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RESEARCH

Skeletal muscle mass, strength, and physical performance gains are similar between healthy postmenopausal women and postmenopausal breast cancer survivors after 12 weeks of resistance exercise training

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Abstract

Purpose Resistance exercise training (RET) effectively increases skeletal muscle mass and strength in healthy postmenopausal women. However, its effects on these parameters in postmenopausal breast cancer survivors are controversial or limited. Therefore, the aim of this study was to compare the effects of a 12-week progressive whole-body RET program on skeletal muscle mass, strength, and physical performance in healthy postmenopausal women versus postmenopausal women who survived breast cancer.

Methods Thirteen healthy postmenopausal women (HEA, 54 ± 3 years, BMI 26.6 ± 2.7 kg·m^2, $n = 13$) and eleven postmenopausal breast cancer survivors (BCS, 52 ± 5 years, BMI 26.8 ± 2.1 kg·m^2, $n = 11$) participated in the study. Before and after the RET program, evaluations were performed on quadriceps muscle thickness, one-repetition maximum strength (1RM) for various exercises, grip strength, and physical performance.

Results Both groups showed significant improvements in quadriceps muscle thickness (time effect, $P < 0.001$); 1RM strength for leg extension, leg press, chest press, horizontal row, and elbow extension (time effect, all $P < 0.001$); as well as handgrip strength (time effect, $P = 0.035$) and physical performance (time effect, all $P < 0.001$) after the 12-week RET program. There were no significant differences between the groups in response to RET for any of the outcomes measured.

Conclusion Twelve weeks of RET significantly increases skeletal muscle mass, strength, and physical performance in postmenopausal women. No differences were observed between healthy postmenopausal women and postmenopausal breast cancer survivors. These findings point out that this study's RET promotes skeletal muscle mass, strength, and performance gains regardless of breast cancer.

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Keywords Cancer · Resistance training · Rehabilitation · Exercise · Atrophy · Muscle mass

Introduction

Breast cancer ranks first in global cancer incidence, with approximately 2.3 million new cases every year as of 2022. Among women, breast cancer constitutes 16% of cancer deaths [1]. The most common age for breast cancer diagnosis is between 51 and 70 years, typically post-menopause [2].

In postmenopausal women, around 80% of breast cancer cases exhibit positive estrogen receptors, frequently resulting in the prescription of endocrine therapy (such as tamoxifen, a selective estrogen-receptor modulator or aromatase inhibitors, which block the production of estrogens) as adjuvant treatment following the primary surgical intervention for localized disease [3]. These medications effectively reduce estrogen exposure in the breast tissue, thus preventing the breast tumor from receiving growth stimuli

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[4]. Consequently, the probability of cancer recurrence is significantly reduced [4] when these therapies are administered for 5 years or longer [5, 6].

Despite the effectiveness of endocrine therapy, the treatment side effects are common and can include increased adipose tissue, skeletal muscle mass loss, and muscle weakness [7, 8]. The loss of skeletal muscle mass, strength, and physical performance is known as sarcopenia. It is commonly associated with aging and is partially attributed to the decline of estrogen in older women [9]. The use of estrogen-effect suppressors such as tamoxifen and aromatase inhibitors hastens the depletion of skeletal muscle during menopause, diminishes mobility, and impacts the overall quality of life for breast cancer survivors undergoing endocrine therapy [10].

Additionally, diseases such as cancer and aging-related factors promote skeletal muscle atrophy, with growth differentiation factor 15 (GDF-15) identified as a potential biomarker for muscle disease [11]. Tumor-derived exosomes containing GDF-15 promote cancer-induced skeletal muscle atrophy through the Bcl-2/caspase-3 pathway [12, 13]. Moreover, serum GDF-15 has been associated with poor physical function in pre-frail older adults with diabetes [14].

To effectively counteract these adverse effects, supervised resistance exercise training (RET) has been shown to improve muscle strength and reduce plasma levels of lipids, inflammatory cytokines, and oxidative stress markers in breast cancer survivors treated with endocrine therapy such as tamoxifen [15]. Although the effectiveness of this type of training has been explored previously in women with breast cancer in terms of skeletal muscle mass, little information is available on the response magnitude in postmenopausal breast cancer survivors compared with postmenopausal healthy women [16].

Recent systematic reviews analyzing data from cancer survivors of advanced age and patients diagnosed with cancer during adjuvant treatment have shown that RET improves muscle strength but does not induce a substantial increase in skeletal muscle mass [17, 18]. These results differ from meta-analyses conducted in healthy postmenopausal women, where it has been demonstrated that this type of training, with or without nutritional supplementation, improves skeletal muscle mass, strength, and physical performance measures in women aged 45 to 80 years [19].

Based on these backgrounds, this study aimed to compare the effects of a 12-week progressive RET on skeletal muscle mass, muscle strength, and physical performance of healthy postmenopausal women versus postmenopausal women who are breast cancer survivors. The correlation of GDF-15 with markers of sarcopenia was also investigated. We hypothesize that the effects of RET on skeletal muscle mass are lower in postmenopausal breast cancer survivors compared to healthy postmenopausal women.

