

Fracture Risk Among Breast Cancer Survivors

Results From the Women's Health Initiative Observational Study

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Background: Breast cancer and its treatment may compromise bone health. We tested the hypothesis in the Women's Health Initiative Observational Study that postmenopausal survivors of breast cancer have a higher risk for fractures compared with women who have no cancer history.

Methods: A prospective cohort (5.1 years' follow-up) study design was used. Breast cancer survivors were women who reported a history of breast cancer (n=5298). A reference group included women who had no cancer history at baseline (n=80848). Fracture occurrence was ascertained from annual self-reports. Hip fractures were confirmed by reviewing medical records.

Results: After adjustment for age, weight, ethnicity, and geographic region of enrollment, the hazard ratios (HRs) of breast cancer survivors to women in the reference group were 0.93 (95% confidence interval [CI], 0.64-1.33) for

hip; 1.36 (95% CI, 1.16-1.59) for forearm or wrist; 1.31 (95% CI, 1.19-1.43) for eligible fractures other than hip, vertebral, and forearm or wrist; and 1.31 (95% CI, 1.21-1.41) for these fractures combined. The increased risk for clinical vertebral fracture was statistically significant only among survivors who had a breast cancer diagnosis before age 55 years (HR, 1.78; 95% CI, 1.28-2.46). After adjusting for factors related to hormone levels, risk of fall, fracture history, medication use, comorbidity, and lifestyle, the increased risk for all fractures studied among survivors was reduced to 15% (HR, 1.15; 95% CI, 1.05-1.25).

Conclusions: Postmenopausal survivors of breast cancer are at increased risk for clinical fractures. Preventions and therapeutic interventions are needed to reduce fracture risk in this large and growing population.

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BREAST CANCER SURVIVORS may be more likely to have further increased risk for bone loss and fractures compared with other women of their age for many reasons. High bone turnover and bone loss may arise because of low estrogen levels from an early menopause induced by adjuvant chemotherapy^{1,2} or oophorectomy in premenopausal women and from contraindication of postmenopausal hormone therapy (HT). It has been suggested that cancer treatments may have direct toxic effects on bone formation cells³⁻⁵ and that breast cancer itself may interfere with bone metabolism without bone metastases.⁶

Studies on the risk of hip fracture in breast cancer survivors are inconsistent, suggesting either an increased⁷ or reduced risk.⁸ A high incidence of vertebral fractures in women with nonmetastatic recurrent breast cancer has been reported in a previous study; however, the vertebral fractures were identified by us-

ing a radiographic evaluation method instead of by clinical diagnosis.⁹ Whether breast cancer survivors have an increased risk for clinical fractures deserves further investigation.

In a prospective cohort of postmenopausal women from the Women's Health Initiative Observational Study (WHI-OS), we tested the hypothesis that postmenopausal breast cancer survivors have a significantly increased risk for clinical fractures.

METHODS

STUDY PARTICIPANTS AND PROCEDURES

The WHI-OS is a large nationwide, longitudinal study, which comprises more than 90 thousand women (N=93 676) enrolled from 1994 to 1998 at 40 clinical centers in the United States.¹⁰ The WHI-OS has been reviewed and approved by human subjects review committees at each participating institution. In this ar-

ticle, we included all WHI-OS participants with follow-up information, excluding those women who reported prior cancer other than breast cancer in the WHI enrollment questionnaire. This left 86 146 participants for the subsequent analyses. These participants were classified into 2 groups, a breast cancer survivor group (n=5298) and a no cancer reference group (n=80848), based on their response in the baseline questionnaire (ever had breast cancer vs no history of any cancer). As of August 31, 2002, the average length of follow-up time in this prospective cohort was 5.1 years.

FRACTURE ASSESSMENTS

During the follow-up, fracture events were reported annually in questionnaires by either WHI participants or proxy respondents. Approximately 79% of the fracture reports were from the participants themselves. The initial question on fracture was phrased as follows: "Since [last reporting date], has a doctor told you that you had a broken, fractured, or crushed bone?" If people selected "Yes," they were asked to answer "Which bone did you break, fracture, or crush?" by marking all that apply from the following list: (1) hip, (2) upper leg (not hip), (3) pelvis, (4) knee (patella), (5) lower leg or ankle, (6) foot (not toe), (7) tailbone (coccyx), (8) spine or back (vertebra), (9) lower arm or wrist, (10) hand (not finger), (11) elbow, (12) upper arm or shoulder, and (13) other (specify). Hip fractures were confirmed by central review of radiology reports at the WHI Bone Density Center at the University of California, San Francisco. All other nonhip clinical fractures used in this article were based on information from self-reports.

