Original Contribution

Maternal Health, Pregnancy and Offspring Factors, and Maternal Thyroid Cancer Risk: A Nordic Population-Based Registry Study

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Thyroid cancer incidence is higher in women than men, especially during the reproductive years, for reasons that remain poorly understood. Using population-based registry data from 4 Nordic countries through 2015, we examined associations of perinatal characteristics with risk of maternal thyroid cancer. Cases were women diagnosed with thyroid cancer ≥2 years after last birth ($n = 7,425$, 83% papillary). Cases were matched to controls ($n = 67,903$) by mother's birth year, country, and county of residence. Odds ratios (ORs) were estimated using conditional logistic regression models adjusting for parity. Older age at first pregnancy, postpartum hemorrhage (OR = 1.18, 95% (confidence interval) CI: 1.08, 1.29), and benign thyroid conditions (ORs ranging from 1.64 for hypothyroidism to 10.35 for thyroid neoplasms) were associated with increased thyroid cancer risk, as were higher offspring birth weight (per 1-kg increase, OR = 1.17, 95% CI: 1.12, 1.22) and higher likelihood of offspring being large for gestational age (OR = 1.26, 95% CI: 1.11, 1.43). Unmarried/noncohabiting status (OR = 0.91, 95% CI: 0.84, 0.98), maternal smoking (OR = 0.75, 95% CI: 0.67, 0.84), and preterm birth (OR = 0.90, 95% CI: 0.83, 0.98) were associated with reduced risk. Several factors (e.g., older age at first pregnancy, maternal smoking, goiter, benign neoplasms, postpartum hemorrhage, hyperemesis gravidarum, and neonatal jaundice) were associated with advanced thyroid cancer. These findings suggest that some perinatal exposures may influence maternal thyroid cancer risk.

benign thyroid disease; cohort study; epidemiology; hormones; observational study; pregnancy; reproductive factors; thyroid cancer

Abbreviations: CI, confidence interval; LGA, large for gestational age; MBR, medical birth registry; OR, odds ratio; SGA, small for gestational age.

In the Nordic countries, thyroid cancer ranks as the fourth most frequently diagnosed malignancy in women of reproductive age (15–44 years), after breast cancer, cervical cancer, and melanoma (1). Few modifiable risk factors for thyroid cancer have been established apart from childhood exposure to ionizing radiation and obesity (2, 3).

Sex steroid hormones have long been hypothesized to play a role in thyroid carcinogenesis because of the higher incidence in women than men, particularly during the reproductive years (2, 4). Reproductive and hormonal characteristics (e.g., parity, age at menarche or menopause, exogenous hormone use) have not been consistently associated with thyroid cancer risk in epidemiologic studies; however, few studies have explored whether hormonal or other exposures in pregnancy are associated with risk of thyroid cancer in women (2, 4, 5). Pregnancy may represent a susceptible period in thyroid cancer development, considering that thyroid cancer risk is elevated following pregnancy (6–8). Maternal diagnosis of hyperemesis gravidarum and greater offspring birth weight, which serve as surrogates for hormonal exposures in pregnancy (9, 10), have also been associated with increased risk of thyroid cancer (11, 12).

On the other hand, many thyroid cancers diagnosed immediately after pregnancy may reflect incidental detection of

thyroid nodules (of which 8%–16% are malignant) owing to more frequent contact with the health-care system (13). Pregnant women generally have more opportunities for thyroid function testing, thyroid palpation, and thyroid ultrasound imaging. Although pregnancy can contribute to modest growth of an existing thyroid nodule, diagnostic workup of some nodules may be delayed until after pregnancy to avoid complications (13). Owing to the slow growth of most benign and malignant thyroid nodules (14, 15), environmental or hormonal exposures contributing to the pathogenesis of thyroid cancer may occur months or years prior to diagnosis. Thus, studies investigating the association of pregnancy-related exposures with thyroid cancer risk should account for a potentially long latency period and incorporate methods to minimize detection bias.

In this study, we linked population-based medical birth and cancer registry data within and across 4 Nordic countries to investigate associations for a wide range of pregnancy characteristics and complications, maternal medical history, and birth outcomes in relation to maternal thyroid cancer risk.

METHODS

A detailed description of the study methods was reported previously for a Nordic registry-linkage study of perinatal exposures and thyroid cancer risk in offspring (5).

Registries and study population

The Nordic countries offer the opportunity to investigate a variety of unique research questions owing to decades of information collected and electronically recorded in high-quality population-based registries (16). Legal residents are assigned unique personal identification numbers that allow linking of information across registries with nearly complete nationwide coverage. The similar health-care systems and data collection and structure across the Nordic registries facilitates pooling of data for research purposes.

National medical birth registries (MBRs) have recorded comprehensive information on maternal and offspring characteristics for all births in Denmark since 1973, in Finland since 1987, in Norway since 1967, and in Sweden since 1973 (17). MBR-derived variables include calendar year and maternal age at delivery, maternal marital status, parity, multiple versus singleton birth, birth weight and gestational age (used to calculate offspring being small/large for gestational age (SGA/LGA): birth weight by mean gestational age below/above 2 standard deviations), preterm birth, delivery type, and maternal pregnancy complications. Data for maternal smoking in pregnancy were available (though largely incomplete) in Denmark since 1991, in Finland since 1987 (for early pregnancy) and 1990 (for late pregnancy), in Norway since 1999, and in Sweden since 1982/1999. Information on prepregnancy body mass index was incomplete and mainly available in Sweden and since 2004 in Denmark. Offspring diagnoses of congenital hypothyroidism and neonatal jaundice were captured during the first year after birth for all countries except Sweden. Linkages with

National Patient Registries (NPRs) in Denmark (covers all hospitals since 1977 and specialist outpatient hospital contacts since 1995) and Sweden (since 1964) provided hospital diagnoses on maternal (Denmark and Sweden) and offspring (Denmark only) medical conditions not available in the MBRs. The cancer registries provide virtually complete information on malignancies, nationwide coverage in Denmark since 1943, Finland since 1953, Norway since 1953, and Sweden since 1958 (18).

