Research Article

Breast Cancer Risk 55+ Years After Irradiation for an Enlarged Thymus and Its Implications for Early Childhood Medical Irradiation Today

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Abstract

Background: Radiotherapy during childhood increases long-term cancer risk, but the risk from radiation as a result of relatively higher dose diagnostic procedures remains less well known. This study, which evaluates breast cancer incidence in a cohort treated with “lower dose” chest radiotherapy over 50 years ago, can assist with estimating lifetime breast cancer risk in young children exposed to radiation from procedures such as chest computed tomography (CT) or treatment with recent “lower dose” chest radiotherapy protocols.

Methods: A population-based, longitudinal cohort of subjects exposed to thymic irradiation during infancy from 1926 to 1957 and of their unexposed siblings was re-established. Previously followed until 1987, we resurveyed cohort members from 2004 to 2008. Poisson regression models compared breast cancer incidence rates between women in the cohort by treatment and dose category groups.

Results: Breast cancer occurred in 96 treated (mean breast dose, 0.71 Gy) and 57 untreated women during 159,459 person-years of follow-up. After adjusting for attained age and treatment/birth cohort, the rate ratio was 3.01 (2.18-4.21). The adjusted excess relative risk per Gy was 1.10 (95% confidence interval, 0.61-1.86). Traditional breast cancer risk factors did not contribute significantly to multivariate model fit.

Conclusion: Our results show that at radiation doses between those received by the breast from chest CT and cancer therapy during early childhood, breast cancer incidence rates remain elevated >50 years after exposure. This implies that increased breast cancer risk will remain a lifelong concern in females treated during childhood with currently reduced radiotherapy doses and for infants receiving multiple chest CTs. Cancer Epidemiol Biomarkers Prev; 19(1); 48–58. ©2010 AACR.

Introduction

Ionizing radiation is a well-established risk factor for breast cancer, particularly when exposure occurs at a young age (1, 2). Substantial evidence for this risk comes from studies of female Hodgkin lymphoma survivors (3-13). Such survivors treated before age 20 years with median doses of ~40 Gy have an estimated cumulative breast cancer incidence as high as 1 in 8 by age 40 years, similar to that of a typical American woman living to 75 years of age (5, 7, 14). In recognition of this increased risk of breast cancer and other morbidities from radiotherapy, the current practice is to generally limit total chest radiation dose to 25 Gy or less during childhood, which exposes the breast to ~1.25 Gy (5% of 25 Gy) when blocking is used. However, this limit is relatively recent, so its effect on breast cancer incidence remains largely unknown.

Furthermore, increased breast cancer risk also occurs in cohorts treated with much lower doses of irradiation for benign conditions such as enlarged thymus (15), skin hemangiomas (16), tinea capitis (17), and tuberculosis (18, 19), but mean follow-up has generally been limited to <50 years. These studies and studies of the atomic bomb survivors have raised concerns about the population risk from the increasing use of “higher-dose” imaging modalities such as chest computed tomography (CT) in young children (20). The reinitiation of a dormant cohort of individuals who received X-ray therapy for an enlarged thymus during infancy between 1926 and 1957 provided the opportunity to indirectly evaluate the breast cancer.
risk from radiation exposures during early childhood from newer methods of chest radiotherapy and chest CT >50 years after exposure, because of the overlap between breast doses received by this cohort and from these procedures (21-23).

Radiation treatment for thymic enlargement during infancy and early childhood was based on misconceptions regarding the normal size range of infant thymus glands and that an enlarged thymus could lead to status lymphaticus and suffocation (24, 25). In 1951, a longitudinal cohort study of individuals treated for this condition in Rochester, NY, between 1926 and 1957 and their untreated siblings was begun to examine cancer incidence (15). Based on follow-up through 1985 to 1987, the thymic-irradiated women had a 3.6 [95% confidence interval (95% CI), 1.8-7.3] times higher risk of breast cancer than the untreated women (15). This increased risk occurred although the average age of the cohort was only 37 years of age and most women were still premenopausal. However, the subsequent breast cancer incidence in middle age and beyond has remained unknown.

Materials and Methods

The Population-Based Cohort

Records were collected from all 10 hospitals and clinics in the Rochester, NY area where thymic irradiation treatments were given except for one practice that closed in 1944 and whose records were destroyed (this practice is estimated to have treated fewer than 400 children). Cumulative air dose to the thymus ranged from 0.25 to 12.50 Gy, with the number of fractions ranging from 1 to 7, although 89% received only one or two treatments. Time between first and last treatment was ≤90 d for 98% of women with the longest time being 4.5 y. All treated subjects received orthovoltage radiation ranging from 57 to 290 KVP, and 96% of individuals were treated at 1 y of age or less. Enrollment was deemed complete after medical records had been searched twice, once in 1952 and again in 1957. Untreated siblings were identified and included in the cohort if they had been born before the third follow-up survey in 1963. As in the last analysis for thyroid cancer incidence (26), children were excluded if follow-up was <5 y after birth, either due to death or loss to follow-up. After these exclusions, the studied cohort included 1,120 girls who had received radiation treatment and 2,382 female siblings (of both treated boys and girls) who did not. This comparison group is called the “untreated” or “nontreated” women throughout this article. Although included in data collection, males were excluded from this analysis, because no breast cancers were reported among treated men.

