The Impact of Hashimoto's Thyroiditis on Thyroid Nodule Cytology & Risk of Thyroid Cancer

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The Impact of Hashimoto's Thyroiditis on Thyroid Nodule Cytology & Risk of Thyroid Cancer

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TITLE: The Impact of Hashimoto's Thyroiditis on Thyroid Nodule Cytology & Risk of Thyroid Cancer

Purpose: The impact of Hashimoto's thyroiditis (HT) upon the risk of thyroid cancer and its accurate detection remains unclear. Prior studies are limited by retrospective design, selection bias, or their narrow definitions of HT. Importantly, the presence of a chronic lymphocytic infiltration imparts a logical mechanism potentially altering neoplastic transformation, while also influencing the accuracy of diagnostic evaluation.

Methods: We performed a prospective, cohort analysis studying 9,851 consecutive patients with 21,397 nodules 1cm who underwent nodule evaluation between 1995-2017. The definition of HT included a) elevated thyroid peroxidase antibody (TPOAb) and/or, b) findings of diffuse heterogeneity on ultrasound, and/or c) the finding of diffuse lymphocytic thyroiditis on histopathology. We then determined the impact of HT on the distribution of cytology, and ultimately upon malignancy risk.

Results: 2,651 patients (27%) were diagnosed with HT. In total, 3,895 HT nodules, and 10,168 non-HT nodules, were biopsied. The prevalence of indeterminate and malignant cytology was higher in the HT vs. non-HT group (Indeterminate 26.3% vs. 21.8%, $p<0.001$; Malignant: 10.0% vs. 6.4%, $p<0.001$). Ultimately, the risk of any nodule proving malignant was significantly elevated in the setting of HT (RR=1.6 95% CI: 1.44-1.79 $p< 0.001$). This increased prevalence was maintained when patients with solitary or multiple nodules were analyzed separately (HT vs. non-HT: 24.5% vs. 16.3% solitary; 22.1% vs. 15.4% multinodular, $p<0.01$).

Conclusions: Hashimoto's thyroiditis increases the risk of thyroid malignancy in any patient presenting for nodule evaluation. Diffuse sonographic heterogeneity and/or TPOAb positivity should be used for risk assessment at time of evaluation.

Glossary of abbreviations

HT: Hashimoto's thyroiditis

FNA: fine needle aspiration

TPOAb: thyroid peroxidase antibody

TBSRTC: The Bethesda System for Reporting Thyroid Cytopathology

AUS: atypia of undetermined significance

SFN: suspicious for follicular or Hürthle cell neoplasm

SUSP: suspicious for malignancy

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Personal Contribution to Work

Scholarly question: Does Hashimoto's thyroiditis confer an increased risk of a thyroid nodule having indeterminate cytology on FNA and/or of that nodule being malignant?

I joined Dr. Erik Alexander and Dr. Nathalie Morais in this project in Spring of 2018. At that point, the project was in the early stages of conception: our team wanted to examine the relationship between Hashimoto's and thyroid malignancy utilizing the Brigham's robust thyroid nodule database, which contains data from all patients who underwent a thyroid FNA at the Brigham Thyroid Nodule Clinic between 1995 and 2017. I helped to flesh out the details of how we would conduct the project, such as how we would define our Hashimoto's population and our malignancy population and how we would address the varying TPO antibody titer thresholds over the years.

From June through August of 2018, I worked on the project full-time. The first half was largely spent doing data collection, as the Hashimoto's status of the patients in the thyroid nodule database was unknown. Dr. Morais and I essentially split up the database such that each of us filled in the missing data for half of the patients. Along the way, we had important conversations about what to do with complex situations, such as when the TPO antibody went from positive to negative, or the sonographic data was discordant with the histopathologic data.

The second half of the summer was spent on analysis and writing. As we had no statistician on our team, I played an integral role in analyzing the data using SPSS. We met with Dr. Alexander frequently and also consulted a BWH statistician to ensure the integrity of our analysis. For the writing, I co-wrote the paper with Dr. Morais and Dr. Alexander's input.

