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Hashimoto's Thyroiditis as a Risk Factor of Papillary Thyroid Cancer May Improve Cancer Prognosis

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Abstract

Objective. Hashimoto's thyroiditis (HT) has been associated with an elevated risk of papillary thyroid cancer (PTC). To investigate the possible influence of HT on the prognosis of PTC patients, we assessed the related clinical factors linking these conditions, especially serum thyroid-stimulating hormone (TSH) concentration.

Study Design. Case-control study.

Setting. The First Hospital of China Medical University.

Subjects and Methods. The demographic and histological characteristics of 2478 patients who underwent thyroidectomy at our center from 2004 to 2012 were analyzed.

Results. Compared with patients with benign thyroid nodular disease, patients with PTC showed a significantly higher prevalence of HT (18.8% vs 7.2%, $P < .001$), mean TSH concentrations (2.02 $\pm$ 1.76 vs 1.46 $\pm$ 1.21 mIU/L, $P < .001$), and positivity rates for anti–thyroglobulin antibodies (TGAB; 40.0% vs 20.4%, $P < .001$) and anti–thyroid peroxidase antibodies (24.8% vs 12.5%, $P < .001$). These differences remained after excluding all HT patients. The TSH concentrations were significantly higher in PTC patients with HT than in those without HT (2.54 $\pm$ 2.06 vs 1.90 $\pm$ 1.66 mIU/L, $P = .001$). Patients with PTC and HT were younger, with a female predominance, and had smaller sized tumors with less advanced TNM stage compared with those without HT, indicating a better prognosis. Multivariate analysis showed that HT, higher TSH concentration, male sex, and TGAB positivity were independent risk factors for PTC development.

Conclusion. Histologically confirmed HT is associated with a significantly higher risk of PTC, due primarily to the higher serum TSH concentrations resulting from the tendency to hypothyroidism in HT. Autoimmunity is another independent risk factor for PTC but may be associated with a better prognosis.

Keywords

Hashimoto's thyroiditis, papillary thyroid cancer, thyroid-stimulating hormone

Thyroid cancer is the most common endocrine malignancy worldwide, with significant increases in incidence in China and East Asia over the past decade.[1,2] About 70% to 80% of thyroid cancers are papillary thyroid cancer (PTC).[3] Despite surgical advances and better long-term results, the underlying pathogenesis of PTC remains unclear. Hashimoto's thyroiditis (HT) is a thyroid-specific autoimmune disease that may be associated with an increased risk of thyroid cancer. It is characterized by an increased serum concentration of thyroid-stimulating hormone (TSH), but the relationship between higher TSH in HT and the development of PTC remains unclear.

A link between HT and thyroid cancer was first proposed in 1955,[4] with several subsequent retrospective studies showing a correlation between these conditions.[5-10] Hashimoto's thyroiditis is the most common cause of hypothyroidism, which is closely related to elevated TSH concentration. Recent studies have suggested that, even within a normal range, a higher serum TSH concentration is associated with the occurrence and extension of PTC.[11-15] Although we hypothesized that HT may lead to neoplastic transformation through higher TSH concentrations, studies to date have yielded conflicting results,[7,12] largely because of different criteria and methods of diagnosis. In several studies, a diagnosis of HT was based only on the presence of thyroid antibodies, whereas in others, HT was diagnosed based on fine-needle aspiration (FNA) and cytological examination. These differences can easily lead to conflicting results.

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Table 1. Reasons for Exclusion from the Study

	Number
Thyroidectomy history	207
No thyroid function test	12
History of thyroid nodule for more than 1 year[a]	98
Other histological types of thyroid malignancies[b]	63
Hyperthyroidism[c]	179
Subacute thyroiditis	24
Parathyroid diseases	11
History of using drugs[d]	13
Total	607

[a]Before thyroidectomy in our hospital.
[b]Including medullary carcinoma, follicular carcinoma, lymphoma, and other rare histological types.
[c]$FT_3 \geq 5.70$ pmol/L and/or $FT_4 \geq 19.05$ pmol/L, including Graves disease, Plummer's disease, and toxic multinodular goiters.
[d]Including thyroid hormones, antithyroid drugs, and iodine.

