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# Associations between body mass index and lymph node metastases of patients with papillary thyroid cancer

## A retrospective study

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**Abstract**

Epidemiological studies suggest that obesity is a risk of thyroid cancer, especially papillary thyroid cancer (PTC). However, the associations of obesity and clinic–pathological features, especially the association of body mass index (BMI) and lymph node metastasis of thyroid cancer are unclear. Seven hundred ninety-six primary patients with PTC were enrolled in this retrospective cohort study. The relationships between BMI and clinic-pathological features of PTC were evaluated by logistic regression models based on the 5-point increase in BMI and BMI quartiles (underweight, normal weight, overweight, and obesity). The 5-point increase in BMI was strongly associated with extra-thyroidal invasion [odds ratio (OR) 2.201, $P<0.001$], primary tumor size larger than 1 cm (OR 1.267, $P=0.027$), advanced tumor node metastasis (TNM) staging (OR 1.479, $P=0.004$), and multifocality (OR 1.31, $P=0.01$) in multivariable-adjusted models. The relationships between BMI and lymph node metastasis of PTC were evaluated by Mann–Whitney *U* test. The mean number of positive central lymph nodes and lateral nodes were increased with the increase of BMI when BMI ≥18.5 kg/m$^2$. It was not shown in underweight group. The present study found that increased BMI was associated with the lymph node metastases (LNMs) of patients with PTC, and other invasive features, including large tumor size, extra-thyroidal invasion, advanced TNM staging, and multifocality. Further studies with long-term follow-up are needed to confirm this finding.

**Abbreviations:** ATC = Anaplastic thyroid cancer, BMI = Body mass index, CI = Confidence intervals, CT = Computed tomography, DTC = Differentiated thyroid carcinoma, ER = Estrogen receptor, FNAC = Fine-needle aspiration cytology, FTC = Follicular thyroid carcinoma, HT = Hashimoto thyroiditis, LN = Lymph node, LNM = Lymph node metastases, OR = Odds ratios, PTC = Papillary thyroid cancer, SD = Standard deviation, TC = Thyroid cancer, TNM = Tumor node metastasis, TSH = Thyroid-stimulating hormone, WHO = World Health Organization.

**Keywords:** body mass index, prognosis, thyroid papillary carcinoma

## 1. Introduction

Thyroid cancer (TC) incidence, specifically papillary TC (PTC), has increased rapidly over the world[1–5]; it is estimated that about 62,980 new cases of TC were diagnosed in the United States in 2014 and this disease accounted for about 1890 deaths.[6] Despite the fact that the majority of newly diagnosed TCs are small PTCs through the use of ultrasound and ultrasound-guided biopsy, it has been suggested that enhanced detection of early-stage tumors cannot completely explain the significant increase of TC rates. Because the growing prevalence of TC has been began before the widespread use of diagnostic ultrasound.[7] In addition, an epidemiologic observation reported that half the overall increase in papillary carcinoma rates was due to increasing rates of very small (≤1.0 cm) cancers, 30% to cancers 1.1 to 2 cm, and 20% to cancers >2 cm since 1992 to 1995.[8] So, the alternative of a true rise in TC incidence should be considered. Obesity has become a mass phenomenon with a pronounced upward trend in most industrialized countries.[9,10] More and more epidemiological data support that obesity is a precipitating factor in cancer development, including TC.[11,12] World Health Organization (WHO) suggests that BMI is used as an index to evaluate the degree of obesity.

In addition, clinically significant prognostic factors for patients with differentiated thyroid carcinoma (DTC) have also been associated with aggressive tumor pathological features and lymph node (LN) metastasis.[13] Some studies suggested that obesity was significantly associated with larger tumor size and marginally associated with advanced tumor stage.[14,15] At the same time, Kim et al[16] believed that the correlation between the 2 was found in a specific group of patients ≥45 years of age. In Chinese population, Liu et al[17] found that increased BMI might elevate the risks of aggressive clinicopathological features, such as extrathyroidal invasion and advanced TNM stage. In contrast, Paes et al[18] reported a negative association between obesity and aggressive histological tumor features, such as the absence of nodal metastasis and tumor invasion. However, the association of body mass index (BMI) and LN metastasis of TC is unclear.

