Published in final edited form as:

Surgery. 2013 December ; 154(6): . doi:10.1016/j.surg.2013.06.019.

Prospective Screening in Familial Non-medullary Thyroid Cancer

Samira M. Sadowski, MD¹, Mei He, MD¹, Krisana Gesuwan, MS¹, Neelam Gulati, BS¹,
Francesco Celi, MD², Maria J. Merino, MD³, Naris Nilubol, MD¹, and Electron Kebebew, MD¹

¹Endocrine Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda
MD 20892

²Diabetes, Endocrinology, and Obesity Branch, National Institute of Diabetes and Digestive and
Kidney Diseases, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892

³Translational Surgical Pathology Section, Laboratory of Pathology, National Cancer Institute,
National Institutes of Health, Bethesda, MD 20892

Abstract

Background—Approximately 8% of non-medullary thyroid cancers are familial. The optimal age for screening in familial non-medullary thyroid cancer (FNMTc) is unknown.

Method—Kindreds with FNMTc (2 or more first-degree relatives affected) were prospectively screened by thyroid ultrasound.

Results—Fifteen kindreds showed an overall prevalence of thyroid nodule(s) ≥ 5 mm of 44.4% at screening; 19.2% in the second generation, and 90% in the generation anterior to the index case. The youngest age of detection was 10 years for thyroid nodules and 18 years for thyroid cancer. Thyroid nodule microcalcification at screening was associated with a higher risk of cancer ($p < 0.05$). Family members diagnosed with thyroid cancer by ultrasound screening were diagnosed at a younger age and had a lower rate of extrathyroidal invasion ($p < 0.05$).

Conclusions—In FNMTc, first-degree relatives 10 years or older, including the generation anterior to the index case, should have thyroid ultrasound screening. This may result in earlier diagnosis.

Keywords

Familial non-medullary thyroid cancer; screening; thyroid nodule

Introduction

Thyroid cancer is the most common endocrine-related cancer in the United States, with an increased incidence of more than 2-fold over the last three decades.^{1, 2} Approximately 95% of thyroid cancers are of follicular cell origin, of which 85% are papillary thyroid cancer. Most non-medullary thyroid cancers (NMTCs) are sporadic. However, approximately 8% of NMTCs are familial.³ Familial non-medullary thyroid cancer (FNMTc) may occur as a minor component of syndromic familial cancer syndromes (Gardner and Cowden syndrome,

Address all correspondence to: Samira M. Sadowski, MD, Endocrine Oncology Branch, National Cancer Institute, NIH Clinical Research Center, Building 10-CRC, Room 3W-5840, Bethesda, MD 20892. Phone: 301-451-1040, samira.sadowskiveuthey@nih.gov.

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Carney complex type 1, Werner and McCune-Albright syndrome) or as nonsyndromic familial disease.⁴

Population studies have shown that the risk of thyroid cancer increases 9-fold in patients with a first-degree relative with thyroid cancer.^{5, 6} FNMTC is defined as when 2 or more first-degree relatives are affected.⁷ When 3 or more first-degree relatives are affected, the probability that their cancer is FNMTC is greater than 95%, as compared with 31–38% when 2 first-degree relatives are affected.⁵

Early screening in at-risk members in kindreds with FNMTC may be beneficial, as the outcome for non-index cases has been observed to be better.^{8, 9} Uchino et al.¹⁰ screened family members when 2 first-degree relatives were affected with thyroid cancer. Of 149 family members screened, more than 77 patients (52%) were found to have thyroid nodules and 15 patients (10%) were found to have thyroid cancer, with lymph node metastases in 6 patients (43%). Rosario and colleagues screened the siblings of patients with thyroid cancer and found that screening was associated with an earlier diagnosis because tumors were detected at a smaller size, and with lower rate of lymph node metastases and extrathyroidal invasion.¹¹

Nonetheless, many questions remain regarding screening for FNMTC in at-risk members. Which at-risk generation should be screened relative to the index case? At what age should FNMTC screening begin in at-risk members? Should screening practices be based on the number of affected members with FNMTC?

Therefore, the aims of this study were to determine the first age of onset of thyroid cancer and nodules in at-risk family members using screening ultrasound.

