

## Does Increased Body Mass Index Lead to Elevated Thyroid Cancer Risk?

Fevzi Balkan, Celil Alper Usluogullari\*, Rifki Ucler, Husniye Baser, Reyhan Ersoy and Bekir Cakir

Atatürk Training and Research Hospital, Clinic of Endocrinology and Metabolism, Ankara, Turkey

\*Corresponding author: Celil Alper Usluogullari, Atatürk Training and Research Hospital, Clinic of Endocrinology and Metabolism, Ankara, Turkey, Tel: 05336585735; Fax: 03422876726; E-mail: calperuslu@yahoo.com

Received date: May 23, 2014, Accepted date: Jun 23, 2014, Published date: Jun 26, 2014

Copyright: © 2014 Usluogullari CA, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

**Purpose:** Obesity is associated with various diseases including thyroid cancer. The relationship between thyroid nodules and obesity is unclear. In this study, patients with a higher-than-population risk of thyroid cancer whose thyroid fine needle aspiration biopsies were suspicious or indeterminate were divided into groups according to their body mass index and their rate of malignancy was examined.

**Method:** In this study, 214 patients who were operated for indeterminate cytology in 2009-2010 at our clinic were reviewed retrospectively. The patients were divided into 4 groups. Group 1 included 47 patients (BMI 18-24, 9 kg/m<sup>2</sup>); Group 2 included 67 patients (BMI 25-29, 9); Group 3 included 85 patients (BMI 30-39, 9); and Group 4 had 15 patients (BMI>40). Patients were classified as benign and malign based on the postoperative histopathological results. Malignancy rates were recorded for each group and the groups were compared.

**Results:** Based on the histopathological results of the 214 patients included in the study, 70 patients were reported to have thyroid cancer (32.7%). When the patients were divided into groups as benign and malign according to the pathology results, age, BMI, height, FT3, TSH, body fat ratios and WC/HC ratios were found to be similar between groups ( $p>0.05$ ). FT4 was found to be significantly elevated in the malign group ( $p<0.05$ ).

**Conclusion:** In this study, malignancy rates increased as the patients' body mass index increased but the difference was not statistically significant ( $p>0.05$ ). Obesity and increased body mass index may be a risk factor for thyroid cancer.

**Keywords:** Obesity; Body mass index; Thyroid cancer

### Introduction

Obesity is associated with increased risk of diabetes, hypertension, cardiovascular disease, metabolic syndrome and cancer. Obesity increases the risk of stomach, esophageal adenocarcinoma, cholangiocarcinoma, pancreas, breast, endometrial, renal, prostate and lung cancer, non-Hodgkin's lymphoma and multiple myeloma. In women, postmenopausal elevated levels of endogenous estrogen lead to increased risk of breast and endometrial cancer. The incidence of Papillary Thyroid Cancer (PTC) is markedly higher in women than men during the reproductive years. *In vitro* studies have suggested that estrogen may play an important role in the development and progression of PTC through Estrogen Receptors (ERs). There is also much evidence that estrogen has direct actions in thyroid cell lines originating from normal thyroid gland tissue and thyroid carcinoma by ER dependent mechanisms such as enhancement of proliferation, modulation of sodium-iodide symporter and thyroglobuline gene expression and upregulation of matrix metalloproteinase 9 production. The above findings indicate that the growth and progression of thyroid malignancies are influenced by female sex hormones, particularly estrogen.

Compared to non-diabetic and thin patients, obese patients have a 2-6 times higher risk of cancer [1-4]. Thyroid cancer is one of the most increasingly prevalent types of cancer around the world. The most important reason for this increase is the rise in the use of diagnostic

ultrasonography and ultrasound-guided thyroid fine needle aspiration biopsy [5]. Studies on thyroid cancer and body mass index (BMI) are heterogeneous. Obesity is influential on the development and progression of thyroid cancer [6]. Many studies compared thyroid cancer patients with healthy groups and showed that increased body mass index led to a predisposition to malignancy [7]. Excessive protein and carbohydrate consumption increases the risk of differentiated thyroid cancer [8]. Long-term physical activity decreases the risk of papillary thyroid cancer in normal-weight and overweight people [9]. Ultrasound-guided fine needle aspiration biopsy of the thyroid (TFNAB) is the first-choice diagnostic method to assess thyroid nodules. According to TFNAB results, the rate of malignancy in nodules is 4.8%, the rate of suspicious cytology is 9.4% and the rate of non-diagnostic cytology is 3.8%. Thyroid fine needle aspiration biopsy gives accurate results with a specificity of 98.7% and sensitivity of 89.1% [10]. In a study evaluating 201 patients with indeterminate cytology, malignancy rates were found to be 33.1% in the Hurthle cell lesion, 23% in the suspicious follicular neoplasm and 53.7% in suspicious malignancies [11].

