Research Article

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Hormonal Factors and the Risk of Papillary Thyroid Cancer in the California Teachers Study Cohort

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Abstract

Background: Despite the increasing incidence of thyroid cancer, there is limited information on its etiology. The strikingly higher rates in young women, compared with men, suggest that sex steroid hormones may be involved in the development of this disease.

Methods: We investigated the effects of menstrual, reproductive, and other hormonal factors on papillary thyroid cancer risk in the prospective California Teachers Study cohort. Among 117,646 women, 233 were diagnosed with invasive histologically confirmed papillary thyroid cancer after cohort enrollment and before January 1, 2008. Relative risks (RR) and 95% CIs were estimated by using Cox proportional hazards regression models.

Results: Among younger women (age <45 years at baseline; approximately one-third of the cohort), but not older women, later age at menarche (age ≥14 years) was associated with increased risk (RR = 1.88, 95% CI: 1.13–3.13; $p_{interaction}$ by age = 0.06). Risk was also increased among young women who had longer (>30 days) adolescent menstrual cycles (RR = 1.78, 95% CI: 1.01–3.14) and whose last pregnancy had ended within five years of cohort enrollment (RR = 2.21, 95% CI: 1.13–4.34). Among older women (age ≥45 years at baseline), ever use of estrogen-only therapy was associated with a statistically nonsignificant increase in risk (RR = 1.69, 95% CI: 0.95–2.98).

Conclusions: The findings from this prospective analysis suggest that several factors related to delayed pubertal development and the transient effects of pregnancy may be particularly important in influencing risk in young women.

Impact: These results suggest the importance of future research into the role of progesterone and the estrogen-to-progesterone ratio. *Cancer Epidemiol Biomarkers Prev; 20(8); 1751–9. ©2011 AACR.*

Introduction

Thyroid cancer incidence has increased substantially over the last decade (1). It is now the seventh most commonly occurring cancer in U.S. women, and the second most common among young women (ages 20–44 years; ref. 1). Overall, thyroid cancer is 3 times more common in women than men, with the greatest gender differences observed between the ages of 25 and 64 (1). Yet, with the exception of radiation exposure and a personal or family history of proliferative thyroid disease (2–4), its causes are still largely unestablished. The striking gender differences in incidence strongly suggest that sex steroid hormones may be involved in the development of this disease. A large pooled analysis of case–control studies found only weak associations between thyroid cancer and several menstrual and reproductive factors, such as later age at menarche, miscarriages, and parity (5). Examination of more complex relationships, such as those that reflect exposure to estrogens unopposed by progesterone (e.g., irregular menstrual cycles), may provide additional information. Indeed, several more recent studies have suggested that irregular menstrual cycles and a pregnancy within the 5 years prior to diagnosis increase risk in young women (6–12).

We investigated the effects of various aspects of menstrual and reproductive factors on papillary thyroid cancer risk in the prospective California Teachers Study (CTS) cohort. Papillary thyroid cancer, including its variant mixed papillary/follicular, is the most common type of thyroid cancer accounting for about 80% to 85% of all thyroid cancers in iodine sufficient, nonendemic goiter areas, including California. Because the etiology of thyroid cancer is likely to differ by histologic type, we focus here on tumors with papillary components only.

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Material and Methods

Study population and data collection

The CTS cohort was established in 1995–96 when 133,479 active and retired female teachers and administrators participating in the California State Teachers Retirement System returned a mailed self-administered questionnaire covering a wide variety of issues related to women's health, including extensive questions on menstrual and reproductive histories and use of exogenous hormones (13). Exposure data used in this analysis are based on responses to this baseline questionnaire. Cohort member were excluded (sequentially) from this analysis if they did not reside in California at baseline ($n = 8{,}867$); restricted their participation to breast cancer research ($n = 18$); reported having been diagnosed with thyroid cancer before completing the baseline questionnaire, were identified by the California Cancer Registry (CCR) as having had a previous thyroid cancer, or did not adequately complete items related to a history of thyroid cancer ($n = 1{,}219$); or were age 80 years or older at baseline ($n = 5{,}729$). Of the 117,646 women included in this analysis, 233 were diagnosed with invasive histologically confirmed papillary thyroid cancer (ICD-O-3 site code: C73.9; histology codes: 8050, 8260, 8340–8344, and 8350) after joining the cohort and before January 1, 2008. Women diagnosed with other histologic types of thyroid cancer or *in situ* thyroid cancer, and women who moved out of California or died before January 1, 2008 were censored at the date of the first of these events.

