

Lack of Associations between Body Mass Index and Clinical Outcomes in Patients with Papillary Thyroid Carcinoma

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Background: Obesity is associated with aggressive pathological features and poor clinical outcomes in breast and prostate cancers. In papillary thyroid carcinoma (PTC), these relationships remain still controversial. This study aimed to evaluate the associations between body mass index (BMI) and the clinical outcomes of patients with PTC.

Methods: This retrospective study included 1,189 patients who underwent total thyroidectomy for PTCs equal to or larger than 1 cm in size. Clinical outcomes were evaluated and compared based on the BMI quartiles.

Results: There were no significant associations between BMI quartiles and primary tumor size, extrathyroidal invasion, cervical lymph node metastasis, or distant metastasis. However, an increase in mean age was associated with an increased BMI (P for trend <0.001). Multifocality and advanced tumor-node-metastasis (TNM) stage (stage III or IV) were significantly associated with increases of BMI (P for trend 0.02 and <0.001 , respectively). However, these associations of multifocality and advanced TNM stage with BMI were not significant in multivariate analyses adjusted for age and gender. Moreover, there were no differences in recurrence-free survivals according to BMI quartiles ($P=0.26$).

Conclusion: In the present study, BMI was not associated with the aggressive clinicopathological features or recurrence-free survivals in patients with PTC.

Keywords: Obesity; Thyroid neoplasms; Prognosis

INTRODUCTION

Obesity is associated with the development and progression of various cancers such as breast cancer, endometrial cancer, colon cancer, esophageal adenocarcinoma, prostate cancer, liver cell carcinoma, leukemia, non-Hodgkin lymphoma, and mela-

noma [1-4]. Recently, several epidemiologic studies have suggested a positive association between obesity and the prevalence of thyroid cancer [5-10].

In addition to the increased prevalence of cancers, obesity is associated with aggressive pathological features and poor clinical outcomes such as increased risk of recurrence and progres-

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sion in breast and prostate cancers [11-14]. The relationships between obesity and clinical outcomes of thyroid cancer remain still controversial. Three studies showed a correlation between obesity and more advanced tumor stages [5,15,16]. A report suggested that overweight or obese patients with papillary thyroid carcinomas (PTC) larger than 1 cm in size had the increased risk of developing loco-regional persistent or recurrent disease [5]. However, other studies reported that a higher body mass index (BMI) was not associated with more aggressive pathological features, or the recurrence or persistence of disease [17,18]. In fact, one study suggested that obesity might be correlated with less aggressive tumor invasion, although this finding was not statistically significant [17].

In the present study, we evaluated the associations of an increased BMI with clinicopathological features and the recurrence-free survivals in patients with PTCs equal to or larger than 1 cm in size.

METHODS

Study subjects and design

This retrospective study included 1,189 patients who underwent total thyroidectomy for PTCs equal to or larger than 1 cm in size at Asan Medical Center in Seoul, Korea between 2000 and 2005. We reviewed medical records of the patients including preoperative body weights, heights, surgical records, pathology reports, and the results of therapeutic whole body scans to assess the initial clinicopathological status for each patient. The tumor node metastasis (TNM) stage was based on the seventh edition of the American Joint Committee on Cancer (AJCC) staging manual [19].

Anthropometric measurements

On the day of admission for thyroid surgery, the heights and weights were measured in patients wearing light clothing without shoes. BMI was calculated using the following formula; the weight in kilograms stratified by square of the height in meters (kg/m^2). For comparisons, patients were stratified into four groups according to gender-specific quartiles for BMI (kg/m^2): Q1 19.4 to 23.0, Q2 23.1 to 24.9, Q3 25.0 to 26.9, and Q4 27.0 to 38.2 for males; Q1 15.8 to 21.7, Q2 21.8 to 23.5, Q3 23.6 to 25.9, and Q4 26.0 to 37.1 for females.

Follow-up protocol for the detection of clinical recurrence

As we previously described, all patients were subjected to regular physical examinations and assessments of serum thyro-

globulin (TG) levels in every 6 to 12 months interval [20]. Neck ultrasonography examinations were performed at least once during the follow-up period. Stimulated TG levels were evaluated in patients with thyroid-stimulating hormone withdrawal approximately 12 months after total thyroidectomy. Additional diagnostic imaging studies including fluorodeoxyglucose positron emission tomography and chest computed tomography scans, were performed in patients whose distant metastases were clinically under suspicions [20]. Clinical recurrence was defined as the reappearance of pathologically proven malignant tissues and/or the appearance of metastatic lesions in the lung, bone, and/or brain in patients initially confirmed to be in remission [20].

