THYROID
Volume 31, Number 4, 2021
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DOI: 10.1089/thy.2020.0217

Birth Characteristics and Risk of Pediatric Thyroid Cancer: A Population-Based Record-Linkage Study in California

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Background: Incidence rates of thyroid cancer in children and young adults (age 0–19 years) have nearly doubled over a recent 15-year period in the United States. Children with thyroid cancer may require long-term therapy and surveillance and are at greater risk for second primary malignancies. High-dose exposure to ionizing radiation is the only known nongenetic risk factor; the vast majority of cases have an unknown etiology.
Methods: We conducted a population-based nested case-control study to evaluate the relationship between a range of birth characteristics and the risk of pediatric thyroid cancer. Using linked birth records and cancer registry data from California, we included 1012 cases who were diagnosed with first primary thyroid cancer at the age of 0–19 years from 1988 to 2015 and 50,600 birth-year matched controls (1:50 case to control ratio). We estimated adjusted odds ratios (OR) and 95% confidence intervals (CI) by using multivariable logistic regression models applied to the full population and stratified by thyroid cancer subtypes (papillary and follicular), race/ethnicity (white and Hispanic), and age at diagnosis (0–14 and 15–19 years).
Results: Hispanic ethnicity (OR: 1.20 [CI 1.01–1.42]), higher birth weight (OR: 1.11 [CI 1.04–1.18] per 500g), and higher maternal education (13–15 years OR: 1.35 [CI 1.09–1.68], 16+ years OR: 1.35 [CI 1.07–1.71]) were associated with an increased risk of pediatric thyroid cancer, while male sex (OR: 0.21 [CI 0.18–0.25]) and higher birth order (third or higher OR: 0.81 [CI 0.68–0.98]) were associated with a decreased risk. Some heterogeneity was observed across subtype, most notably an elevated OR with higher birth order for follicular thyroid cancer, in contrast to the reduced risk for this category among papillary thyroid cancer cases (p-value for interaction = 0.01). Hispanic ethnicity was a risk factor for papillary, but not follicular thyroid cancer (p-value for interaction = 0.07).
Conclusions: In this population-based study of birth characteristics and pediatric thyroid cancer, we identified several important risk factors for pediatric thyroid cancer, including female sex, Hispanic ethnicity, higher birth weight, higher maternal educational attainment, and lower birth order. Our data provide new areas for replication and investigation of biological mechanisms for this poorly understood malignancy.

Keywords: pediatric thyroid cancer, papillary, follicular, epidemiology

Introduction

Incidence rates of pediatric thyroid cancer (ages 0–19 years) have nearly doubled over an ~15-year period, increasing from $4.8/10^6$ in 1998 to $8.8/10^6$ in 2013 in the United States (1). The clinical manifestation of thyroid cancer differs between children and adults. Children tend to present at a more advanced stage with larger tumor sizes, involvement of regional lymph nodes, and pulmonary metastasis (2–4). Although mortality rates are low, children with thyroid cancer may face a lifetime of surveillance and are at a greater risk for second primary malignancies, notably leukemia and salivary gland cancer (5). In addition, the uncertainty surrounding the disease poses challenges to life milestones (e.g., education, employment, family formation) and may lead to adverse psychosocial outcomes, such as anxiety and depression (6–8).

The increasing trend in pediatric thyroid cancer is driven primarily by papillary thyroid cancer, the most common subtype. Increases have also been observed for follicular thyroid cancer (1), while incidence rates of other less common subtypes (medullary and anaplastic) are too low to evaluate for temporal trends (9). In general, similar annual percent changes (APCs) in

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pediatric thyroid cancer incidence have been observed in males and females (4% to 5% per year over recent decades) (1,10), and incidence rates have increased across all racial and ethnic groups: non-Hispanic white (APC: 4–8%), non-Hispanic Black (APC: 2–7%), and Hispanic (APC: 6–9%) children (1,10).

Increasing incidence rates have been observed in adolescent age groups (10–14 years [APC: 5%] and 15–19 years [APC: 4%]), but not in younger age groups (0–9 years [APC: 0.8%]) (1). Incidence rates have increased across stages (APC localized: 4.1%; APC distant 8.5%) and tumor sizes (APC <1 cm: 9.5%, APC 1–2 cm: 6.9%, APC >2 cm: 4.7%) (1). An increasing trend has been observed for pediatric thyroid cancers in the Northeast (APC: 5.8%), South (APC: 4.3%), and West (6.6%) regions of the United States, but not the Midwest region (10).

The increasing trend in pediatric thyroid cancer mirrors the trajectory in U.S. adults. The rising trends in adults are likely due to a combination of a true increase from changing risk factors as well as improvements to and greater usage of diagnostic and imaging methods (11). Although the relative contribution of these different factors is under debate, one analysis found that enhanced diagnostic scrutiny explained only $\sim$50% of the changing thyroid cancer incidence in adults, leaving half of incident cases manifesting from other origins, for example, environmental or lifestyle factors (11,12).

In children, significant increases observed for larger tumors (13) and the low likelihood of screening and imaging for other clinical purposes (14,15) suggest that diagnostic changes are unlikely to be the sole explanatory factor (16,17). Other than being female (18) and high-level exposure to ionizing radiation (19,20), a few risk factors for pediatric thyroid cancer have been identified. Very few studies have considered exposures or factors pertaining to the fetal development period, which is considered a critical window of vulnerability for childhood cancers (21,22).