Manuscript: *In submission to Journal of the Endocrine Society*

Introduction

Hashimoto's Thyroiditis (HT) is the most common autoimmune disease and the most frequent cause of hypothyroidism, affecting up to 2-15% of the population depending on their age (1-4). The pathogenesis of HT involves a chronic inflammatory infiltrate in the thyroid gland as a consequence of a breakdown in immune tolerance. This leads to activation of cellular and humoral immune responses (5). Histologically, Hashimoto's thyroiditis is characterized by diffuse lymphocytic infiltration of the gland, with numerous lymphoid follicles and germinal centers, fibrosis and ultimately parenchymal atrophy (6, 7). Both genetic and environmental factors, such as dietary iodine uptake have been shown to contribute to the development of HT (8).

In 1893, Rudolf Virchow first proposed an association between chronic inflammation and the formation of cancer. Over the ensuing century, this hypothesis has been verified though our understanding of a multitude of human illnesses. Classic examples of this adverse effect of inflammation upon malignancy risk include the predisposition of patients with ulcerative colitis to adenocarcinoma of the colon, and the impact of chronic hepatitis upon development of hepatocellular carcinoma (9, 10).

Given the well-established cause-and-effect relationship between chronic inflammation and risk of malignancy, it has long been postulated that Hashimoto's thyroiditis, a chronic thyroid inflammatory disease, would also be associated with an increased risk of thyroid cancer. While numerous studies have since investigated this hypothesis, nearly all have been

confounded by substantial selection bias, imprecise metrics, and/or retrospective analysis (11-13). For these reasons, the association between HT and papillary thyroid cancer continues to remain controversial. To date, no large, unbiased, and prospective analysis has been performed to examine this important question.

By definition, Hashimoto's thyroiditis is a histological diagnosis. However, it is clinically impractical to necessitate surgical intervention when other means of pre-operative diagnosis have proven highly predictive of the disease. These include the presence of antibodies to thyroid peroxidase (TPOAb), as well as the identification of a diffusely heterogeneous parenchyma upon sonographic imaging of the gland (14). It follows, therefore, that all three means of identifying Hashimoto's thyroiditis (histopathologic, biologic, and sonographic) should be applied to any investigation seeking the broadest inclusion of patients with evidence of inflammation.

Thus, using a large prospectively tracked database of consecutive patients presenting for nodule evaluation, we sought to evaluate the association between HT and thyroid cancer. Separately, we also sought to determine the impact of HT on diagnostic nodule evaluation, and specifically upon the distribution of preoperative cytology.

Materials and Methods

We performed a prospective, cohort analysis studying 10,054 consecutive adult (≥18yo) patients with thyroid nodules 1cm who underwent nodule evaluation between 1995-2017 at the Brigham and Women's Hospital (BWH) Thyroid Nodule Clinic.

All patients were referred for evaluation of a clinically relevant thyroid nodule, and then underwent sonographic and clinical evaluation. Sonographic evaluation was performed by radiologists with expertise in thyroid imaging, using a 5-15mHz transducer. All thyroid nodules were evaluated as previously described (15), and the background thyroid parenchyma was separately assessed. From the ultrasound report, HT was considered present if a diffusely heterogeneous parenchyma or the presence of Hashimoto's thyroiditis was reported (16). Clinical evaluation included a full medical history and physical examination, and assessment of serum TSH. When TSH was elevated, or at the discretion of the clinician, measurement of serum TPOAb was performed. For the purposes of this study, TPOAb was considered positive when elevated above the reference range as defined by the test manufacturer.

Thyroid nodules were treated per the clinical guidelines applicable to the time period, typically performing FNA on solid or partially cystic nodules nodules 1cm. FNA was performed by a thyroidologist under ultrasound guidance using a 25 gauge needle following local anesthesia. Typically, three passes from different areas of the nodule constituted a single aspiration.

For each subject, age at the time of the first FNA and the total number of nodules 1cm were documented. Aspiration specimens were processed using ThinPrep liquid-based cytology preparation (Hologic Corp., Marlborough, MA) and were examined by a cytopathologist with thyroid expertise. Although the period of study partially predates The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), cytologic classification through the entire study period uniformly employed the same criteria and terminology later adopted by the TBSRTC (17). Thyroid FNA cytology was reported as: non-diagnostic, negative for malignant cells

(benign), atypia of undetermined significance (AUS), suspicious for follicular or Hürthle cell neoplasm (SFN), suspicious for malignancy (SUSP), or malignant. For patients with more than one nodule evaluated by ultrasound guided-FNA, the primary cytology was defined as the cytologic result that carried the highest risk of malignancy. Indeterminate cytology collective included those with AUS, SFN or SUSP results. When a thyroidectomy was performed, histopathologic data were also obtained, specifically documenting malignant or benign disease, as well as the histologic evidence of HT.

