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Relation Between Hysterectomy, Oophorectomy and the Risk of Incident Differentiated Thyroid Cancer

The E3N Cohort

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Abstract and Introduction

Abstract

Background: Thyroid cancers are threefold more frequent in women than in men. A role of reproductive or hormonal factors has been suggested but with contradictory results. We investigated potential associations between history of hysterectomy, with or without oophorectomy, and history of benign gynaecological disease (uterine fibroids, endometriosis) and the incidence of differentiated thyroid cancer, in a large French prospective cohort.

Methods: A total of 89 340 women from the E3N cohort were followed up between 1990 and 2012. Gynaecological diseases treated by surgery were self-reported. Thyroid cancers were validated by histological reports. Time-dependent covariates included smoking status, BMI and history of benign thyroid disease. Cox proportional hazard models with age as timescale were used to estimate Hazard Ratios (HR) and 95% confidence intervals (CI).

Results: A total of 412 cases of thyroid cancer were diagnosed during follow-up. A history of hysterectomy was associated with an increased risk of differentiated thyroid cancer (adjusted HR=2.05; 95%CI: 1.65-2.55). The association was not altered after further adjustment for reproductive factors. Endometriosis, uterine polyps, ovarian cysts and oophorectomy without hysterectomy were not associated with the risk of thyroid cancer. A history of fibroids was also significantly related to the risk of thyroid cancer over the follow-up period (adjusted HR=1.91; 95%CI: 1.50–2.44) and the increased risk persisted after adjustment for history of hysterectomy.

Conclusions: Women who had either a history of fibroids or hysterectomy had an increased risk of differentiated thyroid cancer. These findings suggest shared biological mechanisms between fibroids and thyroid cancer, which deserve to be further dissected.

Introduction

Incidence of thyroid cancer has increased worldwide over the recent decades.[1,2] Some established risk factors for thyroid cancer are known, such as ionizing radiation, benign thyroid disease, genetic predisposal and high body mass index (BMI).[1,3,4] Based on epidemiological data, it has long been proposed that hormonal factors may determine or modulate the risk of thyroid cancer. Indeed, thyroid cancers are threefold more frequent in women than in men after puberty and incidence decreases after menopause.[5,6] A role of female hormones in the aetiology of thyroid cancer has been suggested with a direct action of oestrogens, via its receptors (ER), on proliferative and neoplastic disorders.[6] However, the relationship between thyroid cancer risk and reproductive or hormonal factors is still debated, with contradictory and often inconclusive findings on the association between thyroid cancer and age at puberty, menopause, parity, breast-feeding or menopausal hormone therapy.[5,7–9]

Hysterectomy is one of the most common surgical procedures in gynaecology worldwide and is mainly performed in case of a benign disease such as fibroma and endometriosis, conditions which are associated with lifetime sex steroid hormone exposure.[10–12]

Several studies have attempted to determine hormonal and reproductive factors involved in the development of thyroid cancer in women, with conflicting results.[5,9,13] A potential association between hysterectomy and thyroid cancer risk has already been described, but in studies with methodological heterogeneities and potential bias.[7,14–17] Moreover, links between thyroid cancer risk and hysterectomy, oophorectomy or benign gynaecological disease histories have not been investigated simultaneously, despite common aetiological factors and frequent morbid associations. Thus, we aimed to prospectively explore the link between differentiated thyroid cancer (micro- or macro-carcinomas) and a history of hysterectomy, with or without oophorectomy, in a large cohort, according to age and time since gynaecological surgery. In addition, we investigated the relation between a history of benign gynaecological disease (uterine fibroids, endometriosis, ovarian cyst and uterine polyp) and the risk of incident thyroid cancer.

Materials and Methods

The E3N Cohort

TheE3N cohort study (Etude Epidemiologique de Femmes de la Mutuelle Générale de l'Education Nationale) is a prospective cohort of 98 995 French women born between 1925 and 1950 and insured by a national health system primarily covering teachers.18Participants have received 11 follow-up questionnaires (mailed every 2–3 years) and responded to each at a rate of ~80%.[18] The women were enrolled in 1990 after they returned a baseline self-administered questionnaire on their lifestyle and medical history. All women signed an informed consent, in compliance with the rules of the French National Commission for Data Protection and Individual Freedom from which approval was obtained.

Thyroid Disease Assessment

Each questionnaire inquired about cancer occurrence, and requested information and permission to contact participants' physicians. Cases were confirmed by pathology reports.[18] Here, we considered only histologically confirmed first incident primary differentiated thyroid cancer cases (ie, papillary (International Classification of Diseases for Oncology, ICD-O codes: 8050, 8052, 8130, 8260, 8263, 8340- 8344, 8350, 8450) and follicular (8290, 8330–8335, 8480, 8490)), excluding 21 cases of anaplastic or medullary thyroid cancer. Micro- and macro-carcinomas were defined as tumours sized <10 mm and ≥10 mm, respectively.

Each questionnaire also inquired about diagnoses of dysthyroidism (hyperthyroidism or hypothyroidism) and of benign morphological thyroid conditions.

