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A Randomized Controlled Trial of Exercise to Prevent Bone Loss in Premenopausal Women with Breast Cancer

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Abstract

Background/Introduction/Objective: Premenopausal women treated for breast cancer are at high risk for bone loss. This trial examined the effects of a 1-year combined aerobic and resistance exercise program on bone mineral density (BMD) in women treated for premenopausal breast cancer.

Materials and Methods: Premenopausal women (n = 206) age ≤ 55 years at cancer diagnosis who were within two years of receiving adjuvant chemotherapy were randomized to a 12-month exercise program or a control group. BMD was measured by dual-energy X-ray absorptiometry at baseline and after 1 year; blood was drawn for skeletal markers. Change from baseline to end of study was compared within and between treatment groups using paired and unpaired *t*-tests.

Results: Lumbar spine BMD declined in both treatment groups with no significant difference between treatment groups (-0.008 ± 0.003 g/cm^2 exercise vs. -0.014 ± 0.003 g/cm^2 control, $p = 0.24$). However, among the women who did not lose lean mass during the study ($n = 100$, 54 control, 46 exercise), the exercise intervention prevented lumbar spine bone loss (0.001 ± 0.005 g/cm^2 treatment group vs. -0.014 ± 0.005 g/cm^2 control group, $p = 0.03$). Bone turnover markers decreased significantly in both groups with no differences between groups.

Conclusions: Among women who maintained lean mass, our exercise intervention prevented bone loss; however, our intervention did not prevent bone loss among women who lost muscle mass. Additional investigation into exercise regimens that can prevent both bone and muscle loss may help prevent long-term consequences of premenopausal breast cancer treatment.

Keywords: breast cancer, bone density, bone loss, exercise, osteoporosis, premenopausal

Introduction

One in eight women in the United States will develop breast cancer in their lifetime. In 2013, approximately 4800 breast cancer deaths occurred in women <50 years.[1] Screening and treatment options have improved significantly, resulting in improved survival for all women diagnosed with breast cancer, especially premenopausal women. Over the past two decades, breast cancer death rates have decreased by 34%. The decline in death rates has occurred more rapidly in women <50 years (decrease of 3.1%/year) than among women aged 50 years and older (decrease of 1.9%/year).[1]

Up to 70% of premenopausal women with breast cancer treated with adjuvant chemotherapy will develop premature ovarian failure and reduced estradiol levels, resulting in bone loss[2] and an increase in weight and fat mass that appear to be because of a reduction in physical activity.[3,4] These changes put premenopausal women at risk for several long-term health consequences. These include bone loss and metabolic derangements such as insulin resistance, dyslipidemia, and increased oxidative stress and inflammation. It is important to recognize skeletal and cardiovascular risk factors early on, as targeted interventions including exercise may be successful in preventing adverse outcomes.

Although the results of individual exercise trials in premenopausal women have varied, multiple meta-analyses suggest a positive impact of exercise on bone density in this population.[5–10] The few trials of exercise intervention trials

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in premenopausal women with breast cancer have had mixed results.[11–13]

Previous trials generally have been limited by small sample size and/or lack of controls. In addition, all have been conducted in close proximity to adjuvant chemotherapy and none have examined cardiovascular parameters. Thus, the effect of exercise on bone mineral density (BMD) and cardiovascular parameters in premenopausal women who have been treated for breast cancer remains unclear.

In this randomized trial, we hypothesized that physical activity in the form of a 12-month combined weight-bearing and aerobic exercise program would prevent bone loss in young breast cancer survivors, more than 1 year after initial diagnosis, who had been treated with chemotherapy with or without tamoxifen. Additional objectives of this study were to assess participants' menopausal status and determine the effect of exercise intervention on body composition and biochemical parameters, including gonadal steroids, calciotropic hormones (25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, parathyroid hormone), bone turnover markers, and risk factors for the metabolic syndrome and cardiovascular disease (fructosamine, Homeostatic Model Assessment for insulin Resistance [HOMA-IR], lipid profile).

