American Journal of Epidemiology Advance Access published September 30, 2014

American Journal of Epidemiology

DOI: 10.1093/aje/kwu220

Original Contribution

Menstrual and Reproductive Factors in the Risk of Differentiated Thyroid Carcinoma in Young Women in France: A Population-Based Case-Control Study

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Initially submitted March 17, 2014; accepted for publication July 23, 2014.

The incidence of thyroid cancer has increased in eastern Europe since the Chernobyl nuclear power plant accident. Although the radioactive fallout was much less severe and the thyroid radiation dose was much lower in France, a case-control study was initiated in eastern France. The present study included 633 young women who were diagnosed with differentiated thyroid cancer before 35 years of age between 2002 and 2006 and matched with 677 controls. Face-to-face interviews were conducted from 2005 to 2010. Odds ratios were calculated using conditional logistic regressions and were reported in the total group and by histopathological type of cancer ("only papillary" and "excluding microcarcinomas"). The risk of thyroid cancer was higher in women who had a higher number of pregnancies, used a lactation suppressant, or had early menarche. Conversely, breastfeeding, oral contraceptive use, and late age at first pregnancy were associated with a lower risk of thyroid cancer. No association was observed between thyroid cancer and having irregular menstrual cycle, undergoing treatment for menstrual cycle regularity shortly after menarche, having a cessation of menstruation, use of another contraceptive, history of miscarriage or abortion for the first pregnancy, or having had gestational diabetes. This study confirms the role of hormonal and reproductive factors in thyroid cancer, and our results support the fact that exposure to estrogens increases thyroid cancer risk.

case-control study; menstruation; oral contraception; pregnancy; thyroid cancer

Abbreviations: BMI, body mass index; CI, confidence interval; DTC, differentiated thyroid cancer; OC, oral contraceptive; OR, odds ratio.

Over the past 10 years, important progress has been made in understanding risk factors for differentiated thyroid cancer (DTC) as the result of the increasing number of studies on this subject. In addition to the role of exposure to ionizing radiation during childhood, which is well established (1, 2), there is now also a consensus concerning certain other risk factors, namely tall height and large body size (measured as either body surface area or body mass index (BMI; weight in kilograms divided by height in meters squared)) (3–7). Family history studies have suggested that DTC may have a greater familial component than other nonhereditary cancers, with relative risk estimates of 3–4 (or higher) for first-degree relatives of persons with DTC (8, 9). Conversely, certain factors, such as tobacco smoking (10–12) or being black (13), are known to have an inverse association with DTC risk. Because there is familial aggregation of thyroid disease and DTC, genetic factors are thought to contribute to the risk of DTC, but those factors remain unidentified for the most part (14). However, recent genome-wide association studies on genetic risk factors have shown certain correlations between DTC and single nucleotide polymorphisms in the *forkhead box protein E1* (*FOXE1*), *ataxia telangiectasia mutated* (*ATM*), and *disrupted in renal carcinoma 3* (*DIRC3*) genes (14–17).

Because DTC is consistently more common in women, with female-to-male incidence rates of approximately 3-to-1 in the general population, hormonal and reproductive factors

could be of great importance (18). Moreover, the incidence of DTC in women peaks during their reproductive years (19–21), and the female-to-male ratio reaches 5-to-1 in adolescents and young adults (22). In a pooled analysis, the previously reported associations of DTC risk with hormonal and reproductive factors were heterogeneous among different studies, and those that remained were often very weak (23, 24). The only risk factors for which associations have been established are a high parity rate (25), an advanced age at menarche (26, 27), a late first pregnancy (27), and artificial menopause (27). However, these associations are not always consistent between studies (7). For other factors (menstrual cycle regularity, miscarriage, abortion, use of oral contraceptives (OCs), breastfeeding, age at menopause, etc.), no clear associations have been demonstrated to date.

After the Chernobyl nuclear power plant accident in April 1986, an increased incidence of DTC was observed in children living in contaminated areas of Belarus, Ukraine, and the Russian Federation (28, 29). Although the radioactive fallout was much less severe and the thyroid radiation dose was much lower in France than in the previously mentioned contaminated areas, a case-control study was performed to investigate the role of the fallout and of other potential risk factors in the incidence of DTC in young people. The goal of the present study was to investigate the potential role of hormonal and reproductive factors in DTC risk among young women living in eastern France.

