Exercise Effects on Bone Mineral Density in Women With Breast Cancer Receiving Adjuvant Chemotherapy

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Purpose/Objectives: To test the effects of aerobic and resistance exercise on changes in bone mineral density (BMD) in women newly diagnosed with stage I–III breast cancer receiving chemotherapy.

Design: Randomized clinical trial.

Setting: Two National Cancer Institute–designated cancer centers in metropolitan areas.

Sample: 66 women with stage I–III breast cancer beginning adjuvant chemotherapy.

Methods: Participants were randomized to aerobic or resistance exercise and usual care. At the beginning of chemotherapy and at six months, patients completed exercise testing and BMD assessment of the lumbar spine by dual energy x-ray absorptionetry.

Main Research Variables: BMD, aerobic capacity, and muscle strength.

Findings: The average decline in BMD was –6.23% for usual care, –4.92% for resistance exercise, and –0.76% for aerobic exercise. Aerobic exercise preserved BMD significantly better compared to usual care. Premenopausal women demonstrated significantly greater declines in BMD than postmenopausal women. Aerobic capacity increased by almost 25% for women in the aerobic exercise group and 4% for resistance exercise. Participants in the usual care group showed a 10% decline in aerobic capacity.

Conclusions: The data suggest that weight-bearing aerobic exercise attenuates declines in BMD and that aerobic and resistance exercise improve aerobic capacity and muscle strength at a time when women generally show marked declines in functional ability.

Implications for Nursing: Exercise may prevent or at least minimize bone loss observed during chemotherapy and may prevent or delay the long-term effects of osteoporosis.

Key Points . . .

- ➤ Significant bone loss is a side effect of breast cancer treatment that often goes undetected and untreated in pre- and postmenopausal women.
- ➤ Aerobic exercise may reduce bone loss during cancer treatment.
- ➤ Resistance exercise reduces treatment-related bone loss but may be less effective because of noncompliance.
- ➤ Moderate-intensity exercise not only maintains but significantly improves aerobic capacity and muscle strength in women undergoing chemotherapy.

In 2007, an estimated 180,510 women will be diagnosed with invasive breast cancer (American Cancer Society, 2007). Most patients are treated with a combination of surgery, chemotherapy, and radiotherapy. Although breast cancer mortality rates have declined in recent years, long-term treatment-related side effects have a considerable negative effect on morbidity and non–cancer-related risk of mortality (Jemal et al., 2005). The increasingly common use of adjuvant chemotherapy, particularly for breast cancer, has led to improved survival as well as a rise in long-term treatment-related side effects, including early menopause, osteoporosis, and elevated risk for cardiovascular disease (Leedham & Ganz, 1999; Lower, Blau, Gadzer, & Tummala, 1999; Shapiro, Manola, & Leboff, 2001; Sklar, 1999; Van Poznak & Sauter, 2005).

Osteoporosis is a serious public health concern, and as the number of long-term cancer survivors grows, osteoporosis is becoming a costly and common long-term complication of breast cancer. Breast cancer survivors are almost five times more likely to experience a vertebral fracture a year following treatment than their healthy counterparts (Swenson,

