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Thyroid malignancy risk in different clinical thyroid diseases

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Background/aim: To evaluate the malignancy risk of thyroid nodules in different clinical thyroid diseases.

Materials and methods: Patients who underwent thyroidectomy between 2007 and 2014 were grouped as euthyroid, hypothyroid, and hyperthyroid. Further classification was made depending on the presence of solitary/multiple thyroid nodules.

Results: Among 2870 patients, 1719 (59.9%) were euthyroid, 962 (33.5%) were hyperthyroid, and 189 (6.6%) were hypothyroid. Overall malignancy was detected in 980 (34.1%) patients. Malignancy rates were 42.1%, 42.9%, and 18.3% in the euthyroid, hypothyroid, and hyperthyroid groups, respectively ($P < 0.001$). A total 41.4% of patients with euthyroid nodular goiter (ENG) and 46.3% of patients with euthyroid multinodular goiter (EMNG) had thyroid malignancy ($P = 0.169$). Mean tumor size and capsular and vascular invasion were significantly lower in EMNG than in ENG. Among hypothyroid patients, 45.7% with solitary and 42.2% with multiple nodules were malignant ($P = 0.705$). When toxic nodular goiter and toxic multinodular goiter were analyzed together, malignancy rate was 24.7% (104/421), and when Graves with nodule/nodules was considered, it was 19.7% (59/299).

Conclusion: In hypothyroid or euthyroid patients who underwent thyroidectomy, malignancy rate was higher than 40%, and was lower in hyperthyroid patients. Patients with multiple nodules carry a similar risk of malignancy as patients with solitary nodules, independent of the functional status.

Key words: Thyroid cancer, thyroid functions, thyroid nodule

1. Introduction

Nodular thyroid diseases are the most frequent diseases of the thyroid gland. Prevalence of clinically apparent thyroid nodules is 5% in women and 1% in men living in iodine-sufficient regions of the world. However, over the past two decades, the widespread use of ultrasonography (US) has resulted in a dramatic increase in thyroid nodules, estimated at 19%–68% in the general population (1). The high prevalence of thyroid nodules requires evidence-based rational strategies for their differential diagnosis, risk stratification, treatment, and follow-up. These strategies mainly concentrate on the risk of malignancy. Thyroid carcinoma is the most frequent cancer of the endocrine glands and constitutes 1% of human neoplasias. The yearly incidence of thyroid cancer has nearly tripled from 4.9 per 100,000 to 14.3 per 100,000 in approximately 35 years (2). Such incidence is higher if cases of occult carcinoma are taken into account. Advanced age, male sex, radiation exposure, rapidly growing mass in neck, >4 cm nodule, and a family history of thyroid cancer are the main risk factors for malignant thyroid lesions (1,3).

Clinical thyroid diseases can be classified as euthyroid, hypothyroid, and hyperthyroid, according to functional status. Thyroid functions are normal in a considerable amount of patients with thyroid cancer. Measurement of high sensitive thyrotropin (TSH) in serum plays the main role in the diagnosis of thyroid dysfunctions and has a predictive value for thyroid malignancies. In a study consisting of 1500 patients, prevalence of malignancy was significantly lower in patients with serum TSH < 0.4 mU/L, compared to those with TSH > 0.4 mU/L (4). Furthermore, the highest malignancy risk was shown in patients with TSH levels higher than 5.5 mU/L. There are a number of studies reporting an association between increased malignancy and high serum TSH levels even in normal ranges (5,6).

The term goiter refers to the abnormal growth of the thyroid gland. Goiters can be diffuse or nodular,

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depending on the cause, and may be associated with normal, decreased, or increased thyroid hormone production. Additionally, absence or presence of a single or multiple nodules determines the nodular status of the thyroid disease. In contrast to studies suggesting higher malignancy risk in solitary thyroid nodules (7,8), several studies have shown that the risk is similar in patients with multinodular disease and those with solitary nodules (9,10).

In this study, we evaluated malignancy risk in various clinical thyroid diseases classified according to functional and morphological status. Additionally, we compare histopathological features of malignant lesions accompanying different thyroid diseases.

2. Materials and methods

The study was approved by the Clinical Investigations Ethical Committee of the School of Medicine, Yıldırım Beyazit University, Turkey (Chairperson: MD Halil Kara, date: 21.10.2015, Protocol No. 210). Patients who had undergone thyroidectomy in our center between 2007 and June 2014 were evaluated retrospectively in this study. Patients with a previous history of thyroid surgery, or percutaneous invasive procedure for thyroid nodule, or radiotherapy to the head and neck region were excluded from the study. According to the preoperative functional status, patients were classified into 3 groups: euthyroid, hypothyroid, and hyperthyroid. Demographic features, serum TSH levels, presence of thyroid autoantibodies, and use of medication for thyroid dysfunctions were obtained from medical records. Chemiluminescent enzyme immunoassay (Immulite 2000, Diagnostic Products Corp. Los Angeles, CA, USA, and UniCel DXI 800, Beckman Coulter, Brea, CA, USA) were used for measurement of serum TSH, antithyroid peroxidase antibody (antiTPO), and antithyroglobulin antibody (antiTGAb) levels. Normal range for serum TSH was 0.4–4 μIU/mL. The thyroid antibody levels over the upper range were accepted as positive. Patients with a basal TSH level > 4.0 μIU/mL and patients on levothyroxine therapy were defined as having hypothyroidism. Euthyroidism was defined as normal TSH values in the absence of thyroid medication. Patients with TSH values < 0.4 μIU/mL or patients using antithyroid medications were considered to have hyperthyroidism.

Preoperative thyroid US findings were reviewed from medical records. Euthyroid and hypothyroid patients were further classified according to the presence of solitary or multiple nodules preoperatively. The causes of hyperthyroidism were Graves disease, solitary autonomous nodule, or multiple toxic nodules. The differential diagnosis was made by US findings, ^{99m}Tc-pertechnatae scintigraphy, ^{131}I uptake results, and TSH receptor antibody levels. Hyperthyroid patients were further classified according to the presence and number of nodules.