Empirical data on risk factors specific to pediatric thyroid cancer are extremely limited. Several birth and demographic characteristics have been identified as risk factors for other pediatric cancers, adult thyroid cancer, or have been associated with maternal or neonatal thyroid hormone levels (22–26). Elevated or reduced thyroid hormone levels has been hypothesized to cause abnormal proliferation in the thyroid, potentially leading to tumorigenesis in adults (27–30). Adults with high or low thyrotropin (TSH) concentrations compared with the normal range have been observed to have an elevated risk of thyroid cancer (31–33). A case-control study of pediatric thyroid cancer ($n = 29$ cases) observed increased odds of thyroid cancer with TSH levels greater than 2.5 mIU/I compared with lower levels (28).

To address the paucity of information on risk factors for pediatric thyroid cancer, we aimed at evaluating a range of potential risk factors related to demographic and birth characteristics with the purpose of discovering areas for further research.

Methods

Study population

We leveraged the California Linkage Study of Early-Onset Cancers, a data architecture with joined California birth records maintained by the Center for Health Statistics and Informatics, California Department of Public Health (for the birth years 1978–2015), and statewide cancer diagnosis data from the California Cancer Registry for the years 1988–2015. The current study included children whose birth residence was in California and who were diagnosed with their first, primary thyroid cancer by the age of 19 years, as reported to the California Cancer Registry (SEER site recode 32010 or International Classification of Childhood Cancer extended classification code 093).

Thyroid cancer was classified according to the following histological subtypes by using the International Classification of Diseases for Oncology, 3rd ed. [ICD-O-3]: papillary (8050, 8052, 8130, 8260, 8340–8344, 8350, 8450, and 8452), follicular (ICD-O-3 8290, 8330–8332, and 8335), medullary (ICD-O-3 8345, 8346, and 8510), or anaplastic (ICD-O-3 8021). While the overall linkage included birth years from 1978 through 2015, none of the pediatric thyroid cancer cases were born during 2012–2015. For each case, 50 control subjects were randomly selected from children who were born in California during the same year and were not diagnosed with any childhood cancer. The study protocol was approved by the institutional review boards at the California Health and Human Services Agency (Project Number 16-06-2587), the University of California, Berkeley, and Yale University.

Demographic and birth characteristics

We abstracted numerous variables from birth records. Factors were selected because of reported associations with pediatric thyroid cancer, other childhood cancers, adult thyroid cancer, or a plausible influence on thyroid hormone levels (22–26). Variables pertaining to the characteristics of the child included: year of birth in categories (1978–1982, 1983–1987, 1988–1992, 1993–2011), sex (male, female), and race (white, Hispanic, non-White and non-Hispanic), birth weight in grams (modeled continuously per 500 g), and gestational age in weeks (22–36, 37–41, 42–44, unknown). Parental characteristics included maternal age in years (<20, 20–24, 25–29, 30–34, 35+ years), maternal education in years (≤8, 9–11, 12, 13–15, 16+, unknown years), mother's place of birth (United States, foreign), and paternal age in years (<25, 25–29, 30–34, 35–39, 40+ years). Characteristics pertaining to the birth process included: birth plurality (singleton, multiple), birth order (first, second, or third and above), mode of delivery (vaginal, Cesarean section), presence of a congenital abnormality (no, yes), history of miscarriage/stillbirth (never, ever, unknown), history of maternal complications during pregnancy (never, ever, unknown), and history of Cesarean section (never, ever, unknown).

Statistical analysis

In bivariable analyses, we compared characteristics between cases and controls by using Pearson's χ^2 test. In multivariable analyses, odds ratios (OR) and 95% confidence intervals (CI) were obtained from logistic regression models. All possible characteristics previously described were included regardless of statistical significance based on known or suspected associations with other childhood cancers. We chose the full model approach rather than a more parsimonious variable selection method, because the goal was to identify new risk factors, confounders were not known *a priori*, and effect estimates could be biased if confounders were omitted (34–36).

We modeled the full study population and conducted several subgroup analyses stratified by cancer subtype (papillary,

Table 1. Characteristics of Pediatric Thyroid Cancer Cases and Controls, Born in California During the Years 1978–2011

