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Original Contribution

A Prospective Study of Medical Diagnostic Radiography and Risk of Thyroid Cancer

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Although diagnostic x-ray procedures provide important medical benefits, cancer risks associated with their exposure are also possible, but not well characterized. The US Radiologic Technologists Study (1983–2006) is a nationwide, prospective cohort study with extensive questionnaire data on history of personal diagnostic imaging procedures collected prior to cancer diagnosis. We used Cox proportional hazard regressions to estimate thyroid cancer risks related to the number and type of selected procedures. We assessed potential modifying effects of age and calendar year of the first x-ray procedure in each category of procedures. Incident thyroid cancers ($n = 251$) were diagnosed among 75,494 technologists (1.3 million person-years; mean follow-up = 17 years). Overall, there was no clear evidence of thyroid cancer risk associated with diagnostic x-rays except for dental x-rays. We observed a 13% increase in thyroid cancer risk for every 10 reported dental radiographs (hazard ratio = 1.13, 95% confidence interval: 1.01, 1.26), which was driven by dental x-rays first received before 1970, but we found no evidence that the relationship between dental x-rays and thyroid cancer was associated with childhood or adolescent exposures as would have been anticipated. The lack of association of thyroid cancer with x-ray procedures that expose the thyroid to higher radiation doses than do dental x-rays underscores the need to conduct a detailed radiation exposure assessment to enable quantitative evaluation of risk.

radiation; radiography; thyroid gland; thyroid neoplasms; x-rays

The incidence of thyroid cancer has increased more rapidly than the incidence of any other solid tumor in the United States during the last 3 decades and is now the fifth most common cancer diagnosed in women (1). The incidence rate is 3 times higher among women than among men (2). Exposure to ionizing radiation at a young age is the only established environmental risk factor for thyroid cancer. Data supporting the relationship between external sources of ionizing radiation exposure and thyroid cancer are based in large part on studies of atomic bomb survivors and people who were exposed to therapeutic radiation in childhood (3). Less is known about the magnitude of the risks related to medical diagnostic radiation, which has been the fastest growing source of human exposure to ionizing radiation during the last 3 decades (4). Whereas medical x-rays constituted a small fraction (11%) of ionizing radiation exposure in the general population in the early 1980s (5), increasing use of diagnostic radiology has made it a leading source (36%) of ionizing radiation exposure in the United States as of 2006 (4).

Only case-control studies have examined the relationship between thyroid cancer risk and exposure to diagnostic x-rays (6–12). Most studies have relied on information collected from questionnaires or interviews (6–9, 12). Three interview-based studies reported some evidence of an increased risk of thyroid cancer related to an increased number of medical x-ray procedures (6, 7, 9). However, those case-control studies that relied on information abstracted from medical records (10, 11) and 2 studies that relied on data from in-person interviews (8, 12) found no association. Although recall bias may, in part, explain this inconsistency in findings, validation studies comparing documented versus recalled histories of diagnostic x-ray procedures suggest that there is also nondifferential reporting error between cases and controls (13, 14). Additionally, data from medical records may underestimate exposure because of under-ascertainment of procedures during medical record review (11, 14), especially if it is not possible to obtain all medical records from birth. A prospective cohort study design could minimize the potential for recall bias and avoid the under-ascertainment that is possible when relying on medical records.

The US Radiologic Technologists Study is a nationwide, prospective cohort study of 146,022 radiologic technologists, the majority of whom are women. The study has extensive data on self-reported personal medical histories of diagnostic imaging procedures and radiotherapy collected at baseline prior to developing thyroid cancer, as well as detailed records of occupational radiation exposure. Radiologic technologists' occupational expertise may facilitate recall of their own diagnostic radiologic histories compared with the general population. Substantiating this view are data from the US Radiologic Technologists Study showing 1) a correlation of red bone marrow dose scores extrapolated from the self-reported cumulative number of diagnostic x-ray procedures with chromosomal aberrations; and 2) the reproducibility of recall of medical diagnostic procedures for 354 technologists who responded to the same questionnaire twice in a 4-year period (15). This study provides a unique opportunity to investigate the risk of incident thyroid cancer related to the number of diagnostic x-ray procedures of different types in a prospective study.

MATERIALS AND METHODS

Study population

The US Radiologic Technologists Study has been described in detail previously (16). Briefly, the US Radiologic Technologists Study was initiated in 1982, enrolling 146,022 radiologic technologists nationwide who were certified for at least 2 years by the American Registry of Radiologic Technologists between 1926 and 1982. Three different questionnaires were administered (during the periods 1983–1989, 1994–1998, and 2003–2005) to collect information on health outcomes (including self-reports of thyroid cancer), demographic characteristics, medical histories, work practices, and other environmental and lifestyle risk factors. The response rate for each of the questionnaires among living and located cohort members has been approximately 70%, with 110,418 individuals completing 1 or more questionnaires.

The present investigation focused on 75,494 radiologic technologists who responded to the first questionnaire between 1983 and 1989 and who were followed up for thyroid cancer, which was reported by the participants in responses to the second questionnaire (between 1994 and 1998) or the third questionnaire (between 2003 and 2005). We excluded participants who reported a previous cancer (except nonmelanoma skin cancer) on the first questionnaire ($n = 3,416$); those who reported a cancer with an unknown date of diagnosis on any of the questionnaires ($n = 185$); and those who did not respond to both the first questionnaire and at least 1 subsequent questionnaire ($n = 66,922$). Additionally, we excluded 5 subjects who had improbable numbers of multiple cancer reports. The US Radiologic Technologists Study is reviewed and approved annually by the institutional review boards of the National Cancer Institute (Bethesda, Maryland) and the University of Minnesota (Minneapolis, Minnesota).

