OXFORD

JNCI J Natl Cancer Inst (2018) 0(0): pky001

doi: 10.1093/jncics/pky001
Article

ARTICLE

Postmenopausal Fracture History and Survival After Reproductive Cancer Diagnosis

Polly A. Newcomb, Scott V. Adams, Sophie Mayer, Michael N. Passarelli, Lesley Tinker, Dorothy Lane, Rowan T. Chlebowski, Carolyn J. Crandall

Affiliations of authors: Department of Epidemiology, University of Washington, Seattle, WA (PAN, SVA, SM, MNP, LT); Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA (PAN, SVA, SM); Department of Epidemiology, Geisel School of Medicine, Dartmouth College, Hanover, NH (MNP); Department of Family, Population and Preventive Medicine, Stony Brook University, Stony Brook, NY (DL); Department of Medical Oncology and Therapeutics Research, City of Hope National Medical Center, Duarte, CA (RTC); Department of Medicine, University of California, Los Angeles, Los Angeles, CA (CJC).

Correspondence to: Polly Newcomb, PhD, 1100 Fairview Ave. N., M4-B402, Seattle, WA 98109-1024 (e-mail: pnewcomb@fredhutch.org).

Abstract

Background: Postmenopausal bone fracture's have been proposed as a marker of lifetime estrogen exposure and have been associated with decreased risk of breast and endometrial cancer. It is plausible that prediagnostic fractures may be related to survival of estrogen-sensitive cancers.
Methods: We evaluated a cohort of breast (n = 6411), endometrial (n = 1127), and ovarian (n = 658) cancer cases diagnosed between 1992 and 2010 while participating in the Women's Health Initiative. Postmenopausal fracture history was assessed from baseline reports of fractures after age 55 years and incident fractures that occurred at least one year prior to cancer diagnosis during study follow-up. Using Cox regression, we compared women with and without a history of fractures with respect to overall and cancer-specific survival. Estimates were adjusted for participant factors, including hormone therapy use; hormone receptor status was not included in our analysis.
Results: Among women with breast cancer, a history of prediagnostic fractures at any site was associated with poorer overall survival (hazard ratio [HR] = 1.22, 95% confidence interval [CI] = 1.05 to 1.43). A history of hip, forearm, or spine fractures, or hip fracture alone, was associated with increased risk of mortality (HR = 1.26, 95% CI = 1.01 to 1.58, and HR = 2.05, 95% CI = 1.27 to 3.32, respectively). Fracture history was associated neither with cancer-specific survival among breast cancer survivors, nor with overall or disease-specific mortality among endometrial and ovarian cancer survivors.
Conclusions: Postmenopausal breast cancer patients with a history of fractures, especially of the hip, are more likely to die of any cause than breast cancer survivors without a fracture history. Identifying and intervening in fracture risk factors should be standard of care for all women diagnosed with breast cancer.

The risks of osteoporotic fractures and of several reproductive cancers are strongly influenced by exposure to endogenous and exogenous estrogens. Higher lifetime estrogen exposure and factors that contribute to estrogen exposure, including obesity, younger age at menarche, older age at menopause, and postmenopausal hormone use, have been associated with an increased risk of breast (1–7), endometrial (2,8,9), and ovarian cancers (10–13). Estrogen also plays a major role in maintaining bone health, and the decrease in endogenous estrogen during menopause is associated with bone loss and increased risk of osteoporotic bone fractures, most commonly to the hip, spine, and forearm (14). Higher lifetime levels of estrogens, either from exogenous or endogenous sources, are associated with greater bone mineral density (BMD) and reduced risk of postmenopausal fracture (15,16). As proxies for lower lifetime estrogen exposure, lower BMD and osteoporotic fractures have been shown to be inversely associated with breast and endometrial cancer incidence in postmenopausal women (2,17–19). However, in the one study of ovarian cancer, no association was observed between fractures and ovarian cancer incidence (20).

Received: August 14, 2017; **Revised:** December 13, 2017; **Accepted:** January 3, 2018

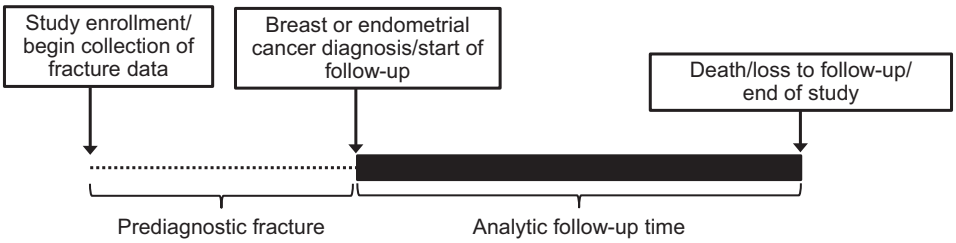

Figure 1. Study diagram.

