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Association between obesity and thyroid cancer in women: a comparative study of malignant and benign nodules

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ABSTRACT

Introduction: Obesity is a disease that induces various changes in the body, including oxidative stress, which can contribute to the development of cancer cells in the thyroid.

Objective: Evaluate whether the presence of obesity and antioxidant defense is associated with the diagnosis of malignant thyroid nodules in adult women. **Methods:** The cross-sectional study consisted of 109 females diagnosed with nodular thyroid disease who underwent thyroidectomy surgery, with benignity or malignancy classification previously defined by Fine Needle Aspiration Biopsy (FNAB) and the Bethesda system. The participants had anthropometric and clinical markers assessed before the surgical process. The prevalence ratio of malignant nodules with obesity and antioxidant markers was determined using Poisson regression analysis.

Results: After biopsy analysis, 70 women were diagnosed with a benign nodule and 39 with a malignant nodule. A significant association was found between body mass index and nodule type ($p < 0.015$). All but one participant had glutathione peroxidase and superoxide dismutase enzyme activity above the reference values. The prevalence of malignant nodules was significantly higher in women diagnosed with obesity (PR=1.94; 95% CI: 1.01 - 3.17; $p = 0.046$) compared to those without obesity. Antioxidant markers showed no association with nodule malignancy. **Conclusion:** The prevalence of malignant thyroid nodules in adult women is higher in those who are obese, and the presence of thyroid nodules, regardless of their type, can influence the increase in antioxidant enzyme activity.

Keywords: women's health; thyroid gland; thyroid neoplasms; anthropometry; oxidative stress; enzymes.

INTRODUCTION

Despite the benign nature of most thyroid nodules, thyroid cancer has seen an increase in prevalence worldwide¹. In Brazil, this type of cancer is considered one of the most common endocrinological tumors, and its incidence is approximately five times higher in women than in men². Part of the increase in incidence is due to advances in more sensitive tests for early detection and diagnosis, but other factors inherent to population health also contribute to these results, such as weight changes³.

Obesity is an emerging public health problem and one of the main factors influencing the appearance of thyroid nodules^{4,5}. Excess weight, independent of insulin resistance, results in endocrine alterations that contribute to cell growth and development. As a result, the thyroid volume expands and nodules form⁶. In addition, the normal functioning of thyroid cells is altered due to the constant, chronic low-grade inflammatory process in the body. The balance between the production of reactive oxygen species (ROS) and intracellular antioxidant defenses tends toward oxidative imbalance, which may contribute to the initiation and progression of thyroid cancer^{7,8}.

The thyroid gland is naturally exposed to relatively high concentrations of ROS, particularly hydrogen peroxide (H₂O₂), which acts as an essential cofactor in the synthesis of thyroid hormones. Although thyroid cells possess robust antioxidant systems that confer greater tolerance to oxidative stress, an imbalance between ROS production and antioxidant defenses—often associated with excess body fat—may lead to damage to genetic material, proteins, and membrane lipids. This condition favors the activation of signaling pathways involved in inflammation, cellular dysfunction, and carcinogenesis^{9,10}.

In addition to high concentrations of ROS, in obesity, adipocyte hypertrophy promotes the dysregulation of signaling pathways associated with growth hormones, chronic

hyperinsulinemia, decreased antioxidant capacity, and increased production and bioavailability of estrogens. Regardless of obesity, benign and malignant thyroid nodules have been associated with reduced enzymatic antioxidant activity, including lower Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPx) activity, as well as decreased selenium concentrations in the body, compared to healthy thyroid tissue^{11,12}. These endocrine alterations associated with obesity induce oxidative stress and further enhance cell proliferation, angiogenesis, and suppression of apoptosis, thereby creating a microenvironment conducive to the development and progression of benign and malignant neoplasms⁸.

One of the mechanisms by which excess body weight may increase the risk of both benign and malignant thyroid nodules is through elevated estrogen concentrations resulting from increased activity of the aromatase enzyme. The upregulation of aromatase activity is associated with adipose tissue expansion and the action of endocrine signaling molecules secreted by adipose cells¹³. High estrogen levels contribute to carcinogenic effects by activating intracellular anti-apoptotic pathways, thereby promoting cell survival and proliferation, as well as increasing the production of ROS. Furthermore, elevated estrogen concentrations, by sustaining oxidative stress, may promote epigenetic modifications that regulate the development and invasiveness of thyroid tumors, including the activation of the PI3K/AKT and MAPK signaling pathways¹³.

