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REVIEW ARTICLE

Effects of aerobic exercise on cancer-related fatigue: a meta-analysis of randomized controlled trials

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Abstract
Background Cancer-related fatigue (CRF) is the most commonly reported and most distressing symptom in cancer patients. Currently, there are no effective strategies for managing this condition.
Objective The purpose of this study is to compare the effects of aerobic exercise on CRF with the standard of care.
Methods A systematic search for randomized controlled trials (RCTs) was performed using the Cochrane Library, JBI Library, Embase, MEDLINE, Web of Science, China Biology Medicine (CBM), and China National Knowledge Infrastructure (CNKI). The risk of bias was critically evaluated, and data were independently extracted by two reviewers. All of the analyses were performed using Review Manager 5.
Results A total of 26 qualified studies that included 2830 participants (aerobic exercise, 1426; control, 1404) were included in the meta-analysis. Cancer patients who completed adjuvant therapy in the aerobic exercise group reported reduced CRF levels relative to patients undergoing the standard of care. Aerobic exercise had a moderate effect on CRF for patients not currently undergoing anticancer treatment. Supervised aerobic exercise, exercise for 20–30 min/session, or exercise three times/week had a small effect on CRF. Exercise for 50 min/session or exercise two sessions/week had a significant effect on patient CRF, whereas 8 weeks of exercise had a moderate effect.
Conclusions Aerobic exercise is effective for the management of CRF, especially for patients who have completed adjuvant therapy.
Implications for practice Cancer patients can make more informed choices regarding their cancer-related fatigue management based on the best available evidence.

Keywords Aerobic exercise · Cancer-related fatigue · Meta-analysis

Introduction

The International Agency for Research on Cancer (IARC) predicts that the total number of cancer cases will reach 22.2 million by 2030. Furthermore, the average age of cancer patients has been decreasing over the past 20 years [1]. With the development of cancer diagnosis and treatment technology, years of survival have been significantly extended. However, patients' quality of life has not been significantly improved as expected, in part due to the cancer-related symptoms. Cancer-related fatigue (CRF) is the most common symptom reported by cancer patients [2]. CRF is a subjective symptom of fatigue (e.g., infirmity, poor endurance, attention deficit) that is experienced by almost all cancer patients due to both the disease process and treatments, including surgery, chemotherapy, and radiation therapy [3, 4]. CRF is typically characterized by sudden onset, does not result from activity or exertion, and is not relieved by sleep or rest [5]. Higher CRF prevalence rates are reported in younger patients; female patients; patients with advanced tumors; and patients with gall bladder,

The authors have full control of all primary data and agree to allow the journal to review the data if requested.

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pancreatic, gynecological, head and neck, and hematological malignancies [6]. CRF is the one of the most disabling outcomes of cancer and is the most distressing symptom during cancer treatment [7, 8].

Aerobic exercise is defined as a rhythmic and continuous activity that uses oxygen and large muscle masses of the body, such as the arms and legs. Aerobic exercise is long in duration yet low to moderate in intensity. Common aerobic exercise activities include walking, biking, jogging, swimming, aerobic classes, and cross-country skiing.

To date, many studies have reported the effects of aerobic exercise on cancer-related fatigue, most of which had positive outcomes. However, there remains substantial ambiguity and variability regarding the relationship between the exercise benefits and the exercise method, intensity, duration, length, and frequency. Therefore, the purpose of this study was to systematically assess and determine the effect of aerobic exercise interventions in the management of CRF.

Methods

PRISMA guidelines for systematic reviews and meta-analyses were followed [9].

Searching strategies

The Cochrane Central Register of Controlled Trials, Embase, MEDLINE, Web of Science, China Biology Medicine (CBM), and China National Knowledge Infrastructure (CNKI) were searched from their inception to December 2014 for relevant randomized controlled trials (RCTs) without language restrictions. Keywords included "exercise," "physical activity," "exercise therapy," "exercise training," "aerobic exercise," "physical training," "cancer," "oncology," "neoplasm," "cancer treatment," "chemotherapy," "radiotherapy," "hormonal therapy," "fatigue," "cancer related fatigue," and "CRF." The electronic database searches included three steps:

1. Search relevant original research in MEDLINE, CBM, and CNKI; analyze the title, abstract, keywords, and MeSH terms of these studies to identify the keywords for further information retrieval.
2. Search databases with all the relevant keywords/MeSH terms and read the abstract; if the abstract conforms to the inclusion criteria, acquire the full text.
3. Research the databases using the references of these acquired studies.

The identified abstracts were screened, and the full-text articles of potentially eligible studies were read in full by the two authors to determine whether they met the inclusion criteria.

Inclusion criteria

Types of studies Only RCTs were eligible.

Types of participants Studies including adult patients (≥18 years) who were diagnosed with any type of cancer, regardless of gender, tumor stage, and type of cancer treatment, were eligible.

Types of interventions Trials that compared aerobic exercise interventions with usual/standard care or no exercise were included, and those that were focused only on improvements in range of motion were excluded.

Types of outcomes Trials regarding fatigue as a primary or secondary outcome and containing fatigue scores that could be extracted were included.

Data extraction

General study information (title, authors, publication source, and publication year), the characteristics of the patient population (age, gender, ethnicity, sample size, cancer type, stage of cancer, and current treatment), the characteristics of the intervention and the control (type, intensity, duration, frequency, program length, and adherence or contamination), the outcome measures, and the results were independently extracted by two reviewers using a predesigned data collection form.

Risk of bias in the individual studies

Two reviewers independently assessed each trial using the 12 criteria (including 5 domains: selection bias, performance bias, attrition bias, reporting bias, and detection bias; rating: yes, no, or unclear) recommended by the Cochrane Back Review Group [10]. The trials that met at least 6 of the 12 criteria and had no serious flaws were rated as low risk of bias; all other studies were rated as high risk of bias [10].

Discrepancies during data extraction and methodology appraisal were assessed with a third reviewer, and consensus was achieved by discussion.

