The Usefulness of Preoperative Thyroid-Stimulating Hormone for Predicting Differentiated Thyroid Microcarcinoma

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Abstract
Objective. Thyroid-stimulating hormone (TSH) is a known thyroid growth factor, but the pathogenic role of TSH in thyroid tumorigenesis is controversial. The aim of this study is to examine the relationship between preoperative TSH and differentiated thyroid microcarcinoma (DTMC).

Data Sources. We searched PubMed, EMBASE, Ovid, Web of Science, and the Cochrane Library from their inception to March 2015 and performed a systematic literature review of original studies.

Review Methods. Published studies that explored the relationship between preoperative TSH and DTMC were included for the review. We calculated odds ratio referring to different TSH concentrations between DTMC and control groups and used random effects model for the meta-analysis.

Results. Nine eligible studies that included 6523 patients were identified. Meta-analysis revealed that DTMC was associated with high TSH concentration (odds ratio = 1.23, 95% confidence interval = 1.03-1.46, \( P = .001 \)). Metaregression analysis indicated that the disparity of control groups was the possible factor resulting in heterogeneity among the studies.

Conclusions. The risk of DTMC increases significantly in parallel with TSH concentration. These results support the hypothesis that TSH is involved in tumorigenesis of differentiated thyroid cancer.

Keywords
thyroid-stimulating hormone, differentiated thyroid cancer, microcarcinoma, risk

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In many regions, the incidence of differentiated thyroid cancer (DTC) is increasing more rapidly than that of any other malignancy.1,2 It may be explained by the increased detection of thyroid micronodule (lesions \( \leq 10 \) mm in diameter), which is confirmed as differentiated thyroid microcarcinoma (DTMC) on final pathology. Since diagnostic options are limited because of these small nodules, additional markers for risk assessment would be very important.3

Thyroid-stimulating hormone (TSH) plays an important role in the abnormal growth of thyrocytes.4,5 DTC has been reported to express TSH receptors,6 and TSH may act as a cancer stimulus as combined with oncogenes and other growth factors in thyroid cancer growth and development.7,8 Recent studies show that high TSH concentration is associated with increased risk of DTC,9 and they propose that TSH may be a novel predictor of malignancy in patients with thyroid nodules. We synthesized data from original studies and performed a systematic literature review to study the association between high TSH concentration and DTMC. We investigated whether high TSH concentration is related to risk for DTMC, by testing the differences of TSH concentrations in patients with and without DTMC who had undergone thyroidectomy for nodular thyroid disease.

Materials and Methods
Search Strategy and Study Selection
A comprehensive literature search of the period up to March 2015 was conducted with PubMed, EMBASE, Ovid, Web of Science, and Cochrane Library. The search algorithm was based on the following combination of keywords:

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“thyroid cancer,” “malignancy,” “thyrotropin,” “thyroid stimulating hormone.” All of the reference lists from the main articles were inspected for additional eligible studies.

Two investigators (T.L. and F.L.)—who were blinded to the journal, author, institution, and date of publication—individually checked the retrieved articles. Discrepancies in the selection were resolved by consensus. Eligible studies fulfilled the following inclusion criteria: (1) the original article was published in English or Chinese; (2) diagnosis of DTC versus control was based on surgical pathology reports; (3) the aim of studies (or a subgroup analysis) was to examine the relationship between preoperative TSH concentration and DTMC, in which data from patients with TSH were measured within 1 year of surgery and were complete for the pooling analysis; and (4) patients enrolled in each study were free of neck surgical history, radiation exposure history, and family history.

Online titles and abstracts were screened initially, and those not meeting the inclusion criteria were excluded. We then obtained the full text of the remaining articles to determine whether they were specifically eligible for the final analysis. Studies were excluded for the following reasons: (1) no data; (2) indeterminate cytology from fine-needle aspiration biopsy and unconfirmed pathologic; (3) investigation of whether TSH concentrations can be used for risk prediction of DTC rather than DTMC; (4) evaluation of preoperative TSH in patients with medullary thyroid cancer (MTC), c-cell hyperplasia, or benign thyroid nodules. As a secondary data analysis, this study did not require ethical approval.

Data Extraction and Quality Assessment

In total, 9 articles met the inclusion/exclusion criteria for the meta-analysis. The following data were extracted: first author and year, study center, study design, sample size, study and control groups, the assay panel and reference ranges for TSH, the preoperative use of thyroid hormone or antithyroid drugs, TSH concentrations, and the proportions of patients within euthyroidism ranges.