Methods

Participants

Thirteen healthy postmenopausal women (HEA, 54 ± 3 years, BMI 26.6 ± 2.7 kg·m^2, n = 13) and eleven postmenopausal women who are breast cancer survivors (BCS, 52 ± 5 years, BMI 26.8 ± 2.1 kg·m^2, n = 11) completed the study (Fig. 1). The study was approved by the scientific ethics committee of Universidad de La Frontera, Temuco, Chile (registration record N°004_23) according to the Declaration of Helsinki and was registered on clinicaltrials.gov as NCT05690295. A signed informed consent was obtained from each participant. One week before the study, the participants completed a routine medical screening and general health questionnaire to ensure their suitability for the study. Inclusion criteria were postmenopausal women between 45 and 59 years of age, healthy and breast cancer survivors who completed primary treatment ≥ 6 months ago with or without endocrine therapy, BMI between 18.5 and 30 kg·m^2, and willingness to participate in the study and follow the proposed intervention scheme. The exclusion criteria were performing regular RET in the previous 6 months, cardiovascular diseases incompatible with physical activity, all comorbidities affecting the mobility of the body and muscle metabolism and that do not allow to safely perform the RET program, smoking, use of nutritional supplementation (leucine, glutamine, casein, whey-protein, fatty acids, and creatine), and use of estrogen replacement therapy.

Study design

All volunteers performed 12 weeks of supervised whole-body RET (three times per week). Before and after 12 weeks of RET, muscle ultrasonography (US) was performed to assess quadriceps muscle thickness as our primary outcome. In addition, fasting blood samples were obtained to determine biochemical and inflammatory markers, and a whole-body bioelectric impedance analysis was performed to determine lean and fat mass. Maximal strength was determined by one-repetition maximum (1RM); functional capacity was assessed through the 6-min walk test and physical performance by the timed up and go (TUG) test and short physical performance battery (SPPB) at the same time points.

Exercise intervention program

Participants in both groups underwent an identical, supervised, progressive whole-body RET program three times a week for 12 weeks, as described previously [20]. During