Data Collection

Historical Follow-up. The cohort was surveyed by mail six times, in 1953 (27), 1959 (28), 1963 (29), 1969 (30), 1975 (31), and 1985 to 1987 (15, 26), before becoming dormant after 1987. The method was similar for all surveys; specific details are provided in the references cited above for each survey. In the 1985 survey, telephone interviews were attempted with those who did not return a survey after three mailings. All respondents provided written informed consent for the 1985 survey and granted permission to contact their medical care providers to verify self-reported tumors. All cases of cancer were confirmed by pathology report, surgical record, or medical record. Survey response rates were very high and similar among treated and untreated cohort members. In the 1985 to 1987 survey, ~85% of both groups responded, 5% had died, and 10% declined to participate or were lost to follow-up.

In the early 1990s, Dr. Stovall and colleagues re-estimated the radiation doses to the breasts of each subject, and these are used in this study. Dose calculations were made by applying data abstracted from the original treatment records of each subject to water and polystyrene phantoms as described previously for other studies (32). Earlier dosimetry had been done with fewer variables (29), so these phantom-based recalculations are likely to be more accurate and more like those used in other similar cohorts (32, 33). Data abstracted from the original records and used for re-estimating doses included cumulative air dose to the thymus, age at each treatment, treatment field size, thickness of lead protection, kilovoltage, and position of treatment (posterior, anterior, or both). If variables besides thymus dose were missing, the most common practice of the institution was imputed. Overall, 67% of women had complete data for dose estimation, whereas another 22% had some missing data in other than treatment field size or thymus dose, the most important determinants of radiation dose in this sample. Treatment field size was imputed for 5%; 5% did not have enough data to estimate the breast dose and were categorized as breast dose unknown. Another 10 women (0.8% of the sample) had complete data but were known to have received other radiation treatments concurrently with thymic irradiation. Their dose for this analysis is based solely on their thymic irradiation.

Current Follow-up. In 2003, we reinitiated follow-up of this cohort. Individuals who returned any of the earlier surveys were eligible for follow-up. We updated contact information by asking cohort members to confirm or update this information for themselves and their siblings, checking publicly available databases, and hiring a search firm to track participants by their social security numbers, which had previously been collected from ~60% of the cohort. About 10% of the cohort had died and another 8% were not locatable.

Between 2004 and 2008, we collected self-reported data from both males and females using a pilot-tested 81-item, 16-page mailed survey. It collected information on outcomes and risk factors for cardiovascular disease and cancer, except family history of cancer. Participants who did not return a survey after two mailings were contacted by telephone if their phone number was on record or if it
could be found using the WhitePages Website.

Up to four calls were made to each subject. Each was asked to complete the survey by phone or to have another survey sent. Written documentation of informed consent was obtained from all respondents. Study and consent procedures were approved by the University of Rochester Research Subjects Review Board.

Participants reporting a cancer (except nonmelanoma skin cancer) were sent a medical release form so we could verify the event from their medical records. In all cases of self-reported malignancies not previously confirmed, we sought confirmation from pathology reports but also accepted concurrent treatment records and National Death Index cause of death as confirmation. For this study, breast ductal carcinoma in situ was considered to be breast cancer (34), whereas breast lobular carcinoma in situ was not. Date of diagnosis was abstracted from the medical records.

Breast cancer risk factor information was collected in the 1985 and the current survey. The most recent information about risk factors that might have changed (e.g., number of full pregnancies, use of hormones) was used in our multivariate analysis. For those risk factors that would not have changed (e.g., age of menarche and age at first giving birth), we used the earliest data provided by the participant on these two surveys, to limit recall bias over time.

**Statistical Analysis**

The primary study hypothesis was that after adjusting for known risk factors, thymic irradiation during early childhood will increase the life-long incidence rate of breast cancer in women. The secondary hypothesis was that the association between radiation and breast cancer risk will persist >37 y after initial exposure. This analysis calculated the breast cancer incidence between the last survey (1985-1987) and the current survey. A third aim was to assess the excess relative risk (ERR) per Gy after adjusting for attained age and other breast cancer risk factors that in our sample were potentially significant.

To calculate person-years at risk for the primary analysis, we used date of birth as the beginning date for both treated and untreated women, because 96% of women had received therapy by 1 y of age. Thus, length of follow-up is nearly equivalent to age at follow-up. The event date was date of breast cancer diagnosis; data were censored at the last survey response or at death. Because this is an incidence study, the date of death was only used if a subsequent survey was received from next of kin or the date of death was the only date we had for breast cancer incidence. For the interval analysis, time to event calculations were the same, except that the start of the follow-up interval was the return date of the 1985 to 1987 survey. Women who had a breast cancer before the beginning of this interval or who did not return a survey during this interval were excluded from the secondary analysis. For both hypotheses, we also evaluated the incidence of breast cancer as a first cancer by censoring at the time of any other first cancer, except nonmelanoma skin cancer, to assess whether increased radiation or chemotherapy treatments for first cancers was the cause of an imbalance in breast cancer incidence.

