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Family History of Cancer and Risk of Sporadic Differentiated Thyroid Carcinoma

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Abstract

BACKGROUND—Thyroid cancer incidence in the United States, particularly in women, has increased dramatically since 1980s. While the causes of thyroid cancer in most patients remain largely unknown, evidence suggests the existence of an inherited predisposition to development of differentiated thyroid cancer (DTC). Therefore, we explored the association between sporadic DTC and family history of cancer.

METHODS—In a retrospective hospital-based case-control study of prospectively recruited subjects who completed the study questionnaire upon enrollment, unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) as estimates of the DTC risk associated with first-degree family history of cancer.

RESULTS—The study included 288 patients with sporadic DTC and 591 cancer-free controls. Family history of thyroid cancer in first-degree relatives was associated with increased DTC risk (adjusted OR = 4.1, 95% CI: 1.7–9.9). All DTC cases in patients with a first-degree family history of thyroid cancer were cases of papillary thyroid carcinoma (PTC) (adjusted OR = 4.6, 95 CI%: 1.9–11.1). Notably, the risk of PTC was highest in subjects with a family history of thyroid cancer in siblings (OR = 7.4, 95% CI: 1.8–30.4). In addition, multifocal primary tumor was more common among PTC patients with first-degree family history of thyroid cancer than among PTC patients with no first-degree family history of thyroid cancer (68.8% vs. 35.5%, p = 0.01).

CONCLUSIONS—Our study suggests that family history of thyroid cancer in first-degree relatives, particularly in siblings, is associated with an increased risk of sporadic PTC.

Keywords

Differentiated thyroid carcinoma; papillary thyroid carcinoma; benign thyroid disease; multifocal; family history of cancer

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INTRODUCTION

Thyroid cancer is the most prevalent endocrine malignancy.[1] In the United States, it was predicted to account for nearly 3% of cancer diagnoses in 2010 (45,000 new cases) and is the fifth most common cancer in women.[1] The incidence of thyroid cancer is increasing more rapidly than that of any other cancer in the United States; the incidence of thyroid cancer today is 2.4 times what it was 3 decades ago.[2, 3] It is argued that the rising incidence of thyroid cancer may largely be attributed to improved diagnostic procedures and advanced screening.[3–5] However, since there has been an increase in the incidence of not only small, clinically insignificant tumors but also larger, clinically significant tumors, improved screening and medical practices alone do not fully explain the observed increase.[4, 5]

Differentiated thyroid carcinoma (DTC) comprises approximately 90% of all thyroid cancers and consists of 3 distinct histological types: papillary (80–90% of cases), follicular (10%), and Hurthle cell.[6, 7] The etiology of DTC is largely unknown and may vary according to histological type.[8] DTC risk has been examined in relation to family history of cancer in a number of epidemiologic studies, many of which reported a family cluster of thyroid cancer,[9–19] suggesting a potential interplay of genetic and environmental factors in thyroid carcinogenesis. However, most of these studies did not provide histology-specific risk. Although several families with a cluster of thyroid cancer reported a more aggressive clinical course,[7,20] epidemiological studies on association between family history of thyroid cancer and patho-clinical feature of DTC are limited.

Thus, to address these issues, we carried out a hospital-based case-control study. To exclusively investigate the association with sporadic DTC, we excluded familial DTC cases according to the standard definition of 3 or more first-degree family members with thyroid cancer in a kindred.[7,20] In the analysis reported here, to assess whether first degree family history of cancer was associated with risk of sporadic DTC, particularly sporadic PTC, we retrospectively compared the proportion of first-degree family history of cancer among 3 groups including: patients with incident DTC, patients with incident benign thyroid disease (BTD), and cancer-free controls. Pathologic characteristics of DTC were also examined to explore the clinical relevance of family history of cancer.

MATERIALS AND METHODS

Study subjects

In this retrospective hospital-based case-control study, cases and controls were prospectively recruited to and enrolled in Institutional Review Board approved studies of cancer susceptibility at The University of Texas MD Anderson Cancer Center, and each participant prospectively provided written informed consent and completed the questionnaire described below. The study included 2 case groups and 1 cancer-free control group. Incident cases with papillary, follicular or Hurthle cell carcinoma of the thyroid composed the DTC case group and incident cases with thyroid benign mass composed the BTD case group (an intermediate-risk comparison group).

