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Risk of Pelvic Fractures in Older Women Following Pelvic Irradiation

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P ELVIC FRACTURES, INCLUDING hip fractures, are common in older people and are a major source of morbidity and mortality, particularly in women. The lifetime risk of a hip fracture after 50 years of age for white women is estimated at 17%.[1] Within the first year after a hip fracture, 10% to 20% more women die than expected for age.[2] In fact, in a Swedish study,[3] more than 1% of deaths from all causes in people aged 50 years or older were causally related to a hip fracture. The number of deaths due to hip fractures is comparable with the number of deaths due to pancreatic cancer and is only slightly lower than the number of deaths due to breast cancer.

It is well recognized that therapeutic radiation can result in bone damage and may increase fracture risks. However, the risks have not been well studied, particularly the risks with standard-course fractionation. The main evidence for the effect of irradiation on fracture risk comes from a long-term follow-up study of 2 European randomized trials (Stockholm I and II)[4,5] evaluating the effect of short-course irradiation in patients with operable rectal cancer.[6] In that follow-up study, patients who underwent short-course irradiation were twice as likely to be admitted to the hospital for hip frac-

For editorial comment see p 2635.

Context Pelvic fractures, including hip fractures, are a major source of morbidity and mortality in older women. Although therapeutic pelvic irradiation could increase the risk of such fractures, this effect has not been studied.

Objective To determine if women who undergo pelvic irradiation for pelvic malignancies (anal, cervical, or rectal cancers) have a higher rate of pelvic fracture than women with pelvic malignancies who do not undergo irradiation.

Design, Setting, and Participants We conducted a retrospective cohort study using Surveillance, Epidemiology, and End Results (SEER) cancer registry data linked to Medicare claims data. A total of 6428 women aged 65 years and older diagnosed with pelvic malignancies from 1986 through 1999 were included. We compared results for women who did (n = 2855) vs did not (n = 3573) undergo radiation therapy. To assess the influence of selection bias, we also evaluated the effect of irradiation on osteoporotic fractures in nonirradiated sites (arm and spine).

Main Outcome Measure We evaluated the effect of irradiation on the incidence of pelvic fractures over time, and adjusted for potential confounders using a proportional hazards model.

Results Women who underwent radiation therapy were more likely to have a pelvic fracture than women who did not undergo radiation therapy (cumulative 5-year fracture rate, 14.0% vs 7.5% in women with anal cancer, 8.2% vs 5.9% in women with cervical cancer, and 11.2% vs 8.7% in women with rectal cancer); the difference was statistically significant and most fractures (90%) were hip fractures. We controlled for potential confounders including age, race, cancer stage, and geographic location. The impact of irradiation varied by cancer site: treatment for anal cancer was associated with a higher risk of pelvic fractures (hazard ratio, 3.16; 95% confidence interval, 1.48-6.73); than for cervical cancer (hazard ratio, 1.66; 95% confidence interval, 1.06-2.59); or rectal cancer (hazard ratio, 1.65; 95% confidence interval, 1.33-2.05). No statistically significant difference was found in the rate of arm or spine fractures between the irradiated and nonirradiated groups (hazard ratio, 1.15; 95% confidence interval, 0.89-1.48).

Conclusions Pelvic irradiation substantially increases the risk of pelvic fractures in older women. Given the high baseline risk of pelvic fracture, this finding is of particular concern.

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tures than patients who did not undergo short-course irradiation. But short-course irradiation (with a high dose per fraction) is generally not used in the United States and many other centers. So, it is unclear whether fracture risk is increased by the standard (in the United States and many other locations) irradiation schedules with a lower dose per fraction, given over 5 to 6 weeks. However, because of the high baseline inci-

dence of fractures in older people and the significant morbidity and mortality associated with fractures, even a small increase in the fracture rate would be an important finding.

