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ORIGINAL REPORT

THE IMPACT OF POST-RADIOTHERAPY EXERCISE ON WOMEN WITH BREAST CANCER: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Objective: **To determine the effect of post-radiotherapy exercise on quality of life, fatigue, pain, depression, and other outcomes for women with breast cancer.**
Methods: **Medline, Embase, Scopus, and Cochrane electronic databases were searched (up to August 2019) for relevant studies. Studies were included if they were randomized controlled trials of the effect of post-radiotherapy exercise on the above outcomes in women with breast cancer. Fixed- or random-effects meta-analyses were performed to pool standard mean differences.**
Results: **Data were extracted from 13 randomized controlled trials; a total of 1,306 patients. Overall quality of life and physical functioning scores were increased via post-radiotherapy exercise (0.28 in QoL and 0.27 in physical function). Risks of developing fatigue, pain, and depression were lower in exercise than control groups. There were no differences in the change in emotional function, social function, and sleep disturbance between exercise and control groups.**
Conclusion: **Post-radiotherapy exercise appears to be tolerated and effective for patients with breast cancer. Physicians and other clinicians should encourage patients to exercise after radiotherapy for breast cancer, in order to achieve a better outcome with regards to QoL, physical functioning, fatigue, pain, and depression. Further research is needed to explore which exercise strategies are effective.**

Key words: radiotherapy; exercise; breast cancer; meta-analysis; randomized controlled trial.

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LAY ABSTRACT

It was still debatable with regards to the efficacy of post-radiotherapy exercise on clinical outcomes for breast cancer. The increase in overall QoL and physical function scores was obviously driven by post-radiotherapy exercise. The risk of fatigue, pain, depression was lower with exercise than with control. But there was no difference in the variation of emotional function, social function, sleep disturbances between exercise and control groups. It suggests the physicians and other clinicians should encourage patients to exercise after radiotherapy for breast cancer, in order to achieve a better prognosis

In 2019 breast cancer was one of the most prevalent cancers worldwide. In the USA there were more than 3.8 million women with a history of invasive breast cancer were alive in 2019, and approximately 268,600 women were newly diagnosed (1) The 5-year (2013–2017) death rate for patients with breast cancer decreased in Hispanic (2.1% per year), black (1.5%), white (1.0%) and Asian/Pacific Islander (0.8%) populations, but remained stable in the American Indian/Alaskan Native population in the USA (2). Almost 64% of patients with breast cancer were older than 65 years, while 7% were younger than 50 years of age. When diagnosed with metastatic breast cancer, the majority of patients usually underwent radiotherapy or chemotherapy, with 25% receiving no treatment (1). Despite the beneficial role of radiotherapy, which reduces the risk of local recurrence and mortality, most patients experienced various physical and mental adverse effects, including fatigue, pain, and depression. These symptoms may result in reduced quality of life (QoL). In recent years, there have been many studies into the impact of exercise on women with breast cancer undergoing radiotherapy (3, 4). However, the conclusions are debated with regards to the efficacy of exercise on clinical outcomes. There is a lack of evidence to assess the accurate effect size of exercise on overall QoL, fatigue, pain, physical function, emotional function, social function, depression, and sleep disturbance in patients with breast cancer.

The aim of this systematic review and meta-analysis of randomized controlled trials (RCTs) was to determine the effects of post-radiotherapy exercise compared with controls in patients with breast cancer.

METHODS

Literature search

Medline, Embase, Scopus, and Cochrane electronic databases were searched up to August 2019 to obtain RCTs of the effect of exercise on patients with breast cancer undergoing radiotherapy. The initial search comprised the following terms: breast cancer, radiotherapy, exercise, resistance training, yoga, and

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randomized controlled trial. The detailed search strategies are shown in Appendix S1[1]. No language or publication status restrictions were specified.

Eligibility and study selection

Inclusion criteria were: (*i*) study was a RCT comparing post-radiotherapy exercise or not in patients with breast cancer; (*ii*) at least one of the following outcomes were available: overall QoL, fatigue, pain, physical function, emotional function, social function, depression, or sleep disturbance; (*iii*) sample size > 10 cases. The title and abstract of each study were screened for relevance according to the inclusion criteria. Relevant articles then underwent further full-text analysis. The search and selection of articles for inclusion were performed by 2 investigators (QS and HCY). In case of disagreement regarding inclusion, this was resolved through discussion by these 2 authors.

