

# A meta-analysis of the influence of body mass index on the clinicopathologic progression of papillary thyroid carcinoma

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## Abstract

**Background:** Papillary thyroid carcinoma (PTC) incidence has been increasing worldwide. Obesity, that is, having a high body mass index, is associated with the incidence of several cancers including colon, breast, esophageal, and kidney cancer. However, the association between obesity and the clinical features of PTC is still unknown. This study aimed to determine the impact of obesity on the clinical features of PTC.

**Method:** A database search was conducted for articles published up to 2020 on obesity and clinical features of PTC. Data were extracted from articles that met the meta-analysis inclusion criteria.

**Results:** A total of 11 retrospective cohorts and 11,729 patients were included. Obesity was associated with the following variables in PTC patients: older age (difference in means = 1.95, 95% confidence interval [CI] 0.16–3.74,  $P = .03$ ), male sex (odds ratio [OR] = 3.13, 95%CI 2.24–4.38,  $P < .00001$ ), tumor size  $\geq 1$  cm (OR = 1.34, 95%CI 1.11–1.61,  $P < .002$ ), multifocality (OR = 1.54, 95%CI 1.27–1.88,  $P < .0001$ ), extrathyroidal extension (OR = 1.78, 95%CI 1.22–2.59,  $P = .003$ ) and advanced tumor, node, metastasis stage (OR = 1.68, 95%CI 1.44–1.96,  $P < .00001$ ). Preoperative serum thyroid-stimulating hormone level (difference in means = 0.09, 95%CI 0.35–0.52,  $P = .70$ ), Vascular invasion (OR = 0.84, 95%CI 0.56–1.26,  $P = .41$ ), lymph node metastasis (OR = 1.07, 95%CI 0.87–1.32,  $P = .50$ ), distant metastasis (OR = 1.14, 95%CI 0.64–2.04,  $P = .66$ ), and recurrence (OR = 1.45, 95%CI 0.97–2.15,  $P = .07$ ) were not associated with obesity.

**Conclusion:** Obesity was associated with several poor clinicopathologic prognostic features: older age, male gender, tumor size  $\geq 1$  cm, extrathyroidal extension, multifocality, and advanced tumor/node/metastasis stage. However, thyroid-stimulating hormone level, vascular invasion, lymph node metastasis, distant metastasis, and recurrence were not associated with obesity in PTC.

**Abbreviations:** BMI = body mass index, CI = confidence interval, LNM = lymph node metastasis, MD = difference in means, OR = odds ratio, PTC = papillary thyroid carcinoma, TNM = tumor/node/metastasis, TSH = thyroid-stimulating hormone.

**Keywords:** body mass index, clinicopathologic progression, papillary thyroid carcinoma

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Ethical standards was not applicable.

The authors have no conflicts of interest to disclose.

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The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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## 1. Introduction

Over the past 20 years, the incidence of thyroid cancer, especially papillary thyroid carcinoma (PTC), has increased significantly worldwide. According to the Surveillance, Epidemiology, and End Results database, incidence of PTC in the USA increased from 4.56 per 100,000 person-years in 1974 to 1977 to 14.42 per 100,000 person-years in 2010 to 2013.<sup>[1]</sup> According to data from the China Cancer Center, thyroid cancer ranks seventh in cancer incidence in China and is the fourth most common malignancy in women.<sup>[2]</sup> The increase in the incidence of PTC is largely due to the application of high-resolution ultrasonography to detect thyroid nodules. Nevertheless, this does not explain why the incidence of thyroid cancer with a larger diameter is on the rise, with studies reporting increased incidence of PTCs, with larger size and at later stage.<sup>[3]</sup> One study based on data from the Surveillance Epidemiology and End Results database showed that environmental and other factors play an important role in the occurrence and development of thyroid cancer.<sup>[3]</sup>

Overweight and obesity, that is, having a high body mass index (BMI), are considered to be associated with incidence of several cancers, including cancer of the colon, breast, esophagus, and kidney.<sup>[4]</sup> Furthermore, high BMI is related to advanced stage or aggressive cancers including prostate, colon and breast cancers.<sup>[5]</sup> However, whether BMI is associated with the incidence or prognosis of PTC is still controversial. Although the current (8th

edition) American Joint Committee on Cancer staging system has stratified prognostic risk factors according to age, tumor size, lymph node metastasis (LNM), grossly extrathyroidal extension, and distant metastasis, the impact of these factors on PTC prognosis is still unknown.<sup>[6]</sup> Some studies have reported a correlation between obesity or elevated BMI with more advanced tumor/node/metastasis (TNM) stage and extrathyroidal extension in PTC.<sup>[7,8]</sup> In contrast, other studies have found no association between obesity and PTC progression.<sup>[9,10]</sup> In light of these conflicting reports, we aimed to conduct a meta-analysis to assess whether obesity was associated with the clinical features and progression of PTC.

## 2. Methods

We performed this meta-analysis according to the preferred reporting items for systematic reviews and meta-analyses statement.<sup>[11]</sup> A systematic search of the PubMed, Web of Science, and China National Knowledge Infrastructure databases was performed to find relevant articles published up to 8<sup>th</sup> February 2020. The following search terms were used: (“thyroid cancer” OR “thyroid neoplasm” OR “thyroid carcinoma”) AND (“obesity” OR “body mass index” OR “weight”). The study selection was done by two independent authors who screened the titles, abstracts, and full text. Relevant references and reviews were also identified. Discrepancies were resolved via discussion. Our study was approved by the Ethics Committee of the First Affiliated Hospital of China Medical University, Shenyang, China.

