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Thyroid Cancer Risk 40+ Years after Irradiation for an Enlarged Thymus: An Update of the Hempelmann Cohort

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Abstract

Although ionizing radiation is a known carcinogen, the long-term risk from relatively higher-dose diagnostic procedures during childhood is less well known. We evaluated this risk indirectly by assessing thyroid cancer incidence in a cohort treated with “lower-dose” chest radiotherapy more than 55 years ago. Between 2004 and 2008, we re-surveyed a population-based cohort of subjects treated with radiation for an enlarged thymus during infancy between 1926 and 1957 and their unexposed siblings. Thyroid cancer occurred in 50 irradiated subjects (mean thyroid dose, 1.29 Gy) and in 13 nonirradiated siblings during 334,347 person-years of follow-up. After adjusting for attained age, Jewish religion, sex and history of goiter, the rate ratio for thyroid cancer was 5.6 (95% CI: 3.1–10.8). The adjusted excess relative risk per gray was 3.2 (95% CI: 1.5–6.6). The adjusted excess absolute risk per gray was 2.2 cases (95% CI: 1.4–3.2) per 10,000 person-years. Cumulative thyroid cancer incidence remains elevated in this cohort after a median 57.5 years of follow-up and is dose-dependent. Although the incidence appeared to decrease after 40 years, increased risk remains a lifelong concern in those exposed to lower doses of medical radiation during early childhood.

INTRODUCTION

The general population is increasingly exposed to higher doses of radiation through more frequent use of relatively “higher-dose” diagnostic imaging techniques, such as computed tomography (CT) (1,2). The potential increased population cancer risk from such procedures has recently received increased attention (3–5), including coverage in the lay press (6).

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Although radiation exposure at a young age is a well-known risk factor for thyroid cancer (7–9), it is less clear to what extent this risk remains more than 40 years after exposure. Thyroid cancer incidence has also been increasing for the last 10 to 15 years; in the United States, the incidence increased by 100% in females and by about 67% in males between 1992 and 2005 (10,11). Although part of this increase may be the result of heightened medical surveillance for thyroid cancer, another possible factor is the increasing use—even among children—of these higher-dose diagnostic procedures. In fact, about 1 million CT scans are performed every year on children 5 years old or younger (3), and the effect of CT scans during childhood is thought to have an impact on population cancer risks in general (12). However, the very long-term impact of such imaging on thyroid cancer incidence remains unclear.

In the first half of the last century, a misconception of the normal size range of infant thymus glands and the mistaken belief that an enlarged thymus could lead to status lymphaticus and suffocation (13,14) led to thousands of infants and children being irradiated for thymic enlargement. In 1951, Louis Hempelmann began a longitudinal cohort study of cancer incidence among subjects treated for this condition in Rochester, NY, between 1926 and 1957 and their untreated siblings (15,16). Based on follow-up through 1985–1987 (when participants were on average 37.5 years old), subjects exposed to thymic radiation had a risk of thyroid cancer that was 18.6 times as high as that of their unexposed siblings and a 24.3 times higher incidence than New Yorkers of the same age and sex (16). However, thyroid cancer incidence in middle age and beyond in this cohort and in other irradiated cohorts has remained unknown since average follow-up in medically irradiated cohorts has been limited.

The re-initiation of this dormant cohort provided the opportunity to estimate the effect of chest and neck CT and of radiotherapy for cancer during childhood on the incidence of thyroid cancer over most of the life span. This cohort received thyroid doses similar to current exposures from these procedures (17–19), thereby allowing such comparisons.

METHODS

The Population-Based Cohort

Records were collected from all Rochester, NY, area hospitals and clinics, where thymic radiation 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.) All exposed subjects received orthovoltage irradiation with the cumulative air dose to the thymus ranging from 0.25 Gy to 12.50 Gy. The number of fractions ranged from one to seven, although 89% received only one or two treatments. Time between first and last treatment was 90 days or less for 98% of subjects; 96% were treated at 1 year of age or less. Nonirradiated siblings born before the third follow-up survey in 1963 were included in the cohort. Subjects were excluded if follow-up ended within 5 years after birth due to either death or loss to follow-up (16). The studied cohort included 2657 thymic irradiated and 4833 non-thymic irradiated siblings, referred to as the irradiated and nonirradiated siblings, respectively, throughout the rest of the paper. Irradiated individuals had a variable number of siblings, including none, so direct matching comparisons of siblings cannot be easily performed; this also explains why factors such as religion can differ between the two groups.