Assessment of Hysterectomy and Benign Gynaecological Diseases

Hysterectomy and oophorectomy status (none, or uni- or bilateral), and age at surgery were recorded in each questionnaire. Benign gynaecological diseases considered in this analysis were endometriosis, ovarian cysts, fibroids and uterine polyps recorded in each questionnaire. Ovarian cysts reported by women diagnosed with endometriosis were not considered, to avoid potentially misdiagnosed ovarian endometrioid cyst cases. For all diseases, diagnostic procedures as laparoscopy, biopsy, hysterography, hysteroscopy or ultrasonography were recorded in the 1992, 1993 and 1994 questionnaires and surgical treatments were available in each questionnaire except the baseline questionnaire. For each gynaecological disease, we separately considered those confirmed by surgery or laparoscopy, confirmed by at least one treatment or diagnosis examination, and only self-reported gynaecological diseases.

Population for Analysis

Follow-up started at the date of return of the 1990 questionnaire. Participants contributed person-years of follow-up until the date of diagnosis of any cancer (except basal cell carcinoma and in situ colorectal cancer), the date of the last completed questionnaire, or December 2011 (date of mailing of the 10th questionnaire), whichever occurred first. Women studied were censored at the date of a first thyroid cancer and we did not consider a hysterectomy or other benign gynaecological diseases which occurred following a first thyroid cancer. Among the 98 995 women included in the study, we excluded those who reported a prevalent cancer at baseline other than a basal cell cancer or in situ colorectal cancer (n = 4844), and women with no follow-up data (n = 2073), with primary amenorrhoea or unknown age at menarche (n = 2209), with missing information on age at hysterectomy or oophorectomy (n = 418), or with unknown date of cancer diagnosis (n = 111), ending up with 89 340 women for analysis.

Statistical Analyses

Cox proportional hazard models with age as timescale were used to estimate Hazard ratios (HR) and 95% confidence intervals (CI) of first differentiated thyroid cancer associated with history of hysterectomy or benign gynaecological disease. Women diagnosed with non-differentiated thyroid cancer were censored at the date of diagnosis. Hysterectomy status or benign gynaecological disease variables were analyzed as time-dependent variables. When the variables were not available at a given questionnaire, the preceding value was considered until the next known value. The proportional hazard hypothesis was verified for all time-independent variables of interest using log-log survivor plots. Covariates included in the models used are listed in and . Information on time-dependent variables was updated at each questionnaire. Missing values for all adjustment variables were replaced by the modal value, as they were missing for less than 5% of women.

Table 2. Hazard ratios (HRs) and 95% confidence intervals (95% CI) for differentiated thyroid cancer according to medical history of hysterectomy. E3N cohort, 1990–2011 (n = 89 340)

	Non-cases (N = 88 928)	Cases (N = 412)	M1	M2	M3
			HR (95% CI)	HR (95% CI)	HR (95% CI)
Hysterectomy					
Never	72 864	295	ref	ref	ref
Ever	16 064	117	2.22 (1.79; 2.76)	2.05 (1.65; 2.55)	2.15 (1.72; 2.69)

Surgical intervention					
No intervention	69 278	283	ref	ref	ref
HT and oophorectomy	8853	65	2.40 (1.82; 3.16)	2.21 (1.67; 2.91)	2.35 (1.77; 3.11)
Oophorectomy alone	3586	12	1.04 (0.58; 1.85)	0.98 (0.55; 1.75)	1.00 (0.56; 1.79)
HT alone	7211	52	2.05 (1.52; 2.76)	1.89 (1.41; 2.55)	1.96 (1.46; 2.65)
Age at HT (years old)					
No HT	72 864	295	ref	ref	ref
≤40	2386	25	2.79 (1.85; 4.20)	2.55 (1.70; 3.85)	2.69 (1.78; 4.08)
40–45	3550	27	2.01 (1.35; 2.98)	1.88 (1.27; 2.79)	1.97 (1.32; 2.93)
>45	10 128	65	2.15 (1.64; 2.82)	1.98 (1.50; 2.60)	2.08 (1.57; 2.74)
P-trend			0.69	0.73	0.89
Time since HT (y)					
No HT	72 864	295	ref	ref	ref
≤5	846	21	2.12 (1.36; 3.32)	2.01 (1.29; 3.14)	2.14 (1.37; 3.35)
5–10	1588	28	2.41 (1.63; 3.56)	2.23 (1.51; 3.29)	2.37 (1.60; 3.51)
10–15	2458	19	1.70 (1.07; 2.72)	1.55 (0.97; 2.48)	1.63 (1.02; 2.61)
>15	11 172	49	2.47 (1.79; 3.40)	2.27 (1.64; 3.12)	2.33 (1.69; 3.22)
P-trend			0.54	0.60	0.74

BMI, body mass index; HT, hysterectomy; MHT, menopausal hormone therapy
M1: Model adjusted for age (timescale), and stratified by 5-year category birth cohort (to consider a potential age-cohort effect).
M2: M1 further adjusted for smoking status (ever/never, time-dependent), history of dysthyroidism (hyperthyroidism or hypothyroidism) (ever/never, time-dependent), history of other benign thyroid disease (nodule or goitre) (ever/never, time-dependent) and BMI (<18.5/[18.5–22.5[/[22.5–25[/[25–30[/≥30, time-dependent).
M3: M2 further adjusted for age at menarche (<13 years/≥13 years), use of oral contraceptives (ever/never, time-dependent), infertility treatment (ever/never, last assessed in 1992), parity and age at first full-term pregnancy (nulliparous/one child at age <30/one child at age ≥30/two children or more, the first at age <30/two children or more, the first at age ≥30), age at menopause and use of MHT (premenopausal/postmenopausal with no recent use of MHT/postmenopausal with recent use of MHT/postmenopausal with use of MHT but unknown recency, time-dependent).

