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REVIEW

Progressive resistance training in breast cancer: a systematic review of clinical trials

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Abstract
Background Progressive resistance training (PRT) may be effective for targeting the sequelae of breast cancer and its treatment given the unique anabolic nature of this exercise modality. Therefore, our objectives were: (1) to systematically review studies that have prescribed PRT after breast cancer surgery, (2) to summarize the efficacy of PRT in this cohort, and (3) to delineate areas for future investigations.
Method A systematic review using computerized databases was performed.
Results The systematic review located 10 trials: Four uncontrolled trials, one controlled trial and five randomized controlled trials (RCTs). PRT was prescribed with aerobic training in 8/10 trials reviewed, and in isolation in 2/10 trials reviewed. Upper body PRT was prescribed in 7/10 trials, including 4/5 RCTs. No exacerbation of objectively measured or subjectively reported lymphedema symptoms was reported in any of these trials. Adverse events were rare, generally musculoskeletal in nature, and were managed effectively by conservative means. Overall, the studies we reviewed suggest that women surgically treated for breast cancer can derive health-related and clinical benefits by performing PRT after breast cancer surgery. Further research may be required to stimulate greater advocacy for PRT among oncologists, and in community care settings.
Conclusions Robustly designed RCTs prescribing targeted PRT regimens throughout various phases of breast cancer treatment are warranted. RCTs with thorough, standardized reporting of interventions and adverse events are required to establish the efficacy of this intervention for the post-treatment management of breast cancer patients and survivors as a means to improve health status and quality of life.

Keywords Women · Upper Body · Exercise · Quality of Life · Lymphedema

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Introduction

Breast cancer is the most commonly diagnosed cancer among women affecting more than 1.2 million individuals per year worldwide [1]. Advances in medical treatment options have improved survival opportunity, but these interventions commonly induce sequelae that can chronically impair health status and quality of life (QOL). Some of the long-term side effects of breast cancer treatment may

include fatigue, [2] depression, [3] weakness, upper extremity lymphedema, [4] immune system dysfunction, [5] neuropathy, [6] bone loss [7], adverse shifts in body composition [8], upper body pain [9] and deficits of upper body strength, flexibility and functioning [10–12].

Over the past 25 years, exercise has been investigated as a therapeutic intervention for targeting the chronic side effects of breast cancer treatment and improving health status and QOL [13]. Empirical evidence to date has overwhelmingly demonstrated that exercise, in general, is safe and beneficial both during and following the administration of adjuvant therapies [13–15]. However, at present, the modalities and dosages of exercise required to optimize post-operative rehabilitation practices in this cohort have not been fully elucidated.

Progressive resistance training (PRT) by definition elicits positive health and performance adaptations by challenging the skeletal muscles with loads that can be lifted repetitively for 8–15 repetitions maximum (RM) per set to the onset of neuromuscular fatigue, the point at which appropriate technique can no longer be maintained [16]. PRT sessions are optimal when followed by periods of recovery ranging from 48 to 72 h to allow for physiological supercompensation (i.e. positive adaptation). To facilitate continued adaptation, training intensity (i.e. load) and training volume (i.e. number of sets) are progressively increased, and exercises are adjusted as indicated throughout the training regimen, to attenuate the onset of a plateau in physiological adaptation. Once the physiological plateau has been reached, health and performance are maintained with continued training, which may involve periodical manipulations of the PRT variables, including training frequency, training intensity (load), training volume (sets), types of exercises, time under tension per repetition, etc.

PRT is well-established as safe and beneficial exercise modality for individuals of all ages and fitness levels, including those afflicted with severe chronic illnesses [17, 18]. PRT is particularly efficacious for adult and elderly cohorts given its efficacy in counteracting sarcopenia, abating osteoporosis and reversing the many physiological and functional impairments that accrue with age [18]. The benefits of PRT are myriad, and are associated with greater quality and quantity of life [18]. Given the adverse effects of breast cancer treatment it makes intuitive sense that PRT may be of significant benefit in this cohort as well.

Strenuous upper body exercise following breast cancer treatment has historically been an area of controversy [19]. The medical community has considered vigorous upper body exercise contraindicated in this cohort as it might induce or exacerbate upper extremity lymphedema [19–21]. However, no empirical evidence exists to substantiate this notion [21]. In 1996, Dr. Don McKenzie, MD, PhD, a sportsmedicine physician from Vancouver, Canada, formed the first all-breast-cancer-survivor dragon boat team, *Abreast in a Boat*, and demonstrated that strenuous, upper body exercise in the form of dragon boat training, a predominantly aerobic form of exercise, did not induce or exacerbate lymphedema symptoms [20]. Dragon boat training is now widely advocated as a safe and beneficial form of exercise for survivors of breast cancer [22].

Currently, advocacy for PRT in breast cancer patients and survivors remains negligible in both the clinical rehabilitation and community setting. This has occurred despite the fact that full-body PRT has been proven to provide health-related benefits not attainable with aerobic training. PRT provides a greater anabolic stimulus than aerobic training and is inherently regarded as the modality of choice for improving muscle strength, endurance, size, quality and power [18]. Prevention of musculoskeletal injuries, reduced risk of falls, reduced frailty, improved self efficacy and improved clinical depression are additional benefits that may be induced by PRT. These benefits provide a robust rationale for the prescription of PRT in breast cancer [18]. PRT may also provide an effective alternative to improving bone mineral density [23] in postmenopausal breast cancer survivors with estrogen-dependent tumors who are at greater risk for osteoporosis but are unable to take hormone replacement therapy.

The lack of advocacy for PRT for breast cancer patients and survivors may be due to a lack of awareness of the PRT literature among oncologists and a lack of understanding of the required research directions in this area. To address this issue, we have undertaken the present systematic review of trials prescribing PRT for the post-operative management of breast cancer patients and survivors. Our objectives were three-fold:

(1) To systematically review studies which have prescribed PRT in breast cancer;
(2) To summarize the safety and effectiveness of PRT in breast cancer; and
(3) To delineate areas for future investigation.

Method

A systematic review of all published literature, regardless of study design was conducted. Given the heterogeneity of the exercise interventions and the paucity of robust randomized controlled trials (RCTs) the pooling of effect sizes across studies in a meta-analysis was not considered appropriate at this stage. Further, due to the lack of robust RCTs there was an inherent need to also discuss interventions and outcomes of several uncontrolled trials.

