Breast Cancer Res Treat (2014) 148:249–268
DOI 10.1007/s10549-014-3162-9

REVIEW

Safety and efficacy of progressive resistance training in breast cancer: a systematic review and meta-analysis

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Received: 16 September 2014 / Accepted: 1 October 2014 / Published online: 17 October 2014

Abstract The purpose of this study was to assess the safety and efficacy of progressive resistance training (PRT) in breast cancer. Randomized controlled trials (RCTs) published to November 2013 that reported on the effects of PRT (>6 weeks) on breast cancer-related lymphedema (BCRL) (incidence/exacerbation, arm volume, and symptom severity), physical functioning (upper and lower body muscular strength), and health-related quality of life (HRQoL) in breast cancer patients were included. Of 446 citations retrieved, 15 RCTs in 1,652 patients were included and yielded five studies on BCRL incidence/exacerbation ($N = 647$), four studies on arm volume ($N = 384$) and BCRL symptom severity ($N = 479$), 11 studies on upper body muscular strength ($N = 1,252$), nine studies on lower body muscular strength ($N = 1,079$), and seven studies on HRQoL ($N = 823$). PRT reduced the risk of BCRL versus control conditions [OR = 0.53 (95 % CI 0.31–0.90); $I^2 = 0$ %] and did not worsen arm volume or symptom severity (both SMD = −0.07). PRT significantly improved upper [SMD = 0.57 (95 % CI 0.37–0.76); $I^2 = 58.4$ %] and lower body muscular strength [SMD = 0.48 (95 % CI 0.30–0.67); $I^2 = 46.7$ %] but not HRQoL [SMD = 0.17 (95 % CI −0.03 to 0.38); $I^2 = 47.0$ %]. The effect of PRT on HRQoL became significant in our sensitivity analysis when two studies conducted during adjuvant chemotherapy [SMD = 0.30 (95 % CI 0.04–0.55), $I^2 = 37.0$ %] were excluded. These data indicate that PRT improves physical functioning and reduces the risk of BCRL. Clinical practice guidelines should be updated to inform clinicians on the benefits of PRT in this cohort.

Electronic supplementary material The online version of this article (doi:10.1007/s10549-014-3162-9) contains supplementary material, which is available to authorized users.

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Keywords Strength · Physical functioning · Quality of life · Rehabilitation · Exercise · Health · Lymphedema · Survival · Fitness

Introduction

Breast cancer is the most frequently diagnosed cancer in women globally (1.68 million new cases estimated in 2012) [1, 2]. The 5-year relative survival rate in many developed countries has improved steadily in recent decades [1, 3]. As the prevalent breast cancer survivor population continues to grow [4], important questions remain regarding long-term standard of care, physical functioning, and health-related quality of life (HRQoL) in this patient group.

Treatment of breast cancer can include surgery to the breast and axilla and adjuvant chemotherapy, radiotherapy, and endocrine therapies. These interventions have increased survival [5–7] but can induce chronic side effects such as breast cancer-related lymphedema (BCRL) [8], upper body functional impairment [9], chronic fatigue [10], weight gain [11, 12], bone loss [13], inflammation [14], immunosuppression [15], peripheral neuropathy [16], and psychological impairments (e.g., depression) [17]. The adverse effects of breast cancer treatment are often associated with decreased physical activity [18] and fitness [9, 19], and impairments of physical functioning [20] and HRQoL [21]. Low physical functioning and HRQoL, in turn, contribute to greater mortality in this population [22, 23].

Progressive resistance training (PRT) is an anabolic exercise modality that can potentially target many of the adverse effects of breast cancer treatment, improving physical functioning and HRQoL [24]. However, there have been concerns regarding the safety of strenuous upper body PRT in women treated for breast cancer, particularly on the risk of BCRL [25]. Since 2006, several randomized controlled trials (RCTs) have investigated the safety and efficacy of PRT regimens involving upper body exertion [26–40]. However, these data have not yet been systematically reviewed; accordingly, recommendations for PRT (and prescribed exercise training in general) remain absent from clinical guidelines [41–43]. We therefore systematically assessed the total body of RCT evidence on the safety and efficacy of PRT to inform clinical guidelines and practice.

Methods

Search strategy and study selection

Search strategy: A systematic review of all published literature using the following electronic databases was conducted up to November 2013: MEDLINE (OvidSP, Wolters Kluwer), PubMed (NCBI, U.S. National Library of Medicine), ScienceDirect (SciVerse, Elsevier), SPORTDiscus (EBSCOhost, EBSCO), Scopus (SciVerse, Elsevier), Web of Science (Web of Knowledge, Thomson Reuters), the Cochrane Library (John Wiley & Sons), Embase (OvidSP, Wolters Kluwer), CINAHL, and Google Scholar. Search syntaxes were developed in consultation with an experienced university librarian taking into account a broad range of terms and phrases used in definitions related to breast cancer (e.g., breast cancer, breast neoplasm, breast carcinoma, breast tumor, mammary carcinoma, etc.) and resistance training (e.g., resistance training, resistance exercise, weight training, weight lifting, strength training, etc.). A sample search strategy (PubMed and Scopus) has been presented in the Electronic Supplementary Material (Appendix S1). Reference lists of retrieved full-text articles and recent reviews were examined to identify additional articles not found by our search strategy.

Study selection: Electronic references were compiled in an Endnote X6© (Thomson Reuters) file, and duplicates were identified and deleted. Two authors (BSC and EA) independently reviewed the titles and abstracts of each reference for potential inclusion. Each reviewer then performed a second screening on the full-text version of these articles, and disagreements were resolved by discussion. RCTs that investigated the isolated effects of PRT on BCRL (number of cases of incidence or exacerbation, arm volume, and severity of BCRL symptoms) and/or upper body strength, and/or lower body strength and/or HRQoL in women surgically treated for primary tumor of the breast were included. PRT interventions may have included but were not restricted to, any form of resistive type exercise using body weight (calisthenics), equipment (machine weights, free weights) or apparatus (elastic bands), and had to have been at least 6 weeks in duration. Studies that prescribed aerobic training plus PRT were excluded, unless a comparison group undertook the same dosage of aerobic training in isolation (i.e., to control for confounding effect of aerobic training). Studies that prescribed flexibility training plus PRT were included given that PRT involves aspects of flexibility training, i.e., loaded movements throughout a complete range of motion. Where multiple PRT prescriptions were tested, higher intensity regimens were prioritised over lower intensity regimens. The review was restricted to articles published in English.

Primary outcomes (safety)

Primary outcomes assessed the effect of PRT on BCRL outcomes, including: (1) cases of BCRL incidence or exacerbation during the trial, (2) arm volume outcomes, and (3) BCRL symptom severity between the treatment and

control group. Where multiple measures of BCRL incidence or exacerbation were reported, we prioritized clinician-defined diagnosis with objective physical measurements over other methods. Data for BCRL incidence and exacerbation were combined given that the physiologic mechanism between cases is identical (i.e., a decrease in lymphatic transport capacity relative to lymphatic load) [44]. Where multiple arm volume outcomes were reported, we prioritized measurements of the inter-limb volume difference, followed by volume of the affected limb. Where multiple BCRL symptom severity outcomes were reported, we prioritized assessments using the arm symptoms subscale of the European Organization for Research and Treatment of Cancer Breast Cancer Module (QLQ-BR23) [45].

