Factors Associated with Malignancy in Hyperthyroid Patients

Rhea Karla P. Panilagao, MD,[1] Ceryl Cindy Y. Tan, MD,[2] Gorgonia P. Panilagao, MD[2]

Abstract

Introduction. Hyperthyroidism was thought to lower thyroid cancer risk due to TSH suppression, potentially leading to overlooked diagnoses. This study examines clinical factors linked to thyroid cancer in hyperthyroid patients who have undergone thyroidectomy.

Objective. This study determined the clinical factors associated with malignancy among patients with hyperthyroidism who underwent thyroidectomy in a tertiary hospital.

Methods. This analytical cross-sectional study reviewed electronic biopsy results of adult patients who underwent thyroidectomy from January 2009 to December 2019 for hyperthyroidism secondary to Graves' Disease, Solitary Toxic Adenoma or Multinodular Toxic Goiter. It considered factors linked to thyroid cancer, its prevalence, and clinical features associated with aggressive tumor behavior.

Results. Sixty hyperthyroid patients who underwent thyroidectomy were included, 12 of whom have thyroid cancer. Each increase in the initial free thyroxine (FT4) leads to increased likelihood of thyroid cancer by 1.02 times (95% CI 1.001-1.03, *p=0.044*). The presence of thyroid nodule is associated with 24 times (95% CI 2.67-3275.62, *p=0.002*) higher risk of thyroid cancer, while every unit increase in mm for nodule diameter increases thyroid cancer odds by 1.04 times (95% CI 1.01-1.07, *p=0.022*). An FNAB pre-op diagnosis of malignancy is associated with having histopathologic diagnosis of thyroid cancer increased by 40 times (95% CI 2.42-6668.98, *p=0.007*). Although aggressive tumor behavior was noted among those with a younger age on average (36.35 vs 46.75 years), higher initial FT4 (95.97 vs 23.55 pmol/L), and those with sizeable diameter of multinodular goiter (95 mm vs 20 mm), only the high FT4 was statistically significant.

Conclusion. Initial FT4, thyroid nodules, nodule size, and pre-operative FNAB finding of a malignancy were the factors associated with thyroid cancer in hyperthyroid patients who underwent thyroidectomy. Furthermore, those with aggressive tumor behavior had higher initial FT4 levels.

Keywords. hyperthyroidism, thyroid malignancy

Introduction

Hyperthyroidism is a state of overactive thyroid gland producing clinical manifestations reflective of excessive thyroid hormones. The common causes are TSH receptor overstimulation by autoantibodies that act as agonists, Graves' Disease, and autonomous thyroid hormone secretion by multinodular toxic goiter or a solitary thyroid adenoma.

In the past, hyperthyroidism was believed to be protective of thyroid cancer since TSH suppression in these patients lead to a lower incidence of malignancy than that observed in euthyroid patients.[1] In contrast, most patients with thyroid cancer are euthyroid or have clinical/subclinical hypothyroidism.[2] This view is slowly being supplanted by reports that hyperthyroidism is associated with notable rates of thyroid malignancy.[3] It has been reported that thyroid cancer occurs in 0.76% to 8.7% of the glands removed for treatment of thyrotoxicosis.[4] Furthermore, in the evaluation of thyroid nodules >1cm, American Thyroid Association (ATA) recommends that radionuclide thyroid scan should be obtained if the serum TSH is subnormal to document whether the nodule is hyperfunctioning ("hot"), iso-functioning ("warm") or non-functioning ("cold"). Since hyperfunctioning nodules rarely harbor malignancy, no cytologic evaluation is deemed necessary.[5] Thus, the

[1] Internal Medicine Department, Chong Hua Hospital
[2] Section of Endocrinology Diabetes and Metabolism, Internal Medicine Department, Chong Hua Hospital
Corresponding Author: Rhea Karla P. Panilagao, MD eMail: rheapanilagao@gmail.com

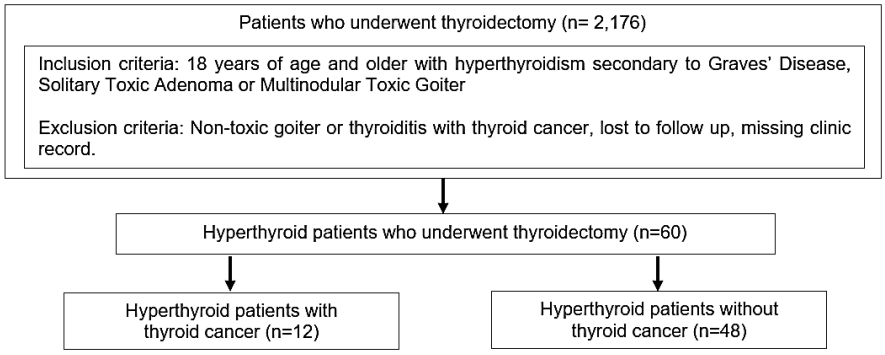

Figure 1. Flow Diagram of the Study Population

diagnosis of thyroid malignancy in hyperthyroid patients may be overlooked.