METHODS
Data
We used data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry that was linked to Medicare enrollment records and utilization data (SEER-Medicare). SEER, a population-based cancer registry sponsored by the National Cancer Institute, collects information on cancer incidence and survival from 11 population-based cancer registries; these 11 registries include incident cancers in about 14% of the US population.[7] The information collected by SEER includes patient characteristics, county of residence, primary tumor site, cancer stage, first course of treatment (through completion of the initial treatment plan, including treatment within the first year after diagnosis or until there is evidence either of disease progression or of treatment failure within the first year), timing of irradiation, and follow-up for vital status.[7]

Medicare provides comprehensive health care for about 98% of the US population aged 65 years or older. Cancer cases reported to SEER have been matched to the Medicare master enrollment file, to facilitate population-based health services research. Medicare eligibility has been identified for 94% of people aged 65 years or older identified by SEER.[8] For Medicare enrollees who do not participate in a managed care plan, claims data for hospitalizations, outpatient visits, and physician services are available through the Medicare Provider Analysis and Review file and the Outpatient Standard Analytic file. SEER-Medicare includes cancer cases reported to SEER from 1973 through 1999 and all Medicare claims for people diagnosed with cancer from 1991 through 2001. Hospitalization data (per the Medicare Provider Analysis and Review file) are available from 1986 through 2001. Be-

cause the majority of patients with pelvic fractures are admitted to hospitals, we were able to determine fracture rate since 1986. In the case of arm or spine fractures, where few patients are admitted to the hospital, we were able to determine the fracture rate since 1991 from the Outpatient Standard Analytic file.

Patients
Included in our study were women aged 65 years or older who were diagnosed with anal, cervical, or rectal cancer from January 1, 1986, through December 31, 1999. We selected these 3 types of cancer because they are relatively common and/or are frequently treated with pelvic irradiation. We limited our analysis to women, because as a group they have the highest baseline fracture risk. Included in our study were women with localized or regional staged cancers.

Excluded from our study were women with a previous cancer diagnosis and women who developed a second cancer; women with in situ, metastatic, or unstaged cancers; women whose cancer was diagnosed by autopsy or first cited on the death certificate; women whose irradiation status was unknown or who received only radioactive implants, radioisotopes, or other forms of irradiation besides conventional therapy; and women who were enrolled in a managed care organization any time after 1 month after cancer diagnosis (because Medicare files do not include insurance claims data on managed care enrollees).

Analysis
SEER routinely collects data on the first course of treatment, including radiation therapy. For our study, women who underwent external-beam irradiation alone or combined with radioactive implants or radioisotopes were defined as the irradiated group. The nonirradiated group was defined as women who were prescribed no radiation therapy or who refused such treatment.

Pelvic fractures were defined from the Medicare Provider Analysis and Re-

view data from 1986 through 2001 using the following *International Classification of Diseases, Ninth Edition* (*ICD-9*) codes[9]: 808 (fracture of pelvis), 805.6, 805.7, 806.6, 806.7 (fracture of sacrum and coccyx), and 820 (fracture of neck of femur).

Arm and spine fractures were defined from the Outpatient Standard Analytic data (as most arm and spine fractures did not require hospital admission) from 1991 through 2001 using the following *ICD-9* codes: 805.2 (fracture of thoracic spine, closed), 805.4 (fracture of lumbar spine, closed), 812 (fracture of humerus), 813 (fracture of radius or ulna), and 814 (fracture of carpal bones). We also reviewed the Medicare Provider Analysis and Review data for arm and spine fractures resulting in hospitalization using the same codes. Of note, if an arm or spine fracture occurred on the same date as a pelvic fracture, we did not include the arm or spine fracture in our analysis because it may have been the consequence of a fall due to the hip fracture; only 15 arm or spine fractures were excluded for this reason. Pathologic fractures of the pelvis, spine, or arm (*ICD-9* code 733.1) were also excluded.

Thus, pelvic fractures were identified through hospitalization data available since 1986, whereas arm and spine fractures were identified primarily through outpatient data, available only since 1991. So, in our multivariable models, we compared the pattern of pelvic fractures occurring from 1986 through 1990 with those occurring in or after 1991 and we found no difference attributable to year of diagnosis. We therefore included all years of available data in our analysis.

