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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

Purpose—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 (BC) incidence in a cohort treated with “lower dose” chest radiotherapy (cRT) over 50 years ago, can assist with estimating lifetime BC risk in young children exposed to radiation from procedures such as chest computed tomography (CT) or treatment with recent “lower dose” cRT 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 reestablished. Previously followed until 1987, we re-surveyed cohort members from 2004 to 2008. Poisson regression models compared BC 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% CI: 0.61-1.86). Traditional BC risk factors did not contribute significantly to multivariate model fit.

Conclusion—Our results demonstrate that at radiation doses between those received by the breast from chest CT and cancer therapy during early childhood, BC incidence rates remain elevated more than 50 years after exposure. This implies that increased BC risk will remain a lifelong concern in

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females treated during childhood with currently reduced RT doses and for infants receiving multiple chest CTs.

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 with median doses of approximately 40 Gy have an estimated cumulative breast cancer incidence as high as 1 in 8 by age 40, 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, current practice is to generally limit total chest radiation dose to 25 Gy or less during childhood, which exposes the breast to about 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 less than 50 years. These studies and studies of the atomic bomb survivors have raised concern about the population risk from the increasing use of “higher-dose” imaging modalities such as chest computed tomography (CT) in young children (20). The re-initiation 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 more than 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 1985-1987, the thymic irradiated women had a 3.6 (95% CI: 1.8 -7.3) times higher risk of breast cancer than the untreated women (15). This increased risk occurred even though 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.

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 Gy to 12.50 Gy, with the number of fractions ranging from 1-7, though 89% received only one or two treatments. Time between first and last treatment was $\leq$ 90 days for 98% of women with the longest time being 4.5 years. All treated subjects received orthovoltage radiation ranging from 57 to 290 KVP, and 96% of individuals were treated at one year 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 less than 5 years after birth, either due to death or loss to follow-up. After these exclusions, the studied cohort included 1120 girls who had received radiation treatment and 2382 female siblings (of both treated boys and girls) who did not. This comparison group

is referred to as the “untreated” or “non-treated” women throughout this paper. 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 6 times, in 1953 (27), 1959 (28), 1963 (29), 1969 (30), 1975 (31), and 1985-1987 (15,26), before becoming dormant after 1987. Methodology 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 report, or medical record. Survey response rates were very high and similar among treated and untreated cohort members. In the 1985-87 survey, approximately 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 previously described 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, while 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 about 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 www.whitepages.com. 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 non-melanoma 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, in order 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 more than 37 years after initial exposure. This “interval 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 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 year 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 the start of the follow-up interval was the return date of the 1985-1987 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 non-melanoma skin cancer, in order 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 percent confidence intervals (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 chi-square 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 performed using SAS version 9.2. All other statistical tests were two-sided with an alpha 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 (approximately 80% of the cohort).

Excess relative risk modeling of radiation dose to the breast was also performed using this same technique and software package. A linear radiation dose response model was used for excess relative risk 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 excess relative risk (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 yrs in treated; 56.5 yrs in non-treated), 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 non-response bias. Age at first birth and oral contraceptive use as reported in 1985 differed between responders and non-responders to the current survey amongst 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. Amongst treated women, 96 had breast cancer, yielding an incidence rate of 17.9 per 10,000 person-years. Fifty-seven untreated 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 non-melanoma 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 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 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; Figure 1).

Modeling excess relative risk (ERR) as a linear function over the entire follow-up period resulted in a 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 more than 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 10^4 person-years per Gy after adjusting for attained age.

The interval analysis of breast cancer incidence rates since the 1985 survey included 1692 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 demonstrate an increased risk with radiation dose (test for trend $p < 0.001$) The ERR/Gy for this period is 0.86 (95% CI 0.36-1.63) after adjustment for attained age and treatment/birth cohort. The interval incidence rates of breast cancer as first cancers are presented in the right hand columns of Table 4b.

Discussion

Women exposed to radiotherapy for an enlarged thymus during early childhood are at increased risk for breast cancer well into the 6^{th} 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.

