Received: 10 December 2023 | Revised: 2 April 2024 | Accepted: 9 April 2024

DOI: 10.1002/ijc.34974

RESEARCH ARTICLE

Cancer Epidemiology

IJC INTERNATIONAL JOURNAL of CANCER | UICC

Early-pregnancy sex steroid and thyroid function hormones, thyroid autoimmunity, and maternal papillary thyroid cancer incidence in the Finnish Maternity Cohort

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Funding information
Intramural Research Program of the Division of Cancer Epidemiology and Genetics; National Cancer Institute; National Institutes of Health; U.S. Department of Health and Human Services

Abstract

Thyroid cancer more commonly affects women than men and is the third most frequently diagnosed cancer among women of reproductive age. We conducted a nested case–control study within the Finnish Maternity Cohort to evaluate prediagnostic sex steroid and thyroid function markers in relation to subsequent maternal papillary thyroid cancer. Cases ($n = 605$) were women ages 18–44 years, who provided an early-pregnancy (<20 weeks gestation) blood sample and were diagnosed with papillary thyroid cancer up to 11 years afterward. Controls ($n = 1185$) were matched to cases 2:1 by gestational age, mother's age, and date at blood draw. Odds ratios (ORs) for the associations of serum thyroid peroxidase antibodies (TPO-Ab), thyroglobulin antibodies (Tg-Ab), thyroid stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), progesterone, and estradiol with papillary thyroid cancer were estimated using conditional logistic regression. TPO-Ab and Tg-Ab positivity (>95th percentile among controls) were associated with more than 3-fold (OR = 3.32, 95% confidence interval [CI] 2.33–4.72) and 2-fold (OR = 2.03, 95% CI 1.41–2.93) increased odds of papillary thyroid cancer, respectively. These associations were similar by time since blood draw, parity, gestational age, smoking status, and age and stage at diagnosis. In models excluding TPO-Ab or Tg-Ab positivity, TPO-Ab (quartile 4 vs. 1: OR = 1.66, 95% CI 1.17–2.37, p-trend = .002) and Tg-Ab (quartile 4 vs. 1: OR = 1.74, 95% CI 1.22–2.49, p-trend = .01) levels were positively

associated with papillary thyroid cancer. No associations were observed for estradiol, progesterone, TSH, fT3, or fT4 overall. Our results suggest that thyroid autoimmunity in early pregnancy may increase the risk of maternal papillary thyroid cancer.

KEYWORDS

autoimmunity, risk factors, sex steroid hormones, thyroid cancer, thyroid function

What's new?

The contributions of reproductive and hormonal factors to thyroid cancer risk in women remain unclear. This nested case–control study examined sex steroid and thyroid function hormones in early pregnancy, a susceptible period for hormonal abnormalities including development of thyroid disease, and subsequent risk of maternal papillary thyroid cancer. Positivity for thyroglobulin and thyroid peroxidase antibodies in early pregnancy was associated with a 2- to 3-fold increased odds for maternal papillary thyroid cancer. These findings linking early-pregnancy thyroid autoimmunity with maternal papillary thyroid cancer may shed light onto mechanisms of thyroid carcinogenesis.

1 | INTRODUCTION

Worldwide, thyroid cancer is the third most frequently diagnosed cancer among women of reproductive age.[1] Because thyroid cancer incidence is higher in women than in men from adolescence through middle adulthood, sex steroid hormones have been thought to contribute to thyroid carcinogenesis, specifically the promotion or progression of existing thyroid tumors.[2–4] However, to date, the few established modifiable risk factors for thyroid cancer are ionizing radiation in childhood and excess adiposity.[2] Epidemiologic studies have yielded conflicting results for reproductive and hormonal factors with thyroid cancer risk in women.[2–4] Meanwhile, there is clear evidence that intense medical surveillance and diagnostic scrutiny play a major (and increasing) role in explaining sex differences in incidence.[5,6]

On the other hand, several studies found elevated thyroid cancer risk in the first few months or years after childbirth.[7–9] Pregnancy is a susceptible period for the development of thyroid autoimmunity, which may manifest as thyroid dysfunction in late pregnancy and the postpartum period.[10,11] Changes in thyroid stimulating hormone (TSH) and thyroid hormones (free thyroxine [fT4], free triiodothyronine [fT3]) occur as a direct result of rising levels of human chorionic gonadotropin (hCG) and estradiol during the first and second trimesters, increased renal iodine loss, and increased fetal iodine requirements.[10,11] TSH stimulates growth of follicular thyroid cells and follicular cell-derived thyroid cancer,[12] and a high proportion of thyroid cancers identified during the perinatal period have been shown to be estrogen receptor positive.[13] Thyroid autoimmunity causes local inflammation in the thyroid gland and impaired thyroid hormone synthesis, eventually resulting in increased production of TSH by the pituitary gland.[14] In clinical practice, high TSH and thyroid autoimmunity are considered predictive indicators for malignancy in patients with thyroid nodules.[12] Therefore, it is conceivable that thyroid autoimmunity or rising levels of estrogen and TSH in early pregnancy contribute to thyroid cancer growth and development.

