Familial nonmedullary thyroid carcinoma is a more aggressive disease: a systematic review and meta-analysis

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Abstract

Objective: There is controversy as to whether familial nonmedullary thyroid carcinoma (FNMTC) is more aggressive than sporadic NMTC (SNMTC). The aim of the study was to evaluate the biological characteristics of patients with FNMTC by a meta-analysis.

Methods: Four databases (PubMed, EMBASE, the Cochrane library databases, and the Web of Science) were searched to identify studies published before September, 2014. All original studies that compared clinical characteristics and prognosis of patients with FNMTC and SNMTC were included. The pooled effect sizes of interesting parameters were calculated by odds ratio (OR), standard mean difference (SMD), or hazard ratio (HR).

Results: Twelve studies with a total of 12,741 participants were included in this analysis. FNMTC patients had an increased rate of recurrence (OR = 1.72, 95% CI: 1.34 to 2.20) and decreased disease-free survival (DFS) (HR = 1.83, 95% CI: 1.34 to 2.52) in comparison with SNMTC patients. FNMTC possessed more aggressive biological behaviors, characterized by younger age at diagnosis (SMD = −0.91, 95% CI: −1.59 to −0.22), higher risk of multifocal (OR = 1.50, 95% CI: 1.32 to 1.71), bilateral (OR = 1.29, 95% CI: 1.00 to 1.66), extrathyroidal invasion (OR = 1.20, 95% CI: 1.02 to 1.41), and lymph node metastasis (OR = 1.18, 95% CI: 1.01 to 1.38).

Conclusion: FNMTC is a more aggressive disease and possesses higher recurrence rate and lower DFS. More attention and careful consideration should be paid regarding the decision about treatment for patients with FNMTC.

Introduction

Thyroid cancer is the most common endocrine cancer and the incidence is increasing all over the world (1, 2). It can be classified into two main groups depending on the cell origination: medullary thyroid carcinoma (MTC), which originates from the thyroid parafollicular calcitonin-producing C cells, and nonMTC (NMTC), which originates from follicular cells. NMTC represents more than 95% of all thyroid cancer, and four histologic subtypes can be distinguished: papillary (85%), follicular (11%), Hürthle cell (3%), and anaplastic thyroid cancers (1%) (3). Usually, most of the NMTC are sporadic without family history. However, population studies have shown an elevated risk of NMTC in individuals with a first-degree relative having thyroid cancer (4, 5).

Familial NMTC (FNMTC), which has been recognized as a distinct clinical entity in the last decade (6, 7), is characterized by one or more first-degree relatives affected by NMTC in the absence of other known familial
syndromes such as Cowden disease (multiple hamartoma syndrome), familial adenomatous polyposis, or Carney complex (8). The reported prevalence of FNMTC varies from 2.5 to 11.3% of all NMTC patients (5, 9, 10, 11). Given the high prevalence of thyroid cancer in the general population, the occurrence of FNMTC may not be rare. However, unlike familial medullary thyroid disease, the biological characteristics of FNMTC are still poorly understood.

Whether the biological behaviors of FNTMC is different from that of sporadic NMTC (SNMTC) remains controversial. A number of researchers have found that FNMTC has more aggressive biological behaviors, characterized by a higher incidence of multifocality, extrathyroidal invasion, bilateral disease, and lymph node metastases, which lead to a higher recurrence rate and decreased disease-free survival (DFS) (11, 12, 13, 14, 15, 16, 17). Therefore, some of them recommended more aggressive initial treatment for patients with FNMTC, including total thyroidectomy (TT) and concomitant prophylactic central compartment node dissection (14, 17). However, certain other studies did not confirm the difference in biological behaviors between FNMTC and SNMTC (18, 19, 20, 21). In addition, results from several published reviews are conflicting, which have only listed major results of available studies and failed to draw conclusions based on quantitative statistical methods (9, 22, 23). Therefore, the exact biological characteristics and the optimal clinical approach for FNMTC are yet to be established (24, 25).