Materials and Methods

Subjects

The Exercise for Bone Health: Young Breast Cancer Survivors study was a randomized controlled trial of an exercise intervention to prevent bone loss in 206 women aged ≤55 years who were premenopausal at the time of cancer diagnosis, who had received adjuvant chemotherapy, and who were at least 1-year postdiagnosis and cancer-free; complete data were available for 188 women. Women were recruited from the California Cancer Registry who had been diagnosed with local or regional stage breast cancer at age 50 or younger in San Francisco, San Mateo, Marin, and Solano counties. The study was approved by the Institutional Review Boards of the University of California San Francisco and California Health and Human Services Agency. All women provided written informed consent and medical clearance from their primary care provider.

Women were randomized to the intervention, a 12-month exercise program with a combination of resistance training and aerobic exercise administered through the Young Men's Christian Association (YMCA) or the control group, which received a monthly health newsletter. Treatments were allocated using a random number table. Randomization and treatment allocation were completed at the Northern California Cancer Center and the study intervention was implemented by study personnel and the YMCA coaches at the individual YMCA sites. Although the nature of the intervention precluded blinding, personnel conducting outcome measures (bone density and laboratory testing) were not informed of treatment assignments.

Community exercise program

Women randomized to the exercise program selected one of the eight participating YMCA sites and were assigned a YMCA coach. YMCA coaches were trained in the ''Coach Approach'' program, a YMCA-developed exercise support program focused on teaching exercisers how to begin an exercise program and maintain adherence. The coaches underwent additional training on exercise in women with breast cancer using ''The Breast Cancer Survivor's Guide to Fitness'' DVD developed by the Brigham and Women's Comprehensive Breast Health Center and training in the specific exercises selected for this study.

The exercise program consisted of resistance exercises targeting 13 major muscle groups and was completed on equipment available at the YMCA. Muscle groups targeted included hamstrings, quadriceps, gluteus, thigh abductors, thigh adductors, pectoralis, latissimus dorsi, biceps, triceps, deltoids, erector spinae, and rhomboids, as well as exercises for back and abdominal muscles tailored to the type of breast cancer surgery the participant had completed. Initially, participants began with one set of the 13 exercises, completing at least 8 repetitions and worked their way up to two sets of the exercises with 8–12 repetitions three times per week. In addition, participants completed 20–30 minutes of self-selected aerobic exercise three times per week, using cardiovascular machines at the YMCA or other aerobic exercises such as walking, running, or bicycling.

Coaches met with study participants initially to review the exercise goals and teach the participants how to use the exercise equipment. Participants signed an ''Exercise Support Process Contract.'' Participants and coaches met for ~1 hour at weeks 2, 6, 10, 18, 26, and at the end of the 1-year study intervention. Participants were asked to keep a log of their exercise either through notebook entries or using the computerized FitLinxx system available through the YMCA.

BMD, body composition, and laboratory measurements

BMD and body composition were measured by Dual energy X-ray absorptiometry (DXA) (Hologic Delphi, Bedford, MA) at baseline and after 1 year. Phantom scanning and quality assurance were performed on site daily. Biological samples were obtained by venipuncture and the Block98 food frequency questionnaire was administered at baseline and after 1 year. Biological samples were processed and stored at –80 degrees until completion of the study. Batched laboratory assays were performed at the Maine Medical Center Research Institute (Scarborough, ME) for all analytes except 1,25-dihydroxyvitamin D that was performed at Heartland Assays (Ames, IA).

Serum 1,25-dihydroxyvitamin D3 was measured by radioimmunoassay (Heartland Assays). Procollagen type I N-terminal propeptide, C-telopeptide, insulin-like growth factor 1, osteocalcin, 25-hydroxyvitamin D were measured by ISYS Autoanalyzer (chemiluminescence; R&D Systems for high-sensitivity C-reactive protein [hsCRP], bone-specific alkaline phosphatase [BSAP], and leptin; Immunodiagnostic Systems for all other analytes); hsCRP, insulin, intact parathyroid hormone (PTH), BSAP, leptin, adiponectin, estradiol, free testosterone, testosterone, estrone, follicle-stimulating hormone (FSH), and urine N-telopeptide (NTX) were measured by enzyme-linked immunosorbent assay (Inverness for NTX, Alpco for all other analytes); comprehensive metabolic panel was measured on an autoanalyzer; phosphorus and lipid were measured by spectrophotometry; and fructosamine was measured using a colorimetric assay.

