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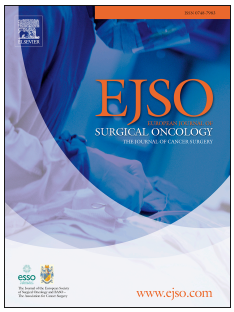

Exercise intervention in people with cancer undergoing adjuvant cancer treatment following surgery: A systematic review

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Exercise intervention in people with cancer undergoing adjuvant cancer treatment following surgery: A systematic review

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ABSTRACT

Background: Remaining physically active during and after cancer treatment is known to improve associated adverse effects, improve overall survival and reduce the probability of relapse. This systematic review addresses the question: is an exercise-training programme beneficial in people with cancer undergoing adjuvant cancer treatment following surgery.

Methods: A systematic database search of Embase, Ovid, Medline without Revisions, SPORTDiscus, Web of Science, Cochrane Library and clinical trials.gov for any randomised controlled trials (RCT) or non-RCT addressing the effect of an exercise training programme in those having adjuvant cancer treatment following surgery was conducted.

Results: The database search yielded 6,489 candidate abstracts of which 94 references included the required terms. A total of 17 articles were included in this review. Exercise training is safe and feasible in the adjuvant setting and furthermore may improve measures of physical fitness and health related quality of life (HRQoL).

Conclusion: This is the first systematic review on exercise training interventions in people with cancer undergoing adjuvant cancer treatment following surgery. Due to the lack of adequately powered RCTs in this area, it remains unclear whether exercise training in this context improves clinical outcomes other physical fitness and HRQoL. It remains unclear what is the optimal timing of initiation of an exercise programme and what are the best combinations of elements within an exercise training programme to optimise training efficacy. Furthermore, it is unclear

if initiating such exercise programmes at cancer diagnosis may have a long-lasting effect on physically activity throughout the subsequent life course.

Keywords: Cancer, Surgery, Adjuvant cancer treatment, Exercise Intervention

BACKGROUND

People with cancer are often faced with the "dual-hit" of surgery and an additional cancer treatment, such as adjuvant chemo- or chemoradio-therapy. Chemo- or chemoradio-therapy in upper and lower gastrointestinal cancer in the neoadjuvant setting has been associated with a decrease in physical fitness (1, 2). Furthermore, this decrease in physical fitness, as a result of such cancer treatments, was found to be related to mortality and morbidity, respectively (1, 2). The reduction in physical fitness appears to be related to the type of treatment they undergo, higher in those receiving surgery and radiotherapy in combination with chemotherapy compared to those who receive radiotherapy alone or surgery(3). Major surgery is associated with significant risk of morbidity and mortality, as recently highlighted in the European Surgical Outcome Study(4). Morbidity has a great impact on the recovery process post-operatively and is associated with long-term health implications including reduced survival(5, 6). Prolonged post-operative morbidity has been associated with an increased risk of death for up to 3 years after surgery(6), however mechanisms for this phenomenon currently remains unanswered. Moreover, the decrease in physical fitness as a result of cancer treatment may have a lasting effect. In a series of cancer studies, cardiorespiratory fitness was ~30% below that of age-matched sedentary healthy women up to 3 years following completion of adjuvant cancer treatment [11, 12, 16].

Higher aerobic capacity has been associated with longer cancer-specific survival and lower cancer related mortality (7). Remaining physically active during and after cancer treatment is known to improve associated adverse effects, as well as improve overall survival and reduce the probability of recurrence (8). However, physical activity levels tend to decrease at diagnosis in people with cancer (9). Furthermore, a

significant decrease in physical activity has been associated to a higher level of fatigue during breast cancer treatment (10). Increasing physical activity levels by 50% following colorectal cancer diagnosis has been shown to decrease both the risk of colorectal cancer-specific and all-cause mortality (11). Additionally, a higher level of physical fitness has been related to longer cancer-specific survival and lower cancer-related mortality (7). It has been suggested that women with breast cancer who exercise at moderate intensity, 30 minutes or more per day on 5 days or more per week, have a lower risk of death (12).

The area of exercise-oncology has attracted great interest over recent years with a number of high-quality clinical trials and systematic reviews conducted in this area. In 2011, Granger and colleagues reported that it was safe to exercise people with non-small cell lung cancer (NSCLC) during and following cancer treatment (13). In 2014, Crandall and colleagues (14) undertook a systematic review specifically investigating exercise interventions in people with NSCLC but in those requiring surgery which showed there was a lack of trials which influenced surgical outcome (14). We aimed to explore all available literature focussing on exercise interventions in people with cancer undergoing adjuvant cancer treatment following surgery.

OBJECTIVES

The objective of this review is to evaluate methods, safety and feasibility, outcomes (including physical fitness, health related quality of life (HRQoL), fatigue, post-operative clinical outcomes), in studies that have tested exercise interventions in people with cancer undergoing both surgery and adjuvant cancer treatment (excluding exercise interventions initiated following adjuvant cancer treatment).

RESEARCH QUESTIONS

1. Is exercise training in people with cancer undergoing adjuvant cancer treatment following surgery safe and feasible?
2. Does exercise training in people with cancer improve some measure of physical fitness (including physical capacity and physical activity), HRQoL and other clinically relevant outcomes such as fatigue and post-operative outcome and what aspects have been reported to be effective?
3. What is the optimal timing of initiation of an exercise intervention, optimal structure and composition of an exercise training programme, optimal approaches to promote adherence and behaviour towards exercise, and whether such an intervention has a long-term effect on physical activity levels?

METHODS

Inclusion Criteria

Type of studies

We considered randomised and non-randomised controlled trials (RCT) investigating exercise training in people with cancer undergoing adjuvant cancer treatment following surgery.

Type of participants

We included studies that recruited human adults (>18 years) with cancer undergoing an exercise intervention,cancer surgery and adjuvant cancer treatment.

