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The Relationship between Body Mass Index and Papillary Thyroid Cancer Pathology Aggressiveness

Song I Yang[1]*, Kwang Kuk Park[2] and Kim Jeong-Hoon[1]

[1]Department of Surgery, Kosin University College of Medicine, Busan, South Korea

[2]Department of Surgery, Park Hospital, Busan, South Korea

Abstract

Purpose: Obesity is a known risk factor for several cancers, including breast, colon, esophagus, kidney, uterus, and thyroid. Recent studies have reported that higher Body Mass Index (BMI) is also associated with more advanced stage. The aim of this study was to investigate the clinicopathological relevance between BMI and Papillary Thyroid Carcinoma (PTC).

Methods: A total of 4,338 patients surgically treated for PTC from January 2005 to December 2015 were included in this study. Medical records and pathologic reports were reviewed retrospectively. According to BMI, patients were divided into four groups: underweight (2.5%), normal (63.2%), overweight (29.7%), and obese (4.6%). Clinicopathological factors were analyzed and compared between normal and other groups.

Results: According to the results, 3,683 patients were women (84.9%) and mean age was 47.1 years. There were significant associations between BMI quartiles and Multifocality, cervical lymph node metastasis, or TNM stage. Increased BMI was strongly associated with Multifocality and extrathyroidal invasion. There were no differences in recurrence according to BMI quartiles.

Conclusion: Increased BMI might elevate the risks of aggressive clinicopathological features, such as extrathyroidal invasion, multifocality and thyroiditis. To confirm this result, further studies with long-term follow-up and more patients are required.

Keywords: Obesity; Body mass index; Papillary thyroid carcinoma

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****Correspondence:***
Song I Yang, Department of Surgery, Kosin University College of Medicine, 262, Gamcheon-ro, Seo-gu, Busan, 49267, Republic of Korea, Tel: 82519906462; Fax: 82512466093; E-mail: tonybin@daum.net

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Introduction

Recently, the prevalence of thyroid cancer, especially Papillary Thyroid Carcinoma (PTC), has shown a significant increase in Korea and around the world. In 1999, thyroid cancer was the seventh most common cancer among women in Korea, but as of 2010, it became the most common cancer among women, accounting for 30.1% of all cancers, while it also became the most common cancer among both men and women with 17.8%. Higher prevalence of thyroid cancer can be explained in part by the fact that development and use of neck ultrasonography and ultrasound-guided fine-needle aspiration have led to increased diagnostic rate for asymptomatic thyroid cancer [1]. Additional aspects, such as changes in exposure to environmental factors, may also play a role in explaining such increase in prevalence. However, considering that increase in prevalence of thyroid cancer coincided with increased number of early cancer with small tumor size, as well as various tumor sizes and stages, it is suspected that there are other unidentified factors besides advances in diagnostic tools [2]. Obesity is a global health issue associated with shorter lifespan and increased incidence of hypertension, type 2 diabetes, heart disease, stroke, and sleep apnea [3]. It is also associated with onset and progression of specific types of cancers, including esophageal, colorectal, breast, endometrial, renal, and thyroid cancer [4]. The relationship between excessive weight and cancer is determined by separate complex pathways, but generally, mechanisms by which obesity affects cancer can be explained by biological or mechanical factors. Biological mechanisms include insulin, Insulin-Like Growth Factors (IGFs), sex steroids, sex steroid-binding globulins, and adipokines, such as adiponectin and leptin. In addition, other biological mechanisms are known to be mediated by obesity-related inflammatory cytokines, nuclear factor κB pathway, and change in immune response, increased oxidative stress, and peroxidation [5]. Mechanical mechanisms include hypertension (renal cancer) and acid reflux (esophageal cancer) [4]. A review of studies on the association between PTC and BMI showed that recent studies are reporting that obesity is one of the factors considered to cause increase in thyroid cancer [6,7]. In addition, some retrospective studies have reported that increase in BMI is associated with aggressive clinicopathological features in patients with PTC [8]. However, the relationship between obesity and poor prognosis associated with PTC is still controversial [9], and while the basis for the correlation between excessive weight and malignant thyroid tumor has not yet been completely identified, the traditional risk factors of thyroid cancer still remain radiation exposure, high iodine intake, and family history of thyroid cancer [10]. For future evident on the potential negative effect of obesity on thyroid cancer, it is determined that clinical intervention including weight loss programs for overweight and obese people and thyroid cancer screening guidelines would play an important role. Accordingly, the present study aimed to investigate the correlation between clinicopathological parameters and being overweight in relation to PTC to use the findings to identify the correlation between BMI and cancer aggressiveness in relation to PTC.