Data Collection

1. Historical follow-up—Between 1953 and 1987, the cohort was surveyed by mail or telephone six times (9,15,16,20–22). Throughout the entire follow-up, all cases of cancer were confirmed by pathology report, or medical record. Survey response rates were high and

similar among irradiated and nonirradiated siblings. In the 1985 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 various organs of each subject, and these values are used in this study. These dose calculations are described more fully in our recent publication on female breast cancer incidence in this cohort (23). In brief, data abstracted from the original treatment records of each subject were applied to water and polystyrene phantoms as described previously (24). Earlier dosimetry employed fewer variables (21), so these phantom-based recalculations are likely to be more accurate and more like those used in other similar cohorts (24,25). 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, kilo-voltage 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, 66% of irradiated subjects had complete data for dose estimation, while another 29% used some imputed data to complete dose calculations. Only 5% had insufficient data to estimate thyroid dose and were classified as thyroid dose unknown. Three subjects in this analysis had received other radiation treatments concurrently with thymic irradiation. Their doses for this analysis are based solely on their thymic irradiation, but none of them developed thyroid cancer.

2. Current follow-up—We re-initiated follow-up of this cohort in 2003 as described previously (23). Briefly, cohort members were eligible for follow-up if they had returned any of the earlier surveys. During the first year of updating contact information prior to sending out any surveys, we determined that about 11% of the cohort had died and another 10% were not locatable.

Between 2004 and 2008, we collected self-reported data using an 81-item survey. The survey collected information on outcomes and risk factors for cardiovascular disease and cancer, except family history of cancer. Up to three mailing attempts and four telephone calls were made to each subject. We obtained and documented each subject's informed consent as a part of the survey procedure. Study and consent procedures were approved by the University of Rochester Research Subjects Review Board.

Participants who reported a cancer (except non-melanoma skin cancer) were sent a medical release form so we could obtain a copy of their relevant medical record. In all cases of self-reported malignancies not previously confirmed, we sought confirmation from pathology reports. We also accepted concurrent treatment records or National Death Index cause of death as confirmation.

Risk factor data were collected in both the current and the 1985 survey. Both surveys assessed smoking and female reproductive factors. Data on thyroid function, benign tumors, education level and religion were obtained in the 1985 survey but not the current survey. The last two factors are specifically mentioned because in the 1985 follow-up of the cohort, these factors, along with maternal age at first birth, were the only factors significantly associated with thyroid cancer incidence ($P < 0.05$) in analyses that included radiation dose and each factor alone in a model (16).

Statistical Methods

We hypothesized that after adjusting for known risk factors, low-dose therapeutic chest radiation will increase the lifelong cumulative incidence of thyroid cancer. We also expected that radiation would continue to be associated with an increased rate of thyroid cancer more

than 37 years after initial exposure, since that was the average age at last follow-up. Finally, we determined the excess relative risk and excess absolute risk of thyroid cancer per gray after adjusting for other thyroid cancer risk factors in our sample.

To calculate person-years at risk, we used date of birth as the beginning date for both irradiated and nonirradiated siblings, because 95% of the exposed had been irradiated by 8 months of age. Thus length of follow-up is nearly equivalent to age at follow-up. The event date was the date of thyroid cancer diagnosis; data were censored at the last survey response. Date of death was used as an end date only if that was the only date we had for an incident thyroid cancer (ONE subject) or if we received a survey subsequently from next of kin.

Incidence rates and their 95% CI were calculated by irradiation status and dose groups, from which rate ratios adjusted for sex and attained age and their 95% CI were calculated (26). Potential thyroid cancer risk factors and demographic variables (attained age, sex, education level, Jewish ethnicity and smoking) were compared by thymic irradiation status using Student's *t* test for continuous variables and Pearson's χ^2 test for categorical variables. Data conformed to the assumptions of the tests used to analyze them. Subjects with and without thyroid cancer were then compared on these same variables. Variables that differed in either of these comparisons with a two-sided *P* value of less than 0.10 were included in the multivariate analysis. Potential confounder analyses were performed using SAS version 9.2.

For primary and secondary analyses, we performed multivariate Poisson regression using the AMFIT module in the statistical package Epicure (27,28). All statistical tests addressing our main hypotheses were two-sided with an α level of 0.05. Person-years were calculated from birth as described above and cross-classified by calendar year, a time-dependent variable of attained age, sex, thyroid radiation dose, treatment/birth cohort (before 1937, 1937 through 1947, after 1947), and potentially significant thyroid cancer risk factors in our cohort. Nonirradiated siblings were assigned to a treatment cohort based on birth year. Model fit was evaluated using two-sided likelihood ratio tests at the 5% significance level (29). Likelihood-based 95% confidence limits were calculated when possible. Reported rate ratios for the entire cohort were adjusted for those factors that were significant in our most parsimonious model for thyroid cancer incidence. Reproductive risk factors that were explored previously in this cohort as potential thyroid cancer risk factors, such as age at first birth, were evaluated in a subset analysis including only female members of the cohort.

