

Original Article

Correlation between body mass index and clinicopathological features of papillary thyroid microcarcinoma

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Received March 6, 2015; Accepted September 10, 2015; Epub September 15, 2015; Published September 30, 2015

Abstract: Objectives: To demonstrate the relationships between body mass index (BMI) and the clinicopathological features of papillary thyroid microcarcinoma (PTMC) and papillary thyroid carcinoma (PTC). Methods: A total of 810 consecutive patients with PTC (501 patients with PTMC) who underwent total thyroidectomy in 2009-2013 were retrospectively reviewed. Height and weight were used to calculate BMI. Results: Increased BMI was strongly associated with i) extrathyroidal invasion ($P < 0.001$) and advanced TNM stage ($P = 0.005$) in patients with PTMC ($n = 501$), and ii) extrathyroidal invasion ($P = 0.001$), advanced TNM stage ($P = 0.001$), and multifocality ($P = 0.002$) in patients with PTC ($n = 810$). As compared with normal-weight patients with PTMC, obese patients with PTMC had greater risks of extrathyroidal invasion (OR = 5.214, $P = 0.0270$), and overweight patients with PTMC had greater risks of extrathyroidal invasion (OR = 2.165, $P = 0.0013$) and advanced TNM stage (OR = 2.019, $P = 0.0137$). As compared with normal-weight patients with PTC, obese patients with PTC had greater risks of extrathyroidal invasion (OR = 3.101, $P = 0.0172$), and overweight patients with PTC had greater risks of extrathyroidal invasion (OR = 1.486, $P = 0.0279$), advanced TNM stage (OR = 1.650, $P = 0.0347$), and multifocality (OR = 1.651, $P = 0.0054$). Conclusions: Increased BMI might elevate the risks of aggressive clinicopathological features, such as extrathyroidal invasion and advanced TNM stage. Obesity control may play an important role in preventing the development of aggressive PTMCs and all PTCs.

Keywords: Body mass index, thyroid papillary microcarcinoma, prognosis

Introduction

Most patients with papillary thyroid microcarcinoma (PTMC) do not exhibit clinical manifestations because of the small sizes of their tumour lesions. However, because high-resolution ultrasound has become a popular component of routine physical examination, the rate of early diagnosis of PTMC has increased dramatically.

Epidemiological studies have reported that being overweight and being obese are associated with increased incidences of numerous cancers, including thyroid cancer. In the European Union, obesity were reported to be associated with 5% of all cancers [1]. In addition

to cancer risk, obesity has also been demonstrated to be associated with more aggressive pathological characteristics of the tumour and worse prognosis in patients with several cancers [2-4]. However, reports regarding the role of body mass index (BMI) in PTMC are lacking.

The aim of this study was to demonstrate the relationships between BMI and the clinicopathological features of PTMC and papillary thyroid carcinoma (PTC). To accomplish this aim, we retrospectively analysed BMI and cancer characteristics for patients who had undergone thyroidectomy plus central lymph node dissection.

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Table 1. Baseline clinico-pathological characteristics of patients with papillary thyroid microcarcinoma

