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Original Scientific Paper

RELATIONSHIP BETWEEN BODY MASS INDEX AND PATOHISTOLOGICAL FEATURES OF THYROID CANCER

Željko Zubčić[1,2], Hrvoje Mihalj[1,2], Anamarija Šestak[1,2], Andrijana Včeva[1,2], Ivan Abičić[1,2] and Tihana Mendeš[1,2]

[1]Department of Otorhinolaryngology and Maxillofacial Surgery, Medical Faculty Osijek, University J.J. Strossmayer Osijek, Osijek, Croatia
[2]Department of Otorhinolaryngology and Head and Neck Surgery, Clinical Hospital Centre Osijek, Osijek, Croatia

SUMMARY – Available studies report conflicting results on the association of body mass index (BMI) and pathohistological features of thyroid cancer. This study aimed to investigate the relationship between BMI and the pathohistological features of different thyroid cancer types. We analyzed the following data from 95 patients with thyroid cancer: age, gender, BMI, pathohistological characteristics of cancer (tumor size, multifocality, lymphovascular invasion, extrathyroidal invasion) and the presence of regional metastases. The BMI of all patients with thyroid cancer was 27.1 ± 4.2. Significantly more patients with obesity class I had cancer size less than 2 cm ($p = 0.02$). There is a significant association between BMI and extrathyroid invasion ($p = 0.03$; OR, 1.18), but not with lymphovascular invasion, tumor size, and multifocality. We can conclude that although obesity is a risk factor for the development of thyroid cancer, higher BMI is only partially associated with more aggressive pathohistological features of thyroid cancer.

Key words: *thyroid cancer; Body Mass Index; lymphovascular invasion; multifocality; extrathyroidal invasion*

Introduction

Thyroid cancer is the most common endocrine cancer, with a global incidence of 6.1 per 100,000 women and 1.9 per 100,000 men[1]. World trends indicate a significant increase in the number of new thyroid cancer cases, and a large part of the increase in the number of new cases is attributed to better diagnosis. In Croatia, there has been a significant increase in the number of new thyroid cancer cases in men and women in the past 15 years, while the mortality rate has remained stable[2]. According to the Croatian Institute of Public Health, the most significant increase in new thyroid cancer cases are women aged 55-64 years and men aged 60-69 years[2,3]. Risk factors for the development of thyroid cancer include exposure to ionizing radiation in childhood, diabetes, and obesity[4-6]. Obesity is one of the most significant and growing problems in the 21st century[7]. According to the World Health Organization, the prevalence of obesity in European countries has tripled since the 1980s[8]. According to the European Health Survey (EHIS) latest results, every second adult in Croatia is overweight or obese[2]. Data from the World Health Organization indicate that 1.9 billion people over 18 are obese[8].

Correspondence to:
Anamarija Šestak, M.D., Ph.D., Department of Otorhinolaryngology and Head and Neck Surgery, Clinical Hospital Centre Osijek, J. Huttlera 4, 31 000 Osijek, Croatia,
Phone: +385 31 512 403; fax.: +385 31 512 203
E-mail: annamarijasestak@gmail.com

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Some epidemiological studies link an increase in the incidence of obesity with a growing incidence of cancer worldwide, as obesity is considered a risk factor for esophageal, colon, kidney, endometrial cancer, and malignant melanoma[9]. Additionally, obesity is associated with more aggressive pathohistological characteristics of these cancers and a poorer prognosis[10]. According to data from the literature, obesity is an independent risk factor for thyroid cancer in men and women, and thus a higher body mass index (BMI) is associated with a higher risk of thyroid cancer[11]. The results of previous studies show an association of BMI, height, and weight with the incidence of thyroid cancer, but looking at cancer there are conflicting results of the studies in the literature regarding the association of BMI and pathohistological features of thyroid cancer[12-22]. Therefore, the question arises as to whether higher BMI is associated with more aggressive pathohistological findings of thyroid cancer, in terms of more frequent lymphovascular or extrathyroidal invasion.

This study aimed to investigate the relationship between BMI and the pathohistological features of different thyroid cancer types.

