Int Surg 2017;**102:**328–333
DOI: 10.9738/INTSURG-D-17-00021.1

Incidence of Thyroid Carcinoma Among Patients With Hyper and Hypothyroidism

Ali Emre Nayci[1], Soykan Arikan[1], Onder Akkus[1], Ozgur Segmen[1], Feray Gunver[2]

[1]*Istanbul Training and Research Hospital, Department of General Surgery, Istanbul, Turkey*

[2]*Istanbul Training and Research Hospital, Department of Pathology, Istanbul, Turkey*

Objective: Our aim was to determine the incidence of thyroid carcinoma in patients with hyperthyroidism and hypothyroidism and to demonstrate whether hyperthyroidism is actually a protective state against carcinoma.

Background: In endemic regions for goiter such as Turkey, the rate of cancer is reported to be lower among patients with hyperthyroidism than those with hypothyroidism. However, we observed in our clinic that carcinoma incidence in patients with hyperthyroidism is at least as high as those with hypo-euthyroidism.

Methods: Cases of bilateral total thyroidectomy performed in the Istanbul Training and Research Hospital General Surgery Clinic between the years 2000 and 2014 were retrospectively examined. Age, gender, hormone levels, and postoperative pathological diagnoses were independently compared.

Results: Data from 1200 patients was analyzed. Mean age was 49.2. Of the patients 220 (17.5%) were male and 990 (82.5%) were female; 722 of the female patients had benign pathologies and 268 had malignant pathologies, whereas 144 of the male patients had benign and 66 had malignant pathologies. Compared by age, no significant difference was detected in pathological diagnoses and hormone levels. Comparing the pathological diagnoses according to hormone levels, rate of malignancy was significantly higher in patients with hyperthyroidism than those with hypothyroidism or euthyroidism.

Conclusions: Unlike what is previously accepted, hyperthyroid patients also carry a risk for thyroid carcinoma. Thus, these patients should be followed up for cancer at least as closely as those with hypothyroidism and euthyroidism.

Key words: Hyperthyroidism – Hypothyroidism – Incidence – Thyroid cancer

Corresponding Author: Ali Emre Nayci, MD, Department of General Surgery, Istanbul Training and Research Hospital, Kasap İlyas Mah. Org. Abdurrahman Nafiz Gürman Cd. 34098, Istanbul, Turkey.
Tel.: +90-532-6487733; E-mail: aliemrenayci@gmail.com

Table 1 Classification of included patients according to age, sex, pathologic diagnoses and hormone status

Categories	Patients, n	Total, %
Sex		
Male	210	82.5
Female	990	17.5
Pathology		
Papillary carcinoma	295	24.6
Follicular carcinoma	23	1.9
Medullary carcinoma	16	1.3
Total number of malignant pathologies	334	27.8
Adenomatous hyperplasia	576	48.0
Lymphocytic thyroiditis	196	16.3
Follicular adenoma	73	6.1
Hashimoto's thyroiditis	21	1.8
Total number of benign pathologies	866	72.2
Hormone status		
Hypothyroid	131	10.9
Euthyroid	718	59.8
Hyperthyroid	351	29.0
Age	Median: 50 (17-82), Mean: 49.2, SD: ±11.8	

Thyroid cancer is the most commonly encountered type of cancer in clinical practice and its incidence is continuously increasing: 1.6% of all new cancer cases are thyroid cancers.[1,2] Improvement in diagnostic methods, especially the detailed investigation of thyroid nodules, has had a major effect on this recent increase in incidence.[3,4]

In endemic regions for goiter such as Turkey, the rate of cancer is reported to be lower among patients with hyperthyroidism.[5] When thyroid gland function is inadequate, continuous overstimulation by the thyroid-stimulating hormone (TSH) results in irregular growth of the thyroid gland. Iodine deficiency, inadequate hormone synthesis by the thyroid gland, dietary or medical goitrogens increase the risk for thyroid cancer by continuously stimulating high levels of TSH.[6] Experimental studies have shown that animals that were fed an iodine-deficient diet for a prolonged period of time, develop follicular hyperplasia, followed by nodules and adenomas at a higher rate than the control groups.[5,6] On the other hand, even though TSH is suppressed in patients with hyperthyroidism, increased TSH stimulation at the early stage results in a toxic state that stimulates tumor development through an oncogenic effect before TSH suppression occurs.[7] Still, the relationship between increased TSH secretion and thyroid cancer is yet to be elucidated.