We categorized fractures into 4 mutually exclusive groups: (1) hip, (2) forearm/wrist, (3) clinical vertebral, and (4) other clinical fractures (excluding fractures of ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae). Only the first fracture event for each of the 4 categories reported by a woman was used in this article. Total fracture is the occurrence of a fracture from any of these 4 categories.

ASSESSMENTS OF COVARIATES

Information on age, age at menopause, race/ethnicity, smoking, fracture history, number of falls in the last 12 months, hysterectomy, postmenopausal hormone use, walking, supplementations, medication uses, and medical history were ascertained from self-administered or interviewer-administered baseline questionnaires. "Don't know" responses were coded as missing. Age at menopause is defined as the minimum age at which the participant last had any menstrual bleeding, had a bilateral oophorectomy, or began using HT. For a hysterectomized woman without a bilateral oophorectomy, age at menopause was the earliest age at which she began using HT or first had menopausal symptoms. If neither occurred and age at hysterectomy was 50 years or older, then age at menopause was her age at hysterectomy. Age at menopause was truncated at age 60 years.

Physical function was measured using the 10-item Medical Outcomes Study Scale,¹¹ with a higher score indicating better physical function. The median value was chosen as a cutoff for analysis. Depression was assessed using the shortened Center for Epidemiologic Studies Depression Scale (CES-D/DIS).¹² Dietary intakes and alcohol consumption were assessed using a semiquantitative food frequency questionnaire.¹³ Weight was measured to the nearest 0.1 kg on a balance beam scale, with the participant dressed in indoor clothing without shoes. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

STATISTICAL ANALYSIS

Selected baseline characteristics of breast cancer survivors were compared with those of the reference group by using χ^2 tests to determine the statistical significance levels of the differences. Age-standardized incidence rates of clinical fractures per 10000 person-years were calculated, using the age distribution of the entire WHI-OS cohort as the standard population.

Multivariate Cox proportional hazard models were used to compute hazard ratios (HRs) and 95% confidence intervals (95% CIs). In the basic multivariate Cox proportional hazard model, age, ethnicity, weight, and region of living were included as covariates using the forced entry approach. Additional models were developed by including the basic model and selected sets of covariates to test whether the differences in fracture risk between breast cancer survivors and the reference group can be explained by variations in factors such as risk of fall, fracture history, lifestyle factors, prior diseases, and medication use in the 2 subgroups of women. In the final model, all these covariates were included.

In an exploratory analysis, separate Cox proportional hazard regression analyses by age at breast cancer diagnosis were also conducted to examine whether the relative risk of fractures, in comparison with the reference group, differ between the earlier cancer diagnosis group (before age 55 years) and the later diagnosis group (age ≥ 55 years). The test for heterogeneity in fracture risk by age at breast cancer diagnosis was conducted using an equality test for the 2 coefficients of the 2 diagnosis groups in the fracture risk model.

Risk factors for fractures among breast cancer survivors were examined in separate Cox proportional hazard models adjusting for age. Because of the large number of covariates, we used separate models for each covariate (adjusting for age) instead of 1 multivariate model including all the risk factors to avoid sparse data in certain strata.

We considered that new cancer diagnosis during the follow-up might have altered fracture risk in the reference group. A sensitivity analysis was repeated after excluding women who developed any form of cancer during the follow-up time from the reference group. To determine the independence of the main association of interest from postmenopausal HT, a sensitivity analysis was also performed by excluding women who were using HT. All analyses were performed using SAS software (version 9.0; SAS Institute, Inc, Cary, NC) using 2-sided tests.

RESULTS

BASELINE CHARACTERISTICS

Most of the bivariate comparison results suggested statistically significant differences ($P < .05$) between the breast cancer survivor group and the reference group. However, some of the group discrepancies in the measurements may have no clinical meaning because they were small and only reflect the large sample size in this study (**Table 1**).