Study quality was independently scored by 2 investigators (T.L. and F.L.) using the Newcastle-Ottawa Scale (NOS). The NOS is frequently used for nonrandom studies, such as case-control studies.

Statistical Analyses

The meta-analysis was performed with STATA 12.0 (StataCorp LP, College Station, Texas) to facilitate the pooling of results across studies. Nominal variables were presented as the number of cases with percentage and continuous variables, as mean ± SD. The association between TSH concentration and DTMC was indicated as odds ratio (OR) referring to different TSH concentrations between DTMC and control groups. The pooled OR was calculated with 95% confidence intervals (CIs). Heterogeneity in each study was assessed with chi-square tests (Q value and P) and I² measures. Significant heterogeneity was defined as a chi-square test P < .05 or as an I² measure >50%. Random effects models were then used for primary analysis in data sets with significant heterogeneity. Sensitivity analysis was performed to test the stability of pooled OR. Reasons for statistical heterogeneity were explored with metaregression models combined with original data provided in the articles and subgroup analysis of studies based on probable sources derived from regression analyses. Publication biases were assessed with Egger’s test.

Results

Baseline Study and Patient Characteristics

The detailed procedure for study selection in this meta-analysis is shown in Figure 1. We found 109 primary studies, of which 15 were excluded after title and abstract review. Eighty-five articles were excluded after complete review; 9 studies including 6523 patients fulfilled the inclusion criteria and were considered for the analysis. Of all patients, 2446 (37.5%) had DTMC on final pathology. In these case-control studies, 8 studies were performed in a single center, while 1 study by Negro et al.9 enrolled patients from 3 district hospitals. The medical records of selected patients in either the study or control group consisted of a serum TSH concentration, which was measured within 3 to 12 months of surgery. Preoperative use of the drug levothyroxine was uncommon; levothyroxine was prescribed for nodule suppression and overt hypothyroidism in only a study by Haymart et al.10 The reference range and intra- and interassay coefficients of variation for TSH concentration varied according to the assay applied in each study. Four studies exclusively included patients with normal thyroid function9,11-13; in the remaining 5 studies, the proportions of

![Figure 1. Flow diagram of article selection for this meta-analysis. DTC, differentiated thyroid cancer; TSH, thyroid-stimulating hormone.](https://example.com/fig1.png)
patients with subclinical hypothyroidism ranged from 2.0% to 22.3%. Table 1 shows the principal characteristics of studies included in this meta-analysis. The NOS was used to assess the quality of the included studies. All NOS scores of the eligible studies were ≥5 for the 9 questions, with an average of 6.2 (range, 5-7), indicating good quality for meta-analysis. The majority of studies did define controls for selection or the nonresponse rate for exposure, thus boosting the scores.

### TSH and Risk of DTMC

Serum TSH concentrations were compared between DTMC patients and controls. Eight studies had control groups with some type of benign nodules (goiter, adenoma, cystic nodule, etc); 3 studies had control groups with benign micronodules.10,12,14 Seven studies reported sufficient data to calculate the OR of DTMC, comparing the high TSH versus the low concentration,9-15 while Gerschpacher et al and Sohn et al provided an adjusted OR in their study.3,16 The OR and 95% CI were calculated with binary logistic regression with original data. Meta-analysis of these studies showed that the risk of DTMC was associated with high TSH concentration (pooled OR = 1.23, 95% CI = 1.03-1.46, \(P = .001\); Figure 2), implying that high TSH concentration did predispose patients to develop a small thyroid cancer. Furthermore, Zafon et al13 performed a receiver operating characteristic analysis for TSH concentration and the presence of malignancy, and the results showed a TSH cutoff value of 1.08 mU/L to differentiate benign from DTC, with a sensitivity of 72% and a specificity of 58% and with an area under the curve of 0.67. They also investigated the association between TSH and the size of the largest nodule; however, high TSH concentration was not found to associate with nodule size, whether benign or malignant.13 Due to the variations for the assays with different sensitivity, as well as the reference range and intra- and interassay coefficients of variation for TSH from each enrolled study, it was difficult to do the receiver operating characteristic analysis based on the original data extracted from studies. Therefore, we calculated only the ORs representing the association between TSH