Women with a record of a pregnancy in an MBR, defined here (for consistency across registries) as a pregnancy with a gestational age of 23 or more weeks, were identified and linked with the cancer registries to identify the cases. Cases were defined as women diagnosed with first primary thyroid cancer (*International Statistical Classification of Diseases and Related Health Problems*, *Tenth Revision*, C73 or equivalent) through 2015 (since 1973 in Denmark, since 1987 in Finland, since 1967 in Norway, and since 1973 in Sweden, as the MBRs were established more recently than the cancer registries). *International Classification of Diseases for Oncology*, *Third Edition*, morphology codes were used to classify cases as papillary (8050, 8260, 8340–8344, 8350, 8450–8460), follicular (8290, 8330–8335), medullary (8345, 8510–8513), or anaplastic (8020–8035) carcinomas. Ten controls identified from the MBR were sampled per case, matched on the affected mother's birth year and county of residence at the time of her last recorded pregnancy before matching. After matching, exclusions were made for controls who had died or emigrated, cases or controls with a prior cancer diagnosis other than nonmelanoma skin cancer, and cases diagnosed (or controls matched) within 2 years of the last recorded pregnancy. The latter exclusion was intended to minimize detection bias, owing to greater medical surveillance of thyroid-related disorders during pregnancy.

This study was approved by ethics committees in Norway and Sweden and the Data Protection Agency in Denmark. In Finland, we obtained permission to use health registry and population data from the Finnish Institute for Health and Welfare, Statistics Finland, and the Digital and Population Data Services Agency after consulting the data protection authority.

Statistical analysis

We used conditional logistic regression models to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for associations between pregnancy characteristics and maternal thyroid cancer, conditioned on matching variables and adjusted for parity (since parity was positively associated with many of the exposures examined in this analysis, as well as maternal thyroid cancer risk). A complete-case approach was used to handle missing values. Additional analyses were conducted separately by histologic type and stage at diagnosis for differentiated (papillary and follicular) thyroid cancers. Two sensitivity analyses were performed for the full set of variables: 1) excluding thyroid cancer cases diagnosed within 5 years (the base analysis excluded 2 years) after the last recorded pregnancy and their matched controls, to further evaluate and limit the potential for detection bias;

Table 1.   Characteristics of 7,425 Thyroid Cancer Cases With Date of Last Recorded Birth >2 Years Prior to Thyroid Cancer Diagnosis, Nordic Countries, 1967–2015

Characteristics	Denmark (n = 1,214)		Finland (n = 1,419)		Norway (n = 2,471)		Sweden (n = 2,321)		Total (n = 7,425)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Histopathological type[a]										
Papillary carcinoma	898	74.0	1,309	92.2	2,027	82.0	1,561	82.2	5,795	82.8
Follicular carcinoma	209	17.2	70	4.9	287	11.6	225	11.8	791	11.3
Medullary carcinoma	60	4.9	21	1.5	71	2.9	59	3.1	211	3.0
Anaplastic carcinoma	22	1.8	N/A[b]		25	1.0	28	1.5	78	1.1
Other	25	2.1	16	1.1	61	2.5	26	1.4	128	1.8
Year of pregnancy										
1923–1949	288	23.7	47	3.3	1,068	43.2	651	28.0	2,054	27.7
1950–1959	408	33.6	454	32.0	668	27.0	701	30.2	2,231	30.0
1960–1969	359	29.6	665	46.9	469	19.0	622	26.8	2,115	28.5
1970–1994	159	13.1	253	17.8	255	10.3	347	15.0	1,025	13.8
Age at diagnosis, years										
18–39	390	32.1	484	34.1	752	30.4	800	34.5	2,426	32.7
40–49	445	36.7	631	44.5	768	31.1	802	34.6	2,646	35.6
50–59	263	21.7	277	19.5	545	22.1	497	21.4	1,582	21.3
60–86	116	9.6	27	1.9	406	16.4	222	9.6	771	10.4
Year of diagnosis										
1967–1989	112	9.2	N/A[b]		534	21.6	302	13.0	952	12.8
1990–1999	239	19.7	254	17.9	458	18.5	472	20.3	1,423	19.2
2000–2009	517	42.6	629	44.3	767	31.0	815	35.1	2,728	36.7
2010–2015	346	28.5	532	37.5	712	28.8	732	31.5	2,322	31.3

Abbreviation: N/A, not available.

[a] 422 unspecified cases from Sweden, mainly diagnosed in the earlier calendar period, were excluded from the denominator.

[b] N/A indicates that the number of cases was <5.

and 2) adjusting additionally for prepregnancy body mass index or maternal smoking (potential confounders of the associations of other pregnancy-related factors and thyroid cancer risk), among women with complete information on those factors. Other sensitivity analyses, including mutual adjustment of related factors that were positively associated with maternal thyroid cancer risk, are described in the Results.

RESULTS

In total, 7,425 first-time primary thyroid cancer cases and 67,903 matched controls with a last pregnancy more than 2 years previously were identified from the registries. The breakdown of cases by known histology was 83% papillary, 11% follicular, 3% medullary, 1% anaplastic, 2% other (Table 1). Overall, most cases (68%) were diagnosed before age 50 years. The age distribution of cases was younger in Finland, with only 2% of cases diagnosed after age 60 versus 10% in the combined study, reflecting the later establishment of the MBR in Finland versus the other countries.

Risk of thyroid cancer was modestly positively associated with parity, although the risks did not increase consistently with each birth (Table 2). All results presented hereafter were adjusted for parity.

