Risk of malignant tumors in first-degree relatives of patients with differentiated thyroid cancer – a hospital based study

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In presented study the risk of incidence of familial differentiated thyroid cancer as well as the risk of other malignant tumors in families of DTC patients was evaluated.

999 patients with differentiated thyroid cancer and 825 persons without any history of malignant disease were evaluated on the occurrence of malignant neoplasm within their families. Information about 6614 first degree relatives of DTC index patients and 4939 first degree relatives of control persons were recorded. The incidence of cancers at various sites was compared between first-degree relatives of index patients and control persons and odds ratio with 95% confidence intervals (CI) were calculated for thyroid cancer and other cancer sites.

Within 999 families of thyroid cancer index patients 23 families with more than one case of DTC were found. The risk of the development of thyroid cancer in the first degree was 6 (95% CI 1.8–19) times greater in the index group than in the control group. No increased risk for development of other malignancies was observed.

Results of our study confirm previous reports of increased risk of thyroid cancer in first-degree relatives of differentiated thyroid cancer patients. However, the relatively small number of first-degree relatives affected with thyroid cancer (24/6614) does not justify at present any screening in the first-degree relatives of patients affected with differentiated thyroid cancer. Simultaneously, no increased risk of other malignant neoplasm was observed in the differentiated cancer families.

Key words: differentiated thyroid cancer, risk of familiar cancer

Genetic predisposition contributes to the development of a number of cancers. Genetic susceptibility to thyroid cancer has been focused mainly on medullary thyroid cancer where, in about 20% of patients, it occurs as a part of the multiple endocrine neoplasia type 2 syndrome or as familiar cancer without other endocrine abnormalities [1, 2]. There is however, increasing evidence that genetic predisposition to thyroid cancer is not restricted to C-cell derived tumors.

The first well-documented case of familial differentiated thyroid cancer (DTC), without coexistence of any hereditary disorder, was reported by NEMEC et al [3]. Since than several dozens of families with two or more cases of DTC have been described. Several studies have reported 4- to 9-fold increased risk of thyroid cancer in relatives of thyroid cancer patients [4–7], placing it among those malignant neoplasm with the most distinct familial predisposition to the occurrence of the same type of cancer [8].

Several groups of investigators have been studying the molecular genetics of familial differentiated thyroid cancer [9–12]. Some of the published pedigrees suggest an autosomal dominant mode of inheritance with incomplete penetrance. MCKAY et al [12] performed a linkage analysis in an independent sample set of 80 pedigrees with DTC indicating the existence of susceptibility locus for familial non-medullary thyroid cancer on chromosome 2q21. Several candidate genes exist in this region, such as *ACVR2,* which has been implicated in thyrocyte growth [13]; *RAB6/RALB,* members of the Ras-like family [14]; and the *LRP-DIT* tumor suppressor [15]. Two other loci predisposing to FNMTC have been identified, *TCO* on 19p13.2, in a French family with an unusual form of NMTC with cell oxyphilia [10] and *MNG1* on locus on 14q, identified in a large Canadian family with multinodular goiter and NMTC [9]. Recently CYBULSKI at al [16] proved positive association between *CHECK 2* pro-

tein-truncating alleles and thyroid cancer. Increased risk of other cancers (breast and prostate) was also demonstrated. Yet, despite extensive molecular investigations, no specific gene responsible for susceptibility to familial thyroid cancer, has been identified so far.

A relationship between genetic predisposition to thyroid cancer and other malignancies has not been clearly established. Well documented relationship exists between thyroid cancer and two forms of inherited colon cancer, familial adenomatous polyposis and Gardner's syndrome [17, 18]. Papillary or follicular thyroid carcinoma may also present as one of many manifestations of Cowden's syndrome [19] characterized by nodular goiter, multiple hamartomas, skeletal abnormalities and 50% risk of developing breast cancer. However, fewer than 0.1% of differentiated cancer cases is associated with either of these cancer syndromes (20). So, the above mentioned familial cancer syndromes are not able to explain excess of breast or other malignancies in relatives of differentiated thyroid cancer patients reported by some [8, 21] but not all authors [5, 22].

Detailed identification and description of familial clustering of DTC and other malignancies should enable prophylactic screening in such families and would be a help to elucidate molecular patomechanism of differentiated thyroid cancer development.

The purpose of our study was to estimate risks of the occurrence of cancers of all types in first degree relatives of patients with differentiated thyroid cancer compared with first-degree relatives of cancer-free controls in a hospital based setting.

Material and methods

Every year more than 500 patients with newly diagnosed thyroid cancer are referred to our Department. In the regular follow-up there are about 5000 patients with differentiated thyroid cancer.