In this study, we conducted a systematic review and meta-analysis of the available literature to further understand the biological behaviors including prognosis of FNMTC. This study might provide a comprehensive and quantitative understanding on the aggressive characteristics of FNMTC and improve the management of individual patients.

Methods

Search strategy

All studies published before September 1, 2014 were identified by searching four databases (PubMed, EMBASE, the Cochrane library databases, and the Web of Science) using the following search terms: ‘nonmedullary thyroid cancer’ or ‘nonmedullary thyroid carcinoma’ or ‘papillary thyroid carcinoma’ or ‘papillary thyroid cancer’ combining with ‘familial’ or ‘genetic predisposition’. The language was limited to English. A manual search of thyroid conference abstracts and publication bibliographies was also performed. Furthermore, the references of the eligible articles and associative reviews were also screened to identify any additional relevant studies.

Study selection

Eligible studies must fulfill the following inclusion criteria: i) studies with case–control or cohort design; ii) comparing the biological behaviors of FNMTC with its sporadic counterpart; and iii) providing sufficient data to enable calculation of an interesting effect estimate and 95% CI. When the same or overlapping data were reported in multiple publications, we selected the most updated or complete report which had the largest sample size. Review articles, letters, case reports, editorials, or comments were excluded.

Data extraction and quality assessment

Two investigators (X Wang and W Cheng) independently evaluated the study eligibility and quality and extracted relevant data from each study using a pretested form. Any disagreement was resolved through discussion. The primary outcomes were recurrence rates and DFS. Recurrence was defined as locoregional or distant disease with detectable basal or stimulated serum thyroglobulin (Tg), and/or evidence of persistent/recurrent disease confirmed by clinical examination, neck ultrasound, diagnostic radioiodine (RAI) whole body scan, histopathologic findings and/or other imaging techniques, based on the American Thyroid Association’s definition of ‘cured or free of disease’: no clinical or imaging evidence of tumor and undetectable serum Tg levels during thyroid-stimulating hormone (TSH) suppression and stimulation without interfering antibodies (26). The term of recurrence includes the recurrent and persistent disease in the present analysis because of the difficulty in differentiating persistence from recurrence of thyroid cancer after initial treatment in a practical sense. The DFS was defined as the period from the date of initiation of therapy to the data of recurrence or metastasis. The secondary outcomes included the age at diagnosis, tumor diameter, multifocal, bilateral, extrathyroidal invasion, and lymph node metastasis.

To assess the quality of included studies, the Newcastle–Ottawa scale for cohort or case–control studies (27) was used, in which a study was judged on three broad perspectives: selection (four items), comparability (one item), and exposure/outcome (three items). A study can be awarded a maximum of one star for each numbered item.
within the selection and exposure/outcome categories. A maximum of two stars can be given for comparability. The full score was nine stars, and the study with awarded stars greater than or equal to seven was defined as a high-quality study.

**Statistical analysis**

The DFS was assessed using hazard ratios (HRs). For studies without HRs for survival, data were extracted following a methodology suggested by Parmar et al. (28). An HR > 1 implied impaired DFS for FNMTC patients, whereas an HR < 1 implied a survival benefit for FNMTC patients. The odds ratios (ORs) were evaluated for binary outcomes based on event rates. For continuous variables (namely age and tumor diameter), we calculated the standard mean differences (SMDs) between patients with FNMTC and SNMTC. Summary effect estimates and corresponding 95% CI were calculated by fixed or random effects meta-analysis based on the heterogeneity test. Heterogeneity among trials was tested by both $I^2$-test and Q-test (29). The $I^2$ more than 50% or Q-test reporting $P$ values $<0.1$ was considered to be heterogeneous. When trials were heterogeneous, random-effects model was used to calculate the pooled effect estimate, otherwise fixed-effects model was used. Sensitivity analyses were performed by excluding one or several studies that were suspicious of causing heterogeneity. We also conducted subgroup analyses stratified by key study characteristics and clinical factors to assess the effects of various confounding factors on our results. Publication bias was assessed by funnel plots, Begg’s rank correlation test, and Egger’s linear regression method (30, 31). A $P$ value $<0.05$ was considered to be statistically significant. All $P$ values were two-tailed. All calculations were performed using RevMan 5.3 (Cochrane Collaboration, Oxford, UK) and Stata 11.0 (Stata Corporation, College Station, TX, USA). This article follows the PRISMA statement (32) and the Cochrane Collaboration guidelines for reporting meta-analysis.