Ages at first and last pregnancy were positively associated with thyroid cancer risk on a continuous scale. In categorical models, however, age at first pregnancy was more clearly associated with maternal thyroid cancer compared with age at last pregnancy. Maternal thyroid cancer risk decreased with time since pregnancy until it was no longer associated after 5 years. Reduced thyroid cancer risk was observed for unmarried/noncohabiting status (OR = 0.91, 95% CI: 0.84, 0.98), maternal smoking (OR = 0.75, 95% CI: 0.67, 0.84), and preterm birth (OR = 0.90, 95% CI: 0.83, 0.98). In contrast, thyroid cancer risk was elevated following an LGA birth (OR = 1.26, 95% CI: 1.11, 1.43). Birth weight was positively associated with risk on a continuous scale (per 1-kg increase, OR = 1.17, 95% CI: 1.12, 1.22); however, a U-shaped relationship was evident in categorical models.

Diagnosis of benign thyroid conditions before or during any pregnancy was positively associated with maternal

Table 2. Association Between Maternal, Pregnancy, and Offspring Characteristics, Neonatal and Maternal Medical Conditions, and the Risk of Thyroid Cancer in Mothers, Excluding Cases Diagnosed <2 Years After Last Birth, and Matched Controls, Nordic Countries, 1967–2015

Exposure	Cases (n = 7,425)		Controls (n = 67,903)		OR[a]	95% CI
	No.	%	No.	%		
Maternal and Pregnancy Characteristics						
Parity						
1	1,238	16.7	11,394	16.8	1.00	Referent
2	3,351	45.1	30,278	44.6	1.09	1.02, 1.17
3	1,893	25.5	17,409	25.6	1.11	1.03, 1.20
4	607	8.2	5,815	8.6	1.09	0.98, 1.22
≥5	336	4.5	3,007	4.4	1.18	1.04, 1.36
Age at first pregnancy, per 1-year increase[b]	7,425	100	67,903	100	1.01	1.01, 1.02
Age at first pregnancy, years[b]						
<25	2,277	42.8	20,655	42.8	1.00	Referent
25–29	1,955	36.7	17,026	35.3	1.12	1.05, 1.21
30–39	1,043	19.6	10,090	20.9	1.13	1.03, 1.24
≥40	51	1.0	445	0.9	1.36	0.96, 1.94
Missing	2,099		19,687			
Age at last pregnancy, per 1-year increase	7,425	100	67,903	100	1.01	1.00, 1.02
Age at last pregnancy, years						
<25	883	11.9	8,158	12.0	1.00	Referent
25–29	2,472	33.3	21,505	31.7	1.20	1.09, 1.31
30–39	3,764	50.7	35,302	52.0	1.19	1.09, 1.31
≥40	306	4.1	2,938	4.3	1.22	1.04, 1.43
Years since last pregnancy						
2–4	1,355	18.2	9,149	13.5	1.16	1.05, 1.28
5–9	1,566	21.1	14,212	20.9	0.99	0.91, 1.07
≥10	4,504	60.7	44,542	65.6	1.00	Referent
Smoked in any pregnancy (yes vs. no)	693	27.6	7,291	33.3	0.75	0.67, 0.84
Missing	4,911		46,026			
BMI[c] before/start of last pregnancy						
<25.0	935	68.2	8,196	69.4	1.02	0.88, 1.18
25.0–29.9	296	21.6	2,576	21.8	1.00	Referent
≥30.0	139	10.1	1,044	8.8	1.15	0.91, 1.44
Missing	6,055		56,087			
Civil status during last pregnancy						
Married/cohabiting	6,123	85.2	55,564	84.5	1.00	Referent
Single/divorced/widowed	1,061	14.8	10,191	15.5	0.91	0.84, 0.98
Missing	241		2,148			
Offspring Characteristics						
Any preterm birth (yes vs. no)	628	8.5	6,350	9.4	0.90	0.83, 0.98
Missing	19		197			
Any multiple birth (yes vs. no)	188	2.5	1,649	2.4	1.06	0.91, 1.24
Missing	0		0			

Table continues

Table 2.   Continued

Exposure	Cases (n = 7,425)		Controls (n = 67,903)		OR[a]	95% CI
	No.	%	No.	%		
Any cesarean delivery (yes vs. no)	1,123	15.1	10,287	15.2	1.00	0.93, 1.07
Missing	9		73			
SGA[d] in last pregnancy (yes vs. no)	141	2.0	1,460	2.2	0.90	0.76, 1.08
Missing	551		4,838			
LGA[d] in last pregnancy (yes vs. no)	283	4.0	2,105	3.2	1.26	1.11, 1.43
Missing	548		4,835			
Birth weight, last pregnancy, per 1-kg increase	7,262	97.8	66,397	97.8	1.17	1.12, 1.22
Missing	162		1,506			
Birth weight, last pregnancy, g						
<1,500	52	0.7	375	0.6	1.43	1.07, 1.92
1,500–2,499	161	2.2	1,959	3.0	0.83	0.71, 0.99
2,500–3,499	2,673	36.8	26,615	40.1	1.00	Referent
3,500–4,499	4,019	55.3	34,727	52.3	1.15	1.10, 1.22
≥4,500	358	4.9	2,721	4.1	1.33	1.18, 1.49
Maternal Thyroid Disorders Diagnosed Prior to or During Any Pregnancy (Yes vs. No)[e]						
Hypothyroidism	40	0.5	222	0.3	1.64	1.17, 2.31
Hyperthyroidism	62	0.8	209	0.3	2.63	1.97, 3.50
Goiter	128	1.7	201	0.3	5.70	4.56, 7.13
Thyroiditis	11	0.1	51	0.1	1.85	0.96, 3.57
Other thyroid disorders	5	0.1	14	<0.1	3.13	1.12, 8.72
Benign thyroid gland neoplasms	21	0.3	18	<0.1	10.35	5.50, 19.48
Maternal Conditions Diagnosed During Any Pregnancy (Yes vs. No)[e]						
Preeclampsia/eclampsia	330	4.4	2,964	4.4	1.02	0.91, 1.15
Gestational hypertension	257	3.5	2,354	3.5	1.00	0.87, 1.14
Gestational diabetes	124	1.7	935	1.4	1.17	0.96, 1.42
Postpartum hemorrhage	613	8.3	4,809	7.1	1.18	1.08, 1.29
Placental abruption	52	0.7	513	0.8	0.93	0.70, 1.24
Placenta previa	51	0.7	413	0.6	1.11	0.82, 1.48
Hyperemesis	160	2.2	1,267	1.9	1.13	0.96, 1.34
Pregnancy anemia	161	2.2	1,222	1.8	1.17	0.99, 1.39
Maternal Conditions Diagnosed Prior to Any Pregnancy (Yes vs. No)[e]						
Diabetes history	47	0.6	434	0.6	0.97	0.72, 1.32
Hypertension history	29	0.4	273	0.4	0.95	0.65, 1.40
Offspring Conditions Diagnosed in First Year of Life, Any Birth (Yes vs. No)[e]						
Congenital hypothyroidism	N/A[f]		19	<0.1	0.47	0.06, 3.54
Neonatal jaundice	78	1.1	595	0.9	1.18	0.93, 1.50