Since obesity is a disease that promotes several changes in the body, including oxidative stress, which can contribute to the development of cancer cells, this study aims to assess whether the presence of obesity and antioxidant defense are associated with the diagnosis of malignant thyroid nodules in adult women.

METHODS

This was an analytical cross-sectional study of female patients diagnosed with nodular thyroid disease and indicated for partial or total thyroidectomy at a hospital in Fortaleza, Ceará. The convenience sample consisted of 109 participants selected on the day they were admitted to the hospital before the surgical procedure. The surgical procedures, as well as the classification of the nodules as benign or malignant, were performed exclusively by the hospital's medical team. Information regarding the diagnosis and nature of the nodules was obtained from the analysis of medical records and patient charts. The process took place between December 2016 and January 2018.

To determine the sample size, the equation proposed by Bassan¹⁴ was applied for finite populations with a 95% confidence level, and a sample of 62 patients was obtained. The total number of thyroidectomies in 2014 and 2015 was used as the basis for the calculation.

The study included women aged between 18 and 60 with a diagnosis of nodular thyroid disease. Patients were not included if they had chronic non-communicable diseases (except obesity), infectious-contagious diseases, or malabsorptive syndromes; if they were using any mineral nutritional supplements or medication for thyroid dysfunctions (hypothyroidism, hyperthyroidism, and Hashimoto's thyroiditis); or if they drank more than two doses of alcohol a day.

The research was approved by the Research Ethics Committee of the State University of Ceará, according to approval number 1,526,420, respecting Resolution 466/2012 of the Brazilian National Health Council. The research stages began after the signing of the Informed Consent Form (ICF).

Social, demographic, and clinical data collection

Data were collected using a structured questionnaire covering social, economic, and demographic characteristics, clinical history, and lifestyle (alcohol consumption, smoking, and physical activity). The preoperative thyroid tests, serum TSH, free thyroxine (T₄), total thyroid volume (TTV), and the cytopathology result were obtained from the hospital records.

The type of nodule, benign or malignant, was determined by the result of the Fine Needle Aspiration Biopsy (FNAB) and classified according to the Bethesda cytology classification system¹⁵.

Anthropometric and nutritional assessment

Anthropometric measurements of weight, height, and waist and hip circumferences were taken. The weight and height measurements were taken on a Filizola balance with a maximum capacity of 150 Kg and divisions of 100g, according to Frisancho's methodology¹⁶.

The results were used to calculate the body mass index (BMI). Waist and hip circumferences were measured using an inelastic, a 2-m inelastic measuring tape with a scale in millimeters, manufactured by Sanny®. Waist circumference (WC) was obtained at the smallest abdominal curvature, and hip circumference at the largest perimeter of the gluteal region. The classification of nutritional status by BMI and risk of cardiovascular disease by WC and waist-to-hip ratio (WHR) was by the World Health Organization¹⁷.

Blood collection, processing of biological material, and determination of blood markers

Blood was collected immediately before surgery, with patients fasting for 12 hours. After collection, the material was sent to the Food and Micronutrient Analysis Laboratory at the State University of Ceará for processing of the biological material and separation of plasma, erythrocytes, and whole blood. The samples were then stored at -80°C for later analysis.

The activity of the glutathione peroxidase enzyme (GPx) was determined in whole blood samples using the commercially available Ransel kit, RANDOX® (Crumlin, County Antrim, BT29 4QY, UK). The reference range was 27.5-73.6 U/g Hb. Superoxide dismutase (SOD) activity was determined in erythrocyte samples using the Ransel Kit, No. SD 125, RANDOX® (Crumlin, County Antrim, BT29 4QY, UK). The reference range considered was 1,102-1,601 U/g Hb. Measurements were performed using a LabMax 240 biochemical analyzer. Analysis of hemoglobin in whole blood on a Mindray® BC-2800Vet hematology analyzer was carried out to express the activity of the enzymes, which was described in units of the enzyme per gram of hemoglobin.