Data about additional PRT-related adverse events (beyond BCRL) were also included for a descriptive synthesis.

Secondary outcomes (efficacy)

Secondary outcomes assessed efficacy data of PRT and included: (1) upper body strength, (2) lower body strength, and (3) HRQoL after intervention (post-treatment) between the treatment and control group. Where multiple upper body muscular strength outcomes were reported, we prioritized the most common measure (i.e., bench press) followed by shoulder press, shoulder flexion, and wrist flexion. Where assessments of upper body strength were completed bilaterally, we prioritized measures of the ipsilateral (affected) extremity over those of the contralateral extremity. Where multiple lower body muscular strength outcomes were reported, we prioritized leg press followed by knee extension. Where multiple HRQoL outcomes were reported, we prioritized domain and then summary scale scores of physical functioning, followed by global scores of HRQoL.

Data extraction

Data extraction of included studies was performed and/or verified independently by three reviewers (BSC, SLK, and PF). Discrepancies were resolved through discussion. Authors of relevant studies were contacted, where possible, for data that could not be extracted from the published articles.

Quality assessment

The following data were extracted from included studies using a standard proforma: study population characteristics, PRT intervention (e.g., specific exercises, number of sets per exercise, number of repetitions per set, intensity (load), frequency, and duration of training and loading progression). Our quality checklist was designed based on established criteria for the assessment of RCTs [46]. Quality items for RCT studies reviewed were (each worth 1.0 numerical point) as follows: (1) evidence of randomization and concealment of treatment allocation, (2) statistical similarity of groups at baseline, (3) specification of eligibility criteria, (4) blinding of outcomes assessors, (5) reporting of compliance, (6) supervision of exercise sessions, (7) reporting of dropouts, (8) presenting data for primary and secondary outcomes, (9) use of intention-to-treat analysis (if data for >90 % of baseline sample were analyzed, a score of 1.0 was given), and (10) reporting of adverse events. Summated scores ranged from 0 to 10 points with higher scores reflecting better quality. The quality assessment was completed and checked by two reviewers (BSC and SLK).

Data synthesis

Three reviewers (BSC, SLK, and EA) independently collated and/or verified extracted data to present a descriptive synthesis of important study characteristics and a quantitative synthesis of effect estimates.

Statistical methods

We pooled and weighted studies first using random effects meta-analysis models and second using fixed effects models for verification [47]. The effect was measured as the difference between groups after the treatment period without correction for possible baseline differences between groups. The mean and standard deviation of the pre- to post-treatment improvement in outcome were unavailable for the majority of papers. While these statistics could have been estimated from the pre- and post-treatment statistics [48], such estimation requires the pre–post correlation. We computed point estimates of correlation for those few papers which provided pre-, post-, and change means and standard deviations [48]. However, as the number of studies with full information was small and the estimated correlations from these studies were not fully consistent, we opted to restrict the analyses to the known post-treatment statistics without correction for possible baseline differences. We checked all studies for differences between groups at baseline and where statistically significant differences were found, we used sensitivity analysis to check the impact of these differences on the pooled results.

To examine the incidence/exacerbation of lymphedema cases, we reported the pooled odds ratio between treatment and control groups and associated 95 % confidence interval (95 % CI). Where articles reported 0 cases in either the

treatment or control group, the Haldane continuity correction was applied by adding 0.5 to all four cells [49]. Articles which reported 0 cases in both the treatment and control groups were excluded from the analysis as differences in group size would produce bias in the continuity correction [50]. To examine the effects of PRT on arm swelling, lymphedema severity, upper and lower body strength, and HRQoL outcomes, the standardized mean difference (SMD) from each study was pooled to produce an overall estimate of effect and associated 95 % CI between treatment and control groups. For each meta-analysis model, the degree of heterogeneity was assessed by visual inspection, the *I*-squared statistic (I^2) (moderate being <50 %) [51], and the χ^2-test of goodness of fit [52]. When evidence of heterogeneity was observed, we checked data extracted from individual outlier studies, qualitatively investigated reasons for their different results, and explored the effects of study exclusion in sensitivity analyses.

We also used sensitivity analysis to investigate the robustness of the meta-analyses models. We variously excluded studies that combined PRT with other exercise modalities or physical therapies, studies that did not include a no-treatment control group, studies that prescribed PRT during the adjuvant chemotherapy treatment phase, studies conducted outside the US, studies of shorter duration (≤12 weeks), studies in older cohorts (≥60 years), studies in which BCRL was an entry criterion, and studies of lower quality (score ≤6.0). Publication bias, which reflects the tendency for smaller studies to be published in the literature only when findings are positive, was assessed visually using funnel plots [53]. All calculations were performed in Stata version 12 (StataCorp, College Station, TX, USA) using the 'metan' and 'metafunnel' commands. A two-tailed *P* value <0.05 was considered statistically significant throughout the analyses.

Results

Figure 1 presents a flowchart summarizing identification of potentially relevant studies and those included. Our search strategy identified 446 citations after duplicates were removed. Of these, 392 citations were excluded after the first screening of titles and/or abstracts for inclusion and exclusion criteria. After further assessment of the remaining 54 citations, 40 were excluded (Electronic Supplementary Material, Appendix S2) for reasons listed in Fig. 1. An expert in the field provided one recent citation not captured by our search. Fifteen citations were included in the present review. Most citations were excluded due to being a conference abstract only or due to being redundant citations of the same study.

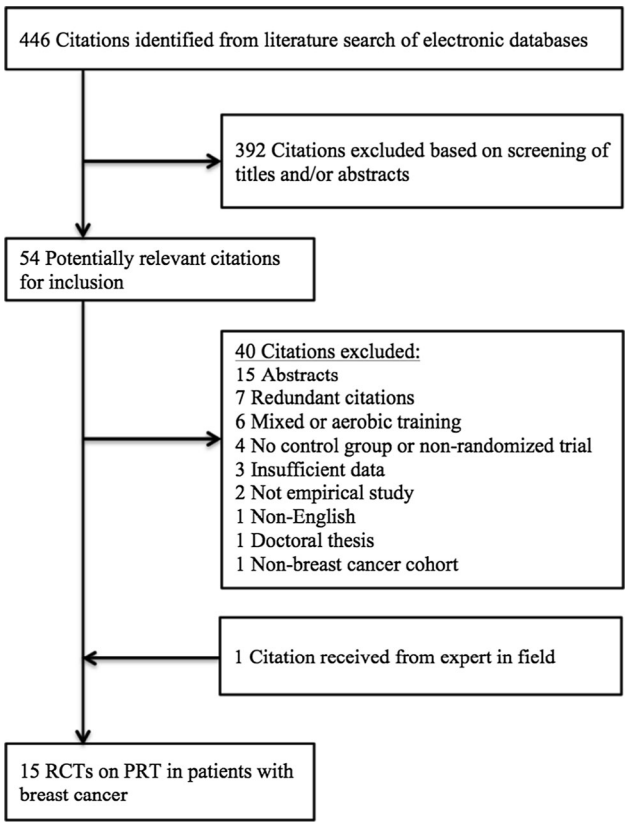

Fig. 1 Flowchart summarizing identification of studies for review. *PRT* progressive resistance training, *RCT* randomized controlled trial

