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Fracture risk increases after diagnosis of breast or other cancers in postmenopausal women ---- Results from the Women's Health Initiative

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Abstract

Summary—Risk for falls and fractures increases after breast cancer or other cancer diagnosis in postmenopausal women. Factors other than falls may be the major causes for the increased fracture risk.

Introduction—Cancer treatment and prognosis may have detrimental effects on bone health. However, there is a lack of prospective investigations on fracture risk among incident cancer cases.

Materials and Methods—In this study, postmenopausal women (N = 146,959) from the Women's Health Initiative prospective cohort, who had no cancer history at baseline were followed for up to 9 years and classified into no cancer, incident breast cancer (BC) and incident other cancer (OC) groups. The main outcomes measured were incident fractures and falls before and after cancer diagnosis. Hazards ratios (HR) and 95% confidence intervals (CI) were computed from Cox proportional hazards models.

Results—While hip fracture risk before a cancer diagnosis was similar between the no cancer and cancer groups, hip fracture risk was significantly higher after BC diagnosis (HR = 1.55, CI = 1.13–2.11) and the elevated risk was even more notable after OC diagnosis (HR = 2.09, CI = 1.65–2.65). Risk of falls also increased after BC (HR = 1.15, CI = 1.06–1.25) or OC diagnosis (HR = 1.27, CI = 1.18–1.36), but could not fully explain the elevated hip fracture risk. Incident clinical vertebral and total fractures were also significantly increased after OC diagnosis ($p < 0.05$).

Conclusions—Postmenopausal women have significantly elevated risks for falls and fractures after a cancer diagnosis. The causes for this increased risk remained to be investigated.

Keywords

Breast cancer diagnosis; Cancer diagnosis; Falls; Fractures; Postmenopausal women; Prospective cohort

Introduction

Approximately four in ten white women age 50 or older in the United States will experience a hip, spine or wrist fracture sometime during the remainder of their lives [1]. Even when women have a higher bone density and lower fracture risk before their breast cancer diagnosis [2,3], bone loss may be accelerated with cancer treatment and the presence of cancer itself [4-7]. Recent findings from the Women's Health Initiative (WHI) study [8] have shown a higher fracture risk among women who reported a breast cancer diagnosis history at the WHI enrollment in comparison to postmenopausal women without a history of cancer. However, fracture risk among incident postmenopausal breast cancer cases, as well as the differences in the fracture risk before and after a breast cancer diagnosis in breast cancer survivors are still unknown. As a diagnosis of other cancers may involve some of the same risk factors, such as chemotherapy use, a higher fracture risk after cancer diagnosis may not be unique to breast cancer [9]. Falls are a major risk factor for fractures since 90% of fractures result from a fall [10]. The susceptibility of women to falls related to a diagnosis of breast cancer or other cancer is also understudied.

This objective of this study was to investigate the risk of falls and fractures following a cancer diagnosis in postmenopausal women. We hypothesized that (1) in comparison to their postmenopausal peers, women who are diagnosed with invasive breast cancer have significantly higher risk for fracture after their breast cancer diagnosis but not before the diagnosis; (2) fracture risk increases in postmenopausal women diagnosed with other cancer; (3) the risk of falls elevates after, but not before, women are diagnosed with either breast cancer or other cancer; and (4) the cancer-related increase in fall does not fully explain the higher fracture risk associated with a cancer diagnosis.

Materials and Methods

Participants

This report was based on the data collected in the WHI. Details regarding the WHI study design and recruitment method have been published elsewhere [11,12]. The primary aim of the WHI was to investigate risk factors of and intervention effects on cancers, cardiovascular diseases, and osteoporotic fractures, in a large multiethnic cohort of postmenopausal women in the United States. WHI included four clinical trials (CT) and one observational study (OS). Participants were recruited at 40 WHI clinic centers across the nation. The major inclusion criteria were being postmenopausal, age between 50 and 79, not participating in other clinical trials at the time of enrollment, and not likely to die or move within 3 years. Additional exclusion criteria were applied to the participants in the CT. Women who had no history of cancers before the WHI enrollment were included in our analyses. Among them, 81,601 women were in the OS and 65,358 in the CT. The average (SD) follow-up time, from randomization in the CT or enrollment into the OS, was 7.8 (1.7) years. In our analysis, women were classified into three groups based on their follow-up result: no cancer, incident invasive breast cancer (BC), and other incident cancer (OC).

