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Benign breast and gynecological conditions, reproductive and hormonal factors, and risk of thyroid cancer

Melissa Z. Braganza[1], **Amy Berrington de González**[1], **Sara J. Schonfeld**[2], **Nicolas Wentzensen**[1], **Alina V. Brenner**[1], and **Cari M. Kitahara**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD

[2]Section of Environment and Radiation, International Agency for Research on Cancer, Lyon, France

Abstract

The higher incidence of thyroid cancer in women compared to men suggests an influence of sex steroid hormones in the etiology of this malignancy. We investigated a comprehensive set of potential indicators of lifetime sex steroid hormone exposure in relation to thyroid cancer risk. Using data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, which enrolled 70,047 women, 50–78 years old, we prospectively examined associations of self-reported history of benign breast and gynecological conditions, reproductive factors, and exogenous sex hormone use with thyroid cancer risk. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated in models using age as the time metric. During follow-up (median=11 years), 127 women were diagnosed with first primary thyroid cancer. Older age at natural menopause (≥55 vs. <50 years: HR=2.24, 95% CI:1.20–4.18), greater estimated lifetime number of ovulatory cycles (≥490 vs. <415 cycles: HR= 2.40, 95% CI:1.33–4.30), greater number of live births (≥5 vs. 1–2: HR=1.72, 95% CI:1.05–2.82), and history of uterine fibroids (HR=1.72, 95% CI:1.18–2.50) were associated with an increased risk of thyroid cancer. Earlier age at menarche, greater number of reproductive years, history of a tubal ligation, and history of ovarian cysts were non-significantly associated with increased thyroid cancer risk. No associations were observed for oral contraceptive use, menopausal hormone therapy, or history of benign breast disease or endometriosis. In general, we found that factors reflecting a greater length of exposure to endogenous hormones, particularly during the reproductive years, were associated with risk of postmenopausal thyroid cancer.

Keywords

thyroid cancer; benign breast disease; uterine fibroids; benign gynecological conditions; ovarian cysts

Introduction

Apart from a few established risk factors (being female, exposure to ionizing radiation, history of benign thyroid disease), little is known regarding the etiology of thyroid cancer. (1) Worldwide, incidence of thyroid cancer is 2–4 times higher in reproductive-age women compared to men. (1) Dietary, environmental, and genetic factors do not fully account for

Address for correspondence and reprints: Melissa Braganza, M.P.H., Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 9609 Medical Center Drive, Bethesda, MD 20892, melissa.braganza@nih.gov, Phone: 240-276-7405, Fax: 240-276-7874.

these sex differences (2), suggesting that sex steroid hormones may play a role in thyroid carcinogenesis. Experimental evidence further supports a role of estradiol in promoting the proliferation and invasiveness of thyroid cells in vitro. (3, 4) However, reproductive factors (e.g., age at menopause) and use of exogenous sex hormones (e.g., oral contraceptives and menopausal hormone therapy) have not been consistently associated with thyroid cancer risk. (1, 5)

Benign breast disease and endometriosis, conditions suspected to have hormonal pathophysiologies (6, 7), have been linked to an increased risk of thyroid cancer in recent studies (8–11). Benign breast disease and endometriosis, along with uterine fibroids, are diagnosed most frequently among reproductive-age women (12, 13) and have also been associated with hormone-related cancers, including breast, ovarian, and uterine cancers (10, 11, 14, 15). Uterine fibroids, which have been associated with an increased prevalence of thyroid nodules (16, 17), proliferate in the presence of estradiol and progesterone (18, 19). In addition to benign breast disease and endometriosis being possible disease precursors (14, 15), benign breast and gynecological conditions could be considered as potential indicators of lifetime sex steroid hormone exposure in epidemiological studies.

Using data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, we examined a comprehensive set of potential indicators of lifetime sex steroid hormone exposure, including history of benign breast disease, benign ovarian tumors/cysts, endometriosis, and uterine fibroids, in relation to thyroid cancer risk in a cohort of mostly postmenopausal women.

Methods

Study population

In 1993, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial began recruiting men and women at 10 screening centers across the United States. (20) By the end of the recruitment process in 2001, 78,215 women, between the ages of 50 and 78 years and with no medical history of lung, colorectal, or ovarian cancer, were enrolled in the study. (20) About 97% of participants completed the baseline questionnaire, which collected information on demographics, smoking history, height, weight, family history of cancer, history of cancer screening, reproductive and hormonal history, and history of benign breast and gynecological conditions. Thyroid cancer cases were ascertained through mailed questionnaires and death certificates, and medical records were used for verification. (20) The Annual Study Update, an annual questionnaire asking participants if they have been diagnosed with any cancer in the previous year, has response rates exceeding 90% for all study years. Study participants provided written informed consent, and the study was approved by the National Cancer Institute and the local institutional review boards. Participants were randomized into an intervention group, who underwent routine screening for lung, colorectal, and ovarian cancer screening, and a control group, who received routine care.