The CTS has been approved by the Institutional Review Boards of the State of California, the Cancer Prevention Institute of California (formerly the Northern California Cancer Center), the City of Hope, the University of Southern California, and the University of California, Irvine.

Follow-up

The CTS cohort is followed annually for cancer diagnoses, death, and changes of address. Annual linkage between the CCR and the cohort membership is used to identify incident cancers occurring among cohort members. The CCR is a population-based cancer registry that is anchored in legislation that mandates reporting. It covers the state of California, has interstate agreements with 13 other states for case-sharing purposes, is estimated to be over 99% complete (14), and is part of the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program. Thus, follow-up for cancer outcomes among cohort members residing in California is virtually complete.

Linkage between the CTS cohort and the CCR database is based on full name, date of birth, address, and social security number and includes manual review of possible matches. Linkages with mortality files, the Social Security death masterfile, and the National Death Index are used to ascertain date and cause of death. Changes of address are obtained by annual mailings, responses from participants, and record linkages with multiple sources, including the US Postal Service National Change of Address database.

Data analysis

Follow-up time was calculated as the number of days between cohort enrollment (i.e., the date the baseline questionnaire was completed) and either the date of invasive papillary thyroid cancer diagnosis, the diagnosis of another type of invasive thyroid cancer or any type of *in situ* thyroid cancer, the date of death, the date (or estimated date) the woman moved out of California, or December 31, 2007, whichever came first. Relative risks (RR; hazard rate ratios) and 95% CIs were estimated by using Cox proportional hazards regression models with age (in days) as the timescale and stratified by age at baseline (in years). As specified in the tables, RRs were adjusted for race/ethnicity (white, non-white, and missing), family history of thyroid cancer in a first degree relative (parent, sibling, or child; yes, no, and adopted/missing), age at menarche (<14 years, $\geq$14 years, and never menstruated/missing), length of adolescent menstrual cycle and time until periods became regular (cycle $\leq$30 days, cycle >30 days with irregular periods for <5 years, cycle >30 days with irregular periods for $\geq$5 years, periods never became regular, never menstruated/missing), years between last pregnancy and joining the cohort ($\leq$5 years, >5 years, never pregnant, and missing), smoking history (never, ever, and missing), alcohol consumption in the year before baseline (nondrinker, <10 g/d, $\geq$10 g/d, and missing), average lifetime (high school to age 54 years or age at joining the cohort if younger than 54 years) moderate and strenuous recreational physical activity (inactive, $\leq$1 h/wk; active, >1 h/wk; missing) and height (<67 inches, $\geq$67 inches, and missing). These covariates were included on the basis of their independent association with risk in our cohort and prior knowledge of thyroid cancer risk factors; variable definitions were chosen which best described the relationship with risk while preserving parsimony. Results are presented for all women combined and separately, for younger (age at baseline <45 years) and older women (age at baseline $\geq$45 years). These age cut-points were chosen for comparability with previous studies, which have suggested age differences in risk factors (8, 10–12), to correspond with the peak of the age-specific incidence curve for papillary thyroid cancer (11), and to reflect the reproductive period.