We compared demographic variables between the irradiated and nonirradiated groups using the χ^2 test for categorical variables and the *t* test for continuous variables. For each cancer site, we calculated Kaplan-Meier curves representing the time from cancer diagnosis to pelvic fracture. For arm and spine fractures, because the overall number of fractures was lower, we cal-

culated Kaplan-Meier curves from cancer diagnosis to fracture for the total cohort.

To control for potential confounders, we constructed a proportional hazards model to evaluate the relationship between irradiation and pelvic fracture for each cancer site, adjusting for age at cancer diagnosis and race, since osteoporosis risk is known to vary with age and race. Race was categorized as African American and non–African American using SEER race classification, which is assigned by medical record abstraction. We also tested for registry effects and for the effect of cancer stage at diagnosis. We tested the model for possible interaction effects between race and irradiation. We constructed a similar proportional hazards model for arm and spine fractures. Follow-up was calculated as the time between diagnosis and fracture. Censoring events included patient death, survival after 12 years of follow-up, and end of follow-up (December 31, 2001).

Because our study used preexisting data with no personal identifiers, the Human Subjects Committee of the University of Minnesota's Institutional Review Board determined that it was exempt from review. We (N.N.B., E.H.,

and B.A.V.) performed the statistical analysis using SAS statistical software version 8.2 (SAS Institute Inc, Cary, NC). All statistical tests were 2-sided and P values less than or equal to .05 were considered significant.

RESULTS

A total of 6428 women met our study's selection criteria. Patient characteristics are summarized in **TABLE 1**. Of these 6428 women, 556 were diagnosed with anal cancer; 1605 cervical cancer; and 4267 rectal cancer. In all, 2855 (44.4%) underwent radiation therapy (irradiated group) and 3573 (55.6%) did not (nonirradiated group).

The average age at diagnosis was 75.9 years. Women in the nonirradiated group were slightly older (average, 76.9 years) than women in the irradiated group (average, 74.5 years) ($P<.001$). Mean follow-up time for the entire cohort was 4.3 years. Mean follow-up time was greater for the nonirradiated group (4.6 years) than the irradiated group (3.9 years) ($P<.001$); this difference may be secondary to the more advanced stage of cancer found in women who underwent radiation therapy. Of the 6428 women in our study, 2449

(38.1%) cases were observed at least 5 years after their cancer diagnosis. Pelvic fractures developed in 554 (8.6%) women; of these 554 pelvic fractures, 499 (90.1%) were hip fractures. Arm or spine fractures developed in 253 (5.4% of the 4702 women evaluated for arm or spine fracture).

Because of differences in length of follow-up between patients in the irradiated and nonirradiated groups, it was essential to evaluate the rate of pelvic fracture over time taking censoring into account. The cumulative incidence of pelvic fractures was greater in the irradiated group than in the nonirradiated group for all 3 types of cancer diagnoses (**FIGURE 1**). Within the first 5 years of our study period, the incidence of pelvic fractures was as follows: of women with anal cancer, 14.0% in the irradiated group vs 7.5% in the nonirradiated group; of women with cervical cancer, 8.2% in the irradiated group vs 5.9% in the nonirradiated group; and of women with rectal cancer, 11.2% in the irradiated group vs 8.7% in the nonirradiated group. The incidence of arm or spine fractures was similar in both groups (**FIGURE 2**).