To avoid selection bias while simultaneously applying the most translatable, real-world protocol, we utilized a holistic definition of Hashimoto's thyroiditis that included a) elevated TPOAb, and/or b) findings of diffuse heterogeneity or Hashimoto's disease on ultrasound, and/or c) diffuse lymphocytic thyroiditis on histopathology. The HT-negative population therefore included all other patients without a single positive finding. Given the decreased accuracy of ultrasound in assessing background thyroid parenchyma in the presence of extensive multinodularity, we excluded from our analysis those patients with >six nodules each ≥1cm. If sonographic reporting was unclear, images were reviewed by a blinded expert. Multinodularity was defined as 2 or more nodules each 1cm. Incidental thyroid microcarcinoma (<1cm) identified separate from the clinically relevant nodule(s) was not considered malignant nor included in our analysis.

Summary statistics are provided as mean ± standard deviation (SD) for continuous, normally distributed variables; median with range and interquartile range (IQR) for non-normally distributed, continuous variables; or numbers and percentages for categorical variables. Comparisons were made using chi-squared ($\chi 2$) or Fisher's exact test for categorical

variables and with the T Student's or Mann-Whitney tests for continuous variables, according to the data distribution as evaluated by Kolmogorov-Smirnov test. For analysis, we calculated the relative risks (RRs), the 95% confidence intervals (CIs), and the pooled effects. A two-sided *p*-value < 0.05 was considered significant. All calculations were performed using IBM SPSS Statistics Software (IBM, Armonk, NY), version 25. Permission for this study was granted by the BWH Institutional Review Board.

Results

Our final study population included 9,851 patients with 21,397 relevant nodules. As expected, the population was predominantly female (83.9%) with a mean age of 52.2 years. Within the evaluable cohort, 14,063 (66%) nodules were aspirated. The remaining non-aspirated nodules were generally cystic, small, noted to have sonographically benign characteristics, or were resected in conjunction with a separate, index nodule prompting concern in the same gland. Baseline patient and nodules characteristics are summarized in **Table 1**.

Evidence of HT (serological, sonographic or histologic) was confirmed in 2,651 patients (27%). A total of 3,895 nodules were evaluated in patients with HT, while the remaining 10,168 nodules were evaluated in patients without evidence of HT.

The influence of Hashimoto's thyroiditis on the diagnostic evaluation and cytology classification is depicted in **Table 2**. The proportion of nodules with indeterminate and malignant cytology was higher in the HT vs. non-HT group. Indeterminate cytology was obtained in 20.6% of patients with nodules in the setting of HT compared to 17.1% of patients

with nodules in a gland not affected by HT (p<0.01; Indeterminate cytology: RR=1.3, 95% CI:1.17-1.44 p<0.01). An increase in malignant cytology was similarly identified in patients with HT (RR=1.7, 95% CI:1.44-1.99 p<0.01) (**Figure 1)**.

Finally, we evaluated the association between Hashimoto's thyroiditis and the risk of malignancy when presenting with clinically relevant thyroid nodular disease. The frequency of a nodule proving cancerous was higher in patients with coexistent HT compared to those without (23.3% vs. 15.9%; RR= 1.6 95% CI: 1.44-1.79; p < 0.01) (**Figure 2)**. This increased cancer prevalence was maintained when patients with solitary or multiple nodules were analyzed separately, suggesting a field effect of HT itself (HT vs. Non-HT groups: 24.5% vs. 16.3% in solitary nodules; 22.1% vs. 15.4% in multinodular glands p< 0.01)**.** The types and proportions of thyroid cancer in both the HT and non-HT groups are shown in **Table 3**.

Given the increased risk of thyroid cancer in the setting of Hashimoto's disease, we also investigated if such malignancy showed signs of increased aggressivity. We investigated the proportion of cancers in both groups showing signs of invasion, local or distant metastasis, or tumor size. Importantly, no significant differences in markers of agressiveness, or malignant pathologic characteristics was identified among patients with or without HT (**Table 4)**.

Though 13 cases of thyroid lymphoma were documented in the entire study cohort, lymphoma alone was not responsible for the increased prevalence of malignant disease in patients with HT. Of the 13 total cases, 9 thyroid lymphoma were documented in the 7,200 patients without HT. Four cases of thyroid lymphoma were detected in the 2,651 patients with HT.

