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Review

Physical exercise results in the improved subjective well-being of a few or is effective rehabilitation for all cancer patients?

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Abstract

Physical exercise as an intervention in cancer patients has attracted increasing interest. This review examines the published randomised controlled trials on physical exercise, during and after cancer treatment, focusing primarily on recruitment of patients, patient compliance, content of the intervention programmes and outcome measures. We performed systematic searches of PubMed, PsychInfo, Cancerlit and the Cochrane Library using the MESH terms *exercise*, *neoplasms*, *cancer*, *rehabilitation* and *intervention*. We identified 12 randomised trials with sample sizes ranging from 21 to 155 patients. Only four studies reported the number of patients assessed for eligibility and the reasons for exclusion; 15% to 30% of patients assessed for eligibility were randomised into the intervention programmes. Drop-out rates in the trials ranged from 0% to 34%. Most studies included female breast cancer patients (nine studies, 62% of total number of patients). Interventions included aerobic exercise training (10 studies) and resistance exercise (two studies). The studies used a wide range of instruments to assess health-related quality of life (HRQOL) and the physical exercise capacity. The studies indicated promising effects on both physiological and psychological outcomes. Randomised clinical studies are few, small in scope, and mainly focus on breast cancer patients. Complete knowledge about the type of physical exercise most beneficial for patients at different stages of the disease progression is still lacking. Future work should identify fewer and more specific endpoints.

Keywords: Physical activity, exercise; Cancer; Rehabilitation; Intervention; Quality of life

1. Introduction

Most diseases affect patients' physical function. Historically, patients with chronic diseases were advised to rest and to avoid physical activity [1]. However, excessive rest and lack of physical activity may result in deconditioning and thus reduce functional capacity and quality of life [2]. Current medical opinion is changing to the belief that patients should be encouraged to be physically active during rehabilitation [3]. Exercise rehabilitation during or after medical treatment is now considered an effective means of restoring physical and psychological function [1].

Cardiology was the first medical speciality in which exercise rehabilitation was implemented and evaluated [4,5]. Physical exercise is now commonly prescribed in cardiac patients and is integral to the rehabilitation programme. Psychological, social and physical benefits of physical exercise after myocardial infarction, coronary artery bypass grafting, heart transplantation and stable congestive heart disease are well documented [6,7]. Physical exercise also has a positive effect on mild to moderate levels of depression in clinically depressed patients [8].

Recruitment of patients into an exercise intervention is a challenge. Exercise presupposes personal commitment

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related to motivation, ability and will. Low participation rates in intervention programmes (e.g., compliance) and motivation to continue training influence the programme's impact, and low compliance with medical treatment is a threat to all types of intervention study.

Despite the high prevalence of physical and emotional impairment in cancer patients, exercise rehabilitation is still not a common component of cancer treatment. However, a growing interest in the field of physical rehabilitation among cancer patients has recently emerged. Some cancer patients are offered systematic physical rehabilitation on an individual basis or as group therapy. Until recently, rehabilitation for cancer patients has mainly been limited to physical treatment addressing specific impairments after surgery or chemotherapy [9,10].

Although some evidence suggests that physical exercise among cancer patients is generally beneficial, there is still a lack of knowledge about the optimal types, duration, frequency, and timing of exercise [11]. The aerobic component has been emphasised in physical exercise programmes and health promotion in general [12]. However, such an approach may over-emphasise the importance of the aerobic component to the detriment of other types of exercise, such as strength training. Studies comparing aerobic and non-aerobic exercise in the treatment of anxiety disorders and muscular skeletal pain suggest that increased aerobic capacity is not the most important mechanism underlying the beneficial effects of physical exercise on non-specific muscular pain and anxiety [13,14]. An important goal for cancer patients is to improve the quality of life (QOL) by maximising functions affected by the disease and its therapy. Therefore, it is important to understand the effect of different exercise regimes on cancer patients at different stages of disease and treatment.

Short-duration interventions are a general problem in exercise programmes. Some interventions are too short to produce any effects. However, this depends on how the primary endpoint of the intervention is defined. For endpoints that include subjective outcomes such as QOL measures, the instrument's dimension(s) or selected endpoint(s) should be identified before subjects are recruited. Data generated from outcomes not defined before the start of the trial should be regarded as hypothesis-generating [15–17].

Previous reviews on different aspects of physical exercise and cancer treatment, have focused mainly on physiological and psychological effects of the interventions [11,18–21]. Some have focused on the effects of exercise on specific symptoms, such as cancer-related fatigue [19]. Open clinical studies have recently called for an update of the 'state-of-the-art' knowledge on this topic [22–25].

Previous reviews have concluded that physical exercise may improve QOL following cancer diagnosis. To our knowledge, no reviews have focused on the important methodological problems concerning patient recruitment and compliance, and the ability to generalise from the results.

