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Indicators of microbial-rich environments and the development of papillary thyroid cancer in the California Teachers Study

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Abstract

Background—Little epidemiologic research has focused on the role of immune function in papillary thyroid cancer risk despite scattered observations suggesting it may be important (e.g, hygiene hypothesis). Here we investigate papillary thyroid cancer risk associated with self-reported living environments across the lifespan reflecting immunologically relevant exposures to microbial-rich environments.

Methods—Among 61,803 eligible participants in the California Teachers Study cohort, 100 were diagnosed with invasive papillary thyroid cancer between 2005 and 2012. Multivariate Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Results—Living in a rural area during early childhood was associated with significantly reduced risk of developing papillary thyroid cancer as an adult (HR=0.51, 95% CI: 0.28–0.94). Specifically, reduced risks were observed for living within a half mile of hoofed animals (HR=0.47, 95% CI: 0.26–0.84), as was having an indoor dog or cat (HR=0.51, 95% CI: 0.32–0.80). Neither sharing a bedroom or living in a rented home as a child nor attending daycare or kindergarten was associated with reduced risk.

Conclusions—Early childhood exposures to hoofed animals or indoor furry pets were associated with reduced risk of subsequently developing papillary thyroid cancer.

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CC, PR, IOG, EL, YL, LB, PHR designed and conducted the research, prepared the manuscript and have responsibility for content; JY and LM analyzed data. All authors read and approved the final manuscript

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Impact—Our findings point to immunologically-relevant, early-life exposures to microbial-rich environments as potentially important in reducing thyroid cancer risk, consistent with the hygiene hypothesis and suggesting that certain, possibly animal-derived, microbial exposures may be important to immune calibration or priming.

Keywords

thyroid cancer; microbial exposures; hygiene hypothesis; early-life exposures; California

Introduction

Thyroid cancer is currently the 5th most commonly diagnosed cancer in United States (US) women (1). Substantial increases in incidence have been observed in US women and men across all ethnic groups (1–3). With an average annual percent increase (AAPI) of 6.6% per year between 1996 and 2010 (compared to an AAPI of 2.5% between 1981 and 1996), incidence rates for thyroid cancer are increasing faster than those for any other cancer in women (1). Improvements in diagnostic technology account for only a portion of the observed increase (2, 4–6). Thus identifying new risk factors for thyroid cancer and understanding temporal changes in both established and new risk factors represent an increasingly important public health priority. At this time, the only well-established risk factors for the papillary (including the papillary/follicular variant) form of thyroid cancer (which comprises 80% of all thyroid cancer) are ionizing radiation, history of proliferative benign thyroid disease (BTD) (e.g., goiter and thyroid nodules), and family history of thyroid cancer or proliferative BTD (7–9). However, these exposures have relatively low prevalence in the US (8, 10). More recent studies have found obesity to increase risk (11–13) and the several years following a full-term pregnancy to be a period of high risk (14, 15). Little research has focused on immunologic correlates of thyroid carcinogenesis despite the fact that half of all autoimmune diseases in women involve the thyroid (16). These autoimmune diseases result from hyperactive cell-mediated immune responses against self tissue (17), and women with autoimmune diseases such as systemic lupus erythematosus (SLE), are at significantly higher risk of developing thyroid cancer (18).

Given the rapid increase, environmental exposures relevant to immune function represent an understudied set of possible risk factors for thyroid cancer. During the last century we have seen unprecedented increases in persons living in more sterile environments and less crowded housing conditions, resulting in diminished exposure to a diversity of microbes (19). This reduction in exposure to microbial-rich environments, especially when it occurs in early life, has been linked to hyperactive immune responses to allergens (e.g., atopic disease) in children and is thought to be detrimental to establishing the appropriate immune “calibration” or “priming” that may be needed for lifelong healthy immune function (19–22). This set of circumstances has been termed the “hygiene hypothesis.” Exposure to microbial-rich environments have been associated with lower risk of other cancers (e.g., daycare and childhood leukemia, occupational exposures to endotoxin-rich agricultural and textile environments and lung cancer (23, 24)) and it is plausible that similar exposures could be related to thyroid cancer development. Here we investigate the association between

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early life self-reported exposures to microbial-rich environments and papillary thyroid cancer risk in a large, prospective cohort of female California teachers.

Materials and Methods

The California Teachers Study (CTS) cohort, established in 1995–96, includes 133,479 active and retired female public school teachers, administrators, and other professionals (25). Participants initially completed a self-administered baseline questionnaire addressing health and medical history, lifestyle, diet, and other behaviors. The fourth follow-up questionnaire, completed in 2005–06, included questions on exposures related to microbial and infectious exposures throughout the lifespan. The study was approved by the Institutional Review Boards of the Cancer Prevention Institute of California, City of Hope National Medical Center, the University of Southern California, the University of California, Irvine, and the California Health and Human Services Agency.

