Updated systematic review of exercise studies in breast cancer survivors: attention to the principles of exercise training

Sarah E Neil-Sztramko,[1] Kerri M Winters-Stone,[2] Kelcey A Bland,[3] Kristin L Campbell[3,4]

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[1]Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada
[2]School of Nursing and Knight Cancer Institute, Oregon Health Sciences University, Portland, Oregon, USA
[3]Rehabilitation Sciences Graduate Program, University of British Columbia, Vancouver, British Columbia, Canada
[4]Department of Physical Therapy, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence to
Dr Sarah E Neil-Sztramko, Faculty of Health Sciences, McMaster University, Hamilton, Ontario L8P 0A1, Canada; neilszts@mcmaster.ca

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ABSTRACT

Objectives To update our previous evaluation of the exercise interventions used in randomised controlled trials of breast cancer survivors in relation to (1) the application of the principles of exercise training in the exercise prescription; (2) the reporting of the components of the exercise prescription; and (3) the reporting of adherence of participants to the prescribed interventions.

Design Systematic review.

Data sources The OVID Medline, Embase, CINAHL and SPORTDiscus electronic databases were searched from January 2010 to January 2017.

Eligibility criteria Randomised controlled trials of at least 4 weeks of aerobic and/or resistance exercise in women diagnosed with breast cancer, reporting on physical fitness or body composition outcomes.

Results Specificity was appropriately applied by 84%, progression by 29%, overload by 38% and initial values by 67% of newly identified studies. Reversibility was reported by 3% anddiminishing returns by 22% of newly identified studies. No studies reported all components of the exercise prescription in the methods, or adherence to the prescribed intervention in the results. Reporting of reversibility has increased from 2010, but no other improvements in reporting were noted from the previous review.

Summary/Conclusion No studies of exercise in women with breast cancer attended to all principles of exercise training, or reported all components of the exercise prescription in the methods, or adherence to the prescription in the results. Full reporting of the exercise prescribed and completed is essential for study replication in research and translating research findings into the community, and should be prioritised in future trials.

INTRODUCTION

Based on the most recent global estimates, 1.7 million new cases of breast cancer are diagnosed worldwide each year, making breast cancer the most commonly diagnosed cancer in women.[1] Survival following a breast cancer diagnosis has greatly increased as a result of treatment advancements, with a five-year survival rate of 87%[2] in developed countries such as Canada. Due to this trend, there is a growing worldwide population of women who are living long after a cancer diagnosis, but who are faced with many late and long-term side effects. Research is now focused on addressing late and long-term cancer treatment side effects along with competing risks of mortality and morbidity. Clinical practice guidelines recommend that breast cancer survivors be continuously monitored for lymphoedema, cardiotoxicity, cognitive impairment, distress, depression and anxiety, fatigue, bone health, pain and peripheral neuropathy, and should receive health promotion counselling related to obesity, physical activity, nutrition and smoking cessation.[3]

There is growing evidence demonstrating the beneficial role of exercise in mitigating several adverse effects of breast cancer and its treatment, and this evidence has been summarised in a number of systematic reviews and meta-analyses.[4–8] However, systematic reviews and meta-analyses tend to aggregate exercise programmes into general categories and rarely investigate the specific features of exercise programmes that may make them more or less effective. While helpful for providing a general consensus regarding the benefits of exercise, this clustering of training programmes may impede translation of effective programmes from research to practice and provides little guidance about the salient features of a training programme for this clinical population.

In 2012, our team published a systematic review evaluating the application of the general principles of exercise training in studies of women diagnosed with breast cancer.[9] This was in response to our observation that the use of well-established exercise training principles in the field of exercise research and practice (see table 1) were not commonly being reported in the exercise oncology literature. We also reviewed the reporting of the exercise prescription components of frequency, intensity, time and type (FITT), and the reporting of adherence to the prescribed intervention. We found that of the 29 studies reviewed, no studies applied all principles of exercise training, or all components of the exercise prescription in their methods or results. We urged researchers in the field to improve their tracking and reporting of these key details.

Since the publication of the 2012 review, many new randomised controlled trials (RCTs) have been published and included more participants and interventions of longer duration and with extended follow-up. Therefore, there was a need to update our previous review to include these new trials. The objective was to highlight potential areas of improvement in exercise prescription methods and reporting in order to move the exercise oncology field forward. We have updated our previous evaluation of the exercise interventions used in RCTs for breast cancer survivors in relation to (1) the application of the principles of exercise training in the development of the exercise prescription; (2) the reporting of the components of the exercise

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Table 1 Exercise training principles

Principle	Criteria for this review	Example
Specificity: Training adaptations are specific to the system or muscles trained with exercise.	Appropriate population targeted and intervention given based on primary outcome	Aerobic exercise such as brisk walking is more appropriate for an intervention aimed at increasing cardiovascular fitness than strength training.
Progression: Over time, the body adapts to exercise. For continued improvement, the volume or intensity must be increased.	Stated exercise programme was progressive and outlined training progression	A walking intervention 2×/week at 60% of maximum heart rate for 30 min, adds 5 min/week over 6 weeks
Overload: For an intervention to improve fitness, it must be greater than what the individual is already doing.	Rationale provided that programme was of sufficient intensity/exercise prescribed relative to baseline fitness.	An individual currently cycles 30 min 2×/week; the exercise intervention must be of greater volume to see a significant improvement in fitness.
Initialvalues: Improvements in the outcome of interest will be greatest in those with lower initial values.	Selected population with low level of primary outcome measure and/or baseline physical activity levels	Those with lowest levels of fitness have greatest room for improvement. A sample with high fatigue levels will be more likely to see a significant change than a sample with low baseline fatigue.
Reversibility: Once a training stimulus is removed, fitness levels will eventually return to baseline.	Performed follow-up assessment on participants who decreased or stopped exercise training after conclusion of intervention	'Use it or lose it'. Strength gains achieved over 1 year of resistance exercise may completely reverse within a number of months of inactivity.
Diminishingreturns: The expected degree of improvement in fitness decreases as individuals become fit, thereby increasing the effort required for further improvements.	Performed follow-up assessment of primary outcomes on participants who continued to exercise after conclusion of intervention.	Non-exercisers who begin an exercise programme are likely to experience large initial gains, but the magnitude of change will decrease over time. This is also known as the 'ceiling effect'.

prescription (ie, FITT) in both the study methods and results; and (3) the adherence of participants to the prescribed interventions.