Abbreviations: BMI, body mass index; CI, confidence interval; LGA, large for gestational age; N/A, not available; OR, odds ratio; SD, standard deviation; SGA, small for gestational age.

[a] ORs and 95% CIs from conditional logistic regressions, conditioned on birth year (of the case), country, and county, with additional adjustment for parity.

[b] Missing for mothers whose first pregnancy was not in the medical birth registries.

[c] Weight (kg)/height (m)^2.

[d] LGA/SGA represent weight by mean gestational age above/below 2 SDs.

[e] Classified as exposed when the diagnosis code was present; otherwise, classified as unexposed.

[f] N/A indicates that the number of cases was <5.

thyroid cancer (Table 2). ORs ranged from 1.64 (95% CI: 1.17, 2.31) for hypothyroidism to 10.35 (95% CI: 5.50, 19.48) for benign thyroid neoplasms. Of the nonthyroid medical conditions diagnosed prior to/during any pregnancy, none were associated with thyroid cancer risk, except postpartum hemorrhage (OR = 1.18, 95% CI: 1.08, 1.29). Results were similar for medical conditions diagnosed only in the last pregnancy (not shown).

Neither offspring diagnosis of jaundice nor congenital hypothyroidism were clearly associated with maternal thyroid cancer risk.

Stratified analyses

Histological type. For some factors (e.g., maternal smoking, unmarried/noncohabiting status, LGA, and birth weight), associations of a similar magnitude and direction were observed with risk of both papillary and follicular carcinoma (Table 3). However, parity, age at last pregnancy, maternal history of certain benign thyroid conditions (e.g., hypothyroidism, hyperthyroidism, goiter, thyroiditis), and pregnancy complications (e.g., gestational diabetes, postpartum hemorrhage, pregnancy anemia) appeared to be more strongly, or clearly, associated with risk of papillary than follicular carcinoma. In contrast, preterm birth and maternal diagnosis of benign thyroid neoplasms appeared to be more strongly associated with risk of follicular than papillary carcinoma. Although some factors appeared to be associated with risk of medullary (e.g., age at first pregnancy, maternal hypothyroidism) or anaplastic thyroid carcinoma (e.g., age at first and last pregnancy), these associations were based on small numbers of cases and confidence intervals were wide.

Stage at diagnosis. Results were largely similar by stage at differentiated thyroid cancer diagnosis (Table 4). However, unmarried/noncohabiting status, preterm birth, multiple births, offspring birth weight, LGA, and maternal thyroid conditions other than thyroiditis were more strongly associated with localized versus regional/distant cases. Associations that were more pronounced for regional/distant than localized cases included age at first pregnancy, very low birth weight, neonatal jaundice, and hyperemesis gravidarum.

Sensitivity analyses

Associations were virtually unchanged after adjustment for prepregnancy body mass index or smoking during pregnancy (data not shown). The postpartum hemorrhage association did not change after adjusting for birthweight, LGA, or SGA (data not shown). Results were similar after restricting to cases diagnosed more than 5 years after last pregnancy (n = 6,070), with the exception of slightly attenuated associations for marital status and papillary carcinoma (OR = 0.96, 95% CI: 0.87, 1.05) and for maternal thyroid conditions and both papillary and follicular thyroid carcinoma; nonetheless, risk of papillary carcinoma remained elevated after hypothyroidism (OR = 1.54, 95% CI: 0.96, 2.47), hyperthyroidism (OR = 1.98, 95% CI: 1.28, 3.04), goiter (OR = 4.85, 95% CI: 3.54, 6.65), and benign thyroid neoplasms (OR = 6.41, 95% CI: 2.78, 14.80), and risk of follicular carcinoma remained elevated after goiter (OR = 2.25, 95% CI: 1.02, 4.94) and benign thyroid neoplasms (OR = 29.63, 95% CI: 3.18, 275.81).

DISCUSSION

We pooled nationwide population-based registry data from 4 Nordic countries to evaluate a wide range of maternal medical histories, pregnancy complications, and birth characteristics in relation to maternal thyroid cancer risk. Several pregnancy-related exposures and characteristics, including parity, age at first pregnancy, hyperemesis gravidarum, postpartum hemorrhage, thyroid disorders, and offspring's birth weight were associated with increased risk of maternal thyroid cancer. Unmarried/noncohabiting status, maternal smoking, and preterm birth were inversely associated with risk.

