Results of Screening in Familial Non-Medullary Thyroid Cancer

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Background: Although a family history of thyroid cancer is one of the main risk factors for thyroid cancer, the benefit of screening individuals with a family history of thyroid cancer is not known.

Methods: A prospective cohort study was performed with yearly screening using neck ultrasound and fine-needle aspiration biopsy of thyroid nodule(s) >0.5 cm in at-risk individuals whose relatives were diagnosed with familial non-medullary thyroid cancer (FNMTc). The eligibility criteria were the presence of thyroid cancer in two or more first-degree relatives and being older than seven years of age. Twenty-five kindred were enrolled in the study (12 families with two members affected, and 13 with three or more members affected at enrollment).

Results: Thyroid cancer was detected by screening in 4.6% (2/43) of at-risk individuals from families with two members affected, and in 22.7% (15/66) of at-risk members from families with three or more patients affected ($p=0.01$). FNMTc detected by screening was characterized by a smaller tumor size (0.7 ± 0.5 cm vs. 1.5 ± 1.1 cm; $p=0.006$), a lower rate of central neck lymph node metastases (17.6% vs. 51.1%; $p=0.02$), less extensive surgery (hemithyroidectomy 23.5% vs. 0%; $p=0.002$), and a lower rate of radioactive iodine therapy (23.5% vs. 79%; $p<0.001$) compared to those affected at enrollment.

Conclusions: Screening of at-risk family members resulted in earlier detection of low-risk FNMTc and was associated with a less aggressive initial treatment. Screening with thyroid ultrasound should be considered in kindred with three or more family members affected by FNMTc. Since active screening might be associated with the risk of overtreatment, it should be implemented with caution, specifically in elderly individuals.

Keywords: familial, thyroid cancer, screening, ultrasound, thyroidectomy

Introduction

THERE HAS BEEN AN INCREASING incidence of thyroid cancer diagnoses worldwide, and it is currently the fastest-growing cancer diagnosis in the United States (1). In 2017, it is estimated that >65,000 new cases of thyroid cancer will occur in the United States. The two main risk factors of thyroid cancer are a family history of thyroid cancer and previous radiation exposure (therapeutic radiation to the head and neck and radioactive isotope) (2). Familial non-medullary thyroid cancer (FNMTc) accounts for 3–9% of all non-medullary thyroid cancer (NMTc) cases. FNMTc may occur as a minor component of syndromic familial cancer syndromes (Gardner and Cowden syndrome, Carney complex type 1, Werner and DICER1 syndromes) or as a non-syndromic familial disease (3).

The majority of FNMTc cases is non-syndromic with unknown susceptibility gene(s), and defined as two or more

first-degree relatives affected with NMTc. Most but not all studies suggest more aggressive clinical behavior of FNMTc, with higher rates of locoregional lymph node metastases, extrathyroidal invasion, multifocal tumors, and higher recurrence rates compared to sporadic NMTc (4–14). A recent meta-analysis that included 12 studies involving 12,741 patients who were followed for 1.5–12.1 years attempted to clarify these controversies (4). The analysis was based on retrospective studies, including eight cohort studies and four case-control studies, of which five were conducted in Asia (7,9,15–17), four in North America (10,18–20), two in Europe (21,22), and one in a combined U.S. and Japanese cohort (8). The study revealed an increased rate of recurrence (odds ratio [OR]=1.72 [confidence interval (CI) 1.34–2.20] and decreased disease-free survival (hazard ratio [HR]=1.83 [CI 1.34–2.52]) in FNMTc cases compared to sporadic disease (4). In this meta-analysis, a younger age at diagnosis

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(2.4 years lower on average for FNMTC patients compared to the sporadic cases), higher risk of multifocal tumor growth (OR = 1.50 [CI 1.32–1.71]), bilateral disease (OR = 1.29 [CI 1.00–1.66]), extrathyroidal invasion (OR = 1.20 [CI 1.02–1.41]), and lymph node metastases (OR = 1.18 [CI 1.01–1.38]) was observed in FNMTC, but no difference in tumor diameter was appreciated (4). Interestingly, FNMTC might be more aggressive, with higher thyroid cancer–specific mortality, in families with three or more members affected by FNMTC compared to families with two members affected (23). To the authors' knowledge, there has been no prospective screening study in patients with FNMTC to determine who should have screening based on the number of affected members, what the impact of screening is on the detection of thyroid cancer, treatment utilization, and/or treatment-associated morbidity and mortality.