### 2.1. Selection criteria and exclusion criteria

BMI was calculated as weight (kilograms) divided by the square of height (meters). On the basis of the standardized guidelines set by the World Health Organization, for enrolled patients with PTC, normal weight was defined as  $18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$  and obesity was defined as  $\text{BMI} \geq 30 \text{ kg/m}^2$ . Studies met the inclusion criteria if the following conditions were met:

- (1) Studies were required to be retrospective or prospective cohort studies;
- (2) included patients had PTC with thyroidectomy and central lymph node dissection or lateral lymph node dissection;
- (3) the relevant BMI records were complete to allow data extraction; and
- (4) data were presented as odds ratio (OR) or hazard ratio with 95% confidence interval (CI) reported.

We excluded studies that met at least one of the following criteria:

- (1) studies with patients who did not accept initial treatment;
- (2) articles that were comments, case reports, reviews, letters, conference abstracts, or expert opinions;
- (3) studies with patients with a family history of thyroid malignancy.

### 2.2. Data extraction and quality assessment

Data extraction was performed by two authors independently. The collected information was extracted and recorded as follows: first author, publication year, country, study design, and case number. Possible risk factors associated with elevated BMI were

investigated and the corresponding numbers of patients were recorded. The identified risk factors were age, sex, tumor size, serum levels of thyroid-stimulating hormone (TSH) before operation, multifocality, extrathyroidal extension, vascular invasion, LNM, advanced TNM stage, distant metastasis, and recurrence. We assessed the quality of each included cohort study using the Newcastle-Ottawa Scale (NOS) which yielded a minimum score of 0 and a maximum score of 9. The quality assessments were performed by two independent reviewers.

### 2.3. Statistical analysis

Review Manager 5.3 (<https://community.cochrane.org>) was used for statistical analyses. The results are presented as ORs with 95% CIs. Unless otherwise specified,  $P$ -values  $< .05$  were considered statistically significant. In addition, the  $I^2$  statistic and the  $Q$  test were used to quantify heterogeneity. When  $I^2$  was  $< 50\%$  and  $P > .1$ , a fixed-effects model was used. To test for possible publication bias, Begg’s funnel plots were used.

## 3. Results

A total of 3,059 studies from PubMed, 6071 studies from Web of Science and 49 studies from China National Knowledge Infrastructure were initially found. After removing duplicate articles, 7,017 articles were included for screening. Following consideration of the inclusion and exclusion criteria for the review, a total of 46 full-text articles were selected after carefully checking the titles and abstracts. After the full-text review, 11 retrospective cohort studies met our selection criteria. A flow chart with details of the study selection process is displayed in Figure 1 and the study characteristics are shown in Table 1.

### 3.1. Age of patients

A total of seven articles were included in the analysis of whether obesity was associated with age in PTC patients. A random-effects model was applied to analyze this risk factor ( $P = .002$ ,  $I^2 = 72\%$ ). Older age was associated with obesity in PTC patients, with a significant difference in age found between the obese group and the normal weight group (difference in means [MD] = 1.95, 95% CI 0.16–3.74,  $P = .03$ ) (Fig. 2A, Figure S1A, Supplemental Digital Content, <http://links.lww.com/MD2/A302>).

### 3.2. Gender

A total of 10 articles and 9,590 patients were included in the analysis of whether obesity was associated with sex in PTC patients. A random-effects model was applied to analyze this risk factor ( $P < .00001$ ,  $I^2 = 82\%$ ). Our results indicated that male PTC patients were more likely to be obese than female patients (38.48% vs 15.53%, OR = 3.13, 95% CI 2.24–4.38,  $P < .00001$ ) (Fig. 2B, Figure S1B, Supplemental Digital Content, <http://links.lww.com/MD2/A302>).

### 3.3. Preoperative serum TSH level

A total of six articles were included in the analysis of whether obesity was associated with preoperative serum TSH level in PTC patients. A random-effects model was applied to analyze this risk factor ( $P < .00001$ ,  $I^2 = 92\%$ ) and our results indicated that

