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The association of preoperative thyroid-stimulating hormone level and the risk of differentiated thyroid cancer in patients with thyroid nodules: A systematic review and meta-analysis

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ABSTRACT

Background: This systematic review and meta-analysis was conducted to determine the value of preoperative thyroid-stimulating hormone (TSH) levels in assessing the risk of differentiated thyroid cancer (DTC) in patients with thyroid nodules.
Methods: This meta-analysis included 23,799 subjects (15,406 non-Chinese and 8,393 Chinese) with thyroid nodules. Multivariate and individual adjusted odds ratios (OR) were calculated for a 1 mU/L increase in preoperative TSH levels to determine the risk of malignant DTC.
Results: The OR for DTC in relation to preoperative TSH levels was significant in Chinese (1.25 [1.11, 1.40], Z = 3.67, p = 0.0002) and non-Chinese subjects (1.12 [1.03, 1.22], Z = 2.72, p = 0.006). The overall random-effects model indicated that there was a significantly increased risk for DTC in patients with thyroid nodules (OR 1.16 [1.06, 1.27], Z = 3.29, p = 0.007).
Conclusions: A significant association between higher TSH levels and risk of DTC was observed in both population groups investigated, with higher ORs for Chinese subjects.

Introduction

Thyroid cancer is one of the most prevalent cancers of the endocrine system; in China, it accounts for approximately 1% of all neoplasms, with an annual incidence of up to 20 per 100,000 people.[1–3] Marked geographic variation exists in the distribution of thyroid cancer, and the incidence is considerably greater in higher-income than middle- or lower-income regions.[4–6] Globally, the incidence of thyroid cancer is increasing in both sexes, and these increases are primarily due to an increased incidence of small, indolent papillary thyroid carcinomas (PTC); however, these increases may also be due to advances in screening technology.[7,8] In China, there is an upward trend in the incidence rates of thyroid cancer in females, which is in part attributed to changes in the Chinese lifestyle that is becoming more Westernized.[9] In line with the increased number of thyroid cancer cases being diagnosed, the overall disease burden is expected to increase substantially in the coming years.[10]

Thyroid cancer typically presents as a nodular goiter, with approximately 3.0% of multinodular goiters and 4.5% of solitary nodules being diagnosed as malignant.[11–13] Given the higher prevalence of solitary nodules, early identification of nodules that represent thyroid cancer is important for improved prognosis. Thyrotropin (thyroid-stimulating hormone; TSH) is an acknowledged thyrocyte growth factor; however, the relationship between TSH levels and differentiated thyroid cancer (DTC) is controversial.[14] Several studies have documented a link between high preoperative TSH levels and an increased risk of thyroid cancer in patients with nodular thyroid disease.[15,16] Furthermore, a recent meta-analysis suggested that a higher serum TSH level was associated with an increased risk of PTC.[17] Therefore, a confirmatory meta-analysis of the association of preoperative TSH level and the risk of DTC in patients with thyroid nodules is necessary for several

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reasons: first, data about thyroid cancer risk factors and strategies for early diagnosis are still insufficient[18–20]; second, serum TSH is the first laboratory test and is still frequently investigated in patients presenting with thyroid nodules[21,22]; third, several important studies have shown that TSH is associated with thyroid cancer[23,24]; and finally, the increased cancer risk in patients with TSH levels within the normal and above-normal reference range remains unexplained.

It is hoped that preoperative TSH screening might help identify a class of patients at an increased risk for thyroid cancer, which could have significant medical and socioeconomic implications. Therefore, the purpose of the current systematic review and meta-analysis was to assess the value of preoperative TSH levels in assessing the risk of DTC in patients with thyroid nodules undergoing fine needle aspiration (FNA) biopsy. The results of this systematic review and meta-analysis can then be incorporated into the rationale and algorithms for diagnosis of DTC and the differential diagnosis of thyroid nodules. Subsequently, our data may assist in improving patient prognosis and may have implications for the cost-effectiveness of DTC diagnosis.

Materials and methods

This was a systematic review and meta-analysis; all aspects of the systematic review process were conducted according to methods described in the Cochrane Handbook for Systematic Reviews of Interventions.[25] The systematic review was registered in PROSPERO, an international prospective register for systematic reviews. The methodology and results were reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews (see *Supplementary Material*).

Search strategy

A comprehensive literature search of the electronic PubMed (MEDLINE), Embase, Web of Science databases, the Cochrane Central Register of Controlled Trials (CENTRAL), and selected Chinese databases (Wangfang and CKNI) was conducted to find relevant studies that reported estimates about TSH levels (and effect sizes; i.e., odds ratio [OR] and relative risk [RR]). No language restriction was used. To expand the search, references of retrieved studies, and references from reviews and meta-analyses, were also screened for additional studies. Medical subject headings (MeSH) and other clinically relevant phrases included: thyroid gland (thyroid neoplasms — thyroid cancer, papillary; follicular thyroid cancer [non-MeSH term]); thyrotropin (preoperative TSH [non-MeSH term]); and thyroid nodules.

Two separate investigators independently selected studies based on the predefined inclusion criteria. First, titles and abstracts of studies retrieved through searches were screened to exclude obviously irrelevant references. Next, full-text publications of potentially relevant studies were obtained and checked against the inclusion criteria. Any disagreement between the investigators was resolved through consensus or by discussion with a third investigator. There was no specific date range or limit. PubMed was searched as the primary database and all available studies from 1975 to March 2019 were included.