Little is known about how lifetime estrogen exposure may affect survival from reproductive cancers, particularly non-breast cancers. Many characteristics that contribute to higher lifetime estrogen exposure levels, such as reproductive time span, obesity, and exogenous hormone use, may be sustained into the postmenopausal period. In turn, these factors may impact a woman's risk of death or recurrence if their cancer's proliferative pathways are sensitive to estrogen levels. Only a few studies have examined BMD as a marker for lifetime estrogen exposure in relation to breast cancer survival, and two have found some evidence of longer disease-free or cancer-specific survival among women with lower bone density (21,22), while one small study found no association (23). Of the previously mentioned studies, only Zambetti et al. incorporated estrogen receptor status into their analyses. In this study, the association between low BMD and disease-free survival was stronger when restricted to women with estrogen receptor–positive cancers, the vast majority of breast cancers in postmenopausal women, suggesting an estrogen-dependent mechanism (22). In this study, we considered whether postmenopausal fracture history, a common and validly described clinical event, may be associated with outcomes in women with breast, endometrial, and ovarian cancer.

Methods

Study Population

The Women's Health Initiative (WHI) enrolled 161 808 postmenopausal women age 50 to 79 years from 40 clinical sites across the United States between 1992 and 1998. In addition to age and menopausal status, eligibility criteria included ability and willingness to provide written informed consent and an agreement to reside in the area for at least three years after enrollment.

The WHI consisted of an observational study (WHI-OS) and a randomized clinical trial (WHI-CT) examining the effects of menopausal hormone therapy, dietary modification, and calcium and vitamin D supplementation on coronary and cancer outcomes and osteoporotic fracture risk. In addition to general screening criteria, for the CT Hormone Therapy trials, women were screened for safety (no history of hypertriglyceridemia or endometrial cancer, normal mammogram) and adherence to the placebo pill run-in during screening; for the CT Dietary Trial, women were screened for dietary fat intake, with a lower fat intake (<32% energy from fat by food frequency questionnaire) being an exclusionary criterion; for the CT Calcium and Vitamin D trial, women were ineligible if they were taking on their own 600 IU vitamin D or more. WHI-OS participants (n = 93 676) were generally similar to those in the WHI-CT (n = 68 132), but were ineligible or unwilling to be included in the randomized trials. Details of the WHI recruitment, eligibility criteria, and protocols have been published elsewhere (24–27). Subsequent to the end of the WHI-CT and WHI-OS, WHI participants were invited to participate in the WHI Extension Study. Thus, 115 400 women were recruited for an additional five years of follow-up through 2010.

In the current analysis, after excluding women missing follow-up information (n = 692) or missing information on fractures at baseline (n = 16 860), as well as those possessing a history of any cancer diagnosis other than nonmelanoma skin cancer at WHI enrollment (n = 14 372), 129 884 women were eligible for the study. From this group, we identified a cohort of incident breast (n = 6411), endometrial (n = 1127), and ovarian (n = 658) cancer cases diagnosed during WHI follow-up for overall and cancer-specific survival. Figure 1 illustrates the overall study design.

The institutional review boards at all WHI institutions approved the protocols and procedures, and all participants provided informed consent. Uniformity of data collection was ensured through centralized training of staff, a standardized written protocol, and quality assurance visits by the clinical coordinating center.

Fracture History Assessment

All WHI participants were personally interviewed and completed baseline screening visits prior to enrollment regarding demographic and health information, including fracture history, prior to enrollment. Baseline fracture ascertainment elicited the anatomic site of any fractures and the age at which any fractures occurred. The WHI also assessed incident hip and other fractures that occurred during the study period through annual (WHI-OS) or semiannual (WHI-CT) questionnaires and interviews. Incident hip fractures occurring during the WHI-OS or WHI-CT were adjudicated by WHI physicians and staff to ascertain site of fracture and exclude pathological fractures (eg, those due to cancer or Paget's disease). Incident fractures of other bones were adjudicated for WHI-CT women, and for a subset (approximately 10%) of WHI-OS women. In the remaining WHI-OS women, fractures other than hip fractures were self-reported only. During the Extension Study, only hip fractures were adjudicated. Fractures that occurred after age 55 years were considered by the WHI to be postmenopausal (regardless of whether they preceded enrollment), and those that occurred more than one year prior to cancer diagnosis were considered in the assessment of postmenopausal fracture history.