Likelihood ratio tests for interaction between age at baseline (<45 years vs. $\geq$45 years) and the reproductive and menstrual factors of interest were computed on the basis of comparing models with and without cross-product terms separately for each of the main effect variables; main effect variables were dichotomized in these models. The proportional hazards assumption for each adjustment variable and main effect was evaluated by using a likelihood ratio test of interaction with the age

time-scale (continuous) on the basis of cross-product terms. There were no violations of the proportional hazards assumption for any of the main effects or adjustment variables.

Results

Table 1 presents the distributions of the factors of interest and potential confounders included in the present analysis for the analytic cohort as a whole and stratified by age at baseline (<45 years and ≥45 years). Twenty-nine percent of the cohort was under age 45 at the time of joining the cohort. Compared with older women, women under age 45 were more likely to be of non-white race/ethnicity, to ever have used oral contraceptives (OC), and to be nulliparous, nonsmokers, non- or light alcohol drinkers, taller, and engage in recreational physical activity. Among older women, more than 50% had used hormone therapy (HT).

Table 2 presents the associations between menstrual factors, use of OCs, HT, and papillary thyroid cancer risk. Later menarche was associated with increased risk of papillary thyroid cancer among younger women (RR = 1.88, 95% CI: 1.13–3.13 for age ≥14 compared with <14 years), but not among older women (RR = 1.01, 95% CI: 0.69–1.48, $p_{interaction} = 0.06$). Younger women who reported experiencing longer (>30 days) menstrual cycles during adolescence were also at greater risk (RR = 1.78, 95% CI: 1.01–3.14) than those reporting shorter cycles, but no such association was observed among older women (RR = 1.21, 95% CI: 0.75–1.95, $p_{interaction} = 0.36$). Additional adjustment for body mass index at age 18 did not affect these estimates. Joint examination of the timing of menarche and adolescent cycle length among younger women showed that, compared with women with earlier menarche and shorter cycle length, women who experienced later menarche and had longer cycle length were at increased risk of papillary thyroid cancer (RR = 3.78, 95% CI: 1.67–8.56), whereas women with later menarche and shorter cycle length (RR = 1.61, 95% CI: 0.85–3.06) or women with earlier menarche and longer cycle length (RR = 1.34, 95% CI: 0.62–2.90) were not. However, the interaction between age at menarche and cycle length was not statistically significant ($p_{interaction} = 0.37$). To further examine the effects of irregular menstrual periods during adolescence, we constructed a variable reflecting both cycle length and how quickly periods of a girl became regular following menarche (Table 2). Among women reporting an adolescent cycle length of 30 days or less, 94% reported having regular periods within 5 years of menarche. Among women with longer adolescent cycles, those whose cycles continued to be irregular for more than 5 years were at increased risk of developing papillary thyroid cancer (RR = 1.92, 95% CI: 1.07–3.47); this finding was similar for both younger and older women. However, women who reported never having had regular cycles were not at substantially increased risk.

Among younger women, OC use, and among older women, use of estrogen-alone therapy (ET), but not combined estrogen–progesterone therapy (EPT), were associated with some elevation in risk of papillary thyroid cancer; however, these estimates did not reach statistical significance (Table 2). For OC use, no trend was observed by duration of use (Table 2) or recency of use (data not shown). Because the prescription of ET alone is often restricted to women who have had an oophorectomy, we additionally evaluated the risk of thyroid cancer because of HT by adjusting for and stratifying by oophorectomy status to assess confounding and effect modification, respectively. Neither of these procedures substantially changed the risk estimates associated with the various types of HT use, although the number of cases with oophorectomy was small and the risk estimates in this stratum were unstable (data not shown). Combining those who used only ET with those who used ET followed by EPT, the RR for ever use of ET was 1.69 (95% CI: 0.95–2.98). Among younger women, but not older women, having had an oophorectomy (either unilateral or bilateral) was associated with a statistically nonsignificant elevation in risk (RR = 2.02, 95% CI: 0.79–5.15 and RR = 1.03, 95% CI: 0.70–1.53 for women age <45 and ≥45 at baseline, respectively; $p_{interaction} = 0.20$). Among older women, those who were premenopausal at baseline were also at a statistically nonsignificant increased risk (RR = 1.64, 95% CI: 0.84–3.18; Table 2).