Crude incidence rates and their 95% CI for both treated and untreated groups were calculated from which the rate ratio was computed. We then compared the two groups' potential breast cancer risk factors and demographic variables using the Pearson χ² test for discrete variables and Student’s t test for continuous variables. Data conformed to the assumptions of the respective tests. Women with and without breast cancer were then compared on these same variables. Variables that differed in either of these comparisons with a P value of <0.10 were included in multivariate analysis. This potential confounders analysis was done using SAS version 9.2. All other statistical tests were two sided with an α level of 0.05.

For primary and secondary analyses, we performed multivariate Poisson regression using the AMFIT module in the statistical package Epicure (35, 36). Person-years were calculated from birth as above and cross-classified by calendar year, a time-dependent variable of attained age, breast radiation dose, treatment/birth cohort (<1937, 1937-1947, >1947), and breast cancer risk factors shown to be potentially different by exposure or outcome group. Untreated women were assigned to a treatment cohort based on year of birth. Model fit was evaluated using two-sided likelihood ratio tests at the 5% significance level (37). Likelihood-based 95% confidence limits were calculated where possible. Reported rate ratios for the entire cohort were adjusted for those factors found to be significant in the most parsimonious model for breast cancer incidence in the subset with complete breast cancer risk factor data (~80% of the cohort).

ERR modeling of radiation dose to the breast was also done using this same technique and software package. A linear radiation dose-response model was used for ERR modeling:

\[
\text{Breast cancer risk} = \exp(\alpha_0 + \sum \alpha_j x_j) \times (1 + \beta D)
\]

where the exponential term represent the baseline risk of breast cancer in the untreated women as a function of categories of attained age, breast cancer risk factors found to add significantly to the model, and year of treatment cohort. D represents the estimated cumulative breast radiation dose in Gy, and the variable β represents the unknown ERR per Gy.

**Results**

Six hundred twenty-five thymic-irradiated and 951 untreated women responded to the current survey, for an overall response rate of 49% after excluding those who were known to be deceased (Table 1). Median
age at follow-up of those who responded to the current survey was 56.8 years (57.3 years in treated; 56.5 years in nontreated), which is equivalent to the median length of follow-up. Table 2 provides the frequency of different traditional breast cancer risk factors as measured in 1985 by response status to the current survey, thus illustrating the potential for nonresponse bias. Age at first birth and oral contraceptive use as reported in 1985 differed between responders and nonresponders to the current survey among both treated and untreated women. Smoking status also differed by response status among untreated women.

During the entire follow-up period of 159,455 person-years, 153 women were diagnosed with breast cancer. Among treated women, 96 had breast cancer, yielding an incidence rate of 17.9 per 10,000 person-years. Fifty-seven treated women developed breast cancer, for an incidence rate of 5.4 per 10,000 person-years. The crude rate ratio for breast cancer comparing treated to untreated women was 3.32 (95% CI, 2.39-4.60). Of the 131 women with breast cancer for which age at menopause was known, 80 (61%) were diagnosed after menopause, with equal proportions among treated and untreated women.

Sixty-nine treated and 44 untreated women had breast cancer as their first cancer (other than nonmelanoma skin cancer). This resulted in rates of 13.0 and 4.2 per 10,000 person-years, respectively, yielding a crude rate ratio of 3.11 (95% CI, 2.13-4.54).

Bivariate analysis revealed potentially significant differences ($P < 0.10$) in the following breast cancer risk factors between treated and untreated women (Table 3, columns 2-4): age at first birth, oral contraceptive use, hormone replacement therapy use, education level, menopausal status at last response, and proportion of population of self-identified as Jewish. Traditional breast cancer risk factors analyzed by breast cancer status were generally in the expected direction (Table 3, columns 4-8). Risk tended to decline with the number of full pregnancies and increase with education level, Jewish religion, and older age at first birth. Treatment/birth cohort was also a significant risk factor with those treated or born between 1937 and 1947 having a higher risk of breast cancer, than the other two groups.

In multivariate analysis that included the above potentially significant risk factors, only treatment/birth cohort added significantly to the fit of the model with treatment status and attained age (Table 3, column 9). Similarly, none of the traditional breast cancer risk factors added significantly to the model of dose category, treatment/birth cohort, and attained age. We therefore calculated dose group rate ratios for the entire cohort by adjusting for attained age, and treatment/birth cohort; a dose-response relationship was observed after these adjustments (Table 4A; Fig. 1).