FRACTURE INCIDENCE RATES

Owing to a higher death rate in breast cancer survivors compared with the reference group (6% vs 3%), the mean \pm SD follow-up time was slightly different: 4.9 ± 1.3 years for breast cancer survivors and 5.1 ± 1.3 years for the reference group. The number of person-years for the time to first fracture or death or last contact was 416 016,

Table 1. Baseline Characteristics of the Study Participants*

Characteristic	Breast Cancer Survivors (n = 5298)	No Cancer Reference Group (n = 80 848)	P Value
Ethnicity			
White	4516 (85.24)	67 027 (82.90)	<.001
Black	477 (9.00)	6641 (8.21)	
Hispanic	140 (2.64)	3225 (3.99)	
American Indian	21 (0.40)	358 (0.44)	
Asian/Pacific Islander	82 (1.55)	2453 (3.03)	
Unknown	62 (1.17)	1144 (1.42)	
US region of enrollment			
Northeast	1007 (19.01)	18 768 (23.21)	<.001
South	1700 (32.09)	20 719 (25.63)	
Midwest	1357 (25.61)	17 691 (21.88)	
West	1234 (23.29)	23 670 (29.28)	
Age group at screening, y			
50-59	1304 (24.61)	26 550 (32.84)	<.001
60-69	2344 (44.24)	35 601 (44.03)	
70-79	1650 (31.14)	18 697 (23.13)	
BMI			
Underweight (<18.5)	50 (0.96)	953 (1.19)	.01
Normal (18.5-24.9)	2020 (38.59)	31 876 (39.89)	
Overweight (25.0-29.9)	1764 (33.70)	27 240 (34.09)	
Obesity I (30.0-34.9)	884 (16.89)	12 444 (15.57)	
Obesity II (35.0-39.9)	340 (6.50)	4603 (5.76)	
Extreme Obesity III (≥40)	176 (3.36)	2789 (3.49)	
Age at menopause, y			
<40	471 (9.35)	6844 (8.81)	.22
40-44	687 (13.64)	9914 (12.76)	
45-49	1283 (25.47)	20 262 (26.09)	
50-54	1911 (37.94)	29 856 (38.44)	
Years since menopause			
<5	436 (8.66)	10 567 (13.60)	<.001
5 to <10	786 (15.60)	14 143 (18.21)	
10 to <15	922 (18.30)	15 321 (19.73)	
≥15	2893 (57.43)	37 639 (48.46)	
Hysterectomy at screening			
No	3028 (57.18)	48 682 (60.27)	<.001
Yes	2268 (42.82)	32 089 (39.73)	
Oophorectomy			
No ovaries removed	3600 (69.10)	57 898 (72.63)	<.001
Partial, 1 or unknown number of ovaries removed	435 (8.35)	6980 (8.76)	
Both ovaries removed before age 55 y	947 (18.18)	12 566 (15.76)	
Both ovaries removed at or after age 55 y	228 (4.38)	2270 (2.85)	
Shortened CES-D/DIS ≥0.06†			
No	4516 (87.69)	70 034 (88.87)	.01
Yes	634 (12.31)	8774 (11.13)	
Time spent walking, min/wk			
None	2247 (42.60)	32 304 (40.42)	.003
>0-150	2220 (42.09)	34 303 (42.92)	
>150	808 (15.32)	13 319 (16.66)	
Physical function score			
≤90 (poor physical function)	3516 (67.82)	48 414 (61.01)	<.001
>90 (better physical function)	1668 (32.18)	30 944 (38.99)	
No. of times fell down in last 12 mo			
None	3517 (66.52)	54 382 (67.91)	.01
1	1045 (19.77)	15 941 (19.91)	
2	484 (9.15)	6450 (8.05)	
≥3	241 (4.56)	3307 (4.13)	
Fracture history (any bone)			
No	3056 (58.01)	49 453 (61.98)	<.001
Yes	2212 (41.99)	30 342 (38.02)	
Broke bone at or after age 55 y			
No	3483 (79.89)	53 251 (83.52)	<.001
Yes	877 (20.11)	10 508 (16.48)	
Myocardial infarction ever			
No	5115 (96.73)	78 917 (97.69)	<.001
Yes	173 (3.27)	1867 (2.31)	

(continued)

