# Multiple Diagnostic X-rays for Spine Deformities and Risk of Breast Cancer

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## Abstract

Background: **Ionizing radiation is a well-established human mammary carcinogen. Women historically monitored by radiography at young ages for abnormal spinal curvature are an exposed population suitable for investigating radiation-related risk and its variation by modifying factors. In this historic cohort, 95% of daily dose increments (when exposure to the breast occurred) were under 2.4 cGy, with mean 1.1 cGy.**

Methods: **A retrospective cohort of 3,010 women, diagnosed with spinal curvature between 1912 and 1965 in 14 U.S. pediatric orthopedic centers and who completed a questionnaire by telephone interview or mail survey in 1992, were studied for risk of breast cancer by radiation dose to the breast (mean, 12 cGy) after adjustment for established breast cancer risk factors.**

Results: **A borderline-significant radiation dose response (excess relative risk/Gy = 2.86; $P$ = 0.058; one-tailed $P$ = 0.029) was observed during 118,905 woman-years of follow-up (median, 35.5 years) based on 78 cases of invasive breast cancer. The dose response was significantly greater ($P$ = 0.03) for women who reported a family history of breast cancer in first- or second-degree relatives (excess relative risk/Gy = 8.37; 95% confidence interval, 1.50-28.16). Radiation-related risk did not vary significantly by stage of reproductive development at exposure.**

Conclusions: **Assuming that repair of radiation-related DNA damage requires at most a few hours, our data argue against existence of a low-dose threshold on the order of 1 to 3 cGy for radiation exposure contributing to breast carcinogenesis. The possibility that a family history of breast cancer may have enhanced a carcinogenic radiation effect requires confirmation in other studies.** (Cancer Epidemiol Biomarkers Prev 2008;17(3):605–13)

## Introduction

Ionizing radiation is an established mammary carcinogen (1-3) and when exposure occurs at young ages in particular (2). Whereas radiation exposure to the breast from diagnostic X-rays has, for the most part, been dramatically reduced over time, the introduction of new technologies (such as computed tomographic scans) that impart higher doses to pediatric and other patients raises new concerns (4). Radiation-related risk of female breast cancer may be influenced by established breast cancer risk factors, such as reproductive history and genetic predisposition, but findings thus far have been conflicting (5-11). A downward gradient in radiation-related risk with increasing exposure age (1) has been variously ascribed to a combination of biological factors, including the undifferentiated sensitive stage of breast tissue cells until puberty, the strongly increased proliferative activity during puberty, and complex hormonal influences during the course of a woman's life (12-15).

We studied a unique population of women whose spinal curvature was monitored by frequent X-ray examinations during childhood and adolescence. Our purposes were to quantify the radiation dose-response relationship for fractionated exposures at a vulnerable age, assess whether known breast cancer risk factors modify dose response, and explore possible developmental intervals of increased radiation sensitivity.

## Materials and Methods

The study population and detailed methods have been described elsewhere (3) and are briefly summarized below.

**Study Population.** We used data from the U.S. Scoliosis Cohort Study. The cohort, comprising 5,573 female scoliosis patients diagnosed between 1912 and 1965 in 1 of 14 large pediatric orthopedic centers in the United States, has been followed for cancer mortality previously (3).

**Personal and Medical Data.** Personal characteristics and information on scoliosis diagnosis and treatment were abstracted from original medical records in the participating medical centers. Characteristics of radiographic exams, retrieved from radiology reports,

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radiographs, radiograph jackets, and radiology logbooks, included date, field, view (e.g., anteroposterior, posteroanterior, and lateral), position, presence of an orthosis (cast, brace, or surgical implant), radiographic size, radiographic machine variables, and position of the breast relative to the beam (3).

**Dosimetry.** Our goal was to reconstruct total radiation dose for every subject by year and age based on 137,711 registered diagnostic radiographs from the pediatric orthopedic centers (3). Assumed depth of breast tissue was 1.0 cm for ages <13 years and 2.5 cm for ages ≥13 years. When the breast was not in the radiation beam for a specific X-ray, it was assumed not to contribute to total breast dose, that is, radiation scatter from such an X-ray was considered to be negligible. Doses were estimated separately by calendar period (1920-1939, 1940-1959, 1960-1975, and 1976-1989) to account for the dramatic changes in radiation technology that occurred during the past century. The average breast dose for a breast-exposed radiograph was 0.45 cGy. The highest estimated dose for a single radiograph (1.56 cGy) corresponded to an anteroposterior full spine X-ray before 1939 to a child under 13 years old. Recent diagnostic radiographs (1976-1989) conferred the lowest doses (≤0.005 cGy). For 245 women (hereafter called minimally exposed), no recorded X-rays were found at the orthopedic center where the patient was enrolled; these patients were included in the dose-response models as having a breast dose of 0 cGy.