METHODS

We used the same protocol as our previously published review[9]; no other protocol for this update has been published. The Medline, CINAHL, SPORTDiscus and Embase electronic databases were searched from January 2010 to January 2017. This overlapped with our previous search (completed in May 2010) to avoid any missed papers that were in the process of indexing during the search. This review includes the papers from the original review with the addition of new papers published between 2010 and 2017. The previous subject heading terms related to breast cancer and exercise, specific to each database, were used and combined with the AND term. The search was then limited to English-language publications in peer-reviewed journals. Key publications, including relevant systematic reviews identified during the literature search, were hand-searched for relevant publications.

We included RCTs with one or more treatment arms involving at least four weeks of aerobic and/or resistance exercise, conducted in women diagnosed with breast cancer. Studies including participants diagnosed with other types of cancer were excluded, as were alternative exercise interventions such as yoga, Pilates or Tai Chi, as well as therapeutic interventions (ie, shoulder rehabilitation). Interventions focused primarily on physical activity behaviour change and those in which the only outcomes reported were physical activity levels or psychosocial outcomes were excluded. To be eligible for inclusion, studies had to report at least one relevant physiological outcome related to exercise (eg, aerobic capacity, muscular strength, functional capacity or body composition). Additional publications from previously included trials were also added to the database of included articles to allow for review of previously extracted data and updates regarding inclusion of information on use of exercise training principles, exercise prescription or adherence to exercise prescription data, particularly the principles of reversibility and diminishing returns reported in follow-up papers.

Two reviewers (SNS and KAB) independently screened the title and abstract of each study identified to determine eligibility. If required, full-text articles were obtained and reviewed for eligibility. Eligibility lists were compared using an online software system (Covidence Systematic Review software, Veritas Health Innovation, Melbourne, Australia). Discrepancies were resolved by consensus and the input of a third reviewer (KLC) when necessary.

Data were extracted in duplicate by the two reviewers using online software (Covidence), including sample size, timing of intervention delivery (during/after treatment), study duration and follow-up, measured outcomes, and study findings. Specific exercise prescription data were abstracted according to the 'FITT' format from each publication's methods section, including frequency (number of sessions per week), intensity (relative or absolute intensity of activity), time (duration of activity) and type of activity.

For each exercise prescription described, a rating was assigned for the application of each principle of exercise training (see table 1). Application of a principle was assigned a '+' when the application was clearly reported, and an 'NR' (not reported) if there was no indication that the principle was used in the exercise prescription. A '?' was assigned when the principle was mentioned but not described, was inconsistently applied or was otherwise unclear. Adequate reporting of the prescription according to the FITT format and reporting of participant adherence to the prescription were also assigned a '+', 'NR' or '?'. For multiarm trials comparing different interventions, the application of the principles of exercise training and the exercise prescription was evaluated separately for each intervention arm. For trials that were previously included, newly identified articles were screened for new information to determine whether the previously assigned ratings should be altered.

The number and percentage of included studies that met each criterion were calculated (1) among newly identified studies and (2) among all studies identified to date. To determine whether there has been an improvement in the reporting of each criteria over time, a χ^2 test was used calculate difference in proportions of those reporting + versus '?' or NR among studies identified in our first review (2010 and prior) and new studies identified in this review (2010 and later).

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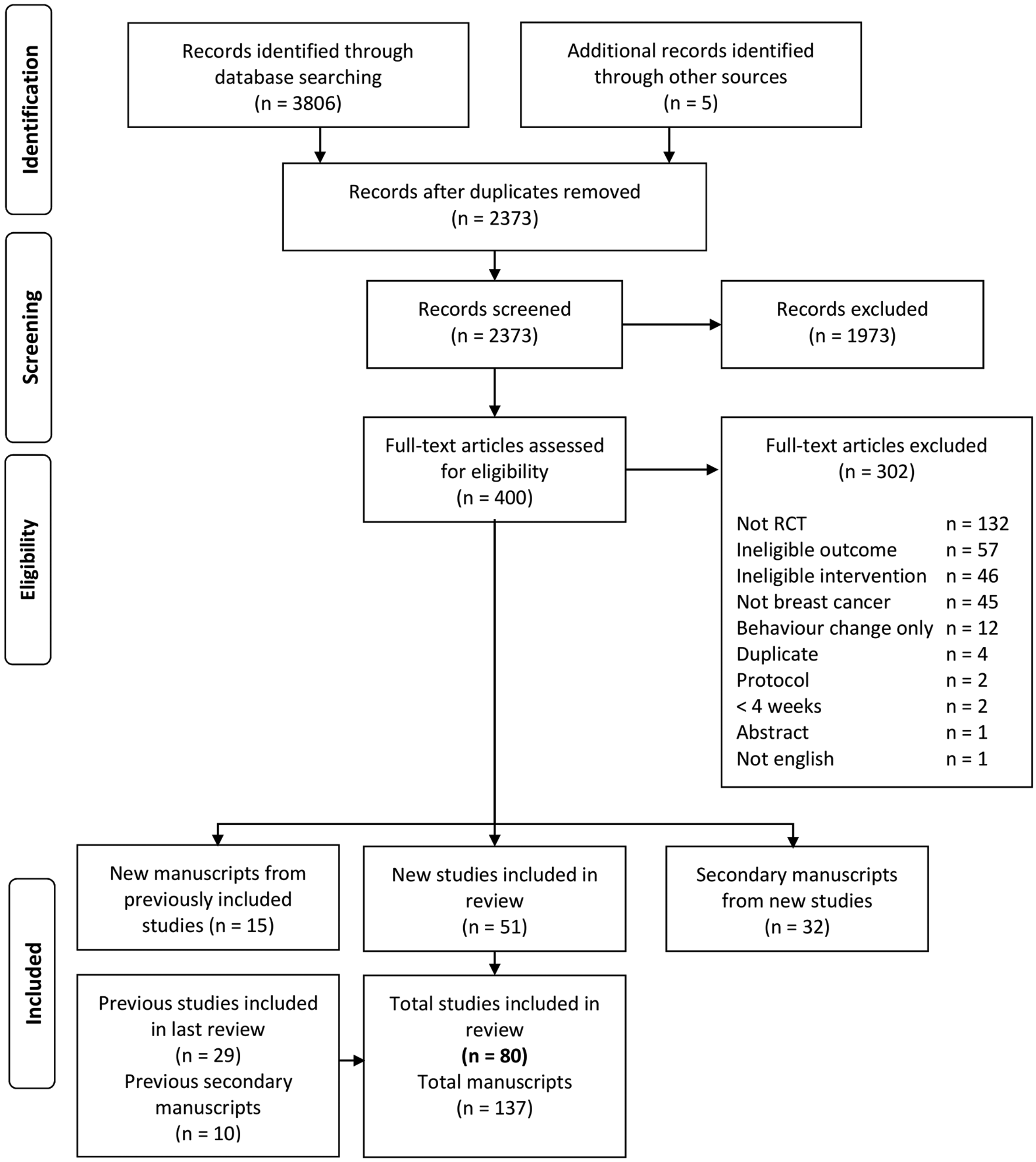