Assessment of diagnostic x-ray exposures

We considered the following diagnostic x-ray procedures to involve potential radiation exposure to the thyroid gland: x-rays to the skull, cervical spine, head and neck, chest, thoracic spine, and lumbar spine, as well as dental x-rays, mammograms, barium swallows, angiograms, and upper gastrointestinal tract series (see Table 1 for estimated radiation doses to the thyroid gland from procedures for which dose data were available). For each of these procedures, participants were asked on the first questionnaire whether they had ever had the procedure, and if so, the approximate number of times and the year they had the procedure for the first time. Information on the type of dental x-ray procedure and the reason for having a diagnostic x-ray procedure was not available. We also evaluated risk related to self-reported therapeutic radiation to the head and neck, which is a known risk factor for thyroid cancer (3, 17). Other x-ray procedures, such as computed tomography scans, expose the thyroid to relatively high doses of radiation, but we did not have information on these types of procedure in the first questionnaire, in part, because they were still relatively rare in the 1980s.

Case ascertainment and follow-up

Incident thyroid cancers were identified by self-report on the second or third questionnaire; of those for which records

Table 1. Estimated Radiation Doses to the Thyroid Gland in the 1970s (Unless Otherwise Indicated) for Selected X-Ray Procedures

X-Ray Procedure	Radiation Dose to Thyroid Gland, mGy
Chest CT	15.5[a]
Cervical spine radiograph	4.0[b]
Skull radiograph	2.2[b]
Head CT	1.5[a]
Thoracic spine radiograph	0.8[b]
Dental radiographs	
Full mouth (F-speed film)	0.7[c]
Panoramic	0.4[c]
Bitewing (F-speed film)	<0.1[c]
Mammogram	0.3[d]
Upper gastrointestinal series	0.07[b]
Chest radiograph	0.007[b]
Lumbar spine radiograph	0.003[b]

Abbreviation: CT, computed tomography.

[a] Derived from Lee et al. (28) and Stern (29) for estimated dose in the United States in 2000.

[b] Derived from Kereiakes and Rosenstein (30); based on surveys conducted in the 1970s.

[c] Derived from Ludlow et al. (31) and Johnson and Goetz (20).

[d] Derived from Thierry-Chef et al. (32) and Whelan et al. (33).

could be obtained, 92% were confirmed by medical records, pathology reports, or cancer registry linkage (16). Follow-up began at the time of answering the first questionnaire and continued until the last questionnaire was completed or a primary cancer (other than nonmelanoma skin cancer) was diagnosed. A total of 251 incident thyroid cancer cases were diagnosed during 1,305,368 person-years of follow-up, with a mean follow-up time of 17.3 years. Of these cases, 187 were papillary carcinoma, 16 were follicular carcinoma, 3 were medullary carcinoma, 44 were of unspecified histology, and 1 was missing information on histology.

Potential confounders

Demographic and anthropometric data and medical and occupational histories were collected on the first questionnaire. Self-reported height, weight, smoking status, family history of thyroid cancer, and personal history of any benign thyroid condition were evaluated as potential confounders. History of any benign thyroid condition was assessed with an "ever/never" question and was confirmed by specific conditions reported, including hyperthyroidism, hypothyroidism, thyroiditis, goiter, and others.

Statistical analysis

By using 2-sided χ^2 tests, we compared the distribution between incident cases and noncases for age at questionnaire completion (<30, 30–39, 40–49, or ≥50 years), year of birth (before 1940, 1940–1949, or 1950 or later), sex, race/ethnicity (white or nonwhite), smoking status (never, former, or current smoker), body mass index (measured as weight (kg)/height (m)^2) (<25.0, 25.0–29.9, ≥30.0), history of any benign thyroid condition, and family history of thyroid cancer in first-degree relatives. Those factors that were associated with both the outcome and diagnostic x-ray procedures were included as potential confounders in our regression analyses of thyroid cancer risk, including sex, year of birth, body mass index, smoking status, and history of a benign thyroid condition. We also adjusted for estimated cumulative occupational radiation absorbed dose to the thyroid gland (18).

For the 11 selected x-ray procedures involving potential exposure to the thyroid gland, we explored the number of subjects who were ever exposed to these specific procedures, the mean and maximum number of procedures reported, and the prevalence of each type of procedure defined as the percentage of subjects who were ever exposed to a specified procedure. We also evaluated the correlations among the different procedure types on the basis of the total number of reported procedures, and we compared the age at first procedure between cases and noncases for each type of procedure.

We estimated the risk of thyroid cancer related to each type of x-ray procedure by using multivariate Cox proportional hazard models with attained age as the time scale and adjustment for the aforementioned variables as well as adjustment for all other types of imaging procedure. Procedures were modeled as continuous variables on the basis of the total number of procedures of each type reported. We evaluated risks for any type of thyroid cancer and specifically for papillary thyroid cancer and censored subjects who developed other histological subtypes of thyroid cancer. Because adjustment for other types of procedure as separate variables in the model did not materially change our point estimates, we did not include them in models stratified by potentially modifying factors. We explored interactions with the calendar year of the first procedure and the subject's age at the first procedure by using the cutoffs of 1970 and 20 years, respectively. In general, x-ray procedures before 1970 conferred higher radiation doses than those performed after 1970 (19, 20), and exposure to ionizing radiation at ages younger than 20 years has been associated with greater increases in thyroid cancer risk than exposure at older ages (17, 21). Diagnostic procedures in the head and neck region may confer higher doses of radiation to the thyroid gland; for these, we examined whether risks were elevated for a given minimum number of x-ray procedures by combining all head and neck procedures together (i.e., skull, cervical spine, and other head and neck x-ray procedures). Although dental x-rays are not considered to deliver substantial radiation doses to the thyroid gland, we also evaluated these separately because reports suggest that they may be associated with risk of thyroid cancer and other tumors (6, 7, 11, 19, 22, 23). Additionally, we evaluated risks related to procedure intensity, which we defined as the cumulative number of procedures divided by the number of years between the time of the first procedure and completion of the first questionnaire.