Statistical analyses

For the statistical analyses, the change in each parameter from baseline to the end of the study was analyzed with

paired *t*-tests for within-group analyses and unpaired *t*-tests for between-group analyses. Changes among subgroups stratified by change in body composition were analyzed using analysis of variance. All statistical tests were two-sided. Sample size calculations demonstrated that 85 subjects per group (total $n = 171$) would provide 80% power to detect a difference in change in bone density between treatment groups of as low as 1.5% with standard deviation of 3.5% and two-sided alpha = 0.05.

Results

Recruitment and randomization

Overall, 206 women were enrolled and randomized into the study; 188 completed the 1-year intervention and had outcome measurements obtained at month 12 including 94 women in the intervention group and 94 in the control group. Reasons for withdrawing from the study included subject preference ($n = 11$), pregnancy ($n = 1$), weight exceeded DXA table limit ($n = 2$), death ($n = 1$), moved out of the region ($n = 2$), and lost to follow-up ($n = 1$). Reasons for withdrawing from the study did not differ by treatment group. One woman in the exercise group began treatment with intravenous bisphosphonate therapy during the study and was excluded from data analysis.

Women were recruited between July 2006 and March 2010. Follow-up continued for 1 year for each participant with the final follow-up visit in March 2011. Only one adverse event, increased nasal discharge after exercising, was considered related to the intervention. This was a long-standing effect the subject noted after any increased physical activity. This subject's research exercise regimen was altered with the involvement of her primary care provider to minimize this side effect.

Characteristics of the study participants are presented in Table 1. Women participating in the study were, on average, in their mid-40s with no differences between the treatment and control groups at baseline in age, BMI, lean mass, 25-hydroxyvitamin D levels, exercise, number of days since completing chemotherapy, percent menstruating, or type of chemotherapy received. The two groups differed in the use of tamoxifen with women randomized to control having a higher prevalence of tamoxifen use (72% control vs. 49% exercise, $p = 0.001$). There were no differences in dietary intakes between groups including intakes of total energy, protein, calcium, phosphorus, or vitamin D. Women in the control group had no change in physical activity as measured by metabolic equivalent of task (MET)-hours per day ($p = 0.3$), whereas the women in the intervention group had a significant increase in MET-hours per day of physical activity ($p < 0.001$).

BMD and body composition

Overall, lumbar spine BMD declined in both the exercise and control groups over the 12-month intervention with no significant difference between the groups in change in lumbar spine bone density (-0.008 ± 0.003 g/cm^2 in the exercise group vs. -0.014 ± 0.003 g/cm^2 in the control group, $p = 0.24$) (Fig. 1). However, among the women who did not lose lean mass during the study ($n = 100$, 54 control, 46 exercise), the exercise intervention was effective in preventing lumbar spine bone loss in the exercise group. The control group, despite maintaining lean mass, manifested a decrease in lumbar spine bone density. Bone density increased by 0.001 ± 0.005 g/cm^2 in the treatment group and decreased by -0.014 ± 0.005 g/cm^2 in the control group, $p = 0.03$ (Fig. 2). There were no statistically significant differences at baseline between the women who did not lose lean mass and those

Table 1. Baseline Characteristics of the Overall Study Population by Treatment Group (Mean ± Standard Deviation)

	Control, n = *103*	*Exercise,* n = *103*	p
Age (years)	45.2 ± 5.9	46.0 ± 5.7	0.36
BMI (kg/m^2)	25.7 ± 6.5	26.2 ± 6.0	0.56
Race (% white)	69	67	0.91
Lumbar spine BMD (g/cm^2)	1.002 ± 0.12	1.005 ± 0.01	0.86
Total hip BMD (g/cm2)	0.936 ± 0.11	0.927 ± 0.11	0.60
25-hydroxyvitamin D (ng/mL)	33.6 ± 13.6	31.9 ± 12.1	0.89
Lean mass (kg)	42.7 ± 7.3	44.0 ± 7.1	0.23
Hours/day exercise	0.93 ± 0.82	0.91 ± 0.89	0.87
Currently menstruating (% yes)	18%	18%	0.99
Days from end of chemotherapy to baseline visit	298 ± 152	317 ± 150	0.38
Treatment includes tamoxifen (% yes)	72%	49%	0.001
Chemotherapy received (%)			0.33
Adriamycin	62%	68%	
Cyclophosphamide	75%	79%	
Fluorouracil	0%	1%	
Methotrexate	0%	1%	
Phenylalanine mustard	0%	0%	
Paclitaxel	54%	58%	
Docetaxel	35%	28%	
Other	19%	19%	
Do not know	6%	4%	

BMD, bone mineral density.

