Bone Health and Falls: Fracture Risk in Breast Cancer Survivors With Chemotherapy-Induced Amenorrhea

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Purpose/Objectives: To describe risk factors for fracture—bone health and falls—among breast cancer survivors with chemotherapy-induced amenorrhea.

Design: Cross-sectional and prospective cohort.

Setting: National Cancer Institute-designated cancer center in the Pacific northwest region of the United States.

Sample: Breast cancer survivors with chemotherapy-induced amenorrhea (N = 35; $\bar{X}$ age = 46 years; one year after chemotherapy) compared to cancer-free controls (N = 26; $\bar{X}$ age = 41 years).

Methods: One two-hour testing session at baseline, 12-month follow-up, monthly postcards.

Main Research Variables: Clinical characteristics and number of falls, leg strength, bone mineral density (BMD), body composition, and bone turnover.

Findings: No significant differences between groups for BMD at either time point. Significantly more breast cancer survivors had low-spine BMD based on T scores and elevated bone turnover versus controls at baseline and follow-up. Breast cancer survivors with low-spine BMD have significantly lower body mass index, lean mass, and leg strength, and had stage II disease more often than breast cancer survivors with normal BMD. Significantly more breast cancer survivors (75%) experienced at least one fall compared to 46% of controls. Among breast cancer survivors, those who had fallen had significantly lower leg strength and calcium intakes than those who had not.

Conclusions: Breast cancer survivors with chemotherapy-induced amenorrhea, particularly those with muscle weakness, may be at increased risk of fracture.

Implications for Nursing: Breast cancer survivors with chemotherapy-induced amenorrhea should be evaluated for low bone mass and fall risk and considered for therapeutic intervention to lower fracture risk.

More than two million breast cancer survivors are living in the United States, with about 24% of them diagnosed prior to menopause (aged 50 years and older) (American Cancer Society, 2007). Although type of treatment varies with disease stage, most breast cancer survivors are treated with chemotherapy and hormone therapy. Although hormone manipulation is reserved for survivors with estrogen receptor-positive tumors, this receptor status is found in most breast cancers (American Cancer Society; Eifel et al., 2001). Premenopausal breast cancer survivors are at risk for chemotherapy-induced amenorrhea (Bruning et al., 1990; Goodwin et al., 1999) that abruptly reduces circulating estrogen levels after menopause. Breast cancer survivors treated with aromatase inhibitors (AIs) experience additional declines in estrogen from nonovarian sources. Low estrogen is associated with bone loss (Shapiro, Manola, & Leboff, 2001) and neuromuscular declines, and chemotherapy for breast cancer may compound these losses with the associated bone and muscle loss (Cheney, Mahloch, & Freeny, 1997; Demark-Wahnefried et al., 2001; Freedman et al., 2004; Greep et al., 2003; Harvie, Campbell, Baildam, & Howell, 2004; Kutynec, McCargar, Barr, & Hislop, 1999), weight gain (Costa, Varella, & del Giglio, 2002; Demark-Wahnefried et al., 2001; Demark-Wahnefried, Rimer, & Winer, 1997; Demark-Wahnefried, Winer, & Rimer, 1993; Hoskin, Ashley, & Yarnold, 1992), and neurologic symptoms such as numbness in extremities (Boehmke & Dickerson, 2005) and cognitive difficulties (Ahles et al., 2002; Schagen, Muller, Boogerd, Mellenbergh, & van Dam, 2006) that could contribute to falls (American Geriatric Society, 2001; Richardson & Hurvitz, 1995). Poor bone health and increased fall risk contribute to heightened risk for fracture (Frost, 2001); therefore, treatment-related side effects could increase fracture risk in prematurely menopausal breast cancer survivors.

More than two-thirds of breast cancer survivors aged 40 years and older and 40% of breast cancer survivors younger than age 40 experience chemotherapy-induced amenorrhea (Bruning et al., 1990; Goodwin et al., 1999). Premenopausal-aged women who stop menstruating during or following cancer therapy have a 10%–15% lower spine bone mineral density (BMD) compared to women who retain menses (Bruning et al.; Headley, Theriault, LeBlanc, Vassilopoulou-Sellin, & Hortobagyi, 1998). Prospective studies report annual rates of bone

loss in women who become menopausal during treatment averaging 3%–8% at the spine and 4%–5% at the hip (Delmas et al., 1997; Saarto et al., 1997; Shapiro et al., 2001; Vehmanen et al., 2001), higher than the average loss observed in non-estrogen–replaced postmenopausal women (Pouilles, Tremollieres, & Ribot, 1995). Treatment with a selective estrogen receptor modulator (SERM), namely tamoxifen, reduces but does not completely prevent bone loss during chemotherapy in patients with postmenopausal breast cancer (Saarto et al., 2001), whereas AIs exacerbate bone loss and increase fractures in this same group (Coombes et al., 2004). Elevated bone turnover is associated with increased fracture risk independent of BMD (Heaney, 2003; Riggs & Melton, 2002) and is observed with chemotherapy-induced amenorrhea (Shapiro et al.) and AI treatment (Coleman et al., 2007).

