

Effects of aerobic exercise on cancer-related fatigue in breast cancer patients receiving chemotherapy: a meta-analysis

Ling-Yun Zou · Liu Yang · Xiao-Ling He · Ming Sun · Jin-Jiang Xu

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Abstract Increasing scientific evidences suggest that aerobic exercise may improve cancer-related fatigue in breast cancer patients, but many existing studies have yielded inconclusive results. This meta-analysis aimed to derive a more precise estimation of the effects of aerobic exercise on cancer-related fatigue in breast cancer patients receiving chemotherapy. The PubMed, CISCOR, CINAHL, Web of Science, Google Scholar, EBSCO, Cochrane Library, and CBM databases were searched from inception through July 1, 2013 without language restrictions. Crude standardized mean difference (SMD) with 95 % confidence interval (CI) was calculated. Twelve comparative studies were assessed with a total of 1,014 breast cancer patients receiving chemotherapy, including 522 patients in the aerobic exercise group (intervention group) and 492 patients in the usual care group (control group). The meta-analysis results revealed that the Revised Piper Fatigue Scale (RPFS) scores of breast cancer patients in the intervention group were significantly lower than those in the control group (SMD=-0.82, 95% CI=-1.04~-0.60, $P<0.001$). However, there was no significant difference in the Functional Assessment of Chronic Illness Treatment-Fatigue scale (FACIT-F) scores between the intervention and control groups (SMD=0.09, 95% CI=-0.07~0.25, $P=0.224$). Subgroup analysis by ethnicity indicated that there were significant differences in RPFS and FACIT-F scores between the intervention and control groups among Asian populations (RPFS: SMD=-1.08, 95% CI=-1.35~-0.82, $P<0.001$; FACIT-F: SMD=1.20, 95 % CI=0.70~1.71,

$P<0.001$), but not among Caucasian populations (all $P>0.05$). The current meta-analysis indicates that aerobic exercise may improve cancer-related fatigue in breast cancer patients receiving chemotherapy, especially among Asian populations.

Keywords Aerobic exercise · Cancer-related fatigue · Breast cancer · Chemotherapy · Meta-analysis

Background

Breast cancer is one of the most common cancers in the world and also the leading cause of cancer death among women, which accounts for 23 % of total cancer cases and 14 % of cancer deaths [1]. However, because of earlier detection and advances in treatment, death rates of breast cancer continue to decrease accounting for 34 % of the total decline in women [2]. New effective chemotherapy, hormone therapy, and biological agents are used to integrate systemic therapy, surgery, and radiation therapy for better treatment of breast cancer [3]. Although these effective therapies improve overall survival, they are also associated with several side effects, such as decreased cardiac function, muscle wasting, reductions in physical and cognitive functioning, and especially cancer-related fatigue (CRF) [4, 5]. Previous studies suggested that regular physical activity especially aerobic exercise can reduce CRF presented after breast cancer diagnosis and treatment [6, 7]. Therefore, exercise intervention may play an important role in improving CRF in patients with breast cancer.

Physical activity has generally been proposed as a potentially appealing intervention that could mitigate sequelae related to cancer and assist patients in returning to the health status they had before treatment, which may improve physiological and psychological effects simultaneously [8–10]. In

L.-Y. Zou · L. Yang · X.-L. He · M. Sun
College of Nursing, Liaoning Medical University, Jinzhou 121000,
People's Republic of China

J.-J. Xu (✉)
Nursing Department, The First Affiliated Hospital of Liaoning
Medical University, Jinzhou 121001, People's Republic of China
e-mail: lljh_xjj@126.com

the past decades, there were plenty of randomized controlled trials focused on the effects of physical activity on cancers [11]. Most of the studies have reached a conclusion that exercise is a rehabilitation treatment which can help cancer patients with common complaints such as CRF, nausea, loss of strength and flexibility, and weight gain [12, 13]. Some studies have suggested that physical activity has significant effects on CRF, body composition, physical functions, psychological outcomes, and quality of life in patients after treatment for breast cancer [14, 15]. The various types of physical activities involved in these studies can mainly be classified into occupational, resistance exercise, recreational, and aerobic exercise [16], among which the efficacy of aerobic exercise on the management of CRF in breast cancer patients has attracted an ever-increasing interest. Aerobic exercise is defined as the rhythmic contraction and relaxation of large muscle groups over a prolonged time [17]. A growing body of scientific evidence supports that moderately intense aerobic exercise may be an effective tool for reducing the progression of CRF in breast cancer patients receiving chemotherapy [18]. Nevertheless, other studies indicated that aerobic exercise could not alleviate CRF in breast cancer patients receiving chemotherapy [11]. The inconsistent conclusions may be due to the limitations in sample size; the inadequate statistical power in genetic studies of complex traits, such as age, ethnicity, and gender; the differentiation on tumor stage; and research methodology. Therefore, we performed a meta-analysis of all eligible case-control studies to reveal the effects of aerobic exercise on CRF in breast cancer patients receiving chemotherapy.

