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Relation between Environmental, Lifestyle, Medical and Hormonal Risk Factors and Thyroid Tumour: A Cross-Sectional Study

*Mariangela Mazzone[1], Maria Carmela Di Marcantonio[1], Emira D'Amico[2], Luisa Stellin[3,4], Margherita Legnini[2,5], Alberto D'Aulerio[1,5], Luca Napolitano[2,5], Roberto Cotellese[2,5], Raffaella Muraro[1], Anna Chiara Frigo[6] and Gabriella Mincione[1]**

[1]Department of Innovative Technologies in Medicine and Dentistry, 'G. d'Annunzio' University of Chieti-Pescara, Italy

[2]Department of Medical, Oral and Biotechnological Sciences, 'G. d'Annunzio' University of Chieti-Pescara, Italy

[3]Department of Medicine and Aging Sciences, G. d'Annunzio' University of Chieti-Pescara, Italy

[4]Division of Emergency Surgery, 'SS Annunziata' Hospital, Italy

[5]Division of General Surgery, 'SS Annunziata' Hospital, Italy

[6]Department of Cardiac-Thoracic-Vascular Sciences, University of Padua, Italy

Abstract

Improvements to diagnostic techniques, medical surveillance and screening have allowed early detection of small asymptomatic thyroid lesions, although incidence of large thyroid cancers has increased. The role of environmental, lifestyle, medical and hormonal factors in thyroid cancer development remain under discussion. The aim of this study was to define associations between environmental, lifestyle, medical history and hormonal factors and thyroid tumors. This retrospective cross-sectional population-based study evaluated 246 patients admitted to the 'SS. Annunziata' Hospital in Chieti (Italy) for total thyroidectomy or lobectomy. Twenty-eight variables were collected using questionnaires and clinical records. Logistic regression analysis was used to analyze associations between these patient variables and thyroid histology, to identify novel risk factors, and to generate a multivariate model for thyroid tumour risk assessment. Univariate logistic regression analysis showed significant difference in median age for goiter versus thyroid tumour (Odds Ratio [OR]: 0.980; 95% Confidence Interval [CI], 0.962-0.998; P=0.033). Multivariate logistic regression analysis showed hyperthyroidism significantly associated with lower risk of thyroid tumour (hyperthyroidism versus hypothyroidism: OR: 0.174; 95% CI, 0.044-0.694; euthyroidism *vs.* hypothyroidism: OR: 1.760; 95% CI, 0.678-4.560; P<0.001). These data are supported by significant association with the respective thyroid treatments (in therapy: OR: 0.242; 95% CI, 0.128-0.458; P<0.001). Higher risk of thyroid tumour was significantly associated with single nodule versus multinodular lesions (uninodular: OR: 4.910; 95% CI, 2.240-10.800; P<0.001). Our results suggest that hyperthyroidism and the presence of multinodular lesions represent conditions infrequently associated with thyroid tumors.

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Correspondence:

Gabriella Mincione, Department of Innovative Technologies in Medicine and Dentistry, 'G. d'Annunzio' University of Chieti-Pescara, Via dei Vestini 31, 66100 Chieti, Italy,

E-mail: gabriella.mincione@unich.it

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Introduction

Thyroid carcinoma is the most common cancer of the endocrine system [1]. Its incidence is nearly four-fold in women compared to men. In 2018, the number of new cases of thyroid carcinoma worldwide among women was 436,344, as the fifth most frequent cancer in the world, excluding non-melanoma skin cancer [2]. Over the years, the introduction of new diagnostic techniques (e.g., ultrasonography, computer tomography, magnetic resonance imaging) combined with improvements in medical surveillance and screening programs (predominantly in young and middle-aged populations) has led to increased detection of small asymptomatic lesions [3], although the incidence of large thyroid cancers has also increased [4].

The main risk factors identified for thyroid carcinoma include exposure to ionizing radiation, low iodine intake and obesity [5]. Strong associations have also been reported for history of benign nodules/adenoma and goiter [6]. Female sex hormones appear to have a role too, according to the higher incidence of thyroid carcinoma (and other thyroid dysfunctions) in women compared to men, although several studies have shown conflicting and/or inconclusive data [7]. The role of

lifestyle in terms of potential risk factors such as food and nutrition [6], smoking tobacco, drinking alcohol [8] and physical activity is still unclear. Therefore, we investigated the relationships between thyroid carcinoma and female sex hormones and other potential risk factors.

Sites of Regional Interest (SIRs) and Sites of National Interest (SINs) in Italy are extensive contaminated areas that have been classified by the Italian State as dangerous, and which require remediation of the soil, subsoil and/or surface and underground waters, to avoid damage to the environment and to human health. The SENTIERI Project (Mortality study of residents in Italian polluted sites) has shown that these sites represent a health risk [9], which is also supported by other studies that have analyzed potential environmental risk factors [10]. In the Abruzzo region of Italy, there are three SIRs and one SIN [11]. Therefore, we also questioned whether the exposure to environmental pollutants in such areas could be associated with the prevalence of thyroid cancer.

The recommended intake of iodine for adults is 150 mg/day [12]. However, this requirement varies according to age, and is higher for pregnant and breast-feeding women. The main food source of iodine is fish [13], and living in a seaside town such as those in Abruzzo is known to promote fish consumption. We also investigated whether the proximity to the sea might be an indirect protecting factor against goiter or thyroid cancer.

