Research Article

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Prospective Study of Ultraviolet Radiation Exposure and Thyroid Cancer Risk in the United States

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Abstract

Background: Thyroid cancer incidence has tripled in the past three decades, yet relatively few risk factors have been identified. Some studies have suggested that ultraviolet radiation (UVR) may affect thyroid cancer risk.

Methods: We conducted a prospective analysis of 44,039 participants in the United States Radiologic Technologists Study (153 thyroid cancer cases) from all 50 states. We examined the association between risk of thyroid cancer and exposure to UVR, estimated by ambient UVR, time outdoors, and a combined variable. Participants reported location of residence and time outdoors during five age periods starting in childhood. Ambient UVR was estimated by linking satellite-based UVR measurements to geocoded residences. We assessed the association of UVR by age and average lifetime UVR with thyroid cancer risk using Cox proportional hazards models, starting at the time of the baseline questionnaire (2003–2005) through 2012–2013.

Results: Combined UVR from the latest age period (age 40+) was associated with a decreased risk of thyroid cancer (HR for 4th vs. 1st quartile = 0.56; 95% CI, 0.31–1.02, $P_{trend} = 0.04$). This was limited to participants with benign thyroid disease and to those with darker complexions, although we found no evidence of effect modification. Thyroid cancer risk was unrelated to all metrics of UVR in earlier age periods and for average lifetime exposure.

Conclusions: Recent UVR exposure was associated with a decreased risk of thyroid cancer. This association appeared to be modified by benign thyroid disease and skin complexion.

Impact: UVR exposure may be associated with a decreased risk of thyroid cancer. *Cancer Epidemiol Biomarkers Prev; 26(5); 684–91. ©2016 AACR.*

Introduction

Since the early 1980s, the incidence of thyroid cancer has tripled in the United States (1). Some have attributed this trend entirely to the introduction and widespread use of diagnostic ultrasound, other imaging modalities, and fine-needle aspiration biopsy, which has led to greater detection of small, indolent papillary thyroid cancers (2, 3). However, the steep rise in the incidence of large and advanced stage papillary thyroid cancer and an increase in thyroid cancer mortality have led some investigators to hypothesize that environmental factors have also contributed to the changing incidence of thyroid cancer (4–6). Apart from ionizing radiation exposure in childhood (7–9), obesity (10), and nonmalignant thyroid disease (11, 12), few potentially modifiable risk factors have been identified.

Two prior studies have evaluated the association between exposure to ultraviolet radiation (UVR) and risk of thyroid cancer, both finding an inverse association between UVR exposure and thyroid cancer incidence (13, 14). These studies relied exclusively on ambient UVR linked to residential location, although exposure to solar UVR depends on ambient UVR, unshielded time spent outdoors, and sun sensitivity factors as well. Prior studies also only estimated UVR exposure at one point in time, while it remains unknown whether exposure at other times during life, including during childhood, may also play a role. Neither study ascertained detailed information on sun sensitivity characteristics or thyroid cancer risk factors which may modify any associations found.

The aim of this study is to evaluate the association between ambient UVR, summer time spent outdoors, and a range of sun sensitivity characteristics in relation to subsequent risk of thyroid cancer using data from the United States Radiologic Technologists (USRT) Study. This is the first study to prospectively assess the association of UVR and thyroid cancer risk in a large, nationwide cohort with comprehensive information on UVR exposure across the life span and a range of thyroid cancer risk factors in a geographically dispersed population.

Materials and Methods

Overview

The United States Radiologic Technologists (USRT) Study is a large, prospective cohort designed to assess cancer and other health risks in radiologic technologists. The cohort is composed of radiologic technologists certified by the American Registry of Radiologic Technologists for at least two years between 1926 and 1982. Methods for this study have been previously published (15, 16). Briefly, participants were mailed questionnaires during the following time periods: 1983–1989, 1994–1998, 2003–2005,

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and 2012–2013. Information on lifetime residential history and time spent outdoors on weekdays and weekends was collected during the third survey (2003–2005) and the technologists have subsequently been followed up for cancer and other serious disease incidence and mortality. This study has been approved annually by the human subjects review boards at the University of Minnesota (Minneapolis, MN) and the National Cancer Institute (Bethesda, MD).