Descriptive data synthesis

Table 1 presents the study characteristics of the 15 RCTs included for review, which were published between 2006 and 2013 [26–40]. Ten studies were conducted in the USA [26, 27, 29–33, 35, 36, 38] with others conducted in Canada [28, 40], Australia [37, 39], and Korea [34]. Major inclusion criteria typically were the completion of all breast cancer-related treatments (except hormonal therapy) [26, 27, 30–33, 35, 36, 38] or the initiation of chemotherapy treatment for breast cancer [28, 40]. Lymphedema-related inclusion criteria were lymph node dissection (or sentinel node biopsy) [26, 31, 32, 37] and/or clinical diagnosis of lymphedema by clinician [31, 34, 39]. Major exclusion criteria primarily emphasized uncontrolled cardiovascular diseases and other chronic illnesses that would contraindicate PRT. Lymphedema-related exclusion criteria included bilateral lymph node dissection [31–33], bilateral lymphedema [34], history of lymphedema [37], unstable lymphedema [39], and incomplete axillary surgery [28, 40]. Analyzed sample sizes ranged from 21 to 232, resulting in a total of 1,652 participants across studies. Mean age of the samples ranged from 46 to 62 years.

Table 1 Characteristics of randomized controlled trials reviewed

Reference	Sample size	Population		Mean age (years)	Treatments	Control	Trial duration (weeks)	Outcomes (assessments, units)	Quality score (out of 10)
		Major inclusion criteria	Major exclusion criteria						
Ahmed et al. [26] USA	45	Completed all cancer treatments (except hormonal therapy); nonsmoker >2 years; sedentary to moderately active with no PRT history; stable body weight over previous year; axillary lymph node dissection or sentinel node biopsy	Medical condition prohibiting PRT, morbid obesity (BMI >40 kg/m^2), SBP > 160 mmHg and/or DBP > 99 mmHg, currently on or planning to start a weight loss plan, pregnant or lactating, planned absence or surgery during study	52	PRT using machine and free weights (9 exercises targeting major muscles of the chest, back, shoulders, buttocks, thighs, and legs). Upper body exercises started with nil or 0.5 lb wrist weights and progressed according to tolerance/symptoms with the smallest weight possible, lower body exercises performed at standard 8–10RM, three sets per exercise after first 2–3 weeks, 2 sessions/week	Usual care (no exercise)	26	Lymphedema incidence (number of cases) reported as three separate measures: (1) ≥2 cm change in ipsilateral-contralateral arm circumference measurement at any of four sites: (i) the metacarpophalangeal joint, (ii) just distal to the ulnar styloid process and (iii and iv) 10 cm distal and 10 cm proximal to the mid-point of the lateral epicondyle, (2) patient self-reported diagnosis assessed via validated survey, and (3) an increase in lymphedema symptoms assessed via validated survey. Note: arm circumferences pre- and post-intervention also measured but as mean (SE)	9
Ohira et al. [27] USA	81	Completed all cancer treatments (except hormonal therapy); nonsmoker >2 years; sedentary to moderately active with no PRT history; stable body weight over previous year	Medical condition prohibiting PRT, morbid obesity (BMI > 40 kg/m^2), SBP > 160 mmHg and/or DBP > 99 mmHg, currently on or planning to start a weight loss plan, pregnant or lactating, planned absence or surgery during study	53	PRT using machine and free weights (9 exercises targeting major muscles of the chest, back, shoulders, buttocks, thighs, and legs). Upper body exercises started with nil or 0.5 lb wrist weights and progressed according to tolerance/symptoms with the smallest weight possible, lower body exercises performed at standard 8–10RM, three sets per exercise after first 2–3 weeks, 2 sessions/week	Usual care (no exercise)	26	Cancer-specific HRQoL (CARES-SF, one global score and 5 sub-domains: physical, psychosocial, medical interaction, marital, sexual; all 0–100)	9

Table 1 continued

Reference	Sample size	Population		Mean age (years)	Treatments	Control	Trial duration (weeks)	Outcomes (assessments, units)	Quality score (out of 10)
		Major inclusion criteria	Major exclusion criteria						
Courneya et al. [28] Canada	164	Stages I–IIIA breast cancer; initiating chemotherapy; ≥18 years; non-pregnant	Incomplete axillary surgery, transabdominal rectus abdominus muscle reconstructive surgery, uncontrolled hypertension, cardiac illness, psychiatric illness, not approved for participation by oncologist	49	PRT (9 exercises: leg extension, leg curl, leg press, calf raise, chest press, seated row, triceps extension, biceps curl, modified curl-up) 2 sets × 8–12 reps starting at 60–70 % estimated 1RM, load increased by 10 % when participants completed >12 reps/set, three sessions/week for the duration of chemotherapy	Usual care (no exercise)	17	Cancer-specific HRQoL (FACT-An); upper body strength (estimated 1RM bench press, kg); lower body strength (estimated 1RM leg extension, kg); lymphedema (ipsilateral-contralateral arm volume difference, mL) pre- and post-intervention; lymphedema cases (≥200 ml difference in the ipsilateral-contralateral arm volume difference, number of incident/exacerbation cases)	9
Schwartz et al. [29] USA	44	Histologically confirmed stages I–III breast cancer; planning to begin chemotherapy with doxorubicin or methotrexate; ambulatory	Use of steroids within previous 6 months; Paget disease, hyperparathyroidism, rheumatoid arthritis, ankylosing spondylitis or other diseases affecting bone metabolism; strenuous regular exercise, women exercise >250 min per week; history of serious psychiatric disease	48	Home-based PRT using resistance bands/tubing, two exercise routines each performed twice per week in rotation (four sessions/week in total). Each routine contained four upper and four lower body exercises (unspecified), 2 sets x 8–10, resistance of each exercise increased by modifying starting grip position on resistance bands/tubing when participant could perform two sets of 10 repetitions	Usual care (no exercise)	26	Upper body strength (1RM shoulder press and seated row, kg); lower body strength (1RM knee extension, kg)	5