Criteria for considering studies

Study designs

RCTs, non-randomized controlled trials and uncontrolled trials published in peer-reviewed journals were included. Abstracts and case reports were excluded, as were unpublished trials.

Subjects

Studies involving adults (>18 years) diagnosed and surgically treated for malignancy of the breast were included.

Intervention

Studies prescribing PRT in isolation or in combination with other exercise modalities (e.g. aerobic training) were included. Studies investigating the effects of single, acute bouts of PRT were not included. Studies prescribing movement exercises without loading against a resistance were excluded.

Timing of the intervention

Studies prescribing PRT post breast cancer surgery were included. Studies prescribing PRT during or post adjuvant therapies (i.e. radiotherapy or chemotherapy), or at any other time post breast cancer treatment were included. Studies prescribing PRT before breast cancer treatment were not considered.

Outcome measures

Studies evaluating outcomes potentially responsive to chronic PRT, based on the empirical evidence of PRT efficacy in other chronically diseased and healthy cohorts were included. These outcomes include a broad spectrum of physiological, functional, and psychological outcome measures.

Search method

We conducted a literature review in May 2007 for the years 1966–2007, limited to the English language, using computerized databases, including PubMed, Medline, CINAHL, SportDiscus, Embase, and Web of Science. The search combined key words related to breast cancer (i.e. breast cancer, oncology, malignancy, neoplasm, tumor), breast cancer treatment (i.e. mastectomy, lumpectomy, radiotherapy, chemotherapy) and exercise (i.e. exercise training, training, physical activity, rehabilitation, resistance training, aerobic training, strength training, lifestyle, muscle, endurance, strength). Articles retrieved were examined for further relevant references.

Assessment of research quality

Study quality was assessed based on the Delphi List [24] for assessing the quality of RCTs, and was extended to the non-randomized controlled and uncontrolled trials. An additional quality variable considered was supervision of training sessions.

Data extraction and analyses

Outcome measures significantly adapted by the intervention were extracted for the assessment of study and intervention quality. Weighted mean difference between group means and 95% confidence intervals assuming equal variances were calculated using a confidence interval calculator (version 4.1, 26 Jan 2004) [25] where appropriate (controlled or comparison studies). Relative ES (mean $\text{change}_{\text{Treatment}}$–mean $\text{change}_{\text{Control}}$) ÷ $\text{SD}_{\text{Pooled baseline}}$ and 95% confidence intervals ($\text{SD}_{\text{Pooled baseline}}$ * bias correction factor (Hedges) +/– z-value * standard error of ES estimate) were calculated for controlled trials [26].

Results

Studies retrieved

The search resulted in 12 articles presenting the findings of 10 trials, including: four uncontrolled trials (4/10, 40%) [27–30], one non-randomized controlled trial (1/10, 10%) [31], and five RCTs (5/10, 50%) [32–38]. The *Weight Training for Breast Cancer Trial* by Schmitz and colleagues is a single RCT that has resulted in three publications to date [35–37].

Study quality assessment

A summary of the study quality assessment is presented in Table 1. All four uncontrolled trials [27–30] involved a time series investigation of a single treatment group evaluated with repeated measures collected before and after training (Table 1). Participant eligibility criteria were presented in all except one uncontrolled trial [27]. None of the uncontrolled trials explicitly stated a primary outcome measure, and only one uncontrolled trial presented statistical power calculations *a priori* [29].

The one non-randomized controlled trial recruited a treatment (exercise) and control (non-exercise) group from independent clinical centers, and did not involve a randomization process as such (Table 1) [31]. This trial did

Table 1 Summary of research quality

Citation	Randomization performed?	Treatment allocation concealed?	Groups / subjects similar at baseline regarding important prognostic values?	Eligibility criteria specified?	Blinded outcome assessors?	Compliance reported?	Supervision of exercise sessions?	Dropouts reported?	Did the analysis include an intention-to-treat analysis?	Were point estimates and measures of variability presented for the primary outcome measures?	Were between groups statistics reported?
Uncontrolled Trials											
Kolden et al. [27]	n/a	n/a	n/a	No	n/a	Yes	Yes	Yes	No	n/a	n/a
Turner et al. [28]	n/a	n/a	n/a	Yes	n/a	No	Partial	Yes	No	n/a	n/a
Lane et al. [29]	n/a	n/a	n/a	Yes	n/a	No	No	Yes	No	n/a	n/a
Cheema and Gaul [30]	n/a	n/a	n/a	Yes	n/a	Yes	Partial	Yes	No	n/a	n/a
Non-randomized Controlled Trials											
Hutnick et al. [31]	No	n/a	Yes	Yes	Not	reported	Yes	Partial	Yes	No	Yes
Yes											
Randomized Controlled Trials											
Nieman et al. [32]	Yes	Not	reported	Yes	No	Not	reported	Yes	Yes	Yes	No	Yes
Yes											
McKenzie and Kalda [33]	Yes	Not	reported	Yes	Yes	Not	reported	No	Yes	No	No	Yes
Yes											
Herrero et al. [34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Ahmed et al. [35] Ohira et al. [36] Schmitz et al. [37]	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	No	Yes	Yes
Courneya et al. [38]	Yes	Yes	Yes	Yes	Not	reported	Yes	Yes	Yes	Yes	Yes
Yes											

not present statistical power calculations, explicitly list primary outcomes, or mention if outcomes were collected by blinded assessors (Table 1).

Five trials involved randomization of participants to either an exercising experimental group or non-exercising control group (Table 1) [32–38]. None of these five RCTs [32–38] met all of the Delphi list quality criteria [24], and the most common deficiencies were in the areas of treatment allocation concealment, the blinded assessment of outcome measures, and the use of an intention-to-treat statistical analysis procedure. However, all of the RCTs conducted appropriate statistical tests between the two or more groups involved in the trial [32–38]. Samples were generally adequately described and were similar between groups at baseline in the five RCTs [32–38]. Only one of the RCTs provided power calculations of the primary outcomes [38]. Two RCTs stated that randomization of patients occurred following baseline testing [32, 35–37], and that blinded assessors were involved in the collection of outcome measures [34–37]. To date, only one RCT has involved an intention-to-treat strategy of analysis [38].