Methods

Search strategy

The PubMed, CISCOM, CINAHL, Web of Science, Google Scholar, EBSCO, Cochrane Library, and CBM databases were searched from inception through July 1, 2013 without language restrictions. The following keywords and MeSH terms were used: ["cancer-related fatigue" or "CRF" or "chemotherapy-related fatigue" or "treatment-related fatigue"], ["breast cancer" or "breast neoplasms" or "breast tumor" or "breast carcinoma" or "mammary cancer" or "mammary carcinoma"], and ["aerobic exercise" or "aerobic sports" or "aerobic training"]. We also performed a manual search to find other potential articles.

Selection criteria

The diagnostic criteria for cancer-related fatigue was defined as a common disease that refers to a continuous stressful feeling of physical or psychological tiredness which could

affect functional level as well as quality of life (QOL) and is not possibly to be relieved by rest or sleep. To be included in the meta-analysis, these studies must meet the following criteria: (1) The type of study should be a clinical comparative study, (2) The study must be focused on the effects between the aerobic exercise and CRF in breast cancer patients receiving chemotherapy, (3) All patients diagnosed with breast cancer should be confirmed by pathohistological examinations, (4) Fatigue scores should be capable of extraction, and (5) The publication should be in English or Chinese. If the study failed the inclusion criteria, it was excluded. When authors published several studies using the same subjects, either the one most recently published or with the largest sample size was included.

Data extraction

Two independent authors extracted data from eligible studies using a standardized form. The following information were collected: surname of first author, year of publication, source of publication, country of origin, ethnicity, language of publication, study type, total number of subjects, exercise time, and fatigue scores. In cases of conflicting evaluations, disagreements on inconsistent data from the eligible studies were resolved through discussions and careful reexaminations of the full text by the authors.

Quality assessment

Methodological quality was independently assessed by two researchers according to the Newcastle-Ottawa Scale (NOS) criteria [19]. The NOS criteria includes three dimensions scored within the following ranges: (1) subject selection 0~4, (2) comparability of subject 0~2, and (3) clinical outcome 0~3. NOS scores range from 0 to 9 with a score of ≥ 7 indicating good quality.

Statistical analysis

We calculated crude odds ratios (OR) with their 95 % confidence intervals (95% CI) to evaluate their relationships under five genetic models. The *Z* test was used to determine inclusive OR significance. The Cochran's *Q*-statistic and *I*² test were used to evaluate potential heterogeneity between studies [20]. The *I*² test was also conducted to quantify the heterogeneity (ranges from 0 to 100 %) [21]. If the *Q* test showed a *P*<0.05 or *I*² test exhibits >50 %, indicating significant heterogeneity, the random effects model was conducted; otherwise, the fixed-effects model was used. We also performed subgroup and meta-regression analyses to explore potential sources of heterogeneity. Sensitivity analysis was performed by omitting each study in turn to evaluate the influence of single studies on the overall estimate. Begger's funnel plots

and Egger's linear regression test were conducted to investigate publication bias [22]. All analyses were calculated using the STATA software, version 12.0 (Stata Corp, College Station, TX, USA).

Results

Baseline characteristics of included studies

A total of 126 articles relevant to the searched keywords were initially identified. Of these articles, 74 were excluded after a review of their titles and abstracts; then, full texts and data integrity were reviewed, and another 40 papers were excluded. Twelve comparative studies met our inclusion criteria for this meta-analysis [11, 23–33]. Publication years of the eligible studies ranged from 2005 to 2012. The flow chart of the study selection process is shown in Fig. 1. The distribution of the number of topic-related literatures in the electronic database during the last decade was showed in Fig. 2. A total of 1,014 breast cancer patients receiving chemotherapy were involved in this meta-analysis, including 522 patients in the aerobic exercise group (intervention group) and 492 patients in the usual care group (control group). Overall, four studies were conducted in Asian populations; the other eight studies were conducted in Caucasian populations. The Revised Piper Fatigue Scale (RPFS) was used in six studies, while the Functional Assessment of Chronic Illness Treatment-Fatigue