The aim of our study was to evaluate pre-diagnostic, early-pregnancy levels of sex steroid and thyroid function hormones and thyroid autoimmunity in relation to maternal papillary thyroid cancer risk using data from the Finnish Maternity Cohort (FMC), a national biological specimen bank that includes sera collected during the first and early-second trimesters for nearly all pregnant women in Finland since 1983. The availability of unique population-identifying numbers assigned to all Finnish residents, linkages between the FMC, the Finnish Cancer Registry, and other national registries allows for nearly complete exposure ascertainment and long-term follow-up for thyroid cancer starting from early pregnancy.

2 | METHODS

2.1 | Study population

We conducted a nested case–control study within the FMC of the Northern Finland Biobank Borealis.[15,16] The FMC covers >90% of pregnancies in Finland during 1983–2016 and includes about 2 million maternal serum samples collected for routine screening tests during the first and early second trimesters (5th to 95th percentile: months 2–4 of pregnancy) from over 950,000 gravidae. Following informed consent, prenatal serum specimens were collected for routine screening for congenital infections. The remaining serum samples (approximately 1–3 mLs of serum from each pregnancy) were stored at −25°C in a protected biorepository at Biobank Borealis in Oulu, Finland, and are available for scientific research. FMC samples can be linked with Finnish nationwide registers using a unique personal identification code (PIC) issued to each citizen and permanent resident of Finland since 1964–1968.

FMC participants who provided at least one early-pregnancy (<20 weeks gestation) blood sample between 1987 and 2015 were linked with the Finnish Medical Birth Register (FMBR), which includes comprehensive and standardized data on all live births in Finland since 1987

during the neonatal period up to 7 days of age, and stillbirths where the fetuses had reached at least 22 weeks of gestation or had a birth weight of ≥500 g. These data include demographic characteristics, reproductive history, maternal health-related behaviors and perinatal events, and information about the newborn (e.g., sex, birth weight and length). Linkage of FMC participants with the Care Register for Health Care (CRHC) provided data on public and private inpatient diagnoses since 1969, all public hospital outpatient diagnoses since 1998, and primary care outpatient diagnoses since 2011.[17] We excluded women with a known diagnosis of hypothyroidism (ICD-10 E03.9, ICD-9 code 244.9, or equivalent; $n = 14{,}056/108{,}252$; 12.4%) or hyperthyroidism (ICD-10 E05.9, ICD-9 = 240.9, or equivalent; $n = 3022/108{,}252$; 2.8%).

The remaining subjects were linked with the nationwide Finnish Cancer Registry (founded in 1952), which allowed for identification and selection of cases and controls through 2015 (Figure 1). Cases were women diagnosed with papillary thyroid cancer (ICD-10 code C73, morphology codes 8050, 8260, 8340–8344, 8350, 8450–8460) up to 11 years after blood draw from most recent pregnancy (hereafter referred to as the *index pregnancy*), with no prior history of cancer except non-melanoma skin cancer, and available data on cancer stage at diagnosis. We randomly matched up to two controls to each case (with resampling) by gestational age at blood draw (±6 days), mother's age at blood draw (±6 months), and date at blood draw (±3 months). Controls must have been alive and without a history of cancer (except non-melanoma skin cancer) at the time of the diagnosis of the matched case. Excluded were blood samples from the index pregnancy drawn >20 weeks gestational age, women <18 or ≥45 years old at blood collection for the index pregnancy, and those with insufficient serum volume for laboratory measurements of all seven biomarkers. In total, 605 cases and 1185 controls met the inclusion criteria. All cases had at least one matched control (580 with two matched controls and 25 with one matched control).

