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Cancer Mortality among Women Frequently Exposed to Radiographic Examinations for Spinal Disorders

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We studied cancer mortality in a cohort of 5,573 women with scoliosis and other spine disorders who were diagnosed between 1912 and 1965 and were exposed to frequent diagnostic X-ray procedures. Patients were identified from medical records in 14 orthopedic medical centers in the United States and followed for vital status and address through December 31, 2004, using publicly available regional, state and nationwide databases. Causes of death were obtained from death certificates or through linkage with the National Death Index (NDI). Statistical analyses included standardized mortality ratios (SMR = observed/expected) based on death rates for U.S. females and internal comparisons using Cox regression models with attained age as the time scale. Diagnostic radiation exposure was estimated from radiology files for over 137,000 procedures; estimated average cumulative radiation doses to the breast, lung, thyroid and bone marrow were 10.9, 4.1, 7.4 and 1.0 cGy, respectively. After a median follow-up period of 47 years, 1527 women died, including 355 from cancer. Cancer mortality was 8% higher than expected (95% CI = 0.97–1.20). Mortality from breast cancer was significantly elevated (SMR = 1.68; 95% CI: 1.38–2.02), whereas death rates from several other cancers were below expectation, in particular lung (SMR = 0.77), cervical (SMR = 0.31), and liver (SMR = 0.17). The excess relative risk (ERR) for breast cancer mortality increased significantly with 10-year lagged radiation dose to the breast (ERR/Gy = 3.9; 95% CI: 1.0–9.3).

INTRODUCTION

Patients with abnormal spinal curvature undergo frequent diagnostic examinations to quantify the magnitude of the curvature and to monitor disease progression. Among the most common spinal disorders is adolescent idiopathic scoliosis (*1*). We studied a cohort of patients with scoliosis and other spine disorders diagnosed between 1912 and 1965. Typically, these conditions are diagnosed in childhood or early adolescence and are monitored closely through the growth spurt. These patients received ionizing radiation exposure before age 20 years, which is a sensitive period for radiation carcinogenesis for the thyroid gland and breast (*2–4*). The estimated median value for cumulative breast dose is of the order of 10–15 cGy in this cohort (*5, 6*), which represents an intermediate exposure between modern diagnostic examinations and that associated with radiotherapy for malignant disease (*4*).We have reported earlier on breast cancer mortality related to spinal disease characteristics and diagnostic radiation (*5*) and on a detailed analysis of the association between breast cancer incidence and radiation exposure as well as on potential modifiers of that association in this cohort (*6*). The current report describes the spectrum of cancer mortality after an average follow-up of 47 years, 8 years longer than in the earlier report (*5*). The present report also evaluates risks for all cancers and assesses potential confounding. Noncancer mortality will be covered in detail in a separate report (Ronckers *et al.*, in preparation).

METHODS

Population and Radiation Exposure

Detailed study procedures have been reported previously (*5*) and are summarized briefly below. Guidelines were followed for the protection of human subjects as set forth by the U.S. National Institutes of Health. The U.S. Scoliosis Cohort Study includes 5,573 female patients who had a confirmed diagnosis of scoliosis, kyphosis,

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lordosis or kyphoscoliosis before 20 years of age in one of 14 orthopedic medical centers in the United States during 1912–1965. Details on personal characteristics and scoliosis diagnosis and treatment were collected from medical records. Data on radiographic examinations were abstracted from several sources, including radiology reports, radiographs, radiograph jackets and radiology log books, and included date, field (e.g. thoracic, lumbar), view (anteroposterior, posteroanterior, lateral), position (e.g. standing, supine), presence of an orthosis (cast, brace or surgical implant), radiograph size, whether the breast was in the radiograph beam, and radiograph machine parameters (*5*). Cumulative radiation doses to the breast, thyroid gland, lung, ovary and bone marrow were estimated for every individual in the study based on her age at examination (<13, ≥ 13), the calendar period at examination (1920–1939, 1940–1959, 1960–1975, 1976–1980), and the characteristics noted above that were recorded for each of the 137,711 radiographs identified.