Table 3. Hazard ratios (HRs) and 95% confidence intervals (95% CI) for differentiated thyroid cancer according to benign gynaecological diseases. E3N cohort, 1990–2011 (n = 89 340)

	Non-cases (N = 88928)	Cases (N = 412)	M1	M2	M3
			HR (95% CI)	HR (95% CI)	HR (95% CI)
History of benign gynaecological diseases					
Never	41 845	166	ref	ref	ref
Self-reported	47 083	246	**1.71 (1.40; 2.09)**	**1.58 (1.29; 1.93)**	**1.59 (1.30; 1.95)**
Medically confirmed	36 793	191	**1.82 [1.47; 2.25]**	**1.63 [1.31; 2.03]**	**1.63 [1.31; 2.02]**
Surgically confirmed	27 465	143	**1.87 [1.48; 2.35]**	**1.67 [1.32; 2.11]**	**1.66 [1.31; 2.10]**

Fibroid history					
Never	60 986	244	ref	ref	ref
Self-reported	27 942	168	**1.87 (1.53; 2.28)**	**1.71 (1.40; 2.08)**	**1.73 (1.41; 2.11)**
Medically confirmed	21 198	127	**1.95 (1.57; 2.43)**	**1.74 (1.40; 2.17)**	**1.75 (1.40; 2.19)**
Surgically confirmed	14 725	94	**2.16 (1.69; 2.76)**	**1.91 (1.50; 2.44)**	**1.93 (1.51; 2.48)**
Endometriosis history					
Never	82 322	376	ref	ref	ref
Self-reported	6606	36	1.39 (0.99; 1.96)	1.26 (0.90; 1.78)	1.27 (0.90; 1.79)
Medically confirmed	5096	27	1.39 (0.94; 2.06)	1.25 (0.85; 1.86)	1.26 (0.85; 1.86)
Surgically confirmed	3922	20	1.32 (0.84; 2.07)	1.20 (0.76; 1.88)	1.19 (0.76; 1.88)
Uterine polyp history					
Never	70 291	329	ref	ref	ref
Self-reported	18 637	83	1.22 (0.96; 1.55)	1.15 (0.90; 1.46)	1.15 (0.90; 1.47)
Medically confirmed	13 700	57	1.19 (0.89; 1.58)	1.09 (0.82; 1.45)	1.09 (0.82; 1.45)
Surgically confirmed	11 436	49	1.21 (0.89; 1.64)	1.11 (0.82; 1.51)	1.11 (0.82; 1.50)
Ovarian cyst history					
Never	73 665	336	ref	ref	ref
Self-reported	15 263	76	**1.32 (1.03; 1.69)**	1.23 (0.96; 1.58)	1.24 (0.96; 1.59)
Medically confirmed	11 121	58	**1.44 (1.09; 1.91)**	1.31 (0.99; 1.74)	1.32 (0.99; 1.75)
Surgically confirmed	8211	41	**1.42 (1.03; 1.97)**	1.29 (0.93; 1.78)	1.30 (0.94; 1.81)

BMI, body mass index; HT, hysterectomy; MHT, menopausal hormone therapy
M1: Model adjusted for age (timescale), and stratified by 5-year category birth cohort (to consider a potential age-cohort effect)
M2: M1 further adjusted for smoking status (ever/never, time-dependent), history of dysthyroidism (hyperthyroidism or hypothyroidism) (ever/never, time-dependent), history of other benign thyroid disease (nodule or goitre) (ever/never, time-dependent) and BMI (<18.5/[18.5–22.5[/[22.5–25[/[25–30[/≥30, time-dependent)
M3: M2 further adjusted for age at menarche (<13 years/≥13 years), use of oral contraceptives (ever/never, time-dependent), infertility treatment (ever/never, last assessed in 1992), parity and age at first full-term pregnancy (nulliparous/one child at age <30/one child at age ≥30/two children or more, the first at age <30/two children or more, the first at age ≥30), age at menopause and use of MHT (premenopausal/postmenopausal with no recent use of MHT/postmenopausal with recent use of MHT/postmenopausal with use of MHT but unknown recency, time-dependent).

We performed stratified analyses to explore associations according to tumour size (micro- (<10 mm) or macro- (≥10 mm) carcinoma) using competing-risk models. Cases with missing values on tumour size were excluded from these analyses, and analyses were performed in each strata by censoring the cases belonged to the other strata at date of diagnosis.

We used homogeneity tests to compare risk estimates across strata using the Wald chi-square statistic.

Smoking status and a history of dysthyroidism were evaluated as potential effect modifiers by adding an interaction term in the final model and testing statistical significance. All tests were two-sided, and statistical significance (*P*-value) was set at the 0.05 level. All analyses were performed using Statistical Analysis Systems (SAS) software, version 9.3 (SAS Institute, Inc, Cary, North Carolina).