Characteristic	Total (n = 501)	BMI < 18.5 n = 27	18.5 ≤ BMI < 25 n = 351	25 ≤ BMI < 30 n = 115	BMI ≥ 30 n = 8	P
Age (years)						.045
≤ 45	239 (47.7%)	20 (74.1%)	163 (46.4%)	52 (45.2%)	4 (50.0%)	
> 45	262 (52.3%)	7 (25.9%)	188 (53.6%)	63 (54.8%)	4 (50.0%)	
Sex						.000
Female	423 (84.4%)	25 (92.6%)	319 (91.4%)	74 (64.9%)	5 (62.5%)	
Male	75 (15.6%)	2 (7.4%)	30 (8.6%)	40 (35.1%)	3 (37.5%)	
Extrathyroidal invasion						.000
Present	140 (27.9%)	3 (11.1%)	85 (24.2%)	47 (40.9%)	5 (62.5%)	
Absent	361 (72.1%)	24 (88.9%)	266 (75.8%)	68 (59.1%)	3 (37.5%)	
Lymph node metastasis						.346
Present	138 (27.5%)	7 (25.9%)	97 (27.6%)	34 (29.6%)	0 (0%)	
Absent	363 (72.5%)	20 (74.1%)	254 (72.4%)	81 (70.4%)	8 (100%)	
TNM staging						.005
Stage I + II	387 (77.2%)	27 (100%)	275 (78.3%)	79 (68.7%)	6 (75.0%)	
Stage III + IV	114 (22.8%)	0 (0%)	76 (21.7%)	36 (31.3%)	2 (25.0%)	
multifocality						.117
Absent	328 (65.5%)	20 (74.1%)	238 (67.8%)	66 (57.4%)	4 (50.0%)	
Present	173 (34.5%)	7 (25.9%)	113 (32.2%)	49 (42.6%)	4 (50.0%)	
Maximum tumor size						.386
≤ 0.5 cm	226 (45.1%)	8 (33.3%)	159 (45.3%)	55 (48.7%)	4 (50.0%)	
> 0.5 cm	275 (54.9%)	19 (66.7%)	192 (54.7%)	60 (51.3%)	4 (50.0%)	
Total tumor size						.566
≤ 1 cm	415 (82.8%)	21 (81.5%)	296 (84.3%)	92 (80.0%)	6 (75.0%)	
> 1 cm	86 (17.2%)	6 (18.5%)	55 (15.7%)	23 (20.0%)	2 (25.0%)	

BMI: body mass index.

Methods

Patients

We retrospectively reviewed the records of a total of 1015 consecutive patients with PTC who underwent total thyroidectomy at Union hospital between 2009 and 2013. This study was approved by the ethics committees of Union Hospital (Approval Number: 20131001-PTMC, Date: Oct 1st, 2012- Oct 1st, 2013). After excluding patients whose BMIs were not available, 810 subjects were eligible for analysis in our study, including 501 patients with PTMC. The medical records and pathology reports of each patients were reviewed to define the initial clinicopathological features that were present after surgery. For each subject, height and weight were used to calculate BMI (weight in kilograms divided by height in metres squared [kg/m²]).

All pathology specimens were reviewed by two experienced pathologists to confirm the diag-

nosis, tumour characteristics, and extent of disease. The tumour-node-metastasis (TNM) staging system was employed, based on the Union for International Cancer Control-American Joint Committee on Cancer (UICC/AJCC) 7th edition classification.

Statistical analysis

Logistic regression models were used to determine the associations between BMI and the clinicopathological characteristics of PTMC and PTC, as expressed in terms of odds ratios (ORs) with 95% confidence intervals (CIs). The clinicopathological characteristics of PTMC and PTC were treated as binary variables: extrathyroidal invasion (present or absent), lymph node metastasis (present or absent), advanced TNM stage (stage I/II or stage III/IV), multifocality (present or absent), maximum tumour size (present or absent), maximum tumour size (PTMC: ≤ 0.5 or > 0.5 cm; PTC: ≤ 1 or > 1 cm and ≤ 2 or > 2 cm), total tumour size (PTMC: ≤ 1 or > 1 cm and ≤ 2 or > 2 cm), PTC: ≤ 1 or > 1 cm and ≤ 2 or > 2 cm). All ORs were adjusted for age and gender.

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Table 2. Baseline clinico-pathological characteristics of patients with papillary thyroid carcinoma

