Association of Autoimmune Thyroid Diseases and Thyroid Cancer

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Abstract

Objective: The relationship between thyroid autoimmunity and thyroid cancer remains controversial. The aim of this study was to evaluate the risk of thyroid carcinoma in patients with Basedow-Graves (BG) and Hashimoto’s Thyroiditis (HT) patients, who subsequently underwent surgical treatment.

Design and Methods: From 2005 to 2014, 1668 patients underwent thyroid surgery at our institution. Of these, 138 patients were diagnosed with HT (126 women, 12 men) and 78 patients were diagnosed with BG (61 women, 17 men).

Results: Thyroid cancer was in 23.1 percent of BG patients, 52.2 percent of HT patients, and 38.7 percent of Nodular Goiter (NG) patients. When BG patients were compared with HT patients, it was determined that thyroid cancer was more often seen (p<0.001) in HT patients. When BG patients were compared with NG patients, it was determined that thyroid cancer was less seen (p=0.008) in BG patients. When HT patients were compared with NG patients, thyroid cancer was more often seen (p=0.003) in HT patients. When HT patients (average age: 46.53) were compared with NG patients (average age: 51.02), it was determined that thyroid cancer was seen in the earlier age (p=0.019) in HT patients. It was found that the frequency of papillary microcarcinoma in patients with BG was higher (p=0.004) in comparison with HT and NG patients. It was seen that tumor size in BG patients was smaller in comparison with HT and NG patients.

Conclusion: These data demonstrate that HT is associated with an increased risk of developing Thyroid Cancer (TC).

Keywords: Thyroid cancer; Hashimoto’s thyroiditis; Basedow-Graves disease; Nodular goiter

Abbreviations

AITD: Autoimmune Thyroid Disease; TC: Thyroid Cancer; PTC: Papillary Thyroid Cancer; TN: Thyroid Nodules; HT: Hashimoto’s Thyroiditis; GD: Graves Disease; DTC: Differentiated Thyroid Cancer; TSH: Thyroid-Stimulating Hormone; Tab: Thyroid autoantibodies; TSAb: Thyroid-Stimulating antibodies; TRAb: TSH Receptors Antibodies; FT³: Free Triiodothyronine; FT⁴: Free Thyroxine; TGAb: Thyroglobulin Antibody; TPOA: Thyroid Peroxidase Antibody; TFT: Thyroid Function Test

Introduction

Autoimmune diseases have a high prevalence in the population. Autoimmune Thyroid Disease (AITD) is one of the most common representatives [1]. Thyroid Cancer (TC) is the most common endocrine malignancy [2]. Hashimoto’s Thyroiditis (HT) is the most common cause of hypothyroidism. HT is seven times more likely to occur in women than in men. Papillary Thyroid Cancer (PTC), the most prevalent form of cancer in the thyroid, is 2.5 times more likely to develop in women than men [3]. HT is usually treated medically; however, thyroidecomy is sometimes indicated [4].

A link between inflammation and cancer is well recognized but HT with TC pathogenesis remains unclear [5,6]. The combination of high Thyroid-Stimulating Hormone (TSH) levels, anti-
TPO, and anti-Tg antibodies was identified as a risk factor for DTC [7]. Many hypotheses exist as to why HT occurs. It is possible that HT is thyroid chronic inflammation, which causes the thyroid gland structural damage and affects thyroid hormone production negative feedback to stimulate TSH secretion. Long-term high levels of TSH stimulation in the goiter may stimulate TC [8]. Several studies have suggested that Thyroid Autoantibodies (TAb) could be used as predictors of thyroid cancer risk, but the correlation between TAb and TC is still a matter of debate [9].

The association of Graves Disease (GD) with Thyroid Nodules (TN) and TC is rarely reported. The incidence seems to be increasing according to recent literature [10,11]. It was previously reported that DTC has higher aggressiveness and poorer prognosis in patients with GD than DTC in euthyroid control patients. Subsequent studies on this issue reached controversial conclusions. Genetic and environmental factors, as well as the lack of appropriate control subjects and/or inadequate patient follow-up, may account for these discrepancies [10,12,13]. Thyroid-Stimulating Antibodies (TSAb) may play a role in determining the high aggressiveness of TC in GD patients [14]. Extensive evidence indicates that thyrotropin stimulates the growth and function of DTC. These responses evidently reflect the presence in thyroid cancer cells of functioning thyrotropin receptors, which, on binding thyrotropin, mediate an increase in the cellular concentration of cyclic AMP, the second messenger for most actions of thyrotropin [15].

