Cancer Causes and Control **15**: 1035–1056, 2004.

Exercise interventions for cancer patients: systematic review of controlled trials

Clare Stevinson[1,]*, Debbie A Lawlor[2] & Kenneth R Fox[1]
[1]*Department of Exercise and Health Sciences, University of Bristol, Centre for Sport, Exercise and Health, Tyndall Avenue, Bristol BS8 1TP, UK;* [2]*Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, UK*

Received 16 April 2004; accepted in revised form 13 July 2004

Key words: cancer, rehabilitation, exercise, walking, fatigue.

Abstract

Objective: To systematically review controlled trials investigating the effects of exercise interventions in cancer patients.
Methods: Studies were located through searching seven electronic databases (Medline, Embase, Cochrane Library, CancerLit, PsycInfo, Cinahl, SportDiscus), scanning reference lists of relevant articles, contacting experts (n = 20), and checking the contents lists of journals available through ZETOC (Electronic Table of Contents). To be included, trials had to be prospective, controlled, involve participants diagnosed with cancer and test an exercise intervention. Types of outcome were not restricted. Two reviewers independently applied the selection criteria.
Results: Thirty-three controlled trials (including 25 randomized trials) were included in the review. There was some evidence that physical function was increased among those who exercised. Furthermore, symptoms of fatigue did not appear to be increased and there were few adverse effects reported. There was insufficient evidence to determine effects on other outcomes, such as quality of life, with results hampered by the heterogeneity between studies as well as poor methodological quality. Data were also lacking on the long term effects of exercise relating to cancer recurrence or survival.
Conclusions: There is preliminary evidence that exercise interventions for cancer patients can lead to moderate increases in physical function and are not associated with increased symptoms of fatigue. However, it is impossible from current evidence to determine whether exercise has long term beneficial effects on survival or quality of life.

Introduction

Exercise has a role in the management or rehabilitation of an increasing number of chronic diseases including coronary heart disease [1], hypertension [2], stroke [3], obesity [4], non-insulin dependent diabetes [5] and musculoskeletal disorders [6]. Although it has also been recommended for helping cancer patients recover from treatment [7], exercise rehabilitation is not generally incorporated into cancer care or discussed with patients [8, 9]. Potential benefits of exercise include helping to preserve or restore cardiopulmonary function, muscle and bone strength, and mobility, all of which can be adversely affected by cancer therapy. Furthermore, exercise may help promote psychological well-being following cancer diagnosis and treatment. Conversely, there may be risks associated with exercise for cancer patients, particularly possible exacerbation of fatigue – an important symptom that affects more than half of all patients to a significant degree [10].

Several reviews of the literature have suggested that exercise is likely to be beneficial for cancer patients [11–17]. However, in addition to not employing fully explicit and systematic methods, these reviews have incorporated studies of various types including retrospective surveys and uncontrolled trials. Clearer indications of the effect of exercise interventions are provided by prospective clinical trials with appropriate control groups [18]. A recent systematic review in this area identified 12 randomized trials and concluded that initial

* Address correspondence to: Clare Stevinson, Department of Exercise and Health Sciences, University of Bristol, Centre for Sport Exercise and Health, Tyndall Avenue, Bristol BS8 ITP, UK. Ph.: +44-117-331-1108; Fax: +44-117-331-1148; E-mail: C.Stevinson@bristol.ac.uk

evidence was promising for both physiological and psychological benefits of exercise [19]. In a more extensive search of the literature we have identified 25 randomized trials and eight non-randomized studies and have performed a statistical synthesis of the data in order to determine the effects of exercise in cancer patients.

Materials and methods

Search strategy

The following electronic databases were searched from their respective inceptions to December 2003: Medline, Embase, Cochrane Controlled Trials Register, CancerLit, Cinahl, PsycInfo, SportDiscus. Search terms included subject headings and text words based on (i) cancer (*e.g.*, neoplasms; tumour; oncology); (ii) exercise (*e.g.*, exercise therapy; physical activity; sports); (iii) clinical trials (*e.g.*, controlled clinical trials; random) and were modified according to the specific vocabulary map of each database. In addition, a simple search of 'cancer AND (exercise OR physical activity)' was set-up *via* ZETOC (Electronic Table of Contents) of all British Library journals, with results received in a daily e-mail notification. Contact was made with 20 experts known to be working in the field to ask if they were aware of any further published or unpublished trials [20]. Finally, the reference lists of review articles on the subject and studies already located were checked for potential trials. Titles and available abstracts of all items identified by the electronic searches were scrutinized by one author (CS) and a random selection of 25% of the titles/abstracts was independently assessed by a second author (DAL) to check for consistency in selection. A kappa score of 0.95 was achieved. Obtained reports were read by two reviewers (100% by CS and 50% each by DAL and KRF) who independently applied the selection criteria. The three authors then met to discuss any disagreements and reach consensus.

Selection criteria

Trials were included if they involved human participants who had been diagnosed with cancer. Participants could be of any age, either sex, have any type or stage of cancer or be at any stage of treatment or recovery. Only prospective trials with a control arm were included. Control arms could comprise no intervention (*e.g.*, normal care), an alternative intervention (*e.g.*, counseling, relaxation) or a different exercise type (*e.g.*, aerobic *versus* flexibility exercises). Trials with healthy or historical control groups were excluded. Non-randomized trials were included as well as randomized ones. This was an *a priori* decision made on the basis that the number of randomized trials might be small and that it was important to appraise all available evidence. Trials were included if they tested interventions involving regular exercise of any type (*e.g.*, aerobic, resistance, flexibility). Exercise could be the sole intervention or combined with other interventions (*e.g.*, diet, counseling). Trials of single exercise sessions that measured acute effects (*e.g.*, [21]) were excluded, as were trials that only investigated the effects of physiotherapy (*e.g.*, [22]). There were no restrictions on the outcomes assessed in trials. Both published and unpublished trials written in any language, in full or abstract form were considered for inclusion.

Data extraction

Included trials were read in full and data were extracted by two reviewers (100% by CS and 50% each by DAL and KRF) using a pre-piloted structured form. Any disagreements or discrepancies were resolved through discussion and checking the original papers. Details on the study design, participants, interventions, outcome measures, results and conclusions were recorded. Where key information was not reported, efforts were made to contact the authors in order to obtain further details.

Quality assessment

In the absence of validated methods of assessing methodological rigor suitable for trials of exercise interventions, trial quality was assessed by recording whether the following features were incorporated in the study design: randomization; allocation concealment; blinding of the main outcome assessment and intention-to-treat analysis. These have been identified as the most important components in minimizing bias in clinical trials [23]. Trials were defined as randomized if the method of allocating participants to intervention and control groups was described using terms such as random, randomly or randomization. Allocation concealment was considered adequate if randomization took place at a remote site or involved drawing sealed sequentially numbered envelopes. Trials were defined as blind if the main outcomes were measured by an assessor who was blind to group allocation. If the main outcomes were measured by a non-blinded assessor or by the participants themselves as with self-report questionnaires, the trial was defined as not blind. Trials were defined as using intention-to-treat analysis if all patients were analysed in the groups to which they were allocated, regardless of completion or adherence. Studies described as using intention-to-treat analysis that excluded participants not completing the intervention, were recorded as not using intention-to-treat analysis.

Data analysis

Included trials were summarized in tables and described in the text. After completion of this descriptive synthesis we examined the data to determine whether there were areas where statistical pooling would be possible. This was determined on the basis of having at least four studies in a similar population group with a similar outcome. On this basis we were able to examine the effect of exercise on physical functioning in patients with breast cancer and also examine the same outcome in a separate pooling of studies that had included patients with any cancer diagnosis. In addition we performed a third meta-analysis of trials (irrespective of cancer type) with fatigue as an outcome. Cancer-related fatigue has been identified as an important outcome and has the potential to be either reduced or increased through exercise. It was considered appropriate therefore to try to quantify this possibility. For each outcome (physical function and fatigue) effect sizes were calculated for each trial using Cohen's method [24] to produce a standardized mean difference for the effect of exercise. It was anticipated that there would be systematic differences (heterogeneity) between the results of studies and a random effects model using DerSimonian and Laird's [25] method was used to calculate the pooled effect size. Heterogeneity between studies was further explored using meta-regression analysis to determine the role of trial type (randomized or not), allocation concealment, blinding of outcome assessment, intention-to-treat analysis and cancer type (for the fatigue meta-analysis only) on difference between studies [26]. Funnel plots were examined and statistical evidence of small study bias (indicative of publication bias) was assessed with Egger and Begg tests [26]. All analyses were undertaken using Stata version 8 [26].

Results

Figure 1 shows the outcome of the search process. From the 80 reports of potential trials that were located, 40 did not meet the eligibility criteria [27–66], and a total of 33 studies reported in 40 different papers were included in the review [67–106]. Data were pooled for 19 trials that assessed physical functioning and 12 trials that assessed fatigue.

Trial characteristics

Table 1 shows the characteristics of included trials. Thirteen trials included breast cancer patients during [67, 70, 72, 74, 76, 77, 79–81], or after [68, 71, 73, 75] adjuvant therapy. Eleven trials involved adult patients with any cancer [85, 87, 90–93, 95–97, 99, 100] and one involved paediatric cancer survivors [94]. The remaining trials included patients undergoing treatment for prostate [82–84], lung [104], colorectal [101], or stomach [105] cancer, multiple myeloma [102] or leukemia [106]. Nineteen studies tested aerobic exercise interventions, of which eight used cycle ergometers [68, 77, 79-81, 93, 96, 105], and eight used walking programs [70, 71, 73, 74, 76, 85, 91, 95]. Three trials tested resistive exercise [82, 83, 106], 10 had combined aerobic and resistive programs [67, 75, 84, 86, 92, 97, 99, 100, 103, 104] and one study was based on team sport activities [94]. Most trials compared an exercise intervention with no intervention; six that did not, used information training [84], psychological therapies [85, 92], stretching [70, 88], or tai chi [71] as comparison arms. Exercise interventions lasted for 10 weeks or longer in 17 trials [67, 68, 72, 73, 76, 77, 79–83, 85, 87, 90, 94, 101, 102], between 4 and 8 weeks in 12 trials [70, 71, 74, 75, 84, 91, 92, 95, 97, 99, 100, 106], and 2 weeks or less in four studies [93, 96, 104, 105]. The longest intervention period of any trial was 26 weeks [72].