Outcome Ascertainment

To determine vital status and cause of death for all WHI participants, data were collected by the WHI through annual clinical

center follow-up of participants. These data were linked with the National Death Index of the National Center for Health Statistics. Cause of death was determined by review of death certificate and medical records at the WHI clinical coordinating center, with oversight from the WHI physician adjudicators and outcomes committee, and was coded according to the International Classification of Diseases, Ninth Revision (ICD-9) (25).

Other Covariates

Demographic and clinical covariates were ascertained through questionnaires, interviews, and physical examinations. Ever use of postmenopausal hormones was assessed at baseline and was updated in years 1 and 3–8 for WHI-OS participants. Women randomly assigned to the hormone treatment arm in the WHI-CT were classified as ever-users from baseline. During the WHI Extension Study, hormone use was updated annually for former participants in the WHI-CT hormone trial placebo arm only.

An inventory of all current, regularly used medications, including oral bisphosphonates, was taken at baseline and at one, three, and six years after random assignment for WHI-CT participants. The same inventory was performed at baseline and three years after enrollment for WHI-OS participants. Women were instructed to provide medication bottles or packaging for drugs taken at least twice per week during the previous two weeks. All medications were matched to the Medi-Span (Indianapolis, IN) Master Drug Data Base (MDDB) to ascertain detailed ingredient information.

Statistical Analyses

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association between fracture history and overall and disease-specific survival, comparing women with history of precancer diagnosis postmenopausal fractures with those without history of fractures. Follow-up time began on the date of cancer diagnosis, and women were followed until death, loss to follow-up, or September 30, 2010 (the end of the Extension Study). Data from participants who did not consent to the Extension Study and were alive at WHI study closeout were censored on that date (September 12, 2005).

We conducted separate analyses by fracture site (any fracture site; fractures to the hip, forearm, or spine; and fractures to the hip alone) and by cancer type. Women with no history of fracture were used as the reference group in all models. Analyses were stratified by study arm and fracture adjudication (yes, no); we adjusted all estimates for age at cancer diagnosis, education, race, alcohol intake, smoking status, postmenopausal hormone use, bisphosphonate use, body mass index (BMI), and Charleston Comorbidity Index (CCI) score (including conditions diagnosed up to the date of cancer diagnosis). Additionally, breast cancer estimates were adjusted for self-reported mammography performed within the two years prior to WHI enrollment. All covariates were categorized as shown in Table 1. Hormone therapy and bisphosphonate use were treated as time-varying never/ever variables and were updated at each available assessment. In sensitivity analyses, we adjusted analyses of any fracture for 10-year fracture probability at enrollment in addition to all other covariates, and in a separate model, we adjusted for 10-year fracture probability, postmenopausal hormone use, bisphosphonate use, and CCI. All analyses were performed using STATA SE 14 (College Station, TX).

Results

Breast Cancer

Overall, 6411 women with invasive breast cancer were identified from eligible WHI participants and followed for an average of 6.2 years after cancer diagnosis. Among breast cancer cases, 1354 (21%) experienced a precancer diagnosis postmenopausal fracture, including 483 with one or more hip, forearm, or spine fractures, and 63 with only hip fractures. Breast cancer patients with fractures were slightly more likely than women without a history of prediagnosis fractures to have been enrolled in WHI-CT (57% vs 43%), to be older than age 65 years at cancer diagnosis (89% vs 69%), and to have had more comorbidities, as represented by a CCI score of 3 or greater (19% vs 13%) (Table 1).

Among breast cancer patients, 907 deaths were observed (Table 2), of which 416 were attributable to breast cancer (Table 3). Prediagnosis postmenopausal fractures to any bone were significantly associated with a 22% higher risk of mortality from any cause (HR = 1.22, 95% CI = 1.05 to 1.43), while fractures to the hip alone were associated with double the risk of all-cause mortality (HR = 2.05, 95% CI = 1.27 to 3.32) (Table 2). Fractures to the hip, forearm, or spine were associated with an increased risk of death from any cause (HR = 1.26, 95% CI = 1.01 to 1.58). A history of precancer diagnosis fractures was not related to disease-specific mortality among women with breast cancer, irrespective of fracture site (Table 3).

