ENDOCRINE TUMOURS

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

Xiaofei Wang^{1,2}, Wenli Cheng³, Jingdong Li², Anping Su¹, Tao Wei¹, Feng Liu¹ and Jingqiang Zhu¹

¹Department of Thyroid and Breast Surgery, West China Hospital, Sichuan University, Chendu 610041, China, Departments of ²General Surgery and ³Otolaryngology–Head and Neck Surgery, Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, China

Correspondence should be addressed to J Zhu
Email
westchinaz@sohu.com

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.

European Journal of
Endocrinology
(2015) 172, R253–R262

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

Review	X Wang and others	Familial nonmedullary thyroid carcinoma	172:6	R254
--------	-------------------	---	-------	------

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 FNMTc are 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 date 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

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 hisopathologic 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.

References	Country	Study design	Arms	No. of patients	Age (years, mean $\pm$ s.d.)	Female (%)	PTC (%)	Operation TT+NTT (%)	LND (%)	Postoperative radioiodine therapy (%)	Follow-up (years, mean $\pm$ s.d.)	Quality score (★)
Uchino <i>et al.</i> (14)	Japan	Cohort study	FNMTc SNMTc	258 6200	49.1 $\pm$ 13.9 48.5 $\pm$ 14.0	88.0 90.7	87.6 84.6	62.0 52.5 ^a	72 66	NR NR	11.7 $\pm$ 10 12.1 $\pm$ 10	9
Mazeh <i>et al.</i> (13)	USA	Cohort study	FNMTc SNMTc	37 321	43 $\pm$ 3 49 $\pm$ 1 ^a	78.4 71.3	100 89.4	100 100	NR NR	NR NR	NR NR	7
Park <i>et al.</i> (11)	Korea	Cohort study	FNMTc SNMTc	318 2733	47 $\pm$ 12 47 $\pm$ 11	85.8 82.5	96.2 94.8	NR NR	NR NR	NR NR	6.2 $\pm$ 6.6 6.2 $\pm$ 6.2	8
Robenshtok <i>et al.</i> (21)	Israel	Case-control	FNMTc SNMTc	67 375	42.8 $\pm$ 16.8 47.2 $\pm$ 16.1	89.6 80.0	88.8 91.0	86.2 89.1	22 15	80.6 88.0	8.6 $\pm$ 10 8.4 $\pm$ 9.1	7
Moses <i>et al.</i> (20)	USA	Cohort study	FNMTc SNMTc	12 124	43 48 ^a	83.3 73.4	100 92.7	NR NR	NR NR	NR NR	1.58 ^{b,c} 7.6 $\pm$ 5 ^b	7
Ito <i>et al.</i> (18)	Japan	Cohort study	FNMTc SNMTc	273 5742	NR NR	NR NR	100 100	69 50 ^a	97 94	NR NR	7.6 $\pm$ 5 ^b 8 ^c	8
Alsanea <i>et al.</i> (12)	Japan + USA	Case-control	FNMTc SNMTc	48 144	39 $\pm$ 11 46 $\pm$ 15 ^a	NR NR	NR NR	73 94 ^a	46 22 ^a	60.4 84.7 ^a	7 ^c > 2 ^{b,d}	6
Maxwell <i>et al.</i> (19)	Canada	Case-control	FNMTc SNMTc	24 519	54.6 $\pm$ 18.5 57.8 $\pm$ 16	79.2 80.7	70.8 63.0	91.7 87.1	71 30 ^a	NR NR	NR NR	7
Lee <i>et al.</i> (15)	Korea	Cohort study	FNMTc SNMTc	113 1149	45.3 $\pm$ 12.9 45.2 $\pm$ 12.4	85.8 88.1	100 100	100 100	99 97	93.8 95.0	8 ^{b,c}	9
Capezzone <i>et al.</i> (34)	Italy + Greece	Cohort study	FNMTc SNMTc	34 235	47.9 $\pm$ 18.2 47.5 $\pm$ 16.6	73.5 77.0	100 100	100 100	NR NR	NR NR	4.2 $\pm$ 2.7 4.7 $\pm$ 3.8	7
McDonald <i>et al.</i> (16)	Canada	Cohort study	FNMTc SNMTc	91 521	41.51 $\pm$ 1.9 44.3 $\pm$ 0.65	79.1 79.5	100 100	NR NR	NR NR	NR NR	5.1 $\pm$ 0.8 4.2 $\pm$ 0.2	8
Pinto <i>et al.</i> (33)	Portugal	Case-control	FNMTc SNMTc	107 107	46.1 46.2	76.6 76.6	66.4 66.3	93.5 94.4	28 36	80.4 74.8	NR NR	7

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.