Thyroid dysfunction is known to contribute to several health issues, including cardiovascular disorders, abnormal glucose intolerance, abnormal liver function, dyslipidemia and psychological symptoms [14]. We therefore examined whether thyroid cancer is associated with any of these disorders. We also investigated potential associations between thyroid conditions (i.e., euthyroidism, hypothyroidism, and hyperthyroidism), nodule numbers, and presence of goiter or thyroid cancer. Finally, we used a multivariate model to determine the predictors of thyroid cancer that are critical for thyroid tumour risk assessment and targeted therapies.

Materials and Methods

Study design

This was a retrospective cross-sectional population-based study that included 246 patients admitted to the Division of General Surgery of 'SS. Annunziata' Hospital in Chieti (Italy) for total thyroidectomy or lobectomy. It was carried out in collaboration with the Department of Innovative Technologies in Medicine and Dentistry of the 'G. D'Annunzio' University of Chieti-Pescara. The study was conducted from 2007 to 2021, with the collection of large numbers of samples from patients undergoing surgical interventions, along with their related medical records. Since 2012, and under our indication, the Residents of the Division of General Surgery administered a questionnaire created specifically for this purpose to patients admitted to the hospital.

The study was approved by the ethical committee of the University "G. D'Annunzio" of Chieti-Pescara.

Study groups

This case study included 466 patients, all local Italians and Caucasians. 220 patients were excluded for lack of complete anamnestic records. For the 246 patients included, 56 showed follicular adenoma, 17 follicular carcinoma, 48 papillary carcinoma, 2 medullary carcinoma and 123 goiters. The term 'goiter' simply refers to the abnormal enlargement of the thyroid gland. It should also be noted that the presence of goiter does not necessarily mean that the thyroid gland was malfunctioning. Goiter can occur under the conditions of hyperthyroidism, hypothyroidism or euthyroidism [15]. Therefore, the patients included were divided into two groups: 123 with thyroid tumors, and 123 with goiter. The patients who showed both goiter and thyroid tumour were only included in the tumour group. Different grouping criteria that have been considered previously were discarded here due to the significant difference between the number of patients affected by follicular adenoma (56), follicular carcinoma (17), papillary carcinoma (48) or medullary carcinoma (2) *vs.* patients affected by goiter (123).

Study sample size determination was not carried out because the number of patients enrolled was conditional on the number of admissions.

Data collection

The patients were individually interviewed by Residents in the Division of General Surgery. The data were collected using a questionnaire created specifically for this purpose. This included questions on the patient demographic data (i.e., name, surname, age, sex, place and date of birth, home town, geographic location, marital status), lifestyle information (i.e., employment, lifetime history of tobacco smoking and number of cigarettes per day, consumption of alcoholic beverages per day, weekly physical activity, daily servings of fruit and vegetables), anthropometric factors, medical conditions, family history of cancer and diabetes, drug treatments and age of onset of thyroid disease. For the female patients, their gynecological and reproductive histories were included (i.e., age at menarche, menopause and first pregnancy, number of pregnancies and full-term pregnancies, oral contraceptives use). The laboratory tests included fasting blood glucose (on venous blood samples collected by venipuncture on the day of hospitalization), complete blood counts, and thyroid function tests (i.e., levels of thyroid-stimulating hormone and its receptor antibody, free triiodothyronine, free thyroxine, and anti-thyroglobulin and anti-thyroid peroxidase antibodies). The histological types of the thyroid tumors were confirmed by histological analysis of the tissue samples.

The data for the patients were anonymized by identifier codes, for privacy reasons. The details that were not included in the analysis here due to lack of complete data were for employment, lifetime history of tobacco smoking, number of cigarettes per day, and oral contraceptives use.

For the statistical analysis, new variables were created from the data collected. The hometown and geographic location were used only to determine the proximity to the sea and whether the patient lived in or near to a SIR or SIN, and then they were deleted from the dataset. The anthropometric factors were used to calculate the Body Mass Index (BMI), and then they were deleted. The reference values used for the BMI were according to the U.S. National Library of Medicine, as (in kg/m^2): BMI<18.5, underweight; 18.5<BMI<24.9, normal; 25<BMI<29.9, overweight; 30<BMI<39.9, obese; and BMI>40, severely obese [16]. The number of pregnancies and full-term pregnancies were used to determine the number of abortions, and then they were deleted. The complete blood counts and drug treatments for non-thyroid diseases were deleted because these were not part of the study purpose. The thyroid function tests were used to establish whether the patients had hyperthyroidism, hypothyroidism or euthyroidism, and then they were deleted. The concurrent diseases were classified according to the system of the human body involved;

Table 1: Demographic, lifestyle and clinical data of the studied groups.

