

Positive thyroid antibodies and risk of thyroid cancer: A systematic review and meta-analysis

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Abstract. Previous studies assessing the association between thyroid antibodies and the risk of thyroid cancer (TC) have produced inconsistent results. The present study therefore conducted a meta-analysis of the available data. PubMed, Embase and the Cochrane Library were searched for the retrieval of relevant studies and a meta-analysis was conducted to systematically evaluate the association between positive thyroid antibodies and the risk of TC. This search identified 16 articles containing 17 studies on thyroglobulin antibodies (TgAb), which involved a total of 34,488 patients. Positive TgAb was associated with an increased risk of TC [odds ratio (OR)=1.93, 95% confidence interval (CI)=1.64-2.27, I²=67.2%]. Whether to adjust for confounding factors (gender and thyroid nodule number) was the main cause of heterogeneity. A stronger association between positive TgAb and an increased risk of TC was identified in the studies with an unadjusted thyroid nodule number (OR=2.14, 95% CI=1.82-2.52), as compared to those with an adjusted thyroid nodule number (OR=1.61, 95% CI=1.29-2.00; P=0.04). In addition, 12 studies on thyroid peroxidase antibodies (TPOAb) involving 30,007 patients were included. Positive TPOAb was associated with an increased risk of TC (OR=1.50, 95%CI=1.16-1.95, I²=83.0%). No significant heterogeneity was observed in the PTC group. Positive TgAb is an independent risk factor for TC. The association between positive TPOAb and increased risk of TC needs to be further studied.

Introduction

Thyroid nodules are a common disease of the neck, with malignant nodules accountings for 5-15% of them (1). The pathological classification of thyroid cancer (TC) includes papillary, follicular and undifferentiated types. Except from painless nodules, TC usually has no other specific clinical symptom, making it harder to detect at an early stage. In recent years, the incidence of TC has gradually increased, ranking 9th among all tumors worldwide (2-5). Early diagnosis of TC and surgical treatment are particularly important for the prognosis of patients.

The most accurate examination for preoperative diagnosis of TC, thyroid fine needle aspiration cytology (FNAC) is unable to distinguish between thyroid follicular carcinoma and follicular adenoma. Recent studies found that measuring TgAb could help differentiate TC from indeterminate nodules subjected to FNAC (6-8).

TgAb, an IgG glycoprotein secreted by lymphoid B cells, and thyroid peroxidase antibodies (TPOAb) usually indicates autoimmune thyroid diseases (AITD) when they are positive. These two antibodies could also be elevated in patients with TC (9). Recently, more and more studies have focused on the relationship between thyroid antibodies and TC. An early study found that the prevalence rate of positive TgAb in patients with TC was 2.5 times as much as in the general population (9). Kim *et al* (10) first reported that TgAb could be used as an independent predictor for TC diagnosis (OR=1.80, 95% CI=1.29-2.58), regardless of the presence of AITD, especially in younger patients (11). Furthermore, TC patients with positive TgAb levels had a worse prognosis after surgery (12,13). However, this issue remains controversial. The present meta-analysis was therefore performed to systematically evaluate the association between positive thyroid antibodies (TgAb and TPOAb) and the risk of TC.

Materials and methods

Search strategy. A systematic search was conducted using three electronic databases (Pubmed, Embase and Cochrane library) to retrieve potentially relevant articles published before October 2018. The search strategy comprised the terms (all fields) 'thyroid cancer', 'thyroid carcinoma', 'thyroid