Methodological quality

Table 2 shows the methodological features of included trials. In general, studies were of poor quality. There were eight trials not using randomized allocation [73, 80, 81, 86, 93–95, 99], and of the 25 that did, only five indicated that concealment of allocation may have been adequate [68, 82, 92, 102, 104]. Two studies appeared to include participants in the control group who had declined to undertake the intervention [94, 99], and for a further five studies it was unclear whether eligibility (including willingness to participate) was determined prior to group allocation or whether the control group may have solely or partly consisted of those who declined to be allocated to exercise [73, 80, 81, 88, 95]. Assessor blinding for a main outcome measure took place in two trials [68, 100]. In 13 studies, the main outcome measure was completed by the participant, so blinding was not possible [72, 73, 79, 83–85, 92, 93, 97, 99, 101, 102, 104]. The other 18 trials for which assessor

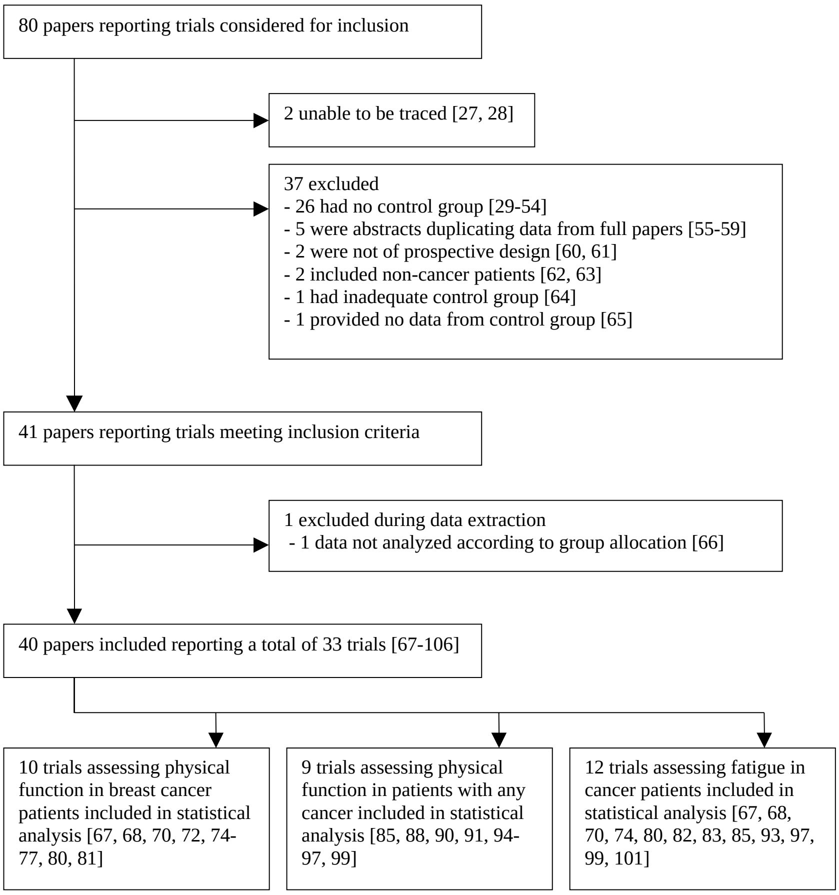

Fig. 1. Process of study selection.

blinding was possible, either did not use blinding [67, 96], or did not state if the assessor was blind to the allocation group [70, 71, 74–77, 80–82, 87, 90, 91, 94, 95, 105, 106]. Four studies analysed data on an intention-to-treat basis [69, 72, 83, 99]. In six other papers intention-to-treat analysis was described [68, 85, 92, 93, 96, 101], but not all the allocated participants were included in the analysis. Other methodological limitations that were common among included trials were small sample sizes and multiple statistical testing. Only eight trials had more than 30 participants per group, [72, 83–85, 92, 97, 101, 104], and 14 trials had 10 or fewer subjects [67, 71, 73, 75, 76, 80–82, 87, 90, 91, 94, 100, 106]. Sample sizes were based on power calculations in only nine trials [67, 68, 72, 74, 83, 85, 89, 94, 104], with two failing to recruit the required number [67, 89], and a further trial reported an insufficient sample size from a *post hoc* power calculation [106]. Seventeen trials did not specifically state the primary outcome measures [70, 73, 74, 76, 84, 87, 90–94, 97, 99, 100, 102, 104, 106], and even among those that did, there were several with numerous secondary outcome measures and sub-group analyses. With many questionnaire measures having additional subscales and with measurements taken at multiple time-points, some studies involved considerable numbers of statistical comparisons [68–70, 72, 76, 82–89, 91, 94, 97, 99, 101, 106]. Conclusions were commonly based on isolated positive findings (those with a *p*-value below the conventional 0.05 level), while the role of chance as an explanation for these and results with higher *p*-values, was disregarded.

Trial outcomes

Physical function

Thirteen trials reported small but statistically significant improvements in tests of aerobic capacity [68, 70, 77, 80, 81, 88, 90, 95, 100] or timed walk distances [67, 74–76] following aerobic exercise programmes lasting from 6 to 25 weeks. In one study, loss of physical performance was attenuated among inpatients

Table 1. Characteristics of controlled clinical trials of exercise interventions for cancer patients

Author Location	Participants [Number allocated/analysed]	Intervention and control arms	Frequency and duration of exercise	Main endpoints	Reported results	Authors conclusion	Reviewers comments
Breast cancer							
Campbell *et al.* [67] United Kingdom	Breast cancer patients receiving adjuvant therapy [22/19]	(1) Supervised group aerobic and resistive exercise (2) Usual care	2 days per week for 12 weeks	QoL (FACT-B); physical function (12-min walk test); fatigue (PFS)	Group 1 increased distance walked by 333 m more than group 2 ($p = 0.001$)	'exercise may be a safe and effective way of improving the QoL for patients with early stage breast cancer'	All outcomes favoured intervention group but study lacked power
Courneya *et al.* [68] Fairey *et al.* [69] Canada	Post-menopausal breast cancer survivors (average 14 months post-treatment) [53/52]	(1) Supervised aerobic cycle ergometer training (2) Usual care	3 days per week for 15 weeks	Physical fitness (VO_2 max); QoL (FACT-B); fasting insulin; other outcomes included fatigue, body composition, insulin resistance, IGFs	Group 1 improved VO_2 by 0.29 l/min more than group 2 ($p < 0.001$) and also improved more on overall and physical QoL, fatigue, self-esteem, happiness; but not body composition or fasting insulin	'beneficial effects on cardiopulmonary function and QoL' … 'no significant effect on fasting insulin… effects on IGF-I, IGFBP-3 … clinical implications remain to be defined'	Suggests improvements in fitness, fatigue and some psychosocial outcomes are possible after treatment; no clear effects on insulin or insulin resistance
Drouin [70] United States	Breast cancer patients receiving radiation therapy [23/21]	(1) Unsupervised walking (2) Stretching	3–5 days per week for 7 weeks	Physical function (VO_2 peak); muscle strength (dynamometry); body composition (calliper); fatigue (PFS); immune function	Group 1 improved VO_2 by 2.0 ml/kg/min more than group 2 ($p = 0.014$); other outcomes not different between groups	'exercise training is means to improve physical function and body composition… immune parameters and oxidative stress values were not compromised'	Suggests that fitness enhancement is possible during radiation therapy
Galantino *et al.* [71] United States	Breast cancer survivors [11/8]	(1) Tai chi classes and video (2) Walking and stretching classes	1 day per fortnight for 6 weeks	Physical function (6-min walk test); body mass index; QoL (FACT-B); fatigue (BRI)	No differences between groups on any outcomes	'study supports the need for further research on the effect of alternative forms of exercise to manage fatigue'	Study design and size precludes determination of relative benefits of interventions
Segal *et al.* [72] Canada	Breast cancer (stage I–II) patients receiving adjuvant therapy [123/123]	(1) Supervised gym-based walking (2) Unsupervised home-based walking (3) Usual care	5 days per week for 26 weeks	Physical functioning (SF-36); other outcomes included QoL, aerobic capacity, body weight	Group 2 increased perceived physical functioning more than group 3; other outcomes not different between groups	'exercise can blunt some of the negative side effects of treatment, including reduced physical functioning'	Well-designed trial with no consistent effect among multiple outcomes measured

Table 1. Continued.

Author Location	Participants [Number allocated/analysed]	Intervention and control arms	Frequency and duration of exercise	Main endpoints	Reported results	Authors conclusion	Reviewers comments
Segar *et al.* [73] United States	Breast cancer survivors (average 3.5 years post-surgery) [30/24]	(1) Unsupervised gym or home-based aerobic activity (2) Aerobic activity plus behaviour modification (3) No intervention	4 days per week for 10 weeks	Depression (BDI); anxiety (SSTAI); self-esteem (RSEI)	Group 1 and 2 combined in analysis; lower depression, state & trait anxiety than group 3; no change in self-esteem	'exercise may be of therapeutic value with respect to depressive and anxiety symptoms but not to self-esteem'	Aspects of study design and analysis preclude interpretation of data
Mock *et al.* [74] United States	Breast cancer (stage I or II) patients undergoing radiation therapy [50/46]	(1) Unsupervised home-based walking (2) Usual care	4–5 days per week for 6 weeks	Physical function (12-min walk test); fatigue (PFS); symptoms (SAS)	Group 1 improved distance walked 87 m more than group 2 ($p = 0.003$) and had lower symptom intensity for fatigue, anxiety and sleep	'walking program can help manage symptoms and improve physical function during radiation therapy'	Implies possible small effect on symptom severity but results may reflect baseline differences
Nieman *et al.* [75] United States	Breast cancer survivors (average 3 years post-diagnosis) [16/12]	(1) Supervised weight training and aerobic activity (2) No intervention	3 days per week for 8 weeks	Change in NK cell cytotoxic activity; physical performance (6-min walk test)	Group 1 improved distance walked 59 m more than group 2 ($p = 0.02$); no change in NK cell activity in either group	'moderate exercise over 8-week period has no significant effect on *in vitro* NK cells in breast cancer patients'	Suggests no effect on NK cell activity in recovered patients
Mock *et al.* [76] United States	Breast cancer (mostly stage II) patients receiving chemotherapy [19/14]	(1) Unsupervised home-based walking (and weekly support group) (2) Usual care	4–5 days per week for 4–6 months	Physical function (KPS; 12-min walk test); pyschosocial adjustment (PAIS; BSI); body image (VAS; TSCS); symptoms (SAS)	Group 1 increased distance walked by 58 m more than group 2 ($p < 0.05$); also superior psychosocial adjustment, body image and symptom tolerance during treatment but not post-test	'physical and psychosocial benefits from a modest walking program and support group are possible'	Implies possible role in symptom management but caveats exist due to inclusion of support group and baseline differences
MacVicar *et al.* [77] Winningham *et al.* [78] United States	Breast cancer (stage II) patients receiving chemotherapy [62/45]	(1) Supervised aerobic cycle ergometer training (2) Stretching and flexibility once a week (3) Usual care	3 days per week for 10 weeks	Functional capacity (VO_2 max); body weight and composition (for sub-group of 24 non-obese patients)	Group 1 improved $VO_2 > 0.4$ l/min than groups 2 and 3 ($p < 0.05$) and also gained 2.7% less fat and 3.3kg more lean tissue than group 3	'intervention effective in improving functional capacity' . . . 'potential for stabilizing weight as well as reducing fat deposition'	Suggests that beneficial effects on fitness and fat distribution are possible during therapy

Table 1. Continued.

