Original Article

Effect of exercise on bone structural traits, physical performance and body composition in breast cancer patients - A 12-month RCT

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Abstract

In this 12-month RCT, we examined whether aerobic impact exercise training (3x/week) could facilitate breast cancer survivors' recovery by enhancing their bone structural strength, physical performance and body composition. After the adjuvant chemo- and/ or radiotherapy, 86 patients were randomly assigned into the training or control group. Structural bone traits were assessed with pQCT at the tibia and with DXA at the femoral neck. Agility (figure-8 running), jump force and power (force platform), grip strength and cardiovascular fitness (2-km walk test) were also assessed. Training effects on outcome variables were estimated by two-way factorial ANCOVA using the study group and menopausal status as fixed factors. Bone structural strength was better maintained among the trainees. At the femoral neck, there was a small but significant 2% training effect in the bone mass distribution (p=0.05). At the tibial diaphysis, slight 1% to 2% training effects (p=0.03) in total cross-sectional area and bone structural strength were observed (p=0.03) among the postmenopausal trainees. Also, 3% to 4% training effects were observed in the figure-8 running time (p=0.03) and grip strength (p=0.01). In conclusion, vigorous aerobic impact exercise training has potential to maintain bone structural strength and improve physical performance among breast cancer survivors.

Keywords: Bone, Breast Cancer, Exercise, Muscle, Rehabilitation

Introduction

Breast cancer is the most common malignant disease of women in Western countries. It affects more than 1.3 million women worldwide every year[1]. Fortunately, the survival rate has improved substantially during the last few decades because of early diagnosis and efficient adjuvant therapy[2]. However, bone loss is one of the negative consequences of adjuvant treatments, which can eventually lead to osteoporosis and related fragility fractures[3]. In addition, cancer treatments also compromise physical performance of these patients.

Besides directly improving physical performance and reducing the risk of falling, physical activity and exercise are among the key preventative strategies to prevent bone loss and osteoporosis, and also to reduce the risk of fractures in population[4-6]. Different training trials have been carried out among breast cancer survivors and some positive effects has been observed in areal bone mineral density (BMD) measured with dual energy X-ray absorptiometry (DXA)[7-10]. However, BMD is difficult to interpret unambiguously[11], and thus it remains open on which bone structural trait (e.g., bone cross-sectional size, cortical geometry, trabecular density) the particular exercise had an effect, if any. It is possible that the bone structural strength can improve without a measurable change in BMD[12]. Therefore, a direct assessment of different bone structural traits is preferred, and peripheral quantitative computed tomography
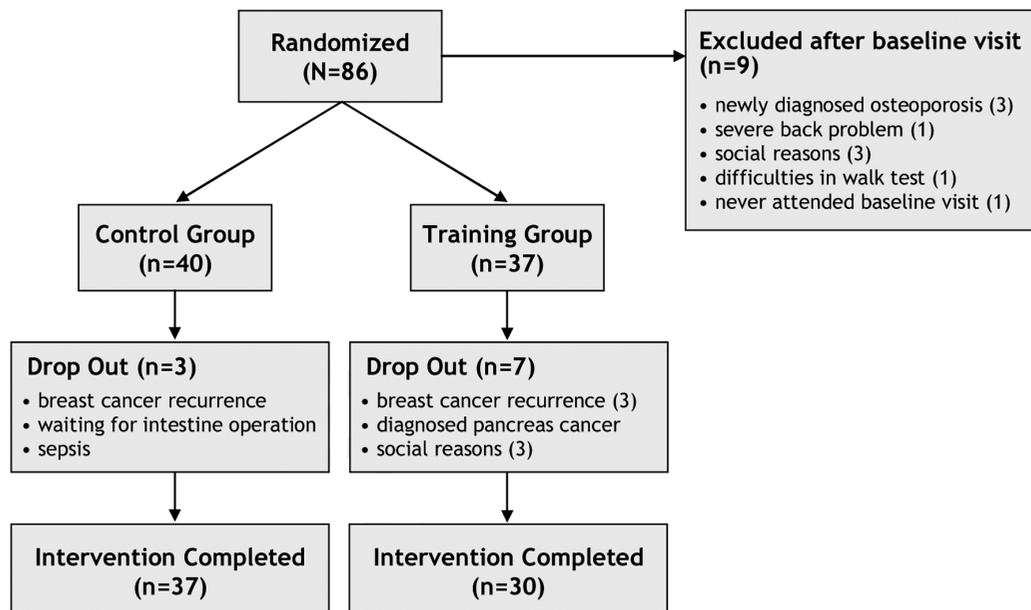
Figure 1. The trial flow diagram.