In sensitivity analyses, we accounted for the possibility that some of the reported x-ray procedures may have been related to the diagnosis of thyroid cancer. Because the dates of all x-ray procedures were not available, we could not use traditional exposure lagging to remove these etiologically irrelevant exposures. As an alternative, we excluded the first 5 years of follow-up. Forty cases, 30 of which were papillary thyroid cancer, were diagnosed in the first 5 years after completion of the questionnaire and were therefore excluded in these sensitivity analyses. All analyses were conducted by using Stata, version 11, software (StataCorp LP, College Station, Texas).

RESULTS

The mean age at study entry was 38.1 (standard deviation, 9.5) years (range, 22–86 years). Among incident cases, the mean age at study entry was 35.7 (standard deviation, 7.2) years. Cases were more likely to be female, nonsmokers, and obese (defined as a body mass index ≥30), and to have a personal history of nonmalignant thyroid disease and/or a family history of thyroid cancer compared with the rest of the study population (Table 2).

Table 3 shows the numbers of participants who reported undergoing specific x-ray procedures and the mean and maximum number of procedures among those exposed. The most common procedures were chest and dental radiographs; the least common were angiograms. Because lumbar spine and thoracic spine radiographs were highly correlated ($r = 0.57$, see Appendix Table 1) and may have been performed together as a single procedure, we treated these procedures as the same procedure in risk analyses. There were 1,348 subjects who reported having received radiotherapy to the head or neck.

Table 2. Baseline Characteristics of Study Participants, US Radiologic Technologists Study, 1983–2006

Characteristic	Noncases (n = 75,243)		Incident Cases (n = 251)		P Value[a]
	No.	%	No.	%	
Age at baseline questionnaire, years					0.04
<30	14,416	19.2	57	22.7	
30–39	35,491	47.2	126	50.2	
40–49	16,504	21.9	52	20.7	
≥50	8,832	11.7	16	6.4	
Year of birth					0.002
Before 1940	14,364	19.1	26	10.4	
1940–1949	25,183	33.5	90	35.9	
1950 or later	35,696	47.4	135	53.8	
Sex					0.001
Female	58,833	78.2	219	87.3	
Male	16,410	21.8	32	12.7	
Race/ethnicity					0.61
White	71,736	95.3	241	96.0	
Nonwhite	3,507	4.7	10	4.0	
Smoking status					0.003
Never smoker	36,273	48.2	140	55.8	
Former smoker	20,761	27.6	72	28.7	
Current smoker	17,529	23.3	36	14.3	
Unknown	680	0.9	3	1.2	
Body mass index[b]					0.005
<25.0	51,585	68.6	169	67.3	
25.0–29.9	16,177	21.5	40	15.9	
≥30.0	5,566	7.4	30	12.0	
Unknown	1,915	2.6	12	4.8	
History of any benign thyroid condition					<0.001
No	67,164	89.3	197	78.5	
Yes	6,709	8.9	48	19.1	
Unknown	1,370	1.8	6	2.4	
Family history of thyroid cancer					<0.001
No	68,593	91.2	218	86.8	
Yes	455	0.6	7	2.8	
Unknown	6,195	8.2	26	10.4	

[a] P value based on χ^2 test excluding any "unknown" category.
[b] Body mass index calculated as weight (kg)/height (m)^2.

Compared with noncases, study participants who developed thyroid cancer had a younger mean age at first diagnostic procedure for skull radiographs (20.8 vs. 23.7 years, $P_{difference} = 0.01$), dental radiographs (15.3 vs. 16.7 years, $P = 0.01$), upper gastrointestinal series (24.1 vs. 26.4 years, $P = 0.01$), and barium swallows (25.3 vs. 29.1 years, $P = 0.03$). The mean age at first diagnostic procedure did not differ substantially between cases and noncases for other types of diagnostic radiographs reported here.

Hazard ratios and 95% confidence intervals for the risk of thyroid cancer associated with a per-unit increase in the number of self-reported medical diagnostic x-rays are presented in Table 4. Dental x-rays were associated with an increased risk of all types of thyroid cancer (hazard ratio = 1.13 per 10 radiographs, 95% confidence interval: 1.01, 1.26) and with the subgroup of papillary thyroid cancer (hazard ratio = 1.18 per 10 radiographs, 95% confidence interval: 1.04, 1.33). Other types of x-ray procedure were not associated with thyroid cancer risk (Table 4). We also examined thoracic x-ray and lumbar x-ray procedures separately and found that neither type was independently associated with an increased risk of thyroid cancer. Any radiotherapy to the head was associated with a 2.7-fold increased risk of thyroid cancer (hazard ratio = 2.74, 95% confidence interval: 1.52, 4.95).

In Table 5, results are stratified by calendar year of first procedure (before 1970 vs. 1970 or later). The observed increase in thyroid cancer risk associated with dental x-rays was apparent only among subjects who were initially exposed before 1970. No other radiologic procedure was associated with an elevated risk of thyroid cancer with initial exposure before 1970. Skull x-ray procedures performed in 1970 or later were associated with an increased risk of thyroid cancer overall (hazard ratio = 1.10 per radiograph, 95% confidence interval: 0.98, 1.24) and of papillary thyroid cancer (hazard ratio = 1.11 per radiograph, 95% confidence interval: 0.98, 1.26) (Table 5).