Study population

The study population consisted of men and women who completed both the third (2003–2005) and fourth (2012–2013) questionnaires and had no history of cancer (except nonmelanoma skin cancer) at the time of the third (baseline) questionnaire ($n = 46{,}114$). As virtually all thyroid cancer cases occurred in white participants (153/155) and skin pigmentation is a potentially strong effect modifier, analyses of UVR and thyroid cancer were restricted to whites ($n = 44{,}039$). Participants were followed until the time of the earlier of the first cancer diagnosis (other than nonmelanoma skin cancer) or completion of the fourth questionnaire.

Outcome

Cases were individuals who reported a first primary thyroid cancer diagnosis on the fourth questionnaire ($n = 153$). Of 110 medical records obtained, 109 cases (99%) were confirmed by medical record review. The remaining cases were not able to be confirmed mainly due to unavailable medical records ($n = 44$) but were still included in the analyses as cases because of the high confirmation rate of self-reported thyroid cancer in this study. Additional analyses were performed limited to papillary thyroid cancer ($n = 101$ cases), defined as International Classification of Diseases for Oncology (ICD-O)-3 codes 8050, 8260, 8340–8344, 8350, and 8450–8460.

Exposure assessment

All UVR-related exposure information used in the current study was collected in the baseline (third) questionnaire. Participants reported sun sensitivity characteristics including skin complexion (dark, medium, light), natural hair color (dark brown, black, light brown, medium brown, reddish-brown, blonde, or red), eye color (brown, hazel, green, or blue), history of blistering sunburn (yes/no), skin reaction to sunlight after 30 minutes (tanned without sunburn or no change in skin color, mild sunburn, severe or painful sunburn), and Celtic or Gaelic ancestry (yes/no). For each age period 0–12 years, 13–19 years, 20–39 years, 40–64 years, and 65 years-end of follow up, participants reported their city and state of residence and the number of hours spent outdoors per day for weekdays and weekends. We estimated UVR exposure with three metrics, accounting for location of residence, time outdoors during summer, and a combined term.

Ambient UVR was estimated by linking geocoded residential locations to NASA's Total Ozone Spectrometer (TOMS) database, which provides satellite-based daily noon-time erythemal UVR exposures on a grid measuring 1.25° longitude by 1° latitude (approximately 110×110 km or 69×69 miles; ref. 17). Satellite measurements were taken during the years 1978–1993 and those values were averaged, as ambient UVR have remained relatively stable since measurement began in the late 1970s (18).

For each age period, we calculated time outdoors, based on the average number of hours per day outdoors in the summer. We combined weekday and weekend time outdoors into a weighted average of 5 weekdays and 2 weekend days to estimate average number of hours spent outdoors per day.

As actual UVR exposure depends on both ambient UVR as well as personal time outdoors, we calculated combined UVR for each age period by multiplying ambient UVR by time outdoors. Because few participants were older than 65 years at baseline, we combined the age categories 40–64 and 65+ years into one category, 40+ years, and generated a weighted average of the two categories. We also calculated average lifetime ambient UVR, time outdoors, and combined UVR by averaging the values across the four age groups, accounting for the number of years spent in each based on the participant's age at study entry.

Lifetime exposure for each metric was divided into four quartiles, and the same quartile cut-off points for lifetime exposure were used to define the cut-off points for ambient UVR and combined UVR in each age period. We categorized time outdoors as follows: <1, 1–2.4, 2.5–3.9, and ≥4 hours/day.

Potential confounders

Information on demographic and physical characteristics (race, height, weight), lifestyle factors (smoking status, alcohol consumption), and history of nonmalignant thyroid disease were also ascertained in the third questionnaire, or in an earlier questionnaire if not available in the third. We also ascertained in the third questionnaire whether participants had a history of autoimmune disease at baseline, including multiple sclerosis, rheumatoid arthritis, lupus, or scleroderma, as they may be related to thyroid cancer risk (19–22).