Table 2 Comparison of pathologic diagnoses and hormone status according to patient age

	Median age (min-max)	Mean age ± SD	*P* value
Pathology			
Malignant (total)	50 (17–82)	49 ± 12.33	0.585
Benign (total)	50 (19–77)	49 ± 11.67	
Malignant pathologies			
Papillary carcinoma	49 (17–82)	49 ± 11.89	0.133
Follicular carcinoma	57 (24–73)	52 ± 15.20	
Medullary carcinoma	59 (19–68)	52 ± 15.46	
Benign pathologies			
Adenomatous hyperplasia	50 (19–77)	50 ± 11.45	0.968
Lymphocytic thyroiditis	50 (22–77)	49 ± 12.26	
Follicular adenoma	49 (22–74)	49 ± 11.73	
Hashimoto's thyroiditis	50 (23–65)	48 ± 12.22	
Hormone status			
Hypothyroid	49 (24–82)	50 ± 11.62	0.633
Euthyroid	49 (19–81)	49 ± 11.89	
Hyperthyroid	51 (17–76)	50 ± 11.88	

In the Istanbul Training and Research Hospital General Surgery Clinic, we observed that carcinoma incidence in patients with hyperthyroidism is at least as high as those with hypo- or euthyroidism. We therefore aimed to retrospectively review cases of bilateral total thyroidectomy in our hospital to investigate if hyperthyroidism has any protective role against carcinoma.

Materials and Methods

The study was approved by the local ethics committee of the Istanbul Training and Research Hospital on May 16, 2014 with Protocol Number 492.

In this study, 1200 cases undergoing bilateral total thyroidectomy in the Istanbul Training and Research Hospital General Surgery Clinic between the years 2010 and 2014 were retrospectively examined. While collecting data, TSH, unbound triiodothyronine (FT3) and unbound thyroxine (FT4) levels at presentation, demographic data such as age and sex, and postoperative pathologic diagnoses were recorded. For categorizing thyroid hormone levels, we used the 2013 Thyroid Disease Diagnosis and Treatment Guidelines[8] of the Turkish Endocrinology and Metabolism Association as reference. Age, sex, hormone level groups, and postoperative pathologic diagnoses were independently compared. Because of the retrospective design of the study, informed consent for anonymous data collection was not taken.

Table 3 Comparison of pathologic diagnoses and hormone status according to patient sex

	Male, n (%)	Female, n (%)	*P* value
Pathology			
Malignant (total)	66 (19.8)	268 (80.2)	0.201
Benign (total)	144 (16.6)	722 (83.4)	
Malignant pathologies			
Papillary carcinoma	53 (18.0)	242 (82.0)	**0.007**
Follicular carcinoma	5 (21.7)	18 (78.3)	
Medullary carcinoma	8 (50.0)	8 (50.0)	
Benign pathologies			
Adenomatous hyperplasia	108 (18.7)	468 (81.3)	**0.014**
Lymphocytic thyroiditis	18 (9.2)	178 (90.8)	
Follicular adenoma	13 (17.8)	60 (82.2)	
Hashimoto's thyroiditis	5 (23.8)	16 (76.2)	
Hormone status			
Hypothyroid	22 (16.8)	109 (83.2)	0.648
Euthyroid	121 (16.9)	597 (83.1)	
Hyperthyroid	67 (19.1)	284 (80.9)	

The collected data was analyzed using commercial software (SPSS v 22.0, Statistical Package for Social Sciences, Inc., Chicago, Illinois). The distribution of the variables was evaluated using the Kolmogorov-Smirnov test. For statistical analysis of quantitative data, Kruskal-Wallis and Mann-Whitney *U*-tests were used whereas χ^2 test was employed for categorical variables.

Results

We examined 1200 patients in total; 210 patients (17.5%) were male and 990 (82.5%) were female. Mean age was 49.2 years (17–82); 718 of the patients (59.8%) had euthyroidism; 351 (29.3%) had hyperthyroidism; and 131 (10.9%) had hypothyroidism (Table 1).

The total number of patients with benign pathologies was 866 (72.2%). Among these, 576 (48.0%) had adenomatous hyperplasia; 196 (16.3%) had lymphocytic thyroiditis; 73 (6.1%) had follicular adenoma; and 21 (1.8%) had Hashimoto's thyroiditis. According to histological type, of the 334 malignant cases, papillary carcinoma made up 88%, follicular carcinoma 7%, and medullary carcinoma 5% of all thyroid malignancies.