Results

Among 89 340 women considered in the present analysis, 412 cases of first primary differentiated thyroid cancer (381 papillary and 31 follicular) were diagnosed during 1 603 264 person-years of observation (median follow-up duration of 9.9 years for cases and 21.4 years for non-cases). Of the 412 cases of thyroid cancer, the information on the micro- or macro-carcinoma status was missing for 9. A total of 166 (41%) were considered as micro-carcinoma (size <10 mm) and 237 were micro-carcinoma (size ≥10 mm).

As shown in , the frequency of goitre/thyroid nodules was similar between women with an history of hysterectomy and those who did not have hysterectomy. The prevalence of excessive weight or obesity was higher among the women with an history of

hysterectomy as compared to those without hysterectomy.

Table 1. Patients characteristics according to baseline hysterectomy status. E3N cohort, 1990–2011 (n = 89 340)

	No hysterectomy (n = 80 197) n (%)	Hysterectomy (n = 9143) n (%)
Age at baseline		
Mean ± SD	48.8 ± 6.5	53.1 ± 6.2
Smoking status		
Never	43 121 (53.8)	5451 (59.6)
Ever	37 076 (46.2)	3692 (40.4)
History of dysthyroidism		
Never	74 838 (93.3)	8292 (90.7)
Ever	5359 (6.7)	851 (9.3)
History of goitre or thyroid nodules		
Never	79 588 (99.2)	9056 (99.0)
Ever	609 (0.8)	87 (1.0)
Body mass index, (kg/m^2)		
<18.5	3479 (4.4)	250 (2.7)
18.5–22.5	43 894 (54.7)	3980 (43.5)
22.5–25	19 659 (24.5)	2607 (28.5)
25–30	10 932 (13.6)	1870 (20.5)
≥30	2233 (2.8)	436 (4.8)
Age at menarche (years)		
<13	36 754 (45.8)	4463 (48.8)
≥13	43 443 (54.2)	4680 (51.2)
Use of oral contraceptives		
Never	33 644 (42.0)	6000 (65.6)
Ever	46 553 (58.0)	3143 (34.4)
Infertility treatment		
Never	74 269 (92.6)	8499 (93.0)
Ever	5928 (7.4)	644 (7.0)
Parity and age at first full-term pregnancy		
Nulliparous	8987 (11.2)	1278 (14.0)
One child at age <30	8956 (11.2)	1201 (13.1)
One child at age ≥30	3848 (4.8)	280 (3.1)
Two or more children, the first at age <30	53 274 (66.4)	6072 (66.4)
Two or more children, the first at age ≥30	5132 (6.4)	312 (3.4)
Menopausal status and use of MHT at baseline		
Premenopausal	51 692 (64.5)	2245 (24.6)
Postmenopausal with no recent use of MHT	16 273 (20.3)	3749 (41.0)
Postmenopausal with recent use of MHT	7446 (9.3)	1875 (20.5)
Postmenopausal with unknown use of MHT	4786 (6.0)	1274 (13.9)

Menopausal status at the end of the follow-up		
Premenopausal	4828 (6.0)	148 (1.6)
Postmenopausal	75 369 (94.0)	8995 (98.4)
Age at menopausal at the end of follow-up		
Mean ± SD	51.0 ± 3.5	47.3 ± 5.7

Hysterectomy/Oophorectomy and Risk of Thyroid Cancer

Women with a history of hysterectomy had an increased risk of differentiated thyroid cancer (HR=2.05, 95%CI 1.65–2.55; model 2), as compared to women without hysterectomy (Figure 1,). When considering types of hysterectomy/oophorectomy, the highest risk was observed for women with hysterectomy and uni- or bilateral oophorectomy (HR=2.21, 95%CI 1.67–2.91). There was no association between oophorectomy alone and thyroid cancer risk. Risks were similar whatever the age at the hysterectomy or the time since hysterectomy. Associations were similar although slightly stronger after adjustment for reproductive factors (model 3) (). Results were similar for papillary and follicular cancers (HR=2.02, 95%CI 1.61–2.53 for papillary, HR=2.52, 95%CI 1.17–5.44 for follicular, $P_{homogeneity}$ =*0*.59, model 2). Both micro- and macro-carcinomas ((HR=1.81, 95%CI 1.28–2.57 and HR=2.16, 95%CI 1.62–2.88 respectively, $P_{homogeneity}$ =*0*.45*,* model 2) were associated with a history of hysterectomy.