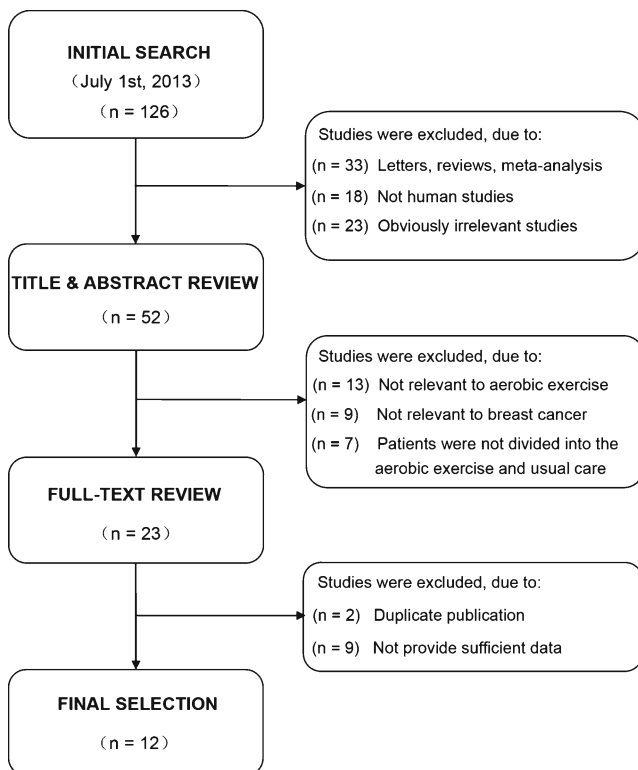


Fig. 1 Flow chart of the literature search and study selection process

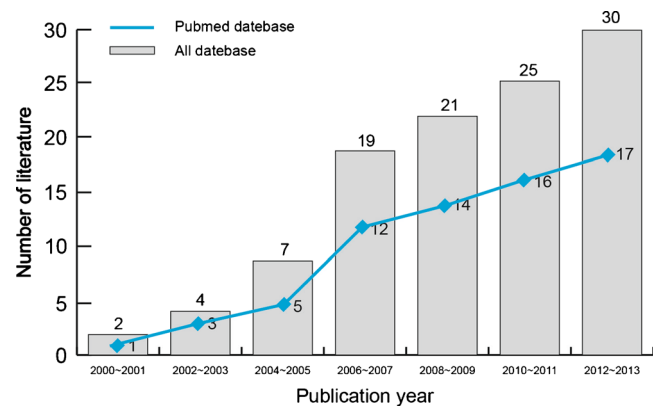


Fig. 2 Distribution of the number of topic-related literatures in the electronic databases during the last decade

scale (FACIT-F) was performed in the other six studies. The characteristics and methodological quality of the included studies are summarized in Table 1.

Quantitative data synthesis

Since heterogeneity obviously existed (all $P < 0.05$), which could be a result of differences in ethnicity and exercise time, the random effects model was conducted. The meta-analysis results revealed that the RPFS scores of breast cancer patients in the intervention group were significantly lower than those in the control group (SMD = -0.82 , 95% CI = $-1.04 \sim -0.60$, $P < 0.001$). However, there was no significant difference in FACIT-F scores between the intervention and control groups (SMD = 0.09 , 95% CI = $-0.07 \sim 0.25$, $P = 0.224$) (Fig. 3). Subgroup analysis by ethnicity indicated that there were significant differences in RPFS and FACIT-F scores between the intervention and control groups among Asian populations (RPFS: SMD = -1.08 , 95% CI = $-1.35 \sim -0.82$, $P < 0.001$; FACIT-F: SMD = 1.20 , 95% CI = $0.70 \sim 1.71$, $P < 0.001$), but not among Caucasian populations (all $P > 0.05$) (Fig. 4). Further subgroup analysis based on exercise time showed significant difference of RPFS scores between the intervention and control groups in the ≤ 8 -week subgroup (SMD = -0.87 , 95% CI = $-1.10 \sim -0.64$, $P < 0.001$) (Fig. 5). Nevertheless, we observed no difference of RPFS scores between the intervention and control groups in the > 8 -week subgroup (SMD = -0.41 , 95% CI = $-1.09 \sim 0.27$, $P = 0.240$). Furthermore, no evidence for any difference in FACIT-F scores was found between the intervention and control groups in both the ≤ 8 -week and > 8 -week subgroups (all $P > 0.05$).