Figure 1 Flow chart of study selection process. (RCTs, randomised controlled trials)

RESULTS

Eighty-three manuscripts describing 51 trials published since 2010 were identified and included (figure 1). Sixteen new manuscripts from previously identified trials were also identified and reviewed for new information provided on relevant methods and outcomes (ie, follow-up). This resulted in a total of 138 articles describing results from 80 trials published between 1994 and 2017 (see online supplementary table 1 , for full list of included articles). Of the 16 newly identified articles from previously included studies, 10 (63%) reported on different outcome measures,[10–19] 3 (19%) reported secondary analysis of already reported outcomes[20–22] and 3 (19%) reported findings from postintervention follow-up.[23–25]

Fourteen new studies (27%) prescribed aerobic exercise only,[26–39] 7 new studies (14%) prescribed resistance exercise only,[40–46] 25 new studies (49%) prescribed aerobic and resistance exercise together,[47–71] and 5 new studies (10%) were multiarm trials (12 intervention arms) comparing aerobic with resistance or aerobic and resistance exercise[72–76] (online supplementary table 1). Eighteen new studies (35%) were conducted in women undergoing adjuvant treatment for breast cancer,[26 30 32 33 35 39 42 44 50 55–57 65 69 71 73 75 76] and 31 new studies (61%) were conducted in women after completion of adjuvant breast cancer treatment.[28 29 31 34 36–38 40 41 43 45 46 48 49 51–54 58–64 66–68 70 72 74] One study included women who had undergone surgery for breast cancer and may or may not have been undergoing chemotherapy and/or radiation therapy,[47] and one study did not report the timing of the intervention.[27] Newly included interventions ranged from 4 to 52 weeks, with follow-up measures taken from 3 weeks to 5 years postintervention.

Application of the principles of exercise training

Table 2 details the ratings of the principles of exercise training for previously included and newly identified studies. After reviewing newly published articles from previously included trials, one study's[77] rating of reversibility and diminishing returns

Table 2 Application of the principles of exercise training and outcomes in exercise intervention studies in breast cancer survivors

Authors, year	Sp	Pr	OV	IV	Rev	DR	Significant results
Aerobic exercise only							
Al-Majid *et al*, 2015[26]	+	+	+	+	?	?	$VO_{2\,peak}$ ↔
Anulika Aweto *et al*, 2015[27]	+	?	NR	NR	NR	+	↓ RBP, SaO_2; ↑ FVC (PostM), ↑ $VO_{2\,peak}$ (PreM)
Courneya *et al*, 2003[85]	+	+	+	NR	NR	NR	↑ $VO_{2\,peak}$*, QoL*, PPO, VO_2 and PO at VEO_2/$VECO_2$
Daley *et al*, 2007[86]	+	NR	NR	+	+	NR	↑ QoL*, Aer fitness
Dolan *et al*, 2016 (Int)[28]	+	+	+	NR	NR	NR	↑ $VO_{2\,peak}$*, 1RM; ↓ BW, WHR, RHR (vs CON)
Dolan *et al*, 2016 (Cont)[28]							↑ $VO_{2\,peak}$*, 1RM; ↓ WHR, RHR (vs CON)
Drouin *et al*, 2005[87]	+	NR	+	+	NR	NR	↑ $VO_{2\,peak}$*
Giallauria *et al*, 2016[29]	+	NR	+	?	NR	NR	↑ $VO_{2\,peak}$, endothelial function; WC, BMI, O_2 pulse
Hornsby *et al*, 2014[30]	+	+	+	+	NR	?	↔ AEs*; ↑ $VO_{2\,peak}$; PPO, endothelial progenitor cells; ↓ O_2 pulse; some serum cytokines; tumour gene expression
Irwin *et al*, 2009[88]	NR	+	?	+	NR	NR	↓ %BF, ↑ LBM
Kim *et al*, 2006[89]	+	?	+	+	NR	NR	↓ RSBP*, RHR*, max SBP*, ↑ $VO_{2\,peak}$*
Matthews *et al*, 2007[90]	?	+	NR	?	NR	NR	None
Mehnert *et al*, 2011[31]	?	NR	?	NR	NR	NR	↑ $VO_{2\,peak}$
Milecki *et al*, 2013[32]	+	NR	NR	+	NR	NR	↓ RBP, ↑ 6MWT
Mock *et al*, 1994[91]	+	?	NR	NR	NR	NR	↑ 12MWT
Mock *et al*, 1997[92]	+	?	?	?	NR	NR	↑ 12MWT
Mock *et al*, 2005[93]	NR	+	?	?	NR	NR	↑ 12MWT
Mowafy *et al*, 2016[33]	+	NR	+	+	NR	NR	↑ $VO_{2\,peak}$, total leucocytes
Murtezani *et al*, 2014[34]	+	?	NR	NR	NR	NR	↑ QoL*, 12MWT
Naraphong *et al*, 2015[35]	+	?	NR	+	NR	?	↑ 12MWT
Nikander *et al*, 2007[94]	?	+	NR	NR	NR	NR	↓ Figure 8 run*, ↑ ground reaction force
Pinto *et al*, 2003[95]	+	+	+	+	NR	NR	↓ BP at rest, 75W, peak, HR at 75W
Pinto *et al*, 2005[96]	+	+	NR	+	?	?	↓ 1MW
Rogers *et al*, 2009[97]	?	?	?	?	NR	NR	↑ Strength, left grip strength, ↓ WHR
Rogers *et al*, 2015[36]	+	+	?	+	?	?	↑ SR PA (3, 6 m)*, objPA (3 m)*, $VO_{2\,peak}$ (6 m)
Saarto *et al*, 2012[37]	+	?	?	+	NR	NR	↑ BMD*, femoral neck (PreM)*; 2kmWT (PreM), figure 8 run, grip strength, femoral neck centroid
Segal *et al*, 2001 (Sup)[98]	+	?	?	+	NR	NR	None
Segal *et al*, 2001 (Home)[98]							None
Swisher *et al*, 2015[38]	?	NR	+	+	NR	NR	↓ BW*, BMI*, BF%*
Wang *et al*, 2011[39]	+	+	?	+	NR	+	↑ 6MWT
Resistance exercise only							
Cormie *et al*, 2013 (High)[40]	+	+	+	+	NR	NR	No ↑ lymphoedema*, ↑ chest press (1RM, endurance), seated row (1RM)
Cormie *et al*, 2013 (Low)[40]							No ↑ lymphoedema*, ↑ chest press (1RM, endurance), seated row (1RM, endurance)
Hagstrom *et al*, 2016[41]	+	+	+	+	NR	NR	↑ 1RM, upper body strength; ↓ NK TNF-a, NKT TNF-a*
Schmidt *et al*, 2012[43]	?	?	?	+	NR	+	↓ RPE at 50, 75, 100W
Schmidt *et al*, 2015[42]	+	+	+	+	NR	NR	↑ IsoM and isoK strength
Schmitz *et al*, 2005[99]	+	+	+	+	NR	+	↓ %BF*, ↑ LBM*, ↓ IGF-2
Schmitz *et al*, 2009[100]	+	+	+	+	NR	NR	No ↑ lymphoedema*, ↑ 1RM
Steindorf *et al*, 2014[44]	+	+	+	+	NR	NR	↑ Strength (knee flex, shoulder internal and external rotation), ↓ fatigue*, HC, IL-6, IL-6/IL-1ra
Twiss *et al*, 2009[101]	+	NR	NR	+	NR	NR	↑ BMD*, strength, balance
Winters-Stone *et al*, 2011[45]	+	+	+	+	+	+	↑ Spine BMD*, bench press, leg press (12-month, 1-year follow-up subset), no ↑ osteocalcin*
Winters-Stone *et al*, 2013[46]	+	+	+	+	+	+	↑ 1RM (chest press); ↓ %BF
Aerobic and resistance exercise							
Anderson *et al*, 2012[47]	+	?	+	NR	NR	NR	↑ 6MWT*
Battaglini *et al*, 2007[102]	+	?	+	NR	NR	NR	↑ LBM, ↓ BF, ↑ sum 1RM
Campbell *et al*, 2005[103]	?	NR	NR	NR	NR	NR	↑ 12MWT
Cantarero-Villanueva *et al*, 2013[48]	+	?	NR	+	?	NR	↓ Fatigue*, ↑ sit-stand, trunk curl
Casla *et al*, 2015[49]	+	+	+	NR	?	?	↑ $VO_{2\,peak}$*, isoM strength, 8RM, muscle endurance, LBM; ↓ FM
Cornette *et al*, 2016[50]	?	?	?	+	?	?	None
DeLuca *et al*, 2016[51]	+	+	+	?	NR	NR	↑ $VO_{2\,peak}$, est 1RM; ↓ %BF
Demark-Wahnefried *et al*, 2008[104]	+	NR	NR	+	NR	NR	↓ %BF without trunk
Do *et al*, 2015[50]	+	?	?	NR	?	+	↔ Aer fitness (EoS and 8 weeks)