(pQCT) permits this with a marginal X-ray dose[13]. So far, specific effects of exercise on bone structure have not been reported among breast cancer survivors.

The present study represents a substudy of a large multicenter exercise trial of breast cancer survivors[10] and was undertaken to assess the effects of a 12-month vigorous aerobic exercise regimen on bone structural traits in pre- and postmenopausal breast cancer patients after adjuvant treatments. The apparent osteogenicity of this exercise regimen was evaluated in a pilot study[14]. We hypothesized that participation in regular vigorous exercise would result in better maintained bone strength and physical performance of breast cancer survivors, as well as facilitate their weight management. The primary outcomes of the present study were bone structural traits of the weight-bearing tibia and femoral neck assessed with pQCT and DXA-based structural analysis, respectively, whereas the secondary outcomes included different traits physical performance and body composition.

Materials and Methods

Study design

The present study is a 12-month prospective randomized controlled, examiner-blinded exercise trial of breast cancer patients that represents a substudy of a multicenter BREX study (NCT00639210). While the multicenter study was carried out in Helsinki, Tampere and Turku University Hospitals[10,15], the present study with a larger set of measurements (including pQCT and dynamic muscle force assessment) than in the parent trial, was carried out in Tampere only. All measurements were done at baseline before randomization and after the 12-month intervention. Further, the examiners were kept blinded to the group allocation. The ethical committee of Helsinki University Hospital approved the study protocol and the participants gave signed informed consent.

Participants

Eighty-six patients aged from 38 to 66 years could be recruited from the Department of Oncology in Tampere University Hospital during a two-year period. The flowchart is presented in Figure 1. All patients were operated with total mastectomy or breast conserving resection with sentinel lymphnode biopsy, or axillary evacuation. Adjuvant treatment was given according to clinical guidelines either with chemotherapy or endocrine therapy or both. Post-operative radiotherapy was given after the breast conserving operation and to regional lymphnodes in node positive patients. The group characteristics are given in Table 1.

Inclusion criteria were histologically proven invasive breast cancer, pre- or postmenopausal breast cancer patient treated with adjuvant chemotherapy or radiotherapy within four months or started adjuvant endocrine therapy no later than 4 months earlier, and age between 35 and 68 years (the trial was primarily designed for women at their working age). Because of ethical reasons, patients were not recruited immediately after getting their cancer diagnosis and primary treatment. The 4 month time frame was set for consistency between participants and to avoid considerable variation in their spontaneous recovery before the intervention. Because the oldest breast cancer patients were excluded, the exercise classes could be designed vigorous enough to be potentially osteogenic but not too demanding and thus feasible for all participants.