Overall, six trials involved complete supervision of the exercise regimen [27, 31–34, 38], while three trials involved partial supervision [28, 30, 35–37] and one trial involved no supervision of PRT [29].

Overview of the participants

Sample size

Five hundred and thirty eight (n = 538) women were enrolled in total in the 10 trials reviewed (Table 2). Five trials (5/10) enrolled ≤20 patients [28, 29, 32–34], while four trials (3/10) enrolled between 31 and 86 patients [27, 30, 31, 35–37]. The RCT by Courneya et al. [38], the largest trial to date, enrolled 242 participants.

No trial to date has involved male breast cancer survivors, who currently account for 1% of all breast cancer cases [39].

Age

Mean age according to group assignment is presented in Table 2. In eight trials that provided an age range [27–32, 35–38] the youngest and eldest patient enrolled were 25 years and 78 years, both participants in the trial by Courneya et al. [38] A broad age range was generally reported in these eight trials.

Menopausal status

Menopausal status has been described in four trials to date [30, 34–38]. One of these trials used postmenopausal status as an entry criterion [34], while in the other three trials the vast majority of participants enrolled were postmenopausal: 85% [35–37], 89% [38], and 93% [30].

Stage of cancer

Stage of breast cancer, reported in eight trials, ranged from ductal carcinoma in situ (DCIS; Stage 0) to Stage III (Table 2). Two trials [28, 32] did not detail the stage of breast cancer (Table 2).

Breast cancer surgery

All participants enrolled in the trials reviewed underwent at least one breast cancer surgery. Of the five trials describing surgical procedure, 87 lumpectomies, 62 modified radical mastectomies, four radical mastectomies, one partial mastectomy, and two unknown cases were reported [27, 29–31, 34]. Courneya et al. mentioned that 59% of their sample (n = 143) received breast conservation surgery [38]. Four trials did not provide data on surgery received prior to enrollment [28, 32, 33, 35–37].

Axillary lymph node dissection

The number of axillary lymph nodes excised during surgery have been provided in only two uncontrolled trials to date [29, 30]. Lane et al. [29] reported a range of 0–24 lymph nodes excised in their sample, while Cheema and Gaul [30] reported a range from 3 to >17.

Adjuvant therapies

Description of adjuvant therapies received was provided in nine trials [27–32, 34–38]. In four of these trials, all patients enrolled had completed both radiotherapy and chemotherapy prior to enrollment [28, 31, 32, 34]. In the other trials, the majority of patients had completed [29, 30, 35–37] or were receiving [27, 38] chemotherapy and/or radiotherapy.

Lymphedema and use of compression sleeves

Unilateral, upper extremity lymphedema diagnoses below stage III was an entry criterion in the RCT by McKenzie and Kalda [33]. Ahmed et al. [35] enrolled 13 of 81 (17%) patients with self-reported, clinical diagnosis of lymphedema at baseline. Two uncontrolled trials have reported two [28] and three [30] self-reported cases of upper extremity lymphedema at baseline. Cases of lymphedema did not preclude participation in these trials [28, 30, 35].

McKenzie and Kalda [33] prescribed the use of professionally fitted compression sleeves during exercise in each participant enrolled. Use of compression sleeves in

Table 2 Overview of participants and interventions

Authors (year) Country	*N*	Study groups (*n*) stage of cancer age	Exercise intervention			
			Timing of exercise	Modality	Exercise prescription	Duration of exercise
Uncontrolled trials						
Kolden et al. [27] (2002) USA	51	Exercise (*n* = 40) Stage I-III 55.3 ± 8.4 years	During radio- or chemotherapy in most patients	Mixed	*Aerobic training:* walking, cycling, step, dance, or aerobics 40–70% of VO_{2max} 20 min per session 3 sessions per week *Resistance training:* unspecified exercises (20 min per session) intensity—method not defined 3 sessions per week	16 weeks
Turner et al [28] (2004)	11	Exercise (*n* = 10) Stage not reported 47 ± 8 years	>4 months post treatment	Mixed	*Aerobic training:* low impact aerobics/water-based exercise 70–90% of maximal heart rate 40–60 minper session 3 sessions per week *Resistance training:* unspecified exercises added at week 6 2–3 sets per exercise 8–12 repetitions per set intensity—method not defined ('moderate') 3 sessions per week	8 weeks
Lane et al. [29] (2005) Canada	18	Exercise (*n* = 16) Stage I-III 52.4 + 6.8 years	>6 months post treatment	Mixed	*Aerobic training:* aerobic activity of subjects choice >60% maximal heart rate 30–45 min per session 3 sessions per week dragon boat training added at week 8 *Resistance training:* 6 upper body exercises 2–3 sets per exercise 10 repetitions per set intensity—method not defined ('to tolerance') 3 sessions per week	20 weeks

Table 2 continued

Authors (year) Country	*N*	Study groups (*n*) stage of cancer age	Exercise intervention			
			Timing of exercise	Modality	Exercise prescription	Duration of exercise
Cheema and Gaul [30] (2006)	31	Exercise (*n* = 31) DCIS – Stage III 57.7 ± 7.2 years	>6 months post treatment	Mixed	*Aerobic training:* aerobic activity of subjects choice 65–85% of maximal heart rate 15–30 min per session 3 sessions per week *Resistance training*: 10 full body exercises 1–3 sets per exercise intensity—8–12 repetitions maximum (RM) 2 sessions per week	8 weeks
Non-randomized controlled trials						
Hutnick et al. [31] (2005) USA	49	Exercise (*n* = 28) Stage I-III 48 ± 10.6 Control (*n* = 21) Stage I-III 52.3 ± 9.2	>2 weeks post treatment	Mixed	*Aerobic training:* unspecified aerobic exercise 60–75% of functional capacity 40–90 min per session 3 sessions per week *Resistance training:* 8 full body exercises using elastic bands 1–3 sets 8–12 repetitions per set intensity—method not defined 3 sessions per week	6 months
Randomized controlled trials						
Nieman et al. [32] (1995) USA	16	Exercise (*n* = 8) Stage not reported 60.8 ± 4.0 years Control (*n* = 8) Stage not reported 51.2 ± 4.7 years	<4 years post treatment[a]	Mixed	*Aerobic training:* walking on an indoor track 75% of maximal heart rate 30 min per session 3 sessions per week *Resistance training* 7 unspecified exercises 2 sets per exercise 12 repetitions per set intensity – method not defined 3 sessions per week	8 weeks