Data analysis

The meta-analysis was performed using Review Manager Software (5.0.1 version). Clinical heterogeneity (variability in the participants, interventions, and outcomes) and methodological heterogeneity (variability in the study design and risk of bias) were evaluated first. Statistical heterogeneity is a consequence of clinical or methodological diversity or both among the studies [10]. If moderate clinical heterogeneity existed, subgroup analysis was conducted when there were at least two studies within a stratum. I^2 was used to measure

the statistical heterogeneity among the trials in each analysis. If $p > 0.1$ and $I^2 < 50\ \%$, a fixed effects model was adopted for the analysis due to the homogeneity of the trials; if $p < 0.1$ and $I^2 \geq 50\ \%$, then a random effects model was adopted. If $p < 0.1$ and the sources of heterogeneity were unknown, a descriptive analysis was adopted without a meta-analysis. For continuous data, the weighted mean difference (WMD) and 95 % confidence interval (CI) were determined for the individual trials. The standardized mean difference (SMD) was used if the outcome assessment tools were different.

Reporting and publication bias were investigated by visually examining the degree of asymmetry of a funnel plot. A sensitivity analysis was performed in light of the fact that some of the trials (e.g., one with a larger sample) might affect the study results. Sensitivity analysis was used to explore the effects of the fixed effects or random effects model analyses for outcomes with heterogeneity and the effects of any assumptions. Subgroup analyses were conducted on different exercise modes, treatment status, and cancer characteristics if there were at least two studies on a stratum, considering that these variables might affect the fatigue outcomes.

Results

Literature search

A total of 1428 records identified through database searching and 3 additional records identified through other sources were retrieved in the literature search, and 763 of them were duplicated (Fig. 1). After an initial review of the title and abstract, 592 records were excluded due to obvious nonconformity to the inclusion criteria. Of the remaining articles, 50 articles were excluded after reading the literature and critical appraisal. Therefore, 26 articles were included in the final meta-analysis [11–36].

Characteristics of the included studies

The characteristics of the patient population, interventions, outcome assessment, and results are presented in Table 1.

Participant characteristics

Among the included studies, 13 were conducted in breast cancer patients, 3 in prostate cancer patients, 2 in colorectal cancer patients, 2 in nasopharyngeal carcinoma patients, 2 in patients with hematological malignancies, 1 in gynecologic cancer patients, and the remaining 3 in various types of malignancy. The mean age of the patients ranged from 40.0 to 70.6 years. Ethnicity was reported in 11 studies; 4 studies involved Asian populations, and most of the patients in the remaining 7 studies were white. Twelve studies reported the cancer stage of the participants, most of which were stage I to III. Only eight studies included patients who had completed active anticancer treatment.

Intervention characteristics

Exercise interventions were supervised or home-based, varied from 15 to 50 min, and took place two–five times per week for 6–24 weeks. Intensity was calculated based on the % heart rate reserve (%HRR), the % maximal oxygen consumption (% VO_{2max}), or the % heart rate maximum.

Risk of bias in individual studies

All of the included 26 studies had a low risk of bias except for two studies [11, 23] (Table 2). Only 13 articles reported detailed random sequence generation, and 9 reported adequate allocation concealment. The risk of performance bias was high in most of the studies; participant blinding was not applicable for aerobic exercise training versus usual care, so only the other two items were appraised. The risk of attrition bias was mixed, and only 13 studies used an intention-to-treat analysis.

The risk of reporting bias and the detection bias were generally low; however, adequate outcome assessor blinding was reported by only one study [36].

Analysis of overall effects

The effect sizes with scores of 0.2–0.5, 0.5–0.8, and >0.8 were considered small, medium, and large effects, respectively [38].

The meta-analysis of the fatigue scores in the 26 studies indicate that aerobic exercise has a small but statistically significant beneficial effect, suggesting that aerobic exercise could mitigate CRF to some extent (SMD = −0.22, 95 % CI (−0.39, −0.04), $P = 0.01$) (Fig. 2). The funnel plot (Fig. 3) indicates that the publication bias is mild, and the sensitivity analysis reveals that the model is relatively stable.

Subgroup and sensitivity analysis

Treatment status

The meta-analysis of the eight studies with only off-treatment patients demonstrates that aerobic exercise has a moderate effect on fatigue compared with the control intervention [(SMD = −0.63, 95 % CI (−0.98, −0.27), $P < 0.01$) (Table 3).

Malignancy type

Aerobic exercise can significantly reduce fatigue of patients with nasopharyngeal carcinoma (SMD = −0.91, 95 % CI

