The impact of post-radiotherapy exercise on women with breast cancer: a meta-analysis of randomized controlled trials

Qian Shen, MS1 and Hongchun Yang, PhD2

From the 1Department of Rehabilitation, The Second Affiliated Hospital of Zhejiang University School of Medicine and 2Institute of Industrial Design, Zhejiang University of Technology, Hangzhou, China

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.

Accepted Aug 25, 2020; Epub ahead of print Sep 17, 2020

J Rehabil Med 2020; 52: jrm00112

Correspondence address: Hongchun Yang, Institute of Industrial Design, Zhejiang University of Technology, Hangzhou, China. E-mail: yhc2016@zjut.edu.cn

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

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...
randomized controlled trial. The detailed search strategies are shown in Appendix S1. 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 (FACT-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 FACT-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 12.0 (Stata Corp LP, College Station, TX). Heterogeneity was assessed using the I² statistic (19). In cases of a high degree of between-study heterogeneity (I² > 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 qi gong (see Table I).

**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,
Impact of post-radiotherapy exercise on women with breast cancer

Table I. Study characteristics of included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient recruitment years</th>
<th>Country</th>
<th>Instrument</th>
<th>Sample size (intervention group/control group)</th>
<th>Stage</th>
<th>Mean age, years (intervention group/control group)</th>
<th>Intervention group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marize I et al. 2017 (34)</td>
<td>2011–2015</td>
<td>Canada</td>
<td>DASH questionnaire</td>
<td>29/30</td>
<td>I–III</td>
<td>39 ± 5</td>
<td>Upper body strength training; weight training; relaxation group</td>
<td></td>
</tr>
<tr>
<td>Ratcliff et al. 2016 (4)</td>
<td>NA</td>
<td>USA</td>
<td>SF-36; CES-D; PSQI</td>
<td>a.53/54, b.56/54</td>
<td>0–III</td>
<td>a.52.38 ± 1.35; b.52.11 ± 1.34; a. Yoga; b. stretching</td>
<td>Usual care</td>
<td></td>
</tr>
<tr>
<td>Schmidt et al. 2016 (27)</td>
<td>NA</td>
<td>Germany</td>
<td>FAQ; CES-D; EORTC QLQ-C30</td>
<td>54/49</td>
<td>0–III</td>
<td>57.1 ± 8.9/57.3 ± 8.8</td>
<td>Resistance exercise; relaxation control</td>
<td></td>
</tr>
<tr>
<td>Steindorf et al. 2014 (3)</td>
<td>Feb 2011–Mar 2013</td>
<td>Germany</td>
<td>EORTC QLQ-C30</td>
<td>77/78</td>
<td>0–III</td>
<td>55.2 ± 9.5/56.4 ± 8.7</td>
<td>Resistance training; relaxation control</td>
<td></td>
</tr>
<tr>
<td>Chen et al. 2013 (33)</td>
<td>2005–2007</td>
<td>China</td>
<td>FAQ; PSQI; FACT-G; CES-D</td>
<td>49/47</td>
<td>0–III</td>
<td>45.3 ± 6.3/44.7 ± 9.7</td>
<td>Qigong; relaxation control</td>
<td></td>
</tr>
<tr>
<td>Reis et al. 2013 (28)</td>
<td>Nov 2008–Jan 2010</td>
<td>USA</td>
<td>FACT-F; FACT-G</td>
<td>22/19</td>
<td>I–III</td>
<td>54 ± 11.1/59 ± 10.7</td>
<td>Nia exercise; usual care</td>
<td></td>
</tr>
<tr>
<td>Chandwani et al. 2010 (24)</td>
<td>NA</td>
<td>USA</td>
<td>BFI; SF-36; PSQI; CES-D</td>
<td>30/31</td>
<td>0–III</td>
<td>51.39 ± 7.97/4.02 ± 9.96</td>
<td>Yoga; usual care</td>
<td></td>
</tr>
<tr>
<td>Oliveira et al. 2010 (29)</td>
<td>Jun 2005–Sep 2006</td>
<td>Brazil</td>
<td>FACT-G; FACT-B</td>
<td>28/27</td>
<td>NA</td>
<td>52.7 ± 11/48.5 ± 10.9</td>
<td>Upper limb kinesitherapy; steps on a 7-day pedometer log</td>
<td></td>
</tr>
<tr>
<td>Cadmus et al. 2009 (36)</td>
<td>Jul 2004–May 2006</td>
<td>USA</td>
<td>FACT-G; SF-36</td>
<td>a.25/25; b.37/38</td>
<td>0–IIIa</td>
<td>a.54.5 ± 8.2/54.0 ± 10.9; b.56.5 ± 9.5/55.1 ± 7.7</td>
<td>Relaxation control; control group</td>
<td></td>
</tr>
<tr>
<td>Hwang et al. 2008 (32)</td>
<td>NA</td>
<td>Korea</td>
<td>BFI; WHOQOL-BREF; VAS</td>
<td>17/20</td>
<td>NA</td>
<td>46.3 ± 7.5/46.3 ± 9.5</td>
<td>Stretching exercises; relaxation control; aerobic exercise</td>
<td></td>
</tr>
<tr>
<td>Mutrie et al. 2007 (30)</td>
<td>Jan 2004–Jan 2005</td>
<td>Great Britain</td>
<td>FACT-F; FACT-G; BDI</td>
<td>99/102</td>
<td>0–III</td>
<td>51.3 ± 10.3/51.8 ± 8.7</td>
<td>Stretching exercise; usual care</td>
<td></td>
</tr>
<tr>
<td>Banerjee et al. 2007 (37)</td>
<td>Jan 2004–Dec 2005</td>
<td>India</td>
<td>HADS</td>
<td>35/23</td>
<td>II–III</td>
<td>47 ± 1.1/43 ± 1.5</td>
<td>Yoga; usual care</td>
<td></td>
</tr>
</tbody>
</table>

