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ORIGINAL PAPER

Family history of malignant and benign thyroid diseases and risk of thyroid cancer: a population-based case–control study in New Caledonia

Christophe Leux · Thérèse Truong · Claire Petit · Dominique Baron-Dubourdieu · Pascal Guénel

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Abstract
Purpose Exceptionally high incidence rates of thyroid cancer have been observed in New Caledonia, particularly in Melanesian women, but familial aggregation of thyroid diseases in this population is unknown. We study the association between family history of malignant or benign thyroid diseases and non-medullary thyroid cancer in this country.
Methods We conducted a population-based case–control study including 332 cases with papillary or follicular carcinoma diagnosed in 1993–1999 and 412 controls, matched by sex and 5-year age-group.
Results Thyroid cancer was associated with a history of thyroid cancer in first-degree relatives (odds ratio (OR), 3.2; 95 % CI, 1.6–6.2) and with a family history of multinodular goiter (OR, 3.6; 95 % CI, 1.9–7.0). The ORs did not change by age at diagnosis and with the number of affected relatives. The study provides evidence that the familial component of thyroid cancer is particularly strong in men. Thyroid cancer was not associated with a family history of thyroid diseases in Melanesians from the Loyalty Islands, the area with the highest incidence rates for thyroid cancer, possibly indicating a high frequency of genetic susceptibility variants and lack of genetic variation in this population subgroup.
Conclusion Overall our findings confirm an elevated risk of thyroid cancer in individuals with a family history of malignant or benign thyroid diseases, particularly in Melanesians where familial aggregation of thyroid cancer had never been investigated before. The study of genetic variants in candidate susceptibility genes for thyroid cancer may help clarifying the absence of an association in the subgroup of Melanesians from the Loyalty Islands.

Keywords Thyroid cancer · Case–control study · Familial cancer · New Caledonia

Abbreviations

CI	Confidence interval
FRR	Familial relative risk
OR	Odds ratio
NMTC	Non-medullary thyroid cancer
SIR	Standardized incidence ratio

Introduction

Worldwide estimates of thyroid cancer age-standardized incidence rates were 4.7 per 100,000 in women and 1.5 per 100,000 in men in 2008 [1], but there is considerable geographic variation in thyroid cancer incidence around the world. Elevated incidence rates were reported in France, Iceland, and Belarus [2] and in some Pacific populations [3]. Marked increases of thyroid cancer incidence,

C. Leux · T. Truong · P. Guénel (✉)
Environmental Epidemiology of Cancer, CESP Centre for research in Epidemiology and Population Health, UMR-S 1018 Equipe 6, INSERM, Université Paris-Sud, 16 Avenue Paul Vaillant-Couturier, 94807 Villejuif Cedex, France
e-mail: pascal.guenel@inserm.fr

C. Leux · T. Truong · P. Guénel
Université Paris Sud 11, UMRS 1018, 94807 Villejuif, France

C. Petit
INSERM U625, Rennes, France

D. Baron-Dubourdieu
Laboratory of Anatomy and Cytopathology, Nouméa, New Caledonia, France

essentially papillary carcinoma, have been observed for several decades in North America, Europe, and Australia [4–11]. The use of more sensitive diagnostic procedures and improved screening of thyroid cancer leading to the detection of occult thyroid tumors may partially explain this time trend [7, 11, 12], but does not totally account for the increased incidence [13, 14].