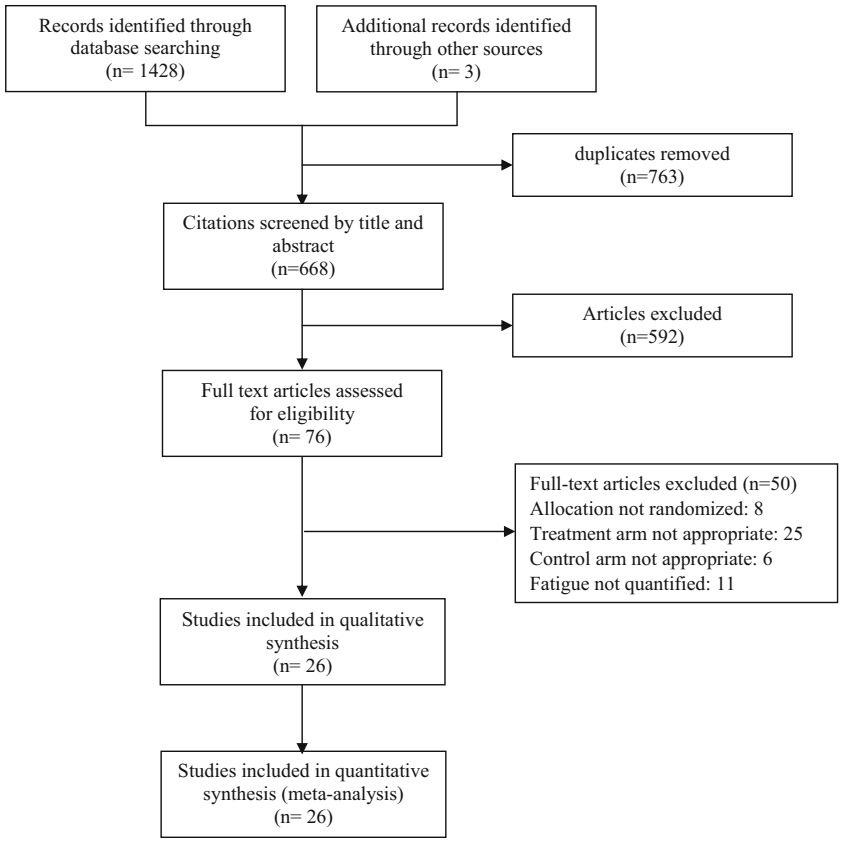

Fig. 1 Flow diagram of trial identification and selection

(−1.27, −0.56), $P < 0.01$) (Table 3), but its impact does not attain significance in breast cancer, prostate cancer, or colorectal cancer patients. The sensitivity analysis indicates that aerobic exercise has a small effect on breast cancer patients (SMD = −0.31, 95 % CI (−0.52, −0.10), $P < 0.01$), i.e., the model is unstable.

Mode of aerobic exercise

Participants who engaged in professionally led (SMD = −0.24, 95 % CI (−0.45, −0.03), $P = 0.02$) aerobic exercise training reported significant changes in their fatigue score compared with those in the control group. The professionally led exercise training lasted for 20–30 min (SMD = −0.36, 95 % CI (−0.63, −0.09), $P < 0.01$) or 50 min (SMD = −1.33, 95 % CI (−2.42, −0.24), $P = 0.02$) in each session, two sessions (SMD = −0.95, 95 % CI (−1.36, −0.54), $P < 0.01$) or three sessions per week (SMD = −0.37, 95 % CI (−0.65, −0.09), $P = 0.01$) for 8 weeks (SMD = −0.73, 95 % CI (−1.19, −0.27), $P < 0.01$). Subgroup analysis of the three studies with a duration of 15–45 min indicates that standard care is more beneficial than aerobic exercise (SMD = 0.25, 95 % CI (0.08, 0.41), $P < 0.01$) (Table 3). No significant difference was found in the subgroup analysis of exercise type; however, sensitivity analysis indicates that walking has a moderate effect on fatigue (SMD = −0.53, 95 % CI (−0.94, −0.11), $P = 0.01$) and that home-based aerobic exercise has a small effect (SMD = −0.43, 95 % CI (−0.61, −0.24), $P < 0.01$).

Adherence and contamination

Nineteen studies reported the adherence to the aerobic exercise intervention; adherence was higher than 80 % in nine studies, and eleven studies reported poor compliance (<80 %); six studies did not report the exercise adherence. Only six studies reported the contamination rate of the control group (14.6 to 52 %) (Table 1).

Adverse events

Twelve studies reported adverse events during the study, but no serious events were directly associated with aerobic exercise (Table 1).

Discussion

This meta-analysis including 2830 participants showed that aerobic exercise had a mild but significant effect on reducing fatigue. Of the included studies, only 23 trials reported the average age of the participants, and in 18 trials, the average

Table 1 Studies included in the meta-analysis

Author, year	Population	Cancer type	Mean age(±SD) gender	Ethnicity	Cancer stage	Current treatment	Treatment group: intervention, intensity[a], duration, frequency, program length, adherence	Control group: intervention, program length, contamination	Fatigue scale	Adverse events
Dimeo, 1999 [11]	EG, 32 CG, 27	Various	EG, 40.0 ± 11 female 18, male 9 CG, 40.0 ± 10.0 female 19, male 13	Not reported	Unclear	Chemotherapy	Supervised: cycling, at least 50 % of the cardiac reserve[b], 30 min, daily, length of hospitalization, 82 % of the hospitalization days	Usual care, length of hospitalization, not reported	POMS	Not reported
Burnham, 2002 [12]	EG, 12 CG, 6	EG: breast 5, colon 1 CG: breast 10, colon 2	EG, 52.5 ± 8.1 female 10, male 2 CG, 56.0 ± 10.1 female 5, male 1	Not reported	Not reported	Off-treatment	Supervised: treadmills, stationary bicycles, stair-climbing machines; 25-60 % HRR[b], 14 to 32 min, 3 times per week, 10 weeks, 95 %	No exercise, 10 weeks, not reported	LASA	None
Courneya, 2003c [13]	EG, 62 CG, 31	Colorectal cancer survivors	EG, 52.9 ± 10.7 male 54.8 % CG, 61.1 ± 9.9 male 64.5 %	Not reported	Not reported	Radiotherapy Chemotherapy	Home-based: walking, cycling, swimming; 65–75 % HR_{max}, 20–30 min, 3–5 times per week, 16 weeks, 75.8 %	No exercise, 16 weeks, 51.6 %	FACT-F	None
Courneya 2003b, [14]	EG, 24 CG, 28	Postmenopausal breast cancer survivors	EG, 59.0 ± 5.0 CG, 58.0 ± 6.0 female	Not reported	I to III	Off-treatment	Supervised: cycling, 70–75 % VO_{2max}, 15–35 min, 3 times per week, 15 weeks, 98.4 %	No exercise, 15 weeks, not reported	FACT-F	EG: lymphedema 3, gynecologic complication 1, fever 1 CG: foot fracture 1, bronchitis 1
Pinto, 2003 [15]	EG, 12 CG, 12	Breast cancer	Not reported	Not reported	0 to II	Off-treatment	Supervised: treadmill walking, arm cycling, stationary cycling, and rowing; 60–70 % HR_{max}, 50 min, 3 times per week, 12 weeks, 88 %	Usual care, 12 weeks, not reported	POMS	Not reported
Windsor, 2004 [16]	EG, 32 CG, 33	Prostate cancer	EG, 68.3 ± 0.9 CG, 69.3 ± 1.3 male	Not reported	Not reported	Radiotherapy	Home-based: walking, 60–70 % HR_{max}, 30 min, 3 times per week, 4 weeks, 100 %	Usual care, 4 weeks, none	BFI	None
Campbell, 2005 [17]	EG, 12 CG, 10	Breast cancer	EG, 48.0 ± 10.0 CG, 47.0 ± 5.0 female	Not reported	Not reported	Radiotherapy Chemotherapy	Supervised: walking, cycling; 60–75 % HR_{max}, 40 min, 2 times per week, 12 weeks, 70 %	Usual care, 12 weeks, not reported	PFS	None
Mock, 2005 [18]	EG, 54 CG, 54	Breast cancer	EG, 51.3 ± 8.9 CG, 51.6 ± 9.7 female	% Caucasian EG, 85.0 % CG, 79.3 %	0 to IIIa	Radiotherapy Chemotherapy	Home-based: walking, 50–70 % HR_{max}, 15–30 min, 5–6 times per week, 6 weeks, 72 %	Usual care, 6 weeks, 39 % were contaminated	PFS	Not reported