Author Location	Participants [Number allocated/analysed]	Intervention and control arms	Frequency and duration of exercise	Main endpoints	Reported results	Authors conclusion	Reviewers comments
Winningham and MacVicar . [79] United States	Breast cancer (stages II–IV) patients receiving chemotherapy [42/42]	(1) Supervised aerobic cycle ergometer training (2) Stretching and flexibility once aweek (3) Usual care	3 days per week for 10 weeks	Nausea, somatization (SCL-90-R)	More from group 1 (n = 8) improved on nausea ratings than group 2 and 3 ($p = 0.03$) and also overall somatisation	'moderate aerobic exercise may provide some relief from nausea in select patients'	Suggests potential anti-nausea effect
MacVicar and Winningham [80] United States	Breast cancer patients receiving chemotherapy [10/10]	(1) Supervised aerobic cycle ergometer training (2) Usual care	3 days per week for 10 weeks	Functional capacity (VO_2 peak); mood (POMS)	Group 1 improved VO_2 by 0.38 l/min more than group 2 and also improved more on mood but group differences not analysed	'small sample size precludes definitive conclusions… trend toward improved mood warrants further study'	Reported findings may reflect selection bias and regression to mean
Winningham [81] United States	Breast cancer (stage II) patients receiving chemotherapy [8/8]	(1) Supervised aerobic cycle ergometer training (2) Usual care	3 days per week for 10 weeks	Functional capacity (maximum estimated METs); perceived control (LLC)	Group 1 increased functional capacity by 0.8 METS more than group 2 and also greater increase in perceived control but group differences not analysed	'patients improved in functional capacity as result of participation in program'	Indicates the feasibility of exercise programmes for cancer patients
Prostate cancer							
Oliver [82] United Kingdom	Prostate cancer patients receiving androgen deprivation therapy [10/9]	(1) Supervised resistive training (2) Usual care	3 days per week for 12 weeks	Body composition (DEXA and BIS); other outcomes included physical function, fatigue and QoL	Group 1 increased appendicular lean mass by 1.2 kg and total lean mass by 2.3 kg more than group 2 ($p = 0.02$)	'resistive training is an effective adjunct treatment of cachexia in prostate patients on androgen deprivation therapy'	Suggests that muscle wastage is reversible. All outcomes favoured exercise group but study lacked power
Segal *et al*. [83] Canada	Prostate cancer patients receiving androgen deprivation therapy [155/155]	(1) Supervised resistive training (2) Usual care	3 days per week for 12 weeks	Fatigue (FACT-F); QoL (FACT-P); other outcomes were muscular fitness and body composition	Group 1 improved more on fatigue, QoL and muscular fitness than group 2; no differences for body composition	'resistive exercise reduces fatigue and improves QoL and muscular fitness'	Well-designed study suggests that small benefits in some areas are possible
Berglund *et al*. [84] Sweden	Prostate cancer patients – 60% on active treatment [211/115]	(1) Supervised group physical training (2) Group information class once a week (3) Combined group physical and information training once a week (4) No intervention	1 day per week for 7 weeks (plus 1 booster session after 2 months)	Perceived benefits of programme (questionnaire)	Group 3 perceived greater relaxation when sitting and breathing than group 1; satisfaction was higher in group 3 than 1 or 2; no assessment of group 4	'benefit of certain aspects of the physical program is greater in the combination group than physical training alone'	Suggests that multi-faceted interventions are preferred by patients

Table 1. Continued.

Author Location	Participants [Number allocated/analysed]	Intervention and control arms	Frequency and duration of exercise	Main endpoints	Reported results	Authors conclusion	Reviewers comments
Mixed cancers							
Courneya *et al.* [85] Canada	Cancer patients (breast; colon; ovarian; stomach etc.) – 56% completed treatment [108/96]	(1) Unsupervised home-based walking (and weekly group psychotherapy) (2) Group psychotherapy weekly	3–5 days per week for 10 weeks	QoL (FACT-G); other outcomes included life satisfaction, depression, anxiety fatigue, fitness, body composition	Group 1 improved more than group 2 on functional QoL; also fatigue and body composition; prior exercise was higher in group 1	'program may improve QoL in cancer survivors beyond the benefits of group psychotherapy, particularly physical and functional well-being'	Suggests possible effect of exercise on functional outcomes that are not addressed by psychotherapy
Hayes *et al.* [86, 87] Hayes *et al.* [88, 89] Australia	Cancer patients after receiving high dose chemotherapy and autologous peripheral blood stem cell transplantation [12/12]	(1) Aerobic and resistive gym-based training (2) Stretching	3 days per week for 12 weeks	Aerobic capacity (VO_2 peak); muscular strength (gym tests); QoL (CARES); body composition (total body water); immune function	Group 1 improved VO_2 by 7.8 ml/kg/min more than group 2 ($p < 0.05$); also improved more on upper and lower body strength and QoL; no different for immune parameters or body composition	'patients able to regain fitness & strength' … 'reduction in number and severity of problems' … 'preserve and increase skeletal mass' … 'did not facilitate faster immune cell recovery'	Most outcomes favour exercise group but baseline differences and small sample hinder interpretation
Burnham and Wilcox [90] United States	Cancer patients (breast; colon) ⩾ 2 months post-treatment [21/18]	(1) Supervised gym-based low-intensity aerobic training (2) Supervised gym-based moderate-intensity aerobic training (3) No intervention	3 days per week for 10 weeks	Aerobic capacity (VO_2 max); flexibility (sit and reach test), body composition (calliper); QoL (QLICP)	Groups 1 and 2 combined in the analysis; improved VO_2 4.6 ml/kg/min more than group 3 ($p < 0.05$) and also improved more on body fat, flexibility, QoL	'low and moderate intensity programs were equally effective in improving physiological and psychological function'	Implies low and moderate intensity exercise produced similar effects on fitness, but sample size may have been insufficient to detect differences
Mello *et al.* [91] Brazil	Cancer patients receiving bone marrow transplants [32/18]	(1) Supervised walking on treadmill and stretching (2) Usual care	Once daily for 6 weeks	Muscle strength (dynamometry)	Group 1 increased hip flexor strength on non-dominant side more than group 2. Other muscle groups not different.	'exercise program was efficient in promoting an increase of muscle strength'	Walking and stretching programme had little effect on muscle strength

Table 1. Continued.

Author Location	Participants [Number allocated/analysed]	Intervention and control arms	Frequency and duration of exercise	Main endpoints	Reported results	Authors conclusion	Reviewers comments
Petersson *et al*. [92] Sweden	Cancer patients (breast, colon, prostate) within 3 months of diagnosis [442/325]	(1) Supervised group physical training (and information, education, cognitive behavioural therapy) (2) Individual support (3) Combination of interventions 1 and 2 (4) Usual care	1 day per week for 8 weeks (plus 1 booster session after 2 months)	Depression (HAD); anxiety (HAD); subjective distress (IES)	No differences between group 1 and 3 compared with 2 and 4 on depression or anxiety. Avoidance reduced in group 1 in breast patients who were 'monitors' and increased in prostate patients who were 'blunters'	'only the monitor concept seems useful for predicting response to rehabilitation with a strong information component'	No apparent effect of exercise component on psychological outcomes beyond psychotherapy
Dimeo *et al*. [93] Germany	Cancer patients (mostly breast) receiving high-dose chemotherapy and autologous peripheral blood stem-cell transplantation [62/59]	(1) Supervised aerobic training on supine cycle ergometer in bed (2) Usual care	Once daily during hospitalization	Psychologic status (POMS; SCL-90-R)	Group 1 reduced global psychological distress while group 2 did not change, but no group differences analysed	'aerobic exercise can reduce fatigue and improve psychologic distress'	Implies that slight improvements in psychological well-being may be possible
Niesen-Vertommen [94] Canada	Paediatric cancer survivors (average 5 years post-treatment) [20/18]	(1) Supervised group sports (soccer, hockey, basketball etc) (2) No intervention	3 days per week for 12 weeks	Pulmonary function (FVC); aerobic fitness (Vo_2max); self perceptions (SPPC)	Group 1 no different to group 2 for any outcomes	'exercise program did not demonstrate a difference in exercise tolerance'	Exercise may not have been sufficient for fitness change
Dimeo *et al*. [95] Germany	Cancer patients (mostly breast) just completed high-dose chemotherapy and autologous peripheral blood stem-cell transplantation [36/32]	(1) Supervised walking on treadmill (2) Usual care	Once daily for 6 weeks	Physical performance (maximum speed on treadmill test); other outcomes included haemoaglobin levels and fatigue	Group 1 improved speed by 0.72 km/h more than group 2 ($p = 0.04$); haemoaglobin increased by 1 g/dl ($p = 0.04$); 4 patients in group 2 reported fatigue in performing daily activities	'aerobic exercise improves the physical performance of cancer patients recovering from high-dose chemotherapy'	Suggests that patients can exercise and improve fitness after high-dose chemotherapy
Dimeo *et al*. [96] Germany	Cancer patients (mostly breast) receiving high-dose chemotherapy and autologous peripheral blood stem-cell transplantation [70/60]	(1) Supervised interval training on supine cycle ergometer 30 minutes daily (2) Usual care	During hospitalization (~ 2 weeks)	Loss of physical performance (maximum speed on treadmill test); other outcomes included haematologic indices and treatment complications	Group 1 decreased speed by 0.37 km/hour less than group 2 ($p = 0.05$), was hospitalised for 1.6 days less ($p = 0.03$), had less pain and diarrhoea and shorter periods of neutropenia and thrombopenia	'aerobic exercise can be safely carried out immediately after high-dose chemotherapy and can partially prevent loss of physical performance'	Implies possible effect in partially preserving fitness during high-dose chemotherapy

Table 1. Continued.

Author Location	Participants [Number allocated/analysed]	Intervention and control arms	Frequency and duration of exercise	Main endpoints	Reported results	Authors conclusion	Reviewers comments
Berglund *et al.* [97] [98] Sweden	Cancer patients (mostly breast) within 2 months of completing treatment [199/176]	(1) Supervised group physical training (and information and coping skills for 7 weeks) (2) No intervention	1 day per week for 4 weeks	Problems with physical activity, symptoms, QoL (questionnaire)	Group 1 improved more than group 2 on perceived physical strength post-test and 3, 6, 12 months later; also physical training post-test, 3 and 12 months and fighting spirit at post-test, 6 and 12 months, but had poorer baseline scores	'results demonstrate several short-term effects' … 'programme seems to be successful with respect to patients' fighting spirit, physical strength and training as late as 1 year after'	Intervention had no effect on most of the outcomes measured (> 70)
Berglund *et al.* [99] Sweden	Cancer patients (mostly breast) within 2 months of completing treatment [60/60]	(1) Supervised group physical training (and information and coping skills for 7 weeks) (2) Usual care	1 day per week for 4 weeks	Problems with physical activity, symptoms, QoL (questionnaire)	Group 1 improved more than group 2 on physical and social activities and physical strength ($p < 0.05$), but for most outcomes had poorer scores before and throughout 1 year of follow up	'participants improved more on physical strength and increased physical training and social activities more'	No effect reported for most of the outcomes measured; (> 60) poor compliance and exercise only one component
Beuttner and Gavon [100] United States	Cancer survivors within 5 years of diagnosis [18/17]	(1) Supervised group aerobic/strength training (2) No intervention	3 days per week for 8 weeks	Fitness (estimated VO_2, heart rate, strength, flexibility); personality (C16PFQ)	Group 1 improved all aspects of fitness and some of personality, but group differences not analysed	'program was sufficient for improvements in physical fitness'	Suggests fitness improvements are possible in cancer survivors
Other cancers							
Courneya *et al.* [101] Canada	Colorectal cancer patients following surgery [102/93]	(1) Unsupervised aerobic exercise 2) Usual care	3–5 days per week for 16 weeks	Quality of life (FACT-C); other outcomes included life satisfaction, depression, anxiety fatigue, fitness, body composition	No differences between groups on any outcomes; reported levels of exercise similar between groups	'increased cardiovascular fitness is associated with improvements in QoL'	High levels of exercise in control group may have masked effects of intervention

Table 1. Continued.