This study aimed to identify clinical predictors of malignancy by evaluating the clinical profiles and histopathologic characteristics of patients with hyperthyroidism who were found to have concurrent thyroid cancer following thyroidectomy. To our knowledge, this is the first study in the Philippines to specifically investigate the coexistence of hyperthyroidism and thyroid cancer.

Methodology

Study Design and Population. In this analytical, cross-sectional chart review, we screened a total of 60 charts of all patients 18 years of age and older who underwent thyroidectomy from January 2009 to December 2019 for hyperthyroidism secondary to Graves' Disease, Solitary Toxic Adenoma or Multinodular Toxic Goiter. A total of 2,116 charts were excluded for patients who underwent thyroidectomy for non-toxic goiter or thyroiditis with thyroid cancer. No patients were excluded for missing clinic record (*Figure 1*). The protocol underwent review and assessment by the Institutional Review Board and Ethics Committee of Chong Hua Hospital and approved by the Medical Director of the same institution.

An a priori calculation indicated that 95 patients were required to detect an odds ratio of 3.53 for the association between preoperative TMNG and malignancy at $\alpha=0.05$ and 80% power.[6,7] Only 60 charts met eligibility criteria and were therefore included in the study.

The charts were meticulously examined to extract pertinent details, focusing on various critical aspects of the patient's care. This comprehensive review included emergency notes (evaluating initial assessments, treatment protocols, and immediate responses to emergency treatments), diagnostic Information (analyzing test results, imaging reports, and clinical evaluations to understand the patient's condition and progress), consultations (reviewing notes from specialist consultations and interdisciplinary team meetings to ensure that expert opinions and recommendations were considered and integrated into the care plan), and discharge reports (assessing the summaries and instructions provided upon discharge to confirm that they accurately reflect the patient's status and provide clear guidance for follow-up care).

This thorough analysis aimed to ensure that all relevant information were captured and that the care provided was consistent, comprehensive, and well-documented. The review elected to include only data relevant to the objectives of the study and omitted personal and identifying information.

Statistical Analysis. Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for categorical variables (nominal/ordinal), mean and standard deviation for normally distributed interval/ratio variables, and median and range for non-normally distributed interval/ratio variables.

Independent t-test, Mann-Whitney U test and Fisher's Exact test were used to determine the difference of mean, median and frequency between groups, respectively.

Odds ratios and the corresponding 95% confidence intervals from binary logistic regression were computed to determine the association between patient features and presence of thyroid cancer, and between patient features and presence of aggressive tumor. A multivariate model was not feasible since many of the factors were highly correlated.

No subgroup, interaction, or sensitivity analyses were performed. All valid data was included in the analysis. Missing variables were neither replaced nor estimated.

A retrospective power calculation was performed for the primary nodule-count comparison (0 vs. 1–2 nodules), using the observed odds ratio (OR 24.56), group sizes (n_1=19 without nodules; n_2=21 with 1–2 nodules), and a 0.5 continuity correction for the zero cell. Using the pwr.2p2n.test() function in R (version 4.2.2), this yielded an achieved power of 89.9% at $\alpha=0.05$. Null hypothesis was rejected at $\alpha=0.05$ level of significance. R 4.2.2 was used for data analysis.

Results

Our study shows that thyroid cancer had a prevalence of 20 per 100 hyperthyroid patients who have undergone thyroidectomy in our hospital (*Table I*). The data offers a comprehensive snapshot of a patient cohort undergoing thyroid treatment. The average age of the patients is

Table I. Prevalence of thyroid cancer among hyperthyroid patients who underwent thyroidectomy.

	n/N	Prevalence (95% CI)
Prevalence	12/60	20 (10.78, 32.33)

40.83 years, with a significant predominance of females (80%) over males (20%). The average BMI is 24.22 kg/m², with 5% classified as underweight, 33.33% as normal weight, 23.33% as overweight, and 38.33% as obese. Most patients have never smoked (91.67%), and only a small fraction has a family history of thyroid cancer (1.67%). The primary causes of hyperthyroidism in the cohort are Grave's disease (46.67%), multinodular toxic goiter (43.33%), and toxic adenoma (10%). Initial FT4 levels vary widely, with a mean of 35.04 pmol/L. The number of thyroid nodules ranges from none in 31.67% of patients to three or more in 33.33%. Nodule sizes vary

Table II. Demographic and clinical features of patients with hyperthyroidism who underwent thyroidectomy.