Meta-regression and sensitivity analyses

Univariate and multivariate meta-regression analyses were used to explore possible sources of heterogeneity among studies. The results showed that no factor could explain the source of heterogeneity (as shown in

Table 1 Main characteristics and methodological quality of all eligible studies

First author [Ref]	Year	Country	Ethnicity	Total number	Group		Age (years)		Exercise time	Fatigue scale	NOS scale
					Intervention	Control	Intervention	Control			
Xu Y [23]	2012	China	Asian	78	39	39	47.3±12.8		8 weeks	RPFS	7
Wang YJ [24]	2011	China	Asian	72	35	37	48.4±10.2 52.3±8.8		6 weeks	FACIT-F	7
Yao MC [25]	2010	China	Asian	120	60	60	(20~65)		8 weeks	RPFS	8
Mustian KM [26]	2009	USA	Caucasian	38	19	19	56.6±13.7 63.3±9.4		4 weeks	FACIT-F	7
Danhauer SC [27]	2009	USA	Caucasian	44	22	22	55.8±9.9		10 weeks	FACIT-F	8
Zhao J [28]	2008	China	Asian	64	32	32	(18~65)		8 weeks	RPFS	6
Courneya KS [11]	2007	USA	Caucasian	160	78	82	(26~78) (30~75)		18 weeks	FACIT-F	8
Daley AJ [32]	2007	USA	Caucasian	72	34	38	51.6±8.8 51.1±8.6		8 weeks	RPFS	6
Moadel AB [31]	2007	USA	Caucasian	128	84	44	55.1±10.1 54.2±9.8		12 weeks	FACIT-F	7
Mutrie N [30]	2007	UK	Caucasian	201	99	102	51.3±10.3 51.8±8.7		12 weeks	FACIT-F	7
Yuen HK [29]	2007	USA	Caucasian	15	8	7	53.1±13.5 55.0±13.4		12 weeks	RPFS	7
Campbell A [33]	2005	UK	Caucasian	22	12	10	48.0±10.0 47.0±5.0		12 weeks	RPFS	6

NOS the Newcastle-Ottawa scale, RPFS the Revised Piper Fatigue Scale, FACIT-F the Functional Assessment of Chronic Illness Treatment-Fatigue scale

Table 2). Sensitivity analysis was performed to assess the influence of each individual study on the pooled SMD by omitting individual studies. The analysis

results suggested that no individual studies significantly affected the pooled SMD, which indicated statistically robust results (Fig. 6).

Fig. 3 Forest plots for the differences in RPFS and FACIT-F scores of breast cancer patients in the aerobic exercise and usual care groups

