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# Advances in Diagnosis and Treatment of Papillary Thyroid Carcinoma with Hashimoto's Thyroiditis

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## Abstract

**Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis, is an autoimmune disease of the endocrine system. Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, with the highest incidence in all thyroid cancers. The relationship between PTC and HT has been exploring in many aspects for the increasing incidence of PTC combined with HT in recent years, the results are controversial though. This review expounds the progress of research on HT combined with PTC in terms of pathogenesis, clinical features, prognosis, treatment and their correlation in epidemiology, in order to offer theoretical basis for the diagnosis and treatment of HT and PTC, and direct future research on them.**

## Keywords

**Hashimoto's Thyroiditis; Papillary Thyroid Cancer; Epidemiology; Pathogenesis.**

## 1. Epidemiological Characteristics of HTPTC

The 2020 Global Cancer Statistical Report shows that thyroid cancer is the most rapidly increasing incidence of endocrine malignancies in the world, and the incidence rate ranks fifth among female cancers in the world and fourth in my country [1]. Papillary thyroid carcinoma (PTC) is the most common pathological type of thyroid cancer. The incidence of HTPTC has also increased rapidly in recent years, which may be related to the increased incidence of PTC. This special type of PTC accounts for 0.5%-38%, which is 1.68 times that of PTC combined with other benign thyroid lesions[2], and some studies have shown that 10%-58% of PTC patients are combined with Hashimoto's thyroiditis[3], the proportion of women in HTPTC patients is much larger than that of men, and the age is smaller than that of pure PTC patients[4]. In short, thyroid cancer combined with HT has attracted widespread attention in recent years, and there are more and more case reports about HTPTC, and there are more Many scholars began to explore the relationship between HT and PTC.

## 2. Pathogenesis of HTPTC

### 2.1 Gene-molecular Correlation of HT Combined with PTC

There are many mechanisms and theories about the correlation between HT and PTC, but the causal relationship between the two is still inconclusive. From a genetic and molecular point of view, the malignant transformation of HT into PTC is associated with some tumor markers, including the rearrangement of the RET/PTC oncogene, the expression of p63 gene, and the heterogeneity of the human 8-hydroxyguanine DNA glycosidase (hOGG1) gene loss of zygosity, etc. [5-7]. These genomic alterations are associated with stimulation by inflammatory cells that infiltrate around thyroid cells during chronic HT, leading to free radical production and interaction with DNA in interstitial cells, which in turn induces PTC. occurred [8]. 1. Rhoden et al [9] found that RET/PTC

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rearrangements existed in a large number of HT cases, and there were similar levels of RET/PTC rearrangements in PTC. This overlapping phenomenon indicated that RET/PTC oncogene rearrangements were mediating HT played a role in the development of PTC. The RET/PTC oncogene after RET gene rearrangement can activate the MAPK signaling pathway, participate in the process of cell proliferation [10], and induce and promote the occurrence and development of PTC. 2. PI3K is a lipid kinase. When PI3K is stimulated by a variety of extracellular signals, it can activate the abnormal P13K/AKT signaling pathway. The PI3K/AKT signaling pathway maintains the balance between pro-apoptotic and anti-apoptotic signals. It can inhibit pro-apoptotic signals and induce tumorigenesis [11].This abnormal signaling pathway is highly expressed in HT, PTC combined with HT, and pure PTC, but not in normal thyroid tissue [12]. 3. hOGG1 is a repair enzyme that can repair oxidative DNA damage, and its loss of heterozygosity is related to the occurrence of head and neck tumors. Royer et al. [5] found that the mutation rate of hOGG1 in HT is as high as 94%, in HT up to 73%, and only 8% in benign nodules. The comparison of the hOGG1 mutation rate in this series further supports the duality of HT and PTC. correlation between them. 4. The p53 homolog p63 protein and other proteins responsible for the stem cell-like phenotype may also interact with HT-related thyroid cancer. The p63 gene is expressed in many epithelial cells, and the higher the expression, the lower the degree of cell differentiation. At present, studies have confirmed that p63 is highly expressed in HT and PTC, while its expression has not been detected in benign thyroid tumors and medullary carcinomas [12]. 5.BRAFV600E is the most commonly mutated gene in PTC, which promotes the growth and proliferation of cancer cells by activating the downstream MAPK signaling pathway[13]. BRAFV600E is associated with the aggressiveness and recurrence of PTC and can be used to predict the prognosis of PTC [14]. BRAF mutation also exists in HT [15], but the incidence of BRAF mutation in PTC combined with HT is lower than that in pure PTC [16]. These studies suggest that BRAF mutations may promote the development of HT to PTC, but can improve the prognosis of PTC.