	Training	Control
	Mean (SD)	Mean (SD)
Age, yrs	53.7 (6.8)	52.6 (7.1)
Height, m	1.65 (0.05)	1.64 (0.05)
Weight, kg	73.4 (14.1)	70.8 (15.5)
Baseline Physical Activity (hours per week)		
Light PA (MET <3)	5.3 (5.0)	5.1 (3.1)
Moderate PA (MET 3 to 6)	2.5 (2.6)	2.0 (2.9)
Hard PA (MET 6 to 9)	0.3 (0.6)	0.5 (1.2)
Very hard PA (MET 9>)	0.0 (0.0)	0.1 (0.5)
6-month Physical Activity (hours per week)		
Light PA (MET <3)	5.5 (4.1)	5.4 (4.8)
Moderate PA (MET 3 to 6)	3.1 (2.6)	2.5 (2.2)
Hard PA (MET 6 to 9)	0.7 (1.4)	0.6 (0.6)
Very hard PA (MET 9>)	0.0 (0.0)	0.0 (0.0)
12-month Physical Activity (hours per week)		
Light PA (MET <3)	6.4 (4.9)	10.8 (6.5)
Moderate PA (MET 3 to 6)	3.8 (3.6)	0.0 (0.0)
Hard PA (MET 6 to 9)	0.6 (0.8)	0.0 (0.0)
Very hard PA (MET 9>)	0.0 (0.0)	0.0 (0.0)
Menopausal Status* (proportion of patients, %)		
Premenopausal	48	50
Postmenopausal	52	50
Histological Grade (proportion of patients, %)		
I	12	20
II	59	60
III	29	20
Operation (proportion of patients, %)		
Breast conserving	56	40
Mastectomy	44	60
Chemotherapy (proportion of patients, %)	88	90
Endocrine therapy (proportion of patients, %)	88	88
aromatase inhibitors (%)	44	43
tamoxifen (%)	44	45
Radiotherapy (%)	79	78

* Of note, it is not known whether some premenopausal women at baseline turned menopausal during the 1-year intervention because of concomitant use of intrauterine devices.

Table 1. Group characteristics.

Exclusion criteria were hematogenous metastases, no systemic adjuvant therapy or only tamoxifen for postmenopausal women, recent pregnancy or lactation (<1 year), severe cardiac disease (NYHA class III or more), myocardial infarction within 12 months, uncontrolled hypertension, verified osteoporosis (T-score<-2.5), other serious illness or medical condition which could be a contraindication for exercise, patients not capable of training (severe knee arthrosis, ligament or cartilage injuries at lower extremities), residence more than one hour from the exercise center, or being a competitive athlete. The eligible participants were then stratified by age and adjuvant endocrine therapy, and randomly assigned by computer program into exercise or control groups.

Exercise intervention

To facilitate broad applicability of the exercise program among breast cancer survivors, the training was designed to be performed in empty classrooms without extensive training equipment. The exercise program was found feasible for breast cancer patients in our earlier pilot study[14]. The weekly training program comprised one guided vigorous aerobic exercise session and three similar home training sessions. Training sessions were arranged in four separate small groups, about ten trainees in each group on average.

The guided training session comprised a 30 to 40 minute effective training period between 10-minute warm-up and cool-down periods. On alternate weeks, the effective part of the guided

training was based either on step aerobics or circuit training. Exercise movements rested on impact training originally found effective in middle age healthy women[16]. These movements were further completed with odd-impact exercise movements, a classification which was originally introduced by Nikander et al. in 2005[17]. The feasibility of selected movements was tested in a pilot study of breast cancer patients[14]. The training included hops and jumps causing peak loading mostly at the level of 4-5 times of body weight (BW) Participants performed around 100 hops and jumps during a typical exercise class, but even 150 to 180 such movements per session were done[14]. In addition, dumbbell exercises were used for upper extremity training between the demanding lower extremity exercises for recovery and also to decrease potential upper extremity swelling, and to improve grip strength. In the beginning of the intervention, the training intensity was kept at the moderate RPE-level of 11-13 (Rating of Perceived Exertion Scale) and was gradually increased to the somewhat hard or hard RPE-level at 14-16. In general, the supervised training was intended to be near to the anaerobic threshold but mostly aerobic. In our study, the highest level of training corresponded to about 80% of patients' maximum heart rate.