Study selection

Studies included in this meta-analysis had to have enrolled adult patients aged $\geq$18 years and had to have the following patient criteria to determine which studies would be extracted before inclusion in the analysis: patients' preoperative TSH levels were measured; patients had thyroid nodules; patients were undergoing FNA biopsy/cytology and operation/surgery, if needed; and patients had DTC (papillary and follicular subtypes were both included; these were analyzed both separately and together). Studies involving patients with any of the following conditions were excluded: diffuse toxic goiter; pure cystic nodules; autonomously hyper-functioning thyroid nodules; any previous thyroid surgery; anaplastic thyroid cancer; or pregnancy.

The following criteria were used to determine which studies would be extracted for inclusion in the meta-analysis: clinical studies (controlled and uncontrolled); cohort, observational and epidemiologic studies (retrospective and prospective); studies where serum TSH level was studied as the prognostic variable (defined as studies with a minimum follow-up from preoperative TSH in order to consider DTC as a binary classification [present/absent] rather than as a time-to-event with censoring); studies reporting OR estimates for DTC for every 1 mU/L increase in serum TSH (studies not meeting this criterion were still included in the systematic review as part of the evidence, but were not suitable for meta-analysis; results of these studies were presented narratively); and studies reporting the standard error (SE) of log odds or confidence intervals (CIs), from which the risk estimate for DTC could be calculated.

The following study types were excluded: reviews; case reports; case series; case–control studies; and meta-analyses. If multiple studies included the same (or overlapping) subjects, the most informative study was chosen for further primary analysis. All ambiguities and discrepancies were resolved by consensus.

Data extraction

Studies meeting the criteria for inclusion in the meta-analysis were analyzed and relevant information from these included studies was presented in the form of tables. Data extraction was performed by two investigators, working independently, and stored in an Excel database accessible to the principal researchers. Again, any disagreement between the investigators was resolved through consensus or by discussion with a third investigator.

The following data were extracted from each of the included studies: basic study information (title, authors, journal, year, digital object identifier); and requested information (study type/design, randomization [yes/no], method of randomization, blinding [single/double/triple/none], method of blinding, duration of study/follow up, total number of subjects, information about subgroups [data stratified by sex, Chinese/non-Chinese, and age], measured variables, endpoints, and main results/effect sizes [OR, RR, SE, and factors/covariates adjusted for in the analysis]).

Risk of bias in individual studies and across studies (and meta-bias)

The potential risk of bias was assessed for each study based on data presented in the published text. The studies were scored and bias graded according to 'leave1out' for cohort/observational studies (R software; R Development Core Team, 2015) and Review Manager (RevMan [Computer program] Version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Publication bias was assessed across studies using Egger's test, a funnel plot analysis, and 'leave1out' cross-validation, as described below.

Statistical methods

Initially, 12 studies were selected for the pooled meta-analysis, which analyzed the risk of DTC in patients with thyroid nodules, and an additional four studies were included in the non-pooled analysis. During the meta-analysis process, three of the initial 12

Table 1
Characteristics of the ten studies included in the meta-analysis.

Lead author	Study type/ design	Duration of study/follow up	Total number of subjects	Measured variables	Primary outcomes and endpoints	Secondary and other outcomes and endpoints	Odds ratio (OR)	Factors/covariates adjusted for in the analysis			Conclusion	Clinical significance
Baser et al. 2016[38]	Retrospective cohort	ND	1,433	Preoperative cytology, nodule size, anti-TgAb, anti-TPOAb, FT3, FT4, Bethesda categories	ND	ND	1.301 (1.101, 1.537), $p = 0.002$ — multivariate logistic regression 1.372 (1.212, 1.554), $p < 0.001$ — univariate logistic regression	Nodule size (multivariate)	Presence of HT (multivariate)	ND	Gender differences between malignant and non-malignant were not significant. Patients with malignant final histopathology had significantly higher TSH levels compared with patients with benign final histopathology ($p < 0.001$). Moreover, TSH levels increased from Bethesda categories II to VI.	Besides cytology, higher TSH levels can be used as a supplementary marker in prediction of malignancy in certain Bethesda categories.
Choi et al. 2015[39]	Retrospective	ND	1,200	FNA, serum TSH, ultrasound features	TSH and malignancy	Nodule size, age	Univariate TSH level crude OR 1.256 (1.16, 1.415). 1.116 (0.947, 1.316) —adjusted	Variables adjusted for nodule size	Age	Sex	Serum TSH did not show a positive association with malignancy for all nodules and the micronodule subgroup in multivariate analysis, although they showed significant association with thyroid malignancy for the macronodule subgroup.	TSH alone is not as useful as ultrasound features in deciding whether or not to perform FNA in patients with micronodules.
Fiore et al. 2011[40]	Cross-sectional study	ND	13,738	TSH, FT3, FT4, TgAb, TPOAb, ultrasound, FNAB.	Frequency of PTC, TSH and thyroid antibodies	Frequency of PTC to TSH in L-T4 treated patients	1.111 (1.048, 1.177) per mU/L	Serum levels of TgAb and TPOAb	ND	ND	The frequency of PTC is significantly higher in nodular HT than in NG and is associated with increased levels of TSH.	Treatment with L-thyroxine, L-T4, reduces TSH and decreases the occurrence of clinically detectable PTC.
Hwang et al. 2016[41]	Retrospective	ND	1,254	Clinical and ultrasound characteristics. FNAB	Family history and malignancy on thyroid nodules	TSH and malignancy	1.415 (1.029, 1.947); $p = 0.033$, TSH grade 2.5–4.99. Serum TSH aOR 1.171 (1.033, 1.327) $p = 0.013$	Age <20 or >60 years	Family history	Solitary lesion	Although multicollinearity existed between US assessment and patient age, first-degree family history of thyroid cancer, and serum TSH values, high-normal serum TSH levels (2.5–4.99 micro IU/mL) did not independently significantly increase the risk of thyroid cancer	Rate of malignancy was higher in males than females
Kim et al. 2011[42]	Prospective cohort	ND	1,329	TSH, FT4, histology post-resection	Presence or absence of malignancy, TSH levels	Male and female ratios, age, tumor size	1.10 (0.99, 1.22) PTC or 0.71 (0.51, 0.99) FTC	HT	ND	ND	No difference in TSH levels was seen in patients with benign disease or PTC. Men and the presence of HT increased the risk of PTC	Clinicians who deal with TNs should pay attention to HT because it is a stronger predictor for PTC than other risk factors.
Lee et al. 2012[43]	Retrospective cohort	ND	164	Tg, TgAb, FT4 and TSH, ultrasound, FNAB	Clinical parameters and malignancy	ND	0.804 (0.410, 1.575) not significant	ND	ND	ND	TSH levels did not differ between benign or malignant groups	Tg levels may be a useful marker for differentiating thyroid cancer from benign thyroid nodules in the cytological diagnosis of indeterminate nodules.
Yazici et al. 2016[44]	Prospective cohort	ND	202	Tg, TSH, FNAB, FT3, FT4, TgAb, TPOAb	Tg, TSH ratios in cancer diagnosis	Histological diagnoses	1.096 (0.770, 1.561)	Gender	Age	ND	Preoperative TSH and Tg levels do not appear to be helpful in identifying patients	