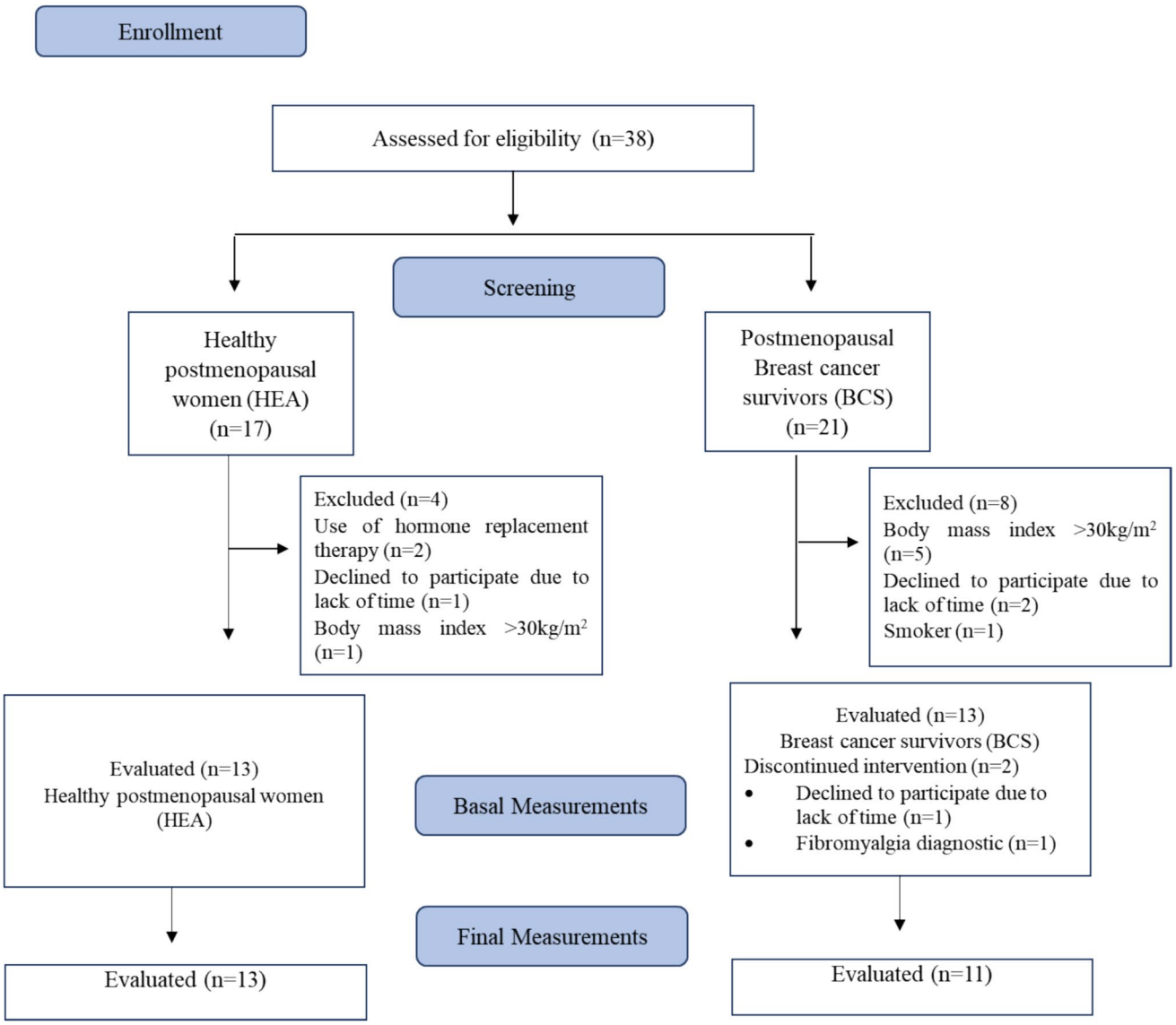

Fig. 1 Flow diagram of study participants

the intervention, 1RM was reassessed to adjust workloads (60–80%) in the sixth week of training. Compliance for the protocol analyses was set at completing at least 80% of the training sessions (i.e., at least 29 of the 36 sessions).

The training regimen began with a 5-min warm-up on a bicycle ergometer followed by global upper limb movements. A series of warm-up exercises were performed followed by four regular sets on the leg press and leg extension machines (TuffStuff Fitness International, California, USA). The upper body exercises comprised three sets for each exercise, including chest press, triceps extension, and horizontal row machines (Fit Tech, Portugal). The cool-down consisted of 5 min of recovery using global muscle stretching exercises.

Dietary intake and physical activity standardization

Participants were instructed to maintain their usual dietary habits and levels of physical activity throughout the exercise program. Before and in week 11 of the RET, participants completed 3-day dietary intake and physical activity records, including two weekdays and one weekend day [20, 21]. These records were reviewed by a blinded nutrition expert and analyzed using FatSecret® software (version 2023, Melbourne, Australia), which has been validated in previous studies for its reliability in estimating macronutrient and caloric intake [22]. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ), widely validated in the Chilean population [23].

Both methods ensured consistent and reliable assessments of dietary intake and physical activity levels during the study. No other dietary control was implemented.

Skeletal muscle mass

All measurements of the thickness were assessed based on the protocol described by Galvão et al. (2006) [24]. The assessment was conducted by an evaluator experienced in measuring muscle thickness using clinical ultrasonography, who was blinded to participant coding. The muscle thickness assessment was performed before and after 12 weeks of the RET program. Ultrasonography equipment (LOGIQTM F8, GE Healthcare, USA) was used with a convex transducer of 5 MHz with water-soluble gel placed on the skin, perpendicular to the tissue interface. In assessing muscle thickness of the rectus femoris, vastus intermedius, and total quadriceps, reference points were established at the anterosuperior iliac spine and the superior border of the patella. For the evaluation of brachial biceps and brachial triceps muscle thickness, the acromion and olecranon were designated as reference points. Consistency in measurements for both upper and lower limbs was maintained by locating the midpoint between these reference points. Participants stayed in a lying position with the head and ankles in a neutral position and the upper and lower limbs fully extended. The measurements were made using the muscle mode preset specific to the ultrasound. The transducer was placed with minimal pressure over the gel so the muscle thickness would not be reduced due to compression. The image was frozen at the reference point, and the measurements were recorded in cm using the same equipment.

Body composition

Whole-body and regional lean mass and whole-body fat mass were determined by bioelectrical impedance analysis (HBF-514C, Omron©, Japan), with participants in an overnight fast and standing position, ensuring they had not engaged in intense physical activity within the previous 48 h. In addition, weight, height, and waist circumference were determined. Waist circumference was measured on exhalation at the midpoint between the lowest rib and the iliac crest on the right half of the body with a SECA® retractable metric measuring tape with a graduation of centimeters (Madison, WI, USA).

Muscle strength

Maximum strength was measured through 1RM strength tests, where repetition was deemed valid only if the entire lift was executed with control and without assistance. The initial estimation through a familiarization trial was conducted to establish maximum strength; subsequently, in a separate session, 1RM strength was determined for both lower (leg press and leg extension) and upper (chest press, elbow extension, and horizontal row) body exercises using the same equipment employed in the training sessions. Additionally, maximal handgrip strength was assessed using a Jamar electronic handheld dynamometer (model Plus+, Patterson Medical) as previously reported [20].

Physical performance measures and functional capacity

Physical performance was measured by performing the timed up and go test (TUG) and short physical performance battery (SPPB); specifically, the 4-m walk time, walk speed, and chair stand test were considered [25]. Functional capacity was assessed through the 6-min walk test, with the maximum distance covered in 6 min [26].