Factor	Group	Categories		OR (95% CI)	*P*-Value
		Goitre (n=123)	Tumor (n=123)		
Age (years) (median [IQR])		57.00 [47.00, 65.50]	52.00 [44.00, 63.00]	0.980 [0.962 - 0.998]	.033*
Sex	M	26 (21.1%)	18 (14.6%)	1	0.185
	F	97 (78.9%)	105 (85.4%)	1.560 [0.807 - 3.030]	
Seaside residence town	yes	31 (25.4%)	41 (33.3%)	1	0.174
	no	91 (74.6%)	82 (66.7%)	0.681 [0.392 - 1.190]	
SIR/SIN residence area	no	80 (65.6%)	90 (73.2%)	1	0.198
	yes	42 (34.4%)	33 (26.8%)	0.698 [0.404 - 1.210]	
Body Mass Index (BMI) (kg/m^2)	underweight + normal	45 (37.2%)	46 (38.7%)	1	0.964
	overweight	46 (38.0%)	45 (37.8%)	0.957 [0.535 - 1.710]	
	obesity + severe obesity	30 (24.8%)	28 (23.5%)	0.913 [0.472 - 1.760]	
Portions of fruit and vegetable (daily)	3-5 portions	48 (41.0%)	53 (46.9%)	1	0.37
	1-2 portions	69 (59.0%)	60 (53.1%)	0.788 [0.467 - 1.330]	
Alcohol consumption (daily)	no	90 (73.8%)	98 (80.3%)	1	0.225
	yes	32 (26.2%)	24 (19.7%)	0.689 [0.377 - 1.260]	
Physical activity (weekly)	regular	23 (19.2%)	18 (15.5%)	1	0.424
	occasional	42 (35.0%)	35 (30.2%)	1.060 [0.497 - 2.280]	
	sedentary	55 (45.8%)	63 (54.3%)	1.460 [0.716 - 2.990]	
Thyroid function	hypothyroidism	12 (9.8%)	12 (9.8%)	1	<.001**
	hyperthyroidism	39 (31.7%)	4 (3.3%)	0.103 [0.028 - 0.378]	
	euthyroidism	72 (58.5%)	107 (86.9%)	1.490 [0.633 - 3.490]	
Type of thyroid disease	multinodular	109 (91.6%)	71 (60.7%)	1	<.001**
	non multinodular	10 (8.4%)	46 (39.3%)	7.060 [3.350 - 14.90]	
Therapy for thyroid disease	no	76 (61.8%)	107 (87.0%)	1	<.001**
	yes	47 (38.2%)	16 (13.0%)	0.242 [0.128 - 0.458]	
Fasting blood glucose (mg/dl) (median [IQR])		95.00 [89.00, 102.00]	92.00 [86.00, 97.00]	0.992 [0.980 - 1.000]	0.187
Diabetes cases in family	no	93 (82.3%)	95 (82.6%)	1	0.951
	yes	20 (17.7%)	20 (17.4%)	0.979 [0.495 - 1.940]	
Metabolic diseases	no	103 (83.7%)	100 (81.3%)	1	0.615
	yes	20 (16.3%)	23 (18.7%)	1.180 [0.613 - 2.290]	
Oncological diseases	no	115 (93.5%)	117 (95.1%)	1	0.583
	yes	8 (6.5%)	6 (4.9%)	0.737 [0.248 - 2.190]	
Neurosensory diseases	no	108 (87.8%)	109 (88.6%)	1	0.843
	yes	15 (12.2%)	14 (11.4%)	0.925 [0.426 - 2.010]	
Cardiovascular diseases	no	72 (58.5%)	80 (65.0%)	1	0.294
	yes	51 (41.5%)	43 (35.0%)	1.320 [0.787 - 2.210]	
Respiratory diseases	no	116 (94.3%)	118 (95.9%)	1	0.556
	yes	7 (5.7%)	5 (4.1%)	0.702 [0.217 - 2.280]	
Gastrointestinal diseases	no	107 (87.0%)	97 (78.9%)	1	0.093
	yes	16 (13.0%)	26 (21.1%)	1.790 [0.907 - 3.540]	
Genital diseases	no	121 (98.4%)	115 (93.5%)	1	0.073
	yes	2 (1.6%)	8 (6.5%)	4.210 [0.875 - 20.20]	
Urinary diseases	no	116 (94.3%)	119 (96.7%)	1	0.361
	yes	7 (5.7%)	4 (3.3%)	0.557 [0.159 - 1.950]	
Other diseases	no	108 (87.8%)	109 (88.6%)	1	
	yes	15 (12.2%)	14 (11.4%)	0.925 [0.426 - 2.010]	0.843

n= number of patients
The continuous variables were expressed as medians with inter quartile ranges and compared using Mann-Whitney U tests.
The categorical data are presented as numbers and percentages, and Pearson's Chi-squared or Fisher's exact tests were used for the statistical analysis.
The odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated using univariate logistic regression.
*P-Value <0.05; **P-Value <0.001

if a system was involved <10 times, the pathologies were classified as "other diseases". No groupings were created for the quantitative variables.

Statistical analysis

The data were collected on a spreadsheet using the Numbers software (version 6; Apple Inc.). Starting from the dataset described above, a subset dataset that included only the female patients was created to investigate the gynecological and reproductive factors. All of the statistical analyses were performed using the R software for Mac OS X (version 3.5.2, GUI 1.70 El Capitan build).

The distributions of the numerical data were tested for normality using Kolmogorov-Smirnov tests. All of the continuous variables showed skewed distributions, and therefore they were expressed as medians with inter quartile ranges and compared using Mann-Whitney U tests. In each category, the categorical data are presented as numbers and percentages, and Pearson's Chi-squared or Fisher's exact tests were used for the statistical analysis. The Odds Ratios (ORs) with 95% Confidence Intervals (95% CIs) were calculated using univariate logistic regression (Table 1, 2).