Table 1 continued

Reference	Sample size	Population		Mean age (years)	Treatments	Control	Trial duration (weeks)	Outcomes (assessments, units)	Quality score (out of 10)
		Major inclusion criteria	Major exclusion criteria						
Twiss et al. [30] USA	221	History of stage 0-II breast cancer; 35–75 years; BMD T-score ≤1.0 at hip, spine or forearm; >6 months post-cancer treatment; >12 months Postmenopausal; physician permission	Recurrence of breast cancer; taking hormone therapy, bisphosphonates, glucocorticosteroids, or other drugs affecting bone; currently engaging in resistance training exercises; BMI ≥ 35 kg/m^2; serum calcium, creatinine, or thyroid stimulating hormone (if on thyroid therapy) outside normal limits; active gastrointestinal problems or other conditions that prohibited exercise; risedronate, calcium, or vitamin D intake	59	PRT + 1,200 mg calcium and 400 IU of vitamin D supplement daily and 35 mg of risedronate weekly. PRT prescribed using ankle cuffs, hand weights and machines (biceps curl, overhead triceps or press, upward row, back and knee extensions, side hip raise, and hip flexion and extension plus two balance exercises (heel and toe stand)), 2 sets x 8–12 reps. Loads increased based on individual response to training. For the first 32 weeks, participants exercised in their homes and were not to lift beyond 20-pound hand or ankle weights because of safety concerns. After 32 weeks, participants exercised using weight machines at a fitness center, 2 sessions/week	1,200 mg calcium and 400 IU of vitamin D supplement daily and 35 mg of risedronate weekly (no exercise)	104	Upper body strength (peak torque at 60-degrees in wrist flexion*/extension, Nm); lower body strength (peak torque at 60-degrees in hip flexion/extension, knee flexion/extension*, Nm)	8
Schmitz et al. [31] USA	139	Unilateral, non-metastatic breast cancer; 1–15 years post-diagnosis; clinical diagnosis of stable lymphedema; free of cancer; >1 lymph node removed; BMI ≤ 50 kg/m^2; >6 months post-pregnancy; >3 months post-lactation; not actively trying to lose weight	Medical condition prohibiting exercise, planned absence or surgery during study; bilateral lymph node dissection; pregnant or lactating or planning to become pregnant; upper body PRT or aerobic exercise within the past year	57	PRT using machine and free weights (9 exercises: seated row, supine dumbbell press, lateral or front raises, bicep curl, triceps extension, leg press, back extension, leg extension, and leg curl). Upper body exercises increased with minimal increment (1/2 pound) after two sessions without change in lymphedema symptoms. If no change in lymphedema symptoms, no upper limit placed on loading (progressed according to tolerance/symptoms). Lower body exercises performed at standard 3 sets × 8–10RM after first 2–3 weeks, 2 sessions/week	Usual care (no exercise)	52	Lymphedema exacerbation (clinician-defined via increase in volume of the affected limb of ≥5 %, accompanied by an increase in the interlimb volume or circumference difference of ≥5 %, and by indications of sustained tissue changes, altered skin color or changes in activities of daily living because of symptoms; number of exacerbation cases); lymphedema (evaluated via interlimb volume difference, %difference) pre- and post-intervention* and number* and severity* of lymphedema symptoms (evaluated via validated survey) pre- and post-intervention; upper body strength (1RM bench press, lb); lower body strength (1RM leg press, lb)	9.5

Table 1 continued

Reference	Sample size	Population		Mean age (years)	Treatments	Control	Trial duration (weeks)	Outcomes (assessments, units)	Quality score (out of 10)
		Major inclusion criteria	Major exclusion criteria						
Schmitz et al. [32] USA	147	Unilateral, non-metastatic breast cancer; 1–15 years post-diagnosis; >2 lymph nodes removed without lymphedema; free of cancer; BMI $\leq$ 50 kg/m^2; >6 months post-pregnancy; >3 months post-lactation; not actively trying to lose weight	Medical condition prohibiting exercise, planned absence or surgery during study; bilateral lymph node dissection; pregnant or lactating or planning to become pregnant; upper body PRT or aerobic exercise within the past year	55	PRT using machine and free weights (9 exercises: seated row, supine dumbbell press, lateral or front raises, bicep curl, triceps extension, leg press, back extension, leg extension, and leg curl). Upper body exercises increased with minimal increment (1/2 pound) after two sessions without change in lymphedema symptoms. If no change in lymphedema symptoms, no upper limit placed on loading (progressed according to tolerance/ symptoms). Lower body exercises performed at standard 3 sets $\times$ 8–10RM after first 2–3 weeks, 2 sessions/week	Usual care (no exercise)	52	Lymphedema onset ($\geq$5 % increase in interlimb volume difference; number of incident cases); lymphedema, clinician-defined onset (via interlimb volume changes, changes in tissue tone or texture, and symptoms; number of incident cases); number* and severity* of lymphedema symptoms (evaluated via validated survey) pre- and post-intervention; upper body strength (1RM bench press, lb); lower body strength (1RM leg press, lb)	9.5
Speck et al. [33] USA	232	Unilateral, non-metastatic breast cancer; 1–15 years post-diagnosis; free of cancer; BMI $\leq$ 50 kg/m^2; >6 months post-pregnancy; >3 months post-lactation; not actively trying to lose weight	Medical condition prohibiting exercise, planned absence or surgery during study; bilateral lymph node dissection; pregnant or lactating or planning to become pregnant; upper body PRT or aerobic exercise within the past year	57	PRT using machine and free weights (9 exercises: seated row, supine dumbbell press, lateral or front raises, bicep curl, triceps extension, leg press, back extension, leg extension, and leg curl). Upper body exercises increased with minimal increment (1/2 pound) after two sessions without change in lymphedema symptoms. If no change in lymphedema symptoms, no upper limit placed on loading (progressed according to tolerance/ symptoms). Lower body exercises performed at standard 3 sets $\times$ 8–10RM after first 2–3 weeks, 2 sessions/week	Usual care (no exercise)	52	HRQoL (SF-36, physical and mental component summary scales)	9.5

Table 1 continued

Reference	Sample size	Population		Mean age (years)	Treatments	Control	Trial duration (weeks)	Outcomes (assessments, units)	Quality score (out of 10)
		Major inclusion criteria	Major exclusion criteria						
Kim et al. [34] Korea	40	Breast cancer survivors with BCRL diagnosed by a physician	>70 years; cancer recurrence within previous 6 months; bilateral lymphedema; cardiovascular disease; neurological signs such as decreased motor power, sensory changes, or decreased deep tendon reflexes; not able to communicate	51	PRT + complete decongestive physiotherapy (i.e., manual lymphatic drainage, compression therapy, and remedial exercise). PRT prescribed using 0.5 lb and 1 lb dumbbells (6 exercises: seated row, bench press, latissimus dorsi pull-down, 1-arm bent-over row, triceps extension, and biceps curl), 2 sets x 10 reps, 5 sessions/week	Complete decongestive physiotherapy only (i.e., manual lymphatic drainage, compression therapy, and remedial exercise)	8	Lymphedema (circumferences of the affected limb assessed at 3 cm intervals and used to compute total, proximal and distal arm volume pre-and post-intervention; cm^3); HRQoL (SF-36, all eight domain scores)	6
Winters-Stone et al. [35] USA	67	Diagnosis of stage 0–IIIA breast cancer at age ≥50 years; postmenopausal; ≥1 years post-chemotherapy or radiotherapy; non-osteoporotic; physician clearance to exercise; physical and cognitive ability to complete study testing	Bone altering medication other than adjuvant hormone therapy; regular participation in resistance and/or impact exercise in the past month	62	PRT plus impact loading exercise using free weights, i.e., dumbbell, weighted vest and barbell, two supervised plus one home-based session per week, 10 exercises: Wall-sits, squats, bent-knee dead lifts, forward and lateral lunges, 1-arm row, chest press, lateral raise, push-ups, two-footed jumps from the ground to height of 1" (bent-knee landing); same exercises at home (except dead lift) but free weights replaced by elastic bands for upper body exercises and lower body exercises performed unloaded, 1–2 sets of 3–4 upper body, and 3–4 lower body exercises plus 1–6 jump sets per session, supervised sessions approx. 60–70 % of 1-RM, 8–12 repetitions per set	Flexibility training (placebo exercise)	52	Lymphedema (arm, wrist and finger circumferences[#] measured pre- and post-intervention; cm); upper body strength (chest press, IRM, lb); lower body strength (leg press, 1RM, lb); HRQoL (SF-36, physical functioning domain)	9.5