Plasma measurements

Blood samples were collected from a superficial vein in the cubital fossa after a 12-h fasting period in the morning. The samples were collected 48 h before the initial RET session and 48 h after completing the final RET session. Samples were drawn into tubes without anticoagulant. After centrifugation at 2500 rpm for 15 min, the resulting serum was aliquoted into microtubes and stored at − 80 °C for subsequent analysis. The lipid and glucose profiles were determined using enzymatic-colorimetric methods with an automatic photometer (Metrolab 2300 plus, Wiener lab, Argentina). Insulin and GDF-15 were assessed via ELISA kits (#KAQ1251 and #BMS2258, respectively, Thermo Fisher Scientific Inc., Waltham, MA, USA) by the manufacturer's guidelines. Insulin sensitivity was evaluated through the HOMA-IS (homeostasis model assessment-insulin sensitivity) calculation, utilizing the formula published by Acosta et al. [27].

Statistics

The results underwent analysis using the statistical software SPSS (IBM SPSS Statistics, v. 21, NY, USA), while the figures were generated utilizing GraphPad Prism 8.2 software (GraphPad Software, San Diego, CA, USA). Data is presented as mean ± standard deviation (SD) and percentage change (from baseline to post-training) to facilitate comparing absolute and relative improvements between the groups. Baseline characteristics between groups were compared using an independent sample *t*-test. Pre- vs. post-intervention data were analyzed using

a repeated-measures analysis of variance (ANOVA) with time (PRE vs. POST) as the within-subject factor and group (HEA vs. BCS) as the between-subject factor. In the case of a significant interaction, separate analyses were performed to determine time effects within groups and independent *t*-tests for group differences in the PRE and POST values. For the main parameters, partial eta squared was used to estimate effect sizes and represented as η^2. Statistical significance was established as $P < 0.05$.

Results

Participants

Participants' characteristics are shown in Table 1. Two breast cancer survivor participants withdrew from the study (Fig. 1).

Skeletal muscle mass

At baseline, upper and lower limb muscle thickness was not different between HEA and BCS participants ($P \geq 0.113$). The results depicting muscle thickness of the vastus intermedius, rectus femoris, and quadriceps before and after 12 weeks RET are illustrated in Fig. 2. Whole-body RET increased muscle thickness of dominant lower limbs after 12 weeks (Fig. 2a, c, e), from 1.5 ± 0.4 to 1.6 ± 0.5 cm (7 ± 15%) in vastus intermedius, from 1.9 ± 0.3 to 2.1 ± 0.3 cm (5 ± 8%) in rectus femoris, and from 3.6 ± 0.6 to 3.9 ± 0.7 cm (5 ± 7%) in total quadriceps after training in HEA participants and from 1.5 ± 0.4 to 1.6 ± 0.4 cm (8 ± 8%) in vastus intermedius, from 1.9 ± 0.2 to 2.0 ± 0.2 cm (8 ± 6%) in rectus femoris, and from 3.5 ± 0.5 to 3.7 ± 0.5 cm (7 ± 4%) in total quadriceps after training in BCS (time effect, all $P \leq 0.007$; $\eta^2 \geq 0.29$) with no differences between groups (time × group, all $P \geq 0.314$; $\eta^2 \leq 0.01$; Fig. 2b, d, f).

Table 1 Participant baseline characteristics

	HEA ($n = 13$)	BCS ($n = 11$)	*P*-value
Age (y)	54 ± 3	52 ± 5	0.155
Weight (kg)	63.8 ± 9.2	67.1 ± 7.2	0.175
Height (m)	151 ± 14.4	158 ± 7.2	0.068
BMI ($kg \cdot m^2$)	26.6 ± 2.7	26.8 ± 2.1	0.539
HR (bpm)	71.2 ± 11.3	73.3 ± 6.3	0.284
SBP (mm Hg)	115.5 ± 11.8	114.2 ± 9.8	0.389
DBP (mm Hg)	79.8 ± 10.7	78.5 ± 7.1	0.365
Type of cancer, n (%)			
Invasive carcinoma		9 (82%)	
Carcinoma in situ		2 (18%)	
Type of surgery			
Mastectomy		5 (45%)	
Quadrantectomy		6 (55%)	
Lymph nodes removed			
Complete axillary dissection		1(10%)	
Sentinel lymph node biopsy		10 (90%)	
Cancer stage			
I		2 (18%)	
II		5 (46%)	
III		4 (36%)	
General treatment received.			
Chemotherapy		6 (55%)	
Radiotherapy		11 (100%)	
Endocrine Therapy			
Tamoxifen		3 (27%)	
Aromatase Inhibitor		3 (27%)	
Without therapy		5 (46%)	
Time since breast cancer surgery (y)		4 ± 4	

Data presented as mean ± SD and as percentages. Data were analyzed using independent samples *t*-tests

HEA healthy group, *BCS* breast cancer survivors' group, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *bpm* beats per minute