Patients and methods

In this retrospective study, we analyzed the data from 320 patients who underwent thyroid surgery for suspicion of cancer at our institution from January 2018 to January 2020. We collected and analyzed the data from medical records on age, gender, BMI, pathohistological characteristics of cancer (tumor size, multifocality, lymphovascular invasion, extrathyroidal invasion) and the presence of regional metastases. The exclusion criterion was if the diagnosis of thyroid cancer was not confirmed pathohistologically. Thyroid cancer was ultimately pathohistologically confirmed in only 95 patients. Central neck dissection was performed in 29 out of 95 patients with thyroid cancer, and regional metastases in the lymph nodes were pathohistologically confirmed in 13 patients. This research was approved by the ethics committee of our institution. As this is a retrospective study, informed patient consent was not obatained.

Body Mass Index

Body mass index value was calculated using the value of weight and height, taken during anesthesiological examinations as part of the preoperative assessment. The value of the BMI was divided into groups according to the World Health Organization classification, which divides the BMI value into underweight (<18.5), normal (18.5-24.9), pre-obesity (25-29.9), obesity class I (30-34.9), II (35-39.9), and III (> 40) (11)[21].

Tumor size

The cancer size was divided into two groups according to the classification of the American Cancer Society: < 2cm and ≥ 2cm[22].

Age groups

The current staging system (8th Edition American Joint Committee on Cancer TNM classification system) uses a cut-off value of age 55 for risk stratification in tumor staging[18].

Statistical analysis

All the data were analyzed using SPSS (IBM Corp. Released in 2013. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The normality of the distribution of numerical variables was tested by the Kolmogorov-Smirnov test. Differences in categorical variables were tested using Fisher's exact test. Differences in numerical variables between the two independent groups were tested using the t-test. Logistic regression (univariate and multivariate) models were used to evaluate the effects of BMI, age, gender, size of cancer, and multifocality on lymphovascular and extrathyroidal invasion. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated for each variable from the logistic regression model results. All p values were two-sided. The significance level was set at $\alpha < 0.05$.

Results

A total of 320 patients underwent surgery for suspicion of thyroid cancer. The pathohistological analysis confirmed thyroid cancer in 95 patients.

The characteristics of patients with thyroid cancer are shown in Table 1.

Comparing the variables of age (< 55 and ≥ 55 years), gender, cancer size, multifocality, lymphovascular invasion, and extrathyroidal invasion within BMI groups (underweight, normal, pre-obesity, obesity class I, and obesity class II), the only significant difference was found in the group of patients with obesity class I, where significantly more patients who had obesity

Table 1. Characteristics of patients with thyroid cancer

Characteristics	**Total, N=95 (100%)**
Gender	
male	18 (19%)
female	77 (81%)
Mean Age total	53.1 (SD±14.4)
mean age male	54.1 (SD±16.2)
mean age female	53 (SD±13.9)
Age group	
<55 years	56 (59%)
≥55 years	39 (41%)
Type of cancer	
papillary cancer	72 (75.8%)
micropapillary cancer	7 (7.4%)
papillary cancer with neck metastasis	5 (5.3%)
follicular cancer	5 (5.3%)
hurthle cell cancer	6 (6.2%)
Tumor size	
< 2 cm	71 (74.7%)
≥ 2 cm	24 (25.3%)
Multifocality	21 (22.1%)
Lymphovascular invasion	20 (21%)
Extrathyroidal invasion	14 (14.7%)
Regional metastases (level VI)	13 (13.6%)
Mean BMI total	27.1 (SD±4,2)
BMI groups	
underweight	2 (2.1%)
normal	32 (32.6%)
pre-obesity	38 (40)
obesity class I	20 (21.1)
obesity class II	4 (4.2%)
obesity class III	0 (0%)

BMI= Body Mass Index

class I had a cancer size of less than 2 cm (Fisher exact test, p = 0.02).

In the univariate analysis, female gender and BMI had a significant impact on extrathyroid invasion, and female gender and tumor size had a significant impact on lymphovascular invasion. In multivariate analysis, BMI (all five groups) had a significant effect on extrathyroid invasion, and tumor size had a significant effect on lymphovascular invasion (Table 2).

