Medical Diagnostic X Rays and Thyroid Cancer

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Background: **Diagnostic x rays are the largest man-made source of exposure to ionizing radiation for the general population. Whether there are meaningful cancer risks associated with such exposures is unclear. Most previous case–control studies have relied on recalled histories of x rays, and there is concern that completeness and accuracy of recall might differ between cancer case and control subjects.** ***Purpose:*** **The present study used information recorded prospectively in hospital charts to address the relationship between medical diagnostic x rays and risk of thyroid cancer.** ***Methods:*** **The Swedish Cancer Registry and the Uppsala-Örebro Regional Cancer Registry were used to identify persons with papillary or follicular thyroid cancer diagnosed from January 1, 1980, through December 31, 1992, among residents of the Uppsala Health Care Region. After histopathologic review, there were 484 such case subjects available for study. An equal number of age-, sex-, and county of residence-matched control subjects from the general population were randomly selected on the basis of the Swedish Registry of the Total Population. Lifetime residential histories were compiled, and radiology records were searched at all Swedish hospitals serving regions where study subjects ever maintained an official residence. Approximate radiation doses to the thyroid gland for specific types of x-ray examinations were assigned on the basis of mean values of measurements made in Sweden in 1973-1975 and in the United States in 1970. Odds ratios were used to evaluate the association between diagnostic radiography and risk of thyroid cancer.** ***Results:*** **A total of 3853 medical diagnostic x rays were ascertained among thyroid cancer case subjects and 4039 among the matched control subjects. There was no tendency for case subjects to have had more of the types of x-ray procedure associated with higher radiation dose to the thyroid gland (i.e., those involving the head or neck area). This finding was true even when analysis was restricted to x rays occurring before 1960, when doses likely were higher than in more recent years, and for examinations occurring in childhood and adolescence, when susceptibility to radiation-induced thyroid cancer is greatest. The relative risk of thyroid cancer was not significantly associated with estimated cumulative dose to the thyroid gland from diagnostic x rays (two-sided *P* for trend = .80).** ***Conclusion:*** **These data indicate that the risk of thyroid cancer due to medical diagnostic x rays, if any, is very small. [J Natl Cancer Inst 1995;87:1613-21]**

Diagnostic radiology is the largest man-made source of exposure to ionizing radiation for the general population *(1,2)*. Except for unusual circumstances in years past, such as repeated chest fluoroscopies in tuberculosis patients *(3)*, cancer risks attributable to diagnostic irradiation are believed to be very small *(4,5)*. However, studies have reported elevated risks of chronic myeloid and monocytic leukemia, meningioma, glioma, parotid gland tumors, and thyroid cancer associated with diagnostic medical and dental x rays, especially for high-dose exposures that occurred several decades ago *(6-10)*. Given the high prevalence and frequency of exposure to diagnostic x rays, any measurable increase in cancer risk would be of considerable public health importance.

An important limitation of most previous studies *(6-10)* was the use of interviews to reconstruct histories of exposure. A study by Graham et al. *(11)* indicated that reliance on interview data alone resulted in substantial underascertainment of diagnostic x rays, and the possibility of differential recall of x rays by case and control subjects usually cannot be ruled out. Errors associated with incomplete or inaccurate recall can be avoided by ascertaining exposure through medical records rather than through interviews, but it is difficult to assemble lifetime x-ray histories in most settings. The few studies that relied on x-ray reports in medical records generally have failed to demonstrate an increased cancer risk associated with diagnostic radiography *(12,13)*.

The thyroid gland is believed to be especially susceptible to radiation carcinogenesis, at least for exposures occurring early in life *(14)*. Indeed, cancer of the thyroid appears to have the highest relative risk (RR) coefficient of any malignancy following irradiation, with estimates ranging between 1% and 32% per cGy (rad) for people irradiated during childhood *(15)*. Using information recorded in hospital charts, we investigated prospectively the relationship between thyroid cancer and lifetime history of medical diagnostic x rays.

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See "'Notes" section following "'References."'

Subjects and Methods

This case–control study was made possible by unique features of the Swedish health care system. At the time of the study, the public medical service in Sweden was divided into 27 financially and administratively independent areas: 25 counties and two cities. Within these areas were the following three categories of hospital: 1) regional hospitals, of which there were 10 (one for each region—a region contains one or more administrative areas); 2) central hospitals, of which there were 23 (generally one per county but, in some instances, the regional hospital served a dual role as central and regional hospital); and 3) community hospitals, of which there were 64 (one to several per county). All individuals resident in a given area were served by at least one such hospital; for those served by a community hospital, the central hospital served as the primary referral center. Highly specialized medical services were provided to several counties by a regional hospital. Charges for medical services were kept low enough to permit all citizens equal access to health care. Only in an emergency or in another unusual situation would a patient obtain care at a hospital outside his or her county of residence. Persons seeking outside nonemergency care without specific authorization had to pay the bill themselves, so there was a strong incentive to use the designated hospital. Because there was no private inpatient treatment in Sweden, apart from two small hospitals in Stockholm and Gothenburg, hospital medical services were population based and referable to the county in which the patient lived. With rare exceptions, diagnostic x-ray procedures were carried out in departments of radiology at the community, county, or regional hospitals. Nonemergency examinations done elsewhere were performed at outpatient clinics run by county authorities and very rarely in private outpatient clinics. Chiropractors in Sweden are not licensed to administer x rays. Leitz et al. *(16)* reported that 95% of all medical diagnostic x-ray examinations in Sweden were given at facilities that were part of the public health care system. Rosters of all diagnostic x-ray procedures are stored in the departments of radiology and are readily available. They are sorted by national registration number, a unique personal identifier assigned to all Swedish citizens at birth, and are stored indefinitely. In the rare instances in which a hospital closed, medical records were transferred to the new hospital serving that community. In principle, therefore, if one can reconstruct a person's lifetime residential history, one knows in which hospitals to look for x-ray reports for particular time intervals. To ensure completeness of retrieval of radiology records, the present study was confined to Swedish-born persons who had not lived outside Sweden for periods exceeding 5 years and who were residents of the Uppsala Health Care Region at the time of thyroid cancer diagnosis. The Uppsala Health Care Region comprises six counties in central Sweden.