Two multivariate logistic regression analyses were built including the significant variables, as one for each dataset (overall, women only), which were identified by the tests above and confirmed by univariate logistic regression analysis. Variables that were statistically significant at P<0.05 in the univariate analysis were introduced into the multivariate logistic regression analysis. Collinearity was evaluated using the generalized variance inflation factor (GVIF), as GVIF^(1/[2*Df]), and confirmed using Fisher's exact tests for categorical variables and by Mann-Whitney U tests between categorical and quantitative variables. The patient age was known to be a potential confounder from previous studies [7], and was included in the overall multivariate model.

On the basis of lower Akaike Information Criterion, the best-fit logistic regression models were established to determine the significant risk factors for thyroid tumors. All of the tests were two-tailed and P<0.05 was considered statistically significant.

Results

Study population

This cross-sectional study included 246 patients, 56 of whom had follicular adenoma, 17 follicular carcinoma, 48 papillary carcinoma and 2 medullary carcinoma, along with 123 patients with goiter. Table 1 summarizes the main demographic, lifestyle and clinical characteristics of the study population. Table 2 shows the menstrual and reproductive characteristics of the subset of the women.

The prevalence of females was higher in the tumour than the goiter group (85.4% *vs.* 78.9%), although this did not reach statistical significance (P=0.185). A significant difference was detected between the median age of patients with goiter and those with tumour in the univariate model (OR: 0.980; 95% CI, 0.962-0.998; P=0.033) (Figure 1), although this significant difference was not confirmed by the multivariate logistic model (OR: 0.992; 95% CI, 0.970-1.020; P=0.508).

The frequency distributions for the BMI categories did not show any significant differences between the patients with goiter and with tumors (overweight: OR: 0.957; 95% CI, 0.535-1.710; obese + severely obese: OR: 0.913; 95% CI, 0.472-1.760; P=0.964).

Geographic characteristics

The prevalence of thyroid tumour and goiter among the different cities of origin of the patients did not show any significant association with exposure to environmental pollutants (OR: 0.698; 95% CI, 0.404-1.210; P=0.198). Furthermore, the proximity to the sea did not have any significant protective effects for these patients against occurrence of thyroid tumors (OR: 0.681; 95% CI, 0.392-1.190; P=0.174).

Lifestyle characteristics

No associations were seen between the main lifestyle characteristics and the occurrence of thyroid tumors, here in terms of daily consumption of servings of fruit and vegetables (OR: 0.788; 95% CI, 0.467-1.330; P=0.370), daily alcohol consumption (OR: 0.689; 95% CI, 0.377-1.260; P=0.225), and weekly physical activity (occasional: OR: 1.060; 95% CI, 0.497-2.280; sedentary: OR: 1.460; 95% CI, 0.716-2.990; P=0.424).

Clinical characteristics

None of the groups of concurrent diseases showed any significative associations with thyroid tumors, according to metabolic diseases (OR: 1.180; 95% CI, 0.613-2.290; P=0.615), oncological diseases (OR: 0.737; 95% CI, 0.248-2.190; P=0.583), neurosensory diseases (OR: 0.925; 95% CI, 0.426-2.010; P=0.843), cardiovascular diseases (OR: 1.320; 95% CI, 0.787-2.210; P=0.294), respiratory diseases (OR: 0.702; 95% CI, 0.217-2.280; P=0.556) gastrointestinal diseases (OR: 1.790; 95% CI, 0.907-3.540; P=0.093), genital diseases (OR: 4.210; 95% CI, 0.875-20.20; P=0.073), urinary diseases (OR: 0.557; 95% CI, 0.159-1.950; P=0.361) or 'other diseases' (OR: 0.925; 95% CI, 0.426-2.010; P=0.843).

The proportions (%) of diabetes in the families of these patients were similar for goiter and thyroid tumors, and hence no significant association was seen (OR: 0.979; 95% CI, 0.495-1.940; P=0.951). No significant association was detected for the median values for fasting blood glucose for goiter and thyroid tumour (OR: 0.992; 95% CI, 0.980-1.000; P=0.187).

Thyroid status

Thyroid function (Figure 2), drug assumption as replacement therapies (Figure 3) and type of thyroid disease all showed significant association between these two patient categories in both the univariate (Figure 4 and Table 1, 2) and multivariate logistic regression analyses, for both the full dataset (Table 3) and the subset analysis (Table 4). However, thyroid function and replacement therapies showed

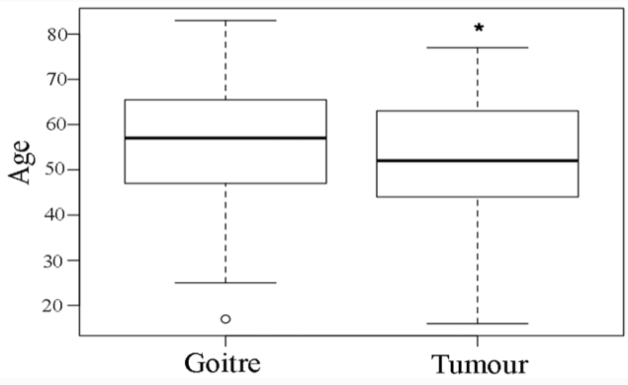

Figure 1: Association between median age of patients and presence of goiter or tumour.
OR: Odds Ratio; 95% CI: 95% Confidence Interval were calculated by univariate logistic regression; *: Statistically significant *vs.* goiter (P<0.05).

Table 2: Demographic, lifestyle and clinical data of the studied groups (women subset).