Table 1. Baseline Characteristics of the Study Participants* (cont)

Characteristic	Breast Cancer Survivors (n = 5298)	No Cancer Reference Group (n = 80 848)	P Value
Myocardial infarction ever			
No	5115 (96.73)	78 917 (97.69)	<.001
Yes	173 (3.27)	1867 (2.31)	
Diabetes			
No diabetes	4918 (92.99)	76 374 (94.6)	<.001
Diabetes, no current insulin	309 (5.84)	3334 (4.13)	
Diabetes, currently using insulin	62 (1.17)	1022 (1.27)	
Arthritis ever			
No arthritis	2302 (44.04)	42 064 (52.77)	<.001
Rheumatoid arthritis	346 (6.62)	4165 (5.22)	
Other arthritis/do not know type	2579 (49.34)	33 490 (42.01)	
Hip replacement			
No	5124 (97.88)	77 919 (98.3)	.02
Yes	111 (2.12)	1348 (1.70)	
Emphysema or chronic bronchitis			
No	5001 (95.53)	76 396 (96.38)	.002
Yes	234 (4.47)	2871 (3.62)	
Osteoporosis ever			
No	4536 (86.48)	73 224 (91.55)	<.001
Yes	709 (13.52)	6755 (8.45)	
HT use status			
Never used	3201 (60.45)	31 841 (39.42)	<.001
Past user	1674 (31.61)	11 007 (13.63)	
Current user	420 (7.93)	37 923 (46.95)	
Oral daily corticosteroid use			
No	5232 (98.75)	79 823 (98.73)	.89
Yes	66 (1.25)	1025 (1.27)	
Thiazide use			
No	4975 (93.90)	76 568 (94.71)	.01
Yes	323 (6.10)	4280 (5.29)	
Anti-estrogen use (tamoxifen citrate or toremifene citrate)			
No	4279 (80.77)	80 831 (99.98)	<.001
Yes	1019 (19.23)	17 (0.02)	
Bisphosphonate use			
No	4987 (94.13)	79 049 (97.77)	<.001
Yes	311 (5.87)	1799 (2.23)	
Calcitonin use			
No	5259 (99.26)	80 561 (99.65)	<.001
Yes	39 (0.74)	287 (0.35)	
Taking calcium supplements			
No	1962 (37.03)	32 627 (40.36)	<.001
Yes	3336 (62.97)	48 221 (59.64)	
Taking vitamin D supplements			
No	2381 (44.94)	39 640 (49.03)	<.001
Yes	2917 (55.06)	41 208 (50.97)	
Total calcium (diet + supplements), mg/d			
<600	1036 (20.27)	16 533 (21.31)	<.001
600-1200	1801 (35.23)	29 326 (37.81)	
>1200	2275 (44.50)	31 710 (40.88)	
Total vitamin D intake (diet + supplements), µg/d			
<5.39	1540 (30.13)	26 006 (33.53)	<.001
5.39-13.38	1685 (32.96)	25 932 (33.43)	
>13.38	1887 (36.91)	25 631 (33.04)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CES-D/DIS, the shortened Center for Epidemiologic Studies Depression Scale; HT, hormone therapy.

*Data are given as number (percentage) unless otherwise specified. Because of missing data for some of the characteristics, the numbers for each characteristic will not sum to the total.

†Shortened CES-D/DIS ≥ 0.06 is an indication of depression.

and the number of fractures included in this study was 9202. Among the 9202 fractures, 722 were reported by the breast cancer survivors, including 31 hip, 74 clinical vertebral, 169 lower arm or wrist, and 514 other fractures; 8480 fractures were reported by women in the ref-

erence group, including 450 hip, 789 clinical vertebral, 1867 lower arm or wrist, and 6108 other fractures. Using the age distribution of the entire WHI-OS cohort, we computed age-standardized fracture rates per 10 000 person-years for breast cancer survivors and the reference