Between November 1999 and November 2010, we prospectively recruited patients who presented to our institution for evaluation of a thyroid gland mass. The final diagnoses of DTC and BTD were assigned by histologic review of the surgical specimen. Patients who did not fit the recruitment criteria (>17 years of age, no prior cancer history except no melanoma skin cancer, no current use of steroids or immunosuppressive medication, no blood transfusion in the previous 6 months) were excluded.

Controls were visitors to our institution using the same exclusion criteria who were recruited in a molecular epidemiologic study of head and neck squamous cell carcinoma between October 2001 and November 2009. For the current study, controls were retrospectively frequency-matched with patients with DTC by sex.

DTC cases, BTD patients, and controls completed the same self-administered questionnaires. Data were obtained on demographic information, environmental exposure, and personal and family history. The family history of cancer included questions about subjects' adoption status; number of first-degree relatives (parents, siblings, and children); current age or age at death of those first-degree relatives; and age at diagnosis of cancer and site of cancer in first-degree relatives with cancer. Subjects who had cumulatively smoked more than 100 cigarettes in their lifetimes were defined as smokers (current or former). Subjects who had drunk alcoholic beverages at least once a week for more than 1 year were defined as drinkers (current or former). Former smokers and former drinkers were those subjects who had quit smoking or these drinking patterns at least 1 year before study enrollment. Radiation exposure was defined as previous whole-body or head-and-neck-specific radiotherapy.

Statistical analysis

We used chi-square test, Fisher's exact test, or *t*-test to compare distributions of characteristics between case and control groups as appropriate. Unconditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) associated with first-degree family history of cancer, using subjects with no family history of cancer as the reference group. To adjust for potential confounders, the variables were included in the final models if they changed the target odds ratio by 10% or more when added to the unadjusted model,[21] including education, family income level, smoking status, and alcohol drinking status. In addition, age at reference date (age at diagnosis for cases and age at recruitment for controls), sex, race, and number of family members (or siblings, children, as appropriate) were fitted into the final regression model. Furthermore, we estimated the adjusted OR and 95% CI for PTC risk in association with a family history of thyroid cancer in different types of relatives and stratified by sex. A p value of less than 0.05 (2-tailed) was considered statistically significant. Statistical analysis was performed using SAS version 9.2 software (SAS Institute Inc., Cary, NC).

RESULTS

We successfully enrolled 290 patients with DTC and 197 patients with BTD. Of these, 1 patient with DTC and 9 patients with BTD had not completed questionnaires. After review of the questionnaire data, 1 patient with PTC was excluded because 2 first-degree relatives had been diagnosed with thyroid cancer. The final study included 288 patients with DTC, 188 patients with BTD, and 591 cancer-free controls.

Compared to cancer-free controls, DTC patients had a higher family income and were less likely to smoke (Table 1). Also, the proportion of non-Hispanic whites was lower in the DTC group than in the control group. DTC and BTD patients were similar in distribution of sex, ethnicity, education, family income, smoking, and alcohol drinking status. The age at diagnosis was significantly greater for controls and BTD patients than the age at recruitment for DTC patients (mean ± standard deviation [SD]: 53.6 ± 13.0 years, 50.3 ± 13.7 years and 44.8 ± 14.1 years, respectively, $p < 0.01$). Only 4 DTC patients, 4 BTD patients, and 8 controls reported a history of radiotherapy, and these differences were not statistically different. The great majority (91.3%) of patients with DTC had PTC, and classic PTC was the most common subtype (71.5%).

Family history of cancer in first-degree relatives was reported by 141 (49.0%) of the patients with DTC, 103 (54.8%) of the patients with BTD, and 343 (58.0%) of the cancer-free controls. No significant association with family history of cancer in first-degree relatives was found for DTC (adjusted OR = 1.0, 95% CI: 0.7–1.4) or BTD (adjusted OR = 0.9, 95% CI: 0.7–1.3).

Table 2 shows the association between self-reported family history of cancer at various sites in first-degree relatives and risk of DTC. The only cancers for which significant associations were found were thyroid cancer and liver cancer. Patients with DTC were significantly more likely than controls to report a family history of thyroid cancer in first-degree relatives (6.3% vs. 1.4%; adjusted OR = 4.1, 95 CI%: 1.7–9.9). A subgroup analysis of the subjects with Texas residence revealed a similar association between a first-degree family history of thyroid cancer and DTC risk (adjusted OR = 4.8, 95% CI: 1.6–14.7). All patients with DTC who had a first-degree family history of thyroid cancer (18 patients) had PTC. The association with first-degree family history of thyroid cancer was slightly stronger for PTC (adjusted OR = 4.6, 95 CI%: 1.9–11.1) (Table 3) than for DTC overall.

