CLINICAL SCIENCES

The Effect of Exercise Training on Lean Body Mass in Breast Cancer Patients: A Systematic Review and Meta-analysis

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ABSTRACT

FRASER, S. F., J. R. GARDNER, J. DALLA VIA, and R. M. DALY. The Effect of Exercise Training on Lean Body Mass in Breast Cancer Patients: A Systematic Review and Meta-analysis. *Med. Sci. Sports Exerc.*, Vol. 54, No. 2, pp. 211–219, 2022. **Purpose:** Reduced lean body mass (LBM) is common during and after treatment for breast cancer, and it is associated with increased treatment-induced toxicity, shorter time to tumor progression, and decreased survival. Exercise training is a potential intervention for maintaining or increasing LBM. We conducted a systematic review and a meta-analysis to investigate the effects of exercise training on LBM in breast cancer. **Methods:** A comprehensive search was performed to November 2020 for randomized controlled trials reporting the effects of structured exercise training on LBM compared with control in women with breast cancer during or after cancer treatment. A random-effects meta-analysis was completed using the absolute net difference in the change in LBM between intervention and control groups as the outcome measure. Sensitivity and subgroup analyses were also performed. **Results:** Data from 17 studies involving 1743 breast cancer survivors were included in the meta-analysis. Overall, there was a significant benefit of exercise training compared with control on LBM (0.58 kg, 95% confidence interval = 0.27 to 0.88, $P < 0.001$). Subgroup analysis showed positive effects for resistance training (0.59 kg) and aerobic training (0.29 kg), and for exercise training conducted during (0.47 kg) or after (0.66 kg) cancer treatment. Exercise training was beneficial in studies enrolling postmenopausal women (0.58 kg) as well as in those with participants of mixed menopausal status (1.46 kg). **Conclusions:** Compared with usual care, exercise training has a beneficial effect on LBM in women with breast cancer, both during and after cancer treatment. Given the physiological and functional importance of LBM in women with breast cancer, oncologists should encourage their patients to engage in regular exercise training, with particular emphasis on resistance training. **Key Words:** BODY COMPOSITION, MUSCLE MASS, RESISTANCE TRAINING, STRENGTH TRAINING, AEROBIC TRAINING, ONCOLOGY

Breast cancer is the most common cancer among women, with an estimated 2.1 million new cases diagnosed worldwide in 2018 (1). Advances in detection and treatment in recent decades have led to improved survival rates, meaning that women are now living longer after diagnosis (2). This has resulted in a growing population of women who may require ongoing care due to the common side effects of breast cancer and its treatment.

Changes in body weight as well as in the different components of body composition are common in breast cancer survivors (3). Adiposity tends to increase with breast cancer treatment, and this effect is most pronounced in women receiving chemotherapy or Tamoxifen (4,5). Conversely, lean body mass (LBM) typically decreases during and after treatment. The greatest losses in LBM tend to occur with chemotherapy, with losses ranging from 0.4 to 1.7 kg (5,6). Reductions have also been observed with radiation therapy and Tamoxifen, whereas treatment with aromatase inhibitors may preserve or increase LBM (5,6). Menopausal status also appears to influence treatment-induced changes in LBM, with the greater declines observed in premenopausal women undergoing treatment, as well as in those who experience treatment-induced menopause (5,6). Importantly, changes in body composition frequently occur independently of overall weight change, as a reduction in LBM can be masked by increasing adiposity (5,6).

The clinical significance of body weight in breast cancer is well documented, with obesity at diagnosis predicting poorer disease prognosis and weight change (either gain or loss) during treatment associated with cancer recurrence and reduced survival (4,7–10). Given that body weight is a poor indicator of body composition in cancer patients (11), it has been proposed that measures of body composition, particularly LBM, may be of greater clinical relevance (5,12,13). In the general

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population and in various other chronic disease states, loss of LBM is associated with physical disability and reduced survival (6,14,15). A recent meta-analysis reported a 36% increase in mortality for each SD decrease in LBM, across a variety of health conditions (15). In cancer patients, decreased LBM is an independent predictor of mortality (12,14–16), and in breast cancer specifically, it is associated with the development of comorbid cardiometabolic conditions, shorter time to tumor progression, and reduced survival (4,6). Reduced LBM in breast cancer is also associated with an increased likelihood of dose-limiting toxicity during chemotherapy (16). Given these links, there is a growing suggestion that LBM should be a consideration in breast cancer treatment, including for determining chemotherapy dosage (12,14,16,17). Consequently, interventions that can preserve or increase LBM in women with breast cancer are important as they may influence both treatment tolerance and prognosis.

Exercise training, particularly resistance training, is widely recognized as a safe and effective intervention for increasing LBM in healthy adults across the life span (18,19), but its efficacy in women with breast cancer is less established. The clinical importance of including exercise training as part of routine cancer care is becoming increasingly recognized throughout the medical community (20–23). In breast cancer specifically, a wide range of physiological, psychological, and functional benefits of exercise training has been demonstrated (24–26). Given the suggested importance of LBM for both breast cancer treatment and prognosis, a detailed understanding of the effects of exercise training on LBM in this specific population is warranted. Therefore, the aim of this systematic review and meta-analysis was to provide a comprehensive overview of the effect of structured exercise training interventions on LBM in women with breast cancer.

METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (27).