We did not observe a difference in thyroid cancer risk with any of the diagnostic procedures according to age at first procedure (less than 20 years vs. 20 years or older) (Table 6). Risk was elevated after exposure to dental x-rays regardless of the reported age at first procedure, although the point estimates within the age strata were not statistically significant except for papillary thyroid cancer with initial exposure before 20 years of age. For several procedures, including barium swallow, mammogram, and angiogram, the number of cases first exposed before the age of 20 years was too small ($n \leq 5$) to reliably estimate risks.

After combining data for diagnostic procedures in the head and neck region (including skull, cervical spine, and other head and neck x-rays), we did not observe a clear dose-response relationship (Table 7). Although we did not observe statistically significant elevated risks for any given category of number of procedures, the point estimates increased with increasing numbers of dental x-rays ($P_{trend} = 0.08$ for all cases; $P_{trend} = 0.05$ for papillary cases only) but not for other diagnostic procedures (Table 7).

Table 8 presents hazard ratios and 95% confidence intervals for thyroid cancer risk related to the intensity of diagnostic x-ray procedures received over time for a given type of x-ray procedure. An increased intensity of dental x-ray procedures and other head and neck x-ray procedures was associated with an increased risk of thyroid cancer overall and of papillary thyroid cancer (Table 8).

Sensitivity analyses excluding the first 5 years of follow-up did not materially change point estimates for any of our results (data not shown).

Table 3. Numbers of Subjects Who Reported Undergoing Specific X-Ray Procedures and Mean and Maximum Numbers of Procedures Among Exposed Persons, US Radiologic Technologists Study, 1983–2006

X-Ray Procedure	Noncases (*n* = 75,243)			Incident Thyroid Cancer Cases (*n* = 251)			Procedure Prevalence, %[a]
	No. of Subjects	Mean No. of Procedures	Maximum No. of Procedures	No. of Subjects	Mean No. of Procedures	Maximum No. of Procedures	
Cervical spine radiograph	23,617	1.9	50	82	1.6	5	31.4
Skull radiograph	22,714	1.8	50	74	1.8	20	30.2
Other head and neck radiograph	13,235	2.4	50	53	2.3	15	17.6
Thoracic spine radiograph	11,795	2.1	50	24	1.5	4	15.7
Angiogram	1,598	1.4	25	7	1.0	1	2.1
Dental radiograph	72,359	12.4	96	247	13.7	75	96.2
Mammogram[b]	15,491	1.8	85	56	1.7	6	26.2
Upper gastrointestinal series	31,505	1.9	30	104	1.8	5	41.9
Barium swallow	9,787	1.7	25	33	1.2	4	13.0
Chest radiograph	74,295	8.8	90	250	7.6	40	98.7
Lumbar spine radiograph	29,469	2.4	50	93	2.4	20	39.2

[a] Procedure prevalence based on those without thyroid cancer (total number of exposed noncases divided by the total number of noncases).
[b] Includes women only.

Table 4. Hazard Ratios and 95% Confidence Intervals for the Risk of Thyroid Cancer Related to Per-Specified-Unit Increase in the Reported Number of Selected Medical Diagnostic X-Ray Procedures, US Radiologic Technologists Study, 1983–2006

X-Ray Procedure	All Incident Cases (*n* = 251)				Papillary Cases Only (*n* = 187)			
	HR[a]	95% CI	HR[b]	95% CI	HR[a]	95% CI	HR[b]	95% CI
Cervical spine radiograph	0.95	0.85, 1.06	0.95	0.85, 1.07	0.96	0.86, 1.09	0.97	0.85, 1.10
Skull radiograph	0.99	0.90, 1.09	1.01	0.92, 1.10	1.01	0.92, 1.11	1.02	0.93, 1.12
Other head and neck radiograph	1.02	0.94, 1.10	1.03	0.95, 1.11	1.03	0.96, 1.12	1.04	0.96, 1.13
Angiogram	1.04	0.64, 1.69	1.10	0.69, 1.74	1.08	0.68, 1.72	1.12	0.69, 1.83
Dental radiograph (per 10 radiographs)	1.11	1.00, 1.24	1.13	1.01, 1.26	1.16	1.02, 1.31	1.18	1.04, 1.33
Mammogram[c]	0.99	0.87, 1.12	1.00	0.88, 1.13	0.97	0.82, 1.15	0.98	0.83, 1.15
Chest radiograph (per 5 radiographs)	0.92	0.82, 1.03	0.91	0.81, 1.03	0.92	0.81, 1.06	0.90	0.78, 1.04
Upper gastrointestinal series	0.98	0.88, 1.08	1.01	0.90, 1.12	1.02	0.93, 1.14	1.07	0.96, 1.19
Barium swallow	0.94	0.76, 1.15	0.95	0.76, 1.19	0.96	0.76, 1.20	0.93	0.73, 1.19
Lumbar/thoracic spine radiograph	0.99	0.93, 1.06	1.01	0.95, 1.08	0.98	0.90, 1.06	0.98	0.90, 1.07

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Cox proportional hazards regression with attained age as the time scale and adjustment for sex, birth cohort, smoking, body mass index, history of benign thyroid condition, and estimated occupational radiation dose to the thyroid.
[b] Cox proportional hazards model as above with additional adjustment for all other diagnostic procedures by adding each of the procedures as a separate variable in the model.
[c] Includes women only.