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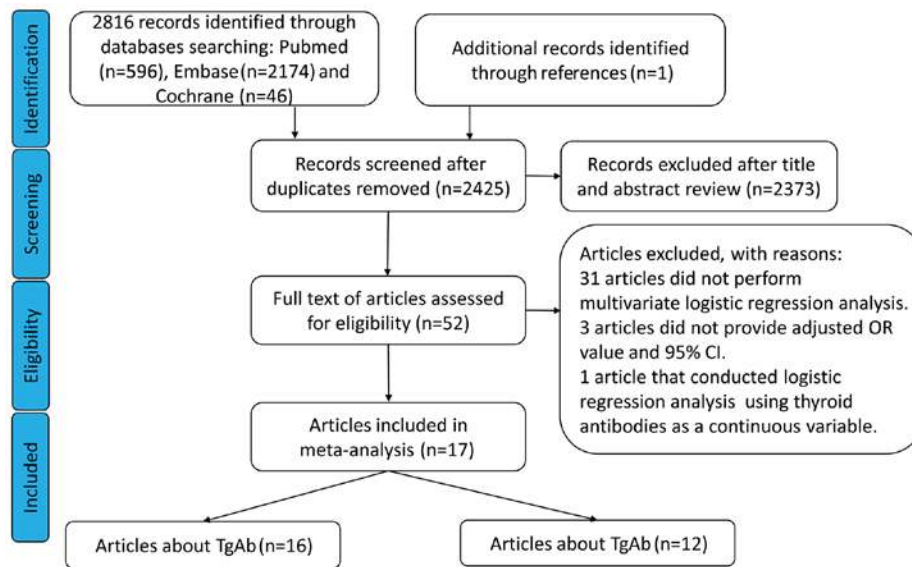


Figure 1. Study selection flowchart for the meta-analysis.

neoplasm', or 'thyroid nodule', and 'thyroglobulin antibody', 'thyroglobulin autoantibody', 'thyroid peroxidase antibody', 'thyroid peroxidase autoantibody', 'thyroid antibody', 'thyroid autoantibody', 'TgAb' or 'TPOAb'. We also searched for relevant articles from references of the original paper and review articles.

Selection criteria. The inclusion criteria were as follows: i) Studies explored the association between preoperative serum thyroid antibodies (TgAb or TPOAb), as a categorical variable, and the risk of TC; ii) patients with TC and thyroid benign nodules were classified into case group and control group, respectively; iii) the diagnosis of TC was based on preoperative FNAC or postoperative histological biopsy. Reviews, duplicate literatures, the meeting abstract and the studies that did not provide odds ratio (OR) and the corresponding 95% confidence intervals (CI) data adjusted by multivariate logistic regression analysis were excluded.

Data extraction. Two researchers independently extracted important information from the selected literature. The extracted data included: The first author, year of publication, study location, sample size, cancer types, confounding factors, OR values and 95%CI adjusted by multivariate logistic regression analysis.

Quality evaluation. The Newcastle-Ottawa Scale (14) was used to evaluate the quality of the selected literature. This scale is three dimensional: Selection, comparability and exposure, with a score range of 0-9. Scores of 0-6 were classified as low-quality studies and scores of 7-9 as high-quality studies.

Statistical analysis. Statistical analysis was carried out using STATA 14.0 software. The heterogeneity across studies was estimated using the I-squared statistic and Cochran's Q-test. If there was significant heterogeneity ($I^2 > 50\%$ or $P < 0.10$), the random effects model was used for meta-analysis. Next, a Galbraith plot was used to investigate the source

of heterogeneity from single studies. At the same time, meta-regression and subgroup analyses were performed based on the characteristics of studies to identify factors that contributed to heterogeneity. Otherwise, the fixed effects model was used. The pooled OR and 95%CI were calculated to evaluate the association between positive thyroid antibodies and the risk of TC. Z test was used to determine the significance of this association. Sensitivity analysis was performed to explore the influence of a single study on the overall risk estimate by omitting one study in each turn. Begg rank correlation test and Egger's regression test were used to estimate the publication bias, and the result of meta-analysis was corrected using the trim-and-fill method, if publication bias was identified. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Literature search and study characteristics. Our search identified 2,817 potentially relevant articles, out of which 392 were duplicates and were deleted (Fig. 1). After reading the title and abstract, 2,373 articles were deleted based on the exclusion criteria. Next, the full text of the remaining 52 articles was reviewed and 35 more were excluded. Finally, 17 articles were included in the meta-analysis (7,8,10,11,15-27). The characteristics of those articles are listed in Table I.