Table 2 continued

Authors (year) Country	*N*	Study groups (*n*) stage of cancer age	Exercise intervention			
			Timing of exercise	Modality	Exercise prescription	Duration of exercise
McKenzie & Kalda [33] (2003) Canada	14	Exercise (*n* = 7) Stage I–II 56.4 ± 10.4 years Control (*n* = 7) Stage I–II 56.9 ± 8.2 years	>6 months post treatment	Mixed	*Aerobic training:* arm ergometer training 8.3–25 watts ≤20 min per session 3 sessions per week *Resistance training:* 6 upper body exercises 2–3 sets 10 repetitions intensity—method not defined ('to tolerance') 3 sessions per week	8 weeks
Herrero et al. [34] (2005) Spain	20	Exercise (*n* = 10) Stage I–II 50 ± 5 years Control (*n* = 10) Stage I–II 51 ± 10 years	24–60 months post treatment	Mixed	*Aerobic training:* exercise cycle 70 to 80% of maximal heart rate 20–30 min 3 sessions per week *Resistance training:* 11 full body exercises 1–3 sets intensity—12–15 RM (first 4 weeks) 8–12 RM (last 4 weeks) 3 sessions per week	8 weeks
Ahmed et al. [35] (2006) Ohira et al. [36] (2006) Schmitz et al. [37] (2005) USA	86	PRT (*n* = 43) Stage DCIS-III 53.3 ± 8.7 years Waitlist control (*n* = 43) Stage DCIS-III 52.8 ± 7.6 years	>4 months post treatment	PRT	*Resistance training:* 9 full body exercises 1–3 sets per exercise 8–10 repetitions per set intensity—method not defined ('to tolerance') 2 sessions per week	6 month RCT, and 6 month cross-over of waitlist controls

Table 2 continued

Authors (year) Country	*N*	Study groups (*n*) stage of cancer age	Exercise intervention			
			Timing of exercise	Modality	Exercise prescription	Duration of exercise
Courneya et al. [38] (2007)	242	Aerobic (n = 78)	During chemotherapy	AER	*Aerobic training group:*	17 weeks (median duration)
		Stage I–IIIa			exercise cycle, treadmill, elliptical trainer	
		Mean age: 49.0 years			60 to >80% of maximal oxygen consumption	
		PRT (n = 82)			15–45 min (progressive)	
		Stage I–IIIa			3 sessions per week	
		49.5 years		PRT	*Resistance training group:*	
		Control (n = 82)			9 full body exercises	
		Stage I–IIIa			2 sets	
		49.0 year			8–12 repetitions per set	
					intensity—60–70% of estimated 1 RM	
					3 sessions per week	

DCIS = ductal carcinoma in situ, Stage 0 breast cancer; PRT = progressive resistance training; AER = aerobic training

[a] all patients enrolled within 4 years of breast cancer treatment, except one (15 years post treatment)

other trials was decided in consultation with a lymphedema specialist [35], or according to personal preference [30]. One trial did not provide information on the use of compression sleeves in participants presenting with lymphedema at baseline [28].

Comorbidities

Comorbidities of the enrolled participants were not thoroughly presented in any of the 10 trials reviewed. Courneya et al. [38] presented data suggesting that 20.7% of their sample were obese while 7.0% were hypertensive at baseline. McKenzie and Kalda [33] noted that 64% of their sample (9/14) were overweight or obese according to normative body mass index data.

Overview of the exercise interventions

Duration

Half of the trials (5/10) prescribed eight weeks of exercise, while other trials employed longer training durations (16 weeks to 6 months; Table 2). One of these trials involved a single crossover in which the control group received 6 months of PRT from the midpoint to the end of the trial [35–37]. Follow-up assessments were conducted in only one uncontrolled trial [28], at six weeks and three months beyond the completion of prescribed exercise.

PRT was prescribed throughout the intervention period in all except one trial where PRT was added for the 'final weeks' of an eight week exercise intervention [28].

Timing relative to breast cancer treatment

Courneya et al. [38] prescribed PRT for the duration of chemotherapy (Table 2). Kolden et al. [27] mentioned that the majority of the participants enrolled in their mixed exercise intervention were concurrently receiving radio- or chemotherapy. All other trials enrolled participants at least 2 weeks after the completion of these adjuvant therapies, not including hormonal therapy (e.g. Tamoxifen) (Table 2). No trial to date has provided data pertaining to the time interval between surgery and the start of exercise.

Exercise modalities prescribed

Two RCTs, the largest trials to date, have prescribed PRT as the sole exercise modality in one of the groups randomized (Table 2) [35–38]. One RCT compared a group receiving PRT to a wait-list control group receiving no exercise for six months [35–37] while the other RCT compared PRT to groups randomized to usual care or aerobic training [38]. All other trials prescribed resistance

training in combination with aerobic training within a mixed exercise intervention (Table 2).

Upper body PRT exercises

Upper body PRT exercises were prescribed in seven investigations (Table 2) [29–31, 33–38]. Other investigations did not define the degree of upper body involvement in their PRT regimen [27, 28, 32]

Resistance training equipment

Standard resistance training equipment (e.g. dumbbells, barbells, cable pulleys, machine weights) appear to have been used in the majority of trials reviewed given the type of exercises described [28–30, 32–38]. One RCT [35–37] used only wrist weights for upper body PRT exercises. One trial prescribed PRT using Flexibands (Jumpstretch Inc., Boardman, OH) [31], while another trial reported using resistance bands, dumbbells and machine weights [27].

Intensity of resistance training

Overall, the intensity of PRT was appropriately described in only 3 trials [30, 34, 38](Table 2). One trial [30] prescribed PRT at 8–12RM (high intensity) throughout the 8-week exercise regimen while another trial [34] prescribed 12–15RM (moderate intensity) for the first four weeks, followed by an increase in intensity to 8–12RM for the latter four weeks (Table 2). Courneya et al. [38] prescribed PRT at 60–70% of 1RM (moderate-high intensity) throughout the exercise regimen.