Material and methods

Patients

Kindreds with FNMTC were enrolled in a prospective observational study performed at the National Institutes of Health (NIH) Clinical Center (Clinicaltrials.gov: NCT-01109420). All participants provided written informed consent. Demographic, clinical, and pathologic data were collected from medical records, family history questionnaires, and patient interview. Patient history, family pedigrees and physical examination, imaging studies and laboratory tests were obtained.

The main study entry criterion was that families had to have 2 or more first-degree relatives who had or have had NMTC. Family members in the generation of the index case (defined as first-generation), in the offspring generation, and in the anterior generation (parents, uncles, and aunts) were included. Syndromic cases with FNMTC were excluded from the study. The study was approved by the Office of Human Subjects Research Protections at the NIH.

Every family member at risk was screened by thyroid ultrasound using a linear 6–15 MHz transducer. The presence of a nodule was defined as a mass larger than or equal to 5 mm. Fine needle aspiration (FNA) biopsy and cytologic examination were performed on clinically suspicious thyroid nodules or cervical lymph nodes per standard guidelines.¹² After their initial evaluation, patients who did not have a malignant thyroid tumor were screened every year by ultrasound. All cases of thyroid cancer were confirmed by histology, and all patients who had had surgery at another institution had their slides reevaluated by our pathologist to confirm their diagnosis. Treatment of patients with a thyroid neoplasm was

performed based on established clinical practice, and all patients were seen once a year for follow-up.

Based on ultrasound screening, cytology of FNA biopsy, and surgical pathology, patients were classified into two groups: affected and unaffected.

Statistical analyses

Data are presented as number and mean $\pm$ standard deviation. Demographic and clinicopathologic data in the affected cases were compared with data from the unaffected cases using Fisher's exact test and the Mann-Whitney test for nonparametric categorical and continuous data, respectively, using SPSS® v18.0 for Windows (SPSS, Inc., Chicago, IL).

Results

Fifteen families with FNMTTC underwent screening, comprising a total of 174 family members, distributed over one to three generations. Of these, 48 family members were affected with papillary thyroid cancer. The prevalence of affected members was 50.9% (28/55) in the first generation and 17.2% (10/58) in the second generation (excluding spouses). Of the 15 families, 7 families had 2 affected first-degree relatives; 2 families had 3 affected first-degree relatives; 3 families had 4 affected first-degree relatives; 2 families had 5 affected first-degree relatives; and 1 family had 6 affected first-degree relatives. Ninety-one of the 174 family members had complete clinical evaluation at the NIH Clinical Center. Of these, 30 (33%) were affected members and 61 (67%) were at-risk family members.

The characteristics of affected family members are summarized in Table 1. The youngest age at diagnosis of thyroid cancer was 18 years old, and 87% were female. Thyroid cancer was detected significantly more often in female patients than in male patients (26/63 females; 4/28 males; $p = 0.015$), and 80% of affected family members had one or more siblings affected with papillary thyroid cancer. Overall, 22 cases of papillary thyroid cancer were diagnosed in the first generation and 5 in the second generation with a younger age at diagnosis in the second generation (41 and 28 years, $p = 0.03$, respectively). When comparing disease characteristics in these two generations, all patients (100%) in the second generation had T1 stage cancers and had no extrathyroidal invasion or recurrences. However, 22.7% of the first-generation patients had T3 stage cancers, and 9.1% had T4 stage; 4 of these patients had extrathyroidal invasion (18.2%), and 2 had recurrences (9.1%). Average follow-up time after surgery was 5.8 years (range 0.2–31 years).

The overall prevalence of thyroid nodules ≥ 5 mm was 56% (44/78). In family members at risk (excluding spouses and those diagnosed as affected at screening), the prevalence of thyroid nodule(s) was 44.4% (24/54), based on ultrasound screening. A solitary thyroid nodule was found in 11 (45.8%) and multiple thyroid nodules in 13 patients (54.2%). Thyroid nodules were present in 19.2% of the second-generation and in 90% of the anterior generation (anterior to the index case generation). The demographic and thyroid nodule ultrasonographic characteristics of family members at risk according to generation are shown in Table 2. The youngest age at which a thyroid nodule was detected was 10 years. The mean age at nodule detection by ultrasound screening in 3 generations was 68.0, 36.7, and 19.4 years for the anterior, first and second generations, respectively, and the mean thyroid nodule size was 10.2, 14.82 and 6.9 mm, respectively. Furthermore, the rate of nodule detection in at risk family members according to the number of family members affected before screening was 40.7% when 4, 50% when 3, and 35.3% when 2 family members were affected. Further, we compared the prevalence of thyroid nodule detection by age range in our study population to that found in population based studies and found younger age at thyroid nodule detection (Fig 1).