The concentration of native thiol (-SH) was determined using the method described by Aksenov and Markesbery¹⁸ in plasma samples. The concentration of sulfhydryl groups was calculated using reduced glutathione as the sulfhydryl group standard, and the result was expressed in $\mu\text{mol/L}$ of plasma. Reading was carried out on an S-2000 spectrophotometer.

Statistical analysis

Initially, the normality and homogeneity of the data were tested using the Kolmogorov-Smirnov and Levene tests, respectively. Numerical data were expressed as means and standard deviation, and categorical data as frequencies and percentages. Student's t-test or the Mann-Whitney test was used to compare means, depending on the distribution of the data. The association between categorical variables was assessed using Pearson's chi-squared test.

Poisson regression was used to assess the association between exposure (presence of obesity and antioxidant defense markers) and the outcome (presence of malignant thyroid tumors) in three models: unadjusted (model 1); adjusted for age, physical activity, smoking, and alcohol consumption (model 2); adjusted for age, physical activity, smoking, alcohol

consumption, waist circumference, and waist-to-hip ratio (model 3). The prevalence ratios (PR) were presented along with their respective 95% confidence intervals (95% CI).

All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) software version 22.0. Data were considered significant when the *p-values* were less than 0.05.

RESULTS

After analyzing the tissue removed during partial or total thyroidectomy, 70 participants were diagnosed with benign nodules and 39 with malignant nodules. To express the data, the patients were divided into two groups: benign and malignant nodules.

The mean age of the benign group was 40 years (SD 11.04) and of the malignant group 42 years (SD 11.11). The sample population was similar in all the social and demographic aspects assessed in this study, as shown in table 1.

According to the BMI classification, 30 (27.5%) participants were eutrophic, and 79 (72.5%) had excess weight, of which 47 (43.1%) had overweight, 25 (22.9%) had class I obesity, 3 (2.8%) had class II obesity, and 4 (3.7%) had class III obesity. Among the anthropometric markers, only BMI was significantly associated with nodule type ($p=0.015$). All the participants diagnosed with obesity had a WC over 80 cm. Concerning WHR, except for eight participants, the women with obesity also had values greater than 0.85 cm. The complete data on the anthropometric variables of the study population are shown in table 2.

Table 3 shows the results of the population's clinical variables. The values of the biomarkers related to thyroid function and antioxidant defense capacity showed no significant differences between the groups. However, all the participants, except for one person, had SOD activity values above the normal range, regardless of whether they belonged to the benign or

malignant group. Regarding GPX, only one participant in the benign group showed values within the normal range.

The results of the regression analysis are shown in table 4. The association between malignant nodules and the presence of obesity remained significant even after adjusting the model. The prevalence of malignant nodules increased by 94% in the presence of obesity compared to the group that was not diagnosed with obesity. Antioxidant markers showed no association with nodule malignancy.

DISCUSSION

According to this study's findings, the prevalence of malignant nodules was 94% higher in women with obesity compared to those without this condition, and antioxidant defense markers showed no association with the type of nodule (malignant and benign).

In agreement with our results, other studies have observed higher BMI values in individuals with malignant nodules when compared to individuals with benign nodules and a higher risk of cancer in people with obesity. Eissa *et al.*¹⁹ and Xu *et al.*²⁰ found a significant increase in BMI in people with malignant thyroid nodules compared to those with benign disease. In another study, carried out only with women, the proportion of patients with BMI ≥ 30 kg/m² (65.9% vs 33.8%, $p < 0.001$) and WC ≥ 88 cm (84.1% vs 47.9%, $p < 0.001$) was significantly higher in the group with a malignant nodule compared to the benign one and the risk of malignancy was 3.819 times higher (95% CI: 2.068-7.054, $p < 0.001$) in the group with BMI ≥ 30 kg/m² compared²¹ to the group with BMI < 30 kg/m².

There is extensive literature that presents obesity as a risk factor for different types of cancer^{22,23}. Evidence suggests that chronic low-grade inflammation and alterations present in the disease, such as elevated concentrations of adipokines (IL-6, TNF- α , and leptin), metabolic

abnormalities (insulin resistance and increased IGF), and oxidative stress, contribute to the development of tumors²². In the thyroid gland, these alterations play key roles in cell proliferation and carcinogenesis, as discussed in several studies²⁴⁻²⁶.