Table 1 (continued)

Author, year	Population	Cancer type	Mean age(±SD) gender	Ethnicity	Cancer stage	Current treatment	Treatment group: intervention, intensity[a], duration, frequency, program length, adherence	Control group: intervention, program length, contamination	Fatigue scale	Adverse events
Pinto, 2005 [19]	EG, 43 CG, 43	Breast cancer	EG, 53.4 ± 9.1 CG, 52.9 ± 10.4 female	% Caucasian EG, 97.7 % CG, 93.0 %	0 to II	Off-treatment	Home-based: brisk walking, biking, swimming; 55–65 % HR_{max}, 30 min, 5 times per week, 12 weeks, not reported	Usual care, 12 weeks, not reported	POMS	Not reported
Courneya, 2007 [20]	EG, 78 CG, 82	Breast cancer	EG, 49.0 (30 to 75) CG, 49.5 (25 to 76) female	Not reported	I to IIIa	Chemotherapy	Supervised: exercise on a cycle ergometer, treadmill, or elliptical; 60–80 % VO_{2max}, 15–45 min, 3 times per week, 24 weeks, 72 %	No exercise, 24 weeks, not reported	FACT-F	EG: lightheaded and nauseous 1; dizziness, diarrhea 1
Daley, 2007 [21]	EG, 34 CG, 38	Breast cancer	EG, 51.6 ± 8.8 CG, 51.1 ± 8.6 female	% Caucasian EG, 100 % CG, 97.4 %	Not reported	Off-treatment	Supervised: aerobic exercise, 65–85 % HR_{max}, 50 min, 3 times per week, 8 weeks, 77 %	Usual care, 8 weeks, not reported	R-PFS	Not reported
Mutrie 2007[22]	EG, 82 CG, 92	Breast cancer	EG, 51.3 ± 10.3 CG, 51.8 ± 8.7 female	Not reported	I to III	Radiotherapy Chemotherapy	Supervised: walking, cycling; 50–70 % HR_{max}, 45 min, 3 times per week, 12 weeks, not reported	Usual care, 12 weeks, not reported	FACT-F	None
Monga, 2007 [23]	EG, 11 CG, 10	Prostate cancer	EG, 68.0 ± 4.2 CG, 70.6 ± 5.3 male	% White EG, 27.3 % CG, 40 %	Not reported	Radiotherapy	Supervised: walking, not reported, 50 min, 3 times per week, 8 weeks, not reported	Usual care, 8 weeks, not reported	R-PFS	None
Yuen, 2007 [24]	EG, 7 CG, 7	Breast cancer	EG, 53.1 ± 13.5 CG, 55.0 ± 13.4 female	% Caucasian EG, 87 % CG, 86 %	Not reported	Off-treatment	Home-based: walking, swimming, biking; unspecified, 20–40 min, 3 times per week, 12 weeks, 72.7 %	Usual care, 12 weeks, not reported	R-PFS	Not reported
Chang, 2008 [25]	EG, 11 CG, 11	Acute myelogenous leukemia	EG, 49.4 ± 15.3 male, 72.7 % CG, 53.3 ± 13.6 male, 36.4 %	Not reported	Not reported	Chemotherapy	Supervised: walking, resting HR plus 30 bpm, 12 min, 5 times per week, 3 weeks, not reported	Usual care, 3 weeks, not reported	BFI	Not reported
Courneya, 2008 [26]	EG, 26 CG, 29	Various	EG, 58 (40 to 77) male, 76.9 % CG, 54 (25 to 77) male, 86.2 %	Not reported	Not reported	Chemotherapy	Supervised: cycling, 60–100 % exercise capacity, unspecified, 3 times per week, 12 weeks, 84.2 %	No exercise, 12 weeks, unclear	FACT-F	Not reported
Courneya, 2009 [27]	EG, 60 CG, 62	Lymphoma	EG, 52.8 (18 to 77)	Not reported	I to IV	Chemotherapy	Supervised: cycling, 60–75 %		FACT-F	3 adverse events related to

Table 1 (continued)