The case series consisted of persons with histologically confirmed papillary or follicular carcinoma diagnosed from January 1, 1980, through December 31, 1992. Only persons with thyroid cancer occurring as the first primary cancer were eligible. Five hundred seventy-four potentially eligible case subjects were ascertained through the Swedish Cancer Registry for the years 1980-1989 and the Up psala-Örebro Regional Cancer Registry for the years 1990-1992. (In Sweden, regional cancer registries compile incidence data, which they then report to the national cancer registry. At the time of this study, the national cancer registry was complete through 1989 only.) Cancer case diagnoses were reviewed by a specialist in endocrine pathology (L. Grimelius). As a result of this review, 90 diagnoses were rejected as incorrect (n = 60) or inadequately supported (n = 30). Reasons for rejection included follicular adenoma misclassified as follicular cancer, medullary or anaplastic cancer coded as differentiated thyroid cancer, diagnosis of papillary cancer that was questioned on review, and absence of histopathologic examination. Four hundred eighty-four case patients with papillary or follicular thyroid cancer were accepted and enrolled in the study.

One control subject was matched to each case subject, based on age (± 1 year), sex, and county of residence at the time of diagnosis, using the Registry of the Total Population, which contains such information on all Swedish residents. We used the registry each year from 1980 onward to match the case subjects diagnosed during that year. Control subjects were randomly selected from among persons in the population who met the matching criteria. Control subjects had not been diagnosed with cancer prior to the date of thyroid cancer diagnosis for the matched case subject. Prior cancers were identified through the Cancer Registry.

Enumeration of residences was made possible through information routinely collected at the parish level. During the study period. a national registration of residences was administered by the Swedish state church. Different parishes were responsible for documenting the residential history of all persons living within their boundaries. Parish authorities retained information about the three most recent places of residence and the dates when an individual moved from one parish to another. Information in the Cancer Registry and the Registry of the Total Population was used to learn in which parish an individual resided at the time of diagnosis. Lifetime residential histories were reconstructed by working backward from parish of current residence and forward from residence at birth.

Based on the residential histories, the list of hospitals to be visited and the roster of subjects and years to be searched at each hospital were determined. Because current residents of Uppsala may have lived elsewhere in Sweden earlier in their lives, it was necessary to include hospitals outside the Uppsala region. Access to records was facilitated through the cooperation and support of the head of the Department of Diagnostic Radiology at University Hospital in Uppsala, Professor Uno Erikson, who wrote letters to heads of radiology departments at hospitals throughout Sweden requesting that they cooperate with the study. We were granted access to records at all hospitals. Histories of x ray(s) were abstracted from radiology records by a person who had been employed previously as an x-ray technician and who was familiar with the terminology and record-keeping procedures. Information about chest x rays sometimes was stored separately from departments of diagnostic radiology, and older radiology files occasionally were stored separately from records for recent patients. However, this situation was known and taken into account during the abstracting. If three or fewer individuals had been served by a given hospital, the information was obtained with the cooperation of hospital staff, who were asked to send copies of the original radiology records. If more than three study subjects had lived in an area served by a particular hospital, that hospital was visited by the study abstractor. A total of 48 hospitals were visited.

The abstractor was not informed of the case or control status of persons in the study, but their status often would become apparent in the course of reviewing radiology records, so blinding cannot be assumed. As a check on the work of the abstractor, a second search for all x-ray procedures was conducted at two departments of diagnostic radiology in Uppsala and Örebro for 40 randomly chosen case and 40 control subjects. Half of each group were known to have resided in Uppsala and half in Örebro, for a median period of 19 years for the case subjects and 20 years for the control subjects. Hospital personnel in each department were recruited to ascertain the x-ray histories of these 80 individuals. These personnel were unaware of results of the abstractor's search. No additional x rays were ascertained for 36 case subjects and 37 control subjects; i.e., the initial ascertainment appears to have been complete. For two case subjects and two control subjects, one additional x ray was found during the reabstraction. For one case and one control subject, the search yielded five previously missed x rays (multiple instances of the same type of x ray); for the remaining case subject, the yield was three additional x rays. On the other hand, for one case subject and two control subjects, x rays that were ascertained by the study abstractor were missed by hospital staff in the validation exercise.

