American Journal of Epidemiology
Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health 2009.

Vol. 171, No. 2
DOI: 10.1093/aje/kwp354
Advance Access publication:
November 30, 2009

Original Contribution

Nonradiation Risk Factors for Thyroid Cancer in the US Radiologic Technologists Study

Cari L. Meinhold*, Elaine Ron, Sara J. Schonfeld, Bruce H. Alexander, D. Michal Freedman, Martha S. Linet, and Amy Berrington de González

* Correspondence to Cari L. Meinhold, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 6120 Executive Boulevard, Rockville, MD 20852 (e-mail: meinholdc@mail.nih.gov).

Initially submitted June 19, 2009; accepted for publication September 29, 2009.

The incidence of thyroid cancer has been rapidly increasing in the United States, but few risk factors have been established. The authors prospectively examined the associations of self-reported medical history, anthropometric factors, and behavioral factors with thyroid cancer risk among 90,713 US radiologic technologists (69,506 women and 21,207 men) followed from 1983 through 2006. Incident thyroid cancers in 242 women and 40 men were reported. Elevated risks were observed for women with benign thyroid conditions (hazard ratio (HR) = 2.35, 95% confidence interval (CI): 1.73, 3.20), benign breast disease (HR = 1.56, 95% CI: 1.08, 2.26), asthma (HR = 1.68, 95% CI: 1.00, 2.83), and body mass index ≥35.0 versus 18.5–24.9 kg/m^2 (HR = 1.74, 95% CI: 1.03, 2.94; *P*-trend = 0.04). Current smoking was inversely associated with thyroid cancer risk (HR = 0.54). No clear associations emerged for reproductive factors, other medical conditions, alcohol intake, or physical activity. Despite few thyroid cancers in men, men with benign thyroid conditions had a significantly increased risk of thyroid cancer (HR = 4.65, 95% CI: 1.62, 13.34), and results for other risk factors were similar to those for women. Consistent with prior studies, obesity and benign thyroid conditions increased and current smoking decreased the risk of thyroid cancer. The novel findings for benign breast disease and asthma warrant further investigation.

body mass index; hormones; motor activity; prospective studies; reproduction; smoking; thyroid diseases; thyroid neoplasms

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; TSH, thyroid-stimulating hormone.

Between 1996 and 2005, thyroid cancer incidence rose annually by 5.8% among men and 7.1% among women in the United States, a more rapid increase than for any other cancer site (1). As a result, thyroid cancer now ranks as the seventh most common cancer in women in the United States (1). While some of this increase may be explained by improved detection of very small papillary tumors and changes in diagnostic criteria, changes in environmental risk factors likely also play a role (2).

The only clearly established risk factor for thyroid cancer is ionizing radiation exposure, particularly in childhood (3). Case-control studies have shown associations for nonradiation risk factors, including benign thyroid conditions, inadequate or excess iodine intake, never smoking, and, particularly in women, obesity (3–5). Worldwide, women have a 3-fold higher incidence of thyroid cancer compared with men, and their age-specific rates rise and peak earlier (median age at diagnosis in the United States: 47 years for women and 53 years for men) (3, 6, 7). These factors suggest a hormonal etiology, but results from case-control studies examining hormonal and reproductive factors in relation to thyroid cancer risk for women have been weak or inconsistent (3). Medical conditions unrelated to the thyroid may also influence the risk of thyroid cancer, biologically or through increased detection (8–11). Although prospective studies avoid recall and selection biases, nonradiation risk factors for thyroid cancer have rarely been investigated prospectively, chiefly because of small numbers of incident thyroid cancers in most studies.

We prospectively examined the associations of potential nonradiation risk factors with thyroid cancer risk in a cohort of more than 90,000 US radiologic technologists. Because of the younger age distribution and the greater frequency of thyroid cancer in women compared with men, the gender and age structure of this cohort provides an opportunity to prospectively examine potential risk factors for thyroid cancer.

MATERIALS AND METHODS

Study population

Details on the study design and methods were published previously (12). In brief, the US Radiologic Technologists Study was initiated between 1983 and 1984 with the primary objective to investigate cancer risks associated with occupational radiation exposure in radiologic technologists. We identified 146,022 individuals who were registered with the American Registry of Radiologic Technologists for at least 2 years between 1926 and 1982 and resided in any of the 50 US states. Between the years 1983–1984, 1994–1998, and 2004–2006, 3 different questionnaires were mailed to participants who were located and thought to be alive. The third questionnaire was sent to respondents of the first or second questionnaire. Nonrespondents to the first survey were contacted by telephone and completed the questionnaire via telephone interview. Response rates were 68% ($n = 90,305$ of 132,454 radiologic technologists located and presumed alive) for the first, 72% ($n = 90,972/126,628$) for the second, and 72% ($n = 73,489/101,694$) for the third questionnaires. Of 110,418 respondents to at least one survey, we excluded from all analyses participants who had a medical history of cancer other than nonmelanoma skin cancer at baseline ($n = 2,808$), were missing the date of any incident cancer diagnosis over follow-up ($n = 144$), had conflicting cancer records ($n = 5$), or did not respond to a second questionnaire or could not be linked to a mortality record with known cause of death ($n = 16,748$). After exclusions, the analytic cohort included 90,713 participants (69,506 women and 21,207 men). The study was approved by the institutional review boards of the National Cancer Institute and the University of Minnesota.