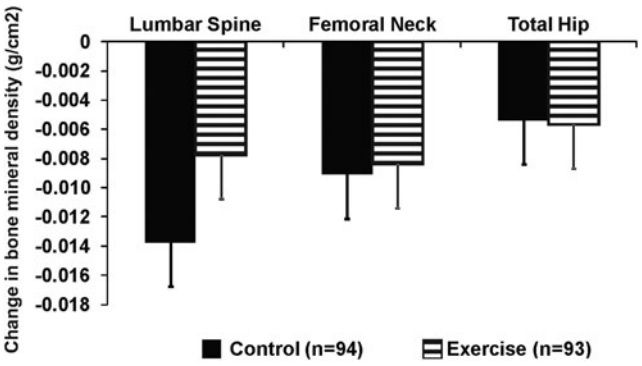

FIG. 1. Change in lumbar spine BMD in 187 women diagnosed and treated for premenopausal breast cancer randomized to a 12-month exercise program or control. BMD, bone mineral density.

who did in terms of age, race, weight, BMI, menstrual status, exercise status, or other parameters (Table 2).

Over the course of the study, there were statistically significant differences in change in weight and BMI between the women who lost lean mass and those who did not lose lean mass with $p < 0.001$ and $p = 0.001$, respectively (Table 3). At the 12-month time-point, the women who lost lean mass tended to report that their health was better than 6 months previously; self-reported health status by the women who maintained lean mass also tended to be improved ($p = 0.06$). Among the women who maintained lean mass, the women in the exercise group reported a higher amount of self-reported hours of exercise per day at month 12 than those in the control group ($p = 0.05$). There was no significant difference in change in bone density by treatment group for the subjects who lost lean mass. BMD declined by 0.013 g/cm^2 in the control group and decreased by 0.016 g/cm^2 in the treatment group ($p = 0.67$) for subjects who lost lean mass during the trial.

Laboratory outcomes

Within-group and between-group comparisons were performed among women who maintained lean mass during the trial for the biological parameters collected in the study. Bone turnover markers including markers of bone formation (osteocalcin, N-terminal propeptide of human procollagen type I), and markers of bone resorption (C-telopeptides and N-telopeptides) decreased significantly in both the exercise and control groups over the study with no significant differences between groups (data not shown). There were no differences between groups in change in any gonadal steroids including total and free testosterone, estrone, and estradiol (data not shown). There were increases in 25-hydroxyvitamin D levels in both the control and exercise groups ($p < 0.01$ and $p = 0.06$, respectively) over the 12-month period; there was no difference between the two groups in terms of change in 25-hydroxyvitamin D levels over the 12-month study. In the exercise group, 1,25-dihydroxyvitamin D increased by 5.3 ± 2.1 pg/mL between baseline to month 12 ($p = 0.0.1$) and was unchanged in the control group. The difference in the change in 1,25-dihydroxyvitamin D between the treatment groups was of marginal statistical significance ($p = 0.08$).

HOMA-IR, an estimate of insulin resistance, increased significantly in both groups with no differences between treatment groups. There was an increase in serum fructosamine in the control group over the 12-month period that approached statistical significance ($p = 0.06$), and no change in fructosamine in the exercise group. There was a significant increase in total cholesterol:HDL ratio in the control group over the 12-month period ($p = 0.03$), but there was no significant change in total cholesterol:HDL ratio in the exercise group.

