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Obesity Does Not Modify the Risk of Differentiated Thyroid Cancer in a Cytological Series of Thyroid Nodules

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Key Words
Thyroid cancer · Morbid obesity · Body mass index · Fine-needle aspiration cytology

Abstract
Background: A possible impact of obesity on the risk of thyroid cancer has been postulated in some studies, but it remains controversial. ***Objective:*** To investigate the association between obesity and differentiated thyroid carcinoma in a population of unselected patients subjected to fine-needle aspiration cytology (FNAC) for thyroid nodules. ***Methods:*** We retrospectively evaluated the results of FNAC of thyroid nodules in 4,849 patients (3,809 females and 1,040 males; mean age 55.9 ± 14.1 years). Patients were stratified according to their body mass index (BMI). There were 1,876 (38.7%) normal-weight patients (BMI 18–24.9), 1,758 (36.2%) overweight (BMI 25–29.9), 662 (13.7%) grade 1 obese (BMI 30–34.9), 310 (6.4%) grade 2 obese (BMI 35–39.9) and 243 (5.0%) grade 3 obese (BMI >40). ***Results:*** The prevalence of suspicious or malignant nodules (Thy4/Thy5) did not differ across the 5 BMI groups, i.e. it was 6.8% in normal-weight patients, 6.3% in overweight patients, 6.3% in grade 1 obese patients, 4.0% in grade 2 obese patients and 4.2% in grade 3 obese patients ($p = 0.29$). The prevalence of Thy4/Thy5 nodules did not differ when males and females were evaluated separately ($p = 0.22$ and $p = 0.12$, respectively). A significant, lower rate of Thy4/5 cytology was observed in female patients with grade 2–3 obesity (odds ratio 0.51; 95% confidence interval 0.284–0.920; $p = 0.009$). ***Conclusions:*** The results of this study, in a retrospective series of patients with thyroid nodules, do not confirm previous findings reporting an association between obesity and differentiated thyroid carcinoma. Thus, obese patients with nodular thyroid disease should be managed the same as normal-weight patients.

Mario Rotondi and Maria Grazia Castagna contributed equally to this work.

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Introduction

An increased incidence of thyroid cancer has been reported in many countries, including the USA and some countries in Europe [1]. This trend may be partially attributable to medical surveillance or environmental factors and/or lifestyle factors [2, 3]. Among well-recognized risk factors for thyroid cancer (previous radiation exposure, iodine intake, family history of thyroid disease and TSH levels), obesity has been added to the list of potential risk factors [4]. In the USA, the prevalence of obesity, defined as a body mass index (BMI) ≥30, increased from 15.3% in 1995 to 23.9% in 2005 [5]. Obesity has been suggested as a predisposing factor in several human cancers, including thyroid cancer [6]. Thus, one could postulate that the increased incidence of obesity may explain, at least in part, the continuous increase in thyroid cancer.

Several case-control [7–10] and cohort studies [11–19] have reported a positive association between obesity and thyroid cancer [7–19]. A recent, pooled analysis of 5 prospective studies showed that BMI is positively associated with the risk of thyroid cancer both in men and women, thus providing evidence for obesity as an independent risk factor for thyroid cancer [20]. Similar results were reported in 2 recent analyses of case-control studies [21, 22]. The association between obesity and thyroid cancer is found in both genders, provided that the number of patients is sufficiently high [7, 9–11, 13, 16, 17, 19]. At variance with the abovementioned studies, Iribarren et al. [23] did not find an association between obesity and thyroid cancer in a large cohort of subjects undergoing a general health check-up [23]. Similarly, no association between obesity and thyroid cancer was reported in 2 other cohort studies [24, 25].

A limitation of the majority of these studies is that the rate of malignancy in obese patients was compared with that of the general population [7, 9–15, 18, 19]. This methodological approach may have introduced a possible diagnostic bias. In fact, in order to compare the prevalence of thyroid cancer in different populations, it is mandatory to apply similar screening procedures. Because most thyroid cancers are slow-growing and asymptomatic malignancies, their incidence would be found to increase in people who undergo specific screening. This could be the case in obese patients who are frequently evaluated for thyroid dysfunction.