Search strategy. An electronic database search was conducted to identify peer-reviewed articles published from January 1980 to the end of November 2020. The databases searched were Cochrane Library, PubMed, EMBASE, PEDro, Academic Search Complete, CINAHL, Health Source (Nursing/Academic Edition), and SPORTDiscus. The exact search strategy was tailored to each database, but all included a combination of relevant search terms relating to (i) breast cancer, (ii) exercise, and (iii) LBM. The complete search strategy is provided in Table S1 (see Supplemental Digital Content 1, Details of search strategy used for electronic database searches, http://links.lww.com/MSS/C435).

Electronic database search results were screened using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Titles and abstracts of electronic search results were screened for relevance against a predefined checklist (see Table S2, Supplementary Digital Content 2, Checklist for title and abstract screening of electronic database search results, http://links.lww.com/MSS/C436), and full-text articles of potentially relevant search results were obtained for more detailed eligibility screening.

Inclusion and exclusion criteria. The inclusion criteria for this systematic review followed the Population, Intervention, Comparator, Outcomes, Study design framework (28). Studies were considered eligible for inclusion if 1) participants included women who were undergoing or had completed active treatment for breast cancer, 2) the intervention involved structured whole-body aerobic and/or resistance exercise training, 3) reported study outcomes included imaging-derived measures of LBM (acceptable measures included lean mass obtained via dual-energy x-ray absorptiometry as well as total LBM estimates derived from computed tomography or magnetic resonance imaging), and 4) the study design was a randomized controlled trial (RCT).

Studies were excluded if 1) they were not published in English in a peer-reviewed journal; 2) they were not full-text articles reporting results of original research (e.g., reviews, letters to the editor, protocol papers, or conference abstracts); 3) study participants included mixed cancer populations, where data from women with breast cancer could not be isolated; 4) interventions involved exercise training in combination with pharmacotherapy or specific dietary manipulation, where the effects of the exercise training intervention could not be isolated; and 5) exercise training interventions were restricted to only one body region (e.g., shoulder mobility exercises).

Data extraction and risk of bias assessment. Data extraction and risk of bias assessment was completed independently by three individuals (J.R.G., J.DV., and Scott Tagliaferri), with any discrepancies resolved by discussion. Information extracted from each study included participant characteristics (age, study inclusion criteria, and treatment information), intervention details (duration, exercise type, intensity, frequency, volume, and progression), and LBM outcomes. Where insufficient or inappropriate data were available from the published manuscript, the corresponding author was contacted to request either individual participant LBM data or the absolute net difference in change in LBM between groups, with 95% confidence interval (CI).

Studies were assessed for risk of bias using the Physiotherapy Evidence Database (PEDro) scale, which is a valid measure of the risk of bias in clinical trials (29). The PEDro scale contains 11 items that require studies to be assessed for internal (item 1) and external (items 2–9) validity, as well as for adequate statistical reporting (items 10–11). Where available, completed risk of bias assessments for included studies were obtained from the PEDro database (https://www.pedro.org.au/).

Data analysis. Absolute net differences for the change in LBM between the intervention and the control groups were used to combine study effect estimates in this meta-analysis. If these values were not available from the original article or not provided by the author upon request, these were calculated using baseline and follow-up values. SD values for these change values were imputed using a correlation coefficient value, calculated using baseline, follow-up, and change values, where presented in other included studies (30). The calculated coefficient used was 0.9, and sensitivity analyses were completed using coefficients of 0.5 and 0.7 to ensure the overall results of the analysis were robust to the use of imputed correlation coefficients (30). SE for the net difference in change between groups was calculated using the imputed SD of change within each group and the sample size of each group. CI for the net difference in change between groups was then calculated using the imputed SE and a corresponding value from a *t* distribution (31). For studies that provided individual participant data for LBM upon request, absolute net differences and 95% CI between groups were calculated using ANOVA, adjusting for multiple comparisons using Tukey's HSD when required.

Once appropriate data were obtained or calculated, we conducted a random-effects meta-analysis, which was chosen as the effect of the interventions on LBM in the included studies may vary because of differences in the study samples and interventions used (31). In studies with more than one intervention group, each intervention group was compared separately within the meta-analysis, but with the control group participant number divided equally between the comparisons. Statistical heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% chosen to indicate low, moderate, and high heterogeneity, respectively (32). Publication bias was evaluated by visual inspection of the funnel plot showing net differences of each study against their corresponding SE and by Egger's regression asymmetry test (33).

To investigate sources of heterogeneity, we performed subgroup analyses based on a list of predefined variables that we anticipated may influence the effect of exercise training on LBM. These were exercise type, menopausal status, whether the intervention was conducted during or posttreatment, and whether the intervention included resistance training. Sensitivity analysis was completed by rerunning the analysis with studies that scored <6 on the PEDro risk of bias assessment omitted. All analyses were conducted using STATA software version 15 (Stata Corp., College Station, TX). A P value of <0.05 was considered statistically significant.

RESULTS

The electronic database search yielded 6489 results after the removal of duplicates. After title and abstract screening, 1124 full-text articles were obtained, with a total of 17 studies meeting our inclusion criteria (see Table S3, Supplementary Digital Content 3, Characteristics of the included studies, http://links.lww.com/MSS/C437). All 17 studies reported estimates of total LBM derived from dual-energy x-ray absorptiometry imaging. Corresponding authors for 12 studies were contacted to request more information, with additional data obtained for eight studies. Overall, 17 studies enrolling a total of 1743 breast cancer survivors were included in our final analysis (34–50). Figure 1 displays a flow diagram of study selection.

Results from the PEDro risk of bias assessment are presented in Table 1. All studies met criteria for reporting study inclusion criteria, random allocation, group similarity at baseline, and point and variability statistics. No study reported participant or therapist blinding to intervention, although this is difficult to achieve in exercise intervention studies. There was variability between studies across all other risk of bias criteria.