Because a possible association with radiologic procedures involving the neck could have been confounded by medical indication, an effort was made to learn the underlying reason for x-ray examinations of soft tissues of the neck occurring 5 or more years before the diagnosis of thyroid cancer. We obtained this information for 92% of the case patients subjected to such a procedure (n = 48) and for 90% of the control subjects (n = 20).

The scheme described above, linking residences with hospitals, was effective for ascertaining most medical diagnostic x rays but not for nuclear medicine procedures (including ^{131}I scans of the thyroid gland), history of radiotherapy, or dental x rays. A substantial part of dental care in Sweden is given in private clinics. Moreover, chest fluoroscopy administered as part of screening programs for early diagnosis of tuberculosis was performed extensively in the 1940s, 1950s, and 1960s, often in mobile clinics at schools and workplaces. In some instances, the records have not been stored in departments of radiology. The same is true, to some extent, for mammography, which was introduced in the 1970s and sometimes carried out in mobile clinics. We attempted to assess the extent of underascertainment in our material by interviewing a sample of recently diagnosed (1985-1992) case and matched control subjects. We obtained telephone interviews for 123 matched pairs. The extent of agreement between documented and self-reported histories of medical x-ray exposure for the full set of 123 case–control pairs will be the subject of a future report. We describe results from the interview here only insofar as they bear on the adequacy of ascertainment of x rays from medical records. Particular attention is given to individuals for whom the radiology record review identified zero x rays, inasmuch as this group is likely to indicate most clearly the types of procedures that were underascertained.

Specific types of x-ray examinations were assigned approximate doses based on mean values of measurements made in 1973-1975 in Sweden *(17)* and in 1970 in the United States *(18)* (Table 1). The Swedish data were used preferentially, if available. These values should not be assumed to accurately represent the dose for an individual from any single examination. Some of the estimates are based on small numbers of dose measurements and are subject to considerable uncertainty. Factors such as field sizes, angles of projections, and numbers of films could not be taken into account. Also, duration of exposure and extent of exposed area were not available for fluoroscopic examinations of the upper gastrointestinal tract. Finally, doses from diagnostic radiography have declined over time, and measurements from one era are not applicable to all time periods. We were not able to locate information by which to quantify this secular trend. The objective here was to sort case subjects and control subjects into ordinal categories based on cumulative radiation dose, not to estimate exact doses for individuals. More than three quarters of the x rays of case subjects and control subjects occurred during the 1960s or 1970s *(see below)*, so the measurements of Bengtsson et al. *(17)* and Kereiakes and Rosenstein *(18)* are relevant to the time period in which most x rays of study subjects occurred.

Odds ratios were used as estimators of RR. Conditional logistic regression models *(19-21)* were used to estimate RRs and associated 95% confidence intervals (CIs) and to test for trend in the RR. Estimates and tests are based on likelihood methods. All *P* values resulted from two-sided tests. Only x-ray examinations that occurred 5 or more years before the date of thyroid cancer diagnosis for the case or matched control subject were included in these analyses, because radiation-induced thyroid cancers rarely are detected until at least 5 years after the relevant exposure *(2)*.

Table 1. Average thyroid doses for common radiographic examinations in Sweden and the United States, based on surveys conducted in the 1970s*

Examination	Thyroid dose, mGy	
	Sweden†	United States‡
Lungs (full size), ribs	0.17	
Lungs (photofluorography)	1.00	
Lungs plus heart	0.24	
Chest		0.065
Ribs		1.54
Head, sinus	7.90	
Skull		2.22
Cerebral angiography	3.00	
Shoulder, clavicle, sternum	<0.50	
Shoulder (one)		0.58
Arm	<0.01	
Cervical spine	1.40	4.04
Thoracic spine	13.0	0.75
Lumbar spine	0.16	0.003
Lumbosacral spine	<0.01	0.0005
Full spine (chiropractic)		2.71
Pelvis	<0.01	<0.0001
Hip and upper femur	<0.01	<0.0001
Pelvimetry	<0.10	
Hysterosalpingography	<0.01	
Abdomen	0.03	
KUB (i.e., kidney, ureter, bladder)		0.0001
Stomach and duodenum	0.29	
Upper gastrointestinal tract		0.070
Small intestine	0.03	
Colon	0.10	
Barium enema		0.002
Cholecystography/cholangiography	0.03	0.010
Urography	0.38	
Retrograde pyelography	0.50	
Intravenous pyelogram		0.0001
Urethrocystography	0.05	
Dental (intraoral, single exposure)	0.03	

*Categories used are as reported in the source publications.

†From Bengtsson et al. *(17)*. Sample sizes for some procedures are very small, and dose estimates among individual patients varied considerably.

‡From Kereiakes and Rosenstein *(18)*.

The study was conducted with the approval of the institutional review board at University Hospital in Uppsala.