To identify families with increased incidence of thyroid and/or other cancers we randomly selected 999 patients with DTC attending their regular check-up. Apart from standard examinations (as required by their follow-up schedule) they were interviewed about their family history. In all the index patients, postoperative diagnosis of differentiated thyroid cancer was confirmed at Pathology Department of our Institute.

Persons admitted to other hospitals due to non malignant diseases were included into the control group. None of the control persons suffered from malignant disease in the past or was admitted to the hospital with suspicion of malignant disease. Information on clinical state was provided by physicians taking care of the control persons.

The family history of all first-degree relatives included current age or age at death and, if any of first-degree relatives suffered from cancer, age of its diagnosis and its site. Only data on blood related relatives were included into the study, and the term "blood relation" was explained to all inquired persons. All questionnaires were filled in during personal talk with the index person. No attempts were made to verify the diagnosis of cancer in first degree relatives. However, if the index person reported cancer in the first degree relative the inquiry was continued to obtain some additional information (e.g. hospital where the relative was treated, kind of therapy) to support the diagnosis of cancer.

Informed oral consent was obtained from all of the inquired persons. None of the patient from the control group refused to participate in the study. From the control group 12 (1.2%) persons declined to answer the questionnaire claiming that no-one in their family suffered from cancer disease.

Statistical analysis. The incidence of thyroid cancer and other malignant tumors was compared between relatives of index patients and control persons using odds ratio (OR). 95% confidence interval (CI) was calculated for each site. Additionally, histopathology-specific OR was calculated for papillary and follicular thyroid cancer.

Results

Most of the inquired thyroid cancer index patients were women with papillary thyroid cancer. There were no statistically significant differences in age or histopathological type of DTC between women and men. However, women had slightly higher number of first degree relatives. The mean time from cancer diagnosis to the interview was 4.3 years (maximum 15 years). Index patients were about 1.6 years younger than the control persons. However, when persons at this extreme age (less then 21 and more than 71) were excluded mean age in the index group and control group was respectively 48.3 and 47.9 and the difference was statistically insignificant. Table 1 describes the distribution of index patients and control persons according to age, sex, place of living as well as number and age of first degree relatives.

29.4% (294/999) of index patients and 27.5% (227/825) of control persons reported cancer disease in a first degree relative. Majority of the cancers in the first-degree relatives originated from digestive tract (n=195), lung (n=94), lymphopoetic system (n=42) or head and neck (n=41). In most cases two persons within a family were affected with cancer, however in about 5% of families there were 3 or more persons. There were no differences in the number of first-degree relatives with cancers between the index and the control group ($p<0.05$, Chi-square test).

Thyroid cancer was diagnosed in 24 first-degree relatives of thyroid cancer index persons. These 24 thyroid cancer cases occurred in 23 different families. Before the diagnosis of thyroid cancer none of persons was treated with radiation therapy. Clinical review of those 23 thyroid cancer families of the index patients was not suggestive of any known familial cancer syndrome (i.e. FAP). Only 3 cases of thyroid cancers were diagnosed in a first-degree relative of control persons. In 19 first-degree relatives of index persons and one

first-degree relative of control person a histopathological confirmation of thyroid cancer was available (Tab. 2). Papillary thyroid cancer was diagnosed in more than 50% of families from the index group. Of note, in the family with three cases of DTC, all were of papillary histopathology.

Among the 6614 first-degree relatives of the thyroid cancer index patients, no general increase of cancer risk was found for all of the sites (OR 1.0; 95% CI 0.8–1.3). The only cancer site that accounted for excess cancer risk was thyroid cancer with odd ratio of 6.0 (95% CI 1.8–19.9). Significantly increased risk was not found for any other site including breast, digestive track or central nervous system. Table 3 shows odds ratio adjusted for age calculated for each cancer site.

When first-degree relatives of patients with papillary and follicular type thyroid cancer were compared there were no differences in risk of malignant neoplasms (Tab. 4). Although thyroid cancer was more prevalent in first-degree relatives of patients with papillary cancer the difference was not statistically significant (95% CI 0.7–4.1). However, there was a slightly decreased risk of head and neck cancer (not originating from thyroid gland) in papillary thyroid cancer.

Discussion

The etiology of differentiated thyroid cancer is not fully understood, but there is some evidence that genetic as well as environmental factors may play a role. However, ionization radiation is the only one well established risk factor for DTC [23].

Familial non-medullary thyroid cancer. Several studies have documented an increased familial occurrence of different cancer types, with thyroid cancer as one of the sites with highest risk among close relatives [6, 8]. The prevalence of familiar DTC ranging from 2.5% to 6.3% has been reported, with mean of 4.2% among 1562 index patients [24]. In the recent series of ORSENIGO et all [25] a familial occurrence of papillary thyroid cancer was found in 2.25% of cases.