**Results**

**Literature search**

As shown in Fig. 1, the search strategy retrieved 1218 articles. Of these, 1165 studies were excluded after the first screening based on titles or abstracts. After further reviewing the full text of the remaining 53 articles, a total of 12 studies finally satisfied the eligibility criteria (11, 12, 13, 14, 15, 16, 18, 19, 20, 21, 33, 34).

![Figure 1](image-url) Flow chart of article selection in this meta-analysis.

**Study characteristics and quality assessment**

Characteristics of the 12 selected studies are given in Table 1. All were retrospective studies, including eight cohort studies (11, 13, 14, 15, 16, 18, 20, 34) and four case-control studies (12, 19, 21, 33), and all of them were hospital-based studies. The included studies were published between 2000 and 2014, and the number of patients ranged from 136 to 6015, for a total of 12 741 subjects across studies, including 1087 cases of FNMTC. Of the 12 included studies, five studies were conducted in Asia (11, 14, 15, 18, 21), four in North America (13, 16, 19, 20), two in Europe (33, 34), and the remaining one included patients from Japan and USA (12). FNMTC was defined as patients with two or more first-degree relatives with NMTC in eight studies, while it was defined as occurring when at least one first-degree relative was affected with NMTC in the other four studies (13, 14, 15, 18). Despite the variations in the diagnosis criteria of recurrence observed in the included studies, most of the authors defined recurrence based on a variable combination of results including clinical, radiographic, and nuclear medicine imaging studies; serum Tg level; and histopathologic findings (11, 12, 13, 15, 18, 19, 21, 34). However, there were three articles which did not provide the information about definition of recurrence (14, 16, 33). The Newcastle–Ottawa scale scores for included studies...
Table 1 Characteristics of studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>References</th>
<th>Country</th>
<th>Study design</th>
<th>Arms</th>
<th>No. of patients</th>
<th>Age (years, mean ± S.D.)</th>
<th>Female (%)</th>
<th>PTC (%)</th>
<th>Operation TT + NTT (%)</th>
<th>LND (%)</th>
<th>Postoperative radioiodine therapy (%)</th>
<th>Follow-up (years, mean ± S.D.)</th>
<th>Quality score (×)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uchino et al. (14) Japan Cohort study FNMTC</td>
<td>258</td>
<td>49.1 ± 13.9</td>
<td>88.0</td>
<td>87.6</td>
<td>62.0</td>
<td>72</td>
<td>NR</td>
<td>11.7 ± 10</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazeh et al. (13) USA Cohort study FNMTC</td>
<td>37</td>
<td>43 ± 3</td>
<td>78.4</td>
<td>100</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Park et al. (11) Korea Cohort study FNMTC</td>
<td>6200</td>
<td>48.5 ± 14.0</td>
<td>90.7</td>
<td>84.6</td>
<td>52.5a</td>
<td>66</td>
<td>NR</td>
<td>12.1 ± 10</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robenshtok et al. (21) Israel Case–control FNMTC</td>
<td>318</td>
<td>47 ± 12</td>
<td>85.8</td>
<td>96.2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6.2 ± 6.2</td>
<td>6</td>
<td></td>
<td></td>
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<tr>
<td>Moses et al. (20) USA Cohort study FNMTC</td>
<td>12</td>
<td>43</td>
<td>83.3</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6.2 ± 6.2</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ito et al. (18) Japan Cohort study FNMTC</td>
<td>5742</td>
<td>NR</td>
<td>NR</td>
<td>100</td>
<td>69</td>
<td>97</td>
<td>NR</td>
<td>7.6 ± 5b</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alsanea et al. (12) Japan + USA Case–control FNMTC</td>
<td>73</td>
<td>39.1</td>
<td>73</td>
<td>73</td>
<td>46</td>
<td>60.4</td>
<td>8c</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxwell et al. (19) Canada Case–control FNMTC</td>
<td>24</td>
<td>54.6 ± 15</td>
<td>79.2</td>
<td>70.8</td>
<td>91.7</td>
<td>71</td>
<td>NR</td>
<td>&gt; 2b</td>
<td>7c</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al. (15) Korea Cohort study FNMTC</td>
<td>113</td>
<td>45.3 ± 12.9</td>
<td>85.8</td>
<td>100</td>
<td>100</td>
<td>99</td>
<td>93.8</td>
<td>8b,c</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capezzone et al. (34) Italy + Greece Cohort study FNMTC</td>
<td>1149</td>
<td>45.2 ± 12.4</td>
<td>88.1</td>
<td>100</td>
<td>100</td>
<td>97</td>
<td>95.0</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McDonald et al. (16) Canada Cohort study FNMTC</td>
<td>235</td>
<td>47.5 ± 16.6</td>
<td>77.0</td>
<td>100</td>
<td>100</td>
<td>NR</td>
<td>4.2 ± 2.7</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pinto et al. (33) Portugal Case–control FNMTC</td>
<td>107</td>
<td>46.1</td>
<td>76.6</td>
<td>60.4</td>
<td>93.5</td>
<td>28</td>
<td>80.4</td>
<td>NR</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FNMTC, familial nonmedullary thyroid carcinoma; SNMTC, sporadic nonmedullary thyroid cancer; PTC, papillary thyroid cancer; TT, total thyroidectomy; NTT, near-TT; LND, lymph node dissection; NR, not reported or available.