Type of exercise intervention

The criterion for study inclusion were evaluation and reporting of the effect of an exercise intervention during adjuvant cancer treatment (defined as cancer surgery followed by adjuvant chemo- or chemoradio-therapy) on safety and feasibility or, a measure of physical fitness (including physical capacity and physical activity) or HRQoL. Other clinical outcomes such as fatigue, post-operative morbidity and mortality, post-cancer treatment morbidity and mortality were also included. The intervention could take place in any setting and be delivered to a group or an individual participant. This also included interventions done alone or in combination: 1) aerobic training (defined as exercise that involves large muscle groups performing continuous or intermittent activity over an extended period of time) (15); 2) prescribed resistance training (defined as exercise that involves performing sets of repeated movements against a resistance during which neuromuscular fatigue occurs within 6-12 repetitions (16)); 3) pelvic floor exercise.

Type of outcome measured

The outcomes of interest assessing the effects of an exercise intervention in the adjuvant setting after cancer surgery were:

1. Safety and feasibility
2. Measure of physical fitness (including physical function, physical capacity and physical activity)
3. HRQoL
4. Clinical outcomes (post-operative morbidity and mortality, post-cancer treatment morbidity and mortality)
5. Other clinically relevant outcomes such as fatigue, and whether such an intervention has a long-term effect on physical activity levels.

The outcomes of interest assessing the elements and composition of an exercise intervention in the adjuvant setting after cancer surgery were:

6. Optimal timing of initiation of exercise intervention
7. Optimal structure and composition of an exercise training programme
8. Optimal approaches to promote adherence and behaviour towards exercise

Search methods for identification of studies

Electronic searches

We performed a comprehensive, systematic search on 23 May 2013 and three further updated searches on 1 October 2014, 1 December 2014 and 1 April 2015. Relevant keywords were categorised under five distinct headings: (i) cancer, (ii) cancer treatment, (iii) exercise, (iv) surgery and (v) outcome. (See appendix 1 for illustration of all search terms and strategy). First, each category was searched separately in the database. A combined search of all the categories was completed and duplicate results were removed. We used the following databases to obtain relevant studies for this review;

- Embase
- Ovid Medline without Revisions
- SPORTDiscus
- Web of Science
- Cochrane Library database
- clinical trials.gov

Searching other resources

- We checked the reference lists of all articles obtained for additional studies.
- A manual title search of references from the previous review articles on exercise and cancer was also conducted.
- We attempted to communicate with the study authors to secure information not presented in the studies.

Data collection and analysis

We conducted a systematic search for all clinical trials that involved people with cancer undergoing any form of adjuvant cancer treatment following surgical intervention who exercise-trained in this setting. Data was extracted by one investigator in accordance with predefined criteria. We retrieved all studies in which the abstract made reference to an exercise intervention in people with cancer undergoing both surgery and adjuvant cancer treatment. Abstracts were screened and reviewed against predefined inclusion and exclusion criteria by two independent assessors (LL and MW), and scored using the Downs and Black quality assessment tool (17). Abstracts that met the inclusion criteria were independently assessed by two reviewers (LL and MW) for descriptive characteristics such as;

- Participant characteristics
- Study design
- Type of cancer and cancer treatment (surgery and adjuvant cancer treatment)
- Type and length of exercise intervention
- An outcome measure

In addition, descriptive data were extracted about the each exercise interventions such as;

- Frequency

- Intensity
- Time
- Type
- Supervision
- Location
- Adherence

Assessment of methodological quality

Two reviewers (LL and MW) independently scored the methodological quality of each study according to the Downs and Black quality appraisal checklist (17). This checklist consists of 27 questions to evaluate internal validity and external validity of both randomised and non-randomised studies. Each question was scored out of 1, except question 5 that was scored out of 2 and question 27 that was scored out of 5, giving a total score of 33. High scores reflect high-quality studies. All discrepancies were resolved by discussion between all authors (see appendix 2)

Meta-analysis

A decision to conduct a meta-analysis was based on the following pre-defined criteria;

- To increase power; detecting a real effect as statistically significant if it exists. However, many individual studies are too small to detect small effects, but when several are combined there is a higher chance of detecting an effect.
- To improve precision; the estimation of an intervention effect can be improved when it is based on more information.
- To answer questions not posed by the individual studies.

- To settle controversies arising from apparently conflicting studies or to generate new hypotheses.

A decision not to conduct a meta-analysis was based on the following pre-defined criteria;

- If studies were clinically diverse
- If there were a mix of comparisons of different treatments with different comparators.
- Decisions concerning what should and should not be combined are inevitably subjective, and are not amenable to statistical solutions but require discussion and clinical judgement. In some cases consensus may be hard to reach.
- If bias is present in each (or some) of the individual studies.

RESULTS

Description of studies

The database search strategy that included exercise interventions in people with cancer undergoing both cancer surgery and adjuvant treatment is shown in appendix 3. This search yielded 6489 candidate abstracts. After review of the candidate abstracts by two independent reviewers (LL and MW), 94 references included the required terms, of which 72 references were excluded as they did not meet all inclusion criteria. 22 references were extracted for full text review, of which 7 references were included. A manual search through all the references from full text papers identified for inclusion resulted in an additional 17 full text papers extracted for review of which, 5 references were eligible for inclusion. 5 additional references were identified for inclusion following the most recent updated searches. After full

text screening and application of all inclusion criteria, 17 articles were eligible for inclusion in this review. Meta-analyses were not performed due to the diverse clinical and statistical heterogeneity of the included studies.

Description of study aims and outcome measures

Summary of study aims and outcome measures is illustrated in table 1.

Description of study characteristics and exercise intervention outcomes

Summary of study characteristics and exercise intervention outcomes is illustrated in table 2.

Physical Fitness Outcomes

A measure of physical fitness was used as a primary outcome in only 4 studies in people with breast cancer (3, 18-20). A measure of physical fitness was used as a secondary outcome in the majority of the studies: physical functioning (21) (22, 23); aerobic capacity (24)); muscular strength (3, 25-28) (19, 24); passive range of movement shoulder rotation (29); cardiopulmonary fitness endpoints (peak workload, ventilatory threshold, oxygen pulse (30)), flexibility (19), lean body mass and percent body fat/body weight (26, 27).