Our results are consistent with the above mentioned reports. Twenty three of 999 (2.3%) patients with DTC had at least one first-degree relative affected with thyroid cancer. We found a 6-fold increase in thyroid cancer in relatives of index patients with differentiated thyroid cancer. Obviously, one is not able to exclude the possibility that some of the excess thyroid cancers observed in relatives are due to attendance at a thyroid scecialist with intention of prophylactic examination or due to thyroid goiter and subsequent diagnosis of very small invasive thyroid carcinoma. Secondly, due to high prevalence of thyroid cancer as evident from post mortem data [26] one can not preclude accidental coexistence of sporadic thyroid cancer in relatives. Yet, in our series of patients and their relatives only one patient had a diagnosis of microcarcinoma (maximum diameter of tumor less than 1 cm).

In most reports familial aggregation of papillary differentiated thyroid cancer is reported. However when, we compared risk of thyroid cancer in first-degree relatives of index patients with papillary and follicular thyroid cancer, there were no statistically significant differences. As the central review of all histopathology results was performed a mistake in histopathology diagnosis of thyroid cancer type can be excluded. We can only speculate on the reason of this observation. For a long time Poland has been considered a region of iodine deficiency [27]. Incidence rate of follicular thyroid cancer tends to be higher in iodine deficient area, while the opposite pattern has been reported for papillary thyroid cancer [28]. It is likely that the familial aggregation of follicular thyroid cancer can be attributed to this environmental factor.

Extrathyreoideal malignancies in first-degree relatives. The Utah Population Database has supported extensive examinations on the familial aggregation of many cancer sites. GOLDGAR at al [8] reported a familial association of breast and thyroid cancer, but it was not confirmed by other epidemiological studies [5, 7, 22]. Other cancers associated with thyroid cancer in the Utah study included soft tissue sarcoma, leukemia and prostate cancer. An excess of all cancers among family members of thyroid cancer index persons has not been supported by others [29, 30]. In the report of PAL et al [7], no increase in incidence for any cancer site except for thyroid

Table 1. Descriptive statistics of study participants and their first-degree relatives.

		Cases n=999	Controls n=825
Age (mean±SD)		48.0±13.8	49.6±14.3
Sex (women)		851 (85%)	654 (79%)
Place of living	seaside	99 (10%)	85 (10%)
	central	747 (75%)	652 (79%)
	highlands	153 (15%)	88 (11%)
First degree relatives	mother (mean age±SD)	997 (68±13.6)	825 (68.2±12.5)
	father (mean age±SD)	998 (65.3±14)	825 (65.7±12.7)
	sister (mean age±SD)	1351 (47.9±15.4)	960 (51±15.8)
	brother (mean age±SD)	1385 (46.5±15.3)	968 (49.2±16.1)
	daughter (mean age±SD)	923 (24.4±12.1)	683 (25.9±13.1)
	son (mean age±SD)	960 (25.0±11.9)	676 (26.4±12.6)

Table 2. Thyroid cancer histopathology in families with two or more cases of DTC

papillary – papillary	12	52%
papillary – follicular	6	26%
papillary – no data	2	9%
follicular – no data	3	13%

Table 3. Odds ratio of malignant neoplasm in first degree relative of thyroid cancer index patients and control persons

Site		Number of malignancies in Ist degree relatives		Odds ratio	95% CI
		of index patients (n=6614)	of control persons (n=4937)		
Thyroid cancers	all	24	3	6.0	**1.8–19.9**
	women	22	3	5.6	**1.7–18.7**
	men	2	0	/	/
Breast cancers (women)		20	27	0.5	0.3–1.01
Female reproductive system cancers (women)		32	26	0.92	0.55–1.56
Prostate cancers (men)		21	18	1.3	0.46–1.61
Cancers of the digestive tract	all	103	92	1.16	0.63–1.61
	women	47	39	0.9	0.59–1.39
	men	56	53	0.7	0.53–1.13
Lung cancers	all	56	38	1.07	0.7–1.62
	women	9	7	0.97	0.36–2.6
	men	47	31	1.12	0.71–1.76
Neoplasms of lymphopoetic system	all	24	18	0.99	0.54–1.83
	women	12	8	1.13	0.46–2.77
	men	12	10	0.88	0.38–2.05
Head and neck*	all	23	18	0.98	0.51–1.77
	women	4	1	5.2	0.58–46.78
	men	19	17	0.82	0.42–1.59
Central nervous system neoplasms	all	13	9	1.07	0.46–2.5
	women	4	6	0.5	0.14–1.78
	men	9	3	2.22	0.6–8.2
Other cancers**	all	33	26	0.84	0.57–1.59
	women	12	11	0.82	0.36–1.87
	men	21	15	1.03	0.53–2.0

