains ranging from 0 to 22 kg influenced by menopausal status, nodal status and the type, duration and intensity of treatment (Demark 1997). Weight gain not only has a similar profound effect on quality of life as fatigue, but in addition represents a potentially poor prognostic factor with higher relapse rates and poorer survival (Camoriano 1990). Evidence suggests that overeating is not a cause of weight gain among breast cancer patients who receive chemotherapy but the result of reduced physical activity. Chemotherapy induced weight gain shows the distinctive pattern of sarcopenic obesity, i.e., weight gain in the presence of lean tissue loss or absence of lean tissue gain (Demark 2001). The development of sarcopenic obesity with evidence of reduced physical activity supports the need for interventions focused on exercise, especially resistance training.

Women treated for breast cancer also frequently experience higher levels of emotional distress than the general population (Spiegel 1997). The rationale for considering exercise as an intervention to reduce distress in women receiving adjuvant therapy for breast cancer is based upon the literature that has demonstrated ameliorating effects of exercise on these problems: results of studies with non-cancer populations indicate that aerobic exercise training has antidepressant and anxiolytic effects and protects against harmful consequences of stress (Salmon 2001). There is evidence that cognitive dysfunction may also occur in women receiving adjuvant chemotherapy for breast cancer (O'Shaughnessy 2003; Rugo 2003; Tchen 2003). A meta-analytic study conducted to examine the hypothesis that aerobic fitness training enhances the cognitive vitality of healthy but sedentary older adults indicated that fitness training has robust benefits for cognition (Colcombe 2003).

The incidence and severity of nausea and vomiting in patients receiving chemotherapy are affected by numerous factors including the specific chemotherapeutic agents used, their dosage, the schedule and route of administration and individual patient variability. Although standard chemo-

therapy regimens for breast cancer are considered as mildly to moderately emetogenic (Dibble 2003), nausea and vomiting occur with these regimens: 73%- 82% of women receiving chemotherapy for breast cancer experience nausea (Dibble 2003) and if emesis is severe it can lead in its turn to anticipatory nausea and vomiting (Morrow 1998). Winningham et al. suggest that aerobic exercise may serve as a potential intervention for controlling or mitigating chemotherapy induced nausea (Winningham 1988).

The role of exercise in breast cancer has been examined in retrospective, cross-sectional and prospective studies (Courneya 2001; Courneya 2002; Courneya 2003; Pinto 1999) with the majority of research focused on rehabilitation and health promotion in women who have completed cancer treatment. This review aims to evaluate the role of exercise in managing common side effects of adjuvant therapy for breast cancer.

OBJECTIVES

To systematically assess the effectiveness and safety of aerobic and/or muscular endurance exercises – administered during adjuvant radiotherapy, chemotherapy or hormonal therapy – on managing the following side effects in women with non-metastatic (stages I to III) breast cancer:

- fatigue
- weight gain
- emotional distress
- nausea and/or vomiting
- muscle weakness
- supression of immune functioning.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized and/or non-randomized controlled trials of exercise training during adjuvant treatment (chemotherapy, hormonal and/or radiotherapy) in women with non-metastatic breast cancer will be considered for inclusion if they make any of the following comparisons:

- Aerobic and/or muscular endurance exercise versus no exercise
- Aerobic and/or muscular endurance exercise versus other interventions (e.g., psychosocial interventions)
- Aerobic and/or muscular endurance exercise alone versus exercise as part of a complex intervention
- Moderate intensity aerobic and/or muscular endurance exercise versus low intensity exercise
- Aerobic exercise versus muscular endurance exercise.

Types of participants

Participants will include women with breast cancer stages I, II and III who are currently undergoing adjuvant (including neo-adjuvant) chemotherapy, hormonal therapy or radiotherapy. Eligible participants will include patients of any age, any reproductive status, any level of physical activity before cancer diagnosis, and any weight/BMI. Patients will be ineligible if they have severe cardiac disease, uncontrolled hypertension, orthopaedic contraindications etc.

Types of intervention

Studies that assess the effects of all forms of repeatedly performed aerobic and/or muscular endurance exercise with program duration of at least six weeks will be considered for inclusion. To be included in this review, the exercise intervention has to coincide with the adjuvant treatment regimen rather than to follow it.

Interventions restricted to local muscular endurance only (e.g., training of shoulders, back or legs only instead of including all major muscle groups) or to stretching exercises as well as to exercises as part of complex interventions (e.g., complete decongestive lymphatic therapy) will be excluded.

Types of outcome measures

Outcomes assessed in this review will be any of the following:

- ***Primary outcome measures***
    - Physical and functional well-being (e.g., fatigue, physical performance, sleep disturbances)
    - Emotional and psychological well-being (e.g., depression, anxiety, self-esteem, coping, physical acceptance, uncertainty in disease)
    - Psychosocial well-being (e.g., sex life, family life, social support, participation in professional activities)
    - Mental functioning (e.g., cognitive functions).

All types of outcome instruments such as interviews, patient self-report and clinical tests will be considered.

- ***Secondary outcome measures***
    - Cardiopulmonary function (e.g., maximum oxygen uptake, forced expiratory volume in one second)
    - Muscle strength
    - Weight
    - Immune function (e.g., natural killer cell activity, white blood count)
    - Adverse effects (e.g., exercise-induced cardiovascular events or orthopaedic injuries).
- ***Effect modifiers***
    - Compliance.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Electronic searching

We will apply the following MEDLINE search strategy (Silver Platter; Edition 2003) – based on the Dickersin strategy for retrieving randomized controlled trials (Dickersin 1994), the CBCG's strategy for the identification of populations with 'breast neoplasms' (Cochrane 2004) and key words to identify exercise interventions. For sensitivity reasons, no keywords for non-metastatic breast cancer and for adjuvant therapy will be applied: all reports retrieved will be checked for stage of breast cancer and time point of exercise intervention.

1.RANDOMIZED-CONTROLLED-TRIAL in PT
2.CONTROLLED-CLINICAL-TRIAL in PT
3.RANDOMIZED-CONTROLLED-TRIALS
4.RANDOM-ALLOCATION
5.DOUBLE-BLIND-METHOD
6.SINGLE-BLIND-METHOD
7.#1 or #2 or #3 or #4 or #5 or #6
8.(TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS))
9.#7 not #8
10.CLINICAL-TRIAL in PT
11.explode CLINICAL-TRIALS/ all subheadings
12.(clin* near trial*) in TI
13.(clin* near trial*) in AB
14.(singl* or doubl* or trebl* or tripl*) near (blind* or mask*)
15.(#14 in TI) or (#14 in AB)
16.PLACEBOS
17.placebo* in TI
18.placebo* in AB
19.random* in TI
20.random* in AB
21.RESEARCH-DESIGN
22.#10 or #11 or #12 or 13 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
23.((TG=ANIMALS) not (TG=HUMAN)) and (TG=ANIMALS)
24.#22 not #23
25.#24 not #9
26.TG=COMPARATIVE-STUDY
27.explode EVALUATION-STUDIES/ all subheadings
28.FOLLOW-UP-STUDIES
29.PROSPECTIVE-STUDIES
30.control* or prospectiv* or volunteer*
31.(#30 in TI) or (#30 in AB)
32.#26 or #27 or #28 or #29 or #31
33.(TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS))
34.#32 not #33
35.#34 not (#9 or #25)
36.#9 or #25 or #35
37.explode "Breast-Neoplasms"/ all subheadings
38.Cancer*
39.Carcinom*
40.Neoplas*

41.Malignan*
42.#38 or #39 or #40 or #41
43.Breast*
44.#42 and #43
45.#37 or #44
46.explode "Exercise"/ all subheadings
47.explode "Exercise-Movement-Techniques"/ all subheadings
48.explode "Exercise-Therapy"/ all subheadings
49.explode "Physical-Education-and-Training"/ all subheadings
50.explode "Physical-Fitness"/ all subheadings
51.explode "Exertion"/ all subheadings
52.explode "Sports"/ all subheadings
53.(sport or sports) in ti, ab
54.physical activit* in ti,ab
55.kinesi?therap* in ti,ab
56.exercise* in ti, ab
57.walking in ti, ab
58.jogging in ti, ab
59.swimming in ti, ab
60.cycling in ti, ab
61.bicycling in ti, ab
62.weight in ti, ab
63.training in ti, ab
64.muscle in ti, ab
65.strengthening in ti, ab
66. endurance in ti, ab
67.#46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or 57# or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66
68.#36 and #45 and #67

Other electronic databases that we will search are: EMBASE, CancerLit, PsycLit, SPORTDiscus, CENTRAL and The System for Information on Grey Literature in Europe (SIGLE). Furthermore, we will search the specialized register maintained by the Cochrane Breast Cancer Group and contact the Cochrane Collaboration Rehabilitation Field for help searching the literature in the rehabilitation and physical therapy field. We will adapt the MEDLINE search strategy according to the query requirements of the other databases.

Handsearching

Additionally, we will handsearch a series of relevant journals: Nursing Research, Oncology Nursing Forum, International Journal of Sports Medicine, Clinical Journal of Sports Medicine, Medicine and Science in Sports and Exercise. Furthermore, we will check reference lists of retrieved studies, reviews, as well as congress proceedings on sports medicine and oncology.

Experts

Relevant national and international experts will be contacted to identify trials either published or unpublished where possible.

METHODS OF THE REVIEW

Two reviewers will perform each of the following steps independently. Disagreements will be resolved by discussion.

Selection of trials

Two reviewers (MM, TB) will independently assess potentially eligible trials for inclusion in the review: first, titles (and abstracts if available) of articles identified will be checked for possible inclusion; second, those believed to meet inclusion criteria will be obtained for a hard-copy review. Discrepancies regarding eligibility will be resolved by discussion and/or a third reviewer. Where it is necessary, additional information will be sought from the principal investigator of the trial concerned.

Assessment of the methodological quality

Both reviewers will independently assess each eligible trial for quality; disagreements on scoring will be resolved by discussion and a third reviewer will be used to resolve any discrepancies regarding quality that cannot be solved by discussion. Methodological assessment will be based on the 19-point methodological quality scale of van Tulder (van Tulder 1997). Because blinding of patients and care providers is not possible in exercise trials, we eliminated the corresponding items from the original Tulder scale and thus reduced the maximum total van Tulder score possible to 17:

Methodological Quality Scale

1. Were the eligibility criteria specified?
2. Was a method of randomization performed?
3. Was the treatment allocation concealed?
4. Were groups similar at baseline regarding most important prognostic indicators?
5. Were interventions explicitly described?
6. Were co-interventions either avoided or comparable?
7. Was compliance acceptable in all groups?
8. Was the outcome assessor blinded to the intervention?
9. Were outcome measures relevant?
10. Were adverse effects described?
11. Was the withdrawal/ drop-out rate acceptable?
12. Was short-term follow-up measurement performed?
13. Was long-term follow-up measurement performed?
14. Was timing of outcome assessment comparable?
15. Was the sample size for each group described?
16. Did the analysis include intention-to-treat analysis?
17. Were point estimates and measures of variability presented for primary outcome measures?

Each criterion will be scored as 'positive', 'negative' or 'unclear'. A total score will be computed by counting the number of positive scores. Van Tulder et al. describe the use of these criteria to

distinguish low and high quality by using an arbitrary preset cut-off point; following this approach of a preset cut-off point, moderate/high quality will be defined as fulfilling 9 (> 50%) or more of the internal validity criteria.

Evaluation of adequacy of exercise dosage

Evaluation of the adequacy of the training stimulus will be based on the American College of Sports Medicine (ACSM) exercise guidelines (ACSM 1998). These exercise guidelines represent widely accepted criteria for achieving improvements in physical fitness; they are developed for healthy individuals, and thus, we have adjusted them for non-metastatic breast cancer patients. We will classify studies as 'trials with an adequate exercise dosage' by either meeting or not meeting the dosage requirements of the ACSM guidelines.

Aerobic exercise: The dosage requirements for aerobic training interventions are:

- Intensity: 55-85% of maximum heart rate or 40-75% of maximum heart rate reserve or 40-75% of maximum oxygen uptake reserve
- Duration of sessions: 20-60 min (minimum of 10 minutes continuous bouts throughout the day) or exercise to tolerance
- Frequency: at least 2 days per week
- Total exercise period: at least 6 weeks.

Resistance exercise: The dosage requirements for muscular endurance training are:

- Intensity: 10-15 repetitions to near fatigue or at least 60% of one Repetition Maximum
- Number of sets completed (intensity): at least 1set
- Frequency: 2 or 3 days per week
- Total exercise period: at least 6 weeks.

Classification of high quality training studies

Studies which we classified as 'methodological sound trials' and as 'trials with an adequate exercise dosage' will be considered as high quality training studies.

Data extraction

We will extract key information from all selected reports on a template data extraction form. Extracted data will include:

- General information: Authors, title, source, contact address, country of performance of the trial, language of publication, year of publication.
- Trial characteristics: Design (randomized controlled, non-randomized controlled), randomization method, concealment of allocation, configuration (parallel groups, waiting list, cross-over), duration of intervention period, length of follow-up.

- Patients: Sampling (random/consecutive/convenience), exclusion criteria, total and group sample sizes, age, clinically relevant information (staging, menopausal status, hormone receptor status, age, weight/BMI, activity level before diagnosis, compliance, attrition rates (reasons/description).
- Experimental intervention: Mode of exercise training, intensity, duration, frequency, supervision (yes/no).
- Control intervention: Detailed description of the control intervention, particularly mode, intensity duration, frequency, if available.
- Co-intervention: Detailed description of the co-intervention, particularly type of adjuvant therapy (radiotherapy, chemotherapy, hormonal therapy, combination).
- Outcomes: Underlying concepts (e.g., depression), specific assessment instruments (e.g., Center for Epidemiologic Studies Depression Scale), score range (e.g., 0-60), direction (e.g., higher values indicate deterioration); we will extract outcome statistics according to the data-entry requirements of RevMan Version 4.2. If the required data can not be extracted directly, we will transform data as proposed in the Cochrane Reviewers' Handbook.

Data combination

Regarding the multiplicity of outcome measures, meta-analysis will be considered where a group of trials is sufficiently homogenous in terms of outcome measures. If the same outcome, e.g., depression or fatigue is assessed in several trials using different psychometric scales (continuous data), the standardized mean difference (SMD) will be calculated; for dichotomous data (e.g., occurrence of adverse events) the relative risk (RR) will be calculated. Heterogeneity in treatment effect will be assessed with a chi square test – provided that trials are enough in number - along with the graphical presentation of confidence intervals of SMD/RR. If heterogeneity exists, we will conduct a subgroup analysis (if at least ten studies will be available for each subgroup) on intervention characteristics (type of exercise, adequacy of exercise, dosage) to explore effect modification. I^2 of more than 50 % will be interpreted as evidence of heterogeneity (Cochrane 2004). The relationship between baseline risk and treatment effect will be elaborated through discussion. Methodological quality will be used as a criterion (besides adequacy of intervention) for inclusion in the quantitative or qualitative data synthesis; a sensitivity analysis may be performed to determine whether overall results are the same when studies above different methodological cut-off points are analyzed. If possible, sensitivity analyses will be conducted on adequacy of exercise dosage and 'high quality training studies'. If meta-analysis is not reasonable data combination will be performed only qualitatively.

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9.2 Appendix 2 – Search Activities

9.2.1 Journals handsearched

Journal	Years
Psycho-Oncology	1997 – 2004
Cancer	1990 – 2004
Breast Cancer Research and Treatment	1990 – 2004
Nursing Research	1996 – 2004
Applied Nursing Research	1994, 2000 – 2004
International Journal of Sports Medicine	1990 – 2004
Medicine & Science in Sports & Medicine	1980 – 2004
Clinical Journal of Sport Medicine	2000 – 2004
Deutsche Zeitschrift für Sportmedizin	1985 – 2004
Oncology Nursing Forum	2000 – 2004
The Physician and Sportsmedicine	1990 – 2003
European Journal of Sport Science	2000 - 2004

9.2.2 Conference proceedings searched

Conference	Years
International Symposium for Adapted Physical Activity	2001
American Public Health Association; annual meetings	2000-2003
American College of Sports Medicine; annual meeting	2004
International society of Behavioral Medicine; annual meetings	2002-2004
International Society for Behavioral Nutrition and Physical Activity; annual conferences	2002-2004
The Cooper Institute Conference Series on Physical Activity	1999-2003
European Congress of Sport Psychology	2003

9.2.3 Study registers searched

Study register	Provider	URL
ClinicalTrials.gov	U.S. National Institutes of Health	http://www.clinicaltrials.gov/
ISRCTN-Register	International Standard Randomised Controlled Trial Number; Current Controlled Trials Ltd.	http://www.controlled-trials.com/isrctn/
metaRegister of Controlled Trials (mRCT)	Current Controlled Trials Ltd.	http://www.controlled-trials.com/mrct/
EORTC Protocols Database	European Organisation for research and Treatment of Cancer, EU	http://www.eortc.be/
Deutsches Krebsstudienregister	Deutsche Krebsgesellschaft, D	http://www.studien.de/index.php
Medical Research Council study register	MRC Clinical Trials Unit, UK	http://www.ctu.mrc.ac.uk/BrowseCancer.asp
Clinical Trials register	National Cancer Institute, US	http://www.cancer.gov/clinicaltrials
National Research Register	Department of Health, UK	http://www.nrr.nhs.uk/search.htm

9.2.4 Experts contacted

American College of Sports Medicine

Cancer Research Interest Group

Center for evidence based Physiotherapy

Cochrane Rehabilitation & Related Therapies Field

Ahlberg, Karin

Ainsworth, Barbara E

Baumann, Freerk

Bie, Rob de

Bolling, C.-O.

Bös, Klaus

Callow, Nichola

Campbel, Anna

Courneya, Kerry S.

Crank, Helen

Crevenna, Richard

Daley, Amanda

Demark-Wahnefried, Wendy

Dimeo, Fernando

Drouin, Jacqueline

Fauteck-Kaskel, Dörte

Fox, Ken

Friedenreich, Christine

Irwin, Melinda L.

Kärki, Anne

Lötzerich, Helmut

Marcora, Samuele

McTiernan, Anne

Mock, Victoria

Mutrie, Nanette

Oldervoll, Liane M.

Peters, Christiane

Pickett, Mary

Pinto, Bernardine M.

Rojas, Roberto

Schüle, Klaus

Schwartz, Anna

Segal, Roanne

Servaes, P

Stevinson, Clare

Uhlenbruck, Gerhard

Wilkie, Diana J

Windsor, Phyllis

Winningham, Maryl L.

9.2.5 Search strategy for electronic databases

Systematic serches employed free text and thesaurus terms (controlled termes) based on individual database thesauri. Since most online databases do not automatically search for all variations of a word, either a truncation symbol (***** at the end) or a wild character (e.g. behavio**?**r) was used to look for variant spellings. A truncation symbol instructs the search engine to look for all words with the specific beginning and a wild character indicates any character or none. Search terms were related to the broad areas of breast cancer, exercise, study design and adjuvant treatment of breast cancer (in two databases).