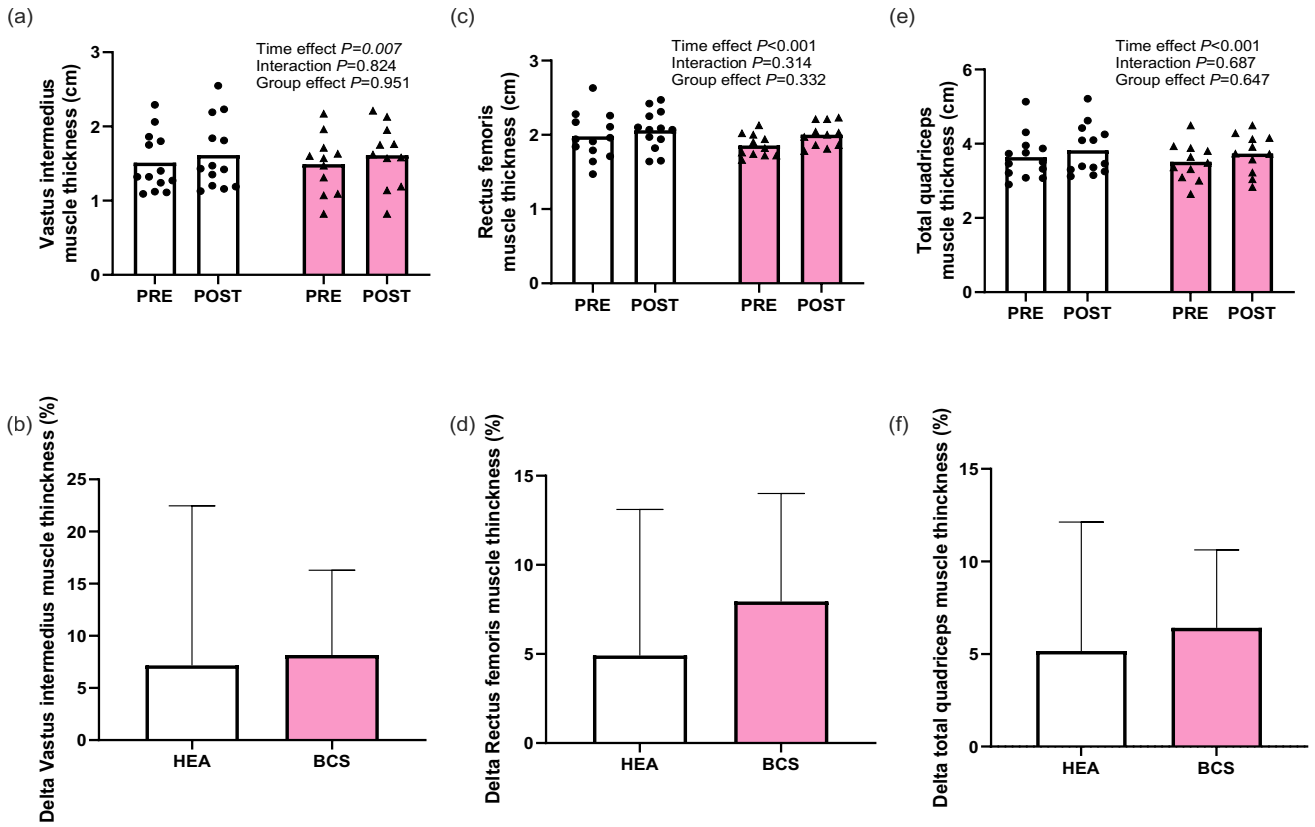

Fig. 2 Thickness of (**a**) vastus intermedius, (**c**) rectus femoris, and **e** total quadriceps muscle of the dominant leg before and after 12 weeks of resistance exercise training. Percentage change in (**b**) vastus intermedius, (**d**) rectus femoris, and (**f**) total quadriceps muscle thicknesses following 12 weeks of training in HEA (healthy group) (n = 13) and BCS (breast cancer survivors group) (n = 11) groups. Data were analyzed using repeated-measures ANOVA (time × group) (**a**, **c**, **e**) and independent t-test (**b**, **d**, **f**), not observing interaction or differences between the groups, respectively

Brachial biceps and brachial triceps muscle thicknesses did not differ between groups, and no changes were observed throughout the 12-week intervention period in either group (supplementary Table S1).

Body composition

Table 2 shows the baseline and post-12-week RET results for body composition. After the intervention, no significant differences over time between groups were observed in terms of body weight, BMI, waist circumference, visceral fat, body fat, and lean body mass percentages.

Habitual dietary intake and physical activity

The data on dietary intake and physical activity are presented in Supplementary Tables S2 and S3, respectively. No significant differences were observed in the macronutrient composition of the diet. Protein intake averaged 0.8 ± 0.2 and 0.7 ± 0.2 g/kg BW·day^{-1} in HEA and BCS participants, respectively. No differences were reported between groups, and no changes were found over time for any dietary intake parameters. Similarly, no significant changes were observed after 12 weeks of RET in the moderate physical activity level (time effect $P = 0.979$) and sedentary behavior (time effect $P = 0.271$). However, vigorous physical activity levels increase after 12 weeks of RET (time effect $P = 0.009$).

