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The Impact of Family History on Non-Medullary Thyroid Cancer

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Abstract

Introduction—Around 10% of patients with non-medullary thyroid cancer (NMTC) will have a positive family history for the disease. Although many will be sporadic, families where 3 first-degree relatives are affected can be considered to represent true familial non-medullary thyroid cancer (FNMTC). The genetic basis, impact on clinical and pathological features, and overall effect on prognosis are poorly understood.

Methods—A literature review identified articles which report on genetic, clinical, therapeutic and screening aspects of FNMTC. The results are presented to allow an understanding of the genetic basis and the impact on clincal-pathological features and prognosis in order to inform clinical decision making.

Results—The genetic basis of FNMTC is unknown. Despite this, significant progress has been made in identifying potential susceptibility genes. The lack of a test for FNMTC has led to a clinical definition requiring a minimum of 3 first-degree relatives to be diagnosed with NMTC.

Although some have shown an association with multi-centric disease, younger age and increased rates of extra-thyroidal extension and nodal metastases, these findings are not supported by all. The impact of FNMTC is unclear with all groups reporting good outcome, and some finding an association with more aggressive disease. The role of screening remains controversial.

Conclusion—FNMTC is rare but can be diagnosed clinically. Its impact on prognostic factors and the subsequent role in influencing management is debated. For those patients who present with otherwise low-risk differentiated thyroid cancer, FNMTC should be included in risk assessment when discussing therapeutic options.

Keywords

Thyroid cancer; familial thyroid cancer; family history

Introduction

Non-medullary thyroid cancer (NMTC) is increasingly common worldwide [1–5]. In addition to exposure to ionizing radiation, family history has been considered a possible risk factor for NMTC. Although the majority of NMTC are sporadic, familial tumors may account for 5–15% of differentiated thyroid carcinoma cases. The presence of multifocal papillary carcinoma is a common feature of familial non-medullary thyroid cancer (FNMTC). Thyroid neoplasia has been reported with increased frequency in familial syndromes, such as familial adenomatous polyposis (FAP), phosphatase and tensin homolog gene (PTEN)-hamartoma tumor syndrome (PHTS), Cowden syndrome, Carney's complex type 1, and Werner's syndrome [6]. Thyroid carcinomas in multitumor genetic syndromes are heterogeneous diseases, tend to share some similar characteristics including early age onset, and are usually bilateral and multicentric. FNMTC syndrome is diagnosed when three

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or more family members have NMTC in the absence of other known associated syndromes. Furthermore, patients with papillary thyroid carcinoma have a higher risk of a second primary tumor at the genitourinary tract, breast, central nerve system, digestive tract, salivary glands and sarcomas [7–9].

Much work on factors prognostic of outcome for NMTC have focused on the impact of age at diagnosis, tumor size, extra-thyroidal extension and the presence of regional and distant metastases. These factors, as well as histological features such as vascular invasion have been incorporated in to widely accepted risk prediction models [10, 11]. Although family history has been suggested as a predictor of poor outcome for patients with NMTC, conflicting evidence has been reported. In addition, in contrast with medullary thyroid cancer, no distinct genetic basis for inherited NMTC has yet been identified. As such, a family history is currently not recognized as important in risk prediction models. The aim of this article is to review our current understanding of the impact of family history on NMTC and to discuss the implications of this diagnosis for clinicians and patients managing this disease.

Familial Non-Medullary Thyroid Cancer

FNMTC represents approximately 3–7% of all thyroid cancers that originate from thyroid follicular epithelial cells [12]. First reported in 1955 in identical twins [13], family history has been shown to have an impact on risk of relatives developing disease, with up to a tenfold increase in risk of NMTC for first degree relatives [14–21]. Histologically, FNMTC is indistinguishable from the sporadic form of the disease. At present, the specific genetic basis for FNMTC is not clear. Studies suggest that FNMTC has an autosomal dominant behavior with incomplete penetrance and variable expressivity [16, 22–33]. Although the specific causative genes are yet to be identified, novel techniques in molecular genetics have identified a number of potential susceptibility genes which may be implicated. These include MNG1 (chromosome 14q31) [34], TCO (chromosome 19p132) [35], NKX2-1 (chromosome 14q13.3) as factor of risk of papillary thyroid carcinoma among patients with familial multinodular goiter [36], or only of FNMTC [37], fPTC/PRN (chromosome 1q21) [23], NMTC1 (chromosome 2q21) [38], DICER1 (chromosome 14q32) [39], FTEN (chromosome 8p23.1-p22) [40], FOXE1 (chromosome 9q22.33) [37], and SRGAP1 (chromosome 12q14) [41]. Li-Fraumeni syndrome is a hereditary cancer predisposition disorder related to germline TP53 mutations. Osteosarcoma, adrenocortical tumors, and central nervous system tumors are usually diagnosed in childhood and breast cancer and soft-tissue sarcomas in adults. Thyroid cancer is rarely reported. However, in Brazil, a specific mutation in this gene (p.R337H), has a high population prevalence (0.3%) and within a cohort composed of R337H mutation positive individuals, thyroid cancer is described in an unexpected high incidence [42]. Despite these advances, no genetic test is yet available for FNMTC.