Starting with these considerations, we aimed to investigate the relationship between obesity and the risk for thyroid cancer in patients with thyroid nodules subjected to fine-needle aspiration cytology (FNAC) and stratified according to their BMI. This selection approach should theoretically avoid the above-reported bias as well as the bias connected to surgical series where the criteria for surgery may not be univocal.

Patients and Methods

We retrospectively evaluated the FNAC results of 4,849 unselected patients diagnosed with thyroid nodules from neck ultrasound and subjected to FNAC with adequate cytological results (3,809 females and 1,040 males; mean age 55.9 ± 14.1 years). The study population consisted of Italian subjects recruited at the Department of Medical, Surgical and Neurological Sciences, University of Siena, the Unit of Internal Medicine and Endocrinology of the Fondazione Maugeri, University of Pavia and the Internal Medicine and Endocrinology Unit, University of Brescia.

According to their BMI, calculated at the time of the FNAC, 1,876 (38.7%) patients were of normal weight (BMI 20–24.9), 1,758 (36.2%) were overweight (BMI 25–29.9), 662 (13.7%) were grade 1 obese (BMI 30–34.9), 310 (6.4%) were grade 2 obese (BMI 35–39.9) and 243 (5.0%) were grade 3 obese (BMI >40).

FNAC was performed under ultrasound guidance using a 23/25-gauge needle. The material was air-dried, stained with May-Grünwald Giemsa stain and interpreted by experienced cytologists. Cytological results were reported according to the criteria of the British Thyroid Association (2007) [26], i.e. benign (Thy2), indeterminate (Thy3), suspicious of malignancy (Thy4) and malignant (Thy5) nodules.

FNAC was performed in a single nodule in 1,731/4,849 (35.7%) patients and in >1 nodule in 3,118/4,849 (64.3%) patients. In multinodular glands, the patient was classified according to the most evident level of cytology (Thy2 < Thy3 < Thy4/5). Nodules with inadequate cytology (Thy1) were excluded unless the result of a second FNAC was informative. Six hundred and forty-one patients out of 4,849 (13.2%) were submitted for surgery. The indication for surgery was Thy4/Thy5 cytology, selected Thy3 nodules and Thy2 nodules with compressive symptoms.

Serological testing was available in the Siena cohort of 2,075 patients (43.0%). Serum TSH was measured by chemiluminescent immunometric assay (Immulite 2000, DPC Diagnostic Products Corp., Los Angeles, Calif., USA). Measurement of thyroglobulin antibody (Tg Ab) and thyroid peroxidase antibody (TPO Ab) was performed with a solid-phase, enzyme-labeled, chemiluminiscent sequential immunometric assay (Immulite 2000, Siemens Medical Solutions Diagnostics, Los Angeles, Calif., USA). Values ≤40 IU/ml for Tg Ab and ≤35 IU/ml for TPO Ab were regarded as negative. For both measurements, values ≥100 were considered clearly elevated. As a standard procedure, all patients had given their consent for using their data for research purposes at the time of the FNAC.

Statistical Analysis

For statistical analysis, the Thy4 and Thy5 categories were combined. Epidemiological data are presented as the mean ± SD. The Student t test for independent data or the Mann-Whitney U test were performed for normal or nonnormal variables, respectively. To evaluate significant differences in data frequency, we analyzed contingency tables. Tables larger than 2 × 2 were examined by the

Table 1. Cytological results according to BMI

Weight category of patients	Thy2 (n = 4,215)	Thy3 (n = 352)	Thy4/Thy5 (n = 282)
Normal weight (n = 1,876)	1,616 (86.2)	142 (7.6)	118 (6.2)
Overweight (n = 1,758)	1,506 (85.7)	150 (8.5)	102 (5.8)
Obese 1 (n = 662)	586 (88.6)	36 (5.4)	40 (6.0)
Obese 2 (n = 310)	281 (90.7)	17 (5.4)	12 (3.9)
Obese 3 (n = 243)	226 (93.1)	7 (2.8)	10 (4.1)

Values are expressed as n (%).