	Mean ± SD; Median (Range); Frequency (%)			*P*
	Total (n=60)	With Thyroid CA (n=12)	No Thyroid CA (n=48)	
Age, years	40.83 ± 13.43	43.25 ± 14.07	40.23 ± 13.35	0.491*
Gender				0.234‡
Male	12 (20)	4 (33.33)	8 (16.67)	
Female	48 (80)	8 (66.67)	40 (83.33)	
BMI, kg/m^2	24.22 ± 3.76	24.23 ± 2.64	24.22 ± 4.03	0.994*
Underweight	3 (5)	0	3 (6.25)	0.700‡
Normal	20 (33.33)	3 (25)	17 (35.42)	
Overweight	14 (23.33)	4 (33.33)	10 (20.83)	
Obese	23 (38.33)	5 (41.67)	18 (37.50)	
Smoking history				0.134‡
Never	55 (91.67)	10 (83.33)	45 (93.75)	
Current	4 (6.67)	1 (8.33)	3 (6.25)	
Past	1 (1.67)	1 (8.33)	0	
Family history of thyroid cancer				>0.999‡
No	59 (98.33)	12 (100)	47 (97.92)	
Yes	1 (1.67)	0	1 (2.08)	
Hyperthyroid or thyrotoxicosis etiology				>0.999‡
Grave's disease	28 (46.67)	6 (50)	22 (45.83)	
Multinodular toxic goiter	26 (43.33)	5 (41.67)	21 (43.75)	
Toxic adenoma	6 (10)	1 (8.33)	5 (10.42)	
Initial FT4	35.04 (11.31-188)	68.89 (11.31-188)	34.21 (11.43-168(	0.108§
Number of thyroid nodules				**0.007**‡
0	19 (31.67)	0	19 (39.58)	
1-2	21 (35)	8 (66.67)	13 (27.08)	
≥3	20 (33.33)	4 (33.33)	16 (33.33)	
Thyroid nodules				
Size, mm				
Grave's disease	0 (0-62)	15.50 (4.50-42)	0 (0-62)	**<0.001**§
Toxic adenoma	20.33 ± 15.50	14 ± 0	21.6 ± 16.98	0.704*
Multinodular goiter**	23 (7-110)	48 (8-110)	23 (7-50)	0.254§
Pre-operative FNAB [n=14]				**0.007**‡
Benign	6 (42.86)	1 (12.50)	5 (83.33)	
AUS/FLUS	0	0	0	
Follicular neoplasm	1 (7.14)	0	1 (16.67)	
Suspicious for malignancy	2 (14.29)	2 (25)	0	
Malignancy	5 (35.71)	5 (62.50)	0	
Non-diagnostic	0	0	0	
Anti-thyroid medication pre-surgery				
Drug				0.692‡
PTU	8 (13.33)	1 (8.33)	7 (14.58)	
Methimazole	46 (76.67)	11 (91.67)	35 (72.92)	
Carbimazole	1 (1.67)	0	1 (2.08)	
Duration, years	4 (0.08-30)	2.50 (0.08-20)	4 (0.08-30)	0.271§
Extent of surgery				
Thyroidectomy				0.182‡
Total	51 (85)	12 (100)	39 (81.25)	
Subtotal	9 (15)	0	9 (18.75)	

Statistical tests used: * - Independent T-test; §–Mann-Whitney U test; ‡–Fisher's exact test

**Largest nodule on Thyroid ultrasound.

AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FNAB, fine needle aspiration biopsy; LN, lymph node; PTU, propylthiouracil.

Table III. Clinical and histopathologic features of thyroid cancer in hyperthyroid patients who underwent thyroidectomy (n=12)

	Frequency (%); Median (Range)
Cancer type	
Papillary	6 (50)
Micropapillary	6 (50)
Tumor size, mm	9.50 (6-30)
Bilaterality	
Unilateral	8 (66.67)
Multifocal	4 (33.33)
Metastasis	
No	8 (66.67)
Yes	4 (33.33)
Regional	4 (100)
Distal	0
Number of RAI treatments	1 (0-2)
Recorded recurrence	
No	11 (91.67)
Yes	1 (8.33)
Regional	1 (100)
Distal	0
Aggressive tumor behavior*	4 (33.33)

*With features of metastasis, ≥2 RAI treatments, or recurrence.
LN, lymph node; RAI, radioactive iodine.

based on the condition, with toxic adenomas averaging 20.33 mm in size. Pre-operative fine needle aspiration biopsies showed a mix of benign cases, suspicious findings, and malignancies. Anti-thyroid medications used pre-surgery include methimazole (76.67%) and PTU (13.33%), with treatment durations averaging four years. The majority of patients underwent total thyroidectomy (85%), while a smaller group had subtotal thyroidectomy (15%).

We grouped the study population into those identified to have thyroid cancer (n=12) and those without (n=48), and found the following to be significantly different between the two: (1) the proportion of patients with 1-2 thyroid nodules were higher among thyroid cancer group (66.67% vs 27.08%, *p=0.007*) and only those without thyroid cancer were noted to have no thyroid nodules (39.58%); (2) likewise, the median thyroid nodule size in mm was higher in the thyroid cancer group, specifically those with Graves' Disease (15.5 [4.5-42) vs 0 [0-62]; *p<0.001*); (3) from those with pre-operative FNAB (n=14), only those with thyroid cancer were assessed to be malignant, with only one patient initially assessed as benign and two patients suspicious for malignancy (*p=0.007*).

