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Long-term pelvic fracture and overall mortality risk after pelvic cancer and pelvic radiation

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Abstract

Background: The association of pelvic radiation with pelvic fracture risk has not been examined in prospective cohort settings with comprehensive fracture risk assessment, cancer-free comparison populations, and long-term follow-up. Our objective is to better characterize pelvic fracture and overall mortality risks in postmenopausal women participating in the Women's Health Initiative.

Methods: A total of 135 743 Women's Health Initiative participants aged 50 to 79 years enrolled from 40 US clinical centers from 1993 to 1998 who had entry Fracture Risk Assessment Tool scores were eligible. Outcomes included pelvic cancer diagnosis, pelvic fracture occurrence, and mortality. Cox proportional hazards regression models were used to examine associations of pelvic cancer and pelvic radiation with pelvic fracture and mortality risk.

Results: After 17.7 years (median) follow-up, 4451 pelvic cancers, 10 139 pelvic fractures, and 33 040 deaths occurred. In multivariable analyses, women with incident pelvic cancer, compared with women who remained pelvic cancer free, had higher pelvic fracture risk (hazard ratio [HR] = 1.26, 95% confidence interval [CI] = 1.11 to 1.43) and higher overall mortality risk (HR = 2.91, 95% CI = 2.77 to 3.05). Women with pelvic cancer treated with pelvic radiation, compared with women with pelvic cancer not treated with pelvic radiation, had higher pelvic fracture risk (HR = 1.98, 95% CI = 1.41 to 2.78) and higher overall mortality after pelvic cancer (HR = 1.32, 95% CI = 1.15 to 1.52).

Conclusions: Postmenopausal women with pelvic cancer, especially those receiving pelvic radiation, are at higher pelvic fracture risk and higher overall mortality risk. As therapeutic advances have reduced cancer mortality, attention to and interventions for pelvic fracture prevention may be important in pelvic cancer survivors.

Pelvic fractures are associated with increased morbidity and mortality, especially in older postmenopausal women (1,2). Retrospective institutional series report an association between radiation and fractures in postmenopausal patients with pelvic cancers treated with radiation (3-6). Baxter and colleagues (7) analyzed data from the Surveillance Epidemiology, and End Results (SEER)–Medicare linked dataset in 6428 women aged 65 years and older with pelvic cancers (anal, cervical, and rectal) to examine pelvic radiation influence on pelvic fracture risk. Information about fracture risk factors was limited to age and race. With a mean follow-up of 4 years, cumulative 5-year fracture rates in irradiated patients compared with nonirradiated patients were substantially increased for anal (14.0% vs 7.5%), cervical (8.2% vs 5.9%), and rectal malignancies (11.2% vs 8.7%).

More recently, pelvic fracture risk by radiation type was examined also using the SEER-Medicare linked dataset (8). The study included patients treated with pelvic radiation for endometrial, cervical, anal, rectal, or prostate cancer. Overall, among 28 354 cancer patients (16 561 with prostate cancer), the 5-year fracture rate was 12.7%. Risk of pelvic fracture was lower in women treated with intensity-modulated radiation therapy (hazard ratio [HR] = 0.85, 95% confidence interval [CI] = 0.73 to 0.99) or brachytherapy alone (HR = 0.43, 95% CI = 0.34 to 0.54) compared with women treated with 3-dimensional conformal radiation therapy.

To our knowledge, no previous study on pelvic cancer and pelvic radiation effects on fracture and mortality has evaluated a prospective cohort of women with comprehensive fracture risk assessment and long-term follow-up. Moreover, no study has included a cancer-free comparison population followed as part of the same study cohort. Therefore, in postmenopausal women participating in the Women's Health Initiative (WHI), we tested the hypothesis that both pelvic cancer and pelvic radiation are associated with higher risk of pelvic fracture and mortality.

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Methods

The WHI enrolled postmenopausal women from 1993 to 1998 at 40 US clinical centers. Of the 161 808 participants, 68 132 women (CT participants) were enrolled in 1 or more of 4 randomized controlled trials while 93 676 (OS participants) were enrolled in an observational cohort study. After the clinical trials were completed in 2005, the CT and OS participants continued in survey-based follow-up in the WHI Extension Study 1 (2005-2010) and Extension Study 2 (2010-2020), which is divided into 2 cohorts: Medical Records and Self-Report. The study design and conduct of the WHI were previously described (9,10). Participant informed consent was obtained, and protocols were approved at all centers.

Baseline demographics included age and self-reported race and ethnicity, which along with medical and reproductive histories, smoking status, alcohol consumption, dietary intake, and physical activity were collected via questionnaires. Prescription and nonprescription drug use, including use of calcium and vitamin D, was collected at baseline and during follow-up. The 10-year risk of pelvic fracture was calculated using the Fracture Risk Assessment Tool (FRAX) scoring system (https://www.sheffield.ac.uk/FRAX/ and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2827823/), which incorporates age, sex, body mass index, alcohol and tobacco use, fracture history, and glucocorticoid use; this score was available for all study participants (11).

For CT participants, information on cancers and fractures was ascertained via semi-annual questionnaires during the 8.5-year (mean) intervention period and annually thereafter, and OS participants had outcomes ascertained annually throughout the original and extension studies. All cancers were initially confirmed through medical record and pathology report review by clinical center physician adjudicators. Final adjudication and coding were performed at the WHI Clinical Coordinating Center following SEER criteria.