Characteristic	Total (n = 810)	BMI < 18.5 n = 42	18.5 ≤ BMI < 25 n = 568	25 ≤ BMI < 30 n = 179	BMI ≥ 30 n = 21	P
Age (years)						.002
≤ 45	405 (50%)	33	278	84	10	
> 45	405 (50%)	9	290	95	11	
Sex						.000
Female	654 (80.7%)	38	494	110	12	
Male	156 (19.3%)	4	74	69	9	
Extrathyroidal invasion						.001
Present	327 (40.4%)	11	210	92	14	
Absent	483 (59.6%)	31	348	97	7	
Lymph node metastasis	347 (42.8%)					.612
Present	347 (42.8%)	18	236	82	11	
Absent	463 (57.2%)	24	332	97	10	
TNM staging						.001
Stage I + II	573 (70.7%)	40	399	120	14	
Stage III + IV	237 (29.3%)	2	159	69	7	
Multifocality	316 (39.0%)					.002
Absent	494	33	353	97	11	
Present	316	9	205	92	10	
Maximum tumor size						.135
≤ 1 cm	501 (61.9%)	27	351	115	8	
> 1 cm	309 (38.1%)	15	217	64	13	
Maximum tumor size						.834
≤ 2 cm	729 (90.0%)	38	514	159	18	
> 2 cm	81 (10.0%)	4	54	20	3	
Total tumor size						.217
≤ 1 cm	414 (51.1%)	21	295	92	6	
> 1 cm	396 (48.9%)	21	273	87	15	
Total tumor size						.103
≤ 2 cm	658 (81.2%)	36	471	136	15	
> 2 cm	152 (18.8%)	6	97	43	6	

BMI: body mass index.

In each model, the independent variable was BMI, age, and gender and one of the clinico-pathological characteristics was the dependent variable. In the logistic regression analyses, BMI was categorised according to the World Health Organization (WHO) classification: underweight (less than 18.5 kg/m²), normal weight (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²), and obese (more than 30 kg/m²). The normal-weight group (18.5-24.9 kg/m²) was used as the reference category.

Analyses were performed using the SPSS Statistics 18.0 software package (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided and P-values less than 0.05 were considered statistically significant.

Results

Baseline clinicopathological features in patients with papillary thyroid microcarcinoma (PTMC)

The clinicopathological features of patients with PTMC are summarised in **Table 1**. Of the 501 patients, 423 (84.4%) were women and 75 (15.6%) were men. Two hundred thirty-nine (47.7%) patients were 45 year old or younger, and 262 (52.3%) were older than 45 years. The normal-weight group included 351 (70.1%) of the 501 patients with PTMC, while the prevalences of underweight BMI, overweight BMI, and obese BMI were 5.4%, 30.0%, and 1.6%, respectively. All 501 of the patients underwent

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Table 3. Risk of more aggressive clinico-pathological features in patients with papillary thyroid micro-carcinoma

	BMI at diagnosis (kg/m ²)			
	BMI < 18.5 N = 27	18.5 ≤ BMI < 25 N = 351	25 ≤ BMI < 30 N = 115	BMI ≥ 30 N = 8
Extrathyroidal invasion				
NO. of patients (%)	3 (11.1%)	85 (24.2%)	47 (40.9%)	5 (62.5%)
OR (95% CI)	0.415 (0.121-1.422)	Reference	2.165 (1.352-3.467)	5.214 (1.206-22.535)
P-value	0.1616		0.0013	0.0270
Lymph node metastasis				
NO. of patients (%)	7 (25.9%)	97 (27.6%)	34 (29.6%)	0 (0%)
OR (95% CI)	0.690 (0.277-1.723)	Reference	0.925 (0.552-)	< 0.001 (< 0.001- > 999.999)
P-value	0.4271		0.7683	0.9850
Advanced TNM staging				
NO. of patients (%)	0 (0%)	76 (21.7%)	36 (31.3%)	2 (25.0%)
OR (95% CI)	< 0.001 (< 0.001- > 999.999)	Reference	2.019 (1.155-3.528)	1.588 (0.253-9.968)
P-value	0.9739		0.0137	0.6217
Multifocality				
NO. of patients (%)	7 (25.9%)	113 (32.2%)	49 (42.6%)	4 (50.0%)
OR (95% CI)	0.771 (0.315-1.889)	Reference	1.566 (0.992-2.472)	2.096 (0.509-8.621)
P-value	0.5698		0.0542	0.3052
Maximum tumor size > 0.5 cm				
NO. of patients (%)	19 (66.7%)	192 (54.7%)	60 (51.3%)	4 (50.0%)
OR (95% CI)	1.739 (1.739-4.118)	Reference	0.906 (0.579-1.420)	0.825 (0.199-3.421)
P-value	0.2084		0.6674	0.7915
Total tumor size > 1 cm				
NO. of patients (%)	6 (18.5%)	55 (15.7%)	23 (20.0%)	2 (25.0%)
OR (95% CI)	1.287 (0.491-3.378)	Reference	1.427 (0.802-2.539)	1.835 (0.351-9.602)
P-value	0.6078		0.2259	0.4722