Only one study reported improvements in oxygen uptake at peak exercise ($\dot{V}o_2peak$), as a primary endpoint, albeit not statistically significant (30). Moderate intensity aerobic training during adjuvant radiotherapy was suggested to preserve or maintain exercise tolerance, although not statistically significant, as measured by 6-minute walk distance test (6MWD). Two studies reported a significant increase in $\dot{V}o_2peak$ as their secondary outcome (19, 25). Courneya and colleagues (26) reported a significant improvement in $\dot{V}o_2peak$ in the aerobic exercise training group but not in

the resistance exercise training group or the usual care group. One home-based exercise programme illustrated a significant improvement in physical fitness as measured by 12-MWD(23). The pectoral stretching programme reported no differences at the 7 month follow-up (29). Other studies illustrated improvements in a measure of physical fitness, although not statistically significant, following the exercise programme (20, 24) (29).

One study in people with breast cancer reported a slight worsening in Karnofsky performance status in both groups following chemotherapy (not significantly significant) (3). Furthermore, there was a significant decrease in physical functioning in women with high fatigue levels during breast cancer therapy (10). Physical functioning was found to improve following initiation of a home-based rehabilitation exercise programme 66-hours post-hospital discharge by 6 weeks, assessed using Medical Outcomes Short Form-36 (SF-36) was illustrated (31). Following the exercise intervention, three studies reported increased physical activity levels, although insignificant (21, 22, 25).

HRQoL Outcome

HRQoL, as the primary outcome, was measured by three included studies (20, 26, 27). HRQoL was used in almost all studies as a secondary outcome measure. Exercise training significantly improved different domains of HRQoL following circuit classes over a 12-week period (22), a 16-week period (19) and aerobic/resistance exercise program over a 17-week period (27). Following the START trial significant improvements in some HRQoL domains were reported, but no significant improvement in cancer-specific HRQoL (fatigue, depression or anxiety) (27). Following the multi-modal high intensity exercise programme, there

was a mixture of HRQoL responses reported (25). There was a decrease in HRQol between pre- and post-surgery and an increase following the 6-week exercise programme with the best results obtained at week-3 in the study in people with NSCLC. However, 5 out of the 7 participants in this trial initiated chemotherapy at week 5 which may account for the slight decrease from week 3 to week 6 (31). There was no statistically significant differences in HRQoL reported following the pectoral training programme, self-directed versus supervised walking intervention or progressive resistance training programme (20, 29, 32).

Fatigue symptoms and other clinical outcomes

Fatigue was used as a primary outcome in five included studies (10, 21, 24, 31) (32). Adamsen and colleagues (25) reported that 65% of study population had a fatigue level greater than that of general population (mean >20) at baseline and that 29% reported severe fatigue (mean >60). Furthermore, they also report that 18% of the participants had a sedentary lifestyle at baseline and suggested that reported fatigue might be primarily due to cancer or the chemotherapy. Schmidt and colleagues (32) illustrated a change in fatigue levels from baseline to post intervention however the results did not reach statistical significance. Husebo and colleagues (21) reported a statistical significant finding in fatigue levels 6 months following completing the exercise programme, initiated during cancer treatment. Moderate intensity home-based walking intervention was found to be effective in managing fatigue levels during both radiotherapy and chemotherapy (10). Moros and Campbell and colleagues (3, 22) reported no statistically significant changes following an aerobic exercise program. Hoffman and colleagues (31) monitored cancer-related fatigue (CRF) and symptom severity from pre-surgery to week-6 of their exercise programme, finding that on average participants experienced 7 symptoms pre-

surgery, 10 symptoms post-surgery and 6 symptoms at week 6. In this study CRF increased from 3.5 to 4.8 pre- to post-surgery and decrease to 2.8 at week 6, with other symptom severity and interference results showing a similar trend (5 out of 7 participants commenced chemotherapy at week 5). Naraphong and colleagues demonstrated an improvement in CRF from baseline to the 10-week follow up, albeit not statistically significant (23).

Naraphong and colleagues(23) also assessed sleep disturbance (General Sleep Disturbance) and mood disturbance (Profile of Mood States-Brief Form). Although participants in the exercise group did demonstrate improvements in mood and symptom distress, results did not reach statistical significance.

Schmidt and colleagues (32) assessed depression (20-item Center for Epidemiological Studies Depression scale) and cognitive function (concentration, cognitive flexibility). There was no statistical significance in either measure with no difference illustrated in depression in either control or exercise group however cognitive performance did improve in the exercise group only.

Behaviour

Only Courneya and colleagues (28) investigated predictors of follow-up exercise behaviour 6 months following a RCT exercise trial as a primary outcome, finding a number of significant predictors such as; demographics, medical, fitness, psycho-social and motivational variables. Moreover, 58% of breast cancer survivors reported meeting at least one exercise guideline and 21% of those reported meeting both following the START trial. At baseline, only 23% were meeting either exercise guideline and only 5% of those were meeting both. The strongest predictor of those exercising at 6-month follow-up in their trial was pre-trial exercise levels.

Additionally, other variables that predict the likelihood of meeting exercise guidelines at follow up included younger age, breast conserving surgery, strength improvements, lower post-intervention fatigue, a more positive attitude and lower post intervention BMI.