Nevertheless, there is some evidence that HABP2 G534E variant (chromosome 10q25.3) is a susceptibility gene for FNMTC and functions as a dominant-negative tumor-suppressor gene [43, 44], although other reports have failed in detecting this association [45, 46]. On the other hand, Yu el al. [47] designed a customized panel to capture all exons of 31 cancer susceptive genes possibly related to FNMTC. Using next-generation sequencing germline

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mutations from eight genes were found matching between paired FNMTC patients from the same family. It is plausible that some of these variants might have contributed to these patients' susceptibility to thyroid cancer.

The lack of a specific laboratory test for FNMTC has resulted in the development of a clinical definition based on family history. The most stringent definition of FNMTC requires 2 first degree relatives to have been diagnosed with NMTC at the time of diagnosis of the patient in question, in the absence of a known familial syndrome (such as Cowden syndrome, FAP, Carney complex, or Werner syndrome, which are associated with an increased risk of NMTC). This definition is based upon the fact that when 2 persons in 1 family (including the index patient) are diagnosed with NMTC there is approximately a 50% chance that the index patient has the familial type of disease. For Charkes [15], if only 2 members of the same family are affected, the probability that it is not *sporadic* event is 38%. This probability that it is not a sporadic event rises to >95% when 3 family members are affected [15, 48]. As such, the clinical definition of "true" FNMTC can only be confirmed when an additional 2 first degree relatives are identified to have also been diagnosed with a malignancy of the same histologic subtype [49].

However, a clinical definition presents a number of problems. Clearly, the first family member (the index case) diagnosed with NMTC cannot be correctly identified as harboring familial disease, nor can the second until 3 cases are identified.

Within large cohorts of NMTC, approximately 5–10% of patients are found to have a positive family history [50–54]. However, further scrutiny reveals that <5% of major series include patients with 2 or more affected first degree relatives, which would meet the more stringent clinical definition of FNMTC [50–52, 54, 55]. The rarity of true FNMTC is one of the reasons that studies have tended to include any patients with a positive family history.

It is important then, when considering reported evidence to distinguish those studies that have analyzed cohorts with a family history of NMTC versus those who report true FNMTC as a distinct entity. In addition, it is important to separate out different aspects of risk. First, the impact on the pattern of established risk factors with respect to family history within NMTC and second, the impact of family history on oncological outcomes including recurrence and survival.

Clinico-Pathological Features of Familial Non-Medullary Thyroid Cancer

The relationship between age and family history is complex. Many groups report no difference in age between familial and sporadic cases [52, 53, 55–58]. In contrast, other groups report a lower average age in familial disease [31, 54]. Whether this finding is explained by increased screening of relatives following a diagnosis which results in identification of occult disease at an earlier stage is unclear.

Age is known as the strongest predictor of survival in NMTC and as such has been the focus of attention, both in terms of observational differences but also the relationship between familial disease, age at presentation and outcome. Some authors have found that in family groups affected, second generation patients present at a younger age with more aggressive

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disease features which results in worse overall outcome, a what is called “clinical anticipation” [59, 60]. Capezzone et al. [59] reported on 47 parent-sibling diagnoses (22 first generation and 25 second generation cases) with earlier age at diagnosis, more men, increased rates of multicentricity, more frequent nodal metastases and higher rates of recurrence in the second generation versus the first. The definition of FNMTC in this study included families with only 2 or more cases, which, as we have seen, may indeed be biased to include fortuitous associations of sporadic tumors. Also, if the index case is a young person with clinical significant disease, screening of parents and older family members for subclinical disease could explain these observations.