Our results for hyperemesis gravidarum and birth weight are consistent with previous studies (11, 12). The inverse association for smoking and thyroid cancer risk is consistent with several previous studies of smoking and thyroid cancer in women, regardless of pregnancy status, and in men (19, 20). Also consistent with other studies (6–8), we found that maternal thyroid cancer risk declined with time since last pregnancy. Some exposures (e.g., married/cohabiting status, preterm birth, multiple birth, LGA and birth weight of the offspring, and benign thyroid conditions) were also more strongly associated with thyroid cancers diagnosed closer in time to the last pregnancy, as well as for localized versus regional/distant stage thyroid cancer, suggesting that at least some of these factors may be surrogates for healthcare access and utilization (and, thus, increased potential for thyroid cancer overdiagnosis). The similar magnitude and direction of association of some exposures (e.g., maternal smoking, unmarried/noncohabiting status, LGA, and birth weight) with risk of both papillary and follicular thyroid cancer may also similarly reflect a detection bias. On the other hand, although previous studies (not limited to pregnant women) have shown a much higher risk of thyroid cancer immediately following benign thyroid disease diagnosis, most likely attributable to diagnostic workup (21, 22), these risks remained significantly elevated for decades after the initial diagnosis. Similarly, we found that several of the factors examined were associated with long-term (>5 years) risks of both total and advanced stage thyroid cancer, including older age at first pregnancy, very low birth weight, maternal goiter and benign thyroid neoplasms, postpartum hemorrhage, hyperemesis gravidarum, neonatal jaundice, and maternal smoking (inverse), suggesting that detection bias may not fully explain these findings.

To our knowledge, our study is the first to evaluate the association between benign thyroid conditions in pregnancy and maternal thyroid cancer risk. In a related Nordic registry linkage study, we demonstrated that maternal hyperthyroidism and goiter, as well as congenital hypothyroidism in the offspring, were strongly associated with risk of thyroid cancer in the offspring (5). The similarity between the results between these 2 studies suggests a potential for shared underlying mechanisms for maternal and offspring

Table 3. Associations Between Maternal, Pregnancy, and Offspring Characteristics, Neonatal and Maternal Medical Conditions, and the Risk of Maternal Thyroid Cancer, Excluding Cases Diagnosed <2 Years After the Last Birth and Matched Controls, Stratified by Histology, Nordic Countries, 1967–2015

Exposure	Papillary Carcinoma (n = 5,795)		Follicular Carcinoma (n = 791)		Medullary Carcinoma (n = 211)		Anaplastic Carcinoma (n = 78)	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
Maternal and Pregnancy Characteristics								
Parity								
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	1.08	1.00, 1.17	1.21	0.97, 1.52	1.31	0.83, 2.07	1.04	0.49, 2.22
3	1.11	1.01, 1.21	1.22	0.96, 1.57	1.30	0.79, 2.14	1.06	0.47, 2.37
4	1.12	1.00, 1.27	1.06	0.76, 1.49	1.05	0.54, 2.04	0.53	0.18, 1.56
≥5	1.18	1.01, 1.38	1.30	0.88, 1.91	0.92	0.39, 2.20	1.08	0.34, 3.44
Age at first pregnancy, per 1-year increase[b]	1.01	1.00, 1.02	1.03	1.00, 1.05	1.03	0.99, 1.08	0.88	0.79, 0.97
Age at first pregnancy, years[b]								
<25	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
25–29	1.10	1.02, 1.19	1.27	1.03, 1.58	1.10	0.69, 1.74	0.40	0.17, 0.99
30–39	1.10	0.99, 1.22	1.28	0.97, 1.71	2.05	1.21, 3.47	0.12	0.02, 0.60
≥40	1.35	0.93, 1.98	2.12	0.71, 6.36	1.92	0.22, 16.58	N/A[f]	
Age at last pregnancy, per 1-year increase	1.01	1.00, 1.02	1.01	0.99, 1.03	1.01	0.98, 1.05	0.93	0.88, 1.00
Age at last pregnancy, years								
<25	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
25–29	1.16	1.05, 1.28	1.28	0.97, 1.69	1.38	0.79, 2.40	1.28	0.50, 3.30
30–39	1.18	1.06, 1.30	1.21	0.91, 1.61	1.44	0.83, 2.52	0.87	0.33, 2.34
≥40	1.26	1.06, 1.51	1.01	0.60, 1.69	0.80	0.27, 2.33	0.70	0.14, 3.54
Years since last pregnancy								
2–4	1.15	1.03, 1.29	1.15	0.84, 1.58	1.15	0.60, 2.22	0.57	0.03, 9.90
5–9	0.99	0.91, 1.09	1.03	0.81, 1.33	0.92	0.54, 1.57	0.98	0.18, 5.44
≥10	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Smoked in any pregnancy (yes vs. no)	0.76	0.68, 0.86	0.65	0.44, 0.96	1.11	0.54, 2.29	N/A[f]	

