Heavy Resistance Training in Breast Cancer Patients Undergoing Adjuvant Therapy

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ABSTRACT

CEŠEIKO, R., S. N. THOMSEN, S. TOMSONE, J. EGLĪTIS, A. VĒTRA, A. SREBNIJS, M. TIMOFEJEVS, E. PURMALIS, and E. WANG. Heavy Resistance Training in Breast Cancer Patients Undergoing Adjuvant Therapy. *Med. Sci. Sports Exerc.*, Vol. 52, No. 6, pp. 1239–1247, 2020. **Background and Purpose:** Adjuvant breast cancer therapy may reduce maximal muscle strength, muscle mass, and functional performance. Although maximal strength training (MST) has the potential to counteract this debilitating outcome and is shown to be superior to low- and moderate-intensity strength training, it is unknown if it can elicit effective adaptations in patients suffering treatment-induced adverse side effects. **Methods:** Fifty-five newly diagnosed stage I to III breast cancer patients (49 ± 7 yr) scheduled for adjuvant therapy were randomized to MST or a control group. The MST group performed 4 × 4 repetitions of dynamic leg press at approximately 90% of one-repetition maximum (1RM) twice a week for 12 wk. **Results:** In the MST group, improvements in 1RM (20% ± 8%; $P < 0.001$) were accompanied by improved walking economy (9% ± 8%) and increased time to exhaustion during incremental walking (9% ± 8%; both $P < 0.01$). Moreover, the MST group increased 6-min walking distance (6MWD; 10% ± 7%), and chair rising (30% ± 20%) and stair climbing performance (12% ± 7%; all $P < 0.001$). All MST-induced improvements were different from the control group ($P < 0.01$) which reduced their 1RM (9% ± 5%), walking economy (4% ± 4%), time to exhaustion (10% ± 8%), 6MWD (5% ± 5%), chair rising performance (12% ± 12%), and stair climbing performance (6% ± 8%; all $P < 0.01$). Finally, although MST maintained estimated quadriceps femoris muscle mass, a decrease was observed in the control group (7% ± 10%; $P < 0.001$). The change in 1RM correlated with the change in walking economy ($r = 0.754$), time to exhaustion ($r = 0.793$), 6MWD ($r = 0.807$), chair rising performance ($r = 0.808$), and stair climbing performance ($r = 0.754$; all $P < 0.001$). **Conclusions:** Lower-extremity MST effectively increases lower-extremity maximal muscle strength in breast cancer patients undergoing adjuvant therapy and results in improved work economy, functional performance, and maintenance of muscle mass. These results advocate that MST should be considered in breast cancer treatment. **Key Words:** EXERCISE ONCOLOGY, CHEMOTHERAPY, STRENGTH TRAINING, WALKING ECONOMY, MUSCLE MASS, NEUROMUSCULAR FUNCTION

Breast cancer is the most frequently diagnosed type of cancer among women, with more than 2 million new cases in 2018 worldwide (1). In combination with surgical resection, adjuvant therapy constitutes the mainstay in the management of breast cancer and is considered a key contributor to the steadily increasing survival rates. Yet, its widespread application comes at the expense of numerous side-effects that adversely affect patients' health and functional performance, and counteracting strategies are requested to advance current breast cancer treatment.

Breast cancer patients are shown to display lower levels of lower-extremity maximal muscle strength after primary adjuvant treatment compared with healthy age-matched individuals (2). Although the cause of this reduction is uncertain, it may, in turn, lead to the impaired walking economy (3,4) and impede the ability to perform force-demanding everyday activities such as stair climbing and chair rising (5). Further, adjuvant breast cancer treatment has been documented to induce skeletal muscle atrophy (6), potentially affecting tolerability to chemotherapy (7). The reduction in muscle strength observed after

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adjuvant treatment is likely attributable to direct effects of antineoplastic therapeutic agents (e.g., anthracyclines) on skeletal muscle fibers (8) and augmented levels of physical inactivity (9).

Strength training has been suggested as a strategy to counteract cancer treatment-induced reductions in maximal muscle strength, muscle mass, and functional performance (10). Importantly, loading intensity is established as a key determinant of neuromuscular adaptions to strength training, with higher intensity (>85% of one-repetition maximum [1RM]) eliciting superior improvements in muscle strength compared with lower intensity (<75% of 1RM) (11). In accordance with this concept, maximal strength training (MST), using three to five repetitions of high loads (85%–90% of 1RM) and maximal indented contraction velocity in the concentric phase, has been shown to induce large improvements in maximal muscle strength and walking economy, and have the potential to improve functional performance (4). Notably, the feasibility and safety of MST extend across a variety of populations, including elderly (4,12), chronic obstructive pulmonary disease (3), coronary artery disease (13), peripheral arterial disease (14), and osteoporosis (15) patients. We recently documented that MST also has the potential to improve breast cancer patients' quality of life when they undergo primary adjuvant therapy (16). Although MST primarily is tailored to target the neural system, Wang et al. (4) recently documented that MST also induces muscle fiber hypertrophy, suggesting that MST may counteract treatment-mediated reductions in muscle mass.

Despite the well-documented neuromuscular and functional adaptations resulting from strength training, very few studies have, somewhat surprisingly, investigated the effects of strength training in the initial critical phase of breast cancer treatment. Furthermore, the few previous studies that have applied strength training also appear to have applied low to moderate loading intensities (<75% of 1RM) (17–19). However, recognizing the adverse early phase side effects of adjuvant therapy, in particular, due to the impact of anthracyclines, it remains unknown whether high-intensity strength training could yield similar neuromuscular and functional effects as observed in other populations, and whether it is feasible in breast cancer patients shortly after surgery. Therefore, the aim of the current study was to examine if leg press MST yielded a typical impact on lower-extremity maximal muscle strength, walking economy, muscle mass, and functional performance in newly diagnosed breast cancer patients scheduled for adjuvant treatment. Specifically, it was hypothesized that lower-extremity maximal muscle strength, walking economy, muscle mass, and functional performance would be superior after the intervention in patients receiving leg press MST as a part of the adjuvant therapy, compared with standard treatment alone.