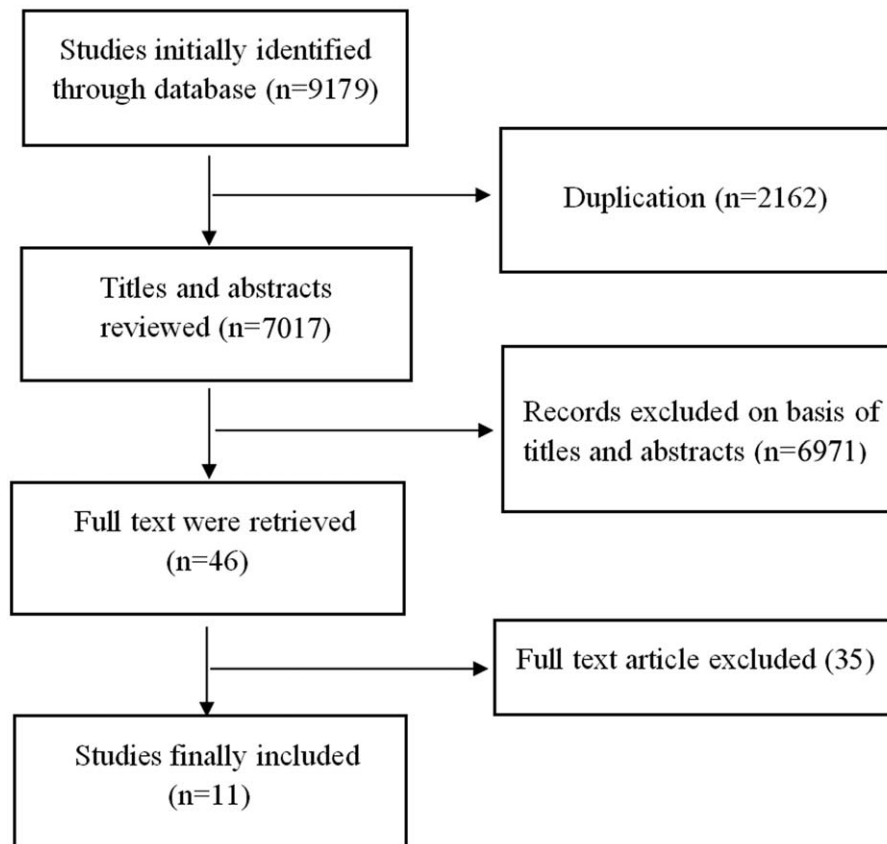


Figure 1. Flow chart of the study selection process.

preoperative serum TSH level was not associated with obesity in PTC patients. No difference in preoperative serum TSH level was found between the normal weight group and the obese group (MD=0.09, 95%CI 0.35–0.52,  $P=.70$ ) (Fig. 2C, Figure S1C, Supplemental Digital Content, <http://links.lww.com/MD2/A302>).

### 3.4. Primary tumor size

A total of nine studies with continuous variables and six articles with dichotomous variables were included in the analysis of

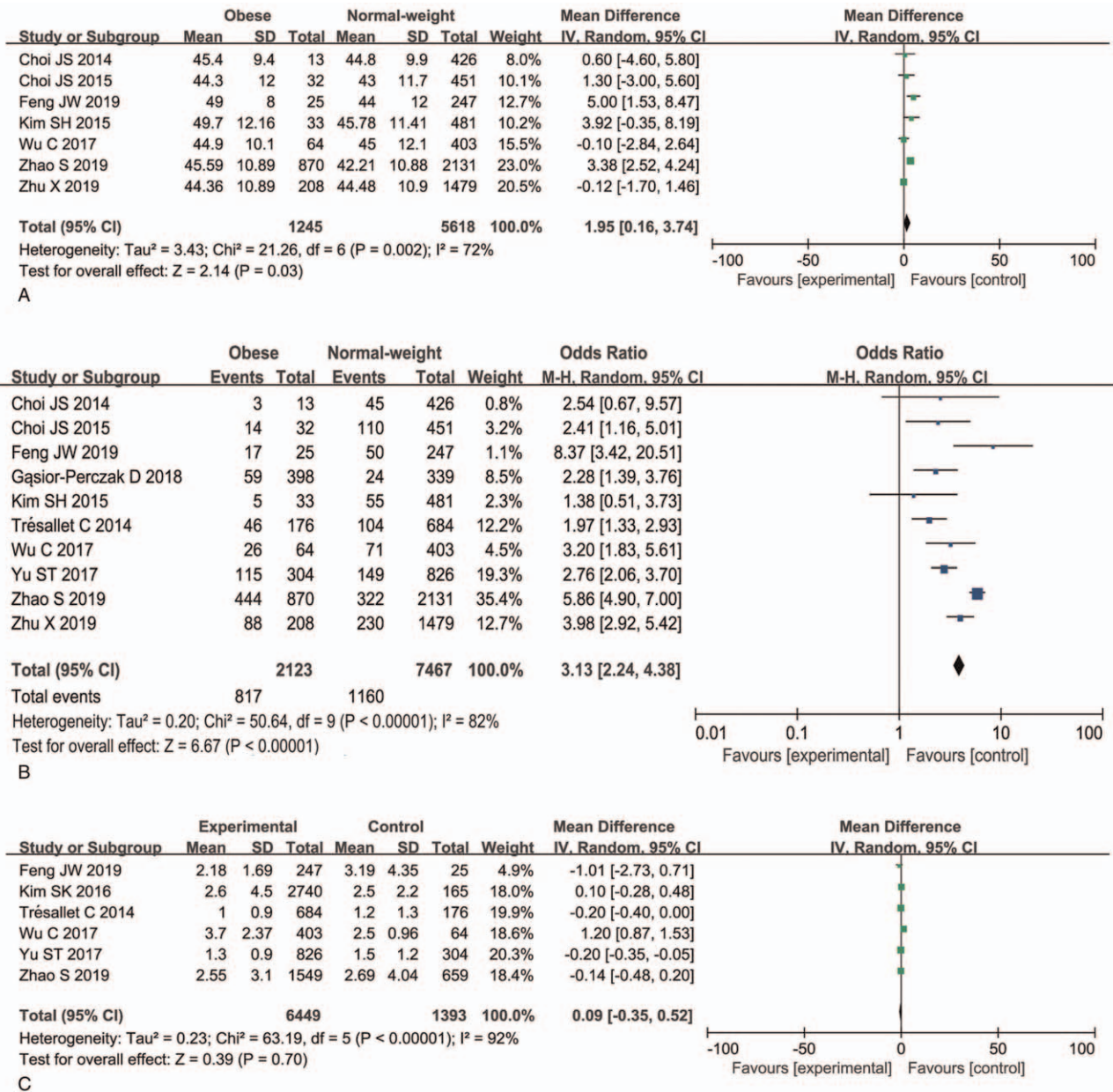
whether obesity was associated with primary tumor size in PTC patients. For the studies with continuous variables, a random-effects model was used to detect this risk factor ( $P=.02$ ,  $I^2=58%$ ); for dichotomous variables a random-effects models was used and 1 cm was used as a cutoff value ( $P=.03$ ,  $I^2=60%$ ). Our meta-analysis indicated that obesity was associated with larger primary tumor size (MD=0.17, 95%CI 0.09–0.24,  $P<.00001$ ; OR=1.34, 95%CI 1.11–1.61,  $P<.002$ ) (Fig. 3A, Figure S2A, Supplemental Digital Content, <http://links.lww.com/MD2/A303> and