Eventually, 9 different clinical thyroid diseases were defined: euthyroid nodular goiter (ENG), euthyroid multinodular goiter (EMNG), hypothyroidism with single nodule (hypothyroid + NG), hypothyroidism with multiple nodules (hypothyroid + MNG), toxic nodular goiter (TNG), toxic multinodular goiter (TMNG), Graves without nodule (Graves), Graves with solitary nodule (Graves + NG), and Graves with multiple nodule (Graves + MNG). No operation was performed on any euthyroid or hypothyroid patient without nodule/nodules. Thus, there was no group of diffuse goiter patients with euthyroidism or hypothyroidism.

Operation indications were classified as giant nodule/compression symptoms, thyrotoxicosis, nondiagnostic cytology, indeterminate (atypia of undetermined significance/follicular lesion of undetermined significance, follicular neoplasm/suspicious for follicular neoplasm, suspicious for malignancy) cytology and malignant cytology results, suspicious US features (hypoechoic texture, solid component, irregular margins, absence of peripheral halo, presence of microcalcification, and anteroposterior/transverse diameter > 1), and other (including increase in nodule size, high nodule number that makes clinical follow-up unfeasible, and coexistent parathyroid adenoma).

Postoperative histopathological diagnosis and malignancy rates were determined in each group. Nodular hyperplasia, colloidal goiter, follicular adenoma, and Hürthle cell adenoma were defined as benign thyroid lesions. Thyroid cancer was classified as PTC, FTC, Hürthle cell cancer, thyroid tumor of unknown malignant potential (TT-UMP), medullary thyroid cancer, and undifferentiated cancer. Tumoral characteristics (size, capsular and vascular invasion, extrathyroidal extension, and lymph node metastasis) were analyzed. A tumor was defined as "incidental" when an unsuspected cancer was identified incidentally during pathologic examination of thyroid tissue removed for benign disease.

3. Results

Data of 2870 patients were analyzed, of which 2203 (76.8%) were female and 667 (23.2%) were male. There were 227 (7.9%) patients in the ENG group, 1492 (52.0%) in EMNG, 35 (1.2%) in hypothyroid + NG, 154 (5.4%) in hypothyroid + MNG, 59 (2.1%) in TNG, 362 (12.6%) in TMNG, 242 (8.4%) in Graves, 55 (1.9%) in Graves + NG, and 244 (8.5%) in Graves + MNG groups.

When groups were organized according to functional status, there were 1719 (59.9%) patients with euthyroidism, 189 (6.6%) with hypothyroidism, and 962 (33.5%) with hyperthyroidism (Table 1). Mean age was similar between groups and the female sex was predominant in all groups. The ratio of female sex in the hypothyroid

Table 1. Comparison of clinical features and histopathology results in patients with euthyroidism, hypothyroidism, and hyperthyroidism.

	Euthyroid n = 1719 (59.9%)	Hypothyroid n = 189 (6.6%)	Hyperthyroid n = 962 (33.5%)	P
Sex				
Male	343 (20.0%)	16 (8.5%)	308 (32.0%)	<0.001
Female	1376 (80.0%)b	173 (91.5%)a,c	654 (68.0%)	
Age (years)	49.09 ± 11.93	48.78 ± 12.37	49.38 ± 13.08	0.767
Thyrotrophin (μIU/mL)	1.46 ± 1.00	5.05 ± 6.72	0.98 ± 4.03	<0.001
AntiTPO positivity (n = 1836)	205 (18.4%)	76 (55.1%)	218 (37.4%)	<0.001
AntiTg positivity (n = 1831)	221 (20.0%)	54 (42.5%)	166 (27.8%)	<0.001
Operation indications				
Giant nodule/compression symptoms	628 (36.5%)	21 (11.1%)	224 (23.3%)	< 0.001
Thyrotoxicosis	0 (0.0%)	0 (0.0%)	514 (53.4%)	
Nondiagnostic cytology	179 (10.4%)	23 (12.2%)	50 (5.2%)	
Indeterminate cytology*	633 (36.8%)	110 (58.2%)	83 (8.6%)	
Malignant cytology	137 (8.0%)	21 (11.1%)	13 (1.4%)	
Suspicious ultrasonography features	34 (2.0%)	1 (0.5%)	7 (0.7%)	
Other	77 (4.5%)	9 (4.8%)	7 (0.7%)	
Unknown	31 (1.8%)	4 (2.1%)	64 (6.7%)	
Histopathology				
Benign	996 (57.9%)	108 (57.1%)	786 (81.7%)	<0.001
Malignant	723 (42.1%)	81 (42.9%)	176 (18.3%)b,c	
Lymph node metastasis (n = 951)	58/700 (8.3%)	11/80 (13.8%)c	8/171 (4.7%)	0.046

AntiTPO: antithyroid peroxidase, AntiTg: antithyroglobulin.
*Indeterminate cytology refers to 'atypia of undetermined significance/follicular lesion of undetermined significance, follicular neoplasm/suspicious for follicular neoplasm, suspicious for malignancy'.
a: P < 0.05 for euthyroid vs. hypothyroid.
b: P < 0.05 for euthyroid vs. hyperthyroid.
c: P < 0.05 for hypothyroid vs. hyperthyroid.

group was significantly higher compared to the euthyroid and hyperthyroid groups (P < 0.001 each). The euthyroid group had a higher ratio of female sex compared to the hyperthyroid group (P < 0.001).

The most common surgical indications were nondiagnostic/indeterminate/malignant cytology results (55.2%) and giant nodule/compression symptoms (36.5%) in euthyroid patients (Table 1). A total 81.5% of hypothyroid patients were operated on for nondiagnostic/indeterminate/malignant cytology results. Thyrotoxicosis was the first (53.4%) and giant nodule/compression symptoms (23.3%) were the second most common operation indications in hyperthyroid patients.