^aThere was a significant difference compared with the FNMTc patients.

^bThe follow-up time for the entire study cohort.

^cThe median of follow-up time.

^dThe minimum follow-up time.

Figure 2

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

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 (FNMTTC, 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 FNMTTC 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 FNMTTC in comparison with SNMTC (OR=1.72, 95% CI: 1.34–2.20, $P < 0.0001$). There was a moderate

heterogeneity among the studies ($\chi^2 = 14.61$, $P = 0.10$; $I^2 = 38\%$), 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 FNMTTC compared with SNMTC. There was a significant heterogeneity among the studies ($\chi^2 = 26.30$, $P < 0.0001$; $I^2 = 81\%$). 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 detail results of recurrence and DFS in subpopulation, we performed stratified analyses according

Figure 3

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 in study), the lymph node dissection rate (reported or not reported), postoperative RAI therapy 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 2 Subgroup analyses for primary outcomes.

Outcomes	Subgroup	No. of studies	Effect estimate	Test for overall effect	Heterogeneity
Recurrence	Cohort studies	6	1.66 (1.29–2.14)	$P<0.01$	$P=0.17$; $I^2=35\%$
	Case-control studies	4	1.75 (0.86–3.56)	$P=0.12^a$	$P=0.08$; $I^2=55\%$
	Eastern countries	4	1.53 (1.18–1.99)	$P=0.001$	$P=0.18$; $I^2=39\%$
	Western countries	5	1.76 (1.15–2.70)	$P=0.009$	$P=0.39$; $I^2=3\%$
	Age (younger in FNMTc group)	2	3.20 (1.86–5.50)	$P<0.01$	$P=0.41$; $I^2=0\%$
	Age (equivalent)	7	1.71 (1.42–2.06)	$P<0.01$	$P=0.74$; $I^2=0\%$
	TT+NTT (= 100%)	2	2.81 (1.41–5.60)	$P=0.003$	$P=0.58$; $I^2=0\%$
	TT+NTT (<100%)	6	1.57 (1.03–2.39)	$P=0.03$	$P=0.04$; $I^2=58\%$
	TT+NTT (not report)	2	1.71 (1.33–2.18)	$P<0.01$	$P=0.93$; $I^2=0\%$
	Report LND rate	6	1.57 (1.03–2.39)	$P=0.03$	$P=0.04$; $I^2=58\%$
	Not report LND rate	4	1.80 (1.30–2.57)	$P<0.01$	$P=0.55$; $I^2=0\%$
	Report postoperative RAI rate	3	1.93 (0.89–4.18)	$P=0.10^a$	$P=0.06$; $I^2=65\%$
	Not report RAI rate	7	1.64 (1.29–2.09)	$P<0.01$	$P=0.22$; $I^2=28\%$
	Follow-up (≥ 5 years)	5	1.71 (1.22–2.38)	$P<0.01$	$P=0.03$; $I^2=62\%$
	Follow-up (<5 years)	3	1.97 (1.00–3.91)	$P=0.05$	$P=0.35$; $I^2=5\%$
	Uniform definition of FNMTc ^b	7	1.85 (1.34–2.56)	$P=0.0002$	$P=0.22$; $I^2=27\%$
	Uniform definition of FNMTc ^c	3	1.56 (0.96–2.54)	$P=0.07^a$	$P=0.06$; $I^2=65\%$
	Overall	10	1.72 (1.34–2.20)	$P<0.01$	$P=0.10$; $I^2=39\%$
DFS	Cohort studies	4	1.95 (1.40–2.72)	$P<0.01$	$P<0.01$; $I^2=78\%$
	Case-control studies	2	1.04 (0.44–2.45)	$P=0.93^a$	$P=0.90$; $I^2=0\%$
	Eastern countries	4	1.95 (1.40–2.72)	$P<0.01$	$P<0.01$; $I^2=87\%$
	Western countries	2	1.04 (0.44–2.45)	$P=0.93^a$	$P=0.90$; $I^2=0\%$
	Age (younger in FNMTc group)	0			
	Age (equivalent)	6	1.83 (1.34–2.52)	$P=0.0002$	$P<0.01$; $I^2=81\%$
	TT (= 100%)	1	1.66 (1.03–2.69)	$P=0.04$	NA
	TT+NTT (<100%)	4	1.55 (0.88–2.73)	$P=0.13^a$	$P<0.01$; $I^2=84\%$
	TT+NTT (not report)	1	2.59 (2.21–3.04)	$P<0.01$	NA
	Report LND rate	5	1.60 (1.03–2.47)	$P=0.04$	$P<0.01$; $I^2=79\%$
	Not report LND rate	1	2.59 (2.21–3.04)	$P<0.01$	NA
	Report postoperative RAI rate	2	1.49 (0.97–2.29)	$P=0.07^a$	$P=0.35$; $I^2=0\%$
	Not report RAI rate	4	2.00 (1.38–2.90)	$P=0.0002$	$P<0.01$; $I^2=86\%$
	Follow-up (≥ 5 years)	4	1.53 (1.18–1.99)	$P<0.01$	$P=0.18$; $I^2=39\%$
	Follow-up (<5 years)	1	1.21 (0.10–15.38)	$P=0.88^a$	NA
	Uniform definition of FNMTc ^b	3	1.83 (0.88–3.78)	$P=0.10^a$	$P=0.12$; $I^2=53\%$
	Uniform definition of FNMTc ^c	3	1.73 (1.06–2.83)	$P=0.03$	$P<0.01$; $I^2=88\%$
	Overall	6	1.83 (1.34–2.52)	$P=0.0002$	$P<0.01$; $I^2=81\%$