Table 1

Basic characteristics of the included studies.

Author	Year	Country	Study design	PTC/PTMC	Case number obese	Case number normal weight
Trésallet C <sup>[7]</sup>	2014	France	retrospective	PTC	176	684
Choi JS <sup>[8]</sup>	2014	Korea	retrospective	PTC	32	451
Choi JS <sup>[36]</sup>	2015	Korea	retrospective	PTMC	13	426
Feng JW <sup>[37]</sup>	2019	China	retrospective	PTC	25	247
Yu ST <sup>[38]</sup>	2017	China	retrospective	PTC	304	826
Kim SH <sup>[39]</sup>	2015	Korea	retrospective	PTC	33	481
Kim SK <sup>[40]</sup>	2016	Korea	retrospective	PTC	165	2740
Wu C <sup>[41]</sup>	2017	China	retrospective	PTC	64	403
Zhao S <sup>[42]</sup>	2019	China	retrospective	PTC	426	1809
Gąsior Perczak D <sup>[43]</sup>	2018	Poland	retrospective	PTC	398	339
Zhu X <sup>[44]</sup>	2019	China	retrospective	PTC	208	1479

PTC = papillary thyroid carcinoma; PTMC = papillary thyroid microcarcinoma.



**Figure 2.** Forest plots of the association between age, gender, preoperative serum TSH level, and obesity in PTC. (A) Age; (B) gender; (C) preoperative serum TSH level. PTC = papillary thyroid carcinoma, TSH = thyroid-stimulating hormone.

Figure S3B, Supplemental Digital Content, <http://links.lww.com/MD2/A304>, Figure S2B, Supplemental Digital Content, <http://links.lww.com/MD2/A303>.

