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TITLE: Exercise and cancer rehabilitation: A systematic review

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Running title: Exercise and cancer rehabilitation

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Abstract

Introduction: Cancer is increasingly being viewed as a chronic illness requiring long-term management, and there is a growing need for evidence-based rehabilitation interventions for cancer survivors. Previous reviews have evaluated the benefits of exercise interventions for patients undergoing cancer treatment and long-term survivors, but none have investigated the role of exercise during cancer rehabilitation, the period immediately following cancer treatment completion. This systematic review summarises the literature on the health effects of exercise during cancer rehabilitation and evaluates the methodological rigour of studies in this area to date.

Methods: Relevant studies were identified through a systematic search of PubMed and Embase to April 2009. Data on study design, recruitment strategy, participants, exercise intervention, adherence rates, and outcomes were extracted. Methodological rigour was assessed using a structured rating system.

Results: Ten studies were included. Breast cancer patients were the predominate patient group represented. Most interventions were aerobic or resistance-training exercise programmes, and exercise type, frequency, duration and intensity varied across studies. Improvements in physical functioning, strength, physical activity levels, quality of life, fatigue, immune function, haemoglobin concentrations, potential markers of recurrence, and body composition were reported. However, all studies were limited by incomplete reporting and methodological limitations.

Conclusions: Although the methodological limitations of studies in this new field must be acknowledged, initial evidence indicates that exercise is feasible and may provide physiological and psychological benefits for cancer survivors during the rehabilitation period. Future studies with rigorous study designs are now required to advance the field.

Key Words: Cancer; Exercise; Rehabilitation; Chemotherapy; Adherence.

Introduction

The population of long-term cancer survivors continues to grow. In 2002 24.6 million people were living with cancer, worldwide.¹ Improvements in treatment are, in part, responsible for the increased survival rates and life expectancies for cancer survivors. However, these treatments can be harmful, with many cancer survivors experiencing long-term negative physical and/or psychological effects from their disease or treatment. For this reason cancer is increasingly being viewed as a chronic illness requiring long-term management,² and the need for evidence-based rehabilitation interventions for this population is growing.

Exercise is increasingly becoming recognised as an important treatment for the recovery and rehabilitation of cancer survivors. The findings from previous reviews and meta-analyses suggest that exercise attenuates a range of physical and psychological complaints after cancer treatment. The benefits are thought to include reductions in fatigue and improvements in immune function, physical functioning, body composition, and quality of life (QoL).³⁻⁵

Courneya and Friedenreich⁶ were the first to provide a framework for examining the short-term and long-term benefits of exercise after cancer treatment. In their most recent physical activity and cancer control framework, they define the period following initial treatment, and ending with recurrence or death, as survivorship.⁷ They then separate survivorship into two time periods: the rehabilitation period, which immediately follows primary treatment, and the disease prevention/health promotion period, which describes longer-term survival. The duration of the rehabilitation period is highly variable but continues until any major loss of function is recovered. Courneya and Friedenreich⁶ suggest that this time period can be defined approximately as the time from treatment completion to 3 to 6 months post-treatment. They argue that exercise and other types of physical activity are important throughout this period, as well as in the longer term survival period.

Early reviews in this field summarised the evidence from all exercise interventions, regardless of whether patients were in the treatment, rehabilitation or survival period. More recent reviews have separated the results of treatment and post-treatment interventions, but to date, no review has evaluated the effects of interventions offered during the rehabilitation period separately from the effects of those offered during the disease prevention/health promotion period. Therefore, little is

known about the specific benefits of exercise immediately following treatment, during which time the goal is to address the acute side-effects of treatment and facilitate a return to pre-treatment health.

In their 2007 summary of the literature on physical activity and cancer control, Courneya and Friedenreich⁷ identified the rehabilitation period as a key focus for future research, particularly research to examine the feasibility and efficacy of exercise interventions. A number of factors explain this interest in offering exercise programmes during this period. First, during treatment, survivors typically experience a significant decline in their participation in exercise and other physical activities. Their levels of activity may not recover, even years after treatments have been completed.⁷

⁸ Considering the de-conditioned state of cancer survivors and the common presence of acute side effects at the completion of treatment, the possibilities for improvements in physical functioning, QoL, and immune function during the rehabilitation period are considerable.³ Second, cancer diagnosis has been described as a life changing event and completion of treatment can serve as a motivator to improve lifestyle risk factors, such as exercise and, more generally, physical activity participation. In a recent pilot study of a multi-strategy rehabilitation intervention for colorectal cancer survivors, cancer diagnosis was identified as a motivator for initiating the lifestyle changes promoted in the intervention.⁹ Participants identified 3 to 5 months post-treatment as their preferred time to start a rehabilitation programme because they felt that they were fit enough to make behavioural changes at that time, while not yet having lost their motivation to change. In another study, more than half the cancer survivors said they would prefer to begin an exercise programme immediately or soon after treatment, rather than during treatment.⁷ A potential reason for this preference could be that after treatment the time constraints imposed by medical appointments decrease. The third factor that could explain the interest in offering exercise during the rehabilitation period is the role of exercise programmes in providing continuing support to cancer survivors. Many cancer patients find this period challenging due to a sudden decline in both medical and social support: for example, they often report experiencing unanticipated fear and emptiness.¹⁰ Exercise programmes that offer social support to cancer survivors during this period could help them transition from the intense levels of support they receive during treatment.