We used a proportional hazards model to evaluate the influence of ra-

Table 1. Patient Characteristics

	Overall		Anal Cancer		Cervical Cancer		Rectal Cancer	
	Nonirradiated Group	Irradiated Group	Nonirradiated Group	Irradiated Group	Nonirradiated Group	Irradiated Group	Nonirradiated Group	Irradiated Group
Total No. of patients	3573	2855	157	399	466	1139	2950	1317
Age, mean (SD), y	76.9 (7.6)*	74.5 (6.8)	78.4 (8.3)*	75.0 (7.0)	74.1 (7.9)	74.2 (6.9)	77.3 (7.4)*	74.7 (6.7)
Race, No. (%)† Non–African American	3302 (92)§	2588 (91)	145 (92)	379 (95)	394 (84.5)	960 (84)	2763 (94)	1249 (95)
African American	271 (8)	267 (9)	12 (8)	20 (5)	72 (15.5)	179 (16)	187 (6)	68 (5)
Stage, No. (%) Localized	2488 (70)*	950 (33)	89 (57)	229 (57)	325 (70)*	283 (25)	2074 (70)*	438 (33)
Regional	1085 (30)	1905 (67)	68 (43)	170 (43)	141 (30)	856 (75)	876 (30)	879 (67)
Follow-up, mean (SD), y	4.6 (3.8)*	3.9 (3.7)	3.6 (3.5)‡	4.5 (3.7)	4.6 (3.9)*	3.7 (3.9)	4.6 (3.8)*	3.9 (3.4)
Pelvic fracture, No. (%) Yes	294 (8)	260 (9)	8 (5)‡	55 (14)	25 (5)	83 (7)	261 (9)	122 (9)
No	3279 (92)	2595 (91)	149 (95)	344 (86)	441 (95)	1056 (93)	2689 (91)	1195 (91)
Arm/spine fracture, No. (%)‖ Yes	144 (6)	109 (5)	10 (9)§	13 (4)	13 (3)	34 (4)	121 (6)	62 (6)
No	2433 (94)	2016 (95)	99 (91)	302 (96)	404 (97)	818 (96)	1930 (94)	896 (94)

*$P<.001$, univariate comparison between pairs.
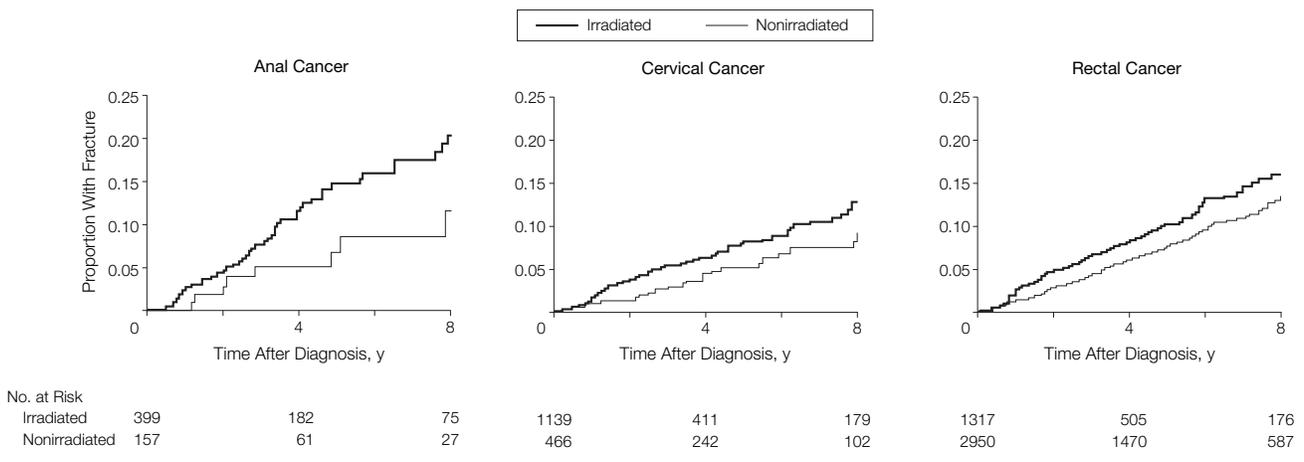†Unknown in 0.7% of patients.
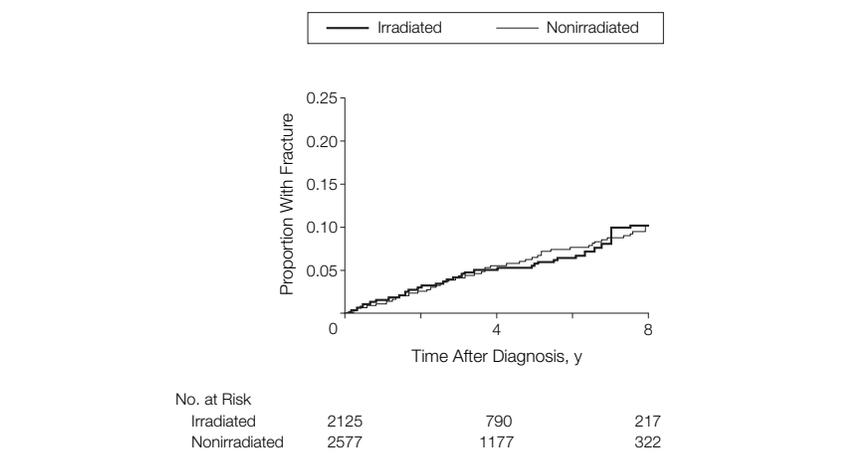‡$P<.01$, univariate comparison between pairs.
§$P<.05$, univariate comparison between pairs.
‖Occurrence of arm/spine fractures could not be determined for patients diagnosed from 1986 through 1990.