Hormone levels and pathologic diagnoses were separately compared with the age of patients and no statistically significant difference was detected (Table 2).

No significant difference was found in the sex distribution of benign and malignant groups. However, analyzing the subtypes of benign and malignant groups, the ratio of male patients was higher in the medullary carcinoma group compared to follicular and papillary carcinomas and lower in the lymphocytic thyroiditis group than in other benign pathologies. Of the 196 patients with lymphocytic thyroiditis, 178 were female. The number of male patients in this group was only 18. The male-to-female ratio of patients with hypothyroidism, euthyroidism and hyperthyroidism did not differ significantly (Table 3).

Comparing hormone status according to the postoperative pathologic diagnoses, 122 (36.5%) of the 334 malignant cases were hyperthyroid. On the other hand, only 26.4% (229/637) of the benign cases were hyperthyroid. Thus, hyperthyroidism was significantly more frequent ($P < 0.05$) among thyroid cancer patients (Table 4, Fig. 2).

Conversely, analyzing the rate of malignancy according to hormone status, 122 (34.8%) of the 351 patients with hyperthyroidism had malignant and 229 (65.2%) had benign diseases. Patients with hypo- and euthyroidism totaled 849, of which 212 (25%) had malignant and 637 (75%) had benign

Table 4 Comparison of pathologic diagnoses according to hormone status

	Hypothyroid, n (%)	Euthyroid, n (%)	Hyperthyroid, n (%)	*P* value
Malignant pathologies				
Papillary carcinoma	29 (9.8)	157 (53.2)	109 (36.9)	
Follicular carcinoma	6 (26.1)	12 (52.2)	5 (21.7)	
Medullary carcinoma	1 (6.3)	7 (43.8)	8 (50.0)	
Benign pathologies				
Adenomatous hyperplasia	57 (9.9)	364 (62.2)	155 (26.9)	
Lymphocytic thyroiditis	25 (12.8)	121 (61.7)	50 (25.5)	
Follicular adenoma	8 (11.0)	49 (67.1)	16 (21.9)	
Hashimoto's thyroiditis	5 (23.8)	8 (38.1)	8 (38.1)	
Malignant (total)	212 (63.5)		122 (36.5)	**0.001**
Benign (total)	637 (73.6)		229 (26.4)	

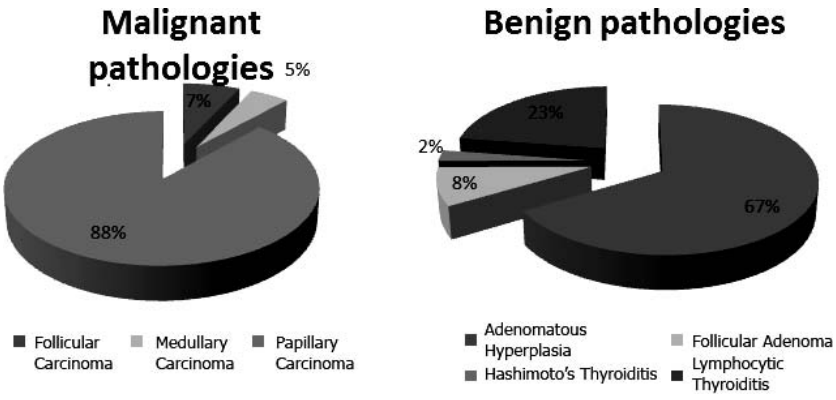

Fig. 1 Distribution of pathologic diagnoses.

diseases. According to this data, risk of malignancy was significantly higher among patients with hyperthyroidism compared to the other 2 groups combined.

Discussion

Numerous hypotheses were proposed for the mechanism of thyroid carcinoma. According to Hancock *et al*,[9] sustained TSH stimulation as a result of goitrogens causes hypertrophy of the thyroid gland, which is followed by neoplasia. However, the mechanism of thyroid cancer development as a result of excess TSH secretion has not yet been clarified.

In patients with Graves' disease, carcinogenic effect is assumed to be caused by the interaction of high levels of thyroid stimulating immunoglobulin (TSI)—instead of TSH—with the TSH receptors on the thyroid tissue. In these patients, because of the constant stimulation by TSI, cancer tends to follow a more aggressive course.[3]

The study by Rieger *et al*,[10] which included 1848 patients, aimed to determine the prevalence of cancer among patients with hyperthyroidism in an endemic goiter region; the rate of cancer was found to be 0.76%. The authors concluded that in regions endemic for goiter, the rate of cancer is lower among patients with hyperthyroidism.[10]

Toward the end of the 90s, Ruggieri *et al*[11] reported a carcinoma incidence of 5% in hyperthyroidism and 14.3% in euthyroidism in their study with 82 patients and declared that this rate of cancer among patients with hyperthyroidism is the highest in the literature. Gabriele *et al*[12] have retrospectively evaluated 425 patients with hyperthyroidism and detected cancer in only 7 (1.65%), thus excluding patients with hyperthyroidism from the risk group.