Strength

At baseline, 1RM of the upper and lower limbs did not significantly differ between the groups (Table 3). After 12 weeks of whole-body RET, 1RM leg extension increased from 57 ± 10 to 80 ± 15 kg (41 ± 12%) in HEA and from 54 ± 13 to 77 ± 18 kg (43 ± 6%) in BCS (time effect, all $P < 0.001$; $\eta^2 = 0.88$). Similar improvements were observed for 1RM leg press, elbow extension, chest press, horizontal row (time effect, all $P < 0.001$; $\eta^2 \geq 0.85$), and handgrip strength (time effect, $P = 0.035$; $\eta^2 = 0.19$) in the HEA and BCS groups (Table 3). For all strength outcomes, no differences in RET response were observed between groups for both

Table 2 Anthropometry and body composition parameters before and after 12 weeks of resistance exercise training

	HEA ($n = 13$)		BCS ($n = 11$)		Statistics (P-value)		
	PRE	POST	PRE	POST	Time	Time × group	Group
Weight (kg)	63.9 ± 9.2	63.9 ± 8.9	67.1 ± 7.2	67.6 ± 8.1	0.420	0.392	0.318
BMI (kg/m^2)	26.6 ± 2.7	26.6 ± 2.7	26.8 ± 2.1	26.9 ± 2.0	0.392	0.594	0.779
Waist circumference (cm)	86.5 ± 9.2	86.2 ± 10.4	91.9 ± 7.7	85.6 ± 8.89	0.285	0.159	0.363
Body fat mass (%)	40.9 ± 4.1	41.0 ± 4.5	41.8 ± 2.7	40.9 ± 3.4	0.172	0.073	0.828
Lean body mass (%)	24.1 ± 1.5	25.3 ± 4.8	23.9 ± 1.3	24.7 ± 1.8	0.197	0.773	0.712
Basal metabolic rate (Kcal)	1301.6 ± 107.3	1303.5 ± 103.9	1349.5 ± 97.2	1356.5 ± 107.9	0.145	0.400	0.250
Visceral fat (kg)	8.2 ± 1.5	8.5 ± 1.4	8.3 ± 1.2	8.5 ± 0.9	0.096	0.659	0.968

Data presented as mean ± SD. Data were analyzed using repeated-measures ANOVA (time × group)

HEA healthy group, *BCS* breast cancer survivors group, *BMI* body mass index

Table 3 Strength parameters before and after 12 weeks of resistance exercise training

	HEA ($n = 13$)		BCS ($n = 11$)		Statistics (P-value)		
	PRE	POST	PRE	POST	Time	Time × group	Group
1RM chest press (kg)	51.2 ± 8.7	62.7 ± 9.0	46.5 ± 12.0	59.0 ± 11.3	**< 0.001**	0.668	0.323
1RM horizontal row (kg)	38.1 ± 5.2	50.4 ± 6.6	39.5 ± 6.9	50.7 ± 7.6	**< 0.001**	0.315	0.325
1RM elbow extension (Kg)	28.5 ± 3.8	36.5 ± 5.8	27.0 ± 4.2	35.8 ± 5.8	**< 0.001**	0.185	0.855
1RM leg extension (kg)	57.1 ± 10.2	80.3 ± 15.0	53.7 ± 13.0	76.8 ± 18.1	**< 0.001**	0.993	0.551
1RM leg press (kg)	85.3 ± 27.8	123.1 ± 34.4	70.7 ± 21.4	102.5 ± 20.4	**< 0.001**	0.314	0.106
Dominant handgrip strength (kg)	27.1 ± 3.2	28.5 ± 4.7	26.6 ± 5.5	27.8 ± 5.9	**0.035**	0.878	0.774

Data presented as mean ± SD. Data were analyzed using repeated-measures ANOVA (time × group)

HEA healthy group, *BCS* breast cancer survivors group, *1RM* 1-repetition maximum

*Bold numbers at the $P < 0.05$ level

the absolute and the relative (i.e., percentage) improvements (time × group, all $P \geq 0.185$; all $\eta^2 \leq 0.09$; Table 3).

Physical performance and physical capacity

At baseline, physical performance (TUG, 4-m walk time, walk speed, and chair stand test) and physical capacity (6-min walk test) did not show a significant difference between groups (Table 4). Twelve weeks of RET promoted a 10 ± 11% (from 6.6 ± 10.7 to 5.9 ± 0.7 s) and 9 ± 16% (from 6.5 ± 0.7 to 5.9 ± 0.7 s) improvement in TUG in HEA and BCS, respectively (time effect, $P < 0.001$; $\eta^2 = 0.45$), with no differences between groups (time × group, $P = 0.891$). In accordance, performance on the 4-m walk time, walk speed, and chair stand tests was improved by RET in both HEA and BCS participants (time effect, all $P \leq$

Table 4 Functional capacity and physical performance before and after 12 weeks of resistance exercise training

	HEA ($n = 13$)		BCS ($n = 11$)		Statistics (P-value)		
	PRE	POST	PRE	POST	Time	Time × group	Group
6MWT (m)	588.8 ± 28	646.5 ± 35	566.6 ± 62	603.9 ± 35	**0.001**	0.277	0.054
TUG (s)	6.6 ± 0.7	5.9 ± 0.7	6.5 ± 0.7	5.9 ± 0.7	**< 0.001**	0.891	0.905
4 m walk time (s)	2.8 ± 0.5	2.6 ± 0.5	2.9 ± 0.5	2.5 ± 0.3	**0.029**	0.451	0.968
Walk speed (m/s)	1.5 ± 0.3	1.6 ± 0.3	1.4 ± 0.2	1.6 ± 0.2	**0.040**	0.471	0.903
Chair stand test (s)	8.8 ± 1.3	7.6 ± 1.5	9.4 ± 1.2	8.0 ± 1.1	**0.002**	0.741	0.214