After excluding participants who did not complete the baseline questionnaire (n=2,094), respondents with a history of any cancer prior to trial entry (n = 5,163), and participants who did not contribute to follow-up time (n=911), our final study population consisted of 70,047 women.

Exposure Assessment

Exposure data were collected from the self-administered baseline questionnaire. Ages at menarche and menopause were defined as the ages at which participants reported having their first and last period, respectively. Type of menopause (natural, surgical, radiation, drug

therapy) was defined as the reason for which the participant's periods stopped. Infertility was defined as ever trying to become pregnant for at least a year without success.

Outcome

Cases were defined as women with a histologically confirmed first primary thyroid cancer and were further categorized by histological subtype: papillary cancer (ICD-O-2 histology codes: 8050, 8260, 8340–8344, 8350, 8450–8460) and follicular cancer (histology codes: 8290, 8330–8335). (21)

Statistical analysis

We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazard regression models, adjusted for education, race/ethnicity, marital status, family history of thyroid cancer, body mass index, and cigarette smoking status, with attained age as the underlying time metric. Missing values were modeled using a separate indicator variable. We also evaluated the effect of mutual adjustment for reproductive and hormonal factors and history of benign breast and gynecological conditions on the respective HRs. Person-time was censored at the first of the following events during follow-up: diagnosis of a first primary cancer, death, withdrawal from the study, no response to attempts at contact, 13 years after randomization, or December 31, 2009.

Number of reproductive years was calculated as the difference between age at natural menopause and age at menarche, restricting to women with natural menopause to avoid confounding by other hormonal factors. (22) Because the questionnaire elicited age at menarche (<10 years, 10–11 years, 12–13 years, 14–15 years, ≥16 years) and age at natural menopause (<40 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years) categorically, we used 1 minus the high end of the range for the lowest categories (e.g., 9 for ages <10 years), the midpoint for the middle categories (e.g., 10.5 for ages 10–11 years), and the bottom end of the range for the highest categories (e.g., 16 for ages ≥16 years) to calculate the number of reproductive years. To estimate lifetime number of ovulatory cycles, we subtracted the duration of oral contraceptive use, 36 weeks for each live birth, 28 weeks for each still birth pregnancy, and 12 weeks for each miscarriage/abortion (23) from the number of reproductive years; for these calculations, we reassigned numerical values for each category of oral contraceptive use using the same method as for number of reproductive years. Because we lacked information on cycle length, we assumed an average cycle length of 28.1 days. (24)

To account for clustering of the benign conditions, we conducted sensitivity analyses excluding women with more than one diagnosis. We also examined reproductive and hormonal factors and benign breast and gynecological conditions in relation to histological subtypes of thyroid cancer. Tests for linear trend were conducted by assigning a numerical value to each category (e.g., 1, 2, 3) and evaluating the statistical significance of the Wald term for this variable. Multiplicative interactions were tested by comparing the fit of a model including a cross-product term to a model not including this term using the likelihood ratio test. All analyses were performed using Stata 11.2 (Stata Corporation, College Station, Texas).

Results

At study entry, the median age was 62 years, and 99% of participants were postmenopausal (Table 1). During a median 11 years of follow-up (range: 1 – 13 years), 127 women were diagnosed with first primary thyroid cancer. The majority of these cases were papillary

(n=99) and follicular (n=20) carcinomas. The median age at thyroid cancer diagnosis was 67 years.

Generally, we observed that indicators reflecting a greater length of exposure to endogenous sex steroid hormones during reproductive years were associated with an increased risk of thyroid cancer (Table 2). There was some evidence that thyroid cancer risk decreased with increasing age at menarche (≥14 vs. <12 years: HR=0.62, 95% CI: 0.36–1.05; P_{trend} = 0.08), and risk of thyroid cancer increased with increasing age at natural menopause (≥55 vs. <50 years: HR=2.24, 95% CI: 1.20–4.18; P_{trend} = 0.02). Greater number of reproductive years was non-significantly associated with an increased risk of thyroid cancer (>40 vs. <35 years: HR=1.71, 95% CI: 0.96–3.07; P_{trend} = 0.05). Greater lifetime number of ovulatory cycles was also associated with an increased risk of thyroid cancer (≥490 vs. <415 cycles: HR= 2.40, 95% CI: 1.33–4.30; P_{trend} = 0.01).