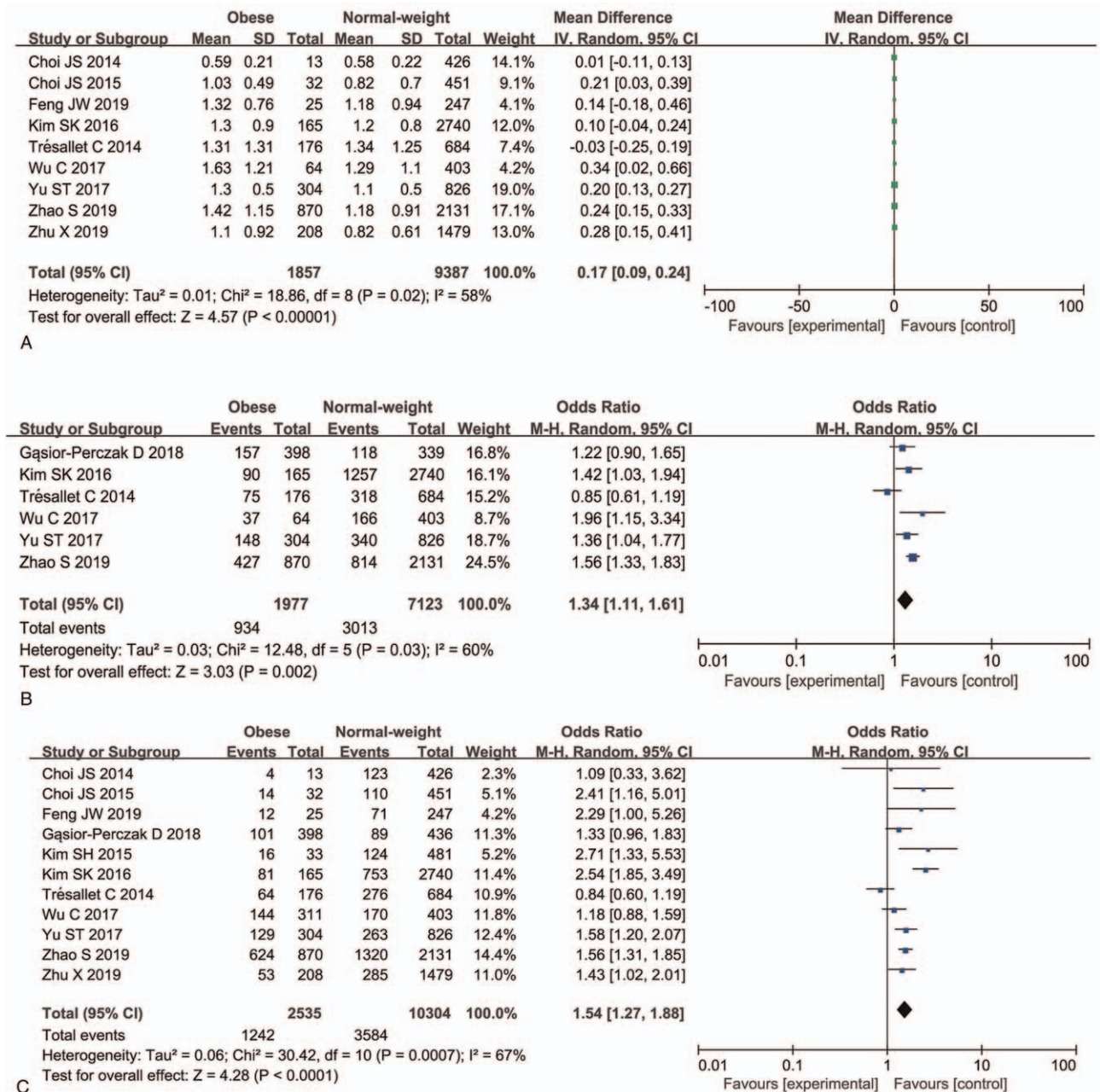
**3.5. Multifocality**

A random-effects model was applied to analyze whether obesity was associated with multifocality in PTC ( $P < .00001$ ,  $I^2 = 81\%$ ). A total of 11 articles with a total of 12,839 patients were included. Our meta-analysis indicated a higher rate of multifocality in the obese group than in the normal weight PTC patients (48.99% vs 34.78%). There was a significant difference in focality between the normal weight group and the obese group (OR = 1.54, 95% CI 1.27–1.88,  $P < .0001$ ) (Fig. 3C, Figure S2C,

Supplemental Digital Content, <http://links.lww.com/MD2/A303>).

**3.6. Extrathyroidal extension**

A total of 10 articles and 6713 patients were included in the analysis of whether obesity was associated with extrathyroidal extension in PTC patients. A random-effects model was applied to analyze this risk factor ( $P < .00001$ ,  $I^2 = 79\%$ ). Meta-analysis indicated that extrathyroidal extension-positive PTC patients were more likely to be obese than extrathyroidal extension-negative PTC patients (29.68% vs 23.23%; OR = 1.78, 95% CI 1.22–2.59,  $P = .003$ ) (Fig. 4A, Figure S3A, Supplemental Digital Content, <http://links.lww.com/MD2/A304>).



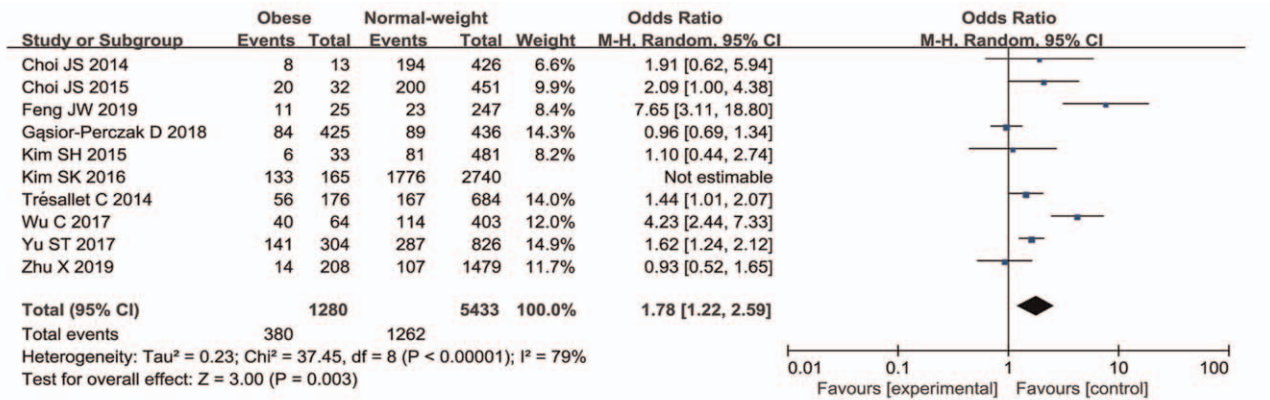
**Figure 3.** Forest plots of the association between primary tumor size, multifocality, and obesity in PTC. (A) Primary tumor size (continuous variable); (B) primary tumor size (dichotomous variable); (C) multifocality. PTC = papillary thyroid carcinoma.

