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CLINICAL STUDY

The association between papillary thyroid carcinoma and histologically proven Hashimoto's thyroiditis: a meta-analysis

Ju-Han Lee, Younghye Kim, Jung-Woo Choi and Young-Sik Kim

Department of Pathology, Korea University Ansan Hospital, 516, Gojan-1 Dong, Danwon-Gu, Ansan-Si, Gyeonggi-Do 425-707, Republic of Korea

(Correspondence should be addressed to Y-S Kim; Email: apysk@korea.ac.kr)

Abstract

Objective: No consensus exists on the association between papillary thyroid carcinoma (PTC) and Hashimoto's thyroiditis (HT). To resolve this controversy, this study aimed to evaluate the relationship between the two conditions using a meta-analysis.

Methods: We searched relevant published studies using citation databases including PubMed, Embase, and ISI Web of Science. The effect sizes of clinicopathologic parameters were calculated by odds ratio (OR), weighted mean difference, or hazard ratio (HR). The effect sizes were combined using a random-effects model.

Results: Thirty-eight eligible studies including 10 648 PTC cases were selected. Histologically proven HT was identified in 2471 (23.2%) PTCs. HT was more frequently observed in PTCs than in benign thyroid diseases and other carcinomas (OR = 2.8 and 2.4; $P<0.001$). PTCs with coexisting HT were significantly related to female patients (OR = 2.7; $P<0.001$), multifocal involvement (OR = 1.5; $P=0.010$), no extrathyroidal extension (OR = 1.3; $P=0.002$), and no lymph node metastasis (OR = 1.3; $P=0.041$). Moreover, PTCs with HT were significantly associated with long recurrence-free survival (HR = 0.6; $P=0.001$).

Conclusions: Our meta-analysis showed that PTC is significantly associated with pathologically confirmed HT. PTC patients with HT have favorable clinicopathologic characteristics compared with PTCs without HT. However, patients with HT need to be carefully monitored for the development of PTC.

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Introduction

Papillary thyroid carcinoma (PTC) is the most prevalent form of thyroid cancers, comprising about 80% of all diagnosed thyroid cancers. Hashimoto's thyroiditis (HT) – chronic lymphocytic thyroiditis or autoimmune thyroiditis – is a well-defined clinicopathologic entity and its incidence has increased over the past 50 years (1). HT is characterized by hypothyroidism, the presence of serum antithyroglobulin and anti-peroxidase antibodies, and widespread lymphocytic infiltration with depletion of follicular cells. In addition to the classical HT, recent studies have proposed that IgG4-related thyroiditis may be considered as a variant of HT (2). The association between HT and PTC has been a subject of long and ongoing debate (1, 2).

HT has shown a wide range of occurrence from 5 to 85% in thyroid specimens resected for PTC (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40). In addition, the clinicopathologic characteristics of PTCs with concomitant HT have not been definitely proposed (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40). Therefore, the present meta-analysis was conducted to clarify the relationship between PTCs and histologically proven conventional HT and to investigate the clinicopathologic features of PTCs with coexistent HT.

Materials and methods

Data collection and eligibility criteria

We searched the following online databases using the keywords 'thyroiditis' and 'cancer': i) Medline using PubMed (http://www.ncbi.nlm.nih.gov/pubmed), ii) Embase (www.embase.com), and iii) ISI Science Citation Index using the ISI Web of Science search interface (http://apps.isiknowledge.com). We also manually searched the reference lists of the identified articles. Duplicate data or overlapping articles were excluded by examining the authors' names and affiliations. The following types of articles were included: i) original articles demonstrating that the association between PTC and classical HT was assessed

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only in thyroid specimens by histopathologic examination; ii) articles published before September 2011; iii) when multiple articles were published by the same authors or institutions, the most recent or informative single article was selected. Articles lacking clinicopathologic data for meta-analysis, review articles without original data, conference abstracts, and single case reports were excluded. Study quality was independently scored by two reviewers using the Newcastle–Ottawa Scale (41). The Newcastle–Ottawa Scale is frequently used for nonrandom studies such as case–control and cohort studies. The maximum scores of case–control and cohort studies are 9 and 13 respectively. Quality scores of the 38 studies ranged from 5 to 7 with a mean of 5.9 (Table 1). All were considered adequate for meta-analysis. Neither language nor geographic restriction was defined. The selection process of the articles is shown in Fig. 1.