Author Location	Participants [Number allocated/analysed]	Intervention and control arms	Frequency and duration of exercise	Main endpoints	Reported results	Authors conclusion	Reviewers comments
Coleman *et al.* [102, 103] United States	Multiple myeloma patients receiving high-dose chemotherapy and autologous peripheral stem-cell transplantation [24/17]	(1) Unsupervised home-based aerobic and resistive training (2) Usual care (including advice to walk for 20 minutes 3 days per week)	5 days per week for 12 weeks pre and post transplant	Fatigue, sleep; other outcomes included aerobic capacity, strength, body composition, mood	Group 1 gained lean body tissue compared with group 2; no differences in other outcomes	'patients can maintain or improve fitness levels' … 'exercise program is feasible and may be effective for decreasing fatigue and mood disturbance and improving sleep'	Most outcomes favoured group 1, but substantial amounts of missing data from analysis preclude interpretation
Wall [104] United States	Lung cancer patients about to undergo surgery [104/97]	(1) Unsupervised pre-operative aerobic, resistive and breathing home-based exercises once daily (2) No intervention	Once daily for 1 week pre-surgery	Hope (HHI); power (PKPCT-VII)	Group 1 increased power more than group 2; no different on hope	'exercise is a form of knowing participation in change'	Importance of outcomes for patients unclear
Na *et al.* [105] South Korea	Stomach cancer patients undergoing surgery [35/32]	(1) Supervised aerobic exercise on arm and cycle ergometers in bed twice daily (2) Usual care	5 days per week for 2 weeks	Change in NK cell cytotoxic activity	Group 1 increased NK cell cytotoxic activity more than group 2	'early moderate exercise has beneficial effect on function of *in vitro* NK cells after curative surgery'	Implies exercise-induced immunologic change following surgery
Cunningham *et al.* [106] United States	Acute leukaemia patients receiving bone marrow transplant [40/30]	(1) Supervised resistive exercises (2) Supervised resistive exercises 5 days per week (3) Usual care	3 days per week for 5 weeks	Body composition (skinfolds); muscle protein (nitrogen balance; creatinine excretion)	Group 1 maintained creatinine status while group 3 decreased, but group differences not analysed; no differences in other outcomes	'lack of physical activity appears to have a negative influence on maintenance of muscle protein, but results are not conclusive'	Implies possible sparing of muscle protein through exercise but not clearly demonstrated

Notes. QoL: quality of life; FACT-B: Functional Assessment of Cancer Therapy – Breast; PFS: Piper Fatigue Scale; IGF: (insulin-like growth factor); SF-36: Medical Outcomes Survey – Short Form-36; BDI: Beck Depression Inventory; SSTAI: Spielberger State Trait Anxiety Inventory; RSEI: Rosenthal Self-Esteem Inventory; SAS: Symptom Assessment Scale; NK: natural killer; KPS: Karnofsky Performance Scale; PAIS: Psychosocial Adjustment to Illness Scale; BSI: Brief Symptom Inventory; VAS: visual analogue scale; TSCS: Tennessee Self-Concept Scale; SCL-9-R: Derogatis Symptom Check List – 90-Revised; POMS: Profile of Mood States; METs: metabolic equivalents; LLC; Levenson Locus of Control; DEXA: dual energy X-ray absorptiometry; BIS: bioelectrical impedance spectroscopy; FACT-F: Functional Assessment of Cancer Therapy – Fatigue; FACT-G: Functional Assessment of Cancer Therapy – General; QLICP: Quality of Life Index for Cancer Patients; CARES: Cancer Rehabilitation Evaluation System; HAD: Hospital Anxiety and Depression scale; IES: Impact of Event Scale; FVC: forced vital capacity; SPPC: Self-Perception Profile for Children; C16PFQ: Cattell's Sixteen Personality Factor Questionnaire; HHI: Herth Hope Index; PKPCT-VII: Power as Knowing Participation in Change Test, version II.

Table 2. Methodological features of included trials

Author	Randomized allocation	Concealment of allocation	Assessor blinding for main outcomes	Intention-to-treat analysis for main outcomes	Other aspects
Breast cancer					
Campbell *et al.* [67]	Yes – computer generated number	Not stated	No	No – 3 not included	Sample size calculation indicated insufficient power for main QoL outcome
Courneya *et al.* [68] Fairey *et al.* [69]	Yes – random number table	Yes – sealed envelopes prepared by person not involved with allocation	Yes for fitness & blood tests; No for self-report QoL	No for fitness & QoL – 3 not included; Yes for insulin – last value carried forward	Sample size calculation reported but lacking details; multiple outcomes assessed
Drouin *et al.* [70]	Yes – random number table	Not stated	Not stated	No – 2 not included	Baseline differences existed
Galantino *et al.* [71]	Yes – random number table	Not stated	Not stated	No – 3 not included	
Segal *et al.* [72]	Yes – random numbers table	No	No – self-report measure	Yes	Multiple outcomes assessed; baseline differences existed
Segar *et al.* [73]	No – rotated sequentially	No	No – self report measures	No – 6 not included	Only half of sample included in results
Mock *et al.* [74]	Yes – random for 1st patient then alternate	No	Not stated	No – 4 not included	Lack of outcome data provided; baseline differences existed
Nieman *et al.* [75]	Yes – no detail	Not stated	Not stated	No – 4 not included	Sample size may have lacked power; baseline differences existed
Mock *et al.* [76]	Yes – cluster randomized – no further detail	Not stated	Not stated	No – 4 not included	Baseline differences existed
MacVicar *et al.* [77] Winningham *et al.* [78]	Yes – stratified on aerobic capacity – no further detail	Not stated	Not stated	No – 17 not included	Lack of outcome data provided
Winningham and MacVicar [79]	Yes – no detail	Not stated	No – self report measure	Not stated – no dropouts reported	Lack of outcome data provided
MacVicar and Winningham [80]	Not stated	Not stated	Not stated	Not stated – no dropouts reported	Baseline differences existed
Winningham *et al.* [81]	No – based on ability to attend exercise sessions	No	Not stated	Not stated – no drop-outs reported	Baseline differences existed
Prostate cancer					
Oliver *et al.* [82]	Yes – computerized random number table	Yes – sealed envelopes prepared by individual not connected with study	Not stated	No – 1 not included	Sample size may have lacked power; multiple outcomes assessed
Segal *et al.* [83]	Yes – random number table	Not stated	No – self-report measures	Yes	Sample size calculation indicated adequate power for main outcome measures
Berglund *et al.* [84]	Yes – no detail	Not stated	No – self report measure	No – 96 not included	

Table 2. Continued.

Author	Randomized allocation	Concealment of allocation	Assessor blinding for main outcomes	Intention-to-treat analysis for main outcomes	Other aspects
Mixed cancers					
Courneya *et al*. [85]	Yes – random numbers table – cluster randomized	No	No – self report measure	No – 12 not included	Multiple outcomes assessed
Hayes *et al*. [86, 87] Hayes *et al*. [88, 89]	No – matched groups	Not stated	Not stated	No – 2 not included for some variables	Sample size calculation reported for some variables but lacking details; baseline differences existed; multiple outcomes assessed
Mello *et al*. [91]	Yes – no details	Not stated	Not stated	Not stated – no drop outs reported	Lack of outcome data provided
Burnham *et al*. [90]	Yes – stratified on aerobic capacity & QoL – no further details	Not stated	Not stated	No – 3 not included	Three groups collapsed into 2 for analysis; baseline differences existed on some variables
Petersson *et al*. [92]	Yes – no detail	Yes – performed by statistics unit	No – self report	No – 117 not included	Four groups collapsed into 2 for analysis
Dimeo *et al*. [93]	No – based on date of hospitalisation	No	No – self report measures	No – 3 not included	No inter-group analysis
Niesen-Vertommen *et al*. [94]	No – based on ability to attend exercise sessions	No	Not stated	No	Power calculation reported but lacking details; baseline differences existed
Dimeo *et al*. [95]	No – based on living close to facility	No	Not stated	No – 4 not included	
Dimeo *et al*. [96]	Yes – no detail	Not stated	No – but yes for some secondary outcomes	No – 10 not included	Multiple outcomes assessed
Berglund *et al*. [97, 98]	Yes – Efron biased coin method for small samples	Not stated	No – self-report measures	No	Baseline differences existed on some variables; multiple outcomes assessed
Berglund *et al*. [99]	No – matched control group selected from those declining intervention	No	No – self-report measures	Yes	Baseline differences existed on some variables; multiple outcomes assessed
Beuttner and Gavon [100]	Yes – drawing names without replacement	No	Yes	No – one not included	Lack of outcome data available
Other cancers					
Courneya *et al*. [101]	Yes – random number table	Not stated	No – self-report measure	No – 9 not included	
Coleman *et al*. [102, 103]	Yes – computerized randomization	Yes – sealed envelopes prepared by research assistant	No – self report measures but yes for some other outcomes	No – 14 not included	Lack of outcome data provided; much missing data
Wall *et al*. [104]	Yes – no detail	Yes – sealed envelopes prepared by statistics unit	No – self-report measures	No – 7 not included	Sample size calculation reported but lacking details
Na *et al*. [105]	Yes – no detail	Not stated	Not stated	Not – 3 not included	Lack of outcome data provided
Cunningham *et al*. [106]	Yes – computer generated number	Not stated	Not stated	No – 10 not included	*Post hoc* calculation indicated insufficient power; baseline differences