The Women's Health Initiative-Observation Study (WHI-OS) reported that postmenopausal breast cancer survivors have a 15% higher overall fracture risk than women with no cancer history (Chen, Maricic, Bassford, et al., 2005). Treatment-related bone loss is presumed to underpin increased fracture risk in breast cancer survivors; however, BMD is an imperfect predictor of fractures in the general population (Frost, 2001). Most fractures are associated with trauma resulting from a fall (Cummings & Nevitt, 1994); therefore, falls should receive equal consideration as a risk factor for fracture as bone mass (Frost). Low muscle mass, weak leg strength, and poor balance are associated with a greater number of falls in older adults (Blake et al., 1988; Campbell, Borrie, & Spears, 1989), and estrogen deficiency is linked to lower muscle strength and balance (Cauley et al., 1987). Data from the WHI-OS suggest that falls play a role in fractures among postmenopausal breast cancer survivors (Chen, Maricic, Bassford, et al.); however, falls remain understudied in this group.

To date, no study has simultaneously evaluated the leading risk factors for fracture in breast cancer survivors with chemotherapy-induced amenorrhea. The current study addressed the following objectives.

- Compare a comprehensive set of objectively measured risk factors for fracture between breast cancer survivors with recent chemotherapy-induced amenorrhea and cancer-free controls.
- Determine the change in risk factors for fracture over the course of one year.
- Describe the differentiating characteristics of breast cancer survivors with low versus normal BMD and of breast cancer survivors who fall versus those who do not.

Methods

Sample and Setting

Women were recruited through the Oregon State Cancer Registry, oncologist referral, community events, posted advertisements, and word of mouth. Eligible women had early-stage breast cancer (I–IIIa), had completed a chemotherapy regimen six months to two years ago, reported 9–12 menstrual cycles in the year prior to the start of chemotherapy, had not had a menstrual cycle since completion of chemotherapy, and were older than age 18. Women were excluded from participation for the documented effects of the following conditions on bone metabolism: skeletal metastasis, current treatment with chemotherapy or radiation, smoking, diabetes mellitus, hyperparathyroidism, hypothyroidism, pregnancy, lactation, or use of bone-active medications (e.g., bisphosphonates, parathyroid hormone, corticosteroids). The authors recruited a control group of premenopausal cancer-free women to represent the expected premenopausal levels of fracture risk factors and changes over time. Control participants had to report 9–12 menstrual cycles or be taking oral contraceptives over the year prior to enrollment and be at least age 18 but were excluded if they were smokers or had conditions or took medications known to affect bone metabolism. Measurements were conducted at the Oregon Health and Science University (OHSU) School of Nursing and the OHSU General Clinical Research Center. The study protocol and informed consent were approved by the OHSU General Clinical Research Center, the OHSU Cancer Institute, and the OHSU institutional review board.

Using BMD as the primary outcome variable and estimating a conservative yet clinically relevant difference of 2% for initial differences between prematurely menopausal breast cancer survivors and controls, a formal power analysis was conducted to determine sample size. The power of the overall analysis of variance is 0.78, with a sample size of 25 per group to detect an effect size of 0.29 at alpha level of 0.05. The associated planned comparisons would be able to detect differences of 2% between groups on BMD.

Procedures

Interested women were contacted in person or by telephone and screened for eligibility. Eligible women were then scheduled for a baseline testing appointment. After written informed consent was obtained, participants underwent initial testing in the following order: blood and urine sample collection, questionnaires, dual energy x-ray absorptiometry (DXA) evaluation, and one-legged stance and one-repetition maximum leg press. Participants were scheduled for testing to repeat measurements 12 months after enrollment. Between measurement periods, participants completed monthly postcards that tracked falls and fractures.

Measures

Demographic and clinical characteristics, including breast cancer stage, date of diagnosis, type and dates of breast cancer treatment, and menstrual history were

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obtained by self-report. Medical records were not obtained for women who could not recall information regarding their clinical history; therefore, these items were coded as "do not know."

Follicle stimulating hormone and estradiol were measured at baseline and 12 months to confirm menopausal status of study groups. Blood samples were collected, centrifuged, and the serum layer was removed and stored at –70°C for analysis. Both hormones were measured by radioimmunoassay, and baseline and 12-month samples were processed in batches to reduce interassay variability within samples. Menopausal status of the group was confirmed by follicle-stimulating hormone levels above 30 mIU/ml and estradiol levels below 20 pg/ml.

BMD (g/cm^2) of the greater trochanter, femoral neck, total hip, and lumbar spine (L_1–L_4) were measured via DXA. A licensed densitometrist conducted and analyzed all scans. Inhouse coefficients of variation, determined from a subsample of women similar to the study population, were above 1% for hip and spine measures (Winters & Snow, 2000a). BMD values also were expressed as T scores and, using the World Health Organization criteria, were categorized as normal (T score above –1) or low (T score below –1) (Binkley et al., 2007).

Bone turnover was assessed by serum osteocalcin, a byproduct of bone formation and urinary deoxypyrodinoline cross-links, a byproduct of bone degradation, adjusted for variations in urine volume (by creatinine). All analyses were performed using ELISA® commercial kits. Markers of bone resorption have been used to detect metastatic disease in patients with breast cancer (Hou et al., 1999). To ensure that biomarkers were primarily reflective of bone turnover changes and not to metastases, data from any woman who developed metastatic disease over the course of the study were excluded, although only one participant developed metastatic disease over the course of the study, and she did not return for follow-up testing.