Study characteristics. Study sample sizes ranged from 20 to 573 participants, with the mean age of participants in each study ranging from 41.8 to 64.9 yr. Eight studies (34,35,37,38,40,43,46,47) enrolled only postmenopausal women, and one study included only women who were premenopausal at study commencement (48). Five studies (39,44,45,49,50) included both pre- and postmenopausal women, and the remaining three studies (36,41,42) did not report menopausal status of participants. Four studies (42,45,48,49) were conducted during adjuvant chemotherapy, with one of these studies (45) continuing for another four to 6 months postchemotherapy. The remaining 13 studies (34–41,43,44,46,47,50) conducted exercise interventions after completion of treatment with chemotherapy and/or radiation therapy, with ongoing endocrine therapy permitted. Exercise intervention duration ranged from 2 to 12 months.

Twelve studies (34,35,37–41,43,44,46,47,50) compared a control group with a single exercise intervention, whereas five studies (36,42,45,48,49) had multiple intervention arms. Three of these studies (36,42,49) compared different exercise interventions against a control group; however, DeNysschen et al. (45) used the same exercise intervention introduced at different time points (either at the commencement of chemotherapy, or once chemotherapy had been completed). Demark-Wahnefried et al. (48) compared a calcium supplementation (attention control) group with a combined calcium and exercise intervention, as well as to the same calcium and exercise intervention with additional dietary modification. As this third intervention arm is not an exercise-only intervention, we did not include these data in our analysis. Schmitz et al. (50) compared a 12-month exercise intervention group with a wait-list control group that received no intervention from baseline to 6 months, and then the exercise intervention from 6 to 12 months. For our meta-analysis, we included only the baseline to 6-month data from this study to compare the intervention with control.

Exercise intervention characteristics. Six studies (34,35,37–39,49) provided entirely supervised exercise training, whereas three studies (36,38,48) had completely unsupervised interventions. Møller et al. (42) had one intervention arm that completed supervised group exercise in a hospital setting, and another that completed an unsupervised walking program at home. The remaining seven studies (40,41,43,44,46,47,50) used a combination of supervised and unsupervised exercise training within their interventions.

Three studies (36,45,47) used solely aerobic training in their exercise interventions, with another (44) involving aerobic training combined with impact-loading exercise. Four studies (35,37,41,50) used only resistance training interventions, whereas another three studies (34,43,46) combined resistance training with impact-loading exercise. Courneya et al. (49) had separate aerobic training–only and resistance training–only intervention arms, whereas another four studies (38–40,48) used

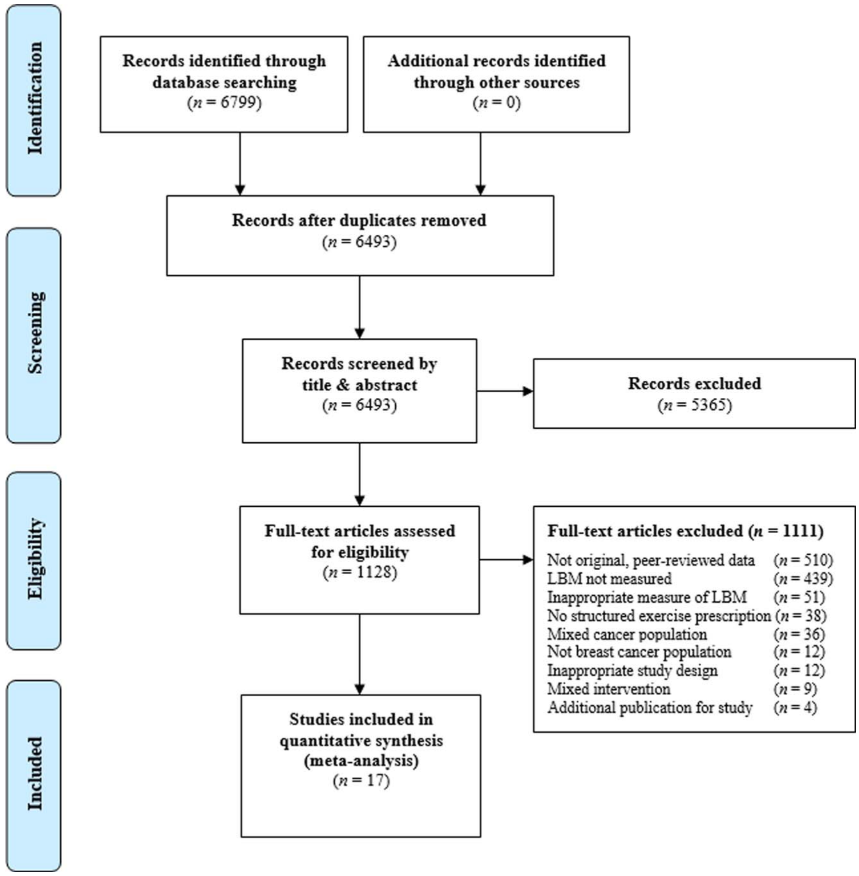

FIGURE 1—Flow diagram of study selection process.

a combined aerobic and resistance exercise intervention. Møller et al. (42) had one aerobic training only intervention arm and one combined aerobic and resistance training arm.