Methods

The study population included 4,338 patients who received surgical treatment at Kosin University Gospel Hospital between January 2005 and December 2015 and were subsequently diagnosed with PTC. All medical records of these patients, including histopathological results, were retrospectively analyzed. BMI of each patient was calculated using the height and weight measured at the time of admission for the surgery. Using the standard BMI categories from the World Health Organization (WHO), the patients were divided into four groups: Underweight (18.5), normal (18.5~24.9), overweight (25.0~29.9), and obese (≥ 30.0) [11]. The clinicopathological factors of the normal group were compared to those of other groups, while tumor size, multifocality, Lymph Node (LN) metastasis, advanced TNM staging, and recurrence were compared as factors suggesting aggressiveness of the tumor. Advanced TNM staging was divided according to the classification system given by the American Joint Committee on Cancer (AJCC; 8th edition) [12], and stages 1 and 2 were compared and analyzed against stages 3 and 4, representing advanced cancer. Recurrence was defined as new pathologically confirmed lesion in a patient who had been determined to be in remission during the follow-up observation period. Univariate analyses including chi-square test and one-way analysis of variance (ANOVA) were performed to determine the significance between BMI and the variables, while multivariate analysis was performed on the factors suggesting cancer aggressiveness. A logistic regression model was used to estimate the Odds Ratio (OR) and 95% Confidence Interval (CI), while adjusted OR was calculated by adjusting for age, gender, and TSH value. All statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA) with statistical significance set to P-value <0.05.

Results

Among a total of 4,338 patients, there were 3,683 females (84.9%) and 655 males (15.1%). The mean age was 47.1 years (14~82 years) and mean BMI was 24.0 ± 3.3 (15.0~41.2). Based on BMI categories, the patients were divided into the underweight (n=109, 2.5%), normal (n=2,741, 63.2%), overweight (n=1,288, 29.7%), and obese (n=200, 4.6%) groups. The mean tumor size was 11.6 mm (2~63 mm), while there were 2,579 cases (59.5%) of papillary thyroid microcarcinoma with tumor size ≤ 1 cm and 1,426 cases (32.9%) showing multifocality. Extrathyroid invasion and LN metastasis was found in 2,037 cases (47.0%) and 1,800 cases (41.5%), respectively, where LN metastasis involved the central neck LN in 1,416 cases (32.6%) and lateral neck LN in 384 cases (8.9%). In advanced TNM staging, the number of cases classified as stage 1, 2, 3, and 4 was 2,684 (61.9%), 74 (1.7%), 1,394 (32.1%), and 186 (4.3%), respectively, while in adjusted TNM staging for statistical analysis, there were 2,758 cases (63.6%) of stages 1 and 2 and 1,580 cases (36.4%) of stages 3 and 4. The mean follow-up period was 1,721 ± 464.2 days, and during the follow-up period, there were 78 cases (1.8%) of recurrences. Of those cases, recurrence found in the central neck LN, lateral neck LN, and contralateral thyroid in 2 cases (2.6%), 61 cases (78.2%), and 15 cases (19.2%), respectively (Table 1).

Table 1: Baseline clinicopathological characteristics of patients diagnosed with papillary thyroid carcinoma.