**Tracing.** Telephone tracers used one-on-one tracing methods by contacting patients and, if necessary, parents or spouses. Social security numbers were obtained for 94.5% of all patients. Several local, state, and national databases were used to obtain vital status and address as of January 1, 1993. Of the total cohort of 5,573 patients, 16% were deceased and 19% were lost to follow-up.

**Medical Follow-up.** We conducted a health survey by telephone among known living subjects with telephone numbers in the United States ($n$ = 3,620). Women who had been included in the original pilot study (16) and those for whom no telephone number was available were initially contacted by mail. The questionnaire obtained information on medical and reproductive history, family history of cancer, and other characteristics (e.g., smoking, alcohol use, and education). In all, 3,121 (86%) women participated in the health survey, 6% refused, 4% were unable to participate due to illness, language problems, or other reasons, and 4% did not respond. By clinic, participation rates ranged from 80% to 91% and refusal rates from 1% to 18%. With patient consent, we solicited written medical confirmation of self-reported breast tumors from treating physicians. For the present analyses, family history of breast cancer was defined as breast cancer in a first- or second-degree blood relative (mother, sister, daughter, grandmother, or aunt) as reported by the scoliosis patient. Although breast budding (thelarche) is known to precede menarche by 2.5 to 3 years, on average (17, 18), self-reported ages at breast budding and menarche were similar. We assumed that the more objective onset of menses was more accurately reported and estimated age at breast budding by subtracting 3 years from the age at menarche (18). Menopausal status at questionnaire survey was unknown for 12 women (0 cases) who reported no menstrual periods at least 6 months before questionnaire completion but who failed to identify the reason. These 12 women were considered to be postmenopausal.

**Analytic Cohort.** The present analyses focus on breast cancer experience among female scoliosis patients who were alive in 1992 and participated in the health survey. Of the total number of 3,121 participants, we excluded 111 congenital scoliosis patients because they were likely to have had radiographic examinations for concomitant medical conditions in other hospitals, for which we did not have records, leaving an analysis cohort of 3,010 subjects. A history of cancer was not an exclusion criterion; however, none of the participants reported a history of Hodgkin's lymphoma, a disease often treated with high-dose chest radiotherapy. The main outcome was a medically confirmed or nondenied invasive breast cancer (*International Classification of Diseases, Ninth Revision* code 174; ref. 19). If a participant had multiple breast cancers, only the first cancer was counted. In one case (a 76-year-old subject who reported a history of two breast cancers), date of diagnosis for breast cancer was unknown and was assumed to have preceded the interview by 10 years.

**Statistical Methods.** Woman-years of follow-up accrued from the date of scoliosis diagnosis until the date of first breast cancer diagnosis or survey completion, whichever came first. All woman-years were cross-classified by time-dependent variables for attained age, total breast dose, and by breast cancer risk factors and scoliosis characteristics. For each of the cells, the sum of the number of breast cancer cases was calculated as well as averages for all relevant covariates. Data analysis was by Poisson regression using the AMFIT module of the statistical package Epicure (20, 21). Model fit was evaluated using two-sided likelihood ratio tests at the 5% significance level (21, 22); however, in interpreting test results for radiation dose response, we considered that a positive dose response is the only serious alternative to the null hypothesis for radiation-related breast cancer. Tests of trend for categorical variables were based on the slope of the corresponding continuous variable or on ordinal scores. Likelihood-based confidence limits were calculated where possible. All analyses were stratified by attained age in eight categories.

A linear radiation dose-response model was used:

$$\text{Breast cancer risk} = \exp(\alpha_0 + \sum \alpha_j x_j) \times (1 + \beta D), \quad (A)$$

where the exponential term represents the background risk of breast cancer as a function of categories of attained age, reproductive history, and other epidemiologic variables; $D$ represents the estimated breast radiation dose in Gy; and the variable $\beta$ represents the (unknown) excess relative risk (ERR) per unit dose. We then evaluated whether the dose response differed according to specific epidemiologic characteristics by allowing the variable $\beta$ to vary by subgroup defined according to the modifying factor of interest and testing for nonhomogeneity of dose response.

Finally, we tested for the possibility of enhanced sensitivity to radiation according to breast development stage. We estimated radiation-related breast cancer risk

for doses received in four developmentally related time windows: (*a*) before breast budding, (*b*) between breast budding and menarche, (*c*) between menarche and birth of a first child, and (*d*) after birth of a first child. Postmenarche person-years of nulliparous women were all allocated to window c. A total of 39 subjects, including two cases, were ineligible for this analysis because of missing information on age at menarche ($n = 31$) or age at first birth ($n = 8$). Most women contributed person-years to more than one time window of exposure because monitoring with X-rays occurred over a period of several years, that is, across the windows that we defined. Total breast dose $D$, after dropping the 39 subjects for which window-specific doses could not be computed, therefore is the sum of window-specific doses $D_1$, $D_2$, $D_3$, and $D_4$ received during the first, second, third, and fourth time windows, respectively. Our analysis for effect modification compared the analysis using model ($A$) to a more general model in which the dose response might depend on the developmental time window during which the dose was received:

$$\text{Breast cancer risk} = \textit{background} \times (1 + \sum \beta_k D_k), \quad (B)$$

where background = $\exp(\alpha_0 + \Sigma\alpha_j x_j)$ as in Eq. A and the variable $\beta_k$ represents the ERR/Gy specifically associated with dose $D_k$ received during time window $k$.