No consistent associations emerged for pregnancy-related factors (Table 2). A history of infertility was not associated with thyroid cancer risk. Compared to women with 1–2 live births, an increased risk was observed for those having had ≥5 (HR=1.72, 95% CI: 1.05–2.82), but not 3–4, live births. Risk of thyroid cancer appeared to decrease with increasing age at first birth among parous women, but the trend was not significant (P_{trend} = 0.09).

Exogenous sex hormone use, including oral contraceptives and menopausal hormone therapy, were not clearly associated with risk of thyroid cancer (Table 2). Although the baseline questionnaire did not elicit information on type of menopausal hormone therapy, we further stratified our models according to hysterectomy status, as a crude measure of type of therapy, because estrogen-only hormone replacement therapy is typically only prescribed to women with a previous hysterectomy and estrogen plus progestin (or progesterone) to women with no history of this surgery. (19) In this study, ever use of menopausal hormone therapy was not associated with risk of thyroid cancer among women with (HR=0.66, 95% CI: 0.35–1.22) or without (HR=0.99, 95% CI: 0.60–1.62) a history of a hysterectomy. History of a tubal ligation was associated with a non-significantly increased risk of thyroid cancer (HR=1.46, 95% CI: 0.99–2.16).

History of uterine fibroids was associated with an increased risk of thyroid cancer (HR=1.72, 95% CI: 1.18–2.50; Table 3); this association was similar in magnitude after restricting to women reporting no other benign condition (HR=1.79, 95% CI: 1.02–3.14). History of benign ovarian tumors/cysts was associated with a non-significant increased risk of thyroid cancer (HR=1.50, 95% CI: 0.95–2.39); this association was more pronounced in women reporting no other benign condition (HR=2.61, 95% CI: 1.32–5.17). No associations were observed for benign breast disease or endometriosis.

Most of the results were similar when restricting the outcome to papillary carcinoma; however, the association for number of reproductive years became more pronounced (>40 vs. <35 years: HR=1.97, 95% CI: 1.00–3.87; P_{trend} = 0.03). The association for uterine fibroids became stronger after restricting the outcome to follicular thyroid carcinoma (HR=2.75, 95% CI: 1.13–6.68), but the number of exposed cases was small (n=9).

Healthcare access and utilization may be associated with history of benign breast and gynecological conditions as well as thyroid cancer detection, and thus may have confounded some of the associations we observed. However, no significant differences were observed by education level, history of mammography use, and screening arm of the trial. Results did not change appreciably after excluding women reporting no mammogram in the previous three years (including 7 cases).

Our results were not substantially different after excluding the first two years of follow-up or excluding women who were unsure of their menopausal status. With the exception of adjusting for history of a hysterectomy in the model for endometriosis, which slightly attenuated the association (HR=1.10), additional adjustment for reproductive and hormonal variables did not appreciably change the results (by >10%) for benign breast and gynecological conditions. Adjusting for age at birth of first child also slightly attenuated the positive association between having ≥5 live births and risk of thyroid cancer (HR=1.57, 95% CI: 0.94–2.61).

Discussion

Although a number of observational studies have investigated reproductive factors (e.g., age at menarche, age at menopause) and use of exogenous sex hormones (e.g., oral contraceptives and menopausal hormone therapy) (9, 25–30), few studies have evaluated other potential indicators of hormone exposure, including benign breast and gynecological conditions, number of reproductive years, and lifetime number of ovulatory cycles. In this prospective study of mostly postmenopausal women, we found that a history of uterine fibroids and greater number of reproductive years and estimated number of ovulatory cycles, factors reflecting a greater lifetime exposure to endogenous hormones, were associated with an increased risk of thyroid cancer.