Excess relative risk modeling with respect to thyroid radiation dose was also performed using Poisson regression. A typical excess relative risk model used to evaluate linear-dose and dose-squared components was

$$ERR = \lambda s \exp \left(\sum \alpha_j x_j \right) (1 + \beta_1 D + \beta_2 D^2),$$

where ERR is the excess relative risk of thyroid cancer, λs is model stratum baseline rates of thyroid cancer (strata by sex and attained age) based on the rates in the nonirradiated siblings, the exponential term x_j represents potentially significant independent risk factors for thyroid cancer and α_j represents their individual coefficient estimates. *D* represents the estimated cumulative thyroid radiation dose in Gy, and β_1 and β_2 represent the coefficients for the dose terms. A typical excess relative risk model to estimate a modifier of radiation risk (i.e. effect modification) was

$$ERR=[\lambda s \exp(\alpha_1 V)](1+D \exp(\beta_3 + \beta_4 V)),$$

where λs is defined as above, V is a potential effect modification variable, α_1 is the coefficient of the effect of V on the background rate, β_3 is the coefficient for the dose-related excess relative risk, and β_4 is the coefficient of the interaction of V with dose.

Excess absolute risk modeling had the following format because the software cannot perform analyses using stratified terms:

$$EAR=\exp(\alpha_2 S+\alpha_3 A+\alpha_i x_i)\exp(\beta_5 D+\beta_6 D^2),$$

where S and A are the potential confounding variables representing sex and attained age with coefficients α_2 and α_3 , and x_i represents other potentially significant independent risk factors for thyroid cancer, such as Jewish religion, with their respective coefficients α_i . β_5 and β_6 are coefficients for dose and dose-squared with all terms on the additive excess risk scale.

RESULTS

Cancer Incidence

A total of 3071 subjects, 1303 irradiated and 1768 nonirradiated siblings, responded to the current survey, for an overall response rate of 46%, after excluding those known to be deceased (Table 1). Median age at follow-up of those who responded was 57.6 years (range: 47.5 to 78.3 years) in the irradiated and 57.5 years (range: 41.2 to 88.8 years) in the nonirradiated siblings. Median estimated thyroid exposure was 0.95 Gy (range: 0.069 to 18.58 Gy; mean 1.29 Gy) among all irradiated siblings in the cohort. This represents a median increase of 0.08 Gy from prior estimates of thyroid exposure.

Since the last follow-up of the cohort, 13 new cancers in the irradiated siblings and eight in the nonirradiated siblings were self-reported. Thus, during the entire follow-up of the cohort, 63 subjects have been diagnosed with thyroid cancer: 50 among irradiated subjects during 123,623 person-years and 13 among the nonirradiated siblings during 210,724 person-years. The resulting thyroid cancer incidence rates for irradiated and nonirradiated siblings are 4.0 and 0.6 per 10,000 person-years, respectively, which yields a sex- and attained age-adjusted rate ratio of 6.6 (95% CI: 3.6 to 12.1). Only four cancers—two in each group—were diagnosed after other malignancies (other than non-melanoma skin cancer). Thus rates of thyroid cancer as first malignancy are 3.9 and 0.52 per 10,000 person-years for irradiated and nonirradiated siblings, respectively, giving a rate ratio of 7.4 (95% CI: 3.9 to 14.6).

Multivariate Adjustment of the Cumulative Incidence of Thyroid Cancer

Bivariate analysis revealed potentially significant differences ($P < 0.10$) in the following factors between irradiated and nonirradiated siblings (Table 2, columns 2 through 4): sex, Jewish religion, history of hypothyroidism, history of goiter and education level. Analyses by thyroid cancer status revealed that Jewish religion, history of hypothyroidism, history of hyperthyroidism, history of goiter, education and age at first birth were each potentially independent risk factors, even after stratifying for attained age (Tables 2, columns 4 through 8). Treatment/birth cohort was not a significant risk factor, and only one subject with thyroid cancer had a preceding benign thyroid tumor diagnosed.

In multivariate analysis, comparing the irradiated and nonirradiated groups, stratified by sex and attained age that included the other potentially significant risk factors, Jewish religion and history of goiter each increased thyroid cancer risk and added significantly to the fit of the stratified model (Table 2, column 9). We therefore calculated dose group rate ratios for the entire cohort by adjusting for these two variables in a model stratified by sex and attained age; a statistically significant dose–response relationship was observed, even after these adjustments (Table 3, Fig. 1).

