Familial Occurrence of Nonmedullary Thyroid Cancer: A Population-based Study of 5673 First-Degree Relatives of Thyroid Cancer Patients from Norway

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Abstract

The purpose of this study was to estimate the occurrence of familial nonmedullary thyroid cancer (FNMT) in a large population-based study. Of the 5274 cases of thyroid cancer on record in the Norwegian Cancer Registry between 1960 and 1995, a total of 1025 patients could be identified with verified thyroid cancer, a unique personal identification number, and a link to at least one parent. For patients with nonmedullary carcinoma, 5457 first-degree relatives in 970 families were found, compared with 216 first-degree relatives in 37 families for the medullary cancers. A standardized incidence ratio (SIR) was calculated among the relatives based on rates from the Cancer Registry of Norway. A significantly increased risk of thyroid cancer was found among the 5457 relatives of nonmedullary index cases, both for males [SIR, 5.2; confidence interval (CI), 2.1–10.7; 7 cases] and females (SIR, 4.9; CI, 3.0–7.7; 19 cases). All of these 26 thyroid cancer cases were of the nonmedullary type. Furthermore, an increased risk was found among 4282 relatives of papillary index cases, for both males (SIR, 5.8; CI, 2.1–12.6; 6 cases) and females (SIR, 4.0; CI, 2.1–7.1; 12 cases). The 36 familial papillary thyroid cancer patients had an average age at diagnosis of 43 years. Genetic influence is probably only modest for the familial nonmedullary cases and clearly weaker than for the classic familial type of medullary thyroid cancer.

Introduction

Medullary thyroid carcinoma, representing 4–5% of all malignant thyroid tumors in Norway (1), has a well-established familial occurrence and tends to be associated with other endocrine disorders, especially multiple endocrine neoplasia (MEN) type 2A and 2B. The hereditary form of medullary carcinoma is caused by germ-line mutations in the ret proto-oncogene (2–4). Regarding the follicular-cell-derived thyroid carcinomas, previous studies have suggested that familial occurrence might be present in a small proportion of the cases. Documented relationships also exist between papillary thyroid cancer and FAP, Gardner’s syndrome, Cowden’s syndrome (multiple hamartoma syndrome), and Peutz-Jeghers syndrome (generalized hamartomatous multiple polyposis of the intestinal tract) (5–7).

Several reports based on small materials (8–15) and recent larger studies (16, 17) indicate an increased familial occurrence of nonmedullary thyroid cancer. Thus, a recent review of 15 case reports/series found the frequency of FNMT to vary between 2.5 and 6.3% of all nonmedullary cases (18). Some authors also claim that FNMT is more aggressive than sporadic nonmedullary thyroid cancer, having a higher incidence of multifocality, extrathyroidal invasion, and local recurrence (19–21) and, hence, should receive more aggressive initial treatment. Others have found no evidence supporting this view (18). The purpose of our study was to test the hypothesis of increased familial occurrence of nonmedullary thyroid cancer in a large and population-based study. We also wanted to examine whether the cases classified as FNMT displayed distinct characteristics of hereditary cancer, especially early age of onset (22), compared with sporadic cases of nonmedullary thyroid cancer.

Materials and Methods

The Cancer Registry of Norway was established in 1951. A compulsory multiple reporting practice, according to which both the diagnosing clinician and the pathology departments report directly to the Registry, ensures nearly complete coverage of all solid malignant tumors since 1953. Classification and coding follows a modified version of ICD-7. Information on cancer cases includes date of diagnosis, site, and histological and/or cytological diagnosis, as well as year and cause of death for deceased persons. A unique 11-digit personal identification number assigned by Statistics Norway to all Norwegian citizens since 1960 identifies the cases. For every newborn child from 1964 and onwards, the personal identification numbers of father and mother were registered in the National Person Registry of

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The abbreviations used are: FAP, familial adenomatous polyposis; FNMT, familial nonmedullary thyroid cancer; SIR, standardized incidence ratio; CI, confidence interval.
Norway. In addition, this information is registered for all Norwegian citizens who in 1970 or later were living with their parents.

A total of 5274 cases of thyroid cancer were recorded in the Cancer Registry between 1960 and 1995, 1364 men (25.9%) and 3910 women (74.1%). Of these, 35 were excluded from the study because of the lack of personal identification number; 4171 persons were excluded because of the lack of personal identification number of the parents. Histology and cytology codes of the thyroid cancer were missing in 28 of the remaining cases, and these were also excluded from further analyses. Fifteen individuals had multiple records in the Registry because of more than one occurrence of thyroid cancer. To ensure that each individual was represented once, only the record of the first primary cancer diagnosis was included. When only cytology codes were available, these were recoded using the appropriate histological code. Finally, a total of 1025 patients remained with histologically or cytologically verified thyroid cancer, a personal identification number, and a link to at least one parent with a personal identification number.