Statistical analyses

To assess the relationship between UVR-related factors and thyroid cancer risk, we used Cox proportional hazards models with age as the time scale (23) to generate HRs and 95% confidence intervals (CI). We evaluated risk of thyroid cancer for each UVR exposure metric in each age period, average lifetime exposure for each metric, and sun sensitivity factors. Models were adjusted for sex, BMI (<18.5, 18.5–25, 25–30, >30 kg/m^2), height (<1.63, 1.63–1.65, 1.68–1.73, >1.73 meters), smoking (never/former/current smoker), and alcohol consumption (0, 1–2, 3–10, 11 or more drinks/week), chosen *a priori* because they have been associated with thyroid cancer risk in earlier studies (24–27). We also evaluated the potential for confounding by autoimmune disease (multiple sclerosis, rheumatoid arthritis, lupus, or scleroderma) by excluding participants with a positive medical history of these conditions, and evaluating the change to the HRs for each UVR metric. As a sensitivity analysis, we re-ran the models with additional adjustment for cumulative occupational ionizing radiation dose to the thyroid. Missing variables (the proportion of missing variables ranged from 0% to 7%) were modeled using a separate indicator variable. P_{trend} values were calculated by modeling the UVR variables as continuous ordinal values.

We tested for effect modification by BMI, functional thyroid disease (goiter, thyroiditis, hypothyroidism, or hyperthyroidism), and sun sensitivity characteristics by testing for multiplicative interaction with a Wald test. All hazard models satisfied the proportionality assumption as tested using Schoenfeld

Table 1. Lifestyle and physical characteristics at baseline in thyroid cancer cases and noncases among 44,039 individuals in the USRT Study

	Thyroid cancer case ($n = 153$)	Thyroid cancer noncase ($n = 43,886$)
Age at entry, mean (SD)	54.1 (7.0)	56.1 (7.6)
Person-years at risk, mean (SD)	4.1 (2.3)	7.8 (1.2)
Sex (%)		
Male	9.8	19.5
Female	90.2	80.5
Smoking status (%)		
Never smoker	59.5	55.3
Current smoker	6.5	10.1
Former smoker	32.7	31.9
Missing	1.3	2.7
Height (%)		
<1.63 meters	22.2	26.5
1.63–1.67 meters	27.5	25.4
1.68–1.73 meters	39.2	28.9
>1.73 meters	11.1	18.9
Missing	0.0	0.2
BMI (%)		
Underweight	0.0	0.8
Normal weight	36.0	36.7
Overweight	34.0	33.2
Obese	20.3	22.5
Missing	9.8	6.9
Functional thyroid disease (%)[a]		
Yes	30.7	14.9
No	68.6	82.2
Missing	0.7	3.0
Goiter (%)		
Yes	12.4	2.6
No	85.6	93.2
Missing	0.7	4.2
Thyroiditis (%)		
Yes	11.8	2.0
No	86.3	93.8
Missing	2.0	4.2
Hyperthyroidism (%)		
Yes	3.9	2.2
No	94.1	93.7
Missing	2.0	4.2
Hypothyroidism (%)		
Yes	15.0	9.6
No	83.0	86.3
Missing	2.0	4.2
Other functional thyroid disease (%)		
Yes	2.0	1.8
No	96.7	93.5
Missing	1.3	4.8
Thyroid adenoma or nodule (%)		
Yes	23.5	4.8
No	75.8	92.2
Missing	0.7	3.0
Complexion (%)		
Light	44.4	38.9
Medium	43.8	45.9
Dark	1.3	2.9
Missing	10.5	12.4
Eye color (%)		
Blue or green	42.5	46.2
Hazel	14.4	14.6
Brown	32.0	26.5
Missing	11.1	12.7
Hair color (%)		
Blonde or red	16.3	18.3
Light brown or reddish-brown	23.5	25.8
Medium brown	28.1	30.2

(Continued on the following column)

Table 1. Lifestyle and physical characteristics at baseline in thyroid cancer cases and noncases among 44,039 individuals in the USRT Study (Cont'd)

	Thyroid cancer case ($n = 153$)	Thyroid cancer noncase ($n = 43,886$)
Dark brown or black	31.4	25.1
Missing	0.7	0.6
Reaction to 30 minutes of strong sunlight (%)		
Severe or painful sunburn	47.1	34.9
Mild sunburn	43.1	52.7
No sunburn	9.2	10.8
Missing	0.7	1.6
Ever had a blistering sunburn (%)		
Yes	65.4	61.7
No	34.6	37.9
Missing	0.0	0.4
Celtic or Gaelic ancestry (%)		
Yes	20.3	20.6
No	58.8	51.8
Missing	20.9	27.6

[a]Defined as goiter, thyroiditis, hyperthyroidism, hypothyroidism, or other functional thyroid disease.

residuals. We considered two-sided *P* values to be significant at $\alpha \leq 0.05$. All analyses were conducted using SAS 9.3 (SAS Institute Inc).