This study reports the screening results of kindred with FNMTC. A high rate of thyroid cancer was found in families with three or more first-degree relatives affected by NMTC. Furthermore, screening resulted in the detection of the disease in a less advanced stage and utilization of less aggressive initial treatment.

Methods

The screening results were analyzed in kindred with FNMTC who enrolled in a prospective cohort study at the National Institutes of Health (NIH) Clinical Center between April 2010 and December 2015 (Clinicaltrials.gov: NCT-01109420). All participants provided written informed consent. The main inclusion criteria were the presence of at least two first-degree relatives affected with NMTC and being older than seven years of age. Individuals with syndromic FNMTC were excluded from the study, and a family history questionnaire was obtained from all kindred. The study was approved by the Office of Human Subjects Research Protections at the NIH.

Demographic, clinical, and pathologic data were collected from medical records, family history questionnaires, and patient interviews. Patient histories, family pedigrees and physical examinations, imaging studies, and laboratory tests were obtained from all patients enrolled in the protocol. All pathology slides were reviewed at the authors' institution to confirm the thyroid cancer diagnoses and histologic subtype.

All at-risk family members who agreed to participate in the study were screened yearly by physical examination and thyroid ultrasound (US) using a linear 7.5 MHz transducer. According to practice guidelines at the time of study initiation, 2009 American Thyroid Association Guidelines, thyroid nodules >5 mm in size were biopsied under US guidance (24). The Bethesda classification system was used to categorize the cytology diagnosis: I, non-diagnostic; II, benign; III, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS); IV, follicular neoplasm; V, suspicious for cancer; and VI, thyroid cancer (25). Treatment of patients with NMTC was consistent with established clinical practices, and all patients were followed annually. Response to treatment was defined as an excellent response if follow-up studies revealed negative imaging and/or suppressed thyroglobulin (Tg) <0.2 ng/mL or stimulated Tg <1 ng/mL with negative anti-Tg antibodies.

The age of diagnosis of FNMTC in the study group was compared to the age of onset of thyroid cancer in the general

population, as reported in the Surveillance, Epidemiology, and End Results (SEER) data on thyroid cancer, representing 28% of the U.S. population. Only NMTC cases ($N=61,523$) were included from the SEER data for the comparison.

Statistical analyses

For parametric and nonparametric data, a two-sided two-sample *t*-test and Mann–Whitney test were used, respectively. A chi-square test of independence and Fisher's exact test were used for categorical data. A *p*-value of <0.05 was considered statistically significant. The data were analyzed using RStudio software (Boston, MA).

Results

Twenty-five kindred with FNMTC were enrolled in the prospective cohort study. Twelve families had two first-degree relatives affected, and 13 families had three or more first-degree relatives affected at the time of enrollment, as documented in 25 pedigrees in Supplementary Figure S1 (Supplementary Data are available online at www.liebertpub.com/thy). The study cohort consisted of 252 individuals: 69 patients with an established diagnosis of thyroid cancer before enrollment, of whom 56 were included in the study (13 patients were excluded, as 10 died before enrollment and three did not provide tissue samples for review), and 183 unaffected at risk relatives among whom 109 (59.6%) underwent screening (Fig. 1). Among patients with FNMTC diagnosed before enrollment, there was no difference in baseline clinicopathologic characteristics between the kindred with two affected members and those with three or more affected members (tumor size 1.8 vs. 1.5 cm, $p=0.49$; gross extrathyroidal extension 9% vs. 8%, $p=0.6$; central neck lymph node metastases 51% vs. 50%, $p=0.99$; lateral neck lymph node metastases 25% vs. 16.7%, $p=0.68$).

Screening thyroid US in 109 at-risk family members detected at least one thyroid nodule in 50.5% (55/109) of individuals. The mean age of individuals with thyroid nodules detected was 36 years (range 7–81 years; Fig. 2). The highest prevalence of thyroid nodules was in the parental generation of the index case (72.7%), but it was also high in the first (57.1%), second (48.9%), and third generation (27.8%; Table 1). Thyroid nodules were detected at the initial screening thyroid US in 53/55 (96.4%) patients, at the third screening thyroid US in 1/55 (1.8%) patients, and at the fifth screening thyroid US in 1/55 (1.8%) patients. Most (47.3%) patients had a single nodule, 10.9% had two nodules, 14.5% patients had three nodules, 7.3% had four nodules, and 20% had five or more nodules. The average size of the thyroid nodule detected at screening was 1 cm (range 0.2–3.8 cm). Thyroid nodules were detected by physical examination in 7/55 (12.7%) patients; none of them were malignant after subsequent evaluation.