To evaluate female reproductive factors (ever given birth, number of full pregnancies, age at first birth, age at menarche, oral contraceptive use, and hormone replacement use) as potential thyroid cancer risk factors, similar modeling was performed with just the women in the cohort. Women had the same factors included in the most parsimonious model of thyroid cancer, as shown in Table 2. However, none of the female reproductive factors evaluated added significantly to this multivariate model, although age at first birth ≥ 25 years, which included nulliparous women, was of borderline significance in this model, increasing the relative risk by 1.9 (95% CI: 0.91–4.2) times.

Excess relative risk was assessed in a model stratified by attained age and sex. A linear model of dose fit the data better than either a linear-quadratic or a quadratic model, resulting in a crude excess relative risk (ERR) per Gy of 4.3 (95% CI: 2.2–8.7) after excluding the 124 subjects with an unknown thyroid radiation dose. Adjusting for Jewish religion and history of goiter produced the best-fitting parsimonious model ($P < 0.001$) with an ERR/Gy of 3.2 (95% CI: 1.5 to 6.6). Neither Jewish religion, history of goiter nor any other collected covariate appeared to have an interactive effect with radiation dose (Table 4). The excess absolute risk estimate for thyroid cancer was 2.2 cases (95% CI: 1.4 to 3.2) per 10,000 person-years per Gy after controlling for attained age, sex, Jewish religion and history of goiter. Female reproductive risk factors did not significantly modify estimates of ERR/Gy or interact with the effects of thymic irradiation (data not shown).

Incidence of Thyroid Cancer by Time Since Irradiation

To evaluate whether radiation exposure during childhood is associated with ongoing differences in thyroid cancer incidence long after therapy, we calculated thyroid cancer rate ratios by attained-age intervals, which as we have already noted is almost synonymous with time since irradiation. We chose our time intervals so that they would reflect the cutoffs using the average attained age at the last follow-up (37.5 years) and the current follow-up (57.5 years) while still providing relatively narrow estimates. Table 5 demonstrates that the rate ratio decreases with time since exposure but still remains elevated at 3.7 (95% CI 1.5–10.4) up to 58 years after irradiation.

All four thyroid cancers that were not a subject's first malignancy occurred after age 38 years. Analyses excluding these four cancers actually provided nonsignificantly higher point estimates of the rate ratio for the interval between 38 and 58 years after radiation exposure. Finally, Table 6 illustrates differences in potential thyroid cancer risk factors among responders and nonresponders by treatment group and is discussed below.

DISCUSSION

Our results indicate that exposure to lower doses of therapeutic chest radiation (median 0.95 Gy, mean 1.29 Gy) during childhood is associated with an increased cumulative incidence of thyroid cancer, even up to a median follow-up of 57.5 years. This association remained even after adjusting for suspected thyroid cancer risk factors and factors previously associated with thyroid cancer in our cohort. Furthermore, our analysis of thyroid cancer incidence by time since radiation exposure indicates that although relative risk decreases with time since

exposure, chest irradiation is still associated with an increased incidence of new thyroid cancers four to six decades after exposure.

Given that only two thyroid cancers occurred in the irradiated siblings after another malignancy had been diagnosed, the increased thyroid cancer incidence cannot be attributed solely to the secondary effects of chemotherapy or secondary radiotherapy. Our findings clearly confirm the results of other cohorts exposed to radiation during childhood, such as the Swedish Hemangioma cohort (30), the Israeli tinea capitis study (31), the Michael Reese Hospital benign head and neck cohort (32), and the data on exposure during childhood from the atomic bomb survivor cohort (33,34).

In comparing these findings to the results from the last follow-up of this cohort, which ended in 1987, it is notable that the unadjusted ERR/Gy fell from 9.0 (90% CI: 4.2–21.7) (16) to the current 4.3 (95% CI: 2.2–8.7). This is most likely due to increasing time since exposure (25,35) and slight differences in dose estimates used. Although revised dose estimates were used for this paper but not prior studies of this cohort, the new dosimetry tended to flatten the dose range by increasing the exposure estimates at the bottom end and decreasing dose estimates at the high end of the exposure range. Modeling using the old dosimetry revealed that the ERR/Gy estimate would be even lower, at 3.4 (95% CI: 1.7 to 6.8).

We again found that a linear model of dose fit the excess relative risk model better than a linear-quadratic or a quadratic model of dose. The linear model also fits better than a more complex radiobiological model, which included a term that allowed for a downturn at high doses as a result of “cell sterilization” (i.e., $ERR(D) = (\beta_1 D + \beta_2 D^2) * [\exp(-\beta_3 D - \beta_4 D^2)]$) (36). Other studies (25,37) suggest that at thyroid doses less than 6.00 Gy, the linear dose model appears to fit thyroid cancer incidence data as well as or better than the other three alternatives above. In our cohort, less than 1% of the irradiated subjects with a known dose had an estimated thyroid exposure greater than 6.00 Gy.