Modeling ERR as a linear function over the entire follow-up period resulted in an ERR/Gy of 1.18 (95% CI, 0.66-1.93), after excluding the 54 individuals with an unknown breast radiation dose and adjusting for attained age. The ERR/Gy decreased to 1.10 (95% CI, 0.61-1.86) after also adjusting for treatment/birth cohort. Inclusion of other risk factors individually or collectively in the model did not alter the point estimate of the ERR/Gy by >3% and did not improve model fit. We found no evidence for significant effect modification of the ERR/Gy by age at first birth, number of live births, Jewish religion, or any other potential breast cancer risk factor. Linear, quadratic, and quadratic models of ERR did not fit the data as well as the linear model. The excess absolute risk was 4.3 (95% CI, 1.2-8.2) per $1 \times 10^4$ person-years per Gy after adjusting for attained age.

The interval analysis of breast cancer incidence rates since the 1985 survey included 1,692 women (30,382 person-years) who were breast cancer free before this period. Seventy treated and 44 untreated women had breast cancer during this period for a crude rate ratio of 2.51 (95% CI, 1.72-3.65). Rate ratios for different dose categories adjusted for attained age and treatment/birth cohort are presented in the left hand columns of Table 4B and show an increased risk with radiation dose ($P_{trend} < 0.001$).
Discussion

Women exposed to radiotherapy for an enlarged thymus during early childhood are at increased risk for breast cancer well into the 6th decade of life with a statistically significant radiation dose-response relationship. This association remained even after evaluating the potential for confounding by multiple breast cancer risk factors. Incidence rate ratios for neither the entire follow-up period nor the interval since the 1985 survey were markedly different when censored for other first cancers, suggesting that the increased breast cancer incidence among thymic-irradiated women did not result solely from a greater exposure to chemotherapy or secondary radiotherapy.

Although our current results suggest a possible decrease in relative risk of breast cancer associated with thymic irradiation over time, the excess absolute risk (EAR) appeared to increase with time. The rate ratio for treated individuals up to 1987 had been 3.6 (15), so the new estimates, using a similar model adjusted for attained age only, of 3.05 represents a 16% reduction and of 2.54 since the 1985 survey represents a 31% reduction. The previously reported ERR/Gy of 3.48 (95% CI, 2.1-6.2) was not adjusted for attained age (15), so similar estimates of 1.96 (95% CI, 1.18-3.08) for the entire follow-up period and of 1.64 (95% CI, 0.85-2.85) since the 1985 survey represent 44% and 53% reductions, respectively. Although models suggested that time since therapy would reduce ERR of breast cancer (1), the longitudinal nature of our data collection has allowed for the confirmation of this within a single cohort. However, the unadjusted excess absolute risk increased from 5.7 (95% CI, 2.9-9.5) to 12.2 (95% CI, 8.2-17.0) cases per 1 × 10^4 person-years per Gy. These opposite trends in relative and absolute risk are not contradictory, because baseline breast cancer incidence increases with age, offsetting the decline over time in the relative risk associated with radiation exposure (1). Although changes in dosimetry might affect comparisons with prior results, analysis using the original dose estimates suggest that any changes in dosimetry would underestimate the decrease in ERR/Gy over time, while having a <5% effect on EAR estimates.

To place the magnitude of the radiation-associated breast cancer risk from our study in perspective, we used the excess absolute risk model for breast cancer diagnosis by 50 years of age from a large pooled analysis of eight cohorts by Preston et al. (1).
cohort with follow-up through the 1985 survey, the atomic bomb survivors cohort, and six others. The authors recommend using the pooled EAR model to transfer risk across different populations (1). Using this pooled model, they estimated that in our cohort, the EAR at age of 50 years would be 30 per $1 \times 10^3$ person-years per Gy (95% CI, 7.7-71), which is remarkably similar to the EAR/Gy of 28.7 per $1 \times 10^3$ person-years (95% CI, 17.6-41.7) we calculated applying this model to the updated data. This would continue to place the EAR/Gy estimate from this cohort among the highest of the eight cohorts studied. This finding is likely due to the relatively greater number of years at risk since exposure, the relatively acute nature of the radiation exposure (i.e., one or two fractions versus multiple fractions), and the relative radiosensitivity of the breast at age of exposure (infancy) compared with other cohorts in the pooled analysis (1).

Although infants are generally thought to be more radiosensitive than older children and adults (20), in terms of breast cancer, the highest risk from radiation may be during puberty and surrounding the first pregnancy, when breast ductal cells are actively developing (2, 38, 39). Comparing our results to those from the recent follow-up of U.S. Scoliosis Study cohort (40) would suggest that breast cancer risk per Gy in infants is not as high as in adolescents and young adults. In this cohort, women received periodic X-rays for scoliosis evaluation resulting in an estimated mean dose to the breast of 0.13 Gy (range, 0.00005-1.11 Gy), over a median of 24 fractions. A vast majority had some radiation exposure from screening between breast budding and first childbirth, whereas only 23% had exposure before breast budding. The estimated EAR/Gy was 176 per $1 \times 10^3$ person-years at age 50 years using the common model from the pooled cohort study compared with our estimate of 28.7. This estimate is much higher than ours, strongly suggesting that the young adult female breast is more radiosensitive. Furthermore, they found that the ERR/Gy was highest for radiation exposure during the period between menarche and birth of the first child and lowest for the period before breast budding, although adjusting for period of exposure did not improve model fit (40).