Histopathologically, 980 (34.1%) patients had thyroid malignancy and 1890 (65.9%) had benign thyroid disease. Considering malignancy rate according to functional status, 723 (42.1%) of euthyroid patients, 81 (42.9%) of hypothyroid patients, and 176 (18.3%) of hyperthyroid patients had malignant thyroid disease (Table 1). Malignancy rate was significantly lower in the hyperthyroid group compared to the euthyroid and hypothyroid groups (P < 0.001 for each).

When the data of patients with thyroid cancer were analyzed, 73.8% of patients with thyroid cancer were euthyroid preoperatively, whereas 17.9% were hyperthyroid and 8.3% were hypothyroid. Overall, there were 1387 carcinoma foci in 980 malignant patients. Among tumoral foci, 1051 (75.8%) were present in the euthyroid group, 115 (8.3%) in the hypothyroid group, and 221 (15.9%) were in the hyperthyroid group (Table 2). The distribution of tumor type was similar in all three groups (P = 0.705). Tumor size was significantly higher in the euthyroid group compared to the hyperthyroid group (P = 0.002). There was no significant difference in terms of tumor size between the euthyroid and hypothyroid groups (P = 0.582), and hyperthyroid and hypothyroid groups (P = 0.371).

Table 2. Comparison of tumoral features of thyroid carcinoma foci in patients with euthyroidism, hypothyroidism, and hyperthyroidism.

Malignant foci n = 1387	Euthyroid n = 1051 (75.8%)	Hypothyroid n = 115 (8.3%)	Hyperthyroid n = 221 (15.9%)	P
Tumor type				
Papillary	979 (93.2%)	109 (94.8)	205 (92.8%)	
Follicular	22 (2.1%)	1 (0.9%)	8 (3.6%)	
Hürthle cell	15 (1.4%)	0	1 (0.5%)	0.705
TT-UMP	18 (1.7%)	1 (0.9%)	5 (2.3%)	
Medullary	12 (1.1%)	2 (1.7%)	1 (0.5%)	
Undifferentiated	5 (0.5%)	2 (1.7%)	1 (0.5%)	
Tumor size (mm)	11.16 ± 12.86b	9.98 ± 9.05	8.09 ± 10.07	0.003
Microcarcinoma	641 (61.0%)	68 (59.1%)	166 (75.1%)b,c	<0.001
Incidental	471 (44.8%)a	46 (40.0%)	147 (66.5%)b,c	<0.001
Capsular invasion	234 (22.3%)	28 (24.3%)	36 (16.3%)	0.419
Vascular invasion	46 (4.4%)	4 (3.5%)	5 (2.3%)	0.508
Extrathyroidal extension	102 (9.7%)	15 (13%)	20 (9%)	0.601

TT-UMP: Thyroid tumor of unknown malignant potential.
a: $P < 0.05$ for euthyroid vs. hypothyroid.
b: $P < 0.05$ for euthyroid vs. hyperthyroid.
c: $P < 0.05$ for hypothyroid vs. hyperthyroid.

Incidental thyroid cancer constituted 47.9% of all malignant lesions. The highest rate of incidental thyroid carcinoma was found in the hyperthyroid group followed by the euthyroid and hypothyroid groups (66.5%, 44.8%, and 40.0%, respectively, $P < 0.001$ for hyperthyroid vs. euthyroid and hyperthyroid vs. hypothyroid, and $P = 0.004$ for euthyroid vs. hypothyroid). Among 1387 carcinoma foci, 875 (63.1%) were microcarcinoma. The rate of microcarcinoma was significantly higher in the hyperthyroid group compared to the euthyroid and hypothyroid groups (61.0% in the euthyroid, 59.1% in the hypothyroid, and 75.1% in the hyperthyroid group, respectively, $P = 0.003$ for hyperthyroid vs. euthyroid, and $P < 0.001$ for hyperthyroid vs. hypothyroid). Capsular invasion, vascular invasion, and extracapsular extension were observed with similar rates in all groups. The only significant difference was in lymph node metastasis, which was higher in hypothyroid patients (13.8%) compared to hyperthyroid patients (4.7%) ($P = 0.011$).

Subgroup analysis was made separately for euthyroid, hypothyroid, and hyperthyroid patients. Among 1719 patients with euthyroidism, 227 (13.2%) had ENG and 1492 (86.8%) had EMNG (Table 3). Higher prevalence was observed in females and mean age was higher in the EMNG group compared to the ENG group ($P < 0.001$ each). Malignancy rates were 41.4% and 46.3% in ENG and EMNG, respectively ($P = 0.169$). There was a statistically significant difference in tumor types between the two groups ($P < 0.001$). PTC constituted 94.4% of tumors in EMNG and 84.2% in ENG groups. A total 25.6% of malignant lesions in ENG and 47.6% of malignant lesions in EMNG were diagnosed incidentally ($P < 0.001$). Mean tumor size, capsular invasion, and vascular invasion were lower in the EMNG group ($P < 0.001$, $P = 0.003$, and $P = 0.015$, respectively).

There were 189 patients with hypothyroidism, of which 35 (18.5%) were in the hypothyroid + NG group and 154 (81.5%) were in the hypothyroid + MNG group (Table 4). Sex distribution, mean age, and malignancy rates were similar in the two groups. In the hypothyroid + NG group, 3 (17.6%) tumors were incidental, and in the hypothyroid + MNG group, 43 (43.9%) tumors were incidental ($P = 0.042$). Tumor size and all tumoral characteristics were identical in the two groups.

There were 962 patients with hyperthyroidism (Table 5). Sex distribution was similar in all subgroups. Mean age was significantly higher in TMNG ($P < 0.05$ for each) and lower in Graves, compared to all other groups ($P < 0.05$ for each). Malignancy rates were similar in TNG, TMNG, Graves + NG, and Graves + MNG groups, but lower in Graves compared to the other groups ($P < 0.01$ for each). When TMNG and TNG were analyzed together, malignancy rate was 24.7% (104/421), and when all Graves patients with/without nodules were considered,

Table 3. Comparison of demographical features, histopathology results, and tumoral characteristics in patients with euthyroid nodular goiter and euthyroid multinodular goiter.