A large single-center study from an iodine-sufficient region in Asia[13] and a meta-analysis of 56 studies from 2016[14] have demonstrated that high TSH levels was not only an independent risk factor for thyroid malignancy, but was also a predictor for advanced stage and aggressive disease characteristics.

On the contrary, some recent studies have remarked the increasing rates of malignancies among patients with hyperthyroidism and reported

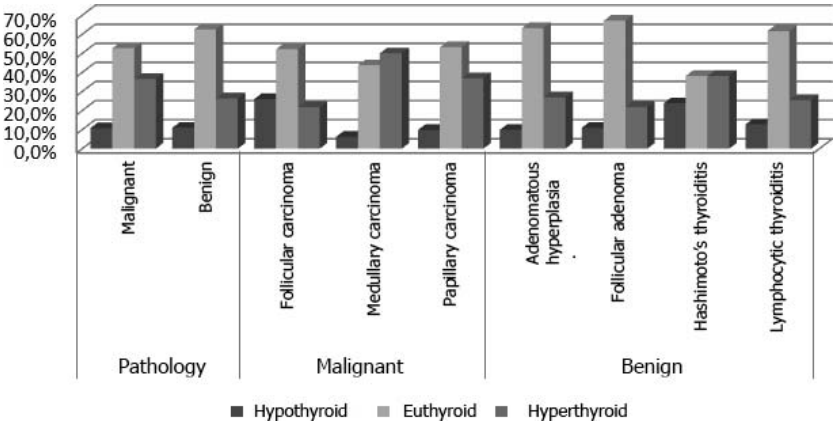

Fig. 2 Comparison of pathologic diagnoses according to hormone status.

malignancy rates close to that of cold nodules in patients with Graves' disease, autonomous nodules and multiple nodules.[15,16]

In our study conducted in an iodine-deficient country, we retrospectively analyzed data from 1200 patients who had undergone bilateral total thyroidectomy and compared the incidence of cancer among patients with hyperthyroidism and those with hypothyroidism. The rate of malignancy among hyperthyroid patients was significantly higher than those with hypothyroidism and euthyroidism. This finding contradicts the classical knowledge and most of the literature that suggest a strong negative correlation between hyperthyroidism and thyroid malignancy.

The fact that Turkey is an iodine-deficient region endemic for goiter might be the key point underlying this deviation from the literature. In the cross-sectional study by Du *et al*,[17] more than 2000 subjects from three regions with different iodine nutrition levels were included and the effects of the iodine status were analyzed. The frequency of both thyroid nodules and hyperthyroidism were independently higher in the iodine-deficient region. It is possible that in our study, the relationship between hormone status and pathologic results was not causative, but that both were related to the iodine level of the patients. Unfortunately, no data was collected in our study regarding the iodine status of the subjects.

In the present study, benign cases consisted of 866 patients in total, of which 576 (67%) had adenomatous hyperplasia; 196 (23%) had lymphocytic thyroiditis; 73 (8%) had follicular adenoma; and 21 (2%) had Hashimoto's thyroiditis. These ratios are consistent with the literature.

The large study population of 1200 patients was one of the strong points of the study. It allowed the analyses of multiple variables and drawing conclusions by increasing the power of the study. Having been conducted in an endemic region for goiter is another aspect of the study that makes it noteworthy.

The major weakness of our study was its retrospective design, resulting in selection bias. Since the study population consisted of patients undergoing bilateral total thyroidectomy, it included all cases with malignant fine needle aspiration biopsy results but not those who had small nodules with benign pathology that are conservatively followed up or those for whom unilateral thyroidectomy was preferred. Many euthyroid patients with small, asymptomatic nodules are likely not diagnosed at all. This situation might have altered our results so that the rate of malignancies appeared higher than it actually is. Similarly, undiagnosed euthyroid patients were not included, causing further inaccuracy.

Larger, multicentric studies are needed to confirm our results. Prospective randomized studies with a screening protocol for subject selection might eliminate the inaccuracies that were inevitable in our study because of its very design.