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.

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

^cFNMTc was defined as patients with at least one first-degree relative affected by NMTC.

Review	X Wang and others	Familial nonmedullary thyroid carcinoma	172:6	R259
--------	-------------------	---	-------	------

Table 3 Meta-analysis for secondary outcomes.

Outcomes	No. of studies	Participants	Effect measure	Effect estimate	Test for overall effect	Heterogeneity
Age	9	13 192	SMD	−0.91 (−1.59 to −0.22)	$P=0.01$	$P<0.01$; $I^2=99\%$
Tumor diameter	5	10 417	SMD	−0.03 (−0.21 to 0.15)	$P=0.74$	$P=0.003$; $I^2=75\%$
Multifocal	9	12 770	OR	1.50 (1.32 to 1.71)	$P<0.01$	$P=0.26$; $I^2=20\%$
Bilateral	4	2356	OR	1.29 (1.00 to 1.66)	$P=0.048$	$P=0.52$; $I^2=0\%$
ET invasion	8	6403	OR	1.20 (1.02 to 1.41)	$P<0.03$	$P=0.27$; $I^2=20\%$
LN metastasis	8	9328	OR	1.18 (1.01 to 1.38)	$P=0.04$	$P=0.48$; $I^2=0\%$

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 ($\chi^2=15.81$, $P=0.003$; $I^2=75\%$). 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 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

Review	X Wang and others	Familial nonmedullary thyroid carcinoma	172:6	R260
--------	-------------------	---	-------	------

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 FNMTC (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

suggests 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.