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Henly, Shapiro, & Schroeder, 2005). Twenty million women are estimated to be at risk for osteoporosis, with 1.3 million osteoporotic fractures occurring annually in the United States, at a cost of $10 billion per year (Greenblatt, 2005). Those figures do not reflect the less conspicuous consequences that affect women's psychological, physical, and social function. The Women's Health Initiative Observational Study reported that more than 77% of breast cancer survivors with osteoporosis were undiagnosed by their healthcare providers (Chen et al., 2005). A follow-up of early-stage breast cancer survivors who were premenopausal when beginning adjuvant chemotherapy with cyclophosphamide found that 71% had undiagnosed osteopenia (McCune, Games, & Espirito, 2005). Four factors place patients with breast cancer at high risk for declines in bone mineral density (BMD) because of treatment: chemotherapy with bone-wasting agents such as doxorubicin, cyclophosphamide, and methotrexate; glucocorticoids; primary ovarian failure (especially in young women); and lack of physical activity (Reichman & Green, 1994; Reyno, Levine, Skingley, Arnold, & Abu Zahra, 1992; Rodriguez-Rodriguez et al., 2005; Shapiro et al., 2001; Shapiro & Recht, 1994; Van Poznak & Sauter, 2005). Muscle wasting, declines in BMD, and obesity are seen frequently in patients receiving glucocorticoids, drugs commonly used in breast cancer treatment protocols (Goodwin et al., 1999; Kaste et al., 2006). The combination of catabolic steroids and chemotherapy increases the potential for considerable physical debilitation and predisposes patients to osteoporosis. No studies have examined the effects of an exercise intervention on the BMD in patients with breast cancer receiving adjuvant or neoadjuvant chemotherapy. Exercise is an intervention that may reduce risks for osteoporosis during cancer treatment (Engelke et al., 2006; Pocock et al., 1989; Talmage, Stinnett, Landwehr, Vincent, & McCartney, 1986; Winters-Stone & Snow, 2006) and has demonstrated many positive effects for patients receiving chemotherapy (Courneya et al., 2003, 2004; Mock et al., 1994, 1997, 2001; Schwartz, 1999, 2000; Schwartz, Mori, Gao, Nail, & King, 2001; Schwartz, Thompson, Masood, & Chahal, 2002; Young-McCaughan et al., 2003). Aerobic and resistance exercise improves bone health in pre- and postmenopausal women (Engels, Currie, Lueck, & Wirth, 2002; Kraemer et al., 2001; Wolff, Van Croonenborg, Kemper, Kostense, & Twisk, 1999), but each has specific effects on physical fitness, namely aerobic capacity and muscle strength. The purpose of the current study was to test the effects of two different exercise interventions (i.e., aerobic and resistance) versus usual care on changes in BMD among women newly diagnosed with stage I–III breast cancer beginning chemotherapy with doxorubicin or methotrexate and receiving a glucocorticoid as part of the antiemetic regimen.

Methods

Setting and Sample

The study was conducted at the University of Washington Cancer Center and Oregon Health and Science University and received human subjects review and approval from both institutions. Women were recruited before beginning adjuvant chemotherapy. Eligible women had histologically confirmed invasive stage I–III breast cancer, were planning to begin chemotherapy with doxorubicin or methotrexate, and were ambulatory. Women who received steroids six months prior to the study were excluded as were patients with Paget disease, hyperparathyroidism, rheumatoid arthritis, ankylosing spondylitis, or other metabolic bone diseases that may affect bone metabolism. Strenuous regular exercisers, women who exercised more than 250 minutes per week, and women with a history of serious psychiatric disease also were excluded.

Procedure

Informed consent was obtained and baseline measures were collected before patients began chemotherapy. At baseline and six months, height, weight, aerobic capacity, and upper and lower body muscle strength were measured. Aerobic capacity was calculated using the 12-minute walk, a timed test that measures how much distance is covered in 12 minutes. Maximal upper- and lower-body strength was determined using a single-repetition maximum test. The exercise tests are used commonly and demonstrate a strong correlation with oxygen consumption tested in the laboratory ($r = 0.90$ and 0.72) and total dynamic strength ($r = 0.84$) (Berger, 1982; Bernstein et al., 1994; Cooper, 1968). Dual-energy x-ray absorptiometry (DEXA) (Hologic QDR-4500A) assessment of the lumbar spine and whole body was conducted within two weeks of the start of chemotherapy and at six months. The coefficient of variation for repeat assessment of BMD is less than 1%. The spine has a high rate of bone turnover because of a high proportion of trabecular bone and is a particularly sensitive site for monitoring catabolic drug effects (Eastell, 1998).

