

# Updates in Familial Non-Medullary Thyroid Cancer

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Familial non-medullary thyroid cancer (FNMTc) may be considered as a separate clinical entity with variable aggressive biologic behaviors on the basis of previously published studies. Therefore, a family history of NMTC should be carefully considered as a possible prognostic factor when endocrine surgeons set a plan regarding the extent of surgery, radioactive iodine treatment, and follow-up strategy for FNMTc patients.

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## INTRODUCTION

Approximately 95% of thyroid cancers are non-medullary thyroid cancers (NMTC) that arise from the thyroid follicular cells.<sup>(1)</sup> Most NMTC arise sporadically. However, it is estimated a familial origin, namely hereditary non-medullary thyroid cancer (HNMTc), is presented in 3.5~6.2% of patients with NMTC.<sup>(1)</sup>

Previous population studies have shown that the risk of thyroid cancer is increased five- to nine-fold in individuals with a first-degree relative with thyroid cancer.<sup>(2-4)</sup> When there are two affected members with NMTC in a family, the risk that the patients have a familial syndrome is between 31% and 53%.<sup>(5,6)</sup> In families having three or more affected members with NMTC, more than 96% have the familial trait.<sup>(5,6)</sup>

Familial non-medullary thyroid cancer (FNMTc) is defined as the diagnosis of two or more first-degree relatives with thyroid cancer of follicular cell origin without another familial syndrome.<sup>(1)</sup> FNMTc has an autosomal dominant mode of inheritance with incomplete penetrance and

variable expressivity.<sup>(1)</sup> Papillary thyroid cancer is the histology seen in more than 90% of cases, and non-malignant thyroid disease (follicular adenoma, Hashimoto's thyroiditis, multinodular goiter, hyperthyroidism, and hypothyroidism) is frequently seen in patients with FNMTc (36~57%).<sup>(2,7)</sup> Patients with FNMTc also appears to be at an increased risk for other malignancies, such as breast, kidney, colon, bladder, melanoma, and lymphoma.<sup>(1,8)</sup>

It is unclear whether FNMTc is due to solely to genetic inheritance or to a combination of genetic predisposition and environmental hazard such as low-dose radiation, and whether FNMTc is more aggressive than sporadic NMTC is controversial.<sup>(1,2,7,9)</sup> Therefore, the optimal clinical approach for FNMTc is yet to be established.

## PRESENTATION OF HNMTc

Hereditary nonmedullary thyroid cancer (HNMTc) may occur as a minor component of familial cancer syndromes or as the predominant features in FNMTc.<sup>(10,11)</sup>

## GENETICS

Although the susceptibility genes for many of the hereditary cancer syndromes with thyroid cancer are known, these cases only account for a small subset of FNMTTC cases. (11)

The genetic causes of most cases of FNMTTC remain poorly understood. Unlike in the case of hereditary medullary thyroid cancer syndromes, the causative genes predisposing to FNMTTC have not been identified. Several linkage studies have identified loci within specific families, including *MNG1*, *TCO1*, *fPTC/PRN*, *NMTC1*, and so forth, but none of these appears to account for a significant number of cases. (1,10-12) These studies were only characterized in one or a few affected families, and almost all examined rare variants of FNMTTC such as Hurthle cell carcinoma and follicular variant of papillary carcinoma. Another important shortcoming is that a less stringent definition for FNMTTC may have diluted the linkage studies with sporadic cases. It is also possible that FNMTTC may be a heterogenous inherited syndrome with more than one susceptibility gene with somatic mutations.

Multiple germline mutation analyses have excluded the most common somatic mutations in genes associated with sporadic thyroid cancers, including *BRAF*, *RET*, *RET/PTC*, *MET*, *MEK1*, *MEK2*, *RAS*, and *NTRK*, as the candidate genes for FNMTTC. (13)

## CLINICAL CHARACTERISTICS

### 1. Early age of onset

There are some that have noted a slightly earlier presentation of FNMTTC. (10,14-18) A meta-analysis found that patients with FNMTTC presented up to a decade earlier than their sporadic counterparts, with a peak age of onset in FNMTTC patients of the fourth decades. (16-18) Moreover, another investigator found that the mean age of onset was 2 years lower for papillary cancer in offspring of affected parents, and 5 years lower for affected siblings. (14) On the basis of these reports, although there is no strict age cutoff at which screening should commence, it has been recommended to begin screening individuals 5 ~ 10 years before

the youngest age of diagnosis within the family and for most families by age 20. (1)