											with thyroid cancer. After multivariate analysis with adjustment for sex and age, this was no longer statistically significant. However, a higher TSH:Tg ratio may hint at an increased thyroid cancer risk.	
Luo et al. 2018[35]	Retrospective analysis	NA	646	TSH, TgAB, TPOAb	NA	NA	Elevated TSH level is an independent risk factor of thyroid cancer: (OR = 2.942, p = 0.031)	Multivariate logistic regression analysis revealed that the development of malignant thyroid nodules was associated with young age, obesity, high dietary iodine intake, and irregular nodule morphology as revealed by ultrasound, abundant blood flow in nodules, longitudinal and transverse diameter ratio of 1 and greater edge angle, calcification and elevated TSH and TPOAb titer levels ($p < 0.05$).			Young age (30–49 years), obesity, high dietary iodine intake, irregular nodule morphology as revealed by ultrasound, abundant blood flow in nodules, longitudinal and transverse diameter ratio of 1 and greater edge angle, calcification, and elevated TSH and TPOAb titer levels are risk factors of malignant thyroid nodules. Notably, abundant blood flow in nodules and calcification are more likely to occur in thyroid cancer with neck lymph node metastasis.	Clinicians should combine multiple indicators to assess whether thyroid nodules are benign or malignant.
Qin et al. 2015[36]	Retrospective cohort	ND	1,638	TSH, TgAb, TPOAb, nodule size and number, tumor stage	Presence of ATAs and DTC	Age, gender, nodule type, TSH as independent risk predictors for PTC	1.24 (1.12, 1.37) $p \leq 0.001$	Age	Gender	Nodule size, TPOAb, TgAb	Elevated TgAb was associated with DTC. Patients with DTC were relatively younger and had higher preoperative TSH levels than those with benign nodules.	High serum TgAb levels may serve as a predictive marker for DTC independent of TSH levels.
Zhang et al. 2012[37]	Retrospective cohort	3–6 m	6,109	Age, gender, nodule size, TSH,	Clinicopathological factors in patients with or without HT	Coexistence of HT with PTC or benign nodules	Risk of PTC, TSH constant 1.303 (1.254 −1.355) p = 0.001, adjusted 1.361 (1.304 −1.421). Risk of metastatic PTC; TSH constant 1.303 (1.254 −1.355) p = 0.001. Adjusted 1.008 (0.962–1.057) p = 0.727	Gender	Age	Nodule size	PTC and HT have a close relationship in this region of highly prevalent HT. Long term HT may lead to elevated TSH which is the real risk of PTC.	More research should be done on raised TSH causing PTC in HT, which could provide more evidence for the correlation of HT and PTC

aOR, adjusted odds ratio; ATA, antithyroid antibody; DTC, differentiated thyroid carcinoma; FNA, fine needle aspiration; FNAB, fine needle aspiration biopsy; FT3, free tri-iodothyronine; FT4, free thyroxine; FTC, follicular thyroid carcinoma; HT, Hashimoto's thyroiditis; L-T4, levothyroxine; ND, no data; NG, nodular goiter; PTC, papillary thyroid carcinoma; Tg, thyroglobulin; TgAb, thyroglobulin antibody; TN, thyroid nodule; TPOAb, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone.

studies were shown to be biased and were excluded; therefore, one additional study was included to meet the Cochrane criteria of 10 studies per meta-analysis.[25] Individual adjusted ORs and their 95% CIs were retrieved for the studies and were used to calculate the log [OR] and SE necessary for the meta-analysis.