Table III showed the clinical and histopathologic features of thyroid cancer in hyperthyroid patients. Half have papillary type and the other half have micropapillary type of cancer. Eight (66.67%) were unilateral only, four (33.33%) have metastasis, all regional; and only one have

Table IV. Association of patient features with presence of thyroid cancer

	Crude OR (95% CI)	*p*
Age, years	1.02 (0.97-1.07)	0.484
Gender		
Male	Reference	-
Female	0.40 (0.10-1.78)	0.206
BMI, kg/m^2		
Underweight	Reference	-
Normal	1.40 (0.10-204.31)	0.831
Overweight	3 (0.22-435.70)	0.454
Obese	2.08 (0.16-296.30)	0.620
Smoking history		
Never	Reference	-
Current	1.50 (0.07-13.19)	0.737
Past	13 (0.65-1953.55)	0.092
Family history of thyroid cancer		
Yes	1.27 (0.01-25.29)	0.889
No	Reference	-
Hyperthyroid or thyrotoxicosis etiology		
Grave's disease	Reference	-
Multinodular toxic goiter	0.87 (0.22-3.33)	0.841
Toxic adenoma	0.73 (0.03-5.84)	0.794
Initial FT4	1.02 (1.001-1.03)	**0.044**
Number of thyroid nodules		
0	Reference	-
1-2	24.56 (2.67-3275.62)	**0.002**
≥3	10.64 (1.02-1449.16)	**0.048**
Thyroid nodule		
Size, mm	1.04 (1.01-1.07)	**0.022**
Pre-operative FNAB		
Benign	Reference	-
AUS/FLUS	-	-
Follicular neoplasm	1.22 (0.01-42.76)	0.916
Suspicious for malignancy	18.33 (0.87-3184.52)	0.062
Malignancy	40.33 (2.42-6668.98)	**0.007**
Non-diagnostic	-	-
Anti-thyroid medication pre-surgery		
Drug		
PTU	Reference	-
Methimazole	2.20 (0.34-43.48)	0.483
Carbimazole	1.67 (0.01-57.02)	0.789
Duration, years	0.95 (0.83-1.06)	0.445
Extent of surgery		
Thyroidectomy		
Total	Reference	-
Subtotal	0.17 (0.001-1.49)	0.125

Note: A multivariate model was not feasible since many of the factors were highly correlated.

recorded recurrence. Four (33.33%) were considered to have aggressive tumor behavior.

The following features were associated with thyroid cancer (*Table IV*): initial FT4, presence of thyroid nodules, nodule size on ultrasound and pre-operative FNAB finding of a malignancy. Specifically, (1) each increase in initial FT4 leads to increased likelihood of thyroid cancer

Table V. Demographic and pre-operative clinical features of hyperthyroid patients with aggressive versus non aggressive tumor behavior

	Mean ± SD; Median (Range); Frequency (%)			
	Total (n=12)	Aggressive (n=4)	Non-aggressive (n=8)	*P*
Age, years	43.25 ± 14.07	36.35 ± 16.23	46.75 ± 12.56	0.240*
Gender				>0.999‡
Male	4 (33.33)	1 (25)	3 (37.50)	
Female	8 (66.67)	3 (75)	5 (62.50)	
BMI, kg/m^2	24.37 ± 2.64	23.77 ± 2.62	24.46 ± 2.80	0.693*
Underweight	0	0	0	0.785‡
Normal	3 (25)	1 (25)	2 (25)	
Overweight	4 (33.33)	2 (50)	2 (25)	
Obese	5 (41.67)	1 (25)	4 (50)	
Smoking history				>0.999‡
Never	10 (83.33)	4 (100)	6 (75)	
Current	1 (8.33)	0	1 (12.50)	
Past	1 (8.33)	0	1 (12.50)	
Family history of thyroid cancer				>0.999‡
No	12 (100)	4 (100)	8 (100)	
Yes	0	0	0	
Hyperthyroid or thyrotoxicosis etiology				0.343‡
Grave's disease	6 (50)	1 (25)	5 (62.50)	
Multinodular toxic goiter	5 (41.67)	2 (50)	3 (37.50)	
Toxic adenoma	1 (8.33)	1 (25)	0	
Initial FT4	68.55 ± 51.86	95.97 ± 54.99	29.55 ± 38.33	**0.044***
Number of thyroid nodules				>0.999‡
0	0	0	0	
1-2	8 (66.67)	3 (75)	5 (62.50)	
≥3	4 (33.33)	1 (25)	3 (37.50)	
Thyroid nodules				
Size, mm				
Grave's disease	15.50 (4.50-42)	35	10 (4.5-42)	0.380§
Toxic adenoma	14 ± 0	14 ± 0	0	-
Multinodular goiter**	48 (8-110)	95 (80-110)	20 (8-48)	0.200§
Pre-operative FNAB [n=8]				>0.999‡
Benign	1 (12.50)	0	1 (16.67)	
AUS/FLUS	0	0	0	
Follicular neoplasm	0	0	0	
Suspicious for malignancy	2 (25)	0	2 (33.33)	
Malignancy	5 (62.50)	2 (100)	3 (50)	
Non-diagnostic	0	0	0	
Anti-thyroid medication pre-surgery				
Drug				>0.999‡
PTU	1 (8.33)	0	1 (12.50)	
Methimazole	11 (91.67)	4 (100)	7 (87.50)	
Carbimazole	0	0	0	
Duration, years	4.97 ± 5.87	6.83 ± 8.99	4.03 ± 4.07	0.462*
Extent of surgery				
Thyroidectomy				>0.999‡
Total	12 (100)	4 (100)	8 (100)	
Subtotal	0	0	0	
LN dissection				0.236‡
Without	9 (75)	2 (50)	7 (87.50)	
With	3 (25)	2 (50)	1 (12.50)	