Patient withdrawal (drop-out) during intervention is a general problem in experimental research, and of special relevance in physical exercise interventions. In healthy populations, approximately 50% of those who start an exercise programme drop out during the first six months [26]. A large drop-out rate may reduce the sample's representation of the larger population, the strength of the findings and the ability to generalize from the results. Medically related drop-out may be controlled through inclusion criteria; although strict inclusion criteria reduces the drop-out rate, it also decreases the ability to generalise from the results [26,27]. A high drop-out rate often results in a biased sample, which may lead to unclear results and conclusions about the direct clinical effects and about the cost versus the benefit of exercise intervention.

This review focuses on physical exercise interventions in cancer patients. The primary aim was to address the methodology used in these controlled studies—specifically patient recruitment and compliance, the content of the interventions and study outcomes. A secondary aim was to discuss the effects of exercise intervention on cancer patients.

2. Methods

Electronic searches of Medline (PubMed), PsychInfo, Cancerlit and Cochrane Library were conducted using the following keywords and combinations: exercise AND (neoplasms OR cancer) AND rehabilitation AND intervention. To be included, the studies had to be randomised clinical trials of physical exercise during or after cancer treatment. The search was limited to the English-language literature, and included studies published up to and including May 2003. Studies with multiple interventions (e.g., exercise combined with other therapies such as cognitive therapy, social support, or diet) and pilot studies were excluded [25,28]. Relevant publications were manually searched for further references. However, the manual search found no further studies. We identified 12 papers that met the inclusion criteria.

The following variables were identified and systematically evaluated in each paper: age, gender, cancer type and oncological treatment (listed in Table 1). Table 2 lists the number of patients assessed for eligibility and reason(s) for the patients declining to participate and/or exclusion by their doctor, the number of patients randomised and the number of patients dropping out during the intervention. Table 3 lists the type, length and intensity of the exercise interventions. Table 4 lists the outcomes and results from these studies.

3. Results

3.1. Patient recruitment

The sample sizes in the 12 studies ranged from 21 to 155 patients (median 49.5). In total, 1697 patients were assessed for eligibility in the randomised studies, of which 973 (57%) declined. Table 2 describes the reasons for the patients declining. Consequently, 724 patients (457 women, 219 men and 48 gender not reported) were randomised to an exercise programme or control (non-exercise) group.

3.2. Patient characteristics

Nine of the studies included female breast cancer patients, of which eight studies included patients with disease stages I or II [29–37]. Thus, most of the patients (62%) were female breast cancer patients. One study included stomach cancer patients, one included acute leukaemia patients and one included prostate cancer patients [38–40]. Three studies included samples with mixed cancer diagnoses (e.g. colon, Hodgkin's disease, non-Hodgkin's disease, small-cell lung carcinoma, testis cancer, and sarcoma/adenocarcinoma) [35–37] (see Table 1).

Table 1
Cancer type, oncology treatment, and patient age, number and sex

Reference	Cancer type	Age (years)	Patient numbers and gender	Type of oncological treatment
Courneya and colleagues, 2003	Breast cancer	Range 50–69 Mean 59	53 female	Surgery, radiotherapy, and/or chemotherapy with or without current hormone therapy
Segal and colleagues, 2003	Prostate cancer	Range NR Mean 68	155 male	Androgen deprivation therapy
Burnham and colleagues, 2002	Breast, colon, and lung cancer	Range NR Mean 52	18 female 3 male	Surgery, radiation or chemotherapy, or a combination of the three
Segal and colleagues, 2001	Stage I and II breast cancer	Range NR Mean 51	123 female	Adjuvant chemotherapy and radiotherapy/hormone therapy
Young-Moo and colleagues, 2000	Stomach cancer	Range 28–75 Mean 55	NR	Curative surgery
Dimeo and colleagues, 1999	Breast carcinoma, metastatic breast carcinoma, seminoma, sarcoma/adenocarcinoma, small-cell lung carcinoma, Hodgkin, non-Hodgkin	Range 18–60 Mean 40	37 female 22 male	High-dose chemotherapy
Dimeo and colleagues, 1997	Breast cancer, metastatic breast cancer, germ cell cancer, sarcoma, small-cell lung carcinoma, non-small-cell lung carcinoma, adenocarcinoma, neuroblastoma	Range 18–60 Mean 39	51 female 19 male	High-dose chemotherapy
Mock and colleagues, 1997	Stage I and II breast cancer	Range 35–65 Mean 49	50 female	Radiation therapy
MacVicar and colleagues, 1989	Stage II breast cancer	Range NR Mean 45	49 female	Standard chemotherapy after surgery
Winningham and colleagues, 1989	Stage II breast cancer	Range 31–66 Mean 45	24 female	Adjuvant chemotherapy
Winningham and colleagues, 1988	Stage I, II and III breast cancer	Range 27–71 Mean 46	42 female	Adjuvant chemotherapy
Cunningham and colleagues, 1985	Acute leukaemia	Range 14–44 Mean 23	10 female 20 male	Chemotherapy/radiation therapy

NR, not reported.