2.2 | Laboratory analyses

Quantitative analyses of thyroid peroxidase antibodies (TPO-Ab), thyroglobulin antibodies (TG-Ab), thyroid hormones (TSH, fT4 and fT3),

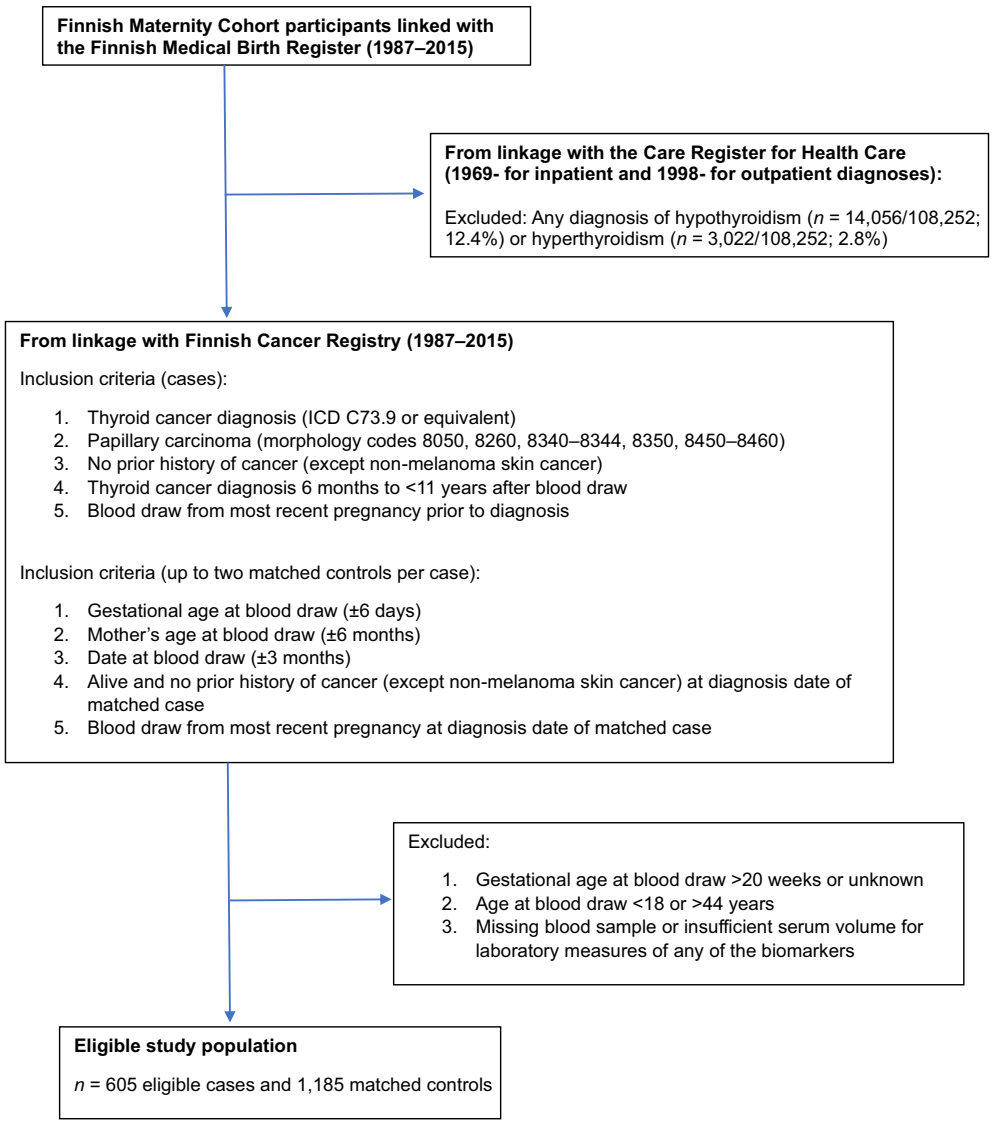

FIGURE 1 Flowchart for selection of eligible thyroid cancer cases and matched controls from the Finnish Maternity Cohort.

progesterone, and estradiol were performed blind to case and control status using chemiluminescent microparticle immunoassays with an Architect i2000 automatic analyzer (Abbott Diagnostics, Abbott Park, IL).

Serum specimens of individually matched case and control subjects were included in the same laboratory batch. Coefficients of variation (CVs) were derived from repeated quality control samples included in the assay with the study samples. Quality controls included manufacturer's controls with low, medium, and high levels of each biomarker, and an internal control of a pool of serum from the cohort inserted at intervals of 100 samples.