Statistical tests used: * - Independent T-test; §–Mann-Whitney U test; ‡–Fisher's exact test
**Largest nodule.
AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FNAB, fine needle aspiration biopsy; LN, lymph node; PTU, propylthiouracil.

by 1.02 times (95% CI 1.001-1.03, *p=0.044*); (2) patients with at least one nodule were at least 24 times (95% CI 2.67-3275.62, *p=0.002*) more likely to have thyroid cancer, while (3) those with three or more are 10 times (95% CI 1.02-1449.16, *p=0.048*) more likely; (4) every unit increase in mm for nodule diameter increases thyroid

Table VI. Association of demographic and pre-operative clinical features with presence of aggressive tumor

	Crude OR (95% CI)	*p*
Age, years	0.94 (0.84-1.03)	.226
Gender		
Male	Reference	-
Female	1.80 (0.14-46.24)	.667
BMI, kg/m^2		
Underweight	-	-
Normal	Reference	-
Overweight	2 (0.09-69.06)	.661
Obese	0.50 (0.01-17.47)	.676
Smoking history		
Never	Reference	-
Current	0.48 (0.003-11.39)	.663
Past	0.48 (0.003-11.39)	.663
Family history of thyroid cancer		
Yes	-	-
No	-	-
Hyperthyroid or thyrotoxicosis etiology		
Grave's disease	Reference	-
Multinodular toxic goiter	3.33 (0.22-92.98)	.398
Toxic adenoma	11 (0.38-2021.25)	.164
Initial FT4	1.02 (0.999-1.08)	.064
Number of thyroid nodules		
0	-	-
1-2	Reference	-
≥3	0.56 (0.02-7.17)	.667
Thyroid nodule		
Size	1.05 (1.004-1.15)	.112
Pre-operative FNAB [n=8]		
Benign	Reference	-
AUS/FLUS	-	-
Follicular neoplasm	-	-
Suspicious for malignancy	0.60 (0.002-142.76)	.821
Malignancy	2.14 (0.07-369.65)	.667
Non-diagnostic	-	-
Anti-thyroid medication pre-surgery		
Drug		
PTU	Reference	-
Methimazole	1.80 (0.08-286.50)	.727
Carbimazole	-	-
Duration, years	1.09 (0.88-1.41)	.435
Extent of surgery		
Thyroidectomy		
Total	-	-
Subtotal	-	-
LN dissection		
Without	Reference	-
With	7 (0.45-211.31)	.184

Note: A multivariate model was not feasible since many of the factors were highly correlated

cancer odds by 1.04 times (95% CI 1.01-1.07, *p=0.022*); (5), while FNAB pre-operative diagnosis of malignancy is associated with having histopathologic diagnosis of thyroid cancer increased by 40 times (95% CI 2.42-6668.98, *p=0.007*).

The initial FT4 level (95.97 vs 23.55 pmol/L, *p=0.044*) was statistically significant between those with the four aggressive and eight non-aggressive tumors, with higher FT4 levels seen in those with aggressive tumor (*Table V*). Clinically, a non-significant trend among those with aggressive tumor behavior was noted among those with a younger age on average (36.35 vs 46.75 years, *p=0.240*), and those with sizable diameter of multinodular goiter (95 mm vs 20 mm, *p=0.200*).

We were unable to determine an association with the selected demographic and pre-operative clinical features with the presence of an aggressive tumor in the 12 patients who underwent thyroidectomy and with thyroid cancer (*Table VI*).

Discussion

Hyperthyroidism is a non-cancerous disease that is usually managed medically with antithyroid medications. In fact, hyperthyroidism was believed to be least likely to be associated with malignancy due to protective effect of TSH suppression. Boelaert et. al. stated in a prospective study involving 1500 patients undergoing thyroidectomy that the risk of thyroid malignancy is increased in those with serum TSH greater than 0.9 mU/liter while the prevalence of malignancy (n = 182) was only 2.8% in subjects with serum TSH below the normal range (<0.4 mU/liter).[8] This suggests that the lower TSH level in patients with hyperthyroidism is also associated with lower incidence of malignancy. This notion however was slowly being supplanted by increasing reports of malignancy among hyperthyroid patients. In one study, thyroid cancer occurred in 0.76% to 8.7% of the glands removed for treatment of thyrotoxicosis.[4]