Table continues

Table 3. Continued

Exposure	Papillary Carcinoma (n = 5,795)		Follicular Carcinoma (n = 791)		Medullary Carcinoma (n = 211)		Anaplastic Carcinoma (n = 78)	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
BMI[c] before/start of last pregnancy								
<25.0	1.01	0.86, 1.19	0.90	0.58, 1.39	2.00	0.61, 6.50	1.40	0.14, 14.08
25.0–29.9	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
≥30.0	1.16	0.91, 1.49	0.82	0.39, 1.76	2.32	0.34, 15.93	N/A[c]	
Civil status during last pregnancy								
Married/cohabiting	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Single/widowed/divorced	0.90	0.83, 0.98	0.93	0.74, 1.18	1.02	0.65, 1.59	1.43	0.71, 2.87
Offspring Characteristics								
Any preterm birth (yes vs. no)	0.91	0.83, 1.00	0.72	0.54, 0.95	1.13	0.71, 1.80	0.79	0.33, 1.89
Any multiple birth (yes vs. no)	1.13	0.95, 1.33	0.92	0.56, 1.50	0.94	0.37, 2.37	N/A[f]	
Any cesarean delivery (yes vs. no)	1.02	0.95, 1.10	0.93	0.75, 1.15	0.90	0.59, 1.33	0.90	0.39, 2.10
SGA[d] in last pregnancy (yes vs. no)	0.88	0.72, 1.08	1.06	0.64, 1.74	1.08	0.38, 3.10	2.44	0.79, 7.55
LGA[d] in last pregnancy (yes vs. no)	1.27	1.10, 1.47	1.30	0.89, 1.89	1.21	0.59, 2.49	2.01	0.66, 6.08
Birth weight, last pregnancy, per 1-kg increase	1.17	1.11, 1.23	1.20	1.05, 1.37	1.18	0.91, 1.53	0.89	0.60, 1.33
Birth weight, last pregnancy, g								
<1,500	1.52	1.09, 2.11	1.38	0.58, 3.27	N/A[f]		N/A[f]	
1,500–2,499	0.79	0.65, 0.96	0.73	0.43, 1.23	2.54	1.25, 5.17	3.81	1.49, 9.79
2,500–3,499	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
3,500–4,499	1.15	1.08, 1.22	1.19	1.01, 1.39	1.51	1.10, 2.07	1.17	0.69, 1.98
≥4,500	1.31	1.15, 1.50	1.41	0.99, 2.00	1.05	0.48, 2.30	2.16	0.76, 6.10
Maternal Conditions Diagnosed Prior to or During Any Pregnancy (Yes vs. No)[e]								
Hypothyroidism	1.70	1.18, 2.45	0.59	0.14, 2.47	6.33	1.04, 38.32	N/A[f]	
Hyperthyroidism	2.84	2.06, 3.89	1.75	0.72, 4.21	4.67	0.85, 25.63	4.92	0.44, 55.43
Goiter	6.75	5.26, 8.66	3.10	1.67, 5.77	3.24	0.65, 16.13	7.12	0.60, 84.94
Thyroiditis	2.30	1.18, 4.50	N/A[f]		N/A[f]		N/A[f]	
Other thyroid disorders	3.97	1.37, 11.48	N/A[f]		N/A[f]		N/A[f]	

Table continues

Table 3. Continued

Exposure	Papillary Carcinoma (n = 5,795)		Follicular Carcinoma (n = 791)		Medullary Carcinoma (n = 211)		Anaplastic Carcinoma (n = 78)	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
Benign neoplasms of thyroid gland	10.20	4.96, 20.98	44.46	5.17, 382.05	N/A[f]		N/A[f]	
Maternal Conditions Diagnosed During Any Pregnancy (Yes vs. No)[e]								
Preeclampsia/eclampsia	1.03	0.90, 1.17	0.88	0.60, 1.29	1.08	0.53, 2.20	1.12	0.33, 3.84
Gestational hypertension	1.03	0.89, 1.19	0.86	0.56, 1.32	1.14	0.51, 2.55	0.49	0.06, 3.79
Gestational diabetes	1.22	0.99, 1.50	0.81	0.40, 1.64	1.49	0.42, 5.26	N/A[f]	
Postpartum hemorrhage	1.18	1.07, 1.31	1.09	0.81, 1.45	1.46	0.87, 2.43	1.08	0.36, 3.21
Placental abruption	0.91	0.66, 1.26	0.87	0.34, 2.19	1.49	0.33, 6.72	N/A[f]	
Placenta previa	1.14	0.81, 1.59	0.79	0.31, 1.97	0.78	0.10, 5.97	N/A[f]	
Hyperemesis	1.16	0.96, 1.39	0.98	0.57, 1.67	1.77	0.66, 4.76	2.04	0.23, 17.81
Pregnancy anemia	1.22	1.01, 1.47	1.01	0.54, 1.87	0.70	0.16, 3.13	2.06	0.42, 9.99
Maternal Conditions Diagnosed Prior to Any Pregnancy (Yes vs. No)[e]								
Diabetes history	1.07	0.77, 1.50	0.76	0.30, 1.93	0.96	0.12, 7.43	4.32	0.38, 49.08
Hypertension history	0.91	0.59, 1.40	1.53	0.59, 4.02	1.26	0.15, 10.31	N/A[f]	
Offspring Conditions Diagnosed in the First Year of Life, Any Birth (Yes vs. No)[e]								
Congenital hypothyroidism	0.55	0.07, 4.16	N/A[f]		N/A[f]		N/A[f]	
Neonatal jaundice	1.17	0.89, 1.53	1.55	0.86, 2.79	0.40	0.05, 3.07	2.17	0.25, 19.15

Abbreviations: BMI, body mass index; CI, confidence interval; LGA, large for gestational age; N/A, not available; OR, odds ratio; SD, standard deviation; SGA, small for gestational age.
[a] ORs and 95% CIs from conditional logistic regressions, conditioned on birth year (of the case), country, and county, with additional adjustment for parity.
[b] Missing for mothers whose first pregnancy was not in the medical birth registries.
[c] Weight (kg)/height (m)^2.
[d] LGA/SGA represent weight by mean gestational age above/below 2 SDs.
[e] Classified as exposed when the diagnosis code was present; otherwise, classified as unexposed.
[f] N/A indicates that the number of cases was <5.