METHODS

Case selection

All patients who were newly diagnosed with DTC between January 1, 2002, and December 31, 2006, were born after January 1, 1971, were less than 35 years of age, and had their main residence in one of the regions of eastern France (Alsace, Champagne-Ardennes, Corse, Franche-Comté, Lorraine, Rhône-Alpes, or Provence-Alpes-Côte d'Azur) were eligible for this study. Incident cases were identified by thoroughly investigating 3 main sources according to the region: 1) the General Cancer Incidence Registry in Champagne-Ardennes, Alsace, and Rhône-Alpes; 2) the National Childhood Cancer Registry (which contains information on children <15 years of age) in all regions; and 3) private and public hospitals in Lorraine, Franche-Comté, Corse, and Provence-Alpes-Côte d'Azur. In these last 4 regions, which are not covered by the General Cancer Incidence Registry, the identification of cancer cases was performed in collaboration with local public health structures. In this way, a collaboration was set up with pathologist networks, specifically with one in the Provence-Alpes-Côte d'Azur region, for which the exhaustiveness and the quality of database has been assessed in previous works (30, 31).

All cases of DTC were histologically confirmed. Information on histopathological diagnosis, the size of the largest cancerous nodule, tumor extension beyond the thyroid capsule, and multifocality were obtained from either the registries or histopathology laboratories. All cases DTC were eligible, regardless of tumor size. Mixed papillary follicular cancers were considered as papillary lesions.

Matching process

Controls were selected from the general population and individually matched to a single case who was the same sex and had the same date of birth (plus or minus 1 year) and region of residence in the year that the case was diagnosed with cancer. Potentially eligible controls were randomly selected in each region from the landline telephone subscriber directory. This was achieved using an SAS random number generator (SAS Institute, Inc., Cary, North Carolina) and a file from France Telecom containing all landline phone numbers (approximately 100 million) in France. Because a large proportion of the population in the targeted age group (10–40 years old at time of interview) only has mobile phones and because a number of people are not included in the directory, controls included not just those selected from the directory but also relatives of those people. Each established contact was asked whether they knew people who fit the selection criteria (year of birth, sex, and region of residence) and whether they could communicate the phone contact details of these potentially eligible controls. This step was done parallel to but independently of the case selection and interview process. This was possible because we used national incidence data to anticipate the age distribution of the cases and therefore the age distribution of the controls required in each region. Only people without DTC were eligible to serve as controls. At the time of the first phone contact, controls were asked about their lack of thyroid cancer, but they did not undergo a medical examination.

Each eligible subject who agreed to participate in the study received an information notice about the study's aims and a consent form to be signed and returned. Once consent forms were received, a database of eligible subjects was compiled so that controls could be selected randomly according to the selection criteria, with at least 1 control per case.

Control contact and interviews

Of the 1,049 eligible persons with DTC, 223 (21%) were not interviewed (Figure 1; Web Table 1, available at http://aje.oxfordjournals.org/). Of the 1,045 contacted controls, 164 (16%) were not interviewed (Figure 1; Web Table 1).

Of the 826 cases who were interviewed, 70 were matched with 2 controls; the others were matched to 1 control. One case who did not live in the region in which he was interviewed and 20 cases who were not matched to a control at the end of this process were excluded. In all, the study consisted of 805 cases, 633 of whom were female. Of the 881 controls who were interviewed, 5 were not matched to a case at the end of this process and were excluded. In all, the study consisted of 876 controls, 679 of whom were female. The median difference in the date of birth between each case and his or her control was 103 (standard deviation, 282) days.

Assurances

The study was approved by the French Data Protection Authority Commission Nationale de l'Informatique et des Libertés