In terms of the pathological presentation of disease, many groups have shown that familial disease is associated with increased rates of multicentric papillary cancers [19, 57, 58, 61]. Although not all groups have found this to be statistically significant due to the already high rate of multifocality in sporadic NMTC [52], the majority of series report rates of multicentricity of approximately 50% in patients with a family history versus 30–40% in sporadic cases [50, 53–56, 59, 62, 63]. Indeed, those groups with a sufficient number of cases to analyze those with 3 or more affected family members report rates of up to 68% in true papillary FNMTC [53].

In contrast, for histologic features included in major risk prediction models such as tumor size and extra-thyroidal extension, most groups report no significant trend towards more aggressive disease [52, 53, 55]. However, a recent Chinese study which applied a strict definition of FNMTC reported both larger tumors and higher rates of extra thyroidal extension in familial cases (88% versus 64%, $p=0.02$ and 82% versus 24%, $p<0.001$, respectively) [56]. Similar results were reported by a group from the United States, who used the less strict definition of at least one other family member affected, and reported extra thyroidal extension in 5.4% of familial versus 0.6% of sporadic cases ($p=0.007$), respectively [54]. Clearly these two groups were dealing with significantly different spectra of disease.

The impact of family history on rates of nodal metastases is also controversial. In the previously mentioned Chinese study [56], patients with FNMTC had a significantly higher rate of metastases than the sporadic cohort (64% versus 34%, $p=0.005$). Zhang et al. [57], in a more recent Chinese study reported similar findings. A group from United States [54] also reported higher rates of nodal disease in patients with a family history (1 or more additional family members affected) than in the sporadic setting (22% versus 11%, $p=0.02$). An Italian group [59] found that in familial disease, second generation papillary thyroid carcinoma was more likely to be associated with nodal metastases than disease in first generation cases (32% versus 5%, $p=0.02$). In addition, Tavarelli et al. [58] found a significant presence of lymph-node metastases in familial tumors (40/151 vs. 113/643, respectively, $p=0.016$). In contrast to these findings, the majority of groups have found no association between family history and nodal disease [31, 50, 52, 53, 55].

In summary, although there is no clear consensus, it may be that FNMTC is characterized by a more aggressive biological behavior with younger age at diagnosis, multifocal disease, and a higher rate of nodal metastases and extrathyroidal tumor extension. A recent meta-analysis

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of Wang et al. [64] reporting 12 studies with a total of 12,741 patients confirmed these findings.

Table 1 summarizes clinical, pathological and outcome data for patients with FNMTC stratified by study [28, 31, 50, 52, 53, 55–59, 61].

Prognosis of Familial Non-Medullary Thyroid Cancer

With no clear consensus on the impact of family history on classic variables associated with risk in NMTC (age, extra thyroid extension, tumor size and nodal metastases) it is hardly surprising that there are conflicting reports of the impact of family history on prognosis. This subject is again further confounded by low patient numbers and various definitions of familial disease.

Ito et al. [50] found no association with recurrence in 273 patients with familial papillary thyroid carcinoma. This group reported higher rates of multicentric disease, and in those familial patients who underwent less than total thyroidectomy, 5% developed disease in the thyroid remnant. This “recurrence” rate was higher than those who underwent total thyroidectomy in this cohort but is in keeping with others’ experience of thyroid lobectomy in the sporadic setting [65]. This study included all patients with a positive family history and did not present a subgroup analysis of those patients who came from families with true FNMTC. It is likely therefore that sporadic cases were included in the “familial” group, lessening the effect associated with true FNMTC [50].

Rosario and Calsolari [51] identified 42 cases of papillary thyroid carcinoma with at least one family member also affected by NMTC. This group treated uninodular disease with thyroid lobectomy and multinodular or metastatic disease with total thyroidectomy. Thirty two patients (76%) had a total thyroidectomy. With a median follow up of 50 months, no patients were diagnosed with recurrent disease [51] suggesting no association between family history and an aggressive disease phenotype. Zhang et al. [57], despite finding more aggressive clinical pathological features of disease reported no recurrences or deaths in 78 patients from 31 families with FNMTC (defined as 2 or more relatives affected with NMTC in addition to the index patient).

Finally, Pinto et al. [61] in matched-case comparative study of a series of 107 patients with FNMTC and 107 with sporadic disease, found that no patient with FNMTC died of disease during follow-up, in contrast to five patients (4.7%) (P=0.06) with sporadic tumors.