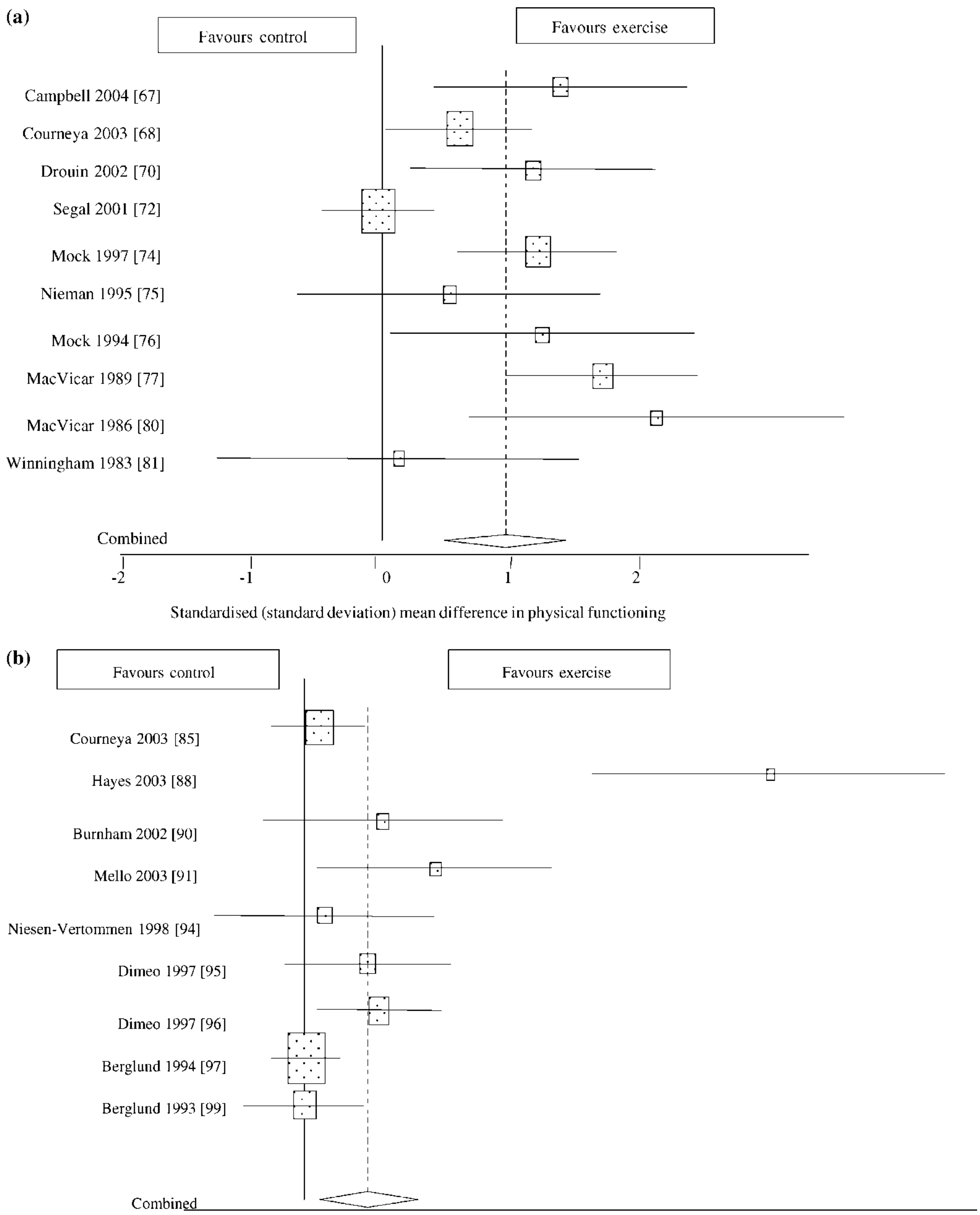

Fig. 2. (a) Effects of exercise on physical function in controlled trials recruiting patients with breast cancer [$n = 10$]; (b) Effects of exercise on physical function in controlled trials recruiting patients with any cancer [$n = 9$].

receiving high-dose chemotherapy who exercised during hospitalization [96]. Increases in muscular strength were recorded after resistive training schedules in three trials [82, 83, 88]. Six other studies reported no differences in fitness parameters [71, 72, 94, 101, 102] or muscle strength [70, 91] following aerobic exercise programmes.

Figure 2 shows the effects of exercise on physical function in 10 trials of breast cancer patients (Figure 2a) and 9 trials of trials that recruited patients with any cancer (Figure 2b). For both groups of patients there was some evidence that exercise improved physical function. For trials that recruited patients with breast cancer the pooled standardized mean difference suggested that those who

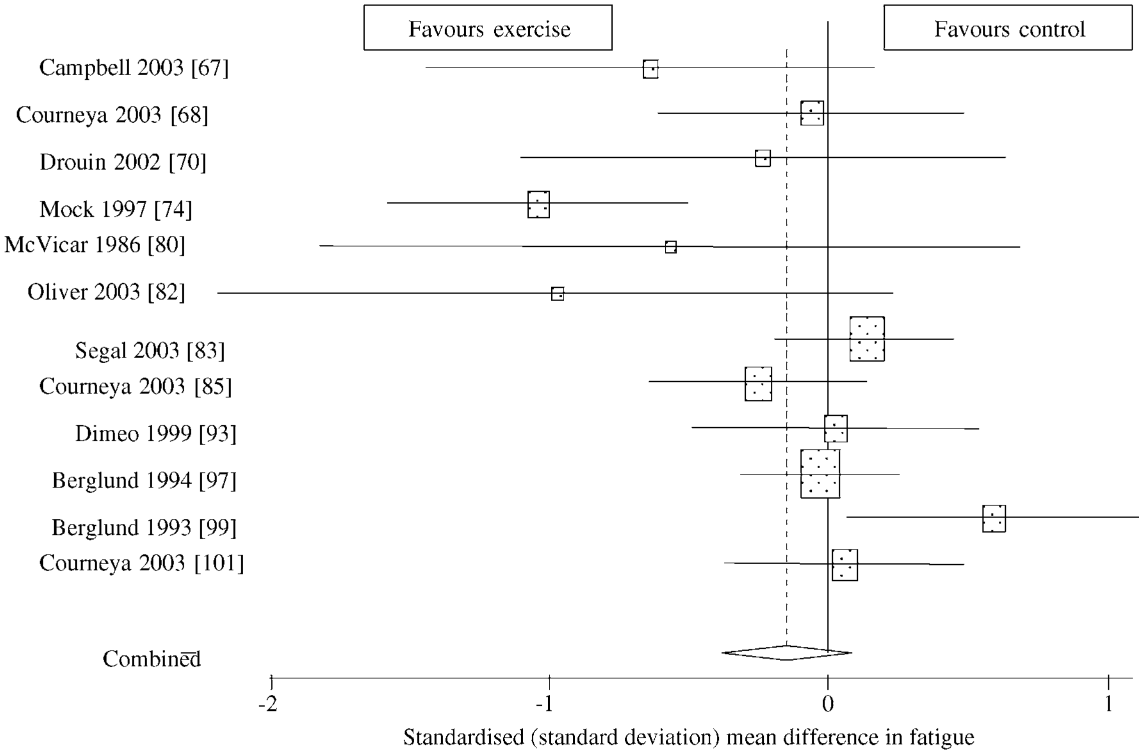

Fig. 3. Effects of exercise on symptoms of fatigue in any cancer trials [$n = 12$]

exercised had on average a 0.96 (95% CI: 0.49, 1.43) standard deviation greater physical function than those who did not. However, there was heterogeneity between studies ($p = 0.001$), which was not explained by whether the trial was randomized ($p = 0.8$), whether there was allocation concealment ($p = 0.5$), blinding of the outcome assessment ($p = 0.5$) or whether there was adequate description of the control group such that it was clear controls were eligible participants ($p = 0.2$). Only one study used intention-to-treat analysis and analysis type was a source of heterogeneity ($p = 0.001$). It should be noted from Figure 2a that the largest study [72], which was also the only study to use intention-to-treat analysis, found no effect of exercise on physical function. There was no evidence of small study bias in this meta-analysis (p-values for Beggs and Egger test both > 0.5). For trials that recruited patients with any type of cancer the pooled standardized mean difference suggested that those who exercised had on average a 0.55 (95% CI: 0.12, 0.97) standard deviation greater physical function than those who did not. However, there was considerable heterogeneity also between these studies ($p < 0.001$), which was mainly due to one small trial that was not randomized, did not blind the outcome assessment and did not undertake intention-to-treat analysis. With this study removed, the pooled standardized mean difference suggested that those who exercised had, on average, a 0.26 (95% CI: 0.03, 0.50) standard deviation greater physical function than those who did not, and there was no heterogeneity between the remaining studies ($p = 0.19$). It should also be noted that two of the largest trials [85, 97], both of which were randomized, showed no effect of exercise on physical function. There was evidence of small study bias in this meta-analysis (both Beggs and Egger test p-value $= 0.01$ with all studies included, and $p = 0.07$ Beggs, and $p = 0.04$ Egger, when the small heterogeneous study was removed).

Fatigue

Reductions in cancer-related fatigue were reported in 10 studies [67, 68, 74, 76, 80, 82, 83, 85, 93, 95], although in three of them, statistical significance was not reached [67, 82] or not tested for [93]. No differences between groups were reported for fatigue in six trials immediately after the intervention or several months later [70, 71, 97–99, 101, 102]. Pooling the data from 12 trials that assessed fatigue suggested that there was no overall effect of exercise on symptoms of fatigue: mean standardized difference −0.15 (−0.38, 0.09) standard deviation (Figure 3). Heterogeneity between studies

($p < 0.001$) was not related to randomization ($p = 0.16$), allocation concealment ($p = 0.65$), intention-to-treat analysis ($p = 0.42$) or choice of control ($p = 0.16$). However, the effect did appear to vary by population type ($p = 0.04$), with some evidence that in trials that recruited patients with any type of cancer [85, 93, 97, 99] finding no effect of exercise on fatigue symptoms: 0.04 (−0.26, 0.35) and those that recruited patients with breast cancer [67, 68, 70, 74, 80] suggesting a modest reduction in symptoms of fatigue among those allocated to exercise: −0.52 (−0.95, −0.09) standard deviation. There was no strong evidence of small study bias in this meta-analysis (Beggs and Egger test both p-values > 0.1).

Body composition

Decreases in skinfold measurements without simultaneous reductions in total body weight were reported in a trial of non-obese breast cancer patients undergoing chemotherapy [78], suggesting that fat mass had been replaced by muscle tissue. Similar findings were reported in two other studies involving breast cancer patients [85, 90]. Increased lean body weight was reported in a trial of patients with multiple myeloma [102], and reductions in body weight and fat mass were described in a sample of breast cancer patients receiving radiation therapy [70]. Appendicular and total lean mass were increased in prostate cancer patients receiving androgen deprivation therapy [82]. Six other studies reported no changes in body weight [72, 86], or skinfold measurements [68, 83, 101, 106]. Changes in muscle protein status of leukemia patients receiving marrow transplants could not be clearly demonstrated [106].

Other physiological parameters

Natural killer cell activity was increased among post-operative stomach cancer inpatients exercising with bed ergometers for 2 weeks [105], but was unchanged in recovered breast cancer survivors following 8 weeks of exercise [75]. T-cell numbers and function were not changed by exercise after high-dose chemotherapy and stem-cell transplantation [87]. No alterations to immune parameters or oxidative stress were observed during exercise in breast cancer patients receiving radiation therapy [70]. In another study of inpatients exercising with bed ergometers while undergoing high-dose chemotherapy and stem-cell transplantation, no changes in haemoglobin or haematocrit were reported [96], but among patients having completed the same treatment, haemoglobin increased by 1 g/dl following a six week walking programme [95]. Fasting insulin, glucose and insulin resistance were not changed by a 15 week training programme in breast cancer survivors [69]. Testosterone and prostate-specific antigen levels of prostate cancer patients did not differ between those following a resistive exercise programme and the control group [83].