Meta-analysis. Sixteen articles containing 17 studies on the association between TgAb and the risk of TC involving 34,488 patients were included, and the pooled OR was 1.93 (95% CI=1.64-2.27, $I^2=67.2\%$), based on the random-effects model (Fig. 2). Twelve studies on the association between TPOAb and the risk of TC involving 30,007 patients were included, and the pooled OR was 1.48 (95% CI=1.15-1.91, $I^2=83.0\%$), based on the random-effects model (Fig. 3).

Heterogeneity analysis. As mentioned above, there was significant heterogeneity across the included studies. In studies about TgAb, the Galbraith radial plot showed that two studies

Table I. Characteristics of the included studies.

Author, year	Country	Sample size (case/control)	Cancer types	Confounding factors adjusted for in the original study	OR or RR (95%CI)	Quality score (Refs.)
Zhu <i>et al.</i> , 2018	China	90/285 ^a ; None ^b	TC	Age, nodule size, TSH	2.59 (1.25-5.37) ^a ; None ^b	8 (15)
Liu <i>et al.</i> , 2018	China	524/2,460 ^a ; 524/2,460 ^b	TC	Age, nodule size, TSH, TPOAb/TgAb	4.435 (1.902-10.345) ^a ; 0.901 (0.346-2.350) ^b	9 (16)
Zhao <i>et al.</i> , 2017 (male)	China	276/193 ^a ; None ^b	PTC	Age, TSH, TPOAb/TgAb, nodule size, nodule number	3.21 (1.36-7.57) ^a ; None ^b	9 (17)
Zhao <i>et al.</i> , 2017 (female)	China	844/728 ^a ; 844/728 ^b	PTC	Age, TSH, TPOAb/TgAb, nodule size, nodule number	1.80 (1.38-2.36) ^a ; 1.98 (1.44-2.73) ^b	9 (17)
Liu <i>et al.</i> , 2017	China	927/927 ^a ; 927/927 ^b	PTC	Age, gender, TSH	2.35 (1.82-3.04) ^a ; 1.58 (1.21-2.05) ^b	6 (11)
Zeng <i>et al.</i> , 2016	China	578/620 ^a ; None ^b	PTC	Age, nodule size	4.894 (2.520-9.505) ^a ; None ^b	8 (18)
He <i>et al.</i> , 2016	China	189/748 ^a ; 194/764 ^b	TC	Age, gender, TSH, TPOAb/TgAb	1.53 (0.91-2.56) ^a ; 0.92 (0.54-1.57) ^b	8 (19)
Qin <i>et al.</i> , 2015	China	237/1,401 ^a ; 237/1,401 ^b	DTC	Age, gender, nodule size, nodule number, TSH, TPOAb/TgAb	2.10 (1.40-3.15) ^a ; 1.2 (0.71-2.04) ^b	9 (20)
Li <i>et al.</i> , 2015	China	1,967/7,228 ^a ; 1,967/7,228 ^b	TC	18 confounding factors ^c	1.20 (1.02-1.42) ^a ; 2.83 (2.39-3.36) ^b	7 (21)
Vasileiadis <i>et al.</i> , 2014	Greece	389/447 ^a ; None ^b	PTC	Age, gender, HT, TSH, nodule size	1.86 (1.21-2.53) ^a ; None ^b	9 (8)
Grani <i>et al.</i> , 2014	Italy	78/1,131 ^a ; None ^b	MIN	Age, nodule size, nodule number, TPOAb/TgAb	0.98 (0.41-2.38) ^a ; None ^b	6 (22)
Azizi <i>et al.</i> , 2014	America	233/1,790 ^a ; 233/1,790 ^b	MIN	Age, gender	2.24 (1.57-3.19) ^a ; 1.19 (0.88-1.61) ^b	7 (23)
Wu <i>et al.</i> , 2013	China	537/1,595 ^a ; 537/1,595 ^b	PTC	Age, gender, TSH, TPOAb/TgAb	1.921 (1.431-2.580) ^a ; 1.945 (1.195-3.165) ^b	9 (24)
Lun <i>et al.</i> , 2013	China	636/1,631 ^a ; 634/1,627 ^b	PTC	Age, gender, HT, TSH, TPOAb/TgAb	1.89 (1.47-2.44) ^a ; 1.19 (0.88-1.61) ^b	8 (25)
Boi <i>et al.</i> , 2013	Italy	189/1,472 ^a ; 189/1,472 ^b	MIN	Age, gender, TSH, TPOAb/TgAb	1.67 (1.05-2.67) ^a ; 2.15 (1.42-3.25) ^b	7 (26)
Azizi <i>et al.</i> , 2011	America	253/2,247 ^a ; 253/2,247 ^b	MIN	Age, gender, nodule number, TSH	1.57 (1.11-2.23) ^a ; 1.12 (0.83-1.51) ^b	7 (7)
Kim <i>et al.</i> , 2010	Korea	296/1,342 ^a ; None ^b	MIN	Age, gender, nodule number, nodule size, TSH	1.61 (1.12-2.33) ^a ; None ^b	6 (10)
Boelaert <i>et al.</i> , 2006	Britain	None ^a ; 91/1,138 ^b	MIN	TSH	None ^a ; 1.19 (0.6-2.35) ^b	7 (27)