There was no association between BMI and tumor size, BMI and tumor multifocality, and BMI and the presence of regional metastases in the central neck compartment (p = 0.23; OR, 0.93; p = 0.87; OR, 1.01; p = 0.16; OR, 0.86).

Table 2. The relationship between the characteristics of patients with thyroid cancer and the pathohistological features of the cancer

	Logistic regression model			
	univariate		multivariate	
	OR (95% CI)	P-value*	OR (95% CI)	P-value*
Extrathyroidal invasion				
Age	1.03 (0.98-1.07)	0.152	1.11 (0.25-4.89)	0.9
Male gender	0.83 (0.2-3.36)	0.798	1.64 (0.37-7.3)	0.51
Female gender	6 (0.2-3.36)	**<0.001**	1.59 (0.36-7.01)	0.53
BMI groups	1.18 (1.01-1.38)	**0.03**	0.84 (0.72-0.98)	**0.02**
Tumor size	0.78 (0.19-3.07)	0.721	1.45 (0.35-6.01)	0.6
Multifocality	0.66 (0.18-2.38)	0.53	1.48 (0.38-5.63)	0.56
Lymphovascular invasion				
Age	1.01 (0.97-1.04)	0.51	0.98 (0.95-1.02)	0.57
Male gender	0.44 (0.14-1.38)	0.16	2.46 (0.73-8.31)	0.14
Female gender	4.5 (0.14-1.38)	**<0.001**	2.36 (0.74-7.48)	0.15
BMI groups	1.07 (0.95-1.21)	0.26	0.94 (0.83-1.07)	0.39
Tumor size	3.27 (1.15-9.32)	**0.02**	0.31 (0.11-0.92)	**0.03**
Multifocality	1.78 (0.47-6.81)	0.39	0.7 (0.17-2.85)	0.62

* Chi squared test; OR: odds ratio; CI: confidence interval; BMI: Body Mass Index

Discussion

This study aimed to determine the relationship between BMI and the pathohistological features of thyroid cancer. Additionally, the relationship between gender, age, and pathohistological features of thyroid cancer was examined. The aforementioned data were analyzed in 320 patients who underwent thyroid surgery due to suspicion of malignancy, but thyroid cancer was pathohistologically confirmed in only 95 patients. The reason that cancer was not ultimately confirmed in such a large number of patients could be the fact that in these patients the findings of fine needle aspiration cytology (FNAC) belonged to categories III and IV according to the Bethesda System. Surgery is usually indicated if the finding of FNAC is category III and above, but the risk of malignancy for category III is only 5-15%, and 15-30% for category IV[23].

The largest number of patients with thyroid cancer were women, which is in line with previous studies[11,24,25]. Since alpha and beta estrogen receptors are expressed in papillary thyroid cancer, the higher incidence of thyroid cancer in women is thought to be due to polymorphisms of these estrogen receptors[26,27]. The mean age of all patients with thyroid cancer was 53.1 ± 14.4 years, which is in line with the Croatian Institute of Public Health's epidemiological data on the age of patients with thyroid cancer[2]. The most common pathohistological diagnosis was papillary carcinoma. Papillary carcinoma accounts for 80% of thyroid cancer cases, and its incidence has almost doubled in the last 30 years, which can be attributed to earlier diagnosis of subclinical disease[28]. The mean value of BMI of patients with thyroid cancer was 27.1 ± 4.2, which belongs to the pre-obesity group. Similar to our data, the mean value of BMI of the patients in the study by Paes et al. also belonged to the pre-obesity group with a value of 27.8[12]. This can be explained by the growing number of people worldwide who are overweight and obese.