	Euthyroid nodular goiter n = 227 (13.2%)	Euthyroid multinodular goiter n = 1492 (86.8%)	P
Sex			
Male	65 (28.6%)	278 (18.6%)	<0.001
Female	162 (71.4%)	1214 (81.4%)	
Age (years)	43.30 ± 12.51	49.97 ± 11.59	<0.001
Histopathology			
Benign	122 (53.7%)	874 (58.6%)	0.169
Malignant	105 (46.3%)	618 (41.4%)	
Lymph node metastasis (n = 700)	12/105 (11.4%)	46/595 (7.7%)	0.205
Malignant foci (n = 1051)	n = 133	n = 918	
Tumor type			
Papillary	112 (84.2%)	867 (94.4%)	<0.001
Follicular	5 (3.8%)	17 (1.9%)	
Hürthle cell	4 (3.0%)	11 (1.2%)	
TT-UMP	4 (3.0%)	14 (1.5%)	
Medullary	6 (4.5%)	6 (0.7%)	
Undifferentiated	2 (1.5%)	3 (0.3%)	
Tumor size (mm)	16.53 ± 15.53	10.38 ± 12.22	<0.001
Capsular invasion	39 (29.3%)	195 (21.2%)	0.003
Vascular invasion	11 (8.3%)	35 (3.8%)	0.015
Extrathyroidal extension	18 (13.5%)	84 (9.2%)	0.168
Incidental	34 (25.6%)	437 (47.6%)	<0.001

TT-UMP: thyroid tumor of unknown malignant potential.

malignancy rate was 13.3% (72/541). Malignancy rate increased to 19.7% when only Graves patients with solitary and multiple nodules were considered. Tumor type was significantly different between groups and this difference was mostly related to the higher rate of FTC in the TNG group. All 16 tumoral foci in Graves disease were incidental, whereas rates of incidental tumors were similar in other groups. There was a significant difference in terms of tumor size between groups with the lowest size (3.53 ± 2.52 mm) in the Graves group and the highest (14.67 ± 16.40 mm) in the TNG group. Capsular invasion was significantly higher in TNG compared to the other groups. Vascular invasion, extrathyroidal extension, and lymph node metastasis were observed with similar frequencies in the groups.

4. Discussion

Approximately 7%–15% of all thyroid nodules are malignant (1). The risk of malignancy in various clinical thyroid disorders, such as Graves disease, toxic nodules, Hashimoto thyroiditis (HT), and solitary/multiple nodules, have been studied extensively in previous studies. However, to the best of our knowledge, malignancy potential under all these conditions had not been evaluated and compared in the same study before. Here, we showed that malignancy is detected at a higher prevalence in patients with preoperative hypothyroidism and euthyroidism compared to patients with hyperthyroidism. Nevertheless, there was a 19.3%–24.9% malignancy rate in patients with preoperative diagnosis of TNG, TMNG, and Graves with solitary/multiple nodules. Presence of solitary or multiple nodules did not change thyroid cancer risk in euthyroid, hypothyroid, and hyperthyroid patients.

Increasing prevalence of thyroid cancer worldwide is partly attributed to increased detection of subclinical cancer resulting from advanced diagnostic techniques. However, recent data suggest that improved surveillance cannot be the only explanation for this; instead, several environmental and habitual factors might contribute (11). In total, we had a higher risk of malignancy (34.1%) than

Table 4. Comparison of demographical features, histopathology results, and tumoral characteristics in patients with hypothyroid nodular goiter and hypothyroid multinodular goiter.

	Hypothyroid nodular goiter n = 35 (18.5%)	Hypothyroid multinodular goiter n = 154 (81.5%)	P
Sex Male Female	 1 (2.9%) 34 (97.1%)	 15 (9.7%) 139 (90.3%)	0.187
Age (years)	48.48 ± 11.57	48.84 ± 12.57	0.877
Histopathology Benign Malignant	 19 (54.3%) 16 (45.7%)	 89 (57.8%) 65 (42.2%)	0.705
Lymph node metastasis (n = 80)	1/16 (6.3%)	10/64 (15.6%)	0.330
Malignant foci (n = 115)	n = 17	n = 98	
Tumor type Papillary Follicular Hürthle cell TT-UMP Medullary Undifferentiated	 16 (94.1%) 1 (5.9%) 0 0 0 0	 93 (94.9%) 0 2 (2.0%) 1 (1.0%) 2 (2.0%) 0	0.157
Tumor size (mm)	12.29 ± 10.40	9.57 ± 8.79	0.256
Capsular invasion	5 (29.4%)	23 (23.5%)	0.598
Vascular invasion	0	4 (4.1%)	NA
Extrathyroidal extension	2 (11.8%)	13 (13.3%)	0.865
Incidental	3 (17.6%)	43 (43.9%)	0.042

TT-UMP: thyroid tumor of unknown malignant potential.

generally expected for a thyroid nodule. In some studies dealing with malignancy risk in thyroid nodules, fine needle aspiration biopsy (FNAB) results were used as the final diagnosis, and the risk was reported to range between 8% and 9.4% (5,12). When histopathological results are taken into consideration, this risk increases to 13.7%–37.6% in different series (6,13,14). Among 3629 patients undergoing surgical treatment, 23.6% were diagnosed with malignant nodules in a study by Lin et al. (15). A possible cause of the high rate of malignancy in our study might be incidental carcinomas and microcarcinomas, which comprise 47.9% and 63.1% of all malignancies, respectively. In addition, iodine deficiency is related to hypertrophy of the thyroid gland and development of nodular goiter. Turkey was a severely iodine-deficient region, and mandatory salt iodination has been carried out since 1999, which has brought our country to a moderate iodine deficiency region. Thus, we commonly come across nodular thyroid diseases in routine clinical practice. Moreover, our center is a reference center, and many patients with nodular goiter and indeterminate or malignant cytology are referred to our clinic for cytological evaluation or thyroidectomy.