To overcome these limitations and shortages, our present study was designed to evaluate the clinical relationship between HT and PTC, with all patients diagnosed histologically. More important, we investigated the association between TSH concentration and HT plus PTC, to determine whether the co-occurrence of HT could influence the prognosis of patients with PTC. We therefore included patients with benign thyroid nodular disease (BTND) and ruled out possible factors that may affect TSH concentration.[6,7]

Patients and Methods

Patients

Of the 3085 patients who underwent thyroidectomy in the First Hospital of China Medical University from 2004 to 2012, 2478 fulfilled our inclusion criteria and were enrolled, whereas 607 patients were excluded (**Table 1**). Patients were included if they underwent thyroidectomy for the first time and if they had not been treated with thyroid hormones, antithyroid drugs, or iodine. Patients who had been diagnosed with hyperthyroidism or subacute thyroiditis were also excluded. In addition, patients with BTND were included if they had been diagnosed with a thyroid nodule within 1 year before surgery.

To rule out possible confounding factors that may affect TSH concentrations and to reduce selection bias, our inclusion criteria were more stringent than in studies from Western countries. Patients with nodular goiter, present in the overwhelming majority of patients in the BTND group, were indicated for surgical treatment, according to current Chinese guidelines and Huang Jiasi Surgery,[16,17] as follows. The first indication for treatment was if their symptoms stemmed from the compression of the trachea, esophagus, and/or recurrent laryngeal nerve. Also, patients were indicated for treatment if they had retrosternal goiter, hyperthyroidism secondary to a nodular goiter, suspected malignancy, or a large nodule that affected a patient's activities of daily living.

Although FNA is helpful in diagnosing thyroid diseases, it has been used in our hospital only during the past 2 years. Prior to its adoption, a suspicion of malignancy was based primarily on morphological data and physical examination, resulting in wider indications for malignancy in China than in Western countries. Our patient cohort therefore consisted of 2478 patients: 1802 in the BTND group and 676 in the PTC group (**Table 2**). The study was approved by the Institutional Review Board of China Medical University and by the local ethics committee.

Laboratory Assays

Thyroid function was evaluated within 2 weeks prior to surgery. All blood samples were tested in the endocrine laboratory of the First Hospital of China Medical University. Serum TSH concentrations were measured using a chemiluminescent microparticle immunoassay (Architect TSH Reagent

Table 2. Characteristics of Patients with BTND and PTC

		PTC (n = 676)					
	BTND (n = 1802)	Total (n = 676)	*P* Value[a]	Microca[b] (n = 247)	*P* Value[a]	No Microca (n = 429)	*P* Value[a]
Existence of HT	129/1802 (7.2)	127/676 (18.8)	<.001	53/247 (21.5)	<.001	74/429 (17.2)	<.001
Male sex	386/1802 (21.4)	138/676 (20.4)	.585	53/247 (21.5)	.989	85/429 (19.8)	.464
Age, y	49.4 ± 11.3	44.2 ± 13.2	<.001	45.2 ± 11.1	<.001	43.6 ± 14.3	<.001
TSH, mIU/L	1.46 ± 1.21	2.02 ± 1.76	<.001	1.88 ± 1.46	<.001	2.10 ± 1.91	<.001
FT_4, pmol/L	13.74 ± 2.01	13.71 ± 2.09	.744	13.83 ± 2.11	.495	13.64 ± 2.07	.351
FT_3, pmol/L	4.37 ± 0.61	4.28 ± 0.62	.001	4.30 ± 0.60	.094	4.27 ± 0.63	.003
TGAB(+)	333/1631 (20.4)	252/636 (40.0)	<.001	85/238 (35.7)	<.001	167/398 (42.0)	<.001
TPOAB(+)	204/1627 (12.5)	157/634 (24.8)	<.001	49/238 (20.6)	.001	108/396 (27.3)	<.001

Values are presented as No. (%) or mean ± SD. Abbreviations: BTND, benign thyroid nodular disease; FT_4, free thyroxine; FT_3, free triiodothyronine; HT, Hashimoto's thyroiditis; Microca, microcarcinoma; PTC, papillary thyroid cancer; TGAB, thyroglobulin antibody; TPOAB, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone.
[a]Compared with the BTND group.
[b]Defined as tumor size ≤1.0 cm.