## Results

A total of 118,905 woman-years of follow-up was accrued. The median follow-up was 35.5 years and the median age at end of follow-up was 47.6 years. The mean estimated dose to the breast was 12.1 cGy for all patients (Table 1), based on an average of 26.8 diagnostic radiographs involving exposure to the breast received over a 6.1-year period. Among women with any breast exposure, the mean estimated dose to the breast was 13.2 cGy. We estimate that daily breast tissue doses, to exposed women, were typically 0.9 cGy (median) or 1.1 cGy (mean), with 90th, 95th, and 99th percentiles of 2.0, 2.4, and 3.7 cGy, respectively.

Eighty-eight women reported breast cancer and one woman reported a nondefined cancer. In all, invasive breast cancer was medically confirmed for 68 women, including 3 subjects with a second contralateral breast cancer. Two subjects had a concomitant confirmed *in situ* breast cancer and another 11 women had a confirmed diagnosis of *in situ* breast cancer only, which was not included in most of our analyses. We did include 10 self-reported breast cancers that were not verified because the patient denied consent ($n = 5$), and could not be contacted ($n = 2$) or because the medical record was not available ($n = 3$). In all, two self-reported breast cancers were denied as a result of the confirmation process, including one second tumor in a patient whose first breast cancer was confirmed. Thus, 78 confirmed or nondenied invasive breast cancers were studied.

**Table 1. Descriptive characteristics of patients who participated in a 1992-1993 U.S. Scoliosis Cohort Questionnaire Survey**

| Characteristics | Median | Mean | Range |
|---|---|---|---|
| All patients ($n$ = 3,010) | | | |
| Age at scoliosis diagnosis (y) | 12.0 | 11.0 | 0-19 |
| Follow-up (y) | 35.5 | 39.5 | 13-68 |
| Age at end of follow-up (y) | 47.6 | 51.3 | 30-84 |
| Total breast dose (cGy) | 9.3 | 12.1 | 0-111 |
| No. breast-exposed radiographs | 21.0 | 26.8 | 0-332 |
| No. years during which breast-exposed radiographs were taken | 4.0 | 6.1 | 0-55 |
| Breast-exposed patients ($n$ = 2,765) | | | |
| Total breast dose (cGy) | 10.3 | 13.2 | 0.005-111 |
| No. breast-exposed radiographs | 24.0 | 29.2 | 1-332 |

Breast cancer risk did not vary appreciably by type of scoliosis or age at diagnosis (data not shown) but rose significantly with indicators of increasing radiation exposure, including spinal curve magnitude (available for 60% of the cohort) and total number of X-rays involving the breast (Table 2). Compared with subjects who had one to nine X-rays, subjects who had ≥60 had a 3-fold risk of breast cancer and minimally exposed subjects (see Materials and Methods) had a 1.3-fold nonsignificant risk. In all subsequent dose-response analyses, minimally exposed subjects are assumed to have had no X-rays, that is, a breast dose of 0 cGy.

Breast cancer risks according to established risk factors were generally as expected (Table 2). Risk declined with increasing number of children and rose with increasing age at first birth. Risk was elevated among women who were postmenopausal at questionnaire completion and was positively associated with family income. It was significantly elevated among women with a family history of breast cancer or of early-onset breast in particular (defined as diagnosis before age 50 years). However, the latter association was not significantly stronger than that associated with family history per se (analysis not shown). There was a borderline negative association with smoking history. Risk was not related to age at menarche, oral contraceptive use, or hormone replacement therapy (data not shown). Adjustment for age at first birth, menopausal status at questionnaire completion, household income, and family history of breast cancer significantly improved the statistical fit of the model and these factors were included as additional baseline term covariates in all subsequent analyses. Compared with women with breast doses less than 10 cGy, those with exposures of 20 to 29 and ≥30 cGy had 2-fold statistically significant breast cancer risks (Fig. 1). Modeling ERR as a linear function of breast dose yielded a borderline statistically significant ERR/Gy of 2.86 [95% confidence interval (95% CI), -0.07 to 8.62; $P = 0.058$; one-tailed $P = 0.029$; Table 3; Fig. 1]. There was no deviation from linearity at higher doses (as evaluated by comparison with pure quadratic, linear-quadratic, or linear-exponential models).