Table 1 continued

Reference	Sample size	Population		Mean age (years)	Treatments	Control	Trial duration (weeks)	Outcomes (assessments, units)	Quality score (out of 10)
		Major inclusion criteria	Major exclusion criteria						
Musanti [36] USA	21	English-speaking; stages I–IIIB breast cancer; >3 month post-chemotherapy; >6 week post-radiation therapy; <24 month post-treatment; hormonal therapy could be ongoing.	Evidence of anemia; uncontrolled hypertension, congestive heart failure, pulmonary disease, diabetes, thyroid or musculoskeletal disease; current enrollment in a weight loss or exercise program; positive response to any question on the PAR-Q	51	Home-based PRT using resistance bands (13 exercises: shoulder flexion, shoulder press, latissimus pulldown, seated row, chest press, triceps extension, biceps curl, hip flexion, hip extension, abdominal crunches, leg press, and squat), RPE up to 7–8/10 seven, 1 set × 10–12 reps, greater resistance bands applied with strength adaptation, 3 sessions/week	Flexibility training (placebo exercise)	12	Upper body strength (6RM bench press, lb; 6RM seated row, lb)	8
Kilbreath et al. [37] Australia	154	Surgery for stages I–III breast cancer that included a sentinel node biopsy or axillary node dissection; able to communicate in English	History of lymphedema; bilateral breast cancer; metastatic breast cancer; pre-existing arm impairments	52	PRT targeting the shoulder muscles, exercises unspecified, performed daily (one supervised session per week using free weights and home-based component performed using elastic bands), 8–15 repetitions per set, intensity = 15 on Borg scale; plus daily upper body stretches in a supine position (arm flexion and abduction), each stretch held for 5–15 min	Usual care (no exercise)	8	Lymphedema (number of cases) evaluated as three separate measures pre- and post-intervention: (1) elevated bioimpedance spectroscopy ratio (affected/non-affected limb) of ≥1.139 when surgery on dominant side or ≥1.066 when surgery on dominant side, (2) interlimb arm circumference difference of ≥2 cm at 2 + sites (circumferences were measured at 4 sites, 10 cm intervals commencing at the ulnar styloid process), (3) elevated arm volume, bilateral difference >10 % (arm volume computed from circumference measures); arm* and breast symptoms (via QLQ-BR23); strength (measured bilaterally in *forward flexion, abduction, external rotation, horizontal extension, N)	8.5

Table 1 continued

Reference	Sample size	Population		Mean age (years)	Treatments	Control	Trial duration (weeks)	Outcomes (assessments, units)	Quality score (out of 10)
		Major inclusion criteria	Major exclusion criteria						
Winters-Stone et al. [38] USA	58	Breast cancer treatment-induced menopause; stages I–IIIA breast cancer; completion of chemotherapy within 6 months–5 years; osteoporosis (hip and spine T scores ≥2.5); physician clearance	Medication to treat bone loss; participation in >60 min/week of resistance training	46	PRT plus impact loading exercise using free weights, i.e., dumbbell, weighted vest and barbell, two supervised plus one home-based session per week, 10 exercises: Wall-sits, squats, bent-knee dead lifts, forward and lateral lunges, 1-arm row, chest press, lateral raise, push-ups, two-footed jumps from the ground to height of 1" (bent-knee landing); same exercises at home (except dead lift) but free weights replaced by elastic bands for upper body exercises and lower body exercises performed unloaded, 1–2 sets of 3–4 upper body and 3–4 lower body exercises plus 1–6 jump sets per session, supervised sessions approx. 60–70 % of 1-RM, 8–12 repetitions per set	Flexibility training (placebo exercise)	52	Lymphedema assessed pre- and post-intervention via bilateral circumference differences[#] (at middle finger, wrist, and distal forearm); upper body strength (chest press, 1RM, lb); lower body strength (leg press, 1RM, lb)	9.5

Table 1 continued

Reference	Sample size	Population		Mean age (years)	Treatments	Control	Trial duration (weeks)	Outcomes (assessments, units)	Quality score (out of 10)
		Major inclusion criteria	Major exclusion criteria						
Cormie et al. [39] Australia	41	Diagnosis of breast cancer >1 yr prior to enrollment; clinical diagnosis of BCRL; medical clearance from general practitioner	Unstable lymphedema (i.e., decongestive therapy or antibiotics for infection) within the previous 3 months; musculoskeletal, cardiovascular and/or neurological disorder that could inhibit exercise	57	PRT (11 exercises: chest press, seated row, lat pulldown, shoulder press, lateral raise, bicep curl, tricep extension, wrist curl, leg press, leg extension, squat/lunge), 6–10RM (~75–85 % of 1RM), 1–4 sets per exercise, loading increased by 5–10 % if participant able to perform more than the repetitions specified, 2 sessions/week	Usual care (no exercise)	12	Lymphedema assessed objectively pre- and post-intervention using five measures: (1) bioimpedance spectroscopy (L-Dex score), (2) affected arm volume via DEXA (mL), (3) interlimb arm volume (% difference), (4) affected arm circumference (measures were taken every 4 cm from the metacarpal-phalangeal joint to the base of the axilla, summed score reported in cm), and (5) interlimb arm circumference (summed score % difference); lymphedema symptom severity assessed via five instruments: (1) DASH, (2) BPI-severity subscale, (3) BPI-interference subscale, FACT-B + 4-arm function subscale, QLQ-BR23-arm symptoms subscale); upper body strength (grip strength-affected arm, kg; 1RM bench press, kg; 1RM seated row, kg); lower body strength (1RM leg press, kg); HRQoL (SF-36 all domain and summary scores)	9

Table 1 continued

Reference	Sample size	Population		Mean age (years)	Treatments	Control	Trial duration (weeks)	Outcomes (assessments, units)	Quality score (out of 10)
		Major inclusion criteria	Major exclusion criteria						
Courneya et al. [40] Canada	198	Stages I–IIIC breast cancer; initiating chemotherapy; ≥18 years; non-pregnant	Incomplete axillary surgery, transabdominal rectus abdominus muscle reconstructive surgery, uncontrolled hypertension, cardiac illness, psychiatric illness, not approved for participation by oncologist	50	PRT (9 exercises: leg extension, leg curl, leg press, calf raise, chest press, seated row, triceps extension, biceps curl, modified curl-up) 2 sets × 10–12 reps at 60–75 % estimated 1RM plus same aerobic exercise prescription as the control group, 3 sessions/week for the duration of chemotherapy	Aerobic exercise on cycle ergometer, treadmill, elliptical, rowing ergometer, or combination. Initial exercise intensity generally began at 55–60 % VO2peak and progressed to 70–75 % of VO2peak by week 6. Initial exercise duration generally began between 15 and 30 min/session and progressed to 25–30 min/session by week 4, 3 sessions/week	16	Upper body strength (estimated 1RM bench press*, kg); lower body strength (estimated 1RM leg press*, kg); HRQoL (SF-36: physical functioning domain*, role physical domain, bodily pain domain, general health domain, and physical component summary scale)	9.5