### 3.7. Vascular invasion

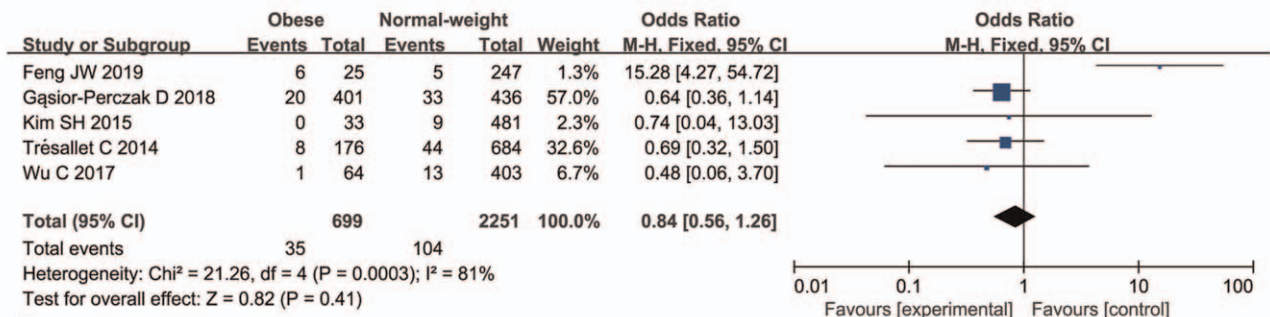
A total of five articles and 2950 patients were included in the analysis of whether obesity was associated with vascular invasion in PTC patients. A fixed-effects model was applied to analyze this risk factor ( $P < .0003$ ,  $I^2 = 81\%$ ) and the meta-analysis indicated that vascular invasion was not associated with obesity in PTC patients (OR=0.84, 95%CI 0.56–1.26,  $P=.41$ ) (Fig. 4B, Figure S3B, Supplemental Digital Content, <http://links.lww.com/MD2/A304>).

### 3.8. Lymph node metastasis

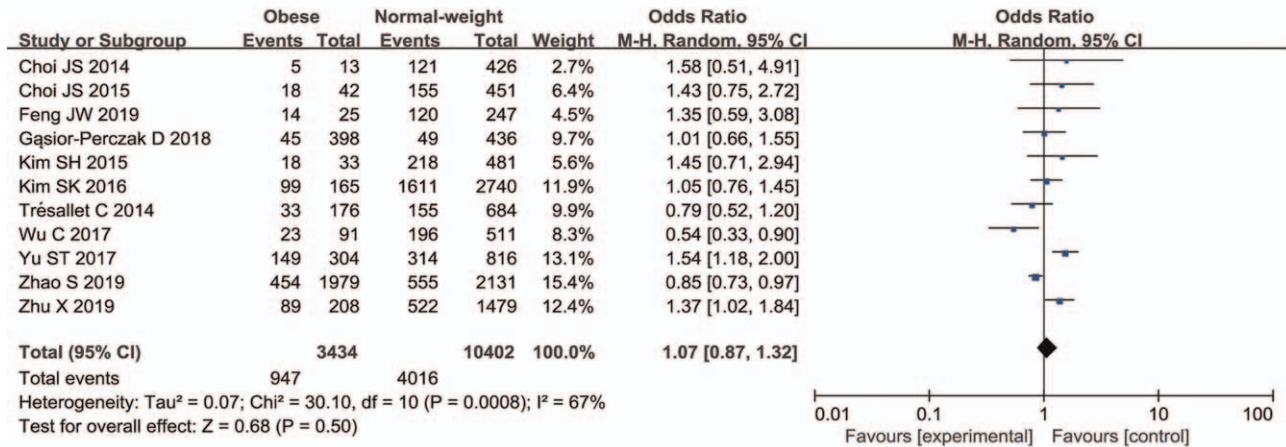
A total of 11 articles and 13,836 patients were included in the analysis of whether obesity was associated with LNM in PTC patients. A random-effects model was applied ( $P < .0008$ ,  $I^2 = 67\%$ ) and the meta-analysis indicated that being LNM positive was not associated with obesity in PTC patients (OR=1.07, 95%CI 0.87–1.32,  $P=.50$ ) (Fig. 4C, Figure S3C, Supplemental Digital Content, <http://links.lww.com/MD2/A304>).



A



B



C

**Figure 4.** Forest plots of the association between extrathyroidal extension, vascular invasion, lymph node metastasis, and obesity in PTC. (A) Extrathyroidal extension; (B) vascular invasion; (C) lymph node metastasis. PTC = papillary thyroid carcinoma.

### 3.9. Advanced TNM stage

A fixed-effects model was applied to analyze advanced TNM stage as a risk factor ( $P = .93$ ,  $I^2 = 0\%$ ). The meta-analysis indicated that advanced TNM stage (III/IV) PTC was associated with obesity in PTC patients (26.32% vs 20.86%; OR = 1.68, 95%CI 1.44–1.96,  $P < .00001$ ) (Fig. 5A, Figure S4A, Supplemental Digital Content, <http://links.lww.com/MD2/A305>).