Endometrial Cancer

A total of 1127 incident endometrial cancer cases were observed during WHI follow-up, and these patients were followed for an average of 5.9 years after cancer diagnosis. Among women with endometrial cancer, 254 (23%) experienced a fracture to any bone, including 83 hip, forearm, or spine fractures, and seven fractures to the hip alone. Endometrial cancer cases with positive prediagnostic postmenopausal fracture history were more likely to be older than age 65 years at their cancer diagnosis (89% vs 71%) and have at least a college education (56% vs 48%) than women without fractures (Table 1).

Among endometrial cancer patients, 192 deaths were observed, of which 83 were due to endometrial cancer (Tables 2 and 3). History of fracture was not associated with all-cause or endometrial cancer–specific mortality, irrespective of fracture site.

Ovarian Cancer

Overall, 658 incident ovarian cancer cases were identified and followed for an average of 3.7 years. Among these women, 138 (21%) experienced a fracture to any bone, including 48 hip, forearm, or spine fractures, and three hip-only fractures. Compared with ovarian cancer patients without a precancer diagnosis fracture history, women with a history of fracture tended to be older than age 65 years at their cancer diagnosis (90% vs 72%), were more likely to be non-Hispanic whites (96% vs 87%), and to have a CCI score of 3 or higher (20% vs 15%) (Table 1).

Among ovarian cancer patients, 334 deaths were observed, of which 306 were due to ovarian cancer (Table 2). History of

Table 1. Study population characteristics at enrollment (1993–1998) of women later diagnosed with reproductive cancers, by fracture status: Women's Health Initiative

	Breast cancer (n = 6411)		Endometrial cancer (n = 1127)		Ovarian cancer (n = 658)	
	No fracture (n = 5057) No. (%)	Fracture (n = 1354) No. (%)	No fracture (n = 873) No. (%)	Fracture (n = 254) No. (%)	No fracture (n = 520) No. (%)	Fracture (n = 138) No. (%)
WHI arm						
Clinical trial	2164 (43)	765 (57)	365 (42)	103 (41)	219 (42)	56 (41)
Observational study	2893 (57)	589 (43)	508 (58)	151(59)	301 (58)	82 (59)
Age at cancer diagnosis, y						
50–65	1587 (31)	154 (11)	251 (29)	28 (11)	147 (28)	14 (10)
65–69	1204 (24)	259 (19)	225 (26)	56 (22)	142 (27)	34 (25)
70–74	1110 (22)	366 (27)	191 (22)	68 (27)	115 (22)	29 (21)
75–79	773 (15)	316 (23)	126 (14)	61 (24)	76 (14)	34 (25)
80+	383 (8)	259 (19)	80 (9)	41 (16)	40 (6)	27 (19)
Education*						
High school or less	958 (19)	208 (15)	166 (19)	38 (15)	112 (21)	27 (20)
Vocational/some college	1834 (36)	502 (37)	285 (33)	73 (29)	177 (34)	48 (35)
College degree or more	2234 (44)	635 (47)	418 (48)	141 (56)	225 (43)	61 (44)
Race/ethnicity						
Non-Hispanic 3hite	4341 (86)	1240 (92)	785 (90)	232 (91)	451 (87)	132 (96)
Other	716 (14)	114 (8)	88 (10)	22 (9)	69 (13)	6 (4)
Alcohol intake at enrollment*						
Nondrinker	1315 (26)	335 (25)	206 (24)	68 (27)	138 (26)	26 (19)
<1 serving/wk	1667 (33)	419 (31)	303 (35)	94 (37)	160 (30)	48 (35)
1–7 servings/wk	1365 (27)	372 (27)	231 (27)	60 (24)	148 (29)	38 (28)
7+ servings/wk	679 (13)	220 (16)	131 (15)	32 (13)	70 (14)	24 (17)
Smoking status at enrollment*						
Never smoked	2424 (48)	672 (50)	465 (53)	133 (52)	251 (48)	63 (46)
Former smoker	2269 (45)	580 (43)	355 (41)	111 (44)	224 (43)	67 (49)
Current smoker	310 (6)	86 (6)	45 (5)	8 (3)	37 (7)	7 (5)
Hormone therapy use at enrollment						
Never	1894 (37)	611 (45)	377 (43)	129 (51)	213 (41)	58 (42)
Ever	3163 (63)	743 (55)	495 (57)	125 (49)	307 (59)	80 (58)
Oral bisphophonate use at enrollment						
No	4999 (99)	1313 (97)	865 (99)	248 (98)	514 (99)	132 (96)
Yes	58 (1)	41 (3)	8 (1)	6 (2)	6 (1)	6 (4)
Body mass index at enrollment*, kg/m^2						
<25	1695 (34)	445 (33)	274 (31)	80 (32)	187 (36)	57 (41)
25–29.9	1708 (23)	487 (36)	242 (28)	75 (29)	192 (37)	38 (28)
30+	1649 (33)	422 (31)	356 (41)	99 (39)	141 (27)	43 (31)
Age at menopause*, y						
23–44	942 (19)	246 (18)	65 (7)	14 (6)	78 (15)	26 (19)
45–49	1200 (24)	305 (23)	191 (22)	51 (20)	130 (25)	26 (19)
50–54	2052 (41)	513 (38)	420 (48)	128 (50)	232 (45)	58 (42)
55+	685 (14)	250 (18)	176 (20)	55 (22)	68 (13)	22 (16)
Mammogram ≤2 y prior to enrollment*						
Yes	4279 (85)	1162 (86)				
No	649 (13)	153 (11)				
Charlson Comorbidity Index at enrollment						
0	1754 (35)	357 (26)	298 (34)	66 (26)	178 (34)	37 (27)
1	1720 (34)	448 (33)	284 (33)	78 (31)	169 (33)	37 (27)
2	938 (19)	294 (22)	166 (19)	62 (24)	93 (18)	37 (27)
3+	645 (13)	255 (19)	125 (14)	48 (19)	80 (15)	27 (20)
Quartiles of 10-y fracture probability at enrollment						
1st	1384 (27)	125 (9)	220 (25)	31 (12)	130 (25)	9 (7)
2nd	1460 (29)	169 (12)	254 (29)	35 (14)	157 (30)	20 (14)
3rd	1423 (28)	238 (18)	247 (28)	42 (16)	148 (28)	22 (16)
4th	790 (16)	822 (61)	152 (17)	146 (57)	85 (16)	87 (63)