In internal control of pooled serum, the CVs were as follows: Tg-Ab 6.8%, TSH 3.2%, fT4 2.9%, and fT3 6.6%. The level of TPO-Ab was universally or uniformly below the lowest level of detection in internal control of pooled serum. In the manufacturer's control samples with "low" TPO-Ab (15 IU/mL), the CV was 4.9%. The lowest limits of detection for TSH, fT3, fT4, TPO-Ab, and Tg-Ab, respectively, were as follows: 0.0025 μIU/mL, 2.304 pmol/L, 4 ng/L, 1.0 IU/mL, and 1.0 IU/mL. CVs for progesterone were less than <6% for medium and high controls and 10.6% for low control. CVs for estradiol were <3.5% for medium and high controls and 8% for low control. The lowest limits of detection were <0.1 ng/mL for progesterone and <25 pg/mL for estradiol. For progesterone and estradiol, similar CVs and median values among controls were obtained in previous measurements from the FMC cohort using high-performance liquid chromatography/tandem mass spectrometry.[18,19]

Although samples have been kept in long-term storage, storage time has not been found to impact measurements of thyroid hormones or sex steroid hormones; however, thyroid autoantibody measures differed after 14 years of storage.[20,21] Freezing/thawing did not appear to affect thyroid hormone or autoantibody measurements[20] or sex steroid hormone measurements.[22]

2.3 | Statistical analysis

As thyroid hormone reference values given by the manufacturer of the analyzer (Abbott) apply to a non-pregnant population, we created cut-points based on hormone level distributions among controls, such that mothers with concentrations of TSH and fT4 between the 5th and 95th percentiles were considered to have normal thyroid function; mothers with values outside of these "normal" ranges were categorized as "high" or "low" for a particular marker as defined in an earlier publication.[23] For these reasons, the same methodology was applied for levels of estradiol, progesterone, and fT3, and subjects were classified as TPO-Ab and TG-Ab positive if antibody concentrations were over the 95th percentile among controls.[23] To examine whether thyroid cancer risk varied within the normal range of these hormones, quartiles of hormone concentrations were defined using the distribution among controls prior to excluding cases and controls with values in the "high" or "low" range. Tests of trends were performed by modeling these quartiles as a continuous (ordinal) variable, with *p*-values derived from the Wald test for that coefficient. Spearman correlations were used to examine associations between hormone levels among controls (Table S1).

For the main analyses, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using conditional logistic regression models, accounting for matched pairs, unadjusted and adjusted for potential confounding factors[24]: cigarette smoking status at blood draw, parity at blood draw, and sex of the neonate. Unconditional logistic regression models adjusted for case–control matching factors were used for subgroup analyses stratified on: (1) the number of years between blood draw and thyroid cancer diagnosis (≥2 vs. <2 years), (2) calendar year of blood draw (before vs. after 2000), (3) smoking status in pregnancy (no smoking vs. any smoking), (4) parity at blood draw (≥1 vs. 0 previous live births), (5) gestational age at blood draw (≥10 vs. <10 weeks), (6) age of the mother at thyroid cancer diagnosis (≥35 vs. <35 years), and (7) stage of thyroid cancer at diagnosis (localized vs. regional/distant). For most of these factors, *p*-values for interaction were based on likelihood ratio tests comparing these unconditional regression models with, versus without, an interaction term. For time since diagnosis, age at diagnosis, and stage, unconditional regression models of the two case groups (i.e., excluding controls) were compared using likelihood ratio tests with, versus without, the main exposure variable. Because thyroid autoimmunity can cause alterations in thyroid hormone synthesis,[10] in a secondary analysis, models for TSH and fT4 additionally excluded TPO-Ab positive status.

3 | RESULTS

Table 1 compares demographic and reproductive characteristics and pre-diagnostic, early-pregnancy hormone levels between cases and controls, as well as diagnostic information for the cases. Few differences were observed, apart from a slightly higher proportion of male versus female neonates (52.9% vs. 49.7%) and lower proportion of non-smokers (88.9% vs. 94.1%) among cases versus controls. Cases were also more likely to be TPO-Ab (14.9% vs. 5.1%) and Tg-Ab positive (10.1% vs. 5.1%). The median age at blood collection for cases and controls was 30.7 (interquartile range [IQR] = 27.9–34.2) and 30.6 years (IQR = 27.8–34.2). Median time between blood draw and thyroid cancer diagnosis was 3.6 years (IQR = 1.8–6.6) and the maximum was 10.1 years. Median age at diagnosis was 35.1 years (IQR = 31.1–39.0). Most cases (76.0%) were localized to the thyroid gland.