For incident fractures, medical records including radiology and surgery reports were requested for all hip fractures in the WHI cohort, for all fractures reported in the clinical trials (N = 68 835), and at 3 bone mineral density centers (N = 11 020). For Extension Study 1, hip fractures were adjudicated; all other fractures were self-reported. For Extension Study 2, hip fractures in Black, Hispanic, and all hormone therapy trial participants were adjudicated, whereas hip fractures of remaining participants and all other fractures were self-reported (12). In the WHI, 71% of the self-reported fractures were confirmed by radiographic report at the exact site; validity of self-reporting varied across fracture site (13). For pelvic fractures, 74.6% were confirmed at the exact or adjacent site.

Hip fractures were initially adjudicated at local clinical centers by trained and blinded physicians, with final adjudication at the clinical coordinating center (14). Agreement between central and local adjudication was 96% (15). Fractures were categorized by site: hip, pelvis, upper leg; lower leg, ankle, knee; foot; upper arm, shoulder, elbow; forearm, wrist, hand; and spine, tailbone. Pelvic fractures were defined as hip, pelvis, and tailbone.

Women with pelvic cancers were further categorized as receiving pelvic radiation by cross-referencing: 1) the WHI's Life and Longevity After Cancer survivorship study (16), and/or 2) Medicare claims information for those and other pelvic cancers. Of the 634 women who received radiation, 116 (18%) were identified by WHI's Life and Longevity After Cancer, 355 (56%) were identified by Medicare, and 163 (26%) were identified by both. Pelvic radiation therapy was considered related to pelvic cancer if it was administered from 1 month preceding and through 12 months following the relevant cancer diagnosis. For pelvic radiation status obtained via Medicare, participants were considered to have not received radiation only if they were continuously enrolled in the fee-for-service Medicare Part B from 1 month preceding through 12 months following cancer diagnosis.

Statistical analysis

Table 1 describes the stepwise identification and sample size of the participants studied. Participant characteristics by pelvic cancer and by pelvic radiation (Table 2) and patient characteristics by pelvic fracture (Supplementary Table 1, available online) are presented with frequencies and percentages for categorical variables and mean with SD for continuous variables. Testing was conducted with χ^2 tests for categorical characteristics and t tests for continuous characteristics. Annualized rates, Cox proportional hazards regression, and Fine and Gray proportional subdistribution competing risk models were used to examine the associations between diagnosis of pelvic cancer and risk of pelvic fracture and overall mortality (Tables 3 and 4) and between receipt of pelvic radiation and risk of pelvic fracture and overall mortality (Table 5). Annualized rates were calculated using a time-dependent pelvic cancer variable, defining the no pelvic cancer group as all participants who did not report a pelvic cancer event as well as the prepelvic cancer follow-up time of those who did have a pelvic cancer event. The pelvic cancer group follow-up time was defined as follow-up time after pelvic cancer event. For comparisons between women with and without pelvic

Table 1. Stepwise selection criteria

Sample	Total No. of participants	No Pelvic cancer, No.	Total Pelvic cancer, No.	Pelvic cancer + radiation[a], No.	Pelvic cancer + no radiation[a], No.	Pelvic cancer + unknown radiation[a], No.	Pelvic fracture, No.	Death, No.
Initial sample	161 808	156 463	5345	770	2171	1949	11 896	39 671
Exclude participants with no follow-up	161 118	155 773	5345	770	2171	1949	11 896	39 671
Not counting cancers/ radiation that occurred after pelvic fracture event	161 118	153 139	5209	753	2115	1907	11 896	39 671
Exclude participants with missing covariate data[b]	135 743	131 292	4451	634	1805	1640	10 139	33 040
Final sample	135 743	131 929	4451	634	1805	1640	10 139	33 040

[a] Pelvic radiation groups do not include n = 372 pelvic cancer cases with no follow-up time after pelvic cancer.
[b] Hormone use, age, race and ethnicity, education, body mass index, physical activity, smoking, alcohol, bisphosphonate use, hip fracture risk score, treated diabetes, hysterectomy, bilateral oophorectomy, history of parental hip fracture.

Table 2. Participant characteristics at screening by pelvic cancer and radiation status