### 2. Aggressive biologic behavior and recurrence

FNMTTC has been shown in several series to have more aggressive biologic behavior and higher rate of recurrence as compared with sporadic thyroid cancer. (7,15-17,19,20) These aggressiveness included multicentricity, bilaterality, an increased incidence of benign thyroid nodules, nodal involvement, larger tumors, perithyroidal soft tissue invasion, and vascular invasion. One study has shown that FNMTTC patients, even in the tumor size of less than 1cm, had significant higher multicentricity (71%), bilaterality (43%), lymph node metastasis (57%), and vascular invasion (43%) than those of patients with sporadic NMTC. The recurrence rate in these patients was also significantly higher at 43% than sporadic counterpart (5%). (20) Another report demonstrated a 10% prevalence of thyroid cancer detected by screening neck ultrasonography and subsequent fine-needle aspiration cytology performed on asymptomatic family members of patients with FNMTTC, with the tumor averaging less than 1cm in diameter. (21) Despite the relatively small size, 47% had multicentricity and 43% had lymph node metastasis. (21) Many authors of these studies consequently recommended that patients with FNMTTC need to be treated more aggressively, regardless of the size of the tumor, including total thyroidectomy combined with prophylactic central compartment node dissection, and radioactive iodine ablation followed by life-long TSH suppression, and to be followed closely as they are at high risk for recurrence.

In contrast to above mentioned studies, some studies did not show that FNMTTC was more aggressive than the sporadic form of NMTC. (9,10,18,22-24) These authors suggested that the therapeutic strategy for FNMTTC might depend on conventional prognostic factors the same as that of sporadic NMTC, but not on whether the cancer is familial or sporadic.

The discrepancy among the results of previous studies regarding the aggressiveness of FNMTTC may have several causes. First explanation is that, albeit the gene responsible for FNMTTC is yet to be identified to date, the genetic defect

related to each study cohort may be different, or that more than one susceptibility gene with somatic mutations may be concerned with the patients with FNMTTC included in each study. Another explanation is ascertainment bias. Patients with relatives affected by thyroid cancer may undergo more careful thyroid examination, more imaging studies, and may be diagnosed earlier. In this case, clinical outcomes may appear comparable to sporadic cases due to earlier diagnosis and treatment and not due to similar biologic behavior. Additionally, the proportion of patients with three or more affected relatives within each FNMTTC cohort may be different. It is important because, as mentioned previously, the disease may actually be sporadic in up to 69% of the families with only two affected members, as opposed to 1~4% in those with three or more affected members. Therefore, relatively lesser proportion of patients with three or more affected members may dilute the aggressiveness of FNMTTC.

## PROGNOSIS

FNMTTC patients have several characteristics that are associated with a worse prognosis. One is the aggressiveness of disease. As described above, FNMTTC may be associated with a higher risk of invasiveness and lymph node involvement. The recurrence rate in FNMTTC is also higher than that seen in sporadic counterpart. Recurrence of thyroid cancer is another factor associated with a worse prognosis, even in a low risk patient.

Several previous studies have tried to examine the impact of FNMTTC on disease-free or overall survival. One study described that FNMTTC patients with three or more affected family members had a shorter survival time than those with two affected members ( $P=0.02$ ).<sup>(25)</sup> Moreover, the cumulative survival of FNMTTC patients with three or more affected members was significantly lower than those of the controls, and the survival of patients in the pre-index group was significantly lower than those of the patients in the post-index group.<sup>(25)</sup> Another study also reported that disease-free survival of patients with FNMTTC was significantly shorter than that of sporadic disease patients, and that disease-free survival was poorer among the subset of

patients with three or more affected members.<sup>(19)</sup> Our own study, published recently, revealed that presence of a family history of NMTC was an independent risk factor for recurrence ( $P<0.001$ ), and that overall disease-free survival in the FNMTTC group was substantially shorter than in the sporadic group, especially in the subgroup aged less than 45 years ( $P<0.001$ ).<sup>(26)</sup> This finding is in line with the results of other recent publication showing that affected members of the second generation of parent-offspring FNMTTC cases were younger at their time of diagnosis ( $38\pm 12$  vs.  $57\pm 11$  years,  $P<0.0001$ ), had more extrathyroidal invasion (58.5% vs. 29.4%,  $P=0.006$ ), a higher recurrence rate (50.0% vs. 19.0%,  $P=0.030$ ), and shorter recurrence-free survival ( $P=0.015$ ) than the preceding generation.<sup>(27)</sup> However, other studies contradict these assertions.<sup>(10,22-24)</sup>

## CONCLUSION

FNMTTC may be considered as a separate clinical entity with variable aggressive biologic behaviors on the basis of previously published studies. Therefore, a family history of NMTC should be carefully considered as a possible prognostic factor when endocrine surgeons lay down a scheme of the extent of surgery, radioactive iodine treatment, and follow-up strategy for FNMTTC patients.

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