Case ascertainment and follow-up

Incident thyroid cancers were identified by self-report on the second or third questionnaire, cancer registry linkage, and death records. Living participants who reported a diagnosis of thyroid cancer were contacted to obtain consent to view their pathology reports or medical records for confirmation. Cases who did not consent to release medical records, or for whom medical records could not be located, were classified as having unconfirmed thyroid cancer. Self-reported, but unconfirmed cancers were included in the case definition because medical records confirmed more than 92% of cases of thyroid cancer self-reported on the second questionnaire (13). Using information obtained from pathology reports, medical records, and cancer registry linkage, we further classified thyroid cancers as papillary, follicular, medullary, or other histology according to *International Classification of Diseases for Oncology*, Third Edition, morphology codes. Participants were followed from the date they responded to the first questionnaire they completed to

Table 1. Select Baseline Characteristics of Women and Men in the US Radiologic Technologists Study, 1983–2006

	Women (n = 69,506)		Men (n = 21,207)	
	No.	%	No.	%
Age at study entry, years				
<30	12,715	18.3	1,863	8.8
30–39	29,672	42.7	8,089	38.1
40–49	16,851	24.2	5,785	27.3
≥50	10,268	14.8	5,470	25.8
Year of birth				
Before 1940	13,122	18.8	6,216	29.3
1940–1949	22,539	32.4	7,351	34.7
1950 or later	33,845	48.7	7,640	36.0
Race/ethnicity				
White	66,711	96.0	19,197	90.5
Black	1,707	2.5	885	4.2
Asian/Pacific Islander	470	0.7	537	2.5
American Indian/Native Alaskan	125	0.2	116	0.6
Other/unknown	493	0.7	472	2.2
Menopausal status				
Premenopausal	57,404	82.6		
Postmenopausal	12,102	17.4		
Smoking status				
Never smoker	35,328	50.8	8,079	38.1
Former smoker	17,869	25.7	7,536	35.5
Current smoker	15,543	22.4	5,216	24.6
Unknown	766	1.1	376	1.8
Body mass index, kg/m^2				
<18.5	2,716	3.9	117	0.6
18.5–24.9	48,006	69.1	9,003	42.5
25.0–29.9	11,876	17.1	9,088	42.9
30.0–34.9	3,762	5.4	2,033	9.6
≥35.0	1,620	2.3	486	2.3
Unknown	1,526	2.2	480	2.3
Alcohol intake				
Nondrinker	12,509	18.0	4,132	19.5
<1 drink/week	29,227	42.1	6,008	28.3
1–6 drinks/week	20,397	29.4	6,702	31.6
≥7 drinks/week	6,078	8.7	3,867	18.2
Unknown	1,295	1.9	498	2.4
History of any benign thyroid condition				
Yes	6,332	9.1	430	2.0
Unknown	1,276	1.8	331	1.6

Table 2. Hazard Ratios and 95% Confidence Intervals for the Association of Thyroid Cancer With Self-reported Medical Conditions, US Radiologic Technologists Study, 1983–2006

	Women			Men		
	No. of Cases[a]	HR	95% CI	No. of Cases[a]	HR	95% CI
Goiter[b]						
Never diagnosed	218	1.00	Reference	35	1.00	Reference
Ever diagnosed	20	4.10	2.58, 6.49	1	9.28	1.25, 69.17
Hyperthyroidism[b]						
Never diagnosed	226	1.00	Reference	36		
Ever diagnosed	11	2.05	1.12, 3.76	0		
Hypothyroidism[b]						
Never diagnosed	213	1.00	Reference	35	1.00	Reference
Ever diagnosed	24	1.31	0.85, 2.02	1	1.72	0.23, 12.69
Thyroiditis[b,c]						
Never diagnosed	214	1.00	Reference	35		
Ever diagnosed	3	1.69	0.54, 5.30	0		
Thyroid nodule/adenoma[b,d]						
Never diagnosed	95	1.00	Reference	13	1.00	Reference
Ever diagnosed	21	6.88	4.28, 11.06	3	32.75	9.12, 117.53
Any benign thyroid condition[b,e]						
Never diagnosed	182	1.00	Reference	32	1.00	Reference
Ever diagnosed	56	2.35	1.73, 3.20	4	4.65	1.62, 13.34
Thyroid hormone use in the past year[b,d]						
No use + never diagnosed with a benign thyroid condition[e]	80	1.00	Reference	12	1.00	Reference
No use + ever diagnosed with a benign thyroid condition[e]	15	3.93	2.26, 6.85	0		
Used	21	2.89	1.77, 4.71	3	16.18	4.45, 58.89
Arthritis, rheumatoid[d,f]						
Never diagnosed	113	1.00	Reference	26		
Ever diagnosed	3	0.92	0.29, 2.90	0		
Arthritis, other[d,f]						
Never diagnosed	94	1.00	Reference	14	1.00	Reference
Ever diagnosed	22	1.31	0.80, 2.15	2	1.10	0.24, 5.01

Table continues

the date of death, date of any cancer diagnosis, or date of last questionnaire completion, whichever occurred first.

In total, 282 incident thyroid cancers (242 in women and 40 in men) were diagnosed over 1,436,541 person-years of follow-up (mean: 15.8). A total of 200 (70.9%) were classified as papillary, 15 (5.3%) as follicular, 3 (1.1%) as medullary, and 16 (5.7%) as "other." Histology was unavailable for 48 (17.0%) cases. The median age at thyroid cancer diagnosis was 46 years (range: 27–78) for women and 50 years (range: 30–75) for men.

Assessment of nonradiation exposures

Exposure data were obtained from the first and second questionnaires, which elicited information on date of birth; sex; race/ethnicity; height; weight; cigarette smoking; alcohol intake; medical history of cancer, benign thyroid conditions, and selected other diseases; reproductive and hormonal history; and occupational and personal radiation exposures. Some exposures were available from only the first (e.g., thyroiditis) or the second (e.g., thyroid adenomas/nodules, some medical conditions, physical activity) questionnaire. Except for alcohol intake, which was assessed separately for beer, wine, and liquor on the second but not the first questionnaire, the level of detail elicited on nonradiation exposures in this analysis was generally similar for both questionnaires.

