ORIGINAL ARTICLE

Positive family history of thyroid disease as a risk factor for differentiated thyroid carcinoma

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KEY WORDS

familial thyroid disease, thyroid carcinoma

ABSTRACT

INTRODUCTION   Apart from the environmental risk factors for differentiated thyroid carcinoma (DTC), such as iodine deficiency and ionising radiation, it seems that there are also other, biological risk factors, for example, familial predisposition to thyroid disease.

OBJECTIVES   The aim of the study was to assess the occurrence of thyroid disease in the families of patients with DTC.

PATIENTS AND METHODS   A case-control study was conducted in a group of 232 patients with DTC and in 342 age- and sex-matched healthy subjects. Eighty patients were diagnosed with follicular thyroid carcinoma, 127 with papillary thyroid carcinoma, and 25 with oxyphilic thyroid carcinoma. The questionnaire included questions on the presence of thyroid diseases in first-degree relatives. The relative risk of DTC and the effect of factors associated with thyroid diseases in the family were assessed by the logistic regression model.

RESULTS   Thyroid disease was more common in the families of DTC patients than in the control group: 18.5% of the patients and 9.6% of the control group had a parent with thyroid disease (OR = 2.12, 95% CI: 1.26–3.55); 16.8% of the patients and 7.7% of the control group had a sibling with thyroid disease (OR = 2.27, 95% CI: 1.31–3.95).

CONCLUSIONS   Familial thyroid disease may be a risk factor for DTC. A positive family history of thyroid disease is associated to a larger extent with the development of papillary thyroid carcinoma than with that of follicular thyroid carcinoma.

INTRODUCTION   Thyroid carcinoma (TC) is a neoplasm derived from the thyroid tissue. It is the most common carcinoma of the endocrine glands and constitutes about 1% of all carcinomas in the world. The incidence depends on the region and ranges from 0.6% to 1.9%. TC affects women 3 times more often than men. Particularly high morbidity is observed in eastern and south-eastern Asia (Japan, Korea, Hong Kong) and in the Pacific Islands. Morbidity is higher in older age groups. About 80% of the cases diagnosed with TC are 30 years of age or older. From

the beginning of the 1990s, a constantly increasing morbidity of TC has been observed, mainly of differentiated thyroid carcinoma (DTC), with the prevalence of papillary carcinoma (PTC).[1-4]

Since the Chernobyl disaster, besides clinical trials and epidemiological studies, there has been a growing interest in the genetic background of thyroid cancer, particularly radiation-induced TC. Protein tyrosine kinases have been reported to play a significant role in the regulation of thyroid cell growth and differentiation.[5-7]

TABLE 1 Incidence of thyroid disease in families

Family history of thyroid disease	Patients with DTC (n = 232)	Controls (n = 343)	P
benign thyroid disease in parents[a], n (%)	40 (17.2)	29 (8.5)	<0.05
benign thyroid disease in siblings[a], n (%)	37 (15.9)	24 (7.0)	<0.05
benign thyroid disease in children[a], n (%)	26 (11.2)	22 (6.4)	NS
thyroid carcinoma in the family[b], n (%)	4 (1.7)	2 (0.6)	NS

a hyperthyroidism, hypothyroidism, thyroiditis, nodular goiter, parenchymal goiter
b in patients with DTC: parents of 2 men, sister of 1 woman, and son of 1 woman; in the control group: daughters of 2 women

Abbreviations: DTC – differentiated thyroid carcinoma, NS – nonsignificant

One of the genes encoding a receptor tyrosine kinase is the proto-oncogene *RET* localized on chromosome 10q11.2. *RET/PTC* rearrangements are predominantly the effect of ionizing radiation.[8]

Molecular research has demonstrated the role of oncogenes in carcinogenesis. Carcinogenesis results from mutations, rearrangements, or amplifications in such proto-oncogenes as *RAS*, *RET/PTC*, *TRK*, *MET*, *GSP*, or from mutations in thyroid-stimulating hormone (TSH) receptor, T3 nuclear receptor, or suppressor genes, e.g., *p53*, whose role was initially discovered in the process of undifferentiation of DTC.[9-14] The *RET* proto-oncogene transforms normal thyrocytes into follicular adenoma, follicular thyroid carcinoma (FTC), and possibly papillary thyroid carcinoma (PTC). The proto-oncogene *TRK* transforms thyrocytes into PTC.