1. **MEDLINE (**Silver Platter MEDLINE)

Breast Cancer	Exercise	Study design
Controlled terms: Breast-Neoplasms. Free text: (Cancer* or Carcinom* or Neoplas* or Malignan*) and Breast*	Controlled terms: Exercise, Exercise-Movement-Techniques, Exercise-Therapy, Physical-Education-and-Training, Physical-Fitness, Exertion, Sports. Free text: Sport*, physical activit*, kinesi?therap*, exercise*, walking or jogging or swimming or cycling or bicycling or weight training or muscle strength* or treadmill or endurance.	Controlled terms: Randomized controlled trial, controlled clinical trial, randomized controlled trials, random allocation, double blind method, single blind method, clinical trials, placebos, comparative study, evaluation studies, follow-up studies, prospective studies. Free text: (clin* near trial*); (singl* or doubl* or trebl* or tripl*) near (blind* or mask*); placebo*, random*; control* or prospectiv* or volunteer*.

2. **EMBASE**

Breast Cancer	Exercise	Study design
Controlled terms: Breast-tumor, Breast cancer, Breast carcinoma. Free text: Breast*and (Neoplas* or carcinom* or cancer* or malignan*).	Controlled terms: Physical education, Physical activity, Fitness, Kinesiotherapy, Muscle training, Muscle exercise, Leg exercise, Treadmill exercise, Dynamic exercise, Exercise-. Free text: Exercise* or walking or swimming or cycling or bicycling or weight training or resistance training or muscle strengthening or endurance or sport* or physical activit*.	Controlled terms: Clinical-research, Clinical-trial, Clinical-study, Controlled-study, Randomized-controlled-trial, Randomization-, Controlled trial. Free text: prospective study or Comparative study.

3. CINAHL

Breast Cancer	Exercise	Study design	Cancer Treatment
Controlled terms: breast-neoplasms. Free text: (cancer* or carcinom* or malignan* or neoplas* or sarcom* or tumo*) and (breast or "breast")	Controlled terms: Physical-activity, Physical-therapy, Endurance-sports, Aquatic-exercises, Aerobic-exercises, Therapeutic exercises, Rehabilitation-Exercise-Saba-HHCC, Recovery-Exercise. Free text: Walking or swimming or cycling or dancing or jogging or muscle strengthening or resistance training or endurance.	Controlled terms: Clinical-trial, Interventions, Research, Trial	Free text: treatment or chemotherap* or radiotherap* or radiation therap* or hormon* therap* or adjuvant therap*

4. PsycInfo

Breast Cancer	Exercise
Free text: (Cancer* or carcinom* or neoplas* or malignan*) and (Breast or Breast cancer)	Controlled terms: Physical-education, Physical-endurance, Physical-fitness, Physical-strength, Aerobic-exercise, Exercise. Free text: Sport* or physical activit* or exercise* or walking or jogging or swimming or cycling or bicycling or weight training or muscle strengthening or endurance.

5. PubMed

Breast Cancer	Exercise	Limits
Controlled terms: Breast Neoplasms. Free text: Breast cancer.	Controlled terms: Sports, Exertion, Weight Lifting, Exercise, Exercise Therapy, Exercise Movement Techniques. Free text : Walking, jogging, swimming, cycling, bicycling, weight training, muscle strength, endurance, exercise*, sport*, aerobic, treadmill.	Randomized Controlled Trial, Clinical Trial, Female, Human, and Cancer.

6. SPORTDiscus

Breast Cancer	Cancer Treatment
Controlled terms: Breast Neoplasm. Free text: Breast cancer	Free text: treatment or chemotherap* or radiotherap* or radiation therap* or hormon* therap* or adjuvant therap*

7. **ProQuest Digital Dissertations:** Free text: Breast cancer and exercise

8. **DissOnline.de**: Free text: Sport und Brustkrebs

9.3 Appendix 3 – Study eligibility form

Assessment for study inclusion				
Study-ID: Reviewer: Date:				
TYPE OF STUDY	Does the study compare two or more groups assigned by trial investigator to exposure?	Yes ⇩ Go to next question	Unclear ⇩ Go to next question	No ⇩ **Exclude**
PARTICIPANTS	Are participants in the study predominantly (>80%) women with non-metastatic breast cancer?	Yes ⇩ Go to next question	Unclear ⇩ Go to next question	No ⇩ **Exclude**
INTERVENTION	Was one of the study groups exposed to either aerobic endurance training (e.g., walking, bicycling, or swimming) or resistance training (e.g., weight lifting, resistance exercise bands or exercise tubings)? Answer 'no' if intervention was restricted to local muscular endurance only, stretching or exercise as part of a complex intervention. Usual care is regarded as a co-intervention: thus, answer 'yes' if exercise is added to usual care.	Yes ⇩ Go to next question	Unclear ⇩ Go to next question	No ⇩ **Exclude**
	Were participants undergoing adjuvant cancer treatment (chemotherapy, hormonal therapy or radiotherapy) during study participation?	Yes ⇩ Go to next question	Unclear ⇩ Go to next question	No ⇩ **Exclude**
	Was exposure to exercise training at least six weeks?	Yes ⇩ Go to next question	Unclear ⇩ Go to next question	No ⇩ **Exclude**
OUTCOMES	Does the study assess one of the following outcomes? Physical fitness (cardiorespiratory fitness, muscular strength, muscular endurance, body composition), quality of life, fatigue, pain, psychological distress, immune function, harm.	Yes ⇩ Go to next question	Unclear ⇩ Go to next question	No ⇩ **Exclude**
FINAL DECISION	**Include**	**Unclear**	**Exclude**	

9.4 Appendix 4 – Data extraction forms

9.4.1 Data extraction of study descriptors

Data extraction	
Study-ID: Reviewer: Date:	
METHODS	Type of trial -
	Configuration of trial
	Method of randomisation
	Allocation concealment
	Outcome assessor blinding
	Timing of outcome assessments after initiation of treatment
	Length of post-intervention follow-up period
	Sample size, total
	Sample size for each group
	Availability of sample size for each group at randomisation
	Withdrawal-/Drop-out rate and reasons
	Adherence
	Type of analysis
	Statistical tests
	Power calculation
PARTICIPANTS	Recruitment
	Inclusion criteria
	Exclusion criteria
	Age
	BMI
	Breast cancer staging
	Menopausal status
	Type of adjuvant cancer treatment
	Physical activity before cancer diagnosis
	Co-morbidity
INTERVENTION	Type of training
	Setting
	Health promotion theory
	Delivery of intervention
	Intensity
	Duration of sessions
	Frequency
	Total exercise period
CONTROL	Type of control
	Intensity
	Duration of sessions
	Frequency
	Total period
CO-INTERVENTION	Type of co-intervention
OUTCOMES	Outcome measure concepts
	Assessment instruments
	Adverse effects
	Similarity at baseline

9.4.2 Instructions for extraction of study descriptors

Data extraction - Instruction for reviewers	
METHODS	
Type of trial	- CCT: any allocation procedure applied? - RCT
Configuration of trial	- Parallel group - Cross over design
Method of randomisation	Enter text
Allocation concealment	- A: Adequate - B: Unclear - C: Inadequate - D: Not used
Outcome assessor blinding	- Yes - No - N/a
Timing of outcome assessments after initiation of treatment	Enter numbers for each occasion of outcome assessment
Length of post-intervention follow-up period	Enter numbers
Sample size, total	Enter numbers used in analysis
Sample size for each group	Enter numbers used in analysis
Availability of sample size for each group at randomisation	- Yes - No - N/a
Withdrawal-/Drop-out rate and reasons	Enter numbers (% and x/n) and text
Adherence	- Describe the mode of monitoring the exercise stimulus (intensity, frequency, duration) - Enter numbers or text (percentage of prescribed exercise sessions which are completed)
Type of analysis	- ITT analysis: participants analysed as randomised, all participants included regardless of whether outcomes collected - Available case analysis: data analysed for every participant for whom outcome was obtained - Per-protocol/ treatment- received analysis: data analysed for only those participants who completed the trial *and* who complied with/or received their allocated treatment
Statistical tests	Enter text (only for outcome measures' analysis)
PARTICIPANTS	
Recruitment	Enter text
Inclusion criteria	Enter text
Exclusion criteria	Enter text
Age	For each group and for all participants: Mean, SD; calculate weighted mean if mean only available per group
BMI	For each group and for all participants: Mean, SD; calculate BMI if weight and height available; calculate weighted mean if mean only available per group
Breast cancer staging	For each group and for all participants - Stage I: x/n (%) - Stage II: x/n (%) - Stage III: x/n (%)

Menopausal status	For each group and for all participants - Pre- menopausal: x/n (%) - Post- menopausal: x/n (%)
Type of adjuvant cancer treatment	For each group and for all participants - Chemotherapy: x/n (%) - Radiotherapy: x/n (%) - Hormonal Therapy: x/n (%) - Combination: x/n (%)
Physical activity before cancer diagnosis	For each group and for all participants - Active: x/n (%) - Sedentary: x/n (%)
Co-morbidity	For each group: enter text
INTERVENTIONS	
Type of training	- Aerobic- or Muscular endurance exercise - Walking, cycling, etc.
Setting	- Laboratory-based - Centre-based - Home-based - Community based
Health promotion theory	Describe the health promotion theory that underpins the intervention
Delivery of intervention	Describe exercise promoting strategies of the intervention
Intensity	- Aerobic endurance exercise: % HR max, % HRR max, % VO_2 max - Muscular endurance exercise: number of repetitions per set, % 1-RM, number of sets completed
Duration of sessions	Enter numbers (minutes)
Frequency	Enter numbers (sessions per week)
Total exercise period	Enter numbers (weeks)
CONTROL	
Type of control	Enter text (e.g., stretching exercise, usual care)
Intensity	Enter text, numbers
Duration of sessions	Enter numbers (minutes)
Frequency	Enter numbers (sessions per week)
Total period	Enter numbers (weeks)
CO-INTERVENTION	
Type of co-intervention	Enter text
OUTCOMES	
Outcome measures concepts	Enter text (e.g., depression)
Assessment instruments	- Specific scale - Score range - Direction of change for improvement
Adverse effects	- Assessment of harm - Reporting of harm - Observation of harm
Similarity at baseline	- Adequate - Inadequate (reviewer determines)

9.4.3 Effect size data coding

Effect size data	
Study-ID: Reviewer: Date:	
Effect size sequence number	
Effect size type	1 Posttest comparison 2 Change score comparison 3 Follow-up comparison
Category of outcome construct	1 Cardiorespiratory endurance 2 Body composition 3 Muscular strength and endurance 4 Quality of life 5 Fatigue 6 Pain 7 Psycho-social distress 8 Immune function 9 Harm 10 Other
Outcome descriptor	
Type of data reported	1 Means and standard deviations 2 t-value or F-value 3 chi-square (df=1) 4 Frequencies or proportions, dichotomous 5 Frequencies or proportions, polychotomous 6 Other
Page number where effect size data found	
Raw difference favours (i.e., shows more success for):	1 Intervention group 2 Neither (exactly equal) 3 Control group 9 Cannot tell or statistically insignificant report only
Sample size	Intervention group sample size Control group sample size
Means and standard deviations	Intervention group mean Control group mean Intervention group standard deviation Control group standard deviation
Proportions or frequencies	n of intervention group with a successful outcome n of control group with successful outcome % of intervention group with a successful outcome % of control group with a successful outcome
Significance tests	t-value F-value (df for the numerator must = 1) Chi-square value
Calculated standard deviations	Intervention group standard deviation Control group standard deviation
In case of coding failure	Available data: Problems/missing data:

9.5 Appendix 5 – Study quality forms

9.5.1 Methodological quality form

Study quality	
Study-ID Reviewer Date	
PATIENT SELECTION	
1. Were the eligibility criteria specified? Descriptive criterion	Yes/No/unable to determine
2. Was a method of randomisation performed? Internal validity criterion	Yes/No/unable to determine
3. Was the treatment allocation concealed? Internal validity criterion	Yes/No/unable to determine
4. Were groups similar at baseline? Descriptive criterion	Yes/No/unable to determine
INTERVENTION	
5. Were interventions explicitly described? Descriptive criterion	Yes/No/unable to determine
6. Were co-interventions either avoided or comparable? Internal validity criterion	Yes/No/unable to determine
7. Was adherence acceptable in all groups? Internal validity criterion	Yes/No/unable to determine
OUTCOME MEASUREMENT	
8. Was the outcome assessor blinded to the intervention? Internal validity criterion	Yes/No/unable to determine
9. Were outcome measures relevant? Internal validity criterion	Yes/No/unable to determine
10. Were adverse effects described? Descriptive criterion	Yes/No/unable to determine
11. Was drop-out rate acceptable and were reasons described? Internal validity criterion	Yes/No/unable to determine
12. Was short-term follow-up measurement performed? Descriptive criterion	Yes/No/unable to determine
13. Was long-term follow-up measurement performed? Descriptive criterion	Yes/No/unable to determine
14. Was timing of outcome assessment comparable in groups? Internal validity criterion	Yes/No/unable to determine
STATISTICS	
15. Was sample size described for each group at randomisation? Statistical criterion	Yes/No/unable to determine
16. Did the analysis include intention-to-treat analysis? Internal validity criterion	Yes/No/unable to determine
17. Were point estimates and measures of variability presented for the primary outcome measures? Statistical criterion	Yes/No/unable to determine
SCORE	

9.5.2 Code of practice for implementing methodological quality criteria

Code of practice for implementing quality criteria
PATIENT SELECTION
1. Were the eligibility criteria specified? To score a 'yes', inclusion and exclusion criteria have to be described appropriately.
2. Was a method of randomisation performed? To score a 'yes', the method used to generate a random allocation sequence has to be specified (e.g., random numbers or computer-generated random sequences). Allocation methods using date of birth, hospital numbers, or alternation should be regarded as quasi-randomised (score 'no').
3. Was the treatment allocation concealed? To score a 'yes', an adequate method has to be used to prevent foreknowledge of group assignment: these methods should allow for preventing researchers from influencing which participants are assigned to a given intervention group. Adequate methods of allocation concealment include: centralised randomisation, sequentially numbered, sealed envelopes each containing the name of the next treatment on a card, generation of assignment by an independent person not responsible for determining the eligibility of the patients.
INTERVENTION
4. Were groups similar at baseline? To score a 'yes', groups should be similar at baseline regarding following factors: adjuvant cancer treatment, physical activity before diagnosis, breast cancer stages, BMI, age, co-morbidity, scores of main outcome measures. The reviewer must be satisfied that the groups' outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount. This criterion may be accomplished even though baseline data are presented of study completers only.
5. Were interventions explicitly described? To score a 'yes', type of exercise intervention, intensity, duration of single sessions, frequency, and programme duration for both the index and control intervention, should be described. Information has to be sufficient to allow an estimate of the exercise stimulus/ dose.
6. Were co-interventions (other than the adjuvant treatment) either avoided or comparable? To score a 'yes', any application of additional diagnostic or therapeutic procedures (besides usual care) should either be avoided or comparable between index and control group; reviewer determines.
7. Was adherence acceptable in all groups? To score a 'yes', reviewer determines whether adherence **(**percentage of prescribed exercise sessions which are completed) was acceptable based on reported programme duration, number of possible sessions and activity levels before cancer diagnosis.
OUTCOME MEASUREMENT
8. Was the outcome assessor blinded to the intervention? To score a 'yes', reviewer determines based on the outcome variable (e. g. fitness evaluation with patient's presence required or self-administered questionnaire) whether enough information about blinding is given.
9. Were outcome measures relevant? To score a 'yes', one of the following outcomes should have been assessed: Physical and functional well-being, Emotional and psychological well-being, Psychosocial well-being, Mental functioning, Muscle strength, BMI, Immune function, Cardiopulmonary function, Adverse effects. Reviewer determines for other outcomes.
10. Were adverse effects described? To score a 'yes', adverse effects should be described and attributed to the allocated intervention; if it is explicitly reported that "no adverse events" have occurred, a 'yes' should be scored, too; if adverse events are described and stated to be unrelated to the intervention, score a 'yes'.
11. Was the withdrawal/ drop-out rate acceptable and were reasons for withdrawal/ drop-out described? To score a 'yes', participants included in the study who did not complete the intervention period or were not included in the analysis must be described (reasons). Furthermore, the percentage of withdrawals and drop-outs must not exceed 20% for short-term follow-up and 30% for long-term follow-up. If analysis of

reasons for withdrawals and drop-outs suggest substantial bias (e. g. drop-outs in control group only due to lacking perceived benefit), a 'no' is scored; reviewer determines.
12. Was short-term follow-up measurement performed? To score a 'yes', outcome assessment has to be performed at the end of the intervention period. Outcome assessment at the end of the intervention period is considered as adequate short-term follow-up, since the review aims at assessing the potentials of exercise in managing common side effects of adjuvant therapy and adjuvant therapy is administered only over a limited period of time.
13. Was long-term follow-up measurement performed? To score a 'yes', outcome assessment has to be performed after the end of the intervention period. Long-Term follow-up may be performed if programme duration is shorter than the period of adjuvant therapy or if side effects (e. g. weight gain or fatigue) of adjuvant therapy are assessed as long-term side effects.
13. Was long-term follow-up measurement performed? To score a 'yes', outcome assessment has to be performed after the end of the intervention period. Long-Term follow-up may be performed if programme duration is shorter than the period of adjuvant therapy or if side effects (e. g. weight gain or fatigue) of adjuvant therapy are assessed as long-term side effects.
14. Was timing of outcome assessment comparable in both groups? To score a 'yes', timing of outcome assessment should be identical for intervention and control group.
STATISTICS
15. Was the sample size for each group described? To score a 'yes', sample size has to be presented for each group at randomisation.
16. Did the analysis include intention-to-treat analysis? To score a 'yes', the following criteria have to be fulfilled (Cochrane 2004): - Trial participants have to be analysed in the groups to which they are randomised regardless of which (or how much) treatment they actually received, and regardless of other protocol irregularities, such as ineligibility. - All participants have to be included regardless of whether their outcomes were actually collected (involves imputing missing data).
17. Were point estimates and measures of variability presented for primary outcome measures? To score a 'yes', both, point estimates and measures of variability should be presented for at least one key outcome based on between-group statistical comparisons.