Fall and fracture incidence were determined by self-report, retrospectively at baseline and prospectively over one year. A fall was defined as a participant's unintentionally coming to rest on the ground or at some other lower level, not as a result of a major intrinsic event (e.g., stroke, syncope) or overwhelming hazard (Tinetti, Speechley, & Ginter, 1988). Retrospective fall history was assessed at baseline, and participants were asked to record the number of falls they experienced in the past year. Previous fracture history also was assessed at baseline. Breast cancer survivors were asked to report the number of fractures they experienced since diagnosis, and controls were asked to report the number of fractures they experienced over the previous two years to better match recall time frames to breast cancer survivors. Prospective assessment of falls and fractures was conducted using monthly postcards. Participants were given 12 preprinted, predated, and postage-paid postcards after baseline testing. Participants were instructed to fill out one postcard each month providing the number of falls or fractures they experienced in the past month and then to mail the postcard to the study team. If a participant recorded a fall or fracture, they were contacted and interviewed about the circumstances surrounding the fall. If postcards were not received within two weeks of their due date, participants were called and information was obtained verbally. If a participant could not be reached within a four-week period, the data were considered missing.

The **Block Food Frequency Questionnaire (FFQ)** was used to determine habitual calcium intake at baseline and 12 months. Total calcium intake was calculated from the sum of calcium ingested from food and beverages and calcium ingested in the form of dietary supplements. The FFQ is a valid and reliable dietary assessment measure (Binkley et al., 2007) and is used as the instrument of choice for National Health and Nutrition Survey Examinations. Fifteen breast cancer survivors and four controls failed to return diet questionnaires at 12-month follow-up; therefore, sample sizes for those analyses are n = 22 and n = 18, respectively. Because of calcium's known effect on bone, the mean value of baseline and 12-month calcium intake was calculated and was included as a covariate in analyses if significant group differences were detected. If the value for month 12 was missing, the baseline value was used in place of a time-averaged value.

Habitual physical activity at baseline and 12 months was determined by the **Kaiser Physical Activity Survey**

Table 1. Cancer and Treatment Characteristics of Breast Cancer Survivors

Characteristic	$\bar{X}$	SD
Age at diagnosis (years)	44.9	3.2
Months since chemotherapy completion	12.6	4.1
Characteristic	**n**	
Stage		
I	11	
II	20	
IIIa	1	
Previous treatment		
Doxorubicin or cyclophosphamide	13	
Doxorubicin or cyclophosphamide plus taxol	11	
Cyclophosphamide, methotrexate, and 5-fluorouracil	2	
Current treatment		
Selective estrogen receptor modulator	17	
Aromatase inhibitors	10	

N = 35

Note. Previous treatment data may not total 35 because some participants were unable to recall treatment information. In addition, not all participants were currently on treatment.

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Table 2. Characteristics of Breast Cancer Survivors and Controls at Baseline and 12-Month Follow-Up

	Breast Cancer Survivors (N = 35)				Controls (N = 26)			
	Baseline		12 Months		Baseline		12 Months	
Characteristic	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Age (years)	46.4	4*	–	–	41.6	6.3	–	–
Body mass index (kg/m^2)	26.6	5.4	26.3	5.8	24.1	3.9	23.6	3.7
Lean mass (kg)	43	5.4	43.8	5.9	43	5.8	43.4	5.6
Fat mass (kg)	27.1	10.5*	28.2	11.3*	21.2	7.8	21.3	7.9
Body fat (%)	36.3	7*	36.8	7.2*	31.2	6.5	31	6.6
Follicle-stimulating hormone (IU)	73.2	29.8*	74.2	34.1*	12.7	13.6	9.5	7.7
Estradiol (pg/ml)	14.1	23.1*	13.3	9.6*	42.9	49.3	66.1	58.4
Maximal leg press (kg)	82.3	17.9	104.3	21.3	84.4	17.9	110.3	22.4
One-leg stance—eyes open	60.6	46.5*	51.3	34.9*	115	67.2	117.9	67.8
One-leg stance—eyes closed	15.7	16.4	13.9	13*	24	28.9	32.5	26.5
Physical Activity Index[a]	10.6	1.8*	10.4	1.5*	11.9	1.7	11.8	1.7
Calcium intake (mg per day)[b]	1,915	628*	1,494	559*	1,375	509	1,015	452

* $p < 0.05$

[a] Physical Activity Index was calculated from the Kaiser Physical Activity Survey; higher scores indicate more physical activity (lowest possible score = 4.3, highest possible score = 21.7).

[b] Calcium intake includes calcium obtained both from dietary sources and from dietary supplements. Sample sizes for 12-month measures are n = 22 for breast cancer survivors and n = 18 for controls.

(KPAS). This survey, an adaptation of the Baecke Usual Physical Activity Survey, is designed specifically to assess activity in women and has acceptable validity and reliability (Ainsworth, Sternfeld, Richardson, & Jackson, 2000). The KPAS provides four activity indices for individual types of physical activity, including housework or caregiving, active living habits, sports, and occupation, as well as a summary score of the four indices. Given the known influence of physical activity on bone (Kohrt, Bloomfield, Little, Nelson, & Yingling, 2004), the authors used the summary index to compare the groups on level of physical activity averaged over both time points. If the value for month 12 was missing, the baseline value was used in place of the time-averaged value.