DISCUSSION

This is the first systematic review aimed to synthesise all available literature of exercise training intervention in people with cancer undergoing adjuvant cancer treatment following surgical resection. Although the area of exercise-oncology is still relatively new with only seventeen studies being considered eligible for review, the principal finding is that exercise training is safe and feasible in the adjuvant setting. The review included studies with various forms of exercise interventions and those that mainly investigated HRQoL as a primary outcome. The evidence does suggest that exercise intervention during adjuvant cancer treatment may improve measures of physical fitness, HRQoL and fatigue, albeit that not all such findings were statistically significant. The question of which is the most effective exercise training programme aimed at improving physical fitness cannot be answered, with only 1 pilot study (in people with breast cancer) reporting a statistically significant increase in physical fitness as a primary outcome measure (19). It remains unclear what the optimal timing of initiation of an exercise programme is and what are the best combinations of elements within an exercise training programme to optimise training efficacy. Furthermore, it also remains unclear whether exercise training in this context improves clinical outcomes and whether such exercise interventions have a long-lasting effect on physically activity throughout the subsequent life course of the patient.

The quality of the included studies in this review were variable. Of the seventeen full text articles, thirteen were reported as an RCT (3, 9, 10, 18, 20-22, 24, 26-29, 32) however three studies were by Courneya and colleagues (26-28) (results from one exercise training trial, the START trial). Of these only 4 studies include >200 patients (9, 26-28) and 3 studies 100-200 patients (10, 20, 32); the remaining 9 studies included 7-67 patients (3, 18, 19, 21-24, 30, 31, 33). All except three studies (19, 30, 31) included a control group. The majority of included studies involved those with breast cancer which suggests more research is required in other

cancer groups. Furthermore, it is difficult to compare such included studies as they were heterogeneous for the type of cancer (breast, NSCLC and one study including 21 different cancer types), cancer treatments and the initiation of the exercise training programme. The exercise training varied in the type of programme (mainly aerobic and resistance exercise training), supervision and setting (supervised in-hospital and unsupervised at home), frequency (2-26 weeks), intensity (mainly moderate aerobic with high intensity in two studies (9)), time (15- 60 minutes) and type (mainly cycle ergometer) of exercise. Adherence ranged between 15 – 90% (home-based and in-hospital exercise training). In comparison, reported adherence rates for surgical prehabilitation studies also range widely, e.g. 16% in colorectal cancer (34) and 81% in people with lung cancer (35) for home-based training programmes and 100% for an in-hospital supervised programme in abdominal aortic aneurysm repair patients (36).

Overall, exercise training during adjuvant cancer treatment has been found to be safe and feasible in people with breast cancer (19, 22) and NSCLC (30). Only Jones (30) and Campbell (22) and colleagues explored fatigue levels in these feasibility studies. Jones and colleagues illustrated a significant improvement following the exercise intervention in people with NSCLC. Although Campbell and colleagues illustrated an improvement in fatigue levels in the intervention group, albeit this did not reach statistical significance. People with cancer encounter worsening symptoms from cancer, cancer treatment and surgery, yet the included studies highlight the efficacy of implementing exercise programmes during this time (30). The feasibility of initiating an exercise programme, even in people with NSCLC, is encouraging as people included in this review were older, had a poor exercise tolerance, a diverse range of co-morbidities and recently underwent surgical interventions (30, 31). Furthermore, this review included a group of participants with NSCLC, of whom, almost one third received platinum-based chemotherapy whilst undertaking exercise training (30). One

study in people with NSCLC tolerated exercise training initiated at 66-hours post hospital discharge (31). Only one study in this review reported a participant becoming unwell during the exercise programme but quickly recovered (26).

It has been suggested that women with breast cancer who exercise at moderate intensity, 30 minutes or more per day on 5 days or more per week, have a lower risk of death (12). Furthermore, exercise training might ameliorate toxicity, completion rate and cancer treatment efficacy (37). However, studies reviewed here provide little insight into detailing the most effective components that might influence such outcomes. Considering the role of strength/muscular training, a recent meta-analysis (38) concluded that resistance training was associated with clinically important improvements in muscular function and body composition in patients undergoing cancer treatment and long term follow-up. Most of the studies included in this review did indeed incorporate a form of resistance exercise although only Battaglini and colleagues (24) reported significant findings. Courneya and colleagues (26, 27) reported that chemotherapy moderated the effects of exercise training on muscular strength with patients receiving non-taxane based chemotherapy increasing muscular strength. Moreover, this resistance exercise training programme improved cancer treatment completion rate. Peripheral muscle strength is known to be related to physical activity in patients with chronic obstructive pulmonary disease (COPD) (39), though this has not been studied in people with cancer .

Preparing for the “dual-hit” treatment including surgery and adjuvant cancer treatment can cause unanticipated fear, anxiety and psychological stresses. HRQoL is much studied in oncology (40). The studies included in this review on the whole support the conclusion of Granger and colleagues (13) such that exercise training is associated with positive benefits on some domains of HRQoL. Exercise training significantly improved different domains of HRQoL following circuit classes (19, 22) and aerobic/resistance exercise programmes (27).

Burke and colleagues (41) explored experiences of participants in an in-hospital exercise programme using semi-structured interviews, finding that it promoted positive changes, as patients viewed their lives in a "fuller, richer and more meaningful way". Campbell and colleagues (22) found over their 12-week exercise intervention period a change in FACT G score of ~15 units, representing the difference between requiring bed rest half the waking day to being fully ambulatory with symptoms (42).

Fatigue is one of the commonest symptoms of cancer and cancer treatment, manifested in the clinic as weakness and exercise intolerance, which can effect quality of life and physical activity (41). Insight into strategies that help patients overcome barriers to exercise may help patients adopt and maintain physical activity (43). It has been suggested that people with cancer interested in participating in physical activity preferred to receive information from a cancer centre or face to face as opposed to leaflets (43). Courneya and colleagues (28) stressed the importance of fully considering demographic, medical, behavioural, fitness, psychosocial and motivational factors when designing behavioural support interventions to promote exercise during the important transition from breast cancer patient to survivor. Encouragingly, Campbell (22) and Adamsen (9) and colleagues reported increased physical activity levels post-exercise training intervention. The first RCT (The CHALLENGE Trial) investigating physical activity levels and survival is currently being conducted among colon cancer survivors following completion of adjuvant chemotherapy (44).