Family history of thyroid cancer in first-degree relatives was associated with an increased risk of BTD (adjusted OR = 3.2, 95% CI: 1.2–8.7). Of the 188 patients with BTD, 9 (4.8%) reported a first-degree family history of thyroid cancer; this proportion was non-significantly lower than the proportion of patients with DTC who reported a first-degree family history of thyroid cancer (6.3%, p = 0.53).

An analysis of the association between first-degree family history of thyroid cancer and PTC risk according to the type of relative was carried out in all subjects and subsequently in women and men separately (Table 3). The PTC risk was more evident in subjects with a family history of thyroid cancer in siblings (OR = 7.4, 95% CI: 1.8–30.4), and the same pattern was found when the analysis was limited to women (OR = 5.9, 95% CI: 1.3–26.2), though the sample sizes of these individual subgroups were limited.

Results of a descriptive analysis of the 18 DTC patients with a first-degree relative diagnosed with thyroid cancer are presented in Table 4. As previously mentioned, all of the patients in this group had histologically confirmed PTC, although the proportion of patients with PTC was not significantly different between DTC patients with and without family history of thyroid cancer (p = 0.38). More interestingly, 68.8% (11 of 16) of PTC patients with a first-degree relative with thyroid cancer had multifocal primary tumors, compared with only 35.2% (86 of 244) of the PTC patients with no family history of thyroid cancer (p = 0.01). There were no significant differences between patients with PTC with and without a first-degree family history of thyroid cancer in age at diagnosis, prevalence of thyroiditis, or distribution of PTC histological subtype. In addition, none of the PTC patients with family history of thyroid cancer in first-degree relatives reported prior history of radiation exposure.

DISCUSSION

This study confirms an association between family history of thyroid cancer in first-degree relatives and risk of sporadic PTC. The excess risk of PTC was greater in subjects who reported a family history of thyroid cancer in siblings. Additionally, among patients with sporadic PTC, those with a family history of thyroid cancer developed multifocal primary tumor more frequently than those without a family history of thyroid cancer.

Increased risk of DTC associated with a family history of thyroid cancer has been observed in most previous case-control[9–16] and cancer family registry[17–19] studies, but some results, particularly those from case-control studies, were not statistically significant.[10, 13, 16] The reported excess risk usually ranges from 2- to 10-fold. This variation in cancer risk estimates

is in part due to variations in the types of relatives assessed: parents only,[11,19] parents and children,[12] first-degree relatives plus grandparents,[10] and all relatives without regard to degree of relationship.[9, 12, 16] Also, these previous studies often did not distinguish between sporadic thyroid cancer and familial thyroid cancer. It has been reported that familial non-medullary thyroid cancer accounts for 5% of thyroid cancers and might be more aggressive in clinical behavior than sporadic cases.[7, 20] We limited our study to patients with sporadic DTC (we excluded 1 patient with PTC with 2 first-degree family members with thyroid cancer from analysis) and reported that the risk of sporadic PTC was 4.6 times as high in subjects with a first-degree family history of thyroid cancer as in those without. This excess risk is in agreement with a recent case-control study in a radiation-exposed population that reported an overall 4.5-fold increase in DTC risk associated with family history of thyroid cancer in first-degree relatives.[15] Moreover, we observed that the risk of PTC associated with a family history of thyroid cancer in siblings was more than double the risk of PTC associated with a family history of thyroid cancer in parents. While this relatives-type effect was not reported in previous case-control studies,[9–16] in the nationwide Swedish Family-Cancer Database, which recorded non-medullary thyroid cancers between 1986 and 2002, the standardized incidence ratio of PTC was more than twice as high in individuals with siblings diagnosed with thyroid cancer as in those with parents diagnosed with thyroid cancer.[22] In our study, further stratified analysis showed that this relatives-type effect was confined to women. Because of the relatively small number of participants in our study who reported a family history of thyroid cancer in first-degree relatives, we cannot conclude whether there is a sex difference in PTC risk associated with a family history of thyroid cancer by type of relative. We also observed an association between family history of liver cancer and DTC risk, whereas this finding may be subject to chance/misclassification and has not been observed in previous studies.