	Cases n = *1012*	*Controls* n = *50,600*	
	n *(%)*	n *(%)*	p-*Value*[a]
Cancer subtype			
Papillary	845 (83)	—	
Follicular	87 (9)	—	
Medullary	53 (5)	—	
Other	27 (3)	—	
Birth year			
1978–1982	131 (12.9)	6550 (12.9)	1.00
1983–1987	157 (15.5)	7850 (15.5)	
1988–1992	279 (27.6)	13,950 (27.6)	
1993–2011	445 (44.0)	22,250 (44.0)	
Age at diagnosis (years)			
0–14	315 (31.1)	—	
15–19	697 (68.9)	—	
Sex			
Female	823 (81.3)	24,565 (48.5)	<0.01
Male	189 (18.7)	26,035 (51.5)	
Race/ethnicity			
White	380 (37.5)	18,235 (36.0)	<0.01
Black	31 (3.1)	4338 (8.6)	
Hispanic	480 (47.4)	22,511 (44.5)	
Asian	116 (11.5)	4955 (9.8)	
Other	5 (0.5)	561 (1.1)	
Birth weight (g)			
250–2499	47 (4.6)	2958 (6)	0.28
2500–2999	159 (15.7)	7743 (15.2)	
3000–3499	362 (35.8)	19,015 (36.8)	
3500–3999	328 (32.4)	15,320 (30.6)	
4000+	116 (11.5)	5564 (11.3)	
Mean (std)	3393 (543)	3367 (581)	0.13
Maternal age (years)			
<20	75 (7.4)	6044 (11.9)	<0.01
20–24	249 (24.6)	13,394 (26.5)	
25–29	324 (32.0)	14,603 (28.9)	
30–34	237 (23.4)	10,924 (21.6)	
≥35	127 (12.5)	5635 (11.1)	
Maternal education (years)			
≤8	72 (7.1)	5009 (9.9)	<0.01
9–11	105 (10.4)	6439 (12.7)	
12	184 (18.2)	10,234 (20.2)	
13–15	171 (16.9)	6779 (13.4)	
16+	154 (15.2)	5840 (11.5)	
Unknown	326 (32.2)	16,302 (32.2)	
Maternal birthplace			
United States	569 (56.2)	30,538 (60.4)	<0.01
Foreign	443 (43.8)	20,062 (39.6)	
Paternal age (years)			
<25	196 (19.4)	11,813 (23.3)	<0.01
25–29	284 (28.1)	13,496 (26.7)	
30–34	244 (24.1)	11,940 (23.6)	
35–39	165 (16.3)	6650 (13.1)	
≥40	85 (8.4)	3822 (7.6)	
Unknown	38 (3.8)	2879 (5.7)	
Gestational age (weeks)			
37–41	93 (9.2)	4784 (9.5)	0.51
22–36	767 (75.8)	37,484 (74.1)	
42–44	89 (8.8)	4925 (9.7)	
Unknown	63 (6.2)	3407 (6.7)	
Birth order			
First	406 (40.1)	20,342 (40.2)	0.05
Second	347 (34.3)	15,823 (31.3)	
Third+	259 (25.6)	14,435 (28.5)	
Mode of delivery			
Vaginal	795 (78.6)	39,618 (78.3)	0.84
C-section	217 (21.4)	10,982 (21.7)	
Miscarriage/stillbirth			
Never	829 (81.9)	41,810 (82.6)	0.55
Ever	183 (18.1)	8790 (17.3)	
Pregnancy complication			
Never	835 (82.5)	41,660 (82.2)	0.91
Ever	155 (15.3)	7811 (15.5)	
Unknown	22 (2.2)	1129 (2.3)	
Previous C-section			
Never	90 (89.5)	45,367 (89.7)	0.76
Ever	89 (8.8)	4306 (8.5)	
Unknown	17 (1.7)	927 (1.8)	

[a]*p*-Value corresponds to χ^2 test.

follicular), race/ethnicity (white, Hispanic), and age at diagnosis (0–14, 15–19 years). In sensitivity analyses, models were run with and without paternal age due to the correlation between maternal and paternal ages ($r_{Spearman} = 0.76$); no other variables were strongly correlated (all other $r_{Spearman} < 0.5$). All tests were two-sided with an α of 0.05; all analyses were conducted in SAS (SAS Institute, Inc., Cary, NC).

Results

Of the 1025 children identified as having a first primary thyroid cancer, 12 (1%) were excluded due to missing information from birth records. Controls were subjected to the same exclusion criteria and were removed at a proportion similar to cases, yielding a final study population of 1012 cases and 50,600 matched controls. Of the 1012 cases with pediatric thyroid cancer, the majority were diagnosed with papillary thyroid cancer ($n = 845$, 83%) followed by follicular ($n = 87$, 9%), medullary ($n = 53$, 5%), and other ($n = 27$, 3%) (Table 1). As there were fewer cases of follicular cancer in our population, results with these subtypes are considered exploratory; there were insufficient case numbers to evaluate risk factors for medullary and anaplastic thyroid cancer.

In bivariable χ^2 tests, cases and controls differed with respect to several factors (Table 1). Cases were more likely to be female, Hispanic, and have a mother with posthigh school education; a greater proportion of controls had parents in the youngest age category. Using multivariable models with all covariates included, we observed evidence for several risk factors for pediatric thyroid cancer, as shown in Tables 2 through 4. The OR did not change more than 5% in magnitude between univariable models and the full multivariable model.