Statistical analysis

All analyses were performed by using Stata version 9 software (Stata Corporation, College Station, Texas). Cox

Table 2. Continued

	Women			Men		
	No. of Cases[a]	HR	95% CI	No. of Cases[a]	HR	95% CI
Asthma[d,f]						
Never diagnosed	99	1.00	Reference	14	1.00	Reference
Ever diagnosed	17	1.68	1.00, 2.83	2	1.49	0.33, 6.62
Benign breast disease (i.e., fibrocystic)[d,f]						
Never diagnosed	63	1.00	Reference			
Ever diagnosed	53	1.56	1.08, 2.26			
Cholesterol, elevated (≥240 mg/dL)[d,f]						
Never diagnosed	110	1.00	Reference	13	1.00	Reference
Ever diagnosed	6	0.47	0.20, 1.09	3	1.63	0.45, 5.90
Chronic bronchitis[d,f]						
Never diagnosed	108	1.00	Reference	16		
Ever diagnosed	8	0.94	0.46, 1.95	0		
Diabetes mellitus[d,f]						
Never diagnosed	112	1.00	Reference	16		
Ever diagnosed	4	1.37	0.49, 3.77	0		
Hypertension[d,f]						
Never diagnosed	113	1.00	Reference	16		
Ever diagnosed	3	1.02	0.32, 3.29	0		
Ulcer[d,f]						
Never diagnosed	105	1.00	Reference	14	1.00	Reference
Ever diagnosed	11	0.88	0.47, 1.65	2	0.99	0.22, 4.54

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Number of cases may be inconsistent because of missing values.
[b] Adjusted for birth year, smoking status, body mass index, number of personal radiographs to the head or neck, and cumulative occupational radiation dose.
[c] Collected in only the first questionnaire (1983–1984) (86.8% of the study population).
[d] Collected in only the second questionnaire (1994–1998) (89.6% of the study population).
[e] Self-reported history of goiter, hyperthyroidism, hypothyroidism, thyroiditis, or benign nodules or adenomas.
[f] Additionally adjusted for medical history of benign thyroid conditions.

proportional hazards models with attained age as the underlying time variable were used to calculate hazard ratios and 95% confidence intervals for thyroid cancer. To account for the time-dependent nature of certain variables, specifically weight, smoking, alcohol intake, benign thyroid conditions, and hormonal factors, we treated the follow-up times before and after the date of completion of a second questionnaire as separate observations. For exposures ascertained on only one of the first 2 questionnaires (i.e., thyroiditis, thyroid adenomas/nodules, some medical conditions, physical activity), we restricted the analyses to participants who responded to the relevant questionnaire and began follow-up on the date of questionnaire completion.

Sex-specific quartiles of exposure were defined based on the entire cohort distribution. Body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) was classified by using the World Health Organization categories of <18.5 (underweight), 18.5–24.9 (normal), 25.0–29.9 (overweight), 30.0–34.9 (obese), and ≥35.0 kg/m^2 (severely obese) (14). We assigned women to be premenopausal if they were younger than 53 years of age, which was the 80th percentile of age at natural menopause in this cohort, and were missing information on menopausal status at either of the first 2 questionnaires ($n = 545$) or had reported having had a hysterectomy without a bilateral oophorectomy ($n = 4,124$). Information on frequency of strenuous physical activity, walking for exercise, and walking at home over the past year was obtained in the second questionnaire and was categorized as never, <1 hour/week, or ≥1 hours/week. Physical activity was summarized as a total activity score by assigning a metabolic equivalent task value for each activity and summing the metabolic equivalent task-hours per week across all 3 activities, as described in a separate study from this cohort (15). Unless otherwise specified, missing values were categorized by using a missing indicator variable.

Models were stratified by sex and were adjusted for birth year (1-year categories with a knot at year 1947), smoking status (never, former, current), BMI (World Health Organization categories), and history of any benign thyroid condition (i.e., goiter, hypothyroidism, hyperthyroidism, adenoma/nodule, or thyroiditis). Although personal and occupational radiation exposures were not associated with nonradiation factors or thyroid cancer incidence in this study, we adjusted for number of personal radiographs to the head or neck (in quartiles) and cumulative occupational radiation dose to the thyroid at baseline (in quartiles) because radiation exposure is the main known risk factor for thyroid cancer. Tests for trend were conducted by modeling categories of exposure as continuous. Interactions were assessed on the multiplicative scale by including cross-product terms in the model. All tests of statistical significance were 2-sided.

RESULTS

The majority of participants were white (94.7%) and female (76.6%) (Table 1). At study entry, men were slightly older than women on average (mean age: 43.3 vs. 39.3 years), and a higher proportion of men than women were born before 1940 (29.3% vs. 18.8%). Women were more likely than men to be never smokers (50.8% vs. 38.1%), to be in the normal BMI (18–24.9 kg/m^2) range (69.1% vs. 42.5%), and to have a history of benign thyroid conditions (9.1% vs. 2.0%). In total, 23.1% of participants were overweight, 8.7% were obese, 28.0% were former smokers, 22.9% were current smokers, and 7.5% reported at study entry having been diagnosed with a benign thyroid condition.

Among women, a history of any previous thyroid condition (hazard ratio (HR) = 2.35, 95% confidence interval (CI): 1.73, 3.20), including goiter (HR = 4.10), benign thyroid nodules/adenomas (HR = 6.88), and hyperthyroidism (HR = 2.05), was associated with an increased risk of thyroid cancer (Table 2). Hypothyroidism was nonsignificantly associated with thyroid cancer risk for women (HR = 1.31, 95% CI: 0.85, 2.02). Thyroiditis was not associated with a significant increased risk of thyroid cancer, but this association was based on only 3 exposed cases. Thyroid hormone use in the past month was associated with an increased risk, but, at least for women, this risk was not greater than that associated with having a history of benign thyroid conditions and no recent thyroid hormone use. Self-reported history of asthma (HR = 1.68, 95% CI: 1.00, 2.83) and benign breast disease (HR = 1.56, 95% CI: 1.08, 2.26) were both associated with an increased risk of thyroid cancer in women.