Table 3. Comparison of Antibodies after Excluding Patients with HT

	BTND without HT, No. (%)	PTC without HT, No. (%)	*P* Value
TGAB(+)	232/1510 (15.4)	140/514 (27.2)	<.001
TPOAB(+)	122/1507 (8.1)	79/513 (15.4)	<.001

Abbreviations: BTND, benign thyroid nodular disease; HT, Hashimoto's thyroiditis; PTC, papillary thyroid cancer; TGAB, thyroglobulin antibody; TPOAB, thyroid peroxidase antibody.

Kit; Abbott Ireland Diagnostics Division, Longford, Ireland; reference interval .35-4.94 mIU/L), as were serum concentrations of free thyroxine (FT_4: Architect Free T_4 Reagent Kit; Abbott Ireland Diagnostics Division; reference interval 9.01-19.05 pmol/L), free triiodothyronine (FT_3: Architect Free T_3 Reagent Kit; Abbott Ireland Diagnostics Division; reference interval 2.63-5.70 pmol/L), anti–thyroglobulin antibodies (TGAB; Architect Anti-Tg Reagent Kit; Thermo Fisher Scientific, Middletown, Virginia; reference interval 0.00-4.11 IU/mL), and anti–thyroid peroxidase antibodies (TPOAB; Architect Anti-Tpo Reagent Kit; Thermo Fisher Scientific; reference interval 0.00-5.61 IU/mL).

Histological Diagnosis

Histological data were obtained from the postoperative paraffin histological reports, provided by the department of pathology of the First Hospital of China Medical University. The results were confirmed by 2 experienced pathologists. The histological criteria for HT included diffuse lymphocytic infiltration, germinal centers, enlarged epithelial cells with large nuclei and eosinophilic cytoplasm (Askanazy or Hürthle cells), and variable amounts of stromal fibrosis throughout the thyroid gland. The overriding feature of HT is the progressive depletion of thyroid epithelial cells, which are gradually replaced by mononuclear cells and fibrosis. On the basis of this key point, and using postoperative paraffin histology, we could histologically distinguish between peri-neoplastic inflammation and true HT combined with PTC, conditions difficult to distinguish on FNA.

Statistical Analysis

Quantitative data were reported as mean ± SD. Independent *t* tests were used to compare continuous values. Counting data were tested by χ^2 tests. Binary logistic regression was used for multivariate analysis. *P* values were 2-sided throughout, and the statistical significance was defined as $P < .05$. All statistical analyses were performed using statistical software (SPSS Statistics version 19; SPSS, Inc, an IBM Company, Chicago, Illinois).

Results

Characteristics of Patients with BTND and PTC

The demographic and laboratory data of the BTND and PTC groups are summarized in **Table 2**. Of the 2478 patients in both groups, 1954 (78.9%) were women and 524 (21.1%) were men, but the proportion of men in each group was identical (21.4% vs 20.4%, $P = .585$). The BTND group was significantly older at the time of surgery (49.4 ± 11.3 years vs 44.2 ± 13.2 years, $P < .001$), with significantly lower TSH (1.46 ± 1.21 mIU/L vs 2.02 ± 1.76 mIU/L, $P < .001$) and significantly higher FT_3 (4.37 ± 0.61 pmol/L vs 4.28 ± 0.62 pmol/L, $P = .001$) concentrations than the PTC group.

The prevalence of HT was significantly higher in the PTC group than in the BTND group (18.8% vs 7.2%, $P < .001$), even after removing patients with papillary microcarcinomas. The PTC group also had higher rates of positivity for TGAB (40.0% vs 20.4%, $P < .001$) and TPOAB (24.8% vs 12.5%, $P < .001$) than the BTND group, but the concentrations of FT_4 did not differ significantly (13.71 ± 2.09 pmol/L vs 13.74 ± 2.01 pmol/L, $P = .744$). Even after removing all patients with HT, the PTC group showed higher positivity rates for TGAB (27.2% vs 15.4%, $P < .001$) and TPOAB (15.4% vs 8.1%, $P < .001$) (**Table 3**) than the BTND group. When we evaluated all 2478 patients, we found that the frequency of PTC increased as TSH concentrations increased (**Figure 1A**). A similar tendency was observed when we evaluated only the 256 patients with HT (**Figure 1B**).