In our study, thyroid cancer was seen in 20 per 100 hyperthyroid patients who have undergone thyroidectomy. The same is true of a study by Aksoy et al., wherein out of 591 patients who had surgery to address hyperthyroidism, 131 (22.6%) had thyroid cancer.[9] An even higher rate of 32.8% was documented by a retrospective study on thyroid cancer in patients with hyperthyroidism.[10] Mohamed et. al. reported an incidence rate of 21.43% among patients with toxic nodular goiter while Yoon et.al reported that malignancy was detected in 1.7% of all patients with Grave's Disease.[11,12]

It is more common in the females in the fourth decade of life.[4] But according to a different study, male gender increases the patient's risk of developing cancer.[11] In our study, age and gender however are not associated with risk for malignancy. Papillary Thyroid Carcinoma was the most common histologic subtype with half of them being a Micropapillary Thyroid Carcinoma (PTC that measures <1cm). This finding is consistent with other previous studies.[4,10,11] But according to Als et al., follicular neoplasm was the most prevalent kind, found in 15 out of 19 TNG patients (79%).[13]

This study established that the factors associated with thyroid cancer include higher initial FT4 levels, the presence of thyroid nodules, nodule size and pre-operative FNAB finding of malignancy. Those with aggressive tumor behavior have higher initial FT4 levels than those with non-aggressive tumor. Although not statistically significant, patients with younger age and larger tumor size tend to have more aggressive tumor behavior. However, a larger sample size may be needed to confirm this observation.

The mechanisms behind hyperthyroidism with concurrent thyroid malignancy have been elucidated in some articles. Fu et. Al. explained that the presence of TSH receptor antibody (TRAb) in patients with Graves' Disease might play a role in stimulating thyroid cancer growth because these malignant cells also express TSH receptors like normal thyroid cells. TRAb stimulates invasiveness and angiogenesis of DTC by upregulating vascular endothelial growth factor, placenta growth factor, and their receptors via the same signaling pathways as TSH-induced cell activation and growth. On the other hand, toxic adenoma and MNTG are the result of focal and/or diffuse hyperplasia of thyroid follicular cells whose functional capacity is independent of regulation by TSH.[14]

Twenty to 80 percent of toxic adenomas and some nodules of MNGs have somatic mutations of the TSH receptor gene.[15] This can lead to TSH-independent (constitutive) activation of the receptor and cause both clonal expansion and hyperthyroidism in a subset of toxic adenomas. Therefore, the TSH receptor is a proto-oncogene that can be activated by a variety of point mutations.[16] According to a study by Krashin, E. et.al., thyroid hormones mediate their effects on the cancer cell through several non-genomic pathways including activation of the plasma membrane receptor integrin αvβ3, a plasma membrane integrin which acts as a membrane receptor for thyroid hormones and facilitates the hormones proliferative action on cancer cells as well as blood vessel cells.[17] This view supports previous reports that hyperthyroidism or thyrotoxicosis is associated with notable rates of thyroid cancer. This may also explain why in contrast to NNTG in which higher TSH levels are associated with higher risk of malignancy, hyperthyroid patients with higher FT4 levels are the ones associated with higher likelihood for malignancy, and even trends towards more aggressiveness.

Consistently, Chao TC et. al. reported that higher serum concentrations of thyroid hormones before antithyroid treatment is associated with an aggressive tumor course as compared with those with lower concentrations.[4] This is in congruence with our study wherein each incremental increase of FT4 level also increases the likelihood of thyroid cancer. Furthermore, a population-based study discovered that having hyperthyroidism for a longer period of time increases the risk of developing thyroid cancer.[18] As a result, sustained FT4 elevation may be associated with an increased risk of thyroid cancer in hyperthyroid patients, and long-term hyperthyroidism may contribute to tumor growth. This study is limited to assess such temporal relationship between length of thyroid hormone exposure and the development of malignancy in this current cross-sectional design. Further prospective investigations will be helpful in elucidating such effects.

Hyperthyroid patients with thyroid cancer usually have 1-2 thyroid nodules and are more likely to have malignant FNAB results preoperatively compared to hyperthyroid patients without thyroid cancer. A systemic review stated that in those patients who had pre-operative imaging, mean malignancy rates were higher in patients with pre-identified nodules (19.8%) compared to those without any nodules (8.7%)[3]. This is also noted in the present study in which the presence of nodule is associated with 24x higher risk of malignancy as compared to those without thyroid nodules. It is also known that thyroid nodule size impacts the risk of thyroid cancer, thus current guidelines include it as part of the criteria when

to do fine needle aspiration biopsy. In this study, the median nodule size was higher in those with thyroid cancer. This was statistically significant in patients with nodular Grave's disease with an average nodule size of 15mm. But in another study, the size of the dominant thyroid nodule was not a significant risk factor of malignancy; rather malignancy rate was higher in those with multinodular toxic nodules than solitary toxic nodules.[10]

Based on the Bethesda Classification of thyroid nodule fine needle aspirations, nodules tagged as malignant have a malignancy risk of 97-99%.[19] Alshahrani AS et. al. established a good concordance between FNAB and histological examination of thyroid nodules, as all malignant nodules detected by FNAC were also determined to be malignant by histopathology.[20] A statistical analysis by Singh et. al. showed that FNAC had a sensitivity of 83.3%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 96.7%.[21] Our study showed that among hyperthyroid patients with cancer, seven out of eight patients who underwent FNAB revealed positive malignant findings which correlate with the final post thyroidectomy histopathology report. Furthermore, FNAB done prior to surgery does not interfere with the accuracy of the final diagnosis which is provided by the histopathology report based on the full tissue architecture obtained after thyroidectomy. FNAB is a preoperative diagnostic tool that guides clinical decisions highlighting the importance of doing FNAB in suspicious nodules among hyperthyroid nodules.