9.5.3 Intervention quality form

Intervention quality	
Study-ID: Reviewer: Date:	
Aerobic endurance training	
60-80% of maximum heart rate or 50-75% of maximum heart rate reserve or 50-75% of maximum oxygen uptake reserve or RPE 11-14	yes, no, unable to determine
20-60 min (minimum of 10 minutes continuous bouts throughout the day) or exercise to tolerance	yes, no, unable to determine
At least 3 days per week	yes, no, unable to determine
At least 6 weeks	yes, no, unable to determine
Score	
Muscular endurance training	
10-15 repetitions to near fatigue or at least 60% of 1-RM	yes, no, unable to determine
At least 1set	yes, no, unable to determine
2 or 3 days per week	yes, no, unable to determine
At least 6 weeks	yes, no, unable to determine
Score	

9.6 Appendix 6 – Identification/critical appraisal of studies of harm

9.6.1 Medline search strategy for studies of harm (WinSPIRS 5.0)

#1	Cancer*
#2	Carcinom*
#3	Neoplas*
#4	Malignan*
#5	#1 or #2 or #3 or #4
#6	Breast*
#7	#5 and #6
#8	(explode "Breast-Neoplasms"/ all subheadings) or #7
#9	explode "Exercise"/ all subheadings
#10	explode "Exercise-Movement-Techniques"/ all subheadings
#11	explode "Exercise-Therapy"/ all subheadings
#12	explode "Physical-Education-and-Training"/ all subheadings
#13	explode "Physical-Fitness"/ all subheadings
#14	explode "Exertion"/ all subheadings
#15	explode "Sports"/ all subheadings
#16	(sport or sports) in ti, ab
#17	physical activit* in ti,ab
#18	kinesi?therap* in ti,ab
#19	exercise* in ti, ab
#20	walking or jogging or swimming or cycling or bicycling or weight training or muscle strength* or treadmill or endurance or aerobic training or resistance training
#21	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22	safe or safety or side-effect* or undesirable effect* or tolerability
#23	adverse adj (effect* or reaction* or event* or outcome*)
#24	lymph?edema
#25	injur*
#26	#25 or #24 or #23 or #22
#27	#26 and #21 and #8

9.6.2 Data extraction form for studies of harm

Studies of harm - data extraction	
Study-ID: Reviewer: Date:	
Type of adverse events	1 injury 2 cardiovascular event 3 lymphedema 4 other
Inclusion criteria for participants	1 post-treatment 2 during treatment 3 lymphedema
Type of exercise	1 aerobic endurance training 2 resistance training 3 aerobic and resistance training
Type of trial	1 randomised controlled trial 2 non- randomised controlled trial 3 Cohort study 4 Case-control study 5 Cross-sectional study 6 Large Databases 7 other
Sample size	Total sample size Intervention group sample size Control Group sample size
Proportions or frequencies	n of intervention group with an adverse event n of control group with an adverse event % of intervention group with an adverse event % of control group with an adverse event
Sample size	Intervention group sample size Control group sample size
Significance tests	T-test ANOVA Chi squared other

9.6.3 Quality assessment form for studies of harm

Studies of harm - quality	
Study-ID: Reviewer: Date:	
Criterion	**Score**
Nonbiased selection	1: Study is properly randomised, controlled trial or observational study with clear, predefined inception cohort 0: Selection not clear or biased selection
Adequate description of population	1: Study reports at least two demographic characteristics, presenting symptoms/syndrome 0: Study does not meet above criteria
Low loss to follow-up, and patients lost to follow-up analysed for adverse events	1: Study reports number lost to follow-up, analyses patients lost to follow-up for adverse events, and has low overall number lost to follow-up 0: Study does not meet above criteria
Adverse events prespecified and defined	1: Study reports explicit definitions for major complications that allow for reproducible ascertainment 0: Study does not meet above criteria
Ascertainment technique adequately described	1: Study reports methods used to ascertain complications, including who ascertained, timing, and methods used 0: Study does not meet above criteria
Nonbiased and accurate ascertainment of adverse event	1: Study provides independent assessment of complication (defined as assessment by someone other than the exercise trainer) 0: Study does not meet above criteria
Adequate statistical analysis of potential confounders	1: Study examines relevant confounders/ risk factors using acceptable statistical techniques, such as stratification or adjustment 0: Study does not meet above criteria
Adequate duration of follow-up	1: Study reports duration of follow-up and duration of follow-up is adequate to identify expected adverse events 0: Study does not meet above criteria
Total quality score = sum of scores (0 - 8)	>6: Good 4-6: Fair <4: Poor

9.7 Appendix 7 – Reference list of excluded studies of benefit

Study-ID	Reference
Aghili 2007	Aghili M, Farhan F, Rade M. A pilot study of the effects of programmed aerobic exercise on the severity of fatigue in cancer patients during external radiotherapy. Eur J Oncol Nurs 11: 179-82; 2007.
Battaglini 2004	Battaglini CL. A randomized study on the effects of a prescribed exercise intervention on lean mass and fatigue changes in breast cancer patients during treatment. PhD [dissertation]. Colorado: University of Northern Colorado; 2004.
Burnham 2002	Burnham TR, Wilcox A. Effects of exercise on physiological and psychological variables in cancer survivors. Med Sci Sports Exerc 34: 1863-7; 2002.
Courneya 2003a	Courneya KS, Friedenreich CM, Sela RA, Quinney HA, Rhodes RE, Handman M. The group psychotherapy and home-based physical exercise (group-hope) trial in cancer survivors: physical fitness and quality of life outcomes. Psychooncology 12: 357-74; 2003.
Courneya 2003b	Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, Fairey AS. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. J Clin Oncol 21: 1660-8; 2003.
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Study-ID	Reference
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9.8 Appendix 8 – Included studies of benefit

9.8.1 Study descriptors and effect size statistics

Battaglini 2007 – Study descriptors	
METHODS	
Type of trial	RCT
Configuration of trial	Parallel group design
Method of randomisation	Quasi-randomised
Allocation concealment	A
Outcome assessor blinding	n/a
Timing of outcome assessments after initiation of treatment	15 weeks
Length of post-intervention follow-up period	0
Sample size, total	20
Sample size for each group	- Intervention group: n=10 - Control group: n=10
Availability of sample size per group at randomisation	Yes
Withdrawal-/Drop-out rate and reasons	- Intervention group: 0/10 (0%) - Control group: 0/10 (0%) - All participants: 0/20 (0%)
Adherence	- Monitoring of intensity (HR) and frequency - Adherence: 100% of all sessions
Type of analysis	ITT
Statistical tests	Two-way mixed model analysis of variance
Power calculation	No
PARTICIPANTS	
Recruitment	Oncology practices in northern Colorado region
Inclusion criteria	- Breast surgery - Designated for adjuvant chemotherapy or radiotherapy - 35-70 years
Exclusion criteria	- Cardiovascular disease - Respiratory disease - Bone, joint or muscular abnormalities - Immune deficiency. - Metastatic disease
Age	- Intervention group: 57.5, SD=23.0 - Control group: 56.6, SD=16.0 - All participants: 57.05
Weight Height BMI	- Intervention group: 77.5 kg; SD=27.3 - Control group: 82.2 kg, SD=25.0 - Intervention group: 168.9 cm, SD=10.2 - Control group: 169.2 cm, SD=10.2 - Intervention group: 27.1 - Control group: 28.5 - All participants: 27.7
Breast cancer staging	n/a
Menopausal status	n/a
Type of adjuvant cancer treatment	- Chemotherapy - Radiotherapy

Battaglini 2007 – Study descriptors	
Physical activity before cancer diagnosis	n/a
Co-morbidity	n/a
INTERVENTIONS	
Type of training	- Aerobic exercise: treadmill, elliptical trainers, cycle ergometer - Resistance exercise: weight machines, free weights, rubber bands, therapeutic balls (lateral and frontal raises, horizontal chest press, lateral pulldown, alternating bizeps curls with dumbbells, triceps extension, leg press, leg extension, leg curl, standing calf raises, and three different types of abdominal exercises)
Setting	Centre based
Health promotion theory	No health promotion theory
Delivery of intervention	- Individualised exercise prescription based on fitness assessments administered at the beginning of the study - Exercise sessions: initial administration of cardiorespiratory activity, followed by whole body stretching sessions, resistance training and a cool-down period that included stretching activities - Participants led and monitored during each exercise session by a trained cancer exercise specialist from the University of Northern Colorado School of Sport and Exercise Science who had participated in an educational seminar prior to the study - Control group: waiting list, explanation of further research needed, reminders to abstain from participating in any regular exercise programme while participating in the study
Intensity	40-60% of predicted maximum exercise capacity for both the cardiorespiratory and strength exercise
Duration of sessions	Total 60 min (6-12 min. cardiovascular, 5-10 min. stretching, 15-30 min. resistance, 8-10 min. cool down) Resistance exercise: 8-12 exercises; 6-12 repetitions, 3 sets per session
Frequency	2 sessions per week
Total exercise period	15 weeks
CONTROL	
Type of control	No exercise
Intensity	n/a
Duration of sessions	n/a
Frequency	n/a
Total period	n/a
CO-INTERVENTION	
Type of co-intervention	n/a
OUTCOMES	
Outcome measure concepts	- Fatigue - Body composition: lean body mass (LBM), body fat (BF) - Muscular fitness - Cardiorespiratory fitness
Assessment instruments	- Revised Piper Fatigue scale (PFS) - Three-site skinfold measurement - Modified Bruce treadmill protocol - Submaximal muscle endurance protocol after Kuramoto and Payne: leg extension, seated leg curl, lateral pull down, seated chest press
Adverse effects	No ("No cases of injury")
Similarity at baseline	Adequate

Battaglini 2007 – Effect size data					
ES No.	1	2	3	4	5
ES type	Post-test	Post-test	Post-test	Post-test	Post-test
Construct	Fatigue	Body composition		Muscular strength	
Instrument	PFS	% LBM	% BF	1-RM* [kg]	1-RM [kg]
N intervention group	10	10	10	10	10
N control group	10	10	10	10	10
Mean intervention	0.84	74.1	25.9	295.59	116.3
Mean control group	3.23	68.9	31.2	260.89	102.7
SD intervention group	1.13	2.9	2.9	22.65	8.9
SD control group	1.16	4.1	4.1	38.76	15.2

* Sum of the results from the predicted 1-RM that was obtained from assessing the exercises of leg extension, seated leg curl, lateral pulldown and seated chest press

Campbell 2005 – Study descriptors	
METHODS	
Type of trial	RCT
Configuration of trial	Parallel group design
Method of randomisation	Computer-generated numbers, stratification by treatment
Allocation concealment	B
Outcome assessor blinding	n/a, questionnaires self-administered and returned to researcher in sealed envelopes
Timing of outcome assessments after initiation of treatment	12 weeks
Length of post-intervention follow-up period	0
Sample size, total	22
Sample size for each group	- Intervention group: n=12 - Control group: n=10
Availability of sample size per group at randomisation	Yes
Withdrawal-/Drop-out rate and reasons	- Intervention group: 2/12 (16.7%) - Control group: 1/10 (10%) - All participants: 3/22 (13.7%) Reasons: travel constraints, secondary cancer
Adherence	- Monitoring of intensity (HR) and frequency - Adherence: 70% of all sessions
Type of analysis	Available case analysis (n=19)
Statistical tests	2-sample t-tests, 2-sided
Power calculation	No
PARTICIPANTS	
Recruitment	Cancer Centre (consultant oncologist, breast care nurse, radiotherapy/chemotherapy nurse)
Inclusion criteria	- Breast surgery - Receiving adjuvant chemotherapy or radiotherapy
Exclusion criteria	- Concurrent major problems (e.g., uncontrolled cardiac or hypertensive disease, respiratory disease, cognitive dysfunction) - Already exercising vigorously three times a week for 20 minutes
Age	- Intervention group: 48, SD=10 - Control group: 47, SD=5 - All participants: 47.5
BMI/weight	n/a
Breast cancer staging	n/a
Menopausal status	n/a
Type of adjuvant cancer treatment	- Intervention group o Chemotherapy: 3/12 (25%) o Radiotherapy: 2/12 (16.7%) o Combination: 7/12 (58.3%) - Control group o Chemotherapy: 3/10 (30%) o Radiotherapy: 4/10 (40%) o Combination: 3/10 (30%) - All participants o Chemotherapy: 6/22 (27.3%) o Radiotherapy: 6/22 (27.3%) o Combination: 10/22 (45.4%) o

Campbell 2005 – Study descriptors	
Physical activity before cancer diagnosis	Scottish Physical Activity Questionnaire (SPAQ), leisure time activity: - Intervention group: 330 minutes, SD=171 - Control group: 421 minutes, SD=191
Co-morbidity	n/a
INTERVENTIONS	
Type of training	Aerobic and resistance exercise: walking, cycling, low-level aerobics, muscle-strengthening exercises, circuits
Setting	Community based: group exercise, supervised
Health promotion theory	Stages of change, self-efficacy
Delivery of intervention	- Group-based exercise classes - Exercise sessions: warm-up, 10-20 minutes exercise (which varied from week to week), cool-down, relaxation period - Workshops addressing health benefits, self-efficacy, exercise barriers, supportive environment, setting goals, finding appropriate activity options
Intensity	60-75% age-adjusted HRmax
Duration of sessions	10-20 minutes aerobic training
Frequency	2 sessions per week
Total exercise period	12 weeks
CONTROL	
Type of control	Monitoring
Intensity	n/a
Duration of sessions	n/a
Frequency	n/a
Total period	n/a
CO-INTERVENTION	
Type of co-intervention	Usual care (both groups)
OUTCOMES	
Outcome measure concepts	- Cancer-specific quality of life (primary outcome) - Cancer-site-specific quality of life, symptoms - Satisfaction with life - Fatigue - Physical fitness - Physical activity - Expectation of treatment
Assessment instruments	- FACT-G - FACT-B - Satisfaction with Life Scale (SWLS) - Perceived expectations and benefits of total care package - R-PFS - Scottish Physical Activity Questionnaire (SPAQ) - 12-minute walk test
Adverse effects	No ("no adverse reactions to taking part in the exercise intervention")
Similarity at baseline	Adequate

Campbell 2005 – Effect size data				
ES No.	1	2	3	4
ES type	Post-test	Post-test	Post-test	Change score
Construct	Cardiorespiratory fitness	Fatigue	Quality of life	Quality of life
Instrument	12-MWT [meter]	PFS	FACT-B	FACT-G
N intervention group	10	10	10	10
N control group	9	9	9	9
Mean intervention group	1423	2.43	111.2	11.9
Mean control group	1083	4.35	94.3	-2.9
SD intervention group	261	1.94	14.1	13.8
SD control group	176	3.48	28.4	16.1

Courneya 2007 – Study descriptors	
METHODS	
Type of trial	- RCT
Configuration of trial	- Parallel group
Method of randomisation	computer-generated programme, stratification by center and chemo-therapy protocol
Allocation concealment	- A: Adequate
Outcome assessor blinding	- No
Timing of outcome assessments after initiation of treatment	mean: 17 weeks, SD=4 weeks
Length of post-intervention fol-low-up period	6 months
Sample size, total	242
Sample size for each group	Intervention group 1 (aerobic): n=78 Intervention group 2 (resistance): n=82 Control group: n=82. Different n according to outcome measure!
Availability of sample size for each group at randomisation	- Yes
Withdrawal-/Drop-out rate and reasons	Intervention group 1 (aerobic): 5.1% (4/78) Intervention group 2 (resistance): 7.3% (6/82) Control group: 11% (9/82) All participants: 7.9% (19/242) Estimated using PRO assessments; Reason (most common): participants unreachable (n=9)
Adherence	- Exercise trainers monitored adherence - Aerobic exercise group: 72% sessions, 95.6% met duration; 87.2% met intensity - Resistance exercise group: 68.2% sessions; 96.8% completed all 9 exercises; 96.9% completed 2 sets each; 94.5% completed 8-12 repetitions
Type of analysis	- Available case analysis
Statistical tests	Mixed model analysis
PARTICIPANTS	
Recruitment	- Cross Cancer Institute (Edmonton, Alberta) - Ottawa Hospital Integrated Cancer Program (Ottawa, Ontario) - British Columbia Cancer Agency (Vancouver, British Columbia)
Inclusion criteria	- Breast cancer stages I-III - Beginning adjuvant chemotherapy - English- or French-speaking - > 18 years
Exclusion criteria	- Incomplete axillary surgery - Transabdominal rectus abdominus muscle reconstructive surgery - Uncontrolled hypertension - Cardiac illness - Psychiatric illness - pregnant
Age	- Aerobic exercise group: 49.0 (30-75) - Resistance exercise group: 49.5 (25-76) - Control group: 49.0 (26-78) - All participants: 49.2 (25-78)

Courneya 2007 – Study descriptors	
BMI	- Aerobic exercise group: 26.7; 5.6 - Resistance exercise group: 26.1; 5.5 - Control group: 27.1; 5.4 - All participants: 26.6; 5.5
Breast cancer staging	- Stage I o Aerobic exercise group: 18/78 (23.1%) o Resistance exercise group: 22/82 (26.8%) o Control group: 20/82 (24.4%) o All participants: 60/242 (24.8%) - Stage II a o Aerobic exercise group: 33/78 (42.3%) o Resistance exercise group: 36/82 (43.9%) o Control group: 30/82 (36.6%) o All participants: 99/242 (40.9%) - Stage II b o Aerobic exercise group: 17/78 (21.8%) o Resistance exercise group: 9/82 (11%) o Control group: 22/82 (26.8%) o All participants: 48/242 (19.8%) - Stage III o Aerobic exercise group: 10/78 (12.8%) o Resistance exercise group: 15/82 (18.3%) o Control group: 10/82 (12.2%) o All participants: 35/242 (14.5%)
Menopausal status	- Post- menopausal o Aerobic exercise group: 27/78 (34.6%) o Resistance exercise group: 35/82 (42.7%) o Control group: 27/82 (32:9%) o All participants: 89/242 (36.8%)
Type of adjuvant cancer treatment	- Chemotherapy
Physical activity before cancer diagnosis	- Current exerciser o Aerobic exercise group: 15/78 (19.2%) o Resistance exercise group: 22/82 (26.8%) o Control group: 27/82 (32:9%) o All participants: 64/242 (26.4%)
Co-morbidity	Obesity, hypertension (no difference between groups)
INTERVENTIONS	
Type of training	- Aerobic- endurance exercise: cycle ergometer, treadmill, elliptical - Muscular endurance exercise: weight machines (set with 9 exercises)
Setting	- Centre-based
Health promotion theory	n/a
Delivery of intervention	- Exercise sessions: supervised at well-equipped fitness centres by qualified staff; warm-up and cool-down periods of 5 minutes with light aerobic activities and stretching - Fitness trainers recorded exercise adherence including attendance, duration and intensity - Fitness trainers monitored harm - Participants who called to cancel the exercise session were asked for a reason why - Fitness centers were open 8:00 a.m. to 5:00 p.m. Monday to Friday; 1 centre made additional accommodations for weekends and evenings if needed.