Risk factors for full study population

In regression models examining all thyroid cancer cases in the full population (Table 2), males had a substantially lower

Table 2. Odds Ratios and 95% Confidence Intervals for Birth Characteristics and Risk of Pediatric Thyroid Cancer in Cases and Controls Born in California, 1978–2011, Overall and Stratified by Subtype

	All thyroid cancer (n = 1012 cases, 50,600 controls)		*Papillary (n = 845 cases, 42,250 controls)*		*Follicular (n = 87 cases, 4350 controls)*	
	OR	*[CI]*	*OR*	*[CI]*	*OR*	*[CI]*
Sex						
Female	1.00		1.00		1.00	
Male	0.21	[0.18–0.25]	0.20	[0.17–0.24]	0.22	[0.13–0.38]
Race/ethnicity						
White	1.00		1.00		1.00	
Hispanic	1.20	[1.01–1.42]	1.20	[1.00–1.45]	0.67	[0.37–1.22]
Black	0.39	[0.27–0.57]	—			
Asian	1.03	[0.80–1.31]	—			
Other	0.48	[0.20–1.17]	—		0.87	[0.48–1.60]
Non-White/non-Hispanic			0.71	[0.57–0.89]		
Birth weight (per 500 g)	1.11	[1.04–1.18]	1.10	[1.03–1.18]	1.06	[0.86–1.31]
Gestational age (weeks)						
37–41	1.22	[0.96–1.54]	1.22	[0.95–1.57]	1.40	[0.65–3.02]
22–36	1.00		1.00		1.00	
42–44	0.88	[0.70–1.10]	0.87	[0.65–1.07]	1.57	[0.82–3.00]
Unknown	0.96	[0.74–1.25]	0.95	[0.71–1.27]	0.93	[0.39–2.22]
Maternal age (years)						
<20	0.65	[0.48–0.87]	0.62	[0.45–0.87]	0.97	[0.34–2.78]
20–24	0.89	[0.74–1.07]	0.87	[0.70–1.07]	1.05	[0.56–1.96]
25–29	1.00		1.00		1.00	
30–34	0.93	[0.78–1.12]	0.97	[0.79–1.18]	0.61	[0.30–1.24]
≥35	0.94	[0.73–1.20]	0.92	[0.70–1.20]	1.47	[0.66–3.26]
Maternal education (years)						
≤8	0.65	[0.48–0.87]	0.67	[0.49–0.91]	0.79	[0.29–2.13]
9–11	0.93	[0.72–1.19]	0.94	[0.72–1.24]	0.79	[0.31–2.01]
12	1.00		1.00		1.00	
13–15	1.35	[1.09–1.68]	1.40	[1.10–1.77]	1.32	[0.62–2.77]
16+	1.35	[1.07–1.71]	1.42	[1.10–1.84]	1.72	[0.78–3.80]
Unknown	1.07	[0.78–1.46]	1.13	[0.81–1.58]	1.04	[0.39–2.81]
Maternal birth place						
United States	1.00		1.00		1.00	
Foreign	1.18	[1.00–1.38]	1.37	[1.16–1.62]	1.01	[0.58–1.76]
Paternal age (years)						
<25	1.00	[0.79–1.28]	0.96	[0.74–1.25]	1.25	[0.54–2.92]
25–29	1.06	[0.88–1.28]	1.01	[0.83–1.25]	1.50	[0.77–2.92]
30–34	1.00		1.00		1.00	
35–39	1.23	[1.00–1.51]	1.29	[1.03–1.62]	1.33	[0.63–2.83]
≥40	1.12	[0.85–1.46]	1.18	[0.88–1.58]	0.70	[0.24–2.08]
Unknown	0.84	[0.59–1.21]	0.81	[0.55–1.20]	1.60	[0.55–4.69]
Birth order						
First	1.00		1.00		1.00	
Second	0.99	[0.84–1.15]	0.94	[0.79–1.11]	1.42	[0.80–2.50]
Third+	0.81	[0.68–0.98]	0.71	[0.58–0.87]	1.82	[0.98–3.39]
Mode of delivery						
Vaginal	1.00		1.00		1.00	
C-section	0.96	[0.80–1.15]	1.01	[0.83–1.22]	0.81	[0.42–1.58]
Miscarriage/stillbirth						
Never	1.00		1.00		1.00	
Ever	1.05	[0.89–1.24]	0.99	[0.82–1.19]	0.91	[0.52–1.61]
Maternal pregnancy complication						
Never	1.00		1.00		1.00	
Ever	1.01	[0.84–1.22]	1.03	[0.84–1.26]	0.76	[0.39–1.50]
Unknown	1.28	[0.49–3.32]	1.66	[0.63–4.38]	0.00	[0–0]
Previous C-section						
Never	1.00		1.00		1.00	
Ever	1.04	[0.79–1.28]	0.98	[0.73–1.31]	1.60	[0.69–3.72]
Unknown	0.75	[0.27–2.09]	0.55	[0.19–1.62]	0.00	[0–0]

Regression models are multivariable models with all variables listed in table included.
CI, 95% confidence intervals; OR, odds ratios.

risk of developing thyroid cancer compared with females (OR: 0.21 [CI 0.18–0.25]), confirming the well-established higher incidence among females. With respect to race and ethnicity, increased risk was observed for children of Hispanic ethnicity compared with white children (OR: 1.20 [CI 1.01–1.42]), while Black children had a decreased risk (OR: 0.39 [CI 0.27–0.57]); OR among Asian children did not differ significantly from white children. An increased risk of thyroid cancer was also observed with increasing birth weight (OR per 500 g: 1.11 [CI 1.04–1.18]).