While our current results suggest a possible decrease in relative risk of breast cancer associated with thymic irradiation over time, the absolute excess risk 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 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 10^4 person-years per Gy. This 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). While 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 less than 5% impact 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 8 cohorts by Preston et al (1). This pooled study included this cohort with follow-up through the 1985 survey, the atomic bomb survivors cohort, and 6 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 would be 30 per 10^4 person-years per Gy (95% CI: 7.7-71), which is remarkably similar to the EAR/Gy of 28.7 per 10^4 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 8 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 vs. multiple fractions), and the relative radiosensitivity of the breast at age of exposure (infancy) compared to 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 child birth, while only 23% had exposure before breast budding. The estimated EAR/Gy was 176 per 10^4 person-years at age 50 using the common model from the pooled cohort study compared to 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 BC 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 then 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 impact 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 though it does not directly modify the effect of a given dose of irradiation (43,44). Findings in Hodgkin lymphoma survivors suggest that decreased estrogen stimulation decreases the breast cancer risk associated with a unit dose of irradiation, at least pre-menopausally (42,45).

Three studies have suggested that family history and particular mutations may affect risk associated with irradiation (40,46,47). 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 (48). 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 non-significantly lower ERR/Gy of 0.63 (95% CI: 0.20-1.36) compared to 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 non-response bias, threatening internal validity. However, differences in breast cancer risk factors amongst responders and non-responders 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 non-responders in the untreated group are similar in magnitude and direction to differences in the treated group between responders and non-responders. 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 non-respondents in the untreated group, but smoking is not consistently associated with breast cancer risk in other studies (49) 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 non-responders to the current survey ($p= 0.25$); further suggesting non-response bias is not a substantial problem in our study.

A related concern is 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 years. 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“– $ERR(D) = (\beta_1 D + \beta_2 D^2) * [\exp(-\beta_3 D - \beta_4 D^2)$ (50)-- 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 (51,52). 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 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, while lower doses may be consistent with scatter from treatment for other malignancies such as Wilms tumor (14,53). 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 (21-23,54). Doses can be twice as high if the settings are not changed from adults levels and a substantial fraction of CT-scanned patients require multiple scan, so if both conditions are met total doses would be close to the median dose of 0.17 Gy in our cohort (55). In fact, exposures at the lower end of the dose range in our cohort were unfractionated, 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 5 years old or younger (55,56). 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 (20,56). 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 3 times 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. While 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.

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Reference List

1. Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD Jr. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. Radiat Res 2002;158:220–35. [PubMed: 12105993]
2. Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: a review of current evidence. Breast Cancer Res 2005;7:21–32. [PubMed: 15642178]
3. van Leeuwen FE, Klokman WJ, Hagenbeek A, et al. Second cancer risk following Hodgkin's disease: a 20-year follow-up study. J Clin Oncol 1994;12:312–25. [PubMed: 8113838]

4. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290:465–75. [PubMed: 12876089]
5. Travis LB, Hill D, Dores GM, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. J Natl Cancer Inst 2005;97:1428–37. [PubMed: 16204692]
6. Hill DA, Gilbert E, Dores GM, et al. Breast cancer risk following radiotherapy for Hodgkin lymphoma: modification by other risk factors. Blood 2005;106(10):3358–65. [PubMed: 16051739]
7. Bhatia S, Robison LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. New Engl J Med 1996;334:745–51. [PubMed: 8592547]
8. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst 1993;85:25–31. [PubMed: 8416252]
9. Aisenberg AC, Finkelstein DM, Doppke KP, Koerner FC, Boivin JF, Willett CG. High risk of breast carcinoma after irradiation of young women with Hodgkin's disease. Cancer 1997;79:1203–10. [PubMed: 9070499]
10. Gervais-Fagnou DD, Girouard C, Laperriere N, Pintillie M, Goss PE. Breast cancer in women following supradiaphragmatic irradiation for Hodgkin's disease. Oncology 1999;57(3):224–31. [PubMed: 10545791]
11. Ng AK, Bernardo MV, Weller E, et al. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors. Blood 2002;100:1989–96. [PubMed: 12200357]
12. Basu SK, Schwartz C, Fisher SG, et al. Unilateral and bilateral breast cancer in women surviving pediatric Hodgkin's disease. Int J Radiat Oncol Biol Phys 2008;72:34–40. [PubMed: 18722264]
13. Tubiana M. Can we reduce the incidence of second primary malignancies occurring after radiotherapy? A critical review Radiother & Oncol 2009;91:4–15.
14. Kenney LB, Yasui Y, Inskip PD, et al. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. Ann Intern Med 2004;141:590–7. [PubMed: 15492338]
15. Hildreth NG, Shore RE, Dvoretsky PM. The risk of breast cancer after irradiation of the thymus in infancy. New Engl J Med 1989;321:1281–4. [PubMed: 2797100]
16. Lundell M, Mattsson A, Karlsson P, Holmberg E, Gustafsson A, Holm LE. Breast cancer risk after radiotherapy in infancy: a pooled analysis of two Swedish cohorts of 17,202 infants. Radiat Res 1999;151:626–32. [PubMed: 10319736]
17. Modan B, Chetrit A, Alfandary E, Katz L. Increased risk of breast cancer after low-dose irradiation. Lancet 1989:629–31. [PubMed: 2564456]
18. Myrden JA, Hiltz JE. Breast cancer following multiple fluoroscopies during artificial pneumothorax treatment of pulmonary tuberculosis. CMAJ 1969;100:1032–4. [PubMed: 5784909]
19. Miller AB, Howe GR, Sherman GJ, et al. Mortality from breast cancer after irradiation during fluoroscopic examinations in patients being treated for tuberculosis. New Engl J Med 1989;321:1285–9. [PubMed: 2797101]
20. Brenner DJ, Elliston CD, Hall EJ, Berdon WE. Estimated Risks of Radiation-Induced Fatal Cancer from Pediatric CT. AJR Am J Roentgenol 2001;176:289–96. [PubMed: 11159059]
21. Pages J, Buls N, Osteaux M. CT doses in children: a multicentre study. Brit J Radiol 2003;76:803–11. [PubMed: 14623782]
22. Fearon T, Vucich J. Normalized pediatric organ-absorbed doses from CT examinations. AJR Am J Roentgenol 1987:171–4. [PubMed: 3491508]
23. Lee C, Staton RJ, Hintenlang DE, Arreola MM, Williams JL, Bolch WE. Organ and effective doses in pediatric patients undergoing helical multislice computed tomography examination. Med Phys 2007;34:1858–73. [PubMed: 17555267]
24. Friedlander A. Status lymphaticus and enlargement of the thymus with report of a case being successfully treated by x-ray. Arch Pedatri 1907;24:491–501.
25. Saenger EL, Silverman F, Sterling T, et al. Neoplasia following therapeutic irradiation for benign conditions of childhood. Radiology 1960;74:904.
26. Shore RE, Hildreth N, Dvoretsky P, Andresen E, Moseson M, Pasternack B. Thyroid cancer among persons given X-ray treatment in infancy for an enlarged thymus gland. Am J Epidemiol 1993;137:1068–80. [PubMed: 8317436]