Courneya 2007 – Study descriptors	
Intensity	- Aerobic exercise: 60-80 % VO_2 max - Resistance exercise: 2 sets of 8-12 repetitions, 60-70% RM, number of sets completed
Duration of sessions	Aerobic exercise: 15-45 minutes Resistance exercise:
Frequency	Aerobic exercise: 3/week Resistance exercise: 3/week
Total exercise period	Aerobic exercise: 17 weeks (SD=4 weeks) Resistance exercise: 17 weeks (SD=4 weeks)
CONTROL	
Type of control	Usual care; women were asked not to initiate an exercise programme
Intensity	n/a
Duration of sessions	n/a
Frequency	n/a
Total period	n/a
CO-INTERVENTION	
Type of co-intervention	n/a
OUTCOMES	
Outcome measures concepts	- Cancer-specific quality of life - Fatigue - Self-esteem - Depression - Anxiety - Aerobic fitness, cardiorespiratory capacity - Strength - Weight - Body composition - Lymphedema - Chemotherapy completion rate
Assessment instruments	- Functional Assessment of Cancer Therapy-Anemia scale (FACT-An) - Rosenberg Self-Esteem Scale - Center for Epidemiological Studies Depression Scale (CES-D) - Spielberger State Anxiety Inventory (STAI) - Peak oxygen consumption in maximal incremental exercise protocol on treadmill (expired gas analysis) - 8-RM on horizontal bench press and leg extension - Balance beam scale - Dual x-ray absorptiometry - Standard volumetric arm measurements based on water displacement - Average relative dose-intensity (RDI) for the originally planned chemotherapy regimen
Adverse effects	- Exercise trainers monitored harm - Reporting of harm: yes - Observation of harm: yes (after baseline maximal treadmill testing)
Similarity at baseline	- Adequate

Courneya 2007 – Effect size data					
ES No.	1	2	3	4	5
ES type	Post-test	Post-test	Post-test	Post-test	Post-test
Construct	QoL	Self-esteem	Fatigue	Anxiety	Depression
Instrument	FACT-An	Rosenberg	FACT-An* Fatigue-subscale	STAI	CES-D
N aerobic exercise	74	74	74	74	74
N resistance exercise	76	76	76	76	76
N control group	73	73	73	73	73
Mean aerobic exercise	144.7	34.5	36.8	35.0	9.7
Mean resistance exercise	140.9	34.7	36.3	36.4	10.6
Mean control group	139.9	33.2	34.9	37.4	10.8
SD aerobic exercise	25.2	5.1	10.4	11.7	9.3
SD resistance exercise	24.8	4.2	9.4	12.7	9.5
SD control group	28.2	5.5	12.5	12.0	9.4

*FACT Fatigue-subscale scores range from 0 to 52, where higher scores represent less fatigue.

Courneya 2007 – Effect size data			
ES No.	6	7	8
ES type	Post-test	Post-test	Post-test
Construct	Cardiorespiratory fitness [ml/kg/min]	Strength leg [kg]	Strength Chest [kg]
Instrument	VO_{2peak}	1 RM	1RM
N aerobic exercise	71	71	71
N resistance exercise	77	77	77
N control group	73	73	73
Mean aerobic exercise	25.7	28.2	24.7
Mean resistance exercise	24.2	32.8	31.9
Mean control group	23.5	27.1	24.6
SD aerobic exercise	7.4	14.2	7.5
SD resistance exercise	6.1	12.6	10.8
SD control group	5.4	14.1	7.8

Courneya 2007 – Effect size data					
ES No.	9	10	11	12	13
ES type	Post-test	Post-test	Post-test	Post-test	Post-test
Construct	Body weight [kg]	Body fat [%]	Fat mass [kg]	Lean mass [kg]	Arm difference [ml]
Instrument					
N aerobic exercise	64	64	64	64	64
N resistance exercise	66	66	66	66	66
N control group	69	69	69	69	69
Mean aerobic exercise	70.3	37.9	27.1	40.9	-7
Mean resistance exercise	71.1	37.2	26.9	41.3	10
Mean control group	73.4	39.8	29.5	40.9	11
SD aerobic exercise	13.8	8.9	11.3	5.1	152
SD resistance exercise	15.4	9.0	12.0	4.9	118
SD control group	15.7	8.8	12.0	5.6	153

Courneya 2007 – Effect size data	
ES No.	10
ES type	Post-test
Construct	Lymphedema
Instrument	Volumetric arm measurements
N aerobic exercise	78
N resistance exercise	82
N control group	82
N aerobic exercise with harm	7
N resistance exercise with harm	3
N control group with harm	6

Courneya 2007 – Effect size data at 6-month follow-up					
ES No.	1	2	3	4	5
ES type	Post-test	Post-test	Post-test	Post-test	Post-test
Construct	QoL	Self-esteem	Fatigue	Anxiety	Depression
Instrument	FACT-An	Rosenberg	FACT-An Fatigue-subscale	STAI	CES-D
N aerobic exercise	68	68	68	68	68
N resistance exercise	73	73	73	73	73
N control group	60	60	60	60	60
Mean aerobic exercise	156.3	35.0	42.1	32.2	7.2
Mean resistance exercise	152.9	35.2	40.8	35.5	9.6
Mean control group	152.4	33.9	41.5	37.4	10.2
SD aerobic exercise	24.0	4.7	10.5	11.2	7.5
SD resistance exercise	26.0	4.6	10.5	13.0	10.4
SD control group	26.4	5.6	9.8	12.0	9.5

Crowley 2003 – Study descriptors	
METHODS	
Type of trial	RCT (p 31)
Configuration of trial	Parallel group design
Method of randomisation	Random numbers table (p 33)
Allocation concealment	A (p 33)
Outcome assessor blinding	Yes (p 34, blinding was not evaluated)
Timing of outcome assessments after initiation of treatment	7 weeks (attention performance, fatigue, physical self-efficacy, functional wellness), 13 weeks (all outcomes); (p 43)
Length of post-intervention follow-up period	0 (p 43)
Sample size, total	22 (p 43)
Sample size for each group	- Intervention group: n=13 - Control group: n=9, (p 43)
Availability of sample size for each group at randomisation	Yes (p 43)
Withdrawal-/Drop-out rate and reasons	- Intervention group: 0/13(0%) - Control group: 0/10 (0%) - All participants: 0/22 (0%) (p 71; 100% retention)
Adherence	- Monitoring of intensity (HR, perceived exertion), frequency, duration - Assessed via activity log to document weekly exercise type, frequency, duration, intensity - Defined as completion of 80% of individual targets for aerobic activity and strength training sessions - Activity level per group: o Intervention group: moderate level of activity (mean: 113 min/week) with a frequency of 3.66 days per week; (21-35 possible sessions >> 3.66 x 7 = 25.62 sessions = 73.2%/sessions) o Control group: low level of activity (mean: 53 min/ week) with a frequency of 1.79 days per week (p 47)
Type of analysis	ITT (available case analysis for strength, p 45)
Statistical tests	Repeated measures analysis of variance, t-tests (p 40)
Power calculation	No
PARTICIPANTS	
Recruitment	- University comprehensive cancer centre - Community hospital oncology practice in a Midwest city (p 32)
Inclusion criteria	- 35-60 years - Breast cancer stages I, II - adjuvant chemotherapy (Adriamycin, Cytoxan) - surgery
Exclusion criteria	- History of cancer treatment - Breast reconstruction - Radiotherapy - Cardiac, pulmonary disease, pregnancy, lactation (p 32)
Age	All participants: range 36 – 58 (p 43)
BMI	n/a
Breast cancer staging	All participants (p 76): - Stage I: 13/22 (59.1%) - Stage II: 9/22 (40.9%);

Crowley 2003 – Study descriptors	
Menopausal status	All participants (p 76): - Premenopausal: 12/22 (54.5%) - Postmenopausal: 10/22 (45.5%)
Type of adjuvant cancer treatment	Chemotherapy: four three-week cycles Adriamycin, Cytoxan (p 32)
Physical activity before cancer diagnosis	Yes, baseline exercise history of 72.7% (self-report, p 62)
Co-morbidity	n/a
INTERVENTIONS	
Type of training	Aerobic and resistance exercise: walking, tubing (p 82-85; 88)
Setting	Home based
Health promotion theory	None
Delivery of intervention	- Week 2: 1 hour exercise instructions through exercise physiologist - Week 8: 30 minutes educational re-enforcement - Week 4, 7, 10, 13: collection of activity logs through nurse researchers at treatment visits
Intensity	- Aerobic exercise: 60% of targeted heart rate?; individualised according to fitness level and post-operative state, RPE 11-13 ("Fairly light" to "somewhat hard") - Resistance exercise: fatigue after 12-15 repetitions
Duration of sessions	- Aerobic exercise: 20-60 min (p 34) - Resistance exercise: ca. 20 minutes, 1-2 sets
Frequency	- Aerobic exercise: 3-5 sessions per week - Resistance exercise : 2-3 sessions per week
Total exercise period	13 weeks (p 34)
CONTROL	
Type of control	No intervention
Intensity	n/a
Duration of sessions	n/a
Frequency	n/a
Total period	n/a
CO-INTERVENTION	
Type of co-intervention	- Usual care - Continuation of ongoing exercise regimens (p 32)
OUTCOMES	
Outcome measure concepts	- Cardiorespiratory fitness - Muscular fitness - Attention performance - Fatigue - Physical self-efficacy - Functional wellness - Quality of life - Adherence (secondary endpoint)
Assessment instruments (p 35f)	- Cornell Treadmill Protocol (VO_2max) - Chest press, leg press (1-RM) - R-PFS - Attentional Functional Index (AFI, 0-100; the larger the score, the greater the perception of ability to function cognitively) - Self-Efficacy to Perform Self-Management Behaviours Scale - Self-Efficacy to Achieve Outcomes scale (10 point scale, higher scores reflecting greater perception of physical self-efficacy) - SF-36 - Functional Wellness Questionnaire (investigator developed, 5-

Crowley 2003 – Study descriptors	
	point scale) - Activity log with exercise type, frequency, duration and intensity
Adverse effects	- 1 fall (unrelated to study) - 1 lymphedema (p 45)
Similarity at baseline	Inadequate

Crowley 2003 – Effect size data	
ES No.	1
ES type	Change score
Construct	Cardiorespiratory fitness
Instrument	Cornell treadmill test
N intervention group	13
N control group	9
Mean intervention group	0.37
Mean control group	-5.38
T-Value	3.41
SD intervention group	3.89
SD control group	3.89

Drouin 2002 – Study descriptors	
METHODS	
Type of trial	RCT
Configuration of trial	Parallel group design
Method of randomisation	Random number chart
Allocation concealment	A (inclusion first, then random assignment; pp 55,70)
Outcome assessor blinding	n/a
Timing of outcome assessments after initiation of treatment	8 weeks (1 week after 7 week intervention, p 72)
Length of post-intervention follow-up period	0
Sample size, total	23 (p 64)
Sample size for each group	- Intervention group: n=13 - Control group: n=10 (p 64)
Availability of sample size per group at randomisation	Yes
Withdrawal-/Drop-out rate and reasons	- Intervention group: 0/23 (0%) - Control group: 2/10 (20%) - All participants: 2/23 (8.7%) Reasons, suspected: too busy with jobs and family
Adherence	- Monitoring of intensity (HR), frequency, duration - Training journals (intensity, duration, frequency, mode of training), heart rate monitors - Adherence defined as 21 minimum sessions out of 35 possible sessions - Adherence per group: o Intervention group: 25.8 sessions, SD=10.1 o Control group: 29.2 sessions, SD=7.7
Type of analysis	Available case analysis
Statistical tests	Wilcoxon-Mann-Whitney U
Power calculation	No
PARTICIPANTS	
Recruitment	Karmanos Cancer Institute (major urban centre for radiation treatment); (p 70)
Inclusion criteria	- Breast cancer stages 0-III (histological established) - Radiotherapy - Surgery - 20-65 years - Sedentary (p 54)
Exclusion criteria	- Uncontrolled cardiac disease or hypertension - Aerobic exercise 3 month before entry in study (p 54)
Age	- Intervention group: 49.4, SD=7 - Control group: 51.9, SD=10 - All participants: 50.5 (p 71)
BMI/weight	BMI - Intervention group: 30.8, SD=7.6 - Control group: 32.0, SD=5.6 - All participants: 31.3 (p 81)
Breast cancer staging	- Intervention group (p 71): o Stage 0: n=3 o Stage I: n=2 o Stage II: n=4 o Stage III: n= 4

Drouin 2002 – Study descriptors	
	- Control group: o Stage 0: n=2 o Stage I: n=1 o Stage II: n=1 o Stage III: n=4
Menopausal status	n/a
Type of adjuvant cancer treatment	Radiotherapy (p 72)
Physical activity before cancer diagnosis	No aerobic exercise 3 month prior to entry in study as inclusion criterion
Co-morbidity	1 x Hypertension (p 72)
INTERVENTIONS	
Type of training	Aerobic exercise: walking (p 72)
Setting	Home based
Health promotion theory	None
Delivery of intervention	- Individualised exercise prescription - Weekly communication with principle investigator to promote adherence, monitor training & safety issues, answer questions.
Intensity	50-70 % HRmax
Duration of sessions	20-45 minutes
Frequency	3-5 sessions per week
Total exercise period	7 weeks
CONTROL	
Type of control	Stretching (1 training session plus booklet); (p 73)
Intensity	n/a
Duration of sessions	n/a
Frequency	3-5 sessions per week (p 75)
Total period	7 weeks
CO-INTERVENTION	
Type of co-intervention	Weekly communication
OUTCOMES	
Outcome measure concepts	- Cardiorespiratory fitness - Muscular fitness - Body composition - Fatigue - Mood - Immune function - Oxidative stress
Assessment instruments	- Modified Bruce protocol (VO_2peak) - Handgrip test (Jaymar Dynamometer) - Waist Hip Ratio - BMI - Lange calliper (skinfold thickness) - R-PFS (p 55 ff) - POMS - CD4+/ CD8+ ratio, NKCA (Natural Killer Cytotoxic Activity) - 8-Isoprostane (Flow cytometry; Chromium release assay; ELISA) - Training journal: intensity, duration, frequency, mode of training
Adverse effects	- 1x increased fatigue and mood disturbance - decrements in strength and shoulder tendonitis due to overtraining - no decrements in immune function (p 93)
Similarity at baseline	Adequate (p 71, 64, 65)

Drouin 2002 – Effect size data					
ES No.	1	2	3	4	5
ES type	Post-test	Post-test	Post-test	Post-test	Post-test
Construct	Cardiorespiratory fitness	Body composition		Muscular fitness	Fatigue
Instrument	Modified Bruce treadmill test	Weight [kg]	BMI	Grip strength [kg]	R-PFS
N intervention group	13	13	13	13	13
N control group	8	8	8	8	8
Mean intervention group	22.6	79.9	30.1	31.3	3.4
Mean control group	16.6	83.3	31.7	32.0	3.9
SD intervention group	6.2	20.9	7.3	6.5	1.9
SD control group	2.2	18.2	6.1	6.4	2.4

Drouin 2002 – Effect size data				
ES No.	6	7	8	9
ES type	Post-test	Post-test	Post-test	Post-test
Construct	Mood	Biological complications		
Instrument	POMS	NKCA [lytic units]	CD4/CD8	8-Iso-prostane serum levels
N intervention group	13	13	13	10
N control group	8	8	8	5
Mean intervention group	5.1	8.5	2.5	244.0
Mean control group	23.9	6.6	1.8	316.4
SD intervention group	22.1	9.2	1.1	132.6
SD control group	32.0	4.2	1.0	118.3

Kim 2006 – Study descriptors	
METHODS	
Type of trial	RCT
Configuration of trial	Parallel group design
Method of randomisation	Computer-generated randomisation lists; stratification by breast cancer stage
Allocation concealment	B
Outcome assessor blinding	n/a
Timing of outcome assessments after initiation of treatment	- 10 weeks for functional ability, cardiorespiratory fitness and exercise level - 16 weeks for exercise level
Length of post-intervention follow-up period	- 0 weeks for functional ability - 6 weeks for exercise level
Sample size, total	41 (p 74)
Sample size for each group	- Intervention group: n=22 - Control group: n=19
Availability of sample size for each group at randomisation	no
Withdrawal-/Drop-out rate and reasons	All participants: 11/74 (15%); Reasons: personal problems, problems at home, problems related to chemotherapy, thrombophlebitis in leg, non-exercise related injuries, death; BMI higher in participants who withdrew or did not complete exercise tests
Adherence	- Monitoring of intensity (HR), frequency, total duration, and duration at target HR - Adherence: 78.3%, SD=20.1% (exercise sessions completed at prescribed level divided by total number of exercise sessions prescribed) - Average weekly frequency of exercise: 2.4, SD=0.6 sessions - Average duration of exercise per session: 42.7 minutes, SD=8.0 - Average duration of exercise within prescribed target HR: 27.8 minutes, SD=8.1 - Overall adherence rate: 78.3%, SD=20.1%
Type of analysis	Available case analysis
Statistical tests	t-tests, Wilcoxon signed-rank test
Power calculation	No
PARTICIPANTS	
Recruitment	- University breast cancer clinics - Interdisciplinary breast Clinic - University affiliated hospitals - Satellite Cancer Clinics
Inclusion criteria	- Women newly diagnosed with breast cancer, all stages - No history of cancer - Older than 40 years - Receiving cancer treatment
Exclusion criteria	- Bone metastasis - High risk of fractures - Psychiatric illness - Uncontrolled cardiopulmonary or other serious medical conditions - Regular exercise at least 2 to 3 times a week in moderate intensity within the past 2 month

Kim 2006 – Study descriptors	
Age	- Intervention group: 51.3, SD=6.7 - Control group: 48.3, SD=8.8 - All participants: 49.9
BMI	- Intervention group: 29.9, SD=5.5 - Control group: 28.0, SD=5.1
Breast cancer staging (n; %)	- **Intervention group**: o Stage 0: 1/22 (4.5%) o Stage I: 10/22 (45.5%) o Stage II: 8/22 (36.4%) o Stage III: 3/22 (13.6%) - **Control group**: o Stage 0: 1/19 (5.3%) o Stage I: 7/19 (36.8%) o Stage II: 7/19 (36.8%) o Stage III: 4/19 (21.1%) - All participants: o Stage 0: 2/41 (4.9%) o Stage I: 17/41 (41.5%) o Stage II: 15/41 (36.6%) o Stage III: 7/41 (17.1%)
Menopausal status	n/a
Type of adjuvant cancer treatment (n; %)	- **Intervention group:** o Chemotherapy: 9/22 (40.9%) o Radiotherapy: 7/22 (31.8%) o Combination: 6/22 (27.3%) - **Control group:** o Chemotherapy: 11/19 (57.9%) o Radiotherapy: 7/19 (36.8%) o Combination: 1/19 (5.3%) - **All participants:** o Chemotherapy: 20/41 (48.8%) o Radiotherapy: 14/41 (34.2%), o Combination: 7/41 (17.1%)
Physical activity before cancer diagnosis	Sedentary (regular exercise at least 2 to 3 times a week in moderate intensity within the past 2 month as exclusion criterion)
Co-morbidity	n/a
INTERVENTIONS	
Type of training	Aerobic exercise: cycling, walking, jogging, or running on a treadmill or track; progressive
Setting	- Centre based: exercise facility within the School of nursing, supervised - home based after the regular intervention (physical activity assessment in 16 weeks follow-up)
Health promotion theory	None
Delivery of intervention	After exercise intervention: biweekly calls of exercise physiologist to collect physical activity data, encouragement to maintain the same pattern of exercise at home or in community setting after supervised training had finished
Intensity	60 – 70%HR reserve; 60 – 70 %VO_2 peak
Duration of sessions	30 minutes (plus warm-up, cool down)
Frequency	3 sessions per week
Total exercise period	8 weeks