Our study confirms the findings of an earlier pooled analysis of five cohort studies of external radiation exposure during childhood, one of which was our cohort with its follow-up until 1987 (25). This pooled analysis demonstrated that ERR began to decline after 30 years of exposure but was still elevated at 40 years after exposure. Our study adds to the literature by showing that, at least in children exposed at a very young age, the increased risk continues at least up to a median 57.5 years after exposure. The pooled analysis, as well as a recent analysis of thyroid cancer incidence in the Childhood Cancer Survivors Study (37), also found that risk decreased significantly with increasing age at exposure, with little risk apparent after 20 years of age. However, we could not assess the effect of age at exposure on ERR, because more than 95% of the thymus cohort was exposed at less than 1 year of age.

In terms of other potential risk factors, only Jewish religion and history of goiter appeared to have an independent association with thyroid cancer incidence when radiation was included in the risk model. The previous report from this cohort found that Jewish religion was an independent risk factor for thyroid cancer but that goiter was not after accounting for concurrent diagnoses of goiter and thyroid cancer (16). Unfortunately, we were unable to adjust for concurrent diagnoses, because records of the date of goiter diagnosis were no longer available. Nevertheless, ERR/Gy estimates were not more than 10% different when we did not include history of goiter in our models, further suggesting that goiter is not a true independent risk factor for thyroid cancer. In terms of modifying the risk of radiation, in this analysis neither Jewish religion nor goiter appeared to have an interactive effect with

radiation dose (Table 4) or exposure, although in the prior report on thyroid cancer in this cohort Jewish religion interacted with radiation dose to modify ERR/Gy (16).

Some (38) but not all studies (39–41) of nonirradiated populations have suggested that older maternal age at first birth increases thyroid cancer risk. The last follow-up of this cohort found that maternal age at first birth ≥ 25 years was an independent risk factor for thyroid cancer after adjusting for thyroid radiation dose and attained age (16). In the current follow-up, we found that the relative risk of age at first birth ≥ 25 years was of only borderline significance after adjusting for attained age and radiation dose, but it was no longer significant after adjusting for Jewish religion and history of goiter as well. There was no evidence for interaction between maternal age at first birth and radiation dose. Unfortunately, no other study of a medically irradiated cohort has evaluated this question.

A limitation of the study is the fairly low response rate, which was differential between the irradiated and nonirradiated siblings. We evaluated whether this response pattern might lead to nonresponse bias, threatening internal validity. However, differences in potential thyroid cancer risk factors among responders and nonresponders by treatment group are minimal and would tend to cancel each other out (Table 6). Certain factors (e.g., female sex, Jewish religion, age at first birth) differed similarly between responders and nonresponders in both groups, which would not introduce analytic bias. Other factors were differential between responders and nonresponders for only one study group (e.g., smoking, hypothyroidism and oral contraceptive use), but those factors have little or no association with thyroid cancer risk, so no impact on the radiation risk estimates is expected.

This study depended on self-report and death-record identification of incident thyroid cancers. Although self-report may lead to bias, we confirmed 75% of the thyroid cancers in the cohort by pathology reports or medical records and attempted to confirm them all. Only one self-reported thyroid cancer turned out to be a benign tumor (which was not included in the current analysis as a thyroid cancer). In collecting medical records for other diagnoses, we found no thyroid cancers that had not been self-reported.

Although irradiated subjects may have known that they were at increased risk, and in the late 1970s to early 1980s free thyroid screening was offered to those who still lived in the area, ascertainment bias is unlikely to have markedly altered our results. First, analyses performed during the last follow-up in this cohort showed that even after adjusting for screening frequency, the estimated excess relative risk was not changed substantially. This analysis was done after the free screening had been offered. Second, since the last article on the cohort was published, the study had been dormant for more than 10 years, so there were no systematic reminders to subjects to have thyroid cancer screening (16), nor has there been a consensus on the screening procedure for those exposed to irradiation of the thyroid.

Our study has several strengths. First, to our knowledge, the median time since irradiation is longer than that of any other radiation-exposed cohort followed for thyroid cancer, other than the atomic bomb survivor cohort (25,31). Among other medically irradiated cohorts, the Israeli tinea capitis study previously had the longest follow-up for thyroid cancer incidence, with a median of 46 years and maximum of 54 years (31). Second, within the cohort, the sibling comparison group helps control for confounding from family history and potential risk factors that were not collected but are related to upbringing. Third, although the 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. Fourth, in our cohort, radiation was not administered in response 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.