χ^2 test, or a numerical approximation of the Fisher exact test when all cell frequencies were >4 or not, respectively. To establish the risk factor for thyroid cancer based on cytology, we performed univariate and multivariate analyses. These were performed in a subgroup of patients (n = 1,885) for whom all variables were available. The following variables were studied by univariate analysis: age at diagnosis, sex, nodule size, TSH levels, single nodule, BMI and antithyroid antibodies. Variables with a p value of <0.1 in the univariate analysis were entered into a multivariate analysis (binary logistic regression) to identify those with independent prognostic significance and to calculate the odds ratio (OR). Statistical analysis was performed using StatView for Windows v5.0.1 (SAS Institute, Cary, N.C., USA) software and SPSS v22.0. A p value of <0.05 was considered statistically significant.

Results

Results of Cytological Series

FNAC was benign (Thy2) in 86.9% of the patients (4,215/4,849), suspicious or malignant (Thy4/Thy5) in 5.8% (282/4,849) and indeterminate (Thy3) in 7.3% (352/4,849). A lower rate of Thy3 and Thy4/Thy5 cytologies was observed in patients with obesity. The prevalence of Thy3 and Thy4/Thy5 nodules, respectively, was: 7.6 and 6.2% in normal-weight patients, 8.5 and 5.8% in overweight patients, 5.4 and 6.0% in grade 1 obese patients, 5.4 and 3.9% in grade 2 obese patients and 2.8 and 4.1% in grade 3 obese patients (table 1). After excluding Thy3 nodules, the prevalence of Thy4/Thy5 nodules was similar in the different BMI groups (p = 0.29; fig. 1), also when males and females were evaluated separately (p = 0.22 and p = 0.12, respectively). However, a trend toward a lower rate of Thy4/Thy5 cytology was observed in grade 2–3 obese patients (fig. 1). As a matter of fact, the prevalence of suspicious/malignant cytology (Thy4/Thy5) in these patients was significantly lower than that observed in the normal-weight patients, i.e. 22/529 (4.1%) versus 118/1,734 (6.8%), respectively (p = 0.029; fig. 1, upper box). The OR using normal-weight patients as a reference (n = 1,734) was 0.59 (95% CI 0.362–0.966; p = 0.01) in patients with grade 2–3 obesity. However, the significance was limited to females patients (OR 0.51; 95% CI 0.284–0.920; p = 0.009).

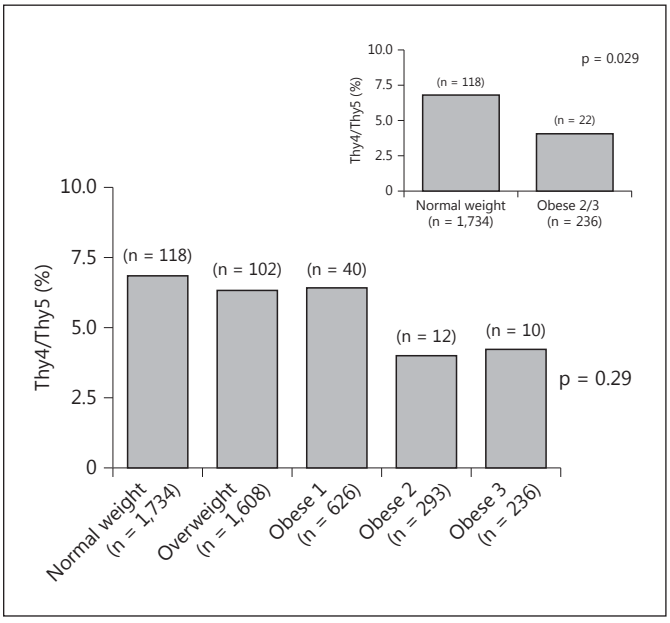

Fig. 1. Prevalence of Thy4/Thy5 cytology according to BMI after excluding Thy3 cytology. The upper box reports the prevalence of Thy4/Thy5 cytology in grade 2 and grade 3 obese patients compared with normal-weight patients.