The meta-analysis was conducted by the Generic Invariance method (DerSimonian and Laird, 1986)[26] in relation to a 1 mU adjusted TSH increase, with two subgroups: Chinese and non-Chinese. Meta-analysis parameters were calculated for: number of patients included in the study, study weight, random effects ORs (95% CI) — DerSimonian and Laird,[26] DTC type and covariates, between-study heterogeneity, degrees of freedom, tau^2, chi^2, z-value, and p values. The risk of bias was assessed by three methods: funnel plot, Egger's test, and 'leave1out' analysis. The funnel plot was used to assess publication bias with numerical representation in Egger's test,[27] while 'leave1out cross-validation' analysis[28,29] was used to exclude the possibility of a type 1 error in the meta-analysis and to cross-validate the results by excluding one study at a time and testing for significance of the model.

In addition, four studies for non-pooled addition to the meta-analysis and with reference range ORs (15 in total) were tabulated with each TSH range OR included. TSH ranges used were those described in the corresponding four studies. Values were calculated relative to the group with the lowest TSH: level 1 < 0.35 mU/L[30] and <0.40 mU/L.[31–33]

IBM Statistical Package for the Social Sciences (IBM SPSS; IBM Corp., released 2012. IBM SPSS Statistics for Windows, version 21.0; Armonk, NY, USA) and Medcalc 17.0 (MedCalc Software, Ostend, Belgium) were used to assess summary results. RGUI 3.6,[34] metafor package,[29] and RStudio IDE (RStudio: Integrated Development for R; RStudio, Inc., Boston, MA, USA) were used to make algebra calculations of log[OR], SE conversion from CIs, and to conduct Egger's test. The meta-analysis plot and the funnel plot were created using RevMan 5.3, and meta-analysis was conducted according to the Cochrane handbook and PRISMA (see Supporting information).

Results

The overall study characteristics of the ten studies included in the meta-analysis are listed in Table 1. Most studies (n = 7) were retrospective meta-analyses, two were prospective analyses, and one was a cross-sectional study. Three studies were conducted in Chinese patients.[35–37] Meta-analysis of 23,799 subjects (15,406 non-Chinese and 8,393 Chinese) with thyroid nodules showed that there was a significant pooled OR in both the non-Chinese and Chinese population regarding the risk of DTC in relation to a 1 mU/L increase in preoperative TSH level (Fig. 1). All included studies contained multivariate and adjusted ORs for a 1 mU/L increase in relation to malignant DTC over the benign type. The OR for DTC in relation to TSH was significant in both population groups and was higher in Chinese (1.25 [1.11, 1.40], Z = 3.67, p = 0.0002) than non-Chinese (1.12 [1.03, 1.22], Z = 2.72, p = 0.006). The overall random effects model showed that there was a significant risk increase for DTC in patients with thyroid nodules (OR 1.16 [1.06, 1.27], Z = 3.29, p = 0.007). Heterogeneity was 41% in non-Chinese studies, 80% in Chinese studies, and 81% overall. Notably, studies adjusted for Hashimoto's thyroiditis[37,38] showed a very strong weight (15.8% and 10.5%), and a higher PTC OR (1.30 [1.10, 1.54] and 1.36 [1.30, 1.42]) with smaller CIs, which indicates high accuracy. This indicates potential implications for including Hashimoto's thyroiditis in assessment of these results.

Risk of bias assessment

The funnel plot (Fig. 2) showed that there was no significant publication bias, although there was some degree of asymmetry in