Discussion

The impact of coexistent Hashimoto's thyroiditis upon the risk of developing thyroid cancer has been unclear. Building off a sound hypothesis and extensive preliminary data, we performed a large prospective cohort analysis investigating this question. Using a highly translatable and broad clinical definition of HT, our data confirm a 45% increased risk that a clinically relevant thyroid nodule will prove malignant when in the presence of this chronic inflammatory process. The risk of a nodule being cancerous in the setting of HT was nearly 1 out of 4, substantially higher than in patients without the disease. Furthermore, the diagnostic evaluation of thyroid nodules is impacted by the presence of Hashimoto's disease, even when the nodule is non-malignant, and a significantly higher risk of indeterminate cytology should be expected. Together, these data provide convincing evidence that Hashimoto's thyroiditis should be viewed as a risk factor for the development of thyroid cancer. Easily obtainable variables, such as measurement of TPOAb and/or identification of a diffusely heterogeneous parenchyma on ultrasound, should be sought at the time of initial thyroid nodule evaluation. The large scale, prospective nature of this 20 year cohort analysis supports the translatability and durability of these findings.

We used the broadest and most practical definition of Hashimoto's thyroiditis. This proved important to our study, as histopathology alone remains an impractical endpoint. Patients recommended for surgery typically represent a highly selected group, and routine thyroidectomy of all patients in any study would be deemed unacceptable. The association of an elevated TPOAb with HT is well established. Furthermore, a diffuse heterogeneous parenchyma on sonographic imaging is highly suggestive of a diffuse inflammatory process,

most notable Hashimoto's thyroiditis (18). Others have similarly used broad-based, holistic diagnostic criteria for HT such as in our study (14, 19).

Together, one or more of these findings confirming HT was present in 27% of our population. While many population estimates of Hashimoto's thyroiditis (typically using only TPOAb measurement to identify HT) are lower (4, 20, 21) , we note that our study cohort was unique. Our population of 9,851 consecutive patients were all being evaluated for clinically relevant thyroid nodules. As expected in such a cohort, the vast majority were women, and the mean age was over 52 years. Together, such a group would be expected to have a higher rate of autoimmune thyroid disease than a broad epidemiologic sampling. It is also well documented that a hypoechoic sonographic pattern or irregular echogenic parenchyma may precede TPOAb positivity in autoimmune thyroid disease, and may thus not be detected in up to 20% of individuals with HT (22). Furthermore, our data note a higher rate of cancer among patients with HT and known nodules. Stemming from this, it is equally plausible that HT itself may therefore predispose to nodule formation. If so, a much higher rate of HT would be expected in any nodule population subsequently studied. In support of our methodology, we note a separate post-mortem histopathologic thyroid analysis on thyroid disease-free individuals which detected evidence of chronic autoimmune thyroiditis in 27% of adult women, a percentage strikingly similar to our findings (1).

Notable to our study were several findings. First, the increased risk of cancer attributable to HT was detected in those with solitary nodules as well as in nodules which were part of a multinodular gland. This supports the rationale that inflammation imparts a field effect through the gland itself. Second, the type, size, and aggressivity of the cancer detected

did not differ from those with or without Hashimoto's thyroidits. Thus, while malignant transformation or formation appears impacted by HT, papillary thyroid carcinoma (by far the most common cancer subtype) remains generally low risk and indolent. Finally, while an increased relative risk of thyroid lymphoma has long been associated with the presence of HT, our data speak to an increase in well-differentiated thyroid cancer, and lymphoma is most certainly not responsibile for the full increased relative risk of malignancy as a whole.

Differentiated thyroid cancer has witnessed a worldwide rise in incidence. According to the Surveillance, Epidemiology, and End Results (SEER) database, the number of new cases of thyroid cancer was 14.5 per 100,000 men and women per year during the period of 2011-2015 (23). Enhanced thyroid nodule detection has been implicated in this, but appears to not fully explain this increase. The concomitant increase in the incidence of HT worldwide (perhaps following iodine supplementation) presents another plausible explanation and reinforces the concept that thyroid chronic inflammation may lead to neoplastic processes (1, 5).