Characteristics of Patients with BTND with or without HT

The TSH concentrations were significantly higher in the 129 patients who had BTND plus HT than in the 1673 patients who had BTND without HT (2.17 ± 1.69 mIU/L vs 1.40 ± 1.15 mIU/L, $P < .001$). In addition, FT_3 (4.24 ± 0.64 pmol/L vs 4.38 ± 0.61 pmol/L, $P = .015$) and FT_4 (13.23 ± 2.39 pmol/L vs 13.77 ± 2.00 pmol/L, $P = .015$) concentrations were significantly lower in BTND patients with HT than without HT. Patients with HT manifested a tendency toward hypothyroidism (**Table 4**).

Characteristics of Patients with PTC with or without HT

Patients with PTC were subdivided into those with HT (n = 127) and without HT (n = 549). Of the 127 PTC patients with HT, 118 were women. Both the average age at operation (41.3 ± 12.5 years vs 44.8 ± 13.3 years, $P = .008$) and the proportion of patients >45 years of age (40.9% vs 51.5%, $P = .031$) were significantly lower in PTC patients with HT than without HT. The TSH concentrations were higher in PTC patients with HT than without HT (2.54 ± 2.06 mIU/L vs 1.90 ± 1.66 mIU/L, $P = .001$), whereas FT_3 and FT_4 concentrations did not differ significantly. Tumors

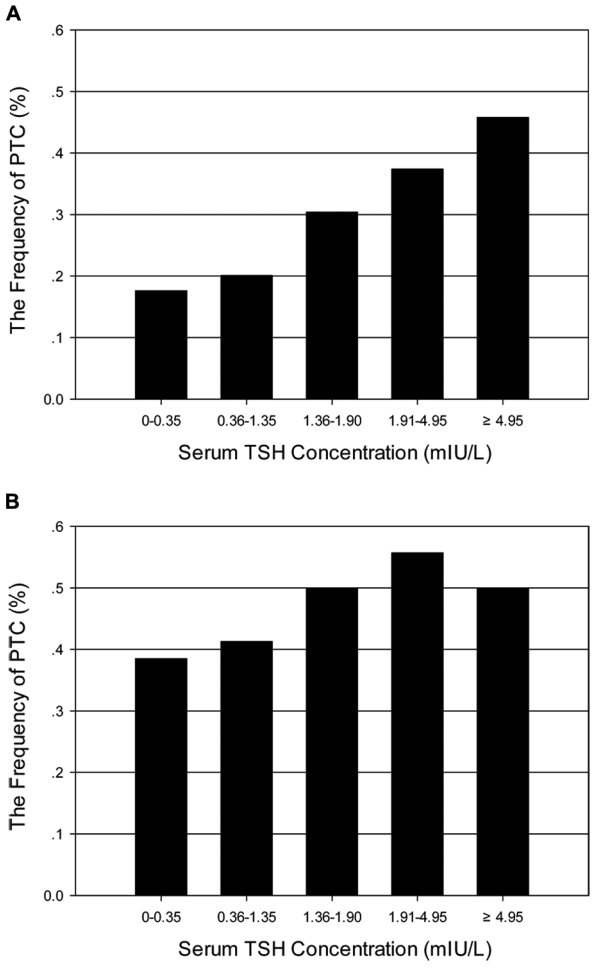

Figure 1. Serum thyroid-stimulating hormone (TSH) concentration was divided into 6 levels. (A) In all of the 2478 patients, the frequency of papillary thyroid cancer (PTC) rises with a higher TSH level. (B) A similar tendency is still observed when only 256 patients with Hashimoto's thyroiditis are considered and the prevalence is much higher.

were significantly smaller (1.84 ± 0.93 cm vs 2.24 ± 1.38 cm, $P < .001$) and tumor stage was less advanced in PTC patients with HT than without HT, but there was no difference in the percentage of patients with lymph node metastases (**Table 5**).

Multivariate Analysis

Variables such as HT, sex, age, FT_3, FT_4, TSH, TGAB, and TPOAB were included in the multivariate analysis. We found that HT (odds ratio [OR] = 1.60; confidence interval [CI], 1.14-2.24; $P = .006$), higher TSH concentration (OR = 1.28; CI, 1.19-1.38; $P < .001$), TGAB (+) (OR = 1.89; CI, 1.47-2.44; $P < .001$), and male sex (OR = 1.34; CI, 1.05-1.71; $P = .020$) were significant independent risk factors for the frequency of PTC (**Table 6**).