Figure 1. Time From Cancer Diagnosis to Pelvic Fracture by Treatment Group

No. at Risk

Irradiated	399	182	75	1139	411	179	1317	505	176
Nonirradiated	157	61	27	466	242	102	2950	1470	587

Figure 2. Total Cohort Time From Cancer Diagnosis to Arm or Spine Fracture by Treatment Group

No. at Risk

Irradiated	2125	790	217
Nonirradiated	2577	1177	322

diation therapy on the timing and incidence of pelvic fractures (**TABLE 2**). After controlling for other factors, we found that radiation therapy remained a statistically significant risk factor for development of pelvic fractures. When included in our initial analysis, registry and cancer stage at diagnosis did not contribute to the analysis, so were not included in our final model. The observed hazard ratio for radiation therapy in women with anal cancer was 3.16. This value can be interpreted as a 3-fold increase in pelvic fracture risk for women with anal cancer who underwent radiation therapy (vs women who did not) at any given time. The observed hazard ratio for radiation therapy in women with cervical cancer was 1.66; in women with rectal cancer, 1.65. These values indicate a lesser effect, but are still consistent with a substantial increase in fracture risk. In contrast, we found no association between pelvic irradiation and arm or spine fractures in our proportional hazards model (Table 2). African Americans had a lower fracture risk than non–African Americans. However, we found no statistical interaction between race and irradiation therapy in our models.

COMMENT

Our population-based, retrospective cohort study demonstrates that pelvic irradiation is associated with an increased risk of pelvic fractures in older women. The increased risk associated with anal cancer was substantial: women with anal cancer who underwent radiation therapy were more than 3 times more likely to develop a pelvic fracture at any point in follow-up, compared with women with anal cancer who did not undergo radiation therapy. The high risk of pelvic fracture after radiation therapy for anal cancer may reflect the radiation therapy technique used to treat this disease. In the treatment of anal cancer, it is usually appropriate to treat the inguinal nodes because of the risk of disease at this site. Because of the location of these nodes with respect to the femoral head and neck, it has been difficult to treat these nodes well without concomitant irradiation of the femur, and thus the femoral heads are exposed to a relatively high irradiation dose in the treatment of anal cancer patients.

