

# Elevated Risk of Papillary Thyroid Cancer in Guatemalan Patients with Hashimoto Thyroiditis

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## ABSTRACT

**Aim and objective:** The relationship between Hashimoto's thyroiditis (HT) and papillary thyroid cancer (PTC) regarding their concurrence and the effect of concurrent HT on the prognosis of PTC has been controversial. In Guatemala, there are no studies of the coexistence of PTC and HT. This study aimed to determine if the presence of HT increased the risk of PTC and to determine if the presence of HT decreases the aggressiveness of PTC.

**Materials and methods:** Clinicopathological data were assessed in all patients ( $n = 381$ ) with thyroid pathology operated by a single surgical team over a period of 1996 to 2014 in Guatemala City. Of these participants, 115 with histologically confirmed PTC, measures of tumor aggressiveness were compared between patients with PTC and HT and PTC without HT.

**Results:** In our study population, 19% (73/381) of the patients presented HT. After adjusting for age, sex, and nodule size; patients with HT presented more coexisting PTC [OR 2.56 (1.35–4.87)] compared to patients without HT. In the subgroup of patients with PTC ( $n = 115$ ), 23% (26/115) had to coexist HT. Nodule size, angiovascular invasion, capsular invasion, lymph node metastasis, and extrathyroidal tissue invasion did not differ between patients with PTC with and without HT.

**Conclusion:** The presence of HT in Guatemalan patients increases the risk of PTC, and the presence of HT does not decrease the aggressiveness of PTC.

**Clinical significance:** High prevalence of PTC in patients with HT requires close clinical monitoring of patients.

**Keywords:** Cohort study, Guatemala, Hashimoto thyroiditis, Papillary thyroid cancer.

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## BACKGROUND

Papillary thyroid carcinoma (PTC) is the most common histologic variant of thyroid cancer in iodine-sufficient areas.<sup>1</sup> Similarly, Hashimoto's thyroiditis (HT) is the most common autoimmune disease of the thyroid gland, with an incidence estimated of 0.3–1.5/1,000 people per year.<sup>2,3</sup> The prevalence of HT in pathology specimens from patients with PTC is 0.05–38%;<sup>4</sup> their coexistence report has increased in recent years.<sup>5</sup>

Both HT and PTC have a high prevalence worldwide, and these conditions may have a close relationship. Although chronic inflammation is known to lead sometimes to neoplastic transformation, a cause-effect relationship between HT and PTC has not been proven. Whether PTC represents a reactive response to HT or HT is a prerequisite tumorigenic event still remains to be determined.<sup>5–7</sup> PI3K/Akt increased expression has been observed in both HT and PTC, suggesting a possible common molecular mechanism for the emergence of HT and thyroid cancer.<sup>6</sup> Moreover, in experimental animals, iodine depletion prevents the development of autoimmune thyroiditis<sup>8</sup> and iodine excess increases the incidence of autoimmune thyroiditis.<sup>9</sup>

In Salta, Argentina, Harach et al. studied epidemiological patterns of cancer and autoimmune thyroid diseases, after implementing programs to increase iodine intake, for preventing the occurrence of endemic goiter. Forty years after these programs started an increase in the incidence of papillary cancer and autoimmune thyroiditis was noticed.

In addition, the clinicopathological characteristics of PTCs with concomitant HT have not been definitely proposed.<sup>5,9–12</sup> In Guatemala, there are no studies of the coexistence of papillary thyroid cancer (PTC) and HT.

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The goals of this study are to determine if the presence of HT increases the risk of PTC and to determine if the presence of HT lessens the aggressiveness of PTC. We performed a retrospective analysis of the relationship between HT and PTC using patients from a private practice sample.