Measurements

General QoL, physical function, emotional function, and social function were estimated using the Short-Form-36 (SF-36) questionnaires (5), European Organisation for Research in the Treatment of Cancer-Quality of Life (EORTC QoL C30) symptom scale (6), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (7), Functional Assessment of Cancer Therapy (FACT-F) (8), Disability of Arm, Shoulder, and Hand questionnaire (DASH) (9), and the World Health Organisation Quality of Life – BREF (WHOQOL-BREF) (10). Fatigue was assessed using the self-administered 20-item Fatigue Assessment Questionnaire (FAQ) (11), Brief Fatigue Inventory (BFI) (12), and FACIT-F (7, 8). The Center for Epidemiological Studies Depression Scale (CES-D) (13), Beck Depression Inventory (BDI) (14), and Hospital Anxiety and Depression Scale (HADS) (15) were used to evaluate depressive symptomatology. Sleep disturbance was judged with the Pittsburgh Sleep Quality Index (PSQI) (16). Severity of pain was assessed with a visual analogue scale (VAS), ranging from 0 (no pain) to 100 (unbearable pain) (17).

Data extraction and quality assessment

The primary outcomes of interest were changes reflecting overall QoL. Secondary outcomes included fatigue, pain, physical function, emotional function, social function, depression, and sleep disturbance. The outcome definitions used in each trial were incorporated. The current review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (18).

Statistical analysis

Standard mean differences (SMD) and 95% confidence intervals (95% CI) were calculated using Stata 1[2].0 (Stata Corp LP, College Station, TX). Heterogeneity was assessed using the I^2 statistic (19). In cases of a high degree of between-study heterogeneity ($I^2 > 50\%$), data were estimated using the random-effects model; otherwise, a fixed-effect model was used. Analysis of primary outcome (overall QoL) and secondary outcomes (fatigue, pain, physical function, emotional function, social function, depression, and sleep disturbance) were stratified. Publication bias was appraised using Egger's intercept (20). Two reviewers independently assessed the risk of bias of clinical trials according to Cochrane guidelines (21). The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (22), and was rated as high, moderate, low, or very low.

RESULTS

Literature search and study characteristics

A total of 525 RCTs of post-radiotherapy exercise for women with breast cancer were found on searching the literature. Of these, some RCTs (23–25) were excluded due to a risk of overlapping participants. Full-text analysis resulted in inclusion of a final total of 13 trials (3, 4, 26–36) (Fig. 1), covering a total of 1,306 patients. Table I describes the baseline characteristics for each study. All European studies were either from Germany (3, 27) or Great Britain (30). Four Asian studies were identified, from China (33), India (26, 36) and South Korea (32). Regarding North America, one study was from Canada (31) and 4 from the USA (4, 28, 34, 35). There was one South American study from Brazil. The mean age of subjects between trials was similar, varying from 39 to 59 years. Of female patients, 74.1%, 7.7%, and 11.2% were diagnosed with stage 0–III, I–III, or IIIII breast cancer, respectively. Two studies did not specify the stage of breast cancer (29, 32). The period of patient recruitment was mostly from 2004 to 2015. Exercises methods included resistance exercise, stretching, yoga, and qigong (see Table I). Most studies recorded a follow-up of 1–6 months. Control group patients received usual care or practised relaxation.

Primary and secondary efficacy endpoints

Post-radiotherapy exercise increased overall QoL as primary endpoint (SMD = 0.28, 95% CI 0.14–0.43) (Fig. 2A). Fatigue, pain and depression were lower in the exercise group than in the control group (fatigue: SMD = –0.76, 95% CI –1.47 to –0.04; pain: SMD = –1.59,

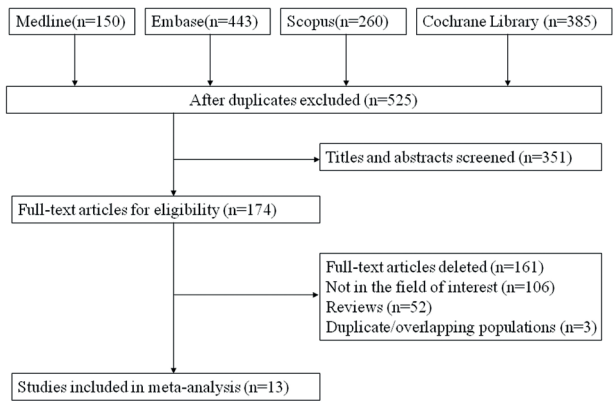

Fig. 1. Selection of studies for inclusion.