In conditional logistic regression models (Table 2), no associations were observed for levels of estradiol, progesterone, TSH, fT3, or fT4 and odds of papillary thyroid cancer. TPO-Ab positivity was associated with a more than 3-fold increase in odds (OR = 3.32, 95% CI 2.33–4.72), while Tg-Ab positivity was associated with 2-fold increased odds of papillary thyroid cancer (OR = 2.03, 95% CI 1.41–2.93). In models excluding TPO-Ab or Tg-Ab positivity, higher levels of TPO-Ab (quartile 4 vs. 1: OR = 1.66, 95% CI 1.17–2.37, *p*-trend = .002) and Tg-Ab (quartile 4 vs. 1: OR = 1.74, 95% CI 1.22–2.49, *p*-trend = .01) were associated with increased odds of papillary thyroid cancer. Additional adjustment for potential

TABLE 1 Reproductive characteristics and pre-diagnostic early pregnancy hormone levels of maternal papillary thyroid cancer cases and matched controls.

Characteristics	Cases ($N = 605$) Median (IQR) or *N* (%)[a]	Controls ($N = 1185$) Median (IQR) or *N* (%)[a]
Calendar year of blood collection	1998 (1993–2005)	1998 (1993–2005)
Age at blood collection, years	30.7 (27.9–34.2)	30.6 (27.8–34.2)
Gestational age at blood collection, weeks	10.4 (9.0–12.3)	10.4 (9.0–12.1)
Gestational age at birth, weeks	39.9 (39.1–40.7)	40.0 (39.0–40.9)
Previous pregnancies	2 (2–3)	2 (2–3)
Previous births	1 (1–2)	1 (1–2)
Nulliparous (no previous births)	147 (24.3%)	285 (24.1%)
Male sex of neonate	320 (52.9%)	589 (49.7%)
Non-smoker	520 (88.9%)	1107 (94.1%)
Unknown	20	9
Birth weight, g	3620 (3264-3990)	3600 (3290–3905)
Birth length, cm	51 (49–52)	50 (49–52)
Estradiol, pg/mL	1624 (981–2522)	1535 (993–2387)
Unknown	2	4
Low (<443 pg/mL)	29 (4.8%)	59 (5.0%)
High (≥4476 pg/mL)	36 (6.0%)	60 (5.1%)
Progesterone, ng/mL	25.1 (19.7–32.2)	25.7 (20.4–32.2)
Unknown	2	4
Low (<13.6 ng/mL)	28 (4.6%)	59 (5.0%)
High (≥47.2 ng/mL)	25 (4.2%)	60 (5.1%)
Thyroid stimulating hormone (TSH), μIU/L	1.06 (0.59–1.72)	1.07 (0.64–1.61)
Unknown	4	0
Low (<0.14 mIU/L)	41 (6.8%)	59 (5.0%)
High (≥3.29 mIU/L)	30 (5.0%)	60 (5.1%)
Free triiodothyronine (fT3), pmol/L	4.62 (4.19–5.05)	4.59 (4.16–5.05)
Unknown	0	1
Low (<3.53 pmol/L)	20 (3.3%)	57 (4.8%)
High (≥5.91 pmol/L)	36 (6.0%)	61 (5.2%)
Free thyroxine (fT4), ng/L	9.9 (9.2–10.7)	10.0 (9.3–10.8)
Unknown	0	1
Low (<8.4 ng/L)	33 (5.5%)	52 (4.4%)
High (≥12.2 ng/L)	38 (6.3%)	64 (5.4%)
Thyroid peroxidase antibody (TPO-Ab), IU/mL	3.76 (2.42–28.58)	3.19 (2.15–5.44)
Unknown	0	2
TPO-Ab positive (≥174.83 IU/mL)	90 (14.9%)	60 (5.1%)
Thyroglobulin antibody (Tg-Ab), IU/mL	9.74 (6.59–17.02)	8.62 (6.08–12.97)
Unknown	0	1
Tg-Ab positive (≥47.09 IU/mL)	61 (10.1%)	60 (5.1%)
Tumor characteristics (cases only)		
Age at diagnosis, years	35.1 (31.1–39.0)	-
Time from blood collection to diagnosis, years	3.6 (1.8–6.6)	
Stage at diagnosis		-
1 (localized)	460 (76.0%)	
2 (non-localized, only regional lymph node metastases)	106 (17.5%)	
3 (metastasized or invaded adjacent tissues)	13 (2.2%)	
4 (non-localized, unknown extent)	23 (3.8%)	
5 (locally advanced, invaded adjacent tissues)	3 (0.5%)	

Abbreviation: IQR, interquartile range.
[a]All percentages exclude unknown values. Unknown value counts are listed separately where applicable.