BMI: body mass index.

total thyroidectomy, 140 (27.9%) of them had extrathyroidal invasion, and 138 (27.5%) of them had lymph node metastasis. One hundred seventy-three (34.5%) patients had multifocal PTMCs and 114 (22.8%) patients showed an advanced TNM stage (stage III or stage IV).

Associations between BMI and the clinicopathological features of PTMC

Increased BMI was strongly associated with extrathyroidal invasion ($P < 0.001$) and advanced TNM stage ($P = 0.005$) in the patients with PTMC. The underweight and normal-BMI groups were younger than the overweight and obese groups. Further, female patients with PTMC were more common in the normal-BMI and underweight groups. However, the presence of metastatic lymph nodes did not differ significantly among these BMI groups. No significant associations were found between BMI and tumour multifocality. BMI was not found to be significantly associated with maximum tumour size (≤ 0.5 cm vs. > 0.5 cm) or total tumour size (≤ 1 vs. > 1 cm).

We further explored the risks of more aggressive clinicopathological features according to the category of BMI (Table 3). As compared with patients who had normal BMIs, patients in the underweight group had an increased risks (ORs > 1) of maximum tumour size > 0.5 cm and total tumour size > 1 cm, which was an interesting finding, although it was not statistically significant (Table 3). Subjects in the overweight group had a significantly greater risk of extrathyroidal invasion (OR = 2.165, $P = 0.0013$), and advanced TNM stage (OR = 2.019, $P = 0.0137$), again as compared with the normal-BMI group. Patients in the obese group only had a greater risk of extrathyroidal invasion (OR = 5.214, $P = 0.0270$).

Multifocality and total tumour size > 1 cm were more common in the overweight group than in the normal-weight group (OR = 1.566 and 1.427, respectively), although the differences were not statistically significant ($P = 0.0542$ and 0.2259, respectively). Advanced TNM stage (OR = 1.588), multifocality (OR = 2.096), and total tumour size > 1 cm (OR = 1.835) were

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Table 4. Risk of more aggressive clinico-pathological features in patients with papillary thyroid carcinoma

	BMI at diagnosis (kg/m ²)			
	BMI < 18.5 N = 42	18.5 ≤ BMI < 25 N = 568	25 ≤ BMI < 30 N = 179	BMI ≥ 30 N = 21
Extrathyroidal invasion				
NO. of patients (%)				
OR (95% CI)	0.624 (0.306-1.275)	Reference	1.486 (1.044-2.115)	3.101 (1.223-7.868)
P-value	0.1961		0.0279	0.0172
Lymph node metastasis				
NO. of patients (%)				
OR (95% CI)	0.819 (0.425-1.578)	Reference	0.944 (0.650-1.37)	1.198 (0.471-3.045)
P-value	0.5503		0.7606	0.7044
Advanced TNM staging				
NO. of patients (%)				
OR (95% CI)	0.213 (0.045-0.998)	Reference	1.650 (1.037-2.625)	1.289 (0.404-4.106)
P-value	0.0497		0.0347	0.6679
Multifocality				
NO. of patients (%)				
OR (95% CI)	0.478 (0.223-1.023)	Reference	1.651 (1.160-2.350)	1.531 (0.635-3.694)
P-value	0.0572		0.0054	0.3427
Maximum tumor size > 1 cm				
NO. of patients (%)				
OR (95% CI)	0.865 (0.446-1.681)	Reference	0.743 (0.512-1.078)	2.169 (0.867-5.427)
P-value	0.6692		0.1178	0.0981
Maximum tumor size > 2 cm				
NO. of patients (%)				
OR (95% CI)	0.927 (0.314-2.742)	Reference	0.917 (0.513-1.641)	1.167 (0.319-4.260)
P-value	0.8914		0.7705	0.8156
Total tumor size > 1 cm				
NO. of patients (%)				
OR (95% CI)	0.978 (0.518-1.849)	Reference	0.902 (0.632-1.287)	2.368 (0.891-6.291)
P-value	0.9464		0.5703	0.0838
Total tumor size > 2 cm				
NO. of patients (%)				
OR (95% CI)	0.750 (0.305-1.846)	Reference	1.349 (0.878-2.073)	1.661 (0.615-4.486)
P-value	0.5311		0.1718	0.3169