Kim 2006 – Study descriptors	
CONTROL	
Type of control	No intervention (waiting list)
Intensity	n/a
Duration of sessions	n/a
Frequency	n/a
Total period	n/a
CO-INTERVENTION	
Type of co-intervention	- Stress management >>> complex intervention, but no influence on functional ability expected! - Usual care - ß-blocker, antihypertensives
OUTCOMES	
Outcome measure concepts	- Cardiorespiratory fitness - Physical activity
Assessment instruments	- Bruce treadmill protocol: Heart rate (resting, maximum), systolic Blood pressure (resting, maximum), VO_2 peak - 7-day physical activity questionnaire: Average weekly frequency of exercise, average duration of exercise per session, average duration of exercise within prescribed target HR, overall adherence rate
Adverse effects	n/a
Similarity at baseline	Yes

Kim 2006 – Effect size data		
ES No.	1	2
ES type	Post-test	Post-test at 4-month post intervention
Construct	Cardiorespiratory fitness	Physical activity
Instrument	Bruce treadmill test [ml VO_2/min]	7-day physical activity log [hours/wk]
N intervention group	22	22
N control group	19	19
Mean intervention group	1810.1	5.68
Mean control group	1630.4	4.35
SD intervention group	369.4	2.28
SD control group	351.5	2.79

MacVicar 1986 – Study descriptors	
METHODS	
Type of trial	Controlled clinical trial (non-randomised)
Configuration of trial	Parallel group design
Method of randomisation	n/a
Allocation concealment	D
Outcome assessor blinding	n/a
Timing of outcome assessments after initiation of treatment	10 weeks
Length of post-intervention follow-up period	0 weeks
Sample size, total	10
Sample size for each group	- Intervention group: n=6 - Control group: n=4
Availability of sample size per group at randomisation	Yes
Withdrawal-/Drop-out rate and reasons	0%
Adherence	n/a
Type of analysis	n/a
Statistical tests	Descriptive statistics: mean scores
Power calculation	No
PARTICIPANTS	
Recruitment	n/a
Inclusion criteria	- Breast cancer, surgery, chemotherapy, younger than 60 years
Exclusion criteria	- Cardiovascular disease or hypertension - Adriamycin
Age	n/a
BMI/weight	n/a
Breast cancer staging	Stage II
Menopausal status	n/a
Type of adjuvant cancer treatment	Chemotherapy
Physical activity before cancer diagnosis	n/a
Co-morbidity	n/a
INTERVENTIONS	
Type of training	Aerobic exercise: cycle ergometer; progressive interval training
Setting	Laboratory based
Health promotion theory	None
Delivery of intervention	Tight supervision
Intensity	60-85% HRmax
Duration of sessions	20-30 minutes
Frequency	3 sessions per week
Total exercise period	10 weeks
CONTROL	
Type of control	No intervention
Intensity	n/a
Duration of sessions	n/a
Frequency	n/a
Total period	n/a
CO-INTERVENTION	
Type of co-intervention	n/a
OUTCOMES	

MacVicar 1986 – Study descriptors	
Outcome measure concepts	- Cardiorespiratory fitness - Mood
Assessment instruments	- Interval-training cycle ergometric protocol (Peak VO_2) - Profile of Mood States (POMS)
Adverse effects	n/a (according to letter no adverse effects)
Similarity at baseline	No

MacVicar 1989, Winningham 1989 – Study descriptors		
Publication	2 reports	
METHODS		
Type of trial	RCT	
Configuration of trial	- Parallel group design - 3 groups (exercise, sham treatment and control)	
Method of randomisation	n/a; stratified by functional capacity (± 1 MET)	
Allocation concealment	B	
Outcome assessor blinding	n/a	
Timing of outcome assessments after initiation of treatment	10 weeks	
Length of post-intervention follow-up period	0 weeks	
Sample size, total	n=45 (MacVicar 1989)	n= 24 (Winningham 1989)
Sample size for each group	- Intervention group: n=18 - Control group placebo: n=11 - Control group: n=16	- Intervention group: n=12 - Control group: n=12 (secondary exclusions)
Availability of sample size per group as randomised	No	No
Withdrawal-/Drop-out rate and reasons	All participants: 17/62 (27.4%) Reasons: equipment breakdown; problems of transport; doxorubicin; extreme reactions to chemotherapy; re-classification of breast cancer stage	
Adherence	- Monitoring of intensity (HR), frequency, duration - Adherence complete (missed sessions repeated)	
Type of analysis	MacVicar 1989: Per protocol analysis (n= 45)	Winningham 1989: Secondary analysis (subsample) per protocol (n= 24)
Statistical tests	MacVicar 1989: Analysis of covariance; covariate: pre-test values	Winningham 1989: Analysis of covariance; covariates: pre-test values and age
Power calculation	No	
PARTICIPANTS		
Recruitment	Outpatient chemotherapy clinics	
Inclusion criteria	- Breast cancer stage II; histological established - Surgery - Chemotherapy (1cycle/4weeks <= intervention <=6month) - Baseline functional capacity of 0-2 on Zubrod scale - Karnofsky 50-100%	
Exclusion criteria	- Cardiotoxic drugs (doxorubicin) - Extreme reactions to chemotherapy - Uncontrolled cardiac, hypertensive or diabetic disease - Regular exercise programme - Secondary exclusions (Winningham 1989) of potential confounders related to body composition: o History of thyroid function o Tamoxifen use o Skinfolds exceeded the capacity of the callipers o Intestinal bypass surgery for obesity	

MacVicar 1989, Winningham 1989 – Study descriptors		
Age	MacVicar 1989:	Winningham 1989:
- Intervention group	- 45.4, SD=10.2	- 45.6, SD=9.6
- Control group placebo	- 46.1, SD=10.3	
- Control group	- 43.8, SD=9.3	- 45.6, SD=9.9
- All participants	- 45.2	- 45.6
Weight	MacVicar 1989:	Winningham 1989:
- Intervention group	- 69.9 kg, SD=14.2	n/a
- Control group placebo	- 64.0 kg, SD=8.8	
- Control group	- 65.7 kg, SD=13.1	
Height		
- Intervention group	- 161.2 cm, SD=7.0	- 161.6 cm; SD=8.0
- Control group placebo	- 155.4 cm, SD=13.0	
- Control group	- 163.2 cm, SD=6.0	- 160.4 cm; SD=11.7
BMI		
- Intervention group	- 26.97	- n/a
- Control group placebo	- 26.5	
- Control group	- 24.67	- n/a
- All participants	- 26.04	
Breast cancer staging	All participants: Stage II	
Menopausal status	MacVicar 1989:	Winningham 1989:
- Intervention group	- n/a	- Pre-menopausal: 5/12 (42%)
- Control group placebo	- n/a	
- Control group	- n/a	- Pre-menopausal: 4/12 (33%)
Type of adjuvant cancer treatment	All participants - Chemotherapy: 41/45 (91%) - Hormonal therapy (Tamoxifen): 4/45 (9%)	
Physical activity before cancer diagnosis	Regular exercise programme as exclusion criterion	
Co-morbidity	n/a	
INTERVENTIONS		
Type of training	Aerobic exercise: cycle ergometer, interval training	
Setting	Laboratory based	
Health promotion theory	None	
Delivery of intervention	Tight supervision	
Intensity	Alternating higher or lower exercise intensity, 60-85% HRmax	
Duration of sessions	20-30 minutes	
Frequency	3 sessions per week	
Total exercise period	10 weeks	
CONTROL	Control group placebo	Control group
Type of control	Flexibility and stretching exercises	No intervention
Intensity	n/a	n/a
Duration of sessions	n/a	n/a
Frequency	n/a	n/a
Total period	n/a	n/a
CO-INTERVENTION		
Type of co-intervention	No subject participated in any other exercise or rehabilitation programme	
OUTCOMES		
Outcome measure concepts	- Cardiorespiratory fitness (aerobic capacity, cardiac function, work load resistance) - Body composition	
Assessment instruments	- Winningham Aerobic Interval Training (WAIT) protocol:	

MacVicar 1989, Winningham 1989 – Study descriptors	
	VO_2max [litre], time to achieve peak oxygen uptake, heart rate, ECG - Weight - Skinfold measurements
Adverse effects	n/a (according to letter no adverse effects)
Similarity at baseline	Adequate

MacVicar 1989 – Effect size data		
ES No.	1	2
ES type	Change score	Change score
Construct	Body composition	Cardiorespiratory fitness
Instrument	Weight [kg]	WAIT-protocol
N intervention group	12	18
N control group	12	16
Mean intervention group	0.82	0.425
Mean control group	1.99	-0.088
F-value (ANCOVA)	1.86	
SD intervention group	2.10	999*
SD control group	2.10	999*

* Transformation of F-value not adequate, since 3 groups were compared with adjustment for pre-test values

Mock 1997 – Study descriptors	
METHODS	
Type of trial	Controlled clinical trial (non randomised)
Configuration of trial	Parallel group design
Method of randomisation	n/a
Allocation concealment	D (alternate assignment)
Outcome assessor blinding	n/a
Timing of outcome assessments after initiation of treatment	- 3 weeks (mid-test) - 6 weeks (post-test)
Length of post-intervention follow-up period	0 weeks
Sample size, total	n=46 (of 50 recruited participants)
Sample size for each group	- Intervention group: n=22 - Control group: n=24
Availability of sample size per group at randomisation	No
Withdrawal-/Drop-out rate and reasons	4/50 (8%) Reasons: time constraints, treatment side effects; withdrawal from radiotherapy
Adherence	- Monitoring of intensity (pulse rates), frequency, duration via diaries - Adherence defined as ≥ 30 minutes of aerobic exercise in 3 or more sessions per week (intervention group) and ≤ 30 minutes in 4 sessions per week (control group) - Adherence: o Intervention group: 86% o Control group: complete adherence
Type of analysis	Available case analysis
Statistical tests	MANCOVA; ANCOVA
Power calculation	Yes
PARTICIPANTS	
Recruitment	- 2 University teaching hospitals - Outpatient departments of radiation oncology
Inclusion criteria	- Breast cancer stages I and II - Breast-conserving surgery - Radiotherapy - 35-65 years
Exclusion criteria	- Concurrent major health problems (e.g., cardiovascular disease, acute or chronic respiratory disease, cognitive dysfunction) - Already participating in structured exercise programme
Age	- Intervention group: 48.09, SD=5.42 - Control group: 50.29, SD=8.47 - All participants: 49.2
BMI	- Intervention group: 24 - Control group: 24 - All participants: 24
Breast cancer staging	- Intervention group: o Stage I: 17/22 (77%) o Stage II: 5/22 (23%) - Control group: o Stage I: 16/24 (67%) o Stage II: 8/24 (33%)

Mock 1997 – Study descriptors	
Menopausal status	n/a
Type of adjuvant cancer treatment	All participants: Radiotherapy
Physical activity before cancer diagnosis	- Control group: several subjects regular walkers - Already participating in structured exercise programme as exclusion criterion
Co-morbidity	n/a
INTERVENTIONS	
Type of training	Aerobic exercise: walking
Setting	Home based
Health promotion theory	None
Delivery of intervention	- Research team taught and monitored exercise program - Exercise session: self-paced, progressive program of brisk walking, followed by 5 minutes slo walking (cool-down) - Subjects walked in their neighbourhoods, at a mall, or in a gym at their own pace and individually prescribed duration - Intensity was purposefully left under the control of the subject to permit individualized adaptation to effects or cancer treatment and to prevent overexertion - Researchers encouraged adherence by recommending that subjects walk with a partner for support - Researchers maintained regular contact by telephone or during clinic visits to assess exercise progress and adjust exercise prescription as indicated and to encourage adherence - Booklet - To prevent a differential intervention effect, the usual care group was contacted regularly to inquire about their health and general response to treatment.
Intensity	60-80% HRmax; self paced; individualized based on level of physical fitness (determined by 12-Minute-Walk Test), history of exercise and age, left under control of subject (Borg Scale for Rating of Perceived Exertion with target rating of 11-13) (cp. Watson and Mock 2004)
Duration of sessions	20-30 minutes
Frequency	4-5 sessions per week
Total exercise period	6 weeks
CONTROL	
Type of control	Usual care
Intensity	n/a
Duration of sessions	n/a
Frequency	n/a
Total period	n/a
CO-INTERVENTION	
Type of co-intervention	Regular contact (both groups)
OUTCOMES	
Outcome measure concepts	- Fatigue - Physical activity - Physical fitness (ability to ambulate and perform ADL) - Emotional distress - Symptom experience (pain, skin change, nausea, vomiting, fatigue, diarrhoea, difficulty sleeping, irritability, depression, mouth sores, anxiety, constipation, satisfaction with body)

Mock 1997 – Study descriptors	
Assessment instruments	- R-PFS, Visual Analogue Scale (VAS) fatigue - 12-minute walk test - Exercise rating scale (0-10) based on self-report of minutes/day and days/week spent exercising - Diaries of exercise periods with pulse rates and subjective data - Symptom Assessment Scales (SAS)
Adverse Effects	No physical injury related to the walking programme
Similarity at baseline	Adequate
COMMENTS	
Conceptual framework	Roy adaptation model

Mock 1997 – Effect size data					
ES No.	1	2	3	4	5
ES type	Post-test	Post-test	Post-test	Post-test	Post-test
Construct	Fatigue	Cardiorespiratory fitness	Anxiety	Depression	Sleep disturbances
Instrument	VAS fatigue	12-MWT [feet]	SAS anxiety	SAS depression	SAS sleep disturbances
N intervention	22	22	22	22	22
N control group	24	22	24	24	24
Mean intervention	26.12	3371	10.44	9.51	12.38
Mean control group	43.05	3089	26.93	21.05	32.58
F-Value (ANCOVA)		9.69	5.11	2.77	5.39
SD intervention group	20.27	300.46	24.70	23.50	29.50
SD control group	36.37	300.46	24.70	23.50	29.50

Mock 2005 – Study descriptors	
METHODS	
Type of trial	RCT
Configuration of trial	Parallel group design
Method of randomisation	Computer-generated
Allocation concealment	A (consecutively numbered sealed opaque envelopes, opened after baseline testing)
Outcome assessor blinding	No
Timing of outcome assessments after initiation of treatment	- Radiotherapy: 6 weeks - Chemotherapy: 3-6 month
Length of post-intervention follow-up period	0 weeks
Sample size, total	119
Sample size for each group	- Intervention group: n=60 - Control group: n=59
Availability of sample size for each group at randomisation	Yes
Withdrawal-/Drop-out rate and reasons	- Intervention group: 6/60 (10%) - Control group: 5/59 (8.5%) Reasons: patient request, moved, chemotherapy problems, chemo-therapy withdrawal
Adherence	- Monitoring of intensity (pulse rates, perceived exertion), frequency, duration via diaries (lack of a physiologic activity monitor) - ACSM definition: 85% of minimum prescription - Coding in trial: o Intervention group: more than 60 minutes per week for more than 2/3 of trial as adherent to exercise prescription o Control group: less than 45 minutes per week for more than 2/3 of trial - Assessment via daily diaries of exercise periods including pulse rates, perceived exertion rates, and fatigue levels - Intervention group: o Not adherent: 15/54 (28%) o Adherent: 39/54 (72 %) exercising 127.43 minutes per week, SD=44.04, with a frequency of 4.59, SD=1.16 sessions per week and a mean of 28.36 SD=9.04 minutes per session - Control group: o Not adherent (= exercising): 21/54 (39%) o Adherent: 33/54 (61%)
Type of analysis	- ITT (Complier-average-causal effect as equivalent to ITT) - Sub-Group Analysis: low exercisers vs. high exercisers
Statistical tests	- 2 sample t-tests - multiple linear regression (with adjustments for baseline covariates) - Instrumental variables with principal stratification (IV/PS) - Complier-average-causal effect (CACE)
Power calculation	Yes
PARTICIPANTS	
Recruitment	- 4 University teaching hospitals of National Cancer Institute - 4 community cancer centres in eastern US

Mock 2005 – Study descriptors	
Inclusion criteria	- 18-70 years - Breast cancer stages 0-III - Surgery - Chemotherapy or radiotherapy - Sedentary (exercising less than 45 minutes per week)
Exclusion criteria	- Concurrent major health problems (e. g. obesity, cardiovascular disease, respiratory disease, cognitive dysfunction) - Active exercising
Age	Intervention group: 51.3, SD=8.9 Control group: 51.6, SD=9.7 All participants: 51.5, SD=9.3
BMI	Intervention group: 25.5, SD=4.0 Control group: 25.8, SD=5.1 All participants: 25.7, SD=4.6
Breast cancer staging	- Intervention group: o Stage 0: 12/60 (20%) o Stage I: 27/60 (45%) o Stage II: 21/60 (35 %) o Stage IIIa: 0/60 (0%) - Control group o Stage 0: 16/59 (27.2%) o Stage I: 24/59 (40.7%) o Stage II: 15/59 (25.4%) o Stage IIIa: 4/59 (6.7%) - All participants o Stage 0: 28/119 (23.5%) o Stage I: 51/119 (42.9%) o Stage: 36/119 (30.2%) o Stage IIIa: 4/119 (3.4%)
Menopausal status	n/a
Type of adjuvant cancer treatment	- Intervention group: o Chemotherapy: 25/60 (41.7%) o Radiotherapy: 35/60 (58.35%) - Control group: o Chemotherapy: 25/59 (42.4%) o Radiotherapy: 34/59 (57.6%) - All participants: o Chemotherapy: 50/119 (42.0%) o Radiotherapy: 69/119 (58.0%)
Physical activity before cancer diagnosis [kcals/week]	- Sedentary (less than 40 minutes per week) - Intervention group: 1657 kcals/week, SD=1262 - Control group: 1918 kcals/week, SD=1806 - All participants: 1789 kcals/week, SD=1559
Co-morbidity	n/a
INTERVENTIONS	
Type of training	Aerobic exercise: walking
Setting	Home based
Health promotion theory	None
Delivery of intervention	- Oncology nurses taught and monitored individualised written prescription of exercise programme - Video - Booklet - Research team contacted participants every two weeks to evaluate the prescription and participant progress