Of 55 patients with thyroid nodules, 41 fulfilled the criteria for fine-needle aspiration biopsy (FNAB; Fig. 3). The biopsy was indicated and performed after the first screening thyroid US in 29/41 (70.8%) patients, the second screening thyroid US in 1/41 (2.4%) patient (initially detected nodule grew in size), the third screening thyroid US in 3/41 (7.3%) patients (in one of the patients, the nodule was not detected initially; in two other patients, the initially detected nodule grew in size), after the fourth screening thyroid US in 5/41 (12.2%) patients (in all patients, nodules were detected after first

FIG. 1. The study design and selection of study population. The deaths were due to thyroid cancer.

screening but initially did not reach the threshold size for biopsy), and the fifth screening thyroid US in 3/41 (7.3%) patients (in all three patients, the nodules were detected at initial screening but reached the size threshold for FNAB after the fifth US; Fig. 3). The FNAB showed a cytological diagnosis of papillary thyroid cancer or features suspicious for papillary thyroid cancer in 12 patients, follicular neoplasm in two patients, and AUS/FLUS in four patients. Four patients had a non-diagnostic FNAB, and the remainder of the patients had benign cytologic diagnosis.

During follow-up (42 ± 15 months), 23 patients were treated surgically. Pathology showed follicular adenoma in six (26%) patients and papillary thyroid cancer in 17 (74%) patients. Among patients found to have thyroid cancer, the final diagnosis was established after initial screening in 8/17 (47.2%) patients, at the second screening US in 1/17 (5.8%), at the third thyroid screening US in 3/17 (17.6%), at the fourth thyroid screening US in 2/17 (11.8%), and at the fifth thyroid screening US in 3/17 (17.6%) patients (Fig. 4). The growth velocity of the nodules ranged between 0.1 and 0.5 cm per year. There were no abnormal lymph nodes detected during this follow up period.

FIG. 2. Rate of thyroid nodule detected at screening and patient age.

The peak incidence of thyroid cancer in the cohort of FNMTc, which occurred between 30 and 39 years of age, was a decade earlier than the peak incidence of thyroid cancer observed in the general population (Fig. 5). Among families with two first-degree relatives affected at enrollment, 43/62 (71.9%) at-risk members were screened, while among the families with three first-degree relatives affected, 66/121 (55%) members were screened ($p=0.06$). Taking into consideration all at-risk family members, thyroid cancer was detected in significantly higher proportion of kindred with three or more first-degree relatives affected (12.4%; 15/121) compared to the ones with two members affected (3.2%; 2/62; $p=0.04$). Among the screened patients, papillary thyroid cancer was detected at a significantly higher rate in kindred with three or more first-degree relatives affected at enrollment compared to kindred who had two first-degree relatives affected (22.7% [15/66] vs. 4.6% [2/43]; $p=0.01$). There was no difference in the screening strategy between patients with two first-degree relatives affected and those with three or more first-degree relatives affected (Supplementary Table S1). There was no difference in the age and sex in the screened subgroups of patients with two first-degree relatives affected and those with three or more first-degree relatives affected by FNMTc (34 ± 19.7 years vs. 36 ± 18.9 years, $p=0.45$; female 55.8% vs. 60.6%, $p=0.69$).

Compared to index cases, FNMTc that was detected by thyroid US screening was characterized by a smaller primary tumor size (0.7 ± 0.5 vs. 1.5 ± 1.1 cm; $p=0.006$) and a lower rate of central neck lymph node metastases (17.6% vs. 51.1%; $p=0.02$; Table 2). Patients diagnosed by screening had less extensive surgery (hemithyroidectomy 23.5% [4/17] vs. 0% [0/56]; $p=0.002$) and a lower rate of radioactive iodine therapy (23.5% vs. 79%; $p<0.001$) than patients with an established diagnosis at enrollment (Table 2). There was no statistically significant difference in complications associated with treatment between those patients diagnosed by screening and those patients with an established thyroid cancer diagnosis at the time of enrollment. However, there were no cases of permanent hypoparathyroidism or permanent vocal cord paralysis in the patients diagnosed by screening, while in