Continued

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Table 2 Continued

Authors, year	Sp	Pr	OV	IV	Rev	DR	Significant results
Hayes *et al*, 2013 (Tele)[56]	+	?	?	+	NR	?	↑ QoL*, Aer fitness
Hayes *et al*, 2013 (FtF)[56]							↑ QoL*, Aer fitness
Galiano-Castillo *et al*, 2016[53]	+	NR	NR	NR	?	?	↑ Strength
Greenlee *et al*, 2013[54]	+	+	?	+	?	?	↓ BW*
Haines *et al*, 2010[55]	+	?	NR	+	?	+	↑ QoL (some domains)*; ↓ 30 cm proximal limb circumference
Heim *et al*, 2007[105]	+	NR	NR	+	NR	NR	↓ Fatigue
Herrero *et al*, 2006[106]	+	+	+	+	NR	NR	↑ $VO_{2\ peak}$, peak PO, leg press, LBM, ↓ sit-stand time, %BF
Husebø *et al*, 2014[57]	?	NR	NR	+	?	?	↓ Fatigue (EoS)
Irwin *et al*, 2015[58]	+	?	?	+	NR	+	↑ LBM, BMD; ↓ arthralgia*, BMI, %BF
Kaltsatou *et al*, 2011[59]	+	?	NR	NR	NR	NR	↑ Grip strength, 6MWT
Kim *et al*, 2016[60]	?	?	NR	+	NR	NR	None
Ligibel *et al*, 2008[107]	+	?	?	+	NR	NR	↓ Fasting insulin*, WC, HC
Martin *et al*, 2013 (Trad)[61]	+	?	NR	?	NR	NR	↑ Muscular endurance (vs CON)
Martin *et al*, 2013 (MVe)[61]							↑ Muscular endurance (vs CON)
Milne *et al*, 2008[108]	+	?	NR	+	NR	NR	↑ QoL*, Aer fitness, strength
Mutrie *et al*, 2007[77]	?	NR	NR	+	+	+	↑ 12MWT
Naumann *et al*, 2012[62]	+	NR	?	+	NR	NR	↑ Bench press, $VO_{2\ peak}$ (ex and ex+couns vs couns)
Nieman *et al*, 1995[109]	+	?	?	NR	NR	NR	↓ 6MWT
Portela *et al*, 2008 (Sup)[63]	+	?	NR	NR	NR	+	None
Portela *et al*, 2008 (Home)[63]							↑ 12MWT
Rahnama *et al*, 2010[64]	+	+	?	+	NR	NR	$VO_{2\ peak}$, HDL; ↓ BW, BMI, WHR, SBP, TG, insulin, glucose, RHR
Rao *et al*, 2012[65]	?	NR	NR	+	NR	NR	None
Rogers *et al*, 2013[66]	+	?	?	+	NR	NR	↑ $VO_{2\ peak}$, ↓ leptin
Rogers *et al*, 2014[67]	+	?	NR	+	NR	NR	None
Scott *et al*, 2013[68]	+	NR	NR	+	NR	NR	↑ Aer fitness, HDL; ↓ WC*, WHR*, RDBP, leptin, TC, HDL, cortisol rhythm, total leucocyte, lymphocyte; CD3+CD4+% cell count
Travier *et al*, 2015[69]	+	?	+	+	?	?	Smaller ↑ fatigue*; ↑ VO_2 and W at VT (18 w), lower body strength
Uhm *et al*, 2017[70]	?	?	?	NR	NR	+	None
Visovsky *et al*, 2014[71]	?	?	NR	+	?	+	None
Aerobic or resistance exercise (multiarm trials)							
Buchan *et al*, 2016 (Aer)[72]	+	?	NR	?	?	+	↔ Lymphoedema*; ↑ lower-body endurance, LBM (12 w); ↑ 6MWT, upper-body strength (24 w)
Buchan *et al*, 2016 (Res)[72]	+	?	NR	?	?	+	↔ Lymphoedema*; ↑6MWT, lower-body endurance, upper-body strength; ↑ upper-body strength (vs Aer)
Courneya *et al*, 2007 (Aer)[110]	+	+	+	+	NR	NR	↑ $VO_{2\ peak}$, no ↑ lymphoedema
Courneya *et al*, 2007 (Res)[110]	+	+	+	+	NR	NR	↑ $VO_{2\ peak}$, 1RM, BW, BF, LBM, no ↑ lymphoedema
Courneya *et al*, 2013 (Low)[73]	+	+	+	+	?	?	↑ 1RM bench press (vs high)
Courneya *et al*, 2013 (High)[73]	+	+	+	+	?	?	↑ $VO_{2\ peak}$ versus Aer+Res
Courneya *et al*, 2013 (Aer+Res)[73]	+	?	+	+	?	?	↑ 1RM, endurance (vs high); ↑ 1RM, upper-body endurance (vs low); ↑ 1RM, endurance, LBM (pre–post)
Musanti *et al*, 2012 (Aer)[74]	+	?	?	?	NR	NR	None
Musanti *et al*, 2012 (Res)[74]	+	?	?	?	NR	NR	↑ 6RM, endurance (chest press, curl-up)
Musanti *et al*, 2012 (Aer+Res)[74]	+	?	?	?	NR	NR	↑ 6RM, endurance (chest press, curl-up)
Schmidt *et al*, 2015 (Res)[75]	+	NR	+	+	NR	NR	↑ Bench press, pull down, ↓ RPE at max
Schmidt *et al*, 2015 (Aer)[75]	+	NR	?	+	NR	NR	↑ Bench press, ↓ RPE at max
Schwartz *et al*, 2007 (Aer)[111]	+	+	NR	?	NR	NR	↑ BMD*, strength, 12MWT
Schwartz *et al*, 2007 (Res)[111]	+	+	NR	?	NR	NR	NR
van Waart *et al*, 2015 (Sup)[76]	+	?	+	+	?	?	↑ PPO*, endurance*, elbow flex*, knee ext*, grip strength*; ↓ fatigue*
van Waart *et al*, 2015 (Home)[76]	+	NR	+	+	?	?	↑ Endurance* (EoS)
Yuen *et al*, 2007 (Aer)[112]	+	NR	NR	+	NR	NR	↓ Fatigue*
Yuen *et al*, 2007 (Res)[112]	NR	NR	NR	+	NR	NR	↑ 6MWT