Variable	Pelvic cancer			Pelvic radiation[a]			
	Pelvic cancer (n = 4451)	No pelvic cancer (n = 131 292)	P[b]	Radiation (n = 634)	No radiation (n = 1805)	Unknown (n = 1640)	P[c]
Age, mean (SD), y	64.0 (6.9)	63.6 (7.2)	.002	64.1 (6.5)	64.4 (6.7)	62.9 (7.2)	.32
Ethnicity, No. (%)			<.001				.64
Not Hispanic	4314 (96.9)	124 820 (95.1)		620 (97.8)	1765 (97.8)	1573 (95.9)	
Hispanic	112 (2.5)	5455 (4.2)		13 (2.1)	33 (1.8)	58 (3.5)	
Unknown/not reported	25 (0.6)	1017 (0.8)		1 (0.2)	7 (0.4)	9 (0.5)	
Race, No. (%)			<.001				.93
American Indian/Alaska Native	12 (0.3)	375 (0.3)		2 (0.3)	4 (0.2)	3 (0.2)	
Asian	64 (1.4)	3394 (2.6)		8 (1.3)	22 (1.2)	22 (1.3	
Black	253 (5.7)	10 444 (8.0)		28 (4.4)	80 (4.4)	121 (7.4)	
Native Hawaiian/Pacific Islander	3 (0.1)	109 (0.1)		1 (0.2)	1 (0.1)	1 (0.1)	
Non-Hispanic White	4046 (90.9)	113 186 (86.2)		590 (93.1)	1675 (92.8)	1457 (88.8)	
>1 race	35 (0.8)	1531 (1.2)		2 (0.3)	12 (0.7)	18 (1.1)	
Unknown/not reported	38 (0.9)	2253 (1.7)		3 (0.5)	11 (0.6)	18 (1.1)	
Education, No. (%)			<.001				.11
≤High school/GED	870 (19.5)	28 309 (21.6)		128 (20.2)	325 (18.0)	322 (19.6)	
School after high school	1576 (35.4)	49 573 (37.8)		199 (31.4)	647 (35.8)	602 (36.7)	
≥College degree	2005 (45.0)	53 410 (40.7)		307 (48.4)	833 (46.1	716 (43.7)	
Body mass index, mean (SD), kg/m^2	28.5 (±6.4)	27.9 (±5.9)	<.001	29.2 (±6.8)	28.0 (±6.2)	28.6 (±6.2)	<.001
<25	1499 (33.7)	47 046 (35.8)		195 (30.8)	646 (35.8)	534 (32.6)	
25 to <30	1451 (32.6)	45 614 (34.7)		196 (30.9)	586 (32.5)	546 (33.3)	
≥30	1501 (33.7)	38 632 (29.4)		243 (38.3)	573 (31.7)	560 (34.1)	
Physical activity (MET-h/wk), mean (SD)	12.7 (±13.7)	12.6 (±13.7)	.46	12.7 (±13.4)	13.3 (±13.5)	12.5 (±14.0)	.33
<5	1556 (35.0)	47 574 (36.2)		230 (36.3)	577 (32.0)	600 (36.6)	
5 to <15	1450 (32.6)	42 098 (32.1)		199 (31.4)	591 (32.7)	531 (32.4)	
≥15	1445 (32.5)	41 620 (31.7)		205 (32.3)	637 (35.3)	509 (31.0)	
Smoking, No. (%)			<.001				.94
Never	2127 (47.8)	66 921 (51.0)		309 (48.7)	869 (48.1)	764 (46.6)	
Past	1991 (44.7)	55 597 (42.3)		283 (44.6)	810 (44.9)	730 (44.5)	
Current	333 (7.5)	8774 (6.7)		42 (6.6)	126 (7.0)	146 (8.9)	
Alcohol use, No. (%)			<.001				.42
Never	389 (8.7)	13 887 (10.6)		53 (8.4)	147 (8.1)	145 (8.8)	
Past	687 (15.4)	23 959 (18.2)		85 (13.4)	281 (15.6)	259 (15.8)	
Current	3375 (75.8)	93 446 (71.2)		496 (78.2)	1377 (76.3)	1236 (75.4)	
Hormone therapy use[d], No. (%)			<.001				.002
Never	1814 (40.8)	49 697 (37.9)		53 (8.4)	693 (38.4)	669 (40.8)	
Past	630 (14.2)	19 066 (14.5)		85 (13.4)	239 (13.2)	245 (14.9)	
Current	2007 (45.1)	62 529 (47.6)		496 (78.2)	873 (48.4)	726 (44.3)	
Total calcium intake, mg/d	1228.3 (±709.1)	1200.8 (±739.4)	.01	1209.7 (±641.9)	1257.8 (±721.3)	1224.3 (±731.2)	.14
Total vitamin D intake, IU/d	386.3 (±281.6)	376.6 (±279.0)	.02	394.8 (±273.6)	397.9 (±281.3)	370.9 (±281.9)	.81
Bisphosphonate use, No. (%)	86 (1.9)	2649 (2.0)	.69	21 (3.3)	39 (2.2)	18 (1.1)	.11
Treated diabetes, No. (%)	187 (4.2)	5542 (4.2)	.95	23 (3.6)	85 (4.7)	58 (3.5)	.26
Hysterectomy, No. (%)	1031 (23.2)	53 941 (41.1)	<.001	112 (17.7)	416 (23.0)	374 (22.8)	.005
Bilateral oophorectomy, No. (%)	445 (10.0)	27 520 (20.4)	<.001	61 (9.6)	151 (8.4)	165 (10.1)	.33
FRAX 10-y hip fracture risk ≥3%, No. (%)	961 (21.6)	26 706 (20.3)	.70	129 (20.3)	425 (23.5)	302 (18.4)	.10
Parental history of hip fracture, No. (%)	657 (14.8)	18 502 (14.1)	.21	87 (13.7)	281 (15.6)	241 (14.7)	.26
WHI calcium/vitamin D arm, No. (%)			.46				.54
Active	508 (11.4)	14 323 (10.9)		70 (11.0)	194 (10.7)	216 (13.2)	
Placebo	495 (11.1)	14 269 (10.9)		79 (12.5)	197 (10.9)	178 (10.9)	
Not randomized	3448 (77.5)	102 700 (78.2)		485 (76.5)	1414 (78.3)	1246 (76.0)	
WHI study component, No. (%)			.27				.61
Clinical trial	1842 (41.4)	53 244 (40.6)		261 (41.2)	722 (40.0)	732 (44.6)	
Observational study	2609 (58.6)	78 048 (59.4)		373 (58.8)	1083 (60.0)	908 (55.4)	