In studies that involved aerobic training (36,38–40,42,44,45,47–49), training frequency ranged from two to five sessions per week, with aerobic exercise volume ranging from 15 to 60 min per session, or a total of 150 to 300 min·wk^{-1}. Aerobic training intensity ranged from 50% to 80% of maximum heart rate, 60% to 80% of maximum oxygen consumption, 40% to 80% of heart rate reserve, or an RPE of 12 to 14 on a 20-point scale. In studies that involved resistance training (34,35,37–43,46,48–50), training frequency ranged from one to three sessions per week, with resistance training volume of four to nine exercises, and one to three sets of 6 to 20 repetitions per exercise. Resistance training intensity ranged from 55% to 80% of one-repetition maximum, or 6- to 14-repetition maximum loads. Artese et al. (34) incorporated resistance and impact exercises within 45-min circuit training sessions, in which resistance exercises were performed in sets of 16 repetitions, and impact exercises were performed in sets of 1 min. Fourteen studies (34,35,37–44,46,47,49,50) provided specific details of exercise progression across the duration of the intervention. Ten studies (34,35,37,39,41,42,46,48–50) reported on adverse events occurring as a result of participation in the exercise interventions. Schmitz et al. (50) reported that one participant sustained a wrist injury resulting in discontinued participation; however, no other studies reported any serious adverse events because of exercise participation.

TABLE 1. PEDro scale risk of bias assessment for included studies.

	PEDro Criteria											
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Total (0–10)**
Artese et al. (34)	N	Y	N	Y	N	N	N	N	N	Y	Y	5
Santagnello et al. (35)	Y	Y	N	Y	N	N	N	N	N	Y	Y	4
McNeil et al. (36)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Santos et al. (37)	N	Y	N	Y	N	N	N	Y	N	Y	Y	5
de Paulo et al. (38)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Dieli-Conwright et al. (39)	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Thomas et al. (40)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Brown and Schmitz (41)	Y	Y	N	Y	N	N	Y	N	Y	Y	Y	6
Møller et al. (42)	Y	Y	N	Y	N	N	Y	N	Y	N	Y	5
Winters-Stone et al. (43)	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	7
Saarto et al. (44)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
DeNysschen et al. (45)	Y	Y	N	Y	N	N	Y	Y	N	N	Y	5
Winters-Stone et al. (46)	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	7
Irwin et al. (47)	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Demark-Wahnefried et al. (48)	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5
Courneya et al. (49)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Schmitz et al. (50)	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	6

1, Specified eligibility criteria; 2, random allocation; 3, allocation concealment; 4, group similarity at baseline; 5, blinding of participants; 6, blinding of therapists; 7, blinding of assessors; 8, outcome measures obtained from at least 85% of participants; 9, intention-to-treat analysis; 10, between-group statistical comparisons; 11, both point and variability measures provided. Y, criterion clearly met; N, criterion not clearly met.

Pooled effects for LBM. Sufficient data for the meta-analysis were available directly from five published studies (35,36,39,44,49), and additional data were provided upon

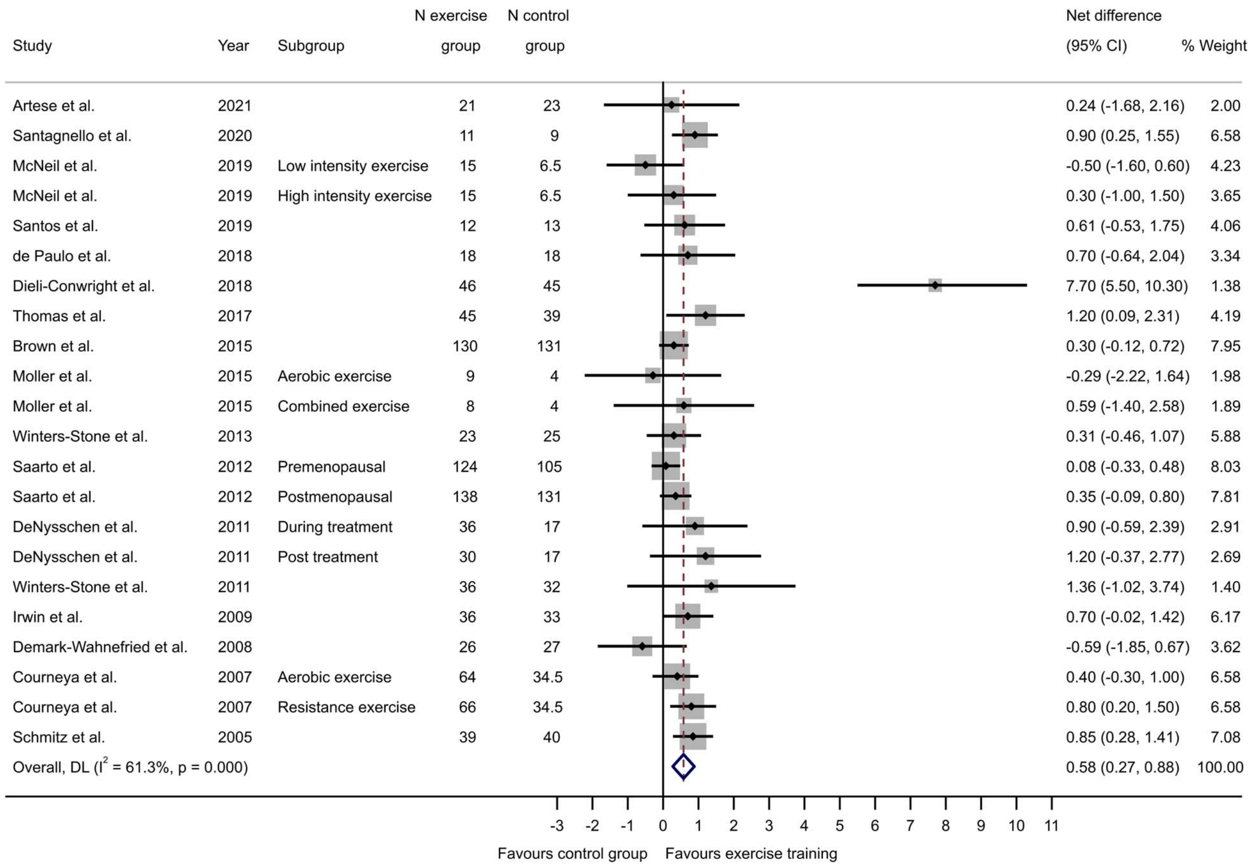

FIGURE 2—Forest plot of absolute net differences for the change in total LBM between exercise training and control groups.