None of the traditional breast cancer risk factors added significantly to model fit in our cohort. This result suggests that even at the “relatively lower” medical doses in the thymus cohort (mean, 0.71 Gy; median, 0.17 Gy), radiation is a much more powerful breast cancer risk factor than other established risk factors. Due to missing risk factor data, we were only able to perform multivariate adjustment using 80% of our sample. The findings from other studies on the effect of traditional breast cancer risk factors on radiation’s effect are mixed (6, 38, 39, 41, 42). In other radiation-exposed cohorts, age at first birth seems to be the most consistent independent risk factor for breast cancer, although it does not directly modify the effect of a given dose of irradiation (41, 43). Findings in Hodgkin lymphoma survivors suggest that decreased estrogen stimulation decreases the breast cancer risk associated with a unit dose of irradiation, at least premenopausally (42, 44).

Three studies have suggested that family history and particular mutations may affect risk associated with irradiation (40, 45, 46). With absent data on family history of breast cancer, we investigated whether Jewish ethnicity might affect risk, given the increased frequency of BRCA1 and 2 mutations in Ashkenazi Jews (47). Jewish subjects in our cohort had also been found to have a greater risk of thyroid cancer per Gy (26). Although significant in univariate analysis, no evidence existed for an independent or interactive effect of Jewish ethnicity in multivariate models that included thymic irradiation status or dose. This result may be due to a true absence of association, our very limited power, and/or the clustering of Jewish families in the practice that tended to use the highest radiation doses (26).

Treatment/birth cohort added to model fit, with the group born or treated between 1937 and 1947 having a much higher risk than the other two groups. This cohort also had a nonsignificantly lower ERR/Gy of 0.63 (95% CI, 0.20-1.36) compared with the group treated before 1937 with an ERR/Gy of 1.97 (95% CI, 0.75-4.49) and the group after 1947 with an ERR/Gy of 2.08 (95% CI 0.44-5.91). These results could be caused by differences in breast cancer risk factors in the different treatment/birth cohorts. However, risk factor distribution varied significantly by treatment/birth cohort but not in a consistent manner (data not shown). There was also more missing data in the earliest cohort, making further analysis difficult. Nevertheless, even in our models without treatment/birth cohort, none of the traditional breast cancer risk factors significantly added to multivariate model fit.

A limitation of our study is the lower-than-desired response rate and the differential response rate between the treated and untreated women. This response pattern might lead to nonresponse bias, threatening internal validity. However, differences in breast cancer risk factors among responders and nonresponders by treatment group are minimal and would tend to cancel each other out (Table 2). For age at first birth and oral contraceptive use, differences in distribution between responders and nonresponders in the untreated group are similar in magnitude and direction to differences in the treated group between responders and nonresponders. Thus, the relative risk comparing the two groups should not be substantially biased by the difference between measured and actual distributions of these factors. Respondents also had a lower rate of smoking than nonrespondents in the untreated group, but smoking is not consistently associated with breast cancer risk in other studies (48) nor in our cohort previously (15). Additionally, the rate ratio for thymic irradiation on breast cancer incidence up until 1987 did not differ significantly between responders and nonresponders to the current survey ($P = 0.25$), further suggesting that nonresponse bias is not a substantial problem in our study.
Table 3. Significance of potential breast cancer risk factors on breast cancer incidence after combining data from the 1985 to 1987 and 2004 to 2008 follow-up surveys