We found no evidence for significant modification of the ERR/Gy by age at first birth, menopausal status, or family income. A significantly higher ERR/Gy ($P = 0.03$) was observed, however, for women with any affected female relative (ERR/Gy = 8.37) compared with women with no affected relatives (ERR/Gy = −0.16; Table 3). The significantly higher risk noted among subjects with family histories of early-onset breast cancer (Table 2), which was based on only six cases in that group, was matched with a nonsignificantly higher estimated ERR/Gy ($P = 0.20$).

**Table 2. Distribution of scoliosis characteristics and established breast cancer risk factors and risk of breast cancer among 3,010 participants of the U.S. Scoliosis Cohort Questionnaire Survey**

| Characteristics | Person-years | *n* cases | Relative risk (95% CI)* | *P* for trend † | Mean total breast dose (cGy) |
|---|---|---|---|---|---|
| Curve magnitude (°) | | | | | |
| <40 | 19,914 | 7 | 1.0 ‡ | 0.42 | 11.8 |
| 40-59 | 22,289 | 11 | 1.45 (0.56-3.79) | | 14.8 |
| 60-79 | 12,575 | 9 | 1.95 (0.71-5.31) | | 16.0 |
| ≥80 | 8,016 | 6 | 1.81 (0.60-5.49) | | 18.8 |
| Unknown | 56,108 | 45 | 1.28 (0.53-3.07) | | 6.4 |
| Total no. X-rays§ | | | | | |
| Minimally exposed‖ | 13,379 | 14 | 1.35 (0.69-2.69) | 0.12 | 0 |
| 1-9 | 32,178 | 21 | 1.0 ‡ | | 3.0 |
| 10-19 | 18,283 | 15 | 1.62 (0.83-3.18) | | 8.3 |
| 20-39 | 28,749 | 10 | 1.97 (0.43-2.18) | | 12.7 |
| 40-59 | 15,527 | 8 | 1.66 (0.67-4.08) | | 19.5 |
| ≥60 | 10,785 | 10 | 3.14 (1.33-7.44) | | 33.5 |
| Age at first live birth (y)¶ | | | | | |
| <25 | 51,665 | 22 | 1.0 ‡ | 0.03 | 10.6 |
| 25-34 | 31,339 | 23 | 1.65 (0.91-2.98) | | 9.2 |
| ≥35 | 3,616 | 4 | 3.02 (1.03-8.87) | | 10.9 |
| Nulliparous | 31,958 | 29 | 2.13 (1.21-3.75) | | 12.5 |
| Unknown | 324 | 0 | — | | 10.4 |
| Parity | | | | | |
| Nulliparous | 31,958 | 29 | 1.0 ‡ | 0.06 | 12.5 |
| 1-2 | 49,754 | 23 | 0.56 (0.32-0.98) | | 10.9 |
| 3-4 | 28,888 | 23 | 0.82 (0.47-1.43) | | 9.0 |
| ≥5 | 8,063 | 3 | 0.32 (0.10-1.05) | | 9.0 |
| Unknown | 239 | 0 | — | | 8.6 |
| Menopausal status** | | | | | |
| Premenopausal | 48,244 | 10 | 1.0 ‡ | 0.004 | 12.7 |
| Postmenopausal | 70,659 | 68 | 3.13 (1.38-7.09) | | 9.4 |
| Highest completed education | | | | | |
| Elementary school | 11,517 | 8 | 1.0 ‡ | 0.29 | 10.9 |
| High school | 74,170 | 48 | 1.16 (0.54-2.49) | | 10.7 |
| College | 32,538 | 21 | 1.47 (0.63-3.40) | | 10.7 |
| Unknown | 709 | 1 | 2.90 (0.28-18.2) | | 11.8 |
| Household income** | | | | | |
| <$30,000 | 51,953 | 31 | 1.0 ‡ | 0.003 | 10.9 |
| $30,000-$59,999 | 37,699 | 18 | 1.13 (0.62-2.07) | | 11.2 |
| ≥$ 60,000 | 18,568 | 18 | 2.84 (1.52-5.30) | | 10.0 |
| Unknown | 10,684 | 11 | 1.66 (0.83-3.32) | | 9.8 |
| Alcohol use** | | | | | |
| <1/wk | 70,862 | 47 | 1.0 ‡ | 0.42 | 10.5 |
| 1-6/wk | 32,854 | 17 | 0.93 (0.53-1.63) | | 11.2 |
| 1-3/d | 11,197 | 12 | 1.65 (0.87-3.12) | | 10.2 |
| ≥4/d | 1,561 | 1 | 0.97 (0.13-7.04) | | 13.8 |
| Unknown | 2,428 | 1 | 0.63 (0.09-4.56) | | 10.3 |
| Smoking | | | | | |
| Never | 66,286 | 51 | 1.0 ‡ | 0.07 †† | 11.1 |
| Past | 32,696 | 20 | 0.77 (0.46-1.30) | | 9.6 |
| Current | 19,723 | 6 | 0.43 (0.19-1.00) | | 11.4 |
| Unknown | 192 | 1 | 4.94 (0.66-36.8) | | 16.8 |
| Family history of breast cancer | | | | | |
| None | 90,233 | 47 | 1.0 ‡ | 0.008 | 10.8 |
| Second-degree affected relatives only | 16,468 | 19 | 2.71 (1.57-4.66) | | 10.8 |
| Any first-degree affected relative | 12,203 | 12 | 1.82 (0.96-3.44) | | 10.1 |
| No. relatives with breast cancer | | | | | |
| 0 | 90,233 | 47 | 1.0 ‡ | 0.0003 | 10.8 |
| 1-2 | 27,551 | 28 | 2.12 (1.32-3.41) | | 10.5 |
| 3-5 | 1,120 | 3 | 5.65 (1.73-18.5) | | 10.5 |
| Family history early-onset breast cancer ‡‡ | | | | | |
| None | 115,618 | 72 | 1.0 ‡ | 0.03 | 10.8 |
| Any | 3,286 | 6 | 2.84 (1.10-6.03) | | 9.6 |