Statistical Analysis

Descriptive data for continuous variables are presented as mean plus or minus standard deviations and for categorical data as a percentage of the sample. Comparisons between breast cancer survivors and controls were determined by repeated measures analysis of covariance (ANCOVA) on baseline and 12-month values. Covariates were included to control for significant group differences on background, clinical, and behavioral variables expected to influence interpretation of outcomes. Group differences for frequency data were determined by chi-square. To assess the effect of hormone therapy on outcomes, the authors categorized breast cancer survivors into three subgroups according to adjuvant hormone therapy status (none, SERM, or AIs) and conducted additional comparisons within the breast cancer survivors group using ANCOVA as described earlier.

Results

Sample

A total of 72 women were enrolled in the study (44 breast cancer survivors and 28 controls). Sixty-one women completed both baseline and 12-month visits (35 breast cancer survivors and 26 controls), and their data were used in analyses. Eleven women completed baseline testing but did not return for 12-month testing. Reasons for not completing the study included: moved outside of study area (n = 4), lack of time (n = 5), recurrence or active treatment (n = 1), and pregnancy (n = 1). Baseline characteristics (age, serum estradiol level, spine and hip BMD, bone biomarkers, strength, balance, calcium intake, and physical activity) of women who dropped out of the study were not significantly different than women who completed the study. On average, breast cancer survivors in this study were aged 45 years at diagnosis and one year past chemotherapy completion. Most women had stage II disease and the majority of women received doxorubicin or cyclophosphamide-containing chemotherapy regimens. About 75% of the sample were on adjuvant hormonal therapy with either a SERM or an AI (see Table 1). Compared to controls, breast cancer survivors were significantly older, had higher follicle-stimulating hormone and lower estradiol levels consistent with menopause, had greater body fat, were less physically active, and had worse balance but consumed more dietary calcium.

Bone Health

No significant group differences existed in BMD between breast cancer survivors and controls at any

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skeletal site at any time point (see Table 2). The rate of bone loss over time did not change significantly within or between groups. Among breast cancer survivors, those who were on an AI and those who were not taking either an AI or a SERM consistently lost BMD over the year compared to slight increases in BMD among SERM users, although no significant group differences were detected (see Table 3). A significantly greater percentage of breast cancer survivors were classified with low BMD at the spine compared to controls, both at baseline and 12-month follow-up. Within breast cancer survivors, the greatest percentage of women classified with low spine BMD were not receiving adjuvant hormone therapy (63%) compared to women taking an AI (40%) or a SERM (26%) ($p = 0.08$). Compared to breast cancer survivors with normal BMD, breast cancer survivors with low scores had significantly lower body mass index, less lean mass and leg strength, and were more likely to have stage II disease (see Table 4). At both baseline and 12 months, breast cancer survivors had significantly elevated levels of bone turnover markers compared to controls. Women on an AI or no adjuvant hormone therapy had the highest initial levels of bone turnover. After one year, the only significant change between groups over time was a 20% decrease in osteocalcin among breast cancer survivors compared to a slight increase in controls ($p < 0.05$), mostly attributable to changes in women on an AI or no adjuvant hormone therapy. More breast cancer survivors reported fractures (11%) than controls (3%) at baseline and, over one year, only one fracture was reported in the breast cancer survivors group (3%) compared to none in controls. The percentage of participants who fractured did not differ significantly between groups at either time point.

Falls

At baseline, a similar percentage of breast cancer survivors and controls reported falling once or more over the previous year (50% versus 45% for breast cancer survivors versus controls, respectively) (see Figure 1). However, significantly more breast cancer survivors ($p = 0.03$) experienced one or more falls (75%) compared to controls (45%) when falls were monitored monthly for one year (see Figure 2). About 50% of the breast cancer survivors who fell over the year reported falling more than once, compared to less than 33% of the controls who reported multiple falls; but these differences were not significantly different. Among breast cancer survivors, those who had fallen were significantly more likely to have lower levels of leg strength and consume less calcium compared to survivors who did not fall (see Table 5). Fall incidence did not differ significantly across categories of adjuvant hormone therapy use (see Table 6).

Discussion

The findings suggest that breast cancer survivors treated with chemotherapy-induced amenorrhea have increased fracture risk factors compared to premenopausal women never treated for cancer. Compared to controls, the breast cancer survivors group had a higher percentage of low spine BMD, higher levels of bone turnover markers, and were more likely to fall. Breast cancer survivors with lower muscle strength were more likely to have low BMD at the spine and to fall compared to breast cancer survivors with greater strength. Additionally, breast cancer survivors with low spine BMD had less lean mass and were more likely to have stage II disease. Breast cancer survivors who fell consumed less calcium than breast cancer survivors who did not.

Breast cancer survivors at risk for treatment-related menopause comprise about 25% of the breast cancer survivor population (American Cancer Society, 2007). The current study is the first to evaluate a comprehensive set of risk factors for fracture among prematurely menopausal breast cancer survivors and to compare risk

Table 3. Bone Health of Breast Cancer Survivors and Controls at Baseline and 12-Month Follow-Up

	Breast Cancer Survivors (N = 35)				Controls (N = 26)			
	Baseline		12 Months		Baseline		12 Months	
Characteristic	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Lumbar spine BMD (g/cm²)	0.996	0.121	0.997	0.112	1.045	0.105	1.043	0.107
Total hip BMD (g/cm²)	0.924	0.116	0.923	0.116	0.927	0.115	0.928	0.116
Greater trochanter BMD (g/cm²)	0.692	0.091	0.693	0.09	0.72	0.09	0.725	0.09
Femoral neck BMD (g/cm²)	0.814	0.114	0.811	0.112	0.803	0.126	0.801	0.116
Osteocalcin (mg/dl)	14.2	8.2*	11.4	6.4**	8.2	3.1	8.5	3.3
Deoxypyridinoline (nmol/mmol creatinine)	8.1	4.7*	6.9	2.3*	4.8	1.6	4.6	1.6