Data collection

At baseline, participants completed a set of questionnaires regarding demographics, medical history, health status, reproductive history, medication, physical activity, dietary intake, fracture history and other lifestyle factors. Height and weight measurements were also conducted during the initial clinical visit. Follow-up information on selected health outcomes, medication, and lifestyle factors was collected from self-administered questionnaires annually in the OS participants and biannually in the CT participants. Self-reported incident cancer diagnoses were adjudicated by physician reviews of medical records and pathology reports at each clinical center. Information on estrogen receptors from pathology reports and selected breast cancer treatment was used in some analyses.

Among CT participants, all self-reported fractures were confirmed by trained physician adjudicators reviewing medical records and reports. For OS participants, only hip fractures were adjudicated and the remaining fractures were based on self-reported information. No study X-rays were examined for the presence of sub-clinical vertebral fractures. In a WHI validation study, agreement between self-reported fracture and clinical chart review was over 70% on average, although it varied by skeletal sites [13]. In this report, the total fracture category included all clinical fractures excluding fractures of face, skull, toe, finger, rib and chest. Data on the number of falls during the follow-up were ascertained from annual or semiannual self-reports.

Statistical analysis

SAS/STAT (version 9.1.3 for Windows, SAS Institute, Cary, NC, USA) program was used. All the tests were two tailed and at a significance level of 0.05. Age-adjusted annual incidence rates were calculated for hip, clinical vertebral, forearm, and total fractures by cancer group and by pre- and post-diagnosis period. The same approach was used to compute age-adjusted annual incidence rates for falls.

Primary analyses used time-to-event methods based on the Cox proportional hazards model, with time from randomization in the CT, and time from enrollment in the OS to time of fracture or fall as the basic time variable. The main exposure variables, incident breast cancer and incident other cancer, were treated as time-varying dichotomous covariates. For example, the covariate breast cancer(t) is equal to 0 for $t \leq \text{time_to_incident_breast_cancer}$ and equal to 1 for $t > \text{time_to_incident_breast_cancer}$, where t is survival time [14]. Women who were diagnosed with breast cancer in situ were included in the Cox proportional hazards model and censored after their breast cancer in situ diagnosis.

The possibility that baseline characteristics may confound the relationship of exposure to the outcome variables was accommodated by including baseline risk factors of fracture previously described [15], we used a slightly finer adjustment by differentiating between estrogen +progesterone and estrogen-alone use and instead of adjusting for body mass index, we adjusted for height (linear and quartiles) and weight (linear and quartiles). We also included family history of cancer (yes/no), Gail risk (linear and quartiles), total calcium intake (linear and quartiles), total vitamin D intake (linear and quartiles), total energy (linear and quartiles), physical activity (linear and quartiles), alcohol intake (linear and quartiles), diet modification (DM) treatment assignment, hormone therapy (HT) assignment, calcium/vitamin D (CaD) supplementation assignment, and history of fracture after the age of 55 and allowed baseline hazard functions to vary by age (5 years).

For the secondary analyses, we divided incident breast cancer by receptor status and differentiated ER+ breast cancer by users and non-users of tamoxifen; these exposure variables were also treated as time varying dichotomous covariates. We investigated whether the number

of falls (≥ 2) and change in height from baseline were intermediate outcomes or independent risk factors by including them as time-varying covariates [16]. To explore possible explanations for an increased fracture or fall risk after a cancer diagnosis, a descriptive analysis was conducted among participants in the WHI CT to show differences in using osteoporotic-related medications and selected cancer treatments.

Results

This study included a total of 146,959 women. Among them, 132,840 had no cancer diagnosis at baseline or during the follow-up; 4,804 were diagnosed with invasive breast cancer; 1,073 with non-invasive breast cancer (in situ); and 8,242 with other types of cancers, including colorectal (16.3% of other cancers), lung (13.1%), endometrial (9.4%), melanoma of the skin (9.2%) and non-Hodgkins lymphoma (6.6%). Given the large sample size, most of the baseline characteristics were statistically different between groups (Tables 1 and 2). However, these groups were comparable in the percentage of parents who ever had a broken bone after age 40 ($p < 0.95$). The percentage of women with a fracture after age 55 in the incident invasive BC group (11.7%) was similar to the non-cancer group (12.0%), but it was higher in the OC group (14.6%, $p < 0.001$).

Age-adjusted annual incidence rates of fractures and falls were presented in Table 3. Fracture incidence rates increased after breast cancer or other cancer diagnosis. Before cancer diagnosis, annualized incident hip fracture rates were 0.13% and 0.15% for the BC and the OC group respectively and these rates were similar to the rate for the non-cancer group (0.15%). After a cancer diagnosis, the annual incidence rates of hip fractures increased to 0.25% in the BC group and 0.40% in the OC group. The age-adjusted incidence rate of falls (two or more falls) was also slightly higher after cancer diagnosis, but not before. We also limited the analysis on the annual percent of total fracture to 2 years as well as 1 year before the cancer diagnosis. The results showed similar patterns as in Table 3, suggesting fracture risk was relatively lower before breast cancer diagnosis, but was higher before other cancer diagnosis in comparison to women without a cancer diagnosis (data not shown).