Risk Factors for Suspicious/Malignant Cytology

We selected potential risk factors for thyroid cancer: age, sex, single nodule, nodule size, TSH levels, BMI and antithyroid antibodies. As shown in table 2, in the univariate analysis, risk factors for cytological diagnosis of suspicious/malignant cytology (Thy4/5) were a younger

Table 2. Univariate/multivariate analysis for risk factors predicting suspicious/malignant cytology in 1,885 patients

	Thy2 (n = 1,780)	Thy4/Thy5 (105)	p value	
			univariate	multivariate[1]
Male sex	314 (17.6)	26 (24.7)	0.06	*0.01*
Age				
Q1 (16–49 years)	433 (24.4)	53 (50.5)		
Q2 (50–60 years)	470 (26.4)	23 (21.9)	*<0.0001*	*0.000*
Q3 (61–69 years)	470 (26.4)	13 (12.4)		
Q4 (70–88 years)	407 (22.8)	16 (15.2)		
TSH, mIU/l				
Q1 (<0.4)	487 (27.4)	24 (22.8)		
Q2 (0.5–0.9)	520 (29.3)	20 (19.1)		
Q3 (1.0–1.6)	364 (20.4)	29 (27.6)	*0.02*	0.21
Q4 (1.7–10)	409 (22.9)	32 (30.5)		
BMI				
Normal weight	699 (39.2)	48 (45.7)	0.05	0.22
Overweight	688 (38.6)	30 (28.5)		
Obese 1	269 (15.2)	21 (20.0)		
Obese 2	91 (5.2)	2 (2.0)		
Obese 3	33 (1.8)	4 (3.8)		
Mean size ± SD, mm	23.3±12.6	20.5±14.9	*0.02*	0.19
Single nodule	323 (18.1)	37 (35.2)	*<0.0001*	*0.01*
TPO Ab-positive (>100 UI/ml)	310 (17.4)	16 (15.2)	0.69	not applicable

Values express n (%) unless otherwise indicated. Thy3 cytology was not included. Italics denote significance.
[1] Binary logistic regression.

age, higher TSH levels, tumor diameter and single nodules but not sex, BMI or antithyroid antibodies. Thy4/Thy5 cytology was significantly higher in single nodules (37/360; 10.2%) than in multinodular goiter (68/1,525; 4.4%; p < 0.0001) and the nodule size was significantly lower in Thy4/Thy5 (20.5 ± 14.9 mm) than in Thy2 cytology (23.3 ± 12.6 mm; p = 0.02). Mean (± SD) TSH levels were 1.55 ± 1.6 mIU/l in patients with suspicious/malignant (Thy4/5) thyroid nodules, i.e. significantly higher (p = 0.016) than in patients with benign cytology (1.48 ± 3.7 mU/l). When TSH levels were divided into quartiles (Q1 <0.4 mIU/l, Q2 0.5–0.9 mIU/l, Q3 1.0–1.6 mIU/l and Q4 1.7–10.0 mIU/l), the prevalence of malignancy (Thy4/Thy5) increased significantly (p = 0.02) with increasing TSH levels, i.e. 4.7% (24/511) in Q1, 3.7% (20/540) in Q2, 7.4% (29/393) in Q3 and 7.3% (32/441) in Q4. Mean (± SD) age was 49.3 ± 17.2 years in patients with suspicious/malignant (Thy4/5) thyroid nodules, significantly lower (p < 0.0001) than in patients with benign cytology (58.8 ± 13.3 years). When age was divided into quartiles (Q1 16–49 years, Q2 50–60 years, Q3 61–69 years and Q4 70–88 years), the prevalence of malignancy (Thy4/Thy5) decreased significantly (p < 0.0001) with increasing age, i.e. 10.9% (53/486) in Q1, 4.6% (23/493) in Q2, 2.7% (13/483) in Q3 and 3.8% (16/423) in Q4. When we evaluated the distribution of TSH levels and age according to BMI, we found that grade 2–3 obese patients were significantly younger (p < 0.001) and had higher serum TSH levels (p = 0.0008; data not shown).

To determine which factors could be considered as independent risk factors for thyroid cancer based on cytology, a binary logistic regression analysis simultaneously analyzing gender, age, type of nodularity, TSH, BMI and nodule size was applied (table 2). Thyroid cancer was inversely related to age (Q1 11–46 years; OR 2.672; 95% CI 1.464–4.877; p = 0.001) and was positively associated with male gender (OR 1.808; 95% CI 1.120–2.919; p = 0.01) and with single nodules (OR 1.766; 95% CI 1.113–2.754; p = 0.01; table 3).