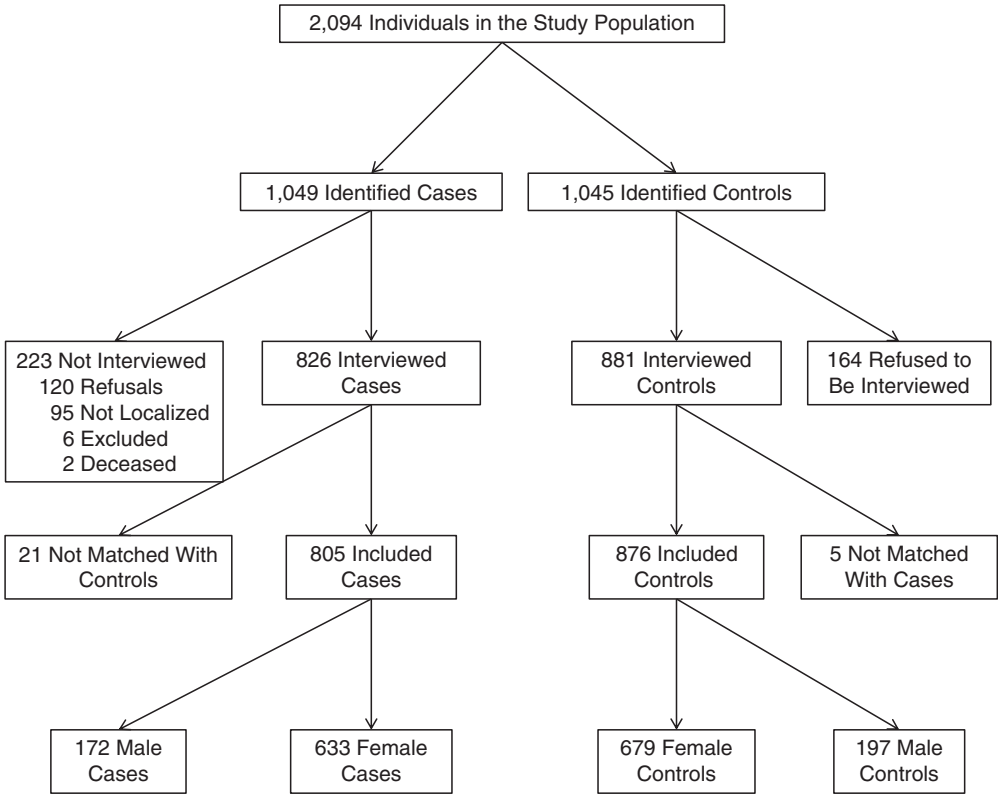

Figure 1. Flow chart of inclusion criteria, eastern France, 2002–2006.

(agreement 05-1120; April 5, 2005). Written consent forms were obtained from all participants.

Data collection

Between July 2005 and October 2010, cases and controls were interviewed face to face by a trained interviewer using a structured questionnaire that was sent to the subjects at least 1 week before the interview so that they could gather documents (e.g., medical examination and radiography results) and ask their parents questions relating to their youth. Interviews were conducted mostly at each subject's place of residence. The same interviewer systematically interviewed all subjects in the same strata.

The questionnaire included items on ethnicity, lifetime weight changes, personal history of thyroid disease, family history of thyroid disease and cancer, places of residence, education and occupation, gynecologic and reproductive factors, medical x-ray exposure, and diet, both at the time of the interview and during childhood. The present report focuses on menstrual and reproductive factors, which included age at menarche, regularity of menstrual cycles, use of OCs, and history of pregnancies.

Web Table 1 contains the general characteristics of the 805 cases by region, and Web Tables 2 and 3 contain the characteristics of the cases and controls. Web Tables 4 and 5 compare the expected (according to each region's statistics) and observed proportions of controls living in rural areas.

Analyzed parameters

Ethnicity was classified into 3 categories according to the participant's own declared ethnic group and their parents' reported ethnic groups, namely: 1) both father and mother of European origin, 2) both father and mother of African origin, or 3) other origin. Level of education, height, and BMI were each divided into 3 categories. For height and BMI, we calculated the different categories according to the tertile values of the variable distribution in the controls.

Statistical analysis

The data were analyzed using conditional logistic regression using SAS, version 9.3. Only events or exposures that occurred before the reference age were considered for analysis. Odds ratios were stratified for age, sex, and region of residence and adjusted for level of education, height, BMI, ethnic group, and smoking status. All statistical tests were 2-sided. For categorical variables, tests for trend were calculated by fitting models with a variable using the ranks of categorization as the values of the variable (e.g., 0, 1, or 2 for a variable in 3 categories).

Table 1. Description of Thyroid Cancer Cases, Eastern France, 2002–2006

Characteristic	Cases ($n = 633$)	
	No.	%
Period of diagnosis		
2002	89	14.1
2003	138	21.8
2004	130	20.5
2005	143	22.6
2006	133	21.0
Age at diagnosis, years	28 (9–35)[a]	
≤15	18	2.8
15–20	63	9.9
21–25	146	23.1
26–30	234	37.0
31–35	172	27.2
Histological type		
Unknown	7	1.1
Papillary	572	90.3
Follicular	53	8.4
Oncocytic	1	0.2
Multifocality		
No	328	51.8
Yes	146	23.1
Missing	159	25.1
Bilateral		
No	443	70.0
Yes	85	13.4
Missing	105	16.6
Extra-thyroidal invasion		
No	498	78.7
Yes	113	17.8
Missing	22	3.5
Associated thyroid disorders[b]		
None	401	63.3
Goiter	209	33.0
Hyperthyroidism	34	5.4
Hypothyroidism	27	4.3
Other pathology	9	1.4

[a] Values are the median age and the range (minimum–maximum) in the 633 cases.
[b] Cases could have more than 1 associated thyroid disorder.