The presence of thyroid nodule microcalcification was associated with a significantly higher risk of cancer ($p < 0.05$) when comparing ultrasound screening thyroid nodule characteristics in unaffected family members (FNA result negative) with those of affected family members. Of 36 patients with a nodule ≥ 5 mm at screening (excluding index cases), 23 patients (63.8%) underwent an FNA (US screening nodule mean size 1.43 ± 0.76 cm). The FNA results, according to the Bethesda classification system¹³, showed one “Nondiagnostic”, 9 “benign”, 1 “Atypia of Undetermined Significance”, 2 “Suspicious for Follicular Neoplasm”, 3 “Suspicious for Malignancy” and 7 “Malignant” cytologic results. Of those, 14 patients underwent thyroidectomy, and 12 had papillary thyroid cancer on histologic examination.

Comparison of the index case to other affected family members (Table 3) showed a trend towards younger age at diagnosis in non-index cases (44 versus 35 years, respectively, $p = 0.057$) and a significantly lower rate of extrathyroidal invasion ($p < 0.05$). The rate of recurrence was lower, but it was not statistically significant. When excluding the index cases, the overall detection rate of papillary thyroid cancer among screened family members at risk was 19.7%. When reporting this rate according to the number of family members affected, the rate of papillary thyroid cancer detection was 18.2% when 4 family members were affected, 44.4% when 3, and 26.1% when 2 were affected.

Discussion

To our knowledge, this is the first prospective study that includes 15 families with FNMTC distributed over one, two or up to 3 generations, with yearly screening and follow-up performed for the entire family, all in one center. Our aim was to determine which family members should be screened when 2 or more first-degree relatives are diagnosed with NMTC, and at what age they should be screened.

Thyroid nodules were present in almost 20% of the second generation and in 90% of the anterior generation, with an overall prevalence of 44.4% in at-risk family members. This rate is similar to that observed in a study by Uchino and colleagues, in which 52% of the screened family members were found to have a thyroid nodule(s).¹⁰ However, Uchino and colleagues did not report screening results according to generation. Thus, our study is believed to be the first to show results of this kind. When comparing the rate of thyroid nodule detected by age in our study to that found in population based-studies (Fig 1), it appears that the rate of thyroid nodule detection occurs at a younger age in FNMTC.¹⁴ This may be an overestimation, as improvements in ultrasound imaging sensitivity have resulted in more frequent detection of smaller thyroid lesions today. More recent studies have shown prevalence between 19% and 67% for ultrasound-detected thyroid nodules in randomly examined populations.^{15, 16}

The high prevalence of thyroid nodules that we observed supports the need for early screening in first-degree relatives of FNMTC patients, both in the anterior generation and second generation. Considering that the youngest age a thyroid nodule greater than 5 mm was detected was 10 years, we believe first-degree relatives at risk for FNMTC should be screened by ultrasound at 10 years and older. The generation anterior to the index case should also have neck ultrasound to detect thyroid cancer, as our findings revealed that 90% of this generation had a thyroid nodule and 20% had thyroid cancer.

The rate of thyroid cancer detection among family members screened by ultrasound was high (19.7%) in our study cohort. Uchino and associates detected thyroid cancer in 10.1% of the cohort their group screened.¹⁰ Furthermore, we found the youngest age thyroid cancer was detected by ultrasound screening was 18 years. Non-index family members affected

were diagnosed at a younger age, with less aggressive disease than in the index cases. These data strongly support the need for ultrasound screening in all first-degree relatives of FNMTC patients and could lead to earlier diagnosis, with subsequent less aggressive disease. Similar results were found in a study that screened siblings of patients with sporadic papillary thyroid cancer cases. In this study, screenings were associated with diagnosis at a younger age, smaller tumor size, and fewer lymph node metastases and extrathyroidal invasion.¹¹ It is unclear, however, whether, in cases with only one family member affected, the disease is familial or sporadic.