What is known about the benefits of exercise during the rehabilitation period comes from the first generation of studies to test the efficacy and effectiveness of exercise programmes for cancer survivors in this period. It is now important to identify directions and challenges learned from these studies to prepare the next generation of studies in this field. Therefore, this study reviews the current literature on the role of exercise during the rehabilitation period. The purposes of this narrative systematic review are: (1) to summarise the literature on the health effects of exercise on cancer survivors in the rehabilitation period and (2) to evaluate the methodological rigour of studies that have examined these effects. The review will discuss: recruitment efforts, participants, interventions, adherence and compliance, analysis, and outcomes.

Methods

Search strategy and selection criteria

Embase and PubMed were searched for articles prior to and including April 2009. Titles and abstracts were searched using the keywords cancer and exercise and clinical trials. The reference lists of located review articles on the topic and of articles describing original research were also checked. RS and KH developed the search strategy. RS then conducted the initial search, and in consultation with KH, determined eligibility of potential articles. WB confirmed the accuracy of the process used to conduct the search and determine eligibility.

Studies were included if they were published in English and in a peer-reviewed journal. ~~Studies that focused on the use of exercise to relieve or control lymphoedema were excluded.~~ The remaining inclusion criteria followed the PIOC (Population, Intervention, Outcomes, Comparison) framework.¹¹ The population under study was defined as: cancer patients who had recently completed adjuvant chemotherapy and/or radiotherapy for any cancer and who had reported no plans for additional treatment (except hormone treatment for breast cancer). ‘Recently completed’ was initially conceptualized as having completed treatment no more than 6 months prior to enrolment. However, it became apparent early in the search process that this criterion was too narrow for such a new field of research. Therefore, this criterion was expanded to: having completed treatment no more than 12 months prior to enrolment. This criterion could be met if: (1) the maximum time between treatment

completion and enrolment was ≤ 12 months for all participants in the study; (2) the mean time between treatment completion and enrolment plus two standard deviations was ≤ 12 months; or (3) the inclusion criteria stated the time between treatment completion and enrolment was ≤ 12 months. Studies were excluded if additional information provided about the recruitment process indicated that the study did not meet one of these criteria, even when the inclusion criterion was reported to be ≤ 12 months since treatment completion.

Interventions that met the criteria were aerobic and/or resistance training programmes, with or without range of motion or flexibility exercises; however, programmes that only included the latter exercises were excluded because these are not expected to lead to physiological improvements. Multi-strategy programmes were also excluded unless one of the intervention groups was an exercise-only group. Studies describing the effects of a single bout of exercise were excluded as were studies that focused on the use of exercise to relieve or control lymphoedema.

Outcomes that met the criteria were all possible health-related effects of cancer and ensuing treatments that would be evident during the rehabilitation period. These included disease- and treatment-related symptoms, QoL, fatigue, body composition, physical function/fitness and exercise behaviour.

Studies that met the 'comparison' criterion of the PIOC inclusion criteria were single group pre-test post-test studies, controlled clinical trials, and randomised controlled trials. It was important to include single-group studies as they are commonly used in newer research areas.

Data extraction and quality assessment

Descriptive characteristics of each study, including time between treatment completion and study enrolment, the study design, participant characteristics, and recruitment details, were extracted. Also extracted were descriptive data about the exercise programme, including the length of the programme; the duration, intensity and frequency of exercise sessions; and adherence or compliance with the programme. Last, the results of evaluating the effects of the intervention on health outcomes were extracted.

The methodological quality of the included studies was assessed using the method described by Stevinson et al.¹² for a review of exercise and cancer throughout the cancer continuum. Four key features of methodological rigour were assessed: the use of randomisation for group allocation, the use of an unbiased randomisation method (e.g. randomisation took place at a remote site or involved drawing sealed sequentially numbered envelopes), the blinding of data collectors from group allocation, and the use of intention-to-treat analysis.

Results

The database searches identified 668 references. Review of their titles and abstracts revealed that 538 did not meet the inclusion criteria. The full texts of the remaining 130 articles were retrieved for more detailed evaluation. Of these, 117 articles were excluded and 13 were included in this review, based on the study criteria (Fig. 1).

INSERT FIGURE 1 ABOUT HERE

Excluded studies

Of the 117 excluded studies, 63 were excluded because they were not exercise interventions post-treatment. Fifty-four of these described interventions for patients during cancer treatment, or for a mix of patients, some in treatment and some in the survival period. Another nine did not describe the evaluation of an exercise intervention (e.g. letters to the editor or protocol papers). The remaining 67 articles described exercise interventions post-treatment. Fifty-four of these were excluded because they did not describe interventions for the rehabilitation period. Two of these 54 were excluded because the primary focus of the interventions was range of motion exercises for lymphodema, following breast cancer treatment,^{13, 14} and another was excluded because the intervention was multi-strategy.¹⁵ For another 25 of these 54 excluded studies, the article did not report the time between treatment completion and study enrolment in a way that met the inclusion criteria: 15 of these only reported time between diagnosis and study enrolment; another six defined participants by time since surgery; and the remaining four reported medians or minimum time between treatment completion and study enrolment. Another 26 of these 54 excluded studies included participants who were >12

months post-treatment. Nineteen of these studies included cancer survivors who were ≤ 5 years post-treatment, and seven included cancer survivors who were >5 years and ≤ 21 years post-treatment.

