

Association of Body Mass Index and Pathologic Features of Adult Filipino Patients Diagnosed with Papillary Thyroid Cancer after Thyroid Surgery Admitted in a Tertiary Hospital in Cebu City

Gerard Ian B. Tan, MD¹, Jovy Louie Anthony R. Vergara, MD¹, Ceryl Cindy Y. Tan, MD¹

Objective. This study aims to determine the association between body mass index and the pathologic features of papillary thyroid cancer among adult Filipinos who underwent thyroid surgery.

Methodology. This is a retrospective cohort study including all patients admitted from January 2014 to December 2020 in a tertiary hospital in Cebu City. Adult Filipino patients who underwent thyroid surgery with a final histopathologic diagnosis of papillary thyroid carcinoma were included in the study and were categorized based on their BMI using the Asian classification. Primary outcome is to identify the association of any BMI category with the clinical features of papillary thyroid cancer using multivariate ordinal logistic regression and Pearson product-moment correlation.

Results. There are 234 patients included in the study. Majority of the participants are middle-aged (mean 42.71), and most are female (82%). The mean anthropometric measurement values include weight of 61 kg, height of 155.47 cm, and BMI of 25.26 kg/m². Majority of the patients are obese. Among the participants more than half showed positive for nodal metastasis, with 1.2% having extrathyroidal invasion. Average tumor size is 2.5 cm and about a third having multifocal features. Among the pathologic features, only the primary tumor size is significantly associated with BMI, the obese or overweight being more likely to have larger tumor size.

Conclusion. Increased BMI may be associated with increased primary nodule size in patients with papillary thyroid carcinoma. It did not show a significant correlation with other pathological features such as lymph node metastasis, extrathyroidal extension and multifocality.

Keywords. Body Mass Index, papillary thyroid cancer, obesity

Introduction

Papillary thyroid carcinoma (PTC) is the most common differentiated thyroid carcinoma and carries the best overall prognosis. Based on the Surveillance, Epidemiology, and End Results (SEER) database from 1975 to 2012, the incidence of PTC increased from 4.8 to 14.9 per 100,000. One of its common features is the ability to invade the lymphatics, and about 10% is seen in patients with metastatic disease.¹

Obesity is a complex, multifactorial and widely preventable disease, which is defined as excess body weight for height, but this simple definition belies an etiologically complex phenotype primarily associated

with excess adiposity, or body fatness, that can manifest metabolically and not just in terms of body size.² In the Philippines, 28.8% are overweight and 9.6% are obese among adults, 20-59 years old, based on BMI. Among elderly, 60 years old and above, the prevalence of overweight was 24.7% and obese is 6.3% at the national level.³

Being obese and overweight greatly increases risk of chronic disease morbidity—namely disability, depression, type 2 diabetes, cardiovascular disease, certain cancers and mortality.³ Cancers such as endometrial cancer, esophageal cancer, gastric cardia cancer, liver cancer, kidney cancer and others with varying degrees of risk involved. The list also includes thyroid cancer which has a slight increase in risk of about 10% for patients with higher body mass index.⁴

¹Section of Endocrinology, Department of Internal Medicine, Chong Hua Hospital, Cebu City, Philippines

Corresponding author: Gerard Ian B. Tan, MD
Email: gerardiano5@gmail.com

Studies have shown that Filipinos, among the other sub-Asian population, have been reported to have higher thyroid cancer rates.⁵ In addition, they also have a more aggressive and recurrent nature.⁶ In a study by Lo, et al, papillary thyroid carcinoma is the most common type identified in Filipinos and is associated with nodal metastasis in 29% of the patients.⁷

Given the prevalence of both conditions noted on the Filipino population, and the reported risks of obesity to the development of thyroid cancer, this study aims to identify any association between the two disorders.

General Objective

This study aims to determine the association between body mass index and the pathologic features of papillary thyroid cancer among adult Filipinos who underwent thyroid surgery.