Tracing and Follow-up

In an earlier phase of the study (*6*), telephone tracers used one-on-one tracing methods to contact patients, spouses and parents, and Social Security numbers were obtained for 94.5% of the cohort. Local, state and national databases were used to obtain vital status and addresses as of January 1, 1993. At that time, 19% of cohort members were lost to follow-up and 16% were deceased. In 1993, a questionnaire survey was administered to the remaining 3620 patients, partly by mail and partly by telephone interview. In all, 3121 women (86%) participated in the survey. Mortality follow-up in this report extends to December 31, 2004, with causes of death obtained from death certificates or through linkage with the National Death Index (NDI). All causes of death were coded to the 9th revision of the International Classification of Diseases (*7*).

Statistical Methods

The main analysis includes the entire cohort of scoliosis patients, except for 60 women with unknown vital status dates, for a total of 5513 women. Dose-specific analyses additionally excluded one patient with incomplete dose information. Woman-years of follow-up accrued from the date of scoliosis diagnosis to the earliest of date of death, date last known alive for those lost to follow-up, or end of study follow-up (December 31, 2004). We also analyzed the risk of dying from cancer in the subcohort of 3121 women who participated in the 1993 questionnaire survey to allow for adjustment for known cancer risk factors. For those analyses, woman-years of follow-up started at the date of questionnaire completion and ended as described above.

The mortality rates of the patients with scoliosis were compared with those of females in the United States (*8*). Numbers of expected deaths, by cause, were calculated by multiplying age- and calendar year-specific woman-years at risk (in 5-year intervals) by the corresponding mortality rates in the general population. Standardized mortality ratios (SMRs) represent the ratio of observed (O) to expected (E) number of deaths. The excess absolute risks (EAR) per 10,000 woman-years (EAR/10,000) is (O – E)*(10,000/total observed number of woman-years). Breast doses were lagged 10 years before cancer diagnosis for cases and study exit for non-cases to allow for latency. Cox proportional hazards models with age as the time scale were used for internal comparisons in the cohort using the PHREG procedure in SAS. Excess relative risks per gray (ERR/Gy) were derived from PEANUTS (Epicure) Cox proportional hazards models that were stratified on birth cohort in 5-year intervals and included dose as a linear term and covariates as log-linear terms. Trend tests were based on the slope estimate of the underlying continuous variable; parentheses indicate a negative slope estimate.

RESULTS

The average (mean) age at scoliosis diagnosis in the analytic cohort of 5513 women was 10.6 years, and the average age at end of follow-up was 58 years (Table 1). After a median follow-up of 47 years, a total of 257,915 woman-years of follow-up accrued. There were 1527 (28%) deaths, 3614 (66%) women were known to be alive on December 31, 2004, and only 372 (7%) were lost to follow-up through December 31, 2004. The average number of radiographs per patient with any exposure to the breast was 22.9, and the range extended from 0 to 553. The estimated mean cumulative breast dose was 10.9 cGy, with a maximum of 1.7 Gy, whereas the average and maximum lung doses were 4.1 and 67.6 cGy, respectively. The average and maximum doses to the active bone marrow were 1.0 cGy and 16 cGy, respectively, and those to the thyroid gland were 7.4 cGy and 1.37 Gy. Survey participants were slightly older at the end of follow-up compared to the entire cohort and had higher average and median radiation doses to organs of interest (Table 1).