^aData from the study on TgAb. ^bData from the study on TPOAb. ^cThe 18 confounding factors included gender, TSH, TPOAb/TgAb, nodule number and nodule size, which were adjusted for in the original study. TC, DTC and PTC were confirmed by postoperative histology TSH, thyroid stimulating hormone; TC, thyroid cancer; DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer; HT, hashimoto thyroiditis; MIN, malignant thyroid nodules, confirmed by thyroid fine needle aspiration cytology; OR, odds ratio; CI, confidence intervals; RR, risk ratio.

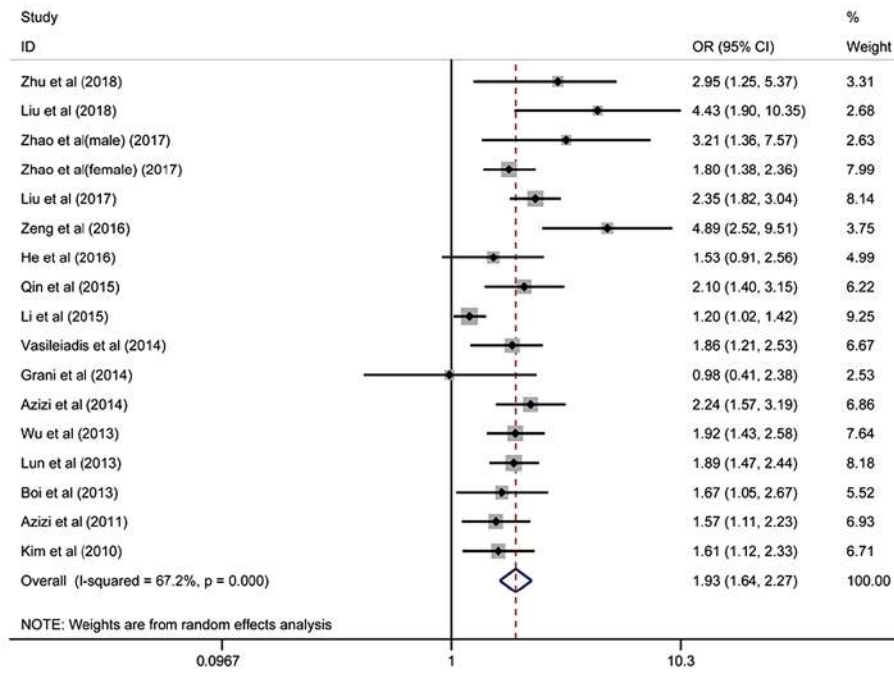


Figure 2. Forest plots for the association between TgAb and the risk of TC. TgAb, thyroglobulin antibodies; TC, thyroid cancer.