The risk of development of Differentiated Thyroid Cancer (DTC) following AITD is still under debate. The aim of this study was to review patients who had surgery for GD and HT associated with TN, and to evaluate the risk of TC.

**Material and Methods**

Between January 2005 and December 2014, of 1668 (1281 female, 387 male) patients treated surgically in a single referral university center (Ege University Medical Faculty Hospital) due to various thyroid diseases. It was determined 79 patients having BG, 138 patients having HT and it was determined having 1452 Nodular Goiter (NG). The study protocol was approved by the ethics committee of the Ege University Medical School.

Primary surgical treatment was Total Thyroidectomy (TT) when preoperative diagnosis was available. Therapeutic central compartment lymph node dissection was always done but prophylactic dissection was not routine. Selective neck dissection of lateral neck nodes clearing nodal stations in Levels II (A&B), III, IV and V was done when metastasis was detected.

Indications for thyroidectomy for GD were suspicious cytology and large volume goiters (>90 ml). All patients underwent high resolution ultrasound imaging and aspiration cytology from the nodules and suspicious lymph nodes.

The inclusion criteria for surgery in the HT group included nodular lesions of the thyroid detected by ultrasound as hypoechoic or hyperechoic nodular pattern at least 5 mm in diameter, identification of a perinodular hypoechoogenic or hyperechogenic halo, and the presence of an anechoic lesion with a reinforced posterior wall. A repeated analysis of Fine-Needle Aspiration Biopsy (FNAB) results based on the Bethesda 2009 classification showed that in the test results, the predominating lesions were these that today would be classified as groups III and IV of the above classification system.

The analyzed group of patients with Hashimoto’s thyroiditis included all individuals meeting the following criteria: (1) lesions visualized by ultrasonography showing a hypoechoic or hyperechoic nodular pattern at least 5 mm in diameter, identification of a perinodular hypoechoogenic or hyperechogenic halo and presence of an anechoic lesion with a reinforced posterior wall, (2) high anti-Thyroid Peroxidase antibodies titers (anti-TPO) or Thyroglobulin Antibody (TgAb) (3) histology: presence of a diffuse lymphocytic infiltrate in the thyroid parenchyma and stroma with reaction foci and lymphatic follicles, presence of small follicles with a decreased colloid volume, foci of fibrosis and oxyphilic cytoplasm-containing cells. The exclusion criteria included patients’ positive for thyroid-stimulating hormone receptor antibodies (TRAb), Graves’ disease in medical history, and absence of clinical, ultrasound, and morphological signs of Hashimoto’s thyroiditis.

In the NG group, indications for surgical treatment included suspicious lesions detected by Fine Needle Aspiration Biopsy (FNAB; Bethesda grades III and IV: III -atypia of undetermined significance or follicular lesion of undetermined significance; IV -follicular neoplasm or suspicious for follicular neoplasm (Hurthle cell)), signs of compression of the trachea and surrounding tissues.

We excluded patients who had been previously exposed to high levels of radiation and patients who reported a history of surgery.

Physical examination, thyroid ultrasonography, and thyroid profiles were performed before surgical procedure. The data were analyzed retrospectively.

**Statistical analysis**

SPSS 20.0 packed software was used to perform statistical analyses. Chi square test, Student-t tests, Post Hoc Test, Kruskal-Wallis Test, Mann-Whitney U and Univariate variance analysis were applied for the examination of the relations between the variables. p values of <0.05 were accepted as statistically significant.

**Results**

In our study, it was determined 78 patients having BG: 61 female, 17 male; average age: 39.42 (19-73). It was determined 138 patients having HT: 126 female, 12 male; average age: 49.24 (22-77). It was determined having 1452 NG: 1094 female, 358 male; average age 53.34 (18-83).

Malignancy was present in 18 out of 78 patients included into the BG (23.1%). Malignancy was present in 72 out of 138 patients included into the HT (52.2%). Malignancy was present in 562 out of 1452 patients included into the NG (38.7%).

Malignancy data of the patients with TC in BG, HT and NG group are shown at Table 1.