Table 2. Hazard ratios (HRs) and 95% confidence intervals (95% CI) for differentiated thyroid cancer according to medical history of hysterectomy. E3N cohort, 1990–2011 (n = 89 340)

	Non-cases (N = 88 928)	Cases (N = 412)	M1	M2	M3
			HR (95% CI)	HR (95% CI)	HR (95% CI)
Hysterectomy					
Never	72 864	295	ref	ref	ref
Ever	16 064	117	2.22 (1.79; 2.76)	2.05 (1.65; 2.55)	2.15 (1.72; 2.69)
Surgical intervention					
No intervention	69 278	283	ref	ref	ref
HT and oophorectomy	8853	65	2.40 (1.82; 3.16)	2.21 (1.67; 2.91)	2.35 (1.77; 3.11)
Oophorectomy alone	3586	12	1.04 (0.58; 1.85)	0.98 (0.55; 1.75)	1.00 (0.56; 1.79)
HT alone	7211	52	2.05 (1.52; 2.76)	1.89 (1.41; 2.55)	1.96 (1.46; 2.65)
Age at HT (years old)					
No HT	72 864	295	ref	ref	ref
≤40	2386	25	2.79 (1.85; 4.20)	2.55 (1.70; 3.85)	2.69 (1.78; 4.08)
40–45	3550	27	2.01 (1.35; 2.98)	1.88 (1.27; 2.79)	1.97 (1.32; 2.93)
>45	10 128	65	2.15 (1.64; 2.82)	1.98 (1.50; 2.60)	2.08 (1.57; 2.74)
P-trend			0.69	0.73	0.89
Time since HT (y)					
No HT	72 864	295	ref	ref	ref
≤5	846	21	2.12 (1.36; 3.32)	2.01 (1.29; 3.14)	2.14 (1.37; 3.35)
5–10	1588	28	2.41 (1.63; 3.56)	2.23 (1.51; 3.29)	2.37 (1.60; 3.51)
10–15	2458	19	1.70 (1.07;	1.55 (0.97;	1.63 (1.02;

			2.72)	2.48)	2.61)
>15	11 172	49	2.47 (1.79; 3.40)	2.27 (1.64; 3.12)	2.33 (1.69; 3.22)
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BMI, body mass index; HT, hysterectomy; MHT, menopausal hormone therapy
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M2: M1 further adjusted for smoking status (ever/never, time-dependent), history of dysthyroidism (hyperthyroidism or hypothyroidism) (ever/never, time-dependent), history of other benign thyroid disease (nodule or goitre) (ever/never, time-dependent) and BMI (<18.5/[18.5–22.5[/[22.5–25[/[25–30[/≥30, time-dependent).
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			3.40)	3.12)	3.22)
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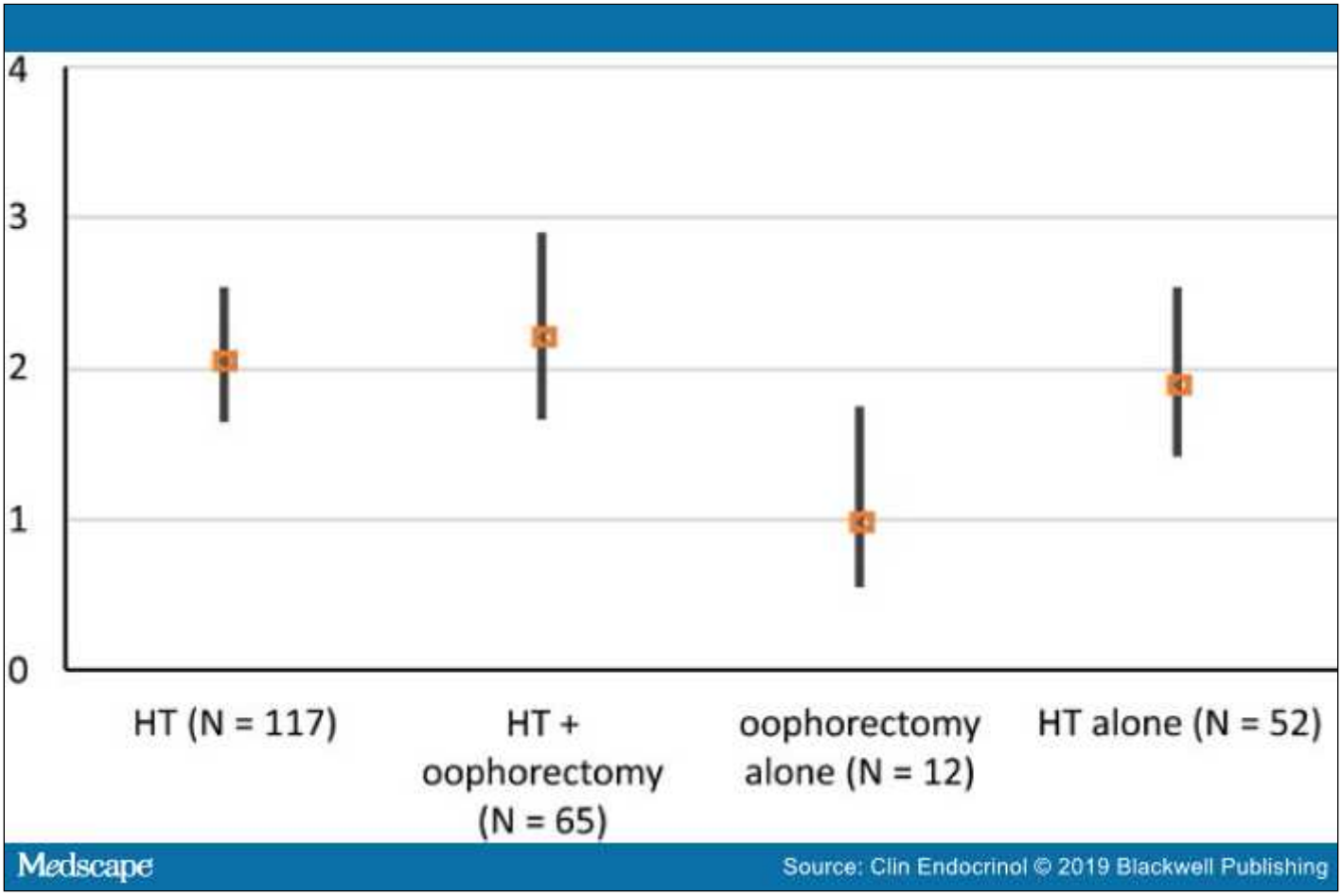

Figure 1.