Author, year	Population	Cancer type	Mean age(±SD) gender	Ethnicity	Cancer stage	Current treatment	Treatment group: intervention, intensity[a], duration, frequency, program length, adherence	Control group: intervention, program length, contamination	Fatigue scale	Adverse events
			male, 61.7 % CG, 53.5 (18 to 80) male, 56.5 %				exercise capacity, 15–45 min, 3 times per week, 12 weeks, 77.8 %	Usual care, 12 weeks, 21 % were contaminated		exercise (back, hip, knee)
Rogers, 2009 [28]	EG, 60 CG, 62	Breast cancer	EG, 52.0 ± 15.0 CG, 54.0 ± 8.0 female	% White EG, 90 % CG, 95 %	I to III	Hormonal therapy	Walking, moderate intensity, unspecified, 3–5 times per week, 12 weeks, 95 %	Usual care, 12 weeks, not reported	FACT-F	None
Segal, 2009 [29]	EG, 40 CG, 41	Prostate cancer	EG, 66.2 ± 6.8 CG, 65.3 ± 7.6 male			Radiotherapy	Supervised: exercise on a cycle ergometer, treadmill, or elliptical; 50–75 % VO_{2max}, 15–45 min, 5 times per week, 24 weeks, 83 %	No exercise, 24 weeks, 14.6 % were contaminated	FACT-F	None
Chen, 2011 [30]	EG, 28 CG, 28	Laryngeal cancer	EG, 52.7 ± 7.5 male, 89.3 % CG, 53.3 ± 13.6 male, 85.7 %	Asian	Not reported	Off-treatment	Power striding, jogging, stair activity; (220 − age − resting HR) × 60 % + resting HR, 20–30 min, 3–5 times per week, 8 weeks, not reported	Usual care, 8 weeks, not reported	R-PFS	Not reported
Donnelly, 2011 [31]	EG, 16 CG, 17	Gynecologic cancer	EG, 53.5 ± 8.7 CG, 52.1 ± 11.8 female	Not reported	I to III	Unclear	Supervised: walking, moderate, 30 min, at least 5 times per week, 12 weeks, 44 %	Usual care, 12 weeks, unclear	FACT-F	EG: 1 lung metastasis, 1 pulmonary embolism, 1 heart palpitations
Wang, 2011 [32]	EG, 35 CG, 37	Breast cancer	EG, 48.4 ± 10.2 CG, 52.3 ± 8.8 female	Asian	I to II	Chemotherapy	Home-based: walking, 40–60 % HR_{max}, 30 min, 3–5 times per week, 6 weeks, poor compliance	Usual care, 6 weeks, 30.4 % were contaminated	FACT-F	EG: 2 dyspnea CG: 1 dizziness, 1 dyspnea
Xu, 2012 [33]	EG, 35 CG, 37	Breast cancer	Not reported female	Asian	Not reported	Chemotherapy	Home-based: walking, stair activity, cycling; 55–65 % HR_{max}, 20–30 min, 3–5 times per week, 8 weeks, not reported	Usual care, 8 weeks, not reported	R-PFS	Not reported
Hu, 2012 [34]	EG, 40 CG, 40	Nasopharyngeal cancer	Unclear	Asian	Not reported	Radiotherapy	Supervised: stair activity, 30–40 % HR_{max}, 30 min, 2 times per day, 7 weeks, not reported	Usual care, 7 weeks, not reported	BFI	Not reported
Sarto, 2012 [35]	EG, 263 CG, 237	Breast cancer	EG, 52 (36 to 68) CG, 52 (35 to 68) female	Not reported	Early stage	Radiotherapy Chemotherapy	Supervised and home training: walking, cycling, swimming,	Usual care, 48 weeks, not reported	FACT-F	Not reported

Table 1 (continued)

Author, year	Population	Cancer type	Mean age(±SD) gender	Ethnicity	Cancer stage	Current treatment	Treatment group: intervention, intensity[a], duration, frequency, program length, adherence	Control group: intervention, program length, contamination	Fatigue scale	Adverse events
							etc.; 86–92 % HR_{max}, 60 min, 1 time per week, 48 weeks, low (unclear)			
Pinto, 2013 [36]	EG, 20 CG, 26	Colorectal cancer	EG, 59.5 ± 11.2 male, 40 % CG, 55.6 ± 8.24 male, 46 %	% White EG, 100 % CG, 96 %	I to III	Off-treatment	Home-based: walking, biking; 64–76 % HR_{max}, 30–50 min, 2–5 times per week, 12 weeks, 76 %	Usual care, 12 weeks, 52 % were contaminated	FACT-F	Not reported

EG aerobic exercise group, *CG* control group, HR_{max} maximal heart rate, *HRR* heart rate reserve, $VO_{2\ max}$ maximal oxygen consumption, *LASA* Linear Analog Self-Assessment, *PFS* Piper Fatigue Scale, *R-PFS* revised Piper Fatigue Scale, *BFI* Brief Fatigue Inventory, *POMS* Profile of Mood States, *FACT-F* Functional Assessment of Cancer Therapy-Fatigue subscale

[a] Several guidelines recommend 50–75 % HRR or $VO_{2\ max}$, 60–80 % HR_{max} as moderate intensity of exercise [37]

[b] Calculated as 220 − age − resting HR

age ranged from 50 to 60 years old, with no stratified analysis according to age; two studies included older participants (66.2 and 70.6 years), and three studies included younger participants (40, 48, 49 years, respectively). Of the 26 studies, 14 were focused on female patients (breast cancer or gynecologic cancer), 3 were focused on male patients (prostate cancer), and the remaining 9 included both genders with no stratified analysis. Only 11 studies reported the ethnicity of the participants; four of the studies were focused on Asian patients, and most of the remaining seven studies were focused on white patients, with no stratified analysis. Only eight studies reported the cancer stage of the participants, and all of them only involved stage I to III patients; however, the included studies did not provide estimates of the effect size that could be pooled for subgroups of age, gender, ethnicity, or cancer stage. Therefore, no subgroup analysis was made according to these stratification factors. The most common CRF measurement tool used was the Functional Assessment of Cancer Therapy-Fatigue subscale (FACT-F); however, among the trials that used this tool, aerobic exercise presented an insignificant effect on CRF (WMD = 1.46, 95 % CI (0.03, 2.89), n = 12 studies, P = 0.05), while the trials using the Brief Fatigue Inventory (BFI) (WMD = −5.27, 95 % CI (−8.38, −2.15), n = 3 studies, P < 0.01) or the revised Piper Fatigue Scale (R-PFS) (WMD = −1.02, 95 % CI (−1.70, −0.34), n = 5 studies, P < 0.01) produced significant results. Although FACT-F, BFI, and R-PFS are all the best validated fatigue instruments [39], this study indicated that FACT-F was not as suitable for measuring CRF of breast and colorectal cancer patients as BFI and R-PFS, which is consistent with the previous research [40].