Discussion

The association between HT and PTC remains uncertain. The heterogeneity of diagnostic criteria for HT may confuse results. We found that the histological prevalence of HT was higher in patients with PTC than with BTND, in agreement with previous results.[5,7] However, the causative relationship between HT and PTC is not yet clear. The risk of malignancy has been shown to be associated with abnormally increased serum TSH concentrations.[13] Moreover, higher TSH concentrations, even within the normal range, have been associated with higher frequencies and more advanced stages of thyroid cancer.[11-15] We observed similar results, with the prevalence of malignancy increasing in patients with HT alone. Recently, the prevalence of PTC was found to be higher in patients with HT than in patients with Graves disease (GD).[18] Hashimoto's thyroiditis and GD are both thyroid-specific autoimmune diseases, suggesting that non-autoimmune factors may play a role in the initiation of PTC. Among patients with PTC, we observed a significant difference in TSH concentrations between those with HT and without HT, suggesting that HT-associated increases in TSH concentrations may enhance the risk of PTC.

Experimental animal models have indicated that TSH stimulation is involved in the pathogenesis of thyroid cancer. In mice and golden hamsters fed a low-iodine diet, thyroid overstimulation with a high TSH leads to hyperplasia and finally to the development of cancer.[19-23] Papillary thyroid cancer frequently presents with 2 genetic alterations, in the

Table 4. Characteristics of Patients with BTND with or without HT

	BTND with HT (n = 129)	BTND without HT (n = 1673)	*P* Value
Male sex	7/129 (5.4)	373/1673 (22.3)	<.001
Age, y	48.97 ± 11.03	49.50 ± 11.25	.606
TSH, mIU/L	2.17 ± 1.69	1.40 ± 1.15	<.001
FT_4, pmol/L	13.23 ± 2.39	13.77 ± 2.00	.015
FT_3, pmol/L	4.24 ± 0.64	4.38 ± 0.61	.015
TGAB(+)	101/121 (83.5)	232/1510 (15.4)	<.001
TPOAB(+)	82/120 (68.3)	122/1507 (8.1)	<.001

Values are presented as No. (%) or mean ± SD. Abbreviations: BTND, benign thyroid nodular disease; FT_4, free thyroxine; FT_3, free triiodothyronine; HT, Hashimoto's thyroiditis; TGAB, thyroglobulin antibody; TPOAB, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone.

Table 5. Characteristics of Patients with PTC with or without HT

	PTC with HT (n = 127)	PTC without HT (n = 549)	*P* Value
Male sex	9/127 (7.1)	130/549 (23.7)	<.001
Age, y	41.3 ± 12.5	44.8 ± 13.3	.008
Age ≥45 y	52/127 (40.9)	283/549 (51.5)	.031
TSH, mIU/L	2.54 ± 2.06	1.90 ± 1.66	.001
FT_4, pmol/L	13.45 ± 2.14	13.74 ± 2.14	.166
FT_3, pmol/L	4.33 ± 0.62	4.26 ± 0.64	.339
Microcarcinoma	53/127 (41.7)	194/549 (35.3)	.177
Tumor size, cm	1.84 ± 0.93	2.24 ± 1.38	<.001
Lymph node metastasis	45/114 (39.5)	199/494 (40.3)	.874
TNM stage III/IV	8/114 (7.0)	101/492 (20.5)	.001

Values are presented as No. (%) or mean ± SD. Abbreviations: FT_4, free thyroxine; FT_3, free triiodothyronine; HT, Hashimoto's thyroiditis; PTC, papillary thyroid cancer; TSH, thyroid-stimulating hormone.

Table 6. Multivariate Analysis for Independent Risk Factors of PTC Using Binary Logistic Regression

	OR	95% CI	*P* Value
Existence of HT	1.60	1.14-2.24	.006
Male sex	1.34	1.05-1.71	.020
Age, y	0.97	0.96-0.98	<.001
FT_3, pmol/L	0.80	0.69-0.94	.005
FT_4, pmol/L	1.04	0.99-1.09	.105
TSH, mIU/L	1.28	1.19-1.38	<.001
TGAB(+)	1.89	1.47-2.44	<.001
TPOAB(+)	1.19	0.88-1.61	.253

Abbreviations: CI, confidence interval; FT_4, free thyroxine; FT_3, free triiodothyronine; HT, Hashimoto's thyroiditis; OR, odds ratio; PTC, papillary thyroid cancer; TGAB, thyroglobulin antibody; TPOAB, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone.