The difference in malignancy between HT and BG group was found to be statistically significant (p<0.001) (Table 2). The difference in malignancy between HT and NG group was found to be statistically significant (p=0.003) (Table 2). The difference in malignancy between NG and BG group was found to be statistically significant (p=0.008) (Table 2).

There was statistical difference HT between malignancy positive and malignancy negative groups in term of the age (p=0.007) (Table 3). There was statistical difference NG between malignancy positive and malignancy negative groups in term of the age (p<0.001) (Table 3). There was no statistical difference GD between malignancy
positive and malignancy negative groups in term of the age (p=0.79) (Table 3). There was no statistical difference between GD malignancy positive and HT malignancy positive groups in term of the age (p=1.000) (Table 2). There was no statistical difference between GD malignancy positive and NG malignancy positive groups in term of the age (p=0.110) (Table 2). There was statistical difference between NG malignancy positive and HT malignancy positive groups in terms of the age (p=0.019) (Table 2).

In our study; malignancy frequency was 43.4% (168/387) in the male group, and 37.8% (484/1281) in the female group; and the difference between these groups was no statistically significant (p=0.054). Malignancy frequency in NG was 43.6% in the male group, and 37.1% in the female group; and the difference between these groups was statistically significant (p=0.034) (Table 4). Malignancy frequency in BG was 29.4% in the male group, and 21.3% in the female group; and the difference between these groups was no statistically significant (p=0.522) (Table 4). Malignancy frequency in HT was 58.3% in the male group, and 51.6% in the female group; and the difference between these groups was no statistically significant (p=0.885) (Table 4).

There was no statistical difference between GD malignancy positive and GD malignancy negative groups in term of the dominant nodule size (p=0.064) (Table 5). There was statistical difference NG between malignancy positive and malignancy negative groups in term of the dominant nodule size (p<0.001) (Table 5).

In our study; tumor size was 0.75 cm (min: 0.1 cm to max: 2.60 cm) based on Table 1: Malignancy data of the patients with thyroid cancer in Basedow-Graves, Hashimoto thyroiditis and nodular goiter group.

**Table 1:** Malignancy data of the patients with thyroid cancer in Basedow-Graves, Hashimoto thyroiditis and nodular goiter group.

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Basedow-Graves (n=78)</th>
<th>Hashimoto thyroiditis (n=138)</th>
<th>Nodular goiter (n=1452)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy (+)</td>
<td>n=18 (23%)</td>
<td>n=72 (52.2%)</td>
<td>n=562 (38%)</td>
</tr>
<tr>
<td>Papillary microcarcinoma</td>
<td>n=15 (83.3%)</td>
<td>n=34 (47.2%)</td>
<td>n=238 (42.3%)</td>
</tr>
<tr>
<td>Papillary carcinoma classic variant</td>
<td>n=2 (11.1%)</td>
<td>n=17 (23.6%)</td>
<td>n=112 (19.9%)</td>
</tr>
<tr>
<td>Papillary carcinoma follicular variant</td>
<td>n=0 (0%)</td>
<td>n=9 (12.5%)</td>
<td>n=146 (25.9%)</td>
</tr>
<tr>
<td>Papillary carcinoma other type</td>
<td>n=1 (5.5%)</td>
<td>n=9 (12.5%)</td>
<td>n=42 (7.4%)</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>n=0 (0%)</td>
<td>n=1 (1.3%)</td>
<td>n=11 (1.9%)</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>n=0 (0%)</td>
<td>n=2 (2.7%)</td>
<td>n=11 (1.9%)</td>
</tr>
<tr>
<td>Anaplastic carcinoma</td>
<td>n=0 (0%)</td>
<td>n=0 (0%)</td>
<td>n=2 (0.3%)</td>
</tr>
</tbody>
</table>

**Table 2:** The relation of Prognostic factors and malignancy in patient with Basedow-Graves, Hashimoto thyroiditis and nodular goiter.