METHODS

Patients. The present study was a part of a study investigating the effects of heavy resistance training on functional performance and quality of life (16), in breast cancer patients undergoing primary adjuvant therapy at the Oncology Centre of Latvia, Riga, Latvia. A total of 55 breast cancer patients were recruited, and inclusion criteria were women between 18 and 63 yr with newly (<3 wk) diagnosed stage I to III invasive breast cancer, assigned for treatment with breast-conserving surgery/mastectomy and adjuvant therapy (radiation therapy and/or chemotherapy). Exclusion criteria were known heart disease, diabetes, musculoskeletal disorders, or any disorder that prohibited participation in the testing procedures or MST. The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Rīga Stradiņš University and the Scientific Department of Rīga East University Hospital. Informed consent was obtained from all patients before inclusion.

Study timeline. The patients attended a standardized 1.5-h testing procedure 2 to 3 wk postsurgery. We aimed to initiate MST as soon as possible after operation, after the surgeon had confirmed that the healing process on the operated site was without complications. After this was confirmed, patients were randomly allocated 1:1 to standard treatment with or without 12 wk of supervised MST. The patients allocated to the MST group started their training 1 to 2 d after the testing and 1 wk before receiving adjuvant therapy, subsequently all patients trained during adjuvant therapy. After 12 wk, the 1.5-h testing procedure was repeated. The testing included assessments of dynamic maximal muscle strength of the lower extremities, walking economy, time to exhaustion (TTE), quadriceps femoris muscle mass, and functional performance.

Maximal muscle strength. After a standardized warm-up consisting of eight repetitions at 50% of predicted 1RM and five repetitions at 70% of predicted 1RM, maximal muscle strength of the lower extremities was assessed as 1RM in a horizontal leg press apparatus (Cybex Eagle 1040, USA). Starting from a near 180° knee-joint angle, the patients were instructed to move slowly to a 90° knee-joint angle, after which they moved concentrically back to the initial position. The load was increased by 2.5 to 7.5 kg until the patients were unable to complete the lift. The 1RM was defined as the heaviest lifted load and was typically obtained within three to six attempts. Rest periods minimum of 3 min were applied between each lift.

Walking economy. After a 5-min warm-up at a self-chosen speed, a 5-min submaximal, steady-rate walking economy test was performed on a motorized treadmill (Spirit CT 100; Jonesboro, AR) at 5% inclination. The speed was calculated to yield a workload of 40 W for the individual patient, using the following equation (20):

$$\text{speed}\ \left(\text{km}\cdot\text{h}^{-1}\right) = \frac{40\ \text{W}}{[m_\text{b}N]\sin\theta} \times 3.6 \qquad [1]$$

where m_b is the individual patient's body mass and θ is the 5% inclination of the treadmill. Thus patients with different body mass would all walk on a work rate corresponding to 40 W, implying different walking speeds. The walking economy was defined as the average HR (Polar Electro FT7, Kempele, Finland) at the last minute of the 5-min 40-W work rate. In addition, the Borg scale (6–20) was used to assess perceived exertion.

Time to exhaustion. After the submaximal walking economy test, the patients commenced directly to the measurement of TTE. The speed was held constant at 3.8 or 4.8 $\text{km}\cdot\text{h}^{-1}$, depending on the patient's condition, and the inclination was increased by 2% every minute. If the patient was able to continue after reaching an inclination of 12%, the speed was increased by 0.5 $\text{km}\cdot\text{h}^{-1}\cdot\text{min}^{-1}$ until voluntary exhaustion. The HR and perceived exertion were recorded immediately after exhaustion.

Functional performance. Functional performance was assessed using three tests. First, the 6-min walking distance (6MWD) was measured. The patients were instructed to walk back, forth, and around two cones separated by 30 m, aiming to walk the longest possible distance in 6 min. Second, chair rising ability was assessed by 30 s sit to stand test. Starting from a seated position with crossed arms, the patients were instructed to rise from a 44-cm high chair as many times as possible in 30 s. Third, the ability to climb stairs was assessed as the time needed to ascend and descend 10 stairs of 18 cm without the use of handrail support. Familiarization was given before all tests.

Anthropometrical measurements. The volume (V) of the left thigh was estimated using the following equation (21):

$$V = L \times 12\pi^{-1} \times \left(\mathrm{C1}^2 + \mathrm{C2}^2 + \mathrm{C3}^2\right) - (S - 0.4) \times 2^{-1} \times L \times (\mathrm{C1} + \mathrm{C2} + \mathrm{C3}) \times 3^{-1} \qquad [2]$$

Utilizing standard measuring tape, the thigh length (L) was measured from the lateral femoral epicondyle to the greater trochanter, and thigh circumferences were measured at the midpoint (C1) and 10 cm distal (C2) and proximal (C3) to the midpoint. Skinfold measurement was taken at the midpoint of the thigh, using skinfold caliper (SH5020; Saehan Corporation, MD, South Korea). Quadriceps femoris muscle mass (M_{qf}) was calculated as $M_{\mathrm{qf}} = 0.307 \times V + 0.353$ kg (22).

Level of physical activity. Patients were asked if they engaged in recreational physical activities weekly, applying the short form of the International Physical Activity Questionnaire (IPAQ-SF). The IPAQ calculates average weekly physical activity level by estimating the metabolic equivalent of task (MET) score, and accounts for the total number of minutes per week spent on low-, moderate-, and vigorous-intensity activities (3.3, 4.0, and 8.0 $\text{MET}\cdot\text{min}\cdot\text{wk}^{-1}$, respectively). The IPAQ has previously been tested and documented to have good validity and reliability (23). The patients were also asked whether they specifically were involved in regular strength training for the last 6 months before diagnosis.