Included studies

The 13 articles¹⁶⁻²⁸ that met the inclusion criteria describe 10 post-treatment intervention studies (Hayes et al.²¹⁻²⁴ reported their study findings in four articles). Characteristics of the studies and their findings are reported in Table 1. Information on the methodological quality of each study and compliance/adherence rates within studies are reported in Table 2.

INSERT TABLE 1 ABOUT HERE

Time since treatment

As required by the inclusion criteria, all the included studies reported the time between treatment completion and study enrolment. However, only four studies reported the *range* of time between treatment completion and study enrolment,^{19, 21, 27, 28} which allowed for accurate estimation of the maximum time between treatment completion and study enrolment. One other study reported the mean and standard deviation,¹⁶ with the remaining five studies only reporting the inclusion criterion for the duration of time since treatment completion.

Even within the tight inclusion criteria, a range of time periods was represented. Time since diagnosis ranged from <1 month to <12 months. Three studies included participants who were <1 month post-treatment.^{21, 25, 26} Three others included participants who were <6 months post-treatment,^{16, 17, 19} and an additional three included participants who were <12 months post-treatment.^{18, 27, 28} The remaining study²⁰ reported the inclusion of participants who were recruited ‘within weeks of completing treatment’.

Study designs

Four of the 10 included studies were randomised controlled trials with participants randomised to an exercise intervention group or a non-exercise control group.^{16-18, 26} Three other studies were controlled clinical trials, but used non-randomised group allocation methods.^{19, 21, 25} Allocation decisions were based instead on proximity to exercise facility,^{19, 25} matching characteristics²¹ or participant

preference.¹⁹ Two studies allocated participants to either a moderate-intensity or high-intensity exercise group (i.e. no control group),^{27,28} and one used a single group design.²⁰

Sample size and recruitment

Power calculations were only reported for four studies,^{16,21,26,27} all of which recruited the intended number of participants (range of 12-111 participants). In the other studies sample sizes ranged from 23-74, with a median of 42, but no information on sample size calculations was provided. Several studies noted the difficulties of recruiting the required number of participants. For example, Hayes et al.²¹ reported 'slow recruitment and low numbers' in a population of high-dose chemotherapy survivors and discussed the subsequent abandonment of the randomisation process. Matthews et al.¹⁸ noted that recruitment was impacted at one site by stringent inclusion criteria. After recruiting only 8% of eligible patients, they changed the inclusion criteria for recruitment at a second site, which improved the recruitment rate to 20% of eligible patients at that second site. In contrast, a high recruitment rate of 71% was reported by Thorsen et al.,¹⁶ who recruited 111 participants. Few studies mentioned *how* they recruited their participants. One study reported recruiting a consecutive series of patients,²⁵ one reported recruiting a convenience sample,²⁰ and one reported recruiting through 'physicians and advertisements'.¹⁹ Recruitment strategies were not reported for the other studies.

Participants

Studies included survivors of a variety of cancers, with most survivors having a breast cancer diagnosis. Four studies included breast cancer survivors only.¹⁷⁻²⁰ Another four included survivors of a range of cancer types (e.g. lymphomas, gynaecological, breast and testicular cancers);^{16,21,25,26} however, three of these included primarily breast cancer survivors.^{16,25,26} The remaining two studies recruited colorectal cancer survivors.^{27,28}

The age of participants ranged from 16-71 years, with most studies including a wide range of ages. Except for the four studies that included only female breast cancer survivors, the studies recruited men and women.

Control groups

Information on control group instructions was reported for four of the seven controlled trials. For two studies, control group participants were told to maintain current levels of physical activity for the duration of the study,^{16,17} and for another study, they were offered a variation of the intervention after the study ended.¹⁸ In a fourth study the control group took part in a stretching programme that provided contact time with a trainer equal to the time given to the exercise group participants, but the contact was not intended to lead to improvements in physiological variables other than flexibility.²¹ Three of the 10 studies had no control group.^{20,27,28}

Interventions

The exercise interventions varied across the 10 included studies. The intervention period ranged from 2 weeks ($n = 3^{26-28}$) to 6 months ($n = 1^{20}$). Eight interventions were supervised exercise programmes.¹⁷⁻²⁸ One of these also encouraged participants to exercise at home.¹⁷ The two remaining interventions were home-based, un-supervised exercise programmes.^{16,18} One of these employed exercise physiologists to prescribe individually-tailored exercise programmes.¹⁶ The investigators of the other study did not specify the qualifications of the person employed to deliver in-person and phone exercise counselling.¹⁸

The frequency, type, intensity and duration of the exercise interventions and the speed and manner in which the prescriptions were progressed also differed among studies. Exercise frequency ranged from daily ($n = 4^{25-28}$) to a minimum of two sessions per week ($n = 2^{16,20}$). A range of 3 to 5 sessions per week was reported for the remaining four studies, with more sessions being required later in the study.