Besides family history, in this study, patients with DTC had higher family income and were less like to smoke than controls. Although the association between DTC and socioeconomic factors is plausible because it is suggested that the rising incidence of thyroid cancer, particularly PTC, is largely attributable to the improved diagnostic practices, only weak associations have been found.[3–5, 23] Consistently, in this study, we did not find strong association with this factor and the significance disappeared when it was entered into a multivariate analysis. Similarly, the association between smoking status and DTC risk was not significant in the multivariate risk model. The protective effect of cigarette smoking for thyroid cancer has been consistently observed. Given that hormonal and reproductive factors may be involved in thyroid carcinogenesis,[24] cigarette smoking is suspected to exhibit its protective effect by lowering the endogenous thyroid-stimulating hormone level,[25, 26] while the exact mechanism remains unclear.

Our finding of an elevated risk of sporadic DTC associated with a family history of thyroid cancer in first-degree relatives may indicate a genetic component in the etiology of thyroid cancer. Previous studies in a subset of the same case-control population revealed that common variants in the *RET* proto-oncogene,[27] DNA repair genes *XRCC1*[28] and *XRCC3*[29], and xenobiotic metabolizing genes *GSTT1* and *GSTM1*[30] were significantly associated with DTC risk. The significance of a genetic component in DTC development is also supported by a large cancer registry-based study,[18] which found a higher familial relative risk of thyroid cancer than other major cancer types, including environmental exposure-related cancers such as lung cancer. In this study, we did not observe the expected difference in age at diagnosis between PTC patients with and without a first-degree family history of thyroid cancer, possibly because the genetic predisposition in these cases may not be as strong as in familial DTC cases to trigger an early onset of disease. Alternatively, the shared environment of families may play a role in these observed excess risks. It is well established that ionizing radiation exposure is an environmental risk factor for PTC.[31] However, only a

few participants in our study reported a radiotherapy history, and the prevalence in patients with DTC was not different from that in controls. Also, while we were unable to obtain exposure information for the relatives of study subjects, adjustment of possible environmental factors, including socioeconomic status, smoking, alcohol drinking, and radiotherapy history, did not modify the association between first-degree family history of thyroid cancer and DTC (or PTC) risk. Therefore, we believe that environmental components are less likely to contribute to the excess DTC (and PTC) risk associated with family history of thyroid cancer in this study. However, we recognize the possibility should be recognized that the familial association of thyroid cancer may be caused by unsuspected or unidentified local environmental factors.

Multifocal primary tumors are common among patients with PTC; previously reported proportions range from 18% to 87%.[32, 33] In this study, 36.9% of newly diagnosed patients had multifocal PTCs. The multiple cancer loci often appear to be a consequence of independent clonal events, implicating a predisposing influence in development of multifocal PTC, including both genetic susceptibility and environmental insult.[34] As expected, multifocal PTC was more common among PTC patients with a first-degree family history of thyroid cancer than among those with no family history of thyroid cancer. Moreover, since multifocal PTC is more likely to have lymph node and pulmonary metastases,[32, 35] a prognostic difference might exist between patients with and without family history of cancer, though we have not explored this possibility here.

Our study has several limitations. First, the study sample size was moderate. As we included only sporadic DTC cases from a mixed background, the small number of subjects with a first-degree family history of thyroid cancer further limited statistical power, especially for stratification analysis. Second, the family history of cancer was self-reported by participants, which might result in recall bias. However, although no attempt was made to verify the diagnoses of cancer in first-degree relatives, those diagnoses are likely to be accurate because several studies have shown a high accuracy of diagnosis in first-degree relatives, and the accuracy proportion was comparable between cases and controls.[36–38] Third, since we used a hospital based case-control design, the possibility of selection bias, especially among controls (visitors to our institution), which could result in the lack of association between family history of cancer and DTC risk, should be considered. Forth, there was a mismatch in age between our patients and controls. However, because our control population was older with a resulting greater possibility for having a positive family history, we may have underestimated the risk of PTC associated with family history of thyroid cancer. Finally, the possibility of screening bias is certainly possible, whereby our cases (both patients with DTC and those with BTD) would have been more likely than controls to have sought thyroid examination and subsequently been diagnosed with PTC or BTD because of a relative (particularly a sibling) with a prevalent thyroid cancer than would a control population with no such family history.

In summary, here we provide evidence suggesting that family history of thyroid cancer in first-degree relatives is associated with a significant increase in sporadic PTC risk and that risk is greater for people whose siblings were diagnosed with thyroid cancer. Such results should be interpreted with caution and confirmation by larger prospective studies is warranted.