Follow-up

The CTS cohort is followed annually for cancer diagnoses, changes of address, and death. Cancer diagnoses are determined by linkage with the California Cancer Registry (CCR), a population-based cancer registry which comprises three of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) 17 registries. Since greater than 99% of all cancer diagnoses among California residents are reported to the CCR (26), cohort members who continue to reside in California are effectively followed for cancer outcomes. Changes of address are obtained by annual mailings, notifications from participants, and record linkages with multiple sources including the US Postal Service National Change of Address database. California and national mortality files are used to ascertain date of death.

Assessment of key exposures

In the 4th questionnaire (hereafter referred to as the 2005–06 questionnaire), participants completed a series of questions about their home environment at age 6 months, at ages 3, 5, 12, and 30 years, and at the present time. These included characteristics of the area where they lived (rural, small town, suburb, or urban); whether they lived within half a mile of barns or stables where horses, cows, pigs, or other hoofed animals were kept (yes, no); whether they had a dog or cat living inside their home (yes, no); whether they lived in a rented apartment or house (yes, no); and the number of siblings or other people who slept in the same bedroom as they did (0, 1–2, 3–5, or 6+). Respondents also indicated if they regularly (at least 30 times/year) attended a preschool, kindergarten, or another regular gathering of at least 4 other children (yes, no) at ages 6 months and 3 and 5 years. In addition to examining exposures at each age/time period, we defined "early childhood" exposure as an affirmative response to the question at any or all ages of 6 months, 3 years, or 5 years.

Study population

For the present analysis, we excluded women who did not respond to the 2005–06 questionnaire (n=61,214). In addition, among those who did complete the 2005–06 questionnaire, we excluded, as of the date the questionnaire was completed, women who

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were not eligible for the evaluation of cancer outcomes due to relocation outside of California (n=9,202),who had a prior or unknown history of thyroid cancer (identified by self-report or by linkage with the CCR) (n=649), consented to participate only in breast cancer studies (n=9), or who did not respond to the relevant questions (n=606). Thus, the resulting analytic cohort included 61,799 women.

Within this analytic cohort we identified 100 women who had been diagnosed with an incident invasive papillary (including its follicular variant) thyroid cancer (International Classification of Diseases for Oncology-3 (ICD-O-3) site code C73.9 and histology codes 8050, 8260, 8340–8344, and 8350) after joining the cohort and before December 31, 2012.

Statistical analyses

Follow-up time was calculated as the number of days between the date when the 2005–06 questionnaire was completed and the first diagnosis of invasive papillary thyroid cancer (n=100), the diagnosis of non-papillary thyroid cancer (n=14), a permanent (over 4 months long) move outside of California (n=2,375), death (n=4,364) or the end of follow-up (December 31, 2012), whichever occurred first.

Multivariable Cox proportional hazards regression was used to estimate hazard rate ratios (HR) associated with development of papillary thyroid cancer. Hazard ratios were used to estimate incidence rate ratios assuming constant hazards and rare events. Age at the time the 2005–06 questionnaire was completed was considered the age at time=0. These models used age (in days) as the time metric, were stratified by age (in years) at the time of the 2005–06 questionnaire, and were adjusted for body mass index (kg/m^2; BMI) based on weight (in pounds) and height (in feet and inches) reported at the 2005–06 questionnaire, age at menarche, and neighborhood SES at the time of the baseline assessment. These covariates were included based on their independent association with papillary thyroid cancer risk in multivariate models in our analytic cohort. We additionally investigated the following variables as potential confounders: race/ethnicity, family history of thyroid cancer, family or personal history of BTD, parity, adolescent menstrual cycle length and time to regular cycles, recency of pregnancy, oral contraceptive use, height, alcohol use, smoking history, and activity during the 3 weeks prior to completing the 2005–06 questionnaire. None of these variables were associated with risk in the multivariable models, nor did their inclusion impact associations with the variables of interest (i.e., the point estimates in unadjusted versus adjusted models were not changed by more than 15%), and therefore were not included in the final models reported here. Models handled ties using the exact method and there were no violations of the proportional hazards assumption. All analyses were conducted using SAS (version 9.3, Cary, NC).