Table 4. Associations Between Maternal, Pregnancy and Birth Characteristics, Neonatal and Maternal Medical Conditions, and Risk of Maternal Differentiated (Papillary and Follicular) Thyroid Cancer, Excluding Cases Diagnosed <2 Years After Last Birth and Matched Controls, Stratified by Stage at Diagnosis, Nordic Countries, 1967–2015

Exposure	Localized (n = 3,348)		Regional and Distant (n = 1,399)	
	OR[a]	95% CI	OR[a]	95% CI
Maternal and Pregnancy Characteristics				
Parity				
1	1.00	Referent	1.00	Referent
2	1.16	1.04, 1.29	1.16	0.98, 1.37
3	1.18	1.05, 1.33	1.13	0.94, 1.36
4	1.13	0.97, 1.32	1.06	0.82, 1.36
≥5	1.13	0.93, 1.38	1.24	0.90, 1.69
Age at first pregnancy, per 1-year increase[b]	1.01	1.00, 1.03	1.02	1.01, 1.04
Age at first pregnancy[b]				
<25	1.00	Referent	1.00	Referent
25–29	1.14	1.03, 1.27	1.08	0.92, 1.27
30–39	1.14	0.98, 1.31	1.16	0.94, 1.43
≥40	0.98	0.54, 1.78	2.17	1.04, 4.51
Age at last pregnancy, per 1-year increase	1.01	1.00, 1.02	1.01	1.00, 1.03
Age at last pregnancy				
<25	1.00	Referent	1.00	Referent
25–29	1.20	1.05, 1.37	1.12	0.92, 1.38
30–39	1.15	1.01, 1.32	1.24	1.01, 1.52
≥40	1.23	0.96, 1.56	1.15	0.79, 1.67
Years since last pregnancy				
2–4	1.11	0.96, 1.28	1.19	0.94, 1.50
5–9	0.93	0.82, 1.04	1.13	0.93, 1.36
≥10	1.00	Referent	1.00	Referent
Smoked in any pregnancy (yes vs. no)	0.74	0.63, 0.88	0.71	0.55, 0.91
BMI[c] before/start of pregnancy				
<25.0	1.08	0.82, 1.43	1.02	0.69, 1.49
25.0–29.9	1.00	Referent	1.00	Referent
≥30.0	0.88	0.57, 1.36	1.03	0.58, 1.81
Civil status during last pregnancy				
Married/cohabiting	1.00	Referent	1.00	Referent
Single/widow/divorced	0.87	0.77, 0.97	0.96	0.81, 1.14
Offspring Characteristics				
Any preterm birth (yes vs. no)	0.89	0.78, 1.01	1.01	0.84, 1.22
Any multiple birth (yes vs. no)	1.37	1.11, 1.68	0.82	0.55, 1.22
Any cesarean delivery (yes vs. no)	1.02	0.92, 1.13	1.01	0.86, 1.19
SGA[d] in last pregnancy (yes vs. no)	0.94	0.73, 1.20	0.97	0.66, 1.45
LGA[d] in last pregnancy (yes vs. no)	1.42	1.19, 1.70	1.04	0.76, 1.43
Birth weight, last pregnancy, per 1-kg increase	1.24	1.16, 1.32	1.04	0.94, 1.15

Table continues

Table 4.   Continued

Exposure	Localized (n = 3,348)		Regional and Distant (n = 1,399)	
	OR[a]	95% CI	OR[a]	95% CI
Birth weight, last pregnancy, g				
<1,500	1.00	0.61, 1.66	2.89	1.70, 4.93
1,500–2,499	0.81	0.63, 1.04	0.76	0.51, 1.14
2,500–3,499	1.00	Referent	1.00	Referent
3,500–4,499	1.18	1.09, 1.27	1.12	0.99, 1.26
≥4,500	1.53	1.29, 1.80	1.03	0.77, 1.38
Maternal Conditions Diagnosed Prior to or During Any Pregnancy (Yes vs. No)[e]				
Hypothyroidism	2.03	1.31, 3.14	1.43	0.67, 3.04
Hyperthyroidism	3.25	2.21, 4.78	1.32	0.56, 3.10
Goiter	6.43	4.74, 8.71	4.83	2.89, 8.06
Thyroiditis	2.19	0.90, 5.35	3.26	0.83, 12.78
Other thyroid disorders	6.57	1.75, 24.62	N/A[f]	
Benign neoplasms of thyroid gland	20.34	7.79, 53.09	9.53	2.38, 38.26
Maternal Conditions Diagnosed During Any Pregnancy (Yes vs. No)[e]				
Preeclampsia/eclampsia	1.09	0.92, 1.29	1.03	0.78, 1.36
Gestational hypertension	1.10	0.90, 1.34	1.02	0.72, 1.44
Gestational diabetes	1.16	0.87, 1.55	1.09	0.65, 1.81
Postpartum hemorrhage	1.23	1.08, 1.41	1.20	0.97, 1.48
Placental abruption	0.96	0.61, 1.52	1.07	0.59, 1.96
Placenta previa	1.27	0.83, 1.94	1.30	0.62, 2.75
Hyperemesis	1.12	0.86, 1.47	1.46	1.00, 2.12
Pregnancy anemia	1.19	0.89, 1.61	1.29	0.79, 2.10
Maternal Conditions Diagnosed Prior to Any Pregnancy (Yes vs. No)[e]				
Diabetes history	1.17	0.76, 1.82	0.86	0.41, 1.79
Hypertension history	1.35	0.82, 2.22	0.34	0.08, 1.41
Offspring Conditions Diagnosed in the First Year, Any Birth (Yes vs. No)[e]				
Congenital hypothyroidism	0.98	0.12, 7.73	N/A[f]	
Neonatal jaundice	1.12	0.80, 1.58	1.93	1.32, 2.83

Abbreviations: BMI, body mass index; CI, confidence interval; LGA, large for gestational age; N/A, not available; OR, odds ratio; SD, standard deviation; SGA, small for gestational age.

[a] ORs and 95% CIs from conditional logistic regressions, conditioned on birth year (of the case), country, and county, with additional adjustment for parity.

[b] Missing for mothers whose first pregnancy was not in the medical birth registries.

[c] Weight (kg)/height (m)^2.

[d] LGA/SGA represent weight by mean gestational age above/below 2 SDs.

[e] Classified as exposed when the diagnosis code was present; otherwise, classified as unexposed.