request for eight studies (40–43,46–48,50). Net differences and CI were imputed from published data for four studies (34,37,38,45). The overall results did not change with either inclusion or exclusion of these studies, nor using different correlation coefficients to impute missing data, so these studies were included in the primary analysis.

Primary analysis. The overall pooled analysis demonstrated a significant absolute net difference for the change in LBM favoring exercise training versus control (0.58 kg, 95% CI = 0.27 to 0.88, P < 0.001) (Fig. 2). There was significant moderate heterogeneity for the effect of exercise training on LBM (I^2 = 61.3%, 95% CI = 38.4% to 75.6%, P < 0.001).

Regarding publication bias, the examination of the funnel plot of net differences by SE (Fig. 3) suggests a fairly even distribution of studies, aside from one outlier. Egger's regression asymmetry test approached significance (P = 0.071).

Sensitivity analysis. Intervention effects remained consistent with the overall analysis when sensitivity analysis excluding studies at greater risk of bias (PEDro score <6) was performed. We also repeated the analysis excluding one study (39) that was a clear outlier in favor of the exercise intervention. Effect sizes were consistently smaller, and CI values were narrower when this study was excluded (for meta-analysis forest plot with outlier excluded, see Fig. S1, Supplementary Digital Content 4, http://links.lww.com/MSS/C438, and for overall and subgroup analysis results with outlier excluded, see Table S4, Supplementary Digital Content 5, http://links.lww.com/MSS/C439); however, the overall results were similar. Heterogeneity was reduced to 0.0% (P = 0.509) with exclusion of this outlier, and there was no suggestion of publication bias based on the funnel plot or Egger's regression asymmetry test (P = 0.281) (for publication bias funnel plot with outlier excluded, see Fig. S2, Supplementary Digital Content 6, http://links.lww.com/MSS/C440).

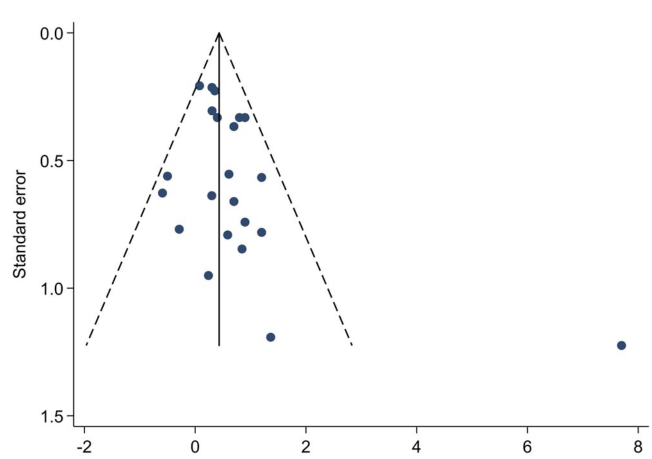

FIGURE 3—Funnel plot of net differences by SE.

Subgroup analysis. The results of the subgroup analyses are presented in Table 2. Separately, resistance training alone (0.59 kg, 95% CI = 0.34 to 0.84, $P < 0.001$) and aerobic training alone (0.29 kg, 95% CI = 0.05 to 0.52, $P = 0.017$) had a positive effect on LBM compared with control. Combined aerobic and resistance training demonstrated a large effect size (1.73 kg, 95% CI = −0.30 to 3.76, $P = 0.094$); however, there was considerable variability and this effect was not significant.

Where exercise interventions included resistance training (either alone or as part of a combined intervention), the magnitude of the effect was larger than for interventions that did not include any resistance training (0.83 kg, 95% CI = 0.32 to 1.34, $P = 0.001$ vs 0.29 kg, 95% CI = 0.05 to 0.52, $P = 0.017$, respectively). Additionally, exercise training had a significant positive effect on LBM whether implemented during treatment (0.47 kg, 95% CI = 0.07 to 0.86, $P = 0.022$) or posttreatment (0.66 kg, 95% CI = 0.28 to 1.04, $P = 0.001$).

Exercise training had a positive effect on LBM in postmenopausal women (0.58 kg, 95% CI = 0.31 to 0.85, $P < 0.001$) and in studies enrolling both pre- and postmenopausal women (1.46 kg, 95% CI = 0.48 to 2.45, $P = 0.004$), but not in premenopausal women alone (0.02 kg, 95% CI = −0.37 to 0.40, $P = 0.935$) or in studies that did not report menopausal status (0.21 kg, 95% CI = −0.16 to 0.57, $P = 0.267$).

Similar positive effects of exercise training on LBM were observed among studies with lower risk of bias (PEDro score ≥6) and higher risk of bias (PEDro score <6) (0.62 kg, 95% CI = 0.24 to 1.01, $P = 0.001$ vs 0.60, 95% CI = 0.17 to 1.03, $P = 0.006$, respectively).