In the full population, children whose mothers were younger at birth (<20 years) in relation to mothers of 25 to 29 years had a decreased risk of thyroid cancer (OR: 0.65 [CI 0.48–0.87]). With respect to father's age, an increased risk was seen in the paternal age category 35 to 39 years relative to 30 to 34 years (OR: 1.23 [CI 1.00–1.51], $p = 0.05$), though there was no difference in risk for the ≥40 years category (Table 2). The strongest magnitude of association with respect to parental factors was that of maternal education. Compared with children of mothers with 12 years of education, children with mothers with higher educational attainment were at an increased risk of thyroid cancer (13–15 years of education: OR: 1.35 [CI 1.09–1.68]; 16+ years: OR: 1.35 [CI 1.07–1.71]), while children of mothers with ≤8 years of education had a lower risk (OR: 0.65 [CI 0.48–0.87]). Compared with children of mothers born in the United States, those with foreign-born mothers had an elevated risk of thyroid cancer (OR: 1.18 [CI 1.00–1.38]; $p = 0.05$). Birth order was an important factor, with children being the third or higher birth having a reduced risk of thyroid cancer (0.81 [CI 0.68–0.98]).

Stratification by thyroid cancer subtype

In analyses stratified by thyroid cancer subtypes (Table 2), the associations observed for papillary thyroid cancer (which constituted 87% of all cases) mirrored those in the full population. The decreased risk in male children was clearly observed across both papillary and follicular subtypes. For the follicular thyroid cancer subtype ($n = 87$ cases), many ORs were of a similar direction and magnitude although not statistically significant, compared with those observed for the papillary subtype. However, some heterogeneity was observed. For follicular thyroid cancer, an elevated OR was observed for birth order of three or higher (OR: 1.82 [CI 0.98–3.39]), in contrast to the reduced risk for this category among papillary thyroid cancer cases (p-value for interaction = 0.01). Hispanic ethnicity was a risk factor for papillary (OR: 2.30 [CI 1.01–1.42]), but not follicular thyroid cancer (OR: 0.67 [CI 0.37–1.22], p-value for interaction = 0.07). In addition, having a foreign-born mother and maternal age were not risk factors for the follicular subtype.

Stratification by race/ethnicity

Due to small numbers in other racial and ethnic groups, we were only able to examine potential differences between white and Hispanic children. In analyses with all thyroid cancer subtypes combined, some differences in the magnitude and direction of the associations were observed when stratified by race/ethnicity, as compared with the full population (Table 3). The decreased risk in male children was robust to stratification. Increased risk for higher birth weight remained a strong risk factor in white children, but not in

Table 3. Odds Ratios and 95% Confidence Intervals for Birth Characteristics and Risk of Pediatric Thyroid Cancer in Cases and Controls Born in California, 1978–2011, Stratified by Ethnicity

	White (n = 380 cases, 7141 controls)		*Hispanic (n = 480 cases, 10,985 controls)*	
	OR	*[CI]*	*OR*	*[CI]*
Sex				
Female	1.00		1.00	
Male	0.22	[0.17–0.28]	0.23	[0.18–0.29]
Birth weight (per 500 g)	1.16	[1.04–1.29]	1.05	[0.96–1.15]
Gestational age (weeks)				
22–36	1.21	[0.80–1.85]	1.26	[0.92–1.73]
37–41	1.00		1.00	
42–44	0.85	[0.59–1.22]	0.83	[0.58–1.17]
Unknown	0.92	[0.59–1.45]	1.07	[0.73–1.57]
Maternal age (years)				
<20	0.86	[0.45–1.64]	0.61	[0.42–0.90]
20–24	1.04	[0.74–1.45]	0.90	[0.69–1.16]
25–29	1.00		1.00	
30–34	0.83	[0.62–1.12]	0.87	[0.64–1.16]
≥35	0.92	[0.62–1.36]	0.75	[0.55–1.12]
Maternal education (years)				
<12	0.70	[0.37–1.31]	0.82	[0.62–1.08]
12	1.00		1.00	
13–15	1.18	[0.82–1.71]	1.58	[1.15–2.16]
16+	1.33	[0.92–1.92]	1.60	[1.04–2.45]
Unknown	0.91	[0.52–1.58]	1.20	[0.75–1.92]
Mother's place of birth				
United States	1.00		1.00	
Foreign	1.25	[0.90–1.73]	1.05	[0.86–1.29]
Paternal age (years)				
<25	0.66	[0.42–1.04]	1.07	[0.77–1.49]
25–29	0.92	[0.68–1.25]	1.06	[0.80–1.41]
30–34	1.00		1.00	
35–39	1.09	[0.79–1.51]	1.29	[0.91–1.83]
≥40	1.10	[0.73–1.66]	1.09	[0.69–1.73]
Unknown	0.75	[0.37–1.51]	0.78	[0.47–1.29]
Birth order				
First	1.00		1.00	
Second	1.00	[0.78–1.29]	0.80	[0.63–1.02]
Third+	0.95	[0.70–1.29]	0.73	[0.56–0.96]
Mode of delivery				
Vaginal	1.00		1.00	
C-section	1.14	[0.86–1.51]	0.89	[0.67–1.17]
Miscarriage/stillbirth				
Never	1.00		1.00	
Ever	1.17	[0.90–1.51]	1.02	[0.79–1.33]
Maternal pregnancy complication				
Never	1.00		1.00	
Ever	1.12	[0.83–1.50]	0.79	[0.58–1.06]
Unknown	1.10	[0.30–4.06]	2.59	[0.51–13.05]
Previous C-section				
Never	1.00		1.00	
Ever	0.87	[0.56–1.35]	1.11	[0.74–1.65]
Unknown	0.73	[0.19–2.79]	0.44	[0.07–2.65]

Regression models are multivariable models with all variables listed in table included.