a There was a significant difference compared with the FNMTC patients.

b The median of follow-up time.

c The minimum follow-up time.
ranged from six to nine stars, with a median seven stars (Table 1). The median score was eight stars for cohort studies and seven stars for case–control studies. All studies but one (12) were scored as high-quality studies (greater than or equal to seven stars).

Recurrence and DFS

Ten studies with a total of 18,158 patients with thyroid cancer (FNMTC, 1256 and SNMTC, 16,902) reported a comparative rate of recurrence. The overall rate of recurrence was 17.8% (range: 4.2–43.8%) for FNMTC and 10.3% (3.4–19.8%) for SNMTC. Figure 2 presents the pooled result, which shows that there is a significant increase in recurrence following FNMTC in comparison with SNMTC (OR = 1.72, 95% CI: 1.34–2.20, P < 0.0001). There was a moderate heterogeneity among the studies (χ² = 14.61, P = 0.10; I² = 38%), maybe resulting from variations in patient characteristics and treatment protocols among studies.

The data of DFS were extracted from six studies. The pooled HR of DFS was 1.83 (95% CI: 1.34–2.52) as shown in Fig. 3, which demonstrated a significantly lower DFS in patients with FNMTC compared with SNMTC. There was a significant heterogeneity among the studies (χ² = 26.30, P < 0.0001; I² = 81%). Sensitivity analysis excluding each study individually confirmed that heterogeneity is mainly related to the inclusion of one study (Ito et al. 18)). Excluding this study, the HR for DFS becomes 2.29 (95% CI: 1.88–2.79), and the heterogeneity drops from 81 to 41% (P = 0.15).

To further explore the potential heterogeneity and inquire into detailed results of recurrence and DFS in subpopulation, we performed stratified analyses according

![Figure 2](image1)

Meta-analysis of the pooled effect of recurrence in patients with FNMTC vs SNMTC.

![Figure 3](image2)

Meta-analysis of the pooled effect of disease-free survival (DFS) in patients with FNMTC vs SNMTC.
to several important confounding factors, including study design (cohort or case–control study), study country (Eastern or Western), mean age at diagnosis (being younger in FNMTC group or equivalent between groups), the rate of TT or near-TT (= 100 or < 100% or not reported), the lymph node dissection rate (reported or not reported), follow-up duration (≥ 5 or < 5 years), and using uniform definition of FNMTC, which is limited to the patients with at least one or two first-degree affected by NMTC (Table 2). All of the stratified analyses, which did not change the pooled orientations, were consistent with the overall results of increased recurrence risk and impaired DFS in FNMTC patients, although several subgroup analyses yielded similar unfavorable but insignificant results of FNMTC compared with SNMTC.