Recent dynamic development of molecular biology allowed to suggest that PTC may be an inherited disorder – not only as a component of Gardner's syndrome, but also as a result of mutations in loci 19p13 and 2q21 as well as mutations and rearrangement of the *RET* proto-oncogene that may be transferred to the offspring.[15-19]

Population-based reports have shown that benign thyroid disorders occur more frequently in certain families, which might be caused by genetic mutations.[20-22] Familial incidence of DTC has also been reported in a number of clinical papers.[23-27]

The aim of the present study was to assess the risk of DTC in patients with a positive family history of thyroid disease.

PATIENTS AND METHODS A questionnaire-based case-control study was conducted at the Department of Endocrinology, Jagiellonian University Medical College in Kraków, Poland, based on the local register of TC, which covered the data of patients from the former provinces of Kraków and Nowy Sącz since 1974.

To reclassify diagnoses established before 1992 and to standardize them according to the International Classification of Diseases 10th Revision, World Health Organization, we evaluated histological thyroid specimen in the years 1999–2000. Laboratory work was coordinated by the Department of Pathomorphology, Jagiellonian University Medical College, Kraków, Poland.

We recruited 362 patients (248 women and 78 men) from the available database; all patients were born before the nuclear accident in Chernobyl. Of all patients, 232 provided written consent and underwent further examination: 201 women (mean age 50.7 ±13.1 years) and 31 men (mean age 60.2 ±12 years).

A control group was drawn from the local population register and included 1090 individuals (834 women and 256 men) matched for age and sex and living in the same area as study subjects. A total of 343 healthy controls provided their consent and were included in the study: 285 women (mean age 53.4 ±14.3 years) and 58 men (mean age 60.2 ±12.0 years). All controls were drawn at the same time.

The ethical committee of the Jagiellonian University approved the study, and the informed consent was obtained from each patient.

All participants completed the same questionnaire with questions concerning thyroid disorders (benign: hyperthyroidism, hypothyroidism, nodular goiter, parenchymal goiter, thyroiditis; malignant: thyroid carcinoma) in their close family (parents, siblings, children).

The relative risk (RR; estimated by the odds ratio [OR]) of DTC was calculated using the unconditional logistic regression model. RR estimates based on conditional logistic regression for matched pairs are similar to those using unconditional logistic regression and controlling for the matching variables. By using unconditional logistic regression, controlling for age and sex, it was possible to use all controls in the subgroup analysis of the cases, thus enhancing the statistical power. $P = 0.05$ was considered statistically significant, and the statistical analysis was conducted using STATISTICA 8.0 PL.

RESULTS The incidence of thyroid diseases in parents, siblings, or children of patients with DTC was more frequent than in those of the controls (**TABLE 1**).

Thyroid disease was reported in 120 family members of the patients and in 82 family members of the controls. There were 108 patients (54.5%) with a negative family history in the DTC group and 174 (71%) in the control group. The difference was statistically significant ($P < 0.001$ and OR = 1.89, 95% CI: 1.27–2.82;

TABLE 2 Family history of thyroid diseases in patients and controls

Family history	Patients with DTC	Controls	P
positive, n (%)	90 (45.5)	71 (29)	<0.001
negative, n (%)	108 (54.5)	174 (71)	

OR: 1.89, 95% CI: 1.27–2.82

Abbreviations: CI – confidence interval, OR – odds ratio

TABLE 3 Risk of DTC in men and women whose father had been diagnosed with benign thyroid disease

	Patients with DTC n (%)	Controls, n (%)	OR	95% CI
thyroid disease				
overall	10 (4.8)	5 (1.0)	5.04[a]	1.34–18.9
goiter	4 (1.9)	2 (0.7)	3.18	0.57–17.7
nodule	2 (1.0)	1 (0.3)	3.36	0.30–38.7
other thyroid diseases[b]	4 (1.9)	2 (0.7)	2.72	0.48–15.4
risk of DTC and type of carcinoma				
FTC	4 (5.7)	3 (1.0)	5.80[a]	1.25–26.9
PTC	5 (4.2)	3 (1.0)	4.03	0.93–17.5
oxyphilic carcinoma	1 (4.5)	3 (1.0)	4.46	0.43–45.9
risk of DTC and sex				
men	2 (8.0)	1 (2.0)	7.16	0.56–91.9
women	8 (4.3)	2 (0.8)	5.17[a]	1.07–24.9

a $P < 0.05$
b   hyperthyroidism, hypothyroidism, thyroiditis

Abbreviations: FTC – follicular thyroid carcinoma, PTC – papillary thyroid carcinoma, others – see **TABLES 1** and **2**

TABLE 2). We did not observe any associations between the age or sex of patients with DTC and either a positive or negative family history of thyroid disease. Moreover, we did not observe any differences between the individual groups.