The incidence of thyroid cancer in New Caledonia, a French overseas territory in South Pacific, is exceptionally elevated. This country counts approximately 200,000 inhabitants of whom 45 % are native Melanesians, 35 % are of European origin, and 20 % are of various ethnic groups, mainly Polynesian or Asian. Very high annual incidence rates have been reported for all ethnic groups in 1985–1999, particularly in Melanesian women (71.4 per 100,000) and men (10.4 per 100,000) [15]. The reasons for the elevated incidence in this group remain unclear. Exposure to ionizing radiations, particularly during childhood, is the only well-established risk factor for thyroid cancer but radioactive fallout from atmospheric nuclear test carried out in French Polynesia in the 1960s and 1970s is not known to have affected New Caledonia located 4,500 km away. It has also been hypothesized that genetic susceptibility factors shared by native Melanesians may explain the occurrence of thyroid cancer in this population, but no data are available to support this hypothesis. In previous papers, we have reported that hormonal, reproductive, anthropometric factors, and history of benign thyroid disease were associated with thyroid cancer in New Caledonia and may account for part of the elevated incidence rates [15–17]. Studies of large databases in other populations have shown that the risk of thyroid cancer among first-degree relatives of thyroid cancer patients was increased threefold to tenfold, and that thyroid cancer is one of the cancers with the highest familial risk [18–23]. Case–control studies have also reported that the risk of thyroid cancer was associated with a family history of thyroid cancer in first-degree relatives [24–30]. The relative contribution in the familial aggregation of a true genetic predisposition or of environmental risk factors shared by family members cannot be determined from these reports. Studies based on a candidate gene approach have identified a few possible genetic polymorphisms conferring slight increased risk of thyroid cancer [31], and a recent genome-wide association study in Iceland reported that genetic variants close to the FOXE1 and the NKX2-1 genes, involved in the biological function of the thyroid gland, conferred marked increased risks [32]. In the present paper, we describe the association between family history of malignant or benign thyroid disease and the incidence of non-medullary thyroid cancer in New Caledonia, to investigate specific patterns of familial risk in this population.

Materials and methods

Case selection

We conducted a population-based case–control study. The cases were patients with a papillary or follicular cancer diagnosed between 1 January 1993 and 31 December 1999 who had been living in New Caledonia for at least 5 years at the time of cancer diagnosis. Thyroid cancer patients were identified from the two pathology laboratories of New Caledonia. Cases were also sought in the cancer registry of New Caledonia and in medical records of head and neck practitioners. All pathology reports were retrieved to determine the histological type of the tumor and the number and diameter of cancerous nodules in the thyroid gland. Data on tumor size, multifocality, and metastases were collected and coded from the original pathology report. The original histological slides were retrieved and reviewed by the pathologist whenever necessary.

Of the 369 cases of thyroid cancer eligible for the study, 37 (10 %) were not included because they refused to participate ($n = 9$), had died ($n = 21$), or could not be contacted ($n = 5$).

Control selection

Controls were randomly selected from recently updated electoral rolls that included the name, sex, address, and date of birth of all New Caledonia residents aged 18 years or older. The controls were frequency matched to the cases by gender and 5-year age-group. To achieve incidence density sampling of the source population, seven control groups were selected to match the seven case groups, each consisting of the cases diagnosed in a given year of the study period (referred to below as the "reference year"). Subjects were eligible as controls if they had been living in New Caledonia for at least 5 years at the reference year and if they had not been diagnosed with a thyroid cancer before or during that year. Of the 473 eligible controls, 61 (13 %) could not be interviewed because they had died ($n = 13$), refused to participate ($n = 24$), or could not be contacted ($n = 24$). The remaining 354 controls were included in the analyses.

Data collection

Data were collected as of 1998 by trained interviewers using a structured questionnaire during in-person interviews. All subjects signed an informed consent. The questionnaire included information on socio-demographic characteristics, reproductive history, previous medical conditions, anthropometric characteristics, residential history, occupations, leisure time activities, and diet.

Pedigrees of cases and controls were obtained. We requested information for all first-degree relatives on sex, date of birth and date of death, history of benign thyroid disease (goiter and nodule), history of thyroid or other cancer, and age at diagnosis. However, the date of birth and/or the date of death of the relatives was frequently missing, particularly among Melanesians. Study subjects were also asked to report on any thyroid disease among second or higher-degree relatives. Thyroid cancers among relatives notified by the study subjects were validated in the New Caledonia cancer registry. This cancer registry was established in the early 1980s, but cancer diagnoses among relatives that occurred before that period could not be retrieved.

Statistical analysis

Malignant or benign thyroid diseases in first-degree relatives were considered in the analysis only if they were diagnosed before or during the year of diagnosis of the index cases or the year of reference for the controls. When two cases of the same family were included in the study, the case with the earlier date of diagnosis was considered as an affected relative of the case with a later date of diagnosis, but the opposite was not true. The odds ratios were calculated using unconditional logistic regression, using R version 2.9.0 [33]. All odds ratios were adjusted for age (5-year age-groups), ethnic group (European, Melanesian, and other), number of siblings, and for gender in the analyses including men and women. In further analyses, we stratified the data by gender, age-group ($\leq$40, $>$40 years), ethnic group (Melanesians, other ethnic groups), and province of residence (North/south provinces, Loyalty islands). We also conducted analyses by tumor type (papillary or follicular carcinoma) and tumor size ($\leq$10, $>$10 mm) using polytomous logistic regression. Multivariate analyses were carried out to account for potential confounders such as body mass index and parity, but the odds ratios were similar and are not shown. Tests for trend were calculated by fitting models with continuous variables, assuming a log-linear relation between the number of affected relatives and cancer incidence.