<table>
<thead>
<tr>
<th>Age</th>
<th>Basedow-Graves</th>
<th>Hashimoto thyroiditis</th>
<th>Nodular goiter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.44 ± 11</td>
<td>46.53 ± 12</td>
<td>51.02 ± 13</td>
</tr>
<tr>
<td>Tumor size</td>
<td>0.7 ± 0.6</td>
<td>1.26 ± 1.04</td>
<td>1.4 ± 1.3</td>
</tr>
<tr>
<td>Papillary microcarcinoma</td>
<td>n=15 (83.3%)</td>
<td>n=34 (49.3%)</td>
<td>n=238 (44.2%)</td>
</tr>
<tr>
<td>Papillary macrocarcinoma</td>
<td>n=3 (16.7%)</td>
<td>n=35 (50.7%)</td>
<td>n=300 (55.8%)</td>
</tr>
<tr>
<td>Multifocal</td>
<td>n=7 (38.9%)</td>
<td>n=30 (41.7%)</td>
<td>n=172 (30.7%)</td>
</tr>
<tr>
<td>Capsule invasion</td>
<td>n=1 (5.6%)</td>
<td>n=7 (9.7%)</td>
<td>n=72 (12.8%)</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>n=0 (0%)</td>
<td>n=0 (0%)</td>
<td>n=15 (2.6%)</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td>n=3 (16.7%)</td>
<td>n=10 (13.9%)</td>
<td>n=75 (13.4%)</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>n=0 (0%)</td>
<td>n=0 (0%)</td>
<td>n=15 (3.3%)</td>
</tr>
</tbody>
</table>

**Table 3:** The relations age of thyroid cancer in patient with Basedow-Graves, Hashimoto thyroiditis and nodular goiter.

<table>
<thead>
<tr>
<th>Age</th>
<th>Malignancy (+)</th>
<th>Malignancy (-)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basedow-Graves</td>
<td>44.44 ± 11 (min:29-max:67)</td>
<td>38.42 ± 12 (min:19-max:73)</td>
<td>0.79</td>
</tr>
<tr>
<td>Hashimoto thyroiditis</td>
<td>46.53 ± 12 (min:22-max:77)</td>
<td>52.20 ± 11 (min:27-max:76)</td>
<td>0.007**</td>
</tr>
<tr>
<td>Nodular goiter</td>
<td>51.02 ± 13 (min:18-max:81)</td>
<td>54.81 ± 12 (min:22-max:83)</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.001
Table 4: The relations sex of thyroid cancer in patient with Basedow-Graves, Hashimoto thyroiditis and nodular goiter.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basedow-Graves</td>
<td>29.4% (n=5)</td>
<td>21.3% (n=13)</td>
<td>0.522</td>
</tr>
<tr>
<td>Hashimoto thyroiditis</td>
<td>58.3% (n=7)</td>
<td>51.6% (n=65)</td>
<td>0.885</td>
</tr>
<tr>
<td>Nodular goiter</td>
<td>43.6% (n=156)</td>
<td>37.1% (n=406)</td>
<td>0.034*</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.001

cm) in the BG group. Tumor size was 1.26 cm (min: 0.1 cm to max: 5 cm) in the HT group. Tumor size was 1.48 cm (min: 0.1 cm to 11 cm) in the NG group. There was statistical difference between GD and HT malignancy positive groups in terms of the tumor size (p=0.048) (Table 2). There was statistical difference between GD and NG malignancy positive groups in term of the tumor size (p=0.010) (Table 5). There was no statistical difference between HT and NG malignancy positive groups in term of the tumor size (p=0.311) (Table 2).

In our study, microcarcinoma frequency was 83.3% (n=15) and macrocarcinoma frequency was 49.3% (n=34) in the BG group. Microcarcinoma frequency was 49.3% (n=34) and macrocarcinoma frequency was 50.7% (n=35) in the HT group.

Microcarcinoma frequency was 44.2% (n=238) and macrocarcinoma frequency was 55.8% (n=300) in the NG group. There was statistical difference between GD and others groups in term of the microcarcinoma (p=0.004) (Table 2).

There was no statistical difference between GD, HT and NG in terms of the vascular invasion; respectively; 0%, 0%, 2.6 (n=15) (p=0.317) (Table 5). There was no statistical difference between GD, HT and NG in term of the lymph node metastases; respectively; 16.7% (n=3), 13.9% (n=10), 13.4% (n=75), (p=0.918) (Table 2).

There was no statistical difference between GD, HT and NG in term of the distant metastases; respectively; 0%, 0%, 2.6 (n=15) (p=0.304) (Table 2).

There was no statistical difference between GD and NG in terms of the tumor size (p=0.311) (Table 2).