Data presented as mean ± SD. Data were analyzed using repeated-measures ANOVA (time × group)

6MWT 6-min walk test, *HEA* healthy group, *BCS* breast cancer survivors group, *TUG* timed up and go

*Bold numbers at the $P < 0.05$ level

0.040; $\eta^2 \geq 0.19$), with no differences between groups (time × group, all $P \geq 0.471$). Moreover, the 12-week RET intervention program effectively increased the distance covered in the 6-min walk test in both groups (time effect, $P = 0.001$, HEA 10% vs. BCS 6%), also with no significant difference between groups (time × group, $P = 0.277$).

Plasma measurements

No changes over time were observed in both groups' cholesterol, triglycerides, HDL, and LDL parameters, including fasting plasma glucose, insulin, and homeostasis model assessment (HOMA) (Supplementary Table S4).

Correlation between GDF-15 and sarcopenia markers

At baseline, no significant differences in GDF-15 levels were observed between groups (Supplementary Table S4). After 12 weeks of RET, no significant change in GDF-15 levels was evident in both HEA and BCS groups (time effect, $P = 0.568$; $\eta^2 = 0.02$). GDF-15 PRE training was negatively correlated with 1RM leg extension when considering all participants ($R = -0.439$, $P = 0.046$) or the HEA group specifically ($R = -0.652$, $P = 0.030$). Also, GDF-15 POST training was correlated negatively with walk speed when including all participants in the analysis ($R = -0.419$, $P = 0.05$) or the HEA group alone ($R = -0.640$, $P = 0.034$) (Supplementary Tables S5 and S6).

Discussion

In the present study, 12 weeks of progressive whole-body RET was shown to effectively increase muscle thickness in the lower limb muscles and muscle strength in the upper and lower body and improve physical performance (TUG and SPPB) and physical capacity (6-min walk test) in both HEA and BCS groups. Importantly, no differences in the beneficial effects of prolonged RET were observed between the HEA and BCS.

The decrease in estrogen production during menopause and the use of endocrine therapy in female BCS is associated with skeletal muscle mass and strength loss, leading to deterioration in physical performance. RET can effectively increase skeletal muscle mass, strength, and physical performance in the healthy postmenopausal population and in breast cancer survivors [28]. We observed an approximate increase of 5 ± 7% and 7 ± 4% in quadriceps muscle thickness in HEA and BCS participants, respectively.

Our results stand out in terms of skeletal muscle mass increase compared to a previous study published, which included women diagnosed with metastatic breast cancer who underwent 12 weeks of concurrent training. The study conducted by Escriche-Escuder et al. (2021) reports a significant 12% reduction in quadriceps muscle thickness, which could be explained by the more advanced progression of the neoplastic disease in the recruited participants and the training protocol that incorporated both aerobic and strength exercises at a lower intensity by recommendations for patients with bone lesions due to metastasis [29].

Additionally, no differences were found in the responses to RET when the data were stratified to specifically compare patients who received endocrine therapy (tamoxifen or aromatase inhibitors) ($n = 6$) with those who did not receive such therapy ($n = 5$).

Scientific evidence has reported difficulties and limitations in increasing skeletal muscle mass through exercise interventions in the oncological population [30–32]. This refers to the heterogeneity of the RET protocols applied, as indicated by the systematic review conducted by Fairman et al. [33]. Therefore, it is crucial to apply a minimal necessary exercise dose to improve skeletal muscle mass. Discrepancies in muscle hypertrophy outcomes have also been described in postmenopausal women who are BCS. Our study hypothesized a lower gain in skeletal muscle mass compared to healthy postmenopausal women.

Lower estrogen concentrations due to menopause and the use of adjuvant endocrine therapy to prevent breast cancer recurrence are currently reported to be associated with a reduction in skeletal muscle mass and strength [30]. Previous studies have shown that estrogen protects skeletal muscle by attenuating muscle damage and inflammation, stimulating muscle repair and regenerative processes, and maintaining satellite cell function [31, 32]. These findings highlight the importance of estrogen for skeletal muscle maintenance in women and suggest that prescribing tamoxifen or aromatase inhibitors could make it even more challenging to preserve muscle health in postmenopausal women [34, 35].

We found no significant differences between the groups after 12 weeks of RET. Schoenfeld et al. (2017) identified that training parameters such as intensity, volume, and frequency of RET are crucial for hypertrophic and strength adaptations in the general population [36, 37]. Therefore, the progressive training regimen with high-intensity resistance exercises applied in the present study effectively improved the skeletal muscle mass of postmenopausal BCS. Our RET protocol and results were comparable to those achieved by Galvão et al. (2006), who showed a 15% increase in quadriceps muscle thickness in men diagnosed with prostate cancer under androgen deprivation treatment after a more extended period of RET compared to our study (20 weeks vs. 12 weeks) [24].