Results

Characteristics of cases and controls

The socio-demographic characteristics of the cases and the controls are shown in Table 1. Due to frequency-matching, the distribution by age-group was similar in the two groups. Proportionally, more cases than controls were of Melanesian origin, reflecting the higher incidence of thyroid cancer in this group. Among Melanesians, more cases than controls were living in the province of Loyalty Islands, reflecting the higher incidence rates in this province [15]. The mean number of siblings among cases and controls was 4.7 and 4.2, respectively.

Pathological characteristics of cases with and without a familial history of thyroid cancer

Table 2 describes pathological characteristics of cases with and without a family history of thyroid cancer among first-degree relatives. Mean age at diagnosis was 47.2 and 48.0 years for cases with and without a family history of thyroid cancer, respectively (Student's t test, $p = 0.72$). The proportion of small-size carcinomas, papillary histological subtype, and multifocal carcinomas was slightly higher in cases with a family history of thyroid cancer, but no statistically significant difference was observed between the two groups.

Family history of thyroid cancer or multinodular goiter

A family history of thyroid cancer in first-degree relatives was reported by 39 cases (11.7 %) and 15 controls (3.6 %) leading to an odds ratio of 3.2 (95 % CI, 1.6–6.2) (Table 3). The odds ratio did not increase with the number of affected first-degree relatives. The odds ratios associated with family history of thyroid cancer in a sibling or a parent were similar. Accounting for first- and higher-degree relatives did not change the association (OR = 3.3; 95 % CI, 1.9–5.9).

The odds ratio associated with a family history of multinodular goiter in first-degree relatives was 3.6 (95 % CI, 1.9–7.0). It increased with the number of affected first-degree relatives (p for trend $<$0.0001) (Table 3). The odds ratio was unchanged when accounting for a history of goiter among first- and higher-degree relatives.

Results of the stratified analyses by age-group, sex, ethnic group, and province are shown in Table 4. The odds ratio of thyroid cancer associated with a family history of thyroid cancer among first-degree relatives was slightly higher in persons aged 40 years or less than in older subjects, but the interaction between age and family history of thyroid cancer was not statistically significant (p for interaction: 0.76). The odds ratio for thyroid cancer in women was 2.6. Among men, there were 5 cases and no control with a family history of thyroid cancer, making the odds ratio virtually infinite (95 % confidence interval based on Fisher's exact test (1.45–∞), $p = 0.0089$). Stratification by ethnic group indicated slightly higher odds ratios in non-Melanesians (p for interaction 0.68). Melanesians from the Southern and Northern provinces (i.e., mainland New Caledonia) had an odds ratio of 6.4 (95 % CI, 2.0–20.2),

Table 1 Socio-demographic characteristics of cases and controls

	Cases (total = 332)		Controls (total = 412)		OR[a]	95 % CI
	No.	%	No.	%		
Gender						
Female	293	88.3	354	85.9		
Male	39	11.7	58	14.1		
Age (years)						
<25	10	3.0	13	3.2		
25–29	21	6.3	31	7.5		
30–34	24	7.2	24	5.8		
35–39	35	10.5	43	10.4		
40–44	33	9.9	42	10.2		
45–49	35	10.5	44	10.7		
50–54	41	12.3	38	9.2		
55–59	39	11.7	55	13.3		
60–64	42	12.7	41	10.0		
65–69	33	9.9	57	13.8		
≥70	19	5.7	24	5.8		
Ethnic group						
Melanesian	244	73.5	189	45.9	1	Ref.
European	42	12.7	133	32.3	0.3	(0.2–0.4)
Other	46	13.9	90	21.8	0.4	(0.3–0.6)
Province (Melanesians only)						
South	75	30.7	81	42.9	1	Ref.
North	68	27.9	52	27.5	1.5	(0.9–2.4)
Loyalty Islands	101	41.4	56	29.6	2.1	(1.3–3.3)
Number of siblings						
0	23	6.9	65	15.8	1	Ref.
1–2	72	21.7	75	18.2	2.7	(1.5–4.8)
3–4	76	22.9	89	21.6	2.4	(1.4–4.3)
5–6	61	18.4	83	20.1	2.0	(1.1–3.5)
7–8	57	17.2	58	14.1	2.6	(1.4–4.8)
≥9	43	12.9	42	19.2	2.8	(1.5–5.3)