In several observational studies (25–29), including recent prospective studies of postmenopausal women (9, 30), reproductive factors and exogenous sex hormone use have been examined in relation to thyroid cancer risk with largely inconsistent results. Thyroid cancer cases appear to have higher postdiagnostic serum estradiol and lower progesterone levels than healthy controls (31), but prospective studies assessing circulating sex steroid hormones in relation to thyroid cancer are lacking. Significant associations between benign breast disease and thyroid cancer risk were observed in two recent prospective studies (HRs=1.47 and 1.56) (8, 9); however, this finding was not replicated in a hospital-based case-control study (32) nor the current study. A population-based case-control study showed some evidence of an elevated risk of thyroid cancer among women surgically treated for benign breast disease. (33) As with breast cancer, risk of thyroid cancer may differ according to benign breast disease sub-type, which may explain differences in results between our study and previous studies. Results from two studies (10, 11) suggest positive associations between endometriosis and risk of thyroid cancer; however, these cohorts consisted of younger women who were primarily premenopausal, thus having a different hormonal profile than postmenopausal women. (34) While a case-control study (32) of premenopausal and postmenopausal women showed no associations for history of ovarian cysts or uterine fibroids, a borderline non-significantly elevated risk of thyroid cancer was observed for women with a history of hysterectomy as treatment for uterine fibroids in a population-based case-control study (35).

Generally, the directions of the associations that we observed for reproductive factors and thyroid cancer risk were consistent with those of other hormone-related cancers. Earlier age at menarche, older age at menopause, and greater number of reproductive years, indicators of greater lifetime exposure to endogenous sex steroid hormones, including estrogens, are consistently associated with breast, endometrial, and ovarian cancers. (22, 36–38) Greater cumulative number of menstrual cycles and lifetime number of ovulatory cycles have also been associated with risk of breast cancer and ovarian cancer. (23, 24, 39, 40, 41) However, the observation in this study of an increased risk of thyroid cancer among women with ≥5 live births contrasts with the results from studies on other hormone-related cancers and is inconsistent with our other results. (36–38) Additionally, oral contraceptive and menopausal hormone therapy use, which have been clearly linked to the risks of breast and other cancers

(36, 37, 42), were not associated with thyroid cancer risk, suggesting that exposure to endogenous hormones in particular, or related hormones other than estrogens and progesterone, may be more relevant in thyroid cancer development. For instance, higher levels of testosterone have been associated with an increased risk of breast cancer. (43) That we observed an increased risk of thyroid cancer among women with a history of uterine fibroids, which grow in the presence of estradiol and progesterone (18, 19) and have been linked to uterine cancer risk (15), additionally supports a potential, yet complicated, role of sex steroid hormones in thyroid carcinogenesis.

Sex steroid hormones may influence thyroid carcinogenesis through promoting the proliferation of thyroid cells and interacting with immune cells. Estradiol enhances the metastatic properties of thyroid cells, including adhesion, migration, and invasiveness, and stimulates proliferation of thyroid tumor cells in vitro. (4) Experimental studies indicate that estrogens act on thyroid cells via estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ), and that thyroid cancer cells exhibit increased expression of ERα, which appears to promote tumorigenesis, and decreased expression of ERβ, which may serve as a tumor suppressor. (3) Elevated expression of ERα has also been observed in lesions of benign conditions, including uterine fibroids (19), and in malignancies, such as breast and ovarian cancers (3), and may indicate common mechanisms between these hormone-related conditions and thyroid cancer. Moreover, estrogens may interact with ER receptors on certain immune cells and alter apoptotic pathways, including Bcl-2 family proteins' and nuclear factor kappa B's activities. (3, 34, 44) Progesterone receptors have also been identified on normal and malignant thyroid cells (45) and some immune cells (34). Progesterone, as it is suspected to promote uterine fibroid growth (19), may play a key role in promoting thyroid cancer development and growth. Additionally, reproductive and hormonal factors may be linked to thyroid cancer through elevated levels of thyroid stimulating hormone (TSH), a hormone involved in regulating thyroid growth, which have been found to be higher during puberty and pregnancy. (1)

The strengths of this study include detailed information on a comprehensive set of indicators of lifetime hormone exposure and available data on history of benign breast and gynecological conditions. All thyroid cancer cases were verified by review of medical records. Exposure data was collected prior to diagnosis of thyroid cancer, thus we avoided potential differential selection and recall biases.

However, misclassification of exposure status is a potential limitation of this study because information on benign breast and gynecological conditions, hormone use, and history of surgery was self-reported. All exposure information was self-reported and was not evaluated for validity or reproducibility. We lacked specific diagnostic information on these benign conditions, including disease sub-type and age at diagnosis. These results may not be generalizable to premenopausal women. In this study, the number of cases was relatively small compared to other prospective studies (9, 30) on this topic. While we adjusted for several potential confounders in our analysis, there may be other factors that we were not assessed or measured with error. It remains unclear whether the associations that we observed for several hormone-related factors represent increased levels of circulating sex steroid hormones (46–49) or other shared factors, such as genetic predisposition. Results were similar across education level and randomization status, implying that screening bias does not fully account for these associations.