[a] Pelvic radiation groups do not include n = 372 pelvic cancer cases with no follow-up time after pelvic cancer event. GED = General Educational Development Test; FRAX = Fracture Risk Assessment Tool; MET = metabolic equivalent; WHI = Women's Health Initiative.
[b] P value compares pelvic cancer with no pelvic cancer groups with *t* tests for continuous variables and χ^2 tests for categorical variables.
[c] P value compares radiation with no radiation groups with *t* tests for continuous variables and χ^2 tests for categorical variables.
[d] Incorporates WHI Hormone Therapy Trial intervention assignment.

fractures, follow-up time began at WHI enrollment and continued until date of pelvic fracture, death, or loss to follow-up, whichever came first. For comparisons between women with pelvic cancer, with or without pelvic radiation, follow-up time began at date of pelvic cancer diagnosis.

The time-dependent pelvic radiation variable used to calculate annualized rates contained 3 groups: radiation, no radiation, and unknown radiation. All models, including unadjusted models, were stratified within the model by hormone therapy use, including WHI hormone therapy trial randomization assignment as well as self-reported use at enrollment and information from the WHI calcium and vitamin D trial by randomization assignment (9). Except for this initial stratification, each model was initially unadjusted, then adjusted for age and race and ethnicity. Finally, a multivariable model was constructed, additionally adjusted for education, physical activity, bisphosphonate use, 10-year risk of hip fracture (FRAX), history of treated diabetes, hysterectomy, bilateral oophorectomy, calcium intake, and vitamin

Table 3. Analysis of pelvic fracture and overall mortality as a function of pelvic cancer[a]

	Pelvic fracture			Mortality		
	No pelvic cancer (n = 131 292)	Pelvic cancer (n = 4451)	P	No pelvic cancer (n = 131 292)	Pelvic cancer (n = 4451)	P
Annualized rates (%)	9892 (0.48)	247 (0.85)		31 201 (1.49)	1839 (6.26)	
Model, HR (95% CI)						
Unadjusted	1.00 (Referent)	1.30 (1.14, 1.47)	<.001	1.00 (Referent)	2.89 (2.76, 3.03)	<.001
Age/race adjusted	1.00 (Referent)	1.23 (1.08, 1.39)	.002	1.00 (Referent)	2.81 (2.68, 2.95)	<.001
Multivariable[b] adjusted	1.00 (Referent)	1.26 (1.11, 1.43)	<.001	1.00 (Referent)	2.91 (2.77, 3.05)	<.001
Competing risk model[c], HR (95% CI)						
Unadjusted	1.00 (Referent)	1.13 (1.00, 1.29)	.05	—	—	
Age/race adjusted	1.00 (Referent)	1.07 (0.94, 1.21)	.33	—	—	
Multivariable[b] adjusted	1.00 (Referent)	1.09 (0.96, 1.24)	.17	—	—	

[a] All models are stratified by WHI HT and CaD intervention arms (active/placebo/not randomized) and WHI study component (clinical trial/observational study). All models are adjusted for WHI study time period (WHI, Extension 1, Extension 2—medical records cohort, Extension 2—self-report cohort), which incorporates adjustment for differences in hip fracture outcome collection during extension 2. CaD = Calcium and Vitamin D; CI = confidence interval; FRAX = Fracture Risk Assessment Tool; HR = hazard ratio; HT = Hormone Therapy; WHI = Women's Health Initiative.
[b] Multivariable models are adjusted for race, ethnicity, education, physical activity, bisphosphonate use, FRAX 10-year hip fracture risk, history of treated diabetes, hysterectomy, bilateral oophorectomy, calcium intake, and vitamin D intake. Mortality multivariable models are additionally adjusted for time-dependent pelvic fracture.
[c] Competing risk models with death using Fine and Gray proportional subdistribution model.

D intake. Stage of pelvic cancer was added for the radiation-stratified fracture and mortality models. All models were further adjusted for WHI study time period (WHI, Extension 1, and Extension 2) to account for hip fracture outcome collection. Mortality models were further adjusted for time-dependent pelvic fracture. Finally, sensitivity analyses were conducted to examine the results after excluding participants with a history of cancer at the time of study enrollment (Supplementary Tables 2 and 3, available online). All adjustment variables were selected a priori based on clinical relevance. For control purposes, similar analyses were completed for arm fracture by pelvic cancer and by pelvic radiation (Supplementary Table 4, available online).

The Kaplan-Meier method was used for graphic displays of pelvic fracture cumulative hazards. The proportional hazards assumption was evaluated both graphically and by fitting a model with pelvic fracture as a function of the interaction between the exposure of interest and log survival time. To visualize event rates over time, cumulative hazard plots of pelvic fracture by pelvic cancer (Figure 1, A) and by pelvic radiation (Figure 1, B) are presented with event totals and the number at risk in 2-year intervals. Likewise, cumulative hazard plots of death by pelvic cancer (Figure 1, C) and by pelvic radiation (Figure 1, D) are shown. Analyses were performed using SAS Version 9.4 and R Version 3.5.3. All *P* values are 2-sided with a statistical significance level cutoff set at .05.