### Table 1. Studies Included in the Meta-analysis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Center</th>
<th>Sample Size</th>
<th>DTMC, %</th>
<th>Study vs Control Group</th>
<th>Assays for Measuring TSH</th>
<th>Preoperative Drugs</th>
<th>Subclinical Hypothyroidism, %</th>
<th>OR (95% CI)</th>
<th>Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haymart10</td>
<td>2008</td>
<td>US</td>
<td>843</td>
<td>28.6</td>
<td>PTMC vs benign micronodule</td>
<td>N/A</td>
<td>Levothyroxine</td>
<td>22.3</td>
<td>1.23 (0.94-1.63)</td>
<td>7</td>
</tr>
<tr>
<td>Gerschpacher3</td>
<td>2010</td>
<td>Austria</td>
<td>87</td>
<td>37.9</td>
<td>PTMC vs MTC</td>
<td>Radioimmuno-assay</td>
<td>None</td>
<td>18.2</td>
<td>0.72 (0.41-1.53)</td>
<td>7</td>
</tr>
<tr>
<td>Moon12</td>
<td>2012</td>
<td>So Korea</td>
<td>483</td>
<td>21.2</td>
<td>DTMC vs benign micronodule</td>
<td>Chemiluminescent assay</td>
<td>None</td>
<td>—</td>
<td>1.50 (1.03-2.03)</td>
<td>6</td>
</tr>
<tr>
<td>Zafon11</td>
<td>2012</td>
<td>Spain</td>
<td>386</td>
<td>19.7</td>
<td>PTMC vs benign micronodule</td>
<td>Chemiluminescent assay</td>
<td>None</td>
<td>—</td>
<td>1.51 (0.72-3.20)</td>
<td>5</td>
</tr>
<tr>
<td>Shi14</td>
<td>2012</td>
<td>China</td>
<td>1870</td>
<td>14.4</td>
<td>DTMC vs benign micronodule</td>
<td>Chemiluminescent assay</td>
<td>None</td>
<td>2.0</td>
<td>1.19 (0.95-1.49)</td>
<td>5</td>
</tr>
<tr>
<td>Negro9</td>
<td>2013</td>
<td>Italy, Switzerland</td>
<td>205</td>
<td>20.0</td>
<td>PTMC vs benign micronodule</td>
<td>N/A</td>
<td>None</td>
<td>—</td>
<td>0.79 (0.48-1.11)</td>
<td>5</td>
</tr>
<tr>
<td>Sohn16</td>
<td>2014</td>
<td>So Korea</td>
<td>1574</td>
<td>93.0</td>
<td>PTMC vs benign micronodule</td>
<td>Chemiluminescent assay</td>
<td>None</td>
<td>9.1</td>
<td>2.21 (0.83-5.88)</td>
<td>7</td>
</tr>
<tr>
<td>Zafon13</td>
<td>2015</td>
<td>Spain</td>
<td>980</td>
<td>10.8</td>
<td>PTMC vs benign micronodule</td>
<td>Chemiluminescent assay</td>
<td>None</td>
<td>—</td>
<td>1.57 (1.38-1.76)</td>
<td>7</td>
</tr>
<tr>
<td>Jiao15</td>
<td>2015</td>
<td>China</td>
<td>365</td>
<td>31.0</td>
<td>PTMC vs benign micronodule</td>
<td>Chemiluminescent assay</td>
<td>None</td>
<td>6.0</td>
<td>1.09 (0.90-1.28)</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DTMC, differentiated thyroid microcarcinoma; MTC, medullary thyroid carcinoma; N/A, not reported; OR, odds ratio; PTMC, papillary thyroid microcarcinoma; TSH, thyroid stimulating hormone.

*Study group vs control group.*
concentration and DTMC and pooled the individual ORs with 95% CIs to assess and examine the relationship between preoperative TSH and DTMC.

**Publication Bias and Sensitivity Analysis**

To determine whether there was a publication bias in a small study, Egger’s test was used to calculate the regress standard normal deviate of intervention and the effect estimate against its standard error. The $P$ value obtained in the meta-analysis was .338, indicating that no significant bias existed.

The sensitivity analysis was conducted to investigate the influence of a single study on the pooled OR, which was considered an overall effect for the association between TSH concentration and DTMC. The value of OR and 95% CI were computed with 1 study omitted in each turn (Figure 3). Regarding the slight variation of each calculated OR versus the pooled OR, the pooled data from 9 eligible studies were considered to be stable in meta-analysis.