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This study aims to clarify the relationship between BMI and aggressive characteristics of patients with papillary TC, especially the association of BMI and LN metastasis.

## 2. Patients and methods

### 2.1. Study population

A total of 823 consecutive patients with PTC who underwent total thyroidectomy or lobectomy at Shandong Cancer Hospital & Institute between 2010 and 2015 were retrospectively reviewed in this study. Only patients with a first primary PTC were included, because their mechanism of cancer development may be different from patients with secondary PTC. The patients with no data of thyroid-stimulating hormone (TSH), serum thyroglobulin, total cholesterol, triglyceride concentrations, and/or fasting glucose level that were used as confounding variables before surgery will be excluded; finally, 796 subjects were eligible for analysis in this study. We reviewed the medical records and pathology reports of each patient to define initial clinic-pathological features, including primary tumor size, gross extra-thyroidal invasion, cervical LN metastasis, multifocality, vascular invasion, and advanced TNM stage after surgery and disease recurrences. Besides that, the generic information such as sex, age, weight, and height were recorded.

BMI was calculated using measurements of weight and height reported on the anesthesia summary as weight in kilograms divided by height in meters squared (kg/m$^2$). Every patient will visit every 3 months during the first year after operation. We recorded BMI and other measurements for every visit, but we only used weight and height of the patients at their first visit. TSH and serum thyroglobulin was measured using an immunoradiometric assay. Total cholesterol, triglyceride concentrations, and fasting glucose were measured with an enzymatic colorimetric method and a nonenzymatic method, respectively.

During each operation, central compartment dissection was performed at the surgeons' discretion. When lateral neck LN metastasis was suspected from the preoperative or intraoperative findings, lateral neck LN dissection was performed. The preoperative assessments for LN metastasis included a high-resolution ultrasound scan, fine-needle aspiration cytology (FNAC), and a computed tomography (CT) scan. The diagnosis, tumor characteristics, and/or the extent of disease were confirmed by cross-checking all pathology specimens. Tumor node metastasis (TNM) staging was based on the AJCC Cancer Staging Atlas (2012).[19]

All patients were followed with a clinical examination including thyroid hormone and ultrasound scan of the neck every 3 months during the first year, and annually thereafter, stimulated serum thyroglobulin levels were evaluated at the same time. Tumor recurrence was defined as high-resolution ultrasound scan and then confirmed by cellular pathology of fine needle aspiration or recorrection in a patient who initially met the criteria for remission. All patients seen in the clinic were offered enrollment in the study and informed consent was obtained. Shandong Cancer Hospital & Institute approved this study.

### 2.2. Statistical analysis

We used logistic regression models to estimate odds ratios (ORs) with 95% confidence intervals (CIs) to analyze the relationship between the BMI and LN metastases. BMI is associated with an increased risk of common and less common malignancies with a 5 kg/m$^2$ increase in BMI.[12] So, BMI with a 5 kg/m$^2$ increase was used as a continuous variable in the initial models. At the same time, the other clinicopathological features were analyzed. All of the following clinicopathological features of PTC patients were used as binary variables such as primary tumor size ($\leq$1 or >1 cm), advanced TNM stage (stage I/II or stage III/IV), extrathyroidal invasion (yes or no), age (<45 or $\geq$45 years), and confounding variables (above reference range or no). All models were adjusted by TSH, serum thyroglobulin, total cholesterol, triglyceride concentrations, and/or fasting glucose level by the mechanism of forward. And, we also performed an analysis using 4 BMI groups in which the normal BMI group was used as a reference category. BMI groups defined by the WHO classification are as follows: underweight (<18.5 kg/m$^2$, n=18), normal weight (18.5–24.9 kg/m$^2$, n=403), overweight (25–29.9 kg/m$^2$, n=311), and obese (>30 kg/m$^2$, n=64). In the model, changes in BMI were defined as an independent variable, while changes in clinicopathological features including LN metastases were dependent variables. The numbers of LN metastases grouped by BMI category without normal distribution were tested using nonparametric test followed by the Mann–Whitney *U* test. Mean±standard deviation was used to represent the quantitative parameters. Differences between categorical or continuous variables were analyzed using the Chi-squared test or Nonparametric test. Statistical differences among four groups were analyzed by ANOVA test. SPSS version 17.0 for Windows was used to conduct all statistical analyses. A $P$ value < 0.05 was considered statistically significant.