It has long been suggested that solitary thyroid nodules carry a higher risk of malignancy compared to MNG. In a study of 300 patients, 46.2% of solitary thyroid nodules were malignant compared to 22.5% of MNG (7,8). However, this was not the case in several other studies, which reported no difference in cancer prevalence between patients with solitary nodules and those with MNG (9,10,16). Independent of thyroid functional status, malignancy rates were similar in patients with MNG and solitary nodules in our study, and we agree that MNG should no longer be considered an indicator of probable benign disease, and that all suspicious nodules, in addition to dominant ones, deserve cytological evaluation.

It is suggested that patients with thyroid cancer are mostly euthyroid (17). In accordance with this observation, the majority (73.8%) of patients with thyroid cancer were euthyroid in our study.

Table 5. Comparison of demographical features, histopathology results, and tumoral characteristics in patients with different clinical diagnosis of hyperthyroidism.

	TNG n = 59 (6.1%)	TMNG n = 362 (37.6%)	Graves n = 242 (25.2%)	Graves + NG n = 55 (5.7%)	Graves + MNG n = 244 (25.4%)	P
Sex						
Male	25 (42.4%)	106 (29.3%)	79 (32.6%)	20 (36.4%)	78 (32.0%)	0.323
Female	34 (57.6%)	256 (70.7%)	163 (67.4%)	35 (63.6%)	166 (68.0%)	
Age (years)	50.59 ± 13.02	55.07 ± 10.92	39.50 ± 10.46	45.27 ± 12.34	51.36 ± 12.77	<0001
Histopathology						
Benign	45 (76.3%)	272 (75.1%)	229 (94.6%)	43 (78.2%) 12	197 (80.7%)	<0.001
Malignant	14 (23.7%)	90 (24.9%)	13 (5.4%)	(21.8%)	47 (19.3%)	
Lymph node metastasis (n = 171)	1/14 (7.1%)	4/88 (4.5%)	0/13 (0.0%)	1/12 (8.3%)	2/44 (4.5%)	0.879
Malignant foci (n = 221)	n = 15	n = 116	n = 16	n = 16	n = 58	
Tumor type						
Papillary	11 (73.3%)	107 (92.2%)	16 (100%)	15 (93.7%)	56 (96.6%)	
Follicular	4 (26.7%)	3 (2.6%)	0	0	1 (1.7%)	
Hürthle cell	0	0	0	1 (6.3%)	0	0.003
TT-UMP	0	4 (3.4%)	0	0	1 (1.7%)	
Medullary	0	1 (0.9%)	0	0	0	
Undifferentiated	0	1 (0.9%)	0	0	0	
Tumor size (mm)	14.67 ± 16.40	8.32 ± 11.23	3.53 ± 2.52	6.02 ± 5.94	7.77 ± 6.53	0.032
Capsular invasion	7 (46.7%)	20 (17.2%)	0	1 (6.3%)	8 (13.8%)	0.048
Vascular invasion	0	3 (2.6%)	0	1 (6.3%)	1 (1.7%)	0.871
Extrathyroidal extension	2 (13.3%)	12 (10.3%)	0	1 (6.3%)	5 (8.6%)	0.676
Incidental	9 (60%)	78 (67.2%)	16 (100%)	11 (68.8%)	33 (56.9%)	0.028

TNG: toxic nodular goiter, TMNG: toxic multinodular goiter, NG: nodular goiter, MNG: multinodular goiter, TT-UMP: thyroid tumor of unknown malignant potential.
*Post-hoc analysis for all variables;
Sex distribution: P > 0.05 for all comparisons of subgroups.
Age: P < 0.05 for all comparisons except TNG vs. Graves + NG and TNG vs. Graves + MNG.
Histopathology: P < 0.001 for comparisons of TMNG vs. Graves, TNG vs. Graves, Graves vs. Graves + NG, and Graves vs. Graves + MNG.
Lymph node metastasis: P > 0.05 or nonapplicable for all comparisons of subgroups.
Tumor type: P = 0.015 for TMNG vs. TNG, P = 0.027 for TNG vs. Graves, P = 0.003 for TNG vs. Graves + MNG.
Tumor size: P > 0.05 for all comparisons of subgroups except TNG vs. Graves (P = 0.017).
Capsular invasion: P = 0.002 for TNG vs. Graves, P = 0.010 for TNG vs. Graves + NG, P = 0.018 for TNG vs. Graves + MNG.
Vascular invasion: P > 0.05 or nonapplicable for all comparisons of subgroups.
Extrathyroidal extension: P > 0.05 for all comparisons of subgroups.

There is growing evidence that serum TSH has a predictor value for malignant thyroid nodules. This was explained by the fact that TSH acts as a growth factor for thyrocytes. In a study of 1870 patients without any thyroid dysfunction, median TSH was found to be significantly higher in DTC patients compared to patients with benign pathology (18). Similar results indicating that TSH levels are significantly higher in PTC compared to benign thyroid diseases were obtained by other studies (5,6,12,13,18,19). In this study, we did not concentrate on the risk of thyroid cancer according to serum TSH levels, but compared malignancy risk in patients with normal and abnormal thyroid functions. Hyperthyroidism was associated with a lower risk of thyroid cancer than euthyroidism and hypothyroidism. The protective role of low TSH, shown in previous studies, might be one of the factors responsible

for this finding. Nevertheless, it should be noted that hyperthyroid patients were operated more frequently for benign diseases such as Graves or toxic nodules, whereas euthyroid and hypothyroid patients were operated on more frequently with indications harboring higher malignancy potential such as malignant, indeterminate, or nondiagnostic cytology results and giant nodules. The higher rate of incidental thyroid tumors and lower tumor size in hyperthyroid patients support this hypothesis.