Finally, thyroid doses in our cohort overlap with those from current medical practices that expose the thyroid to radiation during early childhood. The higher doses in this cohort overlap with exposures to the thyroid from radiotherapy protocols for various childhood cancers (42). The lower doses in this cohort are similar to those to the thyroid of infants from chest and neck CT. In a recent dosimetry study, the thyroid radiation dose from a single torso CT was calculated to be 0.011 Gy in a newborn and 0.014 Gy in a 1-year-old (43). In another study using various pediatric-sized phantoms, the scattered dose to the thyroid from neck CT examinations varied from 0.015 to 0.052 Gy (18). Doses can be twice as high if the settings are not changed from adult levels, and a substantial fraction of CT-scanned patients receive multiple scans (2,44). In fact, exposures at the lower end of the dose range in our cohort were unfractionated, and thus may be more like those from pediatric chest CT than in any other studied cohort.

CONCLUSIONS

Our study adds to the radiation-associated thyroid cancer literature by extending the follow-up of the Hempelmann cohort, providing the longest longitudinal follow-up of any cohort exposed to chest radiotherapy. Our findings suggest that although limiting thoracic radiation exposure during childhood cancer treatment may decrease thyroid cancer risk, survivors will continue to have an increased cumulative incidence of thyroid cancer. These results also suggest that young children undergoing multiple CT scans that expose the thyroid to radiation are at increased thyroid cancer risk well into adulthood. 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 doses in the youngest children whenever possible.

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FIG. 1. Radiation dose response for the incidence of thyroid cancer among 7490 subjects in the Hempelmann (Rochester, NY) Thyroid Irradiation Cohort, with known thyroid radiation dose. The analysis is adjusted for attained age (which is highly correlated with time since radiation exposure), sex, Jewish religion and history of goiter. Dose intervals correspond with categories in Tables 4 and 5. Data shown are mean doses of each category, and cross bars represent 95% confidence intervals. The dashed line is the best-fit linear regression line.

TABLE 1

Response Rates to the 2004–2008 Follow-up Survey of the Hempelmann Cohort by Thymic Irradiation Status

	Total (%)^a	Irradiated (%)	Nonirradiated siblings (%)
Response status	N = 7490	N = 2657^a	N = 4833^a
Deceased ^b	857 (11.4) ^b	345 (13.0) ^b	512 (10.6) ^b
Not known to be deceased	6633 (88.6)	2312 (87.0)	4321 (89.4)
Total surveys mailed	6633 (100)	2312 (100)	4321 (100)
Responded (completed) ^c	3072 (46.3)	1305 (56.4)	1767 (40.9)
Declined ^c	456 (6.9)	107 (4.6)	349 (8.1)
Did not respond ^c	2457 (37.0)	696 (30.1)	1761 (40.7)
Undeliverable ^{c,d}	648 (9.8)	204 (8.8)	444 (10.2)

^aFrom original study population, 199 irradiated and 220 nonirradiated siblings were excluded from the current cohort because they died before age 5 or were untraceable within 5 years after birth.

^bAs a percentage of the entire cohort.

^cAs a percentage of the cohort not known to be deceased. Columns may not sum to 100% as a result of rounding. Note that the Did not respond category may contain individuals lost to follow-up, because we included people who did not respond and whose survey packets were not returned by the post office in the Did not respond category.

^dNo contact information could be confirmed or survey returned by the post office and not known to be deceased.

TABLE 2

Thyroid Cancer Risk Factors by Thyroid Irradiation Group (Both Sexes)

Variable	Irradiated (%)	Nonirradiated (%)	P value (irradiated vs. nonirradiated)	Person-years	No. of thyroid cancers	Relative risk (95% CI) ^a	P value ^b	Adjusted rate ratio for thyroid cancer (95% CI) ^c
Thyroid irradiation								
Yes	100	—	<0.001	123,631	50	6.5 (3.6–12.4)	<0.001	5.6 (3.1–10.8)
No	—	100		210,724	13	Ref		Ref
Sex								
Female	42.1	49.3	<0.001	159,372	36	1.3 (0.82–2.2)	0.243 ^d	N/A ^d
Male	57.9	50.7		174,983	27	Ref		
Religion								
Jewish	8.6	4.9	<0.001	23,920	18	4.6 (2.6–7.9)	<0.001	3.7 (2.1–6.3)
Other	91.4	95.1		310,435	45	Ref		Ref
Hypothyroid								
Yes	5.1	3.5	0.002	13,487	6	2.0 (0.68–4.6)	0.004	NS
Unknown	—	—		33,109	12	3.2 (1.6–5.9)		
No	94.9	96.5		287,759	45	Ref		
Hyperthyroidism								
Yes	1.8	1.3	0.122	5,127	2	2.0 (0.33–6.5)	0.006	NS
Unknown	—	—		32,801	12	3.2 (1.6–5.8)		
No	98.2	98.7		296,427	49	Ref		
Goiter								
Yes	2.0	0.8	<0.001	4,105	6	7.9 (3.0–17.6)	<0.001	5.6 (2.1–12.0)
Unknown	—	—		31,235	10	3.2 (1.6–5.8)		3.0 (1.4–5.7)
No	98.0	99.2		299,015	47	Ref		Ref
Education								
>High school	72.6	67.8	<0.001	231,620	48	1.7 (0.91–3.6)	0.035	NS
Unknown	—	—		13,883	5	4.5 (1.4–12.8)		
High school or less	27.3	32.2		88,852	10	Ref		
Smoke								
Ever	60.6	59.9	0.569	187,102	35	1.2 (0.7–2.1)	0.057	NS