Table 5. Hazard Ratios and 95% Confidence Intervals[a] for the Risk of Thyroid Cancer Related to Per-Specified-Unit Increase in the Reported Number of Selected Diagnostic X-Ray Procedures Stratified by Year of First Procedure Before 1970 or Later, US Radiologic Technologists Study, 1983–2006

X-Ray Procedure	All Cases						Papillary Cases Only					
	First Procedure Before 1970			First Procedure in 1970 or Later			First Procedure Before 1970			First Procedure in 1970 or Later		
	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
Cervical spine radiograph	20	0.72	0.48, 1.08	54	0.98	0.81, 1.18	14	0.76	0.50, 1.16	41	0.99	0.80, 1.21
Skull radiograph	26	0.89	0.66, 1.19	41	1.10	0.98, 1.24	18	0.91	0.66, 1.26	35	1.11	0.98, 1.26
Other head and neck radiograph	12	0.98	0.80, 1.20	38	1.02	0.88, 1.19	9	0.99	0.79, 1.24	30	1.04	0.89, 1.22
Angiogram	2			4			2			3		
Dental radiograph (per 10 radiographs)	153	1.17	1.03, 1.32	70	0.85	0.52, 1.38	116	1.20	1.05, 1.38	52	0.90	0.53, 1.55
Mammogram[b]	1			53	0.97	0.77, 1.22	0			40	0.94	0.70, 1.27
Upper gastrointestinal series	30	0.93	0.74, 1.17	73	1.01	0.82, 1.23	24	0.94	0.74, 1.20	59	1.03	0.84, 1.27
Barium swallow	10	0.65	0.32, 1.32	23	0.54	0.21, 1.43	8	0.63	0.28, 1.42	17	0.66	0.26, 1.66
Chest radiograph (per 5 radiographs)	122	0.93	0.81, 1.07	114	0.97	0.75, 1.25	87	0.93	0.79, 1.09	90	1.02	0.78, 1.33
Lumbar/thoracic spine radiograph	27	0.99	0.89, 1.10	65	1.05	0.97, 1.14	19	1.01	0.92, 1.12	46	1.02	0.89, 1.17

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Cox proportional hazards regression with attained age as the time scale and adjustment for sex, birth cohort, smoking status, body mass index, history of benign thyroid condition, and estimated occupational radiation dose to the thyroid. Results not reported for models in which $n \leq 5$ because models were unstable.

[b] Includes women only.

DISCUSSION

This large, prospective cohort study of US radiologic technologists is the first study to report the relationship between diagnostic x-rays and thyroid cancer risk by using a prospective cohort design. We found no clear or consistent evidence of thyroid cancer risks associated with diagnostic x-ray procedures except for dental x-rays. We observed a 13% increase in thyroid cancer risk for every 10 reported dental radiographs (hazard ratio = 1.13, 95% confidence interval: 1.01, 1.26), which was driven by dental x-rays first received before 1970, but there was no evidence that the relationship between dental x-rays and thyroid cancer was associated with childhood or adolescent exposures as would have been anticipated. The relationship between dental x-rays and thyroid cancer risk was surprising because we found no evidence of an association of thyroid cancer with other types of diagnostic x-rays characterized by higher radiation exposure than dental x-rays. This could be, in part, because other x-ray procedures are not as common at younger ages, which are times of greater vulnerability to the carcinogenic action of ionizing radiation (17, 21). We also observed a 2.7-fold increased risk of thyroid cancer related to self-reported history of radiotherapy to the head and neck, which was expected because of the higher radiation doses for therapeutic radiation.

Our finding that most medical diagnostic x-ray procedures are not associated with the risk of thyroid cancer is consistent with those of the previous case-control studies that relied on medical records to obtain information on diagnostic x-ray exposures (10, 11) and with 2 of the case-control studies that relied on interview data (8, 12). Another study that relied on self-reported procedures reported a 2.6-fold increase in risk related to diagnostic procedures with the highest absorbed thyroid dose (>1 mGy) (9) but subsequently found no increased risk when exposures were later estimated on the basis of information abstracted from medical records (10). Nevertheless, we cannot rule out the possibility that small risks may exist. Doses from medical x-rays are likely to have been higher in the past (19, 20, 24). This is consistent with our findings that dental x-rays were associated with thyroid cancer risk only among participants who received radiography before 1970 (which included 75% of participants in this study) but not among those who received radiography exclusively during and after 1970. Since the first nationwide x-ray exposure study was conducted in 1964, radiation exposures from dental x-rays (namely, bitewing x-rays) have decreased by more than 75% (20). Unlike

Table 6. Hazard Ratios[a] and 95% Confidence Intervals for the Risk of Thyroid Cancer Related to Per-Specified-Unit Increase in the Number of Selected Diagnostic X-Ray Procedures Stratified by Subject Age (<20 years or ≥20 years) at First Procedure, US Radiologic Technologists Study, 1983–2006