Characteristic	Total (N=4338)
Gender	
Female	3683 (84.9%)
Male	655 (15.1%)
Mean Age (years)	47.1 ± 11.4
<45	1820 (42.0%)
≥ 45	2518 (58.0%)
BMI (kg/m^2)	24.0 ± 3.3
Tumor size (mm)	11.6 ± 8.2
≤ 10	2579 (59.5%)
>10	1759 (40.5%)
Multifocality	1426 (32.9%)
Extrathyroidal invasion	2037 (47.0%)
LN metastasis	1800 (41.5%)
Central LN	1416 (32.6%)
Lateral LN	384 (8.9%)
TNM stage	
1	2684 (61.9%)
2	74 (1.7%)
3	1394 (32.1%)
4	186 (4.3%)
Recurrence	78 (1.8%)
central LN	2 (2.6%)
lateral LN	61 (78.2%)
opposite gland	15 (19.2%)
Thyroditis	1152 (26.6%)

Normal group versus underweight group

The mean BMI in the normal and underweight group was 22.3 ± 1.6 and 17.7 ± 0.7, respectively (Table 2), while there were no significant differences between the two groups with respect to tumor size, multifocality, extrathyroid invasion, LN metastasis, recurrence, and thyroiditis. However, in the univariate analysis, the normal and underweight groups showed differences based on TNM staging (P=0.000), but such differences were not found in the multivariate analysis (OR 0.255 [0.062~1.049], P=0.058) (Table 3 and 4).

Normal group versus underweight group

The mean BMI in the overweight group was 26.8 ± 1.3 (Table 2), while there were no significant differences between the two groups with respect to LN metastasis, TNM staging, recurrence, and thyroiditis. However, as compared to the normal group, the overweight group showed differences in tumor size (12.0 mm ± 8.7, p=0.024), multifocality (30.5% *vs.* 36.7%, p=0.000), extrathyroid invasion (44.3% *vs.* 51.6%, p=0.000), and TNM stage (p=0.000) in the univariate analysis and statistically significant differences in multifocality (OR=0.783 [0.677~0.905], P=0.001) and extrathyroid

Table 2: Clinicopathological characteristics of patients diagnosed with papillary thyroid carcinoma.

	Underweight (N=109)	Normal (N=2741)	Overweight (N=1288)	Obese (N=200)	p
Gender					0
Female	106 (97.2%)	2397 (87.4%)	1016 (78.9%)	164 (82.0%)	
Male	3 (2.8%)	344 (12.6%)	272 (21.1%)	36 (18.0%)	
Mean age (years)	40.3 ± 12.9	46.2 ± 11.2	49.8 ± 11.1	46.3 ± 11.8	0
<45	76 (69.7%)	1223 (44.6%)	426 (33.1%)	95 (47.5%)	
≥ 45	33 (30.3%)	1518 (55.4%)	862 (66.9%)	105 (52.5%)	
BMI (kg/m^2)	17.7 ± 0.7	22.3 ± 1.6	26.8 ± 1.3	32.1 ± 2.1	0
Tumor size (mm)	11.9 ± 8.5	11.3 ± 8.0	12.0 ± 8.7	12.1 ± 8.3	0.092
≤ 10	65 (59.6%)	1643 (59.9%)	759 (58.9%)	112 (56.0%)	0.703
>10	44 (40.4%)	1098 (40.1%)	529 (41.1%)	88 (44.0%)	
Multifocality	30 (27.5%)	837 (30.5%)	473 (36.7%)	86 (43.0%)	0
Extrathyroidal invasion	44 (40.4%)	1214 (44.3%)	664 (51.6%)	115 (57.5%)	0
Lymph node metastasis	46 (42.2%)	1132 (41.3%)	535 (41.5%)	87 (43.5%)	0.941
Central LN	35 (32.1%)	895 (32.7%)	418 (32.5%)	68 (34.0%)	0.992
Lateral LN	11 (10.1%)	237 (8.6%)	117 (9.1%)	19 (9.5%)	
TNM stage					0
1	91 (83.5%)	1764 (64.4%)	697 (54.1%)	132 (66.0%)	
2	2 (1.8%)	50 (1.8%)	22 (1.7%)	0 (0.0%)	
3	12 (11.0%)	826 (30.1%)	496 (38.5%)	60 (30.0%)	
4	4 (3.7%)	101 (3.7%)	73 (5.7%)	8 (4.0%)	
Recurrence	3 (2.8%)	45 (1.6%)	27 (2.1%)	3 (1.5%)	0.639
central LN	0 (0.0%)	2 (4.4%)	0 (0.0%)	0 (0.0%)	0.847
lateral LN	3 (100.0%)	34 (75.6%)	22 (81.5%)	2 (66.7%)	
opposite gland	0 (0.0%)	9 (20.0%)	5 (18.5%)	1 (33.3%)	
Thyroditis	34 (31.2%)	757 (27.6%)	321 (24.9%)	40 (20.0%)	0.03