Results

Of 135 743 participants included in this analysis and after a median follow-up of 17.7 years, 4451 pelvic cancers, 10 139 pelvic fractures, and 33 049 deaths occurred. Among women with incident pelvic cancer, 1805 did not receive pelvic radiation, 634 received pelvic radiation, and 1805 had unknown radiation status.

Compared with women with no pelvic cancer, women with pelvic cancer were more likely to be Non-Hispanic White, have higher educational level, have higher body mass index, have tobacco exposure, and be a current alcohol user (Table 2). In addition, women with pelvic cancer were substantially less likely to have undergone hysterectomy (23.2% vs 41.1%, respectively) or bilateral oophorectomy (10.0% vs 20.4%, respectively) (all $P < .001$). At entry, FRAX 10-year hip fracture risk of at least 3% was similar in women with pelvic cancer diagnosed during the follow-up period (21.6% vs 20.3%, respectively, $P = .70$).

The rate of pelvic fracture in participants with and without pelvic cancer was 0.85% and 0.48% per year, respectively (Table 3). On adjusted analyses, the hazard ratio for pelvic fracture in women with pelvic cancer was 1.26 (95% confidence interval = 1.11 to 1.43) relative to women without pelvic cancer. In a competing risk model, the hazard ratio for pelvic fracture in women with incident pelvic cancer was 1.09 (95% CI = 0.96 to 1.24) compared with women who remained pelvic cancer free. The probability of having a pelvic fracture after 20 years from study enrollment was 12% in those with pelvic cancer and 10% in those without pelvic cancer (Figure 1, A).

Pelvic fracture risk in women with incident pelvic cancer who did not receive radiation was like those who remained pelvic cancer free (HR = 1.07, 95% CI = 0.88 to 1.30). However, women with incident pelvic cancer who received radiation therapy were at higher pelvic fracture risk compared with women who remained pelvic cancer free (HR = 2.21, 95% CI = 1.72 to 2.84) (Table 4). Competing risk models showed similar results.

Table 2 outlines participant characteristics by pelvic radiation status in those diagnosed with pelvic cancer. The median time to pelvic cancer diagnosis from study enrollment was 8.6 years, with mean age at diagnosis of 73.3 years (range = 51-99, SD = 8.2). The types and frequencies of the pelvic cancers are listed in Supplementary Table 5 (available online).

Among women with pelvic cancer, the per year rate of pelvic fracture after diagnosis was 1.63%, 0.79%, and 0.68% for the radiation, no radiation, and unknown radiation groups, respectively. In women with pelvic cancer, in the fully adjusted analysis, those with pelvic radiation were twice as likely to sustain a pelvic fracture as those without pelvic radiation (HR = 1.98, 95% CI = 1.41 to 2.78) (Table 5). The competing risk model across the same groups showed a similarly increased risk (HR = 1.90, 95% CI = 1.36 to 2.64). As depicted in Figure 1, B, women with pelvic cancer and pelvic radiation had twice the pelvic fracture risk after 16 years compared with those without radiation or whose radiation status was unknown. To ensure differences in pelvic fracture risk were related to pelvic radiation and not underlying differences in osteoporotic risk factors, radial fracture risk was compared across pelvic cancer and pelvic radiation groups; no statistically significant differences were identified (Supplementary Table 4,

Table 4. Analysis of pelvic fracture and overall mortality as a function of pelvic radiation among all participants[a]

	Pelvic fracture				Overall mortality			
	No pelvic cancer (n = 131 292)	Pelvic cancer			No pelvic cancer	Pelvic cancer		
		No pelvic radiation (n = 1805)	Pelvic radiation (n = 634)	Unknown pelvic radiation (n = 1640)		No pelvic radiation (n = 1805)	Pelvic radiation (n = 634)	Unknown pelvic radiation (n = 1640)
Annualized events (%)	9892 (0.48)	106 (0.79)	62 (1.63)	79 (0.68)	31 201 (1.49)	840 (6.18)	316 (8.04)	683 (5.83)
Model, HR (95% CI)								
Unadjusted	1.00 (Referent)	1.16 (0.96 to 1.41)	2.30 (1.79 to 2.95)	1.10 (0.88 to 1.38)	1.00 (Referent)	2.80 (2.61 to 3.00)	3.34 (2.99 to 3.73)	2.86 (2.65 to 3.09)
Age/race adjusted	1.00 (Referent)	1.01 (0.84 to 1.23)	2.07 (1.61 to 2.66)	1.20 (0.96 to 1.49)	1.00 (Referent)	2.50 (2.33 to 2.68)	3.12 (2.80 to 3.49)	3.19 (2.95 to 3.44)
Multivariable[b] adjusted	1.00 (Referent)	1.07 (0.88 to 1.30)	2.21 (1.72 to 2.84)	1.15 (0.92 to 1.44)	1.00 (Referent)	2.72 (2.54 to 2.92)	3.21 (2.87 to 3.58)	3.05 (2.83 to 3.30)
Competing risk model[c], HR (95% CI)								
Unadjusted	1.00 (Referent)	1.02 (0.84 to 1.24)	1.91 (1.48 to 2.46)	0.98 (0.78 to 1.22)	—	—	—	—
Age/race adjusted	1.00 (Referent)	0.90 (0.74 to 1.09)	1.72 (1.33 to 2.23)	1.03 (0.82 to 1.28)	—	—	—	—
Multivariable[b] adjusted	1.00 (Referent)	0.94 (0.78 to 1.14)	1.83 (1.42 to 2.37)	1.00 (0.80 to 1.25)	—	—	—	—