Table 2 shows the overall and cancer-specific observed numbers of deaths and the SMRs. In the entire cohort, there was a statistically significant 46% higher overall mortality risk compared to the general population (95% CI: 1.39–1.54). The excess absolute risk (EAR) was 18.8 excess deaths per 10,000 woman-years of observation (95% CI: 15.8–21.8). Cancer was listed as the primary cause for 23% of all deaths ($N = 355$) and the overall cancer SMR (1.08) was slightly but not statistically significantly elevated. Breast cancer was the most common cancer listed ($N = 112$), followed by cancers of the lung ($N = 57$), colon ($N = 26$), and ovary ($N = 21$). Several cancer-specific SMR estimates were close to unity. A statistically significant elevated risk was observed only for breast cancer (SMR = 1.68; 95% CI: 1.38–2.02); the risk of dying from all cancers other than breast cancer was nonsignificantly lower than expected, based on 243 observed cases (SMR = 0.93; 95% CI: 0.82–1.05). The EAR for breast cancer was 1.8 excess deaths per 10,000 woman-years of observation (95% CI: 1.0–2.6), whereas the EAR for lung cancer was −0.6 excess deaths per 10,000 woman-years (95% CI: −1.2–0.0).

Mortality risks were below expectation for cancers known to occur in excess among smokers, i.e., lung (SMR = 0.77; 95% CI: 0.57–1.00), liver (SMR = 0.17; 95% CI: 0.00–0.94), and uterine cervix (SMR = 0.31; 95% CI: 0.06–0.92) cancers. In addition, risks were reduced for some other smoking-related cancers (stomach and kidney) though not all (oral cavity, esophageal, pancreatic, bladder) (*9*). Other malignancies known to occur after radiation exposure at relatively low doses include thyroid cancer and leukemia. No thyroid cancer deaths were observed (0.8 expected; 95% CI: 0.00–4.58),

TABLE 1
Descriptive Characteristics of Female Spinal Curvature Patients Diagnosed in Any of 14 U.S. Orthopedic Medical Centers during 1912–1965 and Followed for Mortality through 2004, U.S. Scoliosis Cohort Study

Characteristic	Full cohort (N = 5513)[a]				Survey participants (N = 3121)[b]			
	No.	Mean	Median	Range	No.	Mean	Median	Range
All women								
Age at scoliosis diagnosis (years)	5513	10.6	11.3	0.0–19.9	3121	11.0	11.8	0.0–19.9
Follow-up (years)	5513	46.9	46.5	0.0–91.5	3121	50.8	47.3	29.3–87.4
Age at end of follow-up (years)	5513	58.0	58.3	2.1–96.5	3121	62.6	59.4	39.9–92.4
Number of years during which breast-exposed radiographs were taken (years)	5512	4.0	3.0	0.0–37.0	3121	4.6	4.0	0.0–37.0
Number of breast-exposed radiographs	5512	22.9	14.0	0.0–583.0	3121	27.7	22.0	0.0–413.0
Cumulative breast dose (cGy)	5512	10.9	7.3	0.0–170.3	3121	12.4	9.4	0.0–111.1
Cumulative lung dose (cGy)	5475	4.1	2.8	0.0–67.6	3101	4.7	3.6	0.0–44.7
Cumulative ovary dose (cGy)	5475	2.7	1.8	0.0–33.7	3101	3.0	2.3	0.0–23.5
Cumulative bone marrow dose (cGy)	5475	1.0	0.7	0.0–16.1	3101	1.1	0.9	0.0–11.0
Breast radiation-exposed women[c]								
Number of breast-exposed radiographs	4852	26.0	18.0	1.0–583.0	2876	30.0	24.0	1.0–413
Cumulative breast dose (cGy)	4852	12.4	8.9	0.0–170.3	2876	13.4	10.5	0.0–111.1
Cumulative lung dose (cGy)	4814	4.7	3.5	0.0–67.6	2856	5.1	4.1	0.0–44.7

[a] Excluded from analysis were 60 women for whom tracing efforts failed to render any information about vital status beyond the date of diagnosis of scoliosis, and only for analyses including radiation dose, one additional woman with missing doses.
[b] Based on a health survey conducted during 1992–1993 among 3620 known living patients, of whom 3121 (86%) participated and provided information about cancer incidence and selected cancer risk factors.
[c] Excluding 660 women in the full cohort (245 survey participants) who had no documented radiographic examinations with exposure to the breast at any of the index facilities.

whereas for leukemia, mortality was slightly lower than expected (SMR = 0.87; 95% CI: 0.42–1.60; 10 deaths).

