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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.

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.

1. 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

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

2. Materials and methods

The California Teachers Study (CTS) cohort, established in 1995–1996, 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 2005–2006, 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.

2.1. 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.

2.2. Assessment of key exposures

In the 4th questionnaire (hereafter referred to as the 2005–2006 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 four 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.

2.3. Study population

For the present analysis, we excluded women who did not respond to the 2005–2006 questionnaire (n = 61,214). In addition, among those who did complete the 2005–2006 questionnaire, we excluded, as of the date the questionnaire was completed, women who were not eligible for the evaluation of cancer outcomes due to relocation outside of California (n = 9202), 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.

2.4. Statistical analyses

Follow-up time was calculated as the number of days between the date when the 2005–2006 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 = 2375), death (n = 4364) 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 2005–2006 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 2005–2006 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 2005–2006 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 2005–2006 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

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