## 3. Results

### 3.1. Baseline clinico-pathological features in patients with papillary thyroid cancer

The clinic-pathological characteristics of patients with papillary TC are summarized in Table 1. A total of 796 papillary TC patients (184 men and 612 women) were studied. The mean (SD) age was 46 (11.6) years (range, 12–79 years). The mean (SD) BMI was 25(3.40) kg/m$^2$ (range, 15.62–38.53 kg/m$^2$) and the prevalence of underweight, overweight, and obese patients were 2.3%, 39.1%, and 8.0%, respectively. The mean (±SD) tumor size was 1.37 (±1.11) cm (range, 0.1–9 cm), and the papillary microcarcinoma was shown in 53.3% of tumors. Three hundred and eight patients (38.7%) of the tumors had extra-thyroidal invasion and 239 patients had nodular goiter and/or Hashimoto thyroiditis (HT) at the same time. The prevalence of central neck LN metastasis and lateral neck LN metastasis were 51.3% (n=408) and 35.3% (n=281), respectively; of these, 242 had both central cervical and lateral cervical LN metastasis, and the rest (39 cases) had skip metastasis, in which the lateral cervical LN had metastasis, while the central cervical LNs had no metastasis (Table 1). About 1.5% of patients had distant metastasis. Three hundred forty-eight patients (43.7%) had multifocal PTCs, and 255 patients (32%) showed advanced TNM stage (stage III or stage IV). Twenty-five patients (3.1%) had vascular invasion.

### 3.2. Associations between BMI and lymph node metastasis of papillary thyroid cancer

The 5-point increase in BMI was not statistically associated with cervical LN metastasis, as summarized in Table 2. But in the overweight group and the obese group, subjects had an increased OR for clinicopathological features of PTCs in central neck LN

Table 1

**Baseline clinicopathological characteristics of patients with papillary thyroid carcinoma, at initial diagnosis.**

| | | BMI, kg/m$^2$ | | | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Total n=796** | **Underweight N=18** | **Normal-weight N=403** | **Overweight N=311** | **Obese N=64** | **P** |
| Female sex | 612 (76.9%) | 16 (88.9%) | 332 (79.9%) | 226 (72.7%) | 38 (59.4%) | 0.000* |
| Age, y | 46.17 (±11.5) | 40.94 (±19.3) | 45 (±12.1) | 47.9 (±10.5) | 44.9 (±10.1) | 0.001† |
| BMI, kg/m$^2$ | 25 (±3.40) | 17.5 (±0.74) | 22.7 (±1.65) | 27.1 (±1.35) | 36.69 (±1.62) | 0.000‡ |
| TSH | 2.9 (±1.6) | 2.6 (±1.97) | 3.7 (±2.37) | 3.3 (±2.2) | 2.5 (±0.96) | 0.925† |
| Total cholesterol | 4.38 (±0.692) | 3.98 (±1.33) | 4.14 (±0.89) | 4.28 (±0.72) | 5.3 (±0.78) | 0.726† |
| Fasting glucose level | 5.4 (±2.0) | 4.7 (±0.32) | 5.2 (±1.02) | 5.7 (±2.94) | 5.6 (±1.04) | 0.834† |
| Triglyceride concentrations | 1.37 (±0.564) | 1.04 (±0.96) | 1.29 (±0.64) | 1.73 (±0.88) | 0.86 (±0.34) | 0.235† |
| Primary tumor size, cm | 1.37 (±1.11) | 1.38 (±1.09) | 1.29 (±1.1) | 1.42 (±1.09) | 1.63 (±1.21) | 0.01* |
| ≤1 | 424 (53.3%) | 10 (55.6%) | 237 (58.8%) | 150 (48.2%) | 27 (42.2%) | |
| >1 | 372 (46.7%) | 8 (44.4%) | 166 (41.2%) | 161 (51.8%) | 37 (57.8%) | |
| Extra-thyroidal invasion | 308 (38.7%) | 2 (11.1%) | 114 (28.3%) | 152 (48.9%) | 40 (62.5%) | 0.000* |
| nodular goiter or HT | 239 (30%) | 12 (66.7%) | 121 (30%) | 85 (27.3%) | 21 (32.8%) | 0.005* |
| Cervical lymph node metastasis | | | | | | 0.056* |
| pN0/Nx | 349 (43.8%) | 5 (27.8%) | 196 (48.6%) | 125 (40.2%) | 23 (35.3%) | |
| pN1a | 408 (51.3%) | 10 (55.6%) | 188 (46.7%) | 172 (55.3%) | 38 (59.4%) | |
| pN1b | 281 (35.3%) | 8 (44.4%) | 127 (31.5%) | 119 (38.3%) | 30 (46.9%) | |
| Distant metastasis | 12 (1.5%) | 0 (0%) | 8 (2.0%) | 4 (1.3%) | 0 (0%) | 0.577* |
| Multifocality | 348 (43.7%) | 3 (16.7%) | 170 (42.2%) | 144 (46.3%) | 31 (48.4%) | 0.067* |
| Advanced TNM staging | 255 (32%) | 4 (22.2%) | 105 (26.1%) | 122 (39.2%) | 24 (37.5%) | 0.001* |
| Vascular invasion | 25 (3.1%) | 1 (5.6%) | 13 (3.2%) | 10 (3.2%) | 1 (1.6%) | 0.829* |