Variable	Irradiated (%)	Nonirradiated (%)	<i>P</i> value (irradiated vs. nonirradiated)	Person-years	No. of thyroid cancers	Relative risk (95% CI) ^a	<i>P</i> value ^b	Adjusted rate ratio for thyroid cancer (95% CI) ^c
Unknown	—	—		27,450	8	3.1 (1.2–7.0)		
Never	39.4	40.1		119,803	20	Ref		
Period of treatment (birth in untreated)			0.41				0.138	—
>1947	51.2	53.4		149,951	18	0.51 (0.25–1.01)		
1937–1947	36.5	34.3		131,916	28	0.73 (0.4–1.4)		
<1937	12.3	12.3		52,488	17	Ref		

Notes. Data are from the combined 1985–1987 and 2004–2008 follow-up surveys. Bolded *P* values are for univariate comparisons that are potentially significant and thus tested in building multivariate models. —, not significant in univariate analysis by treatment group or outcome status so placement in multivariate model not attempted. NS, potentially significant in univariate analysis stratified by attained age and sex (when appropriate), but does not add significantly to model with as determined by likelihood ratio test compared to most parsimonious model.

^aRelative risk and 95% CI in this column calculated separately for each variable in Poisson regression model stratified by attained age and sex. Sex evaluated in a model adjusted by attained age only.

^bTest of heterogeneity.

^cAdjusted rate ratios for variables from most parsimonious multivariate Poisson regression model stratified by attained age and sex.

^dNot applicable as multivariate model already stratified by sex. Note, however, that in a model stratified by age only and adjusted for religion and irradiation status, female sex is of borderline significance with an RR = 1.5 (95% : 0.93–2.5).

TABLE 3

Incidence Rates of Thyroid Cancer by Estimated Thyroid Radiation Dose from Hempelmann's Thyroid Irradiation Cohort: Entire Follow-up

Dose (Gy)	Number of people	Person years at risk	Mean dose, Gy (SD)	Median dose (Gy)	Thyroid cancer cases	Thyroid cancer rate (per 10,000 PY)	Stratified rate ratio of thyroid cancer compared to nonirradiated (95% CI) ^a	Adjusted rate ratio of thyroid cancer (95% CI) ^b
Nonirradiated	4833	210,724	—	—	13	0.6	Ref	Ref
Total irradiated	2657	123,623	1.29 (1.3)	0.95	50	4.0	6.6 (3.7–12.7)	5.7 (3.2–11.1)
0.01–0.24	743	30,863	0.13 (0.03)	0.13	3	0.97	1.7 (0.4–5.3)	1.9 (0.4–6.0)
0.25–0.49	117	5,162	0.36 (0.08)	0.37	0	—	—	—
0.50–1.99	1027	49,200	1.17 (0.41)	1.03	14	2.8	4.5 (2.1–9.7)	4.2 (1.9–9.0)
2.00–3.99	544	26,421	2.55 (0.57)	2.35	20	7.6	12.0 (6.0–25.0)	10.0 (4.9–20.9)
4.00–5.99	84	4,418	4.83 (0.58)	4.87	7	15.8	24.5 (9.2–60.3)	15.3 (5.4–40.0)
>=6.00	18	881	7.34 (2.89)	6.39	4	45.4	64.6 (18.1–184)	31.0 (8.0–98.1)
Irradiated but dose unknown	124	6,678	—	—	2	3.0	4.3 (0.7–15.7)	4.4 (0.7–16.0)
							Test of trend ^c <i>P</i> < 0.001	Test of trend ^d <i>P</i> < 0.001

Notes. Analysis was performed with the AMFIT module of Epicure on all 7490 subjects in the thymus irradiation group. Dose categories were chosen to match those in the prior analysis.

^aStratified rate ratio is based on unadjusted dose category model stratified by attained age and sex.

^bAdjusted rate ratio is based on a dose category model stratified by attained age and sex, adjusted for Jewish religion and history of goiter.

^cTest for trend of rate ratios by dose categories stratified by cohort and attained age. Excludes subjects in the unknown radiation dose category.

^dTest for trend of rate ratios by dose categories stratified by cohort and attained age, adjusted by Jewish religion and history of goiter. Excludes subjects in the unknown radiation dose category.

