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Is Hashimoto's Thyroiditis a Risk Factor for Papillary Thyroid Cancer?

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Background. **Hashimoto's thyroiditis (HT) is the most common cause of hypothyroidism and is characterized by gradual autoimmune mediated thyroid failure with occasional goiter development. 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. Given the relatively high prevalence of these diseases and the increased occurrence in women, we analyzed data from our institution to determine if there is a correlation between Hashimoto's thyroiditis and PTC in women.**

Methods. **From May 1994 to January 2007, 1198 patients underwent thyroid surgery at our institution. Of these, 217 patients were diagnosed with HT (196 women, 21 men). The data from these patients were statistically analyzed using SPSS.**

Results. **PTC occurred in 63 of 217 (29%) HT patients and 230 of 981 (23%) patients without HT ($P = 0.051$). Of these groups, 41 (65%) and 158 (69%) patients, respectively, had tumor sizes ≥1.0 cm; 56/196 women (29%) with HT had coexistent PTC compared with 160/730 women (22%) without HT ($P = 0.03$). Among women with any type of thyroid malignancy, 56/59 cases (95%) with HT had PTC compared with 159/196 cases (81%) in women without HT ($P = 0.006$). Additionally, female HT patients with goiters had a significantly lower rate of PTC (9% *versus* 36%, $P < 0.001$) compared with women without goiters. These differences were not observed in men with HT.**

Conclusions. **These data demonstrate that HT is associated with an increased risk of developing PTC. Female patients with HT undergoing thyroidectomy are 30% more likely to have PTC. Thus, more aggressive surveillance for PTC may be indicated in patients with HT, especially in women.**

Key Words: **Hashimoto's thyroiditis; papillary thyroid carcinoma.**

INTRODUCTION

Hashimoto's thyroiditis (HT) is the most common inflammatory thyroid disease as well as the most common cause of hypothyroidism in the United States, as it affects 22 per 100,000 individuals [1–3]. It is characterized by gradual autoimmune-mediated thyroid failure with occasional goiter development. The disease occurs more frequently in females, with published gender prevalence ratios ranging from 5 to 20:1 [1, 3, 4].

Similar to HT, papillary thyroid cancer (PTC) is a relatively common disease. It is the most prevalent manifestation of thyroid cancer, representing 70% to 80% of all diagnosed thyroid cancers [5, 6]. It occurs more frequently in women with prevalence ratios ranging from 2.5 to 4.0:1 [4].

The relationship between HT and papillary thyroid carcinoma was first proposed by Dailey *et al.* in 1955 [7]. Since this initial description, the association between the two diseases has been highly debated in the literature and the relationship remains controversial. Studies to date establish 11% to 36% of patients with coexistent HT/PTC disease [2, 8–11]. Okayasu *et al.* determined a clear association between the two diseases among patients of differing ethnic origin [12]. Due to the ongoing debate, as well as the high prevalence of both diseases, this study was undertaken to determine the association between HT and PTC.

MATERIALS AND METHODS

From May 1994 to January 2007, 1198 patients underwent thyroid surgery at the University of Wisconsin. Of these patients, 217

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TABLE 1

Patient Characteristics*

	HT	No HT	*P*-value**
N	217	981	
Age (years)	46 ± 1	49 ± 1	0.076
Gender			
Male	10%	26%	<0.001
Female	90%	74%	
Gland weight (g)	30.3 ± 2.5	39.8 ± 2.2	0.053
Nodule size (cm)	2.34 ± 0.14	2.71 ± 0.07	0.045
Percent with papillary thyroid cancer			
All patients	29%	23%	0.051
Male	33%	28%	0.379
Female	29%	22%	0.033

* Values reported as mean ± SEM.
** Fisher's exact test.

(196 female, 21 male) were diagnosed with HT, which was confirmed by permanent section. For all patients, data were collected by retrospective chart review for patient demographics, gland weight, nodule size, presence of a goiter, and malignancy.

Data analysis was conducted using statistical software (SPSS Graduate Pack 10.0; SPSS Inc., Chicago, IL.). In analysis of these data, X^2, Fisher's exact test and one-way analysis of variance were used when appropriate. With regard to the results, statistical significance was defined as $P \leq 0.05$. The collection of patient data and subsequent analysis was approved by the University of Wisconsin Human Subjects Institutional Review Board.

RESULTS

Patient Characteristics

Of the 1198 patients who underwent thyroid surgery over a 13-year time span, 18% (217) were diagnosed with HT based on final pathology. When comparing patients with HT with those without HT, there was no significant difference between demographic variables (Table 1) with the exception of females being more likely to have HT and smaller nodule size seen in HT patients. Ninety percent of patients with HT were female while only 74% of patients without HT were female ($P < 0.001$). The nodule sizes between HT patients and patients without HT differed significantly at 2.34 ± 0.14 cm and 2.71 ± 0.07 cm, respectively ($P = 0.045$). Although patients with HT appeared to be slightly younger than those without HT (mean age 46 ± 1 *versus* 49 ± 1); this difference was not significant ($P = 0.076$). Of note, there was a trend toward smaller gland size in patients with HT. The average gland weight of HT patients was 30.3 ± 2.5 g and the average for patients without HT was 39.8 ± 2.2 g ($P = 0.053$). In addition, patients with HT exhibited a higher rate of PTC overall compared with patients without HT (29% *versus* 23%, $P = 0.051$). Thirty-three percent of males with HT also had PTC whereas 28% of males without HT had PTC ($P = 0.379$). Female patients with HT showed a more dramatic difference in the incidence of PTC in contrasted with females without HT (29% *versus* 22%, $P = 0.033$).