Data from this prospective study suggest that history of uterine fibroids and greater lifetime number of ovulatory cycles may be related to an increased risk of thyroid cancer. These novel findings, together with the lack of an association for menopausal hormone therapy use, suggest that exposure to endogenous hormones earlier versus later in life may influence

the development of thyroid cancer. This hypothesis could potentially explain the higher rates of thyroid cancer in women than in men during the reproductive years. Large studies with detailed diagnostic information on breast and gynecological conditions may provide greater insight into the findings from this and previous studies. Furthermore, prospective studies that assess circulating hormones levels in relation to thyroid cancer risk are needed for providing more direct evidence regarding the possible role of sex steroid hormones in thyroid carcinogenesis.

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Table 1

Baseline characteristics of women in the PLCO Cancer Screening Trial

	All Women (%)
Study Participants	70,047
Age at Baseline	62 (median)
Menopause Status[a]	
Definitely postmenopausal	69,362 (99.0%)
Unsure	685 (1%)
Race/Ethnicity	
Non-Hispanic White	61,954 (88.5%)
Non-Hispanic Black	4,035 (5.8%)
Hispanic	1,121 (1.6%)
Asian/Pacific Islander/American Indian	2,911 (4.2%)
Missing	26 (<0.1%)
Education	
Less than High School	4,566 (6.5%)
High School Graduate	44,526 (63.6%)
College Graduate	20,782 (29.7%)
Missing	173 (0.3%)
Body Mass Index	
<25 kg/m^2	27,102 (38.7%)
25–29.9 kg/m^2	23,969 (34.2%)
≥ 30 kg/m^2	17,213 (24.6%)
Missing	1,763 (2.5%)
Family History of Cancer	
No	28,460 (40.8%)
Yes	41,333 (59.2%)
Missing	254 (0.4%)
Family History of Thyroid Cancer	
No	67,610 (97.2%)
Yes	470 (0.7%)
Missing	1,967 (2.8%)
Cigarette Smoking Status	
Never	39,257 (56.0%)
Former	24,070 (34.4%)
Current	6,701 (9.6%)
Missing	19 (<0.1%)
Personal History of Benign Breast Disease	
Never diagnosed	49,302 (70.4%)
Ever diagnosed	19,040 (27.2%)
Missing	1,705 (2.4%)
Personal History of Benign Ovarian Tumor or Cyst	

	All Women (%)
Never diagnosed	58,343 (83.3%)
Ever diagnosed	8,583 (12.3%)
Missing	3,121 (4.5%)
Personal History of Endometriosis	
Never diagnosed	61,105 (87.2%)
Ever diagnosed	5,549 (7.9%)
Missing	3,393 (4.8%)
Personal History of Uterine Fibroid Tumors	
Never diagnosed	52,275 (74.6%)
Ever diagnosed	15,288 (21.8%)
Missing	2,484 (3.6%)

[a]Based on participant responses to questions about age at last menstrual period, reasons that periods stopped, age at baseline, and surgery for ovary removal or hysterectomy

Table 2

Hazard ratios (HRs) and 95% confidence intervals (CIs) for thyroid cancer according to reproductive and hormonal factors.

	All Thyroid		Papillary Carcinoma	
	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]
Age at menarche				
<12 years	33	1.00 (reference)	25	1.00 (reference)
12–13 years	70	0.84 (0.55–1.27)	57	0.91 (0.57–1.46)
≥14 years	24	0.62 (0.36–1.05)	17	0.60 (0.32–1.11)
P-trend[b]		0.08		0.11
Type of menopause				
Natural	74	1.00 (reference)	58	1.00 (reference)
Hysterectomy, both ovaries removed	17	1.21 (0.71–2.06)	16	1.47 (0.84–2.56)
Hysterectomy, still has ≥1 ovaries/unknown	31	1.22 (0.80–1.86)	22	1.13 (0.69–1.85)
Age at natural menopause[c,e]				
<50 years	21	1.00 (reference)	14	1.00 (reference)
50–54 years	34	1.08 (0.62–1.86)	29	1.38 (0.73–2.61)
≥55 years	19	2.24 (1.20–4.18)	15	2.65 (1.28–5.51)
P-trend[b]		0.02		0.01
Number of reproductive years[d,e]				
<35 years	20	1.00 (reference)	14	1.00 (reference)
35–40 years	27	0.83 (0.46–1.48)	22	0.96 (0.49–1.88)
>40 years	27	1.71 (0.96–3.07)	22	1.97 (1.00–3.87)
P-trend[b]		0.05		0.03
Lifetime number of ovulatory cycles[e]				
<415 cycles	22	1.00 (reference)	16	1.00 (reference)
415–489 cycles	28	1.27 (0.73–2.23)	25	1.54 (0.82–2.90)
≥ 490 cycles	24	2.40 (1.33–4.30)	17	2.27 (1.13–4.53)
P-trend[b]		0.01		0.02
Number of live births				
Nulliparous	13	1.40 (0.69–2.85)	9	1.06 (0.44–2.60)