Table 2
Patient recruitment and drop-out

Reference	Number of patients assessed for eligibility	Number (percentage) of patients excluded	Reasons for exclusion (number)	Number of patients randomised	Percentage (number) of patients who dropped out of intervention by group	Number of patients who completed intervention
Courneya and colleagues, 2003	370	317 (86%)	Physician did not reply or did not contact survivors (47), survivors did not reply to recruitment letter or letter returned unopened (232), patients did not meet inclusion criteria (38)	53	Total 2% EG (1)	52
Segal and colleaguesm 2003	507	352 (69%)	NR	155	Total 13% EG (8) CG (12)	135
Burnham and colleagues, 2002	21			21	Total 14% CG (1) LI (1) MI (1)	18
Segal and colleagues, 2001	378	255 (67%)	Patients not interested (62), programme interfered with work (34), doctor would not allow patient to participate (32), medical conditions (8), patients unwilling to be randomized (6), no reason given (113)	123	Total 20% SU (10) SD (7) CG (7)	99
Young-Moo and colleagues, 2000	35			35	NR	35
Dimeo and colleagues, 1999	63	1 (2%)	ECG abnormalities (1)	62	Total 20% EG (5) CG (7)	50
Dimeo and colleagues, 1997	80	10 (13%)	Patients did not fulfil criteria for inclusion (8), ECG abnormalities (2)	70	Total 34% EG (11) CG (13)	46
Mock and colleagues, 1997	65	15 (23%)	Patients not interested (6), patients could handle no more (6), patients had no time to participate (3)	50	Total 8% from both groups	46
MacVicar and colleagues, 1989	62	13 (21%)	Patients reclassified to a more advanced stage of disease (9), patients experienced adverse effects of chemotherapy (2), patients were placed on cardiotoxic drug (2)	49	Total 8% from both groups (4)	45
Winningham and colleagues, 1989	34	10 (29%)	Patients with thyroid dysfunction (4), tamoxifen treatment (3), surgery for obesity (1), skin folds exceeding maximum reading by skin-fold calliper (2)	24	NR	24
Winningham and colleagues, 1988	42	0	NR	42	NR	42
Cunningham and colleagues, 1985	40	0	NR	40	Total 25%: from all three groups (10)	30
All	1697	973 (57%)		724	$N=102$	622

CG, control group; ECG, electrocardiography; LI, low-intensity exercise; MI, moderate-intensity exercise; NR, not reported; SD, self-directed group; SU, supervised group; TG, training group; UC, usual care; EG, exercise group.

Table 3
Description of type, length and intensity of the exercise interventions

Reference	Type of intervention	Duration of sessions and programme, frequency of sessions	Exercise intensity
Courneya and colleagues, 2003	**EG:** Recumbent or upright cycle ergometry. **CG:** Did not train.	15 wk 3× wk 15–35 min each session	70–75% of maximal oxygen consumption in untrained subjects.
Segal and colleagues, 2003	**REG:** Nine supervised strength-training exercises (leg extension, calf raises, leg curl, chest press, latissimus pulldown, overhead press, triceps extensions, biceps curl, and modified curl-ups). Two sets of 8–12 repetitions. **CG:** Waiting list for exercise.	12 wk 3× wk session duration NR	60–70% of 1-RM.
Burnham and colleagues, 2002	**LIG:** Exercise using treadmill, stationary bicycles, and stair-climbing machines. **MIG:** Exercise on treadmill, stationary bicycles, and stair-climbing machines. **CG:** No exercise.	10 wk 3× wk 10–32 min each session	**LIG:** Started at 25–35% HRR, building to 40% by wk 10. **MIG:** Started at 40–50% HRR, building to 60% by wk 10.
Segal and colleagues, 2001	**SD:** Progressive walking programme with standardised series of warm-up and cool-down exercises, 5× wk at home. **SU:** Walking 2× wk at home and 3× wk at hospital; exercise specialist-led 7–10 min warm-up and standard cool-down; participants completed their walking exercise at individually prescribed pace. **CG:** Standard practice. Phone calls every 2 wk to check progress and to help participants overcome any barriers to exercise.	26 wk 5× wk session duration NR	50–60% of predicted VO_{2max}.
Young-Moo, and colleagues 2000	**EG:** Exercise programme in bed, consisting of active ROM exercise, pelvic tilting exercise, and isometric quadriceps-setting exercise for 30 min with supervision; patients encouraged to walk as soon as possible. When ambulatory, patients completed 30 min of supervised aerobic exercise using arm and bicycle ergometry, 2× d. **CG:** NR.	2 wk 2× d 5× wk 30 min each session	NR.
Dimeo and colleagues, 1999	**EG:** Daily programme of aerobic exercise (cycle ergometry in bed), which simulates the cycling motion without patients leaving bed. Interval exercise 1 min exercise followed by 1 min rest to total of 30 min every day. Patients supervised. The mean workload during training programme was 30 ± 5 W. **CG:** standard practice.	30 min each session Every day during hospital stay Workload range 20–40 W	50% HRR.
Dimeo and colleagues, 1997	**EG:** Daily programme of aerobic exercise (cycle ergometry in bed). Interval exercise 1 min followed by 1 min rest to total of 30 min every day. Patients supervised. The mean workload during training programme was 32 ± 5 W. **CG:** Standard practice.	During hospital stay; mean stay 13.6 d in TG, 15.2 d in C every day Workload range 20–40 W	50% HRR.
Mock and colleagues, 1997	**EG:** Self-paced progressive walking programme to avoid overexertion followed by 5 min slow walking (cool-down). Individualised advice based on age, exercise history and fitness level. **CG:** Standard practice.	6 wk programme during radiotherapy 4–5× wk 20–30 min each session	Self-paced.