Six studies incorporated only aerobic exercise,^{17,18,25-28} and four incorporated aerobic and resistance exercises. Most studies prescribed cycling or walking ergometers for the aerobic component of the exercise sessions ($n = 7^{19-21,25-28}$). Two, however, incorporated a range of modalities, including walking, cycling, 'aerobics' exercise (e.g. stepping classes), ball games and swimming,^{16,17} and one study prescribed walking only.¹⁸ Studies incorporating resistance training prescribed either exercises using machines^{20,21} or resistance bands.¹⁹ In one study participants

primarily engaged in aerobic exercise but could also choose to include resistance exercises in whatever way they chose.¹⁶ Flexibility exercises were included as part of the warm-up or cool down in two studies.^{19, 20}

The comparison of exercise intensities is complicated by the variety of methods used to measure intensity. One study used a treadmill speed corresponding to a lactate concentration of 3 ± 0.5 mmol/L in capillary blood (which corresponds to $90 \pm 5\%$ of maximal heart rate).²⁵ Six studies prescribed intensity based on maximum heart rate, assessed with a maximal exercise test,^{19, 21} as heart rate reserve (using the formula $[(220 - \text{age}) - \text{resting heart rate}] \times \text{percent of exercise intensity} + \text{resting heart rate}$ ^{20, 26}), or as maximum power output.^{27, 28} The remaining three studies prescribed an intensity of 6 to 20 on the Borg rating of perceived exertion (RPE) scale.¹⁶⁻¹⁸ Two of these studies also used heart rate monitors to check intensity.^{16, 17} Actual intensities of the exercise prescribed across all the studies ranged from light to moderately-light intensity, described as an RPE of 11 to 13 on the Borg scale,¹⁸ to a moderate to high intensity (described as 70-90% of maximum heart rate^{21, 25}).

Duration of exercise sessions ranged from 30 min ($n = 3$ ^{16, 25, 26}) to 90 min ($n = 1$ ¹⁹). In the seven studies lasting longer than 2 weeks,^{16-21, 25} the exercise prescriptions generally increased in intensity and/or duration gradually over the intervention period. For most of these studies, however, detailed descriptions about the progression in prescriptions were lacking.

Adherence and compliance

Adherence to the exercise protocol was reported fairly consistently, with only three of the 10 studies^{25, 27, 28} neglecting to discuss exercise adherence. Across the seven studies that reported adherence, rates were high (approximately 80-90%). One study reported an adherence rate of approximately 90%, but did not define how this was calculated.²⁰ For the other six studies, adherence was defined in one of two ways: the percentage of prescribed exercise sessions completed or the number or percentage of participants who completed the prescribed number of sessions per week. Adherence to supervised exercise sessions was assessed by attendance logs, and adherence to unsupervised sessions was self-reported.

Three studies reported adherence as the number or percentage of participants who completed the prescribed number of weekly sessions.^{16, 19, 21} In a 14-week intervention trial of unsupervised and supervised exercise, 97% of mixed cancer survivors (57 of 59) self-reported that they had met the goal of two sessions per week.¹⁶ In a study of breast cancer survivors, 82% of participants (23 of 28) completed the goal of three supervised sessions per week over the 12-week intervention.¹⁹ Last, 67% of mixed cancer survivors enrolled in a 12-week supervised exercise programme after completing high-dose chemotherapy (4 of 6), completed all sessions, while 33% (2 of 6) each missed three sessions.²¹

Three studies reported adherence as the number or percentage of prescribed sessions that were completed.^{17, 18, 26} In a study of mixed cancer survivors who were in hospital after completing high-dose chemotherapy, Dimeo et al.²⁶ reported that participants attended daily supervised exercise sessions on 82% of the days they spent in hospital (approximately 2 weeks). Breast cancer survivors enrolled in a 12-week intervention completed 78% of weekly supervised sessions and a mean of 2.1 unsupervised home-based sessions (minimum prescribed = 2 sessions).¹⁷ In another 12-week intervention, breast cancer survivors reported that they completed 94% of unsupervised walking sessions.¹⁸ This was confirmed objectively with a subsample of participants (23 of 36), who wore an Actigraph accelerometer during the sixth and twelfth weeks of the intervention. At the 12-week follow-up, walking frequency and duration, measured with the accelerometer, was strongly correlated with self-reported walking ($\rho=0.65$, $p<0.01$). The investigators also reported a downward trend in self-reported walking adherence over the follow up period (adherence= 108% [walking more than prescribed] at month 1; 88% at month 2; 76% at month 3).

Compliance to the exercise intervention protocol was not reported by any study, and therefore it is not possible to report how well participants followed the exercise prescriptions.

Outcomes

Physical Function

Six studies reported improvements in physical function,^{16, 17, 19, 20, 22, 25} and one study reported reduced loss of physical function.²⁶ In a population of high-dose chemotherapy survivors, patients allocated to

6 weeks of daily exercise had significantly greater improvements in maximum performance (measured in METs) on a treadmill test than did patients in the control group.²⁵ The clinical significance of this is highlighted by the fact that at follow up, only 6% of the exercise group failed to exercise at a level sufficient to perform activities of daily living, compared with 25% of the control group. A similar population of high-dose chemotherapy survivors also showed a significant improvement in maximal performance (measured as VO₂ max), in addition to improvements in upper and lower body strength, after 3 months of aerobic and resistance training.²² No improvements were seen in the control group. Improvements in maximal performance were also reported in populations of mixed cancer survivors¹⁶ and breast cancer survivors,^{19,20} after combined aerobic and resistance training interventions lasting 12 weeks to 6 months. In one of these studies, the combined aerobic and resistance training intervention also led to improved upper and lower body strength.¹⁹ In the other study of breast cancer survivors, which was a single group trial, other improvements reported were increased time to exhaustion during a fitness test, increased percentage of age-predicted forced vital capacity, and decreased resting heart rate.²⁰ In another study of breast cancer survivors¹⁷ greater improvements in dynamic agility and peak jumping power were seen in the exercise group than in the control group, although no significant between-group differences were found for muscle strength or timed 2-km walk distance, after a 12-week aerobic and resistance training intervention. Other outcomes reported by the included studies were an increase in total energy expenditure in the exercise group²⁴ (not assessed in the control group) in a mixed cancer sample and greater increases in walking for exercise over 12 weeks in the exercise group than in the control group in a breast cancer sample.¹⁸