Advanced TNM staging, Stage III + IV, BMI=body mass index, CI=confidence interval, HT=Hashimoto thyroiditis, OR=odds ratio, pN1a=central lymph node metastasis, pN1b=Lateral lymph node metastasis, TNM=tumor node metastasis, TSH=thyroid-stimulating hormone.
* Analysis using Chi-square test.
† Analysis using ANOVA.
‡ Analysis using nonparametric test.

metastasis (OR=1.09, CI: 0.78–1.53, $P=0.601$ in overweight group, OR=1.14, CI: 0.61–2.05, $P=0.605$ in obese group) and lateral neck LN metastasis (OR=1.35, CI: 0.98–1.84, $P=0.06$ in overweight group, OR=1.92, CI: 1.12–3.27, $P=0.017$ in obese group) (Table 3). The sample size is quite small (only 18 patients) in underweight group, so we do not consider doing a statistical test. To further understand the unexpected relationship between BMI and LN metastases, the subjects were categorized into underweight, normal, overweight, and obese according to the WHO. The mean number of LNs removed was 4.09 in the central compartment and 10.88 in the lateral compartment. The mean number of positive nodes was 1.71 (range: 0–17) in the central compartment and 1.76 (range: 0–32) in the lateral compartment.

Table 2

**Adjusted odds ratios (ORs) (with 95% CI) of more severe disease at initial surgery with a 5-point increase in BMI.**

| | Adjusted | |
|---|---|---|
| | **OR (95%)** | **P** |
| Extra-thyroidal invasion | 2.201 (1.691–2.865) | <0.001 |
| Multifocality | 1.31 (1.066–1.61) | 0.01 |
| Central neck lymph node metastasis | 1.033 (0.817–1.308) | 0.785 |
| Lateral neck lymph node metastasis | 0.845 (0.625–1.145) | 0.277 |
| Nodular goiter or HT | 0.877 (0.703–1.096) | 0.249 |
| Advanced TNM staging* | 1.479 (1.13–1.937) | 0.004 |
| Distant metastasis | 0.790 (0.341–1.828) | 0.582 |
| Vascular invasion | 0.848 (0.475–1.513) | 0.576 |
| Primary tumor size† | 1.267 (1.028–1.561) | 0.027 |

BMI=body mass index, HT=Hashimoto thyroiditis, OR=odds ratio, TNM=tumor node metastasis. Adjusted by thyroid-stimulating hormone (TSH), serum thyroglobulin, total cholesterol, triglyceride concentrations, and/or fasting glucose level.
* Advanced TNM staging, Stage III + IV.
† Primary tumor size >1 cm.