Results

Three hundred fifty-seven (74%) of the 484 case subjects had papillary carcinoma, and 127 (26%) had follicular carcinoma. The mean age at diagnosis was 51.5 years for papillary carcinoma, 62.7 years for follicular carcinoma, and 54.4 years overall. Three hundred seventy-one (77%) of the case subjects were female. A female predominance was seen at all ages, but it was more pronounced at the younger ages (85% of case subjects under the age of 40).

A total of 7892 x-ray examinations were ascertained (Table 2), of which 6148 (78%) occurred 5 or more years before the date of thyroid cancer diagnosis. The earliest recorded x ray was given in 1934. Nearly half of the procedures occurred in the 1970s. Excluding the 5 years before diagnosis, case subjects had received an average of 6.1 documented medical x-ray procedures of all types in their lifetimes; the corresponding number for control subjects was 6.6. Maximum numbers of x-ray examinations for individual case and control subjects were 76 and 95, respectively. For 97 case subjects (20%) and 98 control subjects (20%), no radiology record documentation of ever having received diagnostic x rays was found. These numbers increased to 115 (24%) and 117 (24%), respectively, when x rays received during the 5 years preceding the date of thyroid cancer diagnosis were excluded.

Table 3 shows the numbers of case and control subjects ever exposed to specific types of radiographic examinations as well as the mean and maximum numbers of examinations among

Table 2. Number of medical x-ray examinations of all types among 484 thyroid cancer case subjects and an equal number of age- and sex-matched population control subjects

Time interval or population subgroup	Total No. of x-ray examinations	
	Case subjects	Control subjects
Total		
All years	3853	4039
≥5 y before diagnosis of case	2937	3211
Sex*		
Females (n = 371)	2255	2457
Males (n = 113)	682	754
Calendar year of examination*		
<1950	33	73
1950-1959	265	290
1960-1969	906	1043
1970-1979	1368	1459
1980-1987	365	346
Age at examination, y*		
<20	272	237
20-39	947	1079
40-59	1153	1289
≥60	565	606
Year of thyroid cancer diagnosis*		
1980-1985	1341	1628
1986-1992	1596	1583

*Excluding x rays that occurred within 5 years before diagnosis of thyroid cancer in the case subjects and matched control subjects.

Table 3. Numbers of case and control subjects ever exposed to specific radiographic examinations and mean and maximum number of examinations per exposed person*

Examination	Case subjects (n= 484)		Control subjects (n = 484)	
	No. exposed	Examinations per exposed person, mean (maximum)	No. exposed	Examinations per exposed person, mean (maximum)
Head and neck				
Orbits	3	1.33 (2)	3	1.00 (1)
Mandible/jaw	12	1.42 (3)	4	2.00 (3)
Nasal bones/sinuses	48	1.46 (5)	58	1.53 (4)
Other bones of face	4	1.25 (2)	12	1.58 (4)
Skull	30	1.47 (8)	34	1.53 (6)
Teeth, partial†	1	1.00 (1)	2	1.00 (1)
Teeth, full mouth†	6	1.33 (3)	0	—
Neck for soft tissues	47	1.28 (5)	20	1.40 (3)
Computed tomography scan, head	2	1.00 (1)	0	—
Other (head)	2	2.50 (4)	4	1.00 (1)
Head/neck, not otherwise specified	0	—	1	1.00 (1)
Cerebral/carotid arteriogram	1	1.00 (1)	1	1.00 (1)
Any examination of head/neck	110	1.97 (11)	102	2.03 (7)
Chest and shoulder				
Chest, radiograph	217	3.22 (23)	202	3.69 (68)
Chest, photofluorograph	195	2.21 (7)	213	2.53 (14)
Chest, fluoroscopic	1	2.00 (2)	1	1.00 (1)
Heart, plain film	2	1.00 (1)	0	—
Computed tomography scan, chest	3	1.67 (3)	4	1.00 (1)
Ribs	13	1.46 (2)	12	1.25 (2)
Mammogram	7	1.43 (3)	2	1.50 (2)
Other (chest)	0	—	2	1.00 (1)
Clavicle	3	1.00 (1)	2	1.00 (1)
Scapula	2	1.50 (2)	7	1.57 (4)
Shoulder	33	1.61 (7)	40	1.58 (7)
Any examination of chest/shoulder	320	3.82 (26)	314	4.41 (69)
Spine and pelvis				
Full spine	10	1.10 (2)	9	1.11 (2)
Cervical spine	42	1.29 (3)	45	1.27 (3)
Cervicothoracic spine	5	1.00 (1)	12	1.08 (2)
Thoracic spine	7	1.00 (1)	3	1.00 (1)
Thoracolumbar spine	22	1.23 (4)	25	1.12 (2)
Lumbar spine	39	1.26 (3)	59	1.25 (4)
Lumbosacral spine	24	1.21 (2)	22	1.18 (3)
Sacrum and coccyx	8	1.63 (6)	16	1.12 (2)
Pelvis	38	1.61 (9)	53	1.62 (8)
Myelogram	4	1.25 (2)	4	1.25 (2)
Any examination of spine/pelvis	112	2.33 (18)	131	2.44 (12)
Arms and hands				
Humerus, upper arm	5	1.00 (1)	5	1.80 (4)
Elbow	13	1.69 (7)	20	1.25 (4)
Forearm, radius, ulna	4	2.50 (4)	7	2.14 (6)
Hand, wrist, finger(s)	67	2.93 (10)	83	3.24 (21)
Any examination of arms/hands	78	2.99 (10)	100	3.18 (21)
Lower extremities				
Hip	41	3.54 (15)	39	3.00 (10)
Femur, upper leg	3	1.00 (1)	8	1.25 (2)
Knee	58	2.21 (9)	60	2.45 (31)
Tibia, fibula, lower leg	9	3.11 (16)	11	1.91 (8)
Foot, ankle, toe(s)	74	2.12 (10)	79	2.20 (10)
Arteriogram (legs, feet)	1	1.00 (1)	0	—
Venography (legs, feet)	3	2.33 (3)	2	1.00 (1)
Any examination of lower extremities	130	3.61 (20)	138	3.41 (38)
Abdomen				
Abdomen, KUB (i.e., kidney, ureter, bladder)	19	1.05 (2)	34	1.47 (5)
Computed tomography scan, abdomen	0	—	1	1.00 (1)
Abdominal arteriogram	1	1.00 (1)	1	1.00 (1)
Any examination of abdomen	20	1.05 (2)	34	1.53 (6)
Gastrointestinal tract				
Upper gastrointestinal series	83	2.07 (13)	70	2.01 (8)
Colon, barium enema	52	1.52 (5)	46	1.43 (4)
Colonoscopy	6	1.00 (1)	1	1.00 (1)
Cholecystogram	74	1.54 (6)	69	1.36 (6)