TABLE 4
Radiation Dose Response for Thyroid Cancer Incidence 1926–2008 and Evaluation of Effect Modification

Potential effect modifier	Category	Relative risk main effect ^d (95% CI)	Excess relative risk/Gy ^a (95% CI)	Deviance difference ^b	P value ^c
None		–	3.2 (1.5–6.6)	Reference	–
Jewish religion	Yes	2.2 (1.2–3.9)	6.8 (nf–128)	0.907	0.34
	No	1.0	2.7 (1.1–6.0)		
Goiter	Yes	3.1 (1.07–7.3)	682 (nf–nf)	1.472	0.48
	No	1.0	2.7 (1.2–5.9)		
Sex	Female	1.6 (0.96–2.7)	2.6 (nf–nf)	0.555	0.46
	Male	1.0	4.4 (1.4–15.8)		
Age at first birth ^d	≥25 years	1.8 (0.86–4.0)	4.1 (1.2–nf)	1.421	0.49
	<25 years	1.0	1.1 (nf–7.5)		

Note. nf = boundary not found.

^aExcess relative risk/Gy models stratified by attained age and adjusted for Jewish religion, history of goiter and sex. Models include all 7490 subjects except for that of age at first birth, which included only women and did not adjust for sex.

^bRelative to the main effects model without any interaction terms (deviance = 581.043 all subjects; deviance = 418.934 women only).

^cP value is for the likelihood ratio test of homogeneity of excess relative risk/Gy across categories of effect modifiers.

^dNulliparous women were coded as age at first birth of 25 or older.

TABLE 5

Rate Ratio of Thyroid Cancer Incidence by Years of Follow-up

Years of follow-up	Thyroid cancer cases	Person years at risk	Stratified rate ratio of thyroid cancer compared to nonirradiated (95% CI) ^a	Adjusted rate ratio of thyroid cancer (95% CI) ^b
5.0–24.9	Irradiated	17		
	Nonirradiated	1		
25.0–37.9	Irradiated	14	32.6 (6.7–587)	28.0 (5.6–505)
	Nonirradiated	4	6.3 (2.3–22.3)	4.7 (1.6–16.8)
38.0–57.9	Irradiated	15		
	Nonirradiated	6	3.7 (1.5–10.2)	3.7 (1.5–10.4)
≥58.0 years	Irradiated	4		
	Nonirradiated	2	3.2 (0.63–23.1)	3.2 (0.63–23.8)

Note. Years of follow-up calculated from birth, so years of follow-up analogous to age at follow-up.

^a Stratified rate ratio is based on unadjusted dose category model stratified by sex.

^b Adjusted rate ratio is based on a dose category model stratified by sex and adjusted for Jewish religion and history of goiter.

Comparison of Thyroid Cancer Risk Factors Collected in 1985 between Responders and Nonresponders to the 2004–2008 Survey by Thymic Irradiation Status

TABLE 6

		Irradiated		P value	Nonirradiated		P value
		Responders (%)	Nonresponders (%)		Responders (%)	Nonresponders (%)	
Sex	Female	48.0	36.5	<0.001	53.7	46.7	<0.001
	Male	52.0	63.5		46.3	53.3	
Smoking status	Ever	57.9	60.5	0.213	54.7	61.6	<0.001
	Never	42.1	39.5		45.3	38.4	
Hyperthyroidism	Yes	2.0	1.6	0.494	1.5	1.2	0.379
Hypothyroidism	Yes	6.0	3.9	0.026	3.6	3.4	0.762
Goiter	Yes	2.2	1.7	0.386	1.0	0.6	0.089
Jewish	Yes	10.9	6.1	<0.001	6.9	4.3	<0.001
Education (years)	>13	28.9	26.1	0.091	32.8	30.3	0.089
Female reproductive factors							
Ever pregnant	Yes	78.4	78.7	0.884	79.3	78.5	0.664
Number of full pregnancies	0	25.8	28.1	0.361	26.7	26.5	0.972
	1	14.3	16.3		15.7	15.1	
	2	32.7	26.7		28.8	29.6	
	3	17.6	19.6		17.1	16.6	
	4+	9.7	9.3		11.7	12.2	
Age at first birth (years)				0.006			0.008
<20		10.9	17.8		13.5	18.8	
20–24		39.7	43.6		44.5	45.7	
25–29		37.5	26.5		30.8	24.5	
30+		12.0	12.1		11.2	11.0	
OBC ^a	Yes	79.8	77.1	0.323	78.9	73.4	0.003
HRT ^b	Yes	13.8	15.1	0.58	12.3	12.5	0.861
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

Note. Statistically significant results are in bold.

^a Oral birth control use.

^b Hormone replacement therapy.