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Table I. Study characteristics of included trials

Study	Patient recruitment years	Country	Instrument	Sample size (intervention group/control group)	Stage	Mean age, years (intervention group/ control group)	Intervention group	Control group
Marize I et al. 2017 (34)	2011–2015	Canada	DASH questionnaire	29/30	I–III	39.2±5	Upper body strength train-ing; weight training re-sistance	Relaxation group
Ratcliff et al. 2016 (4)	NA	USA	SF-36; CES-D; PSQI	a.53/54 b.56/54	0–III	a.52.38±1.35/52.11±1.34; b.51.14±1.32/52.11±1.34	a. Yoga; b. stretching	Usual care
Schmidt et al. 2016 (27)	NA	Germany	FAQ; CES-D; QLQ-C30	54/49	0–III	57.1±8.9/57.3±8.8	Resistance exercise	Relaxation control
Steindorf et al. 2014 (3)	Feb 2011–Mar 2013	Germany	FAQ; EORTC QLQ-C30; CES-D	77/78	0–III	55.2±9.5/56.4±8.7	Resistance training	Relaxation control
Chen et al. 2013 (33)	2005–2007	China	BFI; PSQI; FACT-G; CES-D	49/47	0–III	45.3±6.3/44.7±9.7	Qigong	Relaxation control
Reis et al. 2013 (28)	Nov 2008–Jan 2010	USA	FACIT-F; FACT-G; FACIT	22/19	I–III	54±11.1/59±10.7	Nia exercise	Usual care
Chandwani et al. 2010 (24)	NA	USA	BFI; SF-36; PSQI; CES-D	30/31	0–III	51.39±7.97/4.02±9.96	Yoga	Usual care
Oliveira et al. 2010 (29)	Jun 2005–Sep 2006	Brazil	FACT-G; FACT-B	28/27	NA	52.7±11/48.5±10.9	Upper limb kinesiotherapy	Relaxation control
Cadmus et al. 2009 (36)	Jul 2004–May 2006	USA	FACT-G; SF-36	a.25/25; b.37/38	0–IIIa	a.54.5±8.2/54.0±10.9; b.56.5±9.5/55.1±7.7	Steps on a 7-day pedometer log	Relaxation control
Vadiraja et al. 2009 (26)	Jan 2004–Jun 2006	India	EORTC QoL C30	44/44	II–III	30–70	Yoga	Usual care
Hwang et al. 2008 (32)	NA	Korea	BFI; WHOQOL-BREF; VAS	17/20	NA	46.3±7.5/46.3±9.5	Stretching exercises, aerobic exercise	Relaxation control
Mutrie et al. 2007 (30)	Jan 2004–Jan 2005	Great Britain	FACT-F; FACT-G; BDI	99/102	0–III	51.3±10.3/51.8±8.7	Stretching exercise, aerobic exercise	Usual care
Banerjee et al. 2007 (37)	Jan 2004–Dec 2005	India	HADS	35/23	II–III	47±1.1/43±1.5	Yoga	Usual care

FAQ: Fatigue Assessment Questionnaire; HADS: Hospital Anxiety and Depression Scale; DASH questionnaire: Disability of Arm, Shoulder, and Hand questionnaire; SF-36: Short-Form-36; CES-D: Center for Epidemiological Studies Depression Scale; PSQI: Pittsburgh Sleep Quality Index; EORTC QLQ-C30: European Organisation for Research in the Treatment of Cancer-Quality of Life; BFI: Brief Fatigue Inventory; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-F: Functional Assessment of Cancer Therapy; WHOQOL-BREF: World Health Organization Quality of Life-BREF; FACT-G: Functional Assessment of Cancer Therapy-General; FACT-B: Functional Assessment of Cancer Therapy-Breast.