*Primary outcome.
1MW, 1 mile walk; 2kmWT, 2 km walk time; 6, 12MWT: 6, 12 min walk test; AE, adverse event; Aer, aerobic; BF, body fat; BMD, bone mineral density; BMI, body mass index; BP, blood pressure; BW, body weight; CON, control; Cont, continuous; Couns: counselling; DR, diminishing returns; EoS, end of study; Ex, exercise; FM, fat mass; FtF, face-to-face; FVC, forced vital capacity; HC, hip circumference; HDL, high-density lipoprotein; HR, heart rate; IGF, insulin-like growth factor; IL, interleukin; Int, intervals; isoK, isokinetic; IsoM, isometric; IV, initial values; LBM, lean body mass; NK, natural killer cell; NR, not reported; obj, objective; OV, overload; PA, physical activity; PO, power output; PostM, postmenopausal; PPO, peak power output; Pr, progression; PreM, premenopausal; QoL, quality of life; RBP, resting blood pressure; Res: resistance; RHR, resting heart rate; RM, repetition max; RPE, rating of perceived exertion; RDBP, resting diastolic blood pressure; Rev, reversibility; RSBP, resting systolic blood pressure; SaO_2, oxygen saturation; SBP, systolic blood pressure; Sp, specificity; SR, self-report; Sup, supervised; TC, total cholesterol; Tele, telephone; TG, triglycerides; TNF-a, tumour necrosis factor-alpha; Trad, traditional; VE, ventilatory equivalend; VO2, volume of oxygen consumed; VT, ventilatory threshold; W, watts; w, weeks; WC, waist circumference; WHR, waist-hip ratio. +, clearly reported; ? unclear; NR, not reported

was changed from NR to + after publication of follow-up data. X^2 tests show no significant difference in the proportion of newly included versus previously identified studies reporting the principles of specificity, progression, overload or initial values. There was a significant difference in the distribution of reporting of the principles of reversibility (P<0.01) and diminishing returns (P<0.001) as more newly included studies were assigned a '?' instead of an 'NR' for these two principles (data not shown).

The following results are presented for newly identified studies, and with a comparison to the total number of studies in the review from both the original search and this update. Among newly identified studies, specificity was appropriately applied by 12 aerobic studies[26–30 32–37 39] (86% vs 75% overall), 6 resistance studies[40–42 44–46] (86% vs 90% overall), 19 mixed studies[47–49 51–56 58 59 61–64 66–69] (76% new and overall) and all 12 intervention arms within multiarm studies[72–76] (100% vs 94% overall). Specificity was unclear in 2 aerobic studies[31 38] (14% vs 18% overall), 1 resistance study[43] (14% vs 10% overall) and 6 mixed studies[50 57 60 65 70 71] (24% new and overall). No new studies were assigned an NR for specificity.

Progression was appropriately reported by 5 aerobic[26 28 30 36 39] (36% vs 43% overall), 6 resistance[40–42 44–46] (86% vs 80% overall), 4 mixed[49 51 54 64] (16% vs 15% overall) and 2 interventions within a multiarm trial[73] (17% vs 33% overall). Progression was unclear in 4 aerobic[27 34 35 37] (29% vs 32% overall), 1 resistance[43] (17% vs 10% overall), 16 mixed[47 48 50 52 55 56 58–61 63 66 67 69–71] (64% vs 59% overall) and 7 interventions within multiarm trials[72–74 76] (58% vs 39% overall). Five aerobic[29 31–33 38] (36% vs 25% overall), 5 mixed[53 57 62 65 68] (20% vs 26% overall) and 2 new multiarm trials[75 76] (25% vs 28% overall) did not report progression.