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are expressed as mean \pm standard deviation. The BMI quartiles were calculated separately for males and females. All data analyses were performed using R version 3.0 and R libraries survival (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org>). The comparisons of continuous variables, such as age and maximal tumor diameter, according to BMI quartiles were conducted using analysis of variance or Student *t* test. Trends across the increases in BMI quartiles were performed using a Cochran-Armitage trend test, except for the nodal metastasis variable. Categorical variables were analyzed using chi-square tests. In the multivariate analyses, the relative associations between BMI quartiles and advanced TNM stage or multifocality were presented as odds ratios (ORs) with 95% confidence intervals (CIs) which were calculated using binominal logistic regression analyses. A log-rank test was used to compare recurrence-free survivals among the BMI quartiles. Hazard ratios (HRs) and 95% CIs were derived from the Cox proportional hazards model. All of *P* values were two-sided. *P* < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Total 1,189 patients (157 males and 1,032 females) were included in the present study. The baseline characteristics of patients are shown in Table 1. The mean age was 45.3 ± 11.9 years and 640 patients (53.8%) were older than 45 years of age. The mean maximal tumor diameter was 2.1 ± 1.2 cm. Extrathyroidal invasion and multifocality of the primary tumors were present in 789

Table 1. Baseline Characteristics of Study Subjects and Associations between Body Mass Index Quartiles and Clinicopathological Features of Papillary Thyroid Carcinoma

Characteristic	Total (n=1,189)	Quartile according to body mass index				P value ^b
		Q1 ^a (n=290)	Q2 ^a (n=293)	Q3 ^a (n=301)	Q4 ^a (n=305)	
Age, yr	45.3±11.9	44.7±11.3	38.4±11.8	48.2±10.1	49.7±11.2	<0.001 ^{cd}
<45	549 (46.2)	146 (50.3)	205 (70.0)	96 (31.9)	102 (33.4)	<0.001 ^d
≥45	640 (53.8)	144 (49.7)	88 (30.0)	205 (68.1)	203 (66.6)	
Gender						
Male	157 (13.2)	39 (13.4)	39 (13.3)	38 (12.6)	41 (13.4)	0.939
Female	1,032 (86.8)	251 (86.6)	254 (86.7)	263 (87.4)	264 (86.6)	
Maximal tumor diameter, cm	2.1±1.2	2.0±1.1	2.2±1.2	2.0±1.0	2.1±1.2	0.209 ^e
≤2	775 (65.2)	199 (68.6)	178 (60.8)	201 (66.8)	197 (64.6)	0.633
>2	414 (34.8)	91 (31.4)	115 (39.2)	100 (33.2)	108 (35.4)	
Extrathyroidal invasion						
Absent	400 (33.6)	92 (31.7)	112 (38.2)	101 (33.6)	95 (31.1)	0.586
Present	789 (66.4)	198 (68.3)	181 (61.8)	200 (66.4)	210 (68.9)	
Multifocal	466 (39.2)	115 (39.7)	85 (29.0)	128 (42.5)	138 (45.2)	0.015 ^d
Lymph node metastasis						
pN0/Nx	427 (35.9)	100 (34.5)	92 (31.4)	121 (40.2)	114 (37.4)	0.330 ^e
pN1a	581 (48.9)	145 (50.0)	148 (50.5)	138 (45.8)	150 (49.2)	
pN1b	181 (15.2)	45 (15.5)	53 (18.1)	42 (14.0)	41 (13.4)	
Distant metastasis, present	25 (2.1)	6 (2.1)	11 (3.8)	5 (1.7)	3 (1.0)	0.145
Staging according to TNM						
I/II	638 (53.7)	165 (56.9)	217 (74.1)	129 (42.9)	127 (41.6)	<0.001 ^d
III/IV	551 (46.3)	125 (43.1)	76 (25.9)	172 (57.1)	178 (58.4)	

Values are expressed as mean±SD or number (%).