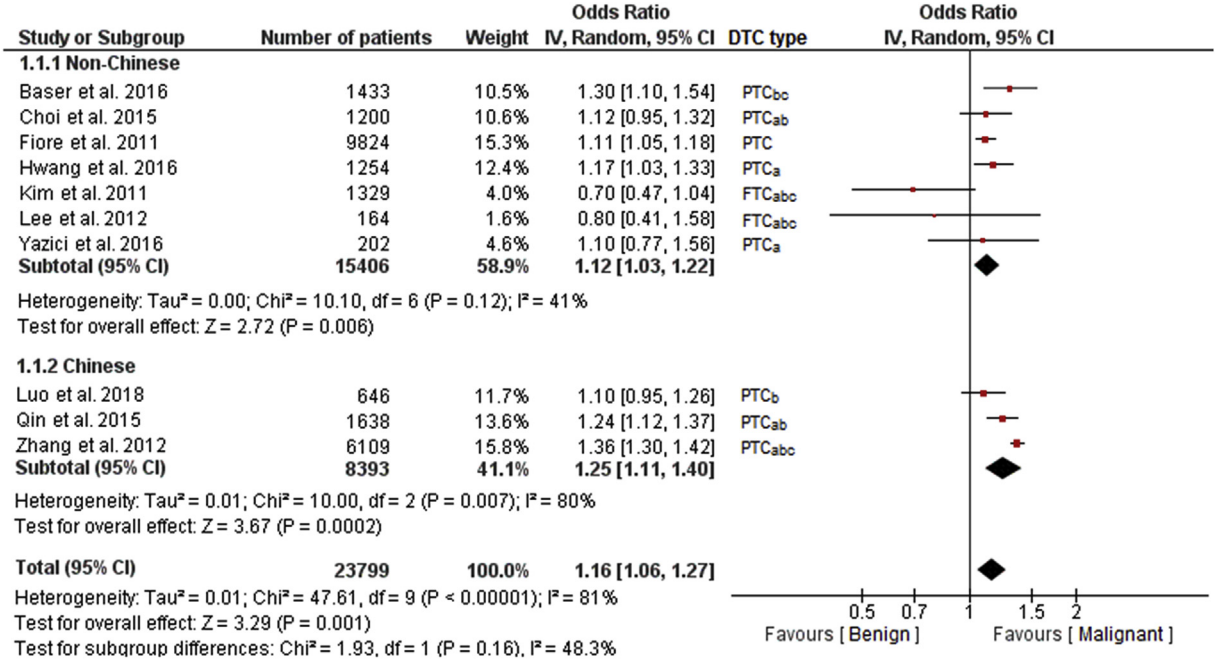

Fig. 1. Risk meta-analysis of differentiated thyroid carcinoma (DTC) in patients with thyroid nodules in relation to preoperative thyroid-stimulating hormone (TSH) level. Values produced from a random effects model (DerSimonian and Laird[26]) in relation to a 1 mu/L increase in TSH.
a Adjusted for age and sex.
b Adjusted for nodule size.
c Adjusted for Hashimoto's thyroiditis.
CI, confidence interval; df, degrees of freedom; p, statistical significance; I^2 between-study heterogeneity; IV, random, inverse variance random effects model; Z, Z statistic.

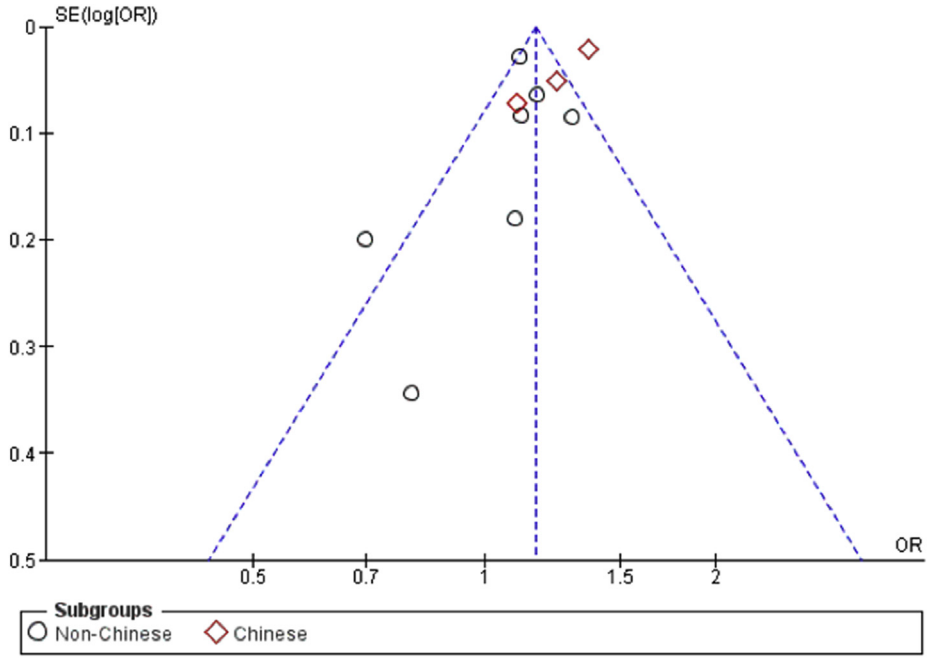

Fig. 2. Funnel plot with bias risk descriptives.
Egger's test p = 0.01 overall; Egger's test p = 0.11 with study 10 (Zhang et al.[37]) excluded; SE, standard error; OR, odds ratio.

the plot. Asymmetry arises generally from the SE range and is expected from varying subject numbers in studies. Both non-Chinese and Chinese studies had ORs on the left and right side of the overall OR, which indicates low publication bias.

The Egger's test result was significant (p = 0.01) for overall effect (which might initially suggest publication bias), but not significant when the Zhang et al., 2012 study was excluded[37]; thus, the construct of the meta-analysis was unbiased. The Egger's test result corresponded to the funnel plot and sample size difference and therefore was not a result of publication bias. All other studies fitted well within the Egger's test and showed no or low publication bias (p = 0.11). Thus, although the Zhang et al., 2012 study was not biased,[37] it was excluded from the funnel plot because of a high OR that affected results in a clinically significant manner: i.e., it showed a strong increase in OR in Chinese patients in a well-designed study with a large number of patients (n = 6,109). Meta-analysis heterogeneity (I^2) and the Egger's test confirmed heterogeneity between population categories regarding the risk of DTC in patients with thyroid nodules relative to TSH level rather than publication bias.

The overall pooled model remained significant (p < 0.05) after exclusion of each study individually (Table 2). This validates the overall result and eliminates the possibility of any significant study-specific bias. Heterogeneity in the meta-analysis was not due to bias, but due to a higher subgroup OR regarding TSH level and the risk of DTC in the Chinese population. Heterogeneity analysis showed that most of the heterogeneity came from the Zhang et al., 2012 study,[37] but this did not influence significance of the model. Moreover, the other nine studies had only 18.7% heterogeneity, thus confirming no publication bias and allocation bias regarding the heterogeneity detected.