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Table 3 (*continued*)

Reference	Type of intervention	Duration of sessions and programme, frequency of sessions	Exercise intensity
Winningham and colleagues, 1989	**EG:** Individualised (Winningham Aerobic Interval Training) using cycle ergometry. **CG:** Maintain normal activities and notify staff if they start exercise or rehabilitation programme.	10–12 wk 3× wk 20–30 min each session	60–85% of MHR attained on symptom-limited GXT.
Winningham and colleagues, 1988	**EG:** Warm-up and cool-down of stretching and flexibility exercises. Exercise prescription based on symptom-limited GXT. Aerobic interval exercise using cycle ergometry. **PG:** Patients met with the exercise leaders weekly for conversational interaction and the same stretching and flexibility exercises used as warm-up and cool-down in the EG. **CG:** Patients instructed to continue normal activities and notify staff if they start exercise on their own or in a group.	10 wk 3× wk	60–85% of MHR attained on symptom-limited GXT.
Cunningham and colleagues, 1985	**PT5:** 15 repetitions of biceps-triceps curls, bench press, shoulder retractions, straight leg raises, hip extensions, hip abductions, sit-ups and knee extensions. **PT3:** Same as PT5, but 3×wk. **CG:** No therapy, usual care.	5 wk 3 or 5× wk 30 min each session	
MacVicar and colleagues, 1989	**EG:** Interval training using cycle ergometry, with a specific ratio of high-to-low workload or resistance for a set time. As fitness improved, patient spent less time exercising at lower intensity and more time at higher intensity. Staff monitored patients and recorded heart rate and blood pressure every 5–7 min. **PG:** Patients performed supervised flexibility and stretching exercises. Heart rate and blood pressure measured every 5–7 min as in EG. **CG:** Patients instructed to carry on with normal activities. No other contact with project staff besides pre- and post-study data collection.	10 wk 3× wk Session duration NR	60–85% of HRR as measured in GXT

1-RM, one-repetition maximum or the maximum amount of weight that can be lifted once; CG, control group; EG, exercise group; GXT, graded exercise test; HRR, heart rate reserve (calculated as 220-age-resting heart rate); LIG, low-intensity exercise group; MHR, maximum heart rate; MIG, moderate-intensity exercise group; NR, not reported; PG, placebo group; PT3, physical therapy three times weekly; PT5, physical therapy five times weekly; REG, resistance exercise group; ROM, range of motion; SD, self-directed group; SU, supervised group; x, number of times exercise completed in the relevant time period (e.g., 2×d is twice daily, 5× wk is five times each week); W, watts.

In 10 studies, the intervention was conducted when the patients were undergoing radiotherapy and/or chemotherapy treatment [22,29–33,36,38–40]. Two trials implemented exercise after the treatment was finished [34,35]. Most patients received treatment with a curative intent (93%). However, one study included a mix of patients receiving treatment with either curative or palliative intent [40].

3.3. Compliance

Forty-three per cent ($n = 724$) of the eligible patients agreed to participate in the interventions. Of these, 102 (14%) patients dropped out during the interventions, and 622 patients completed the exercise period. The drop-out rates across studies ranged from 0% to 34%. Three studies did not report data on drop-outs [32,33,39].

3.4. Adherence to the interventions

Seven studies reported data on the adherence to interventions [29,30,34–37,40]. The adherence rates ranged between 72% and 100%. One study with an adherence rate of 98% reported that missed sessions were rescheduled [34]. Another study comparing a self-directed exercise and a supervised exercise group reported that the participants completed at least 93 of 130 (72%) training sessions in both types of intervention [29].