Table 3 shows the distribution of scoliosis characteristics in the cohort and the risk of dying from breast cancer. Breast cancer risk did not vary significantly by age at curvature diagnosis, type of curvature, etiology, maximum curve magnitude, or number of spinal surgeries. However, risk of dying from breast cancer was strongly associated with the number of X rays involving breast exposure. Compared with women who had 24 or fewer X rays (including 660 women who had no documented breast exposures to X rays), those who had 25–49, or those who had 50 or more were at 1.4- and 2.7-fold risk, respectively, with a borderline significantly increased risk with increasing number of X rays (P trend = 0.05). Table 4 shows results by estimated radiation dose to the breast. The risk of dying from breast cancer was increased significantly for women exposed to 20–29 cGy or 30 or more cGy (1.9- and 2.4-fold, respectively) compared to women who had 0–9 cGy breast exposure, for a highly significant dose response (P trend = 0.001). Using breast dose as a continuous linear variable, the excess relative risk per gray (ERR/Gy) was 4.0 (95% CI: 1.0–9.4).

Similar analyses were conducted for lung cancer. Lung cancer risk varied slightly by scoliosis diagnosis and treatment characteristics, although none of the estimates were statistically significant (Table 3). There was no apparent association with the number of breast-exposed examinations (Table 3), nor was there one with category of estimated lung dose. Compared to subjects whose lungs were on average exposed to <1 cGy, women with doses of 1–4, 5–9 and 10 or more cGy had relative risks of 0.7, 0.3 and 0.5, respectively, with a nonsignificant dose response (P trend = 0.16). The estimated doses to the lungs are less than half the estimated doses to the breasts (Table 1).

Because breast and lung cancer have several established strong risk factors, we then limited the analysis to the 3121 subjects who responded to the health questionnaire survey, in which information on other risk factors (e.g. reproductive history, family history of breast cancer, cigarette smoking) were captured. In all, 443 questionnaire participants died between 1993 and 2004, including 30 from breast cancer and 17 from lung cancer. In the questionnaire subcohort, breast cancer mortality varied by scoliosis characteristics in a manner similar to that reported for the total cohort. After adjustment for breast cancer risk factors, the patterns in risk by number of radiographs involving breast exposure and by estimated breast dose were also similar to those observed for the entire cohort (Table 4). Risk for lung cancer was strongly associated with cigarette smoking and alcohol use but not with scoliosis characteristics or with category of estimated lung dose. There was no evidence of an age-adjusted radiation dose response for lung cancer (ERR = −1.4; 95% CI: −7.1–3.1).

We compared smoking prevalence data among scoliosis patients without a history of breast cancer with that among 11,281 female participants of the 1987

TABLE 2
Observed Deaths through 2004 from All Causes and Malignant Neoplasms among 5513 Female Spinal Curvature Patients, Standardized Mortality Ratios, 95% Confidence Intervals, U.S. Scoliosis Cohort Study