Intervention

Women were randomized to one of three groups (aerobic exercise, resistance exercise, or usual care) and stratified according to menopausal status (premenopausal or postmenopausal). Postmenopausal women were defined as those who had cessation of menses for at least six consecutive months prior to beginning chemotherapy. Women randomized to the home-based aerobic exercise intervention were instructed to choose an aerobic activity they enjoyed (e.g., walking, jogging) and exercise for 15–30 minutes four days per week for the duration of the study, at a symptom-limited, moderate intensity such that they were breathing hard but able to talk. That group also was instructed to use symptoms (e.g., fatigue, pain, breathlessness) to moderate exercise intensity and determine whether to stop exercising. Caloric expenditure during each exercise session was measured using Caltrac Accelerometers™ (Muscle Dynamics Fitness Network) and recorded in exercise logs, which included information about exercise intensity, duration, frequency, and type. Over the course of the study, patients were asked to increase the intensity of their exercise but maintain the duration. However, subjects who wanted to exercise for a longer duration or more frequently were permitted to do so if they recorded the information in their exercise logs. All aerobic exercise subjects continued to exercise.

Resistance exercise subjects were instructed to exercise at home four days per week using Thera-Band™ (Hygenic Corporation) resistance bands and tubing. Subjects were given two different sets of exercises and were asked to complete two sets of 8–10 repetitions and alternate the exercise sets within each week. Both exercise sets included eight different exercises (four upper body and four lower body) that targeted the major muscle groups used in everyday activities. All but one of the exercises were weight bearing; however, women also were shown how to complete the exercises while sitting down if they were too ill or tired to complete them while standing. When women were able to complete two sets of 10 repetitions, they were instructed to increase the resistance on the Thera-Band by modifying the starting grip position or using a band with greater resistance. Subjects in the resistance exercise group maintained an exercise log of the number of repetitions of each exercise, resistance of the band or tubing, and duration of the exercise session. All subjects in the group were asked to record their workouts in their exercise logs. A research associate called aerobic and resistance exercisers at two-week intervals for the first month of the study and then monthly thereafter to answer questions about exercise and assess any barriers and the ability to exercise.

Women in the usual care group were instructed to continue with their usual activities. However, because restricting exercise would be unethical, the subjects were not instructed to avoid exercise but did not receive specific recommendations to exercise. To maintain subject burden across groups and monitor exercise in the control group, the subjects maintained a daily activity log of physical and sedentary activities.

Statistical Analysis

The primary end point was the percent change in BMD in the lumbar spine and whole body from baseline to six months. Secondary outcomes of interest were changes in aerobic capacity and maximum muscle strength.

Baseline subject characteristics in the three groups were compared using one-way analysis of variance. Percent change in lumbar spine BMD from baseline to six months was calculated for each participant. Differences among groups were compared using repeated measures analysis of variance and covariance (menopausal status). Post-hoc analysis was conducted using least significant difference to compare the exercise groups against the control group. A p value of less than 0.05 was used for statistical significance. Secondary measures of aerobic capacity and muscle strength were analyzed in the same way.

Results

Seventy-five women were approached during the recruitment period, and 72 (95%) agreed to participate. Three women declined to participate in the study because of work or family commitments. The groups were equivalent in age, ethnicity, level of education, employment status, stage of disease, and type of treatment. Two subjects from each group dropped out because they were too busy (n = 4) or the location was not convenient (n = 2). Consent was obtained, and the women were randomized to aerobic exercise (n = 22), resistance exercise (n = 21), or usual care (n = 23). No significant differences were found between dropouts and those who completed the study on measures of age, ethnicity, level of education, employment status, stage of disease, or type of treatment. Sixty-six women (93%) completed the study. Fourteen women were premenopausal.

Baseline characteristics of each group are listed in Table 1. At baseline, none of the women had osteopenia (t score < –1.0) or osteoporosis (t score < –2.5). During the study period, women in the aerobic exercise group chose weight-bearing activities most often, with 77% (n = 17) walking and 14% (n = 3) running. Only 9% of the women (n = 2) engaged in non–weight-bearing activities (cycling and swimming). Women in the usual care group reported physical activities of daily living (e.g., shopping, cleaning, gardening) or walking (61%). The resistance exercise group followed the prescribed program, although four women (21%) also reported participation in aerobic exercise.