Risk of thyroid cancer according to the mode of diagnosis of fibroids and the absence of a history of hysterectomy. Hazard ratio and 95% CI are displayed from the multivariate model 2

The association between a history of hysterectomy and thyroid cancer risk was not modified by smoking status nor dysthyroidism history ($P_{interaction}$ =*0*.09 and 0.23, respectively) and was observed in all corresponding strata.

Fibroids

Overall, a history of benign gynaecological disease confirmed by surgery or laparoscopy was associated with increased thyroid cancer risk (HR 1.67, 95%CI 1.32–2.11; model 2;). The increase was driven by the association with uterine fibroids history (HR 1.91; 95% CI 1.50–2.44, model 2;). This association was observed whatever the mode of diagnosis of fibroids and irrespective of a history of hysterectomy (). Women with a confirmed history of fibroids had an increased risk of both micro- (HR=1.54, 95%CI 1.03–2.30, model 2) and macro-carcinomas (HR=2.16, 95%CI 1.57–2.97, model 2). If we consider simultaneously history of hysterectomy and of fibroids in the same multivariate statistical model (model 2), each variable remains statistically

associated with the risk of thyroid cancer [hysterectomy (yes/no): HR=1.70, 95% CI :1.27–2.28; history of fibroids (yes/no): HR=1.33, 95% CI :1.01–1.75].

Table 3. Hazard ratios (HRs) and 95% confidence intervals (95% CI) for differentiated thyroid cancer according to benign gynaecological diseases. E3N cohort, 1990–2011 (n = 89 340)

	Non-cases (N = 88928)	Cases (N = 412)	M1	M2	M3
			HR (95% CI)	HR (95% CI)	HR (95% CI)
History of benign gynaecological diseases					
Never	41 845	166	ref	ref	ref
Self-reported	47 083	246	**1.71 (1.40; 2.09)**	**1.58 (1.29; 1.93)**	**1.59 (1.30; 1.95)**
Medically confirmed	36 793	191	**1.82 [1.47; 2.25]**	**1.63 [1.31; 2.03]**	**1.63 [1.31; 2.02]**
Surgically confirmed	27 465	143	**1.87 [1.48; 2.35]**	**1.67 [1.32; 2.11]**	**1.66 [1.31; 2.10]**
Fibroid history					
Never	60 986	244	ref	ref	ref
Self-reported	27 942	168	**1.87 (1.53; 2.28)**	**1.71 (1.40; 2.08)**	**1.73 (1.41; 2.11)**
Medically confirmed	21 198	127	**1.95 (1.57; 2.43)**	**1.74 (1.40; 2.17)**	**1.75 (1.40; 2.19)**
Surgically confirmed	14 725	94	**2.16 (1.69; 2.76)**	**1.91 (1.50; 2.44)**	**1.93 (1.51; 2.48)**
Endometriosis history					
Never	82 322	376	ref	ref	ref
Self-reported	6606	36	1.39 (0.99; 1.96)	1.26 (0.90; 1.78)	1.27 (0.90; 1.79)
Medically confirmed	5096	27	1.39 (0.94; 2.06)	1.25 (0.85; 1.86)	1.26 (0.85; 1.86)
Surgically confirmed	3922	20	1.32 (0.84; 2.07)	1.20 (0.76; 1.88)	1.19 (0.76; 1.88)
Uterine polyp history					
Never	70 291	329	ref	ref	ref
Self-reported	18 637	83	1.22 (0.96; 1.55)	1.15 (0.90; 1.46)	1.15 (0.90; 1.47)
Medically confirmed	13 700	57	1.19 (0.89; 1.58)	1.09 (0.82; 1.45)	1.09 (0.82; 1.45)
Surgically confirmed	11 436	49	1.21 (0.89; 1.64)	1.11 (0.82; 1.51)	1.11 (0.82; 1.50)
Ovarian cyst history					
Never	73 665	336	ref	ref	ref
Self-reported	15 263	76	**1.32 (1.03; 1.69)**	1.23 (0.96; 1.58)	1.24 (0.96; 1.59)
Medically confirmed	11 121	58	**1.44 (1.09; 1.91)**	1.31 (0.99; 1.74)	1.32 (0.99; 1.75)
Surgically confirmed	8211	41	**1.42 (1.03; 1.97)**	1.29 (0.93; 1.78)	1.30 (0.94; 1.81)