The incidence of central and lateral LN metastases was 55.3% and 37.9% in overweight group, 55.9% and 45.3% in obese group, respectively. The mean number of positive central LNs and lateral nodes also increased with the increase of BMI when BMI ≥18.5 kg/m$^2$ (Table 4). It was not shown in underweight group. It is because the number of cases is too small in the underweight group. The incidence of central and lateral LN metastases was significantly higher in overweight group and obese group than in normal-weight group, but it was not significantly different between underweight group and normal-weight group. Statistical analysis failed to show any significant difference in the number of removed lateral nodes among the groups.

In addition, the 5-point increase in BMI was strongly associated with extra-thyroidal invasion (OR=2.201, CI: 1.691–2.865, $P<0.001$), primary tumor size larger than 1 cm (OR=1.267, CI: 1.028–1.561, $P=0.027$), advanced TNM staging (OR=1.479, CI: 1.13–1.937, $P=0.004$), and multifocality (OR=1.31, CI: 1.066–1.61, $P=0.01$) in multivariable-adjusted models (Table 2). However, there were no statistically significant results between BMI and, distant metastasis, vascular invasion and nodular goiter and/or HT. In our study, the sample size is quite small (only 13 patients) for cancer recurrence, so we do not consider doing a statistical test.

## 4. Discussion

Recently, more and more epidemiologic studies revealed a positive relationship between BMI and the risk of TC,[11,20–22] in particular the papillary thyroid carcinoma.[22] Han et al[21] demonstrated that obesity was associated with a higher prevalence of TC in women when evaluated in a routine health checkup setting. A large Norwegian cohort of more than

**Table 3**

**Risk of more aggressive clinico-pathological features in patients with papillary thyroid carcinoma according to BMI group.**

| | BMI, kg/m² | | | |
|---|---|---|---|---|
| | Overweight OR (95% CI) | (25–29.9 kg/m²) P | Obese OR (95% CI) | (>30 kg/m²) P |
| Extra-thyroidal invasion | 2.42 (1.78–3.3) | <0.001 | 4.23 (2.4–7.3) | <0.001 |
| Multifocality | 1.18 (0.88–1.6) | 0.272 | 1.29 (0.877–1.60) | 0.349 |
| Central neck LNM | 1.09 (0.78–1.53) | 0.601 | 1.14 (0.61–2.05) | 0.605 |
| Lateral neck LNM | 1.35 (0.98–1.84) | 0.06 | 1.92 (1.12–3.27) | 0.017 |
| Nodular goiter and/or HT | 0.88 (0.63–1.22) | 0.431 | 1.14 (0.65–2.0) | 0.653 |
| Advanced TNM staging* | 1.83 (1.33–2.52) | <0.001 | 1.70 (0.98–3.00) | 0.59 |
| Distant metastasis | 0.64 (0.19–2.16) | 0.475 | 0 (0) | 1 |
| Vascular invasion | 1 (0.43–2.30) | 1 | 0.47 (0.06–3.7) | 0.478 |
| Primary tumor size >1 cm | 1.53 (1.14–2.06) | 0.005 | 1.96 (1.15–3.34) | 0.014 |

BMI = body mass index, CI = confidence interval, HT = Hashimoto thyroiditis, LNM = lymph node metastasis, OR = odds ratio, TNM = tumor node metastasis.
* Advanced TNM staging, Stage III + IV.

2 million individuals showed that the risk of TC, especially of the papillary and follicular types, increased moderately with increasing BMI and height in both sexes.[20] In a pooled analysis of 5 prospective U.S. studies, BMI was positively associated with TC risk in both men and women.[11] Besides that, a large prospective cohort study suggests a potential link between early-life factors related to growth and body weight and thyroid carcinogenesis.[23] However, the relationship between BMI and the clinical features of TC is unclear.