95% CI –2.70 to –0.48; pain: SMD = –1.59, 95% CI –2.70 to –0.48; depression: SMD = –0.51, 95% CI –0.97 to –0.04) (Fig. 2B,C and Fig. 3C). More importantly, physical function scores were higher with exercise (SMD = 0.27, 95% CI 0.14 to 0.40) (Fig. 2D). There was no difference in variation in emotional function, social function, or sleep disturbance between exercise and control groups (emotional function: SMD = 0.118, 95% CI –0.018 to 0.255; social function: SMD = 0.11, 95% CI –0.05 to 0.27; sleep disturbance: SMD = 0.11, 95% CI –0.10 to 0.31) (Fig. 3A, B,D). There was significant heterogeneity in the secondary variables measuring of fatigue (I^2 = 95.0%), pain (I^2 = 96.7%), and depression (I^2 = 93.1%) (Fig. 2 and Fig. 3, Table II).

Risk of bias, determined with the Cochrane Risk of Bias Tool, is shown in Fig. 4. A serious methodological limitation resulted from the poor concealment of allocation, and it was difficult to blind participants and personnel due to the nature of the treatment itself. Other biases in the included studies were not clearly set out. It was noted that most of the included studies were relatively small. The GRADE assessment of evidence quality is shown in Table II; most outcomes were rated as moderate or high quality. Although the evidence was from RCTs, the impact of limited sample sizes must be taken into consideration in considering the outcomes.

Sensitivity analyses showed similar results after exclusion of one study at a time (Fig. S1[1] and Fig. S2[1]). The impact of publication bias was explored using Egger's test, with no evidence of publication bias in the outcomes of overall QoL, fatigue, pain, physical function, emotional function, social function, or sleep disturbance ($p > 0.05$). However, there appeared to be a publication bias for depression ($p = 0.008$).

Table II. Outcome of studies of post-radiotherapy exercise and clinical response

Subgroup	Number of trials	SMD (95% CI)	Quality of evidence (GRADE)
Overall QoL (I^2 = 47.7%, p = 0.053)	9	0.28 (0.14 to 0.43)	High
Fatigue (I^2 = 95.0%, p = 0.000)	8	–0.76 (–1.47 to –0.04)	Moderate
Pain (I^2 = 96.7%, p = 0.000)	7	–1.59 (–2.70 to –0.48)	Moderate
Physical function (I^2 = 34.5%, p = 0.122)	11	0.27 (0.14 to 0.40)	High
Emotional function (I^2 = 0.0%, p = 0.788)	10	0.118 (–0.018 to 0.255)	High
Social function (I^2 = 0.0%, p = 0.487)	8	0.11 (–0.05 to 0.27)	High
Depression (I^2 = 93.1%, p = 0.000)	10	–0.51 (–0.97 to –0.04)	Moderate
Sleep disturbance (I^2 = 0.0%, p = 0.564)	4	0.11 (–0.10 to 0.31)	Low

QoL: quality of life; SMD: standard mean difference; GRADE: Grading of Recommendations, Assessment, Development and Evaluation. I^2: Stata version I^2.