TABLE 1. CLINICAL CHARACTERISTICS OF PATIENTS FOUND TO HAVE THYROID NODULES DETECTED BY SCREENING ULTRASOUND

Family members at risk (N = 109)	Parental generation ^a	First generation	Second generation	Third generation
Number of family members at risk	11	35	45	18
Patients with thyroid nodules (%)	72.7%	57.1%	48.9%	27.8%
Mean age at thyroid nodule detection ($\pm$ SD, years)	64 $\pm$ 12	51 $\pm$ 17	31 $\pm$ 12	16 $\pm$ 3.6
Malignant thyroid nodules (%)	26.3%	37.1%	22.7%	0%
Mean age of thyroid cancer diagnosis ($\pm$ SD, years)	75 $\pm$ 2	43 $\pm$ 16	40 $\pm$ 9	NA

^aParental generation was defined relative to the index case in the kindred.
SD, standard deviation; NA, not applicable.

one of the patients with an established diagnosis of thyroid cancer at enrollment, the recurrent laryngeal nerve was sacrificed due to invasion of the nerve (Table 3). Excellent response to initial treatment was more frequently achieved in patients with papillary thyroid cancer detected by screening compared with the index cases (93.3% [16/17] vs. 68.3% [28/41]; $p=0.045$).

FNMTC recurrence rate was 14.3% (8/56), and thyroid cancer-specific mortality was 3.6% (2/56) in patients with an established diagnosis and mean follow-up time of 83 $\pm$ 72 months, and no recurrences or deaths occurred in patients with FNMTC detected by screening, but the follow-up time was shorter (18 $\pm$ 11 months; range 1–36 months).

Discussion

A prospective study was performed that focused on screening for thyroid cancer in at-risk individuals in kindred with FNMTC involving multiple generations. The results demonstrate that screening of at-risk family members identifies thyroid cancer in a greater number of individuals with three or more first-degree relatives. As expected, thyroid cancers diagnosed by screening were less advanced and patients had less extensive initial treatment.

Screening programs in patients at risk of cancer are usually recommended when (i) the patient is indeed at risk of cancer and when the familial disease is more aggressive than sporadic disease, and (ii) when screening results in the detection of the disease at an earlier stage and when early diagnosis has an impact on subsequent treatment and outcome with respect to all-cause mortality, cancer-specific mortality, and/or quality of life. Additionally, it is also important to determine whether screening for cancer is cost-effective.

This study addresses two key components when determining whether screening for thyroid cancer is appropriate in family members at risk for FNMTC, and in whom a screening strategy should be utilized. It was found that the prevalence of thyroid cancer in at-risk individuals from families with two first-degree relatives is the same as for the general population (4.6% vs. 4.5%, respectively) and is significantly lower than the rate of thyroid cancer in kindred with three or more first-degree relatives affected (22.7%) (20). Another prospective study by Rios *et al.* involving nine families with two members affected and one family with three members affected reported that 5% of screened at-risk individuals had thyroid cancer, similar to the present-study cohort in kindreds with two affected members and to the incidence in the general population (26). These results are in agreement with Charkes'

FIG. 3. Summary of indications for fine-needle aspiration biopsy (FNAB) in patients with thyroid nodules.

FIG. 4. Screening strategy in 17 patients for whom the final diagnosis of thyroid cancer was established.

probability estimates that in kindred with two first-degree family members affected, the probability that the disease is sporadic or a chance occurrence is as high as 62%, but that it decreases to <6% when three or more members are affected (27). Taken together, these data suggest that active screening should be considered only in families with three or more first-degree members affected by NMTC, especially in light of the increasing incidence of thyroid cancer worldwide, which is in part due to universal screening implemented by some coun-

tries such as South Korea and increased detection of sub-clinical thyroid cancer (28).

Another important observation from this study is the significantly higher prevalence of thyroid nodules in FNMTC (50.5%) than in the general population (19–35%) that was found when performing screening thyroid US, which is consistent with previous studies by the authors' group (44.4%) and other investigators (52%) (29,30). Furthermore, a high prevalence of thyroid nodules and thyroid cancer was documented not only in the first and second generations, but also in the parental generation (relative to index case). In this study, the prevalence of thyroid nodules in the parental generation was as high as 72.7%, consistent with previous reports documenting thyroid nodules in up to 90% of the parental generation (29). These data suggest that screening, if recommended, should involve all generations. Furthermore, because not all thyroid nodules and thyroid cancers were detected after the initial screening thyroid US or grew after the initial screening thyroid US warranting a FNAB, screening thyroid US should be repeated during follow-up. This study also documents that physical examination is not a sufficient screening tool, since only 12.7% of nodules were palpable and none of them were malignant.