Among newly identified studies, 6 aerobic[26 28–30 33 38] (43% vs 36% overall), 6 resistance[40–42 44–46] (86% vs 80% overall), 4 mixed[47 49 51 69] (16% vs 18% overall) and 6 multiarm trials[73 75 76] (50% vs 44% overall) correctly applied the principle of overload. Overload was unclear in 4 aerobic[31 36 37 39] (29% vs 32% overall), 1 resistance[43] (14% vs 10% overall), 9 mixed[50 52 54 56 58 62 64 66 70] (36% vs 32% overall) and 4 multiarm trials[74 75] (33% vs 22% overall). Overload was not reported in 4 aerobic[27 32 34 35] (29% vs 32% overall), 12 mixed[48 53 55 57 59–61 63 65 67 68 71] (48% vs 50% overall) and 2 arms within multiarm trials[72] (17% vs 33% overall).

The principle of initial values was correctly reported for 9 aerobic[26 30 32 33 35–39] (64% vs 57% overall), all 7 resistance[40–46] (100% new and overall), 16 mixed[48 50 54–58 60 62 64–69 71] (64% vs 65% overall) and 7 multiarm trials[73 75 76] (58% vs 61% overall), and was unclear in 1 aerobic[29] (7% vs 18% overall), 2 mixed[51 61] (8% vs 6% overall) and 5 multiarm trials[72 74] (42% vs 39% overall). Initial values were not reported in 4 aerobic[27 28 31 34] (29% vs 25% overall) and 7 mixed studies[47 49 52 53 59 63 70] (28% vs 29% overall).

Reversibility was correctly reported in 2 resistance studies[45 46] (29% vs 20% overall). Two aerobic[26 36] (14% vs 11% overall), 10 mixed[48–50 52–55 57 69 71] (40% vs 29% overall) and 7 multiarm trials[72 73 76] (58% vs 39% overall) incorrectly reported reversibility. The remaining 12 aerobic[27–35 37–39] (86% new and overall), 5 resistance[40–44] (71% vs 80% overall), 15 mixed[47 51 56 58–68 70] (60% vs 68% overall) and 5 multiarm trials[74 75] (42% vs 61% overall) did not report reversibility.

Diminishing returns were reported by 2 aerobic[27 39] (14% vs 7% overall), 3 resistance[43 45 46] (43% vs 40% overall), 6 mixed[52 55 58 63 70 71] (24% vs 21% overall) and 2 multiarm trials[72] (17% vs 11% overall). Diminishing returns were unclear in 4 aerobic[26 30 35 36] (29% vs 18% overall), 7 mixed[49 50 53 54 56 57 69] (28% vs 21% overall) and 5 multiarm trials[73 76] (42% vs 28% overall). The remaining 8 aerobic[28 29 31–34 37 38] (62% vs 75% overall), 4 resistance[40–42 44] (57% vs 60% overall), 12 mixed[47 48 51 59–62 64–68] (48% vs 59% overall) and 5 multiarm trials[74 75] (42% vs 61% overall) did not report on diminishing returns.

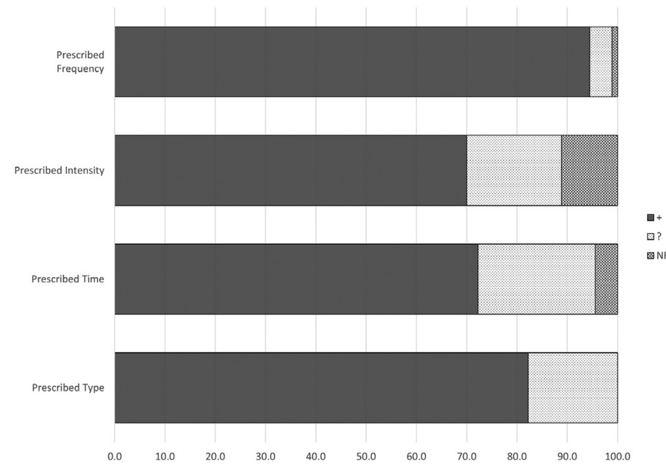

Figure 2 Reporting of components of the exercise prescription. (NR, not reported)

Reporting of the components of the exercise prescription

There were no changes to the reported exercise prescriptions in previously included trials. When comparing ratings between previously included and newly identified trials, there was a significant difference in the proportion who adequately reported exercise intensity (P=0.01) with more new trials assigned an '?' than '+' for prescribed intensity, but no differences for reporting of prescribed frequency, time and type.

Reporting of the components of the exercise prescription for all included studies is displayed in figure 2. Of the newly identified studies, 3 aerobic[29 31 37] (21% vs 32% overall), 18 mixed[48 50 53 55–60 62–68 70 71] (72% vs 67% overall) and 3 multiarm trials[72 74] (25% vs 33% overall) failed to report all components of the exercise prescription. All seven resistance-only interventions[40–46] (100% new and overall) reported all aspects of the exercise prescription. With respect to prescribed frequency in new studies, 1 aerobic[29] (7% vs 6% overall) and 2 mixed interventions[58 70] (8% vs 9% overall) were assigned an unclear rating, and 1 mixed intervention[55] (8% vs 3% overall) did not report frequency. Three aerobic[29 31 37] (21% vs 11% overall), 12 mixed[48 50 55 56 58–60 64 66–68 70] (48% vs 38% overall) and 1 multiarm intervention[72] (8% vs 6% overall) were not clear in their reporting of prescribed intensity, and 5 mixed studies[53 57 62 65 71] (40% vs. 21% overall) did not report intensity at all. Two aerobic[31 37] (14% vs 11% overall), 13 mixed[50 53 55–58 60 62 63 66 67 70 71] (52% vs 50% overall) and 1 multiarm[74] (8% vs 6% overall) intervention were unclear in their reporting of prescribed duration of exercise. One multiarm trial did not report prescribed duration at all[74] (8% vs 17% overall). Three aerobic[29 31 37] (21% vs 18% overall) and 8 mixed studies[53 56 59 62 65 68 70 71] (32% vs 29% overall) were unclear in their reporting of the prescribed exercise type.