Specific Objectives

1. To determine the profile of patients admitted with final histopathologic findings of papillary thyroid carcinoma based on the following characteristics:
 - a. Age
 - b. Gender
 - c. Body mass index (BMI)
 - i. Underweight (<18.5kg/m²)
 - ii. Normal (18.5-22.9kg/m²)
 - iii. Overweight (23-24.9kg/m²)
 - iv. Obese (> 25kg/m²)
 - d. Lymph Node Involvement
 - e. Extrathyroidal Invasion
 - f. Primary Tumor Size
 - g. Multifocality
2. To investigate the association between body mass index and the pathologic features of papillary thyroid cancer among adult Filipinos, specifically:
 - a. Lymph node metastasis
 - b. Extrathyroidal Invasion
 - c. Primary tumor size
 - d. Multifocality

Scope and Limitation of the Study

This study was conducted in a single institution. Data was gathered via review of charts of patients admitted who underwent thyroid surgery with a final histopathological diagnosis of papillary thyroid carcinoma.

Operational Definition

1. **Papillary Thyroid Carcinoma**- a diagnosis based on the pathological report obtained after thyroid surgery.

2. **Asian Body Mass Index (BMI)**- calculated as weight in kilograms divided by height in meters squared (kg/m²) with cut off values adjusted for the Asian population.
 - a. **Overweight** - adult Asians with a calculated BMI of 23-24.9kg/m².
 - b. **Obese** - Adult Asian with calculated BMI of ≥ 25 kg/m².
3. **Pathological feature**- findings in the gross and histologic examination of tissue by means of biopsy.
4. **Lymph Node Involvement**- presence of the papillary thyroid cancer in the adjacent lymph nodes of the thyroid as evidenced by pathological diagnosis.
5. **Extrathyroidal Invasion**- extension of the primary tumor over the adjacent structures of the thyroid or a distal metastatic site as evidenced on preoperative imaging, intraoperative findings, or presence of distal metastasis as seen on pathological diagnosis or post radioactive iodine scan.
6. **Primary Tumor Size**- the size the malignant lesion in the thyroid gland
7. **Multifocality**- presence of two or more individual tumor locations within the thyroid gland.
8. **Thyroid Surgery**- surgical removal of the thyroid by lobectomy, subtotal, or total thyroidectomy

Methodology

Study Design

This study used a retrospective cohort study design.

Study Setting

This study was conducted in Chong Hua Hospital, a tertiary hospital in Cebu City, Philippines.

Inclusion Criteria

The study included all adult Filipino patients who underwent thyroid surgery with a final histopathologic diagnosis of papillary thyroid carcinoma starting January 2014 to December 2020.

Exclusion Criteria

The following were not included in the study:

- a. Patients who were admitted for thyroid surgery with a final histopathologic diagnosis other than papillary thyroid carcinoma.
- b. Patients who were admitted for thyroid surgery with a final histopathologic diagnosis of papillary thyroid carcinoma but before or after the specified period.
- c. Patients who have lost records

Sample Size

To perform the univariate ordinal logistic regression analysis and by assuming 0.10 as the least frequent

outcome for each independent variable, the study needs a sample size of at least 100 patients who satisfy the inclusion criteria.

Data Collection

The study was approved by the Institutional Review Board of Chong Hua Hospital. After acquiring the approval from the board, the researcher conducted a thorough review of the patients' charts and records in the medical records section. The final histopathological reports were obtained from the records from the pathology department. The necessary data were collected and tabulated. Patients were coded numerically to maintain confidentiality. Statistical analysis was then applied to the data gathered.

Data Analysis

Data were documented via Microsoft Excel. The quantitative data were presented through mean and standard deviation, while qualitative data were presented in frequency count and proportion/percentage. Correlation analyses between levels of body mass index and pathologic features of papillary thyroid cancer were performed using multivariate ordinal logistic regression and Pearson product-moment correlation. Statistical analyses were done using Minitab version 17. The statistics with p-values less than 0.05 (the level of significance) were considered significant.

Ethical Consideration

The protocol was submitted and approved by the Institutional Ethics Review Board. The data gathered were kept confidential and was used exclusively for this research. Patients were coded numerically to ensure patient confidentiality.