The impact of HT upon nodule diagnostic evaluation is also perhaps not surprising. HT may result in reactive atypia that mimics PTC, such as increased nuclear size and nuclear contour irregularities and grooves, which can result in an indeterminate FNA diagnoses. (24). Also, the differentiation between follicular neoplasms and HT can be difficult, since some cytological features, such as hyperplastic follicular cells and Hürthle cells, are encountered in both scenarios (25). Previous studies have attempted to link the presence of HT to FNA accuracy with conflicting results. HT was shown to be related to a higher rate of false negative and false positive FNA results (24, 26). Others have demonstrated that the presence of HT

significantly decreased the acuracy and increased the indeterminate rate of cytological results of US-FNA in subcentimeter nodules (27) though data are variable (28).

We acknowledge limitations to our investigation. First, we studied only those patients with at least one thyroid nodule >1cm, and thus our findings are not generalizable to a general population nor do they reflect epidemiologic data regarding HT or thyroid cancer in a broad population. Nonetheless, our data are very translatable to the real-world clinical environment, allowing pre-operative data such as TPOAb or ultrasound appearance to inform individualized risk assessment during thyroid nodule care. Second, we did not measure serum TSH in all patients, and thus we cannot assess to what extent hormonal stimulation may play a role in the risk of thyroid malignancy as others have suggested (29, 30). There remains a possibility that elevated TSH and HT itself may not be mutually independent variables, and this is worthy of further study.

In conclusion, Hashimoto's thyroiditis adversely impacts the diagnostic evaluation, and increases the risk of thyroid malignancy, in any patient presenting for nodule evaluation. The presence of a diffusely heterogeneous sonographic pattern, or TPOAb positivity, should be used for thyroid malignancy risk assessment at the time of nodule evaluation. Future investigation should work to elucidate the relative impact of this finding in relation to other known risk factors such as age and sex.

References

1. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull. 2011;99:39-51.

2. Delemer B, Aubert JP, Nys P, Landron F, Bouee S. An observational study of the initial management of hypothyroidism in France: the ORCHIDEE study. Eur J Endocrinol. 2012;167(6):817-23.

3. McLeod DS, Cooper DS. The incidence and prevalence of thyroid autoimmunity. Endocrine. 2012;42(2):252-65.

4. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf). 1995;43(1):55-68.

5. Ajjan RA, Weetman AP. The Pathogenesis of Hashimoto's Thyroiditis: Further Developments in our Understanding. Horm Metab Res. 2015;47(10):702-10.

6. Hiromatsu Y, Satoh H, Amino N. Hashimoto's thyroiditis: history and future outlook. Hormones (Athens). 2013;12(1):12-8.

7. Caturegli P, De Remigis A, Chuang K, Dembele M, Iwama A, Iwama S. Hashimoto's thyroiditis: celebrating the centennial through the lens of the Johns Hopkins hospital surgical pathology records. Thyroid. 2013;23(2):142-50.

8. McLeod DS, Caturegli P, Cooper DS, Matos PG, Hutfless S. Variation in rates of autoimmune thyroid disease by race/ethnicity in US military personnel. JAMA. 2014;311(15):1563-5.

9. Fung J, Lai CL, Yuen MF. Hepatitis B and C virus-related carcinogenesis. Clin Microbiol Infect. 2009;15(11):964-70.

10. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001;357(9255):539-45.

11. Lai X, Xia Y, Zhang B, Li J, Jiang Y. A meta-analysis of Hashimoto's thyroiditis and papillary thyroid carcinoma risk. Oncotarget. 2017;8(37):62414-24.

12. Resende de Paiva C, Gronhoj C, Feldt-Rasmussen U, von Buchwald C. Association between Hashimoto's Thyroiditis and Thyroid Cancer in 64,628 Patients. Front Oncol. 2017;7:53.

13. Jankovic B, Le KT, Hershman JM. Clinical Review: Hashimoto's thyroiditis and papillary thyroid carcinoma: is there a correlation? J Clin Endocrinol Metab. 2013;98(2):474-82.

14. Grani G, Carbotta G, Nesca A, D'Alessandri M, Vitale M, Del Sordo M, et al. A comprehensive score to diagnose Hashimoto's thyroiditis: a proposal. Endocrine. 2015;49(2):361-5.

15. Angell TE, Vyas CM, Medici M, Wang Z, Barletta JA, Benson CB, et al. Differential Growth Rates of Benign vs. Malignant Thyroid Nodules. J Clin Endocrinol Metab. 2017;102(12):4642-7.

16. Patel S, Giampoli E, Oppenheimer D, Montoya S, Rupasov A, Dogra V. Sonographic Features of Diffuse Hashimoto Thyroiditis: Determining Sensitivity of Features and Predictors of Malignancy. Am J Sonogr. 2018;1(6):1-7.

17. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2009;19(11):1159-65.

18. Pedersen OM, Aardal NP, Larssen TB, Varhaug JE, Myking O, Vik-Mo H. The value of ultrasonography in predicting autoimmune thyroid disease. Thyroid. 2000;10(3):251-9.

19. Castagna MG, Belardini V, Memmo S, Maino F, Di Santo A, Toti P, et al. Nodules in autoimmune thyroiditis are associated with increased risk of thyroid cancer in surgical series but not in cytological series: evidence for selection bias. J Clin Endocrinol Metab. 2014;99(9):3193-8.

20. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87(2):489-99.

21. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160(4):526-34.

22. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 2008;29(1):76-131.

23. Noone AM HN, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/crs/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.

24. Harvey AM, Truong LD, Mody DR. Diagnostic pitfalls of Hashimoto's/lymphocytic thyroiditis on fine-needle aspirations and strategies to avoid overdiagnosis. Acta Cytol. 2012;56(4):352-60.

25. Kollur SM, El Sayed S, El Hag IA. Follicular thyroid lesions coexisting with Hashimoto's thyroiditis: incidence and possible sources of diagnostic errors. Diagn Cytopathol. 2003;28(1):35-8.

26. Kapan M, Onder A, Girgin S, Ulger BV, Firat U, Uslukaya O, et al. The reliability of fine-needle aspiration biopsy in terms of malignancy in patients with Hashimoto thyroiditis. Int Surg. 2015;100(2):249-53.

27. Gao L, Ma B, Zhou L, Wang Y, Yang S, Qu N, et al. The impact of presence of Hashimoto's thyroiditis on diagnostic accuracy of ultrasound-guided fine-needle aspiration biopsy in subcentimeter thyroid nodules: A retrospective study from FUSCC. Cancer Med. 2017;6(5):1014-22.

28. Baser H, Ozdemir D, Cuhaci N, Aydin C, Ersoy R, Kilicarslan A, et al. Hashimoto's Thyroiditis Does Not Affect Ultrasonographical, Cytological, and Histopathological Features in Patients with Papillary Thyroid Carcinoma. Endocr Pathol. 2015;26(4):356-64.

29. Boi F, Minerba L, Lai ML, Marziani B, Figus B, Spanu F, et al. Both thyroid autoimmunity and increased serum TSH are independent risk factors for malignancy in patients with thyroid nodules. J Endocrinol Invest. 2013;36(5):313-20.

30. Fiore E, Rago T, Latrofa F, Provenzale MA, Piaggi P, Delitala A, et al. Hashimoto's thyroiditis is associated with papillary thyroid carcinoma: role of TSH and of treatment with L-thyroxine. Endocr Relat Cancer. 2011;18(4):429-37.

Table 1. Baseline Patient and Nodule Characteristics

Patient Characteristics	
Number of patients	9,851
Gender, n (%)	
Female	8,263 (83.9)
Male	1,588 (16.1)
Age (years)	
Mean ± SD	52.2 ± 15.0
Range	18 – 95
Multinodular gland, n (%)	
Yes	4,495 (45.6)
No	5,356 (54.4)
Thyroidectomy, n (%)	3,186 (32.3)
Hashimoto's thyroiditis, n (%)*	
Yes	2,651 (26.9)
No	7,200 (73.1)
Nodule Characteristics	
Number of nodules	21,397
Largest dimension (cm)	
Mean ± SD	2.6 ± 1.3
Range	1.0 – 12.8
Nodules biopsied, n (%)	14,063 (65.7)

* Hashimoto's thyroiditis criteria: chronic lymphocytic thyroiditis on histopathology and/or elevated thyroperoxidase antibodies and/or diffuse heterogeneity on ultrasound.

Table 2. Influence of HT on Nodule Cytology Classification According to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)

	HT	Non-HT	p-value*
Nodules biopsied, n	3,895	10,168	
Nodule cytology by TBSRTC, n (%)			<0.01
I. Non-diagnostic	168 (4.3)	728 (7.2)	
II. No malignant cells	2,652 (68.1)	7,217 (71.0)	
Indeterminate	791 (20.3)	1,750 (17.2)	
III. AUS, FLUS	307 (7.9)	635 (6.2)	
IV. SFN	249 (6.4)	626 (6.2)	
V. SUSP	235 (6.0)	489 (4.8)	
VI. Positive for Malignancy	284 (7.3)	473 (4.7)	

*P-value for 2x6 χ^2 analysis of 6 Bethesda categories. HT, Hashimoto's thyroiditis; AUS, atypia of undetermined significance; FLUS, follicular lesion of undetermined significance; SFN, suspicious for follicular or Hürthle cell neoplasm; SUSP, suspicious for malignancy.