Multiple potential confounding factors, as suggested by the analyses in Tables 1 and 2, were examined with the fracture and fall outcomes. The following variables were adjusted in all the Cox proportional hazards models: age (linear), years since menopause, ethnicity, education, living with a partner, smoking, general health, parity, duration of E-alone at baseline, duration of E+P at baseline, sedatives or psychotics or hypnotic drug use, depressive symptoms or anti-depressant use, arthritis, corticosteroid use ≥ 2 years, weight (quartiles, linear), height (quartiles, linear), total energy expended from physical activity (linear, quartile), total calcium intake (logged linear, quartiles), total vitamin D intake (logged linear, quartiles), total energy intake (logged linear, quartiles), total alcohol intake (linear, quartiles), high caffeine, parental fracture after age 40, family history of cancer, Gail score (quartiles, linear) and stratified by age (5-year groups), HT trial assignment, DM trial assignment, CaD trial assignment, study participation, hysterectomy status and history of fracture after 55 years of age.

Results from Cox proportional hazards models (Table 4) showed 15% and 27% increased risk for falls after BC or OC diagnosis respectively. The difference in fall risk between the BC and OC was borderline statistically significant ($P = 0.07$). In a secondary data analysis, the risk of falls did not increase in BC who had estrogen receptor negative tumors.

In comparison to the no-cancer group, hip fracture risk significantly increased after BC or OC diagnosis (Table 5). After adjusting for covariates the hazards ratio (HR) of hip fracture was 1.55 (95% confidence interval [95%CI] = 1.13 to 2.11) in women with incident breast cancer and 2.09 (95%CI = 1.65 to 2.65) in women with incident other cancer. The increased hip

fracture risk seemed more obvious in the ER- group. Although fall is a significant risk factor for hip fracture, HR=2.05 (95% CI = 1.82, 2.31 and $p < 0.001$), the increased number of falls did not explain the increased hip fracture risk in incident cancer cases. After adjusting for falls, as a time dependent covariate, the HR (95% CI) were 1.54 (1.13, 2.11) and 2.09 (1.65, 2.64) for BC and OC, respectively, which were very similar to the results in Table 5.

There were apparent increases in clinical vertebral fracture risk in breast cancer cases and in other cancer cases (Table 6), but the increased risk of fracture was only statistically significant ($p < 0.001$) in the OC group (HR = 1.86; 95%CI = 1.49 to 2.32). Falls increased risk of spinal fracture: HR =1.76 (95%CI = 1.58, 1.95). However, the results for clinical vertebral fractures were essentially unchanged: HR (95%) was 1.25 (0.93, 1.68) and 1.86 (1.49, 2.32) for BC and OC, respectively after controlling for falls.

Forearm fracture risk did not increase after breast cancer diagnosis (HR = 1.00) and increased slightly for other cancer diagnosis (HR = 1.07), but the amount of increase was small and did not reach statistical significance (Table 7). A significant increase in total fracture risk (HR = 1.33; 95%CI = 1.18 to 1.49) was found in women diagnosed with cancer other than invasive breast cancer (Table 8).

In an exploratory analysis about the potential explanations for the increased risk of fractures, age adjusted frequencies of selected medication use for the WHI CT was calculated and presented in Table 9. The percentage of tamoxifen use increased to 40.3% and the percentage of aromatase inhibitors use increased to 7.3% after breast cancer diagnosis. The percent of women on tamoxifen and aromatase inhibitors for other cancer was small. The use of bisphosphonates was more common (13.2%) in the no-cancer group than the BC or OC group either before (BC = 2.8%, OC = 4.5%) or after the cancer diagnosis (BC = 10.7%, OC = 6.5%). Less than 0.5% women who were on antiestrogen used Fareston (toremifene citrate) instead of tamoxifen (data not shown).

Though not statistically significant, tamoxifen use was associated with a lower fracture risk. The HR of total fracture was 0.95 (95%CI = 0.72, 1.26) for women without tamoxifen therapy and 0.78 (95%CI = 0.51, 1.18) for women with tamoxifen therapy and ER+ BC. Aromatase inhibitors significantly increased risk of fractures in women with ER+ breast tumors: the HR for the total fractures was 2.76 (95% CI = 1.28, 5.92) for aromatase inhibitors users and 0.83 (95%CI = 0.65, 1.06) for the non-users. It should be noted that the number of fractures was small in these groups; of the 102 total fractures cases in the CT who had an ER+ invasive breast cancer, 51 were tamoxifen users after incident breast cancer while 51 were non-users and 12 were aromatase inhibitor users after incident invasive breast cancer while 90 were not. Fracture risk could not be assessed among the few participants taking raloxifene.