X-Ray Procedure	All Cases						Papillary Cases Only					
	First Procedure When Aged <20 Years			First Procedure When Aged ≥20 Years			First Procedure When Aged <20 Years			First Procedure When Aged ≥20 Years		
	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
Cervical spine radiograph	10	0.37	0.10, 1.31	64	0.95	0.80, 1.12	8	0.26	0.04, 1.65	47	0.98	0.82, 1.16
Skull radiograph	24	0.99	0.82, 1.20	43	1.05	0.91, 1.21	18	0.95	0.70, 1.27	35	1.09	0.97, 1.22
Other head and neck radiograph	10	1.06	0.95, 1.18	40	0.89	0.72, 1.10	8	1.07	0.96, 1.19	31	0.87	0.68, 1.13
Angiogram	1			5			1			4		
Dental radiograph (per 10 radiographs)	156	1.12	0.99, 1.28	67	1.19	0.87, 1.62	119	1.17	1.01, 1.34	49	1.19	0.83, 1.71
Mammogram[b]	3			51	0.98	0.79, 1.20	3			37	0.89	0.64, 1.22
Upper gastrointestinal series	19	1.01	0.80, 1.26	84	0.92	0.76, 1.12	17	1.00	0.79, 1.28	66	0.95	0.78, 1.17
Barium swallow	3			30	0.73	0.43, 1.25	3			22	0.79	0.46, 1.37
Chest radiograph (per 5 radiographs)	161	0.89	0.77, 1.03	75	0.96	0.76, 1.21	122	0.87	0.73, 1.03	55	1.00	0.78, 1.28
Lumbar/thoracic spine radiograph	16	0.99	0.87, 1.13	76	1.04	0.97, 1.12	11	1.01	0.89, 1.15	54	1.04	0.94, 1.14

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Cox proportional hazards regression with attained age as the time scale and adjustment for sex, birth cohort, smoking status, body mass index, history of benign thyroid condition, and estimated occupational radiation dose to the thyroid. Results not reported for models in which there were ≤ 5 cases because models were unstable.

[b] Includes women only.

dental x-rays, the majority of other imaging procedures in our study did not occur until 5–10 years after 1970, when doses were likely to have been much lower (20); therefore, risks may be more difficult to detect.

Our finding of an association between dental x-rays and thyroid cancer risk among subjects who received their first dental radiograph before 1970 is consistent with some (6, 11) but not other (7, 12) reports. Inskip et al. (11) reported an increased risk of thyroid cancer related to panoramic or full-mouth series but no association with bitewing x-rays, which are thought to expose the thyroid gland to a lower dose of radiation than full-mouth series. Preston-Martin et al. (7) reported a decreased risk of thyroid cancer related to wearing a lead apron covering the torso up to the neck during dental radiography (relative risk = 0.6, $P = 0.10$) but no direct association of thyroid cancer with dental x-rays. In contrast, Ron et al. (12) found an inverse association between dental x-rays and thyroid cancer. These studies all relied on self-reported information on dental x-ray procedures after diagnosis and could be subject to recall bias and reporting error more generally. One possible explanation for our findings could be screening bias. That is, subjects who receive more dental x-rays may be greater medical care–seekers and therefore more likely to be screened for thyroid cancer, which is often detected during routine examination prior to the onset of symptoms.

Our finding that thyroid cancer risk is elevated in subjects who report having received radiotherapy to the head or neck is also consistent with those of previous studies (17, 25, 26), including studies that used data collected from in-person interviews (7, 8, 12). Case-control studies in Connecticut (12) and northern Italy (8) reported risk estimates similar to those we found in our study (in the Connecticut study, odds ratio = 2.8, 95% confidence interval: 1.2, 6.9) (159 cases, 19 exposed); in the northern Italy study, odds ratio = 2.6, 95% confidence interval: 0.9, 7.1 (245 cases, 9 exposed). A smaller study in Los Angeles, California, (7) also found an elevated risk (odds ratio = 5.0 ($P = 0.14$) (110 cases, 5 exposed). These similarities in findings lend credence to the external validity of our study.

Our study has several notable strengths. We minimized the potential for reporting bias by conducting a prospective cohort study in which all participants were asked about their diagnostic x-ray procedure history before developing thyroid cancer. We were also able to account for exposures during the period when participants were most vulnerable to the carcinogenic action of radiation, which was more than 20 years in the past for the majority of participants, and which

Table 7. Hazard Ratios and 95% Confidence Intervals for the Risk of Thyroid Cancer by Number of X-Ray Procedures to the Head and Neck Region, US Radiologic Technologists Study, 1983–2006

X-Ray Procedure and No.	All Cases				Papillary Cases Only			
	No. of Cases	HR[a]	95% CI	P_{trend}	No. of Cases	HR[a]	95% CI	P_{trend}
Cervical spine radiograph								
0	168	1.00	Referent	0.79	124	1.00	Referent	0.98
1–2	69	1.09	0.82, 1.44		51	1.10	0.79, 1.53	
≥3	11	0.75	0.40, 1.39		9	0.84	0.42, 1.67	
Skull radiograph								
0	168	1.00	Referent	0.62	123	1.00	Referent	0.96
1–2	60	0.94	0.70, 1.26		47	1.00	0.72, 1.41	
≥3	11	0.91	0.49, 1.67		9	1.02	0.52, 2.01	
Other head and neck radiographs								
0	192	1.00	Referent	0.62	141	1.00	Referent	0.36
1–2	40	1.24	0.88, 1.75		31	1.32	0.89, 1.95	
≥3	12	0.93	0.52, 1.66		10	1.06	0.56, 2.02	
All head and neck radiographs[b]								
0	108	1.00	Referent	0.59	80	1.00	Referent	0.51
1–4	123	1.15	0.88, 1.49		91	1.15	0.85, 1.55	
≥5	20	0.99	0.61, 1.60		16	1.07	0.62, 1.84	
Dental radiograph								
<10	93	1.00	Referent	0.08	66	1.00	Referent	0.05
10–19	74	1.09	0.80, 1.48		58	1.21	0.85, 1.72	
20–29	42	1.24	0.86, 1.79		35	1.47	0.97, 2.22	
≥30	24	1.46	0.93, 2.30		17	1.47	0.86, 2.52	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Cox proportional hazards regression with attained age as the time scale and adjustment for sex, birth cohort, smoking, body mass index, history of thyroid disease, and estimated occupational radiation dose to the thyroid.