3.5. Characteristics of the interventions

The interventions lasted from 2 to 26 weeks. In all studies, the patients performed the exercise individually (i.e. not in a group). In 10 of the studies, an instructor supervised the exercise programmes, which were either for in-patients or out-patients. One study included self-

Table 4
Effects of exercise training on predefined primary and secondary outcomes

Author	Outcomes	Questionnaires and methods of measurement	Results
Courneya and colleagues, 2003	**Primary outcomes:** Peak oxygen consumption and QOL.	**Physiological outcomes:** Peak oxygen consumption: incremental exercise protocol using cycle ergometry, expired gases collected and analysed.	**Peak oxygen consumption:** Significant difference between CG and EG, mean change 0.29 l/min (3.4 mlkg^{-1} min^{-1}) higher in the EG ($P=0.001$).
	Secondary outcomes: Happiness, self-esteem, fatigue and QOL sub-scales.	**QOL outcomes:** Self-esteem Scale RSES, FACT-F, FACT-B, FACT-G.	**Overall QOL:** Significant difference between CG and EG, mean change 8.8 points higher in EG, ($P=0.001$). **QOL outcomes:** Significant differences in happiness ($P=0$ .019), self-esteem ($P=0.010$), fatigue ($P=0.006$), physical well-being ($P=0.001$) in favour of EG.
Segal and colleagues, 2003	**Primary outcome:** Fatigue and disease-specific quality of life.	**QOL outcomes:** FACT-F, FACT-P.	**Fatigue score:** Increased by 0.8 points in the EG, decreased by 2.2 points in the CG ($P=0.002$).
	Secondary outcome: Muscular fitness.	**Physiological outcomes:** Submaximal test of muscular fitness (chest press at 20 kg and leg press at 40 kg at a cadence of 22 repetitions/min); maximum number of repetitions before failing to maintain cadence was recorded.	**Disease-specific HRQOL:** Increased by 2.0 points in EG and decreased by 3.3 points in the CG ($P=0.001$).
			Muscular fitness: Significant difference between CG and EG in muscular fitness for both chest press ($P=0.009$) and leg press ($P=0.001$).
Burnham and colleagues, 2002		**QOL-outcomes:** Quality of Life Index for Cancer patients, LASA.	**QOL:** Significant increase in quality of life ($P=0.001$) and energy in EG compared with CG.
		Physiological outcomes: Aerobic capacity measured during treadmill exercise measured with indirect calorimetry. Lower body flexibility measured with a modified sit-and-reach test. Body composition assessed as sum of subcutaneous skin folds.	**Physiological outcomes:** Compared with CG, EG showed a statistically significant increase in aerobic capacity ($P=0.001$) and lower-body flexibility ($P=0.027$), and decrease in body fat ($P=0.001$).
Segal and colleagues, 2001	**Primary outcome:** Physical functioning.	**QOL-outcomes:** SF-36, FACT-G and FACT-B.	**Physical Functioning:** Significant difference between SD and CG, (9.8 points; $P=0.01$) and borderline significance between SU and CG, 6.3 points; $P=0.09$).
	Secondary outcomes: Remaining seven sub-scales of SF-36, VO_{2max} and QOL.	**Physiological outcomes:** VO_{2max} measured with submaximal stepping ergometer test to predict VO_{2max} (m-CAFT).	**VO_{2max} and QOL:** No significant differences between the groups.
Young-Moo and colleagues, 2000	**Primary outcome:** NKCA.	Blood samples.	NKCA decreased until postoperative day 7 and then increased. At day 14, NKCA of the EG was significantly higher than in CG ($P=0.05$).
Dimeo and colleagues, 1999	**Primary and secondary outcomes:** Not defined. Psychological distress.	POMS and SCL-90R.	**Fatigue:** Fatigue score of 9.6–11.7 ($P=0.28$) in EG and 9.2–11.5 ($P=0.02$) in CG. **Somatic complaints:** Complaints score of 4.2–4.3 ($P=0.97$) in EG and 4.1–6.6 ($P=0.001$) in CG increased significantly.

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Table 4 (*continued*)