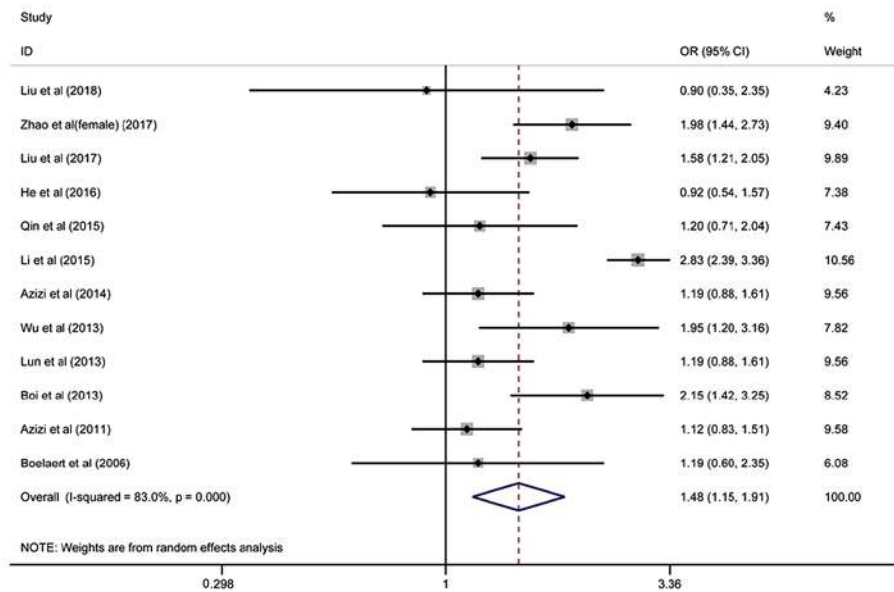


Figure 3. Forest plots for the association between TPOAb and the risk of TC. TPOAb thyroid peroxidase antibodies; TC, thyroid cancer.

caused the heterogeneity (18,21) (Fig. 4). After removing the two studies, we found that the rest of the included studies were homogeneous ($I^2=9.7%$, $P=0.35$) and the association between positive TgAb and the increased risk TC did not change (OR=1.93, 95%CI=1.74-2.14). In addition, meta-regression analysis was conducted based on the characteristics of studies including study location, cancer types, sample size and confounding factors. The results indicated that confounding factors (gender and thyroid nodule number) were responsible for 74.6% of the heterogeneity ($P<0.05$).

In studies on TPOAb, Li *et al* (21) and Zhao *et al* (17) (female) study data were the causes of heterogeneity (Fig. 5). The association between positive TPOAb and increased risk

of TC did not change (OR=1.33, 95%CI=1.13-1.57) and the heterogeneity became not significant ($I^2=36.5%$, $P=0.12$) following the removal of the two studies. Meta-regression analysis did not identify the characteristics of studies that led to heterogeneity. It only showed non-significant heterogeneity in the PTC group.

Subgroup analysis. In studies on TgAb, positive TgAb was associated with an increased risk of TC in all subgroups. A stronger association was found in studies that did not adjust the thyroid nodule number (OR=2.14, 95% CI=1.82-2.52), as compared with studies that did (OR=1.61, 95% CI=1.29-2.00; $P=0.04$).

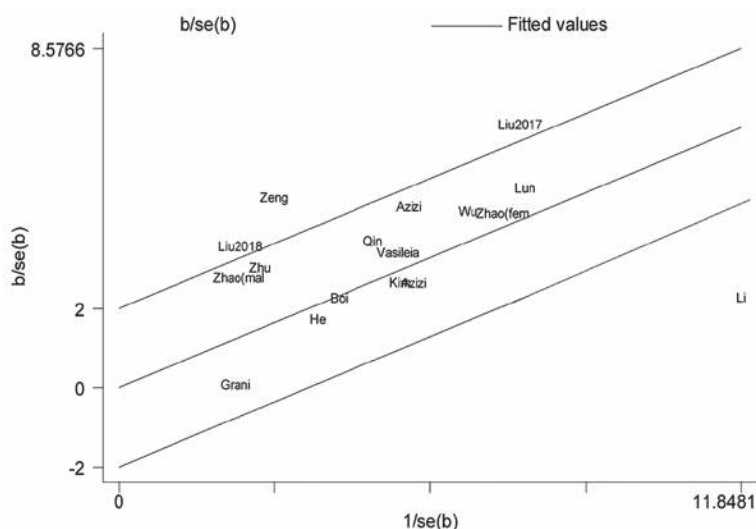


Figure 4. Galbraith radial plot for the heterogeneity across studies on TgAb. TgAb, thyroglobulin antibodies.