27. Simpson CL, Hempelmann LH, Fuller L. Neoplasia in children treated with X-rays in infancy for thymic enlargement. Radiology 1955;64:840–5. [PubMed: 14385062]
28. Pifer JW, Toyooka ET, Murray R, Ames WR, Hempelmann LH. Neoplasms in children treated with x rays for thymic enlargement. I. Neoplasms and mortality. J Nat Cancer Inst 1963;31:1333–56. [PubMed: 14087655]
29. Hempelmann LH, Pifer JW, Burke GJ, Terry R, Ames WR. Neoplasms in persons treated with x rays in infancy for thymic enlargement. A report of the third follow-up survey. J Natl Cancer Inst 1967;38:317–41. [PubMed: 6022610]
30. Hempelmann LH, Hall WJ, Phillips M, Cooper RA, Ames WR. Neoplasms in persons treated with x-rays in infancy: fourth survey in 20 years. J Nat Cancer Inst 1975;55:519–30. [PubMed: 1159831]
31. Hildreth NG, Shore RE, Hempelmann LH, Rosenstein M. Risk of extrathyroid tumors following radiation treatment in infancy for thymic enlargement. Radiat Res 1985;102:378–91. [PubMed: 4070552]
32. Stovall M, Weathers R, Kasper C, et al. Dose reconstruction for therapeutic and diagnostic radiation exposures: use in epidemiological studies. Radiat Res 2006;166:141–57. [PubMed: 16808603]
33. Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995;141:259–77. [PubMed: 7871153]
34. Verkooijen HM, Fioretta G, de Wolf C, et al. Management of women with ductal carcinoma in situ of the breast: a population-based study. Ann Oncol 2002;13:1236–45. [PubMed: 12181247]
35. Pearson, ES.; Hartley, HO. Biometrika tables for statisticians. 3rd. London: Biometrika Trust; 1976.
36. Preston, DL.; Lubin, JH.; Pierce, DA. Epicure User's Guide. Seattle, WA: Hirosoft International; 1991.
37. Breslow, NE.; Day, NE. Statistical Methods in Cancer Research Vol 2 The Design and Analysis of Cohort Studies. Lyon, France: International Agency for Research on Cancer; 1988.
38. Boice, JD., Jr; Stone, BJ. Interaction between radiation and other breast cancer risk factors. Vienna, Austria: International Atomic Energy Association; 1978. Report No.: IAEA-SM-244/713
39. Shore RE, Woodard ED, Hempelmann LH, Pasternack BS. Synergism between radiation and other risk factors for breast cancer. Prev Med 1980;9:815–22. [PubMed: 7454704]
40. Ronckers CM, Doody MM, Lonstein JE, Stovall M, Land CE. Multiple Diagnostic X-rays for Spine Deformities and Risk of Breast Cancer. Cancer Epidemiol Biomarkers Prev 2008;17:605–13. [PubMed: 18349278]
41. Holmberg E, Holm LE, Lundell M, Mattsson A, Wallgren A, Karlsson P. Excess breast cancer risk and the role of parity, age at first childbirth and exposure to radiation in infancy. Brit J Cancer 2001;85:362–6. [PubMed: 11487266]
42. van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst 2003;95:971–80. [PubMed: 12837833]
43. Land CE, Hayakawa N, Machado SG, et al. A case-control interview study of breast cancer among Japanese A-bomb survivors. II. Interactions with radiation dose. Cancer Causes Control 1994;5:167–76. [PubMed: 8167264]
44. Holmberg E, Holm LE, Lundell M, Mattsson A, Wallgren A, Karlsson P. Excess breast cancer risk and the role of parity, age at first childbirth and exposure to radiation in infancy. Brit J Cancer 2001;85:362–6. [PubMed: 11487266]
45. Inskip PD, Robison LL, Stovall M, et al. Radiation Dose and Breast Cancer Risk in the Childhood Cancer Survivor Study. J Clin Oncol 2009;27:3901–7. [PubMed: 19620485]
46. Andrieu N, Easton DF, Chang-Claude J, et al. Effect of Chest X-Rays on the Risk of Breast Cancer Among BRCA1/2 Mutation Carriers in the International BRCA1/2 Carrier Cohort Study. J Clin Oncol 2006;24:3361–6. [PubMed: 16801631]
47. Millikan RC, Player JS, deCotret AR, Tse CK, Keku T. Polymorphisms in DNA repair genes, medical exposures to ionizing irradiation, and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2005;14
48. Chen JJ, Silver D, Cantor S, Livingston DM, Scully R. BRCA1, BRCA2, and Rad51 operate in a common DNA damage response pathway. Cancer Res 1999;59:1752s–6s. [PubMed: 10197592]

49. Egan KM, Stampfer MJ, Hunter D, et al. Active and Passive Smoking in Breast Cancer: Prospective Results from the Nurses' Health Study. Epidemiology 2002;13:138–45. [PubMed: 11880753]
50. Ronckers CM, Sigurdson AJ, Stovall M, et al. Thyroid cancer in childhood cancer survivors: a detailed evaluation of radiation dose response and its modifiers. Radiat Res 2006;166:618–28. [PubMed: 17007558]
51. Land CE, Tokunaga M, Koyama K, et al. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1990. Radiat Res 2003;160:707–17. [PubMed: 14640793]
52. Tokunaga M, Land CE, Tokuoka S, et al. Incidence of female breast cancer among atomic bomb survivors, 1950-1985. Radiat Res 1994;138:209–23. [PubMed: 8183991]
53. Li FP, Corkery J, Vawter G, Fine W, Sallan SE. Breast carcinoma after cancer therapy in childhood. Cancer 1983;51:521–3. [PubMed: 6295605]
54. Fricke BL, Donnelly LF, Frush DP, et al. In-Plane Bismuth Breast Shields for Pediatric CT: Effects on Radiation Dose and Image Quality Using Experimental and Clinical Data. AJR Am J Roentgenol 2003;180:407–11. [PubMed: 12540443]
55. Mettler FA Jr, Wiest PW, Locken JA, Kelsey CA. CT scanning: patterns of use and dose. J Radiol Prot 2000;20:353–9. [PubMed: 11140709]
56. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. New Engl J Med 2007;357:2277–84. [PubMed: 18046031]