BMI, body mass index; HT, hysterectomy; MHT, menopausal hormone therapy
M1: Model adjusted for age (timescale), and stratified by 5-year category birth cohort (to consider a potential age-cohort effect)
M2: M1 further adjusted for smoking status (ever/never, time-dependent), history of dysthyroidism (hyperthyroidism or hypothyroidism) (ever/never, time-dependent), history of other benign thyroid disease (nodule or goitre) (ever/never, time-dependent) and BMI (<18.5/[18.5–22.5[/[22.5–25[/[25–30[/≥30, time-dependent)
M3: M2 further adjusted for age at menarche (<13 years/≥13 years), use of oral contraceptives (ever/never, time-dependent), infertility treatment (ever/never, last assessed in 1992), parity and age at first full-term pregnancy (nulliparous/one child at age <30/one child at age ≥30/two children or more, the first at age <30/two children or more, the first at age ≥30), age at menopause and use of MHT (premenopausal/postmenopausal with no recent use of MHT/postmenopausal with recent use of MHT/postmenopausal with use of MHT but unknown recency, time-dependent).

Table 3. Hazard ratios (HRs) and 95% confidence intervals (95% CI) for differentiated thyroid cancer according to benign gynaecological diseases. E3N cohort, 1990–2011 (n = 89 340)

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Surgically confirmed	14 725	94	**2.16 (1.69; 2.76)**	**1.91 (1.50; 2.44)**	**1.93 (1.51; 2.48)**
Endometriosis history					
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Uterine polyp history					
Never	70 291	329	ref	ref	ref
Self-reported	18 637	83	1.22 (0.96; 1.55)	1.15 (0.90; 1.46)	1.15 (0.90; 1.47)
Medically confirmed	13 700	57	1.19 (0.89; 1.58)	1.09 (0.82; 1.45)	1.09 (0.82; 1.45)
Surgically confirmed	11 436	49	1.21 (0.89; 1.64)	1.11 (0.82; 1.51)	1.11 (0.82; 1.50)
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Fibroid history					
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Never	82 322	376	ref	ref	ref
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Neither self-reported nor confirmed history of endometriosis, uterine polyps or ovarian cysts were associated with thyroid cancer risk (). Results were similar for papillary and follicular thyroid cancers (data not shown).

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Finally, we performed sensitivity analyses by excluding women who had an early diagnosis of thyroid cancer (first 2 years of follow-up) and the results were unchanged: women with a history of hysterectomy had an increased risk of differentiated thyroid cancer (HR=2.01, 95%CI 1.60–2.52; model 2), as compared to women without hysterectomy. Similarly, those who had a history of uterine fibroma were at higher risk of thyroid cancer as well (HR 1.84; 95% CI 1.47–2.30, model 2).

Discussion

In this large prospective study with more than 400 incident thyroid cancer cases occurring in women aged 40–65 at baseline, we found a positive relationship between the risk of differentiated thyroid cancer and a history of hysterectomy, but not with a history of oophorectomy. Results were similar whatever the age at hysterectomy or time since hysterectomy. We observed also an association between a history of fibroids and the risk of thyroid cancer, which appears to be independent of a history of hysterectomy.

Hysterectomy/Oophorectomy Status and Risk of Thyroid Cancer

A recent meta-analysis reported an association between a history of hysterectomy and the risk of thyroid cancer with a summary relative risk (SRR) of 1.43.[5] However, the results were contrasting as only five out of 24 studies found that hysterectomy was associated with an increased risk of thyroid cancer. Other studies focusing specifically on the link between differentiated thyroid cancer risk and a history of hysterectomy were also conflicting.[7,11,14,15,17,19,20] Methodological flaws may partly explain these discrepancies, due to case-control design and retrospective self-reported surgery history. Besides, studies concluding that there was a positive relationship between a history of hysterectomy and thyroid cancer risk did not perform adjustment on history of benign thyroid disease or family history of thyroid cancer, and thus could not discard the possibility of confounding.[14,15,17,19]

In contrast to previous studies,[14,15,17] we did not observe any change in the association between hysterectomy and the risk of thyroid cancer in relation to the time elapsed since hysterectomy or according to the age at hysterectomy. This finding is an argument against a potential detection bias associated with gynaecological surgery. However, we cannot exclude such a detection bias. It could be speculated that thyroid cancer may be more likely to be found among women with hysterectomy or fibroids, because of medical attention received, as compared to those without the conditions. However, the slightly stronger relation observed between hysterectomy or fibroids and macro-cancers compared with micro-cancers is not in favour of a potential screening bias, which involved the detection of a majority of micro-carcinoma.

Surgically induced menopause, often defined in studies as hysterectomy and/or bilateral oophorectomy has previously been associated with an increased risk of thyroid cancer.[8,16,21] When we considered simultaneously hysterectomy and oophorectomy status, we found that a history of oophorectomy was not related to the risk of thyroid cancer and did not substantially affect the association between hysterectomy and thyroid cancer. This is consistent with the WHI cohort for which Kabat et al[7] did not find any association between thyroid cancer risk and bilateral oophorectomy. Some authors found either a higher,[22] a lower[15,17] or a similar[11,14,16] risk of thyroid cancer in women with hysterectomy and bilateral oophorectomy compared to women with hysterectomy alone or hysterectomy with partial oophorectomy.