For patients with rectal or cervical cancer, the inguinal nodes are not routinely treated as they are usually at very low risk of involvement with the

Table 2. Proportional Hazards Model Predicting Time to Fracture*

Fracture Risk	Irradiation Group			Race		
	Nonirradiated	Irradiated	*P* Value	African American	Non-African American	*P* Value
	Pelvic Fracture					
Anal cancer HR (95% CI)	1.00	3.16 (1.48-6.73)	.003	1.00	1.84 (0.25-13.66)	.55
Cervical cancer HR (95% CI)	1.00	1.66 (1.06-2.59)	.03	1.00	3.29 (1.44-7.50)	.005
Rectal cancer HR (95% CI)	1.00	1.65 (1.33-2.05)	<.001	1.00	1.73 (0.89-3.35)	.11
	Arm or Spine Fracture					
All cancers HR (95% CI)	1.00	1.15 (0.89-1.48)	.29	1.00	2.29 (1.12-4.62)	.02

Abbreviations: HR, hazard ratio; CI, confidence interval.
*Adjusted for age at diagnosis.

tumor(s). Thus, sparing of the bony structures in the treatment of these cancers can be accomplished much more easily. In addition, the standard irradiation-sensitizing chemotherapy given to patients with anal cancer differs from standard treatment in rectal and cervical cancers, and this potentially could increase the risk of pelvic fractures. Nevertheless, radiation therapy given for rectal and cervical cancer was also associated with a substantial increase in pelvic fractures.

Given the high baseline rate of fractures in women aged 65 years or older, the hazard ratio of 1.65 that we found in our study may represent an increased lifetime incidence of fractures from the baseline rate of 17% to 27%—a substantial and clinically significant absolute increase. We did not find an increase in osteoporotic fractures in nonirradiated sites, which indicates that the effect of radiation therapy on pelvic fractures is specific to the area treated and is not due to confounding from patient selection.

Pelvic fractures, particularly hip fractures, are common in older women and have a high mortality and substantial morbidity. After a hip fracture, about 50% of women who were able to walk before the fracture will no longer be able to do so independently.[10] About 50% of women who were living independently before the fracture will require long-term care; up to one third become completely dependent.[11] In 1995, the health care expenditures attribut-

able to osteoporotic fractures in the United States were estimated at almost $9 billion.[12] Clearly, pelvic fractures have a dramatic impact on the health and welfare of older women. Because the potential complications of pelvic fractures are so devastating, and because these fractures are common, even small increases in the fracture rate after pelvic irradiation have clinically important implications.

The bony structures of the pelvis and groin lie in close proximity to genitourinary pelvic organs, gastrointestinal pelvic organs, and the lymphatic drainage of these organs. Therefore, when traditional irradiation is used to treat anal, cervical, or rectal cancer, bony structures are also irradiated. It is well-recognized that therapeutic irradiation can result in bone damage. Bone changes after irradiation were first described by Ewing in 1926.[13] A variety of complications from irradiation delivered to the bones in the pelvis have been described, including fractures of the femur, pubic rami, and pubic symphysis; acetabular failure; and avascular necrosis.[14-16] The effects of irradiation on bone are not completely understood; however, damage appears to occur at the bone matrix and cellular level as well as at the vascular level.[17] Irradiation can kill osteoblasts, osteocytes, and osteoclasts, resulting in a reduction in bone matrix production. Reduction of the functional components of bone leads to atrophy and renders the bone more susceptible to fracture at weight-bearing

areas. In addition, irradiation damage to the vascular supply to the bone may lead to further bone loss.[18] Small-vessel damage induced by irradiation leads to microcirculation occlusion and further compromises osteoblastic function. Fractures after radiation therapy are more difficult to treat; hip replacements after radiation therapy have been associated with an increased risk of complications including infection and mechanical insufficiency.[19,20]

Despite the potential of bone injury from pelvic irradiation, the risks to bone have not been well studied. Case series have included relatively small numbers of patients. Even with small sample sizes, pelvic and/or hip fractures have been described after irradiation for cervical cancer,[16,21,22] uterine cancer,[16,23,24] anal cancer,[14,25] and rectal cancer.[6,26] Fractures have occurred as soon as 3 weeks after completion of irradiation.[26] Still, the relatively small numbers of patients in those studies make it difficult to estimate the true fracture rate. Also, few such studies have included a control group, so it is difficult to determine whether pelvic irradiation actually increases the fracture rate above baseline.