Maximal strength training. The MST group attended two supervised training sessions per week for 12 wk. The training was carried at the Oncology Centre of Latvia, Riga, Latvia, and was initiated 3 wk after surgery. As for the testing, MST was performed as a dynamic leg press in the horizontal leg press apparatus using a 90° knee-joint angle. After two warm-up sets, the patients performed four sets of four repetitions at approximately 90% of 1RM. Emphasis was put on slow contraction velocity in the eccentric phase and maximal intended contraction velocity in the concentric phase. A marked stop of approximately 0.5 s was applied between the eccentric and concentric contraction phases. Rest periods minimum of 3 min were used between sets. The load was increased by 2.5 kg when the patients were able to complete all sets. The patients trained in groups of three to five individuals and were supervised by an exercise physiologist. A training session typically lasted for 20 min, and each time the patients attended training they were asked if they experienced MST-related discomfort, pain, or other adverse events during or between the MST sessions, with the exception of the lifted loads feeling heavy when executed. The control group was instructed to perform 3 sets of 10 chair rises twice a week for 12 wk. All patients were encouraged to maintain their typical level of physical activity during the study period.

Breast cancer treatment. The patients were treated according to the European Society for Medical Oncology and the National Comprehensive Cancer Network guidelines. Surgery consisted of oncoplastic breast-conserving surgery or mastectomy and sentinel node biopsy or axillary node dissection. After surgery, patients were scheduled for adjuvant radiation and potentially chemotherapy and Trastuzumab. Chemotherapy consisted of 4–8 cycles of doxorubicin (50–60 $\text{mg}\cdot\text{m}^{-2}$) or epirubicin [60–90 $\text{mg}\cdot\text{m}^{-2}$] and cyclophosphamide (600 $\text{mg}\cdot\text{m}^{-2}$) administered once every third week. After the completion of anthracycline, some patients were furthermore scheduled to four cycles of paclitaxel (135–175 $\text{mg}\cdot\text{m}^{-2}$) or docetaxel (75–100 $\text{mg}\cdot\text{m}^{-2}$) administered once every third week. Patients with HER2-positive tumors were treated with 18 cycles of trastuzumab (600 $\text{mg}\cdot\text{m}^{-2}$) administered once every third week after completion of chemotherapy.

Statistical analysis. Statistical analyses were performed using IBM SPSS (version 25), and figures were made using Graph Pad Prism software (version 8). The power analysis in this study was estimated by setting the standard deviation of a 1RM to 15 kg. Presuming a mean difference of 12 kg between the groups in this study at posttest, we needed a total of 52 patients (n = 26 in each group) to maintain statistical power of 0.80 and alpha 0.05. Data distribution was assessed using Quantile-Quantile plots. All independent and dependent variables were approximately normally distributed for each group at pretest and posttest. Prechanges to postchanges in the 6-min walking test and the walking economy were approximately normally distributed, whereas changes in 1RM, TTE, thigh volume, and M_{qf} were skewed. Changes in dependent variables were examined using a repeated measure two-factor ANOVA, with group (control, MST) and time (pre, post) as factors. Significant interactions were followed up with independent sample t-tests for between-group differences and paired sample t-tests for within-group differences. Spearman's correlation was used to assess associations between pretest to posttest changes in 1RM and pretest to posttest changes in walking economy, TTE, and functional variables for combined groups. For categorical variables χ^2 or Fisher's exact test were used to determine difference between groups. Values are expressed as

TABLE 1. Anthropometric parameters and treatment.

	MST Group (*n* = 27)	Control Group (*n* = 28)	*P*
Age (yr)	48 ± 7	49 ± 8	0.69
Body weight (kg)	77.0 ± 15.2	72.3 ± 17.4	0.29
Height (cm)	170 ± 6	167 ± 6	0.07
Breast cancer stage (%)			0.57
I	9 (33)	13 (46)	
II	12 (44)	9 (32)	
III	6 (23)	6 (22)	
Surgery (%)			0.37
OBCS	16 (59)	22 (78)	
SSM	5 (19)	4 (14)	
AB	4 (15)	1 (4)	
MRM	2 (7)	1 (4)	
Adjuvant therapy (%)			
Radiation	23 (85)	26 (92)	0.42
Anthracyclines	25 (93)	24 (86)	0.70
Cyclophosphamides	14 (52)	17 (61)	0.51
Taxanes	16 (59)	16 (57)	0.88
Trastuzumab	3 (11)	3 (11)	0.99

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as *n* (%).

OBCS, oncoplastic breast-conserving surgery; SSM, skin-sparing mastectomy; AB, amputation of the breast; MRM, modified radical mastectomy.

mean ± standard deviation in text and tables and as mean ± standard error in figures.

RESULTS

Baseline patient anthropometric parameters and adjuvant therapy are presented in (Table 1), and patient characteristics and physical activity levels are presented at (Table 2), and no significant differences between groups were observed for the demographic and clinical factors at baseline. All patients completed adjuvant therapy without interruptions or dose modifications.

Training compliance and adverse events. The MST group completed 23 ± 1 of 24 planned training sessions (96% ± 4%). The targeted training intensity was met during all training sessions, and the sessions were also executed in accordance with the protocol. All included patients completed the study, and except for the repeated lifts typically being perceived as heavy, no patients reported MST-related adverse events during or between the training or testing procedures.

Maximal muscle strength. A group–time interaction was found for leg press 1RM ($P < 0.001$). The MST group increased 1RM by 20% ± 8% ($P < 0.001$) from pretest to posttest. In contrast, 1RM decreased by 9% ± 5% in the control group ($P < 0.001$) from pretest to posttest, resulting in 1RM being higher in the MST group compared with the control group at posttest ($P < 0.001$; Fig. 1). No between-group difference was apparent in 1RM at pretest ($P = 0.187$).

TABLE 2. Patient characteristics and physical activity level at baseline.

	MST Group (*n* = 27)	Control Group (*n* = 28)	*P*
Smoking status (%)			1.00
Current	3 (11)	3 (11)	
Former	1 (4)	2 (7)	
Nonsmokers	23 (85)	23 (82)	
Married, cohabiting, or in a relationship (%)	20 (74)	22 (79)	0.70
Physical activity level (%)			0.59
Low—3.3 METs	22 (82)	21 (75)	
Moderate—4.0 METs	3 (11)	6 (21)	
High—8.0 METs	2 (7)	1 (4)	
Strength training (%)	0 (0)	0 (0)	1.00

Categorical variables are presented as *n* (%). Physical activity level was assessed applying the short form of the International Physical Activity Questionnaire short form.