There are several limitations to our study. The difference in the rate of recurrent disease found in the index and non-index cases may be due to shorter follow-up time in the non-index cases in the second generation. Longer follow-up and additional kindreds screened prospectively need to be enrolled to conclusively determine whether there is a difference in recurrence rates between index and non-index cases of FNMTC. Finally, the classification of a family member as unaffected may require alteration if that family member were later to develop thyroid cancer. This is a shortcoming of any screening study in familial cancer syndromes where one can never reliably determine “affected” status when using clinical screening methods. But for virtually all familial cancer syndromes for which the susceptibility gene had not been identified yet, it is with clinical screening of kindreds that the earliest age of onset and penetrance status were eventually established (e.g. Lynch syndrome colonoscopy and the development of the Amsterdam criteria, familial breast cancer and hereditary medullary thyroid cancer with thyroid ultrasound and serum calcitonin for each of the respective susceptibility genes were identified).

In conclusion, at risk first-degree relatives of FNMTC cases who are age 10 or older should be screened with a thyroid ultrasound, and the screening should include the generation anterior to the index case. This screening strategy could result in earlier diagnosis and result in an improved outcome for the affected members.

Acknowledgments

Financial Support: This research was supported by the intramural research program of the Center for Cancer Research, National Cancer Institute and National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health.

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Abbreviations

FNA	Fine-needle aspiration
FNMTc	Familial non-medullary thyroid cancer

Fig 1. Prevalence of ultrasound-detected thyroid nodules (≥ 5 mm) in the familial population (•) compared to data from Mazzaferri, published in 1993¹⁴, detected by autopsy and ultrasonography (◊), prevalence by age range for each decade.

Table 1
Characteristics of affected family members (N = 30)

Clinical Characteristics	Value
Age at diagnosis [mean years]	41 ± 12, range 18-73
Female	26 (86.7%)
1 sibling affected	24 (80%)
Tumor size [mean in mm] [#]	14.27 ± 11.18
Histological Subtype	
Classic PTC	27 (90%)
Follicular variant PTC	2 (6.7%)
Diffuse sclerosing variant PTC	1 (3.3%)
Lymph node metastases	12/18 (42.9%)
Distant metastases	0
Multifocality	19/29 (65.5%)
Lymphovascular invasion	3/21 (14.3%)
Extrathyroidal extension	5/29 (17.2%)
Recurrence	2/29 (6.8%)
Follow-up after surgery [mean years, range]	5.8 [0.2–31]

[#] Largest tumor size when multifocal; values are mean ± standard deviation or n (%).

PTC: Papillary thyroid cancer.

Table 2
Demographic characteristics in family members at risk by generation (spouses excluded)

Family member at risk N = 54	Anterior generation	First generation (index)	Second generation
Total family members at risk	10	18	26
Thyroid nodules ≥ 5 mm	9/10 (90%)	9/18 (50%)	5/26 (19.23%)
Mean age at thyroid nodule detection by ultrasound [years]	68 [55–75]	36.7 [27–53]	19.4 [10–33]
Screening ultrasound			
Size nodule [mm]	10.2 [5–22]	14.82 [6.9–38]	6.9 [5–13]
Microcalcifications	2	2	0

Table 3
Characteristics of index cases and non-index cases

	Non-index N = 15	Index case N = 14 [#]	p-value
Age at diagnosis [years]	35 ± 10.02	44 ± 12.12	0.057
Female	14/15 (93.3.5%)	12/14 (85.7%)	0.59
Tumor characteristics			
Tumor size [mm]	13.8 ± 11.78	14.5 ± 11.32	0.47
Lymph node metastasis	5/15 (33.3%)	6/13 (46%)	0.7
Multifocality	9/15 (60%)	10/13 (76.9%)	0.43
Extrathyroidal invasion	0/15 (0%)	5/13 (38.5%)	0.011
Recurrence	0/14 (0%)	2/14 (14.3%)	0.48

Values are mean ± standard deviation or n (%).

[#] One case with incomplete data as not evaluated at NIH.