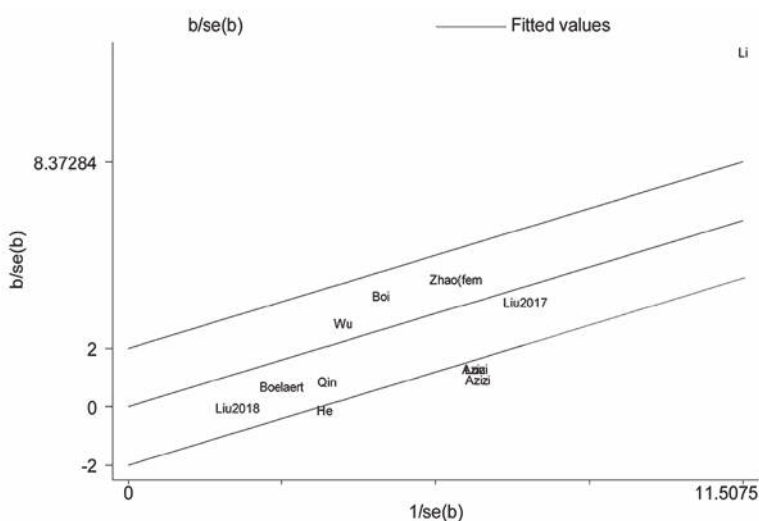


Figure 5. Galbraith radial plot for the heterogeneity across studies on TPOAb. TPOAb, thyroid peroxidase antibodies.

In studies on TPOAb, no association between TPOAb and the risk of TC was observed in the TC group and big sample size group (Table II).

Sensitivity analysis. Sensitivity analysis found that the removal of any studies on TgAb or TPOAb did not affect the pooled OR values and 95% CI, suggesting that the results of our meta-analysis were stable and not influenced by a single study.

Publication bias. In studies on TgAb, the funnel plot was asymmetrical, indicating the presence of potential publication bias ($P=0.02$; Fig. 6), whereas publication bias did not exist ($P=0.28$) following the removal of the data from the study by Li *et al* (21), which was the biggest sample size study and source of heterogeneity. This suggested that the essential difference between smaller and larger studies that arises from heterogeneity across studies was the cause of the asymmetry of the funnel plot (28). Despite that, the trim-and-fill method was used right away and the corrected OR value was found

to be 1.61 (95% CI=1.36-1.91), which was not significantly different from the original OR values, proving the authenticity of the meta-analysis. In studies on TPOAb, both the funnel plot and the Egger test indicated the presence of publication bias ($P<0.01$), but no publication bias was observed ($P=0.11$) following the removal of the data from the study by Li *et al* (21) (Fig. 7).

Discussion

The identification of benign and malignant thyroid nodules has always been in the center of clinical attention. It is controversial whether thyroid antibodies are a risk factor for TC (22,29-31). In the present meta-analysis, TgAb-positive patients were found twice as likely to develop TC as TgAb-negative patients, suggesting that positive TgAb is a risk factor for TC. Though positive TPOAb is associated with an increased risk of TC, this association did not exist in some subgroups, which may have been due to the small sample size of those subgroups.

Table II. Subgroup analysis to probe differences in the pooled OR values between studies included in the meta-analysis.