Author	Outcomes	Questionnaires and methods of measurement	Results
			Psychological distress score of 22.7-17.7 ($P=0.03$) in EG and 19.6–20.7 ($P=0.68$) in CG. Scores decreased significantly in EG, but not in CG.
Dimeo and colleagues, 1997	**Primary outcome:** Loss of MPP.	**Physiological outcome:** Maximal walking speed in km/h on a incremental treadmill exercise test.	**Loss of MPP:** 14% in the EG (7.9 to 6.8 km/h) and 19% in the CG (7.5 to 6.1 km/h), $P=0.05$, resulting in loss of MPP 27% higher in the CG than in the EG. Significant difference ($P=0.04$) between the maximal performance of both groups at discharge.
	Secondary outcomes: Days in hospital, severity of mucositis, diarrhoea, infection, pain and haematological indexes.	Severity of complications measured by WHO scale.	**Days in hospital** significantly lower in EG (15.2 d in CG and 13.6 d in EG; $P=0.03$). **Severity of pain and diarrhoea** significantly lower in EG ($P=0.01$ and $P=0.04$, respectively). **Duration of neutropenia** significantly higher in CG (7.6) than in EG (6.6) ($P=0.01$).
Mock and colleagues, 1997	**Primary and secondary outcomes:** Not defined. Physical functioning, fatigue, emotional distress, difficulty sleeping.	Cooper 12 min walk test, PFS, SAS.	**Physical functioning:** Increased significantly in the walking group compared to the control group (33.7 ft in EG and 30.89 ft in CG, $P=0.003$). Significant differences in fatigue score (24.7 in EG and 45.5 in CG, $P=0.018$), anxiety (10.44 in EG and 26.93 in CG, $P=0.029$) and difficulty sleeping (12.38 in EG and 32.58 in CG, $P=0.027$).
MacVicar and colleagues, 1989	VO_{2max}.	Expired air collected and analysed for fraction of O_2 and CO_2 during an maximal cycle ergometry test.	EG showed significantly increased VO_{2max} compared to PG and CG. VO_{2max} improved by mean of 40% from pre-to post-test (1.02 l/min to 1.45 l/min from start to end of study) in EG. No significant changes in VO_{2max} in PG and CG. $P=0.05$ between the EG and PG and CG.
Winningham and colleagues, 1989	Weight control (balanced beam scale) and body composition.	Skin fold measures: triceps, suprailiac crest, anterior thigh.	Significant difference between the EG and CG in the mean total of three skin fold measures. EG lost 3.19 mm compared with 9.6 mm gain in the CG ($P=0.008$). Body weight: Both groups gained weight from beginning to end of study; mean weight gain 1.99 kg in CG and 0.82 kg in EG ($P=1.888$).
Winningham and colleagues, 1988	Nausea.	SCL-90R.	Significant differences between EG and PG and CG in nausea ($P=0.032$).
Cunningham and colleagues, 1985	**Primary and secondary outcomes:** Not defined. Arm muscle circumference, biochemical parameters, skin fold measure.		No change in arm muscle circumference in either group. Muscle protein-sparing effect of exercise based on significant decrease in creatinine excretion in CG only, suggesting loss of muscle protein in CG.

Abbreviations: CG, control group; CO_2, carbon dioxide; FACT, functional assessment of cancer therapy; FACT-B, FACT-breast; FACT-F, FACT-fatigue; FACT-G, FACT-general; FACT-P, FACT-prostate; HRQOL, health-related quality of life; LASA, linear analogue self-assessment; MPP, maximal physical performance; NKCA, natural killer cell cytotoxic activity; O_2, oxygen; PFS, Piper fatigue scale; PG, placebo group; POMS, profile of mood state; QOL, quality of life; RSES, Rosenberg self-esteem scale; SAS, symptom assessment scale; SCL-90R, Derogatis Symptom Check List; SD, self-directed group; SF-36, medical outcome survey short form; SU, supervised group; VO_{2max}, maximal aerobic capacity; WHO, World Health Organization.

directed exercise programmes at home [30]. Another study compared a self-directed group at home with a supervised group at hospital [29].

3.6. Type of exercise

Two studies used resistance exercise (exercises to increase muscular strength) programmes [38,40], whereas 10 trials used aerobic exercise [30,32–36,39–41] (Table 3).

In the 10 studies using aerobic exercise, the type, intensity and frequency of exercise varied substantially between studies. An exercise bicycle comprised part of (two studies) or the entire (six studies) exercise programme in eight studies [32–36,39,41]. Two studies used a progressive walking programme [29,30]. One study used a treadmill, exercise bicycle and stair-climbing machine [35].

Five studies used an aerobic interval training method with a specific ratio of high-to-low workload for a set number of minutes. Three studies set exercise intensity at 60–85% of the maximal heart rate (MHR) achieved in a symptom-limited, graded exercise test [31–33]. One study used a low-intensity (50% of the MHR) programme with an leg ergometer in bed [36,37].

Five studies included continuous, constant-intensity exercise [29,30,34,35,39]. The intensity varied between 50% and 85% of measured or predicted maximal aerobic capacity (VO_{2max}).

To allow individualised adaptations to the cancer treatment and to prevent over-exertion, two trials allowed patients to control their own exercise intensity [29,30].

3.7. Definitions of outcome measures

Nine studies used one or more outcomes to evaluate the physical effects of the intervention [29–32,34,35,37,38,40]. Six studies measured peak oxygen consumption (VO_{2max}) or cardiovascular capacity, and three specified that this was the primary outcome of the study [31,34,37]. Cardiovascular capacity was assessed using different methods.

One study measured muscular fitness using a standard-load test, which required patients to complete a maximum number of repetitions of the chest press and leg press at a set cadence [40]. One study measured upper arm muscle circumference [38].