Fatigue and Quality of Life

Fatigue was measured in three studies, using a patient interview,²⁵ the fatigue subscale of the EORTC-QLQ QOL questionnaire¹⁶ or the Piper Fatigue Scale.²⁰ In a study of patients who had received high-dose chemotherapy, no patients who were allocated to 6 weeks of daily exercise reported fatigue in patient interviews, compared with 25% of patients allocated to the control group.²⁵ Conversely, in a breast cancer population, scores on the EORTC fatigue scale improved more in the control group than in the intervention group over 14 weeks.¹⁶ Substantial participation in exercise over the intervention

period was noted in the control group; however, no association was found between changes in fatigue and improvements in physical fitness for this sample. The authors hypothesised that the fatigue scale may have been sensitive to acute changes in fatigue rather than long-term chronic fatigue, and, therefore, the scale may not have been appropriate as an outcome measure. In a different population of breast cancer survivors, Hsieh et al.²⁰ reported significant improvements in behavioural, affective, sensory, cognitive, mood and total fatigue, as measured with the Piper Fatigue Scale, after 6 months of aerobic and resistance training. No changes in mental distress and emotional function were found.

QoL was measured in only one study.²³ Using the Cancer Rehabilitation Evaluation System to assess QoL, the investigators reported significantly greater improvements in global and all domains of QoL (physical, psychosocial, medical interaction, marital and sexual) in cancer survivors who completed a 3-month aerobic and resistance training intervention, compared with those in a control group.

Haematological and Immunological Outcomes

A variety of markers has been measured to evaluate the impact of exercise on immune function and haematological outcomes related to recovery and recurrence. Three studies investigated immunological and haematological markers in cancer survivors following high-dose chemotherapy^{21, 25, 26} and one in a population of breast cancer survivors.¹⁹ In cancer survivors who had received high-dose chemotherapy, Hayes et al.²¹ found no change in the speed of immune cell recovery following a 12-week exercise intervention; however, the exercise programme did not negatively impact immune function either. Improvements identified in a similar population after either a 2-week or a 6-week exercise intervention included significantly greater decreases in neutropenia and thrombopenia in the exercise group than in the control group²⁶ and significantly higher haemoglobin concentrations in the exercise group than in the control group.²⁵ In the study of breast cancer survivors the exercise group showed greater lymphocyte activation after a 6-month exercise intervention than did the control group, which may indicate improved immune function.¹⁹

Two other studies examined the effect of low- and high-intensity exercise on potential markers of recurrence.^{27, 28} In the first study, only the higher-intensity exercise group experienced a

shift to a more pro-inflammatory and less anti-inflammatory immune state (which is hypothesised to decrease infection and cancer recurrence rates) after 2 weeks of intervention.²⁸ In the second study, there was a decrease in oxidative DNA damage (a biomarker of cancer recurrence) in the lower-intensity exercise group and an increase in the higher-intensity exercise group.²⁷ The clinical significance of these changes is not known for either outcome.

Body Composition

Two studies reported body composition as an outcome.^{18,24} In one study²⁴ an increase in fat-free mass was associated with a decrease in percentage of body fat, in a sample of cancer survivors who completed a 12-week moderate- to high-intensity aerobic and resistance training intervention after completing high-dose chemotherapy. In contrast, no significant changes in body composition or weight were found for breast cancer survivors who followed a 12-week home-based, unsupervised light- to moderate-intensity walking intervention.¹⁸ However, there was a tendency towards a decrease in fat mass and an increase in fat-free mass in the exercise group (and vice versa in the control group) between baseline and intervention completion.

Methodological evaluation of the studies

The methodological features of the studies are summarised in Table 2. None of the studies met all four criteria used to assess quality in this review. Using the information reported, three of the 10 studies met two criteria;¹⁶⁻¹⁸ three met one criterion,^{19, 26, 28} and four met none of the criteria.^{20, 21, 25, 27} Four studies used randomisation to allocate participants to groups,^{16-18, 26} and of these, only Thorsen et al.¹⁶ reported an unbiased randomisation process, using computerised random assignment from an external site. Four studies analysed data on an intention-to-treat basis.^{17-19, 28} In another five articles, the analyses were described as intention-to-treat; however, data from some participants were not included in the analyses.^{16, 21, 25-27} For all studies information about the flow of participants through the study was provided, and all reported the numbers of participants who dropped out or were lost to follow-up. Blinding of data collectors to group allocation was not reported by any study, and thus this

criterion could not be adequately assessed. Six studies, however, included haematological or immunological outcomes, which were likely to have been assessed by blinded assessors.^{19, 21, 25-28}

INSERT TABLE 2 ABOUT HERE

Discussion

This systematic review summarizes the major results and evaluates the methodological quality of exercise interventions for cancer survivors during the rehabilitation period. To our knowledge this is the first review to focus on this time period, which commences immediately after primary cancer treatment is completed. Only 10 studies (described in 13 articles¹⁶⁻²⁸) were located for inclusion in this review, which illustrates the ‘early’ nature of this work. Although variations in participants, study designs and interventions among the studies do not allow for a synthesis of their data, the findings from this review suggest that exercise can provide a variety of benefits for cancer survivors during the rehabilitation period. These include positive impacts on physical functioning, strength, physical activity levels, QoL, fatigue, immune function, haemoglobin concentrations, potential markers of recurrence, and body composition.