Frequency of resistance training

PRT was prescribed 2–3 times per week in all trials, as presented in Table 2.

Compliance to resistance training

Compliance to exercise ranged from 75.9% [31] to 97.1% [30] according to the seven trials that have presented these data [27, 30–32, 34–38]. However, none of these trials presented *a priori* definition of how compliance was calculated within their respective methods section.

Reasons for participant attrition

Reasons for discontinuation with training have been presented in seven trials reviewed [27–30, 32, 35–38], while two trials did not provide reasons for participant attrition [31, 34] and one trial reported no dropouts [33]. A total of 72 patients dropped out of the 10 trials reviewed, representing approximately 13% of the patients enrolled in these trials (n = 538).

Lymphedema and other adverse events

Lymphedema incidence secondary to exercise training was tracked as an adverse event in three RCTs [33, 35, 38] and three uncontrolled trails [28–30]. No incidence or exacerbation of quantified [28–30, 33, 35, 38] or self-reported lymphedema [30, 35] was attributed to the training regimen. Further, no improvements in lymphedema were reported in any trials presenting this information [28–30, 33, 35, 38].

Four trials did not track adverse events other than lymphedema [28, 29, 31, 33]. Other trials attributed no injuries or adverse events to exercise [27, 30, 32, 34, 38] including three trials which prescribed upper body resistance exercises [30, 34, 38]. One RCT [37] noted several adverse events over the entire 12-month period which were attributed to the exercise regimen, including several back injuries (n = 6), several ankle injuries (n = 3), a wrist injury (n = 1), leg pain (n = 1), heel spurs (n = 1), and a rotator cuff injury (n = 1). The authors reported that "the most severe injuries altered activities of daily living for a period of several weeks, with no known long-term negative effects"[37].

To date, only one uncontrolled trial [30] and two RCTs [37, 38] have provided *a priori* definitions of adverse events within their respective methods section. Each of these trials used a standardized patient interview to collect adverse event data [30, 37, 38]. Neither of the two RCTs [37, 38] performed between groups analyses on adverse events.

Adaptations to exercise involving PRT

Adaptations to exercise regimens involving PRT are presented in Table 3 (a summary of uncontrolled trials) and Table 4 (a summary of non-randomized and randomized controlled trials). Overall, the ten trials reviewed highlight functional, physiological, psychological and clinical adaptations that may be especially important for women recovering from the traumata of breast cancer treatment.

Functional adaptations

The two largest RCTs published to date [35–38] have demonstrated that full body PRT prescribed in isolation of other exercise modalities during chemotherapy [38] or following the completion of adjuvant therapies [35–37] can significantly improve upper body strength. Several other trials have reported improved upper body strength with mixed (aerobic plus resistance) training [27, 29–31, 34].

Table 3 Significant outcomes of uncontrolled trials

Authors (year) Country	Outcomes	PRE	POST	Mean Difference (95% C.I.)	Effect Size	*P*
Kolden et al. [27] (2002) USA	systolic blood pressure (bpm)	124.0 ± 16.4	118.2 ± 16.1	–5.8 (–13.0–1.4)	–0.4	<0.05
	sit & reach flexibility (inches)	14.1 ± 3.7	15.6 ± 3.3	1.5 (–0.1–3.1)	0.4	<0.001
	estimated VO_{2max} (ml $kg^{-1} \cdot min^{-1}$)	30.6 ± 4.3	35.2 ± 5.1	4.6 (2.5–6.7)	1	<0.001
	bench press strength (lbs)	34.0 ± 10.5	45.7 ± 13.5	11.7 (6.3–17.1)	1	<0.001
	leg press strength (lbs)	163.7 ± 56.2	223.8 ± 70.7	60.1 (31.7–88.5)	0.9	<0.001
	depression:					
	Beck Depression Inventory[a]	5.8 ± 4.9	3.9 ± 4.0	–1.9 (–3.9–0.1)	–0.4	<0.01
	Hamilton Depression Scale[b]	9.5 ± 6.0	6.1 ± 5.0	–3.4 (–5.9 to –0.9)	–0.6	<0.001
	mood:					
	positive affect[c]	35.1 ± 5.9	38.2 ± 6.7	3.1 (0.3–5.9)	0.5	<0.01
	negative affect[c]	14.7 ± 5.1	12.7 ± 3.4	–2.0 (–3.9 to –0.1)	–0.5	<0.01
	quality of life/well-being:					
	LFS[d]					
	self management	80.2 ± 13.3	84.7 ± 11.2	4.5 (–1.0–10.0)	0.4	<0.01
	health & grooming	79.9 ± 15.4	87.5 ± 8.9	7.6 (2.0–13.2)	0.6	<0.05
	CARES[e]					
	global score	29.2 ± 19.2	20.6 ± 15.3	–8.6 (–16.3–0.9)	–0.5	<0.05
	medical interaction	2.4 ± 3.2	1.1 ± 1.8	–1.3 (–2.5 to –0.1)	–0.5	<0.05
	physical	6.9 ± 5.9	4.2 ± 4.4	–2.7 (–5.0 to –0.3)	–0.5	<0.05
	psychosocial	11.0 ± 7.9	9.1 ± 5.8	–1.9 (–5.0–1.2)	–0.3	<0.05
	FACT[f]					
	global score	89.9 ± 12.1	94.1 ± 10.9	4.2 (–0.9–9.3)	0.3	<0.05
	physical well-being	22.9 ± 4.5	24.9 ± 3.4	2.0 (0.2–3.8)	0.5	<0.01
Turner et al. [28] (2004)	quality of life:					
Australia	*FACT-B*[g]	98.1 ± 17.4	106.9 ± 17.1	8.8 (–7.4–25.0)	0.5	0.04
Lane et al. [29] (2005) Canada	bench press strength (kg)	55.3 ± 13.6	66.2 ± 9.3	10.9 (2.5–19.3)	0.9	<0.001