Cause of death (ICD-9th revision)	O[a]	SMR[a]	95% CI
All causes[b]	1527	1.46[c]	1.39–1.54
All malignant neoplasms	355	1.08	0.97–1.20
Oral cavity (140–149)	7	1.93	0.77–3.98
Esophagus (150)	4	1.42	0.38–3.63
Stomach (151)	2	0.35	0.04–1.25
Colon (153, 1590)	26	0.99	0.65–1.45
Rectum (1540–1542; 1544–1549)	3	0.66	0.13–1.93
Liver (1550–1551; 1553–1569)	1	0.17[c]	0.00–0.94
Pancreas (1570–1579)	17	1.17	0.68–1.87
Lung (162)	57	0.77	0.59–1.00
Bone (170)	2	1.91	0.21–6.90
Melanoma of skin (172)	6	1.29	0.47–2.81
Connective and soft tissue (171)	2	0.87	0.10–3.12
Breast (174)	112	1.68[c]	1.38–2.02
Uterine cervix[e] (180)	3	0.31[c]	0.06–0.92
Uterine corpus[e] (179, 181–182)	8	1.02	0.44–2.00
Ovary[e] (183)	21	0.99	0.61–1.52
Kidney (189, 1887)	3	0.55	0.11–1.62
Bladder (1880–1886; 1888–1889)	4	1.34	0.36–3.42
Eye[e] (190)	0	0.00	0.00–19.31
Brain and CNS (191–192)	14	1.48	0.81–2.48
Thyroid[e] (193)	0	0.00	0.00–4.58
All lymphoid malignancies (200–204; 2384)	14	0.66	0.36–1.10
Hodgkin disease (201)	2	0.91	0.10–3.29
Non-Hodgkin lymphoma (200; 202)	7	0.59	0.24–1.22
Multiple myeloma (2030, 2386)	4	0.84	0.23–2.16
Leukemia and aleukemia (204–208; 2024, 2031)	10	0.87	0.42–1.60
CLL[d] (2041)	1	0.70	0.01–3.90
Non-CLL (2040, 2042–2089; 2024, 2031)	9	0.88	0.40–1.67

[a] Observed number of deaths (O). Standardized mortality ratio (SMR) equals the number of observed deaths (O) divided by the number of expected deaths based on U.S. population rates from 1925–2002. Follow-up time accrued before 1925 was excluded.
[b] There were six women with an unknown cause of death who contributed to the SMR for "all causes" but did not contribute to any cause-specific category.
[c] $P < 0.05$.
[d] Chronic lymphocytic leukemia.
[e] Mortality rates for periods before 1950 were analyzed using 1950–1954 rates for this category.

National Health Interview Survey (NHIS)[2] who were interviewed at 19–73 years of age and who were without a history of breast cancer. The proportion of ever smokers (defined as having smoked 100 or more cigarettes in lifetime) was 44% among scoliosis patients and 47% in the NIHS cohort. Among the ever smokers, the proportion of heavy smokers (≥40 pack-years) was identical in the two groups at 12%.

DISCUSSION

Women diagnosed with scoliosis between 1912 and 1965 are at higher risk of dying from breast cancer later in life than the general female population of the United States, whereas collective mortality from cancers other than breast cancer is slightly lower than expected. As in previous reports (*5, 6*), a clear dose–response relationship was observed between estimated breast radiation dose from frequent X rays and subsequent breast cancer risk. The ERR/Gy of 4.0 (95% CI 1.0–9.4) is compatible with results from other studies, as was summarized extensively (*4*) and discussed previously (*6*).

Severe scoliosis is associated with compression of organs, depending upon the affected spinal area, for example the uterus and the respiratory tract. Therefore, it is conceivable that the distribution of this cohort across categories of cancer risk factors is not entirely comparable to the general U.S. population. For example, we reported previously that women in this cohort are more likely to be nulliparous and that the parous women were slightly older at first birth than a random sample of the U.S. population (*6*), which would increase their background rate of incident breast cancer. In addition, women in this cohort experienced a total mortality rate approximately 50% higher than women in the general population. Preliminary analyses indicate

[2] Information about the National Health Interview Survey (NHIS) is available at http://www.cdc.gov/nchs/nhis.htm. The 1987 data sets and documentation are at http://www.cdc.gov/nchs/nhis/quest_data_related_1996_prior.htm#1987_NHIS.