In most but not all studies, the mean age of diagnosis for patients with FNMTC is younger than those with sporadic thyroid cancer, with a peak age of onset in the fourth decade of life (4,5,7,16,17,19,22,31,32). Similarly, in this study, the peak incidence of FNMTC was between 30 and 39 years of age compared to the National Cancer Institute's Surveillance, Epidemiology, and End Results Program data in which the peak incidence in the general population is 10–15 years later. This phenomenon might be due to the ascertainment bias associated with the active screening strategy performed in the present cohort, which involved all generations, or it might be due to the different biological behavior of FNMTC. The

FIG. 5. Age at diagnosis of familial non-medullary thyroid cancer (FNMTC) in study group versus general population. The age of diagnosis was earlier compared to the general population ($p < 0.001$), as reported in the Surveillance, Epidemiology, and End Results (SEER) data on thyroid cancer. The data used in the current study were derived from 17 registries at various geographic locations throughout the United States, representing 28% of the U.S. population. Only non-medullary thyroid cancer cases ($N = 61,523$) were included from the SEER data for the comparison.

TABLE 2. COMPARISON OF BASELINE CHARACTERISTIC AND TREATMENT MODALITIES BETWEEN PATIENTS DIAGNOSED WITH NON-MEDULLARY THYROID CANCER BY SCREENING AND THOSE WITH ESTABLISHED DIAGNOSIS AT ENROLLMENT

<i>Clinical and pathologic features</i>	<i>Patients with established diagnosis (N=56)^a</i>	<i>Patients diagnosed by screening (N=17)</i>	<i>p-Value</i>
Age at diagnosis ($\pm$ SD, years)	42 ($\pm$ 14.4)	47 ($\pm$ 15)	0.22
Female (%; number/total number)	71.4% (40/56)	64.7% (11/17)	0.76
Histologic subtype of thyroid cancer (%; number/total number)			0.84
Classic papillary thyroid cancer	91.1% (51/56)	94.1% (16/17)	
Follicular variant of papillary thyroid cancer	7.1% (4/56)	5.9% (1/17)	
Tall-cell variant of papillary thyroid cancer	1.8% (1/56)	0% (0/15)	
Mean tumor size ($\pm$ SD, cm)	1.5 ($\pm$ 1.1)	0.7 ($\pm$ 0.5)	0.006 ^c
Central neck lymph node metastases (%; number/total number)	51.1% (22/43)	17.6% (3/17)	0.02 ^c
Lateral neck lymph node metastases (%; number/total number)	16.3% (7/43)	0% (0/17)	0.1
Extrathyroidal invasion (%; number/total number)	11.6% (5/43)	0% (0/17)	0.3
Multifocal tumor (%; number/total number)	34.9% (15/43)	47% (8/17)	0.3
Bilateral tumor foci (%; number/total number)	75% (6/8) ^b	87.5% (7/8)	0.52
<i>TNM Stage^d</i>			
I	39/49 (79.6%) ^e	15/17 (88.2%)	0.54
II	0/49 (0%) ^e	0/15 (0%)	
III	7/49 (14.3%) ^e	2/17 (11.8%)	
IVa	3/49 (6.1%) ^e	0/15 (0%)	
<i>Surgical and medical treatment</i>			
Hemithyroidectomy	0% (0/56)	23.5% (4/17)	0.002 ^c
Therapeutic central neck lymph node dissection	51.2% (22/43) ^c	41.2% (7/17)	0.68
Therapeutic lateral neck lymph node dissection	16.3% (7/43) ^c	0% (0/17)	0.1
¹³¹ I Treatment	79% (34/43) ^c	23.5% (4/17)	<0.001 ^c

^aTotal number of patients with established diagnosis before enrollment: $n=69$; 10 patients died before enrollment and three did not have pathology slides for review, leaving $n=56$ study participants.

^bData on unilateral versus bilateral multifocal tumors not ascertained for 7/15 patients.

^cData on the exact extent of the surgery were available for 43/56 patients with established thyroid cancer diagnosis at enrollment.

^dTNM: Tumor node metastasis staging according to the American Joint Committee on Cancer 7th Edition.

^eData on the stage were available for 49/56 patients with established thyroid cancer diagnosis at enrollment.

youngest patient in the present cohort found to have a thyroid nodule was seven years old, and the youngest patients with papillary thyroid cancer were 18 years old (five patients from three families). Thus, the present data indicate that initiating screening before 18 years of age might be justified in some families.