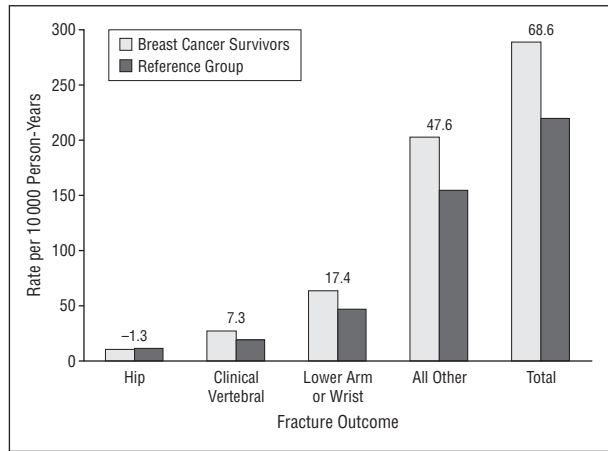


Figure 1. Age-standardized fracture incident rates by survivor status. Standardized rates were calculated using the age distribution of the entire Women's Health Initiative Observational Study cohort. Excess number of fractures per 10,000 person-years are above each set of bars.

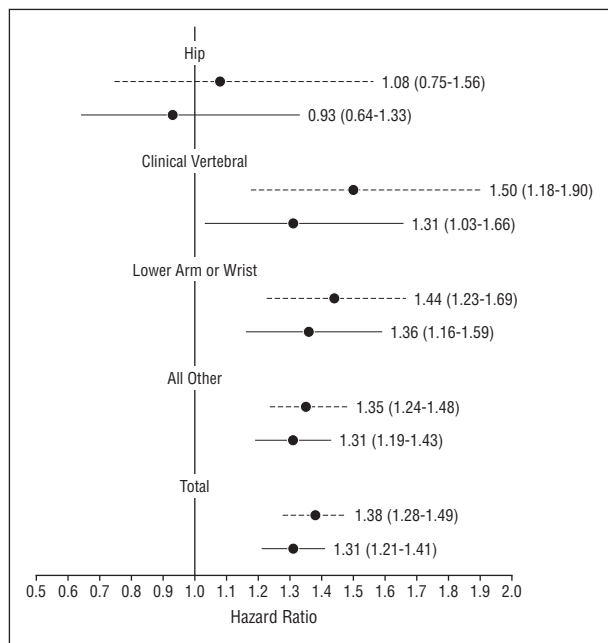


Figure 2. Hazard ratios (95% confidence intervals) of fractures among breast cancer survivors compared with the reference group. The dashed lines indicate the crude estimate, and the solid lines indicate estimates from models adjusted for age, weight, ethnicity, and geographic region of enrollment.

group (**Figure 1**). Except for the hip fracture rate, fracture rates were higher in the breast cancer survivors than in the reference group. Overall, breast cancer survivors may sustain 68.6 excess fractures per 10,000 person-years compared with other women in the same age group.

INCREASED FRACTURE RISK AMONG BREAST CANCER SURVIVORS

The HRs and 95% CIs presented in **Figure 2** further indicate that breast cancer survivors had a significantly increased risk for all the fractures except for hip, even after adjusting for age, ethnicity, body weight, and region of enrollment. The results of Cox proportional hazard regres-

sion from separate analyses by age at breast cancer diagnosis are presented in **Table 2**. After adjusting for age, ethnicity, weight, region of enrollment, the HRs for clinical vertebral fractures were 1.78 (95% CI, 1.28-2.46) for women with breast cancer diagnosis before age 55 years and 1.01 (95% CI, 0.72-1.42) for women who had breast cancer diagnosis at 55 years or older. In a model with 2 covariates for the 2 diagnosis groups, we tested the equality of the 2 coefficients. The results were consistent with the stratified analysis, indicating heterogeneity of fracture risk by age at diagnosis in vertebral fractures but not in any other fracture categories (data not shown).

EXPLANATORY MODELS FOR THE INCREASED TOTAL FRACTURE RISK AMONG BREAST CANCER SURVIVORS

The increased risk for total fractures among breast cancer survivors persisted even after adjustment for hormonal factors, fracture history, lifestyle factors, medication use, and diseases in the multivariate Cox proportional hazard regression models (**Table 3**). The variables age, ethnicity, weight, and geographic region of enrollment were included in all models. There were some small changes in HR after additional variables were entered into each model. The largest change in HR was found in the hormonal model, in which HR was reduced from 1.31 (presented in Table 3) to 1.19 after adjusting for HT, years since menopause, and oophorectomy. The results from the comprehensive model, which included all the variables in the above models, indicated that breast cancer survivors still have a 15% increased risk for total fractures when compared with women in the reference group after adjusting for these multiple risk factors (HR, 1.15; 95% CI, 1.05-1.26). In the sensitivity analysis, similar results were found when excluding women who were receiving HT from the analysis (HR, 1.13; 95% CI, 1.04-1.24), suggesting that the significant difference in total fracture risk between the survivor group and the reference group were independent from the effect of HT.