Results

Thyroid cancer cases were more likely to be female (90.2% vs. 80.5%) and to report having been diagnosed with functional thyroid disease (30.7% vs. 14.9%) or thyroid mass (23.5% vs. 4.8%; Table 1). BMI values were similar between cases and noncases. Cases were also tended to be younger at study entry, and had a higher proportion of people reporting lighter skin and more sensitivity to the sun, were less likely to be current smokers, and were less likely to be either short (<1.63 meters) or tall (>1.73 meters).

UVR exposure was relatively consistent across most characteristics. However, women spent less time outdoors and were less likely to live in an area with high ambient UVR. Taller individuals spent more time outdoors and were more likely to live in areas with higher ambient UVR (Table 2). Lighter-skinned individuals also spent less time outdoors.

UVR exposure before age 40 years was unrelated to thyroid cancer risk apart from a borderline significant inverse association for time outdoors at ages 20–39 years (Table 3). For exposure at age 40+, we found evidence of an inverse association across all three exposure metrics: time outdoors (HR for the 4th vs. 1st quartile = 0.79; 95% CI, 0.39–1.58: $P_{\text{trend}} = 0.14$), ambient UVR (HR = 0.78; 95% CI, 0.51–1.21; $P_{\text{trend}} = 0.16$), and combined UVR (HR = 0.56; 95% CI, 0.31–1.02; $P_{\text{trend}} = 0.04$), but the association was statistically significant only for combined UVR (Table 3).

Although not statistically significant, we found some evidence of effect modification of combined UVR exposure since age 40 by sex, functional thyroid disease, and sun sensitivity (Fig. 1). The inverse association between UVR exposure since age 40 and thyroid cancer risk was limited to women and those with a history of functional thyroid disease. Looking at diseases individually, we found that the association was limited to those with goiter and hypothyroidism. We also found that the association was stronger among darker, less sun-sensitive individuals, as measured by hair color, skin complexion, and reaction to sunlight.

Table 2. Characteristics of study participants according to low, medium, and high lifetime average ambient UVR and lifetime average time outdoors at baseline

	Lifetime average time outdoors[a]			Lifetime average ambient UVR[b]		
Characteristics	**Low-time outdoors**	**High-time outdoors**	***P***	**Low UVR**	**High UVR**	***P***
Age at entry, mean (SD)	56.6 (7.7)	55.5 (7.4)	<0.01	55.7 (7.6)	56.4 (7.6)	<0.01
Person-years at risk, mean (SD)	7.7 (1.2)	7.8 (1.2)	0.23	7.8 (1.2)	7.7 (1.2)	0.03
Sex (%)						
Male	13.8	25.0	<0.01	16.9	22.0	<0.01
Female	86.2	75.0		83.1	78.0	
Smoking status (%)						
Never smoker	57.7	52.9	<0.01	55.6	55.0	<0.01
Former smoker	30.8	33.1		32.2	31.7	
Current smoker	8.3	11.9		9.6	10.5	
Missing	3.2	2.2		2.6	2.8	
Height (%)						
<1.63 meters	28.3	24.7	<0.01	27.8	25.2	<0.01
1.63–1.65 meters	27.1	23.7		26.3	24.5	
1.68–1.73 meters	29.4	28.5		28.8	29.1	
>1.73 meters	14.9	22.8		16.9	21.0	
Missing	0.2	0.2		0.2	0.3	
BMI (%)						
Underweight	0.9	0.7	<0.01	0.7	0.8	<0.01
Normal weight	38.4	35.1		36.3	37.1	
Overweight	32.2	34.2		33.1	33.3	
Obese	22.0	23.1		22.3	22.7	
Missing	6.6	7.0		7.5	6.2	
Functional thyroid disease (%)[c]						
Yes	15.9	14.0	<0.01	14.8	15.1	0.65
No	81.1	83.2		82.3	82.0	
Missing	3.0	2.7		2.9	2.9	
Thyroid adenoma/nodule (%)						
Yes	5.1	4.8	0.10	4.6	91.9	0.01
No	92.0	92.5		92.5	5.2	
Missing	3.0	2.7		2.9	2.9	
Complexion (%)						
Light	44.0	33.8	<0.01	39.8	37.9	0.01
Medium/dark	43.0	54.6		48.5	49.0	
Missing	13.0	11.6		11.7	13.1	
Eye color (%)						
Blue or green	46.5	45.9	0.01	46.2	46.1	0.17
Hazel	14.4	14.8		14.6	14.6	
Brown	25.8	27.4		27.1	26.0	
Missing	13.3	11.9		12.1	13.3	
Hair color (%)						
Blonde or red	18.1	18.6	<0.01	17.5	19.2	<0.01
Light brown or reddish-brown	26.6	25.1		25.8	25.9	
Medium brown	30.5	29.9		31.3	29.0	
Dark brown or black	24.3	25.9		25.1	25.2	
Missing	0.5	0.6		0.4	0.6	
Reaction to 30 minutes strong sunlight (%)						
Severe or painful sunburn	38.7	31.2	<0.01	34.1	35.7	<0.01
Mild sunburn	51.3	54.4		53.8	51.8	
No sunburn	8.6	13.0		10.6	11.1	
Missing	1.5	1.4		1.5	1.4	
Ever had a blistering sunburn (%)						
Yes	62.8	61.0	<0.01	58.7	34.8	<0.01
No	37.0	38.7		41.0	64.9	
Missing	0.3	0.3		0.3	0.3	
Celtic or Gaelic ancestry (%)						
Yes	51.8	20.2	0.04	20.2	21.1	<0.01
No	21.2	52.0		56.5	47.3	
Missing	27.1	27.7		23.4	31.6	