This study demonstrates that FNMTTC detected by screening was characterized by less advanced disease at diagnosis and less extensive initial treatment. In fact, all FNMTTC diagnosed by screening were microcarcinomas. Uchino *et al.*, in a retrospective study of a subgroup of FNMTTC patients, reported that screening was associated with a small primary tumor size (9.1 ± 5.4 mm vs. 0.8 ± 0.6 mm) and a lower rate of multifocal tumors (47% vs. 53.3%) (30).

Thus, screening at-risk individuals in kindred with three or more first-degree relatives affected with FNMTTC is likely to result in the detection of a less advanced disease that would allow less invasive treatment. In fact, none of the patients from the screened cohort had extrathyroidal tumor extension. Thus, in contrast to the patients with an established diagnosis, none of the patient required sacrificing of vital structures such as the recurrent laryngeal nerve in order to achieve complete surgical resection. In the screened cohort, the patients underwent less aggressive initial treatment—less extensive surgery and radioiodine treatment (RAI). Since this observation might be due to the shift in thyroid cancer management guidelines toward less use of RAI therapy, indications for RAI based on the current American Thyroid Association

TABLE 3. TREATMENT-RELATED COMPLICATIONS

<i>Complications</i>	<i>Patients with established diagnosis (N=41)</i>	<i>Patients diagnosed by screening (N=17)</i>	<i>p-Value</i>
Transient hypocalcemia	21.9% (9/41)	11.8% (2/17)	0.09
Permanent hypoparathyroidism	2.4% (1/41)	0% (0/17)	0.51
Vocal cord paresis/paralysis	4.9% (2/41) ^a	0% (0/17)	0.89
Sialadenitis/xerostomia	7.3% (3/41)	0% (0/17)	0.62

^aOne patient had resection of the recurrent laryngeal nerve because of tumor invasion, which was done at another institution. The other patient had a transient vocal cord paresis, which resolved approximately six months after the initial operation done at another institution.

guidelines were analyzed: (i) no RAI for low-risk patients, (ii) individualized approach to RAI treatment in intermediate-risk patients, and (iii) uniform therapy with RAI for high-risk patients (2). Based on the current guidelines, only 51.1% instead of 79% of patients with a thyroid cancer diagnosis established before enrollment and presenting with lymph node metastases would have been treated with RAI. More importantly, a higher proportion of the probands would still require RAI therapy compared to the at-risk individuals diagnosed by screening (51.1% vs. 23.5%; $p=0.05$).

In the cohort of patients with FNMTC detected by screening, four patients with unilateral microcarcinomas were offered and elected to have a hemithyroidectomy as their surgical procedure of choice. Given the predisposition to development of thyroid cancer, these patients will need to be followed closely because of the risk of thyroid cancer in the remnant thyroid.

The cohort was screened at a tertiary referral center. Thus, the surgery was performed by high volume surgeons. The low complication rate in this study might not be generalizable to care at other medical centers, in which the majority of thyroidectomies are performed by low-volume surgeons and as such may be associated with a higher risk of complications. Therefore, it might be justified to offer a watchful waiting strategy to the subset of patients with papillary microcarcinoma diagnosed by screening, especially when detected in older patients. This study was initiated at the time of the 2009 American Thyroid Association guidelines. Therefore, the study design was consistent with the recommendation of performing FNAB in patients with a history of thyroid cancer in at least one relative, when the thyroid nodule was >5 mm in size. In view of the risk of complications associated with overtreatment, the current 2015 American Thyroid Association guidelines recommend a nodule size threshold for FNAB of >1 cm in high-risk patients (2,33). Changing the biopsy threshold from >0.5 cm to >1 cm most likely would not affect the ability of identifying thyroid cancer at an early stage and, as such, current guidelines should be followed. The growth velocity of the nodules harboring thyroid cancer ranged between 0.1 and 0.5 cm per year. There were no abnormal lymph nodes detected during this follow-up period. Consequently, screening at longer intervals than in this study, every two to three years instead of yearly, most likely would not affect the ability to detect the disease at an early stage.

The major limitation of this study is the lack of long-term follow-up to determine the impact of screening on all-cause or cancer-specific mortality, or progression-free survival, and the effect on the long-term quality of life. Another limitation is that the classification of a family member as unaffected may require alteration if that family member was to develop thyroid cancer later. So the rate of thyroid cancer detected by screening may be even higher with long-term follow-up and screening. This is a shortcoming of any prospective screening study in familial cancer syndromes, especially when the susceptibility gene(s) are not known.