In our study, tumoral characteristics were similar in all groups, although lymph node metastasis was higher in hypothyroid patients compared to hyperthyroid patients. A possible reason might be the higher prevalence of incidental tumors in the hyperthyroid group. Moreover, hypothyroid patients were operated more frequently for indeterminate or malignant cytology results.

Age is an independent risk factor for the development of thyroid nodules (20). In our study, the mean age of patients with EMNG was higher compared to patients with ENG. With regard to tumoral characteristics in patients with EMNG and ENG, poor prognostic factors, such as tumor size, vascular invasion, and capsular invasion, were observed at a lower frequency in the EMNG group. This was probably related to a higher incidence of incidental thyroid cancer in this group of patients. We generally prefer to perform US-guided FNAB in all nodules >1–1.5 cm and <1 cm with suspicious US features. However, it seems that, despite all efforts, small tumoral lesions might be left undiagnosed preoperatively in patients with multiple nodules. It is known that the majority of incidental thyroid carcinomas are PTC (21). Higher rate of PTC in EMNG might be attributed to the incidentality of nearly half the malignant lesions in this group of patients.

Thyroid cancer was detected in 42.9% of hypothyroid patients who underwent thyroidectomy in our study. Although there are studies showing no association between HT and malignant thyroid lesions (22), many others show increased prevalence of thyroid cancer in these patients. Prevalence of thyroid cancer was found to be significantly higher in patients with HT than in patients without HT in the metaanalysis by Singh et al. In another study, patients with PTC had a significantly higher prevalence of HT compared to patients with benign thyroid nodular disease (18.8% vs. 7.2%) (23–26). Additionally, we have shown that 34.5% of 919 patients with PTC had histopathologically confirmed HT in a previous study (25). The association between thyroid cancer and HT was attributed to elevated levels of TSH found in hypothyroid patients with HT. We did not determine the underlying causes of hypothyroidism; however, HT, as the leading cause of hypothyroidism in many countries, was probably the most common cause in hypothyroid patients in our study.

Graves disease can affect all ages, but is most common in people between 20 and 50 years of age. In contrast, the most frequent cause of spontaneous hyperthyroidism is TMNG in elderly patients. The mean age of patients with Graves in the present study was significantly lower compared to patients with toxic autonomous nodules. We found that Graves patients were significantly younger than Graves patients with a nodule or nodules. Similarly to our finding, in a study by Kim et al., the mean age of patients with nodular Graves disease was significantly higher compared to Graves patients without nodule (26). Additionally, the authors indicated that the age of the patient was the only significant variable predicting the presence of both nodules and cancer in Graves patients. It seems that increased tendency for development of thyroid nodule with advancing age is also valid for Graves patients (20,27).

Nodules associated with Graves disease have been reported in various studies, with a prevalence ranging from 12.8% to 36.6% (21,26,28,29). However, 55.3% of all Graves patients in our study had nodule/nodules at a higher rate than that reported in the literature. This can be explained by the fact that we only included patients that underwent thyroidectomy. It is probable that surgery was indicated more commonly in Graves patients with nodule/nodules compared to those without nodules, for whom medical follow-up or radioactive iodine treatment are other options.

There is much variability in the prevalence of malignancy in hyperthyroid patients. It has been reported to range between 0.5% and 16.6% in patients with Graves disease, 2.5%–12% in patients with TNG, and 1.6%–16.0% in patients with TMNG (4,30–34). The discrepancy in thyroid cancer prevalence in hyperthyroidism has been explained by differences in treatment strategies, surgical approach, and extent of histopathological examination of the removed thyroid tissue in different centers. Additionally, genetic and environmental factors, such as living in an endemic goiter region and variations in iodine exposure, may have an effect on thyroid cancer rates. In the present study, thyroid cancer in TMNG/TNG patients was observed at a higher frequency compared to that generally reported in the literature. Possible explanations for the high overall prevalence of thyroid cancer in our study are also valid for these patients. In addition, we routinely evaluate nodules in hyperthyroid patients whatever the cause—Graves or autonomously functioning nodule—with FNAB (when euthyroidism is achieved), according to the indications identical to the ones used for nodular goiter. This might have contributed to the detection of cytologically suspicious nodules and increased thyroidectomy decisions, instead of following patients with long-term medical or radioactive iodine therapy. Secondly,

when surgery is indicated in a patient with hyperthyroidism in our center, total/near total thyroidectomy is preferred instead of lobectomy/hemithyroidectomy. This approach might be a factor that causes a high rate of incidental thyroid cancer in hyperthyroid patients.

Considering all 541 Graves patients in our study, malignancy was detected in 72 patients at a rate of 13.3%. This was nearly the same as the study by Ren et al., who showed a malignancy rate of 13.7% in surgically treated Graves disease patients (35). It was reported that when a thyroid nodule was present in Graves, the possibility of finding a carcinoma was 22.2%, whereas it was only 2.9% when the disease was without a nodule (36). In a multicentric study of 557 patients that had undergone thyroidectomy for Graves disease, the incidence of thyroid carcinoma was 3.8%, whereas this incidence was 15% if patients with a nodule were considered (37). In our study, prevalence of thyroid cancer in Graves, Graves + NG, and Graves + MNG groups was consistent with these studies (5.4%, 21.8%, and 19.3%, respectively). These findings suggest that nodules in Graves should be managed in the same way as any other thyroid nodule, including follow-up and consideration of a FNAB to exclude malignancy. There are conflicting results with regard to aggressiveness of thyroid cancer in Graves disease. Increased incidence of aggressive features and locally advanced cancers in these patients were reported in some studies (26,36,37). However, discordant results were obtained by other studies showing similar rates of multifocality, lymph node metastasis, distant metastatis, and mortality of thyroid cancer in patients with Graves disease and EMNG (38,39).