*Relative risk and 95% CI from separate models stratified by attained age (<35, 35-39, 40-44, 45-49, 50-54, 55-59, 60-69, and 70+ years) and calendar year (1925-1929, 1930-1934, . . ., 1990-1995) and adjusted for total number of X-rays (minimally exposed, <10, 10-19, 20-39, 40-59, and ≥60), where appropriate. The variable attained age was calculated in a time-dependent manner.
†Excludes "unknown" category, where applicable.
‡Reference group.
§Refers to X-rays that involved the breast.
‖*n* = 245 women who had no recorded X-rays at the pediatric center where the spinal deformity was diagnosed.
¶Among parous women only.
**At questionnaire completion.
††Trend test contrasting ever and never smokers.
‡‡Diagnose <age 50.

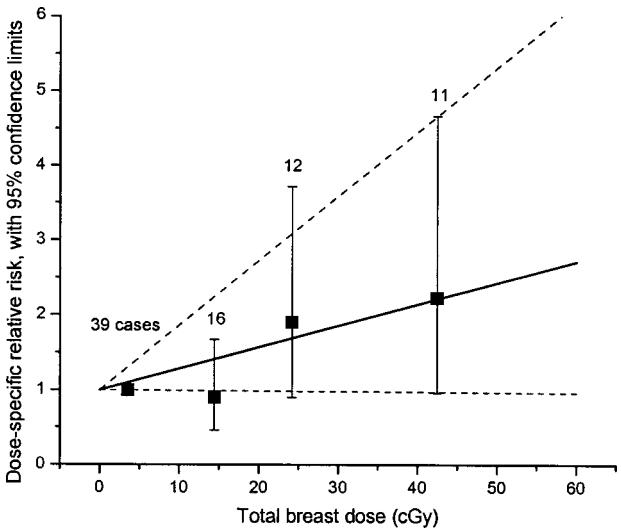


**Figure 1.** Radiation dose response for breast cancer among 3,002 scoliosis patients who were nulliparous or whose age at first birth was known. The analysis is adjusted for attained age, menopausal status at questionnaire completion, age at first birth, household income, and family history of breast cancer. Dose intervals correspond to 0-9, 10-19, 20-29, and 30+ cGy, respectively.

The highest accumulation of radiation dose occurred during the period between menarche and first birth. Including only subjects for which time window doses could be estimated (which resulted in dropping two breast cancer cases), the overall ERR/Gy is 3.30 (95% CI, 0.13-9.63; Table 4). Relatively few subjects had any X-ray exposure before breast budding (24%) or after giving birth to a first child (9%). Table 4 also shows average dose received ($D_k$) during each of the four time windows defined by developmental stage and the corresponding estimated dose response for dose received within that window. Allowing the dose response to depend on time window did not significantly improve the fit ($P = 0.57$, based on a deviance difference of 2.02 with 3 *df*).

Our estimated ERR/Gy of 2.86 was little affected in the following sensitivity analyses (data not shown): Excluding 10 cases for which medical confirmation could not be obtained yielded ERR/Gy = 2.69 (95% CI, −0.19 to 8.46). Including confirmed cases of *in situ* breast tumors ($n = 11$) gave ERR/Gy = 2.01 (95% CI, −0.33 to 6.38). Excluding 245 women (14 cases) with no documented X-ray exposures gave ERR/Gy = 3.06 (95% CI, −0.17 to 10.98). Finally, assuming an exposure lag interval of 5 years yielded ERR/Gy = 2.87 (95% CI, −0.06 to 8.66).

Our analysis is based on a subgroup of the U.S. Scoliosis Cohort (3) of 5,573 women with spine deformities. This subgroup comprises 3,010 women (participants) who completed an epidemiologic survey in 1992. Survey participants, compared with the remainder of the cohort, were more likely (59%; cf. 40%) to have idiopathic etiology, were born later (mean birth year, 1941; cf. 1933), had more breast-exposing X-rays (mean, 27; cf. 16), and had higher total breast dose (mean, 12.1; cf. 8.8 cGy). Participants did not differ markedly from nonparticipants with respect to age at diagnosis (12 years; cf. 10 years) and severity of curvature (51°; cf. 56°).