Supervised step aerobics session consisted of several typical step movements to diverging directions. Circuit training consisted of three rounds of 8 to 10 different vigorous movements such as rope-jumping and skate jumping, resulting in a total of 100 to 150 jumps, hops and leaps during each session. Duration of each circuit training movement varied from 20 to 40 seconds with a similar rest period between consecutive movements. In total, the planned weekly exercise program was intended to consist of one of the guided training sessions described above and at least two home training sessions (three home sessions were recommended, but two sessions were considered sufficient in the study protocol).

The home training session consisted of a modified combination about 100 hops, leaps and jumps similar to those employed in the guided steps and circuit training programs. In addition, brisk endurance training (walking, cycling, swimming etc. based on patients' own preference) at the same RPE level was recommended for improving participants' cardiovascular fitness and facilitating their weight management, and also to attain the recommended 150 minutes of weekly physical activity.

The control group was advised to continue their normal daily routines and activities during the 12-month intervention period.

Measurements
Anthropometry and body composition

Body height and body weight were measured using standard methods. Body fat-% was assessed with DXA (Lunar Prodigy Advance, GE Lunar, Madison, WI, USA). Besides the total body fat-%, site-specific android (approximately corresponds to belly region between the iliac crest and ribcage) and gynoid (approximately corresponds to hip and buttock regions) fat-% was evaluated according to the manufacturer's protocol. In our laboratory, the *in vivo* precision (coefficient of variation, CV%) is 1.3% for total body fat-%, 1.6% for android fat-%, and 2.2% for gynoid fat-%[18].

Physical activity

Crude information on the type, amount and intensity of leisure time physical activity was collected via a recalled questionnaire at baseline and after 6 and 12 months. Leisure time physical activities were classified as low, moderate, hard or very hard intensity activities. Information on amount and intensity of current physical activity just before the start of the exercise intervention, and after 6- and 12-month was collected by a prospective two-week physical activity diary from all patients[19]. Each reported activity was categorised as light intensity (<3 METs), moderate intensity (3 to 6 METs), hard intensity (6 to 9 METs) or very hard intensity activity (>9 METs) based on the compendium of physical activities[20]. Total physical activity amount as MET hours per week (MET-h/wk) was calculated by multiplying the intensity of the activity by the time spent on the activity. MET-h/wk were also analysed separately for moderate to very hard intensity exercise training. In addition, the time spent in supervised and home training and amount of jumps related to home exercise training were collected via separate questions only from the trainees.

Bone traits

The pQCT scans (XCT 3000, Stratec Medizintechnik GmbH, Pforzheim, Germany) of the left distal tibia (5% of the estimated tibial length proximal to the distal endplate) and tibial midshaft (50%) were taken according to our standard measurement and analysis procedures[13]. For the tibial shaft, bone mineral content (BMC, mg), total cross-sectional area (ToA, mm^2), cortical density (CoD, mg/cm^3), and density-weighted polar section modulus (BSI, an index of bone strength against torsion and bending, mm^3) were determined. For the distal tibia, trabecular density (TrD, mg/cm^3) was determined in addition to BMC, ToA, and BSI. In our laboratory, the *in vivo* precision is 1.0% for BMC, 2.0% for ToA, 2.8% for CoA, and 2.3% for BSI at the distal tibia; and 0.6% for BMC, 1.2% for ToA, 0.9% for CoA, and 1.9% for BSI at the tibial shaft.

Femoral neck bone mineral content (BMC) was measured with DXA (Lunar Prodigy Advance). In addition, the femoral neck structure was estimated using the Advanced Hip Analysis (AHA) software of the DXA system. AHA provides data on the cross-sectional area occupied by bone mineral (CSA, mm^2, the amount of load-bearing bone mass and an index of bone strength against compression), section modulus (Z, mm^3, an index of bone strength against bending), distance from the center of mass to the superior neck margin (centroid, mm) and outer diameter (width, mm) for the neck section of minimum cross-sectional moment of inertia. In our laboratory, the *in vivo* precision for CSA is 2.3%, for Z 3.8%, for centroid 2.1% and for width 1.2%.