### 2.2 The Immunological Correlation of HT Combined with PTC

The immune system can distinguish between self and non-self antigens, avoid immune response to self tissues, and at the same time can recognize tumor antigens to generate corresponding anti-tumor immune responses. ① In the thyroid gland tissue combined with HT and PTC, many immune cells, cytokines, chemokines, etc.jointly build the thyroid immune microenvironment, which plays an important role in regulating the occurrence and development of PTC[17] . For example, E-selectin is related to the invasion of PTC capsule, interleukin (IL)-8 contributes to angiogenesis, and then stimulates the occurrence of PTC, while IL-1β can inhibit the proliferation and invasion ability of PTC [18]. ②HT is a common thyroid autoimmune disease. Under the action of various pathogenic factors, the immune tolerance of the gland is destroyed, and then autoimmune damage occurs, which is mostly manifested by T lymphocyte infiltration and the formation of autoantibodies. HT-related antibodies mainly refer to TgAb and TPOAb, both of which are present in almost all HT patients. Among them, TPOAb is highly expressed in 90%-95% of patients, while TgAb is highly expressed in 70%-80% of patients [19]. There appears to be an association between malignancies and autoimmune diseases [8]. A study on the relationship between thyroid antibodies and thyroid cancer showed that the risk of PTMC was significantly associated with serum TPOAb positivity (OR=1.58, P=0.001) and TgAb positivity (OR=2.35, P<0.001) [20].

## 3. Clinicopathological Features and Prognosis of HTPTC

### 3.1 Clinicopathological Features of HTPTC

Numerous studies have shown that compared with pure PTC, PTC combined with HT has a smaller diameter and a lower rate of extracapsular invasion [21]. In contrast, PTC associated with HT is often multifocal and distributed in bilateral glandular lobes [22]. However, Moon et al [23] believed that multifocality is only a clinicopathological feature related to the occurrence of PTC, and has nothing to do with the development and deterioration of PTC. At the same time, this Meta-analysis covered

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71 published studies, with a total of 44,034 PTC patients, of which 11,132 patients were combined with HT. The multi-faceted clinicopathological characteristics of PTC patients combined with HT were comprehensively analyzed, and the PTC group of combined HT was obtained. The conclusion is that the rate of membrane invasion is low, the incidence of central lymph node metastasis is low, and the incidence of distant metastasis is low. Many studies also reported a lower incidence of lymph node metastasis in the central region of HTPTC [24]. However, some studies have shown that HT does not affect the incidence of PTC capsule invasion and the incidence of central lymph node metastasis [25]. There is also a contrary view that compared with patients with negative thyroid autoimmune antibodies, autoimmune antibody-positive PTC patients have more metastatic lymph nodes in the central area, and antibody-positive status may be a risk factor for cervical lymph node metastasis [26]. However, most clinical studies prefer that patients with HTPTC have better clinicopathological characteristics than patients with pure PTC, and there are related theories to demonstrate. The cell infiltration theory [27] believes that there are a large number of cytotoxic T lymphocytes infiltrating around the PTC, and these lymphocytes have immunosuppressive functions, thereby destroying and inhibiting the function of tumor cells, hindering the progress of the tumor, reducing the recurrence rate, and improving the prognosis of HTPTC patients better.