### Materials and Methods

This study was conducted retrospectively at Ankara Atatürk Training and Research Hospital between January 2009 and December 2010 after obtaining the approval of the local ethics committee. The results of the thyroid fine needle aspiration biopsy were evaluated based on the 2007 Bethesda classification. Patients with atypia of undetermined significance/follicular lesion of undetermined

significance (Bethesda 3), Hurthle cell lesion, suspicious follicular neoplasm (Bethesda 4) and suspicious malignancy (Bethesda 5) were included in the study [12]. Height, weight, body mass index (BMI) and fat ratio were measured for each patient included in the study using a Tanita scale in the preoperative period. Waist and hip circumferences were measured. Waist circumference was measured at the midpoint between the lowest rib and iliac crest. WC/HC ratio was calculated by dividing waist circumference (cm) by hip circumference (cm). BMI was calculated with the following formula:  $BMI = \text{Weight (kg)} / \text{height (m)}^2$ . Patients were divided into groups as recommended by the World Health Organization [13]. There were four groups: Group 1 with a BMI of 18.5-24.9; Group 2 with a BMI of 25-29.9; Group 3 with a BMI of 30-39.9 (obese) and Group 4 with a BMI of >40 (morbidly obese). Patients' postoperative pathology reports were reviewed and patients were divided into groups as either benign or malignant. Malignancy rates were calculated for each BMI category. Based on the patients' data, TNM staging was done according to the 2010 guidelines of the American Joint Committee on Cancer (AJCC). (14) Preoperative fT3, fT4 and TSH values of each patient were measured using the Abbott Architect 2000 (Abbott Diagnostics Division, IL, USA) device and the chemiluminescence microparticle immunoassay method.

### Statistical Analysis

SPSS 19 was used for statistical analysis. All mean values were calculated. A Chi-square test was done for both BMI categories. Linear regression analysis was made between BMI and thyroid carcinoma.

### Results

The overall characteristics of patients are summarized in table 1. 214 patients were included in the study. 150 (70.1%) of the patients were females and 64 (29.9%) were males. Mean patient age was  $46.40 \pm 11.17$  (18-65 years). Patients were divided into 4 groups based on BMI: Group 1 (n=47, 21.99%), Group 2 (n=67, 31.3%), Group 3 (n=85, 39.7%) and Group 4 (n=15, 7%). Patients were divided into groups as benign or malignant based on histopathology results. BMI ( $29.60 \pm 6.51$ ,  $30.47 \pm 7.49$ ,  $p=0.38$ ); WC ( $92.03 \pm 11.19$ ,  $94.6 \pm 15$ ,  $p=0.16$ ) and HC ( $103.69 \pm 12.92$ ,  $120.43 \pm 12.20$ ,  $p=0.10$ ) were found to be similar between the two groups. fT4 was found to be significantly elevated in the malignant group ( $1.27 \pm 0.46$ ,  $1.15 \pm 0.32$ ,  $p=0.031$ ).

TSH ( $1.90 \pm 2.93$ ,  $2.34 \pm 4.04$ ,  $p=0.36$ ) and fT3 ( $3.23 \pm 3.83$ ,  $2.96 \pm 0.58$ ,  $p=0.48$ ) levels were similar. Body fat percentage was measured as  $33.74 \pm 9.95\%$  in the malignant group and  $32.55 \pm 9.45\%$  in the benign group; there was no statistical difference between the groups ( $p=0.57$ ). Malignancy was detected in 70 patients (32.7%). In the malignant group, 23 patients had follicular carcinoma (32.8%) and 47 (67.2%) patients had papillary thyroid cancer. Female patients (37/150, 24.6%) and male patients (33/65, 50.7%) had malignancy. Thirty patients had microcarcinoma and 40 patients had macrocarcinoma. Tumor size was measured as  $4.43 \pm 3.61$  mm in the microcarcinoma group and  $18.63 \pm 8.49$  mm in the macrocarcinoma group. Mean tumor size was found to be  $10.51 \pm 9.37$  mm in the malignant group. The malignancy rates of groups are summarized in table 2.

