



# Hormonal and reproductive risk factors of papillary thyroid cancer: A population-based case-control study in France



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## ABSTRACT

The three times higher incidence of thyroid cancer in women compared to men points to a role of female sex hormones in its etiology. However the effects of these factors are poorly understood. We analyzed the association between thyroid cancer and hormonal and reproductive factors among women enrolled in CATHY, a population-based case-control study conducted in France. The study included 430 cases of papillary thyroid cancer and 505 controls frequency-matched on age and area of residence. The odds ratios for thyroid cancer increased with age at menarche ( $p$  trend 0.05). Postmenopausal women were at increased risk, as compared to premenopausal women, particularly if menopause followed an ovariectomy, and for women with age at menopause < 55 years. In addition, use of oral contraceptives and menopausal hormone therapy reduced the association with thyroid cancer by about one third, and breastfeeding by 27%. Overall, these findings provide evidence that the risk of thyroid cancer increases with later age at menarche and after menopause, and decreases with use of oral contraceptives and menopausal hormone therapy. These findings confirm an implication of hormonal factors in papillary thyroid cancer risk, whose mechanisms need to be elucidated.

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## 1. Introduction

Incidence rates of thyroid carcinomas have been increasing regularly over the last decades in most high-resource countries [1]. The rising incidence of thyroid cancer has been attributed mostly to changes in medical practices, like the introduction of neck ultrasonography in the 1980s that enhanced detection of small dormant carcinomas [2]. Actually micropapillary lesions are predominant in this increase, but several epidemiological studies provided evidence of a growing incidence of larger-size carcinomas as well, suggesting a true rise in thyroid cancer incidence [3,4]. In France the estimated age standardized incidence rates of thyroid

cancer were 12.6/100,000 in women and 4.1/100,000 in men according to GLOBOCAN 2012 [5].

Exposure to ionizing radiation during childhood and obesity [6] are recognized risk factors of thyroid cancer. The role of alcohol drinking, tobacco smoking, iodine excess or deficiency, exposure to endocrine disruptors is still unclear [7]. Female sex hormones are likely to play a role, since thyroid cancer is generally three times more frequent in women than in men (5), and the female-to-male incidence ratio has been shown to be greater during reproductive age for papillary thyroid cancer [8]. However, epidemiological studies investigating hormonal and reproductive factors in women in relation to thyroid cancer incidence have provided inconsistent results. Recent meta-analyses showed a possible role for some menstrual and reproductive factors in the etiology of thyroid cancer [9–12], but their findings are difficult to interpret due to heterogeneity between studies [13].

In the present paper we report on the association of hormonal and reproductive factors with papillary thyroid cancer among women who participated in a carefully designed population-based

*Abbreviations:* CI, confidence interval; MHT, menopausal hormone therapy; OC, oral contraceptive; OR, odds ratio.

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case-control study conducted in France, one of the largest studies on thyroid cancer risk conducted so far.

## 2. Subjects and methods

### 2.1. Case selection

The present research was based on the CATHY study, that comprised all patients diagnosed with papillary or follicular thyroid cancer between 2002 and 2007 and residing in the Calvados, Marne or Ardennes, three French administrative areas (*départements*). The data collection started in 2005. As the prognosis of thyroid cancer is very good, incident cases diagnosed in 2002–2004 could be contacted and included in the study, while cases diagnosed in 2005–2007 were recruited prospectively. Cases were identified by the cancer registries in these areas, and only women were included in the present analysis.

The topography and morphology of thyroid cancers were coded according to definitions and rules of the International Classification of Diseases for Oncology, Third edition (ICDO-3). The thyroid cancer cases were classified according to histology and size of the largest cancerous nodule.

Out of 660 eligible cases of thyroid cancer in women, 177 (27%) were not included because the subject refused to participate ( $n = 122$ ), had died at the time of interview ( $n = 15$ ), could not be contacted ( $n = 37$ ), or was too ill to participate ( $n = 3$ ). Only papillary carcinomas ( $n = 430$  cases) were included in the present

analysis, as their etiology may differ from follicular carcinoma ( $n = 53$  cases). Over 56% of the papillary carcinomas had a diameter less than or equal to 10 mm.

### 2.2. Control selection

Controls were selected at random by a polling institute using a telephone directory of all private homes in the study areas. Controls reached by phone who accepted to participate were assigned a year of reference at random from 2002 to 2007, and were frequency-matched by 5-year age group and study area with the cases in the corresponding year of diagnosis. In addition, in order to control for potentially differential participation rates across socio-economic status (SES) categories, the control group was selected to reflect the distribution by SES of the underlying female population of the same age in each study area. Any woman in the household reached by phone was invited to participate in the study, until the predefined number of controls in the strata defined by study area, age, and SES was reached.

The polling institute identified 687 eligible female controls, who initially accepted to be contacted by trained interviewers for an in-person interview. Among them, 182 (26%) finally refused to participate. The remaining 505 controls with completed questionnaires were included in the analyses.

Only variables determined at or before the year of reference (for the controls) or the year of diagnosis (for the cases) underwent subsequent analyses.

**Table 1**  
Socio-demographic Characteristics and Lifestyle Habits of Cases and Controls. The CATHY Study, France, 2002–2007.

	Cases (n = 430)		Controls (n = 505)		OR <sup>a</sup>	95% CI	p trend
	No.	%	No.	%			
<b>Age (years)<sup>b</sup></b>							
<30	23	5.3	37	7.3			
30–39	62	14.4	84	16.6			
40–49	91	21.2	126	25.0			
50–59	148	34.4	128	25.3			
60–69	73	17.0	86	17.0			
≥70	33	7.7	44	8.7			
Mean (SD)	51.2	(12.4)	50.0	(13.6)			
<b>Residence area<sup>c</sup></b>							
Calvados	139	32.33	200	39.6			
Ardennes	88	20.47	84	16.6			
Marne	203	47.21	221	43.8			
<b>Education level (years)</b>							
≤ 5	117	27.2	130	25.8	1	Reference	
6–9	164	38.1	166	33.0	1.16	[0.81–1.66]	
≥ 10	149	34.7	207	41.2	0.91	[0.63–1.33]	0.15
<b>Body Mass Index (kg/m<sup>2</sup>)</b>							
≤ 18.5	12	2.8	19	3.8	0.86	[0.41–1.84]	
[18.5–25[	209	48.9	271	54.1	1	Reference	
[25–30[	128	30.0	129	25.7	1.19	[0.87–1.63]	
≥ 30	78	18.3	82	16.4	1.10	[0.76–1.60]	0.19
<b>Smoking status</b>							
Never	247	57.4	297	58.8	1	Reference	
Current	70	16.3	102	20.2	0.85	[0.58–1.23]	
Past	113	26.3	106	21.0	1.25	[0.90–1.73]	
<b>Alcohol consumption (glass/week)</b>							
Never	141	33.1	142	28.4	1	Reference	
1–10	244	57.3	319	63.8	0.73	[0.54–0.98]	
>10	41	9.6	39	7.8	1.04	[0.62–1.72]	0.57

<sup>a</sup> Odds ratios adjusted for age and residence area.

<sup>b</sup> Chi<sup>2</sup> = 10.36 p = 0.07.

<sup>c</sup> Chi<sup>2</sup> = 5.86 p = 0.05.

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