HT Patients

Within the subgroup of patients with HT, there was no significant difference between pathologic variables such as age, gland weight, and nodule size (Table 2). Among patients with HT, 63 (29%) had concurrent PTC, while 154 (71%) did not have PTC. However, the presence of a goiter was inversely associated with risk of malignancy in those patients with HT. Concerning all HT patients, 63 (29%) also had a goiter. Of HT patients without PTC, 56/154 (36%) had a goiter, while only 7/63 (11%) of patients with PTC had a goiter ($P < 0.001$). Only 5/56 (9%) female HT patients with PTC had a goiter, while 51/140 (36%) female HT patients without PTC had a goiter ($P < 0.001$).

Type of Malignancy

In the subgroup of patients with HT, the majority of all malignancies were PTC (63/67, 94%). Although PTC was also the most common malignancy in patients without HT, it was significantly less common relative to patients with HT (229/298, 76%, $P = 0.001$). There was a significantly greater percentage of PTC occurrence in females with HT compared with females without HT ($P = 0.006$). This trend was not significantly reproducible in male patients (Table 3).

DISCUSSION

Since first being described by Dailey *et al.* in 1955, the association between HT and PTC has been widely disputed and remains so in the literature [2, 7–11]. Given the relatively high incidence of both of these diseases, we further investigated this relationship. At

TABLE 2

HT Patients*

	Papillary thyroid cancer	No papillary thyroid cancer	*P*-value**
N	63	154	
Age (years)	44 ± 2	47 ± 1	0.339
Gland Weight (g)	24.1 ± 3.0	32.8 ± 3.3	0.122
Nodule Size (cm)	2.38 ± 0.35	2.34 ± 0.16	0.912
Goiters			
All Patients	11%	36%	<0.001
Male	29%	36%	0.572
Female	9%	36%	<0.001

* Values reported as mean ± SEM.
** Fisher's exact test.

TABLE 3

Type of Malignancy

	HT	No HT	*P*-value*
N	67	298	
Percent with papillary thyroid cancer			
All patients	63/67 (94%)	229/298 (76%)	0.001
Male	7/8 (88%)	70/102 (69%)	0.245
Female	56/59 (95%)	159/196 (81%)	0.006

* Fisher's exact test.

our institution, of the 217 patients with HT, 63 had coexistent PTC. If subdivided by gender, this was statistically significant for women with HT. Twenty-nine percent of female HT patients had concomitant PTC. When compared with other females without HT, women with HT were found to be 30% more likely to have coexisting PTC. The findings in this patient population support the previous studies linking HT and PTC [2, 8–11]. The data from male patients did not yield statistically significant results. While 33% of male HT patients had coexistent PTC, 28% of male patients without HT also had PTC. The lack of significance is most likely due to a small sampling size. Although the *P*-value did not meet our criteria for statistical significance, the data would possibly change with additional patients to analyze.

This study also found that the presence of a goiter is associated with a lower rate of PTC in HT patients (11% *versus* 36%). However, since all of the patients analyzed in this study underwent thyroid surgery, the selection of these patients must be noted. It is possible that many of the patients with a goiter underwent surgery due to compressive symptoms rather than nodule biopsy that warranted gland resection. That said, the high statistical significance of this result still merits investigation. In 2004, Gasbarri *et al.* determined that the diagnosis of HT actually represents a variety of disease mechanisms which influence the clinical presentation of the disease [13]. Therefore, one may speculate that a particular mechanism may predispose a patient to varying thyroid growth, including goiters or carcinomas.

Since the causative relationship between HT and PTC is not yet clear, careful observation of HT patients is recommended. There have been a number of proposed mechanisms of both of these diseases in the literature, along with some attempts to explain the association. For example, Wirtschafter *et al.* described expression of the RET/PTC1 and RET/PTC3 oncogenes in HT patients [14]. Arif *et al.* also supported this hypothesis, demonstrating both diseases have similar immunohistochemical staining, morphological features and molecular profile in regards to the RET/PTC gene rearrangement [15]. In addition, Unger *et al.* found expression of p63 in HT patients with papillary thyroid cancer [16]. This was further examined by Burstein *et al.* who proposed the two diseases are both initiated by pluripotent p63-positive stem cell remnants [17].

In this study, there was a trend in HT patients for the coexistence of PTC; a finding that becomes statistically significant in female HT patients. Women with HT have a 30% increased risk of having PTC compared with women without HT. In addition, among all HT patients, an overwhelming majority of malignancies were papillary carcinomas. Thus, it is plausible to assume that HT and PTC may be associated diseases. From the data presented above, it can be concluded that a heightened suspicion of PTC may be warranted in patients with HT, especially females. We recommend these patients receive periodic thyroid evaluations to assess any nodules present. If there is a nodule greater than one centimeter, ultrasound-guided FNA is advised.

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