*Numbers do not sum to total due to women with missing information. WHI = Women's Health Initiative.

Table 2. Postmenopausal fractures and all-cause mortality, by cancer and fracture site: Women's Health Initiative

	Breast cancer (n = 6411)			Endometrial cancer (n = 1127)			Ovarian cancer (n = 658)		
	No. of deaths	HR (95% CI)*	HR (95% CI)†	No. of deaths	HR (95% CI)*	HR (95% CI)†	No. of deaths	HR(95% CI)*	HR (95% CI)*
Postmenopausal fracture									
Never at any bone	5057 (680)	Ref.	Ref.	873 (140)	Ref.	Ref.	520 (263)	Ref.	Ref.
Ever at any bone	1354 (227)	1.22 (1.05 to 1.43)	1.23 (1.05 to 1.44)	254 (52)	1.27 (0.91 to 1.78)	1.21 (0.83 to 1.77)	138 (71)	1.15 (0.86 to 1.55)	1.20 (0.88 to 1.63)
Hip, forearm, or spine	483 (87)	1.26 (1.01 to 1.58)	1.25 (1.00 to 1.58)	83 (18)	1.29 (0.77 to 2.15)	1.28 (0.76 to 2.14)	48 (29)	1.01 (0.65 to 1.57)	1.31 (0.84 to 2.03)
Hip only	63 (19)	2.05 (1.27 to 3.32)	1.89 (1.10 to 3.22)	7 (2)	–	–	3 (2)	–	–

*All estimates were stratified by observational study/clinical trial arms and fracture adjudication, and adjusted for categorical age at cancer diagnosis, education, race, alcohol, smoking, hormone therapy use (ever, time-varying), bisphosphonate use (ever, time-varying), body mass index, age at menopause, mammography in the two years prior to cancer diagnosis (breast cancer only), and Charlson Comorbidity Index score (at time of cancer diagnosis).
CI = confidence interval; HR = hazard ratio.
†Cox regression models were additionally stratified by stage (local, regional, or distant).