Table 1. The Baseline Characteristics of Included Patients with Papillary Thyroid Carcinoma n=234

Characteristics	Values
¹ Age (years)	42.71 (13.13)
² Gender	
Male	42 (17.95)
Female	192 (82.05)
¹ Weight (kg)	61.10 (12.55)
¹ Height (cm)	155.47 (8.12)
¹ BMI (kg/m ²)	25.26 (4.77)
² Underweight (<18.5kg/m ²)	12 (5.13)
² Normal (18.5-22.9kg/m ²)	70 (29.91)
² Overweight (23-24.9kg/m ²)	46 (19.66)

² Obese (>= 25kg/m ²)	106 (45.30)
² Lymph node metastasis	
Positive	125 (53.42)
Negative	109 (46.58)
² Extrathyroidal Invasion	
None	231 (98.72)
Paratracheal Mass with Extension to Adjacent Skeletal Muscle	1 (0.43)
Esophagus	1 (0.43)
Anterior cervical mass	1 (0.43)
¹ Primary tumor size (cm)	2.05 (1.40)
² Multifocality	
Present	81 (34.62)
Absent	153 (65.38)

Note: Values presented in ¹Mean (Standard Deviation) and in ²Frequency (Percentage)

Table 2 shows the correlation analysis using multivariate ordinal logistic regression between the body mass index and the pathologic features of papillary thyroid cancer among adult Filipinos. The results show that primary tumor size (p= 0.049) is significantly associated with body mass index. The coefficient and odd ratio suggest that the patients are likely to be obese or overweight as the tumor size increases. The other pathologic features such as lymph node metastasis (p= 0.314), extrathyroidal invasion (p= 0.999) and multifocality (p=0.595) were not significantly associated with the Body mass index.

Table 2. The Correlation Analysis between Body Mass Index and the Pathologic Features of Papillary Thyroid Cancer among Adult Filipinos, n = 234

Response Information			
Variable		Value	Count
Body Mass Index		Underweight	12
		Normal	70
		Overweight	46
		Obese	106

Logistic Regression Table			
Predictor	Coefficient	Odds Ratio	Z-Statistic (P-Value)
Lymph node metastasis (Reference Level: Negative)			
Positive	-0.2533	0.78	-1.01 (0.314)
Extrathyroidal Invasion (Reference Level: None)			
Paratracheal Mass with Extension to Adjacent Skeletal Muscle	-21.0000	0.00	-0.00 (0.999)
Esophagus	-21.0000	0.00	-0.00 (0.999)
Anterior cervical mass	-21.0000	0.00	-0.00 (0.999)
Primary tumor size	-0.1799	0.84	-1.97 (0.049) *
Multifocality (Reference Level: Absent)			
Present	0.1399	1.15	0.53 (0.595)

Note: Significant at 0.05 using Multivariate Ordinal Logistic Regression

The correlation analysis of body mass index and primary tumor size as shown in Table 3 is confirmed using the Pearson product-moment correlation. The coefficient tells that the association is positive ($p=0.032$), that is, as the body mass index increases, the tumor size also increases.

Table 3.: The Correlation f Body Mass Index and Primary Tumor Size, $n=234$

	Correlation Coefficient	P-Value
BMI and Primary Tumor Size	0.140	0.032 *

Note: * Significant at 0.05 using Pearson Product-Moment Correlation

Discussion

Thyroid cancer incidence worldwide reached a total of 255,490 cases. In which approximately 23,880 cases are from Southeast Asia, with an annual standardized incidence rate of 3.55/100,000.⁸ Among, the thyroid cancers, the Papillary Thyroid cancer is the most common and is responsible for the increasing incidence and accounts for 90% of the diagnosed thyroid cancers.⁹ However, the mortality rate (0.059/100,000 population per year) did not increase which can be partly explained with the advancement in diagnostic modality in the past years.^{9,10}

In recent studies, an increase in BMI has been shown to increase the risk of developing papillary thyroid cancer.^{10,11, 12} In addition, a higher BMI is associated with

aggressive pathological features of papillary thyroid carcinoma, such as extrathyroidal extension (OR= 1.32-1.61), multifocality (OR= 1.45-1.58), lymph node metastasis (OR= 1.06- 1.57) and tumor size (OR= 1.31) compared to their normal weight counterparts^{13,14}