TABLE 2 Associations between pre-diagnostic early pregnancy sex steroid and thyroid hormones and risk of maternal papillary thyroid cancer.

				Quartiles (excluding values outside the normal range)[a]				
	Low (<5th percentile)	Normal	High (≥95th percentile)	Q1	Q2	Q3	Q4	*p*-trend
Estradiol, pg/mL	<443	443–4475	≥4476	443–993	993–1534	1535-2386	2387-4475	
Cases/controls	29/59	538/1062	36/60	123/237	131/295	156/295	128/235	
OR (95% CI)	0.96 (0.60–1.55)	1.00 (Ref)	1.24 (0.77–1.99)	1.00 (Ref)	0.86 (0.62–1.19)	1.04 (0.75–1.46)	1.17 (0.80–1.69)	.27
Progesterone, ng/mL	<13.6	13.6–47.1	≥47.2	13.6–20.4	20.4–25.6	25.7–32.1	32.2–47.1	
Cases/controls	28/59	550/1062	25/60	146/238	146/295	135/295	123/234	
OR (95% CI)	0.93 (0.58–1.50)	1.00 (Ref)	0.78 (0.47–1.29)	1.00 (Ref)	0.82 (0.61–1.10)	0.74 (0.55–1.01)	0.89 (0.55–1.01)	.35
TSH, μIU/L	<0.14	0.14–3.28	≥3.29	0.14–0.64	0.64–1.06	1.07–1.60	1.61–3.28	
Cases/controls	41/59	530/1066	30/60	129/238	137/296	123/296	141/236	
OR (95% CI)	1.40 (0.93–2.13)	1.00 (Ref)	1.00 (0.64–1.58)	1.00 (Ref)	0.88 (0.65–1.19)	0.74 (0.54–1.01)	1.11 (0.81–1.53)	.77
fT3, pmol/L	<3.53	3.53–5.90	≥5.91	3.53–4.16	4.16–4.58	4.59–5.04	5.05–5.90	
Cases/controls	20/57	549/1066	36/61	124/248	148/290	162/296	115/232	
OR (95% CI)	0.69 (0.41–1.16)	1.00 (Ref)	1.11 (0.72–1.71)	1.00 (Ref)	1.02 (0.76–1.38)	1.09 (0.81–1.47)	1.01 (0.73–1.38)	.84
fT4, ng/L	<8.4	8.40–12.1	≥12.2	8.4–9.3	9.3–9.9	10.0–10.7	10.7–12.1	
Cases/controls	33/52	534/1068	38/64	135/269	164/295	146/296	89/208	
OR (95% CI)	1.28 (0.81–2.02)	1.00 (Ref)	1.17 (0.77–1.79)	1.00 (Ref)	1.13 (0.84–1.54)	0.97 (0.71–1.31)	0.81 (0.57–1.13)	.16
				Quartiles (excluding values outside the normal range)[a]				
	Normal	Positive (≥95th percentile)		Q1	Q2	Q3	Q4	*p*-trend
TPO-Ab, IU/mL	<174.83	≥174.83		<2.15	2.15–3.18	3.19–5.43	5.44–174.82	
Cases/controls	515/1123	90/60		124/297	116/296	131/295	144/235	
OR (95% CI)	1.00 (Ref)	**3.32 (2.33–4.72)**		1.00 (Ref)	0.96 (0.70–1.32)	1.24 (0.89–1.74)	**1.66 (1.17–2.37)**	.002
Tg-Ab, IU/mL	<47.09	≥47.09		<6.08	6.08–8.61	8.62–12.96	12.97–47.08	
Cases/controls	544/1124	61/60		118/298	143/294	137/296	146/236	
OR (95% CI)	1.00 (Ref)	**2.03 (1.41–2.93)**		1.00 (Ref)	1.33 (0.97–1.84)	1.30 (0.93–1.81)	**1.74 (1.22–2.49)**	.01

Note: Two-sided *p*-values are all < 0.05.

Abbreviations: CI, confidence interval; fT3, free triiodothyronine; fT4, free thyroxine; IQR, interquartile range; OR, odds ratio; Q, quartile; Tg-Ab, thyroglobulin antibody; TPO-Ab, thyroid peroxidase antibody; TSH, thyroid stimulating hormone.

[a]Quartile cut points computed among controls prior to excluding subjects with values outside the normal range.

confounding factors (cigarette smoking status at blood draw, parity at blood draw, and sex of the neonate) did not meaningfully change any of these estimates (data not shown).