RESULTS

Characteristics of cases and controls

The characteristics of the 633 cases are described in Table 1. The mean age at diagnosis was 26.8 years (range, 9–35 years). Papillary carcinoma was the most frequent histological type (572 cases; 91.4%), and 116 of these cases (18.3%) were microcarcinomas (<10 mm without tumor extension and only unifocal tumor). Follicular carcinomas were much less frequent (53 cases; 8.4%), with one of them being an oncocytic variant (0.2%). Microcarcinomas were only of the papillary histological type. In 7 cases (1.1%), the histological type was not available. Information on the associated thyroid disorder was also reported.

Of the known risk factors for DTC for which our analyses have been adjusted, ethnic group, smoking status, height, and educational level were significantly associated with the risk of DTC (Table 2). Only BMI was not significantly different between cases and controls. These results were consistent irrespective of the histological type of the tumor (all cancer, excluding microcarcinomas, or including only papillary).

Hormonal factors

A significantly higher risk of DTC was associated with a younger age at menarche (P for trend < 0.01; Table 3). However, when microcarcinomas were excluded or when only papillary cancers were taken into account, the risk was still higher but was not significant. Hormonal treatments for menstrual cycle regularity shortly after menarche were not related to a higher risk of DTC (Table 3). Regarding the use of contraceptives, OC use showed a nearly significant protective effect irrespective of the duration of use or the time interval between OC use and the year of reference. Other types of contraceptives (patches or implanted devices) were not related to a higher risk of DTC (Table 3).

Reproductive factors

DTC risk increased significantly with an increasing number of pregnancies, but the trend was not significant for the number of children (Table 4). Having a first pregnancy after the age of 25 years was significantly associated with a lower risk of DTC. However, when taking into account only papillary cancer or excluding microcarcinomas, the trend persisted but was not significant.

Among women who had at least 1 child, a longer duration of breastfeeding (≥4 months) was associated with a significantly lower risk of DTC. However, receiving treatment to stop lactation was associated with a significantly higher risk of papillary cancer (Table 4).

DISCUSSION

By analyzing a large-scale case-control study, we found that having a higher number of pregnancies, using lactation suppressants, and having an early menarche were significantly associated with DTC risk in women 35 years of age or younger who lived in eastern France. Conversely, breastfeeding, using OCs, and having a late age at first pregnancy were significantly associated with a lower risk for DTC.

The most important strengths of this study include the large sample size when compared with previously published DTC case-control studies; the homogeneous age range of subjects; a population base that covered all of eastern France; and face-to-face interviews of the cases and controls, who had received the questionnaires by mail in advance. Furthermore,

Table 2. Association of Baseline Characteristics With Thyroid Cancer Risk in Eastern France, 2002–2006

Characteristic	All Cancers					Excluding Noninvasive Microcarcinomas					Papillary Cancers				
	Cases ($n = 633$)	Controls ($n = 679$)	OR[a]	95% CI	*P* for Trend	Cases ($n = 516$)	Controls ($n = 551$)	OR[a]	95% CI	*P* for Trend	Cases ($n = 572$)	Controls ($n = 612$)	OR[a]	95% CI	*P* for Trend
Educational level															
Secondary school level and below	189	131	1.0	Referent	<0.01	150	104	1.0	Referent	<0.01	171	115	1.0	Referent	<0.01
High school diploma	128	136	0.6	0.4, 0.8		100	114	0.5	0.4, 0.8		117	119	0.5	0.4, 0.8	
University	316	412	0.5	0.3, 0.6		266	333	0.5	0.3, 0.7		284	378	0.4	0.3, 0.6	
Height, cm															
<161	172	210	1.0	Referent	0.02	139	163	1.0	Referent	0.01	156	187	1.0	Referent	0.03
161–168	229	235	1.2	0.9, 1.6		176	201	1.1	0.8, 1.5		203	210	1.2	0.9, 1.6	
>168	232	234	1.4	1.0, 1.9		201	187	1.5	1.1, 2.1		213	215	1.4	1.0, 1.9	
BMI[b]															
<20.307	191	220	1.0	Referent	0.10	163	179	1.0	Referent	0.42	171	200	1.0	Referent	0.09
20.307–22.942	177	232	0.9	0.6, 1.1		147	190	0.8	0.6, 1.1		160	206	0.9	0.7, 1.2	
>22.942	265	227	1.2	0.9, 1.6		206	182	1.1	0.8, 1.5		241	206	1.3	0.9, 1.7	
Ethnicity															
European	536	631	1.0	Referent		437	511	1.0	Referent		483	569	1.0	Referent	
African	52	18	2.6	1.5, 4.7		44	13	3.2	1.7, 6.2		49	15	2.9	1.6, 5.4	
Other	45	30	1.5	0.9, 2.5		35	27	1.4	0.8, 2.2		40	28	1.5	0.9, 2.5	
Smoking status															
Never	327	323	1.0	Referent		269	263	1.0	Referent		294	292	1.0	Referent	
Ever	306	356	0.7	0.6, 0.9		247	288	0.7	0.6, 0.9		278	320	0.7	0.6, 1.0	