PTC constituted more than 90% of all tumor types in all subgroups of hyperthyroidism, except TNG, in which 4 of 15 (26.7%) tumoral foci were FTC. In a metaanalysis of solitary hyperfunctioning thyroid nodules harboring thyroid carcinoma, FTC and Hürthle cell carcinoma comprised 36.4% and 7.8% of 76 cases, respectively (40). These rates were much higher than those defined in guidelines for nodular thyroid diseases. No explanation for the high ratio of FTC in such nodules exists to date; however, the authors suggested that cytological diagnosis of follicular neoplasm within a hot nodule may not be as innocuous as previously thought.

In the present study, histopathological characteristics such as vascular invasion, extrathyroidal extension, and lymph node metastasis were similar in subgroups of hyperthyroidism. Exceptionally, capsular invasion was significantly higher in the TNG group compared to others, which can be attributed to a higher rate of FTC in this group. Nevertheless, the number of carcinomas in TNG in this study is not sufficient to conclude that FTC and capsular invasion are seen more frequently in this group of patients.

The main strength of our study is its high number of patients. In addition, to the best of our knowledge, malignancy risk in such a diversity of clinical thyroid diseases was evaluated and compared for the first time in the literature. However, the most significant limitations of our study were its retrospective design and possible selection bias before thyroidectomy. Furthermore, we did not perform further analyses considering the causes of hypothyroidism. Moreover, there might be HT patients with normal thyroid functions included in the euthyroid group. Since the association between HT and thyroid cancer—particularly DTC—was shown previously, the rate of malignancy in the euthyroid group might have been affected by euthyroid HT patients. Another limitation was that we did not analyze scintigraphy results and match hypoactive/hyperactive nodules with malignant nodules in the histopathological examination of hyperthyroid patients. Therefore, it was not possible to determine whether the malignant foci originated from the hyperactive nodule itself or from outside the hot nodule in patients with TMNG/TNG.

In conclusion, although hyperthyroidism has long been suggested to be a protective factor against thyroid cancer, there are growing data contradicting this suggestion. We showed lower prevalence of thyroid cancer in hyperthyroid patients compared to euthyroid and hypothyroid patients, yet the risk was still 18.3% in these patients, increasing to 19.7% when Graves patients without nodule were excluded. Nearly half of the thyroid carcinomas were incidental. Although the clinical significance of incidental thyroid cancer is controversial, we think that when surgery is indicated for some reason, total/near total thyroidectomy may be a reasonable approach in many patients for avoiding surgical risks of a completion thyroidectomy. Additionally, multinodularity in a thyroid gland carries a similar risk of malignancy as with solitary thyroid nodules, independent of functional status, and the risk exceeds 40% in both euthyroid and hypothyroid patients operated for various reasons.

In conclusion:

1) Thyroid cancer was detected less frequently in hyperthyroid patients compared to hypothyroid and euthyroid patients.

2) The rate of thyroid malignancy in hyperthyroid patients, operated for various indications, was 18.3%, which might legitimize total/near total thyroidectomy when surgery is planned.

3) Solitary nodule and multinodular goiter carried a similar risk of thyroid malignancy.

References

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM et al. American Thyroid Association Management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 26: 1-133.
2. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014; 140: 317-322.
3. Hegedus L. Clinical practice. The thyroid nodule. N Engl J Med 2004; 351: 1764-1771.
4. Gelmini R, Franzoni C, Pavesi E, Cabry F, Saviano M. Incidental thyroid carcinoma (ITC): a retrospective study in a series of 737 patients treated for benign disease. Ann Ital Chir 2010; 81: 421-427.
5. Polyzos SA, Kita M, Efstathiadou Z, Poulakos P, Slavakis A, Sofianou D, Flaris N, Leontsini M, Kourtis A, Avramidis A. Serum thyrotropin concentration as a biochemical predictor of thyroid malignancy in patients presenting with thyroid nodules. J Cancer Res Clin Oncol 2008; 134: 953-960.
6. Haymart MR, Repplinger DJ, Leverson GE, Elson DF, Sippel RS, Jaume JC, Chen H. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. Clin Endocrinol Metab 2008; 93: 809-814.
7. Rago T, Fiore E, Scutari M, Santini F, Di Coscio G, Romani R. Male sex, single nodularity, and young age are associated with the risk of finding a papillary thyroid cancer on fine-needle aspiration cytology in a large series of patients with nodular thyroid disease. Eur J Endocrinol 2010; 162: 763-770.
8. Jena A, Patnayak R, Prakash J, Sachan A, Suresh V, Lakshmi AY. Malignancy in solitary thyroid nodule: a clinicoradiopathological evaluation. Indian J Endocrinol Metab 2015; 19: 498-503.
9. Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, Nardi F, Panunzi C, Rinaldi R, Toscano V, Pacella CM. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab 2002; 87: 1941-1946.
10. Belfiore A, La Rosa GL, La Porta GA, Giuffrida D, Milazzo G, Lupo L, Regalbuto C, Vigneri R. Cancer risk in patients with cold thyroid nodules: relevance of iodine intake, sex, age and multinodularity. Am J Med 1992; 93: 363-369.
11. Balasubramaniam S, Ron E, Gridley G, Schneider AB, Brenner AV. Association between benign thyroid and endocrine disorders and subsequent risk of thyroid cancer among 4.5 million U.S. male veterans. See comment in PubMed Commons belowJ Clin Endocrinol Metab 2012; 97: 2661-2669.
12. 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: 4295-4301.
13. Gul K, Ozdemir D, Dirikoc A, Oguz A, Tuzun D, Baser H, Ersoy R, Cakir B. Are endogenously lower serum thyroid hormones new predictors for thyroid malignancy in addition to higher serum thyrotropin? Endocrine 2010; 37: 253-260.
14. Gandolfi PP, Frisina A, Raffa M, Renda F, Rocchetti O, Ruggeri C, Tombolini A. The incidence of thyroid carcinoma in multinodular goiter: retrospective analysis. Acta Biomed 2004; 75: 114-117.
15. Lin JD, Chao TC, Huang BY, Chen ST, Chang HY, Hsueh C. Thyroid cancer in the thyroid nodules evaluated by ultrasonography and fine-needle aspiration cytology. Thyroid 2005; 15: 708-717.
16. McCall A, Jarosz H, Lawrence AM, Paloyan E. The incidence of thyroid carcinoma in solitary cold nodules and in multinodular goiters. Surgery 1986; 100: 1128-1132.
17. Smith D, Thompson AM. Breast and endocrine surgery. In: Lavelle-Jones M, Dent JA, editors. Surgery. Toronto, ON, Canada: Elsevier, 2008. p. 119-141.
18. Shi L, Li Y, Guan H, Li C, Shi L, Shan Z, Teng W. Usefulness of serum thyrotropin for risk prediction of differentiated thyroid cancers does not apply to microcarcinomas: results of 1,870 Chinese patients with thyroid nodules. Endocr J 2012; 59: 973-980.
19. Fiore E, Vitti P. Serum TSH and risk of papillary thyroid cancer in nodular thyroid disease. J Clin Endocrinol Metab 2012; 97: 1134-1145.
20. Gupta KL. Neoplasm of the thyroid gland. Clin Geriatr Med 1995; 11: 271-290.
21. Miccoli P, Minuto MN, Galleri D, D'Agostino J, Basolo F, Antonangeli L, Aghini-Lombardi F, Berti P. Incidental thyroid carcinoma in a large series of consecutive patients operated on for benign thyroid disease. ANZ J Surg 2006; 76: 123-126.
22. Anil C, Goksel S, Gursoy A. Hashimoto's thyroiditis is not associated with increased risk of thyroid cancer in patients with thyroid nodules: a single-center prospective study. Thyroid 2010; 20: 601-606.
23. Singh B, Shaha AR, Trivedi H, Carew JF, Poluri A, Shah JP. Coexistent Hashimoto's thyroiditis with papillary thyroid carcinoma: impact on presentation, management, and outcome. Surgery 1999; 126: 1070-1076.
24. Lun Y, Wu X, Xia Q, Han Y, Zhang X, Liu Z, Wang F, Duan Z, Xin S, Zhang J. Hashimoto's thyroiditis as a risk factor of papillary thyroid cancer may improve cancer prognosis. Otolaryngol Head Neck Surg 2013; 148: 396-402.
25. Baser H, Ozdemir D, Cuhaci N, Aydin C, Ersoy R, Kilicarslan A, Cakir B. Hashimoto's thyroiditis does not affect ultrasonographical, cytological, and histopathological features in patients with papillary thyroid carcinoma. Endocr Pathol 2015; 26: 356-364.