[b] Includes skull, cervical spine, and other head and neck radiographs combined.

is a time period for which medical or dental records may be unavailable or incomplete (13). Although self-reported information on medical history is also subject to uncertainty, radiologic technologists are a population whose occupational expertise may facilitate recall of their own diagnostic radiologic history compared with that of the general population (15).

Our study also has several limitations. We did not have information on the type of dental x-rays received (e.g., panoramic vs. bitewing x-rays). Moreover, we did not validate dental radiology history, an effort that is not feasible on a large scale because no national database of dental procedures exists. Two validation studies have compared recalled dental histories with dental records. The first study of 84 parotid gland cancer cases and 79 controls in Los Angeles, California, (13) reported that cases and controls did not substantially differ in their ability to recall dental histories, and both groups overestimated the number of radiologic visits and underestimated the number of panoramic procedures. The second study of 72 meningioma cases and 75 controls in western Washington State (27) reported accurate recall of panoramic and bitewing x-rays but an overestimation of full-mouth series; the overestimation appeared to be greater for cases for more recent visits and greater for controls for visits in the more distant past (27). Additionally, we were not able to adjust for medical care–seeking behavior, which could lead to screening bias if participants who received more x-ray procedures were also more likely to be screened for thyroid cancer. We also did not account for x-ray exposures after the baseline questionnaire or as a time-dependent exposure. However, because all participants were at least 22 years of age when they entered the study, all participants had the opportunity to report exposures at young ages (i.e., under 20 years), which is the most critical exposure window for thyroid cancer risk related to ionizing radiation (17, 21). Another study limitation is that we did not have thyroid organ doses that would have enabled a quantitative estimate of risk from all exposures combined.

In summary, we found no clear or consistent evidence of thyroid cancer risk associated with diagnostic x-ray procedures except for dental x-rays. The finding for dental x-rays was driven by dental x-ray procedures first received before 1970,

Table 8. Hazard Ratios and 95% Confidence Intervals for the Risk of Thyroid Cancer Related to the Intensity[a] of Diagnostic X-Ray Procedure, US Radiologic Technologists Study, 1983–2006

X-Ray Procedure	All Cases		Papillary Cases Only	
	HR[b]	95% CI	HR[b]	95% CI
Cervical spine radiograph	0.87	0.63, 1.20	0.82	0.62, 1.10
Skull radiograph	1.08	0.77, 1.51	1.13	0.86, 1.50
Other head and neck radiograph	1.17	1.00, 1.38	1.19	1.01, 1.40
Angiogram	2.05	0.91, 4.63	1.81	0.56, 5.88
Dental radiograph	1.23	1.05, 1.44	1.27	1.08, 1.49
Mammogram[c]	0.85	0.57, 1.28	0.95	0.58, 1.56
Upper gastrointestinal series	0.76	0.43, 1.37	1.05	0.50, 2.19
Barium swallow	0.87	0.29, 2.66	0.90	0.27, 3.00
Chest radiograph	1.02	0.75, 1.38	1.02	0.72, 1.44
Lumbar/thoracic spine radiograph	1.15	0.86, 1.53	0.97	0.58, 1.64

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Intensity defined as the reported cumulative number of procedures divided by the total number of years during which the procedures occurred.

[b] Cox proportional hazards regression with attained age as the time scale and adjustment for sex, birth cohort, smoking, body mass index, history of thyroid disease, estimated occupational radiation dose to the thyroid, and all other diagnostic procedures.

[c] Includes women only.

but we found no evidence that the relationship between dental x-rays and thyroid cancer was associated with childhood or adolescent exposures as would have been anticipated. The lack of association of thyroid cancer with childhood or adolescent exposure and with other types of diagnostic x-rays characterized by higher radiation doses underscores the need to conduct a detailed radiation exposure assessment to enable quantitative evaluation of risk, including examination of radiation dose-response.

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REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10–29.
2. Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention*. 3rd ed. New York, NY: Oxford University Press; 2006.
3. Sinnott B, Ron E, Schneider AB. Exposing the thyroid to radiation: a review of its current extent, risks, and implications. *Endocr Rev*. 2010;31(5):756–773.
4. National Council on Radiation Protection and Measurements. Scientific Committee 6–2 on Radiation Exposure of the U.S. Population. *Ionizing Radiation Exposure of the Population of the United States: Recommendations of the National Council on Radiation Protection and Measurements*. Bethesda, MD: National Council on Radiation Protection and Measurements; 2009.
5. National Council on Radiation Protection and Measurements. *Ionizing Radiation Exposure of the Population of the United States: Recommendations of the National Council on Radiation Protection and Measurements*. Bethesda, MD: National Council on Radiation Protection and Measurements; 1987.
6. Memon A, Godward S, Williams D, et al. Dental x-rays and the risk of thyroid cancer: a case-control study. *Acta Oncol*. 2010;49(4):447–453.
7. Preston-Martin S, Bernstein L, Pike MC, et al. Thyroid cancer among young women related to prior thyroid disease and pregnancy history. *Br J Cancer*. 1987;55(2):191–195.
8. Franceschi S, Fassina A, Talamini R, et al. Risk factors for thyroid cancer in northern Italy. *Int J Epidemiol*. 1989;18(3): 578–584.
9. Wingren G, Hallquist A, Hardell L. Diagnostic x-ray exposure and female papillary thyroid cancer: a pooled analysis of two Swedish studies. *Eur J Cancer Prev*. 1997;6(6):550–556.
10. Hallquist A, Nasman A. Medical diagnostic x-ray radiation—an evaluation from medical records and dentist cards in a case-control study of thyroid cancer in the northern medical region of Sweden. *Eur J Cancer Prev*. 2001;10(2):147–152.
11. Inskip PD, Ekbom A, Galanti MR, et al. Medical diagnostic x-rays and thyroid cancer. *J Natl Cancer Inst*. 1995;87(21): 1613–1621.
12. Ron E, Kleinerman RA, Boice JD Jr, et al. A population-based case-control study of thyroid cancer. *J Natl Cancer Inst*. 1987; 79(1):1–12.
13. Preston-Martin S, Bernstein L, Maldonado AA, et al. A dental x-ray validation study. Comparison of information from patient interviews and dental charts. *Am J Epidemiol*. 1985;121(3): 430–439.