[a]Low and high average lifetime hours spent outdoors defined by dividing cohort at the median value.
[b]Low and high average lifetime ambient UVR defined by dividing cohort at the median value.
[c]Defined as goiter, thyroiditis, hyperthyroidism, hypothyroidism, or other functional thyroid disease.

Restricting the outcome to confirmed thyroid cancers (HR for the 4th vs. 1st quartile = 0.53; 95% CI, 0.26–1.07; $P_{\text{trend}} = 0.01$) or papillary thyroid cancer (HR for the 4th vs. 1st quartile = 0.51; 95% CI, 0.24–1.08; $P_{\text{trend}} = 0.02$) did not meaningfully change the magnitude of the thyroid cancer association for combined UVR at age 40+ years, nor did excluding individuals with either a history of autoimmune diseases ($n = 1{,}440$) or missing information on autoimmune diseases ($n = 7{,}771$; HR for the 4th vs. 1st

Table 3. Risk of thyroid cancer associated with ambient UVR exposure, time outdoors, and combined UVR by age at exposure among 44,039 participants in the USRT Study, 2003–2005 through 2012–2013

	Time outdoors				Ambient UVR				Combined UVR[c]			
Age range	**Hours/day**	**Cases**	**Person years**	**HR (95% CI)**	**Quartile[b]**	**Cases**	**Person years**	**HR (95% CI)**	**Quartile[b]**	**Cases**	**Person years**	**HR (95% CI)**
Average lifetime[a]												
	<1	12	31,246	Ref	Q1	43	86,218	Ref	Q1	37	83,592	Ref
	1–2.4	79	162,030	1.25 (0.68–2.29)	Q2	46	82,780	1.10 (0.73–1.67)	Q2	47	83,533	1.27 (0.83–1.96)
	2.5–3.9	50	111,463	1.18 (0.63–2.23)	Q3	32	83,825	0.80 (0.51–1.27)	Q3	38	83,507	1.05 (0.67–1.66)
	≥4	9	29,463	0.89 (0.37–2.13)	Q4	29	83,817	0.77 (0.48–1.23)	Q4	28	83,568	0.84 (0.51–1.39)
	P_{trend}			0.73	P_{trend}			0.15	P_{trend}			0.40
0—12												
	<1	14	28,311	Ref	Q1	52	109,765	Ref	Q1	29	60,594	Ref
	1–2.4	34	81,019	0.83 (0.44–1.55)	Q2	48	89,604	1.12 (0.76–1.67)	Q2	18	36,840	1.04 (0.58–1.87)
	2.5–3.9	49	92,420	1.07 (0.59–1.93)	Q3	21	66,508	0.68 (0.41–1.12)	Q3	29	53,996	1.12 (0.67–1.88)
	≥4	52	130,061	0.83 (0.46–1.51)	Q4	27	61,193	1.01 (0.63–1.62)	Q4	72	172,219	0.92 (0.59–1.42)
	P_{trend}			0.74	P_{trend}			0.53	P_{trend}			0.64
13—19												
	<1	11	31,579	Ref	Q1	53	108,847	Ref	Q1	25	71,561	Ref
	1–2.4	53	108,409	1.37 (0.72–2.63)	Q2	46	88,420	1.06 (0.71–1.58)	Q2	30	53,080	1.60 (0.94–2.73)
	2.5–3.9	46	88,408	1.49 (0.77–2.89)	Q3	23	66,131	0.73 (0.45–1.19)	Q3	33	55,351	1.71 (1.02–2.88)
	≥4	39	103,498	1.16 (0.59–2.28)	Q4	24	64,401	0.83 (0.51–1.35)	Q4	57	143,873	1.22 (0.76–1.96)
	P_{trend}			0.96	P_{trend}			0.23	P_{trend}			0.68
20—39												
	<1	47	84,291	Ref	Q1	50	93,880	Ref	Q1	66	141,376	Ref
	1–2.4	64	157,856	0.76 (0.52–1.11)	Q2	37	76,562	0.90 (0.59–1.38)	Q2	35	71,349	1.10 (0.73–1.65)