Physical performance

Physical performance was assessed with figure-8 running (sec; a measure of dynamic agility), counter-movement jump (N and W/kg; a measure of dynamic muscle performance), maximal isometric muscle force of leg extension (kg), and

Bone traits	Training		Control		Training effect* (Training vs. Control)	p for TE[1]	p for IE[2]
	Baseline Mean (SD)	12-month	Baseline Mean (SD)	12-month	Mean (95% CI)		
Distal Tibia							
BMC, mg	665 (93)	653 (92)	641 (79)	624 (78)	5 (-1 to 10)	0.08	0.74
Total cross-sectional area, mm²	853 (107)	849 (108)	848 (109)	845 (111)	2 (-5 to 8)	0.60	0.38
Cortical Area, mm²	174 (35)	168 (34)	168 (31)	161 (30)	1 (-3 to 4)	0.71	0.96
Trabecular density, mg/ cm³	227 (27)	228 (26)	219 (24)	219 (24)	1 (-0 to 3)	0.09	0.18
Polar section modulus, mm³	1158 (290)	1083 (297)	1096 (291)	1005 (322)	18 (-50 to 86)	0.59	0.25
Tibial Shaft							
BMC, mg	818 (83)	802 (87)	812 (90)	789 (89)	3 (-4 to 11)	0.38	0.21
Total cross-sectional area, mm²	454 (58)	455 (60)	451 (49)	449 (46)	1 (-2 to 4)	0.65	**0.03***
Cortical Area, mm²	287 (28)	287 (29)	285 (31)	282 (30)	2 (-0 to 4)	0.09	0.11
Cortical density, mg/ cm³	1140 (26)	1119 (31)	1138 (25)	1120 (32)	-2 (-8 to 4)	0.49	0.95
Polar section modulus, mm³	1794 (312)	1756 (314)	1760 (262)	1700 (243)	9 (-15 to 34)	0.46	**0.03***
Femoral Neck							
BMC, mg	456 (66)	451 (67)	449 (49)	441 (49)	0 (-0 to 1)	0.30	0.80
Cross-sectional bone area, mm²	143 (21)	142 (22)	142 (16.7)	140 (16)	1 (-2 to 3)	0.64	0.14
Width, mm	32.1 (1.6)	32.1 (1.7)	31.8 (1.9)	31.8 (1.9)	-0.0 (-0.3 to 0.2)	0.71	0.15
Centroid, mm	16.7 (1.1)	16.6 (1.2)	16.2 (1.2)	16.5 (1.3)	-0.3 (-0.6 to -0.0)	**0.05***	**0.02***
Section modulus, mm³	608 (109)	592 (105)	582 (87)	574 (90)	-4 (-22 to 14)	0.64	0.61

[1] The absolute treatment effect between training and control groups with the menopausal status at 12-month follow-up (ANCOVA: the baseline value was used as a covariate, group and menopausal status as fixed factors, Sidak-correction).

[2] The interaction treatment effect (group x menopausal status) between training and control groups at 12-month follow-up (ANCOVA: the baseline value was used as a covariate, group and menopausal status as fixed factors, Sidak-correction).

* Treatment effect p<0.05.

Table 2. Bone traits in the study groups at baseline and at 12-month follow-up, and the observed training effects and p-values for the training effects (TE) and for the interaction effects (IE). Mean (Standard Deviation).

hand grip strength tests (kg). Dynamic maximal take-off force (N) and power (W/kg) were measured with a force-plate (Kistler Ergojump 1.04, Kistler Instrumente AG, Winterthur, Switzerland) during the counter-movement jump with the precision of 3%. Maximal isometric leg extension (kg) and hand grip strength (kg) were measured with isometric leg press (Tamtron, Tampere, Finland) and hand dynamometers (Digitest, Muurame, Finland) with a precision of about 5% and 10%, respectively[21,22]. Walking time (min) and heart rate (beats/min) at the end of the test (measures of cardiorespiratory fitness) were assessed with the 2-kilometer walk test.