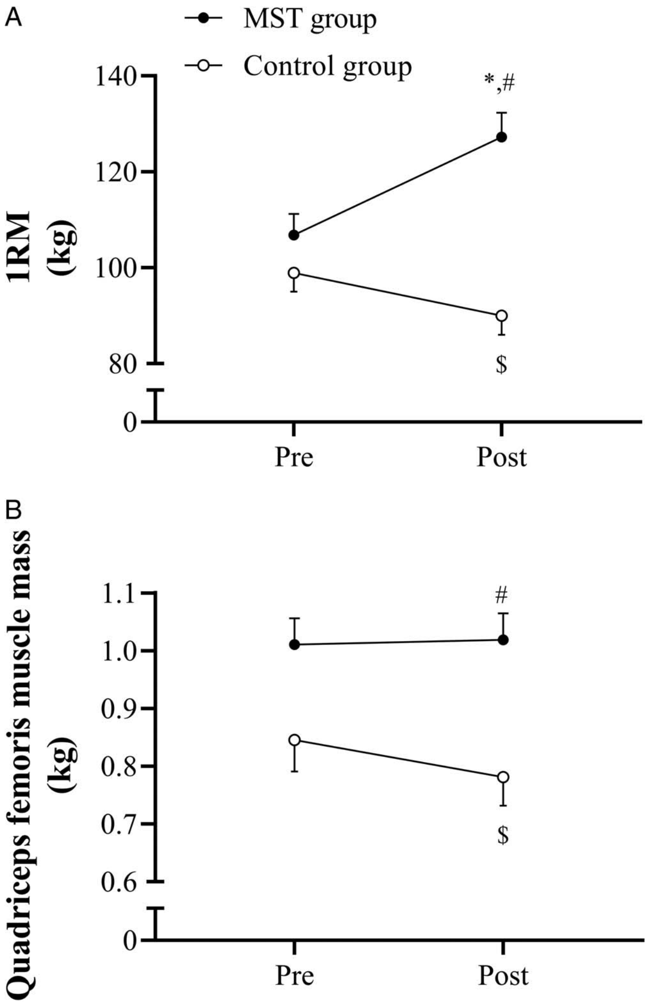

FIGURE 1—A, 1RM and (B) quadriceps femoris muscle mass after 12 wk of adjuvant therapy with and without MST. Data are presented as mean ± SE. *$P < 0.05$, within-group increase from pretest to posttest. \$$P < 0.05$, within-group decrease from pretest to posttest. #$P < 0.05$, the difference between groups from pretest to posttest.

Body mass, thigh volume, and quadriceps femoris muscle mass. No group–time interaction was found for body mass ($P = 0.147$). In contrast, there was a group–time interaction for thigh volumes ($P = 0.045$). A tendency toward a pretest to posttest increase (2% ± 4%) was found in the MST group ($P = 0.076$). No changes (0% ± 4%) occurred in the control group ($P = 0.287$). There was a tendency toward a between-group difference at pretest ($P = 0.068$), whereas a between-group difference was found after the intervention ($P = 0.034$). No correlation was apparent between change in thigh volume and change in 1RM ($r = 0.17$; $P = 0.197$).

A group–time interaction was observed for M_{qf} ($P = 0.004$). In the control group, M_{qf} decrease (7% ± 10%) from pretest to posttest ($P < 0.001$). No changes (1% ± 2%) were found in the MST group ($P = 0.683$), resulting in M_{qf} being higher in the

MST group than the control group at posttest ($P < 0.001$; Fig. 1). Changes in M_{qf} was associated with the training-induced changes in 1RM ($r = 0.45$; $P < 0.001$).

Functional performance. Group–time interactions were found for 6-min walking test ($P < 0.001$), chair rising performance ($P < 0.001$), and stair climbing performance ($P < 0.001$). At posttest, the MST group displayed improvements in the 6MWD (10% ± 7%; $P < 0.001$), chair rising performance (30% ± 20%; $P < 0.001$), and stair climbing performance (12% ± 7%; all $P < 0.001$). Conversely, in the control group, reductions were found in the 6MWD (5% ± 5%, $P < 0.001$), chair rising performance (12% ± 12%), and stair climbing performance (6% ± 8%; $P < 0.001$). As a result, 6-min walking test ($P < 0.001$), chair rising performance ($P < 0.001$), and stair climbing performance ($P = 0.004$) were different between groups at posttest (Fig. 2). No differences in 6-min walking test, chair rising performance, and stair climbing performance were observed between the groups at baseline. Changes in 6-min walking test ($r = 0.807$; $P < 0.001$), chair rising performance test ($r = 0.808$; $P < 0.001$), and stair climbing performance ($r = 0.754$; $P < 0.001$) exhibited an association with changes in 1RM (Fig. 3).

Walking economy and TTE. Pretest and posttest walking economy and TTE are presented in Table 3 with group–time interactions for walking economy, speed at exhaustion, and inclination at exhaustion. Prechanges to postchanges in walking economy ($r = 0.754$; $P < 0.001$) and TTE ($r = 0.793$; $P < 0.001$) were associated with prechanges to postchanges in 1RM (Fig. 3).

DISCUSSION

Adjuvant breast cancer therapy is associated with reduced muscle strength, muscle mass, and physical activity (2,6,9). Despite the well-documented effectiveness of strength training to improve these factors in other populations, evidence of the impact of strength training, particularly applying high intensity, in the important initial phase of breast cancer treatment is scarce. Therefore, this study sought to investigate the effect of strength training performed with high loads (~90% 1RM) and few repetitions (3–5) in newly diagnosed breast patients undergoing adjuvant therapy. The major findings were that 3 months of MST yielded large improvements in lower-extremity maximal muscle strength, walking economy and functional performance, and maintained muscle mass. Conversely, patients assigned to the control group displayed reductions in all assessed variables. The results of the current study advocate that lower-extremity MST should be considered part of breast cancer management postsurgery, starting before initiation of adjuvant therapy, to improve and maintain physical health and functionality.