If a father had a thyroid disease, the risk of DTC significantly increased both in men and women. It increased over 5-fold (OR = 5.04, 95% CI: 1.34–18.9), and the highest risk was observed for FTC (OR =5.8, 95% CI: 1.25–26.9). In male patients whose fathers had any type of thyroid disease, the risk increased over 7-fold, and in female patients more than 5-fold (OR = 5.17, 95% CI: 1.07–24.9; **TABLE 3**). Due to a small size of the group, the risk of developing a particular type of DTC was not analyzed separately for men and women.

If thyroid disease was present in a mother, the risk of DTC significantly increased only in men. The highest risk of DTC was observed in patients whose mother had been diagnosed with thyroid nodules (OR = 9.4, 95% CI: 1.11–79.2) and it was maximum for PTC (OR = 11.2, 95% CI: 1.29-104.0).

The risk of DTC was statistically higher in male patients with a maternal history of thyroid disorders (OR = 16.8, 95% CI: 1.8–154.0; **TABLE 4**).

Thyroid disease diagnosed in either of the parents increased the risk of DTC from 6.5- to 17-fold in men compared with women. A thyroid disease in both parents was reported for 3 patients and 1 control (**TABLE 5**).

A thyroid disease in siblings increased the risk of DTC in both men and women. The incidence of benign thyroid disease in siblings increased the risk of DTC more than 2-fold and was statistically higher for PTC.

Due to a small size of the study group, we did not analyze male patients separately (**TABLE 6**).

There was no correlation between the incidence of DTC in parents and thyroid disease in children.

To sum up, a positive family history of thyroid disease may be a risk factor for DTC. A positive family history of thyroid disease is associated more with PTC than with FTC.

DISCUSSION   Researchers have long been interested in autoimmune thyroid diseases[28] and coexistence of benign and malignant thyroid diseases in families.

Studies on familial predisposition to cancers have reported an increased risk of TC in relatives, particularly first-degree relatives. Patients with familial nonmedullary TC (FNMTC) have more aggressive tumors with earlier age of disease onset compared with the sporadic type.[16,29,30] This proves that there may be genes responsible for DTC formation. The members of families with FNMTC were more often diagnosed with carcinomas and also with adenomas and multinodular goiter.[21,22]

TABLE 4 Risk of DTC in men and women whose mother had been diagnosed with benign thyroid disease

		Patients with DTC, n (%)	Controls, n (%)	OR	95% CI
DTC					
thyroid disease	overall	33 (14.9)	27 (8.9)	1.72	0.99–2.98
	goiter	23 (10.6)	15 (5.0)	2.23[a]	1.13–4.40
	nodule	7 (3.2)	1 (0.3)	9.4[a]	1.11–79.2
	other[b]	3 (1.6)	11 (3.3)	0.44	0.14–1.40
FTC					
thyroid disease	overall	13 (17.3)	27 (8.9)	2.07[a]	1.0–4.28
	goiter	11 (14.7)	15 (5.0)	3.23[a]	1.41–7.41
	nodule	1 (1.4)	1 (0.3)	3.37	0.20–57.1
	other[b]	1 (1.4)	11 (3.3)	0.41	0.12–1.23
PTC					
thyroid disease	overall	16 (13.0)	27 (8.9)	1.40	0.72–2.73
	goiter	10 (8.3)	15 (5.0)	1.61	0.70–3.75
	nodule	6	1 (0.3)	11.2[a]	1.29–104.0
	other[b]	0	11 (3.3)	0.3	0.11–1.01
oxyphilic carcinoma					
thyroid disease	overall	4 (17.4)	27 (8.9)	2.17	0.68–6.99
	goiter	2 (7.7)	15 (5.0)	1.84	0.39–8.70
	nodule	1 (4.3)	1 (0.3)	14.7	0.75–288.0
	other[b]	1 (4.3)	11 (3.3)	0.2	0.68–6.4
risk of DTC and sex					
men		7 (25.0)	1 (2.0)	16.8[a]	1.8–154.0
women		26 (13.5)	26 (10.2)	1.31	0.73–2.35

a   P <0.05
b   hyperthyroidism, hypothyroidism, thyroiditis

Abbreviations: see **TABLES 1**, **2**, and **3**

TABLE 5 Risk of DTC in subjects with at least one parent diagnosed with benign thyroid disease