In a stratified analysis by malignancy type, there were no benefits of aerobic exercise on CRF for breast cancer patients; however, the sensitivity analysis revealed the opposite outcome. These findings do not correspond to the results described by former meta-analyses [41–44], which showed significant positive effects of aerobic exercise on CRF for breast cancer. As to prostate, colorectal, and hematological malignancies, there still lack sufficient evidence to support the aerobic exercise's effect on CRF [44–46]. In addition, we found a significant beneficial effect of aerobic exercise on CRF for nasopharyngeal carcinoma from this study, even if the sample size was too small. "Some physical activity is better than none" [47, 48]; therefore, aerobic exercise should be incorporated into the routine management of CRF, especially for adult breast and nasopharyngeal cancer patients.

In relation to treatment status, benefits of aerobic exercise on CRF were identified for off-treatment patients but not for those undergoing anticancer treatments; however, several other meta-analysis showed the benefits during anticancer treatments [41, 42, 44, 49], but three of them did not specify the type of aerobic exercise [41, 42, 49].

In addition to the mode of aerobic exercise, the type of aerobic exercise (e.g., walking, cycling, swimming) did not influence the effect, while the following moderators remained

Table 2 Methodology quality of included studies

Author, year	Bias												Total (max. 12)[a]
	Selection bias			Performance bias				Attrition bias		Reporting bias	Detection bias		
	Adequate random sequence generation	Adequate allocation concealment	Similar baseline characteristics	Adequate participant blinding	Adequate provider blinding	Similar or no co-intervention	Acceptable compliance	Acceptable and described dropout rate	Inclusion of an intention-to- treat analysis	No selective outcome reporting	Adequate outcome assessor blinding	Similar timing of outcome assessment	
Dimeo 1999 [11]	No	Unclear	Yes	NA	No	No	Yes	No	No	Yes	No	Yes	5
Burnham 2002 [12]	Unclear	Unclear	Yes	NA	No	Yes	Yes	No	No	Yes	No	Yes	6
Courneya 2003 c [13]	Yes	Unclear	No	NA	No	No	Yes	Yes	Yes	Yes	No	Yes	7
Courneya 2003 b [14]	Yes	Unclear	Yes	NA	No	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	9
Pinto 2003 [15]	Unclear	Unclear	Yes	NA	No	Yes	Yes	Yes	Yes	Yes	No	Yes	8
Windsor 2004 [16]	Unclear	Yes	Yes	NA	No	Yes	Yes	No	No	Yes	No	Yes	7
Campbell 2005 [17]	Unclear	Unclear	Yes	NA	No	Yes	Yes	Yes	No	Yes	No	Yes	7
Mock 2005 [18]	Yes	Yes	Yes	NA	No	Yes	Yes	Yes	No	Yes	No	Yes	9
Pinto 2005 [19]	Unclear	Unclear	Yes	NA	No	Yes	Unclear	Yes	Yes	Yes	No	Yes	7
Courneya 2007 [20]	Yes	Yes	Yes	NA	No	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Daley 2007 [21]	Yes	Yes	Yes	NA	No	Yes	Yes	Yes	No	Yes	No	Yes	9
Mutrie 2007 [22]	Yes	Yes	Yes	NA	No	Yes	Unclear	Yes	No	Yes	Unclear	Yes	8
Monga 2007 [23]	Unclear	Unclear	Yes	NA	No	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	5
Yuen 2007 [24]	Yes	Unclear	No	NA	No	Yes	Yes	Unclear	No	Yes	No	Yes	6
Chang 2008 [25]	Unclear	Unclear	Yes	NA	No	Yes	Unclear	Yes	No	Yes	No	Yes	6
Courneya 2008 [26]	Yes	Yes	Yes	NA	No	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Courneya 2009 [27]	Yes	Yes	Yes	NA	No	Yes	Yes	Yes	No	Yes	No	Yes	9
Rogers 2009 [28]	Yes	Unclear	Yes	NA	No	Yes	Yes	Unclear	No	Yes	No	Yes	7
Segal 2009 [29]	Yes	Yes	No	NA	No	No	Yes	Yes	Yes	Yes	No	Yes	8
Chen 2011 [30]	No	Unclear	Yes	NA	No	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	7
Donnelly 2011 [31]	Yes	Yes	Yes	NA	No	Yes	No	Yes	Yes	Yes	No	Yes	9
Wang 2011 [32]	Unclear	Unclear	Yes	NA	Unclear	Yes	No	Yes	Yes	Yes	Unclear	Yes	7
Xu 2012 [33]	Unclear	Unclear	Yes	NA	No	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	7
Hu 2012 [34]	No	Unclear	Yes	NA	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	7
Sarrto 2012 [35]	Yes	No	Yes	NA	No	Yes	No	Yes	No	Yes	No	Yes	7
Pinto 2013 [36]	Unclear	Unclear	Yes	NA	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	8