Mock 2005 – Study descriptors	
	- Prescription was adjusted if an exercise participant was ill or stopped exercising for more than 3 days - Control group: patients were encouraged to maintain current levels of activity; patients were called every 2 weeks by the research team (attentional control) and were asked about their cancer treatment experience; patients reporting unmanaged symptoms or other clinical problems were referred to their health care provider for treatment
Intensity	50-70 % HR max
Duration of sessions	15 minutes increased to 30 minutes as training progressed
Frequency	5-6 sessions per week
Total exercise period	- Radiotherapy: 6 weeks - Chemotherapy: 3 – 6 month
CONTROL	
Type of control	No intervention
Intensity	n/a
Duration of sessions	n/a
Frequency	n/a
Total period	n/a
CO-INTERVENTION	
Type of co-intervention	- Usual care - Regular contact (every 2 weeks)
OUTCOMES	
Outcome measure concepts	- Primary outcome: Fatigue - Physical Function - Cardiorespiratory fitness - Physical activity
Assessment instruments	- PFS - SF-36 (physical function subscale) - 12-minutes walk test - Physical activity questionnaire (PAQ) - Daily diaries of exercise periods, incl. pulse rates, perceived exertion - Borg Rating of Perceived Exertion for monitoring purposes
Adverse effects	No adverse events attributable to walking exercise
Similarity at baseline	Adequate (but difference for 12 min walk, was adjusted for)

Mock 2005 – Effect size data	
ES No.	1
ES type	Post-test
Construct	Fatigue
Instrument	PFS
N intervention group	54
N control group	54
Mean intervention group	3.5
Mean control group	3.7
SD intervention group	2.4
SD control group	2.6

Mutrie 2007 – Study descriptors	
METHODS	
Type of trial	RCT
Configuration of trial	Parallel group design
Method of randomisation	Stratified by hospital and therapy; randomised permuted blocks of length 4 and 6; randomisation performed by telephone to an Interactive Voice Response system implemented by the Robertson Centre for Biostatistics.
Allocation concealment	A
Outcome assessor blinding	Yes (e.g., questionnaires in sealed envelopes, 12 week and follow up measures taken by researchers who had not taught that participant in classes)
Timing of outcome assessments after initiation of treatment	12 weeks and 6 months post intervention
Length of post-intervention follow-up period	6 months post intervention
Sample size, total	201
Sample size for each group	- Intervention group: n=99 - Control group: n=102
Availability of sample size for each group at randomisation	Yes
Withdrawal-/Drop-out rate and reasons	- Intervention group: o Week 12: 17/99 (17.2%) o 6 months post intervention: 17/99 (17.2%) - Control group: o Week 12: 10/102 (9.8%) o 6 months post intervention: 7/102 (6.9%) Reasons: did not start classes, questionnaires not returned, non-contactable, died, too ill
Adherence	- Monitoring of intensity (HR), frequency, duration - Participation in classes: o > 70% classes: 39/99 (38.8%) o 30-69% classes: 30/99 (30.6%) o < 30% classes: 30/99 (30.6%)
Type of analysis	Available case analysis
Statistical tests	Mixed effects linear regression with predictor variables for stratification variables, age, baseline outcome variable measurement, visit-specific effects of intervention; including random participant effect
Power calculation	Yes
PARTICIPANTS	
Recruitment	3 clinical recruiters for outpatient chemotherapy and radiotherapy clinics at three sites
Inclusion criteria	n/a
Exclusion criteria	n/a
Age	- Intervention group: 51.3, SD=10.3 - Control group: 51.8, SD=8.7 - All participants: 51.6, SD=9.5
BMI	- Intervention group: 27.3, SD=5.2 - Control group: 27.5, SD=6.0 - All participants: 27.4, SD=5.6
Breast cancer staging	Early stage

Mutrie 2007 – Study descriptors	
Menopausal status	Periods - **Intervention group:** o None: 82/99 (82.8%) o Irregular: 10/99 (10.1%) o Regular: 7/99 (7.1%) - **Control group**: o None: 87/102 (85.3%) o Irregular: 7/102 (6.9%) o Regular: 8/102 (7.8%) - **All participants**: o None: 169/201 (84.1%) o Irregular: 17/201 (8.5%) o Regular: 15/201 (7.5%)
Type of adjuvant cancer treatment	- **Intervention group:** o Chemotherapy: 8/99 (8.1%) o Radiotherapy: 28/99 (28.3%) o Combination: 63/99 (63.6%) - **Control group**: o Chemotherapy: 7/102 (6.9%) o Radiotherapy: 29/102 (28.4%) o Combination: 66/102 (64.7%) - **All participants**: o Chemotherapy: 15/201 (7.5%) o Radiotherapy: 57/201 (28.4%) o Combination: 129/201 (64.2%)
Physical activity before cancer diagnosis	SPAQ leisure time activity - Intervention group: 367.0 minutes, SD=305.7 - Control group: 364.9 minutes, SD=287.6 - All participants: 365.9 minutes, SD=295.9
Co-morbidity	n/a
INTERVENTIONS	
Type of training	Aerobic and resistance exercise training: warm-up of 5-10 minutes, 20 minutes of exercise (including walking, cycling, low level aerobics, muscle strengthening exercises, or circuits of specifically tailored exercises), a cool down and relaxation period
Setting	Community based
Health promotion theory	Stages of change, self-efficacy
Delivery of intervention	- 24 exercise classes, each week 14 classes - Run by specifically trained exercise specialists - 9 different locations, all accessible by public transport - Time tabled at various times in the day and evening - Individual physical activity counselling - Workshops addressing health benefits, self-efficacy, exercise barriers, supportive environment, setting goals, finding appropriate activity options
Intensity	60-75% age-adjusted heart rate maximum
Duration of sessions	35-50 minutes
Frequency	2 sessions per week
Total exercise period	12 weeks
CONTROL	
Type of control	- Monitoring - Exercise leaflet
Intensity	n/a
Duration of sessions	n/a

Mutrie 2007 – Study descriptors	
Frequency	n/a
Total period	n/a
CO-INTERVENTION	
Type of co-intervention	Usual care (both groups)
OUTCOMES	
Outcome measure concepts	- Primary outcome measure: Quality of Life - Breast-cancer-specific symptoms - Fatigue - Endocrine symptoms - Depression - Emotional distress - Body composition - Cardiorespiratory fitness - Physical activity
Assessment instruments	- **F**unctional **A**ssessment of **C**ancer **T**herapy – **G**eneral (FACT-G) questionnaire - FACT-B; FACT-F; FACT ES - Beck Depression Inventory (BDI) - Positive and negative affect scale (PANAS) - BMI - Scottish Physical Activity Questionnaire (SPAQ) - 12 minute walk test
Adverse effects	n/a
Similarity at baseline	Yes

Mutrie 2007 – Effect size data						
ES No.	1	2	3	4	5	6
ES type	Post-test	Post-test	Post-test	Post-test	Post-test	Post-test
Construct	Cardiorespiratory fitness	Body Com-position	Quality of life	Quality of life	Fatigue	Depression
Instrument	12-MWT [meter]	BMI [kg/m²]	FACT-G	FACT-B	FACT-F	BDI
N intervention group	82	82	82	82	82	82
N control group	92	92	92	92	92	92
Mean inter-vention group	1135	26.9	81.0	106.5	120.8	8.6
Mean control group	984	27.9	77.3	99.7	113.3	11.5
SD interven-tion group	143	4.3	16.8	21.9	26.7	6.8
SD control group	221	6.9	14.4	20.3	25.0	8.6

Mutrie 2007 – Effect size data				
ES No.	7	8	9	10
ES type	Post-test	Post-test	Post-test	Post-test
Construct	Endocrine symptoms	Positive affects	Negative affects	Physical activity
Instrument	FACT-ES	PANAS positive	PANAS negative	SPAQ [min]
N intervention group	82	82	82	82
N control group	92	92	92	92
Mean intervention group	122.1	33.4	15.6	585
Mean control group	117.6	29.3	17.7	416
SD intervention group	24.6	8.5	6.6	385
SD control group	22.2	9.8	7.4	405

Mutrie 2007 – Effect size data at 6-month follow-up						
ES No.	1	2	3	4	5	6
ES type	Post-test	Post-test	Post-test	Post-test	Post-test	Post-test
Construct	Cardiorespiratory fitness	Body Com-position	Quality of life	Quality of life	Fatigue	Depression
Instrument	12-MWT [meter]	BMI [kg/m²]	FACT-G	FACT-B	FACT-F	BDI
N intervention group	82	82	82	82	82	82
N control group	95	95	95	95	95	95
Mean inter-vention group	1127	27.0	83.2	109.4	124.6	8.4
Mean control group	1013	27.0	77.1	101.2	114.3	10.8
SD interven-tion group	166	4.6	12.8	16.5	20.8	7.2
SD control group	190	5.4	17.0	21.7	28.1	7.5

Mutrie 2007 – Effect size data at 6-month follow-up				
ES No.	7	8	9	10
ES type	Post-test	Post-test	Post-test	Post-test
Construct	Endocrine symptoms	Positive affects	Negative affects	Physical activity
Instrument	FACT-ES	PANAS positive	PANAS negative	SPAQ [min]
N intervention group	82	82	82	82
N control group	95	95	95	95
Mean intervention group	123.8	33.0	15.7	492
Mean control group	116.8	29.2	17.4	427
SD intervention group	20.3	8.1	6.1	327
SD control group	24.4	10.5	6.9	370

Payne 2008 – Study descriptors	
METHODS	
Type of trial	- RCT (method unclear)
Configuration of trial	- Parallel group
Method of randomisation	n/a
Allocation concealment	- B: Unclear
Outcome assessor blinding	- N/a
Timing of outcome assessments after initiation of treatment	- 14 weeks
Length of post-intervention follow-up period	- 0 months
Sample size, total	n=20
Sample size for each group	Intervention group: n=10 Control group: n=10
Availability of sample size for each group at randomisation	- Yes
Withdrawal-/Drop-out rate and reasons	Intervention group: 10% (1/10) Control group: 10% (1/10) All participants: 10% (2/20); reasons: worsening health issues
Adherence	- Exercise logs (duration, frequency), pedometer - No adherence data available
Type of analysis	- Available case analysis
Statistical tests	- Repeated measures analysis of variance - repeated measures mixed effect-models
PARTICIPANTS	
Recruitment	University; National Institutes for Health, Comprehensive Cancer Center, Southeastern United States
Inclusion criteria	- Breast cancer - Hormonal therapy with tamoxifen, anastrozole, letrozole - Postmenopausal - Older than 55 years - Fatigue - Karnofsky Performance Scale > 80 - English speaking
Exclusion criteria	- Neuromuscular deficits - Documented history of neurologic deficits or mental illness within the past year
Age	All participants: 65 (range 56-78 years)
BMI	**n/a**
Breast cancer staging	**n/a**
Menopausal status	All participants: postmenopausal
Type of adjuvant cancer treatment	All participants: hormonal therapy
Physical activity before cancer diagnosis	n/a
Co-morbidity	n/a
INTERVENTIONS	
Type of training	walking
Setting	- Home-based
Health promotion theory	n/a
Delivery of intervention	n/a

Payne 2008 – Study descriptors	
Intensity	- moderate
Duration of sessions	20 minutes
Frequency	4 days per week
Total exercise period	14 weeks
CONTROL	
Type of control	Usual care (standard interactions with nurses, physicians and staff)
Intensity	n/a
Duration of sessions	n/a
Frequency	n/a
Total period	n/a
CO-INTERVENTION	
Type of co-intervention	n/a
OUTCOMES	
Outcome measures concepts	- Fatigue - Depressive Symptoms - Sleep disturbances - Biomarkers (cortisol, serotonin, interleukin-6, bilirubin)
Assessment instruments	- Piper Revised Fatigue Scale (R-PFS) - Center for Epidemiological Studies-Depression Scale (CES-D) - Sleep watch actigraphs - Pittsburgh Sleep Quality Index (PSQI) - Routine laboratory measures - Radioimmunoassay analysis (serotonin, interleukin-6)
Adverse effects	- Assessment of harm: n/a - Reporting of harm: no
Similarity at baseline	- n/a

Payne 2008 – Effect size data			
ES No.	1	2	3
ES type	Post-test	Post-test	Post-test
Construct	Sleep disturbances	Fatigue	Depressive symptoms
Instrument	Pittsburgh Sleep Quality Index	Piper Fatigue Scale	Center for Epidemiol-ogical Studies-Depression Scale
N exercise group	9	9	9
N control group	9	9	9
Mean exercise	11.2	4.65	12.7
Mean control group	9.1	3.51	11.4
SD exercise	4.1	2.63	8.7
SD control group	3.8	1.75	7.9

Schwartz 2007 – Study descriptors	
METHODS	
Type of trial	- RCT (method unclear)
Configuration of trial	- Parallel group
Method of randomisation	n/a; stratification according to menopausal status
Allocation concealment	- A: Adequate
Outcome assessor blinding	- N/a
Timing of outcome assessments after initiation of treatment	- 6 months
Length of post-intervention follow-up period	- 0 months
Sample size, total	n=72
Sample size for each group	Intervention group 1 (aerobic): n=22 Intervention group 2 (resistance): n=21 Control group: n=23
Availability of sample size for each group at randomisation	- Yes
Withdrawal-/Drop-out rate and reasons	Intervention group 1 (aerobic): 8,3% (2/24) Intervention group 2 (resistance): 8,7% (2/23) Control group: 8% (2/25) All participants: 8,3% (6/72); reasons: too busy (n=4), location not convenient (n=2)
Adherence	- Exercise logs (intensity, duration, frequency, type for aerobic exercise; number of repetitions per exercise, resistances of the band, duration of session) in intervention groups, daily activity logs in control group, caloric expenditure measured using Caltrac Aceloremeters - No adherence data available
Type of analysis	- Available case analysis (although ITT claimed in report)
Statistical tests	Repeated measures analysis of variance and covariance (menopausal status)
PARTICIPANTS	
Recruitment	University of Washington Cancer Center, Oregon Health and Science University; women were recruited before beginning adjuvant chemotherapy
Inclusion criteria	Breast cancer stages I-III (histologically confirmed); planning to begin chemotherapy with doxorubicin or methotrexate
Exclusion criteria	- Receiving steroids 6 months prior to study - Paget disease - Hyperparathyroidism - Rheumatoid arthritis - Ankylosing spondylitis, or other metabolic bone disease - History of serious psychiatric illness - Strenuous regular exercisers and women who exercised more than 250 minutes per week
Age	Intervention group 1 (aerobic): 48.32, SD=12.6 Intervention group 2 (resistance): 50.1, SD=8.7 Control group: 46.26, SD=9.8 All participants: 48.17

Schwartz 2007 – Study descriptors	
BMI (Weight)	Intervention group 1 (aerobic): 69.80 kg, SD=13.6 Intervention group 2 (resistance): 77.5 kg, SD=17.3 Control group: 68.40 kg, SD=12.3 All participants: 71.76

Breast cancer staging	- Stage I:
	  - Intervention group 1 (aerobic): 4/22 (18%)
	  - Intervention group 2 (resistance): 6/21 (28%)
	  - Control group: 5/23 (22%)
	  - All participants: 15/66 (22.7%)
	- Stage II:
	  - Intervention group 1 (aerobic): 13/22 (59%)
	  - Intervention group 2 (resistance): 11/21 (52%)
	  - Control group: 14/23 (61%)
	  - All participants: 38/66 (57.6%)
	- Stage III:
	  - Intervention group 1 (aerobic): 5/22 (12%)
	  - Intervention group 2 (resistance): 4/21 (19%)
	  - Control group: 4/23 (17%)
	  - All participants: 13/66 (19.7%)

Menopausal status	For each group and for all participants
	- Pre- menopausal:
	  - Intervention group 1 (aerobic): 11/22 (50%)
	  - Intervention group 2 (resistance): 13/21 (61%)
	  - Control group: 12/23 (52%)
	  - All participants: 36/66 (54.5%)

Type of adjuvant cancer treatment	For each group and for all participants - Chemotherapy: 66/66 (100%)

Physical activity before cancer diagnosis	For each group and for all participants
	- Regular exerciser:
	  - Intervention group 1 (aerobic): 13/22 (59%)
	  - Intervention group 2 (resistance): 11/21 (52%)
	  - Control group: 12/23 (52%)
	  - All participants: 36/66 (54.5%)

Co-morbidity	n/a
INTERVENTIONS	
Type of training	- Intervention group 1: Aerobic (participant preferences); 77% weight bearing activities! - Intervention group 2: Resistance exercise (Thera band), 2 sets of 8 exercises (4 upper and 4 lower body)
Setting	- Home-based
Health promotion theory	n/a
Delivery of intervention	- Women in the aerobic exercise intervention group were instructed to choose an aerobic activity they enjoyed (participants preferences) - Group was instructed to use symptoms (e.g., fatigue, pain breathlessness) to moderate exercise intensity and determine whether to stop exercising - Resistance exercise subjects were given 2 different sets of exercises to alternate the exercise sets within each week - Research associate called exercisers at 2 week intervals for the first month and then monthly thereafter to answer questions about exercise and assess any barriers and the ability to exercise.

