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Clinical Thyroidology
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Clinical THYROIDOLOGY

VOLUME 25 • ISSUE 2

FEBRUARY 2013

Clin Thyroidol 2013;25:28–30.

Meta-analysis of Studies of Thyroidectomy Specimens Shows a Positive Correlation between Papillary Thyroid Carcinoma and Hashimoto’s Thyroiditis

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and Jerome M. Hershman

Lee JH, Kim Y, Choi JW, Kim YS. The association between papillary thyroid carcinoma and histologically-proven Hashimoto’s thyroiditis: a meta-analysis. Eur J Endocrinol. December 4, 2012 [Epub ahead of print].

SUMMARY

Background

Hashimoto’s thyroiditis (HT) is found in a high proportion of resected thyroid specimens. There has been considerable controversy as to whether having HT predisposes a patient to papillary thyroid cancer (PTC). This study is a meta-analysis designed to clarify the relationship between PTC and histologically demonstrated HT and to investigate the clinical and pathologic features of PTC with coexistent HT.

Methods

The authors performed an extensive literature search for articles that had primary data showing an association of PTC and “classical HT” based on histopathologic examination of thyroid specimens. Articles lacking pathologic data were excluded. On the basis of these criteria, 38 studies were selected for the meta-analysis.

Odds ratios (OR) with 95% confidence intervals (CI) were calculated and combined using a random-effects model.

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Results

The 38 studies consisted of 37 case-control studies and one cohort study. The number of patients in each study ranged from 6 to 1788, with a total of 10,648 PTC cases. Only 11 studies compared the frequency of HT in cases of PTC and benign thyroid disease. HT was found in 938 of 2317 (40.5%) of PTC cases and in 634 of 3019 (21%) of benign cases (OR, 2.77; 95% CI, 1.95 to 3.93; $P < 0.001$) for the coexistence of HT with PTC, but there was significant statistical heterogeneity among the studies.

In 16 studies comparing the prevalence of HT in PTC and in other thyroid cancers (follicular and medullary), HT was found in 17% of patients with PTC and in only 8% of patients with the other thyroid cancers (OR, 2.43

for the comparison; 95% CI, 1.61 to 3.66; $P < 0.001$). HT with PTC was found in 23% of female patients and in 11% of male patients (OR, 2.678; 95% CI, 1.755 to 4.087; $P < 0.001$). HT in PTC was not associated with the age of the patient or with the size of the tumor. Recurrence-free survival outcomes were provided in four studies including 616 patients who had PTC with HT and 4241 patients who had PTC without HT; HT in PTC was significantly associated with a longer duration of recurrence-free survival (hazard ratio, 0.576; 95% CI, 0.421 to 0.790; $P = 0.001$).

Conclusions

The meta-analysis showed that papillary thyroid cancer is significantly associated with pathologically confirmed Hashimoto's thyroiditis.

ANALYSIS AND COMMENTARY ● ● ● ● ●

The relationship between Hashimoto's thyroiditis and PTC has been a subject of considerable controversy for many decades. The authors of this meta-analysis suggest that PTC is significantly associated with pathologically confirmed HT. Although the incidence of HT is increased in patients with PTC, there has been no evidence suggesting a cause-effect relationship between the two entities. Paradoxically, patients with PTC and concurrent HT have significantly favorable outcomes. Could the immune reaction have a tumor-retarding effect on the PTC instead of being a predisposing factor?

The present study, though comprehensive, has a few shortcomings. It analyzed patients with already diagnosed PTC and calculated the frequency of HT in these cases. It does not explore the risk of PTC developing in patients with HT. Thus, the design of the study creates a considerable bias due to patient selection. The study population consisted of only cases of thyroidectomy, which is not reflective of the general outpatient population.

A retrospective study found that of 10,508 patients referred to an outpatient service for FNA, there was no statistically significant difference in the frequency of observed PTC in patients who had HT versus those who did not have HT (1.9% vs. 2.7%) (1). A prospective study of FNA specimens reported no significant difference between the incidence of PTC in patients who had HT versus those who did not have HT (2). Of 191 nodules from 164 patients with histologically diagnosed HT, only 1% were malignant, similar to the 2.7% malignancy rate in 713 nodules in 551 patients without HT ($P = 0.279$) (2). We conducted a recent literature review and found that the prevalence of PTC in HT is significantly higher among thyroidectomy specimens than among FNA specimens (3). The average prevalence rate of PTC in patients with HT was 1.2% (range, 0 to 2.95) in FNA studies of 18,023 specimens and 27.6% (range, 9.5 to 36.60) in archival thyroidectomy studies of 9884 specimens (3). It appears to us that the FNA studies are more applicable to the population of patients with HT.

Another limitation is the statistically significant heterogeneity between the studies in this meta-analysis
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based on the Q values provided. The authors of the present study sought to examine the clinical behavior of PTC with coexisting HT by investigating sex, age, tumor size, tumor extension, lymph-node metastasis, multifocality, and survival analysis. Among seven clinicopathologic characteristics, survival analysis and tumor extension were the only two that did not have significant heterogeneity, allowing valid conclusions to be reached.

There were two study results that appear to be inconsistent with the conclusions presented by the authors: the results pertaining to tumor extension and lymph-node metastasis. HT was found in 17.5% of 4128 PTCs without extrathyroidal extension and in 17.2% of 2897 PTCs with extrathyroidal extension. The authors concluded that the coexistence of HT in PTCs was associated with no extrathyroidal involvement. However, the equal prevalence of HT in PTC with and without extrathyroidal extension suggests no relationship. Similarly, HT was present in 17.8% of 4185 PTCs

without lymph-node metastasis and in 17.9% of 3462 PTCs with lymph-node metastasis, suggesting no relationship. However, the authors concluded that there was a positive relationship between the coexistence of HT and PTC and the absence of lymph-node metastasis.

This is the second largest meta-analysis to evaluate the association between PTC and HT. It provides a detailed review of the literature about the ongoing debate. However, studies of archival thyroidectomy specimens should be interpreted with caution. Although they provide valuable information about the correlation between the two entities, a significant positive association appears to be observed only in this high-risk population of patients whose disease state leads to a thyroidectomy. We suggest that this association in archived thyroidectomy specimens should not be used in making a decision about management of a thyroid nodule in a patient with Hashimoto's thyroiditis. Instead the decision should be based, as usual, on the result of the FNA cytopathology.

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