### Secondary outcomes

Table 3 summarises the pooled effect estimates of secondary outcomes. Nine studies with a total of 13 192 patients with thyroid cancer (SNMTC, 990 and SNMTC, 12 202) reported the age at diagnosis. The heterogeneity among the studies was particularly prominent for this outcome ($\chi^2 = 715.57$, $P < 0.00001$; $I^2 = 99\%$). The pooled SMD of age was $-0.91$ (95% CI: $-1.59$ to $-0.22$, $P = 0.01$) using a random effects model, which suggested that the age at diagnosis of patients with FNMTC was earlier than

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Subgroup</th>
<th>No. of studies</th>
<th>Effect estimate</th>
<th>Test for overall effect</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$P &lt; 0.01$</td>
<td>$P = 0.03$; $I^2 = 22%$</td>
</tr>
<tr>
<td>DFS</td>
<td>Cohort studies</td>
<td>4</td>
<td>1.04 (1.44–2.45)</td>
<td>$P = 0.03^a$</td>
<td>$P = 0.90$; $I^2 = 0%$</td>
</tr>
<tr>
<td>DFS</td>
<td>Case–control studies</td>
<td>2</td>
<td>1.95 (1.40–2.72)</td>
<td>$P &lt; 0.01$</td>
<td>$P = 0.01$; $I^2 = 78%$</td>
</tr>
<tr>
<td>DFS</td>
<td>Eastern countries</td>
<td>4</td>
<td>1.95 (1.40–2.72)</td>
<td>$P &lt; 0.01$</td>
<td>$P = 0.01$; $I^2 = 87%$</td>
</tr>
<tr>
<td>DFS</td>
<td>Western countries</td>
<td>2</td>
<td>1.04 (1.44–2.45)</td>
<td>$P = 0.93^a$</td>
<td>$P = 0.90$; $I^2 = 0%$</td>
</tr>
<tr>
<td>DFS</td>
<td>Age (younger in FNMTC group)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFS</td>
<td>Age (equivalent)</td>
<td>6</td>
<td>1.83 (1.34–2.52)</td>
<td>$P = 0.002$</td>
<td>$P &lt; 0.01$; $I^2 = 81%$</td>
</tr>
<tr>
<td>DFS</td>
<td>TT (≥ 100%)</td>
<td>1</td>
<td>1.66 (1.03–2.69)</td>
<td>$P = 0.04$</td>
<td>NA</td>
</tr>
<tr>
<td>DFS</td>
<td>TT + NTT (&lt; 100%)</td>
<td>4</td>
<td>1.55 (0.88–2.73)</td>
<td>$P = 0.13^a$</td>
<td>$P &lt; 0.01$; $I^2 = 84%$</td>
</tr>
<tr>
<td>DFS</td>
<td>TT + NTT (not report)</td>
<td>1</td>
<td>2.59 (2.21–3.04)</td>
<td>$P &lt; 0.01$</td>
<td>NA</td>
</tr>
<tr>
<td>DFS</td>
<td>Report LND rate</td>
<td>5</td>
<td>1.60 (1.03–2.47)</td>
<td>$P = 0.04$</td>
<td>$P &lt; 0.01$; $I^2 = 79%$</td>
</tr>
<tr>
<td>DFS</td>
<td>Not report LND rate</td>
<td>1</td>
<td>2.59 (2.21–3.04)</td>
<td>$P &lt; 0.01$</td>
<td>NA</td>
</tr>
<tr>
<td>DFS</td>
<td>Report postoperative RAI rate</td>
<td>2</td>
<td>1.49 (0.97–2.29)</td>
<td>$P = 0.07^a$</td>
<td>$P = 0.35$; $I^2 = 0%$</td>
</tr>
<tr>
<td>DFS</td>
<td>Not report RAI rate</td>
<td>4</td>
<td>2.00 (1.38–2.90)</td>
<td>$P = 0.0002$</td>
<td>$P &lt; 0.01$; $I^2 = 86%$</td>
</tr>
<tr>
<td>DFS</td>
<td>Follow-up (≥ 5 years)</td>
<td>4</td>
<td>1.53 (1.18–1.99)</td>
<td>$P &lt; 0.01$</td>
<td>$P = 0.18$; $I^2 = 39%$</td>
</tr>
<tr>
<td>DFS</td>
<td>Follow-up (&lt; 5 years)</td>
<td>1</td>
<td>1.21 (1.00–15.18)</td>
<td>$P = 0.88^a$</td>
<td>NA</td>
</tr>
<tr>
<td>DFS</td>
<td>Uniform definition of FNMTC</td>
<td>3</td>
<td>1.83 (0.88–3.78)</td>
<td>$P = 0.10^a$</td>
<td>$P = 0.12$; $I^2 = 53%$</td>
</tr>
<tr>
<td>DFS</td>
<td>Uniform definition of FNMTC</td>
<td>3</td>
<td>1.73 (1.06–2.83)</td>
<td>$P = 0.03$</td>
<td>$P &lt; 0.01$; $I^2 = 88%$</td>
</tr>
<tr>
<td>DFS</td>
<td>Overall</td>
<td>6</td>
<td>1.83 (1.34–2.52)</td>
<td>$P = 0.0002$</td>
<td>$P &lt; 0.01$; $I^2 = 81%$</td>
</tr>
</tbody>
</table>