Of these 1025 individuals, 981 had nonmedullary thyroid cancer, and 44 had medullary thyroid cancer. A unique family number was assigned each of these thyroid cancer index patients. Parents were identified using the personal number of the mother and/or father recorded in the National Person Registry on the record of each of the thyroid cancer patients. Siblings were selected by identifying the individuals with the same mother and/or father as the 1025 thyroid cancer cases. Children were identified using similar methods. Data from the Cancer Registry were added to the record of each individual. Relatives of a thyroid cancer index patient were assigned the same family number as the index patient. Related thyroid cancer index patients would initially have been assigned different family numbers, and would identify the same first-degree relatives but with different family numbers. In the case of individuals being represented in more than one family, duplicate families were deleted to ensure that each individual was represented with one record in one family only. Because of the method chosen, each family contained at least one individual with thyroid cancer. If only one thyroid cancer patient existed, this person was selected as an index person and excluded from further study, whereas the first-degree relatives were included in the study. In case of more than one thyroid cancer patient within a family, the individual with the earliest year of diagnosis of thyroid cancer was selected as an index person and excluded from further study. The remaining first-degree relatives from all of the families were divided into groups based on gender and the histological type of thyroid cancer for the index person. For the relatives of nonmedullary thyroid cancer patients, a total of 5457 individuals in 970 families were identified, compared with 216 individuals in 37 families for the medullary cancer cases.

The statistical software package Epicure (23) was used to count person-years and calculate expected numbers of cases of all cancer sites based on 5-year age-specific and gender-specific incidence rates for each year. Person-years and observed cases of cancer were counted from the year of birth of all individuals to the end of follow-up, which was the 31st of December 1997. Deceased patients, or patients with a cancer diagnosis, did not contribute to the person-years after their death or their cancer diagnosis. SIR was calculated as the ratio of observed:expected number of cancer diagnoses for each group. A SIR value of 1.0 signifies that the incidence of cancer in the group is equal to the incidence in the same age- and sex-distributed Norwegian population. 95% CIs were calculated assuming a Poisson distribution.

### Results

Among the 5673 first-degree relatives of the thyroid cancer index cases, no general increased incidence of cancer was found for all of the sites combined for males (SIR, 1.0; CI, 0.9–1.2; 241 cases) or females (SIR, 0.98; CI, 0.9–1.1; 218 cases). A significantly increased incidence of thyroid cancer was present both for males (SIR, 7.9; CI, 4.0–14.2; 4 medullary cases, 7 nonmedullary cases) and for females (SIR, 6.5; CI, 4.2–9.5; 7 medullary cases, 19 nonmedullary cases) (Table 1). Significantly increased incidence was not found for any other sites including colon (SIR, 1.2 for males; SIR, 1.0 for females), kidney (SIR, 0.8 for males; SIR, 1.2 for females), and breast (SIR, 1.0 for females).

A familial component is well established for medullary thyroid cancer. Consequently, the relatives of patients with thyroid cancer were further analyzed in separate groups depending on the histology of the index person. Among the 5457 relatives of nonmedullary index cases, no increased cancer risk was present for all of the sites combined, neither for males (SIR, 1.0; CI, 0.9–1.1; 232 cases) nor females (SIR, 1.0; CI, 0.8–1.1; 205 cases). In contrast, a significantly increased incidence of thyroid cancer was present both for males (SIR, 5.2; CI, 2.1–10.7; 7 cases) and for females (SIR, 4.9; CI, 3.0–7.7; 19 cases).

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Person years</th>
<th>No. of cases</th>
<th>SIR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
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<td></td>
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<tr>
<td>All histological types</td>
<td>90,785</td>
<td>11</td>
<td>7.9</td>
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<tr>
<td>Papillary</td>
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<td>6</td>
<td>5.8</td>
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<tr>
<td>Follicular</td>
<td>10,325</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Medullary</td>
<td>3,196</td>
<td>4</td>
<td>89.9</td>
</tr>
<tr>
<td>Other types</td>
<td>8,571</td>
<td>1</td>
<td>6.7</td>
</tr>
<tr>
<td>Females</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All histological types</td>
<td>90,710</td>
<td>26</td>
<td>6.5</td>
</tr>
<tr>
<td>Papillary</td>
<td>67,795</td>
<td>12</td>
<td>4.1</td>
</tr>
<tr>
<td>Follicular</td>
<td>10,819</td>
<td>2</td>
<td>4.3</td>
</tr>
<tr>
<td>Medullary</td>
<td>3,542</td>
<td>7</td>
<td>44.9</td>
</tr>
<tr>
<td>Other types</td>
<td>8,563</td>
<td>5</td>
<td>12.0</td>
</tr>
</tbody>
</table>