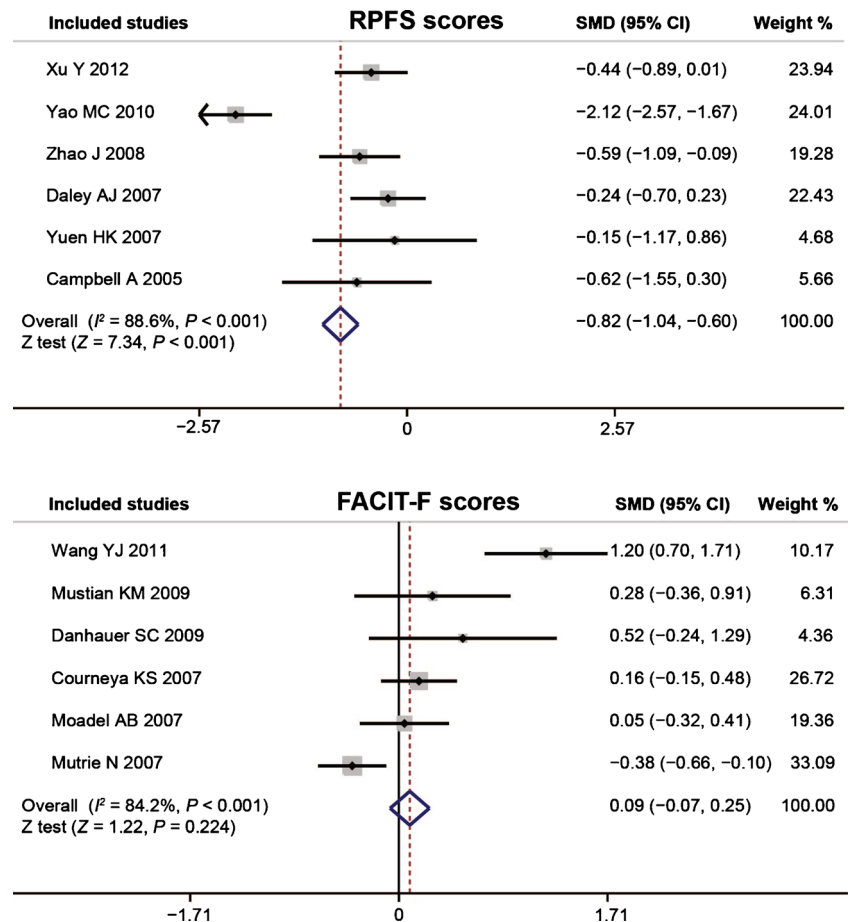
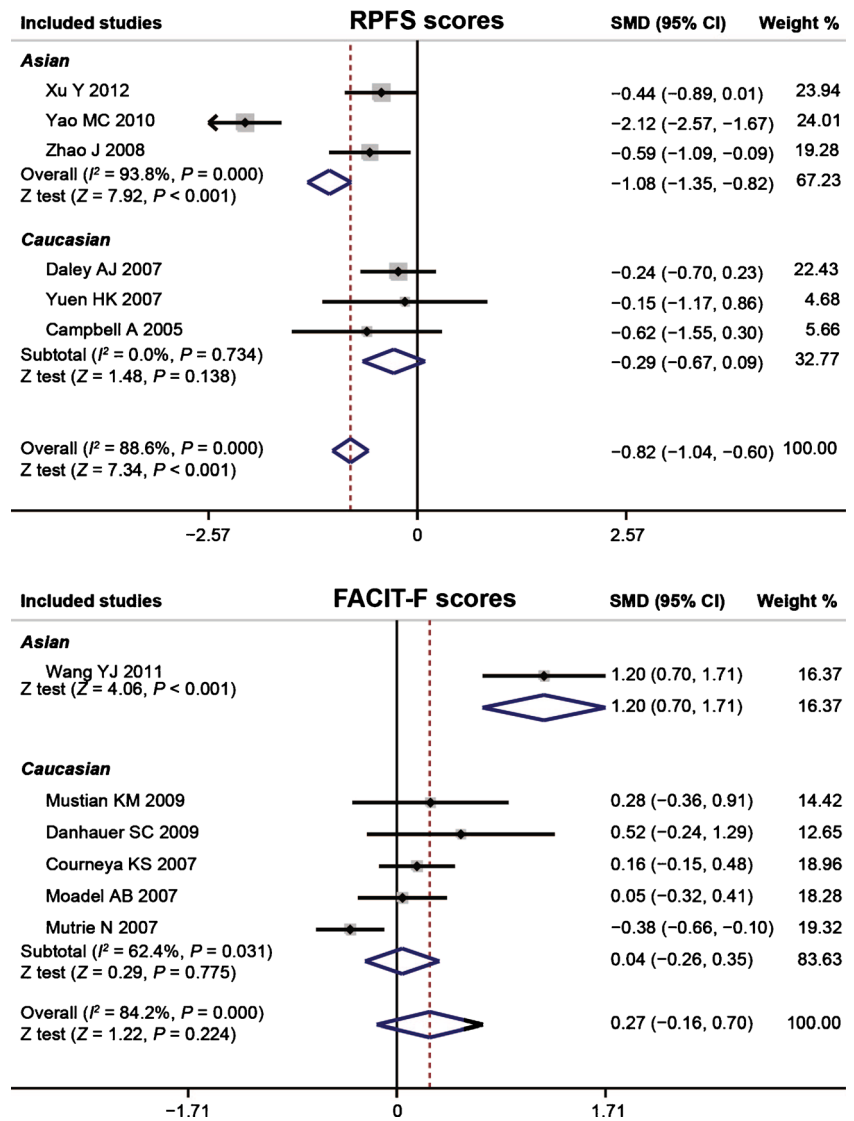


Fig. 4 Subgroup analysis by ethnicity for the differences in RPFS and FACIT-F scores of breast cancer patients in the aerobic exercise and usual care groups