TNM, tumor node metastasis.

^aQuartiles for body mass index (kg/m²): Q1 19.4–23.0, Q2 23.1–24.9, Q3 25.0–26.9, and Q4 27.0–38.2 for males and Q1 15.8–21.7, Q2 21.8–23.5, Q3 23.6–25.9, and Q4 26.0–37.1 for females; ^bP values for trends across the body mass index quartiles were conducted using a Cochran-Armitage trend test, except nodal metastasis variable; ^cP values by analysis of variance; ^dStatistically significant; ^eNodal metastasis variable was analyzed by a chi-square test.

patients (66.4%) and 466 (39.2%), respectively. Of the 1,189 patients, 762 patients (64.1%) had cervical lymph node (LN) metastases, 181 (15.2%) had lateral neck LN metastases (N1b), and 25 (2.1%) had distant metastases at the initial diagnosis.

The mean BMI was 24.1±3.2 kg/m² for all patients, 24.9±3.0 kg/m² for the males, and 23.5±3.3 kg/m² for the females. Of the 1,189 patients, 384 (32.3%) were overweight (BMI, 25.0 to 29.9 kg/m²), and 55 (4.6%) were obese (BMI ≥30.0 kg/m²). The proportion of overweight and obese patients (BMI ≥25 kg/m²) was markedly higher in males than females (48.4% vs. 35.2%, *P*=0.001).

Associations of BMI quartile groups with clinicopathological features of PTC

The clinicopathological features of the PTCs were evaluated

according to BMI quartile categories (Table 1). There were no significant associations for primary tumor size, extrathyroidal invasion, LN metastasis, or distant metastasis according to BMI quartiles. However, the mean age showed a significant increase across BMI quartiles (*P*<0.001). Multifocality and advanced TNM stage (stage III or IV) showed significantly increasing trends with the increases in BMI quartiles (*P* for trend=0.015 and <0.001, respectively).

In multivariate analyses, these associations of increased BMI with multifocality (OR, 1.11; 95% CI, 0.99 to 1.23; *P*=0.067) and advanced TNM stage (OR, 1.11; 95% CI, 0.99 to 1.23; *P*=0.769) were disappeared after adjusting for age and gender. The associations between clinico-pathological features of PTC and BMI quartiles were also evaluated according to gender (Tables 2, 3). The females showed the same patterns as overall

Table 2. Associations between Body Mass Index Quartile and Clinicopathological Features for Females

Variable	Total (n=1,032)	Quartile according to body mass index				P value ^b
		Q1 ^a (n=251)	Q2 ^a (n=254)	Q3 ^a (n=263)	Q4 ^a (n=264)	
Age, yr	45.3±11.9	44.3±11.2	37.6±11.3	48.3±10.0	50.7±10.7	<0.001 ^{c,d}
<45	476 (46.1)	129 (51.4)	187 (73.6)	79 (30.0)	81 (30.7)	<0.001 ^d
≥45	556 (53.9)	122 (48.6)	67 (26.4)	184 (70.0)	183 (69.3)	
Maximal tumor diameter, cm	2.0±1.1	2.0±1.0	2.1±1.1	1.9±1.0	2.0±1.1	0.441 ^c
≤2	695 (67.3)	172 (68.5)	160 (63.0)	185 (70.3)	178 (67.4)	0.751
>2	337 (32.7)	79 (31.5)	94 (37.0)	78 (29.7)	86 (32.6)	
Extrathyroidal invasion						
Absent	345 (33.4)	78 (31.1)	93 (36.6)	91 (34.6)	83 (31.4)	0.928
Present	687 (66.6)	173 (68.9)	161 (63.4)	172 (65.4)	181 (68.6)	
Multifocal	411 (39.8)	99 (39.4)	75 (29.5)	113 (43.0)	124 (47.0)	0.008 ^d
Lymph node metastasis						
pN0/Nx	393 (38.1)	93 (37.1)	83 (32.7)	113 (43.0)	104 (39.4)	0.210 ^c
pN1a	502 (48.6)	126 (50.2)	128 (50.4)	122 (46.4)	126 (47.7)	
pN1b	137 (13.3)	32 (12.7)	43 (16.9)	28 (10.6)	34 (12.9)	
Distant metastasis, present	20 (1.9)	5 (2.0)	9 (3.5)	4 (1.5)	2 (0.8)	0.131
Staging according to TNM						
I/II	559 (54.2)	146 (58.2)	196 (77.2)	111 (42.2)	106 (40.2)	<0.001 ^d
III/IV	473 (45.8)	105 (41.8)	58 (22.8)	152 (57.8)	158 (59.8)	

Values are expressed as mean±SD or number (%).