Hispanic children. The reduced risk with higher birth order and younger maternal age were only observed among Hispanic children. More advanced maternal education was associated with increased thyroid cancer risk in Hispanic children; the OR for mothers attaining more than 16 years of education was elevated in white children, though not statistically significant. None of these differences were statistically significant interactions with ethnicity.

Stratification by age at diagnosis

Associations were similar between the two groups of age at diagnosis (0–14 and 15–19 years) and with all subtypes combined (Table 4). However, ORs tended to be statistically significant in the 15–19 years age group, which had twice as many cases as the 0–14 years ($n=697$ vs. $n=315$ cases). Male sex, increasing birth weight, both more advanced maternal education, and having a foreign-born mother were associated with increased thyroid cancer risk across both groups. Lower maternal education and younger maternal age were linked to a lower risk. A few variations were noted, although none yielded statistically significant interactions. In the 0–14 years age group, younger and older paternal age were associated with an increased risk of thyroid cancer. In the 15–19 years age group, reduced ORs were observed for higher birth order.

Discussion

To our knowledge, this is the largest and among the first population-based studies to examine the association between numerous birth characteristics and pediatric thyroid cancer, and we identified several intriguing risk factors. Overall, associations of increased risk of thyroid cancer were observed for higher birth weight, higher maternal educational attainment, Hispanic ethnicity, and having a mother born outside the United States. Reduced risks were observed for males, young maternal age, lower maternal education attainment, and higher birth order. Some heterogeneity was observed, particularly with respect to subtype. This provides new information on some factors that may be involved in the pathophysiology of thyroid cancer in children.

For childhood cancers, incidence is typically higher among males, though the biological mechanisms underlying these sex disparities are not understood (18). Thyroid cancer is one of the few childhood cancers for which females have a higher incidence (37). In adults, the incidence of thyroid cancer is approximately three times higher in women compared with men worldwide (11,13). Previous reports have observed that the sex disparities were most pronounced after puberty and during the reproductive years, leading to speculation that hormonal changes at the time of puberty could be an underlying factor (38,39). However, we observed that the magnitude and significance of female preponderance was consistent across even the youngest age groups, as well as for all races/ethnicities, and thyroid cancer subtypes.

The consistent sex differences across age groups may suggest that differences in sex hormones beginning in early life may be a driver of this outcome. The observed sex disparity in incidence could also be due to differences at the genetic or molecular levels, such as differences in expression of enzymes that detoxify environmental chemical exposures (40). There may be connections to the predisposition of females to autoimmune thyroid diseases, such as Graves' disease or Hashimoto's disease (41), including among pediatric patients (42) who are hypothesized to have origins related to hormonal factors or genetic factors, including the presence of immune-related genes on the X chromosome (43). Exploration of a shared mechanism in future work may be warranted.

Our diverse study population enabled us to provide new information about disparities in pediatric thyroid cancer incidence with respect to Hispanic ethnicity. Specifically, we observed Hispanic ethnicity to be a risk factor for thyroid cancer overall and for papillary thyroid cancers. This is consistent with observed higher incidences of overall child and adolescent cancers in Hispanic populations (18). This could partially reflect underlying differences in genetic susceptibility or differences in environmental exposures (e.g., thyroid hormone disrupting chemicals), though information in Hispanic populations is limited for both factors (44,45). Black children and adolescents had reduced odds of thyroid cancer, also consistent with reports from other childhood cancers (18), and a descriptive analysis specifically of pediatric thyroid cancer in 39 U.S. states using data from the North American Association of Central Cancer Registries (1). Maternal birth place was also associated with an increased risk of pediatric thyroid cancer overall and among white, but not Hispanic, children. Therefore, birth place may be a reflection of health care access and utilization, culture, reproductive history, and environmental exposures (46,47). Consideration of differences with respect to birth place and race/ethnicity may provide insights into etiology.

Our analysis provides the first evidence of a link between birth weight and pediatric thyroid cancer. Higher birth weight has been implicated in the etiology of other childhood cancers (23,48). The mechanism is unclear, but it could include accelerated fetal growth leading to increased risk of mutations or abnormal methylation patterns, or genetic polymorphisms or epigenetic signatures associated with fetal growth and cancer risk (48,49). Upstream maternal factors that may influence birth weight are numerous and complex and include maternal thyroid function, maternal body composition, nutrition, smoking, alcohol consumption, and environmental exposures. The observed association between birth weight and thyroid cancer could be confounded by these maternal factors. It is also possible that birth weight acted as a mediator of the association between these maternal factors and thyroid cancer.