At the end of the six-month intervention period, the aerobic exercise group had covered a significantly greater distance on the 12-minute walk than the other groups (p = 0.02) and demonstrated greater muscle strength on the single-repetition maximum test for the seated row (p = 0.02) and leg extension press (p = 0.001) than the other groups (see Table 2). Aerobic exercisers increased aerobic capacity almost 25% over six months in contrast to the resistance exercisers who increased only 4% and controls who decreased 10%. Although no differences existed among groups in erythropoietin use, women who received erythropoietin improved aerobic capacity over six months (p = 0.01).

The analysis of variance, by intent to treat, demonstrated significant differences in percent change in lumbar spine BMD (p = 0.02, mean difference = 3.79, 95% confidence interval [CI] = –2.55 to –4.17). Post-hoc analysis with least significant difference detected significant mean differences between only the aerobic exercise and control group (p = 0.02, mean difference = 7.10, 95% CI = –1.98 to 0.14). No significant difference was found in the rate of change in spine BMD between exercise groups (p = 0.09, mean difference = –3.15). A significant difference in lumbar spine BMD change was observed by total dose of dexamethasone (p = 0.04) but not by age (p = 0.73) or baseline lumbar spine BMD (p = 0.06). At baseline, none of the women had bone density in the osteopenic or osteoporotic (t score < –1.0) range. Bone density declined sufficiently at six months to cause osteopenia in 15 women (two in the aerobic exercise group, four in the resistance exercise group, and nine in the usual care control group) and osteoporosis in two women (both in the usual care control group).

When menopausal status was used as a covariate in the analysis, significant differences in lumbar spine BMD were observed by menopausal status (p = 0.001, mean difference = 3.36, 95% CI = –2.56 to –4.16), with a significant difference (p = 0.04, mean difference = –3.79, 95% CI = –7.38 to 0.21) between the aerobic exercise and control groups. No significant differences were observed between the resistance or control groups at six months. When premenopausal and postmenopausal groups were examined separately, premenopausal aerobic exercisers maintained better BMD than the control group (p = 0.03, mean difference = 3.52, 95% CI = –0.50 to –6.54) but were not significantly different from resistance exercisers. Among postmenopausal women, a slight trend was found toward differences between groups, with a significant bone-sparing response observed in aerobic exercise compared to the control group (p = 0.15, mean difference = 2.5, 95% CI = –1.11 to –6). No differences were observed in 12-minute walk distance or muscle strength from baseline to six months between pre- and postmenopausal groups.

Discussion

This prospective study shows that women with breast cancer receiving usual care lose a remarkable amount of spine

Table 1. Baseline Demographic Characteristics by Group

Characteristic	Aerobic Exercise (N = 22)		Resistance Exercise (N = 21)		Usual Care Control (N = 23)	
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Age (years)	48.32	12.6	50.1	8.7	46.26	9.8
Weight (kg)	69.80	13.6	77.5	17.3	68.40	12.3
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Married or partnered	21	95	20	95	23	100
Completed bachelor's degree	10	45	10	48	11	48
Employed full-time	9	41	9	43	10	43
Regular exerciser at baseline	13	59	11	52	12	52
Premenopausal	11	50	13	61	12	52
Stage of disease						
I	4	18	6	28	5	22
II	13	59	11	52	14	61
III	5	12	4	19	4	17
Treatment type						
Cyclophosphamide, methotrexate, and 5-fluorouracil	5	23	5	24	5	22
Doxorubicin and cyclophosphamide	5	23	6	28	7	30
Doxorubicin, cyclophosphamide, and a taxane	12	55	10	48	11	48
Erythropoietin	13	59	11	52	12	52
Tamoxifen	17	77	16	76	18	78
Radiation therapy	15	68	13	61	15	65

Note. Because of rounding, not all percentages total 100.