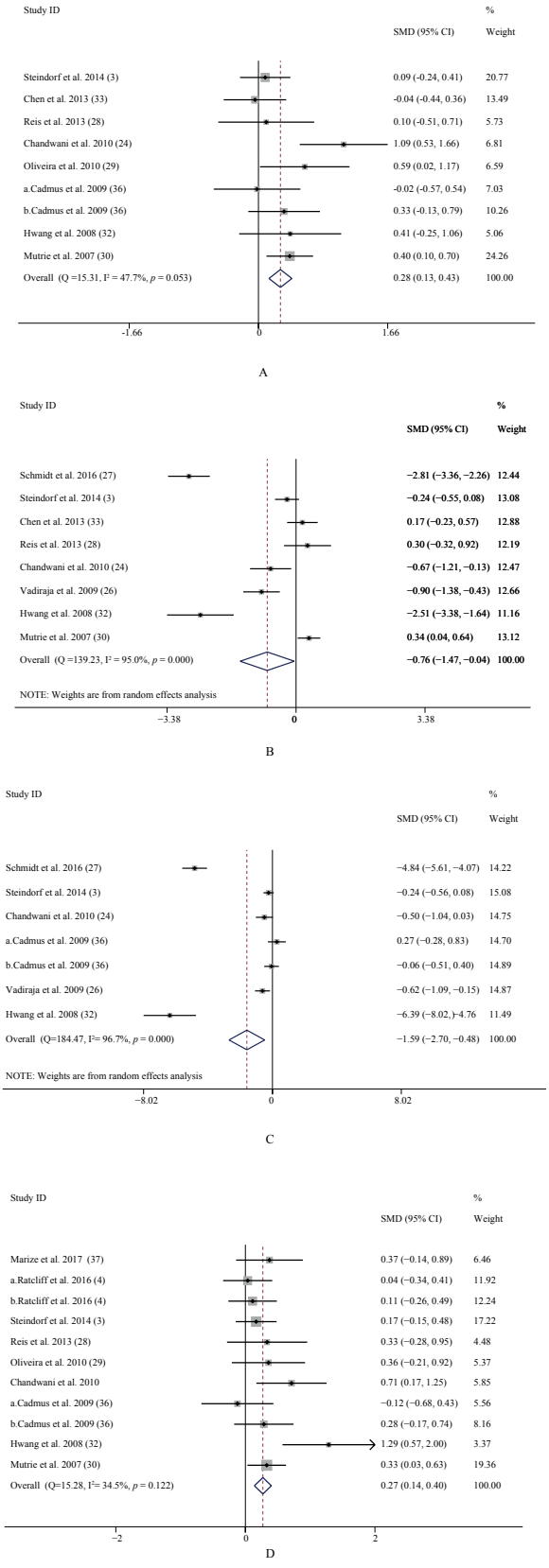

Fig. 2. Effects of post-radiotherapy exercise vs controls in breast cancer. (A) Overall quality of life (QoL), (B) fatigue, (C) pain, and (D) physical function. CI: confidence interval.

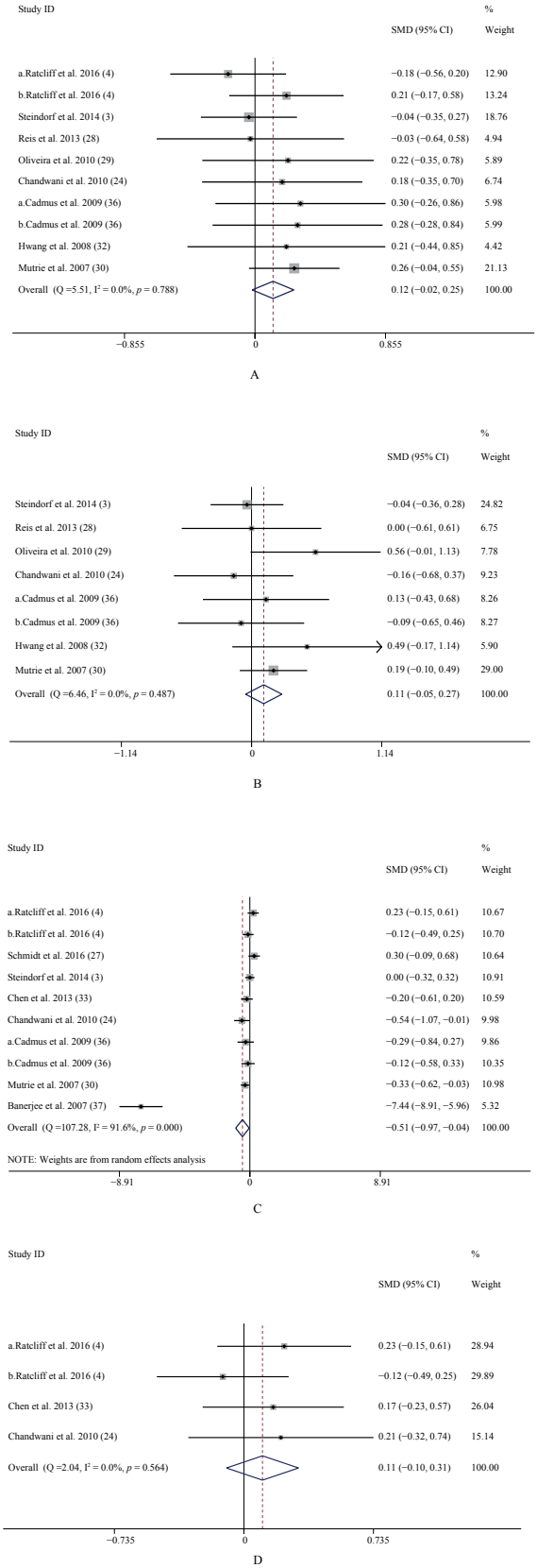

Fig. 3. Effect of post-radiotherapy exercise vs controls in breast cancer. (A) Emotional function, (B) social function, (C) depression and (D) sleep disturbance. CI: confidence interval; SMD: standard mean difference.