Regarding muscle strength, other studies evaluating the effects of a 24-week and a 16-week RET training protocol in postmenopausal breast cancer survivors showed an average increase of 25% and 26% in 1RM of chest press and an increase of 26% and 30% in 1RM of leg extension [38, 39].

It is important to note that these improvements are smaller than those obtained in our study, which, despite a training period of only 12 weeks, but at high intensity, demonstrated a 29% and 43% 1RM increase in the exercises, respectively. These discrepancies could be attributed to a lower number of weekly sessions and the potentially more challenging initial conditions of the participants in the study by Simonavice et al. (2014), as well as a lower volume in the total exercise load in the study by Serra et al. (2018). On the other hand, Serra et al. (2018) also studied physical performance and functional capacity, reporting significant improvements in the chair stand time test and the 6-min walk test without changes in walking speed. As mentioned above, this research team implemented a lower exercise volume and intensity, which could explain the discrepancies in their results compared to our study [39].

Considering that muscle strength serves as a substantial predictor of mortality among BCS [40], the findings from this study hold crucial clinical significance. An improvement in the plasmatic lipid profile of female BCS under treatment with tamoxifen who undergo RET has already been described and is attributed to adaptations in fat oxidation capacity[15]. de Jesus Leite et al. (2021) demonstrated that 12 weeks of RET promoted a significant reduction in triglycerides (15%), total cholesterol (6.8%), and LDL cholesterol (9.7%) levels in addition to an increase in HDL cholesterol (17%) in the described population. These results differ from those obtained by our study, where we observed a slight decrease in lipid profile parameters without statistically significant differences over time and between groups (HEA vs. BCS) [15]. The scientific literature has documented the beneficial hypocholesterolemic and hypotriglyceridemic effects produced by the oral use of tamoxifen, along with decreased mortality related to coronary heart disease observed in patients receiving treatment with this endocrine therapy [15, 41, 42]. On the contrary, the effects of the prescription of aromatase inhibitors on the plasma profile are not apparent yet. However, most studies have shown that the use of this medication unfavorably alters the lipid profile [43, 44]. The reasons above would explain the lower effects on biochemical markers observed in our study because the sample was heterogeneous and included BCS with and without endocrine therapy (tamoxifen or aromatase inhibitors). Therefore, future studies could investigate these differences in detail by comparing each type of endocrine therapy as separate study groups. Finally, a higher concentration of plasma GDF-15 was negatively correlated with muscle strength and walking speed, mainly in healthy postmenopausal women. A decrease in these physical parameters is related to sarcopenia, as is the loss of muscle mass associated with higher concentrations of GDF-15 in other studies [16]. These findings support the potential of GDF-15 as a possible biomarker for changes associated with age-related sarcopenia.

Among the limitations of this study, it is important to note that the findings cannot be extrapolated to premenopausal women diagnosed with breast cancer or those undergoing active chemotherapy and radiotherapy treatment. This study included an optimal number of participants per group, as determined by post hoc statistical power analysis, which demonstrated a 95% power to detect the pre-established difference in total quadriceps muscle thickness between groups. However, a larger sample size of postmenopausal breast cancer survivors is needed to examine results based on the presence or absence of endocrine therapy and to differentiate between specific types of therapy, such as tamoxifen or aromatase inhibitors. Consequently, this study focuses exclusively on comparing the effects of RET between healthy postmenopausal women and postmenopausal women with BCS.

Despite these limitations, our results clearly indicate that RET is beneficial in mitigating the adverse effects of menopause and breast cancer on skeletal muscle mass, strength, physical performance, and overall physical capacity. The strengths of this study include high participant compliance and adherence to the exercise program, stable diet, and moderate physical activity levels, with expected increases in vigorous activity due to the high-intensity RET program. We strongly recommend the implementation of personalized and supervised RET for both healthy postmenopausal women and postmenopausal breast cancer survivors.

In conclusion, this study indicates that 12 weeks of RET increases skeletal muscle mass, strength, and physical performance in postmenopausal women. No differences were observed between healthy postmenopausal women and postmenopausal BCS, suggesting similar benefits for both groups.

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Author contribution M.A-A and G.N.M-N: Study design, M.A-A, A.A-M, N.V-S, R.M-C, J.C-L, A.S-L, N.H, J.S, L.A-S: Experiments' organization and performance, M.A-A, K.F-V, R.C, G.N.M-N: Data analysis, M.A-A, K.F-V, R.C, G.N.M-N: Manuscript drafting, M.A-A and G.N.M-N: Editing and All author: revision of manuscript and Approved of final version.

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Data availability Some data is provided within the manuscript or supplementary information files. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval The protocol and informed consent were approved (registration record N°004_23) by the scientific ethics committee of Universidad de La Frontera, Temuco, Chile.

Consent for publication A signed informed consent was obtained from each participant. The informed consent is available upon request.

Competing Interests The authors declare no competing interests.

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