*other than thyroid cancer, **melanoma, sarcoma, urinary track (excluding prostate)

Table 4. Odds ratio for the diagnosis of a malignant neoplasm in first degree relatives of patients with papillary in relation to follicular thyroid cancer

Site	number of malignancies in Ist degree relatives		Odds ratio	95% CI
	of papillary thyroid cancer (n=4117)	of follicular thyroid cancer (n=2497)		
All cancers	205	144	0.9	(0.8–1.1)
Cancers of the digestive track	58	45	0.8	(0.5–1.2)
Lung cancers	34	22	1.0	(0.5–1.7)
Thyroid cancers	16	8	**1.2**	**(0.5–2.8)**
Neoplasms of limphopoetic system	19	5	2.3	(0.9–6.6)
Breast cancers (women)	13	7	1.2	(0.4–2.8)
Female reproductive track cancers (women)	18	14	0.8	(0.4–1.5)
Prostate cancers (men)	14	7	1.3	(0.5–3.3)
Head and neck*	9	14	**0.4**	**(0.2–0.9)**
Central nervous system neoplasm	10	3	1.9	(0.5–7.1)
Other cancers**	14	19	0.4	(0.2–0.9)

*other than thyroid, **melanoma, sarcoma, urinary track (excluding prostate)

was observed. GALANTI et al [30] reported an increased risk of stomach and thyroid cancer among mothers of differentiated thyroid cancer index-patients. No other association was observed.

In our study we did not observe any excessive risk for malignant tumors, except thyroid cancer, in first-degree relatives of differentiated thyroid cancer patients. However, to our surprise there was a slight, but statistically significant, decrease in head and neck cancer (other than thyroid cancer) in first-degree relatives of papillary thyroid cancer when compared with follicular ones.

Some of the aggregation of the malignancies in families of differentiated thyroid cancer can be explained by familial cancer syndromes like Cowden syndrome or familial polyposis coli. However, both of these syndromes are very rare making their effect very unlikely in our analysis. Less than 1 in 1000 of newly diagnosed DTC is associated with one of these syndromes. Indeed, in our set of 999 index families clinical review was not suggestive of any of those familial cancer syndromes. A few months after the analysis of our results was closed, we diagnosed thyroid cancer in a mother and her daughter, the latter one also suffering from Gardner syndrome.

Although fewer than 0.1% of differentiated thyroid cancers are associated with known cancer syndromes, some information suggest that a relationship exists between thyroid and breast cancer. Both these cancers occur more commonly in women than in man. Geographically, a trend toward increasing incidence of breast cancer with increasing incidence of thyroid cancer has been noted and a higher than expected occurrence of breast cancer in relatives of differentiated thyroid cancer has been reported [8, 21]. However, other studies as well as our, did not confirm an increased risk of breast

cancer in first degree relatives of thyroid cancer index patients [5, 7, 22].

Our hospital based study differs from most of the previous reports that were based on national and/or regional cancer registers [8, 30]. We are well aware of it potential drawbacks. Factor that could underestimate the perceived familial association of thyroid and other types of cancer is that patients may not know that their relatives suffered from malignant disease. We also did not make any attempts to verify the diagnosis of cancer in first-degree relatives. That could both under- and overestimate the reported number of cancer cases in families. However, as reported by others, the diagnosis of cancer reported in first degree relatives is very likely to be accurate [31–34]. Additionally our results were only adjusted for age as a cancer risk factor. Yet, none of the first degree relatives with DTC was treated in the past with radiation therapy; the only well established risk factor for DTC.

In modern oncology afford is aimed at cancer screening and its early diagnosis. It was only intensive screening program that led to breast and cervix cancer down-staging and increased overall survival. Providing evidences of increased cancer risk in first-degree relatives of thyroid cancer patients could enable introduction of prophylactic screening at specific cancer sites. In our study only increased risk of thyroid cancer was proved. However it is doubtful whether the risk of 2.5% of DTC in first-degree relative would justify any screening. The most common cancers in general population (eg. breast, prostate or lung cancer) did not occurred with increased frequency in first-degree relatives of DTC patients, so prophylactic screening seems not to be justified from economical point of view.

To summarize, our study confirms the previous reports of increased risk of thyroid cancer in first-degree relatives of differentiated thyroid cancer patients. This supports the need for further studies to determine this predisposition of differentiated cancer clustering in some families. However, the relatively small number first-degree relatives affected with thyroid cancer does not justify any screening.

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