Table 3 presents the associations between reproductive history and papillary thyroid cancer. Most factors were not associated with risk in either minimally adjusted or fully adjusted models. Among younger women (i.e., those of reproductive age at baseline), however, we observed a statistically significant increased risk among those whose last pregnancy had ended within 5 years of cohort enrollment (RR = 2.28, 95% CI: 1.16–4.45), relative to those whose pregnancies had occurred further in the past. Splitting follow-up time into 2 periods, less than 7 and 7 or more years, the effects associated with a recent pregnancy were generally similar for the earlier and later follow-up periods (RR = 2.53, 95% CI: 0.95–6.77 and RR = 2.07, 95% CI: 0.82–5.22, respectively). Because of small numbers, we were unable to examine these associations within finer subgroups defined by either age at baseline or follow-up time.

Discussion

In this prospective study, we observed independent associations between papillary thyroid cancer and hormonal exposures during adolescence and early adulthood, including later age at menarche, longer menstrual cycle length during adolescence, and a recent pregnancy among younger women. Similar associations were not observed among older women, although risk was somewhat elevated among women who ever used menopausal ET, a finding that was not attributable to having had an oophorectomy.

Table 1. Characteristics of the CTS cohort included in the present analysis ($n = 117,646$)

	All women *n* (%)	Age at baseline <45 y *n* (%)	Age at baseline ≥45 y *n* (%)
Age (y) at baseline			
<35	12,737 (11)	12,737 (37)	
35–44	21,437 (18)	21,437 (63)	
45–54	36,399 (31)		36,399 (44)
55–64	23,440 (20)		23,440 (28)
65–74	17,822 (15)		17,822 (21)
≥75	5,811 (5)		5,811 (7)
Race/ethnicity			
White, non-Latina	101,549 (86)	27,789 (81)	73,760 (88)
Non-white (including Latina)	15,172 (13)	6,157 (18)	9,015 (11)
Not stated	925 (1)	228 (1)	697 (1)
Family history of thyroid cancer (1st degree relative)			
Yes	1,605 (1)	418 (1)	1,187 (1)
No	112,394 (96)	32,572 (95)	79,822 (96)
Adopted/missing	3,647 (3)	1,184 (3)	2,463 (3)
Age at menarche (y)			
<12	26,480 (23)	7,409 (22)	19,071 (23)
12–13	66,049 (56)	19,588 (57)	46,461 (56)
≥14	23,513 (20)	6,892 (20)	16,621 (20)
Never menstruated/missing	1,604 (1)	285 (1)	1,319 (2)
Adolescent cycle length and time to regular menstruation			
≤30 days	94,531 (80)	26,298 (77)	68,233 (82)
>30 days			
Irregular periods <5 y	9,204 (8)	3,483 (10)	5,721 (7)
Irregular periods ≥5 y	2,931 (2)	1,115 (3)	1,816 (2)
Never had regular periods	7,627 (6)	2,409 (7)	5,218 (6)
Never menstruated/missing	3,353 (3)	1,869 (3)	2,484 (3)
OC use			
Never	35,370 (30)	5,664 (17)	29,706 (36)
<5 y duration	35,147 (30)	12,496 (37)	22,651 (27)
≥5 y duration	40,410 (34)	14,235 (42)	26,175 (31)
Never menstruated/missing	6,719 (6)	1,779 (5)	4,940 (6)
Menopausal status and HT use			
Premenopausal	47,854 (41)	32,024 (94)	15,830 (19)
Peri/postmenopausal			
Never used HT	13,880 (12)	220 (1)	13,660 (16)
Used E-only[a]	17,918 (15)	392 (1)	17,526 (21)
Used E+P only[a]	20,895 (18)	433 (1)	20,462 (25)
Other HT use	7,576 (6)	112 (<1)	7,464 (9)
Never menstruated/missing	9,523 (8)	993 (3)	8,530 (10)
Outcome of first pregnancy			
Full-term birth	70,055 (60)	14,773 (43)	55,282 (66)
Miscarriage	9,547 (8)	2,601 (8)	6,946 (8)
Abortion	10,870 (9)	5,812 (17)	5,058 (6)
Ectopic	596 (1)	199 (1)	397 (<1)
Currently primigravid	157 (<1)	156 (<1)	1 (<1)
Never pregnant	23,818 (20)	9,979 (29)	13,839 (17)
Missing	2,603 (2)	654 (2)	1,949 (2)