Publication bias evaluation

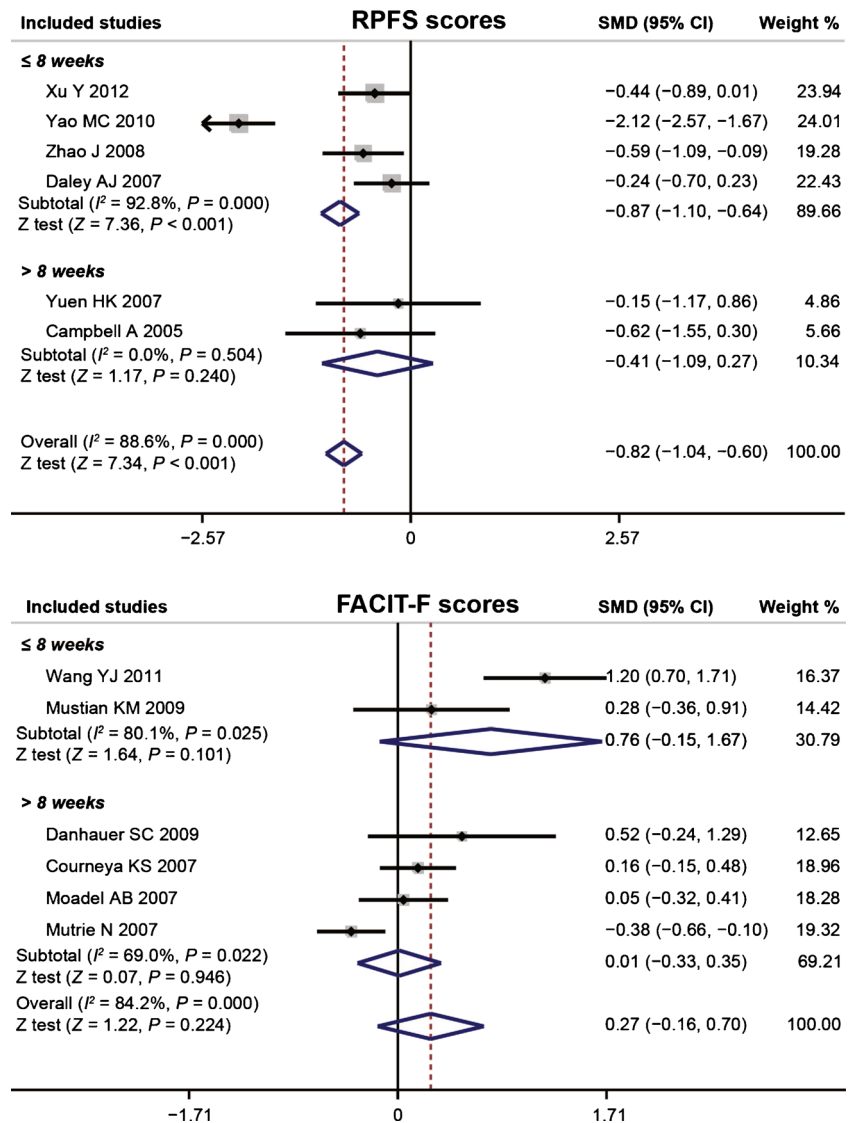
Begger’s funnel plots and Egger’s linear regression test were used to assess potential publication bias in the included studies. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (Fig. 7). Egger’s test also did not display strong statistical evidence for publication bias (RPFS: $t = -1.13$, $P = 0.320$; FACIT-F: $t = -1.43$, $P = 0.225$).

Discussion

CRF is one of the most common and stressful side effects affecting up to 70 to 100 % of cancer patients undergoing treatments such as chemotherapy and radiation therapy [34, 35]. Theoretically, CRF occurs in connection with oncological disease, characterized by feelings of fatigue and lack of energy, and even after successful primary treatment of the

underlying disease, as an independent event in impairment of the health and QOL as well as the ability to work, can lead to vocational disability [36]. Due to the improved management of the previous dominant side effects such as pain, nausea, and vomiting, CRF is increasingly identified as the most burdensome and distinct cancer-related symptom [37]. Nowadays, the exact mechanisms involved in CRF pathophysiology are poorly understood owing to its characteristics as a complex and multifactorial phenomenon which could be induced by a variety of causes and contributing factors [38–40]. Breast cancer is one of the most malignant female death-related cancers worldwide [1]. New effective chemotherapy, hormone therapy, and biological agents are used to integrate systemic therapy, surgery, and radiation therapy for better treatment of breast cancer [3]. However, it is reported in the studies that up to 99 % of breast cancer patients experience some level of fatigue during the course of radiation therapy and chemotherapy, and more than 60 % rate the level of their

Fig. 5 Subgroup analysis by exercise time for the differences in RPFS and FACIT-F scores of breast cancer patients in the aerobic exercise and usual care groups



fatigue as moderate to severe [41]. Evidence has accumulated indicating that CRF may last for months or even years after completion of breast cancer treatment, particularly among patients who have received adjuvant chemotherapy [42]. Previous studies have reported that various methods such as relaxation therapy, group psychotherapy, sleep, and physical exercise have been adopted to effectively manage the influences resulting from the CRF in patients with breast cancer [43–45]. Recent studies have revealed that physical exercise is safe, feasible, and well tolerated by breast cancer patients and owns beneficial effects on improving their QOL, body composition, fitness, and diminishing the side effects of therapy including symptoms of CRF [10]. Among them, aerobic exercise seems to be a preferred intervention to CRF. Aerobic exercise is strongly associated with improved pulmonary function, cardiovascular fitness, and self-esteem, helping patients reduce the feelings of anxiety and depression and facilitating all aspects of health that are typically diminished in