Treatment-related symptoms

Sleep problems were reduced in two studies of breast cancer patients [74, 76], while there was a trend towards improved sleep in a trial of patients with multiple myeloma [103]. Decreased nausea was described in one trial of breast cancer patients [79], but did not differ to the control group in another [76]. Lower severity of treatment-related pain and diarrhoea was reported for inpatients receiving high-dose chemotherapy in one study [96]. In a further trial, no differences in frequency and burden of symptoms were reported following exercise, information and coping skills training [97].

Psychosocial outcomes

Increases in global quality of life measures were reported in four trials [67, 68, 83, 89], while five other studies did not demonstrate significant differences between exercise and control groups [71, 72, 97, 99, 101]. Improvements in specific quality of life dimensions of functional [85] and physical [68] well-being were also reported.

Beneficial effects on depression were reported in three studies [72, 73, 76], but not in five others [74, 92, 97, 99, 101]. Anxiety was reduced in two trials [73, 74], but not in five others [76, 92, 97, 99, 101]. A further trial did not find additional effects of a walking programme on depression, anxiety or other psychological outcomes beyond those provided by psychotherapy [85].

One study reported enhanced self-esteem [68], but three others did not [72, 73, 76]. In two trials, body image remained higher for exercisers during [76] and after [74] treatment than for control participants, but no differences in body image were reported in two other studies [97, 99]. Reported reductions in global psychologic distress [93] and changes in psychosocial adjustment to illness and emotional distress [76] during treatment favoured exercise groups.

Adherence

Adherence to exercise interventions was reported to be over 70% in 19 studies [67, 68, 70, 72–76, 82–86, 90, 93, 94, 96, 102, 104]. One trial reported poor compliance with 20% of the sample attending no more than one exercise session [99]. In another study, 51% of the control group reported exercising to the prescribed intervention level, meaning that average level of activity did not differ between groups [101]. Nine of the remaining trials that did not report adherence, involved exercise interventions that were supervised by study personnel [77, 79, 80, 92, 95, 97, 100, 105, 106].

Tolerability

Adverse events were reported in four trials. Lymphedema ($n = 3$), influenza and a gynecological complication were reported among participants from the exercise group, while bronchitis and a foot fracture were reported in participants from the control group in a study with post-menopausal breast cancer survivors [68]. A trial involving patients with multiple myeloma reported no injuries but one patient broke a central venous catheter stitch [102]. Shoulder tendonitis occurred in one breast cancer patient who reportedly exceeded the exercise prescription of the study [70]. Muscle and joint stiffness ($n = 5$) were reported from the control group in a trial of leukemia patients undergoing bone marrow transplant [106]. Nine studies reported that no adverse events occurred [67, 72, 74–76, 89, 90, 95, 96], while no mention of adverse events was made in the remaining 20 trials [65, 71, 73, 77, 79–83, 85, 91–94, 97, 99–101, 104, 105].

Discussion

A total of 33 controlled trials were identified, with studies of breast cancer patients being most common. There was some evidence of improved physical function due to exercise among patients with breast cancer or those with any type of cancer, although the larger and better quality trials tended to report null effects with this outcome. For other outcomes, including quality of life and psychological symptoms, there was no clear or consistent evidence that exercise was beneficial with trials having conflicting results. We found no evidence that exercise resulted in increased fatigue symptoms in patients with cancer. All of these findings need to be treated with caution because of heterogeneity between studies and methodological limitations. Finally, there is no evidence from clinical trials with which to determine the effect of exercise on long term outcomes relating to cancer recurrence or survival.

Methodological issues

Comprehensive search procedures were adopted when locating studies for this review in the attempt to limit the impact of publication and reporting bias [107]. These can result from the tendency for trials not showing positive results to remain unpublished [108], take longer to reach publication [109], or be published in non-English language journals [110]. Furthermore, coverage bias in the non-indexing of a number of European journals in major literature databases has been reported [111]. The comprehensive search procedures used in this review contributed to the inclusion of 13 studies that have not been reported in previous reviews of the literature.

Conclusions of any review are dependent on the quality of the included studies. Although there are signs in this review that this is improving, with some of the more recent trials demonstrating the greatest rigor [69, 72, 82, 83, 104], most trial findings must be interpreted with caution because of methodological limitations. Although the majority of trials were randomized, very few described using an adequate method of allocation concealment. Both inadequate methods of generating, and concealing, allocation sequences are prone to selection bias and associated with overestimations of the value of interventions [112, 113]. Double blinding is not possible with behavioural interventions such as exercise. However, few of the trials that measured objective endpoints reported blinded assessment, which increases the risk of biased assessment and exaggerated treatment effects [112]. Few studies analysed data on an intention-to-treat basis meaning that the advantages of randomization are lost and estimates of efficacy may be inflated [114]. Many of the studies in the review had only small samples, few of which were based on sample size calculations. Differential outcomes between groups in trials with small samples are more likely to be due to chance [115] leading to a false-positive result (type-I error). Conversely, small samples may lack sufficient power to detect significant differences between intervention groups even if they exist, creating a false-negative finding (type-II error). Multiple outcomes measurement and sub-group analyses were undertaken in many trials. This raises the possibility that significant results reported for one outcome among many others in a single study, are due to chance [116, 117].

Effects of exercise

There was some evidence of improvements in physical function. Minimizing loss of physical function during treatment and regaining it afterwards, are important for patients in terms of facilitating activities of daily living. Prolonged inactivity following surgery and adjuvant therapy exacerbates physical debilitation leading to increased fatigue with even minor exertion. Graded exercise interventions have therefore been recommended for breaking the vicious cycle that can develop between inactivity, physical deconditioning, and fatigue [118]. There is evidence that patients undergoing adjuvant therapy, as well as those who have completed treatment, were able to maintain a regular exercise programme without experiencing major adverse effects or increased fatigue. As is always the case with clinical trials, results may only apply to carefully screened patients who are sufficiently motivated to consent to participate. Within wider clinical practice, uptake and adherence to exercise programmes and physical limitations of patients may be more problematic than for participants in the studies reviewed.

For other outcomes it was not possible to elucidate any clear or consistent effects of exercise. There was considerable heterogeneity between studies in terms of participant, intervention and outcome variables and many methodological weaknesses, all of which may contribute to the inconsistencies among results.

Future directions

One of the purposes of conducting systematic reviews in newly developing research fields is to identify and acknowledge the deficiencies in the literature in order to stimulate further and better research in the future [119]. There are currently several important gaps in the evidence base.

Patient groups

Although a number of trials have focused on patients with breast cancer, there are few studies on the other three most common cancers – colorectal, lung and prostate. It is not always appropriate to generalize findings from one cancer population to another due to the major differences in disease-related factors, treatment regimes and patient demographics.

Outcome measures

A large number of outcomes were assessed in some trials with primary endpoints rarely defined. The most important outcomes for cancer patients relate to recurrence of disease, survival, quality of life and ability to perform activities of daily living. Since studies to date have tended to assess outcomes at the end of the exercise intervention only (rather than longer term follow-up), there is currently no evidence from clinical trials of the effect of exercise on disease recurrence or survival. For quality of life and functional abilities, studies should aim to use the same standardized measures so that findings are comparable. Furthermore, it is essential to pre-define main outcome and the magnitude of a clinically important effect for all measures, rather than simply report statistically significant differences based on arbitrary *p*-values.

Intervention components

There is so far little evidence to help identify the optimum mode, frequency, intensity and duration of activity required for beneficial effects in cancer populations. Existing attempts to compare low *versus* moderate intensity activity [90], or gym *versus* home-based exercise [72] have not produced clear findings. A staged approach may be helpful in addressing these issues such as the framework proposed by the Medical Research Council Health Services and Public Health Research Board in the UK for the development and evaluation of complex health interventions [120].

Methodological design

There are multiple methodological weaknesses among existing studies. Randomization, allocation concealment, blinded assessment, intention-to-treat analysis and sample size calculations are all essential for clinical trials of effectiveness. Other design considerations include the choice of comparison arms in order to control for spontaneous improvements over time and the contextual aspects of an intervention (*i.e.*, additional contact with researchers and other participants). Furthermore, studies combining and comparing exercise with other interventions (*e.g.*, support groups; psychotherapy) will help determine how best to integrate rehabilitation strategies to address the full range of needs of patients. Finally, continuing to monitor patients beyond the end of the structured intervention is essential for establishing the long term effects of interventions in promoting sustained physical activity, increasing survival, preventing recurrence and enhancing quality of life.

Conclusion

From a critical evaluation of data currently available from controlled trials, it appears that cancer patients can benefit from improved physical function without increases in fatigue associated with exercise. It is impossible to determine from current evidence whether exercise has direct effects on survival, recurrence or quality of life.

Nonetheless, on the basis of the rationale for exercise during cancer rehabilitation and preliminary findings from existing studies, further research of this subject is encouraged.

Acknowledgements

We thank the following investigators for providing information on study sources and/or additional information about their work: L Buettner (Florida Gulf Coast University), G Berglund (Uppsala University), A Campbell (University of Glasgow), E Coleman (University of Arkansas for Medical Sciences), K Courneya (University of Alberta), A Daley (Sheffield Hallam University), F Dimeo (Freiburg University Medical Centre), J Drouin (University of Michigan-Flint), E Durak (Medical Health & Fitness), S Hayes (Queensland University of Technology), S Macora (University of Wales – Bangor), A Morgan (Fred Hutchinson Cancer Research Centre), N Mutrie (University of Glasgow), S Oliver (University of Wales – Bangor), L-M Petersson (Uppsala University), D Porock (University of Missouri-Columbia), A Schwartz (Oregen Health Services University), R Segal (Ottawa Regional Cancer Centre), M Segar (University of Michigan), B Stoll (St Thomas' Hospital), P Swan (Arizona State University).

Funding: Clare Stevinson is funded by Cancer Research UK [CUK] grant number C3875/A3887. Debbie A Lawlor is funded by a UK Department of Health Career Scientist Award. The views expressed in this paper are those of the authors and not necessarily those of any funding body.