TABLE 3
Breast and Lung Cancer Mortality Risks among 5512 Female Spinal Curvature Patients Followed through 2004, According to Spinal Curvature History, U.S. Scoliosis Cohort Study

Characteristic	Breast cancer			Lung cancer		
	No. of deaths	RR[a]	95% CI	No. of deaths	RR[a]	95% CI
Age at diagnosis of curvature, years						
≥10 (adolescent) (ref)	77	1.0	—	2	1.0	—
3.1–9.9 (juvenile)	31	0.7	0.4–1.0	32	1.5	0.9–2.9
≤3 (infantile)	4	1.0	0.4–2.8	23	1.6	0.7–3.3
P trend[b]		*(0.84)*			*(0.31)*	
Type of curvature						
Scoliosis (ref)	106	1.0	—	50	1.0	—
Lordosis	1	0.4	0.1–3.3	2	1.3	0.3–5.4
Kyphosis	4	0.9	0.3–2.5	5	1.4	0.5–3.6
Kyphoscoliosis	1	0.8	0.1–5.9	0	–	
Etiology						
Idiopathic (ref)	42	1.0	—	13	1.0	—
Neuromuscular	37	1.7	1.1–2.8	15	1.5	0.7–3.3
Congenital	3	1.4	0.4–4.7	0	–	–
Other	20	1.1	0.6–2.1	27	2.0	0.9–4.5
Maximum curve magnitude, degrees						
<45 (ref)	18	1.0	—	6	1.0	—
45–59	13	1.1	0.5–2.2	2	0.6	0.1–3.1
≥60	14	0.8	0.4–1.6	4	0.9	0.2–3.4
P trend		*(0.42)*			*(0.64)*	
Number of spinal surgeries						
0 (ref)	60	1.0	—	40	1.0	—
1	24	1.0	0.6–1.7	12	1.5	0.7–3.1
2	16	0.8	0.4–1.6	3	0.6	0.2–2.3
≥3	12	0.8	0.4–1.8	2	0.7	0.1–3.4
P trend		*(0.41)*			*(0.49)*	
Number of breast-exposed examinations						
<25 (ref)	74	1.0	—	50	1.0	—
25–49	20	1.4	0.7–2.5	4	0.6	0.9–2.1
≥50	18	2.7	1.3–5.5	3	1.1	0.3–4.8
P trend		*0.05*			*(0.68)*	

[a] Relative risks for each tumor site were estimated from a single Cox proportional hazards multiple regression model that used attained age as the time scale, was stratified on birth cohort in 5-year intervals to allow for secular changes in breast and lung cancer incidence and included all variables shown in this table.

[b] Trend tests were based on the slope estimate of the underlying continuous variable; parentheses indicate a negative slope estimate.

that many different causes of death contribute to this finding. A full examination of the patterns of mortality and the contributing underlying factors is beyond the scope of this work on radiation and cancer mortality and will be reported separately.

We found no evidence of excess lung cancer mortality associated with radiation exposure. In the latest lung cancer incidence data from the atomic bomb survivors, excess incidence of the order of 2% was shown for the dose categories below 10 cGy (*10*), i.e., the dose range that covers 90% of the scoliosis patients and all but three of the lung cancer deaths in our study. Our finding of no dose response in the low-dose region is not statistically incompatible with the data from the atomic bomb survivors. Since only about 70 deaths from lung cancer were expected among scoliosis patients, the statistical power to detect such a small excess in this cohort was low. Our results are consistent with findings in two studies of lung cancer mortality associated with highly fractionated radiation doses from multiple fluoroscopy examinations during pneumothorax treatment for tuberculosis (*11, 12*). In those studies, cumulative breast dose was associated with increased breast cancer risks comparable to those observed among A-bomb survivors exposed to acute radiation doses of similar magnitude, whereas evidence for increased lung cancer risk, which was strong for the A-bomb survivors, was essentially lacking for the tuberculosis patients. Possible explanations include a low-dose threshold or nonlinear radiation dose response for lung cancer or failure to control for the carcinogenic effects of smoking.