A previous mortality follow-up (1937-1996) of the total cohort found 77 cases of lethal breast cancer (3). In all, 57 of 77 patients had already died when the current incidence survey was conducted. Conversely, among 3,010 survey participants included in the current analysis, 10 of 78 women with incident breast cancer died of breast cancer through 1996 and had been included in the earlier mortality survey (3). The radiation dose response (ERR/Gy) for exposed women in the mortality study was 2.7 (95% CI, −0.2 to 9.3).

## Comment

Women with abnormal spinal curvature who were exposed to diagnostic X-rays during childhood and adolescence were at increased risk of breast cancer, with a borderline statistically significant radiation dose-response relationship. Patients who reported having female blood relatives with breast cancer appeared to be at higher risk of radiation-related breast cancer than those who did not report such family history. We were unable to show variations in the risk of radiation-related breast cancer by established reproductive risk factors or by radiation exposure within potentially sensitive time windows related to breast development.

It is surprising that the radiation dose response was positive only among women who reported a family history of breast cancer, and it is conceivable that a recall bias, in which breast cancer cases were more likely than noncases to know about breast cancers among their relatives, might be operating. However, radiation dose did not vary by family history, and inclusion of family history in the model for baseline risk had only a negligible effect on the overall radiation dose response (analysis not shown).

Increased breast cancer risk has been shown following acute radiation exposure from the atomic bombings in Japan (23) and following high cumulative doses associated with treatment for Hodgkin's lymphoma (24-26), benign breast disease (27), tuberculosis (28, 29), postpartum mastitis (30), and, in infancy, treatment for ''enlarged'' thymus gland (31) and hemangioma (32). In these studies, the therapeutic dose fractions tended to be relatively high (especially for Hodgkin's lymphoma), whereas the diagnostic dose fractions were low.

The cumulative exposures experienced by subjects in this study are estimated to have been delivered in daily increments typically around 0.9 cGy (median) or 1.1 cGy (mean), with 90th, 95th, and 99th percentiles at 2.0, 2.4, and 3.7 cGy, respectively. Assuming that repair of radiation-damaged DNA takes place within a few hours (33), the current data argue against the existence of a low-dose radiation threshold, below which there is no radiation-related contribution to breast risk, at dose levels on the order of 1 to 3 cGy.

To put the magnitude of the radiation-related breast cancer risk from our study in perspective, we applied the excess absolute risk model from the large pooled analysis of eight cohorts by Preston et al. (1) for exposure at age 14 years and breast cancer diagnosis at age 51 years, the average ages observed in our study. Although the authors also provide an ERR model, they recommend using the

**Table 3. Radiation dose response for breast cancer and evaluation of effect modification of the established breast cancer risk factors and characteristics of scoliosis diagnosis and treatment**

| Model* | Potential effect modifier | Subgroup | Relative risk (main effect)† | ERR/Gy (95% CI)* | Deviance difference‡ | P§ |
|---|---|---|---|---|---|---|
| Reference | None | All | — | 2.86 (−0.07 to 8.62) | Reference | — |
| 1 | Age at first birth (y) | <25 | 1.0 | 1.25 (<0-9.44)‖ | 1.108 | 0.57 |
| | | 25-34 | 1.23 | 6.21 (−0.55 to 29.61) | | |
| | | ≥35¶ | 2.30 | 2.30 (<0-13.82)‖ | | |
| 2 | Menopausal status at questionnaire completion | Premenopausal | 1.0 | 2.94 (<0-9.89)‖ | <0.001 | 0.99 |
| | | Postmenopausal | 3.82 | 2.84 (−0.21 to 9.03) | | |
| 3 | Household income, dollars | <30,000 | 1.0 | 3.69 (<0-22.29)‖ | 0.868 | 0.83 |
| | | 30,000-59,000 | 1.42 | 1.54 (<0-11.34)‖ | | |
| | | ≥60,000 | 2.74 | 5.14 (<0-24.13)‖ | | |
| 4 | Any family history of breast cancer | No | 1.0 | −0.16 (<0-4.41)‖ | 4.614 | 0.03 |
| | | Yes | 1.20 | 8.37 (1.50-28.16) | | |
| 5 | Family history of breast cancer by degree of family relationship | None | 1.0 | −0.09 (<0-4.60)‖ | 4.610 | 0.10 |
| | | Second degree only | 1.56 | 6.90 (0.23-30.50) | | |
| | | Any first degree | 0.83 | 11.83 (<0-122)‖ | | |
| 6 | Family history of early-onset breast cancer (before age 50 y) | No | 1.0 | 2.76 (−0.12 to 8.50) | 1.32 | 0.25 |
| | | Yes | 2.84 | 17.65 (<0-91.4)‖ | | |