While most researchers reported their *outcomes* reasonably well, methodological details were lacking for most studies. Study characteristics that were not described well included: the timing between treatment completion and study enrolment, the recruitment process (including what strategies were or were not successful), and adherence to the exercise programme. Compliance with the exercise prescription or study protocol was not discussed in any study. These omissions do not allow for a comprehensive assessment of study quality, generalizability of findings, or potential sources of bias, all of which would be valuable to researchers who are developing future intervention studies for cancer survivors post-treatment.

Most studies also suffered from methodological limitations. No study reported whether data collectors were blinded from group allocations, and none met all the three remaining criteria for methodological rigour developed by Stevinson et al.¹² (randomisation of group allocations, unbiased randomisation process, and the use of intention-to-treat analysis). The highest quality score was 2 of 4 criteria, which was achieved by three studies.¹⁶⁻¹⁸ All three were randomised controlled trials. Only

one of these reported power calculations, and it was the largest included study ($n = 111$).¹⁶ Four studies did not meet any criterion, and none of these were randomised controlled trials.^{20, 21, 25, 27}

After examining the quality ratings and other study characteristics (e.g. study design, sample size, type of exercise intervention, reporting of power calculations), it became apparent that no high quality studies of exercise interventions in the rehabilitation period have been published to date. This reflects not only the lack of information reported for each study but also the newness of this field. As the research expands in this area, it is expected that the methodological quality of the studies will improve, as it has for studies of exercise interventions for patients during breast cancer treatment. To improve the quality of research in this area, researchers should address issues of methodological quality, in addition to ensuring all factors are reported accurately.

An additional finding was that studies varied considerably in the exercise prescribed, which makes it difficult to recommend a specific exercise protocol for cancer survivors in the rehabilitation period. Nonetheless, all the prescribed exercise interventions were deemed safe and feasible for the targeted populations. Additionally, adherence rates (reported by 7 of 10 studies) were high, suggesting that cancer survivors who participate in exercise studies are highly motivated, regardless of the exercise prescription. It should be noted, however, that none of the studies reported participant preferences for frequency, type, intensity or duration of exercise sessions. Without evidence about these preferences or the optimal exercise prescription for health benefits, future researchers should continue to prescribe exercise as appropriate for the intended study outcomes (e.g. increased fitness, decreased fatigue). Exercise prescriptions should take into consideration (1) general population prescription guidelines (e.g. American College of Sports Medicine²⁹); (2) successful protocols from previous studies with cancer survivors (such as those included in this review); and (3) the requirements of the specific cancer survivor population (e.g. weight bearing exercise for survivors of treatments that decrease bone strength).

Two further limitations of the studies in this review should be noted. Although it was outside the scope of this review to explore these in detail, they are important for evaluating the quality of the literature in this field. First, as identified in previous reviews of exercise and cancer patients^{12, 30} most of the studies had numerous outcomes, more than the number assessed in the current review. Second,

the studies tended to report only positive findings, arbitrarily defined as those having a p-value of less than 0.05. The biases in making multiple statistical comparisons and reporting only positive findings must be acknowledged.

Limitations of the review

Although a comprehensive literature search was performed, it is possible that eligible studies were missed. Even if every published paper had been included, there could still have been bias arising from the fact that many of the published studies assessed multiple outcomes but reported only the positive findings. In contrast, reliance on published studies probably resulted in the inclusion of the most rigorous studies, which were likely to have their findings reported no matter the outcome. Due to the small number of studies and the heterogeneity in populations, exercise programmes, outcomes and follow-up periods, a meta-analysis, or a discussion of trends in outcomes, was not deemed feasible at this time.

Future directions

To advance the field, researchers evaluating exercise interventions during the rehabilitation period are encouraged to:

- Develop a consistent timeframe to define the rehabilitation period
- Evaluate changes in outcomes most relevant to the rehabilitation period (e.g. physical functioning, QoL, immune/haematological, markers of recurrence, participants feelings of support, PA levels)
- Identify appropriate measures of these outcomes for the target population, and standardise measures to allow for cross-study comparisons
- Undertake further feasibility studies in understudied populations to ensure piloting of interventions and collection of baseline data for future sample size calculations, prior to implementing large scale studies
- Avoid methodological limitations in large-scale studies for which sufficient feasibility data exists (e.g. breast cancer) by using:

- Randomised group allocation
- Unbiased randomisation method for group allocation (e.g. at a remote site or by drawing sealed sequentially numbered envelopes)
- Data collectors blinded to group allocation
- Intention-to-treat analysis

In reporting evaluations of exercise interventions for cancer survivors during the rehabilitation period, researchers are encouraged to report:

- Time (the range of weeks or months) between cancer treatment completion and study enrolment
- Adherence with the intervention protocol and compliance with the exercise prescription
- Power calculations
- Findings from all analyses conducted, including null findings
- Effect sizes and comparisons with pre-determined clinically significant effect sizes
- Successes and failures with recruitment and intervention implementation

Conclusion

Few intervention studies have been conducted with cancer survivors in the rehabilitation period. As might be expected of research in an emerging field, methodological limitations are evident in studies in this field. These make it difficult to draw firm conclusions about the efficacy or effectiveness of exercise interventions for these cancer survivors. Acknowledging these limitations, the initial evidence indicates that exercise programmes are feasible and may provide physiological and psychological benefits for cancer survivors during the rehabilitation period. Future studies with rigorous study designs are now required to advance the field.