Lung cancer mortality in this cohort was 77% of the rate expected among women of similar age in the U.S. population. If women with scoliosis tended to smoke less

TABLE 4
Breast Cancer Radiation Dose Response among Women with Spinal Curvature, U.S. Scoliosis Cohort Study

	Full cohort ($N = 5512$)[a]					
	Breast cancer deaths		Comparison subjects			
Cumulative breast dose (cGy)[e]	No.	%	No.	%	RR[c]	95% CI
0–9	63	56.3	3325	61.6	1.0	–
10–19	23	20.5	1216	22.5	1.2	0.7–2.0
20–29	14	12.5	526	9.7	1.9	1.0–3.5
≥30	12	10.7	333	6.2	2.4	1.2–4.8
P trend[f]					*0.001*	
Linear dose response					ERR/Gy	95% CI[h]
Continuous dose	112	100.0	5400	100.0	3.9	1.0–9.3

[a] Excluded from analysis were 60 women for whom tracing efforts failed to render any information about vital status beyond the date of diagnosis of scoliosis, and one woman with missing doses.

[b] Based on a health survey conducted during 1992–1993 among 3620 known living patients, of whom 3121 (86%) participated and provided information about cancer incidence and selected cancer risk factors.

[c] Relative risks were estimated from PHREG (SAS) Cox proportional hazards regression models that used age as the time scale were stratified on birth cohort in 5-year intervals to allow for secular changes in cancer incidence and included the exposure factor (number of breast exposed X rays or cumulative breast radiation dose) plus age at spinal curvature diagnosis (≤3, 3.1–9.9, ≥10 [ref]) and etiology (idiopathic [ref], neuromuscular, congenital, other, unknown).

[d] Relative risks were estimated from a single Cox proportional hazards multiple regression model as described in footnote *c* above but also included number of live births (0 [ref], 1, 2, ≥3, unknown), age at first live birth (<25 [ref], 25–29, ≥30, unknown), age at menopause (≥50 [ref], 45–49, 40–44, <40, unknown, premenopause), and family history of breast cancer (no [ref], yes, unknown). Number of live births, age at first live birth, and age at menopause were included as time-dependent variables.

[e] Breast doses were lagged 10 years before cancer diagnosis for cases and study exit for non-cases to allow for latency.

[f] Trend tests were based on the slope estimate of the underlying continuous variables.

[g] ERR/Gy = excess relative risk per gray. ERRs derived from PEANUTS (Epicure) Cox proportional hazards models that used age as the time scale were stratified on birth cohort in 5-year intervals, and included dose as a linear term and covariates as log-linear terms. The full cohort model did not include covariates since since addition of scoliosis etiology, age at spinal curvature diagnosis, or amount of spinal curvature did not lead to significant improvement of the model fit ($P > 0.10$ in all three models) nor did such additions materially alter the estimate of the ERR/Gy (change <10%). The model for survey participants was adjusted for age at scoliosis diagnosis and three survey-based variables, i.e., number of live births, age at menopause, and any family history of breast cancer.

[h] Maximum likelihood bounds.

than their age-matched peers in the general population, then a reduced risk would have been expected given that smoking is the strongest risk factor for lung cancer. However, the rate of ever smoking was only slightly lower among the scoliosis questionnaire participants (44%) than among women who participated in the 1987 National Health Interview Survey (47%). Among smokers, the proportion of heavy smokers was identical in the two cohorts. Then again, smoking data were available only for women who had survived at least until the early 1990s. It is quite possible that questionnaire responders represent a relatively healthy subgroup of the entire scoliosis cohort. The mortality analysis concerns the entire cohort, which is almost twice as large, and likely covers a higher proportion of women with severe thoracic curves, who are known to be at increased risk for premature death and for respiratory problems (*1*) and, as a result, may have smoked less than the general population. Therefore, a role of decreased smoking prevalence in the low overall rate of lung cancer deaths cannot be discarded entirely, although we did not find a consistent pattern of decreased risks for mortality from other smoking-related cancers. Within the cohort, smoking is a strong risk factor for lung cancer, because all 17 women who died from lung cancer after participating in the 1993 questionnaire survey were smokers.