Based on the histopathological results of the 214 patients included in the study, 70 patients were reported to have thyroid cancer (32.7%). The rate of malignancy was 27% in Group 1, 32.8% in Group 2, 32.9% in Group 3 and 46.7% in Group 4. There was no significant difference between the groups ( $p>0.05$ ). Malignancy rates were 30.2% (29/96) in patients aged <45 years and 34.7% (41/118) in patients aged >45 years.

There was no statistical difference between groups ( $p=0.55$ ). In the TNM staging of the patients done according to the AJCC-2010 criteria, 13 thyroid cancer cases (stage 1=9, stage 2=2, stage 3=2) were found in group 1. 22 thyroid cancer cases (stage 1=16, stage 2=4, stage 3=2) were found in group 2. 28 thyroid cancer cases (stage 1=19, stage 2=5, stage 3=3, stage 4=1) were found in group 3. 7 thyroid cancer cases (stage 1=5, stage 2=2) were found in group 4. No increase in disease stages was observed as BMI increased ( $p>0.05$ ) (Table 3).

Out of 114 patients with a preoperative cytology diagnosis of Bethesda 3, 12 patients (10.5%) were found to have malignant histopathology. Out of 18 patients with Bethesda 4, 5 patients (27.8%) were found to have malignant cytology. Out of 82 patients with Bethesda 5, 54 patients ( $54/82=65.9\%$ ) were found to have thyroid cancer postoperatively. Correlation analyses were performed within the malignant group itself and the benign group itself. A positive correlation was found between age and waist circumference ( $r=0.47$ ,  $p=0.00$ ), hip circumference ( $r=0.35$ ,  $p=0.00$ ), and BMI ( $r=0.36$ ,  $p=0.00$ ) in the benign group. A positive correlation was found between age and waist circumference ( $r=0.38$ ,  $p=0.001$ ) and BMI ( $r=0.30$ ,  $p=0.01$ ) in the malignant group. A negative correlation was found between age and fT3 (free T3) ( $r=0.24$ ,  $p=0.03$ ). A negative correlation was also found between tumor size and gender in the malignant group ( $r=0.26$ ,  $p=0.025$ ). A negative correlation was found between fT3 and BMI ( $r=0.24$ ,  $p=0.038$ ), and a negative correlation was found between fT3 and age ( $r=0.24$ ,  $p=0.038$ ) in the malignant group. A negative correlation was found between TSH level and fT4 (free T4) level ( $r=0.27$ ,  $p=0.02$ ) in the malignant group.

	Benign (n=144)	Malignant (n=70)	p
Age	46.62 ± 11.47	46.01 ± 11.69	0.72
Height	159.85 ± 8.53	160 ± 7.78	0.90
BMI	29.60 ± 6.51	30.47 ± 7.49	0.38
WC	92.03 ± 11.19	94.6 ± 15	0.16
HC	103.69 ± 12.92	120.43 ± 122.01	0.10
Body fat percentage	32.55 ± 9.45	33.74 ± 9.95	0.57
TSH	1.90 ± 2.93	2.34 ± 4.04	0.36
FT3	3.23 ± 3.83	2.96 ± 0.58	0.48
FT4	1.15 ± 0.32	1.27 ± 0.46	0.031
Tumor Size		10.51 ± 9.37	

**Table 1:** Overall characteristics of patients

	Benign (n=144)	Malignant (n=70)	Malignancy rate
Group 1 (n=47)	34	13	0.27
Group 2 (n=67)	45	22	0.32
Group 3 (n=85)	57	28	0.32
Group 4 (n=15)	8	7	0.46

Total	144	70	0.32
-------	-----	----	------

**Table 2:** Malignancy rates in groups

	Group 1 (n=13)	Group 2 (n=22)	Group 3 (n=28)	Group 4 (n=7)
Stage 1	9	16	19	5
Stage 2	2	4	5	2
Stage 3	2	2	3	0
Stage 4	0	0	1	0

**Table 3:** TNM staging based on AJCC-2010 criteria

N=malignant group patients, pearson Chi-square tests P=0,773 (All groups)