Despite small numbers of males with thyroid cancer, we observed a significantly elevated risk of thyroid cancer for those who reported any history of benign thyroid conditions (n = 4 cases; HR = 4.65, 95% CI: 1.62, 13.34). Statistically significant associations were found for goiter (HR = 9.28, 95% CI: 1.25, 69.17) and benign nodules or adenomas (HR = 32.75, 95% CI: 9.12, 117.53).

We found no clear associations between any of the reproductive factors and thyroid cancer incidence. Refer to Table 3.

Table 3. Hazard Ratios and 95% Confidence Intervals for the Association of Thyroid Cancer With Reproductive and Hormonal Factors, US Radiologic Technologists Study, 1983–2006[a]

	No. of Cases[b]	HR[c]	95% CI
No. of births			
Nulliparous	59	1.00	Reference
1	39	0.95	0.63, 1.42
2	85	0.97	0.69, 1.36
≥3	50	0.87	0.59, 1.29
P-trend*			0.61
Age at menarche, years			
<12	71	1.00	Reference
12–13	122	0.65	0.49, 0.88
14–15	35	0.63	0.42, 0.94
≥16	9	1.45	0.72, 2.92
P-trend*			0.14
Oral contraceptive use			
Never user	44	1.00	Reference
Ever user	197	1.28	0.91, 1.82
<5 years of use	100	1.29	0.89, 1.87
≥5 years of use	90	1.24	0.84, 1.81
Menopausal status			
Premenopausal	196	1.00	Reference
Natural menopause	18	0.69	0.37, 1.28
Hysterectomy, both ovaries removed	18	0.85	0.49, 1.45
Hysterectomy, still has ≥1 ovaries/unknown	4	0.65	0.21, 1.96
Other/unknown reason	6	1.49	0.64, 3.46
Menopausal hormone therapy use[d]			
Never user	13	1.00	Reference
Ever user	33	1.16	0.61, 2.24

Abbreviations: CI, confidence interval; HR, hazard ratio.
**P*-trend based on ordinal score variable.
[a] Women only (n = 69,506).
[b] Number of cases may be inconsistent because of missing values.
[c] Adjusted for birth year, smoking status, body mass index, number of personal radiographs to the head or neck, cumulative occupational radiation dose, and medical history of benign thyroid conditions.
[d] Among postmenopausal women only.

Height was not significantly associated with thyroid cancer risk for women or men (Table 4). Greater weight modestly increased risk for women (*P*-trend = 0.04). BMI ≥35 kg/m^2 (vs. 18.5–24.9 kg/m^2) was associated with an elevated risk, particularly for women (HR = 1.74, 95% CI: 1.03, 2.94; *P*-trend = 0.04). Compared with never smoking, current cigarette smoking was associated with a reduced risk (HR for women = 0.54, 95% CI: 0.35, 0.82; HR for men = 0.31, 95% CI: 0.09, 1.04). There was some evidence that greater smoking intensity, but not duration (data not shown), was associated with a lower risk of thyroid cancer within groups of former and current smokers. Alcohol intake was not clearly associated with risk.

Table 4. Hazard Ratios and 95% Confidence Intervals for the Association of Thyroid Cancer With Anthropometric Factors, Smoking, and Alcohol Intake, US Radiologic Technologists Study, 1983–2006

	Women			Men		
	No. of Cases[a]	HR[b]	95% CI	No. of Cases[a]	HR[b]	95% CI
Height quartile[c]						
1	70	1.00	Reference	13	1.00	Reference
2	47	1.08	0.74, 1.56	13	1.08	0.50, 2.33
3	66	1.19	0.85, 1.67	9	0.73	0.31, 1.71
4	58	1.10	0.78, 1.56	5	0.58	0.20, 1.63
P-trend*			0.46			0.22
Weight quartile[d,e]						
1	52	1.00	Reference	10	1.00	Reference
2	47	1.00	0.67, 1.49	10	1.21	0.49, 2.96
3	69	1.26	0.86, 1.84	6	0.70	0.24, 2.01
4	68	1.43	0.97, 2.11	14	1.81	0.73, 4.50
P-trend*			0.04			0.33
Body mass index, kg/m^2						
<18.5	6	0.96	0.42, 2.18	0		
18.5–24.9	144	1.00	Reference	13	1.00	Reference
25.0–29.9	44	0.90	0.64, 1.27	15	0.89	0.42, 1.90
30.0–34.9	26	1.41	0.92, 2.16	9	1.91	0.80, 4.56
≥35.0	16	1.74	1.03, 2.94	3	2.14	0.60, 7.67
P-trend*			0.04			0.11
Smoking status						
Never smoker	147	1.00	Reference	21	1.00	Reference
Former smoker	64	0.91	0.67, 1.22	13	0.79	0.39, 1.61
Current smoker	26	0.54	0.35, 0.82	3	0.31	0.09, 1.04
Smoking intensity						
Former, <20 cigarettes/day	48	0.99	0.71, 1.37	8	0.96	0.42, 2.21
Former, ≥20 cigarettes/day	15	0.69	0.40, 1.18	4	0.50	0.17, 1.51
Current, <20 cigarettes/day	19	0.64	0.40, 1.04	2	0.43	0.10, 1.86
Current, ≥20 cigarettes/day	7	0.38	0.18, 0.82	1	0.20	0.03, 1.49
Alcohol intake						
Nondrinker	57	1.00	Reference	10	1.00	Reference
<1 drink/week	95	0.86	0.62, 1.20	13	1.03	0.45, 2.38
1–6 drinks/week	66	0.86	0.60, 1.23	9	0.62	0.25, 1.54
≥7 drinks/week	18	0.84	0.49, 1.45	7	0.95	0.35, 2.54
P-trend*			0.45			0.50

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

**P*-trend based on ordinal score variable.

[a] Number of cases may be inconsistent because of missing values.

[b] Adjusted for birth year, smoking status, body mass index, number of personal radiographs to the head or neck, cumulative occupational radiation dose, and medical history of benign thyroid conditions.