In subgroup analyses (Table S2), few meaningful differences were observed for associations of estradiol, progesterone, TSH, fT3, or fT4 with odds of papillary thyroid cancer. Exceptions included elevated odds of papillary thyroid cancer for low versus normal TSH (OR = 2.98, 95% CI 1.04–8.57) and high versus normal fT4 (OR = 2.74, 95% CI 1.13–6.70) among non-parous, but not parous, women (p-interaction by parity = .85 for TSH and .04 for fT4). The ORs for low TSH (OR = 2.04, 95% CI 0.61–6.77) and high fT4 (OR = 2.05, 95% CI 0.74–5.65) among non-parous women were attenuated with mutual adjustment of TSH and fT4. Low versus normal TSH was also associated with elevated odds of localized (OR = 1.67, 95% CI 1.09–2.57) but not non-localized (OR = 0.65, 95% CI 0.26–1.66) papillary thyroid cancer (p-interaction = .03). In addition, low versus normal fT4 was associated with elevated odds of maternal papillary thyroid cancers diagnosed after age 35 (OR = 1.72, 95% CI 1.00–2.95) but not before (p-interaction = .65). Associations for TPO-Ab and Tg-Ab positivity with odds of papillary thyroid cancer were similar by time since blood draw (with highly similar results for ≥2 years and ≥5 years [not shown]), parity, gestational age, smoking status, age and stage at diagnosis, and calendar year of blood draw.

In a sensitivity analysis excluding subjects with TPO-Ab positivity, associations between TSH, fT4, and odds of maternal papillary thyroid cancer were not meaningfully changed (Table S3).

4 | DISCUSSION

To our knowledge, this is the first prospective study to examine associations of pre-diagnostic estradiol, progesterone, thyroid autoantibodies, and thyroid function markers in early pregnancy with subsequent papillary thyroid cancer. Over the follow-up period, we observed 3-fold and 2-fold increased odds of papillary thyroid cancer for women with early-pregnancy TPO-Ab and Tg-Ab positivity, respectively. No associations were observed for estradiol, progesterone, TSH, fT3, or fT4, overall; however, low TSH and high fT4 were associated with increased odds of papillary thyroid cancer in some subgroups (e.g., nulliparous women).

Overall, our results suggest that thyroid autoimmunity in early pregnancy may independently influence the risk of maternal papillary thyroid cancer, possibly mediated by thyroid dysfunction manifesting later in pregnancy or in the postpartum period.[25] Our findings are generally consistent with those from the few previous prospective studies examining pre-diagnostic thyroid function markers and subsequent thyroid cancer risk in non-pregnant women and men.[26–28] In a cohort of US active-duty military personnel, TPO-Ab positivity (>100 IU/mL) and Tg-Ab positivity (>100 IU/mL) measured up to 10 years before thyroid cancer diagnosis were associated with about a 2-fold and 4-fold higher odds of differentiated thyroid cancer, respectively, with positive associations by TPO-Ab antibody titers above 250 IU/mL.[26] The associations did not meaningfully differ by time between blood draw and thyroid cancer diagnosis and or after restricting to subjects without diagnosed thyroid autoimmunity prior to the index date, suggesting that they were unlikely to be explained by detection bias or reverse causation. In a separate evaluation of the same cohort, higher pre-diagnostic TSH within the normal range was inversely associated with papillary thyroid cancer incidence in women and men, although TSH above the normal range was associated with increased incidence in men, while TSH below the normal range was associated with increased incidence in women.[27] In a large European cohort of mostly middle- to older-aged adults, pre-diagnostic TSH was inversely associated with differentiated thyroid cancer, while Tg-Ab positivity was associated with a 50% higher incidence.[28]

Our analysis was specifically designed to examine the novel question of whether alterations in sex steroid and thyroid function hormones in early pregnancy, a susceptible period for hormonal abnormalities including the development of thyroid autoimmunity and thyroid dysfunction, were associated with papillary thyroid cancer incidence. Strengths of our study include the unique data resource—a large nationwide cohort of women in Finland with early-pregnancy blood draws and nearly complete cancer incidence follow-up. To account for the substantial changes in sex steroid hormones and, to a lesser extent, thyroid function markers across the first and second trimesters, we closely matched cases and controls by gestational age, mother's age, and date at blood draw. We were able to control for potential confounding factors, such as parity, smoking status in pregnancy, and sex of the neonate, although additional adjustment of these factors had little impact on our results. To reduce the potential for treatment-related confounding and detection bias, prior to case and control selection, we excluded anyone with a recorded diagnosis of hypothyroidism or hyperthyroidism in the Care Register. This register is considered of very high quality with nearly complete information on hospital outpatient information in recent decades, though it is likely that some inpatient benign thyroid disease diagnoses were not captured by this registry, particularly in the earlier years of the study period.[17] Nonetheless, none of the associations examined were more pronounced after restricting to subjects with earlier (pre-2000) blood draws. Our results also did not change after restricting to subjects with blood samples drawn ≥2 years (or ≥5 years) before papillary thyroid cancer diagnosis, and the associations for TPO-Ab and Tg-Ab positivity remained after restricting to non-localized (regional or distant stage) thyroid cancers. Altogether, these results suggest that neither detection bias nor reverse causation, which would occur if autoantibody levels were influenced by the presence of undiagnosed thyroid cancer, were likely to explain our findings.