USA United States of America, *BCRL* breast cancer-related lymphedema, *BMI* body mass index, *PAR-Q* physical activity readiness questionnaire, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *PRT* progressive resistance training, *RPE* rating of perceived exertion, *RM* repetition maximum, *CARES-SF* Cancer Rehabilitation and Evaluation System short form, *FACT-An* Functional Assessment of Cancer Therapy-Anemia Scale, *HRQoL* health-related quality of life, *SF-36* Medical Outcomes Short Form-36 Quality of Life Questionnaire, *QLQ-BR23* European Organization for Research and Treatment of Cancer - Breast Cancer Module, *DASH* Disability of the Arm, Shoulder, and Hand Questionnaire, *FACT-B4+* Functional Assessment of Chronic Illness Therapy Breast Cancer Questionnaire for Patients with Lymphedema, *BPI* Brief Pain Inventory Questionnaire

* Data requested and received from authors (not available in publication)

Data requested but not received from authors

PRT interventions were prescribed two to three times per week in 12 studies (Table 1). Other studies prescribed a split-routine four sessions per week [29] or lower intensity training for five [34] or seven sessions per week [37]. Upper body training was prescribed in all studies (Table 1), and only two studies did not target lower body musculature [34, 37]. PRT was typically prescribed using machine and/or free weights, while two studies used resistance bands only [29, 36], and three studies incorporated a combination thereof [35, 37, 38]. Training sessions were fully supervised in only three studies [28, 39, 40], while ten studies involved partial supervision [26, 27, 30–35, 37, 38], and two studies did not provide supervision [29, 36]. In general, lower body PRT was prescribed according to standard training principles for healthy adults. Upper body exercises were initiated at low intensities and progressed according to tolerance in most studies, while four studies prescribed upper body PRT at approximately 65–75 % of one repetition maximum (RM) [28, 35, 38, 40], and one study prescribed upper body PRT at 6–10 RM intensity. All studies indicated that training loads were progressively increased with strength adaptation.

Nine studies compared PRT intervention to usual care (no exercise) [26–29, 31–33, 37, 39], while three studies incorporated flexibility training as a sham condition [35, 36, 38]. The other three studies compared PRT plus an additional intervention (i.e., calcium and vitamin D supplement [30], complete decongestive physiotherapy [34], and aerobic training [40]) compared to the latter intervention only. Trial durations ranged from 8 to 104 weeks in duration; six studies were ≥52 weeks, three studies were 26 weeks, and six studies ranged from 8 to 17 weeks.

Primary outcomes were (1) cases of lymphedema incidence or exacerbation evaluated via clinician-defined assessment based on multiple objective tests [31, 32], the interlimb volume [28, 35, 37, 38, 39], or circumference difference [26, 34]; (2) extent of arm swelling outcomes evaluated via the interlimb volume difference [28, 31, 39] or volume of the ipsilateral extremity [34]; and (3) lymphedema symptom severity outcomes evaluated via validated [54] questionnaire [31, 32] or the arm symptoms subscale of the QLQ-BR23 [37, 39]. Secondary outcomes were upper body muscular strength evaluated via bench press [28, 31, 32, 35, 36, 38–40], shoulder press [29], arm flexion [37], and wrist flexion [30], lower body muscular strength evaluated via leg press [31, 32, 35, 38–40] or knee extension [28–30], and HRQoL evaluated via the physical global score on the Cancer Rehabilitation and Evaluation System short form [27], the Functional Assessment of Cancer Therapy–Anemia scale [28], and the physical functioning domain score [34, 35, 39, 40] and physical component summary scale [33] of the *Medical Outcomes Trust Short Form-36* (SF-36). Quality scores ranged from 5.0 to 9.5, and 13 studies received a score of 8.0 or higher (Electronic Supplementary Material, Table S1).

Quantitative data synthesis

Primary outcomes

Figure 2 presents the OR for the incidence and/or exacerbation of BCRL after PRT intervention between the treatment and control groups for five studies in 647 participants [26, 28, 31, 32, 37]. Four studies [34, 35, 38, 39] were excluded from the analysis given that no cases of BCRL were observed in either group. PRT resulted in significantly lower risk of BCRL incidence/exacerbation compared with control conditions [OR = 0.53 (95 % CI 0.31–0.90)]. There was no statistical heterogeneity between studies ($I^2 = 0$ %, $P = 0.80$).

Figure 3 presents the SMD for arm volume (4 studies in 384 participants [28, 31, 34, 39]) and patient-reported severity of BCRL (4 studies in 479 participants [31, 32, 37, 39]) after PRT between the treatment and control groups. PRT did not change arm volume [SMD = −0.07 (95 % CI −0.28 to 0.14)] or patient-reported severity of BCRL [SMD = −0.07 (95 % CI −0.25 to 0.11)] compared with control conditions. There was no evidence of statistical heterogeneity in either of these analyses (both $I^2 = 0$ %, Fig. 3). Funnel plots showed no evidence of publication bias for either outcome (Electronic Supplementary Material, Figs. S1 and S2).

Descriptive synthesis of additional PRT-related adverse events Five studies reported that no adverse events occurred as a consequence of exercise training [31, 34, 35, 39, 40]. Other studies generally reported temporary muscle soreness [30] or musculoskeletal injuries. Winters-Stone et al. [38] reported episodes of back ($N = 2$) and knee pain ($N = 1$) which resulted in one participant discontinuing with lower body training. Adverse events in the study by Ohira et al. [27] have been documented in a separate article [55] which noted back injuries ($N = 4$) in the experimental group; however, none of these participants became unable to exercise. Musanti [36] noted two cases of tendinitis (shoulder and foot) during their study but did not specify the group allocation of the participants affected. Brown et al. [56] have summarized the adverse events encountered in three trials included in our review [31–33]. Nine women randomized to the PRT group reported 10 musculoskeletal injuries related to training that impaired activities of daily living for ≥1 week [56]. Of these, there were a greater number of incidents in women with BCRL (8 injuries) as compared to those at risk for lymphedema ($N = 2$) [56]. Courneya et al. [28] reported on two adverse events unrelated to PRT. Three studies did not report on adverse events beyond lymphedema [26, 29, 37].