Table 3. Postmenopausal fractures and cause-specific mortality, by cancer and fracture site: Women's Health Initiative

	Breast cancer (n = 6411)			Endometrial cancer (n = 1127)			Ovarian cancer (n = 658)		
	No. of deaths	HR (95% CI)*	HR (95% CI)†	No. of deaths	HR (95% CI)*	HR (95% CI)†	No. of deaths	HR (95% CI)*	HR (95% CI)†
Postmenopausal fracture									
Never at any bone	5057 (331)	Ref.		873 (63)	Ref.	Ref.	520 (239)	Ref.	Ref.
Ever at any bone	1354 (85)	1.09 (0.85 to 1.40)	1.09 (0.85 to 1.41)	254 (20)	1.07 (0.62 to 1.85)	1.07 (0.63 to 1.85)	138 (67)	1.22 (0.90 to 1.65)	1.27 (0.93 to 1.75)
Hip, forearm, or spine	483 (26)	0.95 (0.63 to 1.44)	0.87 (0.57 to 1.34)	83 (10)	1.54 (0.76 to 3.11)	1.01(0.54 to 1.89)	48 (28)	1.11 (0.71 to 1.73)	1.45 (0.93 to 2.28)
Hip only	63 (6)	1.75 (0.75 to 4.10)	1.41 (0.54 to 3.68)	7 (0)	–	–	3 (2)	–	–

*All estimates were stratified by observational study/clinical trial arms and fracture adjudication, and adjusted for categorical age at cancer diagnosis, education, race, alcohol, smoking, hormone therapy use (ever, time-varying), bisphosphonate use (ever, time-varying), body mass index, age at menopause, mammography in the two years prior to cancer diagnosis (breast cancer only), and Charlson Comorbidity Index score (at time of cancer diagnosis).
CI = confidence interval; HR = hazard ratio.
†Cox regression models were additionally stratified by stage (local, regional, or distant).

fracture was not associated with any change in all-cause mortality or ovarian cancer–specific mortality, irrespective of fracture site (Table 3).

For all three cancers, sensitivity analyses with adjustment for 10-year fracture probability decreased the precision of estimates but did not meaningfully change hazard ratio estimates or the interpretation of results (Supplementary Tables 1 and 2, available online).

Discussion

In this large cohort of postmenopausal women with reproductive cancers, a history of postmenopausal fractures prior to cancer diagnosis was not associated with breast cancer–, endometrial cancer–, or ovarian cancer–specific survival. Among breast cancer patients, however, postmenopausal fractures, particularly those to the hip, were statistically significantly related to an increased risk of all-cause mortality. Our confidence in these findings is enhanced by the complete ascertainment of deaths, and limiting analyses to fractures prior to cancer diagnoses so that fractures were not related to treatment or metastasis.

To our knowledge, this is the first study to evaluate prediagnosis postmenopausal fracture and survival in women with reproductive cancers. Although we hypothesized that the estrogen deficits assumed present in women with a history of fractures would improve survival after reproductive cancer diagnosis, fracture history did not appear to impact cases' disease-specific prognosis. In fact, our findings indicated that a history of postmenopausal fractures was negatively associated with overall survival in women with breast cancer, the largest case group.

The relationship between postmenopausal fracture and mortality is well-documented in noncancer populations (28–32). Excess mortality risk after hip fracture persists for many years after fracture and has been attributed primarily to postfracture conditions, such as infections and psychiatric conditions, rather than preexisting comorbidities (29). Despite our best efforts to control for health status through adjustment for age, CCI at diagnosis, smoking, alcohol use, and BMI, a history of postmenopausal fractures may reflect persistent frailty and a decline after fracture in overall health unrelated to cancer.

This analysis had several strengths, including the prospective ascertainment of detailed data on cancer, the standardized adjudication of all incident fractures, and the assessment of factors influencing cancer survival. This large cohort also provided complete follow-up for many survival outcomes, including adjudicated cause of death. The interpretation of our findings does require some circumspection. Although we were able to control for the identified putative confounders, we were not able to capture use of some intravenous bisphosphonate formulations, which, along with oral formulations, have been shown to reduce the risk of breast cancer recurrence and mortality in postmenopausal women (33). This use did not become common practice until the recent decade, but may nonetheless have impacted survival following breast cancer diagnosis in some women. We did not control in this analysis for tumor prognostic factors, including hormone receptor expression. Breast cancer and, to a lesser extent, ovarian and endometrial cancers differentially express estrogen and progesterone receptors, which impacts both disease treatment and prognosis (34–38). However, in this postmenopausal population, the majority of these tumors, specifically breast cancers, are likely to be sensitive to estrogen (37), and if anything, inclusion of cancers that did not express hormone receptors likely led to an attenuation of effects specific to hormone-sensitive tumors. We were able to adjust for mammography in the two years preceding breast cancer diagnosis, which in this highly screened population provided some degree of control for stage among breast cancer patients. We also did not include information on cancer treatment, which may differentially affect all-cause and cancer-specific mortality; treatments typically improve survival, but may be contraindicated based on a patient's preexisting condition at diagnosis. Finally, despite the WHI's large size, endometrial and ovarian cancer are fairly uncommon (39), and the relatively small number of fractures among women later diagnosed with endometrial or ovarian cancer limited our ability to detect differences. Therefore, given these limitations, the results of this study should be considered hypothesis-generating.