## Discussion

Our study is a retrospective study on the relationship between BMI and thyroid cancer. In our study, patients were divided into 4 groups based on their BMIs. Malignancy rate was found to be 27% in group 1, 32% in group 2, 32% in group 3, and 46% in group 4. Staging of the patients according to the AJCC-2010 data has shown no increase in the disease stages as BMI increases. Increased BMI leads to an increase in several malignancies including thyroid cancer [15]. In a study conducted in 443 patients operated on for papillary thyroid cancer, patients were assessed after being divided into 4 groups based on their BMI and patients with a higher body mass index were found to have a higher disease stage. Morbidly obese patients were often diagnosed with stage 3-4 papillary thyroid cancer. As BMI increased, tumor size also increased. Obese patients had advanced stage thyroid cancer and aggressive forms [16]. In this study, malignancy rates increased with higher BMI but the difference was not statistically significant ( $p>0.05$ ). Epidemiological studies show that the risk of thyroid cancer increases with excess weight gain. It is not clear if excess weight is a prognostic factor of thyroid cancer. Increased BMI is strongly associated with increased tumor size, extrathyroidal invasion and higher TNM stage. The course of papillary thyroid cancer is more aggressive in overweight people [17]. In our study, no increase in malignancy rates or TNM stages were seen as the BMIs of patients increased. In a retrospective study where 259 papillary thyroid cancer patients were included and followed up for 6.2 years, no relationship was found between BMI and tumor size, lymph nodes, distant metastasis, vascular invasion and disease recurrence [18]. In one recent study, a relationship was found between increased BMI (body mass index) and prevalence of thyroid cancer in women (OR=1.63,  $p<0.001$ ) [18]. According to a meta-analysis, a 5kg/m<sup>2</sup> increase in BMI leads to increased risk of thyroid cancer in males (RR=1.33;  $p=0.02$ ) and females (RR=1.14;  $p=0.001$ ) [15]. In our study, the group with the higher BMI had an increased percentage of thyroid cancer, but the difference was statistically insignificant. There are studies reporting that obese patients with indeterminate cytology have a low risk of malignancy [6]. This study included Group 3-5 patients with a high risk of malignancy according to the Bethesda classification and postoperative histopathology results were found to be consistent with the literature (Bethesda 3: 10.5%, Bethesda 4: 27.8%, Bethesda 5: 65.9%) [12].

Increased body size and physical inactivity are positively related to the risk of several cancers, but only a few epidemiological studies have investigated body mass index (BMI) and physical activity in relation to thyroid cancer, being overweight was related to a suggestive increase of nearly 30% in the risk of thyroid cancer and obesity was associated with an increase of 40% in the risk of thyroid cancer when compared to normal weight [19]. According to a recent systematic review, most studies agree that obesity is positively but modestly correlated with TC risk. However, the risk estimates range widely from 1.1 to 2.3 in men and 1.0 to 7.4 in women (20). In our study, malignancy was detected in 70 patients (32.7%). In the malignant group, 23 patients had follicular carcinoma (32.8%) and 47 (67.2%) patients had papillary thyroid cancer. Female patients (37/150, 24.6%) and male patients (33/65, 50.7%) had malignancy. Thirty patients had microcarcinoma and 40 patients had macrocarcinoma. Potential mechanisms involved in the obesity-thyroid cancer relationship include elevated TSH levels, insulin resistance and adipokine effect. Some studies demonstrate a positive relationship between BMI and TSH while others do not. Leptin and leptin receptor expression has been shown in thyroid cancer [21]. Adipokines, particularly adiponectin, leptin and hepatocyte growth factor are associated with cancer proliferation and cancer progression [22]. The stronger association of obesity with TC in females observed in many studies could point to a direct effect of sex steroids in thyroid carcinogenesis. There are experimental data supporting a mitogenic effect of estrogen in thyroid tumors [4]. In a study conducted in France, increased BMI was found to be associated with differentiated thyroid cancer in women [23]. As a result, the prevalence of thyroid cancer increases with the increase of obesity. It is important to clarify its connection with thyroid cancer as well as the mediating pathways. However, unless this association is confirmed and causation proven, screening for TC in overweight and obese subjects does not seem justified [4].