There was statistical difference between malignancy positive and malignancy negative groups with GD in term of the TSH, FT3, FT4, TSH and calcitonin, respectively (p=0.847, p=0.486, p=0.972, p=0.670). There was statistical difference between malignancy positive (1.4 IU/L) and malignancy negative (5.2 IU/L) groups with GD in term of the TRab (p=0.031). There was no statistical difference between malignancy positive and malignancy negative groups with HD in term of the TSH, FT3, FT4 and calcitonin, respectively (p=0.486, p=0.412, p=0.585, p=0.804).

There was statistical difference between malignancy positive (1.18 mIU/L) and malignancy negative (0.8 mIU/L) groups with NG in term of the TSH (p<0.001). There was no statistical difference between malignancy positive and malignancy negative groups with NG in term of the FT3, FT4 and calcitonin, respectively (p=0.775, p=0.583, p=0.134). There was no statistical difference between malignancy positive groups with GD in term of the autoantibodies Tg-TPO-, Tg-TPO+, T+TPO-., and Tg+TPO+, (p=0.055). There was no statistical difference between malignancy positive groups with HT in terms of the autoantibodies Tg-TPO-, Tg-TPO+, T+TPO-., and Tg+TPO+, (p=0.251). There was no statistical difference between malignancy positive groups with NG in terms of the autoantibodies Tg-TPO-, Tg-TPO+, T+TPO-., and Tg+TPO+, (p=0.724).

Discussion

The aim of the study was to determine the incidence of coexistence of TC and AITD in surgical pathology material. Retrospective study of 1,668 patients undergoing surgery between 2005 and 2014, with a pathological diagnosis of GD, HT and ND. The clinical data and complementary tests performed before surgery are reported.

The risk of TC in patients with TN associated with HT is a debatable issue in evaluation of the available literature [16,17]. Anil et al. evaluated the true malignancy rate of unslected TC in patients with HT who underwent Fine-Needle Aspiration Cytology (FNAC). They found that TN in patients with HT are no more likely to be malignant than in those without HT [17]. On the other hand, Larson SD and colleagues carried out a study and found that patients with HT were three times more likely to have TC. PI3K/Akt expression was increased in both HT and well-differentiated TC in this study. This situation suggested strong link between chronic inflammation and cancer development [18]. The association between TC and GD is controversial. The coexistence of TN and GD is widely described, but its significance is uncertain with regards to the potential risk of malignancy [19]. Terzioglu et al. evaluated concurrent hyperthyroidism and TC. This study found that concurrent carcinoma with GD was 6% [20]. On the other hand, Chen et al. found that the incidence of developing cancer in the GD cohort was 1.37-fold higher than in the comparison cohort (p<0.001) [21].

In our study, malignancy prevalence in NG group was 38.7%. Malignancy frequency in GD and HT groups was determined to be 23.1% and 52.2%, respectively. Thus, the frequency of malignancy in NG is as high as that in GD (p=0.008). The frequency of malignancy in HT is as high as that in NG (p=0.003). On the other hand, frequency of malignancy in HT is as high as that in GD (p<0.01). This result gave rise to thought that HT presence may be a risk factor in malignancy (PTC) development.

PTC, the most prevalent form of cancer in the thyroid, is 2.5 times more likely to develop in women than men. Given the relatively high prevalence of these diseases and the increased occurrence in
women. Repplinger et al. analyzed data from their institution to determine if there is a correlation between HT and PTC in women. Their data demonstrated that HT is associated with an increased risk of developing PTC [3]. Also in our study, similar with the literature the most frequent malignancy type was PTC in HT. On the other hand, Wei et al. investigated in patients with GD who underwent thyroidectomy for TN lesions or GD. They data demonstrated that most of malignancy is low-risk papillary thyroid microcarcinoma without lymph node metastasis or lymphovascular and extrathyroidal invasion [22]. In our study, similar with the literature the most frequent malignancy type was PTC in GD. There was no statistical difference between GD, HT and NG in term of the PTC.

Azizi et al. evaluated association of HT with TC. Their data demonstrated an association of TC with both increased serum TgAb concentration and age <45 years [23]. Also in our study, similar with the literature, there was statistical difference between HT malignancy positive and NG malignancy positive groups in term of the age (46.53, 51.02, respectively) (p=0.019). Similarly, in our study, there was statistical difference HT between malignancy positive and malignancy negative groups in term of the age (p=0.007). In the literature the association between thyroid carcinoma and GD is controversial in terms of the age [24,25]. On the other hand, in our study, there was no statistical difference in malignancy between GD and NG in terms of the age. Similarly, there was no statistical difference malignancy difference between GD and HT in terms of age.