[c] Height quartiles (cm)—women: <161, 161–164, 165–167, ≥168; men: <173, 173–178, 179–183, ≥184.

[d] Weight quartiles (kg)—women: <54.5, 54.5–60.9, 61.0–68.1, ≥68.2; men: <73.0, 73.0–79.9, 80.0–88.5, ≥88.6.

[e] Also adjusted for height.

Table 5. Hazard Ratios and 95% Confidence Intervals for the Association of Thyroid Cancer With Physical Activity Level Over the Past Year, US Radiologic Technologists Study, 1983–2006

	Women			Men		
	No. of Cases[a]	HR[b]	95% CI	No. of Cases[a]	HR[b]	95% CI
Strenuous exercise[c]						
None	57	1.00	Reference	9	1.00	Reference
<1 hour/week	26	0.96	0.60, 1.53	3	0.58	0.15, 2.16
≥1 hours/week	29	0.81	0.51, 1.29	6	0.77	0.26, 2.23
P-trend*			0.40			0.59
Walking/hiking for exercise[c]						
None	24	1.00	Reference	5	1.00	Reference
<1 hour/week	27	0.79	0.45, 1.37	6	0.93	0.28, 3.08
≥1 hours/week	64	0.92	0.58, 1.49	6	0.59	0.18, 1.97
P-trend*			0.94			0.37
Walking at home or work[c]						
None	3	0.52	0.16, 1.64	1	0.86	0.11, 6.65
<1 hour/week	18	1.05	0.64, 1.74	4	1.37	0.44, 4.23
≥1 hours/week	95	1.00	Reference	13	1.00	Reference
P-trend*			0.47			0.82
Total MET-score tertile[c,d]						
1: Low activity	31	1.00	Reference	7	1.00	Reference
2: Medium activity	38	1.33	0.83, 2.14	3	0.50	0.13, 1.94
3: High activity	40	1.37	0.85, 2.20	7	1.11	0.38, 3.20
P-trend*			0.19			0.92

Abbreviations: CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent task.
* *P*-trend based on ordinal score variable.
[a] Number of cases may be inconsistent because of missing values.
[b] Adjusted for birth year, smoking status, body mass index, number of personal radiographs to the head or neck, cumulative occupational radiation dose, and medical history of benign thyroid conditions.
[c] Collected in only the second questionnaire (1994–1998) (89.6% of the study population).
[d] MET tertiles—women: <20, 20–55, ≥56; men: <18, 18–49, ≥50.

None of the types of physical activity we examined were significantly associated with risk. Refer to Table 5.

In sex-specific analyses, we did not observe statistically significant interactions for any of our exposures with smoking status (ever vs. never) or obesity (<30 vs. ≥30 kg/m^2). When we used more specific endpoints, such as confirmed or papillary thyroid cancer, none of our results changed markedly. Because hormonal factors around the time of menopause may play a role in thyroid cancer, we also examined the results for women separately by cancer diagnosed before and after age 50 years. We observed slightly stronger associations for a medical history of benign thyroid conditions for thyroid cancers diagnosed at younger versus older ages. In contrast, the inverse association for cigarette smoking was slightly stronger for cancer diagnosed at older ages. No differences by age at cancer diagnosis were observed regarding other exposures in this study.

DISCUSSION

In this prospective study of US radiologic technologists, we found that a self-reported history of goiter or benign thyroid adenomas and nodules significantly elevated the risk of thyroid cancer for women and men. A significant increased risk was also observed for women reporting hyperthyroidism, asthma, and benign breast disease. Greater weight and obesity were positively associated, while smoking was inversely associated, with thyroid cancer risk for women. Similar associations were observed among men, although they were based on few incident cases. We did not find significant associations for thyroiditis, hypertension, diabetes, reproductive factors, height, alcohol intake, or physical activity.

Because thyroid cancer is a relatively rare malignancy (1–3, 7), most of the epidemiologic studies of nonradiation risk factors for thyroid cancer have used a case-control design. A pooled analysis of 14 thyroid cancer case-control studies, including 2,725 cases and 4,776 controls, investigated a number of factors, including BMI (5), reproductive and hormonal factors (16, 17), benign thyroid conditions (18), diet (19, 20), smoking (21), and alcohol consumption (21) across diverse populations. The strongest and most consistent results from this international pooled case-control analysis were in relation to benign thyroid conditions, particularly goiter, benign nodules/adenomas, and hyperthyroidism, but no association was observed for hypothyroidism (18); the results did not differ according to histology, and relative risks were generally stronger for men.

A prospective study in San Francisco, California, found no association for hypothyroidism and hyperthyroidism, but, similar to our study, goiter increased the risk more than 3-fold (relative risk = 3.36, 95% CI: 1.82, 6.20) (22). Goiter and thyroid nodules are strongly and consistently associated with thyroid cancer in epidemiologic studies and may share similar risk factors with thyroid cancer, including diet, smoking, and iodine deficiency (23). The association we observed for hyperthyroidism may reflect more frequent thyroid examinations among participants with a history of goiter or benign thyroid nodules; in fact, the association was attenuated after excluding participants who also reported a history of goiter (HR = 1.90, 95% CI: 0.94, 3.86) or nodules (HR = 1.73, 95% CI: 0.63, 4.69). Nonetheless, we did not have information on the type of hyperthyroidism or the treatments given for thyroid diseases, and, without diagnostic confirmation, some of these conditions may be subject to misclassification.