Discussion

This study provides new evidence indicating that while incident cancer cases did have a comparable fracture risk as their non-cancer peers of the same age before they were diagnosed with cancer, both fracture and fall risks are significantly elevated after a diagnosis of either breast cancer or any other cancer in postmenopausal women. The increased fracture risk is even more notable after a diagnosis of cancer other than invasive breast cancer.

Several factors have been considered as the potential causes for a higher fracture risk in postmenopausal breast cancer survivors. Chemotherapy, aromatase inhibitor use and the tumor itself may all direct and indirectly interfere with normal bone metabolism [17]. It is well-known that bone metastases increase the risk for pathological fractures. Contraindication of postmenopausal hormone therapy after breast cancer therapy is common, especially in hormonally sensitive breast cancer survivors, and it may increase bone turnover rate and

eventually lead to a higher fracture rate. However, an increased risk of fracture in breast cancer survivors has been identified in some [8,18,19], but not all reports [20]. Previously, we reported that WHI OS participants with a breast cancer history at baseline had a significantly increased risk of clinical fractures (except for hip fractures) in comparison to women who did not have any cancer history [8]. Unfortunately, more than 77% of cancer survivors who had osteoporosis were undiagnosed at the time of WHI enrollment. The results reported here have not only confirmed our findings on a higher fracture risk among breast cancer cases, but also provided the first piece of prospective evidence showing that the higher fracture risk was only evidenced post-cancer diagnosis, not before.

Interestingly, there are some discrepancies on skeletal sites for the increased fracture risk between this current study using incident breast cancer cases and the previous report with the prevalent cases [8]. In the current study, the most remarkably increased fracture risk was found for the hip site, while total fracture risk was not increased after BC diagnosis. In contrast, fracture risk significantly increased for all fractures but not for the hip fracture risk specifically in the previous report with prevalent breast cancer cases. These may be due to the fact that there were fewer hip fractures, but more other fractures among the prevalent cases in comparison to the incident cases. Whether cancer treatment, time since BC diagnosis, age at BC diagnosis and the time period for fracture ascertainment, contribute to these discrepancies are interesting research questions for future investigation.

The association between hormonal receptor status of breast cancer and fracture or fall risk may well be related in part to the commonly used treatment for such cancer types with tamoxifen. As a partial estrogen agonist, tamoxifen decreases bone mineral density in premenopausal women, but has the opposite effect in postmenopausal women [21]. In the National Surgical Adjuvant Breast and Bowel Project P-1 Study, tamoxifen use resulted in a reduction in hip, radius and spine fractures compared to placebo in postmenopausal women. In contrast, the use of aromatase inhibitors in this study seemed to increase fracture risk among women with ER + BC [22]. The elevated fracture risk with aromatase inhibitors use in our study sample is in agreement with the previous findings.

To our knowledge, this is the first paper demonstrating that fracture risk is increased in postmenopausal women after a diagnosis of cancers other than breast cancer. Intuitively, some of the risk factors for increased fracture associated with invasive breast cancer, such as use of chemotherapy and bone metastasis may also contribute to the higher fracture risk in other cancers. Further study is needed to identify high-risk groups of women and to develop strategies to prevent and manage the additional adverse health outcomes associated with cancer.

Falls are a major risk factor for fracture and the etiology of falls is multifactorial, including vitamin D insufficiency; an age-related decrease in muscle size and strength; neurological disorders of vision, balance and coordination; the use of sedatives and other medications which impair cognition [23]; and hospitalization. The cause of increased falls seen in cancer patients in this study is not known, but might include all of the above. Falls are very common in older people. Approximately 10–15% of falls in the elderly result in fracture [24] and more than 90% of fractures are associated with a fall [10]. We found a strong relationship between fall and fractures in this study. However, in spite of the increased number of falls after a cancer diagnosis, this higher rate of falling could not explain the higher fracture risk in cancer cases.

Recent findings have suggested that antiresorptive agents may effectively prevent bone loss in breast cancer survivors [25]. It is striking that in our study the percentage of women on bisphosphonates was even lower in breast cancer cases than in women without a cancer diagnosis in spite of the increased fracture risk. Based on our findings, breast cancer patients who have ER+ breast cancer tumors and are on aromatase inhibitors were at higher fracture

risk. It is recognized that these women should be evaluated and treated as necessary to prevent fractures. However, our study indicates that fracture prevention needs to be improved in this high-risk cancer survivor population.