DISCUSSION

The main finding of this systematic review and meta-analysis is that exercise training had a positive effect on LBM compared with usual care in women with breast cancer, suggesting that exercise training can be used to combat the loss of LBM in this population. Subgroup analysis demonstrated that both resistance training interventions and aerobic training interventions had beneficial effects, but the magnitude of the effect was larger when exercise interventions included resistance training (0.83 vs 0.29 kg). This is consistent with two previous meta-analyses in mixed cancer populations that reported a 0.86- to 1.07-kg benefit of resistance training on LBM compared with usual care (51,52).

An unexpected finding of this meta-analysis was the lack of statistically significant effect of combined aerobic and resistance training on LBM compared with usual care. Although it is possible that combining resistance and aerobic exercise may somehow reduce the beneficial effects of each, caution must be taken when interpreting these results due to the particularly wide CI values observed in this subgroup analysis. Heterogeneity in exercise prescription among these studies may explain some of this variability, particularly the difference in resistance training volume and/or intensity. It is also worth noting that one study (48) included in this subgroup analysis reported an increase in LBM in the control group but a reduction in LBM in the exercise group, which is inconsistent with the pattern observed in all other included studies. Further investigation into the effects of combined aerobic and resistance exercise training on LBM is warranted, particularly as current exercise guidelines for cancer patients recommend multimodal exercise programs including both aerobic and resistance training (20–22).

Regarding the timing of exercise training in relation to cancer treatment, our analysis shows that exercise training has statistically significant beneficial effects on LBM both during and posttreatment compared with usual care. This is valuable information for clinicians, as it demonstrates that exercise training can be used early, with the intention of preserving or increasing LBM during primary treatment. This may be particularly valuable for patients with low physical capacity before commencing treatment, where the consequences of further LBM loss may be of greater concern. Additionally, with growing evidence linking LBM with treatment toxicity, the ability to preserve LBM during treatment may have the potential to improve treatment tolerance and/or completion rates (14,16,53). However, where patients are unable or unwilling to engage in

TABLE 2. Summary of primary and subgroup analyses.

		LBM (kg)		
Category	Subgroup	n^a	Absolute Net Difference for the Change (95% CI)	*P*
Primary analysis				
Overall		22	0.58 (0.27 to 0.88)	<0.001
Subgroup analysis				
Exercise type	Resistance	8	0.59 (0.34 to 0.84)	<0.001
	Aerobic	9	0.29 (0.05 to 0.52)	0.017
	Combined	5	1.73 (−0.30 to 3.76)	0.094
Included resistance training	Yes	13	0.83 (0.32 to 1.34)	0.001
	No	9	0.29 (0.05 to 0.52)	0.017
Timing of exercise intervention	During treatment	6	0.47 (0.07 to 0.86)	0.022
	Posttreatment	16	0.66 (0.28 to 1.04)	0.001
Menopausal status	Premenopausal	2	0.02 (−0.37 to 0.40)	0.935
	Postmenopausal	9	0.58 (0.31 to 0.85)	<0.001
	Mixed	6	1.46 (0.48 to 2.45)	0.004
	Unknown	5	0.21 (−0.16 to 0.57)	0.267
PEDro	<6	8	0.60 (0.17 to 1.03)	0.006
	≥6	14	0.62 (0.24 to 1.01)	0.001

[a]Subgroups and multiple comparisons from a single study included separately.
n, number of studies.

exercise training during treatment, clinicians can still recommend exercise training as an efficacious intervention for LBM once primary treatment has been completed.

The relationship between menopausal status and exercise training effectiveness on LBM was less clear. Our analyses showed that exercise training interventions had a positive effect on LBM in postmenopausal women as well as in study cohorts with mixed menopausal status. No significant effect was observed in premenopausal women, although only two studies (44,48) were included in this subgroup analysis. As the largest declines in LBM during breast cancer treatment have been reported to occur in premenopausal women (5,6), it may be that higher-intensity and/or volume exercise training is necessary to attenuate the loss of LBM in this population. Additional well-designed exercise trials are warranted to explore this further.

It is worth noting that 10 of the studies (36,39–42,44,45,47–49) included in this systematic review and meta-analysis only assessed LBM as a secondary outcome measure. As such, most of the exercise interventions were not designed specifically for increasing LBM. Our analyses demonstrate that exercise training overall had a beneficial effect on LBM compared with usual care, even when this was not the specific focus of the intervention. Greater effects may be possible when exercises interventions are designed with a focus on resistance training in line with specific exercise prescription guidelines for muscle hypertrophy (54); however, this is yet to be thoroughly examined in women with breast cancer.

The key strengths of this systematic review and meta-analysis are that it was conducted in accordance with the PRISMA guidelines (28) and that it included only RCT that used robust, image-derived measurement of total LBM. However, there are also some limitations. First, imputations were made to include data for four studies in the meta-analysis. Despite this, the results were unchanged when these studies were excluded or if more conservative values were imputed. Additionally, there was substantial heterogeneity in the exercise interventions prescribed, limiting the ability to identify the most effective exercise prescription variables for increasing LBM in breast cancer patients and, therefore, to provide evidence-based exercise prescription guidelines.

CONCLUSIONS

In summary, this meta-analysis of 17 RCT indicates that exercise training has a beneficial effect on LBM compared with usual care in women with breast cancer. These effects were observed both during and after treatment, and the largest effects were observed when resistance training was included as part of the exercise intervention. Given that loss of LBM is common in this population, clinicians should encourage all patients to participate in regular exercise training and consider referring to an exercise specialist for assistance with appropriate exercise prescription.