[a] All models are stratified by WHI HT and CaD intervention arms (active/placebo/not randomized) and WHI study component (clinical trial/observational study). All models are adjusted for WHI study time period (WHI, Extension 1, Extension 2—medical records cohort, Extension 2—self-report cohort), which incorporates adjustment for differences in hip fracture outcome collection during extension 2. CaD = Calcium and Vitamin D; CI = confidence interval; FRAX = Fracture Risk Assessment Tool; HR = hazard ratio; HT = Hormone Therapy; ref = reference; WHI = Women's Health Initiative.

[b] Multivariable models are adjusted for race, ethnicity, education, physical activity, bisphosphonate use, FRAX 10-year hip fracture risk, history of treated diabetes, hysterectomy, bilateral oophorectomy, calcium intake, and Vitamin D intake. Mortality multivariable models are additionally adjusted for time-dependent pelvic fracture.

[c] Competing risk models with death using Fine and Gray proportional subdistribution model.

available online). In multivariable analysis, women with incident pelvic cancer were at higher mortality risk compared with women without pelvic cancer (HR = 2.91, 95% CI = 2.77 to 3.05) (Table 3). Among women with pelvic cancer, pelvic radiation was associated with higher mortality risk (HR = 1.32, 95% CI = 1.15 to 1.52) compared with the nonradiation group (Table 5). As graphically depicted, the overall mortality rates were higher in participants with pelvic cancer than those without cancer (Figure 1, C) and, among those with pelvic cancer, those who received pelvic radiation compared with those with did not (Figure 1, D). Table 6 summarizes the cause of death by pelvic cancer and radiation status.

Discussion

Analyzing the long-term follow-up data of postmenopausal women participating in the WHI, we found that women with incident pelvic cancer had a statistically significant 26% higher risk of pelvic fracture compared with women without pelvic cancer. In addition, among women with pelvic cancer, those who received pelvic radiation had an almost twofold higher risk of pelvic fracture compared with those who did not receive pelvic radiation. These findings were independent of demographic and clinical factors such as age, race and ethnicity, FRAX score, and hormone use. In addition, overall mortality risk was statistically significantly higher in women with pelvic cancer who received pelvic radiation compared with those who did not, after adjusting for age, comorbidities, and cancer stage.

A unique component of the current analysis is FRAX fracture risk assessment in all participants. The FRAX algorithm integrates the fracture risk associated with multiple independent, validated clinical factors and is considered the authoritative fracture risk assessment calculator even without bone mineral density information (17,18). The complex issue of integration of other fracture risk factors in modulating the absolute fracture risk prediction is beyond the scope of this study, where demonstration of similar fracture risk in comparison groups is the objective. In addition to closely comparable FRAX fracture risk across study groups, radial fracture rates were also comparable across groups.

Two recent reports addressed the more limited issue of pelvic fractures after pelvic radiation for gynecological cancers. In a meta-analysis of 37 studies in 6488 women with gynecological cancers receiving radiation therapy (19), after 39-month follow-up, pelvic fracture incidence was 9.4% (19). Similarly, in a meta-analysis of 21 studies with 3929 women with gynecological cancers receiving pelvic radiation (20), after 19 months follow-up, pelvic fracture incidence was 14.0% (median time to fracture = 7.1-19 months) (20). Although these findings add to our understanding of radiation-related fracture risk, follow-up was limited and neither report included cancer-free controls. In the first meta-analysis, only 1 of 37 studies had longer than 60 months follow-up (19), and in the second, follow-up did not exceed 20 months in any study (20). Our study expands on these findings by including women with other nongynecologic pelvic cancers, providing comparisons with pelvic cancer-free controls, and examining women with pelvic cancer who were not treated with pelvic radiation. Moreover, the median follow-up of 17.7 years in our study enables analyses of late outcomes.

Although pelvic radiation is indicated for multiple cancers and improves locoregional cancer control, radiation reduces bone remodeling potential, alters bone architecture, and causes bone loss (21,22). The resultant weakened bone in the pelvis is susceptible to insufficiency fractures with associated adverse

Table 5. Analysis of pelvic fracture and overall mortality as a function of pelvic radiation among participants with pelvic cancer[a]

	Pelvic fracture				Overall mortality			
	No pelvic radiation HR (95%CI)	Pelvic radiation HR (95%CI)	Unknown pelvic radiation HR (95%CI)	P[b]	No pelvic radiation HR (95%CI)	Pelvic radiation HR (95%CI)	Unknown pelvic radiation HR (95%CI)	P[b]
No.	1805	634	1640		1805	634	1640	
Annualized events, No. (%)	106 (0.79)	62 (1.63)	79 (0.68)		840 (6.18)	316 (8.04)	683 (5.83)	
Model								
Unadjusted	1.00 (Referent)	2.06 (1.50 to 2.83)	0.90 (0.67 to 1.21)	<.001	1.00 (Referent)	1.25 (1.10 to 1.43)	0.93 (0.84 to 1.03)	<.001
Age/race adjusted	1.00 (Referent)	2.18 (1.59 to 3.00)	1.14 (0.84 to 1.53)	<.001	1.00 (Referent)	1.29 (1.13 to 1.47)	1.11 (1.00 to 1.23)	<.001
Multivariable adjusted	1.00 (Referent)	1.98 (1.41 to 2.78)	1.18 (0.87 to 1.59)	<.001	1.00 (Referent)	1.32 (1.15 to 1.52)	1.43 (1.28 to 1.59)	<.001
Competing risk model[c]								
Unadjusted	1.00 (Referent)	1.96 (1.43 to 2.70)	0.91 (0.68 to 1.22)	<.001	—	—	—	
Age/race adjusted	1.00 (Referent)	2.04 (1.48 to 2.82)	1.10 (0.81 to 1.47)	<.001	—	—	—	
Multivariable adjusted	1.00 (Referent)	1.90 (1.36 to 2.64)	1.09 (0.81 to 1.47)	<.001	—	—	—	