Table 3: Univariate analysis of parameters according to body mass index.

	Underweight (N=109, 2.5%)	Normal (N=2741, 63.2%)	Overweight (N=1288, 29.7%)	Obese (N=200, 4.6%)
Tumor size (mm)	11.9 ± 8.5	11.3 ± 8.0	12.0 ± 8.7	12.1 ± 8.3
P value	0.46	Reference	0.024	0.19
Multifocality	30 (27.5%)	837 (30.5%)	473 (36.7%)	86 (43.0%)
P value	0.572	Reference	0	0
Extrathyroid				
Invasion	44 (40.4%)	1214 (44.3%)	664 (51.6%)	115 (57.5%)
P value	0.477	Reference	0	0
LN metastasis	46 (42.2%)	1132 (41.3%)	535 (41.5%)	87 (43.5%)
P value	0.929	Reference	0.913	0.592
TNM staging				
1	91 (83.5%)	1764 (64.4%)	697 (54.1%)	132 (66.0%)
2	2 (1.8%)	50 (1.8%)	22 (1.7%)	0 (0.0%)
3	12 (11.0%)	826 (30.1%)	496 (38.5%)	60 (30.0%)
4	4 (3.7%)	101 (3.7%)	73 (5.7%)	8 (4.0%)
P value	0	Reference	0	0.287
Recurrence	3 (2.8%)	45 (1.6%)	27 (2.1%)	3 (1.5%)
P value	0.614	Reference	0.374	1
Thyroditis	34 (31.2%)	757 (27.6%)	321 (24.9%)	40 (20.0%)
P value	0.479	Reference	0.078	0.024

Table 4: Multivariate analysis with odds ratio (OR) and 95% confidence interval (CI).

	Underweight (N=109, 2.5%)	Normal (N=2741, 63.2%)	Overweight (N=1288, 29.7%)	Obese (N=200, 4.6%)
Tumor size (mm)				
OR (95% CI)	1.01			
(0.985~1.035)	1	1.007		
(0.998~1.017)	1.012			
(0.994~1.031)				
P value	0.455	Reference	0.113	1.198
Multifocality				
OR (95% CI)	0.862			
(0.558~1.331)	1	1.3		
(1.127~1.499)	1.671			
(1.241~2.251)				
P value	0.502	Reference	0	0.001
Extrathyroid invasion				
OR (95% CI)	0.846			
(0.565~1.267)	1	1.322		
(1.152~1.517)	1.63			
(1.206~2.202)				
P value	0.417	Reference	0	0.001
LN metastasis				
OR (95% CI)	1.098			
(0.733~1.644)	1	0.898		
(0.780~1.034)	0.885			
(0.653~1.198)				
P value	0.651	Reference	0.135	0.428
Advanced TNM staging				
OR (95% CI)	0.255			
(0.062~1.049)	1	0.775		
(0.476~1.261)	0.763			
(0.277~2.097)				
P value	0.058	Reference	0.304	0.599
Recurrence				
OR (95% CI)	1.727			
(0.525~5.675)	1	1.239		
(0.762~2.012)	0.835			
(0.256~2.727)				
P value	0.368	Reference	0.387	0.765
Thyroditis				
OR (95% CI)	1.197			
(0.790~1.813)	1	0.863		
(0.741~1.005)	0.642			
(0.449~0.919)				
P value	0.396	Reference	0.058	0.016