Regarding limitations not already mentioned above, the number of thyroid cancer cases and controls was limited in certain sub-group analyses. We lacked information on some potential confounders (e.g., childhood ionizing radiation exposures, maternal body mass index, and pregnancy weight gain). We also lacked longitudinal measures of thyroid function later across the duration of pregnancy and in the postpartum period, which would have allowed us to examine the downstream effects of thyroid autoimmunity in early pregnancy.[25] Our exclusion of subjects with hypothyroidism or hyperthyroidism, while reducing the potential for detection bias (as discussed above), could have

inadvertently biased our results toward the null due to the exclusion of subjects with early-pregnancy thyroid autoimmunity who went on to develop thyroid dysfunction at a later time point. Although estradiol (Spearman rho 0.32–0.60) and progesterone (Spearman rho 0.39–0.64) are moderately correlated across the first through third trimesters,[29] early-pregnancy levels may be less biologically relevant compared to cumulative exposures or levels in later pregnancy or in other periods in life. Because our study was restricted to women who provided an early-pregnancy blood sample and had a registered live birth or stillbirth in the FMBR, pregnancies that ended due to spontaneous or induced abortion or miscarriage were not included. Because thyroid dysfunction in early-pregnancy is associated with pregnancy loss,[23] our results may underestimate the true influence of these hormones on maternal papillary thyroid cancer. Finally, findings may not be generalizable to men or women who have not (or will not) experience a pregnancy.

In conclusion, we observed that TPO-Ab and Tg-Ab positivity in early pregnancy was associated with a 2- to 3-fold increased odds for maternal papillary thyroid. Our findings may provide insights into the etiology of this disease, which has few established modifiable risk factors apart from childhood exposure to ionizing radiation and obesity. Specifically, a direct influence of early-pregnancy thyroid autoimmunity on maternal papillary thyroid cancer development may at least partly explain the higher incidence of thyroid cancer in women compared to men in the general population.

AUTHOR CONTRIBUTIONS

Cari Kitahara, Heljä-Marja Surcel, Roni Falk, Ruth Pfeiffer, Tuija Männistö, Mika Gissler, and Britton Trabert conceptualized the research project and contributed to the design of the study. Cari Kitahara, Heljä-Marja Surcel, Roni Falk, Ruth Pfeiffer, and Britton Trabert were involved in the data selection and contributed to the study implementation. Heljä-Marja Surcel conducted the laboratory analyses, was responsible for project administration, and provided the data resources. Cari Kitahara, Ruth Pfeiffer, and Britton Trabert contributed to the methodology and statistical analyses. Cari Kitahara acquired funding, conducted the formal analysis, and wrote the original draft. All authors critically reviewed and edited the manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

FUNDING INFORMATION

This work was supported in part by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services.

CONFLICT OF INTEREST STATEMENT

Tuija Männistö reports having received travel reimbursement from Merck. Other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study may be made available from the Northern Finland biobank Borealis upon reasonable request directed to the biobank. Analytic code and a data dictionary can be requested from Northern Finland biobank Borealis. More information on the process to request data is available at: https://oys.fi/biopankki/. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

Our study used de-identified biospecimens and specimen donors were not contacted during the study. The request for biobank serum samples were approved by the responsible Biobank's Scientific Committee (Biobank Borealis of Northern Finland, Oulu University Hospital). The request for register data was approved by the data protection authorities at the National Institute for Health and Welfare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kitahara CM, Surcel H-M, Falk R, et al. Early-pregnancy sex steroid and thyroid function hormones, thyroid autoimmunity, and maternal papillary thyroid cancer incidence in the Finnish Maternity Cohort. *Int J Cancer*. 2024;155(6):1014-1022. doi:10.1002/ijc.34974