Obesity also influences the sex hormone estrogen, which for women can contribute to an increased risk of thyroid cancer¹³. Excess body fat promotes an increase in the activity and concentration of the aromatase enzyme, which, in turn, increases the conversion of testosterone into estradiol⁸. The increase in estradiol levels favors the expression of the estrogen- α receptor in thyroid cells and the activation of pathways mediated by nuclear receptors that increase the capacity for cell growth, proliferation, and survival²⁷.

The prevalence of obesity in women with thyroid cancer is similar to that found in breast cancer in the country. A study in Brazil showed that 29.4% of breast cancer patients were obese at the time of diagnosis²⁸. The figure found is also similar to the prevalence of obesity in adult women in the capital of the state of Ceará, corresponding to 29.8%²⁹. However, it is still lower than the obesity data for adult women in the same state in 2023 (35.38%)³⁰.

Body fat distribution seems to be another important factor in the occurrence of malignant nodules, since central obesity is associated with inflammatory markers and insulin resistance²⁵. Nguyen et al.³¹, in a cohort of 160,650 participants, observed that women with an adequate BMI and WC above the reference values had an increased risk of thyroid cancer (RR=1.54; 95% CI: 1.03-2.32, p 0.027), as did those with an elevated BMI and WC (RR=1.57; 95% CI: 1.23-2.02, p 0.001). Although our study did not find any significant differences in the analyses of WC and WHR between the groups, most of the participants diagnosed with obesity also had WC greater than 80 cm and WHR >0.85. This shows a pattern of metabolically unhealthy obesity in the population with thyroid nodules.

The relationship between oxidative stress and thyroid diseases, whether malignant or benign, is evident in the scientific literature^{10,11}. The presence of benign nodules can reduce the enzymatic activity of enzymes linked to antioxidant defense, as in hypothyroidism, or even have this effect linked to a greater production of ROS, as in hyperthyroidism. Malignant nodules may also influence systemic oxidative stress, as well as affect antioxidant defense^{26,32}.

A wide range of studies aimed at investigating the relationship between antioxidant defense and benign and malignant thyroid diseases have used tissue samples to analyze enzymatic activity^{11,33,34}. Unlike these studies, we set out to evaluate antioxidant activity using serum biomarkers of SOD, GPx, and native thiol, given that different types of thyroid disease can influence antioxidant levels in blood tissue constituents and can also be indicative of thyroid tissue damage³⁵.

Analyses of tissue biopsies have shown that antioxidant activity can decrease, while the production of reactive species can increase in any type of thyroid nodule compared to healthy gland tissues; however, some types of thyroid cancer show these effects more markedly^{11,34,36}. Furthermore, differences can be found when comparing oxidative stress parameters in blood and thyroid tissue, due to the difference between the levels of oxidative stress markers found in these two samples¹¹.

The lack of association of SOD, GPx, and Native Thiol with the type of thyroid nodule observed in this study reinforces that oxidative stress may be an intrinsic process to both types of nodules since both conditions have chronic inflammation in their pathophysiology. Thus, the presence of a nodule of any type could represent a trigger and/or be a potentiator of the production of reactive species, leading to a greater condition of oxidative stress in the thyroid to the detriment of healthy glands³⁷.

It is important to mention that the thyroid has structural and molecular characteristics adapted to resist the permanent and high-level production of reactive species since the very production of thyroid hormones depends on the availability of H_2O_2 produced in thyroid tissue by Double Oxidase 2 (DUOX 2)³⁸. Therefore, serum biomarkers associated with antioxidant enzyme activity, such as SOD and GPx, can make it possible to assess the state of systemic antioxidant defense, where reduced activity can configure a scenario of inadequate redox balance²⁶.