14. Berrington de Gonzalez A, Ekbom A, Glass AG, et al. Comparison of documented and recalled histories of exposure to diagnostic x-rays in case-control studies of thyroid cancer. *Am J Epidemiol*. 2003;157(7):652–663.
15. Bhatti P, Doody MM, Preston DL, et al. Increased frequency of chromosome translocations associated with diagnostic x-ray examinations. *Radiat Res*. 2008;170(2):149–155.
16. Sigurdson AJ, Doody MM, Rao RS, et al. Cancer incidence in the US Radiologic Technologists Health Study, 1983–1998. *Cancer*. 2003;97(12):3080–3089.
17. 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(3):259–277.
18. Simon SL, Weinstock RM, Doody MM, et al. Estimating historical radiation doses to a cohort of US radiologic technologists. *Radiat Res*. 2006;166(1 Pt 2):174–192.
19. Preston-Martin S, Thomas DC, White SC, et al. Prior exposure to medical and dental x-rays related to tumors of the parotid gland. *J Natl Cancer Inst*. 1988;80(12):943–949.
20. Johnson DW, Goetz WA. Patient exposure trends in medical and dental radiography. *Health Phys*. 1986;50(1):107–116.
21. Preston DL, Ron E, Tokuoka S, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat Res*. 2007;168(1):1–64.
22. Preston-Martin S, Paganini-Hill A, Henderson BE, et al. Case-control study of intracranial meningiomas in women in Los Angeles County, California. *J Natl Cancer Inst*. 1980;65(1):67–73.
23. Claus EB, Calvocoressi L, Bondy ML, et al. Dental x-rays and risk of meningioma. *Cancer*. 2012;118(18):4530–4537.
24. Richards AG, Colquitt WN. Reduction in dental x-ray exposures during the past 60 years. *J Am Dent Assoc*. 1981;103(5):713–718.
25. Schneider AB, Ron E, Lubin J, et al. Dose-response relationships for radiation-induced thyroid cancer and thyroid nodules: evidence for the prolonged effects of radiation on the thyroid. *J Clin Endocrinol Metab*. 1993;77(2):362–369.
26. Schneider AB, Sarne DH. Long-term risks for thyroid cancer and other neoplasms after exposure to radiation. *Nat Clin Pract Endocrinol Metab*. 2005;1(2):82–91.
27. Longstreth WT Jr, Phillips LE, Drangsholt M, et al. Dental x-rays and the risk of intracranial meningioma: a population-based case-control study. *Cancer*. 2004;100(5):1026–1034.
28. Lee C, Kim KP, Long D, et al. Organ doses for reference adult male and female undergoing computed tomography estimated by Monte Carlo simulations. *Med Phys*. 2011;38(3):1196–1206.
29. Stern SH. *National Evaluation of X-Ray Trends (NEXT). Tabulation of Graphical Summary of 2000 Survey of Computed Tomography*. Frankfort, KY: Conference of Radiation Control Program Directors, Inc.; 2007.
30. Kereiakes JG, Rosenstein MR. *Handbook of Radiation Doses in Nuclear Medicine and Diagnostic X-Ray*. Boca Raton, FL: CRC Press; 1980.
31. Ludlow JB, Davies-Ludlow LE, White SC. Patient risk related to common dental radiographic examinations: the impact of 2007 International Commission on Radiological Protection recommendations regarding dose calculation. *J Am Dent Assoc*. 2008;139(9):1237–1243.
32. Thierry-Chef I, Simon SL, Weinstock RM, et al. Reconstruction of absorbed doses to fibroglandular tissue of the breast of women undergoing mammography (1960 to the present). *Radiat Res*. 2012;177(1):92–108.
33. Whelan C, McLean D, Poulos A. Investigation of thyroid dose due to mammography. *Australas Radiol*. 1999;43(3):307–310.

Appendix Table 1. Correlation Coefficients (*r*) for the Cumulative Number of Medical Diagnostic Radiograph Procedures Reported on the First Questionnaire, US Radiologic Technologists Study, 1983–2006

Procedure Type	Upper Gastrointestinal	Barium Swallow	Mammogram	Angiogram	Skull	Dental	Cervical Spine	Other Head and Neck	Chest	Thoracic Spine
Barium swallow	0.48	Referent								
Mammogram	0.11	0.07	Referent							
Angiogram	0.10	0.12	0.01	Referent						
Skull	0.15	0.14	0.03	0.08	Referent					
Dental	0.02	0.04	0.06	−0.00	0.07	Referent				
Cervical spine	0.22	0.19	0.08	0.07	0.26	0.08	Referent			
Other head and neck	0.16	0.13	0.05	0.05	0.22	0.07	0.23	Referent		
Chest	0.29	0.23	0.09	0.12	0.17	0.14	0.21	0.16	Referent	
Thoracic spine	0.15	0.13	0.04	0.05	0.16	0.06	0.33	0.16	0.14	Referent
Lumbar spine	0.25	0.20	0.05	0.08	0.21	0.06	0.35	0.18	0.24	0.57