Benign Gynaecological Diseases History and Risk of Thyroid Cancer

Our study revealed a positive association between a history of fibroids and the risk of differentiated thyroid cancer, which is consistent with the relationship between hysterectomy and thyroid cancer as uterine fibroids are the most common cause of hysterectomy.[12] The twofold increased risk of thyroid cancer linked to surgically treated fibroids was similar to results reported in two American studies.[11,15]

Studies on the relationship between endometriosis history and thyroid cancer risk are more conflicting, with HR/SIR varying between 0.85 and 3.09. Only two studies found an increased risk of thyroid cancer in women with an endometriosis evolving from more than 5 years[23] and in parous women.[24] It may reflect discrepancies in the definition of endometriosis cases, differences in the populations and the design of the studies: some used retrospective cohort of infertile women,[25] other used data extracted from inpatient and cancer registers[23,24,26] or self-reported endometriosis history.[12]

As previous studies,[11] we found no relationship between an ovarian cyst history and thyroid cancer risk, which is in line with the lack of link between oophorectomy and thyroid cancer in our study.

Our results seem not to be related to detection bias. Uterine fibroids are the most common pelvic tumours, occurring in nearly 70% of all reproductive-aged women.[12] Hyper- or hypothyroidism both enhance the likelihood of their diagnosis or treatment[27] by causing abnormal uterine bleeding and have been linked with an increased risk of differentiated thyroid cancer.[28,29] However, the fact that we found a similar thyroid cancer risk whatever the time elapsed since surgery argues against this. Moreover, the slightly stronger relation observed between hysterectomy or fibroids and macro-cancers compared with micro-cancers is not in favour of a potential screening bias.

Potential Mechanisms Linking Uterine Fibroids and Differentiated Cancer Thyroid

Uterine fibroids have been associated with thyroid nodules [30,31] and hypothyroidism [32] in transversal studies, suggesting shared mechanisms between fibroids and thyroid diseases. Both fibroids and thyroid cancers are thought to be sex steroid dependent.

If the link between hormonal factors and the risk of fibroids is well established,[11] the relationship between sex hormones and thyroid cancer is much less characterized. Both oestrogen receptors α (ER α) with a proliferative and anti-apoptotic function, and oestrogen receptors β (ERβ) with a pro-apoptotic function, are expressed in normal and thyroid tumour cells. Thyroid cell proliferation and neoplastic development might depend on the imbalance between ER α and ERβ.[6,33] Moreover, progesterone receptors have already been described in thyroid follicular cells, and progesterone has been shown to upregulate genes involved in thyroid function and growth on normal human thyroid cells in vitro.[34] Besides, thyroid cancer cells and fibroids are both able to biosynthesize estradiol in situ through the action of aromatase.[35,36]

However, the link between hormonal factors and thyroid cancer remain inconclusive in several studies[5,7–9] suggesting that not only direct oestrogen action but also other pathways may be shared between fibroids and thyroid cancer, such as growth factors pathways and TSH/thyroid hormones induced pathways. Growth factors and non-genomic estradiol pathways converge towards the aberrant activation of Ras/Raf/MEK/ERK and PI3K/Akt/mTOR signalling in both thyroid and fibroids cells. In addition, due to common nucleotide sequence in ER and thyroid hormone receptor, these receptors can interact and regulate several transcriptional responses to environmental stimuli.[37] Moreover, thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH) and thyroid hormone receptors were shown to be present in monkey uterus.[38] Another study described a smooth muscle cells proliferation after stimulation by TSH.[39]

Somatic genetic mutations play a part in the molecular pathogenesis of both fibroids (MED12 mutations)[12] and differentiated thyroid cancer (eg, *BRAF* mutations).[1] Thus, a chronic reduction in DNA repair capacity might explain partly a common susceptibility to differentiated thyroid cancer and fibroids. The increased risk of both thyroid cancer and fibroids in atomic bomb survivors illustrates this hypothesis.[40] Increased insulin resistance or related hyperinsulinemia might be a common underlying

factor shared by women with uterine fibroids which may predispose to the development of thyroid cancer as recently suggested.[41]

Strengths and Limits

Strengths of our study include its prospective design, large sample size, histological confirmation of all thyroid cancer cases and availability of data for most differentiated risk factors including a history of benign thyroid conditions. Exposure data were collected before diagnosis of thyroid cancer, avoiding potential recall biases. To our knowledge, it is the first study that investigated an association between hysterectomy, uterine fibroids and micro- and macro-thyroid cancer risk.

This cohort is not representative of the French population and our results cannot be extrapolated to the entire French population. As in all observational studies, residual confounding may subsist. Misclassification of exposure status is a potential limitation because of the self-reported assessment of surgery, benign gynaecological and thyroid diseases. Moreover, when we restricted the analysis to the treated cases, the associations remain consistent. Women included in our study, although younger than in the WHI and PLCO studies, were mostly postmenopausal, and our results may not be generalizable to young premenopausal women.

Conclusion

Our findings showed that hysterectomy or a history of fibroids were associated with a twofold increased risk of differentiated thyroid cancer (micro- and macro-carcinomas) in mostly postmenopausal women. This relation might be explained by common signalling pathways regulated by oestrogen, progesterone or TSH/thyroid hormones. Further studies are needed to delineate the underlying molecular mechanisms or pathways.

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