NA not applicable

[a] Higher scores indicate lower risk of bias

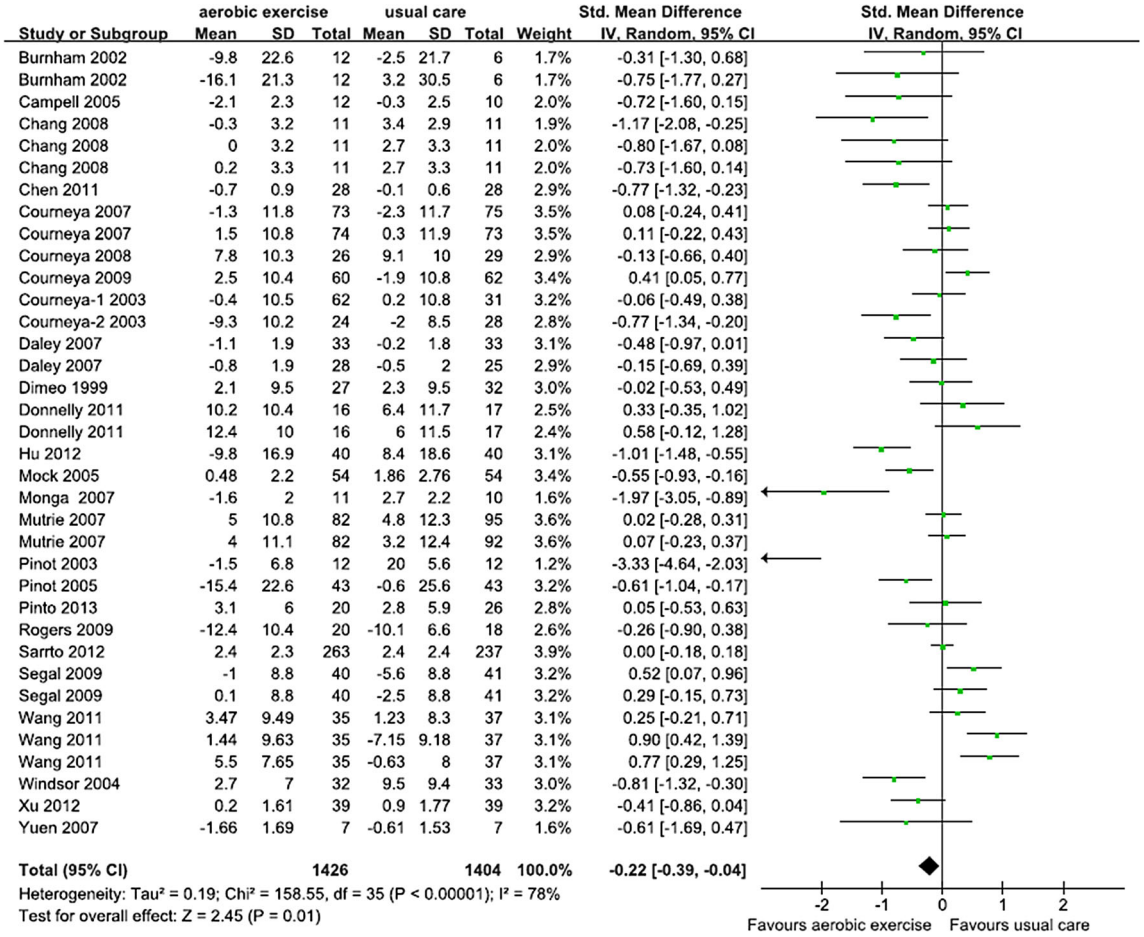

Fig. 2 Forest plot of comparison: overall effect of aerobic exercise versus usual care on CRF changes

significant: delivery mode (supervised), intensity (moderate), duration (20–30 min/session or 50 min/session), program length (8 weeks), and frequency (two times/week or three times/week). Since the exercise type made no difference on the effect, the type of aerobic exercise may be tailored to the specific population [50]. As to the remaining moderators, the American Cancer Society (ACS), the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), and most recently, the American College of Sports Medicine (ACSM) exercise guidelines for cancer survivors have made

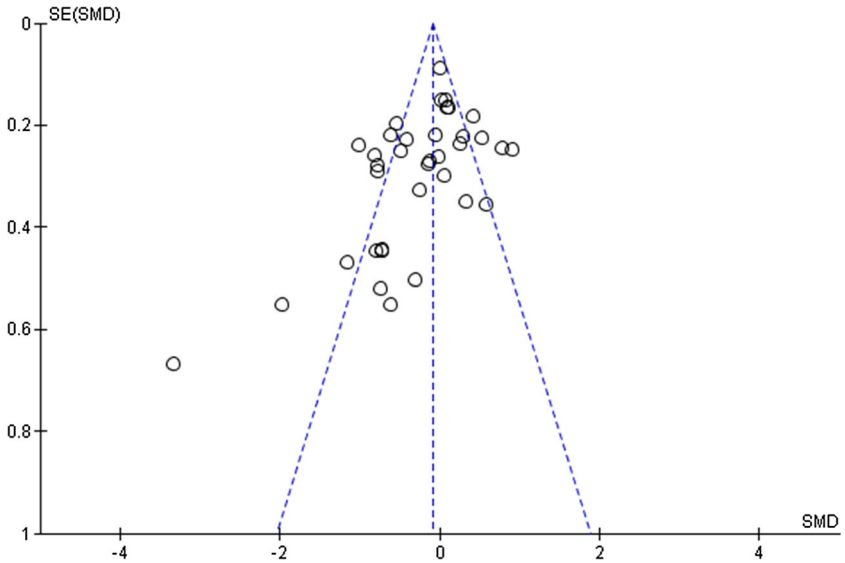

Fig. 3 Funnel plot of comparison: overall effect of aerobic exercise versus usual care on CRF changes. Plotting standard errors of the standardized intervention effect on the vertical axis places the larger, or most powerful, studies towards the top of the plot, while the smaller ones scatter more widely at the bottom of the graph. Visually, this figure reveals some slight asymmetry meaning that there is some publication bias