TNM, tumor node metastasis.

^aQuartiles for body mass index (kg/m²): Q1 15.8–21.7, Q2 21.8–23.5, Q3 23.6–25.9, and Q4 26.0–37.1 for females; ^bP values for trends across the body mass index quartiles were conducted using a Cochran-Armitage trend test, except nodal metastasis variable; ^cP values by analysis of variance;

^dStatistically significant; ^eNodal metastasis variable was analyzed by a chi-square test.

subjects, while the proportion of the males with maximal tumor diameters larger than 2 cm was associated with higher BMI quartile (*P* for trend=0.043). However, its association disappeared after adjusting for age (The data was not shown).

Recurrence-free survivals according to BMI quartiles

After the exclusion of patients with distant metastases at initial diagnosis (*n*=25), the recurrence-free survivals of the PTC patients were evaluated during median 8.4 years of the follow-up period. Total 160 of 1,164 patients (13.7%) experienced PTC recurrence during the follow-up. There were no significant differences in recurrence-free survivals across the BMI quartiles (log rank statistics=4.0, *df*=3, *P*=0.26) (Fig. 1).

DISCUSSION

The present study evaluated associations of the increases in BMI with clinicopathological features and recurrence free sur-

vivals in patients who underwent total thyroidectomy for PTCs. There were no significant relationships between increased BMI and clinicopathological features of PTC. Patients with PTCs that were less than 1 cm in size were excluded because papillary thyroid microcarcinoma has favorable prognoses which included a low rate of distant metastasis and a low risk of disease recurrence [21-23].

In this study, we applied gender-specific BMI quartiles to the data to evaluate possible associations between increased BMI and clinicopathological features of PTC. Gender is an important contributing factor to obesity, and a significant difference in the proportion of obese patients according to gender was observed in our study (males vs. females, 48.4% vs. 35.2%; *P*=0.001). Therefore, gender-specific BMI quartiles were calculated to adjust for the differences in BMI distribution between males and females.

In univariate analyses, an advanced TNM stage was significantly associated with increased BMI. However, this increase

Table 3. Associations between Body Mass Index Quartiles and Clinicopathological Features for Males

Variable	Total (n=157)	Quartile according to body mass index				P value ^b
		Q1 ^a (n=39)	Q2 ^a (n=39)	Q3 ^a (n=38)	Q4 ^a (n=41)	
Age, yr	45.2±12.5	47.1±12.1	43.0±14.1	47.6±11.1	43.5±12.1	0.234 ^c
<45	73 (46.5)	17 (43.6)	18 (46.2)	17 (44.7)	21 (51.2)	0.538
≥45	84 (53.5)	22 (56.4)	21 (53.8)	21 (55.3)	20 (48.8)	
Maximal tumor diameter, cm	2.5±1.5	2.1±1.6	2.7±1.8	2.6±1.1	2.8±1.6	0.200 ^c
≤2	80 (51.0)	27 (69.2)	18 (46.2)	16 (42.1)	19 (46.3)	0.043 ^d
>2	77 (49.0)	12 (30.8)	21 (53.8)	22 (57.9)	22 (53.7)	
Extrathyroidal invasion						
Absent	55 (35.0)	14 (35.9)	19 (48.7)	10 (26.3)	12 (29.3)	0.214
Present	102 (65.0)	25 (64.1)	20 (51.3)	28 (73.7)	29 (70.7)	
Multifocal	55 (35.0)	116 (41.0)	10 (25.6)	15 (39.5)	14 (34.1)	0.838
Lymph node metastasis						
pN0/Nx	34 (21.7)	7 (17.9)	9 (23.1)	8 (21.1)	10 (24.4)	0.570 ^c
pN1a	79 (50.3)	19 (48.7)	20 (51.3)	16 (42.1)	24 (58.5)	
pN1b	44 (28.0)	13 (33.3)	10 (25.6)	14 (36.8)	7 (17.1)	
Distant metastasis, present	5 (3.2)	1 (2.6)	2 (5.1)	1 (2.6)	1 (2.4)	0.815
Staging according to TNM						
I/II	79 (50.3)	19 (48.7)	21 (53.8)	18 (47.4)	21 (51.2)	0.973
III/IV	78 (49.7)	20 (51.3)	18 (46.2)	20 (52.6)	20 (48.8)	

Values are expressed as mean±SD or number (%).