Reporting of adherence to the prescribed intervention

Reporting of adherence to the prescribed interventions or actual exercise completed by participants is displayed in figure 3. Of the newly identified studies, 3 aerobic[26 35 39] (21% vs 11% overall), 1 resistance[45] (14% vs 10% overall) and 1 multiarm trial[73] (8%

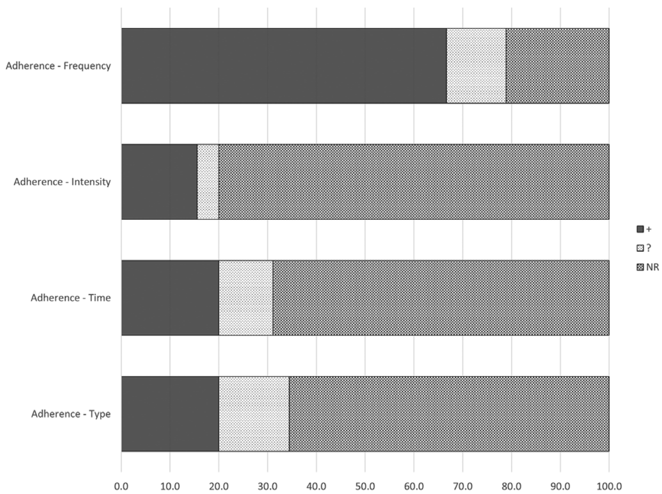

Figure 3 Reporting of adherence to the exercise intervention. (NR, not reported)

vs 6% overall) reported on participants' adherence to all aspects of the prescribed interventions. Four aerobic[27 32–34] (28% vs 21% overall), 1 resistance[43] (14% vs 10% overall), 6 mixed[51 52 59 64 70 71] (24% vs 21% overall) and 2 multiarm[75] trials (17% vs 11% overall) did not report adherence. Frequency of exercise completed was reported in 7 aerobic[26 28 30 35 37–39] (50% vs 64% overall), 5 resistance[40 42 44–46] (71% vs 80% overall), 14 mixed[47–50 53–55 60–63 67–69] (56% vs 65% overall) and 8 multiarm trials[72–74] (67% new and overall). Frequency was unclear in 3 aerobic[29 31 36] (21% vs 11% overall), 1 resistance[41] (14% vs 10% overall), 5 mixed[56–58 65 66] (20% vs 15% overall) and 2 multiarmed trials[76] (17% vs 11% overall). Intensity of exercise completed was reported in 4 aerobic[26 29 35 39] (28% vs 21% overall), 2 resistance[40 45] (29% vs 20% overall), 1 mixed[50] (4% vs 3% overall) and 3 multiarm trials[73] (25% vs 17% overall). Intensity of exercise performed was not reported in 8 aerobic[27 31–34 36–38] (57% vs 71% overall), 4 resistance[41–44] (57% vs 70% overall), 23 mixed[47–49 51–62 64–71] (92% vs 94% overall) and 9 multiarm trials[72 74–76] (75% vs 72% overall). Intensity of exercise completed was unclear in 2 aerobic studies[28 30] (14% vs 7% overall), 1 resistance[46] (14% vs 10% overall) and 1 mixed[63] (4% vs 3% overall). The duration of exercise completed was reported in 5 aerobic[26 28 35 37 39] (36% vs 39% overall), 1 resistance[45] (14% vs 10% overall), 1 mixed[71] (4% vs 9% overall) and 3 multiarm trials[73] (25% vs 17% overall). Duration of exercise completed was not reported in 8 aerobic[27 29 31–34 36 38] (57% new and overall), 5 resistance[40–44] (71% vs 80% overall), 17 mixed[47 48 51–56 59–62 64 65 68–70] (68% new and overall) and 9 multiarm trials[72 74–76] (75% vs 83% overall). The duration of exercise completed was unclear in 1 aerobic[30] (7% vs 4% overall), 1 resistance[46] (15% vs 10% overall) and 7 mixed[49 50 57 58 63 66 67] trials (28% vs 24% overall). The type of exercise performed was reported in 5 aerobic[26 28 30 35 39] (36% vs 39% overall), 2 resistance[45 46] (29% vs 20% overall), 1 mixed[71] (4% vs 6% overall) and 1 multiarm trial[73] (8% vs 17% overall). Mode of exercise was not reported in 8 aerobic[27 29 31–34 36 38] (57% new and overall), 4 resistance[41–44] (57% vs 70% overall), 16 mixed[47 48 51–53 56–59 61 62 64 65 68–70] (64% vs 68% overall) and 9 multiarm trials[72 74–76] (75% vs 72% overall), and was unclear in 1 aerobic[37] (7% vs 4% overall), 1 resistance[40] (14% vs 10% overall), 8 mixed[49 50 54 55 60 63 66 67] (32% vs 26% overall) and 2 multiarm trials[73](16% vs 11% overall).

There were no changes to the reported adherence to exercise interventions in new articles. Compared with reported adherence in the trials included in the previous review, there was a significant difference in reporting of frequency of exercise performed (P=0.02), with fewer new trials adequately reporting the frequency of exercise completed (58% vs 82%). There were no differences in reporting of adherence to exercise intensity, time and type.

DISCUSSION

In almost seven years, 51 new trials meeting our eligibility criteria were identified, bringing the total number of RCTs evaluating the effect of exercise on physiological parameters in women diagnosed with breast cancer to 80 trials (6878 women). Given the now overwhelming evidence on the benefits of exercise during and after breast cancer treatment on a variety of health-related and psychosocial outcomes, there is a need to identify the best exercise prescriptions in terms of FITT to improve specific outcomes at various time points along the cancer continuum. While it is impossible for a single trial to answer this question, findings from multiple trials can be compared. However, the comparison of findings across numerous exercise trials requires best practice in exercise prescription and full reporting of both the exercise intervention prescribed and actual exercise completed by participants.

There was no change (since our 2012 review) in the proportion of studies reporting proper application of the principles of specificity, progression, overload and initial values. Failure to apply these critical points may help to explain some of the heterogeneity in outcomes that have been observed in other systematic reviews and meta-analyses.[4 5 7 8] In some cases, improper exercise prescription, as outlined below, may underestimate some of the benefits of exercise. Improving the reporting of exercise prescriptions in exercise oncology trials will allow for more specific recommendations for types and dose of exercise in published exercise guidelines for breast cancer survivors. This will also assist in translation of these interventions outside of the research setting, allowing for the delivery of appropriate, safe and effective exercise interventions to be delivered in a community or clinical setting.

Application of the principle of specificity was commonly reported, consistent with findings in our previous review. However, nine newly identified studies had not appropriately applied the principle of specificity, as the exercise prescribed did not clearly match the desired study outcomes. For example, one study prescribed resistance exercise to improve fatigue but only measured aerobic capacity (6 min walk test) to determine the effectiveness of the intervention.[57] When inappropriate populations are targeted for improvements in a desired outcome, or the exercise prescription is not well suited to promote change in the primary outcome of interest, the effect of exercise may be underestimated. A lack of statistically significant or clinically meaningful change observed may be due to the exercise prescription chosen, rather than a lack of efficacy of exercise.