## MATERIALS AND METHODS

After obtaining ethical approval, the study included 381 patients with thyroid pathology operated by a single surgical team from 1996 to 2014 in Guatemala. Age, gender, tumor size, presence of histologically proven HT, and PTC were assessed in all patients. In the

subgroup of patients with PTC nodule size, angiovascular invasion, capsular invasion, lymph node metastasis, and extrathyroidal tissue invasion were analyzed.

Results were expressed as mean  $\pm$  standard deviation (SD). Statistical analysis was performed using a Student's *t*-test or Fisher's exact test. ORs with 95% confidence intervals (CIs) for the relationships between the variables and HT were calculated using logistic regression. A *p* value of  $<0.05$  was considered statistically significant. Statistical analysis was performed using STATA version 12.

## RESULTS

In total, 381 patients underwent thyroid surgery in our hospital during the study period (41 males and 340 females), 266 (70%) had a final diagnosis of a benign thyroid nodule, and 115 (30%) had a final diagnosis of PTC. The ages for the patients ranged from 9 to 83 with a mean age of 44 ( $\pm 15.34$ ). The prevalence of HT in our study population was 19%.

We compared the clinicopathological factors between patients with and without HT (Table 1). In univariate analysis, patients with HT were older and had a smaller nodule.

In multivariate analysis, patients with HT are older, have smaller nodules, and presented more coexisting PTC, OR = 2.56 (1.35–4.87) compared to patients without HT (Table 2).

In the subgroup of patients with PTC, we compared clinicopathological factors (Table 3) and the measures of tumor aggressiveness between patients with PTC and HT and PTC without HT. Of the 115 patients, 106 (92%) were female, with a mean age of 44 years (range 14–79) and median nodule size of 1.8 cm (IQR 1–2.3); 61 (53%) had the classical variant of PTC, 46 (40%) follicular variant, 5 (4%) tall cell variant, and the remaining 3 (3%) cribriform and insular. The prevalence of having HT in PTC patients is 23% compared to 18% in patients without PTC.

Among the patients with PTC, none of the clinicopathological factors nor the measures of tumor aggressiveness differ significantly between the groups with and without HT.

## DISCUSSION

After adjusting for age, sex, and nodule size, the presence of HT in Guatemalan patients increases the risk of PTC.

**Table 1:** General characteristic of patients with thyroid surgery

	With Hashimoto	Without Hashimoto	<i>p</i> value
Number of patients	73	308	
Age	48.15 ( $\pm 16$ )	43.53 ( $\pm 15$ )	0.02
Female	69 (94)	271 (88)	0.14
Male	4 (6%)	37 (12%)	
Nodule size	0.63 ( $\pm 1.07$ )	1.99 ( $\pm 1.85$ )	0.00
PTC coexistence	26 (36)	89 (28)	0.26

**Table 2:** Variables associations in patients with and without Hashimoto thyroiditis

	Unadjusted OR	Adjusted OR
Age ( $\leq 45$ vs $>45$ years)	2.06 (1.22–3.47)	1.93 (1.09–3.39)
Sex (male vs female)	0.42 (0.15–1.23)	0.33 (0.11–1.01)
Nodule size ( $\leq 1$ vs $>1$ cm)	0.16 (0.09–0.29)	0.12 (0.06–0.23)
PTC (no coexistence vs coexistence)	1.36 (0.79–2.33)	2.56 (1.35–4.87)

Dailey et al. first reported the coexistence of PTC and HT in 1955.<sup>13</sup> It has been hypothesized that increased iodine intake around the world, has led to increased incidences of PTC and autoimmune thyroid diseases, both separately and together.<sup>14</sup>

The coexistence of PTC and HT may represent a coincidence of two relatively common conditions or be indicative of a causal relationship. One possible mechanism underlying a causal relationship between PTC and HT could be that solid nest thyroid cells (SNCs), composed of pluripotent cells, give rise to follicular cells and C cells, remnants of the last branchial body found in normal thyroid. These SNCs have been observed more often in PTC associated with HT.<sup>15</sup> Also, HT can express the rearrangement RET/PTC, an early and specific marker that is strongly associated with papillary thyroid carcinoma, but it remains unknown whether the rearrangement RET/PTC induces HT to PTC.<sup>7,16</sup>