### 3.2 The BRAFV600E Mutation Rate of HTPTC is Lower

BRAFV600E is the most common oncogene associated with PTC, and its mutation rate is high in PTC patients, and it is significantly associated with tumor extracapsular invasion, lymph node metastasis and postoperative recurrence [28]. In recent years, more and more studies have shown that the BRAFV600E gene mutation rate is lower in the tumors of HTPTC patients [14].

### 3.3 Prognosis of HTPTC Patients

Compared with patients with PTC alone, PTC patients with HT had favorable clinicopathological features, a lower incidence of central lymph node metastasis, and a lower BRAFV600E mutation rate, which predicted earlier TNM staging and a lower incidence of BRAFV600E mutations. good prognosis. Ahn et al [29] found that HTPTC patients had a lower recurrence rate and a higher long-term survival rate during a mean follow-up period of 62 months. Some studies have also shown [30] that the ten-year recurrence-free survival rate of patients with papillary thyroid cancer combined with Hashimoto's thyroiditis is as high as 95%, which is 10% higher than that of patients with simple papillary thyroid cancer. Kimura[31] et al. found that the glands of HTPTC patients were infiltrated with more cytotoxic T cells, and the interleukin-1 produced during the immune response could inhibit the proliferation of malignant tumor cells. Giodarno[32] and other studies found that thyroid follicular epithelial cells in HT-afflicted glands express Fas, which can stimulate apoptosis and destroy tumor cells. These mechanisms may be the reasons for the better prognosis of PTC patients with HT.

## 4. Diagnosis of HTPTC

### 4.1 Laboratory Test

The elevated levels of TPO-Ab and TgAb in the serum of patients are important criteria for the diagnosis of HT. Studies have shown that 80% to 90% of HT patients have serum TPO-Ab levels that exceed the normal range, and TPO-Ab positive has a sensitivity of 90% in diagnosing HT; only 60% to 80% of HT patients have serum TGAb levels that exceed the normal range. The sensitivity of the index to diagnose HT is not as good as that of TPO-Ab [33]. The thyroid function indexes in the serum of patients with pure PTC were generally not abnormal.

### 4.2 Ultrasonography and Ultrasound-Guided Fine Needle Aspiration Biopsy

Ultrasound is the primary imaging technique for detecting thyroid lesions. The main ultrasound manifestations of PTC are microcalcification, marked hypoechoic, aspect ratio greater than 1, blurred and irregular edges, etc. [34]. The most characteristic ultrasound manifestations of thyroid glands with HT are diffuse hypoechoic with heterogeneous echoes, grid-like hyperechoic internal, often accompanied by a large number of tiny nodules. Such coexisting benign and malignant nodules in the

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glands of HTPTC patients, especially HTPTMC patients, have similarities, overlap in ultrasound images, and lack significant differences. A study compared the ultrasound characteristics of HTPTC with that of pure PTC, and the results showed no significant difference [35]. In the case of unclear and difficult ultrasound diagnosis, in order to avoid misdiagnosis of benign nodules and missed diagnosis of PTMC, ultrasound-guided fine-needle aspiration biopsy (US-FNAB) is widely used clinically to evaluate the nature of thyroid nodules. To some extent, unnecessary surgical interference to benign nodules can be avoided, and multiple and multi-needle punctures at the same time can reduce the missed diagnosis rate of PTMC. In recent years, with the development of PTC molecular level research, new markers have been applied to the diagnosis of thyroid nodules. Studies have shown that FNAB specimens combined with BRAFV600E mutation detection have high sensitivity and precision [36]. Some researchers have also found that Galectin-3 and Cytokeratin-19 are highly expressed in PTC tissues, and their detection can improve the diagnostic accuracy of PTC [37].

Elastography can be used as a supplementary diagnostic method for ultrasound examination. At present, common elastography in clinic include strain elastography, transient elastography, and acoustic radiation force pulse imaging [38]. Especially when benign and malignant nodules coexist in the glands of HTPTMC, elastography can still predict malignant nodules confused with small HT nodules through higher elastic strain scores and higher strain rates [39].