Factor	Group	Categories		OR (95% CI)	*P*-Value
		Goitre (n=97)	Tumor (n=105)		
Age (years) (median [IQR])		57.00 [48.00, 64.00]	51.00 [45.00, 64.00]	0.979 [0.958 - 1.000]	.045*
Age at menarche (years) (median [IQR])		12.00 [12.00, 13.00]	12.00 [11.00, 13.00]	0.914 [0.737 - 1.130]	0.412
Age at first pregnancy (years) (median [IQR])		23.00 [20.00, 26.00]	24.00 [21.00, 27.00]	1.040 [0.969 - 1.130]	0.255
Age at menopause (years) (median [IQR])		50.00 [46.00, 50.00]	50.00 [46.00, 51.00]	1.030 [0.964 - 1.110]	0.342
Menopausal status	no	31 (33.3%)	52 (50.0%)	1	.019*
	yes	62 (66.7%)	52 (50.0%)	0.500 [0.281 - 0.891]	
Number of full-term pregnancies	0	11 (11.4%)	16 (15.2%)	1	0.629
	1	14 (14.4%)	20 (19.1%)	0.982 [0.351 - 2.740]	
	2	33 (34.0%)	31 (29.5%)	0.646 [0.260 - 1.610]	
	>2	39 (40.3%)	38 (36.2%)	0.670 [0.276 - 1.630]	
Number of abortion	0	60 (69.8%)	61 (68.5%)	1	0.471
	1	19 (22.1%)	16 (18.0%)	0.828 [0.389 - 1.760]	
	≥2	7 (8.1%)	12 (13.5%)	1.690 [0.622 - 4.570]	
Seaside residence town	yes	24 (25.0%)	35 (33.3%)	1	0.196
	no	72 (75.0%)	70 (66.7%)	0.667 [0.360 - 1.230]	
SIR/SIN residence area	no	64 (66.7%)	78 (74.3%)	1	0.237
	yes	32 (33.3%)	27 (25.7%)	0.692 [0.376 - 1.270]	
Body Mass Index (BMI) (kg/m^2)	underweight + normal	38 (40.0%)	41 (40.6%)	1	0.989
	overweight	32 (33.7%)	33 (32.7%)	0.956 [0.496 - 1.840]	
	obesity + severe obesity	25 (26.3%)	27 (26.7%)	1.000 [0.497 - 2.020]	
Portions of fruit and vegetable (daily)	3-5 portions	41 (45.1%)	44 (46.3%)	1	0.863
	1-2 portions	50 (54.9%)	51 (53.7%)	0.950 [0.534 - 1.690]	
Alcohol consumption (daily)	no	80 (83.3%)	89 (85.6%)		0.662
	yes	16 (16.7%)	15 (14.4%)	0.843 [0.392 - 1.810]	
Physical activity (weekly)	regular	14 (15.2%)	14 (14.0%)	1	0.256
	occasional	36 (39.1%)	28 (28.0%)	0.778 [0.319 - 1.890]	
	sedentary	42 (45.7%)	58 (58.0%)	1.320 [0.570 - 3.050]	
Thyroid function	hypothyroidism	10 (10.3%)	12 (11.4%)	1	<.001**
	hyperthyroidism	32 (33.0%)	4 (3.8%)	0.104 [0.027 - 0.396]	
	euthyroidism	55 (56.7%)	89 (84.8%)	1.350 [0.546 - 3.330]	
Type of thyroid disease	multinodular	85 (91.4%)	58 (58.6%)	1	<.001**
	non multinodular	8 (8.6%)	41 (41.4%)	7.510 [3.280 - 17.20]	
Therapy for thyroid disease	no	57 (58.8%)	89 (84.8%)	1	<.001**
	yes	40 (41.2%)	16 (15.2%)	0.256 [0.131 - 0.500]	
Fasting blood glucose (mg/dl) (median [IQR])		94.00 [88.00, 100.00]	92.00 [86.00, 97.00]	0.997 [0.983 - 1.010]	0.728
Diabetes cases in family	no	73 (83.0%)	78 (80.4%)	1	0.656
	yes	15 (17.0%)	19 (19.6%)	1.190 [0.561 - 2.510]	
Metabolic diseases	no	84 (86.6%)	85 (81.0%)	1	0.28
	yes	13 (13.4%)	20 (19.0%)	1.520 [0.711 - 3.250]	
Oncological diseases	no	94 (96.9%)	100 (95.2%)	1	0.546
	yes	3 (3.1%)	5 (4.8%)	1.570 [0.364 - 6.740]	
Neurosensory diseases	no	87 (89.7%)	92 (87.6%)	1	0.644
	yes	10 (10.3%)	13 (12.4%)	1.230 [0.512 - 2.950]	
Cardiovascular diseases	no	55 (56.7%)	67 (63.8%)	1	0.303
	yes	42 (43.3%)	38 (36.2%)	0.743 [0.422 - 1.310]	