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Abbreviations

DTC	differentiated thyroid carcinoma
PTC	papillary thyroid carcinoma
BTD	benign thyroid disease
OR	odds ratio
CI	confidence interval
SD	standard deviation

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Table 1

Demographic and clinical characteristics of cases and controls

Characteristic	DTC cases (%) n=288	PTC cases (%) n=263	Controls (%) n=591
Sex			
Male	95 (33.0)	83 (31.6)*	228 (38.6)
Female	193 (67.0)	180 (68.4)	363 (61.4)
Age, years			
<45	155 (53.8)*	147 (55.9)*	148 (25.0)
≥45	133 (46.2)	116 (44.1)	443 (75.0)
Ethnicity			
Non-Hispanic Whites	198 (68.7)*	181 (68.8)*	449 (76.0)
Other	90 (31.3)	82 (31.2)	142 (24.0)
Residence			
Texas	229 (79.5)	207 (78.7)	488 (82.6)
Others	59 (20.5)	56 (21.3)	103 (17.4)
Educational level			
High school graduate or less	68 (23.7)	61 (23.3)	178 (30.1)
Some college	89 (31.0)	83 (31.7)	178 (30.1)
College graduate or advanced	130 (45.3)	118 (45.0)	235 (39.8)
Family income ($/year)			
Under 35,000	64 (23.3)*	54 (21.3)*	122 (21.7)
35,000–75,000	74 (26.9)	73 (28.9)	214 (38.0)
Over 75,000	137 (49.8)	126 (49.8)	227 (40.3)
Smoking status			
Never	193 (67.0) *	176 (66.9) *	334 (56.5)
Former	58 (20.1)	51 (19.4)	163 (27.6)
Current	37 (12.9)	36 (13.7)	94 (15.9)
Alcohol drinking status			
Never	165 (57.3)	149 (56.6)	330 (55.9)
Former	25 (8.7)	21 (8.0)	80 (13.5)
Current	98 (34.0)	93 (35.4)*	181 (30.6)
Radiotherapy history			
Yes	4 (1.4)	4 (1.5)	8 (1.4)
No	284 (98.6)	259 (98.5)	583 (98.6)
Histological type			
Papillary	263 (91.0)		
Classic PTC		188 (72.9)	
Follicular variant PTC		60 (23.2)	
Others		10 (3.9)	
Follicular/Hurthle cell	26 (9.0)		

Characteristic	DTC cases (%) n=288	PTC cases (%) n=263	Controls (%) n=591
Multifocal primary			
Yes	100 (35.3)	97 (37.6)	
No	183 (64.7)	161 (62.4)	
Thyroiditis			
Yes	63 (22.3)	57 (22.1)	
No	220 (77.7)	201 (77.9)	

* Chi-square test, $P < 0.05$ using controls as reference group.

Table 2

Family history of cancer in first-degree relatives in DTC cases and controls, by cancer type

Cancer type	DTC cases (%) n=288	Controls (%) n=591	Adjusted OR (95% CI)[a]
Tongue	1 (0.4)	0	-
Salivary gland	1 (0.4)	2 (0.3)	1.3 (0.1–14.5)
Mouth	2 (0.7)	5 (0.9)	0.7 (0.1–3.6)
Pharynx and throat	2 (0.7)	8 (1.4)	0.6 (0.1–2.8)
Esophagus	2 (0.7)	8 (1.4)	0.7 (0.1–3.5)
Stomach	8 (2.8)	9 (1.5)	1.9 (0.7–5.4)
Small intestine	0	2 (0.3)	-
Colon and rectum	11 (3.8)	41 (6.9)	0.8 (0.4–1.5)
Liver	11 (3.8)	12 (2.0)	2.6 (1.1–6.3)
Gallbladder	1 (0.4)	1 (0.2)	8.8 (0.5–148.7)
Pancreas	5 (1.7)	13 (2.2)	1.2 (0.4–3.4)
Larynx	0	3 (0.5)	-
Lung	27 (9.4)	67 (11.3)	1.1 (0.7–1.9)
Bone and joints	2 (0.7)	4 (0.7)	1.9 (0.3–11.0)
Soft tissue	0	5 (0.9)	-
Melanoma	8 (2.8)	30 (5.1)	0.6 (0.3–1.4)
Non-melanoma Skin	9 (3.1)	33 (5.6)	0.7 (0.3–1.6)
Breast	25 (8.7)	76 (12.9)	0.8 (0.5–1.4)
Uterus	6 (2.1)	8 (1.4)	1.6 (0.5–4.9)
Cervix	4 (1.4)	10 (1.7)	0.8 (0.2–2.7)
Ovary	5 (1.7)	10 (1.7)	1.0 (0.3–3.1)
Prostate	24 (8.3)	53 (9.0)	1.2 (0.7–2.0)
Testis	2 (0.7)	4 (0.7)	1.1 (0.2–6.1)
Urinary bladder	4 (1.4)	3 (0.5)	2.5 (0.5–11.6)
Kidney	6 (2.1)	12 (2.0)	1.4 (0.5–4.0)
Ureter and other urinary organs	0	1 (0.2)	-
Eye and orbit	0	1 (0.2)	-
Brain and other nervous system	5 (1.7)	14 (2.4)	0.9 (0.3–2.7)
Thyroid	18 (6.3)	8 (1.4)	4.1 (1.7–9.9)
Lymphoma	3 (1.0)	20 (3.4)	0.4 (0.1–1.4)
Leukemia	6 (2.1)	16 (2.7)	1.1 (0.4–3.1)
Myeloma	0	2 (0.3)	-
Other and unspecified sites	6 (2.1)	10 (1.7)	2.2 (0.7–6.4)
All	141 (49.0)	343 (58.0)	1.0 (0.7–1.4)