This systematic review and meta-analysis also highlights some areas requiring further research. First, additional RCT examining exercise interventions with LBM as a primary outcome measure are needed. These should seek to determine the most effective exercise prescription variables for maintaining or increasing LBM in women with breast cancer, as well as with differing treatment regimens. Second, a more thorough understanding of the influence of menopausal status on the efficacy of exercise training in women with breast cancer is needed. Finally, further research is required to determine whether the beneficial effects of exercise training on LBM lead to improved clinical outcomes such as reduced treatment toxicity, improved treatment completion rates, and improved survival.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
2. American Cancer Society. *Cancer Facts & Figures 2018*. Atlanta: American Cancer Society; 2018.
3. Vance V, Mourtzakis M, McCargar L, Hanning R. Weight gain in breast cancer survivors: prevalence, pattern and health consequences. *Obes Rev*. 2011;12(4):282–94.
4. Gadea E, Thivat E, Planchat E, Morio B, Durando X. Importance of metabolic changes induced by chemotherapy on prognosis of early-stage breast cancer patients: a review of potential mechanisms. *Obes Rev*. 2012;13(4):368–80.
5. Sheean PM, Hoskins K, Stolley M. Body composition changes in females treated for breast cancer: a review of the evidence. *Breast Cancer Res Treat*. 2012;135(3):663–80.
6. McDonald C, Bauer JD, Capra S. Body composition and breast cancer—the role of lean body mass. *Cancer Forum*. 2011;35(2):102–6.
7. Rodriguez San Felipe MJ, Aguilar Martinez A, Manuel-y-Keenoy B. Influence of body weight on the prognosis of breast cancer survivors; nutritional approach after diagnosis. *Nutr Hosp*. 2013;28(6):1829–41.
8. Caan BJ, Kwan ML, Hartzell G, et al. Pre-diagnosis body mass index, post-diagnosis weight change, and prognosis among women with early stage breast cancer. *Cancer Causes Control*. 2008;19(10):1319–28.
9. Bao PP, Cai H, Peng P, et al. Body mass index and weight change in relation to triple-negative breast cancer survival. *Cancer Causes Control*. 2016;27(2):229–36.
10. Playdon MC, Bracken MB, Sanft TB, Ligibel JA, Harrigan M, Irwin ML. Weight gain after breast cancer diagnosis and all-cause mortality: systematic review and meta-analysis. *J Natl Cancer Inst*. 2015;107(12):djv275.