Less than one-third of included studies properly reported the principle of progression, and it was unclear in almost half of the newly included studies. Studies were given a rating of 'unclear' if they stated that the exercise prescription was updated or progression was included, but how this was done was not described. This information, particularly the rate of progression that is well tolerated by participants at various stages (ie, during or after treatment), is critical for those designing future interventions or implementing exercise programmes outside of research settings. A lack of progression could lead to null findings. Full reporting of whether women were progressed more slowly than prescribed should be considered as this information allows for proper interpretation of study findings and better informs future exercise programme implementation within clinical practice and community settings.

Almost 40% of newly identified trials adequately described applying the principle of overload in the exercise prescription. This increases the likelihood that an adequate training stimulus was applied by ensuring the dose of exercise was either greater than self-reported levels of physical activity or prescribed based on fitness levels measured at baseline. Several publications have shown the safety of maximal exercise testing to measure aerobic capacity and muscular strength in women diagnosed with breast cancer,[78–80] which can be used for prescribing adequate workloads. We advocate for the use of these methods whenever possible. The utility of predictive equations or submaximal exercise testing for aerobic and resistance exercise created for the general populations is uncertain in women after a breast cancer diagnosis due to changes in cardiovascular, muscular and metabolic parameters due to breast cancer and its treatment.[81 82] However, these equations or tests could be similarly useful and more practical in community settings. Continued research is needed in this area to understand the best method of exercise prescription in this population.

Approximately two-thirds of studies adequately reported application of the principle of initial values in the exercise prescription. This was typically achieved by excluding participants who were already highly active at baseline. Despite reported low levels of physical activity in both women diagnosed with breast cancer, and the general population, researchers cannot assume that all participants are sedentary at baseline. Those who agree to participate in exercise trials may already be more active, and prescribing a lower dose of exercise than what participants are already doing can result in detraining, lowering the overall estimate of the effect of exercise. Studies including those with the lowest initial values have the greatest potential to show the benefits of exercise. In studies that include participants with higher initial values, exercise prescription should be adjusted to ensure a training stimulus is offered to all participants. Future studies could include additional analysis to understand the influence of baseline values on training responses, so that realistic timelines for training and expectations of benefits are appropriately translated.

Diminishing returns and reversibility were more commonly reported in the newly identified studies. This is due to the publication of studies of longer durations, and those that incorporated a follow-up assessment after the intervention had ended. An important next step in the field of exercise oncology is to understand the long-term effects of exercise, and what 'maintenance-dose' of exercise is sufficient to sustain the benefits seen in short-term interventions. Unfortunately, many of the newly included studies were unclear in the application of diminishing returns and reversibility reported. Either interim or follow-up measures were reported, but they were not examined in the context of the exercise prescribed or adhered to. Future studies that report interim measures during an intervention or follow-up measures after an intervention is complete should also report what dose of exercise was prescribed and/or completed during those periods so that the patterns of change over time can be understood.

Duration of exercise and some indication of the average exercise intensity are necessary to reproduce findings and understand the minimum dose of exercise needed to elicit positive benefits. More studies in the current review were unclear in their reporting of intensity than studies in the original review (28 vs 3%). Fewer studies adequately reported the actual frequency of exercise completed (58 vs 82%). Reporting of the exercise completed by participants is needed for contextualising study findings, and understanding what exercise dose is feasible for participants to complete in future studies and in community settings. Variations in adherence to trials with similar exercise prescriptions may also help to explain some of the variation in results seen across different trials. Researchers may report adherence in terms of an average frequency, intensity and duration of exercise by mode, as well as the proportion of participants who met the exercise prescription. One study reported prescribing a higher than desired frequency of exercise in anticipation that most participants will not adhere to that target.[54] While we do not necessarily advocate for this approach, as it may increase the likelihood of overtraining by some participants, understanding the proportion of adherence to different prescriptions will help to design interventions that are both physiologically beneficial but also acceptable to participants.

Word and page limits in scientific journals limit the amount of information that can be included, which may contribute to information being reported incompletely. We did not contact authors of studies where an unclear or not reported were assigned. Therefore, some of the included trials may have adhered to some of the principles of exercise training, just not reported them. Reporting of the exercise prescription and adherence to the prescribed programme is essential for moving the field forward. Researchers conducting new studies can build on successful interventions or improve on interventions that failed to find significant improvements. Full reporting will also allow for interpretation of differences across studies and will assist in the development of future evidence-based practice guidelines and ultimately translation into community and clinical practice.

Recently, guidelines have been published for reporting of exercise programmes in academic research.[83] We encourage authors of exercise studies in breast cancer survivors to follow the Consensus on Exercise Reporting Template, including the frequency, intensity, duration and type of exercise prescribed under section 13, 'When, How Much', and exercise actually completed under section 16, 'How Well: Planned, actual'. Several articles included in this review also provide excellent examples of how the exercise prescriptions can be reported in either text[35 73] or table format[26 39 45] for both aerobic[26 35 39 73] and resistance[45 73] exercise.

Since the June 2009 round table discussion that led to the publication of the American College of Sports Medicine's exercise guidelines for cancer survivors,[84] there have been at least 50 RCTs of exercise in breast cancer survivors (reviewed here), plus more that did not meet our eligibility criteria. New literature may now be sufficient to make more specific recommendations for women diagnosed with breast cancer—it might be time to revisit these guidelines. Reviewing the strength of the evidence on specific exercise prescriptions to elicit changes in various outcomes of interest is beyond the scope of this review. However, this review may be helpful in identifying trials that report the attention to the principles of exercise training in their study design and fully report the exercise prescription and exercise completed so that the most robust literature can be given appropriate, and potentially preferential, consideration when updating the existing exercise guidelines.

CONCLUSIONS

In conclusion, while the evidence for the benefits of exercise in women diagnosed with breast cancer continues to grow, no studies of exercise in women with breast cancer attended to all key principles of exercise training, or reported all components of the exercise prescription in the methods, or adherence to the prescribed intervention in the results. In order to move this growing evidence into practice, we call for best practices for exercise prescription, as well as full reporting of the exercise prescription used and adherence to the prescribed exercise programme.

What are the findings?

- No studies have reported all components of the exercise prescription in their methods, or adherence to the prescribed intervention in their results.
- The exercise training principles of specificity and initial values are most often applied, while reversibility, diminishing returns and progression are included by <30% of published studies.
- More recent studies have attempted to use reversibility and diminishing returns in their exercise prescription, but there have been no other improvements in use of exercise training principles or reporting since 2010.

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