TT, total thyroidectomy; NTT, near-TT; LND, lymph node dissection; RAI, radioiodine; FNMTC, familial nonmedullary thyroid carcinoma; NA, not applicable.

*aInconsistency with the overall results.

*aFNMTC was defined as patients with two or more first-degree relatives affected by NMTC.

*aFNMTC was defined as patients with at least one first-degree relative affected by NMTC.
Table 3  Meta-analysis for secondary outcomes.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of studies</th>
<th>Participants</th>
<th>Effect measure</th>
<th>Effect estimate</th>
<th>Test for overall effect</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>9</td>
<td>13,192</td>
<td>SMD</td>
<td>-0.91 (-1.59 to -0.22)</td>
<td><em>P</em>= 0.01</td>
<td><em>P</em> &lt; 0.01; <em>I</em>² = 99%</td>
</tr>
<tr>
<td>Tumor diameter</td>
<td>5</td>
<td>10,417</td>
<td>SMD</td>
<td>-0.03 (-0.21 to 0.15)</td>
<td><em>P</em>= 0.74</td>
<td><em>P</em> = 0.003; <em>I</em>² = 75%</td>
</tr>
<tr>
<td>Multifocal</td>
<td>9</td>
<td>12,770</td>
<td>OR</td>
<td>1.50 (1.32 to 1.71)</td>
<td><em>P</em> &lt; 0.01</td>
<td><em>P</em> = 0.26; <em>I</em>² = 20%</td>
</tr>
<tr>
<td>Bilateral</td>
<td>4</td>
<td>2,356</td>
<td>OR</td>
<td>1.29 (1.00 to 1.66)</td>
<td><em>P</em>= 0.048</td>
<td><em>P</em> = 0.52; <em>I</em>² = 0%</td>
</tr>
<tr>
<td>ET invasion</td>
<td>8</td>
<td>6,403</td>
<td>OR</td>
<td>1.20 (1.02 to 1.41)</td>
<td><em>P</em> &lt; 0.03</td>
<td><em>P</em> = 0.27; <em>I</em>² = 20%</td>
</tr>
<tr>
<td>LN metastasis</td>
<td>8</td>
<td>9,328</td>
<td>OR</td>
<td>1.18 (1.01 to 1.38)</td>
<td><em>P</em>= 0.04</td>
<td><em>P</em> = 0.48; <em>I</em>² = 0%</td>
</tr>
</tbody>
</table>

ET, extrathyroidal; LN, lymph node; SMD, standard mean difference; OR, odds ratio.

that of sporadic cases. Both of sensitivity and subgroup analysis cannot explain the source of heterogeneity.