In our study population, 19% of Guatemalan patients presented HT. The prevalence of PTC in patients with HT was 36%, which was a similar rate to in the previous reports.<sup>10,17,18</sup> The high prevalence of PTC in patients with HT has important clinical implications. Patients with HT should be monitored closely, with clinical exams, to be able to identify early-onset PTC. Patients with HT were older and had smaller nodules compared to patients without HT, data that are supported by previous studies linking HT with PTC.<sup>5,10,17</sup>

We also analyzed the relationship of HT in the subgroup of patients with PTC. The prevalence of HT in patients with PTC reported in the literature is 0.05–38%.<sup>10,17,18</sup> We found a prevalence of 23% in our study, within the range of what has been reported.

Several studies have shown that clinical presentation of PTC associated with HT has a better prognosis than PTC alone in terms of recurrence and mortality,<sup>4,10,19,20</sup> suggesting HT as a protective factor in tumoral invasion,<sup>21–23</sup> although other studies show no statistically significant difference.<sup>5,11,24</sup> There have been several hypotheses about the causative mechanisms of better prognosis in patients with PTC and HT. Giordano et al. reported that thyrocytes from HT expressed Fas. Interleukin-1 beta, abundantly produced in HT glands, induced Fas expression in normal thyrocytes resulting in massive thyrocytes apoptosis.<sup>25</sup> Thus, PTC cells originated from follicular cells would express the thyroid-specific antigens and auto-antibodies from coexistence with HT that might destroy the tumor cells in the same way as in HT.<sup>5,26</sup> Zhang et al. hypothesized that long-term HT leads to elevated serum TSH, which is the real risk factor for thyroid cancer.<sup>4</sup> In our study, HT did not play a protective role in PTC patients, none of the clinicopathological factors nor the measures of tumor aggressiveness differ significantly between PTC patients with and without HT.

**Table 3:** Clinicopathological factors in PTC patients

	PTC with Hashimoto	PTC without Hashimoto	<i>p</i> value
Number of patients	26	89	
Age	49.11 ( $\pm 15.93$ )	43.27 ( $\pm 13.84$ )	0.07
Female	26 (100)	80 (89)	0.21
Nodule size	1.77 ( $\pm 1.11$ )	2.16 ( $\pm 1.68$ )	0.16
Angiovascular invasion	6 (23)	12 (13)	0.23
Capsular invasion	42 (47)	11 (42)	0.82
Lymph node metastases	3 (12)	21 (24)	0.27
Extrathyroidal tissue invasion	0 (0)	11 (12)	0.07

It is difficult to explain why HT patients are 2.56 times more likely to have PTC than patients without HT; whereas in the subset of PTC patients, HT shows no correlation with tumor aggressiveness. This study suggests a possible link between HT and the development of PTC rather than the chance of occurrence of two diseases. The cross-link of these two conditions may represent a cause and effect relationship or a predisposing factor.

The association between HT and PTC might be explained by common etiologic factors like genetic mutations present in both conditions or by elevated serum TSH in patients with HT, knowing that PTC is hormone-dependent. This hypothesis needs further study.

The present study has limitations. Because it was based on patients that underwent thyroid surgery, there is a risk of selection bias. Most patients with HT are not treated surgically, so the true prevalence of HT in patients with PTC may have been underestimated. The study was retrospective and rather small; even if we included all the surgically treated patients with thyroid pathology in our institution our sample size is still small. The failure to find associations with statistical significance may represent a type II error (false-negative) due to sample size.

In conclusion, after adjusting for age, sex, and nodule size, the presence of HT increases 2.56 times the risk of PTC and the presence of HT does not lessen the aggressiveness of PTC.

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