Table 3 (continued). Numbers of case and control subjects ever exposed to specific radiographic examinations and mean and maximum number of examinations per exposed person*

Examination	Case subjects (n = 484)		Control subjects (n = 484)	
	No. exposed	Examinations per exposed person, mean (maximum)	No. exposed	Examinations per exposed person, mean (maximum)
Cholangiogram	32	1.09 (2)	25	1.28 (3)
Endoscopic retrograde cholangiopancreatography	2	1.00 (1)	0	—
Any examination of gastrointestinal tract	120	3.40 (25)	119	2.81 (14)
Urinary tract				
Intravenous pyelogram	49	1.31 (3)	58	1.64 (6)
Retrograde pyelogram	2	1.00 (1)	3	1.00 (1)
Cystogram	5	1.00 (1)	4	1.00 (1)
Renal arteriogram	5	1.40 (2)	1	2.00 (2)
Other procedure, urinary tract	1	2.00 (2)	0	—
Any examination of urinary tract	50	1.60 (5)	59	1.76 (6)
Female genital tract				
Pelvimetry	7	1.00 (1)	10	1.10 (2)
Hysterosalpingogram	12	1.25 (3)	5	1.00 (1)
Other	1	1.00 (1)	0	—
Any examination of female genital tract	20	1.15 (3)	15	1.07 (2)
Other/unspecified examinations	0	—	3	1.33 (2)
Any type of examination	369	7.96 (67)	367	8.75 (78)

*Examinations occurring within the 5 years preceding the date of thyroid cancer diagnosis are excluded for case subjects and matched control subjects.
†The x rays were done for medical, not dental, reasons.

those exposed. Examinations of particular interest with regard to potential for exposure to the thyroid gland include those of the neck, upper spine, skull, face, upper gastrointestinal tract, and chest. There was no consistent pattern of case subjects having had more of the types of x-ray procedures associated with higher dose to the thyroid than control subjects. The most common procedures were x rays and photofluorographs of the chest. One case subject had 23 chest x rays, and one control subject had 68 chest x rays. There were more chest x rays among case subjects but more photofluorographs among control subjects. More case than control subjects had received x rays of the jaw and of soft tissues in the neck. Slightly higher percentages of case subjects had received an examination of the thoracic spine or upper gastrointestinal series. Relatively more control subjects, however, had received x rays of the nose, sinuses or face, shoulder, and scapula. Case and control subjects had similar numbers of x-ray examinations of the cervical spine, full spine, and ribs.

The usual reason for the x-ray examinations of soft tissues of the neck was goiter or suspicion of goiter. Twenty-three of 44 case subjects and seven of 18 control subjects for whom reason for referral for x-ray examination was known were given the examination to confirm or rule out a clinical diagnosis of goiter. The clinical diagnosis was confirmed by the x ray in 21 case subjects and six control subjects. Indications for the x rays among the remaining case and control subjects were either pain or discomfort or difficulty in swallowing; in none of these instances did the x ray reveal a goiter as the underlying cause.

With regard to examinations of parts of the body more distant from the neck area, which would have resulted in very small doses to the thyroid, some procedures were more common among case subjects and others were more common among control subjects. This situation is as one might expect if differences were attributable primarily to chance. Examination of results separately for males versus females and for papillary versus follicular cancers did not reveal other notable case–control differences.

Tables 4 and 5 present results separately by calendar year and age at exposure, respectively, for groupings of x-ray procedures corresponding to presumptive high (i.e., in years prior to 1960), medium (in years 1960-1969), and low (in years 1970-1987) exposures. There was no tendency for case subjects to have had more x-ray examinations than control subjects in earlier calendar years. The mean numbers of x-ray examinations before age 20 also were similar for case subjects and matched control subjects.