Results

The average age of women in the analytic cohort was 62 (± 0.1) years at the time they completed the 2005–06 questionnaire; 88% were non-Latina white, 29% were overweight (BMI 25–29.9 kg/m^2), and 18% were obese (BMI >30 kg/m^2). Only 1.4% reported having a family history of thyroid cancer in a first degree relative, but almost 15% had a family history of BTD, and 10% reported a personal history of benign thyroid disease. Women in

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the analytic cohort who were diagnosed with papillary thyroid cancer (n=100) were slightly younger, with an average age of 60 (± 10.4) years, more likely to be obese (31%), parous (80%), and live in areas of higher SES (56%).

Among those women eligible for the analytic cohort, 23% reported living in a rural area during early childhood (at age 5 years or younger) and 25% reported living within a half mile of barns or stables housing horses or other hoofed animals. Rural residence during childhood was associated with a 49% reduced risk of developing papillary thyroid cancer as an adult (HR=0.51, 95% CI: 0.28–0.94) while living near hoofed animals reduced risk by 53% (HR=0.47, 95% CI: 0.26–0.84; Table 1). The reduction in risk waned somewhat for exposure at age 12 years (HR=0.66, 95% CI: 0.37–1.17) and even more so for adult and recent exposure. These associations were independent of each other. Having an indoor dog or cat in early childhood was also associated with reduced risk (HR=0.43, 95% CI: 0.26–0.72) and was independent of the association for living near hoofed animals. Living in a rented home and sharing a bedroom were generally not associated with risk of papillary thyroid cancer risk at the ages assessed. We did not find a significant association with attending daycare or kindergarten during early childhood, but further assessment of age-specific exposures suggested increased risks for exposure at ages 6 months and 3 years.

Discussion

To our knowledge, this is the first study addressing the association between papillary thyroid cancer development and events that could reflect immunologically-relevant microbial exposures during specific periods of life. We examined two types of factors culled from the literature regarding their association with atopic disease: those presumably reflecting exposure to a wide diversity of microbes and microbial byproducts and endotoxins (i.e., living within close proximity to hoofed animals, and with pets), and those presumably reflecting greater exposure to infections from other children (i.e., close contact with siblings or other children). We found that events reflecting early childhood exposures to diverse microbes, but not those reflecting earlier or greater childhood exposure to other children, were inversely associated with papillary thyroid cancer risk. Very early childhood exposure (age ages ≤ 3 years) to other children in daycare, however, increased subsequent thyroid cancer risk. We did not detect important associations with any of these exposures when they occurred during adulthood.

The ‘hygiene hypothesis’ suggests that insufficient microbial exposures in early life can adversely affect immune responsiveness in later life (22). This line of reasoning holds that the immune system evolved to expect early and intense exposure to a diversity of microbes but that the recent, dramatic modification of these exposures associated with the relatively sterile western environment, a reduction in crowded living conditions in modern society, and most recently, widespread use of antimicrobial products, especially in early life, may be detrimental to appropriate priming of immune responses needed for healthy immune function throughout the lifespan (19). It is now thought that the relevant range of microbes extends beyond those responsible for clinically apparent infections, to gastrointestinal microbiome colonization with commensal bacteria and exposures to sterile microbes and bacterial components, including endotoxins (20, 21). To our knowledge, data are lacking to

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corroborate the associations reported here, as little has been published regarding thyroid cancer risk among those living on farms or in rural areas (27), although occupational exposures to agricultural and textile environments rich in microbial byproducts reduce risk of lung cancer in adults (23), and daycare attendance and early life infections have been shown consistently to reduce risk of childhood lymphoid malignancies (24). However, we did not observe any similar, consistent protection from daycare or kindergarten attendance or crowded households, which suggests that the important exposures are animal-derived, perhaps reflecting a greater overall microbial diversity. Our findings are consistent with the notion that key early-life microbial exposures from animals, likely important to immune 'calibration', might be relevant to the etiology of papillary thyroid cancer. Whether microbial exposure patterns are related to worldwide trends of thyroid cancer incidence (4), especially its increasing incidence, is not yet known but warrants further exploration.