The studies included a variety of subjective outcomes, which ranged from 2 to 12, with a median of seven. Four studies defined various QOL measures and five studies defined physical outcomes as the primary outcomes; four studies used a mixture of outcomes, without defining primary or secondary outcomes. Eight studies measured QOL by a variety of generic, disease-specific and symptom-specific questionnaires (Table 4) [29,30,33–37,40]. Three studies specified the domain that was the primary health-related quality of life (HRQOL) outcome. The following dimensions and questionnaires were used: physical functioning by the SF-36, fatigue assessed by the cancer and symptom-specific FACT-fatigue questionnaire, and nausea measured by the Derogatis Symptom Check List (SCL-90R) [29,33,40]. Four studies defined overall QOL as an outcome [29,34,35,40]. Studies also reported a wide range of physiological and psychological variables. These included the physical variables of body composition, body weight, diarrhoea, infection, pain, and biochemical parameters, and the psychological variables of happiness, self-esteem, physical well-being, depression, energy, anxiety, confusion, emotional distress and problems sleeping (Table 4).

Four of the trials specified neither primary nor secondary outcomes [30,35,36,38].

4. Effects

Four studies reported significantly increased cardiovascular capacity in the exercise group compared with the control group [30,31,34,35]. One study found no change in VO_{2max} and no differences between the exercise and control groups; however, in patients not receiving chemotherapy, *post-hoc* analysis showed, that VO_{2max} increased significantly in the supervised exercise group compared with the controls [29]. One study evaluated physical performance after high-dose chemotherapy. Physical performance decreased in both groups, but the decline was significantly higher at discharge from hospital in the control group than in the exercise group [37]. Exploratory analysis in a study on prostate cancer patients showed that resistance exercises improved upper- and lower-body fitness regardless of curative or palliative treatment intent, or whether patients had received androgen deprivation for less than one year or for one year or more [40].

In three studies, overall HRQOL improved significantly in the exercise group compared with the controls [34,35,40], whereas another study failed to find any such difference [29].

Three studies reported a significant reduction in fatigue [30,34,40]. One study observed a significant reduction in fatigue, but the between-group analysis did not reach statistical significance [35]. In another study, no statistical analyses were performed to detect between-group differences [36].

One study found that physical functioning increased in a self-directed exercise group compared with the control group [29].

Three studies showed significant changes in the exercise group, after an exercise programme, on psychological variables such as happiness, general well-being, self-esteem, energy and problems sleeping [30,34,35]. Mock and co-workers reported significantly lower anxiety in the exercise group. Another study observed a non-significant reduction in anxiety, and significant improvements in various other factors such as body composition (percent body fat), natural killer cell activity (NKCA), diarrhoea and duration of neutropenia [35]. Two studies failed to show significant differences between the groups in depression [30,35].

None of the studies performed follow-up assessments of physiological or psychological functioning after termination of the intervention programmes.

5. Discussion

We identified 12 randomised studies from our literature search on physical exercise intervention and cancer treatment. Most samples consisted of female breast cancer patients (62% of the randomised patients), except for one large trial with male prostate cancer patients (21%), resulting in a relatively homogeneous study population. However, the studies were heterogeneous in terms of outcome measures, questionnaires to assess HRQOL, and types of test to determine aerobic capacity. The studies also differed widely in the length of the exercise programme, its intensity, content and frequency, and the timing of the interventions in relation to the patient's disease and treatment. In 10 studies, patients in the intervention groups underwent different oncological treatments, whereas in two studies, the intervention was conducted after termination of therapy. These factors make comparisons difficult and greatly reduce the ability to generalise from the results.

Only the three most recently published papers reported data on patient recruitment according to the CONSORT statement [29,34,40,42]. The earliest trials provided limited information about patient eligibility and their baseline function. Therefore, it is difficult to extrapolate these findings to patients with other cancer diagnoses or different disease disseminations. However, the larger samples in the latest published trials have improved the strength of the statistical analyses for the particular group of cancer patients studied—women with breast cancer and men with prostate cancer. Despite the methodological weaknesses, the recent improved reporting of methodology is promising.

5.1. Recruitment and adherence

As in other study populations, recruitment of cancer patients into physical exercise programmes and their adherence to the programmes represents a challenge for researchers [43,44]. The studies reviewed differed greatly in their descriptions of recruitment and adherence [41]. Not all studies provided information about patient refusal rates and the reasons for refusal. We believe that the results pertain to a select group of patients who were interested in participating in an exercise-based rehabilitation shortly after diagnosis. There are reasons to believe that patients who are willing to participate in an exercise intervention programmes following a cancer diagnosis differ from those who decline participation with regard to characteristics such as age, education, earlier physical exercise habits, fitness level and body mass index. None of the studies provided information about patients who chose not to participate. However, it is important to understand the factors that influence patient recruitment in to an exercise programme following a cancer diagnosis. Patients must exhibit self-effort and motivation to attend an exercise programme. Thus, it is reasonable to assume that the results from the published studies pertain to a select population of cancer patients.