Thyroid cancers in the background of a hyperthyroid gland have an aggressive behavior, with high incidence of local invasion and a worse prognosis than euthyroid patients, especially in patients with Graves' disease.[22] Yoon et. al determined that only lymph node metastasis was an independent prognostic factor for recurrent/persistent disease of thyroid cancer arising in Grave's Disease.[14] Medas et al. found that patients with hyperthyroidism had more aggressive tumors, a greater rate of nodal metastases (12.6% vs. 6.1%), and a worse prognosis (5-year disease free survival of 89.1% compared with 96.6% of euthyroid patients).[22]

In our study, most (66.67%) had unilateral involvement while regional cervical metastasis was seen in four patients with only one recorded recurrence. Four (33.33%) were considered to have aggressive tumor behavior. Although the present study was unable to determine an association with the selected demographic and pre-operative clinical features with the presence of an aggressive tumor in the 12 patients who underwent thyroidectomy and with thyroid cancer, clinically, we can consider that those with aggressive tumor behavior have higher initial FT4 levels (95.97 vs 23.55, $p=0.044$). A younger age on average (36.35 vs 46.75 years, $p=0.240$) and larger nodule size (95 mm vs 20 mm, $p=0.200$) were also observed to have more aggressive behavior as mentioned but this was not statistically significant.

The hyperthyroid state is not completely protective against thyroid malignancy. This study recognizes notable risk (20%) of thyroid malignancy in patients with hyperthyroidism. The risk increases with higher initial FT4 levels in the presence of a thyroid nodule. Thus, hyperthyroid or thyrotoxic patients with thyroid nodule of >1cm and elevated initial FT4 levels (>95 pmol/L) and/or young age (<40yo) should undergo thorough evaluation including long term surveillance using regular ultrasound and ultrasound guided FNAB on nodules with malignant features to assess the risk of malignancy accurately. A finding of malignancy should prompt appropriate management.

This study is limited by its observational design conducted in a single-center. The data obtained from this study were taken for clinical rather than for purely research purpose. Confounders such as autoimmune diseases, exercise, medication or radiation exposure and concomitant malignancies were not originally considered in this study. Attempts were made to statistically adjust for potential confounders, but outcomes were highly correlated, and a multivariate analysis could not be performed. In addition, the follow-up period for thyroid nodules in hyperthyroid patients was relatively short to thoroughly analyze the tumor behavior of patients with thyroid cancer. Finally, and most importantly, post-hoc analysis demonstrated excellent power to detect large effects (e.g., nodule count, ~90%) but only ~5% power to identify the modest FT4 association observed. As a result, the association between initial FT4 and malignancy must be viewed as exploratory. Larger, adequately powered studies are required to confirm this relationship.

Conclusion

In conclusion, initial FT4 level, the presence of thyroid nodules, nodule size, and pre-operative FNAB finding of malignancy were the factors associated with thyroid cancer in hyperthyroid patients. Furthermore, higher initial FT4 level, young age and larger nodule size showed trend towards more aggressive tumor behavior. As such, hyperthyroid patients with these clinical features warrant closer surveillance and more aggressive approach.

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References

1. Fiore E, Vitti P. Serum TSH and risk of papillary thyroid cancer in nodular thyroid disease. J Clin Endocrinol Metab. 2012 Apr;97(4):1134-45. doi: 10.1210/jc.2011-2735. Epub 2012 Jan 25. PMID: 22278420.
2. Kunawudhi A, Promteangtrong C, Chotipanich C. A case report of hyperfunctioning metastatic thyroid cancer and rare I-131 avid liver metastasis. Indian J Nucl Med. 2016 Jul-Sep;31(3):210-4. doi: 10.4103/0972-3919.183616. PMID: 27385894; PMCID: PMC4918487.
3. Varadharajan K, Choudhury N. A systematic review of the incidence of thyroid carcinoma in patients undergoing thyroidectomy for thyrotoxicosis. *Clin Otolaryngol*. 2020;45(4):538-544. doi:10.1111/COA.13527