Statistical analysis

Statistical analysis was performed with SPSS statistics software (version 15.0). Means and standard deviations (SD) are given as descriptive statistics. All patients who attended the 12-month measurements were included in the two-way factorial analysis of covariance (ANCOVA) to estimate the training effect on the outcome variables at the 12-month follow-up. Baseline values were used as covariates, and the group (training vs. control) and menopausal status (premenopausal vs. postmenopausal) were used as fixed factors. The training effect was defined as a mean between-group difference in absolute changes from baseline to 12 months. Besides evaluating the primary training effect, the two-way factorial ANCOVA permitted analysis of whether there was an interaction between training and menopausal status. Sidak-correction was used as a post-hoc test to control for multiple testing. A p-value less than 0.05 was considered statistically significant. The sample size of 86 subjects at the baseline provided the present study an 80% statistical power to detect a training effect that corresponds to about 0.6 (standardized difference) of SD observed in individual responses in traits of interest at significance level of 0.05.

Results

The trial flow diagram is shown in Figure 1. There were 3 drop outs (8%) in the control group and 7 (19%) in the training group. Clinical characteristics of the study groups at baseline and at the 12-month follow-up and general physical activity related to other than the supervised exercise program at baseline, 6-month and 12-month follow-up points are shown in Table 1. Two out of 37 trainees (5%) did not participate in the guided training at all. Also, three trainees attended the super-

	Training		Control		Training effect[1] (Training vs. Control)	p for TE[1]	p for IE[2]
	Baseline Mean (SD)	12-month	Baseline Mean (SD)	12-month	Mean (95% CI)		
Body composition							
Weight, kg	73.4 (14.1)	73.1 (14.7)	70.8 (15.5)	71.5 (16.6)	-0.4 (-2.2 to 1.3)	0.62	0.76
Fat %	40.5 (7.6)	39.9 (7.5)	39.6 (8.2)	40.2 (8.0)	-0.7 (-2.1 to 0.8)	0.36	0.74
Android fat %	45.8 (10.4)	45.5 (9.9)	43.1 (11.4)	44.3 (11.3)	-0.3 (-2.3 to 1.8)	0.80	0.68
Gynoid fat %	46.5 (5.7)	45.9 (6.0)	46.4 (6.1)	47.1 (6.1)	-1.2 (-2.4 to 0.1)	0.06	0.96
Physical performance							
Figure-8 running time, s	17.0 (2.9)	16.0 (1.4)	16.9 (2.7)	17.1 (2.9)	-0.5 (-0.9 to -0.1)	**0.03***	0.11
Counter-movement jump force, N	1426 (247)	1477 (269)	1492 (312)	1443 (242)	67 (-29 to 164)	0.17	0.10
Counter-movement jump power, W/kg	28.9 (4.8)	29.3 (5.0)	29.2 (4.9)	29.5 (4.8)	0.3 (-1.5 to 2.0)	0.77	0.85
Isometric leg extension force, kg	136 (23)	136 (23)	134 (25)	136 (29)	-2 (-11 to 6)	0.54	0.32
Isometric grip strength, kg	31.9 (5.6)	32.7 (5.3)	31.6 (5.3)	30.8 (5.7)	1.3 (0.4 to 2.3)	**0.01***	0.16
2-km walk time, min	17.7 (2.0)	16.9 (1.9)	17.7 (2.2)	17.2 (2.1)	0.0 (-0.5 to 0.6)	0.90	0.31
Heart rate at the end of the 2-km walk	150 (18)	148 (18)	140 (20)	141 (20)	-4 (-9 to 2)	0.22	0.17

[1] *The absolute treatment effect between training and control groups with the menopausal status at 12-month follow-up (ANCOVA: the baseline value was used as a covariate, group and menopausal status as fixed factors, Sidak-correction).*

[2] *The interaction treatment effect (group x menopausal status) between training and control groups at 12-month follow-up (ANCOVA: the baseline value was used as a covariate, group and menopausal status as fixed factors, Sidak-correction).*

* Treatment effect p<0.05.