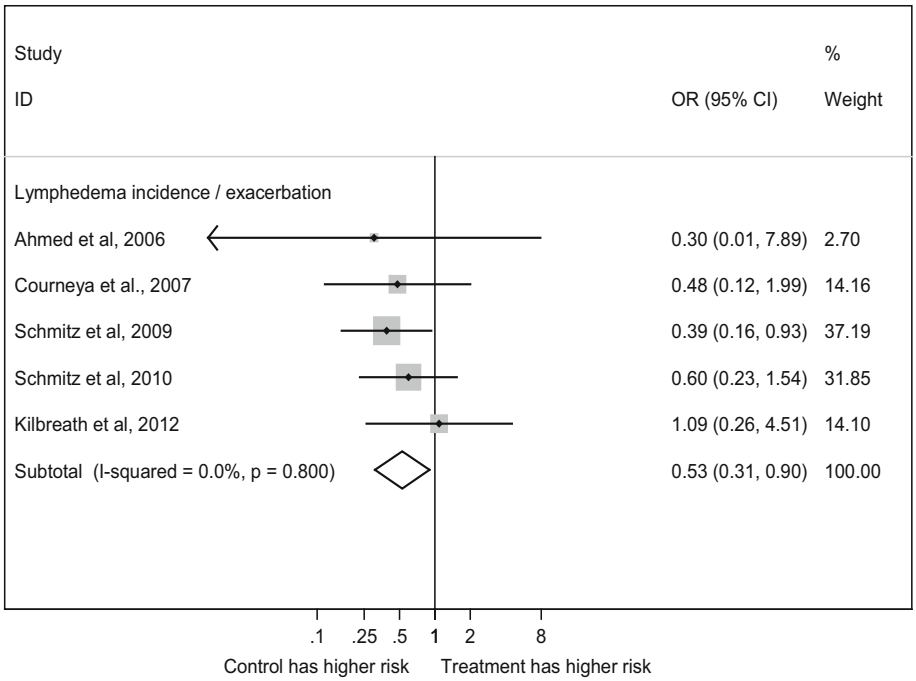

Fig. 2 Odds ratio for the incidence/exacerbation of BCRL outcomes after PRT between the treatment and control groups. *ID* identification, *OR* odds ratio, *CI* confidence interval, *BCRL* breast cancer-related lymphedema

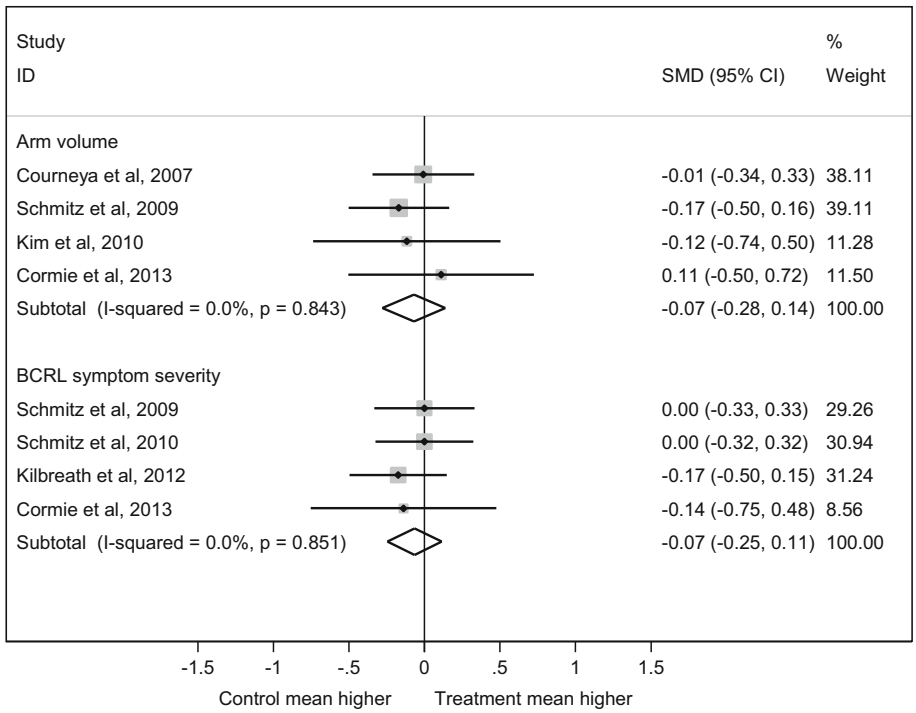

Fig. 3 Standardized mean difference in arm volume and BCRL symptom severity outcomes between the treatment and control groups. *ID* identification, *SMD* standardized mean difference, *CI* confidence interval, *BCRL* breast cancer-related lymphedema

Secondary outcomes

Figure 4 presents the SMD for upper body muscular strength (11 studies in 1,252 participants [28–32, 35–40]), lower body muscular strength (9 studies in 1,079 participants [28–32, 35, 38–40]), and HRQoL outcomes (7 studies in 823 participants [27, 28, 33–35, 39, 40]) after PRT between the treatment and control groups. PRT significantly improved standardized upper body [SMD = 0.57 (95 % CI 0.37–0.76)] and lower body [SMD = 0.48 (95 % CI 0.30–0.67)] muscular strength outcomes compared with control conditions. There was evidence of moderate heterogeneity between studies in each of these analyses. The sensitivity analyses (Electronic Supplementary Material,

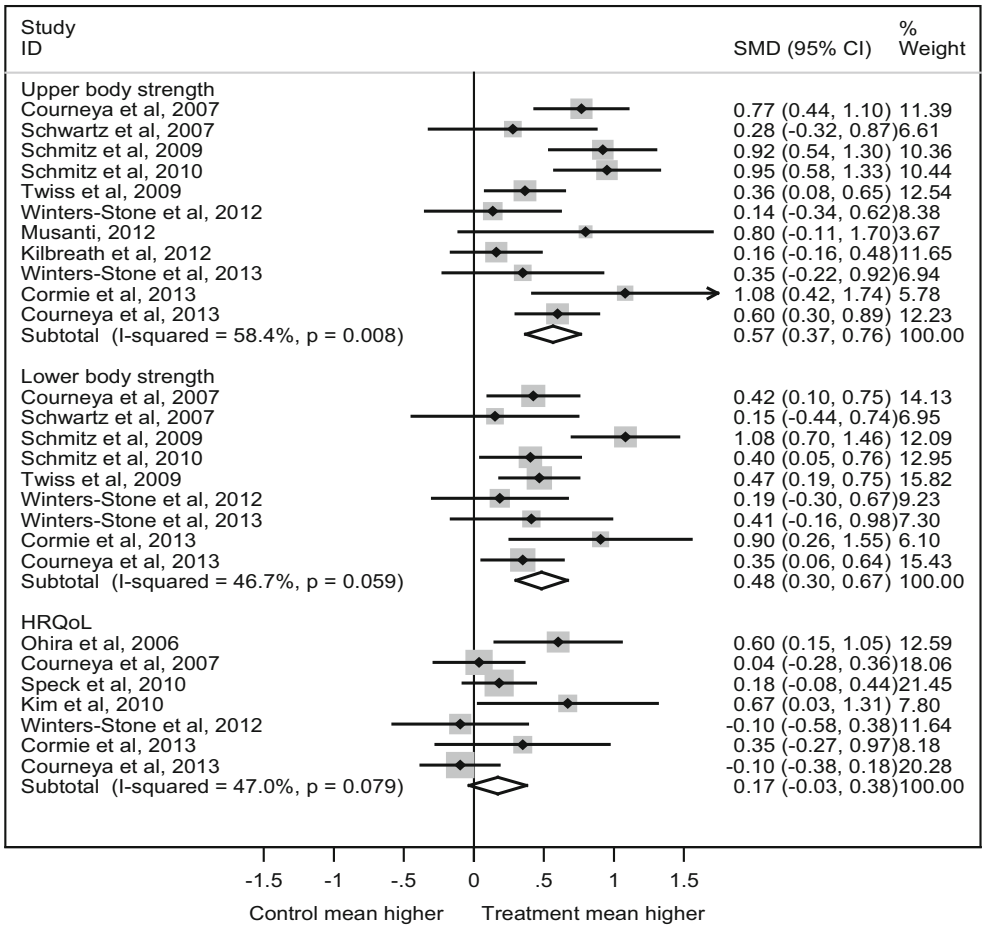

Fig. 4 Standardized mean difference in upper body muscular strength, lower body muscular strength and HRQoL outcomes after PRT between the treatment and control groups. *ID* identification, *SMD* standardized mean difference, *CI* confidence interval, *HRQoL* health-related quality of life