invasion (OR=0.798 [0.669~0.952], P=0.015) in the multivariate analysis (Table 3 and 4).

Normal group versus obese group

The mean BMI in the obese group was 32.1 ± 2.1 (Table 2), while there were no significant differences between the two groups with respect to tumor size, LN metastasis, TNM staging, and recurrence. However, as compared to the normal group, the obese group showed differences in multifocality (OR=0.579 [0.429~0.782], P=0.000), extrathyroid invasion (OR 0.515 [0.353~0.752], P=0.001), and thyroiditis (OR=0.677 [0.471~0.973], P=0.035) in both univariate and multivariate analyses (Table 3 and 4).

Discussion

Thyroid cancer is one of the fastest growing cancers in Korea and the only risk factor that has been established to date is radiation exposure, while diet, accompanying thyroid disease, hormonal influence, and environmental factors are also being considered as possible causes [13]. Recent studies have reported that obesity may also be linked to onset of thyroid cancer. Obesity can cause impairment in the metabolic process within the body and also cause a broad range of endocrine abnormalities involving the pituitary, pancreas, gonad, adrenal glands, and thyroid glands [14]. Moreover, it is also linked to the onset of metabolic syndrome and the overall disease morbidity and mortality rates are known to increase according to obesity [15]. It is also known to be associated with increase in type 2 diabetes, gastroesophageal reflux disease, hypertension, dyslipidemia, and cardiovascular disease, while recent studies are reporting obesity as a risk factor of cancer [15]. Recent studies are also reporting that obesity is associated with increased incidence of thyroid cancer [16]. With respect to the prevalence of thyroid cancer and obesity, a study by Oh et al. [17] on Korean males reported that increase in BMI increased the prevalence of thyroid cancer, while a meta-analysis by Renehan et al. [18] on five prospective studies reported that increase in BMI by 5 kg/m^2 increased the risk of thyroid cancer in males and females by 1.52 (P=0.02) and 1.14 (P=0.001) times. In an analysis conducted in the US, increase in the incidence of thyroid cancer according to increase in BMI was observed in both males and females, while a study conducted in the French Polynesian region with relatively high prevalence of thyroid cancer also confirmed such correlation. Especially in the study from French Polynesian region, BMI ≥ 25 in those aged 18 years or older, the period when they are entering adulthood, showed high probability of thyroid cancer (OR=6.2, P<0.01).(19) Other reports have also indicated that higher BMI manifests more aggressive forms of cancer, including breast cancer [16]. According to Harari et al., [20] in terms of thyroid cancer, obese patients showed higher stage and more aggressive form of PTC. In their study, the percentage of those in stage 3 or 4 among normal, overweight, obese, and morbidly obese groups was 13.2%, 22.7%, 24.3%, and 35.7%, respectively, while the relative risk in overweight, obese, and morbidly obese groups was 1.94, 2.11, and 3.67, respectively (P=0.04).