BMD during treatment. In contrast, women who followed the home-based aerobic exercise intervention maintained lumbar spine BMD over time. The results suggest that chemotherapy, glucocorticoids, and inactivity contribute to rapid declines in bone density, particularly in premenopausal women, and that weight-bearing aerobic exercise may counteract some of the adverse effects of treatment. BMD declines observed in the control and resistance exercise subjects in the present study are similar to declines observed in prospective studies at 6- and 12-month evaluation points in women undergoing chemotherapy (Delmas et al., 1997; Powles et al., 1998; Saarto et al., 1997). Although no differences were found between groups in tamoxifen use, tamoxifen is recognized to be bone sparing in postmenopausal women and bone wasting in premenopausal women (Vehmanen, Elomaa, Blomqvist, & Saarto, 2006). Bone loss over six months was significant enough to observe clinical osteopenia in 39% of the usual care control group, 19% of the resistance exercise group, and 9% of the aerobic exercise group. Two (9%) of the usual care control subjects developed clinical osteoporosis.

The study results support the role of moderate-intensity weight-bearing aerobic exercise to prevent bone loss. Interventions could be tested with bisphosphonates to evaluate their efficacy in reducing bone loss in women who are not receptive to or unable to follow a moderate intensity weight-bearing exercise program. Although the results from the trial are limited by a lack of objective measures of bone turnover (e.g., n-telopeptide) and menopausal status (e.g., follicle-stimulating hormone levels), the findings have important implications for subsequent intervention trials designed to prevent bone loss and point to the immediate effect of chemotherapy, glucocorticoids, and inactivity on bone loss during chemotherapy.

Weight-bearing aerobic exercise creates ground reaction forces, which reflect accelerations of the body's center of mass and the reaction to force the body exerts to the ground. Ground reaction forces have the best effect on increasing BMD; resistance exercise produces joint reaction forces (the result of muscle, ligament inertial, gravitational, and external forces applied to a joint) and more effectively improves lean body mass and strength in postmenopausal women (Kohrt, Bloomfield, Little, Nelson, & Yingling, 2004). In the current study, aerobic exercise appears to improve aerobic capacity, muscle strength, and BMD better than resistance exercise. The women in the aerobic exercise group not only increased their aerobic capacity but also muscle strength and energy expenditure. The increase in physical activity may have been sufficient to offset some of the declines in BMD observed in the other groups.

The aerobic and resistance exercise interventions were designed to improve or maintain functional capacity and were not prescribed to increase BMD according to current recommendations for the general public (Kohrt et al., 2004). The data suggest that moderate levels of weight-bearing exercise may provide an adequate stimulus to the bone to prevent some of the declines incurred from physical inactivity and adjuvant chemotherapy. Because bone loss was so profound in the study group, a lower exercise stimulus that would otherwise be ineffective in women with normal or unchanging bone mass may cause a bone response (Winters-Stone & Snow, 2003). Although previous research has demonstrated that resistance exercise increases BMD (Layne & Nelson, 1999), the resistance exercise program used in the current study was not designed to increase BMD, was likely of insufficient intensity, and did not focus exercises to specifically target the lumbar

Table 2. Effect of Exercise on Aerobic Capacity, Muscle Strength, and Bone Mineral Density