* Significant main effect of group (breast cancer survivors versus controls) controlling for age and the physical activity score; calcium intake and fat mass averaged across time 1 and time 2 for each subject, $p < 0.05$

** Significant group by time interaction, $p < 0.05$

BMD—bone mineral density

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Table 4. Bone Health by Adjuvant Hormone Therapy Treatment in Breast Cancer Survivors

	Selective Estrogen Receptor Modulator (N = 17)			Aromatase Inhibitors (N = 10)			None (N = 8)		
Characteristic	$\bar{X}$	SD	Survivors With Low BMD %	$\bar{X}$	SD	Survivors With Low BMD %	$\bar{X}$	SD	Survivors With Low BMD %
Lumbar spine BMD (g/cm²)			24			40			63
Baseline	1.026	0.126		1.017	0.088		0.904	1.04	
12 months	1.033	0.115		1.013	0.092		0.902	0.091	
Change over one year (%)	0.84	3		–0.5	3.1		–0.1	2.7	
Total hip BMD (g/cm²)			12			20			25
Baseline	0.949	0.116		0.925	0.105		0.87	0.124	
12 months	0.949	0.113		0.919	0.109		0.873	0.132	
Change over one year (%)	0.1	2.2		–0.64	2		0.15	2.1	
Greater trochanter BMD (g/cm²)			18			20			25
Baseline	0.714	0.094		0.693	0.093		0.644	0.077	
12 months	0.718	0.089		0.69	0.097		0.643	0.082	
Change over one year (%)	0.71	3.5		–0.44	2.7		–0.26	3.4	
Femoral neck BMD (g/cm²)			24			10			38
Baseline	0.823	0.123		0.831	0.103		0.774	0.115	
12 months	0.822	0.12		0.825	0.112		0.769	0.108	
Change over one year (%)	0.07	3.5		–0.84	3.7		–0.61	2.8	
Osteocalcin (mg/dl)			–			–			–
Baseline	8.7	4.1*		18.5	7.9		19.2	8.6	
12 months	9.3	3.6*		16.8	9.3		9.8	3.8	
Change over one year (%)	14.8	49.6*		–10.4	33.9		–43.8	23.2	
Deoxypyridinoline (nmol/mmol creatinine)			–			–			–
Baseline	7.1	3.2*		8.3	7.5		10	2.3	
12 months	6.6	2.7*		7.2	2.3		6.6	1.9	
Change over one year (%)	11.9	57.1*		–31.6	23.8		–45.6	66.1	

* Significant differences among groups after adjustment for group differences in age and mean physical activity score, $p < 0.05$

[a] Low BMD defined as a T score less than –1.

BMD—bone mineral density

factors to a control group of premenopausal women. In addition to clinical information, the authors assessed health behaviors and collected objective performance measures related to bone health and risk of falling. The authors are the first to track fall incidence prospectively and to describe characteristics that discriminate between breast cancer survivors who fall and those who do not.

This study also has limitations. The cross-sectional nature of the design precludes the authors from making definitive conclusions that observed differences between breast cancer survivors and controls are attributable solely to cancer treatment. In addition, the sample size was relatively small and was heterogeneous with respect to disease stage and treatment types, potentially limiting the ability to examine treatment-related effects on bone health and falls. To examine trends related to adjuvant hormone therapy use, the authors conducted additional analyses according to treatment type, although sample sizes were underpowered to detect significant group differences. Despite these limitations, the authors were able to evaluate the combined effects of breast cancer, chemotherapy, and early menopause on clinically meaningful T scores, bone turnover, and falls in the early period after treatment and further into recovery. Because most studies to date have focused on bone outcomes before and immediately following chemotherapy, the authors' data provide an extended look at fracture risk factors in survivorship, an important consideration given increased disease-free survival for breast cancer (American Cancer Society, 2007).

Breast cancer survivors in this study had poorer scores on several risk factors related to fracture risk than controls. Breast cancer survivors had significantly lower levels of activity, worse balance, and higher levels of body fat. Others have reported lower physical activity levels and increased body fat after chemotherapy for breast cancer (Cheney et al., 1997; Demark-Wahnefried et al., 2001). The current study is among the first to provide data on balance in breast cancer survivors. Chemotherapy for breast cancer can lead to peripheral neuropathy if the treatment includes a taxane (Boehmke & Dickerson, 2005) and has been linked to poor balance among breast cancer

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survivors (Wampler et al., 2007). The authors also found data linking increased body fat, commonly seen during chemotherapy, to poor balance (Winters & Snow, 2000b). Physical inactivity is linked to bone loss, mobility impairment, and falls (Kohrt et al., 2004), although neuropathies and poor balance increase fall risk (American Geriatric Society, 2001; Richardson & Hurvitz, 1995). Breast cancer survivors consumed significantly more calcium than controls and were well above the recommended dietary intake for calcium and calcium intake reported in a slightly older group of postmenopausal breast cancer survivors (Lindsey et al., 2002).