Conclusions

In this study with a large patient population, the rate of malignancy among patients with hyperthyroidism was significantly higher than those with either hypothyroidism or euthyroidism. Unlike what is previously accepted, hyperthyroid patients also carry a risk for thyroid carcinoma. Thus, these patients should be followed up for cancer at least as closely as those with hypothyroidism and euthyroidism.

Acknowledgments

Disclosure Statement: The authors have nothing to disclose

Sources of support: None received

References

1. Jameson JL, Weetman AP. Chapter 320: disorders of the thyroid gland. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL, eds. *Harrison's Principles of Internal Medicine*. 6th ed. New York, NY: The McGraw Hill Companies, 2005:204–426
2. Hirabayashi RN, Lindsay S. The relationship of thyroid carcinoma and chronic thyroiditis. *Surg Gynecol Obstet* 1965; **121**(2):243–252
3. Mazzaferri EL, Kloos RT. Current approaches to primary therapy for papillary and follicular thyroid cancer. *J Clin Endocrinol Metab* 2001;**86**(4):1447–1463
4. Leenhardt L, Grosclaude P, Cherie-Challine L, *et al*; Thyroid Cancer Committee. Increased incidence of thyroid carcinoma in France: a true epidemic or thyroid nodule management effects? Report from the French Thyroid Cancer Committee. *Thyroid* 2004;**14**(2):1056–1060
5. Urgancıoğlu İ, Hatemi H. Endemik guatr ve Türkiye'de iyot eksikliği: Türkiye'de endemik guatr (Turkish). 3.Baskı. Çetin Matbaacılık. İstanbul. 1996;**5**:5

6. Sadler GP, Clark OH. Thyroid and parathyroid. Schwartz SI, Shires GT, Spencer FC: Principles of surgery. 7th ed. New York, NY: McGraw-Hill, 1999;1661–1667
7. Zanelle E, Rulli F, Muzi M, Sianesi M, Danese D, Sciacchitano S, Pontecorvi A. Prevalence of thyroid cancer in hyperthyroid patients treated by surgery. *World J Surg* 1998;**22**(5):473–478
8. Türkiye Endokrinoloji ve Metabolizma Derneği. Tiroid Hastalıkları Tanı ve Tedavi Kılavuzu (Turkish). Ankara, 2013
9. Hancock BW, Bing RF, Dirmikis SM, Munro DS, Neal FE. Thyroid carcinoma and concurrent hyperthyroidism: a study of ten patients. *Cancer* 1977;**39**(1):298–302
10. Rieger R, Pimpl W, Money S, Rettenbacher L, G. Galvan Hyperthyroidism and concurrent thyroid malignancies. *Surgery* 1989;**106**(1) 6–10
11. Ruggieri M, Scocchera F, Genderini M, Mascaro A. Hyperthyroidism and concurrent thyroid carcinoma. *Eur Rev Med Pharmacol Sci* 1999;**3**(6):265–268
12. Gabriele R, Letizia C, Borghese M. Thyroid cancer in patients with hyperthyroidism. *Horm Res* 2003;**60**(2):79–83
13. Kim SS, Lee BJ, Lee JC, Song SH, Kim BH, Son SM *et al*. Preoperative serum thyroid stimulating hormone levels in well-differentiated thyroid carcinoma is a predictive factor for lateral lymph node metastasis as well as extrathyroidal extension in Korean patients: a single-center experience. *Endocrine* 2011;**39**:259–265
14. Zheng J, Li C, Lu W, Wang C, Ai Z. Quantitative assessment of preoperative serum thyrotropin level and thyroid cancer. *Oncotarget* 2016;**7**(23):34918–34929
15. Gul K, Di Ri Koc A, Ki Yak G, Ersoy PE, Ugras NS, Ozdemi D *et al*. Thyroid carcinoma risk in patients with hyperthyroidism and role of preoperative cytology in diagnosis. *Minerva Endocrinol* 2009;**34**(4):281–288
16. Polyzos SA, Goulis DG. Coincidental thyroid papillary microcarcinoma in a patient treated for a toxic adenoma of the thyroid. *Arch Iran Med* 2011;**14**(2):149–151
17. Du Y, Gao Y, Meng F, Liu S, Fan Z, Wu J *et al*. Iodine deficiency and excess coexist in China and induce thyroid dysfunction and disease: a cross-sectional study. *PloS One* 2014;**9**(11): e111937