<table>
<thead>
<tr>
<th>% treated</th>
<th>% nontreated</th>
<th>P (trt vs nontrt)</th>
<th>Person-years</th>
<th>No. of BC cases</th>
<th>Relative risk (95% CI)*</th>
<th>P†</th>
<th>Adjusted relative risks for breast cancer (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymic irradiation: yes</td>
<td>—</td>
<td>—</td>
<td>&lt;0.001</td>
<td>3.05 (2.15-4.36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time period of treatment (birth in untreated)</td>
<td>0.41</td>
<td>51.2</td>
<td>53.4</td>
<td>58,591</td>
<td>22</td>
<td>1.17 (0.64-2.16)</td>
<td>1.00 (0.55-1.82)</td>
</tr>
<tr>
<td>&gt;1947</td>
<td>36.5</td>
<td>34.3</td>
<td>53,716</td>
<td>81</td>
<td>2.26 (1.48-3.55)</td>
<td>2.05 (1.34-3.20)</td>
<td></td>
</tr>
<tr>
<td>&lt;1937</td>
<td>12.3</td>
<td>12.3</td>
<td>21,330</td>
<td>31</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Attained age</td>
<td>0.78</td>
<td>0.44</td>
<td>0.44</td>
<td>0.44</td>
<td>—</td>
<td>—</td>
<td>1.10 (1.08-1.11)</td>
</tr>
<tr>
<td>Ever pregnant</td>
<td>81.7</td>
<td>82.1</td>
<td>109,852</td>
<td>112</td>
<td>0.83 (0.54-1.35)</td>
<td>1.00</td>
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<tr>
<td>Yes</td>
<td>18.3</td>
<td>17.9</td>
<td>23,785</td>
<td>22</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>Ever given birth</td>
<td>0.46</td>
<td>0.47</td>
<td>0.47</td>
<td>0.47</td>
<td>—</td>
<td>—</td>
<td>1.10 (1.08-1.11)</td>
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<tr>
<td>Yes</td>
<td>76.2</td>
<td>77.4</td>
<td>109,725</td>
<td>112</td>
<td>0.84 (0.54-1.37)</td>
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</tr>
<tr>
<td>No</td>
<td>23.8</td>
<td>22.6</td>
<td>23,913</td>
<td>22</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>No. of full pregnancies</td>
<td>0.24</td>
<td>0.09</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4+</td>
<td>10.7</td>
<td>13.4</td>
<td>20,983</td>
<td>22</td>
<td>0.60 (0.33-1.10)</td>
<td>1.00</td>
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<tr>
<td>3</td>
<td>19.8</td>
<td>18.1</td>
<td>28,053</td>
<td>27</td>
<td>0.79 (0.45-1.41)</td>
<td>1.00</td>
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<tr>
<td>2</td>
<td>31.8</td>
<td>31.9</td>
<td>44,027</td>
<td>53</td>
<td>1.11 (0.69-1.87)</td>
<td>1.00</td>
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<tr>
<td>1</td>
<td>13.9</td>
<td>14.0</td>
<td>16,662</td>
<td>10</td>
<td>0.65 (0.29-1.33)</td>
<td>1.00</td>
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</tr>
<tr>
<td>0</td>
<td>23.8</td>
<td>22.6</td>
<td>23,913</td>
<td>22</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Age at first birth (y)§</td>
<td>0.005†</td>
<td>0.03</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥35</td>
<td>21.3</td>
<td>21.0</td>
<td>25,364</td>
<td>26</td>
<td>1.57 (0.97-2.48)</td>
<td>1.00</td>
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<tr>
<td>25-34</td>
<td>35.1</td>
<td>29.6</td>
<td>43,243</td>
<td>52</td>
<td>1.42 (0.97-2.07)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>43.5</td>
<td>49.4</td>
<td>65,030</td>
<td>56</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Age at menarche (y)</td>
<td>0.71</td>
<td>0.49</td>
<td>—</td>
<td>0.49</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>21.6</td>
<td>22.2</td>
<td>28,970</td>
<td>32</td>
<td>1.15 (0.76-1.69)</td>
<td>1.00</td>
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<tr>
<td>≥12</td>
<td>78.4</td>
<td>77.8</td>
<td>104,667</td>
<td>102</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal at last response</td>
<td>&lt;0.001</td>
<td>&gt;0.50</td>
<td>NS</td>
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<tr>
<td>Yes</td>
<td>59.2</td>
<td>45.2</td>
<td>81,464</td>
<td>114</td>
<td>0.95 (0.57-1.65)</td>
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<tr>
<td>No</td>
<td>40.8</td>
<td>54.8</td>
<td>52,172</td>
<td>22</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>Oral birth control use</td>
<td>0.06</td>
<td>0.49</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>80.0</td>
<td>77.0</td>
<td>102,219</td>
<td>96</td>
<td>1.14 (0.79-1.70)</td>
<td>1.00</td>
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<tr>
<td>No</td>
<td>20.0</td>
<td>23.0</td>
<td>31,418</td>
<td>38</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>Hormone replacement use</td>
<td>&lt;0.001</td>
<td>&gt;0.50</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>37.9</td>
<td>27.3</td>
<td>10,089</td>
<td>48</td>
<td>1.09 (0.74-1.60)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>62.1</td>
<td>72.7</td>
<td>123,549</td>
<td>86</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>0.002</td>
<td>0.03</td>
<td>NS</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grad school</td>
<td>17.6</td>
<td>12.6</td>
<td>45,140</td>
<td>65</td>
<td>2.53 (0.94-10.33)</td>
<td>1.00</td>
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<tr>
<td>4-y college</td>
<td>19.0</td>
<td>18.0</td>
<td>34,071</td>
<td>24</td>
<td>1.46 (0.51-6.15)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Trade and some college</td>
<td>33.0</td>
<td>34.9</td>
<td>11,880</td>
<td>8</td>
<td>1.39 (0.51-6.15)</td>
<td>1.00</td>
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<tr>
<td>High school</td>
<td>24.0</td>
<td>27.5</td>
<td>36,177</td>
<td>34</td>
<td>1.78 (0.64-7.38)</td>
<td>1.00</td>
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<tr>
<td>Less than high school</td>
<td>6.4</td>
<td>6.9</td>
<td>6,369</td>
<td>3</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Jewish ethnicity</td>
<td>&lt;0.001</td>
<td>0.07</td>
<td>NS</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