In contrast to these findings, other groups have found an association between poor outcome and familial disease. Lee et al. [55] reported their experience of 113 Korean patients with a family history of NMTC. All patients were treated with total thyroidectomy and radioactive iodine (RAI) for all patients 45 years or older or with disease >1cm in size. Multifocality (particularly more than 3 deposits) was more commonly seen in patients with familial disease. This feature was more common in patients with 2 or more affected family members than those with only 1 affected family member. The risk of recurrence in the familial group was found to be elevated (HR 1.6 (1.0–2.4), p=0.039) and this was more pronounced in patients <45 years at presentation. Although a true multivariate analysis was not performed,

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the group corrected for variables and found that in addition to young patient age, familial disease was associated with worse outcome in tumors >1cm in size, those with multifocal disease and those disease metastatic to the lateral neck. Cao et al. [53] reported on 372 Chinese patients with NMTC and a positive family history. Again this group found an association with multicentricity. However, when multivariate analysis was used, family history was independently predictive of recurrence only in microcarcinoma. In addition to this finding was the observation that recurrence was more common in second generation than first generation patients. Similar findings were reported by Capezzone et al. [59] who found higher rates of recurrence and lower rates of cure in FNMTC. In this cohort of 34 patients, second generation patients tended to present at a younger age. Despite the normally protective effect of age, rates of metastatic disease and recurrence were higher in this group with fewer second generation than first generation patients cured of disease. Park et al. [63] found smaller tumors with higher rates of multicentricity in those patients with a family history of NMTC. Their numbers were too low to analyze outcome for patients with true FNMTC but their analysis suggested that those patients who were second generation presented at a younger age, had higher rates of extra thyroidal extension (58% versus 29%, p=0.011) and higher rates of recurrence (50% versus 19%, p=0.015).

Mazeh et al. [54] compared 37 patients with a positive family history from the US with 321 controls. This group reported higher rates of multicentric disease, extra-thyroid extension, nodal metastases and recurrence in the familial group. They also reported no difference in prognosis for those patients with 1 family member affected versus those with 2 or more family members affected (recurrence rates 28% versus 21%, p=0.56) although clearly numbers in each group were low. From these data it is impossible to conclude that family history is an independent prognostic factor.

McDonald et al. [52] reported on 91 patients with a family history of NMTC compared with 521 controls. They stratified the group by the number of family members affected and found no clinical-pathological difference between any group and the controls. This group found a significant association between family history and distant metastases, re-treatment and death. The most striking finding was a 15% re-operation rate in patients from families with 3 or more family members affected versus 5% for non-familial cases. Triponez et al. [66] reported on 139 patients who had more than 2 family members affected with NMTC. This group were one of the few to include anaplastic thyroid cancers in the analysis. Although no differences were seen in age at presentation or histology when stratified by family history overall, those patients with 3 or more affected family members were found to have significantly reduced survival. This group is the only one to include survival as an outcome. These results are related to inclusion of de-differentiated disease and are unlikely to apply to well-differentiated tumors within the familial setting. Tavarelli et al. [58] studied 74 FNMTC families (151 affected individuals) compared with 643 sporadic cases. They found a mean age at diagnosis lower in FNMTC ($p < 0.005$); papillary tumors were more frequently multifocal in FNMTC ($p = 0.004$) and with lymph-node metastases ($p = 0.016$). Disease-free survival was shorter in FNMTC vs. Sporadic cases ($p < 0.0001$) with 74.8 vs. 90.8% patients free of disease at the last control ($p < 0.005$). In the above mentioned meta-analysis of Wang et al. [64], FNMTC was found to have an increased rate of recurrence and decreased DFS in comparison to sporadic cancer.

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The conflicting results of current evidence are challenging to interpret. Critics have suggested that the inclusion of patients with only 1 other family member affected by NMTC leads to an enriching of the study group with sporadic cases which may lead such studies to overlook the potential small effect of FNMTC on outcome. This approach tends to be used due to the low number of patients with more than 1 other family member affected available for inclusion. When statistical tests are applied to small patient cohorts, they may overestimate effects which further complicates the interpretation of results [67].