NOTE: An alternative reference model was used for model 4, which includes the ''any family history'' variable as confounder in the background risk term rather than the variable ''family history by degree of relationship'' that is used in all other models in this table.
*All models adjusted for attained age, menopausal status at questionnaire completion, age at first birth, household income, and an indicator of family history of breast cancer in the baseline; all analyses exclude 325 person-years (8 women, 0 cases) for women with unknown age at first birth.
†The main effect relative risks are the coefficients from the log-linear element of the statistical model and reflect the effect of the potential effect modifier on the background risk of breast cancer, whereas the ERR/Gy reflects their effect as modifier of the radiation dose-response relationship for radiation-related breast cancer risk.
‡Relative to the main reference model (deviance 855.544) for models 1, 2, 3, and 5 and to an alternative reference model (deviance 856.848) for model 4.
§Likelihood ratio test of homogeneity of ERR/Gy across categories of effect modifier.
‖Lower confidence bound could not be obtained using likelihood-based methods.
¶Includes nulliparous women.

excess absolute risk model to transfer radiation-related breast cancer risk across different populations (1). The model predicts an excess absolute risk/Gy of 17.6 per 1,000 woman-years with 95% confidence limits of 12.6 to 24.7. We then divided that excess absolute risk estimate by the background breast cancer rate for 50- to 54-year old women, averaged over the relevant calendar period (1973-1992) from the U.S. SEER cancer registries (ref. 34; 2.089 per 1,000 woman-years) to obtain a predicted ERR/Gy of 8.46 (95% CI, 6.04-11.84). Thus, our estimated ERR/Gy of 2.86 (95% CI, -0.07 to 8.62) is somewhat lower than is predicted based on the pooled analysis.

As discussed in detail previously (3), breast radiation doses may be slightly underestimated and risk estimates may be correspondingly overestimated in our study. Also, Preston et al. (1) concluded that variation in background rates of breast cancer can lead to differences in estimates of radiation-related risk and relative risk in particular. Our nonsignificantly lower ERR/Gy could reflect higher background rates of breast cancer among scoliosis patients generally due to risk factors other than radiation exposure. We compared reproductive characteristics for scoliosis patients without a history of breast cancer with averages obtained from 13,378 non-Black

**Table 4. Analysis of radiation dose-response by exposure received in time windows defined by reproductive events to reflect stages of breast tissue development**

| Model | Breast development window | *n* (%) any dose* | Mean dose $D_{kx}$ in selected window (cGy)† | ERR/Gy in specified window $D_x$ (95% CI) | Deviance difference (*df*), *P*-value‡ |
|---|---|---|---|---|---|
| Reference | All windows combined | 2,971 (100) | 11.6 | 3.30 (0.13-9.63) | — |
| Window 1 | Before breast budding | 690 (23) | 1.7 | −0.24§ | 2.02 (3 *df*), *P* = 0.57 |
| Window 2 | Between budding and menarche | 1,215 (41) | 2.7 | 1.73§ | |
| Window 3 | Between menarche and giving birth to first child | 2,312 (78) | 7.1 | 15.94§ | |
| Window 4 | After giving birth to first child | 258 (9) | 0.1 | 4.36§ | |

NOTE: Excludes *n* = 31 subjects with missing data on age at menarche or age at first birth; includes 117,039 person-years and 76 cases.
*Percentage of total number of scoliosis patients (*n* = 3,010) who had any dose to the breast in the respective time window.
†Window doses are not time dependent; the dose in all windows combined is the sum of the four window doses as used in these analyses.
‡Likelihood ratio test for improvement in model fit when the window-specific doses are given separately.
§Likelihood-based confidence limits could not be calculated.

female National Health Interview Survey participants in 1987 and 2000.[4] Scoliosis patients were more often nulliparous than National Health Interview Survey participants, both for women ages 35 to 44 years (31% versus 16%, respectively) and for women older than 44 years at questionnaire completion (24% versus 13%, respectively). Among parous women, scoliosis patients appeared to have a first birth slightly later than the National Health Interview Survey participants (data not shown). Thus, in terms of reproductive history, scoliosis patients might be expected to have somewhat higher breast cancer baseline rates than the general population of U.S. women. However, this observation does not necessarily imply that ERR/Gy should be lower among scoliosis patients than among the general U.S. population: a large nested case-control study among atomic bomb survivors suggests that at least some reproductive history factors, including early first full-term pregnancy and multiple births, interact multiplicatively with radiation dose as breast cancer risk factors, yielding values of ERR/Gy similar to those for women with a late first birth or who were nulliparous but lower values of excess absolute risk/Gy (7). In our cohort, ERR/Gy was similar across subgroups of age at first birth, parity, and age at menarche, in agreement with the A-bomb survivor study (7) and with an evaluation of breast cancer risk among Swedish women treated for hemangioma in infancy (32).