(Continued on the following page)

Table 1. Characteristics of the CTS cohort included in the present analysis (n = 117,646) (Cont'd)

	All women *n* (%)	Age at baseline	
		<45 y *n* (%)	≥45 y *n* (%)
Parity			
Nulliparous	30,909 (26)	13,407 (39)	17,502 (21)
1–2	56,054 (48)	16,281 (48)	39,773 (48)
≥3	28,587 (24)	4,002 (12)	24,585 (29)
Missing	2,096 (2)	484 (1)	1,612 (2)
Age at first full-term pregnancy (y)			
<25	30,966 (26)	4,428 (13)	26,538 (32)
25–29	34,376 (29)	9,109 (27)	25,267 (30)
≥30	19,298 (16)	6,745 (20)	12,553 (15)
Nulliparous	30,909 (26)	13,407 (39)	17,502 (21)
Missing	2,097 (2)	485 (1)	1,612 (2)
Years since last pregnancy			
≤5 (including currently pregnant)	11,594 (10)	11,020 (32)	574 (1)
>5	80,132 (68)	12,688 (37)	67,444 (81)
Never pregnant	23,818 (20)	9,979 (29)	13,839 (17)
Missing	2,102 (2)	487 (1)	1,615 (2)
Smoking			
Ever	39,681 (34)	6,771 (20)	32,910 (39)
Never	77,285 (66)	27,236 (80)	50,049 (60)
Missing	680 (1)	167 (<1)	513 (1)
Alcohol consumption (g/d)			
None	37,230 (32)	11,437 (33)	25,793 (31)
<10	40,829 (35)	12,530 (37)	28,299 (34)
≥10	33,675 (29)	8,141 (24)	25,534 (31)
Missing	5,912 (5)	2,066 (6)	3,846 (5)
Average lifetime physical activity[b]			
Inactive	19,665 (17)	2,730 (8)	16,935 (20)
Active	97,316 (83)	31,347 (92)	65,969 (79)
Missing	665 (1)	97 (<1)	568 (1)
Height (inches)			
<65	56,241 (48)	14,901 (44)	41,340 (50)
66–67	32,039 (27)	9,111 (27)	22,928 (27)
≥67	29,001 (25)	10,115 (30)	18,886 (23)
Missing	365 (<1)	47 (<1)	318 (<1)

[a]E-only: estrogen-only; E+P: estrogen plus progesterone.

[b]On the basis of average lifetime (high school to age 54) strenuous and moderate activity: ≤1 h/wk (inactive) versus >1 h/wk (active).

The substantially greater incidence of thyroid cancer in women compared with men and the peak incidence during the reproductive years in women has led to the investigation of the influence of menstrual and reproductive events in several previous studies, including the international pooled analysis of 14 case–control studies with data on almost 1,800 women with papillary thyroid cancer (15). Individually, the studies included in this pooled analysis had found conflicting and often weak results. However, it had been observed that aspects of pubertal development and, particularly among younger women (age < 45 years), parity increased a woman's risk of developing thyroid cancer in most studies (6–8, 11, 12). In the pooled analysis, weak associations were observed between increased thyroid cancer risk and later age at menarche, having had a miscarriage (particularly as the outcome of the first pregnancy), and having had a full-term pregnancy, but no association was observed for age at first and last birth (5). More recent studies have consistently suggested that the critical aspect of parity may be an elevation in risk during the 5 years following a pregnancy, particularly when a subsequent pregnancy occurs during that period, but with risk diminishing thereafter (8–11). The findings from this prospective study are