	2.5–3.9	21	53,588	0.78 (0.47–1.31)	Q3	25	65,078	0.73 (0.45–1.19)	Q3	17	44,955	0.88 (0.51–1.49)
	≥4	18	36,856	1.03 (0.60–1.78)	Q4	31	91,003	0.69 (0.44–1.08)	Q4	25	65,649	0.94 (0.59–1.49)
	P_{trend}			0.81	P_{trend}			0.07	P_{trend}			0.68
40+												
	<1	74	129,542	Ref	Q1	47	92,435	Ref	Q1	97	181,412	Ref
	1–2.4	53	137,919	0.72 (0.51–1.03)	Q2	36	70,544	0.99 (0.64–1.53)	Q2	20	59,567	0.68 (0.42–1.10)
	2.5–3.9	14	40,474	0.71 (0.40–1.25)	Q3	24	66,590	0.73 (0.44–1.19)	Q3	14	35,923	0.82 (0.47–1.43)
	≥4	9	24,599	0.79 (0.39–1.58)	Q4	36	98,138	0.78 (0.51–1.21)	Q4	12	47,807	0.56 (0.31–1.02)
	P_{trend}			0.14	P_{trend}			0.16	P_{trend}			0.04

NOTE: Models are Cox proportional hazards models, using age as the time scale, adjusting for sex, BMI, height, smoking, and alcohol consumption.
[a]Average lifetime values for each exposure are the weighted average, calculated by multiplying the reported exposure for each age group by the number of years spent in each age group and dividing by the total number of years.
[b]Cut-off points were based on equally sized quartiles of the average lifetime exposure. Units are arbitrary. Cut-off points are as follows: Ambient UVR: Q1 <100.3, Q2 100.3–110.2, Q3 110.3–135.5, Q4 >135.5. Combined UVR: Q1 <175.9, Q2 175.9–257.2, Q3 257.3–358.3, Q4 >358.3.
[c]Combined UVR was calculated by multiplying ambient UVR × time outdoors for each age range, or average lifetime.

quartile = 0.62; 95% CI, 0.32–1.21; $P_{trend} = 0.06$). Additional adjustment for occupational ionizing radiation dose did not result in any meaningful changes (data not shown).

Because our measure of time outdoors was based on time outdoors in the summer, which may be a more or less accurate representation of average exposure throughout the year for participants in the northern versus southern latitudes, we evaluated the associations for time outdoors separately by the latitudes <40 versus ≥40 degrees. In general, we found that inverse associations for time outdoors were stronger for participants in the lower latitudes (further south) than those in the higher latitudes. For ≥4 versus <1 hours outdoors at age 40+ years, the HR was 0.31 (95% CI, 0.07–1.28; $P_{trend} = 0.01$) for latitudes <40 degrees and 1.40 (95% CI, 0.61–3.19; $P_{trend} = 0.66$) for latitudes ≥40 degrees.

Discussion

This is the first study to prospectively evaluate exposure to UVR over the life span in relation to thyroid cancer. We found that higher UVR exposure at age 40+ years, but not at younger ages, was associated with a significantly lower risk of thyroid cancer. Average lifetime UVR exposure was not associated with thyroid cancer risk in this cohort.