Table 3 continued

Authors (year) Country	Outcomes	PRE	POST	Mean Difference (95% C.I.)	Effect Size	*P*
Cheema and Gaul [30] (2006)	VO_{2max} (ml/kg·min^{-1})	24.3 ± 4.9	25.8 ± 5.2	1.5 (–1.4–4.4)	0.3	<0.01
	sum of five skinfolds (mm)	117.6 ± 43.7	101.8 ± 36.3	–15.8 (–38.6–7.0)	–0.4	<0.01
	waist circumference (cm)	85.0 ± 12.3	82.2 ± 12.2	–2.8 (–9.5–3.9)	–0.2	<0.01
	hip circumference (cm)	105.6 ± 9.5	103.1 ± 9.4	–2.5 (–7.7–2.7)	–0.3	<0.01
	upper body strength (kg)	29.8 ± 6.6	39.7 ± 16.4	9.9 (2.9–16.9)	0.8	<0.01
	upper body endurance (repetitions)	10.7 ± 2.1	28.4 ± 6.6	17.7 (15.0–20.4)	3.6	<0.01
	lower body strength (kg)	134.8 ± 29.3	199.1 ± 46.6	64.3 (42.2–86.4)	1.6	<0.01
	lower body endurance (repetitions)	10.4 ± 1.6	38.2 ± 13.0	27.8 (22.3–33.3)	3	<0.01
	ipsilateral arm ROM (°)					
	flexion	152.4 ± 10.2	157.2 ± 8.8	4.8 (–0.2–9.8)	0.5	<0.01
	extension	38.6 ± 9.0	47.7 ± 7.2	9.1 (4.8–13.4)	1.1	<0.01
	abduction	138.8 ± 9.8	148.6 ± 8.9	9.8 (4.9–14.7)	1	<0.01
	contralateral arm ROM (°)					
	flexion	153.8 ± 9.8	160.8 ± 8.2	7.0 (1.9–12.1)	0.8	<0.01
	extension	41.0 ± 8.6	48.6 ± 8.2	7.6 (2.8–12.4)	0.9	<0.01
	abduction	144.2 ± 7.7	151.0 ± 9.3	6.8 (1.9–11.7)	0.8	<0.01
	lower body flexibility (cm)	31.9 ± 8.9	33.9 ± 7.7	2.0 (–2.5–6.5)	0.2	<0.01
	quality of life:					
	WHOQOL-BREF[h]	71.0 ± 8.9	76.2 ± 9.4	5.2 (0.2–10.2)	0.6	0.01
	overall QOL	8.2 ± 0.9	8.8 ± 0.8	0.6 (0.1–1.1)	0.7	<0.01
	psychological					

[a] Ref [40]

[b] Ref [41]

[c] PANAS = Positive And Negative Affect Schedule; Ref [42]

[d] LFS = Life Functioning Scales; Ref [43]

[e] CARES = Cancer Rehabilitation Evaluation System; Ref [44]

[f] FACT = Functional Assessment of Cancer Treatment; Ref [45]

[g] FACT-B = Functional Assessment of Cancer Treatment-Breast; Ref [46]

[h] WHOQOL-BREF = World Health Organization Quality of Life Assessment-Abbreviated Version; Ref [47]

Additional functional adaptations of the upper body as documented by Cheema and Gaul [30] include increased upper body muscular endurance, and increased flexibility of the ipsilateral (surgical) and contralateral shoulder joint with 8 weeks of training.

Improvements of lower body strength [30, 32, 34–38] endurance [30], and flexibility [27, 30] have also been documented with exercise regimens involving PRT. Herrero et al. [34] documented improved sit-to-stand movement time with 8 weeks of mixed training [34].

Courneya et al. [38] determined that PRT significantly improved upper and lower body strength versus aerobic training only.

Physiological adaptations

Significantly improved body composition, including reduced sum of five skinfolds [30], reduced waist and hip circumferences [30], reduced percent body fat [34], and increased muscle mass [34] have been observed in trials involving mixed training. Increased muscle mass [38] and reduced body fat [35–37] have also been documented the RCTs that have prescribed PRT in isolation. Adaptations of body composition have been found to be independent of a change in body weight [30].

Several studies have reported improved cardiorespiratory fitness (VO_{2max}) secondary to mixed training [30, 31, 34]. Significantly increased peak ventilation, power output [34] and indirect measurement of cardiorespiratory fitness have also been observed [27, 32]. Significantly improved immune system functioning has been documented with six months of mixed training, including increased percent activation of T-helper lymphocytes ($CD4^+$), total activated $CD4^+$ cells, lymphocyte proliferation, and IFNγ:IL-6 ratio [31]. Increased circulating insulin-like growth factor II has been observed with six months of PRT within a large scale RCT [35–37].

Psychological adaptations

Several trials prescribing mixed training have documented significantly improved aspects of QOL [27, 28, 30, 34]. Depression and mood (positive and negative affect) have also been shown to significantly improve following 16 weeks of mixed training in one small uncontrolled trial [27]. Trials have also demonstrated that PRT prescribed in isolation can significantly improve self esteem [38] and aspects of quality of life [35–37].

Clinical adaptations

Courneya et al. [38] have demonstrated that participants receiving PRT during chemotherapy significantly improved chemotherapy average relative dose intensity (i.e. chemotherapy dose tolerance) as compared to participants receiving usual care only.

Discussion

To our knowledge, this is the first systematic review of PRT in breast cancer. Overall, the literature review suggests that PRT prescribed in isolation or in combination with aerobic training is safe and beneficial for women recovering from the traumata of breast cancer surgery. Exercise regimens involving PRT have resulted in robust functional, physiological, psychological and clinical benefits that are of particular importance in breast cancer care (Table 3 and 4). These adaptations have occurred in the absence of serious adverse events including upper extremity lymphedema. Compliance to training was reportedly high, ranging from 75.9% to 97.1%, according to the trials reviewed, and dropout rates lower than in many other trials of exercise in clinical cohorts.

Although the available literature supports the prescription of PRT in breast cancer patients and survivors, many methodological limitations exist within this body of literature and many research questions remain to be investigated. Effectively designed RCTs prescribing appropriate, targeted interventions and investigating a broad spectrum of relevant outcome measures may be required to stimulate advocacy for PRT as an essential therapeutic adjunct for the post-operative management of breast cancer patients and survivors. The development of applicable general exercise prescription guidelines should remain the overall objective of future research.