Respiratory diseases	no	94 (96.9%)	100 (95.2%)	1	0.546
	yes	3 (3.1%)	5 (4.8%)	1.570 [0.364 - 6.740]	
Gastrointestinal diseases	no	82 (84.5%)	82 (78.1%)	1	0.244
	yes	15 (15.5%)	23 (21.9%)	1.530 [0.747 - 3.150]	
Genital diseases	no	95 (97.9%)	97 (92.4%)	1	0.089
	yes	2 (2.1%)	8 (7.6%)	3.920 [0.811 - 18.90]	
Urinary diseases	no	95 (97.9%)	103 (98.1%)	1	0.936
	yes	2 (2.1%)	2 (1.9%)	0.922 [0.127 - 6.680]	
Other diseases	no	87 (89.7%)	92 (87.6%)	1	0.644
	yes	10 (10.3%)	13 (12.4%)	1.230 [0.512 - 2.950]	

n= number of patients
The continuous variables were expressed as medians with inter quartile ranges and compared using Mann–Whitney U tests.
The categorical data are presented as numbers and percentages, and Pearson's Chi-squared or Fisher's exact tests were used for the statistical analysis.
The odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated using univariate logistic regression.
*P-Value <0.05; **P-Value <0.001

Table 3: Multivariate logistic regression analysis predicting tumour.

Factor	Group	OR	95% CI	*P*-value
Age		0.99	0.970 - 1.020	0.508
Thyroid function	hypothyroidism	1		**<.001****
	hyperthyroidism	0.17	0.044 - 0.694	
	euthyroidism	1.76	0.678 - 4.560	
Type of thyroid disease	multinodular	1		**<.001****
	non multinodular	4.91	2.240 - 10.800	

The dependent variable was the presence of goitre or thyroid tumour.
Variables that were significant at P<0.05 in the univariate analysis of Table 1 were introduced in the model as independent variables.
**P-Value <0.001

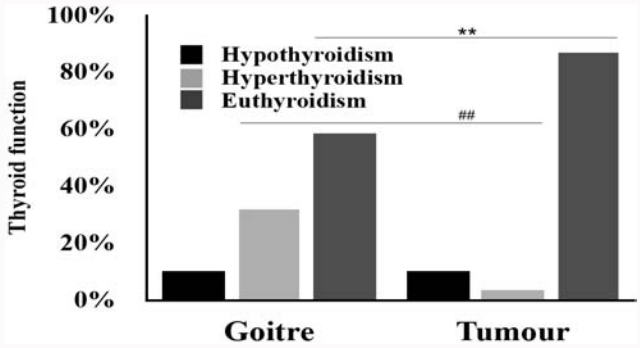

Figure 2: Association between thyroid functions of patients and presence of goiter or tumour.
OR: Odds Ratios; 95% CI: 95% Confidence Intervals were calculated by univariate logistic regression; **: Statistically significant *vs.* goiter (P<0.001); ##: Statistically significant *vs.* goiter (P<0.001)

a collinear relationship and were clinically linked; therefore, the replacement therapies were not included in the multivariate logistic model.

Gynecological and reproductive characteristics

The analysis of the subset of data for the female patients did not show any significant associations between most of the gynecological and reproductive characteristics defined here and thyroid tumors, including for age at menarche (OR: 0.914; 95% CI, 0.737-1.130; P=0.412), age at first pregnancy (OR: 1.040; 95% CI, 0.969-1.130; P=0.255), age at menopause (OR: 1.030; 95% CI, 0.964-1.110; P=0.342), number of pregnancies (1: OR: 0.982; 95% CI, 0.351-2.740; 2: OR: 0.646; 95% CI, 0.260-1.610; >2: OR: 0.670; 95% CI, 0.276-1.630; P=0.629), and number of abortions (1: OR: 0.828; 95% CI, 0.389-1.760; ≥ 2: OR: 1.690; 95% CI, 0.622-4.570; P=0.471).

Table 4: Multivariate logistic regression analysis predicting tumour (women subset).

Factor	Group	OR	95% CI	*P*-value
Menopausal status	no	1	-	0.337
	yes	0.71	0.347 - 1.440	
Thyroid function	hypothyroidism	1	-	**<.001****
	hyperthyroidism	0.19	0.046 - 0.791	
	euthyroidism	1.82	0.657 - 5.020	
Type of thyroid disease	multinodular	1	-	**<.001****
	non multinodular	4.57	1.900 - 11.000	

The dependent variable was the presence of goitre or thyroid tumour.
Variables that were significant at P<0.05 in the univariate analysis of Table 2 were introduced in the model as independent variables.
**P-Value <0.001

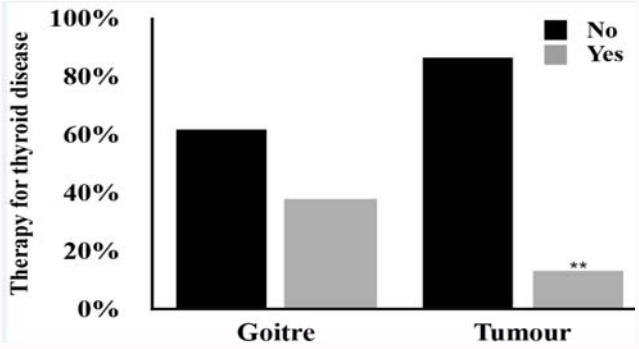

Figure 3: Association between drug assumption by patients as replacement therapies and presence of goiter or tumour.
OR: Odds Ratio; 95% CI: 95% Confidence Interval were calculated by univariate logistic regression; **: Statistically significant *vs.* goiter (P <0.001)

However, and as expected, there was a significant difference for menopausal status between patients with goiter and those with thyroid tumour (OR: 0.502; 95% CI, 0.269-0.926; P=0.019) (Figure 5), although this significant difference was not confirmed by multivariate analysis.