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.
[a] Adjusted for educational level, height, BMI, ethnicity, and smoking status.
[b] Weight (kg)/height $(m)^2$.

Table 3. Odds Ratios of Thyroid Cancer Associated With Menstrual Factors and Hormone Use in Eastern France, 2002–2006

Menstrual and Hormonal Factors	All Cancer					Excluding Noninvasive Microcarcinomas					Papillary Cancers				
	Cases ($n = 633$)	Controls ($n = 679$)	OR[a]	95% CI	*P* for Trend	Cases ($n = 516$)	Controls ($n = 551$)	OR[a]	95% CI	*P* for Trend	Cases ($n = 572$)	Controls ($n = 612$)	OR[a]	95% CI	*P* for Trend
Age at menarche, years															
9–11	165	132	1.3	1.0, 1.8	<0.01	127	110	1.2	0.9, 1.7	0.07	149	118	1.3	0.9, 1.8	0.01
12–14	317	367	1.0	Referent		261	301	1.0	Referent		288	328	1.0	Referent	
15–18	142	175	0.8	0.6, 1.1		119	136	0.8	0.6, 1.2		128	161	0.8	0.6, 1.0	
Unknown	2	0				2	0				0	0			
Not yet menstruated	6	5				6	4				6	5			
No menstruation (operation)	1	0				1	0				1	0			
Treatment for menstrual cycle regularity after menarche															
No	492	534	1.0	Referent		405	436	1.0	Referent		451	479	1.0		Referent
Yes	132	140	1.0	0.7, 1.3		104	111	1.0	0.7, 1.4		114	128	0.9	0.7, 1.3	
Oral contraception use[b]															
Duration															
Never	120	94	1.0	Referent	0.16	105	80	1.0	Referent	0.22	107	87	1.0	Referent	0.14
≤7 years	269	309	0.7	0.5, 1.0		224	262	0.6	0.4, 1.0		283	268	0.7	0.4, 1.0	
>7 years	237	271	0.7	0.4, 1.0		180	205	0.7	0.4, 1.1		219	252	0.7	0.4, 1.0	
Current vs. former use															
Never	120	94	1.0	Referent	0.17	105	80	1.0	Referent	0.14	107	87	1.0	Referent	0.36
Former >1 year	313	342	0.7	0.5, 1.1		252	271	0.7	0.5, 1.1		283	312	0.7	0.5, 1.1	
Current or former ≤1 year	193	238	0.7	0.5, 1.1		152	196	0.7	0.5, 1.1		175	208	0.8	0.5, 1.2	
Other hormonal contraceptive[b]															
No	601	648	1.0	Referent		493	526	1.0	Referent		540	584	1.0	Referent	
Yes	25	26	0.9	0.5, 1.6		16	21	0.7	0.3, 1.5		25	23	1.0	0.5, 1.9	

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Adjusted for ethnic group, level of education, height, body mass index, and smoking habits.

[b] ORs were adjusted for ethnic group, level of education, height, body mass index, smoking habits, and number of pregnancies.