Our findings showed that postmenopausal fractures were not associated with survival from breast, endometrial, or ovarian cancer, counter to our hypothesis. Indeed, breast cancer survivors with history of fracture, especially of the hip, were more likely to die of any cause than breast cancer survivors without history of fracture. This study considered fractures to be primarily the consequence of low estrogen; however, genetics and family history are also important risk factors that should be considered in future studies (40). Understanding more about the mechanisms specific to survival in a cancer population may help to develop strategies to mitigate any increased mortality risk associated with fractures for women diagnosed with breast cancer.

Funding

This work was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, HHSN271201100004C, NIH K05 CA152715 (PAN), and NIH P30 CA015704 (PAN).

Notes

The authors thank the Women's Health Initiative (WHI) investigators and staff for their skill and dedication, and the study participants for making the research program possible.

Program Office: National Heart, Lung, and Blood Institute, Bethesda, Maryland: Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller.

Clinical Coordinating Center: Fred Hutchinson Cancer Research Center, Seattle, Washington: Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg.

Investigators and Academic Centers: Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts: JoAnn E. Manson; MedStar Health Research Institute/Howard University, Washington, DC: Barbara V. Howard; Stanford Prevention Research Center, Stanford, California: Marcia L. Stefanick; The Ohio State University, Columbus, Ohio: Rebecca Jackson; University of Arizona, Tucson/Phoenix, Arizona: Cynthia A. Thomson; University at Buffalo, Buffalo, New York: Jean Wactawski-Wende; University of Florida, Gainesville/Jacksonville, Florida: Marian Limacher; University of Iowa, Iowa City/Davenport, Iowa: Jennifer Robinson; University of Pittsburgh, Pittsburgh, Pennsylvania: Lewis Kuller; Wake Forest University School of Medicine, Winston-Salem, North Carolina:

Sally Shumaker; University of Nevada, Reno, Nevada: Robert Brunner; University of Minnesota, Minneapolis, Minnesota: Karen L. Margolis.