The findings from this study support previous research reporting an inverse association between UVR exposure and thyroid cancer incidence (13, 14). Boscoe and colleagues reported decreased incidence and mortality from thyroid cancer among women living in the southern United States compared with women living in the northern United States, with no differences seen in men (14). However, this study relied on an ecologically derived measure of ambient UVR based on county of residence at time of diagnosis. In addition, individual-level data on major thyroid cancer risk factors was not available. Lin and colleagues also reported a decrease in thyroid cancer incidence with higher ambient UVR in the prospective NIH-AARP cohort which comprised participants aged 50 years and older residing in six U.S. states and two metropolitan areas (13). Neither study had information on sun sensitivity factors, time spent outdoors, or ambient exposure over the life span. However, our findings of reduced risk in participants aged 40+ years are consistent with these earlier findings of reduced thyroid cancer risk in relation to UVR exposure relatively close in time to thyroid cancer diagnosis.

The role of UVR exposure is well-established in both the production of vitamin D and as a cause of DNA damage to skin cells. UVR-induced DNA damage also results in the release of a number of immune mediators into circulation, some of which can suppress immune reactions in sites not directly exposed to UVR

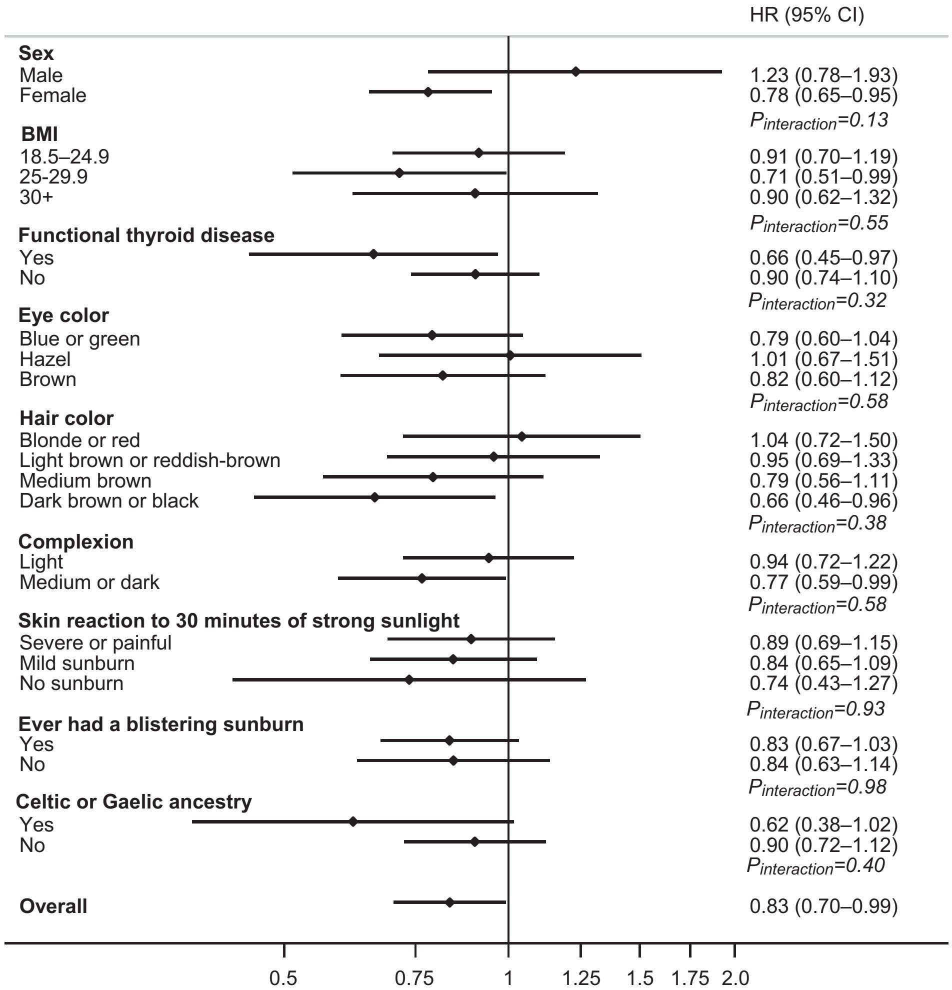

Figure 1.