4. Chao TC, Lin J Der, Jeng L Bin, Chen MF. Thyroid Cancer with Concurrent Hyperthyroidism. *Archives of Surgery*. 1999;134(2):130-134. doi:10.1001/ARCHSURG.134.2.130
5. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. doi:10.1089/thy.2016.0229
6. Hsieh FY, Bloch DA, Larsen MD. Stat Med. 1998;17(14):1623–34. doi:10.1002/(SICI)1097-0258(19980730)17:14<1623: AID-SIM871>3.0.CO;2-S
7. Mohamed TZ, Sultan AAEA, Tag El-Din M, Mostafa AAE, Nafea MA, Kalmoush AE, et al. Incidence and risk factors of thyroid malignancy in patients with toxic nodular goiter. Int J Surg Oncol. 2022; 2022:1054297. doi:10.1155/2022/1054297.
8. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. *J Clin Endocrinol Metab*. 2006;91(11):4295-4301. doi:10.1210/JC.2006-0527
9. Aksoy SÖ, Sevinç Aİ, Durak G. Hyperthyroidism with thyroid cancer: more common than expected? *Ann Ital Chir*. 2019;91. Accessed September 7, 2023. www.annitalchir.com
10. Kunjumohamed FP, Al-Busaidi NB, Al-Musalhi HN, Al-Shereiqi SZ, Al-Salmi IS. The prevalence of thyroid cancer in patients with hyperthyroidism. Saudi Med J. 2015 Jul;36(7):874-7. doi: 10.15537/smj.2015.7.11463. PMID: 26108596; PMCID: PMC4503911.
11. Mohamed TZ, Sultan AAEA, Tag El-Din M, Mostafa AAE, Nafea MA, Kalmoush AE, Nassar MS, Abdalgaleel MA, Hegab AM, Ibrahim AH, Baheeg M. Incidence and Risk Factors of Thyroid Malignancy in Patients with Toxic Nodular Goiter. Int J Surg Oncol. 2022 May 23; 2022:1054297. doi: 10.1155/2022/1054297. PMID: 35656410; PMCID: PMC9152398.
12. Yoon JH, Jin M, Kim M, Hong AR, Kim HK, Kim BH, Kim WB, Shong YK, Jeon MJ, Kang HC. Clinical Characteristics and Prognosis of Coexisting Thyroid Cancer in Patients with Graves' Disease: A Retrospective Multicenter Study. Endocrinol Metab (Seoul). 2021 Dec;36(6):1268-1276. doi: 10.3803/EnM.2021.1227. Epub 2021 Nov 26. PMID: 34823306; PMCID: PMC8743582.
13. Als C, Gedeon P, Rösler H, Minder C, Netzer P, Laissue JA. Survival analysis of 19 patients with toxic thyroid carcinoma. J Clin Endocrinol Metab. 2002 Sep;87(9):4122-7. doi: 10.1210/jc.2001-011147. PMID: 12213859.
14. Fu H, Cheng L, Jin Y, Chen L. Thyrotoxicosis with concomitant thyroid cancer. *Endocr Relat Cancer*. 2019;26(7):R395-R413. doi:10.1530/ERC-19-0129
15. Treatment of toxic adenoma and toxic multinodular goiter - UpToDate. Accessed September 7, 2023. https://www.uptodate.com/contents/treatment-of-toxic-adenoma-and-toxic-multinodular-goiter/print?search=abnormal-uterine-bleeding-in-reproductive-age-women-terminology-and-palm-coein-etiology-classification&topicRef=7835&source=see_link
16. Vargatu I. WILLIAMS TEXTBOOK OF ENDOCRINOLOGY. *Acta Endocrinologica (Bucharest)*. 2016;12(1):113. doi:10.4183/AEB.2016.113
17. Krashin E, Piekiełko-Witkowska A, Ellis M, Ashur-Fabian O. Thyroid Hormones and Cancer: A Comprehensive Review of Preclinical and Clinical Studies. *Front Endocrinol (Lausanne)*. 2019;10(FEB). doi:10.3389/FENDO.2019.00059
18. Yeh NC, Chou CW, Weng SF, Yang CY, Yen FC, Lee SY, Wang JJ, Tien KJ. Hyperthyroidism and thyroid cancer risk: a population-based cohort study. Exp Clin Endocrinol Diabetes. 2013 Jul;121(7):402-6. doi: 10.1055/s-0033-1341474. Epub 2013 Apr 24. PMID: 23616188.
19. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1. doi:10.1089/THY.2015.0020
20. Alshahrani AS, Algazlan AG, Junaid M, Aldosari AA, Amer KA, Mubarki MH, Alharbi SM, Al-Qannass AM. Association of Fine-Needle Aspiration of Thyroid Nodules With Final Histopathology in Diagnosing Thyroid Malignancy: A Single Institute Retrospective Study. Cureus. 2022 Nov 21;14(11):e31733. doi: 10.7759/cureus.31733. PMID: 36569680; PMCID: PMC9769783.
21. Singh P, Gupta N, Dass A, Handa U, Singhal S. Correlation of fine needle aspiration cytology with histopathology in patients undergoing thyroid surgery. Otolaryngol Pol. 2020 Aug 3;75(2):1-5. doi: 10.5604/01.3001.0014.3433. PMID: 33724232.
22. Medas F, Erdas E, Canu GL, ¿et al. Does hyperthyroidism worsen prognosis of thyroid carcinoma? A retrospective analysis on 2820 consecutive thyroidectomies. *Journal of Otolaryngology - Head & Neck Surgery*. 2018;47(1). doi:10.1186/S40463-018-0254-2