radiotherapy patients, to recover to a relatively stable level [33]. Mock et al. reported that adherence to a home-based moderate-intensity walking exercise program could mitigate high levels of CRF in treatment of breast cancer [46]. Nevertheless, there are few clinical studies to examine the clinical values of aerobic exercise on CRF for breast cancer. Therefore, our meta-analysis aims to provide insight into the effects of aerobic exercise on CRF in breast cancer patients undergoing chemotherapy.

In the present meta-analysis, twelve clinical comparative studies were included with a total of 522 patients in the aerobic exercise group and 492 patients in the usual care group. When all the eligible studies were pooled into the meta-analysis, the results showed that the RPFS scores of breast cancer patients in the aerobic exercise group were significantly lower than those in the usual care group, which indicated that aerobic exercise may improve cancer-related fatigue in breast cancer patients receiving chemotherapy.

Table 2 Univariate and multivariate meta-regression analyses of potential source of heterogeneity

Heterogeneity factors	RPFS						FACIT-F					
	Coefficient	SE	Z	P	95% CI		Coefficient	SE	Z	P	95% CI	
					LL	UL					LL	UL
Publication year												
Univariate	-0.101	0.147	-0.69	0.493	-0.388	0.187	0.301	0.144	-0.58	0.339	-0.136	0.467
Multivariate	0.0367	0.472	0.08	0.938	-0.889	0.962	0.210	0.158	1.33	0.184	-0.100	0.520
Country												
Univariate	0.371	0.446	0.83	0.405	-0.503	1.245	-0.709	0.433	-0.33	0.568	-0.969	0.448
Multivariate	-0.395	2.199	-0.18	0.857	-4.705	3.915	-0.450	0.183	-0.27	0.107	-0.860	0.139
Ethnicity												
Univariate	0.725	0.609	1.19	0.234	-0.470	1.919	-1.063	0.190	-2.99	0.223	-1.927	0.400
Multivariate	1.321	2.558	0.52	0.605	-3.692	6.336	0.252	0.504	0.50	0.616	-0.735	1.239
Exercise time												
Univariate	0.455	0.752	0.60	0.545	-1.019	1.928	-0.358	0.381	-0.99	0.146	-0.505	0.120
Multivariate	0.082	1.943	0.04	0.937	-3.728	3.890	0.544	0.674	-1.29	0.092	-0.222	1.864

RPFS the Revised Piper Fatigue Scale, FACIT-F the Functional Assessment of Chronic Illness Treatment-Fatigue scale, SE standard error, 95%CI 95 % confidence interval, LL lower limit, UL upper limit

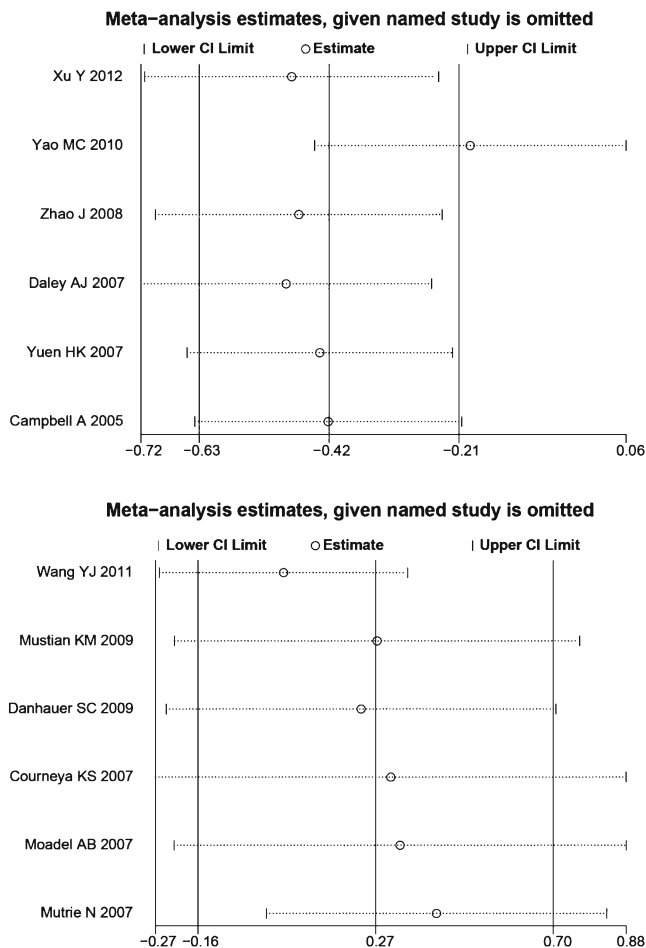


Fig. 6 Sensitivity analyses for the effects of aerobic exercise on cancer-related fatigue in breast cancer patients receiving chemotherapy