HR and 95% CIs for thyroid cancer per quartile of combined UVR exposure during age 40-baseline by selected characteristics. All models are adjusted for attained age, sex, height, BMI, smoking, and alcohol consumption and stratified by selected characteristics. Tests for multiplicative interaction were calculated using a Wald χ^2 test.

(28, 29). A number of studies have reported an increased risk of thyroid cancer in patients with autoimmune conditions of the thyroid gland (e.g., Hashimoto's thyroiditis; refs. 24, 30, 31) and a role of an inflammatory microenvironment in the pathogenesis of thyroid cancer (32) has been proposed. To our knowledge, associations between UVR and inflammatory thyroid conditions have not been reported; however, epidemiologic studies have found an inverse association between UVR exposure and a number of other systemic inflammatory/autoimmune conditions, such as multiple sclerosis and type I diabetes (33). Higher levels of circulating vitamin D have also been examined in relation to thyroid cancer risk, with some suggesting an inverse association (34–37), and others reporting no association (38, 39). Unfortunately, information on vitamin D supplementation, which is likely to be the strongest predictor of circulating vitamin D in this cohort (40), was not collected at baseline for this study population.

We examined effect modification of combined UVR at age 40+ years to assess whether the significant association was limited to individuals with certain characteristics related to either sun sensitivity factors or thyroid cancer susceptibly. While we found no statistically significant interactions between our estimate of combined UVR and sun sensitivity factors, the inverse association between UVR exposure and thyroid cancer was somewhat stronger among individuals with darker hair, darker skin complexion, and reporting less sensitivity to sunlight. If the association between UVR and thyroid cancer is modified by skin complexion, then one possible explanation for the lack of an association between UVR and thyroid cancer among lighter-skinned individuals is they may be more likely to avoid sunlight while spending time outdoors by wearing more clothing, staying in the shade, or wearing sunscreen. In this study population, lighter-skinned and more sun-sensitive individuals report spending less time outdoors, suggesting that sun sensitivity may influence sun-seeking behaviors. Unfortunately, the baseline questionnaire did not ascertain outdoor sun shielding or sun avoidance behaviors, thus preventing an evaluation of whether risk differs by sun sensitivity characteristics when behavior is taken into account.

We also found a nonsignificantly stronger inverse association between combined UVR and thyroid cancer among individuals with functional thyroid disease (goiter and hypothyroidism), which is associated with increased risk of thyroid cancer (41). One possible explanation is that UVR may play a role in limiting disease progression by attenuating the inflammatory response associated with some of these conditions (30).

The strengths of this study include a large, geographically diverse population with information on a wide range of UVR exposures across the lifetime, a prospective study design, and information on many known risk factors for thyroid cancer.

Although our study used data from an occupational cohort, we have no reason to suspect that the associations observed for UVR and thyroid cancer risk are not generalizable to other populations. Limitations include reliance on self-reported UVR exposures and lack of information on sun-shielding behaviors. While participants likely report residential histories accurately, remembering and synthesizing information on time outdoors in the more distant past is problematic. This could also explain why we only saw an association of time outdoors with thyroid cancer risk for the most recent age period. The baseline questionnaire inquired about time outdoors only during the summer. Our finding of a stronger inverse association for time outdoors and thyroid cancer risk in participants in the lower versus higher latitudes suggests that time outdoors in the summer may be a better measure of UVR exposure throughout the year for individuals living in the southern versus northern United States. In addition, while vitamin D may explain the association between UVR exposure and thyroid cancer, we do not have information on vitamin D levels or vitamin D consumption over the participants' lifetimes. Finally, the relatively small number of cases limited our ability to detect statistically significant associations, particularly in stratified analyses.

In summary, this is the first study to comprehensively evaluate the role of UVR exposure in relation to thyroid cancer. We found an inverse association between UVR exposure at age 40+ years and thyroid cancer risk, but no association for UVR exposure during other periods. This finding should be confirmed in other studies before any firm conclusions can be drawn about the role of UVR and thyroid cancer risk. To clarify potential mechanisms, future studies could collect prospective biomarkers of vitamin D and immune function in addition to a wide range of UVR and sun sensitivity factors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.S. Linet
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R.D. Zamoiski, E.K. Cahoon, D.M. Freedman, C.M. Kitahara
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