The studies that reported adherence to the exercise programme obtained a high level of adherence and a low drop-out rate. A high drop-out rate might be an indicator that the exercise programme was inappropriate for the patient group. The adherence rates in the two studies performed after completion of the cancer treatment were 95% or higher [34,35]. The compliance rates of the interventions performed during active therapies were somewhat lower (72–86%), which is still an acceptable level. We expect lower adherence rates among patients during active treatment, when the patients are experiencing more symptoms. The average attendance rates reported in the exercise studies among patients with muscular-skeletal pain and myocardial infarction are in the same range of 75–80% [43,44].

There is good evidence supporting the advice for cancer patients to be physically active when receiving treatment. Physical activity is likely to alleviate the side-effects of prolonged bed-rest, by helping to maintain muscle mass, physical capacity and physical function. Structured rehabilitation might benefit patients with many or severe symptoms and who struggle to regain their 'normal' function, such as those unable to resume work, or who suffer from chronic fatigue and low physical function after the end of treatment. These patients will probably benefit most from a structured rehabilitation. The effect size should increase in research studies selecting patients most likely to benefit from physical exercise intervention, rather than including the entire patient population. This approach is also likely to be the most cost-effective intervention.

Fatigue is one of the most common symptoms experienced by cancer patients, during and after treatment [45]. Some patients suffer from persistent fatigue for months and years after their cancer is cured. In a pilot study among cured cancer patients suffering from chronic fatigue, fatigue was alleviated after a period of physical exercise [46]. A recently published systematic review on treatment and management of chronic fatigue syndrome concluded that behavioural therapy and graded exercise therapy showed the most promising results [47]. Future research should find ways to identify patients needing a longer period of convalescence after treatment.

Many of the studies were conducted in the laboratory setting, although some used self-initiated exercises at home or in a gym [29,30]. Future studies should attempt to simulate real-life situations to see if this can improve recruitment and adherence rates.

5.2. Content of the exercise programme

Most studies included aerobic training; only two studies used resistance exercises. The characteristics of the different exercise programmes have received little attention, and the influence of exercise frequency and intensity training remain unclear. Segal and colleagues [40] recently reported on resistance exercise training in prostate cancer patients receiving either palliative or curative treatments. To our knowledge, this is the first randomised study to use a structured resistance exercise programme, and to include both palliative and potentially curable prostate cancer patients. Resistance exercise significantly improved the symptoms of fatigue and QOL in both treatment groups. This is also the first study to demonstrate that resistance exercise improves QOL and reduces the fatigue related to cancer treatment. Resistance exercise may be an important component of supportive care for cancer patients, irrespective of the treatment intent.

Retaining physical function and independence in activities of daily living are important factors in palliative patients [48,49] Resistance exercise is a potent physiological intervention to increase muscle mass and attenuate muscle-wasting associated with various catabolic conditions. Resistance exercise consists of relatively few repetitions performed against relatively high resistance, and does not have the same cardio-respiratory effect as endurance exercise. Cancer-induced muscle-wasting is a multi-factorial process influenced by factors such as energy intake and cytokines. The reduced physical activity accompanying cancer fatigue can further accelerate muscle-wasting. We suggest that more studies are needed to investigate the potential benefits of resistance exercise training during cancer treatment, to compare the benefits of aerobic versus resistance exercise, and to include patients with various cancer diagnoses, as well as other patients suffering from disease-related fatigue. Further work is also needed to identify the optimal type(s) of exercise at different stages of cancer treatment.

5.3. Outcomes

Overall, the reviewed studies showed some promising effects of physical exercise on overall quality of life (three studies), fatigue (three studies), physical function (one study), and physical capacity and/or muscular fitness, during and after cancer treatment (six studies).

In many of the studies reporting data on QOL, too many outcome variables were listed (range 2 to 12, median 7) and only four of the trials defined which variables were the primary endpoints [29,33,34,40]. It is essential to decide in advance on a principal QOL endpoint, and if there are additional endpoints, to rank these in order of importance. The POMS-questionnaire and the SCL-90R include several scales, yielding many possible outcomes, not all of which are equally relevant as endpoints after an intervention with physical exercise. For example, phobic anxiety, hostility and obsessive-compulsive traits are outcomes that are, theoretically, not affected by exercise. In a formal analysis, outcome measures should be confined to no more than four or five variables.

The studies used various methods to measure aerobic capacity (VO_{2max}), making direct comparisons difficult. Measuring VO_{2max} gives useful information about the physiological effects of the programme, but yields no direct information about the patients' symptoms, well-being and physical function. We believe that aerobic capacity is best regarded as a proxy variable, and not as a primary endpoint.

The reviewed studies suggest that cancer patients benefit from maintaining physical activity balanced with efficient rest periods. However, follow-up data are absent from these studies. Further research is warranted to focus on the effects of resistance exercises, a combination of aerobic and resistance exercise, and other exercise regimes.

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