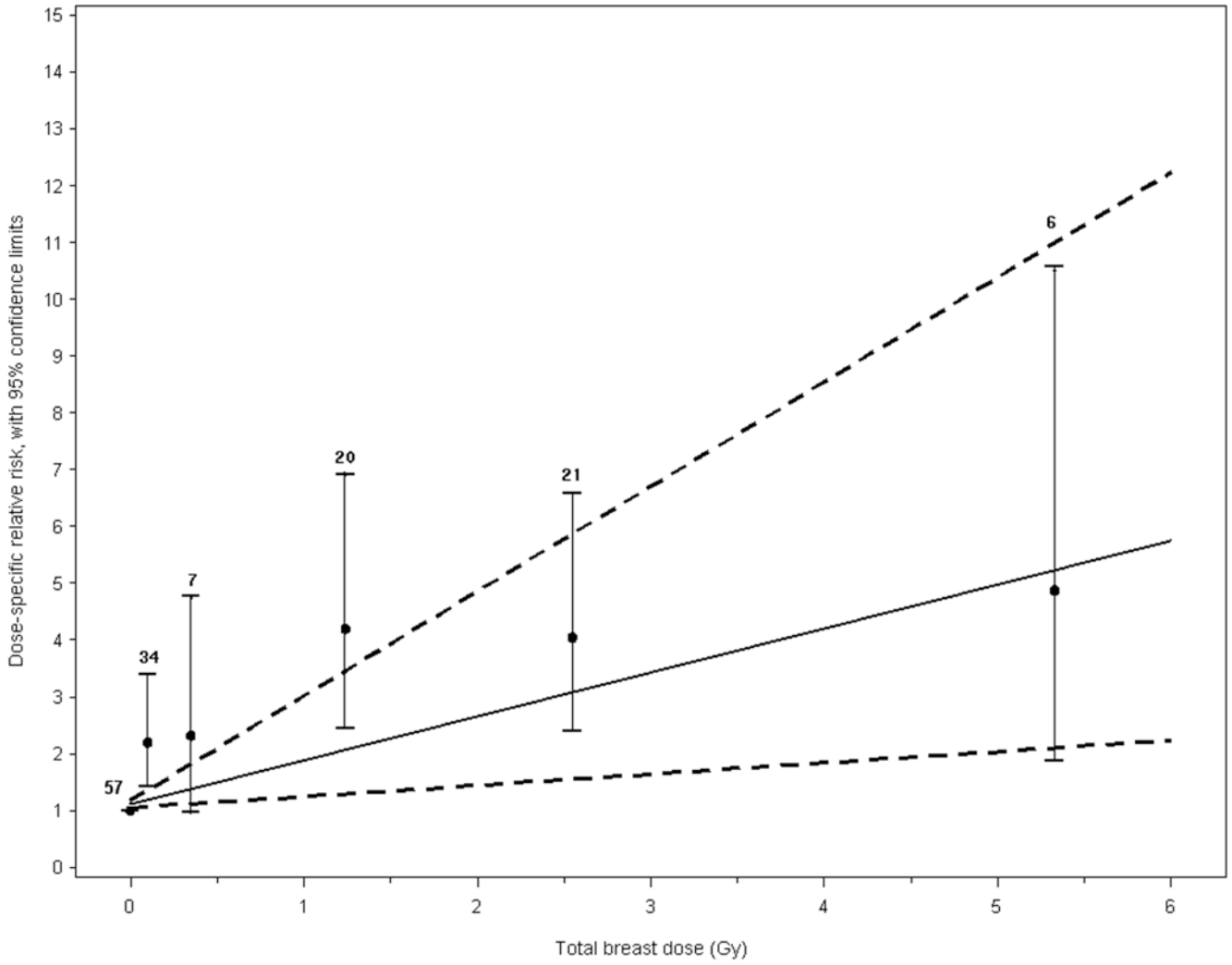

Figure 1.

Radiation dose response for breast cancer incidence among 3449 women in the Rochester, NY Thymus Irradiation Cohort, with known thymic irradiation dose. The analysis is adjusted for attained age (which is highly correlated with time since radiation exposure) and treatment/birth cohort. Dose intervals correspond with categories in Table 4 with data points at mean dose of each category and cross bars representing 95% confidence intervals. Solid line represents best fit linear regression line with dotted lines representing upper and lower 95% CI of regression line

Table 1

Response Rates to the 2004-2008 Follow-up Survey of Women in the Rochester Enlarged Thymus Cohort by Treatment (Thymic Irradiation) Status

Response Status	Total (%) N = 3503[1]	Treated (%) N = 1120[1]	Non-Treated (%) N = 2383[1]
Deceased[2]	314 (9.7)[2]	123 (11.3)	191 (8.0)
Not known to be deceased (Total Surveys Mailed)	3189	997	2192
Responded (Completed) [3]	1576 (49.4)	625 (62.7)	951 (43.4)
Declined[3]	217 (6.8)	36 (3.6)	181 (8.3)
Did not Respond[3]	1096 (34.3)	251 (25.2)	845 (38.5)
Undeliverable[3]	300 (9.4)	85 (8.5)	215 (9.8)

[1] From original sample, 92 treated and 103 untreated girls were excluded from the current cohort because they died before age 5 or were untraceable within 5 years after birth.