According to literature data, obesity is a risk factor for thyroid cancer in men and women[11]. Furthermore, in several observational studies, a higher BMI value was associated with an increased risk of thyroid cancer[29-32]. A study by Shin et al. from 2022 analyzed data on an Asian population of a total of 538,857 subjects with a mean follow-up period of 15.1 years. The authors concluded that BMI between 25 and 29.9 kg/m^2 was associated with an increased risk of thyroid cancer[32]. In contrast, some literature data do not associate increased BMI and obesity with a higher risk of thyroid cancer[33-35]. A prospective study by Ahmadi et al. from 2022, conducted on 1259 patients, showed that there was no correlation between BMI and the risk of thyroid cancer, with the average BMI being 28.6 kg/m^2 [35]. Given the conflicting results of the available studies on the association between BMI and the more aggressive form of thyroid cancer, we can conclude that this association is still unclear[12-22]. We obtained mixed results in our study. According to our results, there was an association between higher BMI and extrathyroid invasion, but not with lymphovascular invasion, tumor size, multifocality and presence of regional metastases in central neck copmartment. Therefore, our results partially concur with the results of other studies linking higher BMI with the more aggressive form of thyroid cancer[17-20,22]. Notably, the results from a recent study by Kim from 2022, which, in contrast to our results, showed a significant association between overweight or obesity and multifocality of papillary carcinoma, while there was no significant association with age, gender, tumor size and extrathyroidal invasion[36]. A possible explanation of the difference in the results may be that in the study by Kim, only patients with papillary carcinoma were included and data were analyzed on a much larger number of patients. According to the literature, men usually have a more aggressive form of the disease at diagnosis[24]. According to our results, female gender was significantly associated with extrathyroid and lymphovascular invasion. In this study, the higher likelihood of more aggressive tumor characteristics in women can be explained by the generally higher incidence of thyroid cancer in women and the influence of hormones. According to in vitro studies, estrogen is associated with increased adherence, invasion, and migration in thyroid cancer cell lines[37-39].

This study's primary limitation was the number of patients. Approximately 350 thyroid surgeries are performed annually due to various indications in our institution, while in this study, 320 patients with suspected malignancy were surgically treated during the study period. Although FNAC is the gold standard in diagnostic processing with an accuracy of 89.46%[40], and the indications for surgery were determined according to the Bethesda system, it does not carry significant risks of malignancy in certain categories. According to the data itself, only 95 patients were ultimately diagnosed with thyroid cancer, and this further demonstrated the shortcomings of the diagnostic procedures. Another limitation is the lack of data on the value of BMI before diagnosis, which could not be collected in this retrospective study. Additionally, BMI is not the best indicator of obesity, such as body fat percentage or waist to hip ratio, but these data were not available to us.

According to the results of this study, we can conclude that higher BMI is only significantly associated with extrathyroid invasion but not with other aggressive pathohistological features of thyroid cancer.

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Sažetak

POVEZANOST INDEKSA TJELESNE MASE I PATOHISTOLOŠKIH ZNAČAJKI KARCINOMA ŠTITNJAČE

Ž. Zubčić, H. Mihalj, A. Šestak, A. Včeva, I. Abičić i *T. Mendeš*

Dostupne studije pokazuju oprečne rezultate povezanosti indeksa tjelesne mase (ITM) s patohistološkim značajkama raka štitnjače. Cilj ove studije bio je istražiti odnos između ITM-a i patohistoloških značajki različitih tipova karcinoma štitnjače. Analizirali smo sljedeće podatke od 95 bolesnika s karcinomom štitnjače: dob, spol, ITM, patohistološke karakteristike karcinoma (veličina tumora, multifokalnost, limfovaskularna invazija, ekstratireoidna invazija) i prisutnost regionalnih metastaza. ITM svih bolesnika s karcinomom štitnjače bio je 27,1 ± 4,2. Značajno više pacijenata s klasom pretilosti I imalo je veličinu raka manju od 2 cm (p=0,02). Postoji značajna povezanost ITM-a i ekstratireoidne invazije (p=0.03; OR, 1,18), ali ne i s limfovaskularnom invazijom, veličinom tumora i multifokalnosti. Možemo zaključiti da iako je pretilost čimbenik rizika za razvoj raka štitnjače, viši ITM je samo djelomično povezan s agresivnijim patohistološkim značajkama raka štitnjače.

Ključne riječi: *karcinom štitnjače; indeks tjelesne mase; limfovaskularna invazija; multifokalnost; ekstratiroidna invazija*