The values for SOD and GPx enzyme activity were high, except for one participant, given the reference range. In agreement with Ramli et al.³⁵, who observed an increase in the activity of serum enzymes (SOD and Catalase) in the benign condition of multinodular goiter and papillary thyroid cancer, we believe that the increase in SOD and GPx activity is a protective response and is related to an increase in the production of the reactive species of Superoxide Anion ($O_2^{\cdot-}$) and H_2O_2 . Given that thyroid hormones regulate mitochondrial oxidative function, any disorder in the gland could also compromise mitochondrial oxidative processes and influence the increase in $O_2^{\cdot-}$ production. When $O_2^{\cdot-}$ is neutralized by SOD, it induces the production of H_2O_2 , which could also explain the increase in this reactive species^{39,40}.

We also point out that the chronicity of this condition of oxidative stress could result in a subsequent reduction in antioxidant enzyme activity, a condition also pointed out by other studies and which can generate a redox imbalance, increasing the oxidative stress seen in benign and malignant thyroid conditions¹¹.

Excess weight could be indirectly responsible for the increase in SOD and GPx, since it is well documented in the literature that excess weight can contribute to the production of reactive species, consequently inducing oxidative stress. However, to reinforce the hypothesis

that the increase in SOD and GPx activity may be linked to the oxidative stress generated by the presence of a thyroid nodule of any kind, we would like to point out that this result was independent of the nutritional status of the participants, with a higher antioxidant enzyme activity in almost all the women in the study.

Our study presents some limitations. One of them is the absence of imaging data (such as ultrasound findings), data from FNAB, information regarding the type of thyroid nodule, and data on the body composition of the women who participated in the study. These aspects, combined with the anthropometric variables already collected, could have contributed to a more comprehensive assessment of nutritional status. Another limitation is the lack of biomarkers related to oxidative damage, such as lipid peroxidation, protein oxidation, or DNA damage. Evaluating these parameters would have provided a deeper understanding of oxidative stress in different types of thyroid nodules.

However, the research has strong points in its methodology. The homogeneity of the groups ensures that the results show reduced interference from factors that may influence the variables of interest. Another potential is the evaluation of systemic antioxidant markers in the group in question, since there is a lot of research on these markers at the tissue level, and a lack of data on these serum markers in thyroid nodular disease.

In conclusion, the prevalence of malignant thyroid nodules in adult women was higher in those diagnosed with obesity when compared to those who did not have obesity, and BMI was the only anthropometric marker evaluated that was associated with the presence of malignant disease. Although serum antioxidant markers (SOD, GPx, and native thiol) were not associated with the prevalence of malignant nodules, we suggest that the presence of the nodule, regardless of its type, may influence the increase in antioxidant defense.

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Table 1: Sociodemographic characteristics of women according to the type of thyroid nodule.

Variables	Total n=109	Type of nodule		p-value*
		Benign n=70	Malignant n=39	
Place of residence, n (%)				
Capital	32 (29.4)	19 (59.4)	13 (40.6)	0.496
Interior	77 (70.6)	51 (66.2)	26 (33.8)	
Schooling, n (%)				
Elementary school	22 (20.2)	14 (63.6)	8 (36.4)	0.949
High school/higher education	87 (79.8)	56 (64.4)	31 (35.6)	
Number of children, n (%)				
0 to 1 child	55 (50.5)	38 (69.1)	17 (30.9)	0.284
≥2 children	54 (49.5)	32 (59.3)	22 (40.7)	
Income, n (%)				
More than 2 MW	26 (23.9)	20 (76.9)	6 (23.1)	0.122
Up to 2 MW	83 (76.1)	50 (60.2)	33 (39.8)	
Physical activity, n (%)				
Yes	33 (30.3)	17 (51.5)	16 (48.5)	0.068
No	76 (69.7)	53 (69.7)	23 (30.3)	
Alcohol consumption, n (%)				
Yes	18 (16.5)	14 (77.8)	4 (22.2)	0.189
No	91 (83.5)	56 (61.5)	35 (38.5)	
Smoking, n (%)				
Yes	2 (1.8)	1 (50.0)	1 (50.0)	0.672
No	107 (98.2)	69 (64.5)	38 (35.5)	

*Pearson's chi-squared test. *P*-value considered significant at less than 5%. *MW*: Minimum Wage.

Table 2: Anthropometric characteristics of women according to type of thyroid nodule.