The main strength of this review is that it provides an up-to-date comprehensive review of all studies using an exercise programme in people with cancer undergoingadjuvant cancer treatment following surgery. The review was conducted in a rigorous manner using selected search terms over several databases. Searches were updated over several time points. Furthermore, two independent assessors screened candidate articles using predefined search terms which minimised bias. The quality of each study was evaluated by using a checklist

designed to assess randomized and non-randomized trials. The main limitation of this review is the limited number of reports available (of which 3 referred to a single exercise programme, the START trial (26-28)). Not all studies reported initial baseline fitness levels, and some studies excluded people with cancer who were already vigorously exercising 3 times a week for 20 minutes or more. Furthermore, not all studies specified the timing of assessments, duration of exercise programmes and the nature of the cancer treatment received. Some studies offered incentives such as massages [35] to continue the exercise programme which limits future application of such exercise interventions. Due to the nature of the literature, only three of the seventeen included studies included mixed genders, all other studies included females with breast cancer which limit generalisability. Finally, due to the clinical and statistical heterogeneity of the included studies, a meta-analysis was not performed

CONCLUSION

This is the first systematic review including all people with cancer undergoing adjuvant cancer treatment following surgery. Consistent with findings presented in a recent review (37), we agree that the majority of work conducted in the adjuvant setting mainly includes people with breast cancer. This review included 1370 people with breast cancer and 296 people with other cancer types. However, in comparison our review has focussed on all people with cancer undergoing adjuvant cancer treatments following surgery. Of the 17 included studies, 6 have been conducted in the past 5 years. Because of the lack of adequately powered RCTs in this area, it remains unclear what is the optimal time to initiate an exercise programme and the kind of programme effective in improving clinically important outcome measures. Future studies should focus on the mechanisms of cancer treatment and a comparison of different exercise programmes. It remains unclear whether exercise training in

this context improves clinically important outcomes other than measures of physical fitness, HRQoL and fatigue. The question of what is the optimal timing of initiation of an exercise programme and what the best combination of elements within an exercise-training programme to optimise training efficacy remain currently unanswered. It is also unclear if initiating such exercise programmes at cancer diagnosis may have a long-lasting effect on long term physical activity and survivorship. Finally, it is encouraging that people with cancer undergoing the "dual-hit" can tolerate exercise training and perhaps global exercise guidelines for people with cancer can be further specified and recommended.

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Table 1. **Summary of study aims and outcome measures**

Author, year, (Country)	**Cancer type, Cancer treatment**	**Exercise Programme**	**Study aim**	**1. Primary outcome measure** **2. Secondary outcome measure**
Segal et al, 2001 (Canada)	Breast, Adjuvant chemo/ other adjuvant cancer treatment	Walking	Evaluate the effect of exercise on physical functioning and other dimensions of HRQoL. Self-directed and supervised exercise were compared with usual care	1. Physical functioning (SF-36) 2. Changes in other scales of SF-36, FACT-General and FACT-Breast, aerobic capacity and body weight
Kolden et al, 2002 (USA)	Breast, Adjuvant radiotherapy	Aerobic/ Resistance/ stretching	Feasibility, safety and tolerability, benefits of a comprehensive group exercise intervention	1. Recruitment and retention and safety and tolerability report 2. Secondary outcome measures are listed below; • Aerobic capacity; a single-stage submaximal treadmill walking test • Flexibility; Sit-And-Reach Test • Strength; estimated 1-RM tests on bench press and leg press • HRQoL- Mood/distress; Beck Depression Inventory (BDI), State-Trait Anxiety Inventory, Positive and Negative Affect Schedule (PANAS), Hamilton Rating Scale for Depression (HRSD) • HRQoL- Well-being; Functional Assessment of Cancer Treatment (FACT), the Life Functioning Scales (LFS) • HRQoL- Functioning; Cancer Rehabilitation Evaluation System (CARES), Global Assessment Scale (GAS)
Campbell et al, 2005	Breast, Adjuvant radiotherapy &	Circuit aerobics	Evaluate physical functioning, fatigue and QoL outcomes	1. Cancer-specific QoL scales; FACT-General and FACT-Breast 2. Secondary outcome measures are listed below; • Global QoL tool; Satisfaction with Life Scale (SWLS) • Fatigue; Revised Piper Fatigue Scale (PFS)

Author, year, (Country)	Cancer type, Cancer treatment	Exercise Programme	Study aim	1. Primary outcome measure 2. Secondary outcome measure
(UK)	chemo			• Physical; Scottish physical activity questionnaire (SPAQ) and 12MWT
Mock et al, 2005 (USA)	Breast Adjuvant radiotherapy	Walking	To determine the effects of a home-based walking exercise programme on levels of fatigue	1. Fatigue; total score of Piper Fatigue Scale (PFS) 2. Physical functioning and activity levels: 12-MWD, Medical Outcomes SF-36 and physical activity questionnaire (PAQ)
Battaglini et al, 2006 (USA)	Breast Adjuvant Chemo, radiation or both	CV/ Resistance/ flexibility	To identify the possible benefits that an individualised exercise programme composed primarily of resistance training would have on muscular strength and fatigue levels	1. Fatigue; total score of Piper Fatigue Scale (PFS) 2. Fitness assessment; VO_2peak/max test using the Bruce treadmill protocol and maximum capacity for muscular strength
Courneya et al, 2007 (Canada)	Breast, Adjuvant chemo	Aerobic/ Resistance	Evaluated the effects of aerobic and resistance exercise on physical functioning, body composition, psychosocial functioning and QoL	1. Functional assessment of cancer therapy-anaemia scale (FACT-An scale) and Psychosocial functioning; Rosenberg Self-esteem scale 2. Secondary outcome measures are listed below; • Aerobic fitness; maximal incremental exercise treadmill protocol • Muscular strength; 8-repetition maximum on horizontal bench press and leg extension.
Lee et al, 2007 (Australia)	Breast, Adjuvant radiotherapy	Pectoral muscle stretching programme	To investigate whether a stretching programme reduced acute musculoskeletal impairments	1. Passive range of movement for horizontal extension 2. Secondary outcome measures are listed below; • Passive range of movement for forward flexion and external rotation • Active range of movement for abduction, • Strength of shoulder muscles • Arm swelling