References

1. Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet*. 1997;350(9084):1047–1059.
2. Newcomb PA, Trentham-Dietz A, Egan KM, et al. Fracture history and risk of breast and endometrial cancer. *Am J Epidemiol*. 2001;153(11):1071–1078.
3. CollaborativeGroup. Breast cancer and hormonal contraceptives: Further results. Collaborative Group on Hormonal Factors in Breast Cancer. *Contraception*. 1996;54(3 Suppl):1S–106S.
4. Newcomb PA, Longnecker MP, Storer BE, et al. Long-term hormone replacement therapy and risk of breast cancer in postmenopausal women. *Am J Epidemiol*. 1995;142(8):788–795.
5. Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer*. 2002;87(11):1234–1245.
6. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: Individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol*. 2012;13(11):1141–1151.
7. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: Collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet*. 1996;347(9017):1713–1727.
8. Newcomb PA, Trentham-Dietz A. Patterns of postmenopausal progestin use with estrogen in relation to endometrial cancer (United States). *Cancer Causes Control*. 2003;14(2):195–201.
9. Karageorgi S, Hankinson SE, Kraft P, De Vivo I. Reproductive factors and postmenopausal hormone use in relation to endometrial cancer risk in the Nurses' Health Study cohort 1976-2004. *Int J Cancer*. 2010;126(1):208–216.
10. Olsen CM, Green AC, Whiteman DC, Sadeghi S, Kolahdooz F, Webb PM. Obesity and the risk of epithelial ovarian cancer: A systematic review and meta-analysis. *Eur J Cancer*. 2007;43(4):690–709.
11. Lacey JV Jr, Mink PJ, Lubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA*. 2002;288(3):334–341.
12. Danforth KN, Tworoger SS, Hecht JL, Rosner BA, Colditz GA, Hankinson SE. A prospective study of postmenopausal hormone use and ovarian cancer risk. *Br J Cancer*. 2007;96(1):151–156.
13. Anderson GL, Judd HL, Kaunitz AM, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: The Women's Health Initiative randomized trial. *JAMA*. 2003;290(13):1739–1748.
14. Clarke BL, Khosla S. Physiology of bone loss. *Radiol Clin North Am*. 2010;48(3):483–495.
15. Cummings SR, Browner WS, Bauer D, et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of Osteoporotic Fractures Research Group. *N Engl J Med*. 1998;339(11):733–738.
16. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: The Women's Health Initiative randomized trial. *JAMA*. 2003;290(13):1729–1738.
17. Nelson RL, Turyk M, Kim J, Persky V. Bone mineral density and the subsequent risk of cancer in the NHANES I follow-up cohort. *BMC Cancer*. 2002;2(1):22.
18. Buist DS, LaCroix AZ, Barlow WE, White E, Weiss NS. Bone mineral density and breast cancer risk in postmenopausal women. *J Clin Epidemiol*. 2001;54(4):417–422.
19. Qu X, Zhang X, Qin A, et al. Bone mineral density and risk of breast cancer in postmenopausal women. *Breast Cancer Res Treat*. 2013;138(1):261–271.
20. Danforth KN, Schairer C, Schatzkin A, Lacey JV. Bone fractures and incident epithelial ovarian cancer in a prospective cohort study. *J Womens Health*. 2009;18(11):1777–1782.
21. Ganry O, Baudoin C, Fardellone P, Peng J, Raverdy N. Bone mass density and risk of breast cancer and survival in older women. *Eur J Epidemiol*. 2004;19(8):785–792.
22. Zambetti A, Tartter PI. Bone mineral density is a prognostic factor for postmenopausal caucasian women with breast cancer. *Breast J*. 2013;19(2):168–172.
23. Fraenkel M, Novack V, Liel Y, et al. Association between bone mineral density and incidence of breast cancer. *PLoS One*. 2013;8(8):e70980.
24. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative study design. *Ann Epidemiol*. 2003;13(9 Suppl):S5–S17.
25. Curb JD, McTiernan A, Heckbert SR, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol*. 2003;13(9 Suppl):S122–S128.
26. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol*. 2003;13(9 Suppl):S18–S77.
27. Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR. The Women's Health Initiative postmenopausal hormone trials: Overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9 suppl):S78–S86.
28. Magaziner J, Lydick E, Hawkes W, et al. Excess mortality attributable to hip fracture in white women aged 70 years and older. *Am J Public Health*. 1997;87(10):1630–1636.
29. Vestergaard P, Rejnmark L, Mosekilde L. Increased mortality in patients with a hip fracture-effect of pre-morbid conditions and post-fracture complications. *Osteoporos Int*. 2007;18(12):1583–1593.
30. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: A systematic epidemiological review. *Osteoporos Int*. 2009;20(10):1633–1650.
31. von Friesendorff M, McGuigan FE, Wizert A, et al. Hip fracture, mortality risk, and cause of death over two decades. *Osteoporos Int*. 2016;27(10):2945–2953.
32. Haentjens P, Magaziner J, Colon-Emeric CS, et al. Meta-analysis: Excess mortality after hip fracture among older women and men. *Ann Intern Med*. 2010;152(6):380–390.
33. Early Breast Cancer Trialists' Collaborative Group, Coleman R, Powles T, et al. Adjuvant bisphosphonate treatment in early breast cancer: Meta-analyses of individual patient data from randomised trials. *Lancet*. 2015;386(10001):1353–1361.
34. Saso S, Chatterjee J, Georgiou E, Ditri AM, Smith JR, Ghaem-Maghami S. Endometrial cancer. *BMJ*. 2011;343:d3954.
35. Sieh W, Kobel M, Longacre TA, et al. Hormone-receptor expression and ovarian cancer survival: An Ovarian Tumor Tissue Analysis Consortium study. *Lancet Oncol*. 2013;14(9):853–862.
36. Jongen V, Briet J, de Jong R, et al. Expression of estrogen receptor-alpha and -beta and progesterone receptor-A and -B in a large cohort of patients with endometrioid endometrial cancer. *Gynecol Oncol*. 2009;112(3):537–542.
37. Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. *J Clin Oncol*. 2010;28(20):3271–3277.
38. Purdie CA, Baker L, Ashfield A, et al. Increased mortality in HER2 positive, oestrogen receptor positive invasive breast cancer: A population-based study. *Br J Cancer*. 2010;103(4):475–481.
39. Howlader N, Noone AM, Krapcho M, et al., eds. *SEER Cancer Statistics Review, 1975-2013*. Bethesda, MD: National Cancer Institute; 2016.
40. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. *N Engl J Med*. 1995;332(12):767–774.