11. Di Sebastiano KM, Mourtzakis M. A critical evaluation of body composition modalities used to assess adipose and skeletal muscle tissue in cancer. *Appl Physiol Nutr Metab*. 2012;37(5):811–21.
12. Yip C, Dinkel C, Mahajan A, Siddique M, Cook GJR, Goh V. Imaging body composition in cancer patients: visceral obesity, sarcopenia and sarcopenic obesity may impact on clinical outcome. *Insights Imaging*. 2015;6(4):489–97.
13. James FR, Wootton S, Jackson A, Wiseman M, Copson ER, Cutress RI. Obesity in breast cancer—what is the risk factor? *Eur J Cancer*. 2015;51(6):705–20.
14. Tsai S. Importance of lean body mass in the oncologic patient. *Nutr Clin Pract*. 2012;27(5):593–8.
15. Koon-Yee Lee G, Chun-Ming Au P, Hoi-Yee Li G, et al. Sarcopenia and mortality in different clinical conditions: a meta-analysis. *Osteoporos Sarcopenia*. 2021;7(1 Suppl):S19–27.
16. Prado CM, Antoun S, Sawyer MB, Baracos VE. Two faces of drug therapy in cancer: drug-related lean tissue loss and its adverse consequences to survival and toxicity. *Curr Opin Clin Nutr Metab Care*. 2011;14(3):250–4.
17. Prado CM. Body composition in chemotherapy: the promising role of CT scans. *Curr Opin Clin Nutr Metab Care*. 2013;16(5):525–33.
18. Peterson MD, Sen A, Gordon PM. Influence of resistance exercise on lean body mass in aging adults: a meta-analysis. *Med Sci Sports Exerc*. 2011;43(2):249–58.
19. Liberman K, Forti LN, Beyer I, Bautmans I. The effects of exercise on muscle strength, body composition, physical functioning and the inflammatory profile of older adults: a systematic review. *Curr Opin Clin Nutr Metab Care*. 2017;20(1):30–53.
20. Cormie P, Atkinson M, Bucci L, et al. Clinical Oncology Society of Australia position statement on exercise in cancer care. *Med J Aust*. 2018;209(4):184–7.
21. Hayes SC, Newton RU, Spence RR, Galvão DA. The Exercise and Sports Science Australia position statement: exercise medicine in cancer management. *J Sci Med Sport*. 2019;22(11):1175–99.
22. Campbell KL, Winters-Stone KM, Wiskemann J, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. *Med Sci Sports Exerc*. 2019;51(11):2375–90.
23. Patel AV, Friedenreich CM, Moore SC, et al. American College of Sports Medicine roundtable report on physical activity, sedentary behavior, and cancer prevention and control. *Med Sci Sports Exerc*. 2019;51(11):2391–402.
24. Kirkham AA, Bland KA, Sayyari S, Campbell KL, Davis MK. Clinically relevant physical benefits of exercise interventions in breast cancer survivors. *Curr Oncol Rep*. 2016;18(2):12.
25. Battaglini CL, Mills RC, Phillips BL, et al. Twenty-five years of research on the effects of exercise training in breast cancer survivors: a systematic review of the literature. *World J Clin Oncol*. 2014;5(2):177–90.
26. Zhu G, Zhang X, Wang Y, Xiong H, Zhao Y, Sun F. Effects of exercise intervention in breast cancer survivors: a meta-analysis of 33 randomized controlled trails. *Onco Targets Ther*. 2016;9:2153–68.
27. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1.
28. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009;151(4):W65–94.
29. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother*. 2009;55(2):129–33.
30. Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol*. 1992;45(7):769–73.
31. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons; 2011.
32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J*. 2003;327(7414):557–60.
33. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–34.
34. Artese AL, Hunt RL, Ormsbee MJ, Kim JS, Arjmandi BH, Panton LB. Effect of functional impact training on body composition, bone mineral density, and strength in breast cancer survivors. *Med Sci Sports Exerc*. 2021;53(1):90–101.
35. Santagnello SB, Martins FM, de Oliveira Junior GN, et al. Improvements in muscle strength, power, and size and self-reported fatigue as mediators of the effect of resistance exercise on physical performance breast cancer survivor women: a randomized controlled trial. *Support Care Cancer*. 2020;28(12):6075–84.
36. McNeil J, Brenner DR, Stone CR, et al. Activity tracker to prescribe various exercise intensities in breast cancer survivors. *Med Sci Sports Exerc*. 2019;51(5):930–40.
37. Santos WDND, Vieira A, de Lira CAB, et al. Once a week resistance training improves muscular strength in breast cancer survivors: a randomized controlled trial. *Integr Cancer Ther*. 2019;18:1534735419879748.
38. de Paulo TRS, Winters-Stone KM, Viezel J, et al. Effects of resistance plus aerobic training on body composition and metabolic markers in older breast cancer survivors undergoing aromatase inhibitor therapy. *Exp Gerontol*. 2018;111:210–7.
39. Dieli-Conwright CM, Courneya KS, Demark-Wahnefried W, et al. Effects of aerobic and resistance exercise on metabolic syndrome, sarcopenic obesity, and circulating biomarkers in overweight or obese survivors of breast cancer: a randomized controlled trial. *J Clin Oncol*. 2018;36(9):875–83.
40. Thomas GA, Cartmel B, Harrigan M, et al. The effect of exercise on body composition and bone mineral density in breast cancer survivors taking aromatase inhibitors. *Obesity (Silver Spring)*. 2017;25(2):346–51.
41. Brown JC, Schmitz KH. Weight lifting and physical function among survivors of breast cancer: a post hoc analysis of a randomized controlled trial. *J Clin Oncol*. 2015;33(19):2184–9.
42. Møller T, Lillelund C, Andersen C, et al. The challenge of preserving cardiorespiratory fitness in physically inactive patients with colon or breast cancer during adjuvant chemotherapy: a randomised feasibility study. *BMJ Open Sport Exerc Med*. 2015;1(1):e000021.
43. Winters-Stone KM, Dobek J, Nail LM, et al. Impact + resistance training improves bone health and body composition in prematurely menopausal breast cancer survivors: a randomized controlled trial. *Osteoporos Int*. 2013;24(5):1637–46.
44. Saarto T, Sievänen H, Kellokumpu-Lehtinen P, et al. Effect of supervised and home exercise training on bone mineral density among breast cancer patients. A 12-month randomised controlled trial. *Osteoporos Int*. 2012;23(5):1601–12.
45. DeNysschen CA, Brown JK, Cho MH, Dodd MJ. Nutritional symptom and body composition outcomes of aerobic exercise in women with breast cancer. *Clin Nurs Res*. 2011;20(1):29–46.
46. Winters-Stone KM, Dobek J, Nail L, et al. Strength training stops bone loss and builds muscle in postmenopausal breast cancer survivors: a randomized, controlled trial. *Breast Cancer Res Treat*. 2011;127(2):447–56.
47. Irwin ML, Alvarez-Reeves M, Cadmus L, et al. Exercise improves body fat, lean mass, and bone mass in breast cancer survivors. *Obesity (Silver Spring)*. 2009;17(8):1534–41.
48. Demark-Wahnefried W, Case LD, Blackwell K, et al. Results of a diet/exercise feasibility trial to prevent adverse body composition change in breast cancer patients on adjuvant chemotherapy. *Clin Breast Cancer*. 2008;8(1):70–9.
49. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol*. 2007;25(28):4396–404.

50. Schmitz KH, Ahmed RL, Hannan PJ, Yee D. Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. *Cancer Epidemiol Biomarkers Prev*. 2005;14(7):1672–80.
51. Padilha CS, Marinello PC, Galvao DA, et al. Evaluation of resistance training to improve muscular strength and body composition in cancer patients undergoing neoadjuvant and adjuvant therapy: a meta-analysis. *J Cancer Surviv*. 2017;11(3):339–49.
52. Strasser B, Steindorf K, Wiskemann J, Ulrich CM. Impact of resistance training in cancer survivors: a meta-analysis. *Med Sci Sports Exerc*. 2013;45(11):2080–90.
53. Hopkins JJ, Sawyer MB. A review of body composition and pharmacokinetics in oncology. *Expert Rev Clin Pharmacol*. 2017;10(9):947–56.
54. Ratamess N, Alvar BA, Evetoch TK, et al. American College of Sports Medicine Position Stand: progression models in resistance training for healthy adults. *Med Sci Sports Exerc*. 2009;41(3):687–708.