SIR of thyroid cancer among the 4282 relatives of papillary thyroid cancer index persons was significantly increased both for males (SIR, 5.8; CI, 2.1–12.6; 6 cases) and for females (SIR, 4.0; CI, 2.1–7.1; 12 cases). Males, ages 40–55 years at diagnosis, had an especially high risk of thyroid cancer (SIR, 13.5; CI, 2.8–39.3; 3 cases). Among females, a significantly increased risk was found in the age groups of 40–55 years at diagnosis (SIR, 4.8; CI, 1.3–12.3; 4 cases) and ≥70 years at diagnosis (SIR, 7.3; CI, 1.5–21.4; 3 cases) (Table 2). Of these 18 thyroid cancers, 11 were of the papillary type, 3 of the follicular type, and 4 of other/unknown types. None were classified as medullary thyroid cancer. These 18 thyroid cancers occurred in 18 different families. Adding the 18 corresponding index persons with papillary thyroid carcinoma in each family, a total of 36 familial papillary thyroid cancer patients were detected, with 2 cases occurring in each family. Average age at diagnosis in these 36 patients was 43 years. Nineteen of the patients had no metastasis, 12 had lymph node metastasis, 1 distant metastasis, 1 local tumor infiltration, and
3 were unknown. Regarding other cancer sites, increased risk of borderline significance was also found for larynx in men (SIR, 2.8; CI, 1.0–6.0; 6 cases), and cancer of the ovary for women ages 0–40 years at diagnosis (SIR, 3.7; CI, 1.0–9.4; 4 cases). No significant increased incidence was found in all of the other sites.

Among the 662 relatives of patients with follicular thyroid cancer, an increased risk for all of the cancer sites was detected for males (SIR, 1.4; CI, 1.0–1.9; 38 cases) but not for females. Increased risk was also indicated for males ages ≥70 years at diagnosis for colon (SIR, 4.4; CI, 1.2–11.3; 4 cases), kidney (SIR, 9.7; CI, 2.0–28.3; 3 cases), and bladder and other urinary organs (SIR, 4.9; CI, 1.3–12.6; 4 cases). Statistically, males age 0–40 years at diagnosis also had an increased risk of bone tumors, with only 2 cases observed (SIR, 34.4; CI, 4.2–124.3; 2 cases). An increased risk of malignant tumors in the eye among women ages 55–70 years at diagnosis was also found (SIR, 41.3; CI 1.0–230.0; 1 case). However, a significantly increased risk of thyroid cancer was not present either in males (SIR, 0.0; CI, 0.0–23.1; 0 cases) or in females (SIR, 4.3; CI, 0.5–15.4; 2 cases). One of these cases was a papillary thyroid carcinoma, the other a follicular thyroid carcinoma. Average age at diagnosis in these 2 patients and the 2 corresponding index cases, had an average age at diagnosis of 43 years, compared with 27 years for medullary cancer cases, which indicated that early age of onset is not a dominating feature.

The background for familial clustering of nonmedullary thyroid carcinomas appears to be heterogeneous, and multiple syndromes and susceptibility genes are probably involved (29). Some studies indicate that the transmission of FNMTC is compatible with autosomal dominant inheritance with reduced penetrance or with complex inheritance (15, 30–32). Considering the different syndromes and subgroups, previous reports show an increased risk of nonmedullary carcinomas in patients with FAP (33, 34), which is caused by alterations of the APC gene (35, 36), and these thyroid carcinomas seem to have specific pathological features (37). In addition, thyroid tumors are associated with Cowden’s disease (multiple hamartoma syndrome; Ref. 38), which is caused by germ-line mutations in the PTEN tumor suppressor gene (39). Thyroid tumors might be involved in familial clustering in rare cases, being associated with the TCO locus (31, 42, 43). In our registry-based study, patients with familial cancer syndromes