We observed a significant increased risk of thyroid cancer for women with a medical history of asthma. However, results from other epidemiologic studies are equivocal. Two case-control studies showed no associations for medical history of asthma (9, 10) or other allergic conditions (10). Inverse associations for history of asthma and other allergic disorders were observed in a Swedish case-control study, particularly among women (11), and a positive association between history of allergies and medullary thyroid cancer risk was shown in the pooled case-control study (8). A history of allergies has been suggested to reduce cancer risk through a heightened immunologic response, but this hypothesis has received little support and is considered controversial (24). Although smoking is less common among individuals with asthma (24), adjustment for smoking did not change the results. Restricting the results to never smokers did attenuate the association for asthma slightly among women (HR = 1.43, 95% CI: 0.73, 2.81), but the number of cases also decreased appreciably (119 to 79). Similar to patients with thyroid disease, asthma patients may be under close medical surveillance and therefore may have a greater chance than the general population of thyroid cancer being diagnosed.

Our finding of an association between benign breast disease and thyroid cancer risk, if not the result of detection bias, may provide further evidence of a common underlying mechanism for breast and thyroid diseases. An increased risk of breast cancer has been observed for individuals with a history of thyroid cancer (25) and certain types of benign breast disease (26). Currently, it is unclear whether the association between benign breast disease and thyroid cancer in this study is attributable to a biologic exposure, such as circulating hormone levels (27), or to greater medical surveillance. Misclassification of benign breast disease was also a concern in this study; benign breast disease encompasses a wide range of conditions (27), and we did not have detailed information on the specific types of benign breast disease.

While most (10, 28–30), but not all (9, 31, 32), case-control studies of thyroid cancer and cigarette smoking, including the pooled case-control study (21), support an inverse association, prospective studies have been less consistent (22, 33, 34). This difference may reflect a greater potential for residual confounding in most prospective studies, which are less likely to have information on thyroid cancer risk factors, including benign thyroid conditions and radiation exposure. In our prospective study, which had detailed covariate information, current smoking was associated with a reduced risk of thyroid cancer, and there was some evidence that the risk decreased with greater intensity, but not duration, of smoking.

The pooled thyroid cancer case-control study found a positive, but small, association for BMI, particularly among women (highest to lowest tertile, odds ratio = 1.2, 95% CI: 1.1, 1.5) (5). A positive association between BMI and thyroid cancer risk was also observed in several subsequent case-control (28, 35, 36) and prospective (37–39) studies, including those restricted to men (38, 39). However, no clear association was observed among Swedish male construction workers ($\geq$30 vs. 18.5–24.9 kg/m^2; relative risk = 0.98, 95% CI: 0.49, 1.96; P-trend = 0.48) (40). There was also no association between BMI ($\geq$25 vs. $<$25 kg/m^2) and thyroid cancer risk for men and women in the San Francisco study (relative risk = 1.08, 95% CI: 0.74, 1.56) (22). Nonetheless, our results are supported by a recent meta-analysis based on prospective observational studies, which found a relative risk of 1.33 (95% CI: 1.04, 1.70) for men and 1.14 (95% CI: 1.06, 1.23) for women for each 5-unit increase in BMI (41). Assuming a causal relation between obesity and thyroid cancer, we estimate that 6% of thyroid cancer is attributable to obesity in this cohort, based on our results and the 11% prevalence of obesity. In the general US adult population, where the prevalence of obesity was 33% in 2004 (42), this figure translates to a population attributable risk of 17% (43). The increasing prevalence of obesity may be one explanation for the increasing incidence of thyroid cancer in the United States over the past 3 decades, but this hypothesis should be explored in future prospective studies.

Some biologic mechanisms have been proposed that may explain the associations we observed in this cohort. In laboratory studies, thyroid-stimulating hormone (TSH) has been shown to regulate the growth and differentiation of thyroid cells (44). Current smokers may have lower levels of TSH compared with former or never smokers (45, 46), and TSH levels may be elevated in people who are obese (47–51). TSH may also increase during puberty, during pregnancy, or while taking oral contraceptives (23, 52). Nonetheless, prospective studies examining levels of TSH in relation to thyroid cancer risk for humans are lacking. In addition, prospective studies on the association of TSH with potential thyroid cancer risk factors, particularly obesity (47), are needed to elucidate whether TSH is a cause or a consequence of these conditions. Estrogen may also play a role in thyroid carcinogenesis given the large sex difference in thyroid cancer incidence; however, epidemiologic evidence linking reproductive or hormonal factors to thyroid cancer has been inconsistent (16, 17, 22, 33, 53–57).

Although estrogen receptors have been found on thyroid tumors (58), and estrogen promotes thyroid carcinogenesis in rats (59), studies of circulating estrogens and thyroid cancer risk have not been conducted to our knowledge. Our study generally does not support a clear role for reproductive or hormonal factors in thyroid carcinogenesis. However, we had limited numbers of thyroid cancer cases to assess the risk for menopausal status and use of hormone therapy.

Despite the relatively large size of this prospective study, the number of male cases was still small. The fairly young age distribution of the cohort also resulted in a limited number of postmenopausal women in this study. A strength of this study compared with several previous prospective studies (33, 34, 37–40) is the availability of information on several established and potential thyroid cancer risk factors, including benign thyroid conditions, radiation exposure, cigarette smoking, and BMI, as well as information on thyroid cancer histology. Furthermore, because of their training, radiologic technologists may more accurately report medical history information compared with the general population. For instance, although studies relying primarily on self-report may underestimate the number of incident cases, the accuracy of self-reported thyroid cancers was high in this cohort (positive predictive value = 92.3%) (13). Misclassification over the follow-up period is a potential limitation given the approximate 10-year interval between questionnaires, but we had updated exposure information for participants who responded to a second questionnaire.

Internal comparisons within this cohort showed that occupational radiation generally did not increase thyroid cancer risk (60), and personal and occupational radiation exposures were not associated with the nonradiation factors examined in this study. The relative homogeneity of this group with regard to socioeconomic status, occupational exposures, and thyroid cancer screening most likely reduced the potential for bias within the study. However, because radiologic technologists may be monitored more closely for thyroid abnormalities, the generalizability of these findings may be limited.