RISK FACTORS FOR TOTAL FRACTURES AMONG BREAST CANCER SURVIVORS

Fracture risk was significantly and positively associated with age among breast cancer survivors. After adjustment by age group at baseline, breast cancer survivors were more likely to sustain fractures if they had any of the following characteristics: non-Hispanic white, an indication of depression (shortened CES-D/DIS ≥ 0.06), more than 2 falls in the past 12 months, a fracture history before the time of enrollment, diabetes (currently using pills or insulin), arthritis, hip replacement, emphysema or chronic bronchitis, and osteoporosis. However, BMI, number of years since menopause, age at breast cancer diagnosis, and HT use were not significantly associated with total fracture risk in breast cancer survivors (data not shown).

There were 4619 women in the reference group who developed cancer during the follow-up period. Excluding these women from the analyses did not change the results of this study (data not shown).

Table 2. Adjusted HRs* of Fractures Among Breast Cancer Survivors by Age at Breast Cancer Diagnosis Compared With the Reference Group

Fracture Outcomes	Breast Cancer Diagnosis, Age <55 y		Breast Cancer Diagnosis, Age ≥55 y	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Hip	1.07 (0.60-1.90)	.82	0.88 (0.55-1.40)	.58
Clinical vertebral	1.78 (1.28-2.46)	<.001	1.01 (0.72-1.42)	.96
Lower arm or wrist	1.29 (1.02-1.65)	.04	1.42 (1.15-1.74)	.001
All other	1.34 (1.18-1.52)	<.001	1.28 (1.13-1.45)	<.001
Total	1.36 (1.22-1.52)	<.001	1.27 (1.14-1.41)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

*Adjusted for age, weight, ethnicity, and geographic region of enrollment.

COMMENT

Several small studies have found low bone density among postmenopausal breast cancer survivors^{14,15} and accelerated bone loss after chemotherapy for breast cancer,^{1,16,17} suggesting an increased risk for fractures among breast cancer survivors. Adami and colleagues⁷ observed a slightly increased risk (10% higher) of hip fracture among a cohort of breast cancer survivors in Sweden. However, a 37% reduction in risk of hip fracture among US elderly breast cancer survivors was reported.⁸ Similar to the latter study, we also found a slightly lower hip fracture rate (7% lower) among breast cancer survivors, but the reduced risk was not statistically significant, which may be owing to the small number of hip fractures (only 31 hip fractures occurred in breast cancer survivors) during the follow-up period. Hip fractures rarely occur before age 70 years. The inconsistent results on hip fracture risk in the reported studies may be due to the composition of the survivors by age at breast cancer diagnosis.

Kanis and colleagues⁹ have reported a 20-fold increased incidence for vertebral fractures identified using a radiographic method among breast cancer survivors who had soft tissue recurrences but no evidence of bone metastases. Because the radiographic method in their study is primarily used for research purposes and not for the clinical diagnosis of fractures, the finding from Kanis and colleagues⁹ is limited to subclinical fractures in a selective group of breast cancer survivors. In contrast, our study focused on clinical fractures among postmenopausal survivors of breast cancer and provided direct evidence of an increased fracture risk in a wide range of breast cancer survivors.

An increased risk for total fractures was observed in all ages of breast cancer survivors in this study regardless of the time of breast cancer diagnosis. The vertebral fracture risk was significantly higher among women whose breast cancer was diagnosed before age 55 years, but not among women diagnosed as having breast cancer at 55 years or older. Differential risks of vertebral fractures among the 2 survivor groups are possible because the large percentage of trabecular bone in vertebrae is highly responsive to hormonal changes, and women with a breast cancer diagnosis before age 55 years are more likely to experience a dramatic decline in endogenous estrogen levels secondary to chemotherapy-induced ovarian failure

Table 3. Explanatory Models for the Increased Risk for Total Fractures Among Breast Cancer Survivors

Model†	Adjusted HR (95% CI) for Total Fractures
(1) Hormonal	1.19 (1.10-1.29)
(2) Fall history	1.30 (1.20-1.40)
(3) Fracture history	1.28 (1.18-1.38)
(4) Lifestyle	1.30 (1.20-1.40)
(5) Prior disease	1.30 (1.21-1.41)
(6) Medication	1.28 (1.19-1.38)
(7) Comprehensive	1.15 (1.05-1.26)

Abbreviations: CI, confidence interval; HR, hazard ratio.