Variables	Total n=109	Type of nodule		p-value
		Benign n=70	Malignant n=39	
BMI, kg/m ² , mean (SD)	27.74 (5.39)	27.04 (4.13)	29.00 (7.00)	0.264 ^b
BMI classification, n (%)				
Without obesity	77 (70.6)	55 (78.6)	22 (56.4)	0.015^a
With obesity	32 (29.4)	15 (21.4)	17 (43.6)	
WC, cm, mean (SD)	86.75 (10.65)	86.13 (9.63)	87.85 (12.32)	0.422 ^c
WC classification, n (%)				
Without risk	28 (25.7)	19 (27.1)	9 (23.1)	0.641 ^a
With risk	81 (74.3)	51 (72.9)	30 (76.9)	
WHR, cm, mean (SD)	0.84 (0.07)	0.84 (0.08)	0.83 (0.07)	0.361 ^c
Classification of WHR, n (%)				
Without risk	53 (48.6)	37 (69.8)	16 (30.2)	0.236 ^a
With risk	56 (51.4)	33 (58.9)	23 (41.1)	

a - Pearson's chi-squared test; b - Mann-Whitney test; c - independent Student's t-test. P-value considered significant at less than 5%. SD: standard deviation. BMI: body mass index. WC: waist circumference. WHR: waist-to-hip ratio. Reference values: BMI without obesity <30 kg/m²; BMI with obesity ≥30 kg/m²; WC without risk <80 cm; WC with risk ≥80 cm; WHR without risk ≤0.85 cm; WHR with risk >0.85.

Table 3: Clinical characteristics of women according to the type of thyroid nodule.

Variables	Total		Benign		Malignant		p-value
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	
TSH, mU/L	83	3.19 (12.50)	56	3.62 (15.18)	27	2.3 (2.08)	0.654 ^a
Free T ₄ , ng/dL	65	0.98 (0.22)	42	1.00 (0.21)	23	0.95 (0.22)	0.433 ^a
TTV, cm ³	36	31.04 (20.13)	27	30.76 (19.14)	9	31.85 (24.11)	0.891 ^a
Native Thiol, μmol/l	104	528.24 (78.36)	65	528.68 (80.36)	39	528.00 (75.96)	0.966 ^a
SOD, U/g Hb	76	2949.79 (559.11)	53	2977.32 (570.68)	23	2886.37 (538.40)	0.518 ^a
GPx, U/g Hb	76	138.64 (29.35)	53	136.08 (25.81)	23	144.56 (36.19)	0.591 ^b

a - independent Student's t-test; b - Mann-Whitney test. P-value considered significant at less than 5%. SD: standard deviation. TSH: thyroid-stimulating hormone. T₄: thyroxine. GPx: glutathione peroxidase. SOD: superoxide dismutase. TTV: total thyroid volume.

Table 4: Prevalence ratio (PR)* and 95% confidence interval of the presence of a malignant thyroid nodule in women according to nutritional status and antioxidant defense.

Variables	Malignant nodule					
	Model 1		Model 2		Model 3	
	PR (CI 95%)	p	PR (CI 95%)	p	PR (CI 95%)	p
Nutritional status						
Absence of obesity	Ref.		Ref.		Ref.	
Presence of obesity	1.86 (1.15 – 3.01)	0.011	1.76 (1.10 – 2.82)	0.018	1.94 (1.01 – 3.17)	0.046
Antioxidant defense						
SOD	1.00 (0.99 – 1.00)	0.495	1.00 (0.99 – 1.00)	0.669	1.00 (0.99 – 1.00)	0.599
GPx	1.01 (0.95 – 1.02)	0.257	1.01 (0.96 – 1.02)	0.140	1.01 (0.96 – 1.02)	0.216
Native Thiol	1.00 (0.97 – 1.03)	0.965	1.00 (0.97 – 1.03)	0.964	1.01 (0.98 – 1.05)	0.512

P-value considered significant at less than 5%. *PR*: prevalence ratio; *CI*: confidence interval; *Ref*: reference; *SOD*: superoxide dismutase; *GPx*: glutathione peroxidase. *Poisson regression in three models: unadjusted (model 1), adjusted for age, physical activity, smoking, and alcohol consumption (model 2), adjusted for age, physical activity, smoking, alcohol consumption, waist circumference, and waist-to-hip ratio (model 3).