In conclusion, screening with thyroid US should be considered in kindred with three or more first-degree relatives affected by FNMTC. Fifteen percent of the study population was diagnosed with FNMTC at <25 years old, while peak incidence occurred between 30 and 39 years of age. Therefore, it might be justified to start screening 10 years before the peak incidence—between 20 and 29 years old or 10 years

before the earliest age of the diagnosis in the family, whichever occurs first. The data indicate that screening should be performed in all generations of kindred affected by FNMTC at regular intervals (every two to three years), as only 47% of thyroid cancer cases were detected at the initial screening.

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Author Disclosure Statement

No competing financial interests exist.

References

1. Chen AY, Jemal A, Ward EM 2009 Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. *Cancer* **115**:3801–3807.
2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L 2016 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* **26**:1–133.
3. Vriens MR, Suh I, Moses W, Kebebew E 2009 Clinical features and genetic predisposition to hereditary non-medullary thyroid cancer. *Thyroid* **19**:1343–1349.
4. Wang X, Cheng W, Li J, Su A, Wei T, Liu F, Zhu J 2015 Endocrine tumours: familial nonmedullary thyroid carcinoma is a more aggressive disease: a systematic review and meta-analysis. *Eur J Endocrinol* **172**:R253–262.
5. Mazeh H, Sippel RS 2014 Aggressiveness in familial non-medullary thyroid carcinoma—the controversy continues. *Thyroid* **24**:783–784.
6. Malchoff CD, McDonald TJ 2014 Is familial nonmedullary thyroid carcinoma more aggressive than sporadic non-medullary thyroid carcinoma? *Thyroid* **24**:782–783.
7. Park YJ, Ahn HY, Choi HS, Kim KW, Park DJ, Cho BY 2012 The long-term outcomes of the second generation of familial nonmedullary thyroid carcinoma are more aggressive than sporadic cases. *Thyroid* **22**:356–362.
8. Alsanea O, Wada N, Ain K, Wong M, Taylor K, Ituarte PH, Weier HU, Freimer N, Siperstein AE, Duh QY, Takami H, Clark OH 2000 Is familial non-medullary thyroid carcinoma more aggressive than sporadic thyroid cancer? A multicenter series. *Surgery* **128**:1043–1050; discussion 50–51.
9. Uchino S, Noguchi S, Kawamoto H, Yamashita H, Watanabe S, Yamashita H, Shuto S 2002 Familial nonmedullary thyroid carcinoma characterized by multifocality and a high recurrence rate in a large study population. *World J Surg* **26**:897–902.