Thyroid cancer is known to occur after exposure to relatively low doses in childhood, i.e., of the order of 10–20 cGy (*3*). In our study, the average thyroid dose was 7.5 cGy, but no deaths from thyroid cancer were observed, which was in line with expectation (0.80 deaths expected) given the excellent survival rates for this disease. In all, 10 deaths from leukemia were observed, which was slightly below expectation. The small number of deaths and the low average dose to the active bone marrow (1 cGy) did not allow for detailed analyses by radiation dose.

The strongly decreased risk of cervical cancer is remarkable. Because the expected number of cases was only 10, this may be a chance finding. On the other hand, the main risk factor for cervical cancer is HPV infection, which is known to be a sexually transmitted virus. In a small Swedish study (*13*), scoliosis patients reported twice the rate of sexual dysfunction compared to control subjects (33% compared to 15%). Therefore, it is possible that women with severe scoliosis have fewer

TABLE 4
Extended

Survey participants ($N = 3121$)[b]					
Breast cancer deaths		Comparison subjects			
No.	%	No.	%	RR[d]	95% CI
14	46.7	1620	52.4	1.0	–
6	20.0	877	28.4	0.9	0.3–2.4
5	16.7	353	11.4	1.6	0.5–4.8
5	16.7	241	7.8	1.9	0.6–6.1
				0.01	
				ERR/Gy[g]	95% CI[h]
30	100.0	3091	100.0	4.5	0.03–20.4

sexual partners and thereby a lower probability of contracting an HPV infection. As with lung cancer, a role of decreased smoking prevalence in the entire cohort cannot be excluded since cervical cancer rates are known to be positively associated with smoking (*9*).

Strengths of our study include (a) high completeness of follow-up for vital status, despite the fact that initial potential for follow-up depended upon availability of maiden names and address information at age 19 years or less; (b) near complete ascertainment of cause of death among those known to be deceased (99.6%); (c) good radiation dosimetry based on abstracted information from nearly 140,000 radiographs; (d) availability of information on cancer risk factors other than radiation exposure; and (e) an intermediate level of radiation exposure compared to low-dose occupational/environmental studies (*14*) and those based on populations exposed to high doses from radiotherapy (*15*), which are relevant for diagnostic exposures from new techniques used in medicine in general (*16*).

By relying on cancer mortality, it was not feasible to study cancers with low lethality, such as thyroid cancer. It is theoretically possible that patients with severe scoliosis are less able than their female counterparts in other segments of the general population to deal with aggressive treatments for cancer and have worse survival rates. If so, this could inflate their cancer-specific mortality rates, without a true increase in incidence or a true causal effect of scoliosis, radiation or other underlying disorder (e.g., polio). Such an effect is unlikely to be strong because there is an established increased risk of new breast cancer diagnoses in this population, including a radiation dose response. Also, overall cancer mortality, excluding breast cancer, was slightly below expectation in this cohort. While general mortality rates for most cancers were not available until 1925, and for a few cancers (cervix, corpus, eye, and thyroid) until 1950, and rates were extrapolated backwards for the interim period in the current analysis, exclusion of person-time before 1950 did not appreciably alter any of the SMRs.

When interpreting the results of this study for patients with scoliosis in current times, it should be kept in mind that radiation doses from diagnostic radiographs have decreased substantially in the past century as technology and procedures have changed (*5*). The clinical community has also altered the frequency of radiographic monitoring as well as the selection criteria for intensive monitoring (*17*), so that individual breast radiation doses are very low for most patients.

In conclusion, women who were diagnosed with scoliosis before 1965 have increased risk of breast cancer, clearly related to radiation exposure from diagnostic radiographs during the period 1920–1980, when doses were much higher than they are today. Mortality rates from cancers other than breast cancer were lower than expected.

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