In the literature the association between TC and HD is controversial in terms of the gender [23]. Mazokopakis et al. did not found statistically significant gender difference in HT with TC [26]. Similarly, in our study, there was no statistical difference in with HT malignancy groups in terms of the gender. In the literature, the malignancy frequency of GD for women is as high as that in male [27]. In our study, we did not find statistically significant gender difference in with GD thyroid carcinoma.

In our study, similar with the literature, there was no statistical difference between GD malignancy positive and GD malignancy negative groups in term of the dominant nodule size. Similarly, in our study, there was no statistical difference HT between malignancy positive and malignancy negative groups in terms of the dominant nodule size. In the literature, the size of tumors in the patients with GD was significantly smaller than in the euthyroid group [28]. In our study, similar with the literature, the size of tumors in the patients with GD was significantly smaller than in the HT group (p=0.048). Similarly, in our study, the size of tumors in the patients with GD was significantly smaller than in the NG group (p=0.01). On the other hand, in our study, there was no statistical difference between HT and NG malignancy positive groups in term of the tumor size. In the literature, the microcarcinoma in the patients with GD was significantly prevalent than NG [25-27]. In our study, similar with the literature, the microcarcinoma with GD was significantly prevalent than in the HT and ND group (p=0.004).

Azizi et al. found an association of TC in HT group with increased serum TgAb concentration [23]. On the other hand, in our study, there was no statistical difference neither HT nor BG malignancy positive groups in term of the serum TgAb and TPOAb.

Azizi et al. found an association of TC in HT group with elevated serum concentration of TSH ≥ 1 μIU/ml [23]. Similarly, in the literature, Haymart et al. found TC incidence correlates with higher

TSH [29]. In our study, there was no statistical difference in with HT malignancy groups in term of the elevated serum concentration of TSH, calcitonin and other TFT.

In our study, there was statistical difference between malignancy positive and malignancy negative groups with GD in term of the TRAb (p=0.019). On the other hand, in our study, there was no statistical difference between malignancy positive and malignancy negative groups with GD in term of the TSH, FT3, FT4, TSH and calcitonin. There was statistical difference between malignancy positive and malignancy negative groups with NG in term of the TSH (p<0.001).

Yano et al. found that no significant correlations were found between the TRAB levels in the GD group and multifocality or the presence of lymph node metastasis. The results in this series of patients do not support the claim that TC is more aggressive in GD patients than in euthyroid patients [30]. In our study, similar with the literature, there was no statistical difference between GD, HT and NG in term of the multifocality.

Konturek et al. found that multifocal PTC in patients with HT is associated with an increased risk of LNM [31]. Also, in Konturek et al. another study found that the spread of PTC to level VI lymph nodes was four times more frequent in HT than in non-HT patients [32]. In our study; there was no statistical difference between GD, HT and NG in term of the capsule invasion. Also in our study, there was no statistical difference between GD, HT and NG in term of the vascular invasion. Similarly, in our study, there was no statistical difference between GD, HT and NG in term of the distant metastases. Cappelli et al. found that cancers associated with GD seem to be more aggressive than those associated with multinodular toxic goiter or uninodular toxic goiter [36]. Kikuchi et al. found that patients with small TC in GD have an excellent prognosis [37]. In the literature, the association between TC and GD is controversial in term of the distant metastases.

In conclusion, we examined the clinico-pathological correlations between HT and GD in terms of the TC in our region in the Western part of Turkey. When BG patients were compared with HT patients, it was determined that thyroid cancer was more often seen in HT patients. When BG patients were compared with NG patients, it was determined that TC was less seen in BG patients. When HT patients were compared with NG patients, TC was more often seen in HT patients. When HT patients were compared with NG patients, it was determined that TC was seen in the earlier age in HT patients. It was found that the frequency of papillary microcarcinoma in patients with BG was higher in comparison with HT and NG patients. It was detected that TRAB was lower in BG patients being TC. It was stated that thyroid antibodies and TSH had no effect on TC development in AIID.

These data demonstrate that HT is associated with an increased risk of developing Papillary Thyroid Cancer (PTC). Nevertheless, a pathogenesis linking these diseases remains unclear. Further long-
term follow-up studies and multicenter research are needed to better understand these risk factors. No association was found between HT and follicular, medullary, or anaplastic thyroid cancer.

**References**