We evaluated differences in the diameter of tumor, multifocal, bilateral, extrathyroidal invasion, and lymph node metastasis rates as potential causes of increased recurrence and impaired DFS. Patients with FNMTC had a higher risk of multifocal based on nine studies (OR = 1.50, 95% CI: 1.32 to 1.71, *P* < 0.00001), bilateral based on four studies (OR = 1.29, 95% CI: 1.00 to 1.66, *P* = 0.05), extrathyroidal invasion based on eight studies (OR = 1.20, 95% CI: 1.02 to 1.41, *P* = 0.03), and lymph node metastasis based on eight studies (OR = 1.18, 95% CI: 1.01 to 1.38, *P* = 0.04).

However, for tumor diameter, there was no difference based on five studies (SMD = -0.03, 95% CI: -0.21 to 0.15, *P* = 0.74), and significant heterogeneity was identified (χ² = 15.81, *P* = 0.003; *I*² = 75%). Sensitivity analysis as described above suggested this is due to the inclusion of a study by Park et al. (11). After excluding this study, the SMD for tumor diameter is -0.08 (95% CI: -0.19 to 0.02), and the heterogeneity drops from 75 to 0% (*P* = 0.74). There was no significant heterogeneity for any of the secondary outcomes except tumor diameter and age at diagnosis.

Publication bias

Only the meta-analysis of multifocality and extrathyroidal invasion showed potential publication bias with *P* values of 0.048 and 0.009 given by Begg’s test. There was no evidence of publication bias for other results, with a symmetrical appearance on funnel plot shape and *P* values ranging from 0.06 to 0.902 given by Begg’s test and *P* values ranging from 0.097 to 0.948 by Egger’s test.

Discussion

This study is, to the best of our knowledge, the first systematic review to quantitatively investigate the cumulative data on biological characteristics of FNMTC. A number of comparative studies have yielded conflicting results about the aggressive risks of FNMTC. This study examined this conflict using a systematic review and meta-analysis, which allows one to aggregate evidence and potentially minimize bias. The present analysis suggests that the patients with FNMTC have a higher risk of recurrence and a lower DFS in comparison with patients with SNMTC. In view of the fact that a great number of studies have confirmed several clinicopathologic characteristics, such as age, tumor size, multifocality, extrathyroidal invasion, bilateral disease, and lymph node metastases at presentation, which are particularly associated with recurrence and survival of thyroid cancer, we also investigated the difference of these relapse correlation factors besides the recurrence rate and then found FNMTC was more aggressive, characterized by younger age at diagnosis, a higher incidence of multifocality, extrathyroidal invasion, bilateral disease, and lymph node metastases at presentation.

Although thyroid cancer is a highly indolent tumor and has an excellent prognosis, recurrence following thyroidectomy develops in 15–30% patients with well-differentiated thyroid carcinoma (35), which may require additional intervention and affect patients’ quality of life, thus increasing the economic burden and social health care resources demand. Based on our meta-analysis, FNMTC possesses a higher risk for multifocality, extrathyroidal invasion, bilaterality, and lymph node involvement, which lead to an increased risk of recurrence. Therefore, the FNMTC patients should be benefit from undergoing TT with routine central lymph node dissection at initial operation.