Multiple mechanisms are proposed as to the development of cancer among obese individuals. Adipokines, such as leptin and adiponectin, secretion is altered especially in the setting of obesity where there is increased leptin and decreased adiponectin. Binding of adiponectin to its receptors results to negative regulation of proliferation with and inhibits cell division activation by way of PI3K/Akt/mTOR, JAK/STAT, and ERK1/2 stimulation. Compared to leptin which stimulates the activation pathways leading to alterations in intracellular growth and proliferation.¹⁵ Leptin receptors are also expressed in papillary thyroid cancer which can affect tumor aggressiveness and result to greater incidence of lymph node metastasis and tumor size.¹⁶ Obesity can also cause hyperinsulinemia by way of insulin resistance causing excess insulin binding in the IGF-1 receptor in the thyroid increasing proliferation of thyroid cancer cells.¹⁷ TSH production is also increased with increased insulin which also promoted thyroid cell proliferation.¹⁸

Majority of patients with papillary thyroid carcinoma are females are with age range in the mid 40's which is similar to our study population.¹⁹ The BMI cut off used by this study is based on the WHO Asian category which is different from the other studies where they used higher cut off values.^{11, 14, 20} The pathological features evaluated in the study included four variables, the lymph node metastasis, extrathyroidal invasion, multifocality and primary tumor size, which is similar characteristics being examined by the other authors,^{11,13,14,20,21}

Results from our study only showed a positive correlation between an increasing BMI and increase tumor size, similar findings to the study of Kim¹⁴, Zhao²⁰ and Harari¹¹. Contrary to other studies which showed association of BMI with multifocal tumors¹⁵, lymph nodes metastasis and extrathyroidal invasion,^{13,14} our study was not able to show a significant correlation between these pathological factors. Discrepancy in results could be due to use of different BMI cut off.

Conclusion

Increased BMI may be associated with increased primary nodule size in patients with papillary thyroid carcinoma. It did not show a significant correlation with other pathological features such as lymph node metastasis, extrathyroidal extension and multifocality.

Limitations and Recommendations

Limitation in the study include the retrospective nature of the study where data is only limited to the available data on chart review. This study did not include other risk factors including Lifestyle: such duration of obesity, smoking, alcohol consumption or degree of physical activity, and family history of cancer.

The author recommends for further studies to include lifestyle factors such as smoking, alcohol intake and exposure to radiation; include clinical laboratory results such as Thyroid stimulating hormone, fasting blood glucose and cholesterol levels and to include other anthropometric measurements such as waist circumference, waist-hip ratio, skin fold thickness.