A, TgAb				
Variables	Pooled OR (95%CI)	Test of heterogeneity		P-value
		I ² (%)	P-value	
Study location				0.34
Occident (n=5)	1.78 (1.48-2.14)	0.2	0.405	
Asia (n=12)	2.05 (1.66-2.53)	75.4	0	
Cancer type				0.29
TC (n=4)	1.99 (1.14-3.46)	78.8	0.003	
DTC (n=1)	2.10 (0.89-2.65)	-	-	
PTC (n=7)	2.11 (1.77-2.50)	42.8	0.105	
MN (=5)	1.72 (1.42-2.07)	2.6	0.392	
Sample size				0.16
>1,200 (=12)	1.81 (1.52-2.15)	68.3	0	
<1,200 (=5)	2.48 (1.65-3.75)	58.4	0.048	
Adjusted for nodule number				0.04
Yes (n=7)	1.61 (1.29-2.00)	60.8	0.018	
No (n=10)	2.14 (1.82-2.52)	38.9	0.099	
Adjusted for nodule size				0.76
Yes (n=10)	2.04 (1.54-2.70)	76.1	0	
No (n=7)	1.95 (1.72-2.20)	0	0.489	
Adjusted for gender				0.18
Yes (n=13)	1.80 (1.56-2.09)	61.00	0.002	
No (n=4)	2.90 (1.48-5.69)	67.10	0.028	
B, TPOAb				
Variables	Pooled OR (95%CI)	Test of heterogeneity		P-value
		I ² (%)	P-value	
Study location				0.53
Occident (n=4)	1.35 (1.00-1.82)	57.3	0.071	
Asia (n=8)	1.55 (1.13-2.12)	84.2	0	
Cancer type				0.66
TC (n=3)	1.41 (0.56-3.51)	89.9	0	
DTC (n=1)	1.20 (0.71-2.03)	-	-	
PTC (n=4)	1.60 (1.27-2.02)	50	0.112	
MN (=4)	1.35 (1.00-1.82)	57.3	0.071	
Sample size				0.85
>2,000 (=6)	1.46 (0.95-2.26)	90.6	0	
<2,000 (=6)	1.54 (1.21-1.95)	48.3	0.085	
Adjusted for nodule number				0.46
Yes (n=4)	1.69 (1.03-2.78)	91	0	
No (n=8)	1.39 (1.14-1.69)	43.2	0.091	
Adjusted for nodule size				0.27
Yes (n=4)	1.79 (1.14-2.79)	80	0.001	
No (n=8)	1.36 (1.13-1.63)	47.5	0.064	

P-values were used to assess the subgroup differences. TC, DTC and PTC were confirmed by postoperative histology. TC, thyroid cancer; DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer; MN, malignant thyroid nodules (confirmed by thyroid fine needle aspiration cytology).

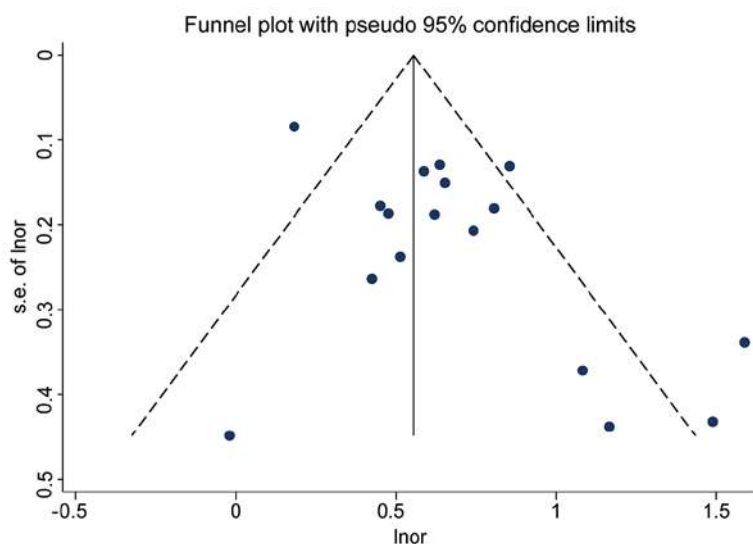


Figure 6. Funnel plot for publication bias test in the meta-analysis on TgAb. TgAb, thyroglobulin antibodies.