[a] OR adjusted for age and gender

whereas Melanesians from the Loyalty Islands had an odds ratio of 1.3 (95 % CI, 0.4–4.6). The interaction between province of residence and family history of thyroid cancer was statistically significant ($p = 0.027$).

The association between thyroid cancer and a family history of multinodular goiter was higher in subjects aged less than 40 years (OR = 5.0, 1.6–16.1) than in older subjects (OR = 2.8, 1.2–6.3) (p for interaction 0.20). The odds ratio for a family history of multinodular goiter was 4.9 in Melanesians living in the South and North Provinces (95 % CI, 1.5–15.5), but it was only 1.5 in Melanesians from the Loyalty Islands (95 % CI, 0.3–7.4).

Results of the analyses by pathological characteristics are shown in Table 5. A family history of thyroid cancer was strongly associated with papillary carcinoma (OR = 3.6, 95 % CI, 1.8–7.1) but not follicular carcinoma (OR = 1.3, 95 % CI, 0.3–5.2). Higher odds ratios were observed for multifocal than for unifocal thyroid cancers, and for microcarcinomas than for carcinomas >10 mm, but the differences were not statistically significant.

The association of thyroid cancer with a family history of multinodular goiter was somewhat higher for carcinomas >10 mm than for microcarcinomas. Odds ratios for papillary and follicular histological types were similar.

Discussion

We found a 3.2-fold increased odds ratio of non-medullary thyroid cancer in individuals with a family history of

Table 2 Histological characteristics of thyroid cancer among study cases ($n = 332$)

	With a family history of thyroid cancer among first-degree relatives ($n = 39$)		Without a family history of thyroid cancer among first-degree relatives ($n = 293$)		p
	n	%	*n*	%	
Tumor size (mm)					
≤10	22	56.4	145	49.5	0.790[a]
>10	17	43.6	144	49.1	
Missing			4		
Histology					
Papillary	36	92.3	252	86.0	0.276[a]
Follicular	3	7.7	41	14.0	
Multifocality					
Yes	25	64.1	164	56.7	0.383[a]
No	15	34.9	125	43.3	
Missing			4		
Extrathyroidal invasion					
Lymph nodes	3	7.7	30	10.4	0.860[b]
Metastasis	0	0	3	1.0	
No	36	92.3	256	88.6	
Missing			4		

[a] Pearson's chi-squared test

[b] Yates' chi-squared

Table 3 Odds ratio of non-medullary thyroid cancer associated with a family history of thyroid cancer or multinodular goiter

	Family history of thyroid cancer			Family history of multinodular goiter		
	Ca/Co (332/412)	OR[a]	95 % CI	Ca/Co (332/412)	OR[a]	95 % CI
First-degree relatives[b]						
No	231/322	1	Ref.	236/326	1	Ref.
Yes	39/15	3.2	(1.6–6.2)	40/16	3.6	(1.9–7.0)
Parents[b,c]						
No	270/352	1	Ref.	267/352	1	Ref.
Yes	10/5	2.3	(0.7–7.3)	19/8	3.0	(1.3–7.3)
Siblings[b]						
No	282/365	1	Ref.	289/367	1	Ref.
Yes	30/12	2.9	(1.4–5.9)	23/10	3.0	(1.3–6.9)
Number of affected first-degree relatives[b]						
0	231/322	1	Ref.	236/326	1	Ref.
1	29/11	3.2	(1.5–6.8)	26/10	3.4	(1.5–7.8)
≥2	6/3	1.9	(0.5–8.0)	11/2	9.5	(1.8–50.2)
All relatives[d]						
No	220/318	1	Ref.	221/319	1	Ref.
Yes	52/20	3.3	(1.9–5.9)	57/23	3.6	(2.1–6.3)