Only five trials to date have involved randomization of participants to exercising and non-exercising groups [32–38]. Of these, three enrolled 20 or fewer participants [32–34] while the other two RCTs, conducted by Courneya et al. [38] and Schmitz and colleagues [35–37] were of larger scale (n = 242 and n = 86, respectively) and therefore may have been adequately powered to test the stated primary and secondary endpoints (Table 4). These trials should provide impetus for the direct application of PRT interventions in the clinical setting, particularly given such findings as PRT-induced improvement of chemotherapy dose tolerance [38], and should be used to stimulate further research. The RCTs by Courneya et al. [38] and Schmitz and colleagues [35–37] were methodologically robust compared to the smaller RCTs reviewed [32–34] according to the current standards of reporting [52] but still did not satisfy all of the Delphi List criteria (Table 1).

Findings of the small-scale RCTs [32–34], non-randomized trials [31], and uncontrolled trials [27–30] should be considered for the development of larger scale, robustly designed RCTs. Important training adaptations have been

Table 4 Significant outcomes of non-randomized controlled trials and RCTs

Authors (year)	Outcomes	Pre Experimental	Post experimental	Pre control	Post control	Relative effect size (95% C.I.)	*P*
Non-randomized controlled trials							
Hutnick et al. [31] (2005) USA	*At 6 months:*						
	VO_{2max} ($L \cdot min^{-1}$)	1.46 ± 0.25	1.60 ± 0.30	1.36 ± 0.35	1.43 ± 0.30	0.29 (–0.42–1.00)	<0.05
	grip strength, left (lb)	23.4 ± 7.5	27.0 ± 6.3	23.0 ± 4.4	21.9 ± 4.9	0.74 (0.02–1.42)	<0.05
	grip strength, right (lb)	25.3 ± 6.9	29.0 ± 6.6	25.1 ± 4.2	23.7 ± 4.0	0.87 (0.14–1.60)	<0.05
	biceps curl strength (lb)	17.0 ± 4.3	19.1 ± 3.5	16.6 ± 3.5	16.9 ± 3.3	0.43 (–0.28–1.14)	<0.05
	triceps curl strength (lb)	23.0 ± 5.7	25.6 ± 7.6	22.0 ± 5.8	20.9 ± 6.8	0.55 (–0.16–1.26)	<0.05
	activation of T-helper lymphocytes ($CD4^+$) (%)	1.40 ± 4.00	0.51 ± 0.46	0.63 ± 0.82	0.34 ± 0.61	0.08 (–0.57–0.73)	<0.05
	lymphocyte proliferation (count)						
	phytohemagglutinin ($50\ \mu g \cdot mL^{-1}$)	34,600 ± 27,227	39,321 ± 1,207	23,694 ± 17,630	26,444 ± 18,296	0.09 (–0.58–0.76)	<0.05
	concanavalin ($25\ \mu g \cdot mL^{-1}$)	14,128 ± 10,437	17,445 ± 9,587	10,289 ± 8,038	9,669 ± 6,274	0.40 (–0.28–1.08)	<0.05
	pokeweed mitogen ($5\ \mu g \cdot mL^{-1}$)	4,345 ± 3,077	6,754 ± 5,426	5,501 ± 10,184	4,192 ± 2,741	0.71 (0.02–1.40)	<0.05
Randomized controlled trails (RCTs)							
Nieman et al. [32] (1995) USA	6 min walk distance[‡] (m)		+60.8 ± 8.4		+12.0 ± 17.8	3.24 (1.52–4.96)	0.02
McKenzie and Kalda[33] (2003) Canada	no sig. adaptations reported						
Herrero et al. [34] (2005) Spain	*quality of life (EORTC QLQ-C30)*[b]						
	global scale	not reported	not reported	not reported	not reported	not applicable	0.002
	physical function	not reported	not reported	not reported	not reported	not applicable	0.04
	muscle mass (kg)	27.3 ± 2.4	28.0 ± 2.7	28.6 ± 2.5	28.3 ± 2.9	0.36 (–0.63–1.35)	<0.05
	body fat (%)	24 ± 6	22 ± 5	22 ± 5	22 ± 4	–0.34 (–1.33–0.65)	<0.05
	muscle mass (%)	41 ± 5	43 ± 5	43 ± 3	42 ± 3	0.59 (–0.41–1.59)	<0.05
	VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$)	23.7 ± 5.8	25.9 ± 4.5	27.4 ± 3.9	25.7 ± 3.7	0.82 (–0.20–1.84)	<0.05
	peak power output (W)	85 ± 24	110 ± 16	91 ± 12	94 ± 12	0.92 (–0.11–1.95)	<0.05
	peak ventilation ($L \cdot min^{-1}$)	54 ± 13	60 ± 9	63 ± 13	59 ± 13	0.80 (–0.22–1.82)	<0.05
	sit-to-stand test (s)	7.9 ± 0.8	7.2 ± 0.7	7.5 ± 0.5	7.5 ± 0.6	–0.88 (–1.91–0.15)	<0.05
	bench press strength (reps)	0.0 ± 0.0	2.0 ± 2.0	0.3 ± 0.8	0.5 ± 1.2	1.15 (0.09–2.21)	<0.05
	leg press strength (reps)	10.1 ± 6.8	26.3 ± 6.2	16.9 ± 5.5	15.2 ± 4.7	2.04 (0.83–3.25)	<0.05