[a] All models are stratified by WHI HT and CaD intervention arms (active/placebo/not randomized) and WHI study component (clinical trial/observational study). All models are adjusted for WHI study time period (WHI, Extension 1, Extension 2—medical records cohort, Extension 2—self-report cohort), which incorporates adjustment for differences in hip fracture outcome collection during extension 2. Multivariable models are adjusted for race, ethnicity, education, physical activity, bisphosphonate use, FRAX 10-year hip fracture risk, history of treated diabetes, hysterectomy, bilateral oophorectomy, calcium intake, Vitamin D intake, age at pelvic cancer diagnosis, and pelvic cancer stage. Mortality multivariable models are additionally adjusted for time-dependent pelvic fracture. Pelvic radiation models include pelvic cancer participants with at least 1 day of follow-up after pelvic cancer diagnosis. CI = confidence interval; FRAX = Fracture Risk Assessment Tool; HR = hazard ratio; ref = reference; WHI = Women's Health Initiative.

[b] *P* values compare radiation vs no radiation groups.

[c] Competing risk models with death using Fine and Gray proportional subdistribution model.

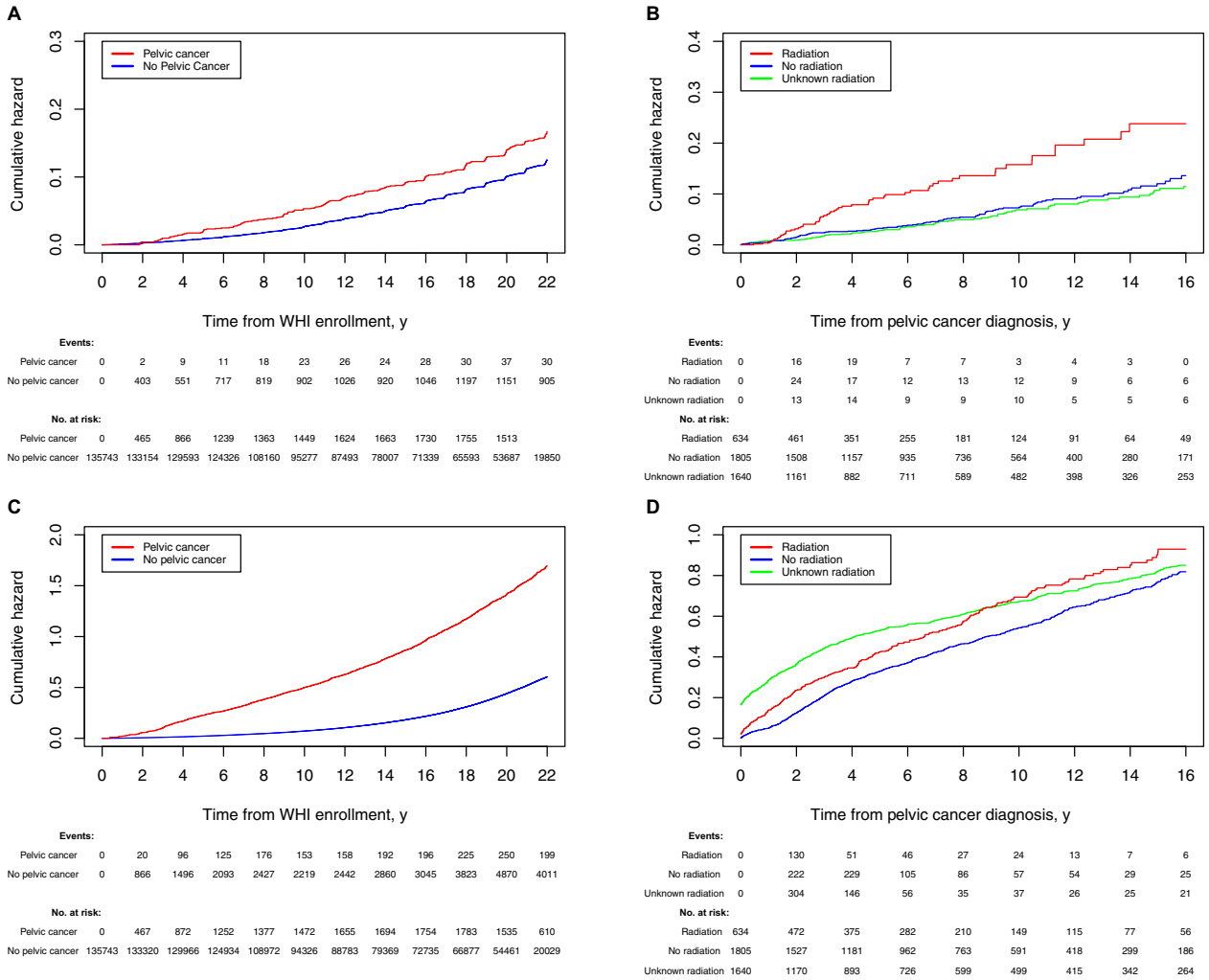

Figure 1. Cumulative hazard plots of (**A**) pelvic fracture by pelvic cancer, (**B**) pelvic fracture by pelvic radiation from date of pelvic cancer diagnosis, (**C**) death by pelvic cancer status, and (**D**) death by pelvic radiation status. Follow-up time from pelvic cancer diagnosis.

Table 6. Cause of death by pelvic cancer and radiation status

Cause of death	Pelvic cancer		Pelvic radiation		
	No No. (%)	Yes No. (%)	No No. (%)	Yes No. (%)	Unknown No. (%)
Cancer	8897 (28.5)	1295 (70.4)	581 (69.2)	221 (69.9)	493 (72.2)
Cardiovascular	9861 (31.6)	207 (11.3)	104 (12.4)	37 (11.7)	66 (9.7)
Other known cause	10 596 (34.0)	259 (14.1)	119 (14.2)	49 (15.5)	91 (13.3)
Unknown/not yet adjudicated	1847 (5.9)	78 (4.2)	36 (4.3)	9 (2.9)	33 (4.8)
Total deaths	31 201 (100.0)	1839 (100.0)	840 (100.0)	316 (100.0)	683 (100.0)

morbidities, impact on quality of life, and mortality risk (16). Our data demonstrate that the risk of pelvic fractures in pelvic cancer patients who are not treated with radiation is like women without pelvic cancer; the increased pelvic fracture risk is seen only in participants with pelvic cancer who receive pelvic irradiation. Given the importance of this clinical problem and the available pharmacologic interventions proven effective in fracture prevention in other clinical settings, a recent Cochrane Database of Systematic Reviews examined the evidence regarding interventions for the prevention of insufficiency fractures with pelvic radiotherapy (16). A literature search for randomized or nonrandomized studies with concurrent comparison groups addressing this issue revealed only 2 randomized trials evaluating zoledronic acid in men undergoing pelvic radiation for nonmetastatic prostate cancer and "provided no evidence on the primary outcomes of the review" (16). Our current findings of long-term risk of pelvic fracture and mortality following pelvic radiation further amplify the Cochrane authors' call for prospective clinical trials evaluating interventions to prevent radiation-related bone morbidity and pelvic insufficiency fractures (23). Given the dearth of controlled evidence regarding interventions to reduce insufficiency fracture risk, comprehensive survivorship care plans for cancer patients receiving pelvic radiation are limited beyond attention to and recognition of the problem. However, use of approaches successful for fracture prevention in other settings would be reasonable for consideration in clinical practice.