[a] OR adjusted for age, gender, ethnic group, and number of siblings

[b] First-degree relatives with a diagnosis prior to the diagnosis of the case or to the reference year of the control

[c] OR adjusted for age, gender, and ethnic group

[d] Independently of the date of diagnosis

Table 4 Odds ratio of non-medullary thyroid cancer associated with a family history of thyroid cancer or with a family history of multinodular goiter in first-degree relatives

	Affected first-degree relatives	Family history of thyroid cancer			Family history of multinodular goiter		
		Ca/Co (332/412)	OR	95 % CI	Ca/Co (332/412)	OR	95 % CI
Age (*years*)[a]							
<40	No	71/102	1	Ref.	72/104	1	Ref.
	Yes	14/6	3.7	(1.2–11.7)	15/5	5.0	(1.6–16.1)
≥40	No	160/220	1	Ref.	164/222	1	Ref.
	Yes	25/9	2.9	(1.3–6.5)	25/11	2.8	(1.2–6.3)
Sex[b]							
Female	No	204/275	1	Ref.	207/279	1	Ref.
	Yes	34/15	2.6	(1.3–5.2)	38/16	3.2	(1.7–6.3)
Male	No	27/47	1	Ref.	29/47	1	Ref.
	Yes	5/0	–	–	2/0	–	–
Ethnic group[c]							
Melanesians	No	160/143	1	Ref.	170/149	1	Ref.
	Yes	34/11	3.2	(1.5–6.7)	29/7	3.5	(1.5–8.6)
Other	No	71/179	1	Ref.	66/177	1	Ref.
	Yes	5/4	5.1	(1.0–26.7)	11/9	4.5	(1.5–13.7)
Province[c] (*Melanesians only*)							
Loyalty islands	No	64/35	1	Ref.	71/41	1	Ref.
	Yes	14/7	1.3	(0.4–4.6)	10/3	1.5	(0.3–7.4)
South/north	No	96/108	1	Ref.	99/108	1	Ref.
	Yes	20/4	6.4	(2.0–20.2)	19/4	4.9	(1.5–15.5)

[a] OR adjusted for age, gender, ethnic group, and number of siblings

[b] OR adjusted for age, ethnic group, and number of siblings

[c] OR adjusted for age, gender, and number of siblings

Table 5 Odds ratio of non-medullary thyroid cancer associated with a family history of thyroid cancer or with a family history of multinodular goiter by pathological characteristics

	Affected first-degree relatives	Family history of thyroid cancer			Family history of multinodular goiter		
		Ca/Co (332/412)	OR[a]	95 % CI	Ca/Co (332/412)	OR[a]	95 % CI
Histology							
Papillary	No	197/322	1	Ref.	203/326	1	Ref.
	Yes	36/15	3.6	(1.8–7.1)	35/16	3.6	(1.8–7.1)
Follicular	No	34/322	1	Ref.	33/326	1	Ref.
	Yes	3/15	1.3	(0.3–5.2)	5/16	2.8	(0.8–9.8)
Multifocality							
Unifocal	No	104/322	1	Ref.	105/326	1	Ref.
	Yes	14/15	2.9	(1.3–6.6)	13/16	2.6	(1.2–5.9)
Multifocal	No	124/322	1	Ref.	128/326	1	Ref.
	Yes	25/15	3.6	(1.7–7.6)	27/16	4.4	(2.0–9.5)
Tumor size (mm)							
≤10	No	117/322	1	Ref.	127/326	1	Ref.
	Yes	22/15	3.8	(1.8–8.0)	15/16	2.8	(1.2–6.2)
>10	No	117/322	1	Ref.	87/326	1	Ref.
	Yes	17/15	2.5	(1.1–5.5)	20/16	4.9	(2.3–10.4)

[a] OR adjusted for age, gender, ethnic group, and number of siblings

thyroid cancer among first-degree relatives. The odds ratio was 5.1 in non-Melanesians, and 3.2 in all Melanesians. This study confirms a familial component of thyroid cancer risk in this population, a genetically distinct group of Pacific islanders [34], that had never been investigated previously with regard to familial cancer risk. We also found an odds ratio of 3.6 for thyroid cancer in individuals with a family history of multinodular goiter in first-degree relatives, a disorder predisposing to malignant thyroid tumors.