To date, this is the largest and most comprehensive prospective study addressing fracture risk, a significant health problem in millions of cancer survivors. The large multiethnic cohort, confirmed cancer diagnosis, adjudicated hip fractures in all women, fracture information before and after cancer diagnosis, and detailed information on tumor receptors and medication use in BC are some major strengths of this study. Nevertheless, the current study has several limitations. Not all fractures used in the analyses were adjudicated. However, we have repeated all the analyses using only the adjudicated fractures in the CT participants and results were similar, suggesting errors in self-reported fractures did not significantly alter the findings of this study. We could not distinguish pathological fractures from other fractures in this analysis. We have used self-reported falls in this study and the validity of this fall assessment tool is uncertain. Assuming the measurement errors in self-reported falls are random, then the relationship between fractures and fall is likely to be underestimated in this study. These limitations have reflected the challenges in prospective investigations on fracture and fall risk in the cancer survivor populations.

In conclusion, a significant increase in fracture risk at selected skeletal sites is seen in postmenopausal women following a diagnosis of invasive breast cancer or other cancer. Despite the higher rate of falls in women with diagnosed cancer, falls are less likely to be the major cause of the increased risk of fracture associated with a cancer diagnosis. Further study is needed to inform development of strategies to reduce the burden of fracture to the large number of cancer survivors in the United States and worldwide.

Appendix

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Table 1Baseline characteristics in the WHI CT and OS (n=146,959^a) – Categorical Variables

	No-cancer (N=132,840)	Incident Other Cancer (N=8242)	Incident Invasive BC (N=4804)	P-Value ^b
	N (%)	N (%)	N (%)	
Ethnicity				
White	10,854 (81.7)	7152 (86.8)	4186 (87.1)	
Black	12,431 (9.4)	608 (7.4)	328 (6.8)	
Hispanic	5746 (4.3)	196 (2.4)	124 (2.6)	<0.001
American Indian	594 (0.4)	30 (0.4)	16 (0.3)	
Asian/Pacific Islander	3649 (2.7)	148 (1.8)	105 (2.2)	
Unknown	1877 (1.4)	108 (1.3)	45 (0.9)	
Education				
0-8 years	2272 (1.7)	119 (1.5)	38 (0.8)	
Some high school	4887 (3.7)	328 (4.0)	139 (2.9)	<0.001
High school diploma/GED	22,859 (17.3)	1477 (18.1)	760 (15.9)	
School after high school	49,952 (37.9)	3117 (38.1)	1740 (36.5)	
College degree or higher	51,870 (39.3)	3139 (38.4)	2088 (43.8)	
Number of pregnancies				
Never pregnant	11,794 (8.9)	815 (9.9)	516 (10.8)	
1	9100 (6.9)	541 (6.6)	341 (7.1)	<0.001
2-4	78,227 (59.2)	4707 (57.3)	2863 (60.0)	
5+	33,063 (25.0)	2145 (26.1)	1053 (22.1)	
Parent broke bone after age 40	48,359 (36.4)	3014 (36.6)	1746 (36.3)	0.95
Corticosteroid Use >= 2 years	687 (0.5)	47 (0.6)	22 (0.5)	0.68
Current smoker at baseline	8851 (6.8)	904 (11.1)	290 (6.1)	<0.001
Unopposed Estrogen Duration by Category				
None	85,925 (64.7)	5459 (66.2)	3158 (65.7)	
< 5 Years	17,579 (13.2)	1051 (12.8)	595 (12.4)	<0.001
5 - < 10 Years	9293 (7.0)	505 (6.1)	308 (6.4)	
10 - < 15 Years	7308 (5.5)	386 (4.7)	252 (5.2)	
15+	12,733 (9.6)	841 (10.2)	491 (10.2)	
Estrogen + Progest Duration by Category				
None	97,356 (73.3)	6219 (75.5)	3147 (65.5)	
< 5 Years	18,210 (13.7)	919 (11.2)	703 (14.6)	<0.001
5 - < 10 Years	9587 (7.2)	546 (6.6)	493 (10.3)	
10 - < 15 Years	5246 (3.9)	368 (4.5)	296 (6.2)	
15+	2439 (1.8)	190 (2.3)	165 (3.4)	
Baseline current HT user by duration				
Not current HT user	78,129 (58.9)	5275 (64.1)	2495 (52.0)	<0.001
Current HT <5yr	15,926 (12.0)	725 (8.8)	598 (12.5)	
Current HT >= 5yr	38,674 (29.1)	2230 (27.1)	1706 (35.5)	
Broke bone at/after 55	15,979 (12.0)	1204 (14.6)	564 (11.7)	<0.001