Table 4. Odds Ratios of Thyroid Cancer Associated With Reproductive Factors in Eastern France, 2002–2006

Reproductive Factor	All Cancers					Excluding Noninvasive Microcarcinomas					Papillary Cancers				
	Cases ($n = 633$)	Controls ($n = 679$)	OR[a]	95% CI	*P* for Trend	Cases ($n = 516$)	Controls ($n = 551$)	OR[a]	95% CI	*P* for Trend	Cases ($n = 572$)	Controls ($n = 612$)	OR[a]	95% CI	*P* for Trend
No. of pregnancies															
0	347	409	1.0	Referent	0.05	293	338	1.0	Referent	0.29	306	369	1.0	Referent	0.03
1	119	144	0.9	0.7, 1.3		97	112	1.0	0.7, 1.4		112	130	1.0	0.7, 1.4	
2	97	83	1.3	0.9, 2.0		75	67	1.2	0.7, 1.8		87	76	1.3	0.9, 2.0	
3	47	28	1.7	1.0, 3.0		34	21	1.4	0.7, 2.6		46	25	1.9	1.0, 3.4	
≥4	23	15	1.4	0.7, 2.9		17	13	1.3	0.6, 2.8		21	12	1.6	0.7, 3.6	
No. of children															
0	387	444	1.0	Referent	0.36	324	366	1.0	Referent	0.96	344	400	1.0	Referent	0.40
1	124	138	0.9	0.6, 1.2		101	106	0.9	0.6, 1.3		116	126	0.9	0.6, 1.2	
2	91	80	1.1	0.8, 1.7		71	66	1.0	0.6, 1.5		83	71	1.2	0.8, 1.8	
≥3	31	17	1.5	0.7, 3.0		20	13	1.2	0.5, 2.6		29	15	1.4	0.7, 3.0	
Age at first pregnancy, years															
<25	174	122	1.0	Referent		134	101	1.0	Referent		159	107	1.0	Referent	
≥25	112	148	0.5	0.3, 0.9		89	112	0.7	0.3, 1.3		107	136	0.5	0.3, 1.0	
OR per year			0.9	0.8, 1.0	0.01			0.9	0.9, 1.0	0.27			0.9	0.8, 1.0	0.02
Breastfeeding duration for all children[b]															
None	93	69	1.0	Referent		69	57	1.0	Referent		87	61	1.0	Referent	
<4 months	72	79	0.9	0.4, 2.0		55	60	1.1	0.5, 2.8		65	75	0.8	0.4, 1.9	
≥4 months	81	87	0.3	0.1, 0.7	<0.01	69	68	0.4	0.2, 1.0	0.05	76	76	0.3	0.1, 0.8	<0.01
OR per month			0.7	0.5, 1.0	0.08			0.8	0.6, 1.3	0.43			0.7	0.5, 1.1	0.11
Used lactation suppressants[b]															
Never	116	145	1.0	Referent		99	114	1.0	Referent		105	136	1.0	Referent	
At least once	130	90	1.6	0.9, 2.9		93	71	1.4	0.7, 2.8		123	76	2.2	1.1, 4.4	

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Adjusted for ethnic group, level of education, height, body mass index, and smoking status.

[b] For women who had at least 1 child. ORs were adjusted for ethnic group, level of education, height, body mass index, smoking status, and number of children.

reproductive factors were not significantly impacted by anamnesis bias.

No similar study has focused on DTC and reproductive risk factors in women younger than 35 years of age. Because these risk factors may change based on age and menopausal status, our findings must be compared with those from other studies that focused on premenopausal DTC.

The most important limitation of our study comes from potential bias in control selection. We initially established a first contact by randomly selecting people from an exhaustive database of landlines, inquiring about the existence of people who fit the selection criteria (year of birth, sex, and region of residence) in their family, and requesting the phone numbers of these potentially eligible controls. The first contacts were almost exclusively established after working hours. Among this list of "family-declared" potential controls, the proportion of refusals was low (16%; 164 of 1,049), but we were not able to document the bias introduced in declarations of such potential controls by first contacts. Indeed, people who are reluctant to participate in such a study are not likely to provide information about potential controls even if they exist in the family. This reluctance is known to be more frequent in persons from low social classes. The over-representation of control women living in rural areas (24%; 95% confidence interval (CI): 20, 27) versus the expected representation from age-adjusted regional statistics (17%) shows that bias was introduced in the selection of controls, but we are not able to directly quantify the consequences of this bias. Furthermore, the absence of DTC among controls was determined based on self-reporting. In France, DTC is not frequent in young populations; fewer than 2 people per 1,000 are expected to have developed DTC before the age of 35 years (32). Consequently, in our study, fewer than 2 people selected as controls may have had DTC. This misclassification of the controls may have induced a less than 2% variation in odds ratios when the exposure prevalence among controls was more than 20% and had an odds ratio in the 1.5–2 range.

Moreover, our study focused on clinical DTC discovered in the absence of a screening program for thyroid cancer in France. Our purpose was to compare characteristics considered to be potential risk factors in DTC cases with the same characteristics in the overall French population rather than with the same characteristics in the French subpopulation who do not have occult DTC. The exclusion of these cancers among controls would introduce a bias.