**Heterogeneity Assessment and Subgroup Analysis**

Tests for heterogeneity that calculated the overall $P$ value and $I^2$ value indicated significant heterogeneity among the study results ($I^2 = 66.9\%$, $P = .002$). Metaregression analysis was performed to explore the sources of heterogeneity in the studies. We used a multivariate regression model with a backward stepwise algorithm. The evaluated variables included year of publication, research center, sample size, assay for measuring TSH, quality score, different control groups, and the proportions of patients with subclinical hypothyroidism within each study. The results revealed that no significant factor was responsible; however, the different control groups trended toward heterogeneity ($P = .170$). Subgroup analysis showed similar results of pooled OR (pooled OR = 1.36, 95% CI = 1.11-1.68, $P = .001$) among 3 studies with benign micronodule as control but without statistical heterogeneity, indicating that disparity of controls might be the primary factor underlying the heterogeneity (Figure 4).

**Discussion**

The recent rise in the incidence of thyroid cancer elicits the studies designed to explore the risk factor for malignancy in patients with a thyroid nodule. TSH as a main regulator of thyroid hormone has been reported to positively correlate with the initiation of differentiated thyroid neoplasms mediated by TSH receptors in most of the previous studies. Despite the negative data suggesting that TSH was involved in only the progression of existing tumors, our

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haymart (2008)</td>
<td>1.23 (0.94, 1.62)</td>
<td>13.89</td>
</tr>
<tr>
<td>Genschopacher (2010)</td>
<td>0.72 (0.41, 1.55)</td>
<td>5.31</td>
</tr>
<tr>
<td>Moon (2011)</td>
<td>1.50 (1.03, 2.03)</td>
<td>11.80</td>
</tr>
<tr>
<td>Zafon (2012)</td>
<td>1.51 (0.72, 2.32)</td>
<td>4.38</td>
</tr>
<tr>
<td>Shi (2012)</td>
<td>1.19 (0.95, 1.49)</td>
<td>15.67</td>
</tr>
<tr>
<td>Negro (2013)</td>
<td>0.76 (0.49, 1.11)</td>
<td>9.57</td>
</tr>
<tr>
<td>Sohn (2013)</td>
<td>2.21 (0.83, 5.88)</td>
<td>2.79</td>
</tr>
<tr>
<td>Zafon (2015)</td>
<td>1.57 (1.30, 1.76)</td>
<td>15.17</td>
</tr>
<tr>
<td>Jiao (2015)</td>
<td>1.08 (0.96, 1.28)</td>
<td>17.41</td>
</tr>
<tr>
<td>Overall ($I^2 = 66.9%$, $p = .002$)</td>
<td>1.23 (1.03, 1.44)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Figure 2.** The random effects model of the effect size (ES) of the odds ratio for the association between thyroid-stimulating hormone and differentiated thyroid microcarcinoma is shown with 95% confidence intervals (CIs).

**Figure 3.** Sensitivity analysis for the influence of a single study on the meta-analysis estimates.
systematic review revealed that patients with DTMC had significantly higher TSH concentrations did than subjects without it. The TSH concentration was confirmed to be an independent risk factor for DTMC in patients with a nodule; given that DTMC is thought to be an early stage in the development of DTC, we also hypothesized that TSH might exert an influence on the origin of differentiated malignancy. Measurement of TSH concentration might be highly recommended in the initial evaluation of patients presenting thyroid nodule, even a tiny nodule detected by ultrasonography.