	Patients with DTC, n (%)	Controls, n (%)	OR	95% CI
DTC				
overall	40 (18.5)	29 (9.6)	2.12[a]	1.26–3.55
men	8 (29.6)	2 (3.8)	11.3[a]	2.05–62.2
women	32 (16.9)	27 (10.5)	1.69	0.97–2.94
FTC				
overall	16 (21.9)	29 (9.6)	2.59[a]	1.31–5.11
men	3 (37.5)	2 (3.8)	17.0[a]	2.01–144.0
women	13 (24.6)	27 (10.5)	2.05	0.98–4.29
PTC				
overall	19 (15.8)	29 (9.6)	1.70	0.91–3.20
men	3 (20.0)	2 (4.2)	6.55	0.89–48.4
women	16 (15.2)	27 (10.6)	1.47	0.75–2.88
oxyphilic carcinoma				
overall	6 (25.0)	29 (9.6)	2.47	0.84–7.23
men	2 (40.0)	2 (3.8)	14.0[a]	1.23–160.0
women	4 (21.1)	27 (10.5)	1.58	0.43–5.87

a   P <0.05

Abbreviations: see **TABLES 1**, **2**, and **3**

Despite the development of molecular techniques, the genetic risk factors are still poorly understood.

Numerous studies have contributed to our understanding of the mechanisms that underlie tumor transformation in tissues. Now it is

TABLE 6 Risk of DTC in cases whose siblings have been diagnosed with benign thyroid disease

Type of disease in siblings	Patients with DTC OR 95% CI	Women OR 95% CI
thyroid disease		
all types of DTC	2.27[a] (1.31–3.95)	2.03[a] (1.15–3.57)
FTC	1.41 (0.62–3.22)	1.21 (0.51–2.85)
PTC	2.73[a] (1.45–5.12)	2.41[a] (1.26–4.59)
oxyphilic carcinoma	3.13[a] (1.02–9.56)	3.40[a] (1.10–10.5)
goiter		
all types of DTC	2.17 (0.99–4.75)	1.86 (0.83–4.16)
FTC	1.30 (0.39–4.33)	0.91 (0.24–3.46)
PTC	2.74[a] (1.16–6.51)	2.45[a] (1.01–5.93)
oxyphilic carcinoma	2.29 (0.45–11.7)	2.64 (0.51–13.6)
nodules		
all types of DTC	1.58 (0.56–4.48)	1.58 (0.56–4.48)
FTC	1.05 (0.21–5.18)	1.04 (0.21–5.18)
PTC	2.28 (0.74–7.05)	2.28 (0.74–7.05)
oxyphilic carcinoma	–	–
hyper- and hypothyreosis		
all types of DTC	2.64[a] (1.03–6.77)	2.38 (0.92–6.21)
FTC	2.17 (0.61–7.66)	2.17 (0.61–7.68)
PTC	2.17 (0.71– 6.67)	1.73 (0.53–5.64)
oxyphilic carcinoma	6.09[a] (1.43–26.0)	6.47 (1.50–27.8)

a $P < 0.05$

Abbreviations: see **TABLES 1**, **2**, and **3**

important to find alterations in the human genome that might predispose to malignancy.

Proto-oncogene mutations in inherited medullary carcinoma have been recognized in isolated medullary carcinoma and in the multiple endocrine neoplasia syndrome. DTC has been also described in Gardner's syndrome and in familial adenomatous polyposis. Preventive activity is therefore possible even in asymptomatic mutation carriers. After have been undertaken, mainly on PTC, confirming that different genetic changes – mutations, polymorphisms, rearrangements – are more often present in patients with DTC than in control groups. However, there is still no consensus as to which genes are responsible for the higher risk of DTC.

In vitro and animal studies have pointed to numerous genes (e.g., BRAF, CYP2D6, MNG1, TCO, thyroglobulin, TSH- and NIS-encoding genes, T3 nuclear receptor gene), the mutations and polymorphisms of which are linked with an increased risk of DTC. This allows to predict the dynamism of carcinoma growth and local recurrence after treatment.[16,30] Polymorphisms of *TNF* and *CTLA4* genes are typical for autoimmune disorders although not only autoimmune thyroid diseases. They can also determine a more aggressive course of some types of neoplasms or angioinvasion.[31,32] The most recent studies based on the evaluation of microRNA in the tumor tissue have provided important data not only for diagnosis but also for the prediction of prognostic factors in DTC.[33,34] Moreover, the polymorphisms of genes that play a role in biotransformation during carcinogenesis may participate in the pathogenesis of TC.[35] Hopefully, molecular biology and genetic engineering will change the way of targeted therapy of TC by modifying genes involved in carcinogenesis, apoptosis, angioinvasion, and metastasis.[36] Family history-based epidemiologic studies have allowed to define populations with high risk of developing thyroid diseases including TC.