Strengths of this study include the novel hypothesis, the large and diverse CTS cohort, and complete and accurate outcome assessment based on linkage of the cohort to the statewide cancer registry and monitoring of residential address and mortality (25). An important limitation of this study is that the exposure questions were answered only by cohort members who completed the 10 year follow-up questionnaire. We opted to limit the analytic cohort to those women who completed this questionnaire and to carry out a prospective analysis, despite the relatively small number of cases even though the exposures of interest occurred during childhood. Alternative analyses including the full cohort and including both prevalent and incident thyroid cancers yielded very similar result s to those shown here. This secondary analysis is reassuring in terms of generalizability given that the prospective cohort is substantially older than the average population which develops thyroid cancer, i.e., women during their reproductive and early menopausal years, whereas the retrospective analysis includes women at a younger average age. The smaller number of cases available for stratified analyses also means that some of our observations are based on small numbers and limited our ability to test formally for statistical interactions. Having nested this study within the prospective cohort did allow us to compare characteristics of women who responded and those that did not respond to the 2005–06 questionnaire. This comparison showed that the two groups of women were generally similar, although responders were somewhat younger than non-responders at baseline (mean age 52 vs. 56 years, respectively). A related limitation is that some incomplete control for confounding may still be present, since while information on BMI was updated on the 2005–06 questionnaire, parity was not. However, given the older average age of the cohort, this may not be a substantial issue as the majority of the women were likely to have completed their childbearing prior to joining the cohort.

Unfortunately, our questionnaire included only a small subset of all possible markers of relevant early-life microbial exposures. Future studies should address a more detailed set of exposures to children, animals, farming and other relevant environments. Future studies should also address alternative exposures that could explain associations of thyroid cancer with early life environments including iodine intake and exposure to diagnostic X-rays or other medical radiation. Studies with sufficient numbers to mutually adjust exposures could potentially tease out their independent effects. We did not have prospective blood samples with which we could have measured antibody profiles to specific antigens. A final limitation

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is the potential for misclassification of self-reported early life exposures. While few data validating such self-reports are available, Nicholas et al. (28) did find that 18-year olds could recall pet ownership at ages 1 to 6 relatively well (between 77% and 89%) compared to parental reports from 12–18 years earlier, with errors towards underreporting. Svanes et al. also reported that adults age <45 years of age recalled childhood pet ownership with 81% to 86% accuracy (29).

In summary, we found that early childhood exposure to certain household pets and hoofed animals were associated with reduced risk of subsequently developing papillary thyroid cancer in women. This finding is consistent with the broader notion that diverse microbial inputs in early life may affect the priming or calibration of immune responses in later life, which in turn could affect the risk of cancer development. This new area of inquiry deserves further study as a novel pathway for understanding the rapid increases in thyroid cancer occurrence observed in many developed populations worldwide.

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Highlights

- First examination of early life exposures and later thyroid cancer development
- We found significant associations with early exposure to hoofed animals and furry pets.
- Our findings are possibly consistent with the hygiene hypothesis for atopic disease.

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Table 1

Distribution of characteristics and risk factors in analytic cohort and women diagnosed with papillary thyroid cancer.

	Analytic cohort		Papillary Thyroid Cancer Cases	
	N	%	N	%
All	61,799	100.0%	100	100.0%
Age at the 2005–06 questionnaire				
<35	117	0.2%	0	0.0%
35–44	4,705	7.6%	6	6.0%
45–54	10,796	17.5%	26	26.0%
55–64	20,530	33.2%	39	39.0%
65–74	13,768	22.3%	18	18.0%
>=75	11,883	19.2%	11	11.0%
mean (SD)	62.7	(12.3)6	59.7	(10.4)
median (interquartile)	62	(54–72)	59	(54–67)
Race at baseline				
White	54,473	88.1%	88	88.0%
Non-white	6,913	11.2%	12	12.0%
Unknown	413	0.7%	0	0.0%
Family history of thyroid cancer at baseline				
No	59,362	96.1%	95	95.0%
Yes	843	1.4%	1	1.0%
Adopted/no info	1,594	2.6%	4	4.0%
Family history of benign thyroid disease (BTD) at baseline				
No	51,640	83.6%	78	78.0%
Yes	9,130	14.8%	20	20.0%
Adopted/no info	1,029	1.7%	2	2.0%
Personal history of BTD at baseline				
Never benign thyroid disease	55,192	89.3%	91	91.0%
Ever benign thyroid disease	6,397	10.4%	9	9.0%
Unknown	210	0.3%	0	0.0%
BMI at the 2005–06 questionnaire				
<25	31,988	51.8%	38	38.0%
25–<30	18,053	29.2%	30	30.0%
30+	11,068	17.9%	31	31.0%
Unknown	690	1.1%	1	1.0%
Age at menarche (baseline data)				
<14	48,799	79.0%	88	88.0%
14+	12,219	19.8%	10	10.0%
Unknown	781	1.3%	2	2.0%
Parity at baseline				
Nulliparous	15,218	24.6%	17	17.0%

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	Analytic cohort		Papillary Thyroid Cancer Cases	
	N	%	N	%
Parous	45,586	73.8%	80	80.0%
Unknown	995	1.6%	3	3.0%
Age at first full-term pregnancy (baseline data)				
Nulliparous or NTP	15,218	24.6%	17	17.0%
<20	2,226	3.6%	5	5.0%
20–<25	14,241	23.0%	28	28.0%
25–<30	18,600	30.1%	27	27.0%
30+	10,519	17.0%	20	20.0%
Unknown	995	1.6%	3	3.0%
Neighborhood SES at baseline				
Q1, Q2-low SES	12,404	20.1%	23	23.0%
Q3	19,821	32.1%	20	20.0%
Q4-high SES	28,839	46.7%	56	56.0%
Unknown	735	1.2%	1	1.0%

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Table 2

Associations between indicators of microbial exposures, socioeconomic status, and greater chance of infection and risk of papillary thyroid cancer in women.