Although the authors failed to detect significant differences in BMD between groups, using clinically relevant T scores, a greater percentage of breast cancer survivors had low BMD at the spine compared to controls. Few studies have compared BMD in postmenopausal breast cancer survivors to matched controls. Using Z scores from the DXA that could include women with a history of breast cancer, Crandall, Petersen, Ganz, and Greendale (2004) reported higher total body BMD but similar hip and spine BMD between menopausal breast cancer survivors and the reference population supplied with the DXA. The discrepant findings among skeletal sites in that study suggest that breast cancer treatment may have affected skeletal regions with a high proportion of trabecular bone, typical of estrogen deprivation (Arlot, Sornay-Rendu, Garnero, Vey-Marty, & Delmas, 1997). Chen, Mericic, Pettinger, et al. (2005) reported significantly lower hip BMD and a greater prevalence of osteoporosis at the hip (10%) among postmenopausal breast cancer survivors aged 50–79 years compared to controls and similar trends for poorer bone health at the spine in breast cancer survivors compared to controls (Chen, Mericic, Pettinger, et al.). In a single-group study of postmenopausal breast cancer survivors aged 42–65 years, Twiss et al. (2001) detected osteopenia

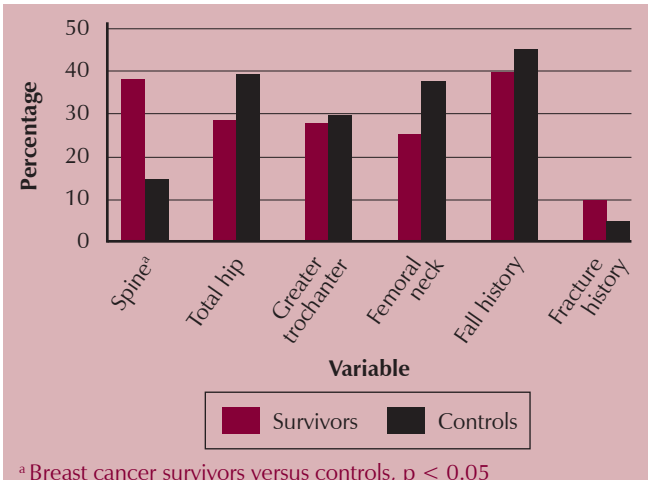

Figure 1. Percentage of Breast Cancer Survivors and Controls With Low Bone Mass (T Score Less Than –1), History of Falls, or History of Fracture at Baseline

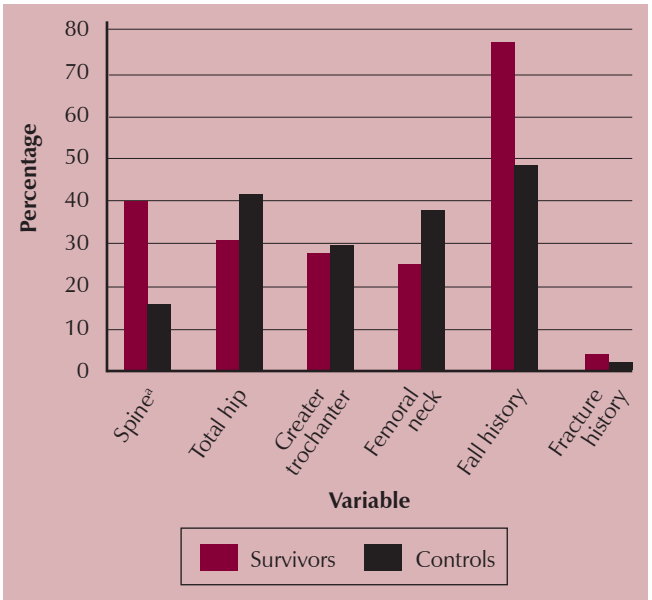

Figure 2. Percentage of Breast Cancer Survivors and Controls With Low Bone Mass (T Score Less Than –1) at Follow-Up or Who Fell or Fractured Bones Over the 12-Month Study Period

in the spine and hip in 53% and 43% of women, respectively, and osteoporosis in the spine and hip in 3% and 6% of women, respectively. Data from the current study are consistent with that of other researchers suggesting that low BMD is a concern for breast cancer survivors (Chen, Maricic, Bassford, et al., 2005a; Chen, Maricic, Pettinger, et al.; Twiss et al.). The higher rates of osteoporosis and osteopenia in other studies reflect the older age of their cohorts. In the current study, BMD did not change significantly in either group over time, which may reflect the mix of adjuvant hormone therapy use among the sample. Almost 50% of the participants were receiving tamoxifen, a SERM expected to increase BMD, and their BMD increased slightly over time. Participants receiving an AI or not receiving any adjuvant hormone therapy experienced BMD losses over the same timeframe.

Breast cancer survivors had significantly elevated levels of bone turnover markers compared to controls both at baseline and one year. Bone turnover is elevated with chemotherapy-induced amenorrhea (Shapiro et al., 2001) and AI administration (Coleman et al., 2007), and lowered with tamoxifen (Kristensen et al., 1994; Love et al., 1992). Over one year, osteocalcin declined significantly in breast cancer survivors compared to no change in controls, while deoxypyrodinoline cross-links decreased (but not significantly). Reductions in bone turnover occurred in women on an AI and to the greatest extent in women on no adjuvant hormone therapy. A trend for decreasing bone turnover with increasing time since menopause has been observed in chemotherapy-induced amenorrhea (Coleman et al.; Shapiro et al.) and

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Table 5. Characteristics of Breast Cancer Survivors With Low Versus Normal Spine BMD[a] at Baseline