## References

1. Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni JF Jr (2006) Relation of body mass index to cancer risk in 362,552 Swedish men. *Cancer Causes Control* 17: 901-909.
2. Smith HO, Tiffany MF, Qualls CR, Key CR (2000) The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States--a 24-year population-based study. *Gynecol Oncol* 78: 97-105.
3. Huang Y, Dong W, Li J1, Zhang H, Shan Z, et al. (2014) Differential expression patterns and clinical significance of estrogen receptor- $\alpha$  and  $\beta$  in papillary thyroid carcinoma. *BMC Cancer* 14: 383.
4. Pappa T, Alevizaki M (2014) Obesity and thyroid cancer: a clinical update. *Thyroid* 24: 190-199.
5. Hodgson NC, Button J, Solorzano CC (2004) Thyroid cancer: is the incidence still increasing? *Ann Surg Oncol* 11: 1093-1097.
6. Pazaitou-Panayiotou K, Polyzos SA, Mantzoros CS (2013) Obesity and thyroid cancer: epidemiologic associations and underlying mechanisms. *Obes Rev* 14: 1006-1022.
7. Mijović T, How J, Pakdaman M, Rochon L, Gologan O, et al. (2009) Body mass index in the evaluation of thyroid cancer risk. *Thyroid* 19: 467-472.
8. Marcello MA, Sampaio AC, Geloneze B, Vasques AC, Assumpção LV, et al. (2012) Obesity and excess protein and carbohydrate consumption are risk factors for thyroid cancer. *Nutr Cancer* 64: 1190-1195.
9. Cash SW, Ma H, Horn-Ross PL, Reynolds P, Canchola AJ, et al. (2013) Recreational physical activity and risk of papillary thyroid cancer among women in the California Teachers Study. *Cancer Epidemiol* 37: 46-53.
10. Gul K, Ersoy R, Dirikoc A, Korukluoglu B, Ersoy PE, et al. (2009) Ultrasonographic evaluation of thyroid nodules: comparison of

- ultrasonographic, cytological, and histopathological findings. *Endocrine* 36: 464-472.
11. Tutuncu Y, Berker D, Isik S, Akbaba G, Ozuguz U, et al. (2014) The frequency of malignancy and the relationship between malignancy and ultrasonographic features of thyroid nodules with indeterminate cytology. *Endocrine* 45: 37-45.
  12. Cibas ES, Ali SZ; NCI Thyroid FNA State of the Science Conference (2009) The Bethesda System For Reporting Thyroid Cytopathology. *Am J Clin Pathol* 132: 658-665.
  13. [No authors listed] (2000) Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 894: i-xii, 1-253.
  14. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, et al. (2010) *AJCC cancer staging manual*. (7th edn), New York: Springer 1-646.
  15. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 371: 569-578.
  16. Harari A, Endo B, Nishimoto S, Ituarte PH, Yeh MW (2012) Risk of advanced papillary thyroid cancer in obese patients. *Arch Surg* 147: 805-811.
  17. Kim HJ, Kim NK, Choi JH, Sohn SY, Kim SW, et al. (2013) Associations between body mass index and clinico-pathological characteristics of papillary thyroid cancer. *Clin Endocrinol (Oxf)* 78: 134-140.
  18. Paes JE, Hua K, Nagy R, Kloos RT, Jarjoura D, et al. (2010) The relationship between body mass index and thyroid cancer pathology features and outcomes: a clinicopathological cohort study. *J Clin Endocrinol Metab* 95: 4244-4250.
  19. Leitzmann MF, Brenner A, Moore SC, Koebnick C, Park Y, et al. (2010) Prospective study of body mass index, physical activity and thyroid cancer. *Int J Cancer* 126: 2947-2956.
  20. Peterson E, De P, Nuttall R (2012) BMI, diet and female reproductive factors as risks for thyroid cancer: a systematic review. *PLoS One* 7: e29177.
  21. Uddin S, Bavi P, Siraj AK, Ahmed M, Al-Rasheed M, et al. (2010) Leptin-R and its association with PI3K/AKT signaling pathway in papillary thyroid carcinoma. *Endocr Relat Cancer* 17: 191-202.
  22. Kitahara CM, Platz EA, Freeman LE, Hsing AW, Linet MS, et al. (2011) Obesity and thyroid cancer risk among U.S. men and women: a pooled analysis of five prospective studies. *Cancer Epidemiol Biomarkers Prev* 20: 464-472.
  23. Rinaldi S, Lise M, Clavel-Chapelon F, Boutron-Ruault MC, Guillas G, et al. (2012) Body size and risk of differentiated thyroid carcinomas: findings from the EPIC study. *Int J Cancer* 131: E1004-1014.