	Age 6 mo			Age 3 yrs			Age 5 yrs			Early childhood[b]			Age 12 yrs			Age 30 yrs			Years 2005–2006		
Exposure	**cases**	**RR[a]**	**95% CI**	**cases**	**RR[a]**	**95% CI**	**cases**	**RR[a]**	**95% CI**	**cases**	**RR[a]**	**95% CI**	**cases**	**RR[a]**	**95% CI**	**cases**	**RR[a]**	**95% CI**	**cases**	**RR[a]**	**95% CI**
Lived in a rural area																					
no	86	1.00		85	1.00		87	1.00		83	1.00		86	1.00		90	1.00		91	1.00	
yes	9	0.52	0.26–1.03	10	0.61	0.31–1.18	8	0.50	0.24–1.05	12	**0.51**	**0.28–0.94**	7	0.51	0.24–1.12	5	0.68	0.27–1.71	5	0.46	0.18–1.14
Lived within 1/2 mile of hoofed animals																					
no	85	1.00		85	1.00		86	1.00		80	1.00		81	1.00		84	1.00		79	1.00	
yes	8	**0.45**	**0.22–0.93**	9	**0.45**	**0.23–0.90**	9	**0.42**	**0.21–0.83**	13	**0.47**	**0.26–0.84**	14	0.66	0.37–1.17	11	0.78	0.41–1.47	16	0.91	0.53–1.57
Lived with a cat or dog																					
no	76	1.00		70	1.00		68	1.00		66	1.00		44	1.00		38	1.00		51	1.00	
yes	17	0.71	0.42–1.21	23	0.75	0.47–1.21	24	**0.53**	**0.33–0.84**	26	**0.51**	**0.32–0.80**	50	0.82	0.54–1.23	56	0.98	0.65–1.48	44	0.77	0.51–1.17
Lived in a rented home																					
no	56	1.00		61	1.00		68	1.00		52	1.00		81	1.00		82	1.00		95	1.00	
yes	40	0.87	0.58–1.31	35	1.03	0.68–1.57	28	1.08	0.69–1.69	44	0.85	0.57–1.28	15	0.94	0.53–1.64	14	**0.56**	**0.32–0.99**	4	0.92	0.33–2.50
Shared a bedroom																					
no	50	1.00		35	1.00		37	1.00		27	1.00		49	1.00		18	1.00		32	1.00	
yes	46	0.99	0.67–1.49	63	1.21	0.80–1.84	61	0.99	0.66–1.49	71	1.15	0.73–1.79	49	1.15	0.77–1.71	81	1.55	0.93–2.59	67	1.18	0.77–1.82
Attended daycare or kindergarten																					
no	83	1.00		74	1.00		18	1.00		15	1.00										
yes	13	**2.59**	**1.44–4.66**	22	**1.69**	**1.04–2.75**	81	1.16	0.69–1.97	82	1.39	0.79–2.45									
Residence Type																					
Rural	9	0.53	0.25–1.15	10	0.57	0.27–1.18	8	0.50	0.22–1.12				7	0.54	0.23–1.31	5	0.60	0.23–1.59	5	0.45	0.17–1.21
Town	37	1.19	0.72–1.96	33	0.97	0.57–1.63	31	0.97	0.56–1.67				24	0.89	0.48–1.65	20	0.87	0.48–1.55	19	0.92	0.50–1.71
Suburban	23	0.87	0.49–1.54	27	0.82	0.47–1.44	34	1.00	0.58–1.73				44	1.24	0.71–2.17	43	0.82	0.51–1.33	50	1.02	0.62–1.69
Urban	26	1.00		25	1.00		22	1.00					18	1.00		27	1.00		22	1.00	

[a] Relative risks (RR; hazard rate ratios) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression models with age (in days) as the time-scale and stratified by age at baseline (in years), the models were adjusted for BMI at Q4, age at menarche, and neighborhood SES.

[b] Exposure at 6 mos, 3 yrs, or 5 yrs of age.