Table 2. Menstrual factors, hormone use, and papillary thyroid cancer risk in the CTS cohort

	All women		Age at baseline			
			<45 y		≥45 y	
	Cases	RR[a] (95% CI)	Cases	RR[a] (95% CI)	Cases	RR[a] (95% CI)
Age at menarche (y)[b]						
<14	174	1.0	46	1.0	128	1.0
≥14	56	1.24 (0.91–1.68)	23	1.88 (1.13–3.13)	33	1.01 (0.69–1.48)
Adolescent cycle length and time to regular menstruation[c]						
≤30 d	174	1.0	48	1.0	126	1.0
>30 d	36	1.42 (0.99–2.03)	16	1.78 (1.01–3.14)	20	1.21 (0.75–1.95)
Irregular periods <5 y	23	1.23 (0.80–1.91)	11	1.69 (0.87–3.26)	12	0.99 (0.54–1.79)
Irregular periods ≥5 y	12	1.92 (1.07–3.47)	5	2.12 (0.84–5.37)	7	1.76 (0.82–3.78)
Never had regular periods[d]	16	1.15 (0.69–1.93)	5	0.98 (0.38–2.48)	11	1.23 (0.66–2.28)
OC use[c]						
Never	56	1.0	9	1.0	47	1.0
Ever	170	1.06 (0.75–1.50)	61	1.51 (0.73–3.11)	109	0.90 (0.60–1.36)
<5 y duration	88	1.22 (0.83–1.78)	32	1.80 (0.84–3.84)	56	1.02 (0.65–1.60)
≥5 y duration	78	0.95 (0.64–1.40)	29	1.40 (0.65–3.04)	49	0.78 (0.49–1.25)
Menopausal status and HT use[b,c]						
Premenopausal					51	1.64 (0.84–3.18)
Peri/postmenopausal						
Never used HT					16	1.0
Only used E alone[e]					33	1.68 (0.92–3.05)
Only used E+P[e]					30	1.07 (0.57–1.98)
Used both types of HT					14	1.71 (0.83–3.51)

[a]Adjusted for race/ethnicity, family history of thyroid cancer, time since last pregnancy, smoking, alcohol consumption, physical inactivity, height; age was the time-scale and analyses were stratified by age at baseline.
[b]Also adjusted for adolescent cycle length and time to regular menstruation.
[c]Also adjusted for age at menarche.
[d]Women who reported never having regular periods were not asked about adolescent cycle length.
[e]E-only: estrogen-only; E+P: estrogen plus progesterone.

consistent with these observations and show that several aspects of pubertal development have independent effects on risk.

Later age at menarche has been associated with irregular and anovulatory menstrual cycles (16). Both later menarche and irregular cycle length have been associated with increased risk of thyroid cancer (5, 7, 10), although when examined by age, the elevated risk associated with later age at menarche has been largely found among older (age ≥45 years) women (8, 12), whereas the risk for irregular cycles has been more consistently observed for younger women (6, 12). We found both later menarche and longer adolescent cycle length to be independently related to risk in women who were under age 45 years at baseline. The independence of the 2 factors in our findings suggests that later age at menarche may reflect an impact on risk other than through cycle length. Our menarche finding is consistent with a recently published cohort study of thyroid cancer in radiologic technicians, most of whom were younger than age 50 years at cohort entry (17). To the extent that longer cycle length in adolescence is related to irregular cycles, our finding is consistent with the majority of the available literature. Our results for irregular periods, however, are mixed: women whose periods became regular more than 5 years after menstruation began were at increased risk of thyroid cancer, whereas those whose periods never became regular were not. Whether this is indicative of a perception or reporting difference or reflective of biologic differences is not clear.