Schwartz 2007 – Study descriptors	
Intensity	- Aerobic exercise: symptom-limited, moderate intensity, breathing hard, but able to talk; progressive via increasing intensity vs. duration - Resistance exercise: 8-10 repetitions per exercise, 2 sets
Duration of sessions	Aerobic exercise: 15-30 minutes
Frequency	Aerobic exercise: 4 days per week
Total exercise period	6 months (24 weeks)
CONTROL	
Type of control	Usual care
Intensity	women were instructed to continue usual activities, were not instructed to avoid exercise
Duration of sessions	n/a
Frequency	n/a
Total period	n/a
CO-INTERVENTION	
Type of co-intervention	n/a
OUTCOMES	
Outcome measures concepts	- Bone mass density - Aerobic fitness - Strength
Assessment instruments	- Dual-energy x-ray absorptiometry (lumbar spine, g/cm^2) - 12-minute walk test - 1 repetition Maximum
Adverse effects	- Assessment of harm: n/a - Reporting of harm: yes - Observation of harm: no new onset of lymphedema or acute flares
Similarity at baseline	- Adequate

Schwartz 2007 – Effect size data				
ES No.	1	2	3	
ES type	Post-test	Post-test	Post-test	Post-test
Construct	Cardiorespiratory fitness	Bone mineral density	Strength (leg extension) [kg]	Strength (over-head press) [kg]
Instrument	12-MWT [meter]	Dual x-ray absorptiometry [g/cm^2]	1 RM	1 RM
N aerobic exercise group	22	22	22	22
N resistance exercise gr.	21	21	21	21
N control group	23	23	23	23
Mean aerobic exercise	1228	0.98	78.6	13.7
Mean resistance exercise	1055	0.99	75.3	10.8
Mean control group	944	0.97	70.5	9.5
SD aerobic exercise	322	0.069	30.5	6.4
SD resistance exercise	177	0.120	34.5	5.1
SD control group	241	0.105	28.1	4.1

Segal 2001 – Study descriptors	
METHODS	
Type of trial	RCT
Configuration of trial	Parallel group design
Method of randomisation	Random numbers table
Allocation concealment	A (Study coordinator revealed group assignment after baseline testing)
Outcome assessor blinding	n/a
Timing of outcome assessments after initiation of treatment	26 weeks
Length of post-intervention follow-up period	0 weeks
Sample size, total	123
Sample size for each group	- Intervention group home based: n=40 - Intervention group centre based: n=42 - Control group: n=41
Availability of sample size per group at randomisation	Yes
Withdrawal-/Drop-out rate and reasons	- Intervention group home based: 7/40 (17.5%) - Intervention group centre based: 10/42 (23.1%) - Control group: 7/41 (17.5%) No reasons given
Adherence	- Monitoring of intensity, frequency - Assessment via exercise diaries - Adherence in intervention groups: o Home based: 93/130 sessions (71.5%) o Centre based: 93/130 sessions (71.5%)
Type of analysis	ITT (most recent observed)
Statistical tests	- 1-way ANOVA to compare change scores between groups - Dunnett's t-test where the 2 exercise groups were each compared against the control group
Power calculation	Yes
PARTICIPANTS	
Recruitment	Medical oncologists
Inclusion criteria	- Breast cancer stages I and II - Radiotherapy, hormonal therapy, or chemotherapy
Exclusion criteria	- Dose-intensity chemotherapy regimen - Severe cardiac disease, uncontrolled hypertension
Age Age total	- Intervention group home based: 51.0, SD=8.7 - Intervention group centre based: 51.4, SD=8.7 - Control group: 50.3, SD=8.7 - All participants: 50.9
Weight [kg]	- Intervention group home based: 65.6kg, SD=13.6 - Intervention group centre based: 73.4kg, SD=15.0 - Control group: 71.6kg, SD=17.9
Breast cancer staging	Breast cancer stages I, II
Menopausal status	n/a

Segal 2001 – Study descriptors	
Type of adjuvant cancer treatment	- Chemotherapy o Intervention group home based: 32/40 (80.0%) o Intervention group centre based: 34/42 (81.0%) o Control group: 30/41 (73.2%) - Radiotherapy - Hormonal therapy
Physical activity before cancer diagnosis	- Intervention group home based: 20/40 (50.0 %) - Intervention group centre based: 25/42 (60.0 %) - Control group: 19/41 (47.6 %)
Co-morbidity	n/a
INTERVENTIONS	
Type of training	1. Aerobic exercise: walking, self directed 2. Aerobic exercise: walking, supervised
Setting	1. Home based 2. Centre based
Health promotion theory	None
Delivery of intervention	1. Prescription of an individualised walking programme, exercise specialists showed a series of warm-up and cool-down exercises, contact every 2 weeks; exercise specialist conducted interim fitness evaluation at 13 weeks; contacted participants by telephone every 2 weeks, checked progress and addressed barriers 2. Supervised progressive walking programme; exercise sessions with warm-up and cool-down
Intensity	1. 50-60% VO2max 2. 50-60% VO2max
Duration of sessions	1. 7-10 minutes warm-up, walking, cool down; n/a 2. 7-10 minutes warm-up, walking, cool down (20-30 minutes walking; based on protocol information of 35-45 minutes total session)
Frequency	1. 5 sessions per week 2. 5 sessions per week (3 supervised +2 self directed)
Total exercise period	1. 26 weeks 2. 26 weeks
CONTROL	
Type of control	Usual care (general advice from oncologist about benefits of exercise)
Intensity	n/a
Duration of sessions	n/a
Frequency	n/a
Total period	n/a
CO-INTERVENTION	
Type of co-intervention	Regular contact (all groups)
OUTCOMES	
Outcome measure concepts	- Quality of life (generic and cancer, cancer-site-specific) - Cardiorespiratory fitness - Body composition (weight)
Assessment instruments	- **Primary outcome**: SF-36 physical functioning scale - SF-36 other scales - FACT-G, FACT-B - Modified Canadian Aerobic Fitness test (mCAFT): ml/kg/min - Scale
Adverse effects	No ("no adverse events recorded")
Similarity at baseline	Adequate (but baseline differences in physical functioning)

Segal 2001 – Effect size data			
ES No.	1	2	3
ES type	Post-test	Post-test	Change Score
Construct	Cardiorespiratory fitness	Fatigue	Body composition
Instrument	mCAFT	SF-36 vitality	Weight [kg]
N self-directed exercise	40	40	40
N supervised exercise	42	42	42
N control group	41	41	41
Mean self-directed exercise	26.3	60.8	0.4
Mean supervised exercise	26.2	55.8	-1.4
Mean control group	25.1	61.6	0.6
CI self-directed exercise			-0.7 - 1.6
CI supervised exercise			-3.3 - 0.5
CI control group			-1.3 - 2.5
SD self-directed exercise	5.3	23.5	3.71
SD supervised exercise	5.1	24.0	6.28
SD control group	6.1	17.7	6.21

Winningham 1988 – -Study descriptors	
METHODS	
Type of trial	RCT
Configuration of trial	- Parallel group design - 3 groups (exercise, sham treatment and control)
Method of randomisation	Matching on age and functional capacity
Allocation concealment	B
Outcome assessor blinding	n/a
Timing of outcome assessments after initiation of treatment	10 weeks
Length of post-intervention follow-up period	0 weeks
Sample size, total	42
Sample size for each group	- Intervention group: n=16 - Control group placebo: n=14 - Control group: n=12
Availability of sample size per group at randomisation	Yes
Withdrawal-/Drop-out rate and reasons	0
Adherence	n/a
Type of analysis	ITT
Statistical tests	Repeated measures ANOVA, Duncan's Multiple Range Test (post hoc), Chi^2 to compare nausea response between groups
Power calculation	No
PARTICIPANTS	
Recruitment	- University Medical Centre - Medical clinics - Private practices in a large Midwestern city
Inclusion criteria	- Breast cancer, histological established - Surgery - Chemotherapy (3 treatments <= intervention <=6month), responding to adjuvant treatment - Baseline functional capacity of 0-2 on Zubrod scale - Karnofsky 60-100%
Exclusion criteria	- Uncontrolled cardiac or hypertensive disease - Doxorubicin - Other regular exercise programme
Age	- Intervention group: 46.1, SD=12.4 - Control group placebo: 48.2, SD=11.3 - Control group: 45.3, SD=9.0 - All participants: 46.6
Weight (kg) **Height** **BMI**	- Intervention group: 66.7 kg, SD=8.6 - Control group placebo: 65.6 kg, SD=9.3 - Control group: 64.6 kg, SD=13.5 - Intervention group: 161 cm, SD=7 - Control group placebo: 155 cm, SD=12 - Control group: 163 cm, SD=6 - Intervention group: 25.7 - Control group placebo: 27.3 - Control group: 24.3 - All participants: 25.8

Winningham 1988 – -Study descriptors	
Breast cancer staging	- Intervention group: o Stage II: 81% o Stage III: 6% o Stage IV: 13% - Control group placebo: o Stage II: 79% o Stage III: 7% o Stage IV: 14% - Control group: o Stage II: 92% o Stage III: 0% o Stage IV: 8%
Menopausal status	n/a
Type of adjuvant cancer treatment	Chemotherapy
Physical activity before cancer diagnosis	Other regular exercise programme as exclusion criterion
Co-morbidity	n/a
INTERVENTIONS	
Type of training	Aerobic exercise: cycle ergometer training, interval training
Setting	Laboratory based
Health promotion theory	None
Delivery of intervention	Winningham Aerobic Interval Training (WAIT) protocol, tight supervision
Intensity	60-85% HRmax
Duration of sessions	20-30 minutes per session
Frequency	3 sessions per week
Total exercise period	10 weeks
CONTROL	
Type of control	- Control group placebo: conversational interaction; mild stretching and flexibility exercise. - Control group: Normal activities
Intensity	- Control group placebo: mild - Control group: n/a
Duration of sessions	- Control group placebo: n/a - Control group: n/a
Frequency	- Control group placebo:1 session per week - Control group: n/a
Total period	- Control group placebo: 10 weeks - Control group: n/a
CO-INTERVENTION	
Type of co-intervention	None (esp. no anti-emetic medication)
OUTCOMES	
Outcome measure concepts	- Nausea - Somatisation
Assessment instruments	Derogatis Symptom Check List-90 Revised (SCL-90-R) somatisation (SOM) scale
Adverse effects	n/a (no worsening of nausea in experimental group; according to letter no adverse effects at all)
Similarity at baseline	Adequate

Winningham 1988 – Effect size data	
ES No.	1
ES type	Post-test
Construct	Physiological side-effects (nausea)
Instrument	Nausea relief: Derogatis Symptom Check List-90 Revised (SCL-90-R)
N intervention group	16
N control group	26
N intervention group with a successful outcome	8
N control group with successful outcome	3

9.8.2 Intervention quality

		Aerobic training*				Resistance training†			
Study-ID	Score	1	2	3	4	1	2	3	4
Battaglini 2007	4			✓	✓		✓	✓	✓
Campbell 2005	3	✓	✓		✓				
Courneya 2007	4	✓	✓	✓	✓	✓	✓	✓	✓
Crowley 2003	4		✓	✓	✓	✓	✓	✓	✓
Drouin 2002	4	✓	✓	✓	✓				
Kim 2006	4	✓	✓	✓	✓				
MacVicar 1986	4	✓	✓	✓	✓				
MacVicar 1989	4	✓	✓	✓	✓				
Mock 1997	4	✓	✓	✓	✓				
Mock 2005	4	✓	✓	✓	✓				
Mutrie 2007	3	✓	✓		✓				
Payne 2008	3		✓	✓	✓				
Schwartz 2007	3		✓	✓	✓	✓	✓		✓
Segal 2001	4	✓	✓	✓	✓				
Winningham 1988	4	✓	✓	✓	✓				

* Aerobic training: 1=intensity, 2=duration, 3=frequency. 4=program duration

† Resistance training: 1=repetitions (intensity), 2=sets (duration), 3=frequency. 4=program duration

9.9 Appendix 9 – Characteristics of studies adressing harm

9.9.1 Reference list of included studies of harm

Study-ID	Reference
Schmitz 2005	Schmitz KH, Ahmed RL, Hannan PJ, Yee D. Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. Cancer Epidemiol Biomarkers Prev 14(7):1672-80; 2005. Ahmed RL, Thomas W, Yee D, Schmitz KH. Randomized controlled trial of weight training and lymphedema in breast cancer survivors. J Clin Oncol 24: 2765-72; 2006.
Basen-Engquist 2006	Basen-Engquist K, Taylor CL, Rosenblum C, Smith MA, Shinn EH, Greisinger A, Gregg X, Massey P, Valero V, Rivera E. Randomized pilot test of a lifestyle physical activity intervention for breast cancer survivors. Patient Educ Couns 13: 13; 2006.
McKenzie 2003	McKenzie DC, Kalda AL. Effect of upper extremity exercise on secondary lymphedema in breast cancer patients: a pilot study. J Clin Oncol 21: 463-6; 2003.

9.9.2 Reference list of excluded studies of harm

Study-ID	Reference
Cheema 2006	Cheema BS, Gaul CA. Full-body exercise training improves fitness and quality of life in survivors of breast cancer. J Strength Cond Res 20: 14-21; 2006.
Harris 2000	Harris SR, Niesen-Vertommen SL. Challenging the myth of exercise-induced lymphedema following breast cancer: a series of case reports. J Surg Oncol 74: 95-8; 2000.
Johansson 2005	Johansson K, Tibe K, Weibull A, Newton RC. Low intensity resistance exercise for breast cancer patients with arm lymphedema with or without compression sleeve. Lymphology 38: 167-80; 2005.
Turner 2004	Turner J, Hayes S, Reul-Hirche H. Improving the physical status and quality of life of women treated for breast cancer: a pilot study of a structured exercise intervention. J Surg Oncol 86: 141-6; 2004.

9.9.3 Quality of studies of harm

Basen-Engquist 2006	
Criterion	**Score**
Nonbiased selection	1
Adequate description of population	1
Low loss to follow-up, and patients lost to follow-up analysed for adverse events	0
Adverse events prespecified and defined	1
Ascertainment technique adequately described	1
Nonbiased and accurate ascertainment of adverse event	1
Adequate statistical analysis of potential confounders	1
Adequate duration of follow-up	1
Total quality score = sum of scores (0 - 8)	**7: Good**

McKenzie 2003	
Criterion	**Score**
Nonbiased selection	1
Adequate description of population	1
Low loss to follow-up, and patients lost to follow-up analysed for adverse events	0 (n/a)
Adverse events prespecified and defined	1
Ascertainment technique adequately described	1
Nonbiased and accurate ascertainment of adverse event	0 (n/a)
Adequate statistical analysis of potential confounders	0
Adequate duration of follow-up	1
Total quality score = sum of scores (0 - 8)	**5: Fair**

Schmitz 2005; Ahmed 2006	
Criterion	**Score**
Nonbiased selection	1
Adequate description of population	1
Low loss to follow-up, and patients lost to follow-up analysed for adverse events	0
Adverse events prespecified and defined	1
Ascertainment technique adequately described	1
Nonbiased and accurate ascertainment of adverse event	1
Adequate statistical analysis of potential confounders	1
Adequate duration of follow-up	1
Total quality score = sum of scores (0 - 8)	**7: Good**

9.9.4 Study descriptors and effect size data of studies of harm

Basen-Engquist 2006 – Study descriptors and effect size data	
Type of adverse events	
3 lymphedema	3
Inclusion criteria	
1 post-treatment	1
Type of exercise	n/a
Type of trial	
1 randomised controlled trial	1
Sample Size	
Total sample size	60
Intervention group sample size	35
Control Group sample size	25
Significance Tests	No. of increases in arm circumference
Mann-Whitney U	U=222.5, p=0.124 right arm; U=252.5, p=0.411 left arm.

McKenzie 2003 – Study descriptors and effect size data	
Type of adverse events	
3 lymphedema	3
Inclusion criteria	
1 post-treatment	1
Type of exercise	
2 resistance training	2
3 lymphedema	3
Type of trial	
1 randomised controlled trial	1
Sample Size	
Total sample size	14
Intervention group sample size	7
Control Group sample size	7
Significance Tests	"no significant differences in the percentage change of measured arm volume" between groups
ANOVA	

Schmitz 2005; Ahmed 2006 – Study descriptors and effect size data	
Type of adverse events	
1 injury	1
Inclusion criteria	
1 post-treatment	1
Type of exercise	
2 resistance training	2
Type of trial	
1 randomised controlled trial	1
Sample Size	
Total sample size	85
Intervention group sample size	42 (immediate exercise intervention)
Control Group sample size	43 (delayed intervention, by 6 month)
Proportions or Frequencies	
- % of intervention group with an adverse event	- 10.5% per 6 month, 22.5% over 1 year
- % of control group with an adverse event	- 20% over first 6 month

Schmitz 2005; Ahmed 2006 – Study descriptors and effect size data	
Type of adverse events	
3 lymphedema	3
Inclusion criteria	
1 post-treatment	1
Type of exercise	
2 resistance training	2
Type of trial	
1 randomised controlled trial	1
Sample Size	
Total sample size	45
Intervention group sample size	23
Control Group sample size	22
Proportions or Frequencies	
- n of intervention group with an adverse event	- 2 (incidence of lymphedema)*
- n of control group with an adverse event	- 1 (incidence of lymphedema)
- n of intervention group with an adverse event	- 0 (self reported symptoms)
- n of control group with an adverse event	- 3 (self reported symptoms)
Significance Tests	
Chi squared	p=0.40 (incidence) p=0.22 (symptoms

* "incidence" refers to clinician diagnosis of lymphedema

9.10 Appendix 10 – Outcome assessment instruments

Name of tool	Author/Year	Domains or factors	Items	Scaling	Scoring
Functional assessment of cancer therapy (FACT-G)	Cella 1993	1. Physical well-being (PWB) 2. Social well-being (SWB) 3. Relationship with doctor (RWD) 4. Emotional well-being (EWB) 5. Functional well-being (FWB). FACT-G = sum of PWB, SWB, RWD, EWB, FWB scores	7 7 2 6 7 29	5-point Likert rating scale (0-4)	0-112 Subscales and total scores are the sums of items. High scores indicate higher quality of life.
Functional assessment of cancer therapy - Breast (FACT-B)	Brady 1997	Breast cancer subscale (BCS). FACT-B = sum of PWB, SWB, RWD, EWB, FWB, BCS scores	9 38	5-point Likert rating scale (0-4)	0-152 High scores indicate higher quality of life.
Functional assessment of cancer therapy - Fatigue (FACT-F)	Cella 1998	Fatigue subscale (FS). FACT-F = sum of PWB, SWB, RWD, EWB, FWB, and fatigue subscale	13 41	5-point Likert rating scale (0-4)	0-164 High scores indicate higher quality of life.
Functional assessment of cancer therapy - endocrine symptoms (FACT-ES)	Fallowfield 1999	Endocrine subscale (ES). FACT-ES = sum of PWB, SWB, RWD, EWB, FWB, BCS, ES	18 56	5-point Likert rating scale (0-4)	0-224 High scores indicate higher quality of life.
Functional assessment of cancer therapy-Anemia scale (FACT-An)	Cella 1997	Anemia subscale (An). FACT-An= sum 13 items FS and 7 items An FACT-An= sum of FACT-G and An	 20 48	5-point Likert rating scale (0-4)	0-192 0-52 FACT Fatigue subscale scores range from 0 to 52, where higher scores represent less fatigue
Revised Piper Fatigue Scale (R-PFS)	Piper 1998	6. Behavioural/severity 7. Affective meaning 8. Sensory 9. Cognitive/mood. Total fatigue score	6 5 5 6 22	11-point numerical self-report, five open-ended	The 22-item are added together and divided by 22 "0" to "10" scale Severity Codes: 0 none 1-3 mild 4-6 moderate
Piper Fatigue Scale (PFS)	Piper 1989		40		7-10 severe