Table 3. Body composition and physical performance in the study groups at baseline and at 12-month follow-up, and the observed training effects and p-values for the treatment effects (TE) and for the interaction effects (IE) (group x menopause). Mean (Standard Deviation).

vised sessions no more than 5 times (of all 52 weekly possibilities). The average adherence to the weekly supervised sessions among the remaining 30 trainees was 76%. As regards to the intervention based on home exercises, 27 trainees returned their training diaries reporting that they had accomplished vigorous home training 1.2 times per week and endurance training 1.7 times per week. The average time spent doing an endurance training session was 88 minutes. No severe side-effects were reported that related to the supervised exercise classes. However, four moderate overuse injuries were reported to cause joint and muscle pain and muscle stiffness to the lower extremities. However, all these symptoms were relieved after 1-2 weeks break from the exercise training, after which all these participants returned to their classes.

Training effects on bone traits

Bone traits at baseline and at the 12-month follow-up, and the observed training effects are shown in Table 2. In general, bone loss was evident in both groups, but bone structural strength was better maintained among the trainees. At the femoral neck, there was a small, but significant 2% training effect in the bone mass distribution (p=0.05). At the tibial diaphysis, slight 1% to 2% training effects (p=0.03) in total cross-sectional area and bone structural strength were observed (p=0.03) among the postmenopausal trainees.

Training effects on physical performance

Physical performance at baseline and at the 12-month follow-up, and the observed training effects are also shown in Table 3. In general, the physical performance improved slightly in both groups. The trainees' figure-8 running time improved by 0.5 seconds, (~3% between-group difference, p<0.03), whereas the changes, if any, in the lower extremity muscle force and power were similar between the groups. However, the trainees' grip strength increased ~1 kg, while it decreased by a similar degree in the control group (~4% between-group difference, p=0.01). No significant training effect was observed on cardiorespiratory performance. Be it noted, however, that the 2 km walking time was about half a minute shorter (3-5%) in both groups at the end of intervention compared to its beginning.

Training effects on body composition

Body composition at baseline and at the 12-month follow-up, and the observed training effects are shown in Table 3. The mean body weight in both groups remained almost unchanged (within ±1 kg of the baseline weight) during the 12-month study period. Also, total body and android fat-% were not affected by training, whereas trainees' gynoid fat-% showed a trend (p=0.06) for decreased 1.2 percentage units compared to the controls' gynoid fat-%.

Discussion

Multiple small, but positive health-related training effects on bone structural traits (~1-2%), physical performance (~3-4%) and body composition (~1-3%) were observed among breast cancer patients who took part in a 12-month vigorous aerobic exercise training regimen. However, the observed exercise effects remained mostly small and indicative only. Further studies with greater number of participants would be needed to confirm the results and evaluate their clinical relevance.

In this substudy of the multicenter parent BREX trial[10], we used pQCT for the structural analysis of distal tibia and mid-diaphysis, and DXA-based Advanced Hip Analysis for the coarse structural analysis of the femoral neck. Interestingly, all significant changes in bone structural traits showed interaction with menopausal status. First, the total cross-sectional area at the tibial diaphysis expanded slightly among the postmenopausal trainees. This kind of adaptation leads to increased resistance of bone shaft against bending forces. Bending, in turn, is a typical loading type for tibia that occurs in habitual loading such as walking and running. In the large parent trial[10], we observed that femoral neck bone loss was completely prevented among the premenopausal trainees, while the premenopausal controls showed a 1-2% loss in femoral neck BMD. In the present substudy, the treatment effect on the centroid of the femoral neck bone mass distribution suggested that the pre- and postmenopausal trainees better maintained their bone mass in the superior region of the femoral neck than the controls. Relatively greater bone mass in the upper region is relevant because hip fractures usually originate from the weakened upper region[23]. Even though small, this kind bone mass distribution at the femoral neck observed among the trainees may have some clinical bearing in terms of risk of fracture in older age. Obviously, further studies are needed.