Category	Baseline			Six Months			Difference Between Groups	
	$\bar{X}$	SD	p[a]	$\bar{X}$	SD	$\bar{X}$ Change	95% Confidence Interval	p[b]
12-minute walk (meters)			0.84			94.500	81.2–104.6	0.02
Aerobic exercise	983.60	289.00		1228.00	322.000			
Resistance exercise	1020.00	357.00		1055.00	177.000			
Usual care	1035.00	257.00		944.00	241.000			
Overhead press (kg)			0.57			0.970	0.75–1.06	0.02
Aerobic exercise	12.20	5.90		13.72	6.400			
Resistance exercise	9.50	6.90		10.80	5.100			
Usual care	9.60	4.50		9.50	4.100			
Seated row (kg)			0.81			4.800	4.3–5.4	0.05
Aerobic exercise	32.30	12.10		40.10	13.600			
Resistance exercise	32.70	12.50		38.10	8.600			
Usual care	30.50	10.80		30.70	9.100			
Leg extension (kg)			0.80			12.030	10.1–14.02	0.01
Aerobic exercise	64.00	26.00		78.60	30.500			
Resistance exercise	60.40	31.80		75.30	34.500			
Usual care	65.90	27.70		70.50	28.100			
Bone mineral density L-spine (g)			0.35			0.032	–0.025 to 0.39	0.000
Aerobic exercise	0.99	0.11		0.98	0.069			
Resistance exercise	1.02	0.15		0.99	0.120			
Usual care	1.04	0.14		0.97	0.105			

[a] Difference between groups at baseline

[b] Difference between groups from baseline to six months

spine; a more vigorous resistance exercise intervention that specifically includes exercises to increase BMD may change the results. Previous studies of resistance exercise have demonstrated that at sufficient intensity, bone is preserved in the hip and spine in postmenopausal women who are not osteoporotic (Kerr, Morton, Dick, & Marcus, 1996; Nelson et al., 1994; Pruitt, Taaffe, & Marcus, 1995; Snow, Shaw, Winters, & Witzke, 2000) and increased at both sites in premenopausal women (Lohman et al., 1995; Winters-Stone & Snow, 2006). However, the load needs to be relatively high. Intensities greater than 70% of a woman's single-repetition maximum (i.e., the most weight an individual can lift at one time) have the strongest effect on preserving bone, are well tolerated, are safe for older adults, and demonstrate the best adherence in a supervised setting (Evans, 1999; Nelson et al.). Neither the single-repetition maximum nor the resistance exercise program was associated with any new onset lymphedema or acute flares. The better bone response in the aerobic exercise group may be related, in part, to a general increase in activity levels, particularly weight-bearing activities outside the intervention such as gardening, lifting groceries, and other physical activities of daily living.

The inclusion of bone turnover measures may have provided additional information about the effect of exercise on bone health. Elevated bone turnover is an independent risk factor for fracture, beyond bone density, that reflects an increase in bone fragility resulting from a greater presence of resorption cavities over a given time span (Garnero, Sornay-Rendu, Claustrat, & Delmas, 2000). If exercise reduced bone turnover, it would suggest an additional protective effect of exercise to reduce fracture risk. Recording the number of women who became amenorrheic from chemotherapy may have provided an explanation for some of the decline in BMD among premenopausal women. Interventions to reduce bone loss during adjuvant chemotherapy, as well as longitudinal follow-up studies, are important given the growing number of long-term breast cancer survivors. Many questions remain as to the pattern of bone change in the months following chemotherapy, the degree to which bone remodeling can occur with exercise alone, and whether the upfront use of a bisphosphonate is indicated during adjuvant chemotherapy. Some research suggests that bone density at the beginning of chemotherapy may predict women at highest risk for ovarian failure and, perhaps, development of osteoporosis (Shapiro et al., 2005). Those questions are important given the intent to cure women with breast cancer and the adverse long-term health effects of bone loss and related fractures.

Nursing Implications

Evidence suggests that exercise, particularly aerobic exercise, may preserve bone, minimize some of the bone loss observed during chemotherapy, and reduce the risk of osteoporosis. Nurses play a pivotal role in motivating patients to begin and continue exercise during treatment. As breast cancer treatments become more effective and the number of long-term survivors grows, healthcare professionals need to consider methods for health promotion and disease prevention during and following cancer treatment as well as early osteoporosis screening. Pretreatment workup protocols may include DEXA scans. Osteoporosis is a long-term side effect of treatment that nurses may be able to minimize by teaching patients the importance of exercise during treatment or by collaborating with multidisciplinary teams (e.g., physical therapy, rehabilitation medicine, exercise physiologists) to develop programs for their patients.

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