Discussion

In recent decades, the incidence of small asymptomatic thyroid

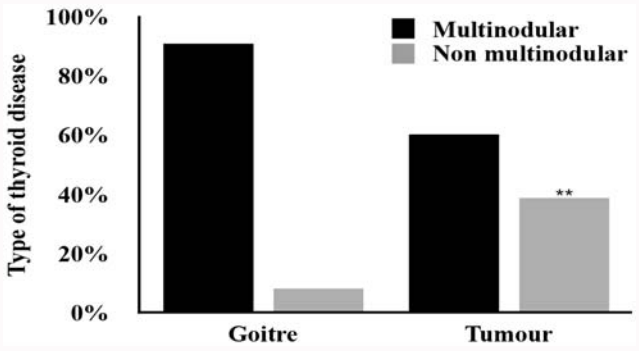

Figure 4: Association between multinodular or non-multinodular thyroid disease and presence of goiter or tumour.
OR: Odds Ratio; 95% CI: 95% Confidence Interval were calculated by univariate logistic regression; **: Statistically significant *vs.* goiter (P<0.001)

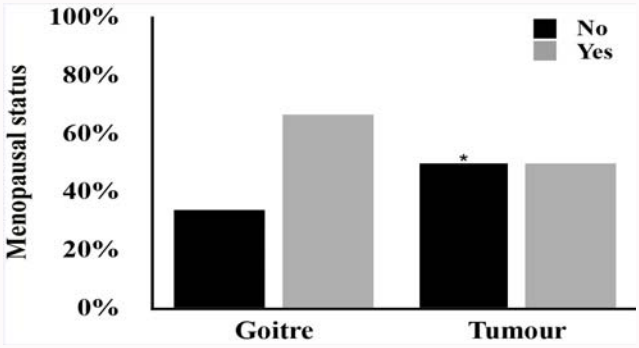

Figure 5: Relationship between women patient menopausal status and presence of goiter or tumour.
OR: Odds Ratio; 95% CI: 95% Confidence Interval were calculated by univariate logistic regression; *: Statistically significant *vs.* goiter (P<0.05)

lesions and large thyroid cancers has increased [3,4]. Despite these changes, to date, the role of environmental, lifestyle, medical and hormonal factors in thyroid cancer development remain poorly defined, with conflicting findings reported in the literature. In the present population-based cross-sectional study, we aimed to evaluate and define any associations between 28 potential risk factors and thyroid tumors.

These data confirmed the greater prevalence of thyroid tumors in women compared to men, as has been described in several studies [2,17]. The median age for patients with goiter was significantly higher than for patients with thyroid tumors, and consequently, the proportion of menopausal women was significantly higher for goiter compared to thyroid tumors. These data suggest that estrogen levels have a critical role in the proliferation and invasion of thyroid cancer cells, through molecular mechanisms that have yet to be defined [18]. However, we showed that there were no significant associations with thyroid tumors seen for number of pregnancies, abortions, and age at menarche, first pregnancy and menopause.

Several studies have investigated the roles of female sex hormones in terms of thyroid cancers in different study cohorts of women, such as in Japan [7] and Europe [1], but to date, these have generally shown conflicting and/or inconclusive data. This is also reported by Cao et al. in their systematic review and meta-analysis, based on 25 epidemiological studies on the association between hormonal and reproductive factors and thyroid cancer risk [19]. Some studies have demonstrated significant associations between late age at menopause and increased risk of papillary thyroid cancer [5,20]. Others have reported positive associations between artificial menopause and thyroid cancer risk [1,6,7], although with conflicting findings for the history of infertility [1,6]. Finally, an epidemiological review showed that the number of births and spontaneous or induced abortions are not associated with thyroid carcinoma risk [6]. In their close examination, Cao et al. could only suggest an association between older age at menopause and parity and increased risk of thyroid cancer, and the potential protective role against thyroid cancer provided by longer duration of breast feeding [19]. The bidirectional relationship between breast and thyroid cancer and their higher incidence in women suggest and support common putative roles for estrogen levels and hormonal signaling pathways [21,22]. The close association between thyroid disorders, especially Hashimoto's thyroiditis, and polycystic ovary syndrome provide further evidence of complex molecular mechanisms and genetic susceptibility behind the still undefined cross-talk between sex hormones and the thyroid gland [23]. The potential reason for these conflicting and/or inconclusive data might be attributed to different study designs with differing inclusion and exclusion criteria, varying ethnic backgrounds of the patients enrolled, with distinct habits, different administrations of contraceptive and hormone therapy, and others [19]. In our opinion, further studies can improve the current knowledge through accurate measurement of sex hormones levels and investigation of their putative association with thyroid disease.

The major findings of this study concern thyroid function, drug assumption for replacement therapy, and type of thyroid disease. The data from the multivariate logistic regression analysis show that hyperthyroidism is significantly associated with lower risk of thyroid tumors, and this is supported by the significant associations with the respective thyroid treatments. Thyroid hormones can induce or inhibit gene transcription, and many pathways that are influenced by thyroid hormones will have roles in tumorigenesis. Indeed, the Rotterdam Study showed positive association between higher free thyroxine levels and increased risk of any solid cancers [24].