Maximal muscle strength, adjuvant therapy, and MST. Primary adjuvant treatment, without strength training, resulted in reductions in lower-extremity maximal muscle strength, muscle mass, and functional performance in the current study. The approximately 9% decrease in leg press maximal muscle strength, apparent after only 12 wk of adjuvant therapy, corresponds to more than one decade of typical aging (24). This is in accordance with several previous studies (2,18), which has documented especially chemotherapy to reduce the main determinants of muscle strength such as muscle

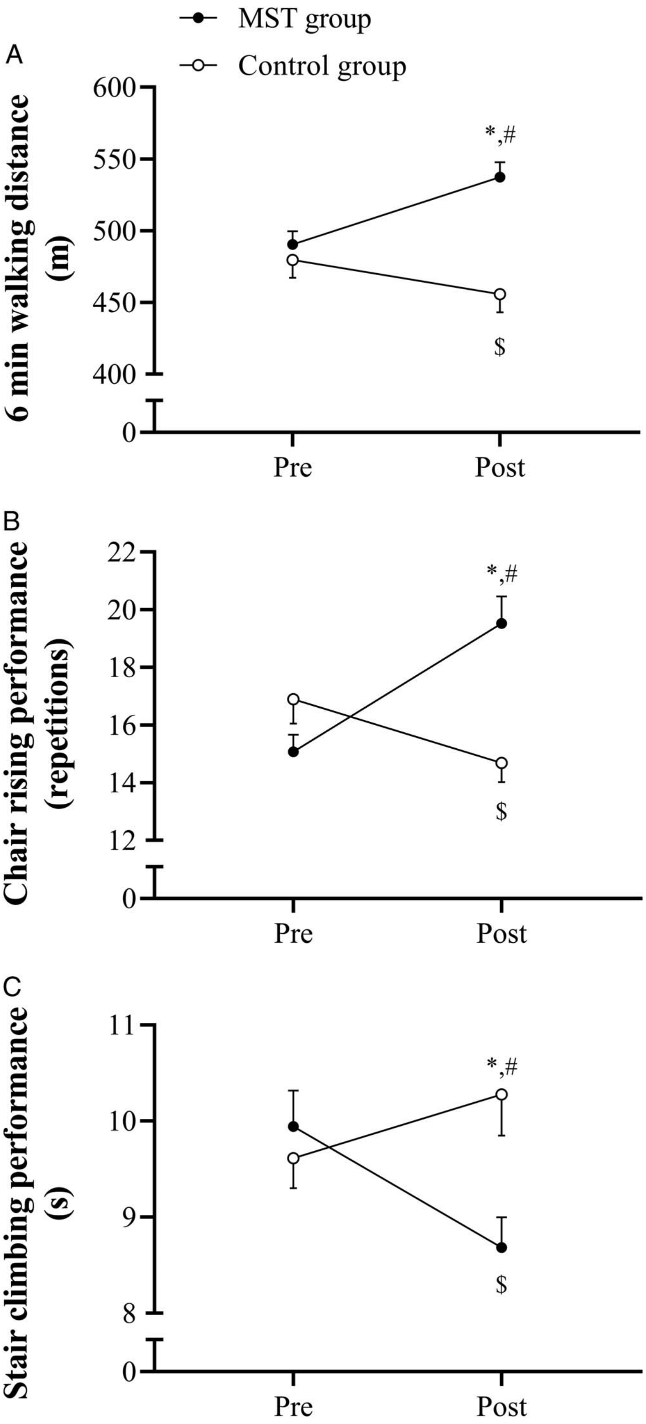

FIGURE 2—A, 6MWD (m), (B) chair rising performance (repetitions), and (C) stair climbing performance (s) after 12 wk of adjuvant therapy with and without maximal strength training (MST). Data are presented as mean ± SE, *$P < 0.05$, increase within-group from pretest to posttest. \$$P < 0.05$, decrease within-group from pretest to posttest. #$P < 0.05$ difference between groups from pretest to posttest.