Table 4 continued

Authors (year)	Outcomes	Pre Experimental	Post experimental	Pre control	Post control	Relative effect size (95% C.I.)	*P*
Ahmed *et al.* [35] (2006) Ohira *et al.* [36] (2006) Schmitz *et al.* [37] (2005) USA	*At 6 months:*						
	leg press strength[†] (lb)	50.7 ± 2.7	83.0 ± 2.8	56.1 ± 2.7	63.0 ± 2.7	not applicable[†]	<0.0001
	bench press strength[†] (lb)	214.8 ± 9.8	296.6 ± 10.2	218.5 ± 9.6	238.9 ± 9.9	not applicable[†]	<0.0001
	lean mass (kg)	37.9 ± 0.8	38.8 ± 0.8	37.6 ± 0.8	37.7 ± 0.8	0.99 (0.38–1.60)	0.008
	body fat (%)	42.0 ± 1.3	40.9 ± 1.3	42.1 ± 1.3	42.3 ± 1.3	–0.98 (–1.59 to –0.37)	0.003
	IGFII (ng/dL)	898.0 ± 34.9	871.8 ± 34.9	891.3 ± 34.4	919.5 ± 34.4	–1.55 (–2.06 to –1.04)	0.02
	quality of life (CARES-SF)[c]						
	-physical global score	46.4 ± 7.2	44.2 ± 5.6	47.1 ± 6.8	48.3 ± 7.7	–0.5 (–0.95 to –0.05)	0.006
	-psychosocial global score	48.0 ± 7.5	45.6 ± 8.2	48.7 ± 8.7	48.2 ± 8.2	–0.36 (–0.80–0.08)	0.02
Courneya *et al.* [38] (2007) Canada	*Resistance training group:*						
	Rosenberg self-esteem[d]	34.1 ± 4.2	34.7 ± 4.2	34.1 ± 4.6	33.2 ± 5.5	0.32 (0.01–0.63)	0.018
	leg strength (kg)	24.4 ± 11.2	32.8 ± 12.6	25.6 ± 12.6	27.1 ± 14.1	0.59 (0.28–0.90)	<0.001[φ]
	chest strength (kg)	23.2 ± 7.2	31.9 ± 10.8	22.8 ± 8.9	24.6 ± 7.8	0.73 (0.41–1.05)	<0.001[φ]
	lean body mass (kg)	40.3 ± 4.6	41.3 ± 4.9	40.8 ± 5.3	40.9 ± 5.6	0.19 (–0.12–0.50)	0.015
	chemotherapy relative dose intensity (%)		89.80%		84.10%	not applicable	0.033

All data presented as mean ± standard deviation, except:

[‡] data presented as post-pre change score ± standard deviation;

[†] data presented as mean ± standard error of estimate

P-values correspond to differences between exercise and control group, except [φ]significantly different between both comparison groups

NS = non-significant (*P*-value set at 0.01 by investigators)

[a] SF-36=Medical Trust Outcomes Short-Form 36 Quality of Life Questionnaire; [48]

[b] *EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer QLQ-C30*; [49]

[c] CARES = Cancer Rehabilitation Evaluation System – Short Form; [50]

[d] Ref [51]

Relative ES (mean changeTreatment – mean changeControl) ÷ SDPooled baseline and 95% confidence intervals (SDPooled baseline * bias correction factor (Hedges) ± *z*-value * standard error of ES estimate) were calculated for controlled trials 26

reported and some of these trials have provided evidence of the efficacy of upper body PRT (Tables 3 and 4) [29, 30, 33] findings later confirmed by Courneya et al. [38] and Schmitz and colleagues [35–37].

In general, the PRT interventions prescribed in the trials reviewed were not well defined. Several investigations did not outline the specific exercises performed [27, 28, 32], while others provided inadequate description of the relative training intensity (i.e. loading) [27–29, 31–33, 35–37]. Loads that elicit 8–15 repetitions (to a point at which appropriate technique can no longer be maintained; i.e. 8-15RM) are recommended for optimizing training adaptation [16] yet only three trials to date have prescribed PRT accordingly in breast cancer patients and survivors [30, 34, 38].

PRT interventions in future trials must be thoroughly defined with respect to frequency, intensity, volume, specific exercises performed, equipment used, and training supervision. These data are required to determine the dose of PRT required for adapting specific clinical and health-related outcomes. Notably, only two RCTs to date have prescribed PRT in isolation in breast cancer [35–38]. Studies isolating PRT are required to determine which training-induced adaptations can be assigned to the PRT regimen specifically. The improvement of upper body functioning specifically may be of utmost importance following breast cancer surgery, and this review suggests that the improvement of upper body functioning is concomitant with psychological adaptations including improved quality of life and self esteem (Tables 3 and 4). The findings of Courneya et al. [38] suggest that PRT may be more beneficial than aerobic training for eliciting functional adaptations such as improved strength, and as such, presents a rationale for further investigation of PRT as a therapeutic intervention in breast cancer.

Thorough and standardized reporting [52] is required of future RCTs. Accordingly, subject characteristics must be clearly described, including menopausal status, stage of breast cancer, surgeries and adjuvant therapies received including extent of axillary lymph node dissection, comorbidities, and prevalence of lymphedema. The time interval between surgery and the initiation of exercise must also be adequately presented. No trial to date has presented these data, yet the timing of exercise relative to surgery may be the most important consideration related to side effects, exercise tolerance, wound dehiscence, pain sensations, and dropout.

Compliance to training should be defined *a priori* to determine the feasibility and generalizability of prescribing exercise training in this patient population. The efficacy of unsupervised training is largely unknown, as only one trial has used this type of intervention [29], which has important cost and feasibility implications for the dissemination of this adjunctive therapy. Thorough reporting of adverse events, including *a priori* definitions and statistical comparisons between groups, is necessary to determine the risk to benefit ratio of PRT in this cohort, which is suggested to be favourable among many other clinical populations [18].

The documented adaptations to exercise regimens involving PRT in the 10 trials reviewed represent important areas of benefit to breast cancer patients and survivors. These adaptations may be associated with reduced cardiovascular risk profile, reduced risk of recurrence, improved QOL, and a longer lifespan [27–38]. Robustly designed RCTs are required to confirm these findings and evaluate many of other health-related and clinical outcomes which are pertinent in this cohort, including osteoporosis, inflammation, lymphedema, immune system functioning, depression, self-efficacy, QOL, and survival rates. Future investigations should also be conducted explicitly with targeted subpopulations within this cohort, including those suffering from clinical depression, obesity, hypertension, and insulin resistance/diabetes. Further, no trials have specifically targeted patients of specific age ranges (i.e. >65 years, < 40 years), and no trial to date has enrolled a male breast cancer survivor.

In summary, PRT is currently widely advocated and prescribed for health benefits in various healthy and chronically diseased cohorts. However, at present there is minimal advocacy for PRT in breast cancer patients and survivors. The modest amount of available literature supports the prescription of PRT in this cohort, though methodological shortcomings and gaps in knowledge are clearly evident. Further research is required to advance general knowledge of this research area toward the development of position stands, and foster the prescription of PRT as a component of mainstream medical practice in breast cancer.

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