BMI: body mass index.

each more frequent in the obese group than in the normal-weight group, but none of these associations was significant.

Baseline clinicopathological features in patients with papillary thyroid carcinoma (PTC)

In the patients with PTC, increased BMI was strongly associated with extrathyroidal invasion (P = 0.001), advanced TNM stage (P = 0.001), and multifocality (P = 0.002). The underweight and normal-BMI groups were younger than the

overweight and obese groups. Female patients were more common in the normal and underweight groups. However, the presence of metastatic lymph nodes did not differ significantly among these BMI groups. Further, no significant associations were found between BMI tumour multifocality. BMI was not found to be significantly associated with maximum tumour size (≤ 1 cm vs. > 1 cm), maximum tumour size (≤ 2 cm vs. > 2 cm), total tumour size (≤ 1 cm vs. > 1 cm), or total tumour size (≤ 2 cm vs. > 2 cm).

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The clinicopathological features of patients with PTC are summarised in **Table 2**. Of the 810 patients, 654 (80.7%) were women and 156 (19.3%) were men. Four hundred five (50%) patients were 45 years old or younger, and 405 (50%) were older than 45 years. The normal-weight group included 351 (70.1%) of the 810 patients with PTC, while the prevalences of the underweight BMI, overweight BMI, and obese BMI were 5.2%, 22.1%, and 2.6% respectively. All 810 of the patients underwent total thyroidectomy, 327 (40.4%) of them had extrathyroidal invasion, and 347 (42.8%) of them had lymph node metastasis. Three hundred sixteen (39.0%) patients showed multifocal PTMCs and 237 (29.3%) patients showed advanced TNM stage (stage III or stage IV).

Associations between BMI and the clinicopathological features of PTC

The risk of more aggressive clinicopathological features was also investigated according to the category of BMI (**Table 4**). As compared with patients who had normal BMIs, patients in the underweight group had decreased risks (ORs < 1) of all aggressive clinicopathological features, such as extrathyroidal invasion, lymph node metastasis, and advanced TNM stage. However, the risk reduction was only statistically significant for advanced TNM stage (**Table 4**). Subjects in the overweight group had significantly greater risks of extrathyroidal invasion (OR = 1.486, $P = 0.0279$), advanced TNM stage (OR = 1.650, $P = 0.0347$), and multifocality (OR = 1.651, $P = 0.0054$), as compared with normal-weight patients. Patients in the obese group only had an elevated risk of extrathyroidal invasion (OR = 3.101, $P = 0.0172$).

Among the patients with PTC, total tumour size > 2 cm was more common in the overweight group than in the normal-weight group (OR = 1.349), although the differences were not statistically significant ($P = 0.1718$). Further, lymph node metastasis (OR = 1.198), advanced TNM stage (OR = 1.289), multifocality (OR = 1.531), maximum tumour size > 1 cm (OR = 1.167), total tumour size > 1 cm (OR = 2.368) and total tumour size > 2 cm (OR = 1.661) were each more frequent in the obese group than in the normal-weight group, but none of these associations was significant ($P > 0.05$).

Discussion

Papillary thyroid cancer is the most frequent type of thyroid malignancy according to the

World Health Organization [5], and the incidence of papillary thyroid cancer has been increasing dramatically [6-10]. Papillary microcarcinoma of the thyroid is defined as thyroid cancer that measures ≤ 1 cm in its greatest dimension [11, 12]. Microcarcinoma accounts for between 35.7% and 48.8% of papillary thyroid cancers in different countries [13-15].