Tables S2 and S3) showed that the pooled SMD was similarly medium to large in the fixed effect model and after each of the various studies was excluded (SMD = 0.49–0.68 and 0.40–0.59 for upper and lower body muscular strength outcomes). Heterogeneity in upper body strength outcomes (I^2 = 58.4 %) could not be explained by our sensitivity analysis, whereas heterogeneity in lower body strength outcomes (I^2 = 46.7 %) was reduced with the exclusion of one study [31] that noted a significant difference between groups at baseline. Funnel plots were produced and showed little evidence of publication bias (Electronic Supplementary Material, Figs. S3 and S4).

Our primary analysis revealed that PRT induced a small improvement in HRQoL [SMD = 0.17 (95 % CI −0.03 to 0.38)] compared with control conditions, but this effect was not statistically significant, and there was evidence of moderate heterogeneity (I^2 = 47.0 %). The sensitivity analyses presented in Table S4 showed that the pooled SMD was similarly small in the fixed effect model and after each of the various studies was excluded (SMD = 0.11–0.24). Notably, the findings became significant, and heterogeneity was reduced, when studies conducted during adjuvant chemotherapy [SMD = 0.30 (95 % CI 0.04–0.55), I^2 = 37.0 %] and studies that did not include a no-treatment control group [SMD = 0.24 (95 % CI 0.01–0.46), I^2 = 29.2 %] were excluded. The corresponding funnel plot showed little evidence of publication bias (Electronic Supplementary Material, Fig. S5).

Discussion

Summary of the evidence

Based on RCT evidence in women surgically treated for breast cancer, our results for safety outcomes were consistent. PRT reduced the risk of BCRL and did not exacerbate arm volume or patient-reported severity of BCRL

versus control conditions (Figs. 2, 3). Our finding that PRT nearly halves the odds of BCRL incidence/exacerbation is clinically relevant given that studies have consistently shown that women with a diagnosis of BCRL suffer greater impairments of upper body functioning [57, 58] and HRQoL [59, 60] compared to their non-affected peers. Further, the null effect of PRT on measures of arm volume and BCRL symptom severity indicates that PRT does not worsen lymphedema symptoms, in contrast to prior assertions [25].

For efficacy data, our results indicate that PRT significantly improved upper and lower body muscular strength and induced a small improvement of HRQoL (Fig. 4). The mean improvement in upper body muscular strength was more than half a standard deviation in our primary and sensitivity analysis (SMD = 0.49–0.68) and is clinically relevant. A recent prospective study [61] showed that mean upper body strength of both the affected and unaffected extremity is significantly reduced from pre-surgery to 2.5 years post-treatment in women who received axillary lymph node dissection (both SMD = −0.42). The mean PRT-induced improvement of upper body muscular strength documented in our study (SMD = 0.57) is therefore greater than the expected long-term (2.5 year) decline [61] indicating that PRT can, on average, counteract treatment-induced upper body morbidity [57, 58].

The mean improvement in lower body muscular strength approached half a standard deviation in our primary and sensitivity analysis (SMD = 0.40–0.59) and is also clinically relevant. Breast cancer survivors suffer from significantly reduced leg strength compared to healthy controls (SMD = −1.16) [62]. Moreover, prospective studies have shown that mean lower body strength declines rapidly with age (2.6–3.0 % per year) [63], and the loss of lower body strength (SMD = −0.44) is a powerful predictor of all-cause mortality [64, 65]. Poor leg strength is therefore an important target for rehabilitation in the breast cancer population.

The small effect of PRT on mean HRQoL noted in our primary and sensitivity analysis is also clinically relevant. HRQoL is reduced in women with breast cancer, both at diagnosis and post-treatment, compared to the general population [66, 67]. However, higher levels of physical activity pre- or post-breast cancer treatment can contribute to higher HRQoL, particularly in the physical domains of HRQoL [68, 69]. For example, in a cancer registry study [67] that identified and recruited women at 5, 10, and 15 years post-breast cancer diagnosis, the mean score of the physical functioning domain of HRQoL was reduced at the 5-year (SMD = −0.27) and 10-year timepoint (SMD = −0.18) compared to healthy controls. The magnitude of change of HRQoL in our study was SMD = 0.30 exclusive of two studies conducted during adjuvant chemotherapy [28, 40], suggesting that women engaging in PRT post-chemotherapy can experience an improvement of HRQoL beyond the levels expected in healthy peers.

The effect of PRT on upper and lower body muscular strength remained robust in fixed effect models and after exclusion of studies that combined PRT with other exercise modalities (or therapies), studies without a no-treatment control group, studies prescribed PRT during chemotherapy treatment, studies conducted outside the US, studies of shorter duration, studies in older cohorts, studies in which BCRL was an entry criterion, and studies of lower quality.

In summary, our primary results indicate that that PRT does not exacerbate measures of BCRL and may lower risk. PRT also improves upper and lower body muscular strength, and elicits a small improvement in HRQoL. No serious PRT-induced adverse events were reported in the studies reviewed. These findings are clinically relevant. Therefore, clinical practice guidelines should be updated to inform clinicians on the benefits of PRT in this patient group.

Limitations

Several limitations require careful consideration. First, our analysis of arm volume and patient-reported severity of BCRL outcomes was based on a limited number of studies (Fig. 3), and only three of these studies included a clinical diagnosis of BCRL as a participant entry criterion. Women without BCRL are unlikely to improve these outcomes, and therefore additional studies limited to women with BCRL are warranted. Second, we did not distinguish the affected and non-affected extremity in the assessment of upper body muscular strength outcomes. There is evidence that bilateral strength deficits may be incurred by breast cancer treatment [70], and future research is required to distinguish the effect of PRT on both the surgically treated and non-treated side. Third, there was heterogeneity with respect to the exercise prescriptions, including the level of supervision, training equipment, and training frequency and intensity (Table 1); training intensity was also not quantitatively defined in many studies. We did not investigate any dose–response effects in the present review; accordingly, the optimal dosages of PRT to adapt the specific outcomes in this patient group remain unknown and require further research.

Conclusion

Our meta-analytic results are sufficiently reliable to recommend that clinicians consider PRT for reducing the risk of BCRL and improving upper and lower body muscular strength and HRQoL outcomes in women treated for breast cancer.

Acknowledgments We sincerely thank Ms Katrina Chaudhary for her work in developing the database searches.

Funding All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work.

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

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