Results of Surgical Series

A total of 641/4,849 (13.2%) patients were sent to surgery, including all patients with Thy4/Thy5 cytology (n = 282), the majority of patients with Thy3 cytology (239/352;

Table 3. OR for thyroid cancer risk according to age, sex and type of nodularity

	OR (95% CI)	p value
Age		
Q1 (16–49 years)	*2.672 (1.464–4.877)*	*0.001*
Q2 (50–60 years)	1.173 (0.605–2.275)	0.63
Q3 (61–69 years)	0.654 (0.309–1.385)	0.26
Q4 (70–88 years)	1	
Male gender	*1.808 (1.120–2.919)*	*0.015*
Single nodule	*1.766 (1.133–2.754)*	*0.012*

Italics denote significance.

67.9%) and selected patients with Thy2 cytology and/or compressive symptoms (140/4,215; 3.3%). Differentiated thyroid carcinoma was confirmed at histology in 323/641 (50.3%) patients (7.8% in Thy2, 25% in Thy3, 71.4% in Thy4 and 100% in Thy5 patients). Also in this subgroup of surgical patients, the rate of thyroid cancer was not different between normal-weight, overweight, grade 1 obese, grade 2 obese and grade 3 obese patients (52.5, 46.7, 55.5, 44.8 and 57.9%, respectively; p = 0.47).

Discussion

Although several case-control [7–10, 23–25] and cohort prospective studies [11–19] have evaluated the association between BMI and thyroid cancer, to our knowledge, this is the first study to investigate this association in a large series of FNAC cytologies. In both the large cytological and the small surgical series, our study does not confirm an association between thyroid cancer and obesity. On the contrary, we observed a trend toward a lower rate of malignancy in more severe obesity (grades 2 and 3) in the cytological series. Our results are at variance with previous studies reporting a positive association between obesity and thyroid cancer [7–22]. Different methodologies may explain the discrepancies. To evaluate the effect of obesity on thyroid cancer risk, the majority of authors performed population-based studies [11–15, 18, 19]. Cancer information and anthropometric data were obtained through different sources such as self-reported, cancer register linkage or death certificates. Participants were considered to be cases if they were diagnosed with primary thyroid cancer during follow-up. The same methodological approach was used in some case-control studies [7, 9, 10] in which thyroid cancer patients were matched with healthy controls selected using different databases (lists of residents, birth registries and electoral rolls). In this setting, anthropometric data and medical history in the control groups were collected during face-to-face interviews using structured questionnaires, which are prone to referral bias concerning both the diagnosis and anthropometric measurements. More importantly, obese patients could represent a population more likely to be screened for thyroid dysfunction, in view of the common belief that hypothyroidism might favor/promote weight gain [27].

This study was specifically designed to avoid selection bias by including unselected patients undergoing FNAC for the discovery of thyroid nodules. An additional strength of our study is that the anthropometric data were collected by physicians in the outpatients clinic at the time of FNAC.

The influence of the age of the patients on thyroid cancer risk remained poorly defined, with conflicting results [28–30]. At multivariate analysis, a highly significant negative correlation between the risk of thyroid cancer and age was observed. Our results are in agreement with a recent prospective study confirming a reduced risk of thyroid cancer with advancing age [31]. Surprisingly, severe obesity that was associated with younger age was associated with a lower rate of thyroid cancer (OR for thyroid cancer: 0.51; 95% CI 0.284–0.920; p = 0.009), suggestive of possible protective role.

We confirmed that Thy4/Thy5 cytology is more frequent in single nodules than in multinodular goiter (OR 1.766; 95% CI 1.113–2.754; p = 0.01). Our results are in agreement with some studies [29, 32], while others report no difference in thyroid cancer prevalence between single nodules and multinodular goiter [33–35]. A recent meta-analysis reported that thyroid cancer is less frequent in multinodular goiter than in single nodules, particularly outside the USA and perhaps in iodine-deficient areas [36]. Male gender (OR 1.808; 95% CI 1.120–2.919; p = 0.01) was also an independent risk factor for thyroid cancer as previously reported in a large cohort of patients with nodular thyroid disease (papillary thyroid cancer in 3.2% of males and in 2.4% of females; p < 0.0001) [29].

In conclusion, all together, our findings indicate that obese patients do not represent a population with a higher risk of thyroid cancer. Whether severe obesity might exert a possible protective role against thyroid cancer is an attractive model, similarly described in premenopausal women with breast cancer [6, 37], which deserves further confirmatory studies.

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Disclosure Statement

The authors state the absence of any conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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