Birth weight has also been positively associated with cord TSH concentrations and free thyroxine (T4) concentrations (50,51). The importance of this observation is underscored, because weight at birth has recently been associated with thyroid cancer in adults in studies conducted in Denmark (24,52). These observations are consistent with evidence from other hormone-related cancers. For example, many studies of birthweight and subsequent breast cancer risk in adulthood suggest a positive relationship, particularly for younger women (53). In addition, adult body mass index has been established as a risk factor for adult thyroid cancer (54). One other study of birth-related factors found no association between pediatric thyroid cancer (≤14 years) and birth weight ($n=159$ cases) (22).

Younger maternal age was associated with a decreased risk, while advanced material age was not generally associated with an increased risk of pediatric thyroid cancer. Advanced maternal age has been identified as a risk factor for

Table 4. Adjusted Odds Ratios and 95% Confidence Intervals of Child, Parental, and Birth Characteristics and Risk of Pediatric Thyroid Cancer in Cases and Controls Born in California, 1978–2011, Stratified by Age Group

	0–14 years (n = 315 cases, 15,750 controls)		*15–19 years (n = 697 cases, 34,850 controls)*	
	OR	*[CI]*	*OR*	*[CI]*
Sex				
Female	1.00		1.00	
Male	0.29	[0.22–0.38]	0.18	[0.14–0.22]
Race/ethnicity				
White	1.00		1.00	
Hispanic	1.21	[0.89–1.63]	1.18	[0.96–1.45]
Non-White, non-Hispanic	0.73	[0.50–1.06]	1.01	[0.75–1.35]
Birth weight (per 500 g)	1.15	[1.03–1.28]	1.09	[1.01–1.17]
Gestational age (weeks)				
37–41	1.34	[0.89–2.01]	1.15	[0.87–1.53]
22–36	1.00		1.00	
42–44	1.06	[0.72–1.56]	0.80	[0.61–1.05]
Unknown	1.03	[0.60–1.62]	0.95	[0.69–1.31]
Maternal age (years)				
<20	0.69	[0.40–1.19]	0.61	[0.43–0.87]
20–24	1.06	[0.76–1.47]	0.80	[0.64–1.01]
25–29	1.00		1.00	
30–34	0.92	[0.65–1.31]	0.96	[0.77–1.19]
≥35	1.04	[0.66–1.63]	0.92	[0.69–1.24]
Maternal education (years)				
≤8	0.68	[0.41–1.12]	0.61	[0.43–0.87]
9–11	0.72	[0.46–1.13]	1.02	[0.75–1.38]
12	1.00		1.00	
13–15	1.41	[0.98–2.03]	1.34	[1.03–1.75]
16+	1.61	[1.08–2.40]	1.32	[0.99–1.77]
Unknown	0.80	[0.42–1.53]	1.18	[0.82–1.68]
Mother's birth place				
United States	1.00		1.00	
Foreign	1.24	[0.95–1.62]	1.39	[1.15–1.67]
Paternal age (years)				
<25	1.57	[1.02–2.43]	0.82	[0.62–1.10]
25–29	1.67	[1.17–2.37]	0.87	[0.70–1.09]
30–34	1.00		1.00	
35–39	1.30	[0.87–1.96]	1.21	[0.94–1.54]
≥40	1.44	[0.89–2.33]	0.98	[0.71–1.36]
Unknown	0.96	[0.49–1.88]	0.79	[0.52–1.21]
Birth order				
First	1.00		1.00	
Second	1.04	[0.78–1.38]	0.95	[0.79–1.15]
Third+	0.91	[0.66–1.26]	0.75	[0.60–0.93]
Mode of delivery				
Vaginal	1.00		1.00	
C-section	1.15	[0.85–1.57]	0.87	[0.70–1.09]
Miscarriage/stillbirth				
Never	1.00		1.00	
Ever	0.97	[0.72–1.33]	1.07	[0.88–1.30]
Maternal complication during pregnancy				
Never	1.00		1.00	
Ever	0.92	[0.66–1.28]	1.05	[0.84–1.31]
Unknown	1.60	[0.33–7.86]	1.20	[0.36–4.05]
Previous C-section				
Never	1.00		1.00	
Ever	0.92	[0.58–1.46]	1.09	[0.79–1.51]
Unknown	0.40	[0.06–2.57]	0.90	[0.25–3.25]

Regression models are multivariable models with all variables listed in table included.

other childhood cancers, including thyroid cancer (22) and childhood leukemia (55,56). Older maternal age is associated with lower free T4 concentrations, which may also have some correlation with birth order (25). Older maternal age could represent socioeconomic status, lifestyle choices, or fertility issues. Another potential explanatory mechanism is the increased prevalence of chromosomal abnormalities and birth defects among children born to older mothers (56). It is also hypothesized that older mothers may have had a greater cumulative exposure to environmental pollutants known to dysregulate thyroid hormones (57–59), which can be transferred to the child *in utero* through placental transfer (60) and postnatally via breast milk (61).

Higher maternal educational attainment was associated with an increased risk of thyroid cancer in our study. Higher maternal education has been positively associated with other common childhood cancers, such as acute lymphoblastic leukemia, lymphomas, and central nervous system tumors, as reported in a previous analysis in the state of California (62), and population-based studies from other countries (63,64). Maternal education is frequently used in epidemiologic studies as a proxy for socioeconomic status, as it is believed to reflect familial intellectual assets and factors such as occupation and income (64). Maternal education could also reflect other factors related to cancer risk, such as nutritional status, compliance with infant immunization schedules, and breastfeeding, or factors related to diagnosis such as greater access to health care and screening (65,66). In addition, maternal education may be associated with certain occupational or environmental exposures, such as to polybrominated flame retardants (67), which have been hypothesized to play a role in thyroid cancer.