The literature search in the present study revealed that 9 original articles had analyzed the relationship of TSH concentration with DTMC. Moon et al.\(^{12}\) reported that, for the first time, the risk of malignancy was observed to be significantly associated with higher TSH in a cohort of patients with micronodules. This finding was subsequently confirmed by others.\(^{13}\) Alternatively, Gerschpacher et al.\(^{3}\) compared a cohort of patients with papillary thyroid microcancers and a control group of patients whose thyroid glands had been removed as a treatment for MTC, but they found no significant differences in TSH concentration. Moreover, Shi et al.\(^{18}\), Negro et al.\(^{9}\), and Sohn et al.\(^{16}\) found no preoperative TSH differences between patients with papillary thyroid microcancers and patients with benign nodular diseases. The first reason for the conflicting results (ie, that they did not detect a significant difference) might be the small sample sizes. In addition, patients taking medications that interfered with thyroid function were included to evaluate the influence of TSH on thyroid malignancy; we also did not exclude patients with biochemical and histologic evidence of autoimmunity. The presence of autoimmunity might be a confounding factor mainly because it was associated with higher TSH concentrations. Last, although the control groups were consistently designed as patients with benign nodular diseases among 8 studies, 1 study by Gerschpacher et al.\(^{3}\) involved MTC, and 3 studies had benign micronodular patients as control groups. The metaregression and subgroup analyses also indicated that disparity of controls might be the primary factor underlying the heterogeneity. Finally, the variation among the studies could be due to the retrospective design, which limited patient selection and control group setting; in addition, this variability might have led to the heterogeneity for the meta-analysis. In fact, obvious heterogeneity was observed under investigation. Sensitivity analysis and Egger's test suggested that the included studies were highly qualified, without significant publication bias. Thus, in terms of the possibly heterogeneous factors, we focused on published year, study design, sample size, control group, and subclinical hypothyroidism; the metaregression and subgroup analysis indicated that the possible factor contributing to heterogeneity was the variation of different control groups among studies. A series of large prospective studies is needed to provide reliable information and validate the particular risk for DTMC with high TSH concentration in a cohort of patients with nodular thyroid disease.

It is improbable that TSH acts alone in cancer induction, because thyroid cancer has been known to occur at a range of TSH concentrations, even in the lobe under suppression due to hyperfunctioning nodules. However, the biological mechanisms underlying the influences of high TSH and the interaction of TSH with other carcinogenic factors (long-term inflammatory stimulations, oncogenes, etc) on thyroid tumorgenesis remain unknown so far. According to in vitro studies, genetic mutations such as \(BRAF^V600E\) are known to be the trigger for the initiation of DTC.\(^{19,20}\) while TSH may
play a role in tumor development rather than in its initiation. Franco et al. first crossed LSL-BRAFV600E/TPO-Cre with TSH-receptor knockout mice. The BRAFV600E oncogene was activated in follicular cells, but they had a lower mitotic index and were not transformed without TSH stimulation. Recent advances in research on thyroid carcinogenesis have also yielded applications of these molecular biomarkers and profiling panels in the preoperative evaluation of thyroid nodules, specifically for the 7-gene mutation tests of a panel of mutations (BRAF, N-/H-/K-RAS) and for translocations of the RET/PTC and PAX8/PPARY genes in genomic DNA from thyroid nodules or gene expression profiling based on RNA. In clinical practice, a higher TSH concentration was also found to be associated with an advanced stage of thyroid cancer at diagnosis. These data provide support for an association between high TSH and thyroid cancer progression; considering issues of the present study, we suggest that a higher TSH is not only associated with the risk of DTMC but also correlated with its development.

The first limitation of this study is that it includes case-control trials. To some extent, the quality of the reports could be improved. The second limitation is the fact that we did not establish a risk evaluation system to predict the quantitative odds of DTMC in a nodular disease patient with a certain high TSH concentration. A recent review found that the dose-response model OR was 1.72 (95% CI = 1.42-2.07) per TSH levels <1 mU/L, changing to an OR of 1.16 (95% CI = 1.12-1.21) per TSH levels ≥1 mU/L; however, this model was only possible as applied in patients with larger nodules. Hence, we believe that a prospective study with sufficient data is necessary.

In conclusion, the existing data provide evidence favoring a significant relationship between high TSH concentration and DTMC. Therefore, the determination of preoperative TSH concentrations contribute to clinical risk estimation in the assessment of small thyroid nodules. However, further prospective research is required to clarify the impact of TSH on the initiation of papillary cancer.

Author Contributions
Rong-liang Shi, data collection, interpretation, drafting, revision, final approval, accountability for all aspects of the work; Tian Liao, data collection, drafting, revision, review of article, final approval, accountability for all aspects of the work; Ning Qu, data collection, interpretation, drafting, revision, final approval, accountability for all aspects of the work; Fei Liang, data collection, drafting, revision, review of article, final approval, accountability for all aspects of the work; Jia-ying Chen, data collection, drafting, revision, review of article, final approval, accountability for all aspects of the work; Qing-hai Ji, study design, critical review of article, final approval, accountability for all aspects of the work.

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