Thyroid volume and thyroid stimulating hormone levels vary across the menstrual cycle, however, how these changes relate to thyroid carcinogenesis remains unclear (18–20). Increased thyroid volume has been associated with later age at menarche and diminished progesterone levels in adolescent girls (21). Irregular cycles are characterized by an increase in the length of the follicular (preovulatory) phase of the cycle and a progesterone deficit related to a lack of the normal progesterone surge that occurs during the luteal (post-ovulatory) phase (22). Thus, the menstrual-related

Table 3. Reproductive factors and papillary thyroid cancer risk in the CTS cohort

	All women		Age at baseline			
			<45 years		≥45 years	
	Cases	RR[a] (95% CI)	Cases	RR[a] (95% CI)	Cases	RR[a] (95% CI)
Outcome of first pregnancy						
Full-term birth	137	1.0	30	1.0	107	1.0
Miscarriage	20	1.04 (0.65–1.67)	5	1.03 (0.40–2.66)	15	1.07 (0.62–1.83)
Abortion	23	1.05 (0.67–1.66)	11	1.06 (0.52–2.13)	12	1.08 (0.59–1.99)
Never pregnant	48	1.02 (0.72–1.43)	23	1.20 (0.66–2.16)	25	0.91 (0.59–1.42)
Parity[c]						
Nulliparous	59	0.73 (0.39–1.36)	29	1.08 (0.45–2.60)	30	0.58 (0.24–1.44)
1–2	126	1.0	34	1.0	92	1.0
≥3	47	0.81 (0.57–1.14)	7	0.82 (0.36–1.87)	40	0.78 (0.53–1.14)
Age at first full-term pregnancy (y)[b]						
<25	60	1.08 (0.76–1.53)	7	0.95 (0.39–2.31)	53	1.08 (0.73–1.59)
25–29	70	1.0	19	1.0	51	1.0
≥30	43	1.00 (0.68–1.48)	15	0.93 (0.46–1.90)	28	1.01 (0.63–1.61)
Nulliparous	59	0.79 (0.41–1.49)	29	1.08 (0.43–2.74)	30	0.65 (0.26–1.63)
Years since last pregnancy[c]						
≤5 (including currently pregnant)			29	2.28 (1.16–4.45)		
>5			18	1.0		
Never pregnant			23	1.92 (0.96–3.84)		

[a]Adjusted for race/ethnicity, family history of thyroid cancer, age at menarche, adolescent cycle length and time to regular menstruation, smoking, alcohol consumption, physical inactivity, and height; age was the time-scale and analyses were stratified by age at baseline.
[b]Also adjusted for years since last pregnancy.
[c]Relative to completion of the baseline questionnaire.

papillary thyroid cancer risk factors observed in this study are consistent with the hypothesis that reduced progesterone exposure may increase thyroid cancer risk.

Recent pregnancy has been associated with increased risk of thyroid cancer in our study as well as others (8–11). Although both estrogen and progesterone increase substantially throughout pregnancy, the progesterone-to-estrogen ratio is highest during the first trimester and significant between-group variation has been observed. Potischman and colleagues (23) found that, compared with white women, African American women (who experience substantially lower thyroid cancer rates than white women during the reproductive years) had higher levels of progesterone during the first trimester of pregnancy, but estradiol and estrone levels did not differ between the 2 groups. These observations are generally consistent with the hypothesis that reduced thyroid cancer risk is associated with higher progesterone levels, although the progesterone-to-estrogen ratio may be equally or more important. Our findings in older women of increased risk with ET use, but not EPT use, also support the progesterone-to-estrogen ratio hypothesis. In older women in whom endogenous hormones are at substantially lower levels than earlier in life, exogenous hormones may have greater influence. The use of EPT would thus increase both estrogen and progesterone levels, whereas the use of ET would increase only estrogen levels, thus, reducing the progesterone-to-estrogen ratio and increasing thyroid cancer risk. Previous research on the association between HT and thyroid cancer risk have generally been null, however, none of the prior studies have evaluated type of HT preparation (6, 9, 11, 12, 17, 24–27).