Until now, the long-term follow-up study of the Stockholm I[4] and Stockholm II trials[5] provided the most compelling evidence of an association between pelvic irradiation and fracture risk. The Stockholm trials were randomized studies evaluating the effect of short-course radiation therapy on op-

erable rectal cancer. In both trials, patients in the irradiation group received a total dose of 2500 cGy over 5 or 7 days. The Stockholm I trial used a 2-field (AP-PA) technique; the Stockholm II trial, a 4-field box technique (AP-PA, R/L laterals). The long-term follow-up study focused on the 1027 curatively treated patients in the 2 trials.[6] A total of 27 patients (5.3%) in their irradiated group and 13 patients (2.4%) in their nonirradiated group were hospitalized with a femoral neck or pelvic fracture during follow-up, a statistically significant doubling of the fracture risk. Short-course radiation therapy (with a high dose per fraction that may be associated with an increased fracture risk[27]) is not standard in many centers (including the United States) and is known to increase late toxicity in many tissues. In addition, short-course radiation therapy is generally used only for rectal cancer; thus the findings of this study were not widely generalized.

Any increase in late effects, such as the hip fracture risk in our study, must be put into the context of the benefit from irradiation. For example, the alternative to irradiation in women with anal cancer is an abdominoperineal resection with a permanent colostomy and probably a lower chance of cure. In women with locally advanced cervical cancer, there are no good treatment alternatives to primary irradiation (now routinely combined with chemotherapy). In women with rectal cancer, omission of irradiation would lead to an increased risk of local failure, an increased colostomy rate, and potentially decreased survival. However, the use of irradiation is increasing[28] and therefore it is essential that long-term risks are understood. Increasing our knowledge regarding the long-term consequences of irradiation will improve our ability to inform patients of the risks and benefits of treatment, may lead to changes in therapy that decrease the risk, and will prompt research evaluating potential preventive strategies and the benefits of early detection.

Our study has several limitations. First, information about the type and method of radiation therapy delivery was limited, with no available data on dosage or fields. Changes in radiation therapy delivery techniques over time may have affected risk. Today's more sophisticated approaches of conformal irradiation and intensity-modulated irradiation use smaller irradiation fields, and have the potential to reduce the irradiation dose to bone, particularly to the femoral neck and head. Further studies evaluating the effect of irradiation dosage, fields, and techniques on fracture risk are needed. Because our study relied on observational data, rather than on the results of a randomized trial, the potential for patient selection bias, although small, remains. Likewise, we had no information about risk factors for fracture other than age and race, although it is unlikely that such risk factors would have resulted in differential treatment selection. Therefore, it is unlikely that these limitations would have altered our final conclusion, namely that pelvic irradiation for anal, cervical, and rectal cancer in older women results in an increased risk of pelvic fractures over time. However, these findings should be confirmed using other data sources. In addition, as the pelvic fracture events were determined using data from hospitalizations, untreated pelvic insufficiency fractures, or those treated in the outpatient setting were not included in our evaluation. Such fractures may be a source of great morbidity to patients, and should be studied further.

It is important to note that our study population (older, predominantly white women) was already at high risk for pelvic fractures. Therefore, our results cannot be generalized to other populations (eg, men, younger age groups). The risk of pelvic fractures after irradiation in other populations should be the focus of future studies.

In conclusion, older women undergoing irradiation therapy for anal, cervical, or rectal cancer should be counseled with respect to fracture risks from irradiation. Potentially, these women could be targeted for preventive strategies, such as bone mineral densitometry screening, medical regimens aimed at preventing osteoporosis, and fall prevention. Such strategies should be evaluated in prospective studies. In addition, changes in irradiation techniques for high-risk individuals to minimize the irradiation dose received by bone should be investigated.

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>
> —Lord David Cecil (1902-1986)