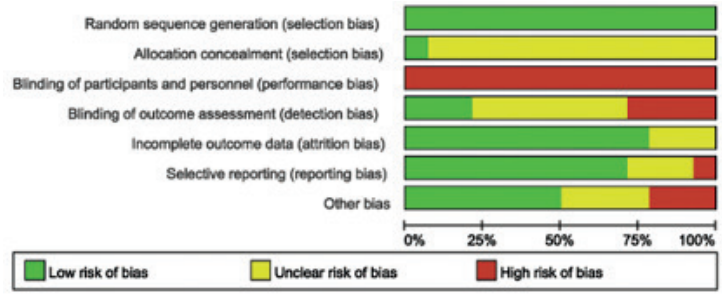

Fig. 4. Risk of bias graph.

DISCUSSION

Improvements in healthcare may improve patients' QoL. This meta-analysis of 14 trials, including 1,306 patients, provides evidence that post-radiotherapy exercise has a positive impact on overall QoL, fatigue, pain, and physical function in women with breast cancer (34).

In terms of QoL as the primary outcome, a previous study by Chandwani et al. found that a 3-month yoga programme for breast cancer patients undergoing radiotherapy was associated with significant improvements (35). Steindorf et al. reported that a 12-week resistance training programme had a positive effect on fatigue and QoL compared with usual care (3). In another study, women in a qigong group who participated in a 5-week class during 5- or 6-weeks of radiotherapy had less fatigue and better overall QoL (33). In contrast, another study concluded that exercise was not associated with QoL (36). However, we consider that careful attention should be paid to the effect of post-radiotherapy exercise on QoL in patients with breast cancer.

In the current study, secondary outcomes were examined in order to determine the effects of post-radiotherapy exercise. The findings were similar to previous results. It has been reported previously that Nia intervention post-radiotherapy resulted in significantly less fatigue at 12 weeks, compared with a control group (28). In another study, there was significant reduction in pain after resistance training in breast cancer patients (3). Subgroup analysis based on 8 studies indicated a reduction in depression (3, 4, 27, 30, 33–37). These results support the physiological and psychological improvement in patients.

The positive effects of exercise may be due to changes in immune function, including reduction in inflammation and enhancement of anti-tumour immunity (38). Exercise accelerates the production of adiponectin, which has an anti-inflammatory effect. Furthermore, exercise may reduce inflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) (39, 40). For cancer prevention and therapy, it is suggested that exercise might reduce the risk of the disease developing further (41, 42).

However, many reports show that it is challenging to encourage cancer patients to participate in physical activity and sports programmes. Many people believe that patients treated for cancer need more rest than exercise, in order to avoid fatigue and pain induced by physical activity (43). In addition, there may be a lack of motivation or time to perform individual exercise, due to personal factors such as economic hardship or child rearing responsibilities.

Study limitations

This meta-analysis has several limitations. First, data for primary and secondary outcomes were provided through self-report measures, which are prone to report and recall biases. Thus, the effects of post-radiotherapy exercise may be under- or over-estimated in this meta-analysis. Secondly, many studies used a range of different scales to quantify the prognosis of the treatment. Thirdly, due to the nature of the treatment, it is not possible to blind patients to exercise programmes. Fourthly, the reference scales for the endpoint variables were different; e.g. fatigue evaluated by FAQ, BFI, FACIT-F, QoLC30, and FACT-F, pain estimated by QLQ-C30, SF-36, and VAS, depression evaluated by CES-D, BDI, and HADS-D. In addition, there was obvious heterogeneity in the secondary variables measuring fatigue, pain, and depression. Thus, the current analysis used standardized mean difference and a random-effects model given within-study and between-study differences. Finally, the small sample size in this analysis may be a crucial methodological shortcoming.

Overall, these factors may cause considerable heterogeneity in the results. Further research is necessary to determine the long-term effectiveness of exercise in these patients, since the follow-up period was short in the studies analysed here.

CONCLUSION

Overall QoL for breast cancer patients was found to improve over time with exercise after radiotherapy. This result highlights the importance of implementing post-radiotherapy exercise. Physicians and other clinicians should encourage patients to exercise after radiotherapy for breast cancer, in order to improve outcomes.

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The authors have no conflicts of interest to declare.

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