Addition to the meta-analysis

A non-pooled analysis of four studies relative to the lowest TSH level showed an increase in the level 2 TSH group (L2) in all four studies (Table 3) (OR 1.72 [1.33, 2.22]; OR 2.11 [1.63, 4.18]; OR 1.169 [0.759, 1.798]; and OR 1.31 [0.45, 3.81]).[30–33] The risks of DTC in the L3 TSH group were also markedly increased: OR 2.76 (2.12, 3.60); OR 3.14 (1.60, 6.15); OR 1.74 (1.09, 2.79); and OR 2.72 (1.02, 7.27).[30–33] There was a moderate increase in DTC risk in the L4 range of TSH levels: OR 3.32 (2.54, 4.35); OR 2.34 (1.53, 3.75); and OR 3.88 (1.48, 10.19).[30,31,33] In the L5 TSH group, TSH level was outside the reference range in all four studies and showed the greatest risk of DTC in patients with thyroid nodules: OR 4.12 (2.83,

Table 2
'Leave1out' cross-validation of the model.

'Leave1out'	OR (DTC)	Lower 95% CI	Upper 95% CI	p value	I^2 (%)
Baser et al. 2016[38]	1.14	1.06	1.23	0.0008	76.70
Choi et al. 2015[39]	1.16	1.08	1.25	0.0002	76.50
Fiore et al. 2011[40]	1.17	1.08	1.25	0.0002	67.20
Hwang et al. 2016[41]	1.15	1.07	1.24	0.0007	77.80
Kim et al. 2011[42]	1.18	1.11	1.25	<0.0001	69.29
Lee et al. 2012[43]	1.16	1.09	1.24	<0.0001	74.60
Yazici et al. 2016[44]	1.16	1.08	1.24	<0.0001	75.90
Luo et al. 2018[35]	1.17	1.08	1.25	<0.0001	75.20
Qin et al. 2015[36]	1.14	1.05	1.23	0.015	76.70
Zhang et al. 2012[37]	1.14	1.08	1.19	<0.0001	18.70

CI, confidence interval; DTC, differentiated thyroid carcinoma; I^2 heterogeneity; OR, odds ratio (values relative to a 1 mU/L increase in TSH).

Table 3
Non-pooled analysis of differentiated thyroid carcinoma risk in patients with thyroid nodules according to different ranges of thyroid-stimulating hormone (TSH).

Study		Reference range OR (95% CI) relative to low TSH L1 <0.35 < 0.40 mU/L			
	n	L2 (TSH)	L3 (TSH)	L4 (TSH)	L5 (TSH)
Retrospective cohort		(0.40–1.35 mU/L)	(1.36–2.12 mU/L)	(2.13–4.20 mU/L)	(>4.20 mU/L)
1. Sohn et al. 2014[31]	3,791	OR 1.72 (1.33, 2.22)	OR 2.76 (2.12, 3.60)	OR 3.32 (2.54, 4.35)	OR 4.12 (2.83, 5.99)
Retrospective cohort		(0.40–1.34 mU/L)	(1.34–4.00 mU/L)	NA	(>4.00 mU/L)
2. Yang et al. 2011[32]	1,685	OR 2.11 (1.63, 4.18)	OR 3.14 (1.60, 6.15)	NA	OR 2.99 (1.26, 7.08)
Prospective cohort		(0.36–1.35 mU/L)	(1.36–1.90 mU/L)	(1.91–4.95 mU/L)	(>4.95 mU/L)
3. Wu et al. 2014[30]	2,132	OR 1.169 (0.759, 1.798)	OR 1.74 (1.09, 2.79)	OR 2.34 (1.53, 3.75)	OR 4.11 (1.83, 9.23)
Retrospective cohort		(0.40–0.90 mU/L)	(1.00–1.70 mU/L)	(1.80–5.50 mU/L)	(>5.50 mU/L)
4. Boelaert et al. 2006[33]	1,183	OR 1.31 (0.45, 3,81)	OR 2.72 (1.02, 7.27)	OR 3.88 (1.48, 10.19)	OR 11.18 (3.23, 38.63)

Values presented as odds ratios (95% CI) relative to the group with lowest TSH, L1 <0.35 mU/L (Wu et al. 2014[30]) and <0.40 mU/L (Sohn et al. 2014[31]; Yang et al. 2011[32]; Boelaert et al. 2006[33]).
CI, confidence interval; L(2–5), different ranges of TSH levels; NA, not applicable; OR, odds ratio.

5.99); OR 2.99 (1.26, 7.08); OR 4.11 (1.83, 9.23); and OR 11.18 (3.23, 38.63).[31–33] Finally, there was a large increase in the risk of DTC in patients with thyroid nodules evident in the L2, L3, and L4 TSH ranges, which were all within reference values, relative to L1 (<35 mU/L and <40 mU/L) and below the reference level.

Discussion

This meta-analysis of 23,799 subjects (15,406 non-Chinese and 8,393 Chinese) with thyroid nodules showed a significant pooled OR in both non-Chinese and Chinese populations regarding the risk of DTC in relation to preoperative TSH increase (1 mU/L). In the meta-analysis, the overall OR of 1.16 indicates that each 1 mU/L increase in TSH increases the risk of DTC by 16%. This increased risk is even higher in Chinese patients: OR 1.25, or a 25% increase for each 1 mU/L increment in TSH. Heterogeneity was high (81%), but its effects were minimized by use of the random effects model: all results were statistically significant ($p < 0.05$ for all models).