[2] As a percentage of the entire cohort

[3] As a percentage of the cohort not known to be deceased. Columns may not sum to 100% as a result of rounding

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Table 2

Comparison of Breast Cancer Risk Factors Collected in 1985 in Responders vs. Non-responders to 2004-2008 Survey by Treatment Group (Females)

	Treated			Non-Treated		
Risk Factor	**Responders n(%)**	**Non-Responders n (%)**	**P**	**Responders n (%)**	**Non-Responders n (%)**	**P**
Pregnant Yes (vs. No)	485 (78.4)	289 (78.7)	0.88	738 (79.3)	922 (78.5)	0.66
Number of full pregnancies			0.36			0.97
0	157 (25.8)	103 (28.1)		245 (26.7)	307 (26.5)	
1	87 (14.3)	60 (16.3)		144 (15.7)	175 (15.1)	
2	199 (32.7)	98 (26.7)		264 (28.8)	343 (29.6)	
3	107 (17.6)	72 (19.6)		157 (17.1)	193 (16.6)	
4 +	59 (9.7)	34 (9.3)		107 (11.7)	142 (12.2)	
Age at 1st Birth			**0.02**			**0.02**
< 25 yrs of age	232 (50.5)	162 (61.3)		394 (58.0)	553 (64.5)	
25-34 yrs of age	220 (47.9)	98 (37.1)		277 (40.8)	290 (33.8)	
≥ 35 yrs of age	7 (1.5)	4 (1.5)		8 (1.2)	14 (1.6)	
Smoking Status						
Ever	365 (59.3)	216 (58.7)	0.84	505 (54.4)	685 (58.7)	**0.047**
Never	250 (40.7)	152 (41.3)		423 (45.6)	481 (41.3)	
Oral Birth Control Use	493 (79.8)	283 (77.1)	**0.003**	733 (78.9)	857 (73.4)	**0.003**
Yes (vs. No)						
Hormone Replacement Therapy Yes (vs. No)	85 (13.8)	55 (15.1)	0.58	114 (12.3)	145 (12.5)	0.91
Mean (SD) Age at Menarche	12.7 (1.5)	12.5 (1.5)	0.17	12.5 (1.4)	12.5 (1.6)	0.74
Mean (SD) Age at 1985-1987 response	38.9 (6.8)	38.7 (6.8)	0.65	37.6 (8.1)	37.9 (9.3)	0.51
Median (Range) Radiation Dose to Breast, Gy	0.16 (0.02-6.15)	0.18 (0.02-7.45)	0.48			

Table 3

Significance of Potential Breast Cancer Risk Factors on Breast Cancer Incidence After Combining Data from the 1985-1987 and 2004-2008 Follow-up Surveys

	% Treated	% Non-Treated	P-value (Trt vs. non-trt)	Person-Years	# BC Cases	Relative Risk (95%CI) [1]	P –Value[2]	Adjusted Relative Risks for Breast Cancer (95%CI)[3]
Thymic Irradiation-- Yes	-	-	-				**< 0.001**	**3.05 (2.15-4.36)**
Time period of treatment (birth in untreated			0.41				**< 0.001**[2]	
>1947	51.2	53.4		58,591	22	1.17 (0.64-2.16)		1.00 (0.55-1.82)
1937-1947	36.5	34.3		53,716	81	2.26 (1.48-3.55)		2.05 (1.34-3.20)
< 1937	12.3	12.3		21,330	31	Ref		Ref
Attained Age				--	--	--		1.10 (1.08-1.11)
Ever Pregnant			0.78				0.44	--
Yes	81.7	82.1		109,852	112	0.83 (0.54-1.35)		
No	18.3	17.9		23,785	22	Ref		
Ever given birth			0.46				0.47	--
Yes	76.2	77.4		109,725	112	0.84 (0.54-1.37)		
No	23.8	22.6		23,913	22	Ref		
Number of Full Pregnancies			0.24				**0.09**	**NS**
4+	10.7	13.4		20,983	22	0.60 (0.33-1.10)		
3	19.8	18.1		28,053	27	0.79 (0.45-1.41)		
2	31.8	31.9		44,027	53	1.11 (0.69-1.87)		
1	13.9	14.0		16,662	10	0.65 (0.29-1.33)		
0	23.8	22.6		23,913	22	Ref		
Age at 1st Birth (yrs of age) [4]			**0.005**[2]				**0.03**	**NS**
≥35	21.3	21.0		25,364	26	1.57 (0.97-2.48)		
25-34	35.1	29.6		43,243	52	1.42 (0.97-2.07)		
< 25	43.5	49.4		65,030	56	Ref		
Age at Menarche (yrs of age)			0.71				0.49	--
< 12	21.6	22.2		28,970	32	1.15 (0.76-1.69)		
≥ 12	78.4	77.8		104,667	102	Ref		
Postmenopausal at last response			**< 0.001**				> 0.50	**NS**