(Continued on the following page)
A related concern is the accuracy of risk factor data collected. Although we incorporated breast cancer risk factor data from the 1985 and the current surveys into our analysis, the inclusion of the former would minimize misclassification only for those risk factors unlikely to change after 1985, when the average age was 37 years and the minimum age was 22 year. These risk factors would include age at menarche, factors regarding pregnancy, and use of oral contraceptives, which were all remarkably consistent between the two surveys at the individual level. Data on menopausal status, age at menopause, and hormone replacement therapy, however, likely changed after 1985. Thus, the effect of these factors on the association between radiation and breast cancer risk should be interpreted with caution, as there were fewer respondents to the current survey. As breast cancer risk factors were first collected in 1985, we could not adjust for these variables in the person-years provided by people who were no longer in the cohort by 1985. Finally, we note that complex radiobiological models were not applied to these data, as the linear dose model proved to fit better than linear quadratic or pure quadratic models, and a more complex model including a term that allowed for a downturn at high doses due to “cell sterilization”—ERR(D) = (β1D + β2D2) * [exp(−β3D −β4D3)]; ref. 49—could not be fit statistically. The latter is probably because of the limited number of breast cancer cases.

This study has several strengths. First, to our knowledge, the median follow-up of this cohort is longer than that of any other radiation-exposed cohort, other than the atomic bomb survivors’ cohort (49, 50). As such, it is one of the first studies of individuals exposed to medical irradiation during childhood known to have a significant proportion of breast cancer events occur after menopause. Second, the cohort has an internal comparison group made up of siblings from the same community as those exposed to irradiation. Third, although radiation received by our cohort differs from that used today in terms of dose distribution and less-precise techniques, this exposure is more similar to the therapeutic and diagnostic radiation received by patients today than is the whole-body radiation received by atomic bomb survivors with its different exposure pattern and sources of radioactivity. Our cohort also has the advantage that their radiation exposure was not due to cancer, so our findings are not confounded by the possibility that an initial malignancy may be a marker of cancer susceptibility or by chemotherapy effects.

Our results therefore highlight the potential for increased breast cancer risk from current medical practices that
### Table 4. Breast cancer incidence and rates

#### A. Breast cancer incidence and rates by estimated radiation dose since thymic irradiation

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>No. of women</th>
<th>Person-years at risk</th>
<th>Mean dose Gy (SD)</th>
<th>Median dose Gy</th>
<th>Breast cancer cases, n</th>
<th>Breast cancer rate (per 10,000 person-years)</th>
<th>Rate ratio of breast cancer compared with untreated (95% CI)*</th>
<th>Person years at risk for BC as first cancer</th>
<th>Breast cancer as first cancer†</th>
<th>Rate of BC as first cancer (per 10,000 person-years)</th>
<th>Rate ratio of first breast cancer (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontreated</td>
<td>2,383</td>
<td>105,723</td>
<td>—</td>
<td>—</td>
<td>57</td>
<td>5.4 Reference</td>
<td>105,486 44 4.2 Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total treated</td>
<td>1,120</td>
<td>53,732</td>
<td>0.71 (1.20)</td>
<td>0.17</td>
<td>96</td>
<td>17.9 3.01 (2.18-4.21) 53,196 69 13.0 2.84 (1.95-4.17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.01-0.24</td>
<td>694</td>
<td>31,906</td>
<td>0.10 (0.08)</td>
<td>0.06</td>
<td>34</td>
<td>10.7 2.23 (1.43-3.44) 31,792 27 8.5 2.31 (1.40-3.77)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25-0.49</td>
<td>79</td>
<td>3,891</td>
<td>0.35 (0.08)</td>
<td>0.33</td>
<td>7</td>
<td>18.0 2.37 (0.98-4.87) 3,860 5 13.0 2.15 (0.74-4.94)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0.5-1.99</td>
<td>119</td>
<td>6,153</td>
<td>1.24 (0.43)</td>
<td>1.22</td>
<td>20</td>
<td>32.5 4.23 (2.47-6.98) 6,054 16 26.4 4.51 (2.45-7.91)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2.00-3.99</td>
<td>148</td>
<td>7,462</td>
<td>2.55 (0.49)</td>
<td>2.29</td>
<td>21</td>
<td>28.1 4.13 (2.45-6.71) 7,279 13 17.9 3.43 (1.77-6.18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4.00</td>
<td>26</td>
<td>1,384</td>
<td>5.33 (2.03)</td>
<td>4.72</td>
<td>6</td>
<td>43.4 4.74 (1.82 to 10.2) 1,352 5 37.0 5.05 (1.74-11.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irradiated but dose unknown</td>
<td>54</td>
<td>2,936</td>
<td>—</td>
<td>—</td>
<td>8</td>
<td>27.2 2.70 (1.18-5.35) 2,859 3 10.5 1.37 (0.33-3.76)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for attained age and treatment/birth cohort (three periods). Analysis was performed with the AMFIT module of Epicure.
†First cancer other than nonmelanoma skin cancer.
‡Test for trend of rate ratios adjusted for treatment/birth cohort and attained age. Excludes unknown radiation dose category.