26. Kim WB, Han SM, Kim TY, Nam-Goong IS, Gong G, Lee HK, Hong SJ, Shong YK. Ultrasonographic screening for detection of thyroid cancer in patients with Graves' disease. Clin Endocrinol 2004; 60: 719-725.

27. Faggiano A, Del Prete M, Marciello F, Marotta V, Ramundo V, Colao A. Thyroid diseases in elderly. Minerva Endocrinol 2011; 36: 211-231.

28. Carnell NE, Valente WA. Thyroid nodules in Graves' disease: classification, characterization, and response to treatment. Thyroid 1998; 8: 647-652.

29. Mishra A, Mishra SK. Thyroid nodules in Graves' disease: implications in an endemically iodine deficient area. J Postgrad Med 2001; 47: 244-247.

30. Kang AS, Grant CS, Thompson GB, van Heerden JA. Current treatment of nodular goiter with hyperthyroidism (Plummer's disease): surgery versus radioiodine. Surgery 2002; 132: 916-923.

31. Negro R, Valcavi R, Toulis KA. Incidental thyroid cancer in toxic and nontoxic goiter: is TSH associated with malignancy rate? Results of a meta-analysis. Endocr Pract 2013; 19: 212-218.

32. Preece J, Grodski S, Yeung M, Bailey M, Serpell J. Thyrotoxicosis does not protect against incidental papillary thyroid cancer. Surgery 2014; 156: 1153-1156.

33. Pazaitou-Panayiotou K, Michalakis K, Paschke R. Thyroid cancer in patients with hyperthyroidism. Horm Metab Res 2012; 44: 255-262.

34. Gul K, Di Ri Koc A, Ki Yak G, Ersoy PE, Ugras NS, Ozdemir D, Ersoy R, Cakir B. Thyroid carcinoma risk in patients with hyperthyroidism and role of preoperative cytology in diagnosis. Minerva Endocrinol 2009; 34: 281-288.

35. Ren M, Wu MC, Shang CZ, Wang XY, Zhang JL, Cheng H, Xu MT, Yan L. Predictive factors of thyroid cancer in patients with Graves' disease. World J Surg 2014; 38: 80-87.

36. Pacini F, Elisei R, Di Coscio GC, Anelli S, Macchia E, Concetti R, Miccoli P, Arganini M, Pinchera A. Thyroid carcinoma in thyrotoxicosis patients treated by surgery. J Endocrinol Invest 1988; 11: 107-112.

37. Cappelli C, Braga M, De Martino E, Castellano M, Gandossi E, Agosti B, Cumetti D, Pirola I, Mattanza C, Cherubini L et al. Outcome of patients surgically treated for various forms of hyperthyroidism with differentiated thyroid cancer: experience at an endocrine center in Italy. Surg Today 2006; 36: 125-130.

38. Edmonds CJ, Tellez M. Hyperthyroidism and thyroid cancer. Clin Endocrinol (Oxf) 1998; 28: 253-259.

39. Yano Y, Shibuya H, Kitagawa W, Nagahama M, Sugino K, Ito K, Ito K. Recent outcome of Graves' disease patients with papillary thyroid cancer. Eur J Endocrinol 2007; 157: 325-329.

40. Belfiore A, Garofalo MR, Giuffrida D, Runello F, Filetti S, Fiumara A. Increased aggressiveness of thyroid cancer in patients with Graves' disease. J Clin Endocrinol Metab 1990; 70: 830-835.