Our study confirmed that risk of DTC in children is increased if parents are affected by benign thyroid disease. Franceschi et al.[37] obtained similar data based on multicenter trials from 12 European and Asian countries and from the United States. The authors confirmed an increased risk of DTC in patients whose parents had been diagnosed with benign thyroid disease.

A parental history of thyroid disease increased the risk of TC (about 40-fold if it was a father and 6-fold if it was a mother).[37] Memon et al.[38] suggested that a family history of benign thyroid diseases is associated with increased risk of thyroid cancer, and described familial susceptibility to benign thyroid disease and TC in the Kuwait population. Similarly, Cross et al.[39] observed a higher incidence of goiter and hypothyroidism in the relatives of patients with PTC when compared with the control group. In our study, thyroid disease in a father increased the risk of DTC 5-fold both in men and women. Thyroid disease

in a mother increased the risk of DTC 16-fold in men. The incidence of TC in the family increased the risk of DTC over 3-fold and the risk of developing follicular or oxyphilic thyroid carcinoma even 5-fold.

Galanti et al.[40] observed that the questionnaire-based studies investigating a family history of different diseases, including thyroid disorders, have limited credibility, particularly in older patient groups. This fact could be responsible for the underestimation of thyroid disease incidence in families.

When analyzing the risk factors for DTC, diverse other carcinogenic factors should be considered. However, such analysis is beyond the scope of the present paper.

Our study has several limitations, but it is impossible to discuss them in detail. Generally, we did not consider other factors that might have influenced a higher DTC risk in this patient group, such as genetic disorders, iodine deficiency, the effect of environmental or occupational factors, diet, reproductive history in women, or exposure to radioactivity after the Chernobyl disaster.

Our study was the first population-based examination in the former provinces of Kraków and Nowy Sącz – the area that was classified as having moderate iodine deficiency during the years 1980–1997. Our study was also the first to have assessed the risk of DTC in patients from this region, who had a positive family history of thyroid disease.

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Rodzinne występowanie chorób tarczycy jako czynnik ryzyka zróżnicowanego raka tarczycy

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STRESZCZENIE

WPROWADZENIE   Oprócz środowiskowych czynników ryzyka zróżnicowanego raka tarczycy (*differentiated thyroid carcinoma* – DTC), takich jak niedobór jodu i promieniowanie jonizujące, prawdopodobnie istnieją także inne, biologiczne czynniki ryzyka, np. rodzinna predyspozycja do chorób tarczycy.

CELE   Celem pracy była ocena występowania chorób tarczycy w rodzinach chorych z DTC.

PACJENCI I METODY   Badanie kliniczno-kontrolne przeprowadzono w grupie 232 chorych z DTC oraz u 342 osób z grupy kontrolnej dobranych pod względem płci i wieku. Raka pęcherzykowego rozpoznano u 80 osób, raka brodawkowatego – u 127 osób, a raka oksyfilnego – u 25 osób. Pytania ankietowe dotyczyły występowania chorób tarczycy wśród krewnych w pierwszym stopniu pokrewieństwa. Względne ryzyko wystąpienia DTC oraz wpływ czynników związanych z chorobami tarczycy w rodzinie oceniono za pomocą analizy regresji logistycznej.

WYNIKI   Choroby tarczycy były częstsze w rodzinach chorych z DTC niż w grupie kontrolnej: choroba jednego z rodziców występowała u 18,5% chorych i u 9,6% osób z grupy kontrolnej (OR 2,12; 95% CI: 1,26–3,55); choroba rodzeństwa – u 16,8% chorych i u 7,7% osób w grupie kontrolnej (OR 2,27; 95% CI: 1,31–3,95).

WNIOSKI   Choroby tarczycy w rodzinie mogą stanowić czynnik ryzyka wystąpienia DTC. Dodatni rodzinny wywiad w kierunku chorób tarczycy w większym stopniu związany jest z wystąpieniem raka brodawkowatego niż raka pęcherzykowego.