Furthermore, the multivariate logistic regression analysis here shows that significantly higher risk of thyroid tumors is associated with presence of a single nodule, rather than for multinodular lesions. In agreement with this, Kwong et al. [25] demonstrated that the prevalence of multinodularity increases with age, but also that multinodularity reduces the risk that these nodules will be cancerous in a population of adult American patients. Also, for patients with multiple nodules, the cancer rate per nodule were shown to be inversely proportional to the number of nodules present [26]. Finally, a retrospective analysis of thyroid nodules in a China population study drew attention to an association between younger patients with nodular thyroid disease (nodules ≤ 1 cm) with higher TSH levels and TgAb positivity and the increased risk of thyroid cancer [27].

The frequency distribution for the full range of BMI categories showed no significant differences between the patients with goiter and those with thyroid cancers, which is not in agreement with the previous identification of obesity as a risk factor [6]. Similarly for alcohol consumption and thyroid tumors, with no significant association seen in the present study. Indeed, the true effects of alcohol consumption on thyroid tumors is elusive, with two recent meta-analysis [28,29] and a systematic literature review reporting an inverse association between alcohol consumption and thyroid cancer

risk [30]. However, the mechanism of action behind any protective effects that alcohol might have against thyroid tumors remains poorly understood.

The present study also did not show any correlation between physical activity and thyroid tumors. The health benefits of physical activity are well established, although very few studies have investigated associations between physical activity and thyroid cancers specifically. However, a recent Italian case-control study showed that daily walking duration is associated with lower risk of thyroid cancer [31]. It would be interesting to analyze this association in more detail, by including specific laboratory tests, such as circulating levels of the thyroid hormones pre-workout and post-workout, which might clarify the potential biological mechanisms behind this.

Potential antiproliferative roles of specific vegetable constituents, such as flavonoids, phenols and carotenoids, on cancer cells have been described, while potential protective effects of fruit consumption on thyroid tumour onset remain controversial [6]. In the present study, the diet habits did not appear to have any significant roles on thyroid tumour occurrence.

The carcinogenic potential of exposure to several toxic compounds in the SIRs and SINs in the Abruzzo region of Italy are well established, such as metals (arsenic, cadmium, and manganese), nitrates and dioxins. The SENTIERI report showed causal associations only for malignant pleural cancer and residence in SIRs and SINs contaminated by asbestos or other mineral fibers, and around mines and quarries. However, this was based on some limited evidence for causal associations between 17 causes of death and a total of 7 categories of environmental exposure in polluted area [9]. An up-to-date review by Fiore et al. [32] described how several environmental agents can act as cancer promoters. Particularly with regard to metals, their mechanism of action consists of induction of secretion of T-helper (Th) 1 chemokines into the thyroid and increase of the effects of important Th1 cytokines, with a consequent inflammatory reaction in the thyroid gland [32]. In contrast, high levels of nitrates can lead to overproduction of cellular nitric oxide, genomic instability and thyroid hypertrophy [32]. The data for the present study did not show any significative associations between environmental pollutants and thyroid tumors, although in light of the results from other studies, further research using appropriate epidemiological data would be required.

In the present study, the proximity to the sea did not appear to have any indirect protective effects on the occurrence of thyroid tumors. A decade ago, several studies supported the hypothesis that iodine deficiency is a risk factor for goiter and follicular thyroid carcinoma [6,33]. Recent studies have also demonstrated that higher intake of iodine has positive effects on papillary thyroid carcinoma [34,35], especially in patients from high iodinated regions [34]. The diet of coastal areas is rich in fish and other seafood, and has been associated with increased incidence of thyroid cancer [6,36]. A putative protective role of fish and seafood consumption occurred only in an endemic goiter area with iodine deficiency [6]. Furthermore, fish can contain several contaminants that might represent risk factors for thyroid cancer [33]. Therefore, the protective role of iodine in thyroid cancer development is still unclear and deserves further investigation.

Thyroid dysfunction can lead to different health problems, including dyslipidemia, cardiovascular disorders, abnormal glucose intolerance, psychological symptoms, and others [14]. Furthermore, several studies have shown significant association between increased thyroid cancer risk and presence of insulin resistance, dysglycemia and hypertension [37], hepatitis C virus infection [38], diabetes mellitus [39] and Crohn's disease [40]. In the present study, none of the concurrent diseases of these patients showed any significant associations with thyroid tumors, which is contrary to what is indicated by the European Society for Medical Oncology Clinical Practice Guidelines [41]. Furthermore, in the present study, the presence of diabetes in a family did not have any effects on the occurrence of thyroid tumors. A significant difference was indicated for median values of fasting blood glucose between the patients with goiter and those with tumors, although this was not confirmed in the univariate logistic regression.

Although this study has some limitations, which are mainly related to the study size and that it is not possible to infer causality due to the cross-sectional nature of the research design, it highlights that the presence of hyperthyroidism and of multinodular lesions represent conditions infrequently associated with thyroid tumors. This addition of these data to the literature can provide a risk assessment for thyroid tumorigenesis and nodules evolution and further assistance to doctors and patients for the available management options, and in particular, for the treatment of nodules. Furthermore, although our study did not find any statistically significant association between the exposure of patients to several toxic compounds in the SIRs and SIN in the Abruzzo region and the onset of thyroid diseases, to the best of our knowledge, it is the first to investigate this particular association in this area.

This study can be considered as preliminary, such that it indicates the need for follow-up with another larger study. However, the data here are useful towards the formulation of first hypotheses that can be further supported by subsequent experimental studies.

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