Conflict of interest statement

None of the authors have any financial and personal relationships with other people or organisations that could inappropriately influence this work.

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Table 1. Characteristics and results of studies that evaluated the effects of exercise on cancer survivors during the rehabilitation period (sorted by 'months since treatment').

Study	Months since treatment ^a (criteria)	Type of study	No. of Patients	Sex	Age (years)	Types of Cancer	Duration (wks of exercise)	Exercise Programme	Intensity	Frequency	Results
Dimeo et al. ²⁶	≤5 (criteria)	RCT	Ex: 33 C: 37	M, W	39-40 (mean)	Mixed - mainly breast cancer following HDC & PBST	~2	Cardiovascular cycling 30 minutes (intervals) (15 x [1 minutes cycling at intensity + 1 minutes recovery]) (supervised)	50% HRR	Daily while in hospital	- ↓drop in maximal performance - ↓neutropenia & thrombopenia duration - ↓symptoms - ↓duration of hospitalisation
Dimeo et al. ²⁵	≤5 (criteria)	CCT	Ex: 16 C: 16	M, W	39-42 (mean)	Mixed – mainly breast cancer and non-Hodgkin's lymphoma following HDC & PBST	6	5 x 3min – 1 x 30 minutes treadmill walking (supervised)	Treadmill speed matched to lactate concentration of 3 mmol/L Corresponding to 80% APMHR or 90% MHR	Daily	- ↑ maximum performance - ↑ Haemoglobin concentration - ↓ self-reported fatigue
Hayes et al. ²¹⁻²⁴	.6 (maximum)	CCT	Ex: 6 C: 6	M, W	16-64 (range)	Mixed	12	20-40 minutes treadmill walking or stationary cycling & 3-6 resistance machine exercises (supervised)	70-90% MHR	3 aerobic sessions/wk 2 resistance sessions/wk	- ↑ VO ₂ & peak aerobic capacity - ↑ strength in upper body, lower body, & handgrip - ↑ global, physical and psychosocial QOL - ↔ immune parameters - ↑total energy expenditure - ↑fat-free mass with ↓ in % body fat
Thorsen et al. ¹⁶	1 ±.25 (mean & SD)	RCT	Ex: 59 C: 52	M, W	18-50 (range)	Mixed – mainly breast cancer (plus gynaecological, lymphoma and testicular)	14	At least 30min/ session Choice of exercise (usually walking, but also included cycling, strength training, water activities, ball games) (programme developed with exercise physiologist, but exercise was unsupervised)	RPE 13-15 Some patients used HR monitors: 60-70% APHMR	≥2 sessions/wk	- ↑ VO ₂ (predicted ^b) - ↔ mental distress and emotional function - greater ↓ in fatigue in control group N.B. mean number of days exercise was not different between exercise and control groups. Dose-response relationship identified in all patients between minutes exercise/ week and cardiovascular fitness

Hutnick et al. ¹⁹	2 (maximum)	CCT	Ex: 28 C: 21	W	29-71 (range)	Breast cancer	12	(total sessions = 40-90 minutes) 5 minute warm-up 4 x upper and lower body resistance exercises (8-12 repetitions x 1-3 sets) 20 minutes aerobic treadmill exercise (supervised)	Aerobic training: 60-75% functional capacity (based on VO2 max) Resistance Training: Not reported	3 sessions/ wk	- ↑ VO2max - ↑ upper body strength - ↑ % of proliferating CD4 ⁺ CD69 ⁺ T-helper cells (immunologic indicators) - ↑ DNA synthesis - ↔ Plasma and mitogen-stimulated IL-6 and IFN-γ production
Nikander et al. ¹⁷	≤6 (criteria)	RCT	Ex: 14 C: 14	W	41-65 (range)	Breast cancer	12	10 minute warm-up and cool-down 30-40 minutes aerobic exercise (supervised: circuit based skipping and jumping, step-aerobics/ unsupervised: walking, cycling, swimming etc) (Supervised and unsupervised)	RPE 11-16 (HR monitors were used to check intensity. Intended to be just below anaerobic threshold.)	1 session/ wk supervised 2-3 sessions/ wk home-based unsupervised	- ↑ physical performance (dynamic agility: figure-8 running test) - ↑ dynamic muscle performance (peak jumping power) - ↔ maximal isometric muscle force (leg extension & elbow flexion) - ↔ timed 2 km walk distance
Allgayer et al. ²⁸	9 (maximum)	RT	Moderate intensity Ex: 13 Low Intensity Ex: 10	M,W	49-60 years (mean)	Colorectal cancer	2	30-40 minutes aerobic exercise (type not defined, stationary bike used for testing) (not reported but probably supervised since in hospital)	30-40% or 55-65% maximum power output depending on group.	Daily individual exercise	Moderate-intensity group vs. low-intensity group - ↓ anti-inflammatory response
Allgayer et al. ²⁷	9 (maximum)	RT	High intensity Ex: 29 Moderate Intensity Ex: 19	M,W	58-59 years (mean)	Colorectal cancer	2	30-40 minutes aerobic exercise (type not defined, stationary bike used for testing) (not reported but probably supervised since in hospital)	° 30-40% or 50-60% maximum power output depending on group.	Daily individual exercise	Moderate Intensity Group: - ↓ oxidative DNA damage (indicator of risk of recurrence) High Intensity Group: - ↑ DNA damage