Characteristic	Low BMD (N = 13)			Normal BMD (N = 22)		
	$\bar{X}$	SD	%	$\bar{X}$	SD	%
Age (years)	46.3	5.7	–	46.5	2.7	–
BMI (kg/m^2)	24	3.1*	–	28.2	5.9	–
Lean mass (kg)	39.9	3.8*	–	44.6	5.6	–
Fat mass (kg)	22.5	7.3	–	29.6	11.2	–
Estradiol (ng/ml)	20.8	34.9	–	9.7	10.4	–
Osteocalcin (ng/ml)	16.5	7.2	–	12.9	8.6	–
Deoxypyridinoline (nmol/mmol creatinine)	9.4	3.5	–	7.4	5.3	–
Maximal leg press (kg)	72	14.4*	–	88.5	17.9	–
One-leg stance—eyes open	74.1	49.7	–	52.6	43.6	–
One-leg stance—eyes closed	22.9	24	–	11.8	10.8	–
Physical activity index	10.6	2	–	10.5	1.7	–
Calcium intake (mg per day)	2,027	602	–	1,850	647	–
Treatment with doxorubicin or cyclophosphamide plus taxol	–	–	90	–	–	94
Stage II[b]	–	–	92*	–	–	45
Currently using SERM	–	–	31	–	–	61
Currently using AI	–	–	33	–	–	27

* Low BMD group different from normal BMD group, $p < 0.05$

[a] Low BMD defined as a T score of less than –1

[b] Comparisons based on frequency of women with low versus normal BMD with either stage I or stage II disease

AI—aromatase inhibitors; BMD—bone mineral density; BMI—body mass index; SERM—selective estrogen receptor modulator

natural menopause (Suresh & Naidu, 2006). Despite the potential for some recovery in bone turnover, levels of both markers remained greater in breast cancer survivors than controls at the one-year follow-up. Because elevated bone turnover is an independent risk factor for fracture (Riggs & Melton, 2002), the trajectory of changes in bone turnover in breast cancer survivors with chemotherapy-induced amenorrhea should be determined to better evaluate long-term fracture risk.

Among breast cancer survivors, women with low BMD at the spine had lower body mass index, leaner mass, less leg strength, and were more likely to have stage II disease than women with normal bone density. Lean mass and strength are significantly correlated to one another and each is positively associated with spine and hip BMD (Beck & Snow, 2003; Winters & Snow, 2000a). Chemotherapy and estrogen deprivation are linked to loss of muscle mass (Cheney et al., 1997; Demark-Wahnefried et al., 2001; Freedman et al., 2004; Greep et al., 2003; Harvie et al., 2004; Kutynec et al., 1999) and strength (Beck & Snow, 2003). Although all breast cancer survivors in the study received chemotherapy, a subgroup of women may be particularly prone to loss of muscle mass and strength from treatment or, alternatively, women may have had lower muscle mass and strength prior to treatment. The higher percentage of women with stage II disease among breast cancer survivors with low BMD is interesting. A greater proportion of women with stage II disease rather than stage I disease were taking neither a SERM nor an AI, and these breast cancer survivors not on adjuvant hormone therapy had the lowest BMD among hormone treatment groups. The low estrogen levels among breast cancer survivors with chemotherapy-induced amenorrhea and no adjuvant hormone therapy may explain their poorer musculoskeletal health and may indicate a subgroup of breast cancer survivors that may be vulnerable to fractures.

Despite similar fall rates at baseline, breast cancer survivors reported almost twice as many falls as controls when falls were tracked prospectively. Prospective falls monitoring using diaries or postcards avoids issues of recall accuracy and erroneous classification of accidental falls compared to a retrospective falls history (Ganz, Higashi, & Rubenstein, 2005) because participants are aware that they are to track falls, the recall time frame of 30 days is shorter than the 12-month time frames used in other studies and at the baseline interview, and the authors used telephone reminders to prompt completion of the monthly diary form. This methodologic difference may explain why breast cancer survivors recorded more falls when followed over one year compared to controls, despite similar fall rates at enrollment. A history of multiple falls is a well-recognized and independent risk factor for fracture in the general population and also has been observed as contributing to fractures in breast cancer survivors (Chen, Maricic, Bassford, et al., 2005). An increase in distal forearm fracture and falls among women in their perimenopausal years suggests that declining estrogen levels may be linked to fall risk (Winner, Morgan, & Evans, 1989). Torgerson, Garton, and Reid (1993) reported a greater risk of falls among perimenopausal women who were closer to menopause compared to women with regular cycles. Given the sudden and severe estrogen decline among prematurely menopausal breast cancer survivors, particularly women also receiving adjuvant hormone therapy with an AI, the link between hypoestrogenism and increased fall risk is worth additional study.