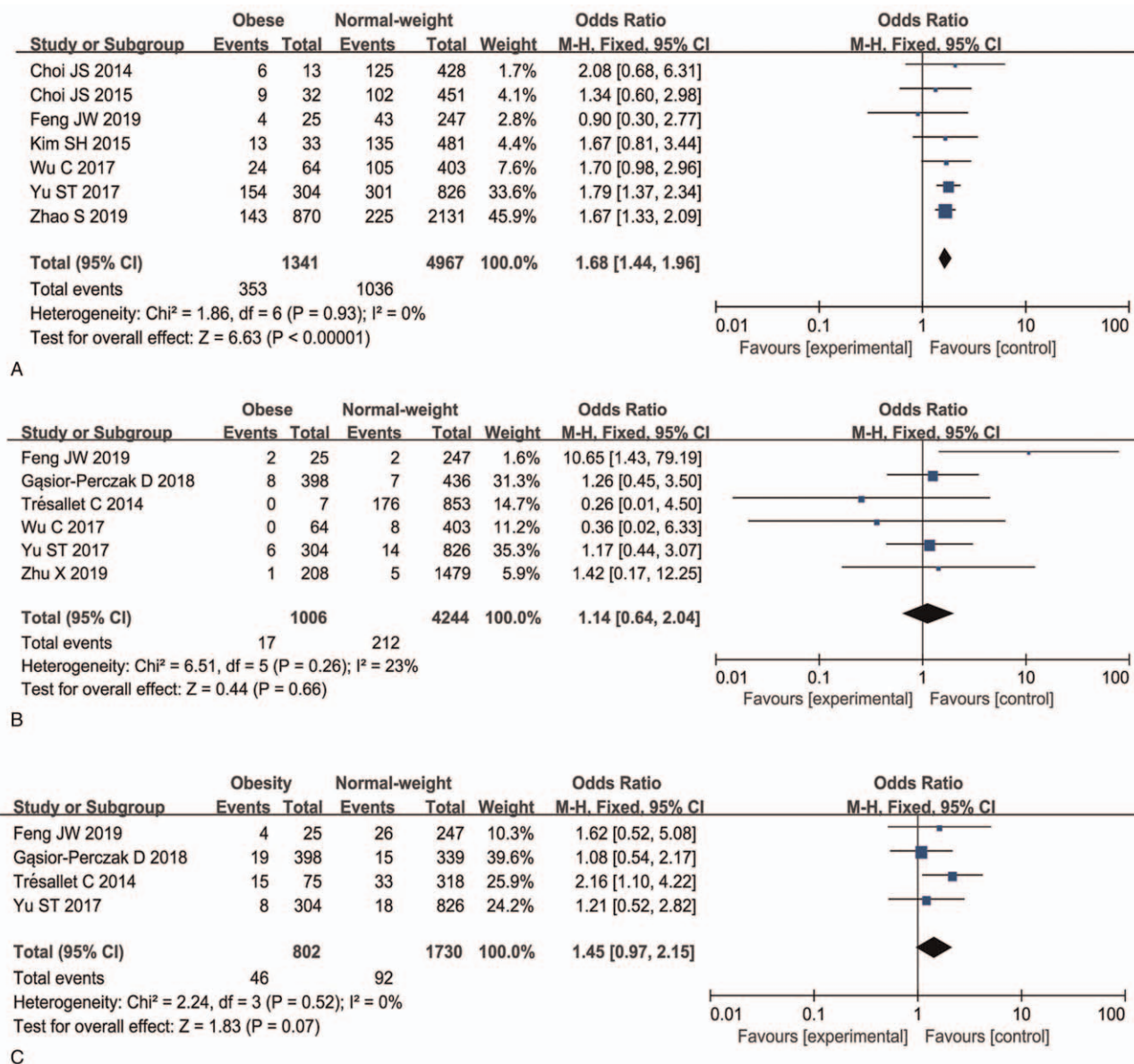
### 3.10. Distant metastasis

A total of six articles and 5250 patients were included in the analysis of whether obesity was associated distant metastasis in PTC patients. A fixed-effects model was applied to the analysis of

this risk factor ( $P < .26$ ,  $I^2 = 23\%$ ) and indicated that distant metastasis was not associated with obesity in PTC patients (OR = 1.14, 95%CI 0.64–2.04,  $P = .66$ ) (Fig. 5B, Figure S4B, Supplemental Digital Content, <http://links.lww.com/MD2/A305>).

### 3.11. Recurrence

A total of four articles and 2532 patients were included in the analysis of whether obesity was associated with recurrence of disease in PTC patients. A fixed-effects model was applied ( $P < .52$ ,  $I^2 = 0\%$ ) and the meta-analysis indicated that recurrence was not associated with obesity in PTC patients (OR = 1.45, 95% CI 0.97–2.15,  $P = .07$ ) (Fig. 5C, Figure S4C, Supplemental Digital Content, <http://links.lww.com/MD2/A305>).



**Figure 5.** Forest plots of the association between advanced TNM stage, distant metastasis, recurrence, and obesity in PTC. (A) Advanced TNM stage; (B) distant metastasis; (C) recurrence. PTC = papillary thyroid carcinoma, TNM = tumor/node/metastasis.

### 4. Discussion

Thyroid cancer incidence has increased rapidly across the world in the last several decades. PTC is the most common type, representing approximately 85% to 90% of all cases.<sup>[12]</sup> In the USA, thyroid cancer incidence increased from 4.56 per 100,000 person-years in 1974 to 1977 to 14.42 per 100,000 person-years in 2010 to 2013, an average increase of 3.6% per year between 1974 and 2013.<sup>[1]</sup> In China, the age-standardized incidence was 3.21/105 in 2005, and had increased to 9.61/105 in 2015. This represents an average annual percentage change of 12.4% for the period 2005 to 2015.<sup>[13]</sup> However, the cause of the increasing incidence of thyroid cancer is still unclear.