Study strengths include a large, well-characterized cohort of postmenopausal women with comprehensive fracture risk assessment and prospective long-term follow-up, a cancer-free comparison group, and a radiation therapy-free pelvic cancer comparison group. Serial National Death Index (NDI) linkage enhanced mortality findings, and information on fractures outside of the pelvic region, allowed for a comparative analysis in participants without incident pelvic cancer or without pelvic radiation to ensure that findings were related to pelvic cancer and/or pelvic radiation.

This study has limitations. First, although all hip fractures from 1993 to 2012 were adjudicated and all subsequent hip fractures were adjudicated in Black and Hispanic women and in the 27 347 hormone trial participants, not all pelvic fractures are adjudicated. Second, information on pelvic radiation is limited to a subset of participants. However, the pelvic fracture incidence is similar in those with known "no radiation" status compared with those with "unknown radiation" status, suggesting that participants who received radiation are captured while participants who were "unknown" did not receive radiation. Third, although the multivariable models adjust for cancer stage, a key predictive factor of overall mortality, the fraction of patients with unknown stage is much higher in the "unknown" radiation group (20%) than the "no radiation" (1.3%) and "radiation" (4.8%) (data not shown). This may account for the higher overall mortality risk in the "unknown" radiation group shown in Figure 1, D. Fourth, radiation therapy regimens are not available. Because current radiation therapy options include intensity-modulated radiation therapy, a technique associated with a lower pelvic fracture risk (8), this study's findings may be less applicable to contemporary pelvic cancer management, a common issue occurring with long-term cancer outcomes. Finally, the observational and nonrandomized nature of the WHI study design precludes causal inferences; potential unmeasured confounding factors may exist, and careful interpretation of results is warranted.

Overall, this study provides the longest follow-up of associations between pelvic cancer, pelvic radiation, and pelvic fracture risk. Women with pelvic cancer treated with pelvic radiation had a durable increased risk of pelvic fracture and death. Because advances in cancer therapy have enabled more women to survive a pelvic cancer diagnosis, there is an urgent need for clinical studies of fracture risk reduction interventions in survivors of these cancers.

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Data availability

Data are available through the WHI online resource, https://www.whi.org/datasets, while the WHI remains funded and indefinitely through BioLINCC, https://biolincc.nhlbi.nih.gov/studies/whi_ctos/.

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