BRAF and *RET*/*PTC* genes. Using a mouse model with thyroid-specific knock-in of oncogenic *BRAF*, TSH was recently shown to have a key role in the pathogenesis of *BRAF*-induced PTC,[24] suggesting that the TSH signaling pathway may predispose thyroid cells to *BRAF*-induced transformation. Moreover, these results provide experimental support for recent clinical findings in humans regarding the strong association between TSH concentrations and thyroid cancer.

This issue becomes much more complicated when autoimmunity is included. After removing all HT patients from analysis, we compared the rates of positivity for the autoantibodies TGAB and TPOAB, again observing differences between patients with BTND and PTC. We also found that both types of autoantibodies were associated with PTC, but only TGAB was significant in multivariate analyses. Two recent studies also reported that only TGAB was associated with PTC,[6,7] with TPOAB being less relevant to PTC than TGAB. However, in PTC patients, circulating TGAB can represent either the expression of a coexistent HT or a reaction to a structural modification of thyroglobulin resulting from the neoplastic process.[25] In agreement with the latter, it has been shown that TGAB recognizes different thyroglobulin epitopes in patients with PTC and those with HT.[26] The overlapping host immune responses to tumor and autoimmunity may explain the higher titer of TGAB than TPOAB in PTC patients with than without HT.

Interestingly, we observed that PTC patients with HT were younger in age, were more likely to be female, and had a smaller tumor size and less advanced TNM stages than PTC patients without HT. This suggests that the patients with HT had a better prognosis. Indeed, HT also has been found to have a protective effect in patients with PTC. Follicular cells in HT express both Fas and Fas ligand, which probably activate the Fas-mediated apoptotic pathway that also results in the destruction of tumor cells.[27] The infiltrating lymphocytes are likely to be cytotoxic T cells, along with natural killer cells and lymphokine-associated killer cells that act to kill carcinoma cells.[28] We deduce that the initial autoimmune injury by infiltrating T cells leads to hypothyroidism with elevated TSH as a reflection. This is associated with the occurrence of PTC and then accompanied by the tumor with T-cell infiltration to some extent. The interplay and overlap between these 2 types of T cells may shift the autoimmune response to tumor immune, which acts as a predominant one.

The immune microenvironment of the thyroid is affected by 3 factors: TSH, reactive oxygen species (ROS), and iodine. Shenyang, where our hospital is located, is in an iodine-sufficient area, and an assessment in 2010 of 3 other Chinese cities with the same iodine status found that the normal TSH range in China was 0.71 to 6.25 mIU/L, much higher than the reference interval provided by the Abbott Corporation and the data published in 2006.[29] During the same period, the prevalence of subclinical hypothyroidism increased from 2.9% to 5.6%, an increase that may be due to the accumulation of iodine, especially since increased iodine intake, autoimmune thyroiditis, and PTC are interrelated.[30,31] Iodine consumption status may also influence the association between HT and PTC, but this warrants further investigation.

Our case-control study has several of the biases inherent in a retrospective analysis. The natural history of HT is characterized by fluctuations in thyroid function, but since we could only choose one determination for comparison, patients with small nodules were not enrolled. In addition, conservative treatment is indicated for large numbers of HT patients without nodules but not for patients with nodules highly suspicious of malignancy. These limitations may be overcome by a prospective cohort study in the general population.

In conclusion, we found that histologically confirmed HT was associated with a significant increase in the frequency of PTC. The higher TSH concentration associated with HT was the most important factor in the association between HT and PTC. Even if current LT4 replacement therapy in HT is not designed to reduce cancer risk, our findings should be used in designing the treatment of patients with HT based on clinical and/or histological findings. Autoimmunity is another independent factor that increases cancer risk but may also improve patient prognosis. We recommend that HT patients undergo periodic thyroid examinations to evaluate their risk of developing malignancy.

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Author Contributions

Yu Lun, designed study, wrote article, analyzed data, data collection; **Xiaoyu Wu**, designed study, data collection; **Qian Xia**, data collection; **Yanshuo Han**, data collection; **Xiaoyu Zhang**, data collection; **Zhimin Liu**, data collection; **Fengyi Wang**, data collection; **Zhiquan Duan**, revised the article; **Shijie Xin**, revised the article; **Jian Zhang**, designed study, revised the article.

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