Obesity has been linked to many threats to health. Recent epidemiological studies of the association between obesity and cancer risk have suggested that BMI is positively associated with the risks of many types of cancers, such as cancers of the uterus, gallbladder, kidney, and thyroid [16-21]. Li Xu et al. demonstrated that BMI and body fat percentage were significantly associated with increased risks of papillary thyroid cancer. In a pooled analysis of 5 prospective studies, Cari et al. concluded that BMI was positively associated with thyroid cancer risk in both men and women. In summary, most of the relevant studies have demonstrated that higher BMI leads to a higher risk of PTC.

Although a few studies have investigated the relationships between BMI and the clinical features of thyroid cancer, these studies have not drawn the same conclusion [22-27]. Krishnan et al. suggested that BMI is associated with cancer risk, with substantial population-level effects [22]. Kim et al. reported that, in the subgroup of patients ≥ 45 years old, higher BMI was correlated with more aggressive tumour features, such as lymph node metastasis ($P = 0.004$), lymphatic invasion ($P = 0.003$), and tumour multiplicity ($P = 0.008$) [24]. However, Paes et al. concluded that higher BMI was neither associated with more aggressive tumour features, nor a greater likelihood of disease recurrence or persistence [26]. Small numbers of cases, differences in race and/or ethnicity, and differences in degrees of obesity may explain these conflicting results regarding the relationship between BMI and the clinical prognosis of thyroid cancer. Therefore, the relationship between BMI and the clinicopathological features of this disease remain controversial.

Our study is the first to show that higher BMI is strongly associated with extrathyroidal and advanced TNM stage in PTMCs. Further, patients in the overweight group had significantly greater risks of extrathyroidal invasion and advanced TNM stage, as compared with

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patients who had normal BMIs. Patients in the obese group also had an elevated risk of extra-thyroidal invasion. All of these findings demonstrate that high BMI might elevate the risk of aggressive clinicopathological features. Similar results were also found for all PTCs.

There are many potential explanations for the association between PTC and obesity. One of these potential explanations is hormonal changes, such as in insulin, leptin, adiponectin, and thyroid stimulating hormone [28-30]. Insulin resistance is a state in which tissues have reduced responsiveness to the physiological actions of insulin. This state could lead to a compensatory rise in plasma insulin levels, as affected by both adiposity and physical activity. Intra-abdominal obesity is associated with insulin resistance. Insulin resistance may play an important role in the growth of thyroid cancer cells because these cells may be encouraged to proliferate by the direct binding of insulin to insulin receptors, or by the stimulation of insulin-like growth factor. Therefore, obesity may affect the thyroid cancer cells' proliferation, resulting in aggressive clinical features [31]. Furthermore, leptin, blood glucose, and adiponectin, have been implicated as mediators of the effects of obesity on thyroid cancer development [32, 33]. Even in an in vitro analysis, leptin has been shown to stimulate cell proliferation, inhibit apoptosis, and promote angiogenesis and tumour invasion via activation of the P13K/AKT signalling pathway.

There were some limitations to our study. First, even though BMI is the most used measurement in medical research on obesity, waist-to-hip ratio and skin-fold thickness may be more accurate measures. Second, because this study had a retrospective design, various biases could not be excluded. In addition, it was not possible for us to include information on recurrence and survival, which prevents us from determining the association between BMI and the recurrence or survival of papillary microthyroid cancer. Moreover, the obesity threshold of BMI ≥ 30 kg/m² in Han patients is not representative of the same level of obesity in patients of other ethnicities, because of ethnic heterogeneity in body shape and build.

Conclusion

In conclusion, the results of our study support the hypothesis that obesity control can play an important role in preventing the development of aggressive PTMC and all PTCs. However, fur-

ther studies are necessary to confirm both the causal role of obesity and the potential prognostic value of BMI.

Disclosure of conflict of interest

None.

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