Table 3. Association Between Hashimoto's Thyroiditis and Thyroid Cancer

	Total (n=9851)	HT (n=2651)	Non-HT (n=7200)	p-value
Benign disease, n (%)	8,140 (82.7%)	2,045 (77.2%)	6,095 (84.5%)	
Thyroid Cancer, n (%)				
All subtypes	1,711 (17.3%)	606 (22.8%)	1,105 (15.4%)	<0.01
PTC	1521 (88.9)	547 (90.3)	974(88.1)	
FTC	118 (6.8)	39 (6.4)	79 (7.1)	
MTC	14 (0.8)	5 (0.8)	9 (0.8)	
Anaplastic	18 (1.1)	3 (0.5)	15 (1.4)	
Poorly differentiated	18 (1.1)	4 (0.7)	14 (1.3)	
Non-thyroid malignancy	22(1.3)	8 (1.3)	14 (1.3)	

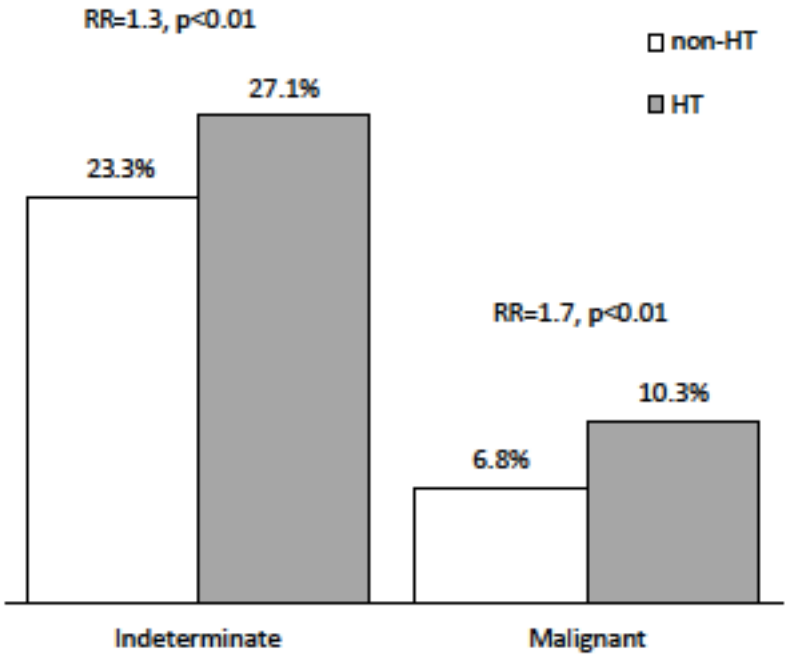
HT, Hashimoto's thyroiditis; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; MTC, medullary thyroid cancer.

Table 4. Differences in Cancer Pathologic Characteristics Between Patients With and Without Hashimoto's Thyroiditis

	HT (n=2651)	Non-HT (n=7200)	p-value
Micro Invasion, n (%)	122 (20.4%)	192 (18.6%)	0.39
Gross Invasion, n (%)	44 (6.7%)	87 (7.2%)	0.70
Lymph Node Metastasis, n (%)	108 (22.3%)	177 (26.7%)	0.09
Distant Metastasis, n (%)	23 (5.8%)	41 (6.1%)	0.89
Multifocal, n (%)*	85 (15.1%)	122(12.5%)	0.16
Tumor size – largest dimension			0.04
≤2 cm	430 (66.0%)	729 (61.9%)	
> 2cm, ≤ 4cm	182 (27.9%)	339 (28.8%)	
>4cm	40 (6.1%)	109 (9.3%)	

*Multifocal: 2 or more nodules each >=1cm. HT, Hashimoto's thyroiditis.

Figure 1. Nodule Cytology and Hashimoto's Thyroiditis



RR, relative risk of indeterminate/malignant cytology vs. benign cytology given Hashimoto's thyroiditis (HT). Indeterminate cytology includes Bethesda 3,4 and 5 categories. Malignant cytology includes Bethesda 6 category.