Matthews et al. ¹⁸	≤12 (criteria) [median = ~10 months)	RCT	Ex: 22 C: 14	W	51-57 (mean)	Breast cancer	12	20-40 minutes of walking [Home-based, unsupervised – + 1 x 30 minute in-person counselling visit & 5 brief phone calls over the 12 weeks)]	RPE 11-13	3-5 walks/ wk	- ↑ walking for exercise - ↔ body composition/weight
Hsieh et al. ²⁰	‘within weeks of completing treatment’ (criteria)	Pre-test, Post-test	Ex: 74 (n = 96 but 22 did not have adjuvant treatment, results from this group are not included here)	W	57.9 ± 10.4 years (mean)	Breast cancer	~26	60 minutes “whole-body” exercise individually prescribed (e.g. 10 min warm-up, 40 minutes aerobic/ resistance/ flexibility training, 10 minute cool-down) Aerobic exercise included treadmill, stationary cycling, recumbent stepping, underwater treadmill. Resistance/ flexibility exercises targeted major muscle groups. (supervised)	40-75% HRR	2-3 individual sessions/ wk	- ↑ predicted VO2 - ↑ timed treadmill fitness test - ↑ % of age predicted forced vital capacity - ↓ resting HR - ↓ fatigue

RCT: randomised clinical controlled trial, CCT: controlled clinical trial (non-randomised), RT: Randomised Trial (comparing exercise groups of different intensities), Ex: exercise/intervention group, C: control group, HRR: heart rate reserve, HDC: High-dose chemotherapy, PBST: peripheral blood stem-cell transplantation, ↔ no change, ↑ increase, ↓ decrease, APMHR: age predicted maximum heart rate (220 beats per minute - age), MHR: maximum heart rate (based on exercise testing), VO2: oxygen consumption (based on exercise testing), RPE: Borg’s Rating of Perceived Exertion scale (6-20), HR: Heart rate, wk: week, QoL: Quality of Life

^a The most accurate method reported for the study (maximum, mean & SD, or inclusion criteria)

^b ‘Predicted’ VO2 is determined using a submaximal exercise test and extrapolation.

^c Although given different names, the prescribed exercise in Allgayer²⁸ and Allgayer²⁷ was very similar. Low-intensity in Allgayer²⁸ and moderate-intensity in Allgayer²⁷ are defined as 30-40% of maximum power output. Moderate-intensity in Allgayer²⁸ is defined as 55-65% and high-intensity in Allgayer²⁷ is defined as 50-60% maximum power output.

Table 2. Methodological quality of studies that have evaluated the effects of exercise on cancer survivors during the rehabilitation period

(sorted by 'months since treatment').

Study	Randomisation	Unbiased randomisation process	Blinding of data collectors	Intention-to-treat analysis	Adherence with exercise protocol
Dimeo et al. ²⁶	Yes	NR	NR	No – 10 dropouts not included	Participants completed 82% (±10%) of sessions
Dimeo et al. ²⁵	No – group allocation based on proximity to facility	No	NR	No – 4 dropouts not included	NR
Hayes et al. ²¹⁻²⁴	No – matched groups (age, gender, marriage status, exercise history, weight, living distance from centre, diagnosis, number of transplants, chemotherapy regime)	NR	NR	No – 1 drop out not included	67% of participants attended 100% of sessions. 33% participants missed 1/12 weeks.
Thorsen et al. ¹⁶	Yes – stratified for sex & diagnosis	Yes	NR for fitness; No for Questionnaires (self-report)	No – 28 drop outs not included. ^a	97% of participants met the exercise frequency minimum of 2 sessions/week. N.B. 69% of control group participants also met this target.
Hutnick et al. ¹⁹	No – group allocation based on geography and/or preference	No	NR	Yes	82% of intervention participants attended all sessions in the first 3 months.
Nikander et al. ¹⁷	Yes – stratified by age	NR	NR	Yes	Participants attended 78% of all supervised exercise sessions. Mean home sessions completed = 2.1 (meets study protocol)
Matthews et al. ¹⁸	Yes – (2:1, intervention to control)	NR	NR – some outcomes were self-report	Yes	Participants completed 94% of the required number of walking sessions
Allgayer et al. ²⁸	No – based on week of treatment completion and some patients were allowed to switch to the alternate group after allocation	NR	NR – possibly since all outcomes were lab based	Yes	NR
Allgayer et al. ²⁷	No – based on week of treatment completion and some patients were allowed to switch to the alternate group after allocation	NR	NR – possibly since all outcomes were lab based	No – 4 drop outs not included	NR
Hsieh et al. ²⁰	Single group design	NA	NR	NA	~90% adherence to exercise intervention (no further details were provided)

NR: not reported, NA: not applicable

^a Intention-to-treat analysis: “to some extent, ascertained that dropouts... had no significant effect on the results reported”