The following mechanisms have been suggested for the effect of excessive weight on thyroid cancer. First, potential biological mechanisms may affect overweight and obese people, including increased levels of endogenous hormones (steroid hormones, adipokines, estrogen, and insulin-like growth factor-1) [6,18,21]. Obesity-related hormonal changes appear to be associated with cancer aggressiveness of leptin and its receptors. Adipokines, such as leptin, can promote the production of pituitary production of Thyroid-Stimulating Hormone (TSH), [22] where PTC patients tend to show elevated leptin level [23]. Moreover, leptin stimulates cell proliferation and inhibits apoptosis through activation of phosphatidylinositide 3-kinase/protein kinase B (PI3K/AKT) pathway, which is believed to facilitate angiogenesis and tumor invasion [8]. Second, factors or mechanisms association with differentiation of thyroid cancer, such as oxidative stress and nuclear factor κB system, may also have an effect. Third, increase in BMI results in increased volume of thyroid, and thus, people with high BMI may be more susceptible to malignancy due to the presence of more cells with risk of mutation. In addition, it was reported that increase in physical activities, including outdoor activities, may have a potential impact on incidence of thyroid cancer [24]. It was also discovered that lifestyle factors, including consumption of fruits, fresh vegetables, and tea, are associated with lowering the risk of thyroid cancer [25]. However, unlike these studies, Paes et al. [9] reported that obesity may be correlated with the prevalence of thyroid cancer, but the results did not show more aggressive form of cancer or higher recurrence rate during the analysis period. Therefore, it is determined that the correlation between obesity and aggressiveness of thyroid cancer may be established after more studies are reviewed.

Overweight patients are known to show lower serum 1,25-hydroxyvitamin D levels. In a study that examined incidence of thyroid cancer per BMI in all males and females aged 45 years or younger diagnosed with thyroid cancer by fine-needle aspiration biopsy [26,27] and other recent studies have reported that serum 1,25-dihydroxyvitamin D level was significantly lower when BMI was increased [28,29]. In addition to calcium homeostasis, this hormone is known to play an important role in regulating the proliferation and differentiation of various cell types [30]. Meanwhile, some in vitro studies demonstrated that serum 1,25-dihydroxyvitamin D showed dose-dependent inhibition of the proliferation of well-differentiated thyroid cancer cells [30]. Ultimately, it was identified by serum 1,25-dihydroxyvitamin D has a protective effect against the exposure to risk of cancer onset, indicating that lower serum 1,25-dihydroxyvitamin D levels in overweight patients may increase their risk of cancer.

In the present study, the results demonstrated that BMI was closely associated with aggressive oncologic features of PTC, such as tumor multiplicity and extrathyroid invasion. Tumor multiplicity is not a strong prognosticator of PTC, but based on this, it was determined that obesity can affect the aggressive tendency of PTC (invasive metastasis) and cancer susceptibility of patients, such as multifocality. Moreover, the univariate and multivariate analyses results in the present study confirmed that the obese group had higher rate of multifocality and extrathyroid invasion than the normal group, while the rate of thyroiditis was actually lower. In the comparison between the overweight and normal groups, the univariate analysis results also confirmed higher rate of multifocality, extrathyroid invasion, and advanced TNM staging, while the multivariate analysis results confirmed higher rate of only multifocality and extrathyroid invasion. In the comparison between the underweight and normal groups, there were no factors that showed significant differences.

Thyroiditis being lower in the obese group has not been mentioned in existing reports, and thus, additional studies on this topic are needed. The present study had the limitations of being a retrospective study with relatively short follow-up period. Moreover, the study did not fully account for confounding factors, such as smoking, drinking, activity level, and diabetes. However, a major significance of the study can be found in the fact that it analyzed the correlation between obesity and aggressiveness of PTC, including recurrence, using a high number of cases and confirmed that BMI is closely associated with aggressive oncologic features, such as multifocality and extrathyroid invasion.

Conclusion

Retrospective analysis of the association between BMI and cancer aggressiveness in patients with PTC showed that the obese group showed higher rate of multifocality and extrathyroid invasion than the normal group. Although various causes may play a role in the onset of

PTC, maintaining BMI at an appropriate level may be a method for preventing the onset of PTC with more aggressive tendencies, such as multifocality and extrathyroid invasion.

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