Author, year, (Country)	Cancer type, Cancer treatment	Exercise Programme	Study aim	1. Primary outcome measure 2. Secondary outcome measure
				• QoL
Courneya et al, 2008, (Canada)	Breast, Adjuvant chemo	Aerobic/ Resistance	Personal and clinical factors that may predict exercise training responses	1. Qol; functional assessment of cancer therapy-anaemia (FACT-An scale) 2. Secondary outcome measures are listed below; • Aerobic fitness; maximal incremental exercise treadmill protocol • Muscular strength; 1-RM equation using 8-RM horizontal bench press • Lean body mass; DEXA scan • Percent body fat; Hologic QDR-4500 in Vancouver and the General Electric Lunar Expert in Ottawa and Edmonton
Jones et al, 2008 (Canada)	Lung, Adjuvant chemo & some received no chemo	Cycle	Assess feasibility study examining the effects of a supervised aerobic exercise training on aerobic fitness	1. Change in VO2peak; CPET 2. Secondary outcome measures are listed below; • Secondary cardiopulmonary endpoints; peak workload, ventilatory threshold, O_2 pulse and secondary QoL endpoints were overall fatigue and QoL subscale. endpoints; • QoL; Functional Assessment of Camcer Therapy-Lung (FACT-L), Lung Cancer Subscale (LCS), • Fatigue; Fatigue Scale of the FACT measurement system
Adamsen et al, 2009 (Denmark)	21 different cancers, 59 different chemo regimens	Resistance, relaxation, body awareness and massage	To assess the effect of a multimodal group exercise intervention, as an adjunct to conventional care on fatigue, physical capacity, general wellbeing, physical activity and QoL.	1. Fatigue; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) 2. Secondary outcome measures are listed below; • QoL; Other scales on EORTC QLQ-C30 General well-being was further assessed by Medical Outcomes Study Short Form (MOS SF-36) • Leisure time physical activity level; questionnaire • Muscular strength; 1-RM • Aerobic capacity; VO_2max
Courneya et al, 2009	Breast,	Aerobic/	To identify key predictors of aerobic and resistance exercise	1. Predictors of follow-up exercise behaviour 2. Variables such as;

Author, year, (Country)	Cancer type, Cancer treatment	Exercise Programme	Study aim	1. Primary outcome measure 2. Secondary outcome measure
(Canada)	Adjuvant chemo	Resistance	during the follow-up phase of the START Trial.	• Demographics and behavioural • Medical • Post-intervention • Change scores for physical fitness and body composition • Motivational variables
Moros et al, 2010 (Spain)	Breast, Adjuvant chemo	Aerobic / resistance	To assess functional capacity, QoL and pyshco-social status of patients. Assess the influence of physical exercise programme throughout the course of chemotherapy.	1. Functional capacity; Karnofsky performance status 2. Secondary outcome measures are listed below; • Psychological wellbeing; General Health Questionnaire (GHQ) • QoL; The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
Milecki et al, 2013 (Poland)	Breast, Adjuvant radiotherapy	Aerobic Endurance, Respiratory muscle training	Examine whether moderate-intensity endurance training would have a positive effect on aerobic capacity in comparison with those women who were not taking any physical activity during postoperative radiotherapy	1. Functional capacity; 6MWD 2. Breathlessness; Modified Borg scale (0-10)
Hoffman et al, 2014 (USA)	NSCLC, Chemo (initiated week 5 in 5/7 patients)	Walking and balancing program (Nintendo Wii Fit Plus)	Describe the effects of a home-based rehabilitation exercise intervention on CRF, other symptoms, functional status and QoL for post-surgical NSCLC patients starting within days after hospital discharge	1. CRF; Brief Fatigue Inventory (BFI) 2. Secondary outcome measures are listed below; • Symptom severity and interference was assessed using M.D. Anderson Symptom Inventory Core and Lung Module (MDASI) • Functional status; Medical Outcomes SF-36 • QoL; Ferrans and Powers Quality of Life Index (QLI) (assessing satisfaction and important aspects of life to the person)

Author, year, (Country)	Cancer type, Cancer treatment	Exercise Programme	Study aim	1. Primary outcome measure 2. Secondary outcome measure
Schmidt et al, 2014 (Germany)	Breast, Adjuvant chemo	Resistance exercise training	To investigate whether progressive resistance training in breast cancer patients during chemotherapy provides beneficial effects on fatigue and QoL beyond the potential effects of a supervised group-based training	1. Fatigue; Fatigue Assessment Questionnaire (FAQ) 2. Secondary outcome measures are listed below; • QoL; EORTC QLQ-C30 • Depression; 20-item Center for Epidemiological Studies Depression scale) • Cognitive function (concentration, cognitive flexibility); trail-making-test
Naraphong et al, 2014 (Thailand)	Breast, Adjuvant chemo	Walking programme	To preliminarily examine the effects of an exercise programme on the symptoms of fatigue, sleep disturbance, mood disturbance, symptom distress and physical fitness for Thai women	1. Fatigue; Revised Piper Fatigue Scale (PFS) 2. Secondary outcome measures are listed below; • Sleep disturbance; General Sleep Disturbance) • Mood disturbance; Profile of Mood States-Brief Form • Distress; Memorial Symptom Assessment Scale (MSAS)
Husebo et al, 2014 (Norway)	Breast cancer, Adjuvant chemo	Walking programme and strength exercise	Investigate the effects of a scheduled home-based exercise intervention on CRF, physical fitness and activity level.	1. CRF; Schwartz Cancer Fatigue Scale-6 2. Secondary outcome measures are listed below; • Physical activity; International Physical Activity Questionnaire • Physical fitness ; 6-MWT • Exercise volume; exercise diaries • Exercise adherence; extent to which the women in the