While the training effects on body composition remained rather small and of borderline statistical significance, gains were observed in physical performance. Besides improved grip strength, the trainees improved their agility as could be judged from the better figure-8 running time. Since over 90% of hip fractures are caused by falls in elderly people[24], improved agility through better control of dynamic balance may account not only for preventing falls but also for preventing fractures. A recent meta-analysis showed that leg extension strength can be improved by aerobic and resistance training in breast cancer patients[25]. However, we did not observe any improvement in leg extension strength, which may be explained by the fact that the present intervention did not include resistance training but aerobic impact exercises only[14]. In previous interventions of breast cancer patients, both resistance training and weight-bearing aerobic training have been successfully employed[26-27]. Schmitz et al. showed that resistance training increased upper- and lower-body muscle strength, whereas Schwartz et al. showed that aerobic training was more effective in maintaining bone density than resistance training[26-27]. In this study, we mainly concentrated on aerobic weight-bearing impact exercises, and utilized sufficiently high ground impacts that have been found effective in improving bone density and structural strength among middle-aged women[14,16,28].

After enrollment into the study, the weekly time spent in leisure time physical activity increased in both groups (Table 1). In the training group, the mean amount of total physical activity increased from baseline to 12-months by 33% (2.7 hours) and in the control group slightly more – by 40% (3.1 hours). While the mean total amount of leisure time physical activity was equal between the groups at the 12-month follow-up, the mean intensity was higher in the training group. However, the possibility that the increased amount of physical activity also among the controls attenuated the observed treatment effects cannot be ruled out. With respect to the potential of breast cancer patients to improve healthy lifestyle, Szabo et al.[29] found in their cross-sectional study that only 37% of breast cancer patients but 71% of their healthy matched controls reported that they had participated in leisure time physical activity. Moreover, their breast cancer patients participated in less strenuous sports and weight-bearing activities and patients' tibial bone strength index was 6 % lower than in healthy matched controls. Similarly, we found that the controls preferred light activities and lost more bone in contrast to the trainees who performed more moderate to vigorous activities and better maintained their bone structural strength. As a wider perspective, leisure time activity can be crucial since physically active patients have also a lower cancer recurrence rates and a better survival rate[8].

The major strengths of the present study are the randomized controlled, examiner-blinded design and several measurements of bone structure, physical performance and body composition. Further, the feasibility of applied impact exercise training regimen was fairly good in this study. Those trainees who successfully completed the entire 12-month intervention period (81% of the total exercise group) adhered to supervised exercise program reasonably well, attending at least 75% of available sessions. On the other hand, the adherence to the home impact training was 60%, but together with endurance home training, the overall adherence to home training met the study protocol satisfactorily. The main limitations of the study are the relatively small sample size and heterogeneity of the patient group in terms of age and variation of adjuvant treatments. Thus, the present study remained apparently underpowered to detect potential training effects regarding the body composition, for example. A larger sample would also have allowed the possibility to assess dose-response relationships between the amount and intensity of exercise and respective changes in outcome variables of interest.

In conclusion, vigorous aerobic exercise resulted in small benefits in bone structural traits and physical performance of breast cancer survivors. However, since the findings were small on average and the strength of evidence remained limited despite the strong study design, larger exercise intervention trials with a longer follow-up periods and appropriate methods for assessment of bone structural strength and physical performance are needed to confirm the clinical relevance of the present findings.

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