	No-cancer (N=132,840)	Incident Other Cancer (N=8242)	Incident Invasive BC (N=4804)	P-Value ^b
	N (%)	N (%)	N (%)	
Living w/partner	83,031 (62.8)	4857 (59.2)	3015 (63.0)	<0.001
Excellent/VG/Good v. Fair/Poor health	120,477 (91.3)	7393 (90.2)	4407 (92.3)	<0.001
History of arthritis	61,300 (46.6)	4087 (50.0)	2248 (47.4)	<0.001
Sedatives, psychotics or hypnotics drug use	7899 (5.9)	525 (6.4)	278 (5.8)	0.25
CESD>=0.009 or anti-depressant use	36,729 (28.4)	2290 (28.5)	1291 (27.5)	0.36
Years since menopause				
<10	41,053 (32.8)	1869 (24.3)	1515 (33.3)	<0.001
10 – 20	46,128 (36.9)	2846 (36.9)	1646 (36.2)	
≥ 20	37,822 (30.3)	2990 (38.8)	1388 (30.5)	
4th quartile of height (>161.9 cm) vs. others	32,199 (24.4)	2106 (25.7)	1269 (26.5)	<0.001
4th quartile of weight (>70.5 kg) vs. others	32,926 (24.9)	2197 (26.8)	1300 (27.1)	<0.001
4th quartile of FFQ caffeine intake (>188 mg) vs. others	32,196 (25.0)	2151 (26.9)	1156 (24.7)	<0.001
Family history of cancer	83,196 (62.6)	5474 (66.4)	3207 (66.8)	<0.001
Study				
E active	4642 (3.5)	293 (3.6)	108 (2.2)	
E placebo	4663 (3.5)	293 (3.6)	138 (2.9)	
E+P active	7467 (5.6)	525 (6.4)	278 (5.8)	<0.001
E+P placebo	7193 (5.4)	494 (6.0)	204 (4.2)	
CT not randomized to HT	34,929 (26.3)	2220 (26.9)	1391 (29.0)	
OS	73,946 (55.7)	4417 (53.6)	2685 (55.9)	
Hysterectomy at randomization				
Yes	53,894 (40.6)	3052 (37.1)	1705 (35.5)	<0.001
No	78,878 (59.4)	5184 (62.9)	3095 (64.5)	
Broke bone at/after 55	15,979 (12.0)	1204 (14.6)	564 (11.7)	<0.001

^a Baseline characteristics of the 1073 participants with non-invasive breast cancer are not displayed

^b From a chi-square test of association

Table 2

Baseline characteristics in the WHI CT and OS – Continuous Variables

	No-cancer (N=132,840)		Incident Other Cancer (N=8242)		Incident Invasive BC (N=4804)		P-Value ^a
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Age at screening, years	132,840	62.9 (7.2)	8242	65.2 (7.0)	4804	63.6 (7.0)	<0.001
Weight, kg	132,408	73.5 (16.9)	8211	74.3 (17.2)	4791	74.5 (16.7)	<0.001
Height, cm	132,038	161.7 (6.7)	8196	162.0 (6.6)	4784	162.2 (6.6)	<0.001
Gail 5 year risk	132,840	1.7 (1.0)	8242	1.9 (1.0)	4804	2.0 (1.1)	<0.001
Dietary Energy (kcal)	128,808	1645.1 (646.2)	8013	1647.5 (641.9)	4674	1654.0 (622.1)	0.63
BL Total expend from phys act (kcal/week per kg)	126,444	12.4 (13.8)	7743	12.2 (13.7)	4528	12.1 (12.9)	0.05
Dietary Alcohol (g)	128,808	5.1 (10.4)	8013	5.7 (11.4)	4674	6.0 (11.3)	<0.001

^aFrom a one-way ANOVA

Table 3
Events and age-adjusted annualized percentages of hip fracture and falls before and after incident cancer in the WHI CT and OS (n=146,959)