	% Treated	% Non-Treated	P-value (Trt vs. non-trt)	Person-Years	# BC Cases	Relative Risk (95%CI) [1]	P –Value[2]	Adjusted Relative Risks for Breast Cancer (95%CI)[3]
Yes	59.2	45.2		81,464	114	0.95 (0.57-1.65)		
No	40.8	54.8		52,172	22	Ref		
Oral Birth Control Use			**0.06**				0.49	**NS**
Yes	80.0	77.0		102,219	96	1.14 (0.79-1.70)		
No	20.0	23.0		31,418	38	Ref		
Hormone Replacement Use			<**0.001**				> 0.50	**NS**[5]
Yes	37.9	27.3		10,089	48	1.09 (0.74-1.60)[5]		
No	62.1	72.7		123,549	86	Ref		
Education			**0.002**				**0.03**	**NS**
Grad school	17.6	12.6		45,140	65	2.53 (0.94-10.33)		
4 yrs college	19.0	18.0		34,071	24	1.46 (0.51-6.15)		
trade and some college	33.0	34.9		11,880	8	1.39 (0.51-6.15)		
high school	24.0	27.5		36,177	34	1.78 (0.64-7.38)		
<high school	6.4	6.9		6369	3	Ref		
Jewish Ethnicity			<**0.001**				**0.07**	**NS**
Yes	8.3	5.1		9240	19	1.60 (0.95-2.54)		
No	91.7	94.9		124,398	115	Ref		
Smoking Status			0.25				0.35	--
Ever	59.8	57.7		79,569	85	1.09 (0.76-1.54)		
Never	40.2	42.3		54,068	49	Ref		
Mean Radiation Dose to Breast (Range) Gy	0.72 (0.02-14.44[6])	--	--					

Bolded p-values are for univariate comparisons that are potentially significant and thus tested in building multivariate models.

[1] Relative risk and 95% CI in this column calculated separately for each variable in Poisson regression models which adjusted for attained age. These models included data on the 2786 women with complete data on the variables evaluated; 134 of whom had breast cancer.

[2] Test of heterogeneity for variables with two categories; test of trend for variables with more than two categories except for treatment/birth cohort which is test of heterogeneity (Test of trend p=0.32)

[3] Relative risks for variables from most parsimonious multivariate Poisson regression model

[4] Nulliparous women were classified in oldest age group for purposes of modeling

[5] Analyzed as a time dependent covariate so that HRT became positive at time of last menstrual period

[6] Note person with dose of 14.44 Gy to breast died in 1972 so not included in table 2, but provided follow-up data until 1972

-- Not significant in univariate analysis by treatment group or outcome status so placement in multivariable model not attempted

NS Potentially significant in univariate analysis adjusted for age, but does not add significantly to model with as determined by Likelihood ratio test versus most parsimonious model.

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Table 4

Table 4a: Breast Cancer Incidence and Rates by Estimated Radiation Dose since Thymic Irradiation