## 5. Surgical Treatment of HTPTC

With the publication of more and more studies on the clinicopathological characteristics of HTPTC, the surgical treatment of HTPTC has also become a hot topic of discussion, especially the treatment of cervical lymph nodes, which is still controversial. The principle of surgical treatment of HTPTC mainly follows the treatment guidelines for thyroid cancer. The size, number, location of the tumor, and the presence or absence of cervical lymph node metastasis before and after surgery determine the surgical method. However, in view of the unique clinicopathological characteristics of HTPTC compared with pure PTC, HT is easy to induce the incidence of PTC and the postoperative complications caused by the operation. After full communication with patients and their families, individualized selection should be considered comprehensively The optimal surgical method takes the maximization of patient benefit as the ultimate goal.

### 5.1 Treatment of Primary Tumor

Some scholars[40] believe that HTPTC often presents as multifocal cancer, and preoperative and intraoperative assessment is unilateral PTC. Postoperative pathology may confirm that there is accidental cancer on the contralateral side, and it is easy to miss the diagnosis. Therefore, it is recommended that preoperative assessment be bilateral multiple cancers. Total/subtotal thyroidectomy is more secure in patients with nodules. This is also in line with the guidelines for indications for total thyroidectomy. Some scholars have suggested[41]: (1) unilateral PTC, with a diameter of ≤1 cm, can perform unilateral glandular lobe + isthmectomy; (2) unilateral PTC, with a diameter of >1 cm or with contralateral benign nodules, can perform full Thyroidectomy; (3) bilateral tumors require total thyroidectomy.

### 5.2 Management of Cervical Lymph Nodes

For patients with pure PTC, the ipsilateral prophylactic central lymph node dissection is routinely performed. For patients with confirmed lateral neck lymph node metastasis, in addition to central lymph node dissection, curative lateral neck dissection is also required. For HTPTC patients, the management of central lymph nodes is still controversial. At present, most studies have shown that the incidence of central lymph node metastasis in HTPTC patients is lower than that in pure PTC patients, so the necessity of preventive dissection of the central region remains to be explored. And HT makes the thyroid gland more brittle and easier to bleed, and the gland adheres more tightly to the surrounding tissue. These factors may reduce the benefit of central lymph node dissection, increase the damage of recurrent laryngeal nerve and parathyroid gland, and cause a series of

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postoperative complications. CT and ultrasonography can be used as means for preoperative evaluation of central lymph nodes, but due to the factors of anatomical location, the diagnostic accuracy of ultrasonography for central lymph node metastases is low [42], and chronic inflammation of HT often leads to central lymph node reactivity Hyperplasia and enlargement make it more difficult to distinguish inflammatory lymph nodes from metastatic lymph nodes by ultrasound and CT. In recent years, some studies have begun to analyze the risk factors of central lymph node metastasis in HTPTC, and use preoperative clinical data to predict whether central lymph nodes have metastasized, providing a clinical basis for individualized and precise treatment of such patients, thereby reducing unnecessary Central area cleaning, narrowing the central area cleaning range. In conclusion, a large number of clinical studies, especially prospective studies, are needed to provide recommendations for the management of central lymph nodes in HTPTC.

## 6. Summary and Outlook

The incidence of HT combined with PTC shows an increasing trend, and there is a close relationship between the two. There are many theories on the pathogenesis of HTPTC, such as immune theory, endocrine theory, common etiology theory and precancerous lesion theory, but there is no definite research result. It shows the causal relationship between HT and PTC, and it is more inclined to think that HT is one of the risk factors for the occurrence of PTC. Therefore, in the treatment of thyroid glands with HT, if relevant characteristic nodules appear on ultrasonography and elastography, malignancy should be highly suspected and further combined with FNA for accurate evaluation. The prognosis of PTC with HT is better, so it is necessary to understand the exact pathogenesis to formulate and develop new preventive measures and treatments.

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