A smaller limitation comes from the 11% (120 of 1,049) refusal rate and the 9% (95 of 1,049) of potential cases who could not be located. Nevertheless, these quantities are not important enough to have a significant impact on our results.

A younger age at menarche was significantly associated with a higher risk of DTC in our study (for girls 11 years of age or younger vs. those 12–14 years old, odds ratio (OR) = 1.3, 95% CI: 1.0, 1.8). Our results are the direct opposite of the findings of a pooled analysis (for girls 15 year of age or older vs. those younger than 13 years, OR = 1.2, 95% CI: 1.0, 1.4) (23) and those from a cohort study conducted in California in which the analysis was restricted to women less than 45 years of age (for girls 14 years of age or older vs. those younger than 13 years, relative risk = 1.88, 95% CI: 1.13, 3.13) (26). No such association with age at menarche was observed in several other studies, including one conducted in Serbia on subjects less than 20 years of age (33) and 3 in which the analysis was restricted to subjects less than 45 years of age in New Caledonia (21), French Polynesia (25), and California (34). These differences between age at menarche and DTC risk may be due to the age and ethnicity of subjects (21, 34).

We found that the risk of DTC was significantly higher (P for trend = 0.05) in women who had a higher number of pregnancies. However, our study lacked the power to provide evidence regarding the role of the number of children because very few women had 3 children or more. As in our study, a large national survey performed in Norway and 2 case-control studies performed in China (35) and New Caledonia (21) revealed evidence of a higher risk in women who had been pregnant. In contrast, cohort studies performed in China (36) and Japan (37) did not report a higher risk, and another study performed in Thailand that was based on only 17 cases showed a lower risk (38). Results in other populations were heterogeneous (7). This heterogeneity does not seem to be attributable only to differences in the number of children between the studied populations and was observed between recent studies (7, 27), as well as between studies performed more than 20 years ago (24).

We found that breastfeeding was significantly associated with a decreased risk of DTC (OR per month = 0.7, 95% CI: 0.5, 1.0). The protective role of breastfeeding has already been observed in a case-control study conducted in California (for duration of breastfeeding, P for trend = 0.04) (19). However, another case-control study performed in the United States found the opposite result (for 1–12 months of breastfeeding vs. no breastfeeding, OR = 3.1, 95% CI: 1.0, 9.1) (39). In a majority of the other studies that have tested this correlation, no significant associations were found (23, 40).

The use of lactation suppressants was significantly associated with papillary thyroid cancer risk in our study (for ever used vs. never used, OR = 2.2, 95% CI: 1.1, 4.4). Although not frequently investigated, use of lactation suppressants was found to be significantly associated with DTC in a pooled analysis of 13 studies (OR = 1.5, 95% CI: 1.1, 2.1) (24). In 2 other case-control studies published after that meta-analysis, nonsignificant higher risks were shown (OR = 3.2, 95% CI: 0.2, 159 (41) and OR = 1.7, 95% CI: 0.7, 5.0 (19)).

In the present study, OC use was significantly associated with a lower risk of DTC irrespective of the duration of use. The relationship between OC use and DTC has never been clearly documented and varies across studies, with the majority of studies not finding any such relation (10, 19, 21, 40, 42). However, in the pooled analysis (24), the authors found that OC use conferred a slightly higher risk (OR = 1.2, 95% CI: 1.0, 1.4), particularly among current users (OR = 1.6, 95% CI: 1.1, 2.4). Conversely, other studies reported results similar to ours, in which OC use was inversely associated with DTC risk (27, 34). Sakoda and Horn-Ross reported a decrease in risk with OC use (OR = 0.73, 95% CI: 0.52, 0.97) (34), but without a correlation with duration of OC use, similar to what we observed in our study.

Because DTC is much more frequent in women than in men and because luteinizing hormone, human chorionic gonadotropin, follicle-stimulating hormone, and thyroid-stimulating hormone have the same α-subunit coded by the same gene

(43), reproductive events are strongly suspected to play a role in DTC.

The role of estrogens and estrogen receptors in thyroid tumorigenesis, reprogramming, and progression may explain the higher DTC incidence in women. A small case-control study comparing the ratio of estrogen-DNA adducts to estrogen metabolites and conjugates between 40 cases and 40 controls showed that estrogen metabolism was unbalanced, which suggests that the formation of estrogen-DNA adducts may be the initiating event for women who develop DTC (44). A recent review focused on the role of estrogen receptors and estradiol in DTC. The authors reported that estrogen receptors have been shown to influence the development and progression of thyroid cancer cells and that in vitro studies have demonstrated that estradiol stimulates the proliferation of papillary thyroid cancer cells (45).