TNM, tumor node metastasis.

^aQuartiles for body mass index (kg/m²); Q1 19.4–23.0, Q2 23.1–24.9, Q3 25.0–26.9, and Q4 27.0–38.2 for males; ^bP values for trends across the body mass index quartiles were conducted using a Cochran-Armitage trend test, except nodal metastasis variable; ^cP values by analysis of variance; ^dStatistically significant; ^eNodal metastasis variable was analyzed by a chi-square test.

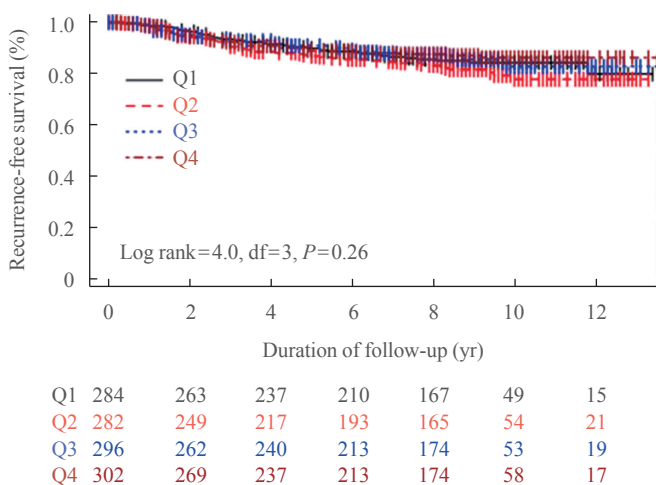


Fig. 1. Recurrence-free survivals across the body mass index (BMI) quartiles. There were no significant differences in recurrence-free survivals of papillary thyroid carcinoma patients across the BMI quartiles. The numbers of patients who remained no evidence of disease at each time point were described at the bottom.

was also associated with older age. Age at the time of diagnosis was a major variable when assessing tumor staging based on the AJCC TNM staging system [19]. Therefore, age might be a confounding factor when assessing the impact of obesity in the TNM stage of PTC. In our multivariate analysis, the positive association between BMI and advanced TNM stage disappeared after adjusting for age and gender.

The World Health Organization defined obesity as BMI ≥ 30.0 kg/m² [24]. Tresallet et al. [5] suggested that overweight or obese patients with PTC larger than 1 cm in size had an increased risk of developing loco-regional persistent or recurrent disease (OR, 3.8; P=0.03). Using Western standards, these authors categorized 14.5% of patients as obese (BMI ≥30.0 kg/m²) and 29.3% of patients as overweight (BMI, 25.0 to 29.9 kg/m²). However, only 55 of 1,189 patients (4.6%) in the present study had BMI ≥30.0 kg/m². The Korean Endocrine Society defined obesity as BMI ≥25.0 kg/m² [25]. Using this definition, approximately 36% of patients in the present study were

categorized as the obese group. This difference in the prevalence of obesity between Western countries and Korea may explain the lack of associations between obesity and clinico-pathological features of PTC. Therefore, BMI quartiles were used for analyses in this study.

This retrospective study has several limitations. First, information such as waist to hip ratio, percentage of body fat, skin-fold thickness, and assessments of intra-abdominal fat were unavailable. Thus, the present study defined obesity based only on BMI. Similarly, other potential contributing factors including the history of diabetes mellitus, dyslipidemia, smoking, and physical activity could not be obtained. However, this study did include a large, homogenous, and well-defined population of subjects ($n=1,189$) with PTC equal to or greater than 1 cm in size. Moreover, the study subjects underwent total thyroidectomy and followed by same strategy at one institution for long term period. And, we applied gender-specific BMI quartiles.

In conclusion, the present study found that increased BMI was not associated with the clinical outcomes of patients with PTC, including their clinicopathological features and recurrence-free survivals.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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