Clinical and pathological characteristics of familial cases

In our study, pathological characteristics were not significantly different between cases with and without a family history of thyroid cancer. However, there was an indication of a greater frequency of family history in the papillary than in the follicular subtype, which is consistent with previous studies [22, 35–37]. It has been postulated that thyroid cancer is more aggressive and occurs at a younger age in familial cases of thyroid cancer than in thyroid cancer patients without a family history [38–41] and these patients might need a more aggressive initial treatment [39–42]. However, this question remains controversial as other authors found no differences in tumor characteristics or in prognosis between familial and sporadic cases [37, 41, 43, 44].

Family history of thyroid cancer

Our findings in New Caledonia are consistent with findings in other populations that reported strong familial aggregation of non-medullary thyroid cancer. The relative risk of thyroid cancer in first-degree relatives of thyroid cancer patients ranged from 3 to 9 in studies based on large population databases conducted in Utah, Iceland, and Norway [18, 19, 21, 23]. In these studies, the familial relative risk of thyroid cancer was among the highest familial risk of all cancer sites. Studies from Norway and Sweden that compared the incidence of thyroid cancer in individuals with a family history of thyroid cancer among first-degree relatives to that in the general population reported standardized incidence ratios ranging from 3 to 6 [20, 22]. Case–control studies in populations of various ethnic groups also reported elevated odds ratios ranging from 3 to 8 for thyroid cancer in individuals with a family history of thyroid cancer [24, 26, 28–30, 45, 46].

Genetic predisposition or environmental factors

Familial aggregation of thyroid cancer could arise from genetic predisposition factors, from non-genetic lifestyle or environmental exposures shared by family members, or from both [22, 28, 47, 48]. No clear pattern of genetic predisposition has been demonstrated for familial aggregation of thyroid cancer. Several linkage studies have identified several susceptibility loci on chromosomes 1q21, 2q21, 14q31 and 19p32 [49–53], but none of these loci accounts for a significant fraction of familial form of non-medullary thyroid cancer pedigrees [49–55]. Somatic mutations of *BRAF* and *RAS* were also identified in Portuguese families with several individuals affected with non-medullary thyroid cancer [56]. More recently, genetic variants associated with thyroid cancer have been studied in a genome-wide association study conducted in 378 and 37,196 Icelandic cases and controls. Two common gene polymorphisms associated with thyroid cancer were detected at chromosomes 9q22.33 and 14q13.3 [32]. In homozygous carriers of the rare allele for both variants, the estimated risk of thyroid cancer was 5.7-fold greater than that of non-carriers. These variants involved, respectively, the *FOXE1* and the *NKX2-1* genes, which encode for a thyroid transcription factor. It is of primary interest to replicate these findings in the Melanesian population of New Caledonia to see whether these genetic variants may account for the elevated incidence of thyroid cancer in this country.

Familial aggregation may also be related to environmental or lifestyle factors shared by family members. These factors may include iodine deficiency, a relatively common condition among Melanesians of New Caledonia, or frequent consumption of cruciferous vegetables that have high content of goitrogenic substances. We reported in an earlier paper that these exposures were associated with the incidence of thyroid cancer in our study [57]. It is also possible that interaction between genetic predisposition factors and environmental or lifestyle factors explain the familial aggregation of thyroid cancer. A high frequency of predisposing variant alleles combined with frequent exposures to environmental or lifestyle risk factors may explain the very high incidence of thyroid cancer in the country.

Disparities among Melanesians across geographical areas in New Caledonia

Overall, our results confirm a familial component of thyroid cancer risk in Melanesians, an ethnic group where, to our knowledge, it had never been reported before. Intriguingly, the odds ratio of thyroid cancer associated with a family history of the disease among Melanesians varied widely depending on the geographical area in New Caledonia. The odds ratio was 6.4 in Melanesians of mainland New Caledonia (North and South provinces), but it was close to unity in Melanesians of the Loyalty Islands,

the population subgroup with the highest incidence rates of thyroid cancer [15]. To explain this finding, it can be hypothesized that thyroid cancer is related to a few specific predisposing alleles shared by most Melanesians of the Loyalty Islands, an isolated population with possibly little genetic admixture. It is thus possible that highly prevalent deleterious alleles account for the elevated incidence of the disease in this specific population, while the lack of genetic variation prevents a familial component of thyroid cancer from being detected. Only few studies on the genetic structure of Melanesian population have been carried out [34], and to our knowledge, no such studies were conducted in the population of New Caledonia or Loyalty Islands. Genotyping candidate genes such as *FOXE1* in these populations may be of particular interest and will help clarifying this intriguing finding.