In subgroup analyses, breast cancer survivors who fell were weaker and consumed less dietary calcium than breast cancer survivors who did not fall. Lower extremity weakness is the leading risk factor for falls among

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Table 6. Baseline Characteristics of Breast Cancer Survivors Who Fell During the 12-Month Study Period Versus Survivors Who Did Not Fall

Characteristic	Survivors Who Fell (N = 26)			Survivors Who Did Not Fall (N = 9)		
	$\bar{X}$	SD	%	$\bar{X}$	SD	%
Age (years)	46.4	4.3	–	46.6	3.2	–
BMI (kg/m²)	26.5	5.9	–	26.8	3.9	–
Lean mass (kg)	42.6	5.3	–	43.9	6.4	–
Fat mass (kg)	26.3	11	–	29.2	9.1	–
Estradiol (ng/ml)	15.3	26.5	–	10.9	8.9	–
Maximal leg press (kg)	170.4	37*	–	212.2	34.1	–
One-leg stance—eyes open	68.9	50.9	–	36.4	13.4	–
One-leg stance—eyes closed	16.8	18.8	–	12.6	12	–
Physical activity level	10.6	1.8	–	10.5	1.8	–
Calcium intake (mg per day)	1,771	617*	–	2,332	472	–
Stage II	–	–	62	–	–	56
Treatment with doxorubicin or cyclophosphamide plus taxol	–	–	94	–	–	88
Currently using SERM	–	–	50	–	–	44
Currently using AI	–	–	28	–	–	33

* Low BMD group different from normal BMD group, $p < 0.05$

[a] Comparisons based on frequency of women with low versus normal BMD with either stage I or stage II disease

AI—aromatase inhibitors; BMD—bone mineral density; BMI—body mass index; SERM—selective estrogen receptor modulator

community-dwelling older adults (American Geriatric Society, 2001). Muscle weakness also was linked to falls in a study that tracked falls among inpatient cardiac patients and patients with cancer, although strength assessments were subjective and the examiner was not blinded to the fall status of patients (O'Connell, Baker, Gaskin, & Hawkins, 2007). Overcash (2007) reported lower perceived physical functioning as a risk factor for falls among older adult cancer survivors, although participants who fell may have subsequently appraised themselves as functioning more poorly because they had fallen as opposed to the lower level of functioning leading to the fall. In the current study, the authors used an objective measure of maximal muscle strength—the one-repetition maximum test, a validated and well-accepted technique—and tested participants at two time points. Lower extremity weakness in breast cancer survivors could be the result of treatment-related loss of lean mass, physical inactivity, or subclinical peripheral neuropathies. Lean mass was lower, but not significantly so between breast cancer survivors who fell and breast cancer survivors who did not fall, and physical activity levels between subgroups were similar, although the authors did not specifically look at strength-promoting activities. The authors did not measure symptoms of peripheral neuropathy in this sample and, therefore, the cause of muscle weakness among the fallen remains unclear. Calcium intake was significantly lower among breast cancer survivors who fell compared to those who did not; however, no known link exists between poor calcium intake and increased fall risk. Lower calcium intake may reflect overall poorer nutritional status that could include vitamin D (Twiss, Gross, Waltman, Ott, & Lindsey, 2006), a nutrient increasingly linked to fall risk (Jackson, Gaugris, Sen, & Hosking, 2007). Given the complexity and intensity of medical treatment for breast cancer and the multiple, persistent side effects that remain after treatment ends, falls and their determinants should be specifically studied in breast cancer survivors, preferably before, during, and after treatment.

Epidemiologic studies have reported both a reduced risk (Lamont & Lauderdale, 2003) and an increased risk of fracture among breast cancer survivors (Adami et al., 1990; Chen, Maricic, Bassford, et al., 2005; Kanis et al., 1999). The most recent prospective study from the Women's Health Initiative reports a 15% increase in the risk of overall fractures among postmenopausal breast cancer survivors (Chen, Maricic, Bassford, et al.). In the current study, more breast cancer survivors reported having a fracture since diagnosis compared to controls reporting a fracture since age 40, although differences were not significantly different. The average observation time for fracture history at enrollment was similar between groups at one and two years (breast cancer survivors $\bar{X}$ age = 46.4, $\bar{X}$ age at diagnosis = 44.6; controls $\bar{X}$ age = 41.3), but the mean absolute age at enrollment was significantly higher in breast cancer survivors. Because breast cancer survivors were almost six years older than controls over the comparison periods, the higher fracture rate may be related to the older age of the breast cancer survivors, not to breast cancer or its treatments. Over one year, only one breast cancer survivor had a fracture compared to no one in the control group. This low incidence rate reflects the small sample and the short observation period of the study because fractures remain a relatively rare event.

Conclusion

In conclusion, the data show that breast cancer survivors who become menopausal from chemotherapy have greater fracture risk factors compared to premenopausal women with no cancer history. That is, the prevalence of low BMD, elevated bone turnover, and falling each were greater in breast cancer survivors than controls. Little evidence exists that musculoskeletal health recovers as time past treatment increases, because risk factors remain greater

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than controls even two years after completing breast cancer chemotherapy. Women with lower levels of muscle strength were a subgroup of breast cancer survivors in the study and they were most likely to have both poor bone health and an increased numbers of falls. Adjuvant hormone therapy may differentially affect musculoskeletal health among these breast cancer survivors and should continue to be studied, particularly among women who are not on adjuvant hormone therapy. Fractures in breast cancer survivors are costly (Zhou, Redaelli, Johnell, Willke, & Massimini, 2004) and threaten quality of life in survivorship. Breast cancer survivors who are at risk of fracture should continue to be studied longitudinally and efforts should be focused on developing and testing targeted interventions to decrease identified risk factors. In the meantime, suggesting that breast cancer survivors with chemotherapy-induced amenorrhea be screened for low bone mass and a history of falls is reasonable. If positive, lifestyle strategies aimed at bone health and fall prevention, including physical activity that includes lower body strengthening exercises and proper nutrition, should be suggested. Nurses may play a pivotal role in both screening and making appropriate recommendations during follow-up.

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