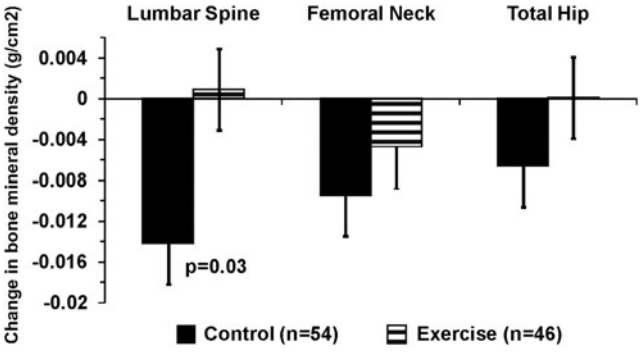

FIG. 2. Change in lumbar spine BMD in the subset of women diagnosed and treated for premenopausal breast cancer randomized to a 12-month exercise program or control who maintained or gained lean mass during the trial ($n = 54$ control, 46 exercise).

Discussion

Premenopausal women are at increased risk for bone loss after breast cancer treatment. Chemotherapy, nutritional changes, weight loss, and premature loss of estrogen are all potential mediators of bone loss. Previous studies have been inconsistent in terms of the effects of aerobic versus resistance exercise on bone density and the effects on different bone density sites, but overall studies have suggested possible beneficial effects of exercise on BMD in women with breast cancer.

A recent study in 124 premenopausal breast cancer survivors showed that a 12-month exercise intervention including aerobic and resistance training instituted within 4 months of adjuvant chemotherapy prevented bone loss at the femoral neck, but was ineffective at the lumbar spine.[12] In contrast, an aerobic exercise intervention in 14 premenopausal women with stage I–III breast cancer actively undergoing chemotherapy showed that aerobic, but not resistance, training reduced bone loss at the lumbar spine at 6 months compared with usual care.[13] Aerobic exercise may have slowed bone loss at the total hip among 41 premenopausal women with breast cancer who were being treated with goserelin and tamoxifen, but there was no control group in this study so the slowing of bone loss with time may not have been related to the intervention.[11]

In our study, premenopausal women diagnosed with breast cancer continued to lose bone although they were more than a year after diagnosis and treatment. In the overall cohort, the exercise intervention was not sufficient to prevent bone loss. However, among women who maintained lean mass in our study, the 12-month exercise intervention prevented bone loss at the lumbar spine. The exercise intervention did not prevent bone loss among women who lost muscle mass. Some studies of exercise and bone density suggest that the spine may be more responsive to resistance exercise than the

Table 2. Baseline Characteristics of the Study Population by Loss or Maintenance of Lean Mass During the Trial and Treatment Group

		No lean mass loss, n = *100*		
	Lean mass loss, n = *87*	*Control,* n = *54*	*Exercise,* n = *46*	p
Age (years)	45.8 ± 5.0	45.0 ± 5.9	46.9 ± 5.7	0.21
BMI	26.7 ± 6.8	26.3 ± 6.4	26.6 ± 6.1	0.72
Race (% white)	65%	59%	69%	0.53
Lumbar spine BMD (g/cm^2)	0.995 ± 0.109	1.01 ± 0.134	1.005 ± 0.092	0.61
Total hip BMD (g/cm2)	0.920 ± 0.111	0.962 ± 0.122	0.915 ± 0.097	0.06
25-hydroxyvitamin D (ng/mL)	33.6 ± 14.1	33.6 ± 11.8	30.4 ± 12.0	0.37
Lean mass (kg)	43.0 ± 7.3	43.5 ± 7.7	43.0 ± 6.1	0.38
Hours/day exercise	0.97 ± 0.80	0.82 ± 0.88	0.92 ± 0.94	0.59
Currently menstruating (% yes)	20%	17%	15%	0.48
Days from end of chemotherapy to baseline visit	288 ± 138	292 ± 153	324 ± 150	0.38
Treatment includes tamoxifen (% yes)	69%	69%	46%	0.09
FSH	46.0	39.3	41.9	0.51
Race				0.53
AA	1%	2%	7%	
Asian	25%	26%	11%	
White	65%	59%	69%	
Hispanic	5%	11%	9%	
Other	4%	2%	7%	

AA, African-American; FSH, follicle stimulating hormone.

hip. It is possible that the trabecular bone of the spine is more sensitive to changes because of mechanical strain and, thus, responds more rapidly.