### Table 2

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>Person years</th>
<th>No. of cases</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All age groups</td>
<td>68,693</td>
<td>6</td>
<td>5.8</td>
<td>2.1–12.6</td>
</tr>
<tr>
<td>0–40</td>
<td>45,770</td>
<td>1</td>
<td>4.0</td>
<td>0.1–22.5</td>
</tr>
<tr>
<td>41–55</td>
<td>12,038</td>
<td>3</td>
<td>13.5</td>
<td>2.8–39.3</td>
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<td>56–70</td>
<td>7,961</td>
<td>1</td>
<td>2.8</td>
<td>0.1–15.6</td>
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<tr>
<td>70+</td>
<td>2,925</td>
<td>1</td>
<td>4.8</td>
<td>0.1–26.9</td>
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<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All age groups</td>
<td>67,795</td>
<td>12</td>
<td>4.1</td>
<td>2.1–7.1</td>
</tr>
<tr>
<td>0–40</td>
<td>44,189</td>
<td>3</td>
<td>3.0</td>
<td>0.6–8.9</td>
</tr>
<tr>
<td>41–55</td>
<td>11,965</td>
<td>4</td>
<td>4.8</td>
<td>1.3–12.4</td>
</tr>
<tr>
<td>56–70</td>
<td>8,217</td>
<td>2</td>
<td>2.7</td>
<td>0.3–9.8</td>
</tr>
<tr>
<td>70+</td>
<td>3,424</td>
<td>3</td>
<td>7.3</td>
<td>1.5–21.4</td>
</tr>
</tbody>
</table>

### Discussion

Several studies have documented an increased familial occurrence of different cancer types, with thyroid as one of the sites with high risk among close relatives (16, 24, 25). Whereas familial aggregation of medullary thyroid carcinoma is well recognized (26, 27) and is now known to be caused by mutations in the ret proto-oncogene (2–4), early studies also indicated that a familial component was present for nonmedullary thyroid carcinomas, although some of these reports were based on relatively few patients (8, 9, 11, 12, 20, 28). Recently, familial clustering of nonmedullary carcinomas has been found in population-based materials as well (16, 17).

As expected, we found a markedly increased incidence among first-degree relatives of patients with medullary thyroid carcinoma, with a SIR of 89.9 for males and 44.9 for females, in line with previous studies (17). Among 5457 first-degree relatives of nonmedullary thyroid cancer patients, we also found a statistically significant increased incidence of nonmedullary carcinomas, which confirmed indications from other reports in a large and population-based study with complete follow-up. Thus, the SIR for relatives of patients with papillary thyroid carcinomas was 5.8 in males and 4.0 in females. A recent study based on the Family Cancer Database in Sweden found similar figures for papillary and follicular carcinomas combined (17), and corresponding results were reported from the Utah Population Database (16, 24). By using registry data, confounders associated with retrospective collection of data were avoided. However, because of limited information on first-degree relatives, and some missing histological or cytological diagnoses, only 1025 patients could be identified with verified thyroid cancer, a unique personal identification number, and a link to at least one parent. Other families with clusters of thyroid cancer may not have been detected, and the incidence of FNMTC is probably underestimated in our study.

One could expect an early age of onset among patients with familial papillary thyroid carcinoma. Male and female relatives ages 40–55 years at diagnosis and females above 70 years of age, had an especially increased risk of thyroid cancer in our study, whereas high risk at early age was not evident. The relatives of papillary thyroid cancer patients, and the corresponding index cases, had an average age at diagnosis of 43 years, compared with 27 years for medullary cancer cases, which indicated that early age of onset is not a dominating feature.

As expected, we found a markedly increased incidence among first-degree relatives of patients with medullary thyroid carcinoma.
(multiple endocrine neoplasia type 2, Cowden’s disease, FAP including Gardner’s syndrome, or Peutz-Jeghers syndrome) could not be identified and analyzed in separate subgroups because the Cancer Registry contains information on malignant tumors only, and no data on specific syndromes. Information on relevant tumors such as pheochromocytomas, hamartomas, or colon polyps was not available. However, these cancer syndromes probably account for a minor proportion of FNMT cases, and recent studies have not been able to establish consistent links between familial papillary thyroid cancer and known mutations in PTEN, APC (31, 44), or other candidate genes such as ret, MNG1, and TCO (32, 41, 45). Whereas increased incidence of other cancers among relatives of non-medullary thyroid cancer patients have been reported for colon and other abdominal organs (11), breast (16), kidney (46, 47), uterus, and stomach (48), no excess risk of these sites was found in our present study.

Familial aggregation of cancer depends on several factors, such as incidence in the general population of the cancer sites examined, and study design (16). Clustering of cancer may be caused by inherited predisposition or shared environmental factors such as diet, use of tobacco and alcohol, and socio-economic or cultural factors like age at first birth (49). We had no information on possible environmental risk factors, and the methods used do not allow us to determine to what degree genetic susceptibility, environmental factors, or both, contribute to the observed familial clustering. A segregation analysis might probably add some information.

In conclusion, our study supports a significantly increased familial occurrence of nonmedullary thyroid cancer, with an excess of cases among relatives of patients with papillary thyroid carcinoma. However, the modest increase in SIR and excess of cases among relatives of patients treated during 1946 through 1970. Mayo Clin. Proc., 63: 947–954, 1988.


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