There was no association between thyroid cancer and numbers of x-ray examinations of the head, neck, or upper spine (Table 6). In addition, there was not a statistically significant trend in the RR for thyroid cancer with increases in the estimated cumulative dose from all medical diagnostic x rays (Table 7). The highest quartile of the cumulative dose distribution corresponds approximately to a thyroid dose of 10-80 mGy, or 1-8 cGy. The mean overall estimated cumulative dose was 5.9 mGy for case subjects and 5.7 mGy for control subjects. These figures include persons for whom the medical record review identified no x rays. If we underascertained x-ray procedures, the actual doses would have been somewhat higher. The excess RR, based on a straight-line dose–response model, was 0.02 per cGy (95%CI = –0.11 to 0.15).

For 115 case subjects and 117 control subjects, there was no medical record documentation of diagnostic x rays during the period 5 or more years before the date of thyroid cancer diagnosis. Of these persons, telephone interviews were completed for 27 case subjects and 23 control subjects. Abstract data were compared with data obtained through the telephone interview,

Table 4. Average numbers of x-ray examinations of different parts of the body for case and matched control subjects, separately by decades m which examinations occurred*

	Mean No. of radiographic examinations per individual							
	<1960		1960-1969		1970-1987		All years†	
Part of body examined	Case subjects	Control subjects	Case subjects	Control subjects	Case subjects	Control subjects	Case subjects	Control subjects
Head, neck, upper spine	0.08	0.09	0.21	0.25	0.34	0.28	0.62	0.61
Chest, shoulders, upper gastrointestinal tract	0.39	0.50	0.95	1.05	1.63	1.70	2.92	3.20
Abdomen, pelvis, arms, legs	0.19	0.21	0.75	0.90	1.61	1.74	2.53	2.82
Total (entire body)	0.66	0.80	1.91	2.20	3.58	3.72	6.07	6.63

*Examinations occuring within the 5 years preceding the date of thyroid cancer diagnosis are excluded for case subjects and matched control subjects.

†The mean number of examinations for all years combined does not equal the sum of the means for each time interval because means for each interval are based on study subjects alive during that interval. For example, persons born after 1959 are not included in the calculation for the interval "<1960."

Table 5. Average numbers of x-ray examinations of different parts of the body for case and matched control subjects, separately by age interval*

	Mean No. of radiographic examinations per individual					
	Age <20 y		Age ≥20 y		All ages†	
Part of body examined	Case subjects	Control subjects	Case subjects	Control subjects	Case subjects	Control subjects
Head, neck, upper spine	0.06	0.04	0.57	0.58	0.62	0.61
Chest, shoulders, upper gastrointestinal tract	0.22	0.20	2.77	3.08	2.92	3.20
Abdomen, pelvis, arms, legs	0.28	0.25	2.30	2.64	2.53	2.82
Total (entire body)	0.56	0.49	5.64	6.30	6.07	6.63

*Examinations occurring within the 5 years preceding the date of thyroid cancer diagnosis are excluded for case subjects and matched control subjects.

†The mean number of examinations for all ages combined does not equal the sum of the means for each age group because the means for age >=20 years do not include persons under age 20 at the time of thyroid cancer diagnosis.

Table 6. Relative risk (RR) of thyroid cancer by numbers of x-ray examinations of different parts of the body*

Part of body examined	Relative dose to thyroid†	No. of x rays	No. of case subjects	No. of control subjects	RR‡	95% confidence interval	*P* for trend‡
Head, neck, upper spine	Highest	0	349	345	1.00	Reference	.54
		1-5	126	131	1.02	0.76-1.38	
		≥6	9	8	1.22	0.46-3.34	
Chest, shoulders, upper gastrointestinal tract	Medium	0	157	159	1.00	Reference	.50
		1-5	244	240	1.06	0.78-1.46	
		6-10	63	62	1.11	0.67-1.87	
		>10	20	23	0.99	0.47-2.08	
Abdomen, pelvis, arms, legs	Lowest	0	254	225	1.00	Reference	.42
		1-5	153	182	0.75	0.56-1.00	
		6-10	49	44	0.99	0.60-1.62	
		>10	28	33	0.75	0.42-1.35	

*Examinations are grouped in terms of their relative radiation dose to the thyroid gland; x rays occurring within the 5 years preceding the date of thyroid cancer diagnosis are excluded for case subjects and matched control subjects.

†Assignment of specific x-ray examinations to high, medium, or low dose category was based on dose measurements given by Bengtsson et al. *(17)* and Kereiakes and Rosenstein *(18)* (Table 1).