Genetic characteristics may affect susceptibility to radiation-related tumors to some degree. A recent European study of BRCA1/2 carriers showed an unusually strong association between self-reported X-rays and breast cancer risk (40). A large case-control study (35) showed increased risk of breast cancer associated with postdiagnosis self-reported lifetime number of mammograms among women who had 2 to 4 variant genotypes for genes involved in DNA double-stranded repair, but not among women who had 0 or 1 variant genotypes, and a less clear risk pattern by genotype for chest X-rays. As in most other observational studies of radiation-exposed populations (8, 10), we could evaluate only a crude surrogate measure of genetic factors, that is, family history of breast cancer. In agreement with one (10) but not other (8, 11, 36) studies, we found a stronger dose response for patients who had any female blood relative with breast cancer than for patients who had no affected female relative after adjustment for the main effect of family history *per se* on breast cancer risk. Having a female blood relative with breast cancer is not necessarily indicative of genetic predisposition given the high lifetime breast cancer risk (12.5%) in western countries (37) and because siblings also share environmental factors (38, 39). Finally, idiopathic scoliosis is known to have a genetic component (40). There is no direct evidence of the unidentified genetic characteristics that predispose to idiopathic scoliosis also carrying inherently increased risk of breast cancer in affected individuals, yet the possibility cannot be excluded (41). Although our findings on family history are intriguing, they require confirmation in other studies that have validated information on family history of disease as well as adequate radiation dosimetry. Future collection and evaluation of biological samples should be considered to advance knowledge of gene-radiation interactions in the occurrence of radiation-related breast cancer in this unique population.

In our study, the overall breast cancer dose response was mostly accounted for by doses received in adolescence and only 25% of the cohort had any dose before age 10 years. Given the skewed distribution of the doses, careful interpretation is warranted. Also, because exposure assessment was based on information in pediatric medical files, X-rays received in adulthood were not captured. Although earlier studies suggested that girls in the second decade of life are most sensitive to radiation-related breast cancer, recent data are more consistent with the notion that exposure anytime before age 20 years confers a high dose-specific risk (2, 23, 36). [But we note that a recent comprehensive analysis of site-specific cancer incidence among atomic bomb survivors suggests that higher radiation-related breast cancer risks among women, in that population, exposed at young ages mainly reflect strong secular increases in age-specific baseline breast cancer rates among women born between 1925 and 1945 (42)].

Several factors should be considered when interpreting our findings. We relied on initial self-reports for both breast cancer and cancer family history. A personal history of breast cancer is among the most accurately reported cancers across study populations (43, 44). Also, quality of reporting is unlikely to differ by exposure status in this cohort. For family history, some (45, 46) but not all (47-49) validation studies found breast cancer patients more likely than healthy women to report complete family histories of the disease, in particular for distant second-degree relatives. Therefore, risks associated with family history of breast cancer might be slightly overestimated in our study. With respect to internal validity, women had to have survived until 1993 to participate in the questionnaire survey. Because scoliosis patients have elevated death rates compared with the general population (3), our findings might not be entirely representative of all scoliosis patients treated in the study period. In addition, patients with late-stage breast cancers are likely underrepresented in our sample because of a higher lethality compared with early-stage breast cancer. For exposed women, the similarity of our overall dose response (ERR/Gy = 3.06; 95% CI, −0.17 to 10.98) to that based on breast cancer mortality in this cohort (ERR/Gy = 2.7; 95% CI, −0.2 to 9.3; ref. 3) is reassuring.

Strengths of this study include the large cohort size, a high rate of survey participation, and concomitant availability of breast cancer risk factor information and detailed dosimetry, which is important because scoliosis patients differ from the general population with respect to breast cancer risk factors, such as parity. In addition, we collected information on radiographs from an objective source (medical records) and before ascertainment of breast cancer status, thereby minimizing recall and/or ascertainment bias that can affect studies on diagnostic radiation exposure and cancer risk (50-52). It should be emphasized that the radiation exposures described herein are not representative of radiation exposure associated with low-dose conventional techniques used to monitor scoliosis patients in current medical practice. Also, increased awareness among physicians

[4] Dr. C. Schairer, personal communication, September 2005.

has lead to less frequent exposures of young girls with scoliosis (53). For women exposed to multiple X-rays in the past, compliance with current breast cancer screening guidelines is warranted. Health-care practitioners should be aware that women with a history of scoliosis may be at increased risk of breast cancer.

In conclusion, scoliosis patients exposed to multiple radiographic examinations in adolescence were at increased risk of breast cancer with a borderline-significant dose-response relationship. Reproductive factors did not affect the dose response, but women with a family history of breast cancer had a stronger dose response than women who did not have such family history. The implication of the latter finding is unclear at present and it requires replication in other studies. Although some variation in dose response was seen by breast development stage at exposure, it was not statistically significant. Further follow-up is recommended because most women were still relatively young with respect to breast cancer risk.

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# Multiple Diagnostic X-rays for Spine Deformities and Risk of Breast Cancer

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