Some findings from this prospective study warrant further investigation, particularly the positive associations for history of asthma and benign breast disease. Consistent with previous studies, we found that benign thyroid conditions (except thyroiditis) and obesity increase and current smoking reduces the risk of thyroid cancer in men and women. These findings provide additional evidence that obesity may partially contribute to the rising frequency of thyroid cancer.

ACKNOWLEDGMENTS

Author affiliations: Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland (Cari L. Meinhold, Elaine Ron, Sara J. Schonfeld, D. Michal Freedman, Martha S. Linet, Amy Berrington de González); and Division of Environmental Health Sciences, University of Minnesota School of Public Health, Minneapolis, Minnesota (Bruce H. Alexander).

This research was supported in part by the Intramural Research Program of the National Institutes of Health/ National Cancer Institute.

Conflict of interest: none declared.

REFERENCES

1. Jemal A, Thun MJ, Ries LA, et al. Annual report to the nation on the status of cancer, 1975–2005, featuring trends in lung cancer, tobacco use, and tobacco control. *J Natl Cancer Inst*. 2008;100(23):1672–1694.
2. Enewold L, Zhu K, Ron E, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005. *Cancer Epidemiol Biomarkers Prev*. 2009;18(3):784–791.
3. Ron E, Schneider AB. Thyroid cancer. In: Schottenfeld D, Fraumeni J, eds. *Cancer Epidemiology and Prevention*. New York, NY: Oxford University Press; 2006:975–994.
4. Preston-Martin S, Franceschi S, Ron E, et al. Thyroid cancer pooled analysis from 14 case-control studies: what have we learned? *Cancer Causes Control*. 2003;14(8): 787–789.
5. Dal Maso L, La Vecchia C, Franceschi S, et al. A pooled analysis of thyroid cancer studies. V. Anthropometric factors. *Cancer Causes Control*. 2000;11(2):137–144.
6. Surveillance Epidemiology and End Results (SEER). SEER stat fact sheet—cancer of the thyroid. Bethesda, MD: National Cancer Institute, National Institutes of Health; 2009. (http://seer.cancer.gov/csr/1975_2006/results_single/sect_01_table.11_2pgs.pdf). (Accessed April 19, 2009).
7. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55(2):74–108.
8. Negri E, Ron E, Franceschi S, et al. Risk factors for medullary thyroid carcinoma: a pooled analysis. *Cancer Causes Control*. 2002;13(4):365–372.
9. 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.
10. Nagano J, Mabuchi K, Yoshimoto Y, et al. A case-control study in Hiroshima and Nagasaki examining non-radiation risk factors for thyroid cancer. *J Epidemiol*. 2007;17(3): 76–85.
11. Hallquist A, Hardell L, Degerman A, et al. Thyroid cancer: reproductive factors, previous diseases, drug intake, family history and diet. A case-control study. *Eur J Cancer Prev*. 1994;3(6):481–488.
12. Boice JD Jr, Mandel JS, Doody MM, et al. A health survey of radiologic technologists. *Cancer*. 1992;69(2):586–598.
13. 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.
14. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser*. 1995;854:1–452.
15. Howard RA, Leitzmann MF, Linet MS, et al. Physical activity and breast cancer risk among pre- and postmenopausal women in the U.S. Radiologic Technologists cohort. *Cancer Causes Control*. 2009;20(3):323–333.
16. Negri E, Dal Maso L, Ron E, et al. A pooled analysis of case-control studies of thyroid cancer. II. Menstrual and reproductive factors. *Cancer Causes Control*. 1999;10(2): 143–155.