Exposure	Phase	Mean (SD) Follow- up time- yrs	Hip Fracture			Forearm Fracture ^d			Vertebral Fracture ^d			Total Fracture ^d			>= 2 Falls ^b	
			N of Events	Annualized % ^c	N of Events	Annualized % ^c	N of Events	Annualized % ^c	N of Events	Annualized % ^c	N of Events	Annualized % ^c	N of Events	Annualized % ^c	N of Events	Annualized % ^c
No-Cancer (N = 132,840)		7.8 (1.6)	1,449	0.15%	4,676	0.47%	1,868	0.19%	11,996	1.24%	40,085	4.72%				
Incident Other Cancer (N = 8,242)	Before	4.3 (2.4)	61	0.15%	157	0.42%	127	0.34%	513	1.45%	1584	5.06%				
	After	2.7 (2.5)	96	0.40%	116	0.53%	109	0.48%	396	1.89%	982	5.76%				
Incident Breast Cancer (N = 4,804)	Before	4.2 (2.4)	25	0.13%	84	0.43%	31	0.16%	216	1.12%	854	4.89%				
	After	3.9 (2.3)	48	0.25%	92	0.50%	56	0.30%	240	1.36%	753	5.30%				

^a OS data based on self-report

^b Based on self-report

^c Adjusted for age at baseline by 1-year groups

Table 4
Risk of ≥ 2 falls after incident cancer in the WHI CT and OS (n=146,959)

	Number of Events	(Annualized Percent) ^a	Hazard Ratio (95% CI) ^b	P-value ^c	P-value ^d
No-Cancer	42,708 ^e	(4.73%)	1.00		
Incident Other Cancer	982	(5.76%)	1.27 (1.18, 1.36)	<0.001	
Incident Breast Cancer	753	(5.30%)	1.15 (1.06, 1.25)	<0.001	0.07
ER+	568	(5.33%)	1.17 (1.06, 1.28)	0.001	0.16
ER-	100	(4.72%)	1.02 (0.82, 1.27)	0.86	0.07
Other	85	(5.66%)	1.21 (0.96, 1.53)	0.11	0.73

^aAdjusted for age at baseline by 10-year groups.

^bFrom a proportional hazards model, where incident cancer status is fit as time-dependent variable, adjusted for age (linear), years since menopause, ethnicity, education, living with partner, smoking, general health, parity, duration of E-alone at baseline, duration of E+P at baseline, sedatives or psychoactives or hypnotic drug use, depressive symptoms or anti-depressant use, arthritis, corticosteroid use ≥ 2 yrs, weight (quartiles, linear), height (quartiles, linear), total energy expended from physical activity (linear, quartile), total calcium intake (logged linear, quartiles), total vitamin D intake (logged linear, quartiles), total energy intake (logged linear, quartiles), total alcohol intake (linear, quartiles), high caffeine, parent broke bone after age 40, family history of cancer, Gail score (quartiles, linear) and stratified by age (5 year groups), HT trial assignment, DM trial assignment, CaD trial assignment, study participation, hysterectomy status and history of fracture after 55 years of age.

^cFrom the described proportional hazards model testing whether the hazard ratio is different from unity.

^dFrom the described proportional hazards model testing whether the hazard ratio for breast cancer, or breast cancer type, is different from the hazard ratio for other cancer.

^e42768 falls (≥ 2) = 40085 incidents of falling ($>=2$) from the no-cancer group + 1584 incidents of falling (≥ 2) prior to incident other cancer + 854 incidents of falling ($>=2$) prior to incident invasive breast cancer + 245 incidents of falling (≥ 2) prior to incident non-invasive breast cancer.

Table 5
Risk of hip fracture after incident cancer in the WHI CT and OS (n=146,959)

	Number of Events	(Annualized Percent) ^a	Hazard Ratio (95% CI) ^b	P-value ^c	P-value ^d
No-Cancer	1,539^e	(0.15%)			
Incident Other Cancer	96	(0.40%)	2.09 (1.65, 2.65)	<0.001	
Incident Breast Cancer	48	(0.25%)	1.55 (1.13, 2.11)	0.006	0.12
ER+	35	(0.24%)	1.44 (1.00, 2.06)	0.05	0.08
ER-	8	(0.34%)	2.02 (0.90, 4.55)	0.09	0.94
Other	5	(0.25%)	1.89 (0.78, 4.62)	0.16	0.83

^a Adjusted for age at baseline by 10-year groups.

^b From a proportional hazards model using covariates and stratification variables described in Table 4.

^c From the described proportional hazards model testing whether the hazard ratio is different from unity.

^d From the described proportional hazards model testing whether the hazard ratio for breast cancer, or breast cancer type, is different from the hazard ratio for other cancer.

^e 1,539 hip fractures = 1,449 fractures from the no- cancer group + 61 fractures prior to incident other cancer + 25 fractures prior to incident invasive breast cancer + 4 fractures prior to incident non-invasive breast cancer.