10. Mazeh H, Benavidez J, Poehls JL, Youngwirth L, Chen H, Sippel RS 2012 In patients with thyroid cancer of follicular cell origin, a family history of nonmedullary thyroid cancer in one first-degree relative is associated with more aggressive disease. *Thyroid* **22**:3–8.
11. Jiwang L, Zhendong L, Shuchun L, Bo H, Yanguo L 2015 Clinicopathologic characteristics of familial versus sporadic papillary thyroid carcinoma. *Acta Otorhinolaryngol Ital* **35**:234–242.
12. Leux C, Truong T, Petit C, Baron-Dubourdieu D, Guenel P 2012 Family history of malignant and benign thyroid diseases and risk of thyroid cancer: a population-based case-control study in New Caledonia. *Cancer Causes Control* **23**:745–755.
13. Pitoia F, Cross G, Salvai ME, Abelleira E, Niepomniszcze H 2011 Patients with familial non-medullary thyroid cancer have an outcome similar to that of patients with sporadic papillary thyroid tumors. *Arq Bras Endocrinol Metabol* **55**:219–223.
14. Tavarelli M, Russo M, Terranova R, Scollo C, Spadaro A, Sapuppo G, Malandrino P, Masucci R, Squatrito S, Pellegriti G 2015 Familial non-medullary thyroid cancer represents an independent risk factor for increased cancer aggressiveness: a retrospective analysis of 74 families. *Front Endocrinol (Lausanne)* **6**:117.
15. Lee YM, Yoon JH, Yi O, Sung TY, Chung KW, Kim WB, Hong SJ 2014 Familial history of non-medullary thyroid cancer is an independent prognostic factor for tumor recurrence in younger patients with conventional papillary thyroid carcinoma. *J Surg Oncol* **109**:168–173.
16. Ito Y, Kakudo K, Hirokawa M, Fukushima M, Yabuta T, Tomoda C, Inoue H, Kihara M, Higashiyama T, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Miyauchi A 2009 Biological behavior and prognosis of familial papillary thyroid carcinoma. *Surgery* **145**:100–105.
17. Robenshtok E, Tzvetov G, Grozinsky-Glasberg S, Shraga-Slutsky I, Weinstein R, Lazar L, Serov S, Singer J, Hirsch D, Shimon I, Benbassat C 2011 Clinical characteristics and outcome of familial nonmedullary thyroid cancer: a retrospective controlled study. *Thyroid* **21**:43–48.
18. McDonald TJ, Driedger AA, Garcia BM, Van Uum SH, Rachinsky I, Chevendra V, Breadner D, Feinn R, Walsh SJ, Malchoff CD 2011 Familial papillary thyroid carcinoma: a retrospective analysis. *J Oncol* **2011**:948786.
19. Maxwell EL, Hall FT, Freeman JL 2004 Familial non-medullary thyroid cancer: a matched-case control study. *Laryngoscope* **114**:2182–2186.
20. Moses W, Weng J, Kebebew E 2011 Prevalence, clinicopathologic features, and somatic genetic mutation profile in familial versus sporadic nonmedullary thyroid cancer. *Thyroid* **21**:367–371.
21. Pinto AE, Silva GL, Henrique R, Menezes FD, Teixeira MR, Leite V, Cavaco BM 2014 Familial vs sporadic papillary thyroid carcinoma: a matched-case comparative study showing similar clinical/prognostic behaviour. *Eur J Endocrinol* **170**:321–327.
22. Capezzone M, Marchisotta S, Cantara S, Busonero G, Brilli L, Pazaitou-Panayiotou K, Carli AF, Caruso G, Toti P, Capitani S, Pammolli A, Pacini F 2008 Familial non-medullary thyroid carcinoma displays the features of clinical anticipation suggestive of a distinct biological entity. *Endocr Relat Cancer* **15**:1075–1081.
23. Triponez F, Wong M, Sturgeon C, Caron N, Ginzinger DG, Segal MR, Kebebew E, Duh QY, Clark OH 2006 Does familial non-medullary thyroid cancer adversely affect survival? *World J Surg* **30**:787–793.
24. American Thyroid Association Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM 2009 Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* **19**:1167–1214.
25. Cibas ES, Ali SZ; NCI Thyroid FNA State of the Science Conference 2009 The Bethesda System For Reporting Thyroid Cytopathology. *Am J Clin Pathol* **132**:658–665.
26. Rios A, Rodriguez JM, Navas D, Cepero A, Torregrosa NM, Balsalobre MD, Parrilla P 2016 Family screening in familial papillary carcinoma: the early detection of thyroid disease. *Ann Surg Oncol* **23**:2564–2570.
27. Charkes ND 2006 On the prevalence of familial non-medullary thyroid cancer in multiply affected kindreds. *Thyroid* **16**:181–186.
28. Ahn HS, Kim HJ, Welch HG 2014 Korea's thyroid-cancer "epidemic"—screening and overdiagnosis. *N Engl J Med* **371**:1765–1767.
29. Sadowski SM, He M, Gesuwan K, Gulati N, Celi F, Merino MJ, Nilubol N, Kebebew E 2013 Prospective screening in familial nonmedullary thyroid cancer. *Surgery* **154**:1194–1198.
30. Uchino S, Noguchi S, Yamashita H, Murakami T, Watanabe S, Ogawa T, Tsuno A, Shuto S 2004 Detection of asymptomatic differentiated thyroid carcinoma by neck ultrasonographic screening for familial nonmedullary thyroid carcinoma. *World J Surg* **28**:1099–1102.
31. Loh KC 1997 Familial nonmedullary thyroid carcinoma: a meta-review of case series. *Thyroid* **7**:107–113.
32. Sippel RS, Caron NR, Clark OH 2007 An evidence-based approach to familial nonmedullary thyroid cancer: screening, clinical management, and follow-up. *World J Surg* **31**:924–933.
33. Oda H, Miyauchi A, Ito Y, Yoshioka K, Nakayama A, Sasai H, Masuoka H, Yabuta T, Fukushima M, Higashiyama T, Kihara M, Kobayashi K, Miya A 2016 Incidences of unfavorable events in the management of low-risk papillary microcarcinoma of the thyroid by active surveillance versus immediate surgery. *Thyroid* **26**:150–155.

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