[f] N/A indicates that the number of cases was <5.

thyroid cancer, including a possible role of iodine deficiency or thyroid autoimmunity (23, 24). Pregnancy is a time of profound physiological changes contributing to thyroid gland enlargement (particularly in iodine-deficient regions) and substantial increases in thyroid hormone, fetal iodine requirements, and renal iodine loss (24). Dietary intake of iodine, an essential nutrient in thyroid hormone synthesis, is often inadequate in pregnancy, and residing in regions characterized by mild-to-moderate iodine deficiency (e.g., Denmark before mandatory iodine supplementation in the early-2000s) greatly increases the risk of developing severe iodine deficiency in pregnancy (23–25). Iodine deficiency increases the risk of maternal (and fetal) thyroid dysfunction and goiter, particularly in the presence of thyroid autoimmunity (present in about 18% of pregnancies); consequently, overt thyroid dysfunction is prevalent in about 4% of all pregnancies (24). Experimental and ecological studies have suggested a link between iodine deficiency and increased risk

of thyroid cancer, particularly follicular thyroid carcinoma (23). Among the cases in our study, iodine deficiency may explain the relatively high proportion of follicular (17%) and low proportion of papillary (74%) thyroid carcinoma in Denmark versus the other 3 countries (25). In addition to iodine deficiency, thyroid autoimmune disorders such as Graves disease and Hashimoto thyroiditis may trigger the development of thyroid dysfunction, which may, in turn, contribute to an increased risk of maternal thyroid cancer (21, 22). Suppression of thyroid autoantibodies and thyroid stimulating hormone have been proposed as possible biological mechanisms underlying the inverse association between smoking and thyroid cancer (26). Consistent with our findings for maternal thyroid disorders and papillary thyroid cancer risk, positive thyroid peroxidase (TPO) antibody status and TPO antibody titer were positively associated with papillary thyroid cancer in a recent nested case-control study of US active-duty personnel (27).

In addition to thyroid dysfunction and autoimmunity, the results from this analysis suggest a possible role of sex steroid and growth hormones in thyroid cancer development. Estradiol and progesterone rise substantially over the course of gestation and may directly influence thyroid cancer progression by increasing proliferation of existing thyroid cancer cells, or indirectly by influencing thyroid hormone synthesis (28). Experimental studies have shown greater estrogen receptor (ER) expression in thyroid cancer versus normal thyroid tissue; they have also shown that estradiol directly regulates thyroid cancer cell proliferation by binding to ER-α and ER-β (29). Overt thyroid diseases in pregnancy have been linked to increased risk of miscarriage and other adverse obstetrical and fetal outcomes, such as preterm birth, both low and high birth weight, and some outcomes that were not associated with maternal thyroid cancer risk in our study (e.g., preeclampsia, gestational diabetes, and placental abruption) (24, 30). Hyperemesis gravidarum also has been associated with increased risk of maternal hyperthyroidism (9). Birth weight is positively associated with concentrations of maternal and fetal growth hormone, including insulin-like growth factor-I (IGF-I) (10), and prediagnostic IGF-I has been positively associated with differentiated thyroid cancer risk (31). Higher birth weight is also associated with more circulating maternal estriol and progesterone (10). Prospective studies that directly evaluate prediagnostic measurements of thyroid hormones and autoantibodies, sex steroid hormones, and growth hormones in relation to maternal thyroid cancer risk may provide additional insights about the biological mechanisms contributing to thyroid carcinogenesis.

Strengths of this study include the large number of thyroid cancer cases and controls identified over a study period spanning several decades, made possible by combining high-quality, nationwide birth, hospital, and cancer registry data from 4 Nordic countries. Mandatory reporting of pregnancy and birth information to the MBRs allowed for nearly complete data for most variables of interest.

Study limitations include potential underascertainment of some maternal or offspring medical diagnoses. Diagnoses occurring under the care of nonspecialists (e.g., general practitioners) and not referred to hospital specialists were not included in the National Patient Registries (16). In general, underascertainment of these conditions was expected to bias associations toward the null. Data on prepregnancy body mass index and smoking in pregnancy were not available across all the countries and the entire study period. Thus, we had limited statistical power to assess these factors as main exposures or potential confounding factors; these findings also may not be generalizable to the full study population. In addition, we were unable to evaluate maternal thyroid cancer risk in relation to breastfeeding, which is highly prevalent in the Nordic countries and increases susceptibility to iodine deficiency (24). As mentioned above, detection bias is also a major concern in epidemiologic studies of thyroid cancer. In addition to serving as surrogates for hormonal exposures, some perinatal characteristics examined in this study could reflect greater health-care access and utilization, thereby increasing the likelihood of incidental detection. We used various statistical approaches, such as excluding cases diagnosed within 2 (or 5) years after pregnancy, to minimize this bias. However, such exclusions may inadvertently have hindered our ability to detect true causal associations of pregnancy hormones, which could have contributed to growth and progression of existing tumors to the point of clinical detection. Individual matching of cases and controls by county of residence helped to minimize detection bias by reducing variation in access to health care and thyroid diagnostic practices, while also controlling for other potential sources of confounding, including regional differences in iodine intake. Furthermore, incidental detection/ overdiagnosis appears to be less pervasive in the Nordic countries compared with other high-income countries (32). Another limitation was the lack of information on childhood exposure to ionizing radiation and genetic predisposition to thyroid cancer. Still, these factors were unlikely to have been associated with the perinatal characteristics examined and would therefore not have been expected to act as strong confounders. Finally, we lacked data on disease severity and treatments for the medical conditions examined. Additional linkages with national hospital, patient, and prescription registries, which cover a more limited timespan than the birth registries, would be more costly and time-consuming to conduct but would allow for a more in-depth investigation of the associations examined here.

In summary, the results of this large population-based registry linkage study support a link between pregnancy-related hormonal exposures and maternal thyroid cancer risk. Future studies are needed to confirm these findings and to better understand the potential underlying mechanisms.

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