Screening for Familial Non-Medullary Thyroid Cancer

The recognition that family history of NMTC may confer poor prognosis, in particular for second generation patients diagnosed with the condition, has led authors to explore the place of screening for this condition. This way, preventive screening will allow earlier detection, more timely intervention, and hopefully improved outcomes for patients and their families. Musholt et al. [29] recommend screening of all family members once a hereditary predisposition for papillary thyroid carcinoma is suspected. When Rios et al. [68] screened families of patients with 2 first degree relatives affected by NMTC they demonstrated higher rates of malignancy in the study group than the control group (6% versus 1%, p=0.0182). They also found higher rates of thyroid disease in first degree than second degree family members (64% versus 46%, p=0.0482). However, more than half of the patients suspected of having malignant disease in this cohort were confirmed benign after surgery, suggesting a significant risk of overtreatment.

Uchino et al. [69] screened 149 patients with at least 1 first degree relative affected by NMTC. This group reported nodular disease in 52% of participants. Eighteen patients required surgery (12%) and of those, 15 (10%) were malignant. The histopathology confirmed metastatic nodes in 7 patients (47%) which is still compatible with the rate of nodal metastases in sporadic.

Sippel et al. [70] recommend using clinical history and examination to screen first degree relatives of patients diagnosed with NMTC. They suggest proceeding to ultrasound only if indicated by the results of this preliminary screen. For patients with 2 or more family members affected be NMTC they recommend ultrasound screening as routine and in the absence of positive findings, that this should be repeated annually.

Stephenson et al. [71] screened 30 parents of 15 children diagnosed with papillary thyroid carcinoma and found 1 micropapillary carcinoma following 6 fine needle aspirations and 2 surgeries. The authors conclude that screening of affected families is unlikely to be useful.

However, authors have not searched for the clinical characteristics and methods used at the moment of diagnosis of the second and third familial cases that gives support to the definition of FNMTC. It is clear that a relative who is diagnosed with subclinical disease immediately after the diagnosis of the index case with a random ultrasound and which tumor size is lower than 1 cm does not offer the same burden to support a familiar pattern in comparison with a relative diagnosed before with a clinically palpable nodule or with lymph node metastases.

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The place of screening is therefore not clear. Screening relatives of patients with true FNMTC yields higher rates of malignancy than screening the population but whether that translates in to clinical benefit is unclear, particularly with high rates of false positive cases in the generated surgical cohort [72] and the consequent adverse effects of surgical treatment as postoperative hypothyroidism and laryngeal nerve injuries or definitive hypoparathyroidism. Besides, the recommendation of screening for FNMTC could increase the actual high rate of over diagnosis of thyroid cancer [73].

Treatment of Familial Non-Medullary Thyroid Cancer

Having identified disease in a patient with a family history of at least 2 additional first degree relatives affected by NMTC, the next challenge is knowing whether this feature of disease should impact management. For patients with demonstrable extra thyroidal extension or regional or distant metastases, total thyroidectomy, appropriate neck dissection and post-operative RAI will be recommended as for sporadic disease [11, 70, 74]. However, for uninodular tumors without regional or distant disease, the position is less clear [54]. The majority of authors cite high rates of multifocality as an argument against thyroid lobectomy in favor of total thyroidectomy [50]. In addition, the suggestion that rates of lymph node metastases are higher than in sporadic disease leads many groups to recommend prophylactic central neck dissection [66]. However, not all groups agree, and those who report low rates of recurrence and minimal impact on outcome do not recommend altering the treatment approach based on family history alone [50, 51].

At present, prophylactic thyroidectomy is not recommended for patients considered at risk of FNMTC in the absence of nodular disease. If a nodule is identified and clinical, ultrasound or cytological features suggest malignancy surgical treatment is recommended. The role of “prophylactic” thyroidectomy for patients with benign nodular disease is debatable. Efforts should be made to confirm the pre-operative diagnosis with cytology and an individualized treatment decision should be made. In the absence of confirmed malignancy, some authors still recommend total thyroidectomy in this situation even without evidence of multi-nodular disease [70]. This is based on the relatively low accuracy of cytology in some instances [28, 75], high rates of multicentric disease and the concept that in FNMTC the entire gland is “high risk”. Other groups do not support this approach but recommend serial screening of benign nodules [29] and lobectomy for indeterminate lesions [51].

When considering management of the neck, patients with FNMTC should undergo the same diagnostic work up in terms of ultrasound +/− fine needle aspiration. In those who have demonstrable regional disease, compartment-orientated therapeutic neck dissection is recommended [76]. The situation regarding elective neck surgery is less clear. Higher rates of metastatic disease have been reported in FNMTC but no group has yet shown that elective neck dissection is beneficial. Current guidelines recommend considering elective central neck surgery in cases with higher risk of occult nodal disease. Some authors do recommend prophylactic central neck dissection in the setting of familial disease which is over 1 cm at the time of diagnosis [70].