Funding

This review did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

- Davies L & Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. *Journal of the American Medical Association* 2006 **295** 2164–2167. (doi:10.1001/jama.295.18.2164)
- Udelsman R & Zhang Y. The epidemic of thyroid cancer in the United States: the role of endocrinologists and ultrasounds. *Thyroid* 2014 **24** 472–479. (doi:10.1089/thy.2013.0257)
- Alsanea O & Clark OH. Familial thyroid cancer. *Current Opinion in Oncology* 2001 **13** 44–51. (doi:10.1097/00001622-200101000-00009)
- Goldgar DE, Easton DF, Cannon-Albright LA & Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *Journal of the National Cancer Institute* 1994 **86** 1600–1608. (doi:10.1093/jnci/86.21.1600)
- Pal T, Vogl FD, Chappuis PO, Tsang R, Brierley J, Renard H, Sanders K, Kantemiroff T, Bagha S, Goldgar DE *et al.* Increased risk for nonmedullary thyroid cancer in the first degree relatives of prevalent cases of nonmedullary thyroid cancer: a hospital-based study. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 5307–5312. (doi:10.1210/jcem.86.11.8010)
- Musholt TJ, Musholt PB, Petrich T, Oetting G, Knapp WH & Klempnauer J. Familial papillary thyroid carcinoma: genetics, criteria for diagnosis, clinical features, and surgical treatment. *World Journal of Surgery* 2000 **24** 1409–1417. (doi:10.1007/s002680010233)
- Charkes ND. On the prevalence of familial nonmedullary thyroid cancer in multiply affected kindreds. *Thyroid* 2006 **16** 181–186. (doi:10.1089/thy.2006.16.181)
- Sturgeon C & Clark OH. Familial nonmedullary thyroid cancer. *Thyroid* 2005 **15** 588–593. (doi:10.1089/thy.2005.15.588)
- Loh KC. Familial nonmedullary thyroid carcinoma: a meta-review of case series. *Thyroid* 1997 **7** 107–113. (doi:10.1089/thy.1997.7.107)
- Hemminki K, Eng C & Chen B. Familial risks for nonmedullary thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 5747–5753. (doi:10.1210/jc.2005-0935)
- Park YJ, Ahn HY, Choi HS, Kim KW, Park do J & Cho BY. The long-term outcomes of the second generation of familial nonmedullary thyroid carcinoma are more aggressive than sporadic cases. *Thyroid* 2012 **22** 356–362. (doi:10.1089/thy.2011.0163)
- Alsanea O, Wada N, Ain K, Wong M, Taylor K, Ituarte PH, Treseler PA, Weier HU, Freimer N, Siperstein AE *et al.* Is familial non-medullary thyroid carcinoma more aggressive than sporadic thyroid cancer? A multicenter series. *Surgery* 2000 **128** 1043–1050 (discussion 1050–1051). (doi:10.1067/msy.2000.110848)
- Mazeh H, Benavidez J, Poehls JL, Youngwirth L, Chen H & Sippel RS. 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* 2012 **22** 3–8. (doi:10.1089/thy.2011.0192)
- Uchino S, Noguchi S, Kawamoto H, Yamashita H, Watanabe S, Yamashita H & Shuto S. Familial nonmedullary thyroid carcinoma characterized by multifocality and a high recurrence rate in a large study population. *World Journal of Surgery* 2002 **26** 897–902. (doi:10.1007/s00268-002-6615-y)
- Lee YM, Yoon JH, Yi O, Sung TY, Chung KW, Kim WB & Hong SJ. Familial history of non-medullary thyroid cancer is an independent prognostic factor for tumor recurrence in younger patients with conventional papillary thyroid carcinoma. *Journal of Surgical Oncology* 2014 **109** 168–173. (doi:10.1002/jso.23447)
- McDonald TJ, Driedger AA, Garcia BM, Van Uum SH, Rachinsky I, Chevendra V, Breadner D, Feinn R, Walsh SJ & Malchoff CD. Familial papillary thyroid carcinoma: a retrospective analysis. *Journal of Oncology* 2011 **2011** 948786. (doi:10.1155/2011/948786)
- Hillenbrand A, Varhaug JE, Brauckhoff M, Pandev R, Haufe S, Dotzenrath C, Koberle R, Hoffmann R, Klein G, Kadmon M *et al.* Familial nonmedullary thyroid carcinoma—clinical relevance and prognosis. A European multicenter study. ESES Vienna presentation. *Langenbeck's Archives of Surgery* 2010 **395** 851–858. (doi:10.1007/s00423-010-0696-0)
- Ito Y, Kakudo K, Hirokawa M, Fukushima M, Yabuta T, Tomoda C, Inoue H, Kihara M, Higashiyama T, Uruno T *et al.* Biological behavior and prognosis of familial papillary thyroid carcinoma. *Surgery* 2009 **145** 100–105. (doi:10.1016/j.surg.2008.08.004)
- Maxwell EL, Hall FT & Freeman JL. Familial non-medullary thyroid cancer: a matched-case control study. *Laryngoscope* 2004 **114** 2182–2186. (doi:10.1097/01.mlg.0000149454.91005.65)
- Moses W, Weng J & Kebebew E. Prevalence, clinicopathologic features, and somatic genetic mutation profile in familial versus sporadic nonmedullary thyroid cancer. *Thyroid* 2011 **21** 367–371. (doi:10.1089/thy.2010.0256)
- Robenshtok E, Tzvetov G, Grozinsky-Glasberg S, Shraga-Slutsky I, Weinstein R, Lazar L, Serov S, Singer J, Hirsch D, Shimon I *et al.* Clinical characteristics and outcome of familial nonmedullary thyroid cancer: a retrospective controlled study. *Thyroid* 2011 **21** 43–48. (doi:10.1089/thy.2009.0406)
- Mazeh H & Sippel RS. Familial nonmedullary thyroid carcinoma. *Thyroid* 2013 **23** 1049–1056. (doi:10.1089/thy.2013.0079)
- Sippel RS, Caron NR & Clark OH. An evidence-based approach to familial nonmedullary thyroid cancer: screening, clinical management, and follow-up. *World Journal of Surgery* 2007 **31** 924–933. (doi:10.1007/s00268-006-0847-1)
- Mazeh H & Sippel RS. Aggressiveness in familial nonmedullary thyroid carcinoma – the controversy continues. *Thyroid* 2014 **24** 783–784. (doi:10.1089/thy.2014.0076)
- Benbassat C. Evidence is not sufficient to recommend a more aggressive approach to familial nonmedullary thyroid cancer. *Thyroid* 2014 **24** 781–782. (doi:10.1089/thy.2013.0592)
- American Thyroid Association (ATA) 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 *et al.* Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009 **19** 1167–1214. (doi:10.1089/thy.2009.0110)
- Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle–Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [webpage on the Internet] Ottawa, ON: Ottawa Hospital Research Institute; 2011. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
- Parmar MK, Torri V & Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival end-points. *Statistics in Medicine* 1998 **17** 2815–2834. (doi:10.1002/(SICI)1097-0258(19981230)17:24<2815::AID-SIM110>3.0.CO;2-8)