#### B. Breast cancer incidence and rates for the interval between the 1985 to 1987 survey and the current survey

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>No. of women</th>
<th>Person-years at risk</th>
<th>Mean dose Gy (SD)</th>
<th>Median dose Gy</th>
<th>Breast cancer cases</th>
<th>Breast cancer rate (per 10,000 person-years)</th>
<th>Rate ratio of breast cancer compared with untreated (95% CI)*</th>
<th>Person years at risk for BC as first cancer</th>
<th>Breast cancer as first cancer†</th>
<th>Rate of BC as first cancer (per 10,000 person-years)</th>
<th>Rate ratio of first breast cancer (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontreated</td>
<td>1,024</td>
<td>18,595</td>
<td>—</td>
<td>—</td>
<td>44</td>
<td>23.7 Reference</td>
<td>18,414 31 16.8 Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total treated</td>
<td>668</td>
<td>11,787</td>
<td>0.70 (1.13)</td>
<td>0.16</td>
<td>70</td>
<td>59.4 2.52 (1.73-3.69) 11,534 47 40.7 2.43 (1.55-3.86)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.01-0.24</td>
<td>422</td>
<td>7,681</td>
<td>0.10 (0.07)</td>
<td>0.06</td>
<td>27</td>
<td>35.1 1.90 (1.15-3.08) 7,590 20 26.4 1.94 (1.08-3.41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0.25-0.49</td>
<td>42</td>
<td>750</td>
<td>0.36 (0.09)</td>
<td>0.33</td>
<td>6</td>
<td>80.0 2.40 (0.81-5.24) 727 4 55.0 2.27 (0.67-5.77)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5-1.99</td>
<td>64</td>
<td>1,061</td>
<td>1.24 (0.43)</td>
<td>1.24</td>
<td>13</td>
<td>122.5 3.41 (1.75-6.24) 1,033 10 98.8 4.06 (1.86-8.15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.00-3.99</td>
<td>89</td>
<td>1,515</td>
<td>2.55 (0.51)</td>
<td>2.29</td>
<td>14</td>
<td>92.4 3.34 (1.76-5.95) 1,456 9 61.8 3.23 (1.44-6.53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4.00</td>
<td>16</td>
<td>204</td>
<td>5.33 (2.03)</td>
<td>4.72</td>
<td>3</td>
<td>147.1 3.59 (0.87-9.93) 197 2 101.5 3.36 (0.54-11.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated but dose unknown</td>
<td>35</td>
<td>576</td>
<td>7</td>
<td>121.5 2.98 (1.22-6.27) 532 2 37.6 1.35 (0.22-4.50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
expose the chest to irradiation during early childhood. As previously mentioned, the higher breast doses in the thymus cohort overlap with exposures to the breast from current radiotherapy protocols for childhood Hodgkin’s lymphoma, whereas lower doses may be consistent with scatter from treatment for other malignancies such as Wilms tumor (14, 51). More importantly, the lower doses in this cohort are similar to those to the breast of infants from chest CT. Typical breast doses for an infant from a single chest CT range between 0.014 and 0.03 Gy (21-23, 52). Doses can be twice as high if the settings are not changed from adult levels and a substantial fraction of CT-scanned patients require multiple scans; so if both conditions are met, total doses would be close to the median dose of 0.17 Gy in our cohort (53). In fact, exposures at the lower end of the dose range in our cohort were unfractonated, and thus, may be the most like that from pediatric chest CT than in any other studied cohort to date. Recent studies suggest that an estimated 930,000 body CTs are performed on children ages 5 years or younger (53, 54). Our findings, by adding information on breast cancer risk, support the earlier concern that the population risk of cancer from children undergoing a single CT is not negligible (20, 54). In fact, when we limited our analysis to breast exposures of <1 Gy, the estimated ERR per Gy was even higher at 4.80 (95% CI, 1.71-9.56). Although at lower doses, the error in dose estimation is larger as a percentage of total dose, so ERR estimates may not be as accurate.

In conclusion, our study adds to the radiation-associated breast cancer literature by extending the follow-up of the Rochester, NY thymic irradiation cohort, providing the longest longitudinal follow-up of any cohort exposed to chest radiotherapy. The breast cancer incidence rate associated with the average radiation dose of 0.71 Gy remains about thrice higher than it is among untreated women from the same communities and families. Our findings suggest that while limiting thoracic radiation exposure during childhood cancer treatment may decrease breast cancer risk, survivors will continue to have an increased cumulative incidence of breast cancer. These findings along with those of others also suggest that female infants undergoing chest CT may be at increased breast cancer risk as adults. Although the risks and benefits of radiation exposure for medical purposes must be weighed on an individual basis, these results underscore the importance of limiting radiation exposure in the youngest children as much as possible.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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**References**

Breast Cancer Risk 55+ Years After Irradiation for an Enlarged Thymus and Its Implications for Early Childhood Medical Irradiation Today


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