Conflicts of Interest

All authors have no conflict of interest

References

1. Limaïem F, Rehman A, Mazzoni T. Papillary Thyroid Carcinoma. [Updated 2020 Oct 16]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan.
2. Hruby A, Hu FB. The Epidemiology of Obesity: A Big Picture. *Pharmacoeconomics*. 2015;33(7):673-689.
3. Department of Science and Technology, Food and Nutrition Research Institute: Overweight and obesity is top nutrition concern in 8 Metro Manila cities-FNRI Survey, (Set 20, 2019). <https://www.fnri.dost.gov.ph/index.php/programs-and-projects/news-and-announcement/769-overweight-and-obesity-is-top-nutrition-concern-in-8-metro-manila-cities-fnri-survey>
4. National Cancer Institute: Obesity and Cancer (January 17, 2017). <https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet#r6>
5. Kim BH. Differentiated Thyroid Cancer in Asians. *Endocrinol Metab (Seoul)*. 2016;31(1):62-63.
6. Kus LH, Shah M, Eski S, Walfish PG, Freeman JL. Thyroid cancer outcomes in Filipino patients. *Arch Otolaryngol Head Neck Surg*. 2010 Feb;136(2):138-42.
7. Lo TE, Canto AU, Maningat PD. Risk Factors for Recurrence in Filipinos with Well-Differentiated Thyroid Cancer. *Endocrinol Metab (Seoul)*. 2015;30(4):543-550.
8. Deng Y, Li H, Wang M, et al. Global Burden of Thyroid Cancer From 1990 to 2017. *JAMA Netw Open*. 2020;3(6):e208759.
9. Rossi, E. D., Pantanowitz, L., & Hornick, J. L. (2021). A worldwide journey of thyroid cancer incidence centred on tumour histology. *The Lancet Diabetes & Endocrinology*, 9(4), 193-194.
10. Zhao ZG, Guo XG, Ba CX, Wang W, Yang YY, Wang J, Cao HY. Overweight, obesity and thyroid cancer risk: a meta-analysis of cohort studies. *J Int Med Res*. 2012;40(6):2041-50.
11. Harari A, Endo B, Nishimoto S, Ituarte PHG, Yeh MW. Risk of Advanced Papillary Thyroid Cancer in Obese Patients. *Arch Surg*. 2012;147(9):805-811.
12. Shin A, Cho S, Jang D, Abe SK, Saito E, Rahman MS, Islam MR, Sawada N, Shu XO, Koh WP, Sadakane A, Tsuji I, Sugawara Y, Ito H, Nagata C, Park SK, Yuan JM, Kim J, Tsugane S, Cai H, Wen W, Ozasa K, Matsuyama S, Kanemura S, Oze I, Wada K, Wang R, Yoo KY, Potter JD, Ahsan H, Boffetta P, Chia KS, Matsuo K, Qiao YL, Rothman N, Zheng W, Inoue M, Kang D. Body Mass Index and Thyroid Cancer Risk: A Pooled Analysis of Half a Million Men and Women in the Asia Cohort Consortium. *Thyroid*. 2022 Jan 11
13. Yu, S., Chen, W., Cai, Q., Liang, F., Xu, D., Han, P., ... Huang, X. (2017). Pretreatment BMI Is Associated with Aggressive Clinicopathological Features of Papillary Thyroid Carcinoma: A Multicenter Study. *International Journal of Endocrinology*, 2017, 1-7.
14. Kim HJ, Kim NK, Choi JH, Sohn SY, Kim SW, Jin SM, Jang HW, Suh S, Min YK, Chung JH, Kim SW. Associations between body mass index and clinicopathological characteristics of papillary thyroid cancer. *Clin Endocrinol (Oxf)*. 2013 Jan;78(1):134-40.
15. Lohmann, A. E., Goodwin, P. J., Chlebowski, R. T., Pan, K., Stambolic, V., & Dowling, R. J. O. (2016). Association of Obesity-Related Metabolic Disruptions With Cancer Risk and Outcome. *Journal of Clinical Oncology*, 34(35), 4249-4255.
16. Cheng SP, Chi CW, Tzen CY, Yang TL, Lee JJ, Liu TP, Liu CL. Clinicopathologic significance of leptin and leptin receptor expressions in papillary thyroid carcinoma. *Surgery*. 2010 Jun;147(6):847-53
17. Harikrishna, A., Ishak, A., Ellinides, A., Saad, R., Christodoulou, H., Spartalis, E., & Paschou, S. A. (2019). The impact of obesity and insulin resistance on thyroid cancer: a systematic review. *Maturitas*.
18. Marcello, M. A., Cunha, L. L., Batista, F. A., and Ward, L. S. (2014). Obesity and thyroid cancer. *Endocrine-Related Cancer* 21, 5, T255-T271
19. Economides Aliki, Giannakou Konstantinos, Mamais Ioannis, Economides Panayiotis A., Papageorgis Panagiotis. Association Between Aggressive Clinicopathologic Features of Papillary Thyroid Carcinoma and Body Mass Index: A Systematic Review and Meta-Analysis. *Frontiers in Endocrinology VOLUME 12 YEAR 2021*
20. Zhao, Sitong MDa; Jia, Xiaomeng PhDa; Fan, Xiaojing MDa; Zhao, Ling PhDa; Pang, Ping MDb; Wang, Yajing MDa; Luo, Yukun PhDc; Wang, Fulin PhDd; Yang, Guoqing PhDa; Wang, Xianling PhDa; Gu, Weijun PhDa; Zang, Li PhDa; Pei, Yu PhDa; Du, Jin PhDa; Ba, Jianming PhDa; Dou, Jingtao PhDa; Mu, Yiming PhDa; Lyu, Zhaohui MD, PhDa,* Association of obesity with the clinicopathological features of thyroid cancer in a large, operative population, *Medicine*: December 2019 - Volume 98 - Issue 50 - p e18213
21. Zaman SU, Awan MS, Sulaiman MA. Obesity and High Risk Pathological Features of Papillary Thyroid Carcinoma: A Retrospective Analysis of a University Hospital in Pakistan. *Gulf J Oncolog*. 2018 May;1(27):6-10.