* $P < .001$ for all.

†(1) Hormonal model: adjusted for age, weight, ethnicity, geographic region of enrollment, hormone therapy use (never, past, current), oophorectomy, and number of years since menopause. (2) Fall history model: adjusted for age, weight, ethnicity, geographic region of enrollment, and number of falls. (3) Fracture history model: adjusted for age, weight, ethnicity, geographic region of enrollment, fracture history ever, and broken bone at or after age 55 years (at baseline). (4) Lifestyle model: adjusted for age, weight, ethnicity, geographic region of enrollment, smoking, physical function score. (5) Prior disease model: adjusted for age, weight, ethnicity, geographic region of enrollment, diabetes (with the use of treated pills or shots), arthritis ever, hip replacement, and emphysema or chronic bronchitis. (6) Medication model: adjusted for age, weight, ethnicity, geographic region of enrollment, bisphosphonate use, and calcitonin use. (7) Comprehensive model: adjusted for all the variables in models 1 through 6.

and/or avoidance of HT at menopause. However, it should be noted that vertebral fractures are often undiagnosed, and physicians may detect vertebral fractures more often among breast cancer survivors owing to the more intensive evaluation of complaints for this special population.

It is known that postmenopausal breast cancer occurs more often among women with higher bone density¹⁸⁻²⁰ and lower risk of bone fracture.²¹ The higher bone fracture rates observed among survivors of postmenopausal breast cancer are possibly due to a combination of factors other than initial bone mineral density. The relationship between bone density and premenopausal breast cancer is unknown, so we cannot exclude the possibility of preexisting low bone density contributing to higher fracture risks among these women. It has been suggested that breast carcinoma may increase osteoclastic activity by increasing the release of transforming growth factors α or β ⁶; however, this hypothesis remains to be tested. Chemotherapeutic agents, such as methotrexate, have a direct toxic effect on bone formation cells,³⁻⁵ which may contribute to the increased risk of bone frac-

tures in the survivors of breast cancer. In addition, chemotherapy-induced ovarian failure among women who are premenopausal at the time of breast cancer diagnosis may have further detrimental effects on bone metabolism.^{1,2} After menopause, most breast cancer survivors are advised not to receive HT, especially women who have estrogen receptor-positive tumors. In the present study, only 8% of breast cancer survivors reported receiving HT at baseline, in contrast to 47% of current users of HT in the reference group at baseline. However, after adjustment for HT use, the increased risk of fractures among breast cancer survivors was still significantly higher than that of the reference group. This finding suggests that the lower frequency of HT use among breast cancer survivors was not the major cause of the increased fracture rates among survivors.

Hip fractures were confirmed through review of medical records, but nonhip fractures used in this study were all self-reported, thus subject to overreporting or underreporting. Previous data suggest that underreporting of fractures rarely occurs in a prospective study among postmenopausal women²²; however, overreporting is common in all epidemiological studies on fracture risk. According to a substudy of the WHI, the overall agreement rate between self-reports of fractures and medical records was approximately 70% for total fractures.²³ This information bias on fractures may have little impact on our study results because there is no evidence that the rate of overreporting is differential by survivor status. Other limitations in this study include no information on the exact age at breast cancer diagnosis, stage of cancer, treatment regimens, and bone metastasis.

In summary, we found increased fracture risks among breast cancer survivors. If our study results are confirmed by others, the excess number of fractures may be as high as 13 000 per year for the 2 million postmenopausal breast cancer survivors in the United States.²⁴ Clearly, more research is needed to understand the fracture risk in this special population and to develop strategies to reduce the number of fractures among breast cancer survivors.

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information about the WHI investigators can be found at <http://www.whi.org/about>.

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