In vitro studies by using papillary thyroid cancer cell lines have shown that exposure to estradiol increases cell proliferation via the estrogen receptor (ER), whereas the addition of tamoxifen, an antiestrogen, halts proliferation (28). Thyroid tissue is responsive to steroid hormones. Estrogen and progesterone receptors have been identified in papillary thyroid tumors and normal thyroid tissue (29) and ERα has been shown to be more highly expressed in papillary thyroid cancer in younger women than in older women, men, or in normal thyroid tissue (30). On the basis of risk factor patterns observed in this study, particularly the risk associated with a recent pregnancy and use of menopausal ET, the influence of steroid hormones on the development of thyroid cancer may be most important in the later, promotional stage of carcinogenesis (31).

Strengths of this study include its prospective nature which minimizes any recall bias and the examination of both standard measures of menstrual and reproductive events as well as more detailed variables, such as characteristics of adolescent menstrual cycles. Limitations include the relatively small number of papillary thyroid cancer cases ($n = 233$). However, because of the design of our cohort, which included a substantial number of women under the age of 45 compared with most other cohorts that recruited only women over that age, we were able to prospectively evaluate thyroid cancer risk factors in this group of high-risk women. Another limitation is lack of information on pregnancies occurring after enrollment. However, our analysis of the effects of recency of pregnancy at baseline by length of follow-up (<7 vs. ≥7 years) serves to partially address this issue.

Two areas of potential bias should also be noted. It is also possible that greater medical attention during pregnancy may result in thyroid tumors being diagnosed during this period that would have gone undiagnosed otherwise. Although we have no information on how tumors came to light in this study, the similar RRs for recency of pregnancy regardless of follow-up period also provides evidence that surveillance bias is not the sole reason for this finding. In addition, in our previous case–control study, we found that the RR associated with the number of pregnancies occurring within the previous 5 years was stronger for women who first found the tumor themselves as opposed to tumors which were first found by a physician (11). There is also concern that greater reporting errors by older women may result in differential misclassification by age group influencing our age-specific findings for menstrual factors and OC use. Although we found several menstrual-related factors (i.e., age at menarche, cycle length, and OC use) to be more strongly associated with risk in younger women than older women, we found similar RRs for both age groups associated with the time until regular menstruation was established. It is unlikely that reporting of this latter factor among older women would be more accurate than the former factors; thus, providing some evidence that our age group differences are not solely because of misclassification error. In addition, although the findings for age at menarche by age group are mixed, studies that have examined irregular menstruation and OC use have generally found these effects to be stronger in younger women (6, 12, 24).

Finally, although missing data for most of the variables of interest was small, we conducted sensitivity analyses for those factors for which missing data was 3% or greater. We observed less than 10% change in the RRs for adolescent cycle length and time to regular menstruation. Although changes in the RRs for ever use of OCs and the use of various HT preparations were larger (23% and 13%–14%, respectively, when assuming that all missing data were in truth never users of these compounds), the observed patterns remained quite similar to those reported and our conclusions with regard to the effects of these compounds on risk did not change.

In summary, the increasing incidence of thyroid cancer serves to underscore the public health importance of identifying factors which may predispose young women to developing this cancer. The findings from this prospective analysis suggest that several factors related to delayed pubertal development and the transient effects of pregnancy may be particularly important in influencing risk. Together they point to the likely importance of a progesterone deficit or, equivalently of estrogen unopposed by progesterone, in the etiology of papillary thyroid cancer.

Disclosure of Potential Conflicts of Interest

The ideas and opinions expressed herein are those of the authors and endorsement by the State of California, Department of Health Services, the NCI, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

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