[a] Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression adjusted with age, sex, race, and number of first-degree family members.

Table 3

Family history of thyroid cancer in first-degree relatives in PTC cases and controls, by type of relative

	All patients		Women		Men	
Type of relative	**Case/Control 263/591**	**Adjusted OR (95% CI) [a]**	**Case/Control 180/363**	**Adjusted OR (95% CI) [a]**	**Case/Control 83/234**	**Adjusted OR (95% CI) [a]**
First-degree relative	18/8	4.6 (1.9–11.1)	14/6	4.4 (1.6–12.2)	4/2	5.3 (0.9–30.8)
Parent	10/4	3.3 (1.0–11.0)	9/3	3.4 (0.9–13.3)	1/1	1.9 (0.1–32.6)
Sibling	7/3	7.4 (1.8–30.4)	5/3	5.9 (1.3–26.2)	2/0	-
Child	1/1	2.4 (0.1–57.7)	0/0	-	1/1	2.8 (0.2–49.8)
First-degree female relative	14/7	4.5 (1.7–11.8)	11/6	3.6 (1.2–10.4)	3/1	9.9 (1.0–102.6)
Mother	8/4	2.8 (0.8–9.7)	7/3	2.9 (0.7–11.6)	1/1	1.9 (0.1–32.6)
Sister	5/3	5.9 (1.3–26.2)	4/3	4.8 (1.0–23.1)	1/0	-
Daughter	1/0	-	0/0	-	1/0	-
First-degree male relative	4/1	4.6 (0.5–42.9)	3/0	-	1/1	1.7 (0.1–29.0)
Father	2/0	-	2/0	-	0/0	-
Brother	2/0	-	1/0	-	1/0	-
Son	0/1	-	0/0	-	0/1	-

[a] Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression adjusted with age, sex, race, and number of first-degree family members (parents, sibling, children, as appropriate).

Table 4

Description of patients with DTC and first-degree family history of thyroid cancer

Relatives	Patients with DTC				
Relationship	**Age at diagnosis**	**Gender**	**Histology**	**Multifocal primary**	**Thyroiditis**
Mother	30	Male	Classical PTC	Yes	No
Mother	33	Female	n.a.	n.a.	n.a.
Mother	34	Female	Follicular variant PTC	No	No
Mother	37	Female	Follicular variant PTC	No	No
Mother	40	Female	Classical PTC	Yes	No
Mother	44	Female	Follicular variant PTC	Yes	No
Mother	46	Female	Classical PTC	Yes	Yes
Mother	51	Female	Classical PTC	No	No
Father	31	Female	Classical PTC	Yes	No
Father	35	Female	Classical PTC	Yes	No
Sister	42	Female	Follicular variant PTC	Yes	No
Sister	58	Female	n.a.	n.a.	n.a.
Sister	60	Female	Classical PTC	No	Yes
Sister	63	Female	Classical PTC	Yes	No
Sister	64	Male	Classical PTC	No	No
Brother	31	Male	Follicular variant PTC	Yes	No
Brother	54	Female	Classical PTC	Yes	No
Daughter	66	Male	Classical PTC	Yes	No