Within the exercise group, PTH and 1,25-dihydroxyvitamin D levels increased; however, the long-term pattern of changes in calciotropic hormones during exercise and their effects on the skeleton are unknown. Bone turnover markers decreased significantly in both the exercise and control groups, with no significant difference between the groups. This may reflect decreasing bone remodeling as the subjects became farther removed from their breast cancer treatment. As there was no difference by treatment group, changes in these markers do not seem to explain the observed effects of our exercise intervention on bone density.

Breast cancer survivors are more likely to have a higher BMI, larger waist circumference, and higher blood pressures than noncancer subjects.[14] Our study showed no significant differences in change in HOMA-IR, fructosamine, and total cholesterol:HDL ratio between the control and exercise groups at 12 months. However, within the control group, there was an increase in serum fructosamine (marker of glycemic control) and total cholesterol:LDL ratio over the 12-month period, whereas there was no change in either parameter in the exercise group. This suggests that exercise may offer some protection against adverse changes in metabolic and cardiovascular parameters. Previous studies have not examined these parameters in this population. Further studies are needed to evaluate the effects of different types of exercise (aerobic vs. resistance) on these types of biochemical parameters and to examine longer term cardiovascular outcomes.

Our study had limitations, including lack of formal assessment of compliance to the exercise program. Women in the exercise group had higher levels of self-reported exercise. A meta-analysis of 36 studies using exercise interventions showed that greater compliance to exercise was associated with being women, home or facility-based exercise versus both, and shorter study duration, whereas higher dropout rates were associated with premenopausal versus postmenopausal women, younger versus older participants, and longer study duration.[15] In the exercise group, the women who lost lean muscle mass may have been less compliant to the exercise intervention although this was not evident from the self-reported exercise measures in our study. Another

Table 3. Change in Body Composition and Health Parameters Over 12-Month Study and at 12 Months by Loss or Maintenance of Lean Mass

		No lean mass loss, n = *100*		p	
	Lean mass loss, n = *87*	*Control,* n = *54*	*Exercise,* n = *46*	*Overall*	*Control vs. exercise*
Hours/day exercise at month 12	1.1 ± 0.9	1.0 ± 0.9	1.4 ± 1.0	0.11	0.05
Weight change (kg)	−1.8 ± 5.8	2.2 ± 3.7	2.3 ± 3.0	<0.001	0.99
BMI change	−1.0 ± 3.5	0.6 ± 2.1	0.6 ± 1.8	0.001	1.0
% fat change	0.5 ± 2.4	0.3 ± 2.4	0.5 ± 2.0	.87	0.99
Lean mass change (g)	−885 ± 852	1056 ± 996	1143 ± 839	<0.001	0.95
Self reported health = very good/excellent	67%	59%	61%	0.64	1.0
Health better than 6 months ago	60%	39%	52%	0.06	0.46

possibility is that the women who lost lean muscle mass were too debilitated by medical comorbidities to benefit from exercise although their self-reported health in our study was actually higher at the 12-month time-point. It is important to note that maintaining lean mass by itself did not prevent loss of bone density; only women who maintained lean mass and exercised had no bone loss. This appears to support the importance of resistance exercises aiming to maintain or improve lean mass in maintaining bone mass.

Another limitation to our study was that participants were not stratified by tamoxifen use. In the Breast Cancer Prevention Trial, tamoxifen use was associated with a 45% reduction in hip fracture.[16] Tamoxifen treatment has been shown induce ovarian suppression in premenopausal breast cancer patients (low estradiol and low gonadotropin levels).[17] It is possible that tamoxifen treatment resulted in reduced bone loss and low FSH levels in a subset of participants. In our study, FSH was not significantly different across treatment groups or between women who lost or maintained lean mass, suggesting no difference in ovarian function. Of importance, the higher tamoxifen use in our study was in the control group, which would have biased against our findings.

Women with premenopausal breast cancer are at risk for adverse cardiovascular and skeletal changes. Exercise may provide an effective intervention to ameliorate this risk, but the relationship appears complex and the effectiveness of exercise may depend on the maintenance of lean muscle mass. Additional investigation into exercise regimens that can prevent both bone and muscle loss may aid in the development of treatments to prevent long-term consequences of breast cancer treatment in premenopausal women.

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Author Disclosure Statement

No competing financial interests exist.

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