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; FACT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; 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 –0.48 (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 (I² = 95.0%), pain (I² = 96.7%), and depression (I² = 93.1%) (Fig. 2 and 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 and Fig. S2). 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

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of trials</th>
<th>SMD (95% CI)</th>
<th>Quality of evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall QoL (I² = 47.7%, p = 0.053)</td>
<td>9</td>
<td>0.28 (0.14 to 0.43)</td>
<td>High</td>
</tr>
<tr>
<td>Fatigue (I² = 95.0%, p = 0.000)</td>
<td>8</td>
<td>–0.76 (–1.47 to –0.04)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pain (I² = 96.7%, p = 0.000)</td>
<td>7</td>
<td>–1.59 (–2.70 to –0.48)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Physical function (I² = 34.5%, p = 0.122)</td>
<td>11</td>
<td>0.27 (0.14 to 0.40)</td>
<td>High</td>
</tr>
<tr>
<td>Emotional function (I² = 0.0%, p = 0.788)</td>
<td>10</td>
<td>0.118 (–0.018 to 0.255)</td>
<td>High</td>
</tr>
<tr>
<td>Social function (I² = 0.0%, p = 0.487)</td>
<td>8</td>
<td>–0.11 (–0.05 to 0.27)</td>
<td>High</td>
</tr>
<tr>
<td>Depression (I² = 93.1%, p = 0.000)</td>
<td>10</td>
<td>–0.51 (–0.97 to –0.04)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Sleep disturbance (I² = 0.0%, p = 0.564)</td>
<td>4</td>
<td>0.11 (–0.10 to 0.31)</td>
<td>Low</td>
</tr>
</tbody>
</table>

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.
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, FACT-T, 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.

ACKNOWLEDGEMENT

This study was supported by Ministry of Education Humanities and Social Sciences Research and Planning Fund Project (No.19YJA890028).

The authors have no conflicts of interest to declare.
REFERENCES