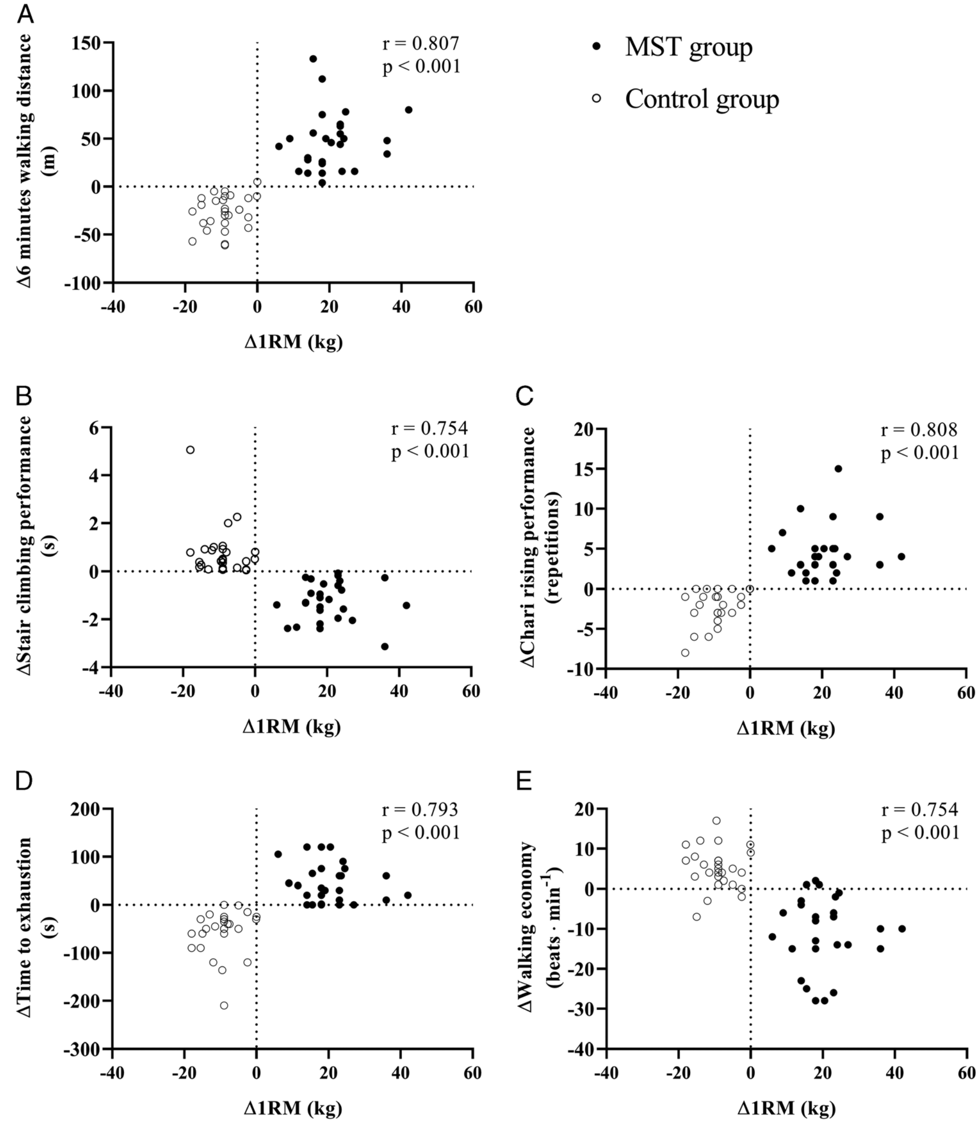

FIGURE 3—Associations between changes in maximal strength (leg press 1RM) and changes in (A) TTE during incremental walking, (B) walking work economy, (C) 6-min walking distance, and (D) chair rising performance after 12 wk of breast cancer adjuvant therapy with and without MST.

fiber cross-sectional area (25) and diminish motoneuron excitability (26). However, strength reductions are not always observed (27–29). Of importance, the latter studies applied single-joint isometric measurements of muscle strength, whereas we applied dynamic leg press, and the equivocal findings may partly be explained by the application of different measurement techniques. Additionally, a discrepancy between studies may be attributable to type, duration, and dose of chemotherapy. Indeed,

TABLE 3. Endurance performance before and after maximal strength training.

	MST Group (n = 27)			Control Group (n = 28)			Interactions (Time–Group)	Between Groups	
								P	
	Pre	Post	*P*	Pre	Post	*P*	*P*	Pre	Post
Walking economy									
HR (bpm)	140 ± 16	128 ± 15	**<0.001**	134 ± 12	149 ± 12	**0.002**	**<0.001**	0.150	**0.009**
RPE (6–20)	12 ± 1	10 ± 2	**<0.001**	12 ± 2	13 ± 1	0.184	**<0.001**	0.289	**<0.001**
Graded walking test									
TTE (s)	536 ± 71	571 ± 68	**<0.001**	531 ± 73	476 ± 63	**<0.001**	**<0.001**	0.814	**<0.001**
HR_{max} (bpm)	172 ± 8	172 ± 7	1.000	167 ± 11	166 ± 11	0.275	0.443	**0.042**	**0.013**
E_{speed} (km·h^{-1})	4.8 ± 0.4	5.1 ± 0.4	**<0.001**	4.8 ± 0.5	4.7 ± 0.3	**0.002**	**<0.001**	0.454	**0.001**
$E_{inclination}$ (%)	11 ± 1	12 ± 1	**0.009**	11 ± 1	10 ± 2	**0.003**	**<0.001**	0.402	**0.010**
RPE (6–20)	17 ± 1	18 ± 1	0.120	17 ± 1	17 ± 1	0.563	0.475	0.975	0.372

Data are presented as mean ± standard deviation.

E_{speed}, treadmill speed at exhaustion; $E_{inclination}$, treadmill inclination at exhaustion.

reductions in muscle strength induced by therapeutic agents typically applied in breast cancer treatment (e.g., anthracyclines) have been shown to be dose-dependent (30).

Compared with the control group that received standard adjuvant treatment, the patients that performed strength training two times a week had approximately 30% higher lower-extremity maximal muscle strength after 3 months. This MST-induced effect is similar to what has been observed after a comparable volume of leg press MST in healthy individuals (31) and other patient populations (3,14,32). The approximately 20 kg improvement in leg press 1RM in the current study is about 2.5 times larger compared with the approximately 8 kg 1RM increase observed in a previous study were the patients exercised three times a week with an intensity corresponding to 60% to 70% of 1RM (17), and even similar to improvements observed after 1 yr of home-based training 4 d·wk^{-1} (18). Albeit, again, direct comparison between studies should be made with caution due to differences in type, dose, and duration of chemotherapy. Importantly, although MST may be considered strenuous, the 96% completion rate in the present study clearly indicates that breast cancer patients are, despite suffering adverse side effects of early phase adjuvant therapy, capable of performing strength training of the lower extremities with a targeted intensity of approximately 90% of 1RM. Furthermore, the intervention was completed without any reported difficulties or injuries, indicating that the feasibility and safety of leg press MST during breast cancer treatment should be considered satisfactory. Of notice, it is only the concentric phase of movement during MST that is carried out with high intensity. This is a likely reason why MST may be safely performed, as the high-impact force associated with eccentric muscle action is avoided (33).

Muscle mass, adjuvant therapy, and MST. Although breast cancer patients undergoing adjuvant therapy typically are weight stable or gain weight, recent data reveal that chemotherapy may cause muscle fiber atrophy (34). Accordingly, in the present study, the control group displayed reductions in M_{qf}, indicating that muscular alterations contributed to the reduction in lower-extremity maximal muscle strength. Indeed, our results revealed a tendency for alterations in M_{qf} to be associated with changes in lower-extremity maximal muscle strength. Although MST primarily is tailored to induce neural adaptions, it may also cause muscle hypertrophy (4), and thus potentially counteract chemotherapy-induced reductions in muscle mass. In line with this finding, muscle mass was preserved in the MST group. Depletion of muscle mass can lead to chemotherapy toxicity, which in turn may necessitate dose reduction or delayed administration (7).