Author, year, (Country)	Cancer type, Cancer treatment	Exercise Programme	Study aim	1. Primary outcome measure 2. Secondary outcome measure
				intervention group performed the prescribed exercise regimen

Abbreviations: Chemo – chemotherapy, HRQoL – health related quality of life, QoL – quality of life, 1-RM – repetition maximum, SF-36; The Short Form (36) Health Survery, VO_2Peak – oxygen uptake at peak exercise, VO_2max – oxygen uptake at max exercise, CPET – Cardiopulmonary exercise test, 12 MWD- 12 minute walk distance test, 6MWD – 6 minute walk distance test, CRF – cancer related fatigue

Table 2. **Summary of study characteristics and exercise intervention outcomes**

Author,	Study	N	Gender	Cancer type,	Exercise	Supervision,	Frequency	Intensity	Duration	Adherence	Primary

year, (Country)	**design**			**Cancer treatment**	**Programme**	**Location**					**outcome**
Segal et al, 2001 (Canada)	RCT	123	Female	Breast, Adjuvant chemo/ other adjuvant cancer treatment	Walking programme	Supervised & home based	Home; 5times/week x 26 weeks. In-hospital; 3times x 26weeks	50-60% VO_2Peak	NR	71.5%	*Physical functioning (in UC)
Kolden et al, 2002 (USA)	Pilot study	40	Female	Breast, Adjuvant radiotherapy	Aerobic/ resistance training	Supervised	3times/week x 16 weeks	Prog: 40-70% VO_2Max	60min	78.4%	*Fitness & QoI flexibility
Campbell et al, 2005 (UK)	Pilot RCT	22	Female	Breast, Adjuvant radiotherapy & chemo	Aerobic training	Supervised	2times/week x 12 weeks	60-75% MHR	NR	70%	* QoI measure (in EG)
Mock et al, 2005 (USA)	RCT	119	Female	Breast Adjuvant radiotherapy	Walking programme	Home-based Unsupervised	5-6times /week x 6-weeks during RET or 3-6months	50-70% MHR	15-30 min	EG: 72% UG: 61%	Fatigue & physical functioning
Battaglini et al, 2006 (USA)	RCT	20	Female	Breast Adjuvant Chemo, radiation or both	CV/ resistance/ flexibility training	Supervised	2times/week x 16 weeks	40-60% max exercise capacity	60min	NR	*Muscular strength, fatigue
Courneya et al, 2007 (Canada)	RCT	242	Female	Breast, Adjuvant chemo	Aerobic/ resistance training	Supervised In-hospital	Duration of chemo	Prog: 60-80% VO_2Peak/1RM	15-45min	70.2%	↑ QoL measure, *↑ chemo completion rate in RET
Lee et al, 2007	Single-blind	61	Female	Breast, Adjuvant	Pectoral muscle	Unsupervised Home based	2times/day X 7days	NR	10min	90%	Range of motion

(Australia)	RCT			radiotherapy	stretching programme		x 6 weeks				
Courneya et al, 2008 (Canada)	RCT	242	Female	Breast, Adjuvant chemo	Aerobic/ resistance training	Supervised In-hospital	3 times/week x 17 weeks	60-80% VO_2Peak/ 60-70% 1RM	15- 45 min	A; 72% R; 68.2%	Measure of QoL
Jones et al, 2008 (Canada)	Pros. single group	20	Mixed gender	Lung, Adjuvant chemo & some received no chemo	Aerobic training	Supervised: short term	3 times/week x14 weeks	Prog: 60-70% WRpeak	15-45 min	©93% and 72%, NC;85%	Feasible, *↑Qol and select CP (in NC only)
Adamsen et al, 2009 (Denmark)	RCT	269	Mixed gender	21 different cancers, 59 different chemo regimens	Resistance training, relaxation, body awareness and massage	Supervised In-hospital	9hours/week x 6weeks	Low & high intensity	90min	70.8%	*Fatigue, Variety of QoL measures, Other QoL measures
Courneya et al 2009 (Canada)	Pros. RCT	242	Female	Breast, Adjuvant chemo	Aerobic/ Resistance training	Supervised In-hospital	3 times/week x 17weeks	60-80% VO_2Peak/ 60-70% IRM	60min	A;72% R;68.2%	Measure of exercise patterns
Moros et al, 2010 (Spain)	RCT	22	Female	Breast, Adjuvant chemo	Aerobic/ muscle strength/ coordination training	Supervised In-hospital	3 times week x 18-22-weeks	60-70% HR	60min	91%	Functional capacity, *QoL
Milecki et al, 2013 (Poland)	RCT	46	Female	Breast, Adjuvant radiotherapy	Aerobic/ endurance, respiratory muscle training	Supervised, In-Hospital	5times / week x 6 weeks	65-70% MHR	40-45 min	NR	6MWD
Hoffman	Pilot	7	Mixed	NSCLC,	Walking and	Home based	5times/week	Prog:	Light	NR	CRF, other

et al, 2014 (USA)			gender	Chemo (initiated week 5 in 5/7 patients)	balancing program (Nintendo Wii Fit Plus)		X 6weeks	5-30min	intensity		symptoms, functional status, QoL
Schmidt et al, 2014 (Germany)	Prop. RCT	101	Female	Breast, Adjuvant chemo	Resistance exercise training	Supervised, Training facility	2/week x 12 weeks	60-80% IRM	60 min	71%	Fatigue, QoL, depression, cognitive function, effect modification
Naraphong et al, 2014 (Thailand)	Pilot	23	Female	Breast, Adjuvant chemo	Walking programme	Home based	3-5 days/week x 12 weeks	Prog; 20-30min	Prog; light to moderate	Reported as increase in mean 5920 steps	Feasibility, CRF, physical fitness, mood and sleep disturbance
Husebo et al, 2014 (Norway)	RCT	67	Female	Breast cancer, Adjuvant chemo	Strength/ aerobic training	Home based	Daily x 17weeks	Self-reported	30 min	Walking-17% Strength-15%	CRF, physical fitness, physical activity