The prevalence of obesity is also increasing worldwide and the impact of obesity on cancer risk has been extensively studied.<sup>[14]</sup> Epidemiologic studies of the relationship between excess body weight and cancer risk have shown that BMI is positively

associated with incidence of and poor pathologic prognosis for multiple cancers, including colon, esophageal, and breast cancer, among others. However, the relationship between BMI and the clinical features of PTC remains unclear. Some studies have reported a positive association between BMI and PTC. Higher BMI has been associated with extrathyroidal extension, LNM, and advanced tumor stages.<sup>[15,16]</sup> However, the possible associations between BMI and clinicopathologic features of thyroid cancer have remained controversial, and some studies have found no association between obesity, stages of PTC, and clinical features of thyroid cancer.<sup>[9,10]</sup> In addition, Paes et al<sup>[17]</sup> reported that higher BMI was not associated with more aggressive tumor features, and that obesity may be correlated with less nodal metastases. Although many studies have focused on the relationship between high BMI and the clinicopathologic features of PTC, the results are inconsistent. Thus, we performed

a meta-analysis to assess the correlation between obesity and clinicopathologic factors in patients with PTC.

Age and male sex were two prognostic factors in PTC. Age > 55 years has been found to be associated with extrathyroidal extension and the significant factors that affect overall survival in patients with PTC.<sup>[118–20]</sup> The incidence of thyroid cancer is nearly three times higher in women than in men.<sup>[21]</sup> However, the aggressive histologic subtypes of thyroid cancer are more common in men.<sup>[21]</sup> In this meta-analysis, we concluded that obesity was associated with older age and male sex in PTC patients.

Preoperative serum TSH has been reported to play a major role in carcinogenesis, and several studies have reported an association between TSH level and thyroid cancer. TSH cooperates with insulin and IGF-1 signaling to activate the downstream MAPK and PI3K pathways that are central in thyroid carcinogenesis.<sup>[22,23]</sup> TSH level has been regarded as a factor that promotes aggressiveness of PTC in obese patients.<sup>[24]</sup> However, we found that obesity was not associated with preoperative serum TSH level in PTC patients.

Tumor size is considered a critical factor according to AJCC staging, and larger tumors are prone to being more aggressive.<sup>[25]</sup> From our data, we observed that tumor size  $\geq 1$  cm was 1.4 times more frequent in obese patients than in normal-weight patients. Whether multifocality is related to central lymph node metastasis in clinical lymph node-negative patients remains controversial. Multifocal PTC may be more aggressive than unifocal PTC, and multifocality is an independent risk factor for PTC recurrence after total thyroidectomy.<sup>[26]</sup> In this study, we found that obesity was associated with larger tumor size and multifocality in PTC patients.

The progression of PTC is slow and the primary tumor may break through the thyroid capsule and invade the surrounding strap muscles, the recurrent laryngeal nerve, and the internal jugular vein. It is widely believed that macroscopic extrathyroid extension has an important impact on the poor prognosis of PTC.<sup>[27]</sup> Some studies have reported that serum leptin levels are elevated in patients with PTC, and that PTC with expression of leptin and/or its receptor is associated with tumor aggressiveness.<sup>[28]</sup> Adiponectin levels are inversely associated with obesity, and low adiponectin level in obesity has been found to have an association with risk of several malignancies, including thyroid cancer.<sup>[29]</sup> Our results showed that obese patients had a higher probability of extrathyroid extension. However, vascular invasion may not be associated with obesity in PTC.

LNM is frequent in PTC, seen in 20% to 90% of patients.<sup>[30]</sup> It occurs in the central or lateral compartments and is an important determinant of the locoregional recurrence of PTC. Although there is controversy, some recent studies have reported that LNM can affect survival, particularly in elderly PTC patients.<sup>[31]</sup> In this study, LNM was not detected more frequently in obese patients than in normal weight PTC patients.

TNM stage is the most commonly used staging system applied in PTC. Classification is elaborated on by the AJCC, and allows prediction of the risk of cancer-related death. Our study was limited by the included studies, all of which used TNM staging according to the AJCC 7<sup>th</sup> edition. At the III/IV TNM stage of the AJCC, the 5-year survival rate is 41.4% to 82% for PTC.<sup>[32]</sup> In our study we found that high BMI was associated with advanced TNM stage. Distant metastasis and local recurrence are two important factors that may lead to a poor prognosis for PTC. Local recurrence has an effect on the survival of patients, and the

10-year overall survival rate is 78%–97%.<sup>[33,34]</sup> The 5-year and 10-year specific survival rates of patients with distant recurrence are 71% and 50%, respectively.<sup>[35]</sup> In our meta-analysis, we found that obesity was not associated with local recurrence and distant metastasis.

In conclusion, this study demonstrated that obesity was associated with several clinicopathologic features for poor prognosis of PTC: older age, male gender, tumor size  $\geq 1$  cm, extrathyroidal extension, multifocality, and advanced TNM stage. However, Preoperative serum TSH level, vascular invasion, LNM, distant metastasis, and recurrence were not associated with obesity in PTC.

## Author contributions

**Data curation:** Qian Sun.

**Investigation:** Ningning Cui, Qian Sun.

**Methodology:** Ningning Cui.

**Resources:** Li Chen.

**Software:** Ningning Cui.

**Validation:** Li Chen.

**Writing – original draft:** Ningning Cui.

**Writing – review & editing:** Ningning Cui.

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