‡Adjusted for numbers of x rays in the other two relative dose categories.

so that we might assess possible underascertainment associated with the abstraction process. Four case subjects and four control subjects reported no x rays. An additional 18 case subjects and 13 control subjects reported having received one to three x rays, and five case subjects and six control subjects reported having had four or more x rays. As expected, most of the discrepancy was due to photofluorographic examinations of the chest, which were reported by 18 case subjects (67%) and 16 control subjects (70%), and mammograms. which were reported by five case subjects (19%) and five control subjects (22%). Several persons

Table 7. Distribution of case and control subjects by estimated cumulative radiation dose to thyroid gland from diagnostic x-ray examinations, excluding the 5 years before thyroid cancer diagnosis

	Cumulative dose group*			
	1†	2	3	4
Case subjects	133	116	114	121
Control subjects	137	114	114	119
Relative risk‡	1.00†	1.05	1.04	1.05
95% confidence interval	†	(0.73-1.52)	(0.70-1.55)	(0.73-1.52)

*Dose groups are ordered from low (l) to high (4). Categories are defined by quartiles of distribution of cumulative dose among control subjects. The approximate range (and mean values) of thyroid doses in the four cumulative dose groups were as follows: category 1, 0.00-0.00 cGy (0.00 cGy); category 2, 0.003-0.16 cGy (0.08 cGy); category 3, 0.17-0.68 cGy (0.32 cGy); category 4, 0.70-7.53 cGy (1.95 cGy).

†Reference category; estimated dose from diagnostic x rays equals zero.

‡ *P* for trend = .80.

also reported having received x rays of the arms or legs secondary to trauma, none of which would have had much of an influence on thyroid dose.

The only information available about dental x rays was from the interview. Among case–control pairs for whom telephone interviews were completed for both members of the matched set, 23 case subjects and 11 control subjects reported having had one or more Panorex x rays or full-mouth series of dental x rays (RR = 2.3; 95% CI = 1.1-4.8). The average number of bite-wing x rays, however, was greater among control subjects (8.7) than among case subjects (8.2). In addition, based on results from the telephone interview, an identical percentage (2.5%) of case and control subjects reported having been given diagnostic ^{131}I 5 or more years before the date of diagnosis of thyroid cancer.

Discussion

This study is unique among those that have considered cancer risks associated with diagnostic radiography. Characteristics of the Swedish health care system made it possible to assemble lifetime histories of medical x rays based on information recorded prospectively in hospital charts. Limitations of previous studies that relied on recalled history of exposure or that had access to documented histories of exposure for only limited parts of the lifetimes of study subjects were avoided. The sample size was large (484 case–control pairs), and the case diagnosis review by a specialist in endocrine pathology minimized the likelihood of misdiagnosis among the thyroid cancer case subjects enrolled in the study.

The pivotal validity issue concerns the method used to ascertain x-ray history. Although the approach represents a considerable improvement over previous studies, the sensitivity was not 100%. Many study subjects for whom we found no record of x rays reported having had one or more x-ray examinations. Photofluorographic examinations of the chest, mammograms, and x rays of the upper or lower extremities, in particular, appear to have been underascertained in the abstraction process. It is likely that many of these examinations occurred outside the hospital setting, such as in screening programs, and therefore escaped detection. We also would have missed other x-ray procedures that took place outside the hospital serving a person's residential area, e.g., emergency care while away from home, such as due to trauma, highly specialized care at a distant referral center, or, possibly, during times when a person maintained more than one residence, such as while at college. Such underascertainment, however, would be expected to be nondifferential for case and control subjects, and results from the telephone interview suggest that this was so. Moreover, the abstraction process appears to have been reproducible, as indicated by the generally good agreement when x rays were reabstracted for a sample of case and control subjects. In summary, evidence supports the belief that the ascertainment of medical x-ray examinations was unbiased and nearly complete for most procedures, particularly those most relevant to assessing thyroid exposure. This conclusion does not include thyroid scans, inasmuch as nuclear medicine procedures generally were not documented in radiology records. However, diagnostic ^{131}I has not been shown to cause thyroid cancer *(22)*.

The somewhat greater overall frequency of x rays among control subjects than among case subjects could be due either to chance or to some unidentified confounding factor. It is not clear, however, what this hypothetical confounding variable might be. Access to the medical care system was not limited by the ability to pay. Control subjects were randomly selected and matched to case subjects on county of residence at the time of thyroid cancer diagnosis, as well as on age and sex. There was no evidence of an increasing trend in the RR with increasing numbers of examinations. There is no readily identifiable bias that would nullify or undermine the validity of these data for addressing the risk of medical diagnostic radiography. Further credence to the validity of the data is given by the fact that more case subjects than control subjects had hysterosalpingograms (Table 3), which are given for infertility. Positive associations have been reported between infertility and the risk of thyroid cancer *(23,24)*.