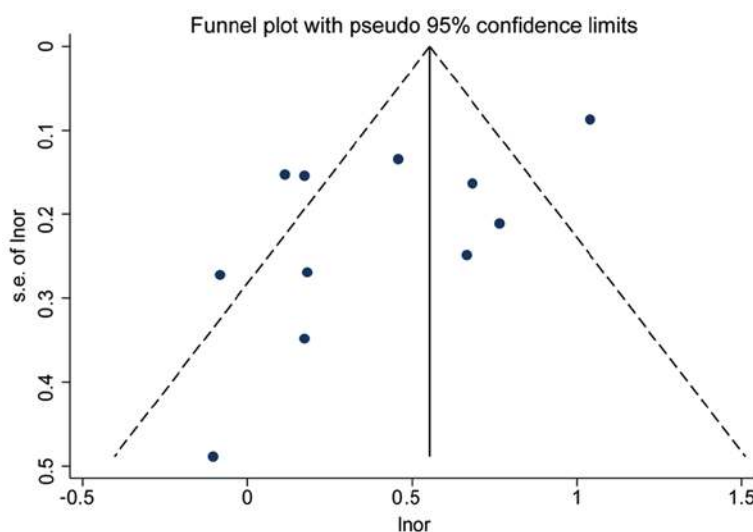


Figure 7. Funnel plot for publication bias test in the meta-analysis on TPOAb. TPOAb thyroid peroxidase antibodies.

Furthermore, the result of the meta-analysis was consistent with a diagnostic study conducted by Hosseini *et al* (29), which found that the sensitivity and specificity of TgAb for the diagnosis of TC was 16.04% (95% CI=11.37-21.68) and 90.67% (95% CI=85.66-94.38), respectively. Therefore, positive TgAb is specific for TC, although negative TgAb has little value in eliminating the diagnosis of TC. Certain studies reported that the lower sensitivity of TgAb may arise from the limitations of assay methods, since using different TgAb assays could discover discrepancies in the TgAb status (32-34).

It is well-known that TgAb, combined with TPOAb, used to be a hallmark of AITD. Several studies have discovered an obvious association between AITD with TC, and reported that the coexistence with AITD may be one cause of the elevated serum thyroid antibodies in patients with TC (35-37). However, positive TgAb remained a risk factor for TC in studies which excluded AITD patients (24,25). A study showed that the exposure of thyroglobulin antigen

during tumor formation could cause an increase in serum TgAb through immune responses (38). Other studies found that thyroglobulin had ~40 antigenic sites, which were different between TC and AITD patients (39,40). TC patients exhibited clearly higher core fucose content and an increasing trend of TgAb sialylation (41). Further research could improve the predictive value of TgAb for TC by detecting TC-specific TgAb fragments.

The present meta-analysis had several following advantages: First, all included studies had performed a multivariate logistic regression analysis that controlled the effects of confounding factors, which fully demonstrated the independent predictive value of TgAb for TC. Secondly, our analysis included a large sample data from a total of 34,488 thyroid nodules patients in 17 studies on TgAb. Although a moderate to high heterogeneity was observed among those studies ($I^2=67.2%$), the pooled OR value did not change following the removal of the two studies that caused the heterogeneity. It was also found that the differences in confounding factors (thyroid nodule

number and gender) controlled by the study caused 74.6% of the heterogeneity. This may be due to differences in cancer rates among people with different genders or thyroid nodule numbers. Nevertheless, the results of both the sensitivity analysis and the trim-and-fill method supported the accuracy of our meta-analysis on the association between positive TgAb and the increased risk of TC.

However, the present meta-analysis also had certain limitations. First, most of the included studies were retrospective case-control studies and cross-sectional studies, which were unable to articulate the causal relationship between TgAb and TC. As a result, a multi-center and prospective cohort study is required to further investigate this issue. Secondly, publication bias was identified in our meta-analysis on TgAb. Even though the heterogeneity across studies, particularly that by Li *et al* (21) that had too big a sample size and was the main source of heterogeneity, led to this bias (28), the result of the trim-and-fill method supported the authenticity of our meta-analysis. Finally, in studies on TPOAb, even though we discovered that the high heterogeneity was derived from single studies ($I^2=83.0\%$), we failed to identify the characteristics of these studies that led to heterogeneity. We therefore did not conduct a meta-analysis on the association between TPOAb and the risk of TC.

In conclusion, positive TgAb is an independent risk factor for TC. The association between positive TPOAb and the risk of TC remains to be elucidated.

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Availability of data and materials

The datasets used and analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YaX, QZ, QAL and SLY conceived and designed the experiments. YaX, QZ, QAL, SLY and YoX performed the experiments. YaX and QZ analyzed the data. YaX, QAL, SLY, QZ and YoX wrote the paper.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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