Interestingly, in two studies of patients with follicular thyroid carcinoma, the OR was <1, which means that increased TSH was associated with a reduced risk of DTC; however, these findings were from two studies only, and definitive conclusions cannot be drawn. Nonetheless, it is pertinent that all studies of papillary thyroid carcinoma demonstrated an association between increased TSH and increased DTC.

In general, studies with larger sample sizes have more weight, which is why the Zhang et al., 2012 study was not considered to be biased, as this study has one of the highest weights and the lowest CI range.[37] In the risk of bias assessment, studies were present on both sides of the reference line in the funnel plot; however, most studies fitted the funnel plot, thus suggesting only limited bias in the meta-analysis. An initially significant ($p < 0.05$) Egger's test result conveyed the impression of bias, but exclusion of the Zhang et al., 2012 study provided more accurate data, a nonsignificant Egger's test result, and highlighted a lack of bias in the model.[37] The robustness of the model was confirmed by the 'leave1out' analysis, which excluded studies one-by-one and endorsed that the overall significance of the pooled data was not due to results from a single over-weighted study.

The meta-analysis used a standardized 1 mU/L increase in TSH as a reference to avoid bias. However, it is also interesting to consider a reference TSH range to examine how the risk of DTC varies across TSH ranges outside of the meta-analysis. For example, in the level 5 (L5) TSH range, various studies demonstrated an approximately 4-fold[30,31] or 11-fold[33] increase in DTC risk. An exponential link may therefore exist between TSH level and DTC risk; however, it should be remembered that the latter risk increases were relative to a level 1 TSH group (<0.35 or <0.40 mU/L) and not to a standardized TSH increment of 1 mU/L.

Conclusions

In summary, the OR for DTC in relation to TSH was significant in both population groups and was higher in Chinese 1.25 (1.11, 1,40), $Z = 3.67$ ($p = 0.0002$) compared to non-Chinese: 1.12 (1.03, 1.22), $Z = 2.72$ ($p = 0.006$). An overall random effects model showed a significant risk increase for DTC in patients with thyroid nodules: OR = 1.16 (1.06, 1.27), $Z = 3.29$ ($p = 0.007$).

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Declaration of competing interest

Meifang Ruan is an employee of Merck Serono Co., Ltd, China (an affiliate of Merck KGaA Darmstadt, Germany). All other authors declare that they have no conflicts of interest to report in relation to this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2020.01.009.

References

1. Du L, Wang Y, Sun X, et al. Thyroid cancer: trends in incidence, mortality and clinical-pathological patterns in Zhejiang Province, Southeast China. *BMC Canc*. 2018;18:291.
2. Lee KL, Chen TJ, Won GS, et al. The use of fine needle aspiration and trends in incidence of thyroid cancer in Taiwan. *J Chin Med Assoc*. 2018;81:164–169.
3. Li K, Lin G, Zhou Q, Wu X. Time trends of the incidence of thyroid cancer in urban Guangzhou, 2000-2011. *Zhonghua Yufang Yixue Zazhi*. 2015;49:142–146.
4. La Vecchia C, Malvezzi M, Bosetti C, et al. Thyroid cancer mortality and incidence: a global overview. *Int J Cancer*. 2015;136:2187–2195.
5. Jegerlehner S, Bulliard JL, Aujesky D, et al. Overdiagnosis and overtreatment of thyroid cancer: a population-based temporal trend study. *PLoS One*. 2017;12, e0179387.
6. Shulin JH, Aizhen J, Kuo SM, et al. Rising incidence of thyroid cancer in Singapore not solely due to micropapillary subtype. *Ann R Coll Surg Engl*. 2018;100:295–300.
7. Lubitz CC, Sosa JA. The changing landscape of papillary thyroid cancer: epidemiology, management, and the implications for patients. *Cancer*. 2016;122:3754–3759.