It is suspected that FNMTC is associated with an earlier age at diagnosis. FNMTC patients were diagnosed approximately a decade earlier compared with SNMTC cases in some studies (12, 13). On the other hand, some researchers found that the age at diagnosis is similar in patients with FNMTC or SNMTC. In our meta-analysis, we found the
mean age at diagnosis was 2.4 years lower for FNMTC patients (SMD = −0.91, 95% CI: −1.59 to −0.22). However, a prudent attitude toward this result should be required, because the heterogeneity amongst the studies is particularly prominent for this outcome and both sensitivity and subgroup analysis can not explain the source of heterogeneity. This is not surprising due to the variations in the study design and study population across studies. The different proportion of second generation across studies may be also a significant source of heterogeneity. When comparing the first (parent) and second (offspring) generation in parent–offspring FNMTC, Capezzone et al. (34) found that the second generation was diagnosed at a mean of 29.3 years earlier. Similar results were observed in several (11, 17) but not all (21) studies. However, we could not further analyze the exact age difference between the first and second generation, because the data provided by individual study was limited. Further studies investigating this issue should be needed. In addition, there may be ascertainment bias because individuals with positive familiar history of NMTC may be investigated more aggressively for thyroid disease than the control populations, which lead to an early diagnosis in FNMTC patients. Nevertheless, based on the current available evidence, it may be rational that screening individuals with relatives affected by thyroid cancer commence at an earlier age. However, there is no strict age cutoff at which screening should begin; some authors (17, 22, 23) recommend that screening should commence at the age of 18–20 years, or 5–10 years earlier than the youngest age of diagnosis with the family, which remains to be further elucidated.

As given in Table 2, most of subgroup analyses did not show significant difference to the overall conclusion. Study design may have an impact on the overall conclusion. When restricting included case–control studies, we found that the patients with FNMTC had potential unfavorable recurrence rate and DFS compared with SNMTC patients, although this trend did not reach statistical significance, maybe owing to the small sample size. A parallel was observed in the subgroup analysis only included studies with reported data of postoperative RAI ablation. In addition, we did find unfavorable results in FNMTC patients compared with the control group in terms of the subgroup analysis included the studies without reported data of RAI ablation. It emphasized the effects of postoperative RAI ablation on prognosis. However, there is inadequate data to determine whether RAI therapy has more benefit for FNMTC, which needs to be confirmed in future research with well-designed cohort or intervention studies. Notably, the definition of FNMTC did not seem to markedly influence the results, but studies that met more strict definition criteria tended to report a slightly stronger association of impaired prognosis with FNMTC patients. When defining FNMTC as patients with two or more first-degree relatives affected by NMTC, the pooled OR for recurrence is 1.82, while that decreases to 1.20 when defining FNMTC as patients with one or more affected relatives. A similar tendency was observed in pooled results for DFS. Maybe it is due to the dilution of the familial cases with sporadic ones by using a less stringent definition of FNMTC. Charkes et al. (7) has estimated that 62–69% of patients with two affected relatives may suffer from the sporadic rather than the familial form of the disease, whereas the chance of a sporadic case in families of three or more affected members is <6%. It can be speculated that there will be a higher chance of sporadic in FNMTC patients with one affected relative, which will significantly underestimate the true difference. At present, a few molecular genetic analyses have identified several predisposing genes to FNMC (36, 37, 38); however, genetic testing is not available because the association between specific genes with FNMTC is still under dispute. The identification of FNMTC still relies on clinical data. Therefore, further study investigating the clinical and genetic research should choose the patients with three or more affected members to represent the familial form of the disease in order to reduce the potential selection bias as some authors have recommended (7).

There are some limitations in the current study. First, the potential confounding factors, such as extent of thyroidectomy and lymph node dissection, the indications of radioactive iodine ablation, and postoperative TSH suppression, were present because of the variations at different centers and regional; and quantitative weighing of these factors could not be performed due to data insufficiency. Second, the mean follow-up durations differed from 1.5 to 12.1 years and the definition of FNMTC was not unified in each trial. However, stratified analyses showed pooled ORs/HRs consistently >1 across a number of clinical factors. Third, the different definition for recurrence of each study should be a major limitation for this meta-analysis, although most of the authors defined recurrence based on the combination of radiographic and nuclear medicine imaging studies. Finally, although the Egger’s test did not detect significant publication bias for most analyses, potential publication bias might be present, because unpublished and non-English language published studies were not included in the meta-analysis.

In conclusion, the systematic review confirmed that FNMTC patients are more aggressive at presentation and possess higher recurrence rate and decreased DFS. This
suggestions that more attention and careful consideration should be paid on decision about treatment for patients with familial history of thyroid cancer.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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