Table 3 Subgroup analyses of aerobic exercise on CRF changes

Outcome type	k	Sample size		SMD	95 % CI		*P* value
		EG	CG		L	U	
Treatment status							
Off-treatment	8[b]	219	214	−0.63	−0.98	−0.27	<0.01
Chemotherapy	7[c]	437	454	0.04	−0.24	0.31	0.78
Radiotherapy	4[d]	163	164	−0.52	−1.28	0.24	0.18
Chemotherapy/radiotherapy	5[e]	292	282	−0.06	−0.18	0.06	0.34
Malignancy type							
Breast cancer	13[f]	951	952	−0.17	−0.39	0.05	0.14
Prostate cancer	3[g]	123	125	−0.38	−1.24	0.47	0.38
Colorectal cancer	2	82	57	−0.02	−0.37	0.33	0.92
Nasopharyngeal carcinoma	2	68	68	−0.91	−1.27	−0.56	<0.01
Mixed	3[h]	77	73	−0.17	−0.49	0.16	0.31
Aerobic exercise type							
Walking	7[i]	287	291	−0.22	−0.66	0.23	0.34
Cycling	4	137	151	−0.10	−0.59	0.40	0.70
Mixed	13[j]	901	864	−0.17	−0.38	0.03	0.09
Delivery method							
Home-based	8[k]	362	406	−0.09	−0.46	0.28	0.64
Supervised	16[l]	976	908	−0.24	−0.45	−0.03	0.02
Intensity of aerobic exercise							
Mild	4[m]	208	202	−0.05	−0.64	0.55	0.88
moderate	18[n]	911	919	−0.23	−0.43	−0.04	0.02
Vigorous	2	289	266	−0.01	−0.18	0.15	0.88
Aerobic exercise duration (min)							
15–45[a]	3[o]	287	292	0.25	0.08	0.41	<0.01
20–30[a]	3	129	98	−0.36	−0.63	−0.09	<0.01
30	6[p]	279	293	0.03	−0.45	0.51	0.90
50	3[q]	84	80	−1.33	−2.42	−0.24	0.02
Program length (weeks)							
6	2	89	91	0.10	−1.19	1.40	0.87
8	4	111	110	−0.73	−1.19	−0.27	<0.01
12	11	391	417	−0.16	−0.50	0.18	0.35
24	5	240	248	0.13	−0.05	0.30	0.17
Frequency of aerobic exercise (per week)							
2 times	2	52	50	−0.95	−1.36	−0.54	<0.01

Table 3 (continued)

Outcome type	k	Sample size		SMD	95 % CI		*P* value
		EG	CG		L	U	
3 times	11[r]	578	586	−0.37	−0.65	−0.09	0.01
3–5 times	5[s]	254	227	0.07	−0.38	0.52	0.76
5 times	4[t]	188	192	−0.14	−0.59	0.31	0.55

k number of studies, *EG* aerobic exercise group, *CG* control group, *SMD* standardized mean difference effect size, *L* lower, *U* upper

[a] Duration of each session increases gradually throughout the intervention

[b] 8 studies provided a total of 10 effect sizes

[c] 7 studies provided a total of 12 effect sizes

[d] 4 studies provided a total of 5 effect sizes

[e] 5 studies provided a total of 6 effect sizes

[f] 13 studies provided a total of 18 effect sizes

[g] 3 studies provided a total of 4 effect sizes

[h] 3 studies provided a total of 4 effect sizes

[i] 7 studies provided a total of 12 effect sizes

[j] 13 studies provided a total of 17 effect sizes

[k] 8 studies provided a total of 10 effect sizes

[l] 16 studies provided a total of 24 effect sizes

[m] 4 studies provided a total of 7 effect sizes

[n] 18 studies provided a total of 25 effect sizes

[o] 3 studies provided a total of 5 effect sizes

[p] 6 studies provided a total of 9 effect sizes

[q] 3 studies provided a total of 4 effect sizes

[r] 11 studies provided a total of 15 effect sizes

[s] 5 studies provided a total of 7 effect sizes

[t] 4 studies provided a total of 8 effect sizes

the similar correlated recommendations, i.e., cancer survivors "should be as physically active as their abilities and conditions allow," and an overall volume of weekly aerobic activity should be at least 150 min of moderate-intensity exercise or 75 min of vigorous-intensity exercise or an equivalent combination [47, 48]. Therefore, clinical professionals could make exercise prescription according to the above results based on the patients' status, e.g., moderate-intensity aerobic exercise, 50 min/session, three times/week.

As to the other factors influencing the effect of aerobic exercise on CRF, exercise adherence and group contamination should be considered. Exercise adherence not only includes exercise frequency and duration but also includes exercise intensity. Adherence to aerobic exercise during cancer treatment may be lower due to the treatment-associated adverse effects, while higher exercise adherence could realize the largest effects of aerobic exercise on CRF during adjuvant therapy [51]. Group contamination may occur when the control participants undertake exercise or the exercise group does not adhere to the program. Further contamination may occur when participants do not perform the exercise at the prescribed intensity or for the prescribed duration [46]. Monitoring group contamination is more difficult when the prescribed program is home-based.

Limitations of the current study

Despite our comprehensive review of the literature on CRF in all types of cancer, the present study still has some limitations. First, the large number of breast cancer patients limits the generalizability to other types of cancer patients. Second, 10 of the included studies had a sample size smaller than 30. Third, the NCCN panel recommends other contributing factors, including pain, emotional distress, sleep disturbance, anemia, nutrition, activity level, medication side effects profile, alcohol/substance abuse, and comorbidities [2]. However, the individual studies involved in the present study did not report information regarding these factors, which may have significantly influenced the outcome. Therefore, there remains a need for further studies with adequate blinding, larger sample sizes, multicenter design, more rigorous inclusion criteria, and control groups.

Conclusions

Exercise should be considered as part of the cancer care standards to mitigate the effects of CRF, especially in adult breast and nasopharyngeal cancer patients who have completed adjuvant therapy. From this study, supervised aerobic exercise, exercise for 20–30 min/session, or exercise three times/week had a small effect on CRF. Exercise for 50 min/session and exercise two sessions/week had a significant effect, and 8 weeks of exercise had a moderate effect. Clinical professionals could make the exercise prescription referring to the above results with the patients' status combined. In addition, exercise adherence is very important for the management effect; future research should focus on the monitoring methods and improvement of the aerobic exercise adherence. BFI and R-PFS are more appropriately used in assessing CRF of the breast and colorectal cancer patients.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

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