	All Thyroid		Papillary Carcinoma	
	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]
1 or 2	34	1.00 (reference)	26	1.00 (reference)
3	27	0.98 (0.59–1.63)	22	1.06 (0.60–1.87)
4	19	1.04 (0.59–1.83)	13	0.94 (0.48–1.85)
≥5	34	1.72 (1.05–2.82)	29	1.98 (1.14–3.43)
P-trend[b,f]		0.04		0.03
Age at birth of first child among parous women[d]				
<20 years	26	1.00 (reference)	19	1.00 (reference)
20–24 years	60	0.83 (0.51–1.34)	47	0.89 (0.51–1.56)
≥25	27	0.60 (0.34–1.08)	23	0.68 (0.35–1.33)
P-trend[b]		0.09		0.26
Tried becoming pregnant without success				
Never	107	1.00 (reference)	84	1.00 (reference)
Ever	20	1.10 (0.68–1.77)	15	1.05 (0.60–1.82)
Oral contraceptive use				
Never	51	1.00 (reference)	42	1.00 (reference)
Ever	76	1.15 (0.79–1.68)	57	1.05 (0.69–1.60)
Hormone therapy status				
Never	41	1.00 (reference)	33	1.00 (reference)
Former	18	0.86 (0.50–1.50)	14	0.83 (0.45–1.56)
Current	68	0.99 (0.67–1.49)	52	0.94 (0.60–1.48)
Tubal Ligation				
Never	89	1.00 (reference)	70	1.00 (reference)
Ever	38	1.46 (0.99–2.16)	29	1.42 (0.91–2.23)

[a] Adjusted for education (less than high school graduate, high school graduate, college graduate), race (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander/American Indian), marital status (married or living as married, widowed, divorced/separated, never married), family history of thyroid cancer, baseline BMI status (<25 kg/m^2, 25–29 kg/m^2, ≥30 kg/m^2), and smoking status (never smoked, former smoker, current smoker) with attained age as the underlying time variable

[b] P-trend calculated by modeling the categorical variable as continuous

[c] Age at natural menopause defined as when the participant reported having their last period

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[d] Number of years between age at menarche and age at natural menopause

[e] Restricted to women with natural menopause

[f] Excludes participants reporting never pregnant or no live births

Table 3

Hazard ratios (HRs) and 95% confidence intervals (CIs) for thyroid cancer according to benign breast and reproductive conditions.

	All Thyroid		Papillary Carcinoma	
	Cases	**HR (95% CI)[a]**	**Cases**	**HR (95% CI)[a]**
Benign breast/fibrocystic disease				
Never diagnosed	85	1.00 (reference)	66	1.00 (reference)
Ever diagnosed	38	1.15 (0.78–1.69)	30	1.17 (0.76–1.82)
Benign ovarian tumors/cysts				
Never diagnosed	99	1.00 (reference)	76	1.00 (reference)
Ever diagnosed	22	1.50 (0.95–2.39)	18	1.61 (0.96–2.69)
Endometriosis				
Never diagnosed	109	1.00 (reference)	83	1.00 (reference)
Ever diagnosed	13	1.25 (0.70–2.23)	12	1.52 (0.83–2.79)
Uterine fibroids				
Never diagnosed	81	1.00 (reference)	64	1.00 (reference)
Ever diagnosed	42	1.72 (1.18–2.50)	31	1.60 (1.04–2.46)

[a] Adjusted for education (less than high school graduate, high school graduate, college graduate), race (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander/American Indian), marital status (married or living as married, widowed, divorced/separated, never married), family history of thyroid cancer, baseline BMI status (<25 kg/m^2, 25–29 kg/m^2, ≥30 kg/m^2), and smoking status (never smoked, former smoker, current smoker) with attained age as the underlying time variable