Endurance performance, adjuvant therapy, and MST. In accordance with previous interventions (4,14), the increments in lower-extremity maximal muscle strength were associated with improvements in the walking economy, one of three major determinants of aerobic endurance (35). When lower-extremity maximal muscle strength is improved, the load imposed by each stride becomes relatively lower and may lead to decreased reliance on the less efficient high-threshold type II muscle fibers and to lower motor unit recruitment (4). The improved walking economy is likely to have implications for the patients' everyday function as a given submaximal workload now requires less energy compared with before the intervention. In accordance with previous findings (14), the improved walking economy likely also led to the observed improvements in TTE observed in the present study. This implies that the breast cancer patients that had performed leg press MST not only were able to walk with a lower energy cost but also that they increased their maximal walking effort.

Functional performance and MST. Importantly, MST-induced improvements in lower-extremity maximal muscle strength were accompanied by improved functional performance in the current study. Particularly the chair rising performance, stair climbing, and 6MWD tests exhibited strong relationships with the changes in lower-extremity maximal muscle strength. These findings are in accordance with previous observations, documenting changes in muscle strength to occur in conjunction with changes in functional performance. Especially functional tasks involving upward displacement of the body are shown to be susceptible to change with enhanced lower-extremity muscle strength (36). In contrast, low-force activities, such as walking, appear to be less dependent on muscle strength (36). The MST-induced increases in chair climbing performance and chair rising in the current study are in accordance with this notion, whereas the improved 6MWD may to a greater extent be attributable to the improved walking economy. In contrast to their strength training counterpart, the control group displayed impaired functional performance, further consolidating the close relationship between lower-extremity muscle strength and physical functioning.

Strengths and limitations of the study. Few studies have investigated the effects of strength training in the initial phase of breast cancer treatment. A strength of the present study is the application of effective high-intensity strength training of functionally relevant muscle groups of the lower extremities. Maximal strength training is time- and cost-efficient, demanding less than an hour of training per week, and patients may train in groups of three to five individuals per training apparatus during the same training session. Despite adverse early phase side effects of adjuvant therapy, the patients had a completion rate of 96%, suggesting leg press MST to be a feasible exercise modality in this critical phase of breast cancer treatment. Importantly, the strength training was also carried out without any observed injuries during the training period. Ultimately, the major strength in the current study was that the large improvements in lower-extremity muscle strength were strongly associated with improvements in the patients' functional performance. A limitation with the current study is the lack of measurements of neural and muscular components. This may have provided important information about the origin of the strength training-induced improvements, and if certain components of adjuvant therapy possibly affected some factors more than others. As breast cancer patients may suffer attenuated bone health, it would also have been beneficial to include musculoskeletal measurements. Increased lower-extremity muscle strength has previously been documented to result in enhanced bone formation and bone mineral density (37), and it would have been of great value to investigate if this was also the case in our study. Finally, the relatively short duration of the study also represents a limitation, as information on long-term effects would have provided a better understanding of the role of exercise in breast cancer treatment and survival rate.

Clinical implications. The present study clearly demonstrates the importance of counteracting the detrimental effects of adjuvant breast cancer therapy on neuromuscular function. Indeed, although patients commencing leg press MST improved lower-extremity maximal muscle strength, walking economy, functional performance, and maintained muscle mass, the control group was subject to reductions in all these variables. Notably, 40 min of leg press MST per week was sufficient to gain lower-extremity muscle strength and functionality, and we recently documented that it also improved the patients' overall quality of life (16). In fact, only one exercise, dynamic leg press, was performed. Although it would be beneficial to include strength training of other muscle groups, the lower extremities should be prioritized due to their weight-bearing function. It is noteworthy that MST appears to be safe, despite the heavy loads applied in the training. Of importance, only the concentric phase of movement has a high intensity. The eccentric phase, which is more associated with muscle soreness and microdamage to the muscle (33), is carried out in a slow and controlled fashion. In combination with few repetitions (4) and sets (4), and low actual velocity also in the concentric phase, this is a likely explanation of why MST can be carried out safely. Taken together, the findings in the current study and the Cešeiko et al. (16) study certainly support previous suggestions of implementation of strength training in adjuvant breast cancer treatment and extend recommendations to include effective high-intensity MST of the lower extremities.

CONCLUSIONS

In conclusion, the present study showed that 3 months of leg press MST effectively improved lower-extremity maximal muscle strength in breast cancer patients receiving adjuvant treatment and that the changes were associated with improvements in walking economy and functional performance. These results advocate that lower-extremity high-intensity strength training should be considered a part of breast cancer treatment to not only counteract the typically observed decline in lower-extremity muscle strength but also to improve physical health and functionality from the time of diagnosis.