Table 6
Risk of vertebral fracture after incident cancer in the WHI CT and OS (n=146,959)

	Number of Events	(Annualized Percent)	^a	Hazard Ratio (95% CI) ^b	P-value ^c	P-value ^d
No-Cancer	2,033 ^e	(0.19%)		1.00		
Incident Other Cancer	109	(0.48%)		1.86 (1.49, 2.32)	<0.001	
Incident Breast Cancer	56	(0.30%)		1.26 (0.94, 1.69)	0.12	0.03
ER+	44	(0.31%)		1.23 (0.88, 1.72)	0.22	0.04
ER-	7	(0.31%)		1.62 (0.77, 3.42)	0.21	0.73
Other	5	(0.25%)		1.04 (0.39, 2.79)	0.94	0.26

^a Adjusted for age at baseline by 10-year groups.

^b From a proportional hazards model using covariates and stratification variables described in Table 4.

^c From the described proportional hazards model testing whether the hazard ratio is different from unity.

^d From the described proportional hazards model testing whether the hazard ratio for breast cancer, or breast cancer type, is different from the hazard ratio for other cancer.

^e 2,033 vertebral fractures = 1,868 fractures from the no-cancer group + 127 fractures prior to incident other cancer + 31 fractures prior to incident invasive breast cancer + 7 fractures prior to incident non-invasive breast cancer.

Table 7

Risk of lower arm fracture after incident cancer in the WHI CT and OS (n=146,959)

	Number of Events	(Annualized Percent) ^a	Hazard Ratio (95% CI) ^b	P-value ^c	P-value ^d
No-Cancer	4,938^e	(0.46%)			
Incident Other Cancer	116	(0.53%)	1.07 (0.87, 1.31)	0.54	
Incident Breast Cancer	92	(0.50%)	1.00 (0.79, 1.26)	0.97	0.66
ER+	72	(0.52%)	0.99 (0.76, 1.29)	0.94	0.66
ER-	9	(0.37%)	0.89 (0.44, 1.78)	0.74	0.62
Other	11	(0.56%)	1.16 (0.60, 2.24)	0.66	0.81

^a Adjusted for age at baseline by 10-year groups.

^b From a proportional hazards model using covariates and stratification variables described in Table 4.

^c From the described proportional hazards model testing whether the hazard ratio is different from unity.

^d From the described proportional hazards model testing whether the hazard ratio for breast cancer, or breast cancer type, is different from the hazard ratio for other cancer.

^e 4,938 lower arm fractures = 4,676 fractures from the no-cancer group + 157 fractures prior to incident other cancer + 84 fractures prior to incident invasive breast cancer + 21 fractures prior to incident non-invasive breast cancer.

Table 8
Risk of total fracture after incident cancer in the WHI CT and OS (n=146,959)

	Number of Events	(Annualized Percent) ^a	Hazard Ratio (95% CI) ^b	P-value ^c	P-value ^d
No-Cancer	12,775 ^e	(1.24%)			
Incident Other Cancer	396	(1.89%)	1.33 (1.18, 1.49)	<0.001	
Incident Breast Cancer	240	(1.36%)	1.02 (0.89, 1.18)	0.74	0.005
ER+	180	(1.35%)	0.99 (0.84, 1.17)	0.87	0.004
ER-	33	(1.44%)	1.18 (0.81, 1.70)	0.39	0.54
Other	27	(1.44%)	1.12 (0.73, 1.70)	0.61	0.44

^a Adjusted for age at baseline by 10-year groups.

^b From a proportional hazards model using covariates and stratification variables described in Table 4.

^c From the described proportional hazards model testing whether the hazard ratio is different from unity.

^d From the described proportional hazards model testing whether the hazard ratio for breast cancer, or breast cancer type, is different from the hazard ratio for other cancer.

^e 12,775 total fractures = 11,996 fractures from the no- cancer group + 513 fractures prior to incident other cancer + 216 fractures prior to incident invasive breast cancer + 50 fractures prior to incident non-invasive breast cancer.

Table 9
Medication use during baseline or follow-up WHI CT (n=64,838)

	Number and Percent ^a of Participant Using Each Agent					
	Non cancer n=58,894	Breast Cancer Pt n=2,119		Other Cancers n=3,825		
		Before	After diagnosis	Before	After Diagnosis	
Tamoxifen	50 (0.1%)	1 (<0.1%)	855 (40.3%)	4 (0.1%)	10 (0.3%)	
Aromatase Inhibitors	1 (<0.1%)	0	155 (7.3%)	0	4 (0.1%)	
Raloxifene	1834 (3.1%)	30 (1.4%)	34 (1.6%)	40 (1.0%)	58 (1.5%)	
Bisphosphonates	7560 (13.2%)	58 (2.8%)	227 (10.7%)	175 (4.5%)	259 (6.5%)	

^a Adjusted by age at baseline.