Review	X Wang and others	Familial nonmedullary thyroid carcinoma	172:6	R262
--------	-------------------	---	-------	------

- 29 Higgins JP & Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002 **21** 1539–1558. (doi:10.1002/sim.1186)
- 30 Begg CB & Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994 **50** 1088–1101. (doi:10.2307/2533446)
- 31 Egger M, Davey Smith G, Schneider M & Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997 **315** 629–634. (doi:10.1136/bmj.315.7109.629)
- 32 Moher D, Liberati A, Tetzlaff J, Altman DG & Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009 **339** b2535. (doi:10.1136/bmj.b2535)
- 33 Pinto AE, Silva GL, Henrique R, Menezes FD, Teixeira MR, Leite V & Cavaco BM. Familial vs sporadic papillary thyroid carcinoma: a matched-case comparative study showing similar clinical/prognostic behaviour. *European Journal of Endocrinology* 2014 **170** 321–327. (doi:10.1530/EJE-13-0865)
- 34 Capezzone M, Marchisotta S, Cantara S, Busonero G, Brilli L, Pazaitou-Panayiotou K, Carli AF, Caruso G, Toti P, Capitani S *et al*. Familial non-medullary thyroid carcinoma displays the features of clinical anticipation suggestive of a distinct biological entity. *Endocrine-Related Cancer* 2008 **15** 1075–1081. (doi:10.1677/ERC-08-0080)
- 35 Magarey MJ & Freeman JL. Recurrent well-differentiated thyroid carcinoma. *Oral Oncology* 2013 **49** 689–694. (doi:10.1016/j.oraloncology.2013.03.434)
- 36 Bevan S, Pal T, Greenberg CR, Green H, Wixey J, Bignell G, Narod SA, Foulkes WD, Stratton MR & Houlston RS. A comprehensive analysis of MNG1, TCO1, fPTC, PTEN, TSHR, and TRKA in familial nonmedullary thyroid cancer: confirmation of linkage to TCO1. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 3701–3704. (doi:10.1210/jcem.86.8.7725)
- 37 Cantara S, Pisu M, Frau DV, Caria P, Dettori T, Capezzone M, Capuano S, Vanni R & Pacini F. Telomere abnormalities and chromosome fragility in patients affected by familial papillary thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E1327–E1331. (doi:10.1210/jc.2011-2096)
- 38 Cavaco BM, Batista PF, Sobrinho LG & Leite V. Mapping a new familial thyroid epithelial neoplasia susceptibility locus to chromosome 8p23.1-p22 by high-density single-nucleotide polymorphism genome-wide linkage analysis. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 4426–4430. (doi:10.1210/jc.2008-0449)

Received 6 November 2014

Revised version received 27 December 2014

Accepted 30 January 2015