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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. Klassen O, Schmidt ME, Ulrich CM, et al. Muscle strength in breast cancer patients receiving different treatment regimes. *J Cachexia Sarcopenia Muscle*. 2017;8(2):305–16.
3. Hoff J, Tjonna AE, Steinshamn S, Hoydal M, Richardson RS, Helgerud J. Maximal strength training of the legs in COPD: a therapy for mechanical inefficiency. *Med Sci Sports Exerc*. 2007;39(2):220–6.
4. Wang E, Nyberg SK, Hoff J, et al. Impact of maximal strength training on work efficiency and muscle fiber type in the elderly: implications for physical function and fall prevention. *Exp Gerontol*. 2017;91:64–71.
5. Unhjem R, van den Hoven LT, Nygard M, Hoff J, Wang E. Functional performance with age: the role of long-term strength training. *J Geriatr Phys Ther*. 2019;42(3):115–22.
6. Mijwel S, Cardinale DA, Norrbom J, et al. Exercise training during chemotherapy preserves skeletal muscle fiber area, capillarization, and mitochondrial content in patients with breast cancer. *FASEB J*. 2018;32(10):5495–505.
7. 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.
8. Hayward R, Hydock D, Gibson N, Greufe S, Bredahl E, Parry T. Tissue retention of doxorubicin and its effects on cardiac, smooth, and skeletal muscle function. *J Physiol Biochem*. 2013;69(2):177–87.
9. Irwin ML, Crumley D, McTiernan A, et al. Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. *Cancer*. 2003;97(7):1746–57.
10. Christensen JF, Jones L, Andersen J, Daugaard G, Rorth M, Hojman P. Muscle dysfunction in cancer patients. *Ann Oncol*. 2014;25(5):947–58.
11. Heggelund J, Fimland MS, Helgerud J, Hoff J. Maximal strength training improves work economy, rate of force development and maximal strength more than conventional strength training. *Eur J Appl Physiol*. 2013;113(6):1565–73.
12. Unhjem R, Lundestad R, Fimland MS, Mosti MP, Wang E. Strength training-induced responses in older adults: attenuation of descending neural drive with age. *Age*. 2015;37(3):47.
13. Karlsen T, Helgerud J, Stoylen A, Lauritsen N, Hoff J. Maximal strength training restores walking mechanical efficiency in heart patients. *Int J Sports Med*. 2009;30(5):337–42.
14. Wang E, Helgerud J, Loe H, Indseth K, Kaehler N, Hoff J. Maximal strength training improves walking performance in peripheral arterial disease patients. *Scand J Med Sci Sports*. 2010;20(5):764–70.
15. Mosti MP, Kaehler N, Stunes AK, Hoff J, Syversen U. Maximal strength training in postmenopausal women with osteoporosis or osteopenia. *J Strength Cond Res*. 2013;27(10):2879–86.
16. Ceseiko R, Eglitis J, Srebnijs A, et al. The impact of maximal strength training on quality of life among women with breast cancer undergoing treatment. *Exp Oncol*. 2019;41(2):166–72.
17. 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.
18. Schwartz AL, Winters-Stone K. Effects of a 12-month randomized controlled trial of aerobic or resistance exercise during and following cancer treatment in women. *Phys Sportsmed*. 2009;37(3):62–7.
19. Courneya KS, McKenzie DC, Mackey JR, et al. Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. *J Natl Cancer Inst*. 2013;105(23):1821–32.

20. Høydal KL, Helgerud J, Karlsen T, Støylen A, Steinshamn S, Hoff J. Patients with coronary artery-or chronic obstructive pulmonary disease walk with mechanical inefficiency. *Scand Cardiovasc J*. 2007; 41(6):405–10.
21. Layec G, Venturelli M, Jeong E-K, Richardson RS. The validity of anthropometric leg muscle volume estimation across a wide spectrum: from able-bodied adults to individuals with a spinal cord injury. *J Appl Physiol*. 2014;116(9):1142–7.
22. Radegran G, Blomstrand E, Saltin B. Peak muscle perfusion and oxygen uptake in humans: importance of precise estimates of muscle mass. *J Appl Physiol (1985)*. 1999;87(6):2375–80.
23. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381–95.
24. Lindle RS, Metter EJ, Lynch NA, et al. Age and gender comparisons of muscle strength in 654 women and men aged 20-93 yr. *J Appl Physiol (1985)*. 1997;83(5):1581–7.
25. Mijwel S, Backman M, Bolam KA, et al. Highly favorable physiological responses to concurrent resistance and high-intensity interval training during chemotherapy: the OptiTrain breast cancer trial. *Breast Cancer Res Treat*. 2018;169(1):93–103.
26. Kneis S, Wehrle A, Freyler K, et al. Balance impairments and neuromuscular changes in breast cancer patients with chemotherapy-induced peripheral neuropathy. *Clin Neurophysiol*. 2016;127(2): 1481–90.
27. Cornette T, Vincent F, Mandigout S, et al. Effects of home-based exercise training on VO2 in breast cancer patients under adjuvant or neoadjuvant chemotherapy (SAPA): a randomized controlled trial. *Eur J Phys Rehabil Med*. 2016;52(2):223–32.
28. Travier N, Velthuis MJ, Steins Bisschop CN, et al. Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial. *BMC Med*. 2015;13:121.
29. Nikander R, Sievanen H, Ojala K, et al. Effect of exercise on bone structural traits, physical performance and body composition in breast cancer patients—a 12-month RCT. *J Musculoskelet Neuronal Interact*. 2012;12(3):127–35.
30. Hydock DS, Lien CY, Jensen BT, Schneider CM, Hayward R. Characterization of the effect of in vivo doxorubicin treatment on skeletal muscle function in the rat. *Anticancer Res*. 2011;31(6):2023–8.
31. Hoff J, Gran A, Helgerud J. Maximal strength training improves aerobic endurance performance. *Scand J Med Sci Sports*. 2002;12(5):288–95.
32. Helgerud J, Karlsen T, Kim WY, et al. Interval and strength training in CAD patients. *Int J Sports Med*. 2011;32(1):54–9.
33. Toien T, Pedersen Haglo H, Unhjem R, Hoff J, Wang E. Maximal strength training: the impact of eccentric overload. *J Neurophysiol*. 2018;120(6):2868–76.
34. Guigni BA, Callahan DM, Tourville TW, et al. Skeletal muscle atrophy and dysfunction in breast cancer patients: role for chemotherapy-derived oxidant stress. *Am J Physiol Cell Physiol*. 2018;315(5): C744–c56.
35. Pate RR, Kriska A. Physiological basis of the sex difference in cardiorespiratory endurance. *Sports Med*. 1984;1(2):87–98.
36. Salem GJ, Wang MY, Young JT, Marion M, Greendale GA. Knee strength and lower- and higher-intensity functional performance in older adults. *Med Sci Sports Exerc*. 2000;32(10):1679–84.
37. Nygard M, Mosti MP, Brose L, et al. Maximal strength training improves musculoskeletal health in amphetamine users in clinical treatment. *Osteoporos Int*. 2018;29(10):2289–98.