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

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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.

KEY WORDS
familial thyroid disease, thyroid carcinoma
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, n (%)                 | 40 (17.2)                   | 29 (8.5)          | <0.05 |
| benign thyroid disease in siblings, n (%)                | 37 (15.9)                   | 24 (7.0)          | <0.05 |
| benign thyroid disease in children, n (%)                | 26 (11.2)                   | 22 (6.4)          | NS    |
| thyroid carcinoma in the family, n (%)                   | 4 (1.7)                     | 2 (0.6)           | NS    |

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. 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. 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.

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

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;
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 and co-existence 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. 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.

### Table 2

| Family history | Patients with DTC | Controls | OR (95% CI) |
|---------------|-------------------|---------|-------------|
| 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

**Discussion**

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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. 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.

### Table 3

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

| Thyroid disease | Patients with DTC n (%) | Controls, n (%) | OR (95% CI) |
|----------------|-------------------------|----------------|-------------|
| 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<sup>b</sup> | 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 (<i>P</i> < 0.05) 1.25–26.9
  - PTC: 5 (4.2) 3 (1.0) 4.03 (0.93–17.5)

- **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 (<i>P</i> < 0.05) 1.07–24.9

- Abbreviations: FTC – follicular thyroid carcinoma, PTC – papillary thyroid carcinoma, others – see Tables 1 and 2
Numerous studies have contributed to our understanding of the mechanisms that underlie tumor transformation in tissues. Now it is despite the development of molecular techniques, the genetic risk factors are still poorly understood.

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

| Thyroid Disease | Patients with DTC, n (%) | Controls, n (%) | OR      | 95% CI |
|-----------------|-------------------------|----------------|---------|-------|
| DTC overall     | 33 (14.9)               | 27 (8.9)       | 1.72    | 0.99–2.98 |
| goiter          | 23 (10.6)               | 15 (5.0)       | 2.23*   | 1.13–4.40 |
| nodule          | 7 (3.2)                 | 1 (0.3)        | 9.4*    | 1.11–79.2 |
| other*          | 3 (1.6)                 | 11 (3.3)       | 0.44    | 0.14–1.40 |
| FTC overall     | 13 (17.3)               | 27 (8.9)       | 2.07*   | 1.0–4.28  |
| goiter          | 11 (14.7)               | 15 (5.0)       | 3.23*   | 1.41–7.41  |
| nodule          | 1 (1.4)                 | 1 (0.3)        | 3.37    | 0.2–57.1   |
| other*          | 0                      | 11 (3.3)       | 0.41    | 0.12–1.23  |
| PTC 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    | 1.29–104.0 |
| other*          | 0                      | 11 (3.3)       | 0.3     | 0.11–1.01  |
| oxyphilic carcinoma 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*          | 1 (4.3)                 | 11 (3.3)       | 0.2     | 0.68–6.4   |
| risk of DTC and sex overall | 7 (25.0) | 1 (2.0) | 16.8* | 1.8–154.0 |
| men             | 26 (13.5)               | 26 (10.2)      | 1.31    | 0.73–2.35 |
| women           | 7 (25.0)                | 1 (2.0)        | 16.8    | 1.8–154.0 |

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

| Thyroid Disease | Patients with DTC, n (%) | Controls, n (%) | OR      | 95% CI |
|-----------------|-------------------------|----------------|---------|-------|
| DTC overall     | 40 (18.5)               | 29 (9.6)       | 2.12*   | 1.26–3.55 |
| men             | 8 (29.6)                | 2 (3.8)        | 11.3*   | 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*   | 1.31–5.11 |
| men             | 3 (37.5)                | 2 (3.8)        | 17.0*   | 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*   | 1.23–160.0 |
| women           | 4 (21.1)                | 27 (10.5)      | 1.58    | 0.43–5.87 |

a P <0.05
b hyperthyroidism, hypothyroidism, thyroiditis

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.\textsuperscript{30,32} 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.\textsuperscript{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.\textsuperscript{33,34} Moreover, the polymorphisms of genes that play a role in bio-transformation during carcinogenesis may participate in the pathogenesis of TC.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{37} Memon et al.\textsuperscript{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.\textsuperscript{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.
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. 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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SŁOWA KLUCZOWE
choroby tarczycy w rodzinie, rak tarczycy

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. rodzina predyspozycja do chorób tarczycy.

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

PACJENTI I METODY Badanie kliniczno-kontrolne przeprowadzono w grupie 232 chorych z DTC oraz u 342 osób z grupy kontrolnej dobrych pod względem płci i wieku. Raka pęcherzykowego rozpoznano u 80 osób, raka brodawkowego – 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 w grupie 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 brodawkowego niż raka pęcherzykowego.