Name of tool	Author/Year	Domains or factors	Items	Scaling	Scoring
Beck Depression Inventory (BDI)	Beck 1961	Depression	21	4-point Likert rating scale (0-3)	0-63 Severity Codes: 11-17 moderate 18 clinically relevant
Center for Epidemiological Studies–Depression Scale (CES-D)	Radloff 1977	Depression	20	4-point Likert rating scale (1-4)	0-60 Higher scores indicate more impair-ment
Pittsburgh Sleep Quality Index (PSQI)	Buysse 1989	Sleep disturbances 1. Subjective sleep quality 2. Sleep latency 3. Sleep duration 4. Habitual sleep efficiency 5. Sleep disturbances 6. Use of sleep medications 7. Daytime dysfunction	19 5	4-point Likert rating scale (0-3) 0 no difficulty; 3 severe difficulty Additional items rated by a bed partner	0–21 Component scores are summed to produce a global score; Higher scores indicate higher sleep disturbances; A PSQI global score >5 is considered to be suggestive of significant sleep disturbance.
Spielberger State Anxiety Inventory (STAI)	Spielberger 1983	State anxiety	20	4-point Likert rating scale (1-4)	20-80
Rosenberg Self-Esteem Scale	Rosenberg 1965	Self-esteem	10	4-point Likert rating scale (0-3)	0-30 The higher the score, the higher the self esteem
Profile of mood states (POMS)	McNair, Lorr, and Dropple-man 1992	10. Tension-anxiety 11. Depression-dejection 12. Anger-hostility 13. Vigour-activity 14. Fatigue-inertia 15. Confusion-bewilderment.	65	Respondents rate 65 adjectives on a 5-point intensity scale, in terms of how they have been feeling in the past week (0=not at all and 4=extremely).	-32-200 Subscales and total scores are the sums of items. Total mood disturbance (TMD): sum of the scores on the six subscales, with vigour-activity negatively weighted. Except for vigour-activity, the higher the score, the greater the mood dis-turbance/more distress.
Positive and Negative Affect Schedule (PANAS)	Watson, Clark, and Tellegen 1988	Two 10-item mood scales 1. Positive affects (PA) 2. Negative affects (NA)	 10 10	5-point Likert rating scale (1-5) 1 very slightly/ not at all 5 very much	 PA: 10-50 NA: 10-50

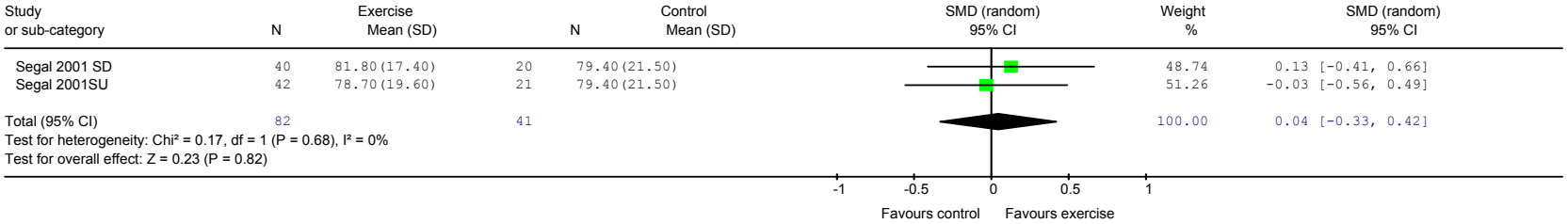
9.11 Appendix 11 – Effect size calculation: inputs into meta-analyses

Outcome	Study_ID	Instrument
Body composition	- Battaglini 2007	- % BF
	- Drouin 2002	- BMI
	- Courneya 2007 AET	- % BF
	- Courneya 2007 RET	- % BF
	- Mutrie 2007	- BMI
Fatigue	- Battaglini 2007	- PFS
	- Campbell 2005	- PFS
	- Courneya 2007 AET	- FACT-An (reversed)
	- Courneya 2007 RET	- FACT-An (reversed)
	- Drouin 2002	- R-PFS
	- Mock 1997	- VAS fatigue
	- Mock 2005	- PFS
	- Mutrie 2007	- FACT-F (reversed)
	- Payne 2008	- R-PFS
	- Segal 2001 SD	- SF-36 vitality (reversed)
	- Segal 2001 SU	- SF-36 vitality (reversed)
Strength	- Battaglini 2007	- 1-RM (4 exercises, kg)
	- Drouin 2002	- 1-RM (grip, kg)
	- Courney 2007 AET	- 1-RM (chest, kg)
	- Courneya 2007 RET	- 1-RM (chest, kg)
	- Schwartz 2007 AET	- 1-RM (overhead press; kg)
	- Schwartz 2007 RET	
Aerobic fitness	- Campbell 2005	- 12 MWT (m)
	- Courneya 2007 AET	- VO_2 (ml/kg/min)
	- Courneya 2007 RET	- VO_2 (ml/kg/min)
	- Drouin 2002	- VO_2 (ml/kg/min)
	- Kim 2006	- VO_2 (ml/min)
	- Mock 1997	- 12 MWT (feet)
	- Mutrie 2007	- 12 MWT (m)
	- Schwartz 2007 AET	- 12 MWT (m)
	- Schwartz 2007 RET	- 12 MWT (m)
	- Segal 2001 SD	- VO_2 (ml/kg/min)
	- Segal 2001 SU	- VO_2 (ml/kg/min)
Depression	- Courneya 2007 AET	- CES-D
	- Courneya 2007 RET	- CES-D
	- Payne 2008	- CES-D
	- Mock 1997	- SAS depression
	- Mutrie 2007	- BDI
Cancer-site-specific QoL	- Campbell 2005	- FACT-B
	- Courneya 2007 AET	- FACT-An
	- Courneya 2007 RET	- FACT-An
	- Mutrie 2007	- FACT-B

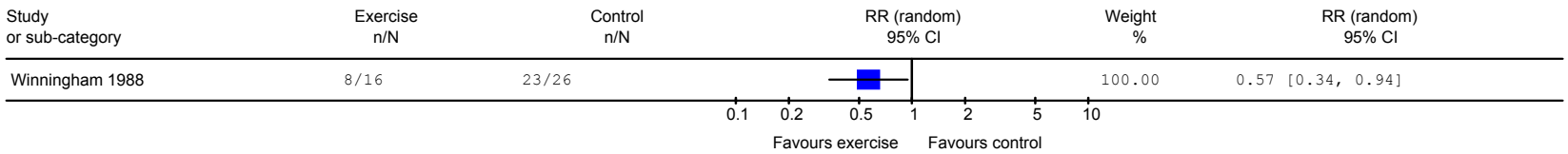
9.12 Appendix 12 – Forest plots

9.12.1 Immediate post-intervention outcomes

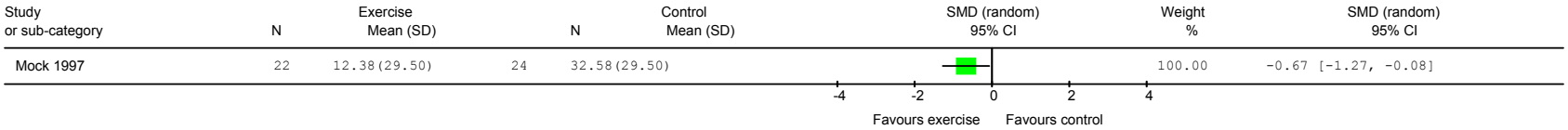
Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 01 Exercise versus control
Outcome: 15 Physical functioning



Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 01 Exercise versus control
Outcome: 20 Nausea

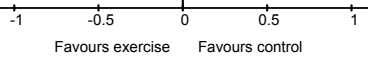


Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 01 Exercise versus control
Outcome: 14 Sleep disturbances



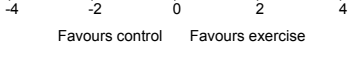
Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 01 Exercise versus control
Outcome: 09 Endocrine symptoms

Study or sub-category	N	Exercise Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Mutrie 2007	82	-41.60(9.10)	92	-40.30(9.70)		100.00	-0.14 [-0.44, 0.16]



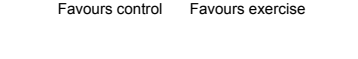
Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 01 Exercise versus control
Outcome: 10 Natural killer cells

Study or sub-category	N	Exercise Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Drouin 2002	13	8.50(9.20)	8	6.60(4.20)		100.00	0.24 [-0.65, 1.12]



Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 01 Exercise versus control
Outcome: 11 T-cells

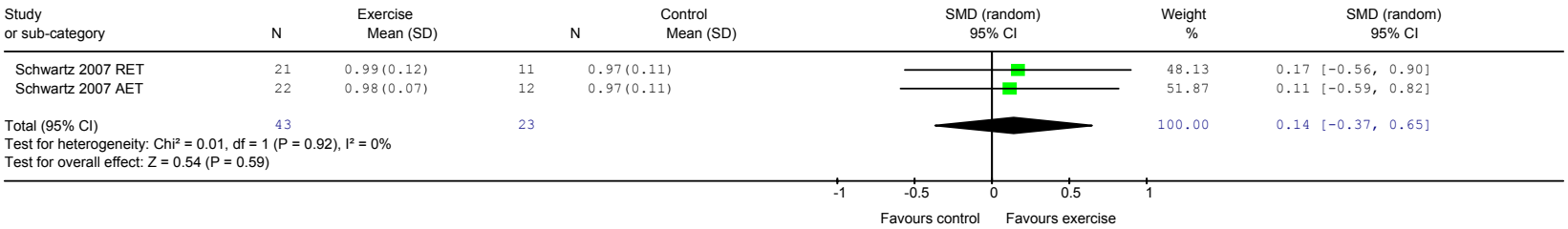
Study or sub-category	N	Exercise Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Drouin 2002	13	2.50(1.10)	8	1.80(1.00)		100.00	0.63 [-0.27, 1.54]



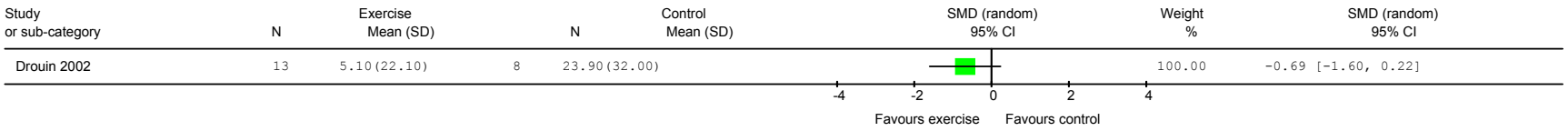
Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 01 Exercise versus control
Outcome: 12 Oxidative stress

Study or sub-category	N	Exercise Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Drouin 2002	10	244.00(132.60)	5	316.40(118.30)		100.00	-0.53 [-1.63, 0.57]

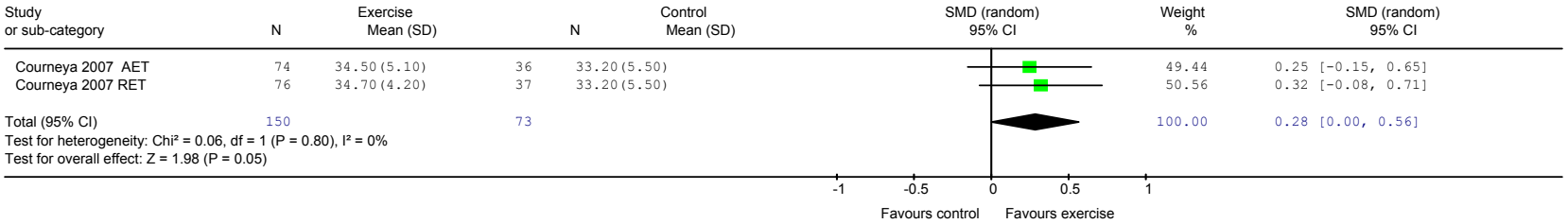
Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 01 Exercise versus control
Outcome: 21 Bone mineral density



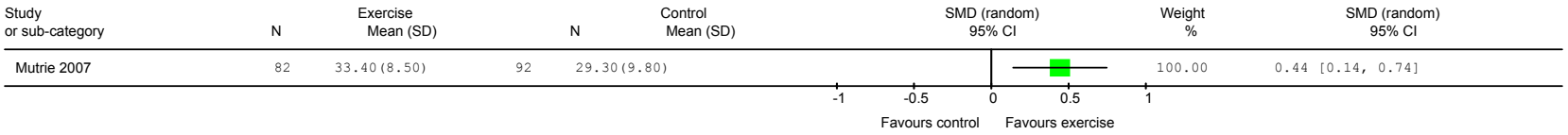
Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 01 Exercise versus control
Outcome: 08 Mood disturbance



Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 01 Exercise versus control
Outcome: 16 Self esteem

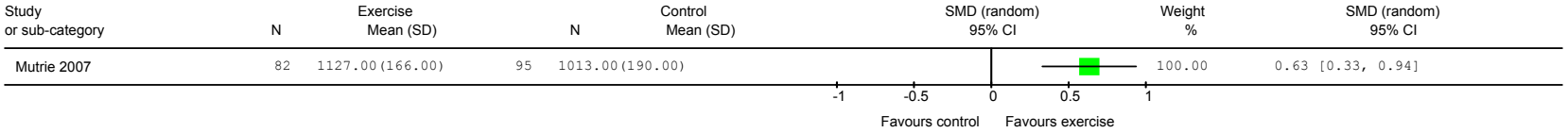


Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 01 Exercise versus control
Outcome: 18 Positive affects

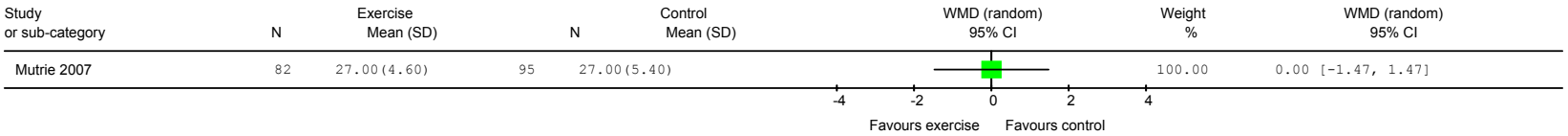


9.12.2 Long-term outcomes

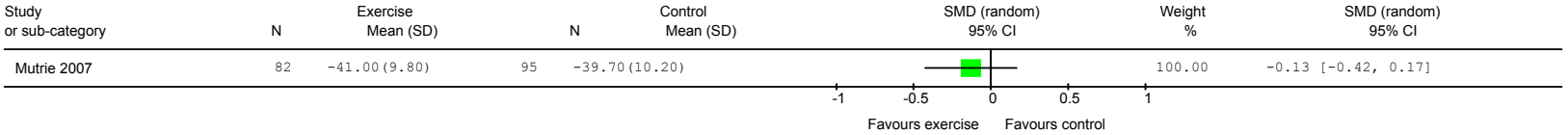
Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 02 Long-term effects
Outcome: 04 Cardiorespiratory fitness



Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 02 Long-term effects
Outcome: 05 BMI



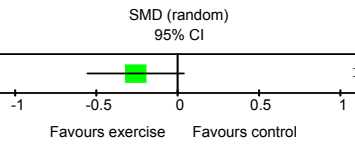
Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 02 Long-term effects
Outcome: 06 Endocrine symptoms



Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 02 Long-term effects
Outcome: 07 Positive affects

Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 02 Long-term effects
Outcome: 08 Negative affects

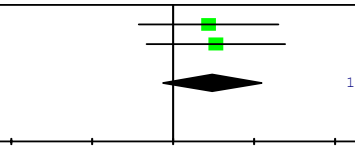
Study or sub-category	Exercise N	Exercise Mean (SD)	Control N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Mutrie 2007	82	15.70(6.10)	95	17.40(6.90)		100.00	-0.26 [-0.56, 0.04]



Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 02 Long-term effects
Outcome: 10 Self esteem

Study or sub-category	Exercise N	Exercise Mean (SD)	Control N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Courneya 2007 AET	68	35.00(4.70)	30	33.90(5.60)		49.52	0.22 [-0.21, 0.65]
Courneya 2007 RET	73	35.20(4.60)	30	33.90(5.60)		50.48	0.26 [-0.16, 0.69]
Total (95% CI)	141		60			100.00	0.24 [-0.06, 0.54]

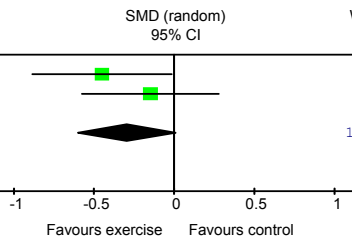
Test for heterogeneity: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%
Test for overall effect: Z = 1.56 (P = 0.12)



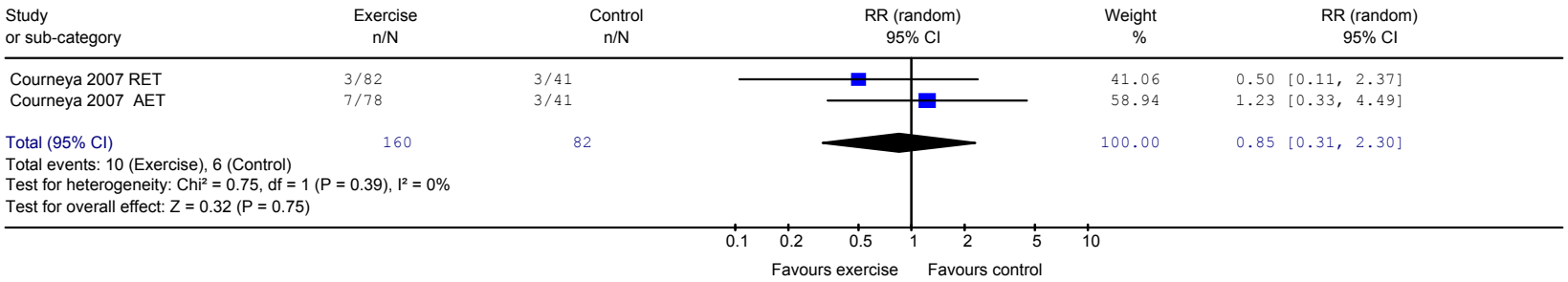
Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 02 Long-term effects
Outcome: 12 Anxiety

Study or sub-category	Exercise N	Exercise Mean (SD)	Control N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Courneya 2007 AET	68	32.20(11.20)	30	37.40(12.00)		48.97	-0.45 [-0.89, -0.02]
Courneya 2007 RET	73	35.50(13.00)	30	37.40(12.00)		51.03	-0.15 [-0.57, 0.28]
Total (95% CI)	141		60			100.00	-0.30 [-0.60, 0.01]

Test for heterogeneity: Chi² = 0.95, df = 1 (P = 0.33), I² = 0%
Test for overall effect: Z = 1.91 (P = 0.06)



Review: Exercise for women receiving adjuvant therapy for breast cancer
Comparison: 02 Long-term effects
Outcome: 09 Lymphedema incidence



Eidesstattliche Erklärung

Ich versichere hiermit, dass ich diese Arbeit selbst angefertigt habe und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt sowie die wörtlich oder inhaltlich übernommenen Stellen als solche kenntlich gemacht habe.

Ich habe keine Promotionsversuche an anderen Universitäten unternommen.

.....

Datum, Unterschrift