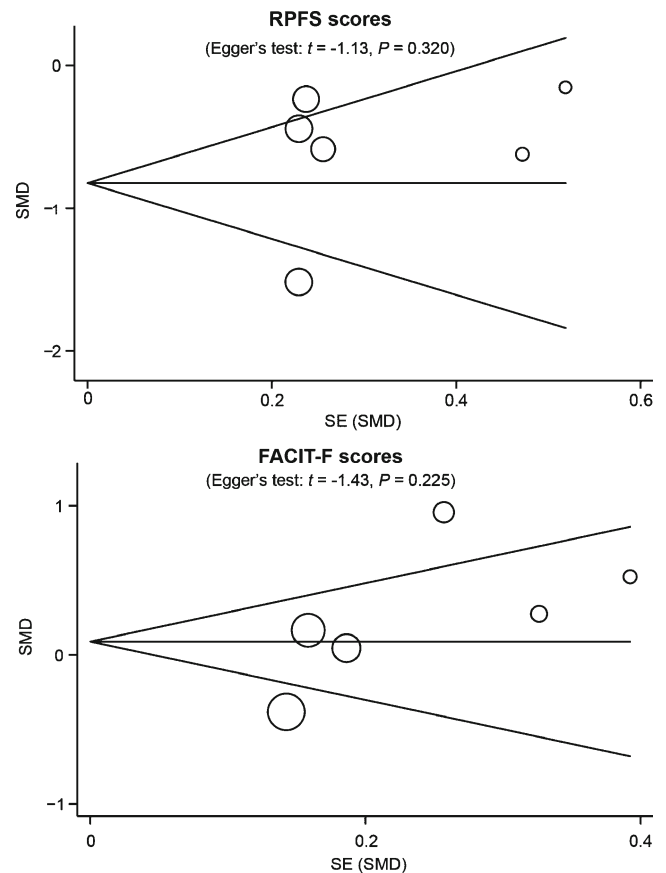


Fig. 7 Beggler's funnel plot for the effects of aerobic exercise on cancer-related fatigue in breast cancer patients receiving chemotherapy

However, there was no significant difference in FACIT-F scores between the aerobic exercise and usual care groups. One possible reason for these results could be the difficulty to determine what frequency, intensity, and duration may be most effective and safe in improving CRF for breast cancer patients, thereby possibly explaining inter-individual difference in improving CRF [47, 48]. In the subgroup analysis by ethnicity, it indicated that there were significant differences in RPFs and FACIT-F scores between the aerobic exercise and usual care groups among Asian populations, but not among Caucasian populations. A possible reason for the ethnic difference could be that large differences in aerobic exercise which improve CRF are mostly due to cultural factors and natural selection. Previous studies have reported that various methods such as relaxation therapy, group psychotherapy, sleep, and physical exercise have been adopted to effectively manage the influences resulting from the CRF in patients with breast cancer. Our findings are partially consistent with the previous studies, suggesting that aerobic exercise may improve CRF in breast cancer patients receiving chemotherapy.

In interpreting our current meta-analysis results, some limitations need to be addressed. First, the sample size is still relatively small and may not provide sufficient statistical power to estimate the effects of aerobic exercise on CRF in breast cancer patients receiving chemotherapy. Therefore, more studies with larger sample size are needed to accurately provide a more representative statistical analysis. Second, as a retrospective study, a meta-analysis may encounter recall or selection bias, possibly influencing the reliability of our results [49]. Third, our lack of access to the original data from the included studies limited further evaluation of potential effects of aerobic exercise on QOL and clinical outcomes of breast cancer patients receiving chemotherapy. Finally, although all included studies were well defined with similar inclusion criteria, there may be other potential factors that were not taken into account that might have influenced our results.

In conclusion, this meta-analysis provides strong evidence that aerobic exercise may improve CRF in breast cancer patients receiving chemotherapy, especially among Asian populations. Based on the limitations mentioned above, detailed studies are still needed to confirm our findings. Further studies are still needed to warrant and validate the effects of aerobic exercise on QOL and clinical outcomes of breast cancer patients receiving chemotherapy.

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Conflicts of interest None

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