17. La Vecchia C, Ron E, Franceschi S, et al. A pooled analysis of case-control studies of thyroid cancer. III. Oral contraceptives, menopausal replacement therapy and other female hormones. *Cancer Causes Control*. 1999;10(2):157–166.
18. Franceschi S, Preston-Martin S, Dal Maso L, et al. A pooled analysis of case-control studies of thyroid cancer. IV. Benign thyroid diseases. *Cancer Causes Control*. 1999;10(6): 583–595.
19. Bosetti C, Kolonel L, Negri E, et al. A pooled analysis of case-control studies of thyroid cancer. VI. Fish and shell-fish consumption. *Cancer Causes Control*. 2001;12(4): 375–382.
20. Bosetti C, Negri E, Kolonel L, et al. A pooled analysis of case-control studies of thyroid cancer. VII. Cruciferous and other vegetables (International). *Cancer Causes Control*. 2002;13(8): 765–775.
21. Mack WJ, Preston-Martin S, Dal Maso L, et al. A pooled analysis of case-control studies of thyroid cancer: cigarette smoking and consumption of alcohol, coffee, and tea. *Cancer Causes Control*. 2003;14(8):773–785.
22. Iribarren C, Haselkorn T, Tekawa IS, et al. Cohort study of thyroid cancer in a San Francisco Bay area population. *Int J Cancer*. 2001;93(5):745–750.
23. Dal Maso L, Bosetti C, La Vecchia C, et al. Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors. *Cancer Causes Control*. 2009;20(1):75–86.
24. Turner MC, Chen Y, Krewski D, et al. An overview of the association between allergy and cancer. *Int J Cancer*. 2006; 118(12):3124–3132.
25. Curtis RE, Freedman DM, Ron E, et al, eds. *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000*. Bethesda, MD: National Cancer Institute; 2006. (NIH publication no. 05-5302).
26. Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. *N Engl J Med*. 2005;353(3): 229–237.
27. Meisner AL, Fekrazad MH, Royce ME. Breast disease: benign and malignant. *Med Clin North Am*. 2008;92(5):1115–1141.
28. Suzuki T, Matsuo K, Wakai K, et al. Effect of familial history and smoking on common cancer risks in Japan. *Cancer*. 2007; 109(10):2116–2123.
29. Galanti MR, Hansson L, Lund E, et al. Reproductive history and cigarette smoking as risk factors for thyroid cancer in women: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 1996;5(6):425–431.
30. Rossing MA, Cushing KL, Voigt LF, et al. Risk of papillary thyroid cancer in women in relation to smoking and alcohol consumption. *Epidemiology*. 2000;11(1):49–54.
31. Guignard R, Truong T, Rougier Y, et al. Alcohol drinking, tobacco smoking, and anthropometric characteristics as risk factors for thyroid cancer: a countrywide case-control study in New Caledonia. *Am J Epidemiol*. 2007;166(10):1140–1149.
32. Mack WJ, Preston-Martin S, Bernstein L, et al. Lifestyle and other risk factors for thyroid cancer in Los Angeles County females. *Ann Epidemiol*. 2002;12(6):395–401.
33. Navarro Silvera SA, Miller AB, Rohan TE. Risk factors for thyroid cancer: a prospective cohort study. *Int J Cancer*. 2005; 116(3):433–438.
34. Jee SH, Samet JM, Ohrr H, et al. Smoking and cancer risk in Korean men and women. *Cancer Causes Control*. 2004;15(4): 341–348.
35. Suzuki T, Matsuo K, Hasegawa Y, et al. Anthropometric factors at age 20 years and risk of thyroid cancer. *Cancer Causes Control*. 2008;19(10):1233–1242.
36. Brindel P, Doyon F, Rachédi F, et al. Anthropometric factors in differentiated thyroid cancer in French Polynesia: a case-control study. *Cancer Causes Control*. 2009;20(5): 581–590.
37. Engeland A, Tretli S, Akslen LA, et al. Body size and thyroid cancer in two million Norwegian men and women. *Br J Cancer*. 2006;95(3):366–370.
38. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. *J Clin Oncol*. 2005;23(21):4742–4754.
39. Samanic C, Gridley G, Chow WH, et al. Obesity and cancer risk among white and black United States veterans. *Cancer Causes Control*. 2004;15(1):35–43.
40. Samanic C, Chow WH, Gridley G, et al. Relation of body mass index to cancer risk in 362,552 Swedish men. *Cancer Causes Control*. 2006;17(7):901–909.
41. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612): 569–578.
42. Ogden CL, Yanovski SZ, Carroll MD, et al. The epidemiology of obesity. *Gastroenterology*. 2007;132(6):2087–2102.
43. Greenland S, Rothman KJ. Measures of effect and measures of association. In: Rothman KJ, Greenland S, eds. *Modern Epidemiology*. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1998: 47–64.
44. Hard GC. Recent developments in the investigation of thyroid regulation and thyroid carcinogenesis. *Environ Health Perspect*. 1998;106(8):427–436.
45. Belin RM, Astor BC, Powe NR, et al. Smoke exposure is associated with a lower prevalence of serum thyroid autoantibodies and thyrotropin concentration elevation and a higher prevalence of mild thyrotropin concentration suppression in the Third National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2004;89(12): 6077–6086.
46. Asvold BO, Bjøro T, Nilsen TI, et al. Tobacco smoking and thyroid function: a population-based study. *Arch Intern Med*. 2007;167(13):1428–1432.
47. Fox CS, Pencina MJ, D'Agostino RB, et al. Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. *Arch Intern Med*. 2008;168(6):587–592.
48. Knudsen N, Laurberg P, Rasmussen LB, et al. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. *J Clin Endocrinol Metab*. 2005;90(7):4019–4024.
49. Galofré JC, Pujante P, Abreu C, et al. Relationship between thyroid-stimulating hormone and insulin in euthyroid obese men. *Ann Nutr Metab*. 2008;53(3-4):188–194.
50. De Pergola G, Ciampolillo A, Paolotti S, et al. Free triiodothyronine and thyroid stimulating hormone are directly associated with waist circumference, independently of insulin resistance, metabolic parameters and blood pressure in overweight and obese women. *Clin Endocrinol (Oxf)*. 2007;67(2): 265–269.
51. Bastemir M, Akin F, Alkis E, et al. Obesity is associated with increased serum TSH level, independent of thyroid function. *Swiss Med Wkly*. 2007;137(29-30):431–434.
52. Glinoer D. What happens to the normal thyroid during pregnancy? *Thyroid*. 1999;9(7):631–635.
53. Akslen LA, Nilssen S, Kvåle G. Reproductive factors and risk of thyroid cancer. A prospective study of 63,090 women from Norway. *Br J Cancer*. 1992;65(5):772–774.

54. Sakoda LC, Horn-Ross PL. Reproductive and menstrual history and papillary thyroid cancer risk: the San Francisco Bay Area thyroid cancer study. *Cancer Epidemiol Biomarkers Prev*. 2002;11(1):51–57.
55. Truong T, Orsi L, Dubourdieu D, et al. Role of goiter and of menstrual and reproductive factors in thyroid cancer: a population-based case-control study in New Caledonia (South Pacific), a very high incidence area. *Am J Epidemiol*. 2005;161(11):1056–1065.
56. Memon A, Darif M, Al-Saleh K, et al. Epidemiology of reproductive and hormonal factors in thyroid cancer: evidence from a case-control study in the Middle East. *Int J Cancer*. 2002;97(1):82–89.
57. Brindel P, Doyon F, Rachédi F, et al. Menstrual and reproductive factors in the risk of differentiated thyroid carcinoma in native women in French Polynesia: a population-based case-control study. *Am J Epidemiol*. 2008;167(2):219–229.
58. Chaudhuri PK, Prinz R. Estrogen receptor in normal and neoplastic human thyroid tissue. *Am J Otolaryngol*. 1989;10(5):322–326.
59. Mori M, Naito M, Watanabe H, et al. Effects of sex difference, gonadectomy, and estrogen on N-methyl-N-nitrosourea induced rat thyroid tumors. *Cancer Res*. 1990;50(23):7662–7667.
60. Zabel EW, Alexander BH, Mongin SJ, et al. Thyroid cancer and employment as a radiologic technologist. *Int J Cancer*. 2006;119(8):1940–1945.