Conflicts of interest: None

References

1. Jolliffe J, Rees K, Taylor RS, Thompson D, Oldridge N, Abrahim S (2004) Exercise-based rehabilitation for coronary heart disease [Cochrane Review]. *The Cochrane Library* Issue 2. Oxford: Update Software.
2. Pescatello L, Franklin, BA, Fagard R, Farquhar WB, Kelley GA, Ray CA, American College of Sports Medicine (2004) American College of Sports Medicine position stand. Exercise and hypertension. *Med Sci Sports Exerc* **36**: 533–553.
3. Gordon N, Gulanick M, Costa F, *et al*., American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council (2004) Physical activity and exercise recommendations for stroke survivors. *Stroke* **35**: 1230–1240.
4. Jakicic J, Clark K, Coleman E, *et al*., American College of Sports Medicine (2001) American College of Sports Medicine position stand. Appropriate intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc* **33**: 2145–2156.
5. Albright A, Franz M, Hornsby G, *et al*. (2000) American College of Sports Medicine position stand. Exercise and type 2 diabetes. *Med Sci Sports Exerc* **32**: 1345–1360.
6. Vuori I (2001) Dose-response of physical activity and low back pain, osteoarthritis, and osteoporosis. *Med Sci Sports Exerc* **33**: S551–S586.
7. Schneider C, Dennehy C, Carter S (2003) *Exercise and Cancer Recovery*. Champaign, IL: Human Kinetics.
8. Jones L, Courneya KS (2002) Exercise discussions during cancer treatment consultations. *Cancer Pract* **10**: 66–74.
9. Stevinson C, Fox K (2004) Role of exercise for cancer rehabilitation in UK hospitals: a survey of oncology nurses. *Eur J Cancer Care* (in press).
10. Curt G (2001) Fatigue in cancer. *BMJ* **322**: 1560.
11. Smith S (1996) Physical exercise as an oncology nursing intervention to enhance quality of life. *Oncol Nurs Forum* **23**: 771–778.
12. Thune I, Smeland S (2000) Is physical activity important in treatment and rehabilitation of cancer patients? [Norwegian]. *Tidsskr Nor Laegeforen* **120**: 3302–3304.
13. Pinto B, Maruyama NC (1999) Exercise in the rehabilitation of breast cancer survivors. *Psychooncology* **8**: 191–206.
14. Courneya K, Friedenreich CM (1999) Physical exercise and quality of life following cancer diagnosis: a literature review. *Ann Behav Med* **21**: 171–179.
15. Courneya K, Mackey JR, Jones LW (2000) Coping with cancer: can exercise help? *Phys Sportsmed* **28**: 49–73.
16. Courneya K (2001) Exercise interventions during cancer treatment: biopsychosocial outcomes. *Exerc Sport Sci Rev* **29**: 60–64.
17. Courneya K, Mackey JR, McKenzie DC (2002) Exercise for breast cancer survivors: research evidence and clinical guidelines. *Phys Sportsmed* **30**: 33–42.
18. Sibbald B, Roland M (1998) Why are randomised controlled trials important? *BMJ* **316**: 201.
19. Oldervoll L, Kaasa S, Hjermstad MJ, Lund JA, Loge JH (2004) Physical exercise results in the improved subjective well-being of a few or is effective rehabilitation for all cancer patients? *Eur J Cancer* **40**: 951–962.
20. McManus R, Wilson S, Delaney BC, *et al*. (1998) Review of the usefulness of contacting other experts when conducting a literature search for systematic reviews. *BMJ* **317**: 1562–1563.
21. Blanchard C, Courneya KS, Laing D (2001) Effects of acute exercise on state anxiety in breast cancer survivors. *Oncol Nurs Forum* **28**: 1617–1621.
22. Schultz I, Barholm M, Grondal S (1997) Delayed shoulder exercises in reducing seroma frequency after modified radical mastectomy: a prospective randomized study. *Ann Surg Oncol* **4**: 293–297.
23. Jüni P, Altman G, Egger M (2001) Assessing the quality of controlled clinical trials. *BMJ* **323**: 42–46.
24. Rosenthal R (1994) Parametric measures of effect size. In: Cooper H, Hedges LV, eds. *The Handbook of Research Synthesis*. New York: Russell Sage Foundation, pp. 231–244.
25. DerSimonian R, Laird N (1986) Meta-regression analysis in clinical trials. *Control Clin Trials* **7**: 177–188.
26. Sterne J, Bradburn MJ, Egger M (2001) Meta-analysis in Stata™. In: Egger M, Davey Smith G, Altman DG, eds. *Systematic Reviews in Health Care: Meta-analysis in Context*. London: BMA Books, pp. 347–369.
27. Turchetta A, Calzolari A, Donfrancesco A, Drago F, Miano C (1990) Physical activity and competitive sport in youngs with leukemia 'off therapy' [abstract]. Proceedings of the World Congress on Sport for All: Tampere, Finland.
28. Whittaker J, Baracos VE, Haennel RG, Brown BE, Humen DP (1991) Exercise training in the posttreatment remission period of patients with limited small cell lung cancer [abstract]. Proceedings

of the 24th Annual Meeting of the Canadian Association of Sport Sciences: Kingston, Ontario.

29. Adamsen L, Rasmussen JM, Pedersen LS (2001) 'Brothers in arms': how men with cancer experience a sense of comradeship through group intervention which combines physical activity with information relay. *J Clin Nurs* **10**: 528–537.
30. Decker W, Turner-McGlade JT, Fehir KM (1989) Psychosocial aspects and the physiological effects of a cardiopulmonary exercise program in patients undergoing bone marrow transplantation for acute leukemia. *Transplant Proc* **21**: 3068–3069.
31. Derman W, Coleman KL, Noakes TD (1999) Effects of exercise training in patients with cancer who have undergone chemotherapy [abstract]. 46th Annual Meeting of the American College of Sports Medicine: Seattle. *Med Sci Sports Exerc* **31**: S368.
32. Dimeo F, Bertz H, Finke J, Fetscher S, Mertelsmann R, Keul J (1996) An aerobic exercise program for patients with haematological malignancies after bone marrow transplantation. *Bone Marrow Transplant* **18**: 1157–1160.
33. Dimeo F, Rumberger G, Keul J (1998) Aerobic exercise as therapy for cancer fatigue. *Med Sci Sports Exerc* **30**: 475–478.
34. Durak E, Lilly PC (1998) The application of an exercise and wellness program for cancer patients: a preliminary outcomes report. *J Strength Cond Res* **6**: 3–6.
35. Durak E, Lilly PC (1999) A 5 year follow-up survey on health and exercise habits in women breast cancer survivors [abstract]. 2nd Annual Meeting of the American Society of Exercise Physiologists: Albuquerque. *Breast Cancer Res Treat* **57**: 92.
36. Durak E, Lilly PC, Hackworth JL (1999) Physical and psychosocial responses to exercise in cancer patients: a two year follow-up survey with postate, leukemia and general carcinoma. *J Exerc Physiol Online* (http://www.css.edu/users/tboone2/asep/jan12b.htm. Accessed Oct 30, 2002).
37. Gaskin T, LoBuglio A, Kelly P, Doss M, Pizitz N (1989) STRETCH: a rehabilitative program for patients with breast cancer. *South Med J* **82**: 467–469.
38. Kolden G, Strauman TJ, Ward A, *et al.* (2002) A pilot study of group exercise training (GET) for women with primary breast cancer: feasibility and health benefits. *Psychooncology* **11**: 447–456.
39. Kramer MM (1996) The effects of exercise on psychological well-being in women recovering from breast cancer [abstract]. *Diss Abstr Int* **57**: 2157.
40. Loetzerich H, Peters C, Niemeier B, Schule K, Hoff HG, Uhlenbruck G (1994) Influence of endurance training on natural cytotoxicity and behaviour in cancer patients. *Psychologische-Beitraege* **36**: 47–52.
41. Peters C, Lotzerich H, Niemeier B, Schule K, Uhlenbruck G (1995) Exercise, cancer and the immune response of monocytes. *Anticancer Res* **15**: 175–180.
42. Peters C, Lotzerich H, Niemeier B, Schule K, Uhlenbruck G (1994) Influence of a moderate exercise training on natural killer cytotoxicity and personality traits in cancer patients. *Anticancer Res* **14**: 1033–1036.
43. Peters C (1992) Ausdauersport als Rehabilitationsmassnahme in der Krebsnachsorge: Immunologishce und Psychologische Aspekte [dissertation]. Köln: Deutschen Sporthochschule.
44. Porock D, Kristjanson L, Tinnelly K, Duke T, Blight J (2000) An exercise intervention for advanced cancer patients experiencing fatigue: a pilot study. *J Palliat Care* **16**: 30–36.
45. Schulz K, Szlovak C, Schulz H, *et al.* (1998) Implementation and evaluation of an exercise rehabilitation training for breast cancer patients [German]. *Psychother Psychosom Med Psychol* **48**: 398–407.
46. Schwartz A (1998) The relationship of exercise to fatigue and quality of life in women with breast cancer [dissertation]. Salt Lake City: University of Utah.
47. Schwartz AL (2000) Exercise and weight gain in breast cancer patients receiving chemotherapy. *Cancer Pract* **8**: 231–237.
48. Schwartz AL, Mori M, Gao R, Nail LM, King ME (2001) Exercise reduces daily fatigue in women with breast cancer receiving chemotherapy. *Med Sci Sports Exerc* **33**: 718–723.
49. Schwartz AL (1999) Fatigue mediates the effects of exercise on quality of life. *Qual Life Res* **8**: 529–538.
50. Schwartz AL (2000) Daily fatigue patterns and effect of exercise in women with breast cancer. *Cancer Pract* **8**: 16–24.
51. Sharkey A, Carey AB, Heise CT, Barber G (1993) Cardiac rehabilitation after cancer therapy in children and young adults. *Am J Cardiol* **71**: 1488–1490.
52. Segal R, Reid R, Johnson D, *et al.* (1996) Pilot study of physical fitness and quality of life in patients with breast cancer [abstract]. 32nd Annual Meeting of the American Society of Clinical Oncology: Philadelphia, Pennsylvania.
53. Yoshioka H (1994) Rehabilitation for the terminal cancer patient. *Am J Phys Med Rehabil* **73**: 199–206.
54. Shore S, Shepard RJ (1999) Immune responses to exercise in children treated for cancer. *J Sports Med Phys Fitness* **39**: 240–243.
55. Earle C, Reid B, Johnson D (1996) Exercise may ameliate the effects of adjuvant breast cancer treatment on physical fitness and quality of life [abstract]. *Clin Invest Med* **19**: 417.
56. Segal R, Reid B, Johnson D (1996) Effects of exercise on body composition in breast cancer patients receiving adjuvant therapy [abstract]. *Clin Invest Med* **19**: 426.
57. Segal R, Reid B, Johnson D (1997) Progressive resistance exercise training in men with advanced prostate cancer [abstract]. *Clin Invest Med* **20**: S58.
58. Segal R, Evans WK, Gayton J, Woodard S, Wells G, Reid, R (2000) Structured exercise improves physical functioning in women with breast cancer (BC): results of a randomized controlled trial [abstract]. *Breast Cancer Res Treat* **64**: 128.
59. Segar M, Katch VL, Roth RS, *et al.* (1995) Aerobic exercise reduces depression and anxiety, and increases self-esteem among breast cancer survivors [abstract]. *Med Sci Sports Exer* **27**: S212.
60. Seifert E, Ewert S, Werle J (1992) Physical training in the aftercare of patients with cancer of the head and neck [German]. *Rehabilitation (Stuttg)* **31**: 33–37.
61. Durak E, Lilly PC (1999) Preliminary results of exercise in breast cancer: a two year follow up survey. *J Rehabil Outcomes Meas* **3**: 53–60.
62. Lazowski DA, Ecclestone NA, Myers AM, *et al.* (1999) A randomized outcome evaluation of group exercise programs in long-term care institutions. *J Gerontol* **54**: M621–M628.
63. Pfalzer L (1990) The responses of bone marrow transplant patients to graded exercise testing prior to transplant and after transplant with and without exercise training [dissertation]. Columbus: Ohio State University.
64. Schwartz AL, Thompson JA, Masood N (2002) Interferon-induced fatigue in patients with melanoma: a pilot study of exercise and methylphenidate. *Oncol Nurs Forum* **29**: E85–E90.
65. Petersson LM, Berglund G, Brodin O, Glimelius B, Sjoden PO (2000) Group rehabilitation for cancer patients: satisfaction and perceived benefits. *Patient Educ Couns* **40**: 219–229.