The association between maternal education and other child cancers is sometimes attenuated after adjustment with other socioeconomic or risk factors, such as race/ethnicity and parental age, and the direction of the association is not always consistent (68). The interplay between maternal age and maternal education may be difficult to disentangle. Younger (<20 years) mothers are both less common and more limited as to their educational attainment; for example, a 16-year-old mother could only have $\sim$10 years of education. However, these two variables were only weakly correlated in our population ($r_{Spearman} = 0.35$). Overall, maternal education is a complex variable potentially capturing many factors and its role in risk of childhood thyroid cancer is poorly understood and needs to be studied further.

Birth order has been associated with other childhood cancers, such as leukemia, although relationships have been inconsistent (69). In our analysis, higher birth order yielded a reduced risk of papillary thyroid cancer, but an increased risk of follicular thyroid cancer. Birth order may be linked to differences in hormone levels, because later pregnancies tend to have lower levels of estrogen and progesterone (70). Moreover, neonates of nulliparous women tend to have higher TSH concentrations and lower T4 concentrations compared with babies of a higher birth order (25,71), which could influence their thyroid cancer risk. This could be due to increased stress associated with first pregnancies in nulliparous women (72) and the subsequent impact of stress on thyroid hormone levels (73). It could also be that children with higher birth order may be exposed to lower concentrations of thyroid hormone disrupting contaminants *in utero* or during breastfeeding, as environmental chemicals may have been transferred to the children born earlier (74). For example, concentrations of the thyroid hormone disrupting chemicals, perfluoroalkylated substances, were significantly lower in women who breastfed for at least six months compared with those who had not breastfed and in women with two or more children compared with nulliparous women (75).

Delivery method was not associated with pediatric thyroid cancer, although studies have reported higher concentrations of umbilical cord TSH in neonates born by vaginal delivery compared with Cesarean section (25,50,71,73,76). These observations are hypothesized to be related to stress during vaginal delivery, such as the downregulating effect of stress on thyroid hormone distributor proteins subsequently altering circulating thyroid hormone levels (50,73).

The strengths of this study include a large sample size (>1000 cases), a racially and ethnically diverse population, and detailed individual-level information on multiple potential risk factors. The record-linkage design obviated the need for participant contact and therefore all eligible subjects were included, leading to a low probability of selection bias that may arise with low response rates and loss to follow-up. The study design leveraged the appropriate temporal relationship by examining factors present at birth with the subsequent incidence of thyroid cancer. Information was ascertained from birth records, and no recall was needed.

In terms of limitations, we were constrained by data available on the birth records and therefore did not have information on environmental exposures, or the occupation, diet, and physical activity of the parents. We were not able to adjust for socioeconomic status, which could change the results for maternal education, parental age, birth order, and race/ethnicity. We also had limited information on the father's characteristics. It is also possible that some controls moved out of California after birth and developed thyroid cancer in another state, which would not be captured in our database. However, because pediatric thyroid cancer is a rare malignancy, only four children would have been expected to develop thyroid cancer from among the 50,600 controls if they were followed until age 19 years, based on age-adjusted incidence rates. In addition, there is no reason to believe that the likelihood of misclassifying actual cases as controls would be different based on a child's birth characteristics, and nondifferential misclassification would have biased the risk estimates toward the null.

Our CALSEC dataset captures more than 70% of all pediatric thyroid cancer cases diagnosed in California, yielding a sizable population. The majority of the 30% of cases not included were born outside of California, are not part of the source population, and are not eligible for this study. As such, the validity of this study is not compromised. Finally, there is the possibility that some observed associations could have been false positives occurring by chance, given the testing of multiple risk factors in the absence of an *a priori* hypothesis. Alternatively, residual confounding by unmeasured factors is possible. For example, the observed association between birth weight and risk of pediatric thyroid cancer may be influenced by maternal weight gain during pregnancy and gestational diabetes, which we were unable to assess.

In conclusion, pediatric thyroid cancer is on the rise, but knowledge of risk factors remains extremely limited. In this large nested case-control study, we report on several newly identified risk factors for pediatric thyroid cancer. Except for female sex, many of the observed risk factors are also

associated with other pediatric cancers, suggesting common pathways across multiple cancer sites in children. This work provides new areas for replication and investigation of biological mechanisms.

Disclaimer

The ideas and opinions expressed herein are those of the author(s), and endorsement by the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is neither intended nor should be inferred. This study used birth data obtained from the State of California Center for Health Statistics and Informatics. The California Department of Public Health is not responsible for the analyses, interpretations, or conclusions drawn by the authors regarding the birth data used in this publication.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

This research was buoyed by the American Cancer Society (ACS) grants RSGM-10-038-01-CCE and 127509-MRSG-15-147-01-CNE. The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute); and the Centers for Disease Control and Prevention's National Program of Cancer Registries (agreement U58DP003862-01 awarded to the California Department of Public Health).

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