Results are, by and large, reassuring in that they confirm that the risk of thyroid cancer due to medical diagnostic x rays is very small. If such exposures were important etiologic factors for thyroid cancer, one would expect case–control differences to have been greatest for those procedures that deliver the greatest doses to the thyroid gland, for examinations occurring in earlier calendar years, when doses were higher, and at younger ages of exposure, when susceptibility to radiation-induced thyroid cancer is greatest. The results do not fit these patterns. There was no general tendency for case subjects to have had more x rays of parts of the body close to the thyroid gland, such as of the head, neck, spine, shoulder, or chest areas, nor were the differences any greater for examinations at young ages or in early decades. The more frequent occurrence of x rays of the jaw and teeth among the case subjects is balanced by a greater frequency of other types of x-ray examination of the head among control subjects. More case subjects than control subjects had had an x ray of soft tissues of the neck, but some of these examinations were associated with goiter. History of goiter is strongly associated with risk of thyroid cancer *(25-28)*. The difference between case and control subjects persists even after allowances are made for the presence of goiter, but the interpretation is unclear because the presence of thyroid enlargement other than diffuse nontoxic

goiter cannot be ruled out. In any case, results are strongly at odds with the suggestion that scatter radiation from diagnostic x rays of parts of the body remote from the thyroid gland increases the risk of thyroid cancer *(9)*.

The radiation dose–response relationship could be evaluated only semiquantitatively, because it was not possible to accurately estimate cumulative dose to the thyroid gland from all x-ray procedures combined for individual people. Some degree of misclassification of thyroid doses is certain to have occurred, and this would have made it difficult to detect a small radiation effect. No evidence of an association between diagnostic irradiation and risk of thyroid cancer was seen, however, either on the metric of cumulative dose or that of number of procedures. These negative findings are not surprising in light of the magnitude of doses. Even with allowance for a degree of underascertainment, the most highly exposed individuals appear to have received doses to the thyroid that were of the same order of magnitude as experienced from natural background sources over the course of a lifetime, about 70 mSv, or 7 cGy *(2)*. The observed RR for the 1-8 cGy group in the present study was 1.05, and the excess RR was estimated as 0.02 per cGy with a 95% CI upper bound of 0.15 per cGy. While it is unclear whether there was any radiation effect in the present study, the data are compatible with the range of excess RR estimates reported in the literature (0.04-0.35/cGy) *(15)*. Values toward the higher end of this range tended to be for exposures occurring during childhood *(15)*.

The absence of a demonstrable effect might be attributable not only to the generally small thyroid doses from diagnostic radiography, but also to the fractionated and protracted nature of the exposure. Studies linking thyroid cancer to prior irradiation generally have involved relatively high dose and high dose rate exposures *(15)*. Protraction of exposure would allow more time for repair mechanisms to operate and, possibly, result in less cancer induction relative to the same dose given briefly *(15)*. Other large-scale studies of thyroid cancer or modularity following exposure to high-dose diagnostic ^{131}I *(22)* or living in areas of high background radiation *(29)* have failed to find evidence of increased risks, possibly because of the low dose rates involved.

Although results from the present study do not support the view that medical diagnostic radiography is an important cause of thyroid cancer, they leave open the possibility that there is a small risk associated with examinations of the jaw, mouth, or neck, possibly contingent on the specific projections used, as well as the number of exposures. Very few persons in the present study received x-ray doses to the thyroid gland in excess of 2 cGy, so results do not bear directly on risk among persons with exceptionally high exposures to diagnostic radiation. Furthermore, we did not have documented histories of dental x rays and so could not assess this type of exposure in a way that was immune from deficient or biased recall. More case subjects than control subjects reported having had full-mouth or Panorex dental examinations, but the reverse was true for bite-wing examinations.

A recent analysis of thyroid cancer incidence among atomic bomb survivors underscores the importance of age at exposure *(30)*. Data from that study indicate that the risk of radiation-induced thyroid cancer is low for exposures occurring in adulthood but that the risk is much greater for exposures among children. In the present study, there was little evidence of case–control differences even for x-ray examinations given before age 20 (Table 5), but the number of x rays among children and adolescents was small (Table 2). At the same time, the low risk of radiation-induced thyroid cancer in adult atomic bomb survivors gives further reason to believe that risks due to diagnostic radiography in adulthood are minimal.

The approach used for ascertaining diagnostic x rays in this study of thyroid cancer could be applied to studies of other cancers, such as childhood leukemia. Whereas the thyroid gland is within the irradiated field for relatively few x-ray procedures, the active (red) bone marrow is exposed to radiation in varying degrees from many types of examination. The cumulative dose to the bone marrow from diagnostic radiography would be higher than that to the thyroid gland. A previous study of leukemia among members of a prepaid health plan did not find an association between diagnostic x rays and leukemia *(l3)*, but only leukemias occurring among adults were included in that study.

In light of the inability to rule out the possibility of cancer risks associated with diagnostic radiography, efforts should continue to be discriminating in the use of x rays and to avoid their use when there is no likely clinical benefit *(31)*. Similarly, the use of shielding and implementation of advancements in equipment and techniques that provide high-quality images while delivering low doses to the patient *(32)* are to be encouraged. It also should be noted, however, that studies relying on prospectively recorded information about diagnostic x-ray procedures, rather than on the memories of study subjects or their proxies, have failed to find an association with either thyroid cancer or leukemia *(12,13)*. Only for multiple myeloma, a cancer not associated with radiation exposure among survivors of the atomic bomb explosions *(33)*, has a positive association with diagnostic x-ray exposure as ascertained from medical records been reported *(13)*. Although it would be irresponsible to presume the cancer risks of modern radiography to be zero, they certainly appear to be very small—smaller than many risks that people commonly accept in everyday life *(34)*.

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Notes

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