66. Mock V, Pickett M, Ropka ME, *et al.* (2001) Fatigue and quality of life outcomes of exercise during cancer treatment. Cancer Pract **9**: 119–127.
67. Campbell A, Mutrie N, White F, McGuire F, Kearney N (2004) A pilot study of a supervised group exercise program as a rehabilitation treatment for women with breat cancer receiving adjuvant treatment. Eur J Oncol Nurs (in press).
68. Courneya K, Mackey JR, Bell GJ, Jones LW, Field CJ, Fairey AS (2003) Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *J Clin Oncol* **21**: 1660–1668.
69. Fairey AS, Courneya KS, Field CJ, Bell GJ, Jones LW, Mackey JR (2003) Effects of exercise training on fasting insulin, insulin resistance, insulin-like growth factors, and insulin-like growth factor binding proteins in postmenopausal breast cancer survivors: a randomized controlled trial. *Cancer Epidemiol Biomarkers Prev* **12**: 721–727.
70. Drouin J (2002) Aerobic exercise training effects on physical function, fatigue and mood, immune status, and oxidative stress in subjects undergoing radiation treatment for breast cancer [dissertation]. Detroit: Wayne State University.
71. Galantino ML, Capito L, Kane RJ, Ottey N, Switzer S, Packel L (2003) The effects of Tai Chi and walking on fatigue and body mass index in women living with breast cancer: a pilot study. *Rehabil Oncol* **21**: 17–22.
72. Segal R, Evans W, Johnson D, *et al.* (2001) Structured exercise improves physical functioning in women with stages I and II breast cancer: results of a randomized controlled trial. *J Clin Oncol* **19**: 657–665.
73. Segar ML, Katch VL, Roth RS, *et al.* (1998) The effect of aerobic exercise on self-esteem and depressive and anxiety symptoms among breast cancer survivors. *Oncol Nurs Forum* **25**: 107–113.
74. Mock V, Dow KH, Meares CJ, *et al.* (1997) Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. *Oncol Nurs Forum* **24**: 991–1000.
75. Nieman DC, Cook VD, Henson DA, *et al.* (1995) Moderate exercise training and natural killer cell cytotoxic activity in breast cancer patients. *Int J Sports Med* **16**: 334–337.
76. Mock V, Burke MB, Sheehan P, *et al.* (1994) A nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. *Oncol Nurs Forum* **21**: 899–907.
77. MacVicar MG, Winningham ML, Nickel JL (1989) Effects of aerobic interval training on cancer patients' functional capacity. *Nurs Res* **38**: 348–351.
78. Winningham ML, MacVicar MG, Bondoc M, Anderson JI, Minton JP (1989) Effect of aerobic exercise on body weight and composition in patients with breast cancer on adjuvant chemotherapy. *Oncol Nurs Forum* **16**: 683–689.
79. Winningham ML, MacVicar MG (1988) The effect of aerobic exercise on patient reports of nausea. *Oncol Nurs Forum* **15**: 447–450.
80. MacVicar M, Winningham, ML (1986) Promoting the functional capacity of cancer patients. *Cancer Bull* **38**: 235–239.
81. Winningham M (1983) Effects of a bicycle ergometry program on functional capacity and feelings of control in women with breast cancer [dissertation]. Columbus: Ohio State University.
82. Oliver S (2003) Physiological and psychological effects of progressive resistance training in elderly prostate cancer patients undergoing androgen deprivation therapy: a pilot study [dissertation]. Bangor: University of Wales – Bangor.
83. Segal R, Reid RD, Courneya KS, *et al.* (2003) Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol* **21**: 1653–1659.
84. Berglund G, Petersson L-M, Eriksson KRN, Häggman M (2003) 'Between men': patient perceptions and priorities in a rehabilitation program for men with prostate cancer. *Patient Educ Couns* **49**: 285–292.
85. Courneya K, Friedenreich CM, Sela RA, Quinney A, Rhodes RE, Handman M (2003) The group psychotherapy and home-based physical exercise (GROUP-HOPE) trial in cancer survivors: physical fitness and quality of life outcomes. *Psychooncology* **12**: 357–374.
86. Hayes S, Davies PSW, Parker TW, Bashford J (2003) Total energy expenditure and body composition changes following peripheral blood stem cell transplantation and participation in an exercise programme. *Bone Marrow Transplant* **31**: 331–338.
87. Hayes SC, Rowbottom D, Davies PSW, Parker TW, Bashford J (2003) Immunological changes after cancer treatment and participation in an exercise program. *Med Sci Sports Exerc* **35**: 2–9.
88. Hayes S, Davies PSW, Parker TW, Bashford J, Green A (2004) The role of a mixed type, moderate intensity exercise program following peripheral blood stem cell transplantation. *Br J Sports Med* **38**: 304–309.
89. Hayes S, Davies PSW, Parker TW, Bashford J, Newman B (2004) Quality of life changes following peripheral blood stem cell transplantation and participation in a mixed-type, moderate intensity exercise program. *Bone Marrow Transplant* **33**: 553–558.
90. Burnham TR, Wilcox A (2002) Effects of exercise on physiological and psychological variables in cancer survivors. *Med Sci Sports Exerc* **34**: 1863–1867.
91. Mello M, Tanaka C, Dulley FL (2003) Effects of an exercise program on muscle performance in patients undergoing allogeneic bone marrow transplant. *Bone Marrow Transplant* **32**: 723–728.
92. Petersson L-M, Nordin K, Glimelius B, Brekkan E, Sjödén P-O, Berglund G (2002) Differential effects of cancer rehabilitation depending on diagnosis and patients cognitive coping style. *Psychosom Med* **64**: 971–980.
93. Dimeo FC, Stieglitz RD, Novelli-Fischer U, Fetscher S, Keul J (1999) Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. *Cancer* **85**: 2273–2277.
94. Niesen-Vertommen S (1999) The recovery patterns and effects of exercise rehabilitation on the physiological and psychological health of children who have survived treatment for a malignancy [dissertation]. Vancouver: University of British Columbia.
95. Dimeo FC, Tilmann MH, Bertz H, Kanz L, Mertelsmann R, Keul J (1997) Aerobic exercise in the rehabilitation of cancer patients after high-dose chemotherapy and autologous peripheral stem cell transplantation. *Cancer* **79**: 1717–1722.
96. Dimeo F, Fetscher S, Lange W, Mertelsmann R, Keul J (1997) Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. *Blood* **90**: 3390–3394.
97. Berglund G, Bolund C, Gustavsson U-L, Sjoden P-O (1994) A randomized study of a rehabilitation program for cancer patients: the 'starting again' group. *Psychooncology* **3**: 109–120.
98. Berglund G, Bolund C, Gustafsson UL, Sjoden PO (1994) One-year follow-up of the 'Starting Again' group rehabilitation programme for cancer patients. *Eur J Cancer* **30**: 1744–1751.
99. Berglund G, Bolund C, Gustavsson UL, Sjoden PO (1993) Starting again – a comparison study of a group of rehabilitation program for cancer patients. *Acta Oncol* **32**: 15–21.
100. Buettner L, Gavon SJ (1981) Personality changes and physiological effects of a personalized fitness enrichment program for

cancer patients [dissertation]. Bowling Green: Bowling Green State University.
101. Courneya K, Friendenreich CM, Quinney HA, Fields ALA, Jones LW, Fairey AS (2003) A randomised trial of exercise and quality of life in colorectal cancer survivors. *Eur J Cancer Care* **12**: 347–357.
102. Coleman E, Hall-Barrow J, Coon S, Stewart CB (2003) Facilitating exercise adherence for patients with multiple myeloma. *Clin J Oncol Nurs* **7**: 529–535.
103. Coleman E, Coon S, Hall-Barrow J, Richards K, Gaylor D, Stewart CB (2003) Feasibility of exercise during treatment for multiple myeloma. *Cancer Nurs* **26**: 410–419.
104. Wall LM (2000) Changes in hope and power in lung cancer patients who exercise. *Nurs Sci Q* **13**: 234–242.
105. Na YM, Kim MY, Kim YK, Ha YR, Yoon DS (2000) Exercise therapy effect on natural killer cell cytotoxic activity in stomach cancer patients after curative surgery. *Arch Phys Med Rehabil* **81**: 777–779.
106. Cunningham BA, Morris G, Cheney CL, Buergel N, Aker SN, Lenssen P (1986) Effects of resistive exercise on skeletal muscle in marrow transplant recipients receiving total parenteral nutrition. *J Parenter Enteral Nutr* **10**: 558–563.
107. Egger M, Dickersin K, Davey Smith G (2001) Problems and limitations in conducting systematic reviews. In: Egger M, Davey Smith G, Altman DG, eds. *Systematic Reviews in Health Care: Meta-analysis in Context*, 2nd edn. London: BMJ Publishing Group, pp. 43–68.
108. Easterbrook P, Berlin JA, Gopalan R, Matthews DR (1991) Publication bias in clinical research. *Lancet* **337**: 867–872.
109. Ioannidis JPA (1998) Effect of the statistical signficance of results on the time to completion and publication of randomized efficacy trials. *JAMA* **279**: 281–286.
110. Egger M, Zellweger-Zahner T, Schneider M, Junker C, Lengeler C, Antes G (1997) Language bias in randomised controlled trials published in English and German. *Lancet* **350**: 326–329.
111. Nieminen P, Isohanni M (1999) Bias against European journals in medical publication databases. *Lancet* **353**: 1592.
112. Schulz KF, Chalmers I, Hayes RJ, Altman DG (1995) Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* **273**: 408–412.
113. Moher D, Pham B, Jones A, *et al*. (1998) Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* **352**: 609–613.
114. Hollis S, Campbell F (1999) What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* **319**: 670–674.
115. Moore R, Gavaghan D, Tramer MR, Collins SL, McQuay HJ (1998) Size is everything – large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* **78**: 209–216.
116. Bland J, Altman DG (1995) Multiple significance tests: the Bonferroni method. *BMJ* **310**: 170–172.
117. Smith D G, Clemens J, Crede W, Harvey M, Gracely EJ (1987) Impact of multiple comparisons in randomized clinical trials. *Am J Med* **83**: 545–550.
118. Dimeo F (2001) Effects of exercise on cancer-related fatigue. *Cancer* **92**: 1689–1693.
119. Alderson P, Roberts I (2000) Should journals publish systematic reviews that find no evidence to guide practice? Examples from injury research. *BMJ* **320**: 376–377.
120. Campbell M, Fitzpatrick, R, Haines, A, *et al*. (2000) Framework for design and evaluation of complex interventions to improve health. *BMJ* **321**: 694–696.