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The role of RAI and thyroid stimulating hormone (TSH) suppression is also currently unclear. Again, those groups who find higher rates of recurrence in FNMTC recommend RAI for all with lifelong TSH suppression. Whether this approach is associated with improved outcomes may never be resolved. Despite that, it seems fair to say that the chance of identifying disease features in FNMTC which are recognized indications for RAI (extra-thyroid extension and nodal disease) may be higher and as a result such patients are more likely to be offered RAI within the framework of contemporary international guidelines [11]. The role of long term TSH suppression has been questioned, particularly in the era of dynamic risk stratification [77]. It seems likely although patients with FNMTC may be considered at higher early risk of recurrent disease by some groups, this assessment is likely to change with time allowing patients to revert to a lower risk approach during long term follow up.

When considering treatment options for any patient with NMTC (irrespective of the family history), clinicians must weigh patient and tumor variables against the risk of later recurrence and surgical complications. While a positive family history alone is unlikely to alter that risk benefit calculation significantly, for patients with true FNMTC (>=2 first degree relatives affected) consideration should be given to this as a risk factor when individualizing treatment decisions.

Conclusions

FNMTC is a rare but recognized condition. In family groups with 3 or more members affected, there is a hereditary basis for the disease in almost all cases. In this situation the term FNMTC should be applied. In contrast, for patients with a single first-degree family member affected, or someone more distant on the family tree, the situation is less clear. Many such patients will have sporadic disease, although some will ultimately be diagnosed with FNMTC following identification of disease within the family group. There is no current evidence that screening is beneficial in the setting of FNMTC although, particularly in first-degree relatives, clinicians should have a low threshold for investigating nodular disease.

True FNMTC may present with features of more aggressive disease including multifocality and lymph node metastases. Patients are often younger than average, but despite this generally favorable finding, there is an association with worse outcomes in terms of recurrence. The position in relation to survival is less clear and with such a rare form of disease it is unlikely that robust evidence will ever be available. In contrast, a family history of NMTC is a less clear predictor of aggressive disease. Evidence is conflicting and this may represent the different inclusion criteria applied in the studies reported. It is not clear from most studies if family history is truly an independent risk factor.

Patients with true FNMTC should be considered for a more aggressive therapeutic approach to primary surgery with total thyroidectomy rather than thyroid lobectomy given the high rate of multifocality reported. Although some groups have reported an increased rate of nodal metastasis in FNMTC, no group has demonstrated improved outcome related to elective neck dissection, and as such the approach to the neck should be as for sporadic disease. For those patients with a family history of NMTC but without 2 or more first degree

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relatives affected, there is little evidence that more aggressive approach is beneficial. As the incidence of thyroid cancer increases it is important for clinicians to understand the role of family history in assessment and management of patients with NMTC. For the majority of patients without true FNMTC, the family history should be recorded but this should not impact on the approach to initial therapy. In contrast, those with a true hereditary condition, characterized by 2 or more first degree family members affected, may be considered at higher risk and treated appropriately.

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Table 1

Summary of clinical, pathological and outcome data for patients with Familial Non-Medullary Thyroid Cancer stratified by study

Author	Definition Applied**	Younger Age	Male Gender	Increased Size	Increased Multi Centricity	Increased Extra Thyroidal Extension	Increased Lymph Node Metastases	Worse Prognosis
Uchino et al. [28]	>1*	−	−	−	+	−	−	+
Moses et al. [31]	>2	+	−	−	−	−	−	−
Ito et al. [50]	>1*	−	−	−	+	−	−	−
McDonald et al. [52]	>1*	−	−	−	−	−	−	+
Cao et al. [53]	>1*	−	−	−	+	−	−	−
Lee et al. [55]	>1*	−	−	−	+	−	−	+
Lei et al. [56]	>2	−	−	+	+	+	+	+
Zhang et al. [57]	>2	−	−	−	−	+	+	−
Tavarelli et al. [58]	>1	+	−	−	+	−	+	+
Capezzone et al. [59]	>1	−	−	−	+	−	−	+
Pinto et al. [61]	>2	−	−	−	+	−	−	−

** Number of first degree relatives affected by non-medullary thyroid cancer in order to be classed as familial disease

* subgroup analysis of families with >2 affected first degree relatives is provided.

+ positive association found

− no association found