A possible explanation for the higher risk of DTC in women who have had a high number of pregnancies could be the proliferation of thyroid cells, as maternal thyroid activity increases during pregnancy (46). Estrogens, which are elevated during pregnancy, could have a function in the proliferation of malignant thyroid cells (47, 48). Repeated pregnancies may increase the risk of DTC by revealing DNA damage due to carcinogens, such as ionizing radiation, that may have remained silent without pregnancies (49). We hypothesize that OC use and breastfeeding (both of which inhibit ovulation) may reduce the risk of DTC by shortening the exposure to endogenous estrogens.

Two main drugs are used in France as lactation suppressants; both are dopamine activators that induce the decrease of prolactin. The higher risk of DTC in women who use lactation suppressants may be mediated by the complex interaction between dopamine, prolactin, estrogen, and thyroid hormones.

In conclusion, despite some inconsistencies between studies, the role of hormonal and reproductive factors in the risk of DTC has been well established. Our results on early age at menarche, number of pregnancies, and breastfeeding support the hypothesis that estrogen exposure increases DTC risk. Nevertheless, our findings of a lower DTC risk in women who use OCs show that the relationship between estrogen exposure and DTC risk may be more complex.

ACKNOWLEDGMENTS

Author affiliations: Institut National de la Santé et de la Recherche Médicale (INSERM), Center for Research in Epidemiology and Population Health (CESP), U1018, Radiation Epidemiology Group, Villejuif, France (Constance Xhaard, Carole Rubino, Enora Cléro, Stéphane Maillard, Yan Ren, Elisabeth Adjadj, Florent de Vathaire); Institut Gustave Roussy, Villejuif, France (Constance Xhaard, Carole Rubino, Enora Cléro, Stéphane Maillard, Yan Ren, Martin Schlumberger, Elisabeth Adjadj, Florent de Vathaire); University of Paris-Sud, Villejuif, France (Constance Xhaard, Carole Rubino, Enora Cléro, Stéphane Maillard, Yan Ren, Elisabeth Adjadj, Florent de Vathaire); Fédération d'Endocrinologie, Hospices Civils de Lyon, Groupement Hospitalier Lyon-Est, Bron, France (Françoise Borson-Chazot); Rhône-Alpes Thyroid Cancer Registry, Cancerology Research Center of Lyon (UMR INSERM 1052, CNRS 5286), RTH Laennec Faculty of Medicine, University of Lyon, Lyon, France (Geneviève Sassolas); Thyroid Cancer Registry of Champagne-Ardennes, Institut Jean Godinot, Reims, France (Claire Schvartz); Cancer Registry of Isère, Meylan, France (Marc Colonna); French National Childhood Solid Cancer Registry, CHU, Nancy, France (Brigitte Lacour); Cancer Registry of Doubs EA 3181, Université de Franche-Comté, Besançon, France (Arlette Danzon); Cancer Registry of Bas-Rhin, Faculty of Medicine, University of Strasbourg, Strasbourg, France (Michel Velten); Cancer Registry of Haut-Rhin, Mulhouse, France (Antoine Buemi); Public Health Department, University Hospital Nice, France (Laurent Bailly, Eugènia Mariné Barjoan); and Service d'endocrinologie, Groupement Hospitalier Lyon-Sud, Hospices Civils de Lyon et Université Claude Bernard Lyon1, France (Jacques Orgiazzi).

This study was supported by the Ligue Nationale Contre le Cancer (LNCC), the Agence Nationale pour la Recherche (ANR), the Institut National de Veille Sanitaire (InVS), the Institut National de la Santé et de la Recherche Médicale (INSERM), and the Direction Générale de la Santé (DGS).

We thank the Association Centre de Regroupement Informatique et Statistique en Anatomie Pathologique en Provence-Alpes-Côte d'Azur (CRISAP PACA), as well as Dr. Christophe Sattonnet, Dr. Jean-Luc Lassalle, Dr. Z. Hafdi-Nejjari, Dr. P. Delafosse, Kami-Marie Morerau, Cyrielle Orenes, Laurianne Sarrazin, Stéphanie Bonnay, Frédérique Chatelain, Maryse Barouh, Evelyne Rapp, Julie Festraëts, Julie Valbousquet, Yusuf Atilgan, Jean Chappellet, Lallia Bedhouche, Florent Dayet, and Ziyan Fami.

Conflict of interest: none declared.

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