Dose (Gy	Number of Women	Person Years at Risk	Mean Dose Gy (Std Dev)	Median Dose Gy	Breast Cancer Casesn	Breast Cancer Rate (per 10,000 p-yrs)	Rate Ratio of Breast Cancer Compared to Untreated (95%CI)[1]	Person Years at Risk for BC as 1st Cancer	Breast Cancer as 1st Cancer[2]	Rate of BC as 1st Cancer (per 10,000 p-yrs)	Rate Ratio of 1st Breast Cancer (95% CI) [1]
Non-treated	**2383**	**105,723**	**--**		**57**	**5.4**	**Ref**	**105,486**	**44**	**4.2**	**Ref**
Total Treated	**1120**	**53,732**	**0.71 (1.20)**	0.17	**96**	**17.9**	**3.01 (2.18-4.21)**	**53,196**	**69**	**13.0**	**2.84 (1.95-4.17)**
0.01-0.24	694	31,906	0.10 (0.08)	0.06	34	10.7	2.23 (1.43-3.44)	31,792	27	8.5	2.31 (1.40-3.77)
0.25-0.49	79	3,891	0.35 (0.08)	0.33	7	18.0	2.37 (0.98-4.87)	3,860	5	13.0	2.15 (0.74-4.94)
0.5-1.99	119	6,153	1.24 (0.43)	1.22	20	32.5	4.23 (2.47-6.98)	6,054	16	26.4	4.51 (2.45-7.91)
2.00-3.99	148	7,462	2.55 (0.49)	2.29	21	28.1	4.13 (2.45-6.71)	7,279	13	17.9	3.43 (1.77-6.18)
≥ 4.00	26	1,384	5.33 (2.03)	4.72	6	43.4	4.74 (1.82- 10.2)	1,352	5	37.0	5.05 (1.74-11.7)
Irradiated but dose unknown	54	2,936	--		8	27.2	2.70 (1.18-5.35)	2,859	3	10.5	1.37 (0.33-3.78)
							Test for trend: $p < 0.001$[3]				Test for trend: $p < 0.001$[3]

Table 4b: Breast Cancer Incidence and Rates for the Interval between the 1985-87 Survey and the Current Survey

Dose (Gy)	Number of Women	Person Years at Risk	Mean Dose Gy (Std Dev)	Median Dose Gy	Breast Cancer Cases	Breast Cancer Rate (per 10,000 p-yrs)	Rate Ratio of Breast Cancer Compared to Untreated (95% CI) [1]	Person Years at Risk for BC as 1st Cancer	Breast Cancer as 1st Cancer [2]	Rate of BC as 1st Cancer (per 10,000 p-yrs)	Rate Ratio of 1st Breast Cancer (95%CI) [1]
Non-treated	**1024**	**18,595**	**--**		**44**	**23.7**	**Ref**	**18,414**	**31**	**16.8**	**Ref**
Total-Treated	**668**	**11,787**	**0.70 (1.13)**	**0.16**	**70**	**59.4**	**2.52 (1.73-3.69)**	**11,534**	**47**	**40.7**	**2.43 (1.55-3.85)**
0.01-0.24	422	7,681	0.10 (0.07)	0.06	27	35.1	1.90 (1.15-3.08)	7,590	20	26.4	1.94 (1.08-3.41)
0.25-0.49	42	750	0.36 (0.09)	0.33	6	80.0	2.40 (0.91-5.24)	727	4	55.0	2.27 (0.67-5.77)
0.5-1.99	64	1,061	1.24 (0.43)	1.24	13	122.5	3.41 (1.75-6.24)	1,033	10	96.8	4.06 (1.86-8.15)
2.00-3.99	89	1,515	2.55 (0.51)	2.29	14	92.4	3.34 (1.76-5.95)	1456	9	61.8	3.23 (1.44-6.53)
≥ 4.00	16	204	5.33 (2.03)	4.72	3	147.1	3.59 (0.87-9.93)	197	2	101.5	3.36 (0.54-11.2)
Treated but dose unknown	35	576			7	121.5	2.98 (1.22-6.27)	532	2	37.6	1.35 (0.22-4.50)
							Test for trend: $p< 0.0013$				Test for trend: $p = 0.005$[3]

Dose (Gy	Number of Women	Person Years at Risk	Mean Dose Gy (Std Dev)	Median Dose Gy	Breast Cancer Casesn	Breast Cancer Rate (per 10,000 p-yrs)	Rate Ratio of Breast Cancer Compared to Untreated (95%CI)[1]	Person Years at Risk for BC as 1st Cancer	Breast Cancer as 1st Cancer[2]	Rate of BC as 1st Cancer (per 10,000 p-yrs)	Rate Ratio of 1st Breast Cancer (95% CI) [1]

[1] Adjusted for attained age and treatment/birth cohort (3 periods). Analysis performed with AMFIT module of Epicure on all 3503 women in the Thymus irradiation cohort

[2] First cancer other than non-melanoma skin cancer.

[3] Test for trend of rate ratios adjusted for treatment/birth cohort and attained age. Excludes unknown radiation dose category.

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