Gender disparities

Although the small number of cases in men did not allow a formal comparison of the odds ratios between genders, we found that 5 cases (including 4 Melanesians) versus 0 controls had a family history of thyroid cancer among men, possibly indicating that the risk of thyroid cancer associated with a family history of the disease is much higher in males than in females. Previous studies have pointed to a greater heritability of thyroid cancer in males than in females [23, 58]. In the Swedish Family-Cancer Database, thyroid cancer was 2.5 more frequent in male than in female offspring of thyroid cancer patients and was the only cancer site with an elevated familial sex ratio [58]. A greater familial risk in men could be accounted for by a lower susceptibility than women to non-genetically determined risk factors of thyroid cancer (e.g., hormonal and reproductive risk factors), making the relative contribution of genetic susceptibility.

Family history of benign thyroid disease

We reported a 3.6-fold increased risk of non-medullary thyroid cancer in study subjects with a family history of multinodular goiter. Previous studies reported a twofold to fourfold increased risk of thyroid cancer in individuals with a familial history of benign thyroid disease [25, 27, 28, 59–67]. Multinodular goiter is a relatively common disease among Melanesians of New Caledonia, possibly related to iodine deficiency [57], and it is strongly associated with thyroid cancer in epidemiological studies [16, 68]. The odds ratio for thyroid cancer related to a family history of multinodular goiter was noticeably higher in individuals with two or more affected relatives than in individuals with only one affected relative. It was also more elevated in individuals aged less than 40 years than in older individuals, suggesting the role of a genetic predisposition. In another case–control study in Kuwait, Memon et al. [28] reported similar results. These findings suggest that common genetic predisposition factors may play a role in multinodular goiter and thyroid cancer, possibly in interaction with environmental factors such as iodine deficiency.

Study strengths and limits

Strengths of the study include a population-based design with exhaustive identification of thyroid cancer cases and a high participation rate among cases and controls. Another strength lies on a careful review of pathologic reports and slides. It allowed classifying thyroid tumors according to the size of carcinoma and assessing the effects of a possible detection bias due to improved diagnoses of small-size thyroid cancers. The effect of a detection bias may be limited as our results showed a similar distribution of tumor sizes in cases with and without a family history of thyroid cancer. Knowledge of the composition of the family of each subject was another important feature. It allowed us to take into account the role of family size as a potential confounder for the estimates of familial risk. The large number of siblings in Melanesians families of New Caledonia also increased the probability of observing familial cases of thyroid cancer or benign thyroid diseases among first-degree relatives.

Limitations of the study include small numbers of cases and controls that yielded low statistical power, particularly in stratified analyses by gender, ethnic group, or geographical area. There was also a potential for recall bias since family history data were self-reported by participants. Family history data were not validated from registry data except when affected relatives were also included as cases in the case–control study. Accuracy of reporting a family history of cancer was assessed in several case–control studies, but no substantial difference was generally observed between cases and controls in reporting familial cancers cases [69–71] suggesting that recall bias is more likely to be non-differential.

Conclusion

We have shown that the risk of thyroid cancer in New Caledonia was strongly associated with a family history of thyroid cancer or of multinodular goiter. This is the first study reporting results on the familial component of thyroid cancer in Melanesians of New Caledonia, a population where extremely high incidence of thyroid cancer has been reported. There was also indication that the familial component of thyroid cancer may be stronger in males than in

females. Although the familial aggregation of thyroid diseases in New Caledonia may be accounted for by environmental or lifestyle risk factors shared by family members, or by gene–environment interactions, genotyping studies of candidate genes among Melanesians are essential for a better understanding of the thyroid cancer incidence in this country. DNA samples are being collected among Melanesians of New Caledonia and will allow elucidating the present findings.

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Conflict of interest The authors declare that they have no conflict of interest.

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