Abbreviations: RCT – randomised controlled trial, Prop – prospective study, NR – not report, Chemo – chemotherapy * - significant findings, RCT- randomised controlled trial, chemo-chemotherapy, VO_2Peak – oxygen uptake at peak exercise, VO_2max – oxygen uptake at max exercise, VO_2 at LT- oxygen uptake at lactate threshold, 1RM – 1 rep maximum, UC- Usual care, Prog-progressive, IG/EG; Intervention group, CG; Control group, MHR- max heart rate, Min- minute, Prog – progressive increase, RET – resistance training, QoL; quality of life, CP –Cardiopulmoanry endpoints, Note# - UC offered 1month supervised exercise post intervention, AET- Aerobic exercise training, RET- resistance exercise training, Pros –prospective, WRpeak – peak work rate, 6MWD-6 minute walk distance test, CRF – cancer related fatigue. * - significant findings, RCT- randomised controlled trial, $\dot{V}O_2$ at $\hat{\theta}_L$- oxygen uptake at lactate threshold, Prog-progressive, Min- minute.

APPENDIX 1. **Literature review search terms**

Search terms
i) CANCER
1. expNeoplasm
2. Canc*.tw.
3. Neoplasm*.tw.
4. expTumor
5. Tumo*.tw.
6. expCarcinoma
7. Carcin*.tw.
8. expMalignant
9. expOncology
10. Oncol*tw.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
ii) CANCER TREATMENT
12. expNeoadjuvant
13. Neoadjuvant*.tw.
14. expChemo
15. Chemo*.tw.
16. expRadiotherapy
17. expCancer treatment
18. 12 or 13 or 14 or 15 or 16 or 17
iii) EXERCISE
19. expExercise
20. Exercise*.tw.
21. expFitness
22. Fit*.tw.
23. expOxygen consumption
24. expAerobic
25. Aerobic*.tw.
26. Anaerobic
27. Anaerobic*.tw.
28. 19 or 20 or 21 or 21 or 22 or 23 or 24 or 25 or 26 or 27
i) and ii) and iii)
iv) SURGERY
29. Surgery
30. Surg*.tw.
31. Surgical (including Anatomy, drainage, mortality, patient, science, stress, wound, ward all terms)
32. 30 or 31 or 32
33. **I) and ii) and iii) and iv)**
v) OUTCOME
34. Morb*.tw.
35. Mort*.tw.
36. Recurrence*.tw.
37. Outcom*.tw.
38. 34 or 35 or 36 or 37
i) and ii) and iii) and iv) and v)

APPENDIX 2. **Quality assessment**

	Lee et al. 2007	***Courneya et al.2009***	***Campbell et al.2005***	***Kolden et al.2002***	***Courneya et al. 2007***	***Adamsen et al.2009***	***Mock et al.2005***	***Courneya et al.2008***	***Moros et al. 2010***	***Jones et al. 2008***	***Segal et al.2001***	***Battaglini et al .2005***	***Milecki et al. 2013***	***Hoffman et al. 2014***	***Husebo et al. 2014***	***Naraphon g et al. 2014***	***Schmidt et al. 2014***
Reporting																	
Is the hypothesis/aim/objective of the study clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are the main outcomes to be measured clearly described in the introduction or methods section?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are the characteristics of the patients included in the study clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are the interventions of interest clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are the main findings of the study clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Does the study provide estimates of the random variability in the data for the main outcomes?	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Have all important adverse events that may be a consequence of the intervention been reported?	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1
Have the characteristics of patients lost to follow-up been described	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
Have actual probability values been reported for the main outcomes except where the probability value is less than 0.001?	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1
External validity																	
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

	Lee et al. 2007	***Courneya et al.2009***	***Campbell et al.2005***	***Kolden et al.2002***	***Courneya et al. 2007***	***Adamsen et al.2009***	***Mock et al.2005***	***Courneya et al.2008***	***Moros et al. 2010***	***Jones et al. 2008***	***Segal et al.2001***	***Battaglini et al .2005***	***Milecki et al. 2013***	***Hoffman et al. 2014***	***Husebo et al. 2014***	***Naraphong et al. 2014***	***Schmidt et al. 2014***
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Internal validity bias																	
Was an attempt made to blind study subjects to the intervention they have received?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Was an attempt made to blind those measuring the main outcomes of the intervention?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
If any of the results of the study were based on data dredging, was this made clear?	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for case controls?	1	0	0	0	0	1	0	0	0	0	0	0	1	1	1	1	1
Were the statistical tests used to assess the main outcomes appropriate?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
Was compliance with the intervention/s reliable?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Were the main outcome measures used accurate (valid and reliable)?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Internal validity - confounding (selection bias)																	
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1

	Lee et al. 2007	***Courneya et al.2009***	***Campbell et al.2005***	***Kolden et al.2002***	***Courneya et al. 2007***	***Adamsen et al.2009***	***Mock et al.2005***	***Courneya et al.2008***	***Moros et al. 2010***	***Jones et al. 2008***	***Segal et al.2001***	***Battaglini et al .2005***	***Milecki et al. 2013***	***Hoffman et al. 2014***	***Husebo et al. 2014***	***Naraphong et al. 2014***	***Schmidt et al. 2014***
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1
Were the study subjects randomised to intervention groups?	1	1	1	0	1	1	1	1	1	0	1	1	1	0	1	1	1
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1
Were losses of patients to follow-up taken into account?	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
Power																	
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	1	0	0	0	1	1	1	1	0	0	1	1	1		1	0	1
Total	**23**	**20**	**21**	**17**	**23**	**24**	**23**	**23**	**22**	**19**	**23**	**23**	**21**	**21**	**24**	**21**	**24**

APPENDIX 3. **Search results conducted for this systematic review**