8. Lim H, Devesa SS, Sosa JA, et al. Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. *J Am Med Assoc*. 2017;317:1338–1348.
9.. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66:115–132.
10. Wang Y, Wang W. Increasing incidence of thyroid cancer in Shanghai, China, 1983–2007. *Asia Pac J Public Health*. 2015;27:NP223–NP229.
11. Knobel M. Etiopathology, clinical features, and treatment of diffuse and multinodular nontoxic goiters. *J Endocrinol Investig*. 2016;39:357–373.
12. Perri F, Giordano A, Pisconti S, et al. Thyroid cancer management: from a suspicious nodule to targeted therapy. *Anti Cancer Drugs*. 2018;29:483–490.
13. Smith JJ, Chen X, Schneider DF, et al. Toxic nodular goiter and cancer: a compelling case for thyroidectomy. *Ann Surg Oncol*. 2013;20:1336–1340.
14. Shi RL, Liao T, Qu N, et al. The usefulness of preoperative thyroid-stimulating hormone for predicting differentiated thyroid microcarcinoma. *Otolaryngol Head Neck Surg*. 2016;154:256–262.
15. Besler E, Citgez B, Aygun N, et al. The relationship of clinicopathological factors of the tumor with preoperative TSH Level in papillary thyroid cancers. *Eurasian J Med*. 2019;51:8–11.
16. Zafon C, Obiols G, Mesa J. Preoperative TSH level and risk of thyroid cancer in patients with nodular thyroid disease: nodule size contribution. *Endocrinol Nutr*. 2015;62:24–28.
17. Hu N, Li ZM, Liu JF, et al. An overall and dose-response meta-analysis for thyrotropin and thyroid cancer risk by histological type. *Oncotarget*. 2016;7:47750–47759.
18. Raue F, Frank-Raue K. Thyroid cancer: risk-stratified management and individualized therapy. *Clin Cancer Res*. 2016;22:5012–5021.
19. Nabhan F, Ringel MD. Thyroid nodules and cancer management guidelines: comparisons and controversies. *Endocr Relat Cancer*. 2017;24:R13–R26.
20. Tufano RP, Noureldine SI, Angelos P. Incidental thyroid nodules and thyroid cancer: considerations before determining management. *JAMA Otolaryngol Head Neck Surg*. 2015;141:566–572.
21. Paschou SA, Vryonidou A, Goulis DG. Thyroid nodules: alpha guide to assessment, treatment and follow-up. *Maturitas*. 2017;96:1–9.
22. Wong R, Farrell SG, Grossmann M. Thyroid nodules: diagnosis and management. *Med J Aust*. 2018;209:92–98.
23. Golbert L, de Cristo AP, Faccin CS, et al. Serum TSH levels as a predictor of malignancy in thyroid nodules: a prospective study. *PLoS One*. 2017;12,e0188123.
24. Kim HJ, Mok JO, Kim CH, et al. Preoperative serum thyroglobulin and changes in serum thyroglobulin during TSH suppression independently predict follicular thyroid carcinoma in thyroid nodules with a cytological diagnosis of follicular lesion. *Endocr Res*. 2017;42:154–162.
25. Cochrane handbook for systematic reviews of Interventions [updated March 2011]. In: Higgins JPT, Green S, eds. *The Cochrane Collaboration*; 2011. Version 5.1.0. http://handbook.cochrane.org. Accessed July 22, 2019.
26. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials*. 1986;7:177–188.
27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
28. Viechtbauer W, Cheung MW. Outlier and influence diagnostics for meta-analysis. *Res Synth Methods*. 2010;1:112–125.
29. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36:1–48.
30. Wu X, Lun Y, Jiang H, et al. Coexistence of thyroglobulin antibodies and thyroid peroxidase antibodies correlates with elevated thyroid-stimulating hormone level and advanced tumor stage of papillary thyroid cancer. *Endocrine*. 2014;46:554–560.
31. Sohn SY, Kim HJ, Jang HW, et al. Lack of association between high serum thyroid-stimulating hormone level and risk of papillary thyroid microcarcinomas. *Head Neck*. 2014;36:43–46.
32. Yang Y, Li Q, Guo L, et al. A retrospective analysis of thyroid cancer in China. *Asian Pac J Cancer Prev APJCP*. 2011;12:2245–2249.
33. Boelaert K, Horacek J, Holder RL, et al. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. *J Clin Endocrinol Metab*. 2006;91:4295–4301.
34. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2018. https://www.R-project.org/.
35. Luo J. Study on clinical characteristics of thyroid nodules. *Chin J Gen Pract*. 2018;21:4445–44452+58.
36. Qin J. *High thyroglobulin antibody levels increase the risk of differentiated thyroid carcinoma*2015. Disease Markers; 2015:648670.
37. Zhang L, Li H, Ji QH, et al. The clinical features of papillary thyroid cancer in Hashimoto's thyroiditis patients from an area with a high prevalence of Hashimoto's disease. *BMC Canc*. 2012;12:610.
38. Baser H, Topaloglu O, Tam AA, et al. Higher TSH can be used as an additional risk factor in prediction of malignancy in euthyroid thyroid nodules evaluated by cytology based on Bethesda system. *Endocrine*. 2016;53:520–529.
39. Choi JS, Nam CM, Kim EK, et al. Evaluation of serum thyroid-stimulating hormone as indicator for fine-needle aspiration in patients with thyroid nodules. *Head Neck*. 2015;37:498–504.
40. Fiore E, Rago T, Latrofa F, et al. Hashimoto's thyroiditis is associated with papillary thyroid carcinoma: role of TSH and of treatment with L-thyroxine. *Endocr Relat Cancer*. 2011;18:429–437.
41. Hwang SH, Kim EK, Moon HJ, et al. Risk of thyroid cancer in euthyroid asymptomatic patients with thyroid nodules with an emphasis on family history of thyroid cancer. *Korean J Radiol*. 2016;17:255–263.
42. Kim KW, Park YJ, Kim EH, et al. Elevated risk of papillary thyroid cancer in Korean patients with Hashimoto's thyroiditis. *Head Neck*. 2011;33:691–695.
43. Lee EK, Chung KW, Min HS, et al. Preoperative serum thyroglobulin as a useful predictive marker to differentiate follicular thyroid cancer from benign nodules in indeterminate nodules. *J Korean Med Sci*. 2012;27:1014–1018.
44. Yazici P, Mihmanli M, Bozkurt E, et al. Which is the best predictor of thyroid cancer: thyrotropin, thyroglobulin or their ratio? *Hormones (Basel)*. 2016;15:256–263.