Although a few studies have made great efforts to investigate the relationships between BMI and the clinical features of TC, these studies have not got the same conclusion.[14–16,18,24] Our study has shown at the first time that higher BMI is strongly associated with extra-thyroidal invasion and universally associated with multifocality, advanced TNM staging, and primary tumor size >1 cm in our study. Further, those had been shown at the same time in the overweight group and/or in the obese group.

Although these findings demonstrate that high BMI might elevate the risk of aggressive clinicopathological features,[14,15] the molecular mechanism is unclear. The carcinoma risk in patients with thyroid nodules increased with increasing serum thyroid-stimulating hormone concentration, with a significant elevation in patients with serum thyroid-stimulating hormone levels above 1.64 mU/L ($P < 0.001$).[25] Furthermore, Betry et al[26] confirmed an increase of thyroid-stimulating hormone in conjunction with BMI in obese subjects and this increase was correlated with leptin independently of BMI.

There is an association between insulin resistance and thyroid nodules,[27] which may be worked through the combination of insulin receptor and insulin directly[28] or insulin-like growth factor indirectly.[29] There was a strong correlation of leptin expression with Ob-R expression in papillary TC (PTC), follicular thyroid carcinoma (FTC), and anaplastic TC (ATC). For PTC, leptin expression was strongly correlated with larger tumor size, nodal metastasis, and advanced stage.[30] An in vitro analysis showed that leptin plays an important role in PTC pathogenesis through PI3K/AKT pathway via Ob-R.[31] Also, a few agents modulating leptin signaling to inhibit cancer cell growth have been described.[32] In addition, Liu et el[33] demonstrated that the positive rates of serum estrogen level and the expression of estrogen receptor (ER) were significantly greater in patients with various types of thyroid neoplasms than that in normal controls, which reveals that thyroid neoplasms might be sex hormone dependent. Autophagy induced by estrogen/ER is associated with generation of reactive oxygen species, activation of ERK1/2, and the survival/growth of PTC cells.[34] However, more research on the molecular mechanism of the relationship between obesity and thyroid carcinoma is needed.

Our current study has some limitations such as the follows: first, it is a retrospective study and the subjects in the underweight group are never enough, so it leads to the un-foreseeing outcome. In addition, not all the extra-thyroidal invasions were demonstrated by the postoperative pathological report but the surgical

**Table 4**

**Lymph node metastases grouped by BMI category.**

| | BMI, kg/m² | | | |
|---|---|---|---|---|
| | Underweight | Normal-weight | Overweight | Obese |
| No. of patients | N = 18 | N = 403 | N = 311 | N = 64 |
| No. with positive central lymph nodes (%) | 10 (55.5) | 188 (46.6) | 172 (55.3) | 38 (59.4) |
| Mean no. of central lymph nodes removed | 3.28 | 4.28 | 3.9 | 4.13 |
| Mean no. of positive central lymph nodes | 1.67 | 1.5 | 1.88 | 2.3 |
| Mann–Whitney *U* test* | 0.532 | Reference | 0.014 | 0.013 |
| No. with positive lateral lymph nodes (%) | 8 (45.5) | 126 (31.3) | 118 (37.9) | 29 (45.3) |
| Mean no. of lateral lymph nodes removed | 11.3 | 9.21 | 11.81 | 16.8 |
| Mean no. of positive lateral lymph nodes | 2.5 | 1.51 | 1.87 | 2.53 |
| Mann–Whitney *U* test† | 0.177 | reference | 0.053 | 0.017 |

BMI = body mass index.
* *P* value versus normal weight group of no. of positive central lymph nodes.
† *P* value versus normal weight group of no. of positive lateral lymph nodes.

judgment in the operation. Second, some information is unfortunately lacked such as physical activity and medical history of diabetes. Information such as waist-to-hip ratio, percentage of body fat, skinfold thickness, and assessments of intra-abdominal fat were unavailable. So, obese patients were evaluated by BMI only. We also lack the information to explore the role of insulin resistance, adiponectin, and sex hormone in the progress of TC.

In conclusion, the present study found that increased BMI was associated with the LN metastases of patients with PTC, and other invasive features, including large tumor size, extra-thyroidal invasion, advanced TNM staging, and multifocality.

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