Data pooling and statistics

Meta-analysis was performed as previously described (42, 43). Briefly, effect sizes for each study were calculated by odds ratio (OR) or weighted mean

Table 1 Characteristics of individual studies included in the meta-analysis.

References	Year	Country	Study design	Study objective	HT/PTC (%)	Quality score
(3)	2011	Korea	Case–control	Association between PTC and HT	307/1028 (29.9)	6
(4)	2010	Italy	Case–control	Association between PTC and HT	25/101 (24.8)	6
(5)	2010	Greece	Case–control	Association between PTC and HT	12/32 (37.5)	6
(6)	2009	Italy	Case–control	Serum thyroid autoantibody in PTC with HT	257/304 (84.5)	6
(7)	2007	Turkey	Case–control	Association between PTC and HT	37/199 (18.6)	6
(8)	2006	Japan	Case–control	Niban expression in thyroid tumor and HT	6/54 (11.1)	5
(9)	2005	Italy	Case–control	Association between PTC and HT	19/71 (26.8)	6
(10)	2002	Saudi Arabia	Case–control	Association between PTC and HT	34/59 (57.6)	6
(11)	1997	Ireland	Case–control	Thyroid diseases in west Ireland	1/14 (7.1)	6
(12)	1995	USA, Japan	Case–control	Association between PTC and HT in three races	210/312 (67.3)	6
(13)	1998	USA	Case–control	Association between PTC and HT	30/143 (21.0)	6
(14)	2011	Taiwan	Case–control	Association between PTC and HT	85/1788 (4.8)	6
(15)	2008	USA	Case–control	Association between PTC and HT	63/292 (21.6)	6
(16)	2004	USA	Case–control	HT in pediatric thyroid tumor	3/6 (50.0)	6
(17)	2002	Argentina	Cohort	PTC and HT in relation to iodine prophylaxis	31/87 (35.6)	7
(18)	1999	USA	Case–control	Association between PTC and HT	125/564 (22.2)	6
(19)	1999	USA	Case–control	Association between PTC and HT	57/388 (14.7)	6
(20)	1998	Germany	Case– control	Association between PTC and HT	23/92 (25.0)	6
(21)	1993	Italy	Case–control	HT in thyroid tumor	4/22 (18.2)	5
(22)	1983	Italy	Case–control	Pathologic characteristics in thyroid cancer	14/79 (17.7)	6
(23)	1957	USA	Case–control	HT in thyroid lesion	2/16 (12.5)	6
(24)	2012	Korea	Case–control	Association between PTC and HT	56/195 (28.7)	6
(25)	2010	Italy	Case–control	Association between PTC and HT	128/343 (37.3)	6
(26)	2010	Korea	Case–control	Association between PTC and HT	105/323 (32.5)	6
(27)	2010	USA	Case–control	FoxP3+ regulatory T cell frequency in PTC	37/100 (37.0)	6
(28)	2009	Korea	Case–control	Association between PTC and HT	214/1441 (14.9)	6
(29)	2009	Korea	Case–control	BRAF mutation in PTC and HT	37/101 (36.6)	6
(30)	2009	Norway	Case–control	PDGFC expression in PTC	7/18 (38.9)	5
(31)	2009	Turkey	Case–control	HT and tumor infiltrating lymphocytes in PTC	16/61 (26.2)	6
(32)	2007	Japan	Case–control	Ultrasonographic finding in PTC with HT	29/83 (34.9)	6
(33)	2001	Austria	Case–control	Latent thyroid cancer in Austria	6/10 (60.0)	6
(34)	2001	USA	Case–control	Association between PTC and HT	41/136 (30.1)	6
(35)	1998	Japan	Case–control	Association between PTC and HT	281/1533 (18.3)	6
(36)	1998	Japan	Case–control	Association between PTC and HT	15/69 (21.7)	6
(37)	1997	Spain	Case–control	Association between PTC and HT	6/129 (4.7)	6
(38)	1995	Japan	Case–control	Association between PTC and HT	36/95 (37.9)	6
(39)	2008	Italy	Case–control	Association between PTC and HT	72/189 (38.1)	6
(40)	2010	Turkey	Case–control	Association between PTC and HT	40/171 (23.4)	6
Total					2471/10 648 (23.2)	

HT, Hashimoto's thyroiditis; PTC, papillary thyroid cancer.

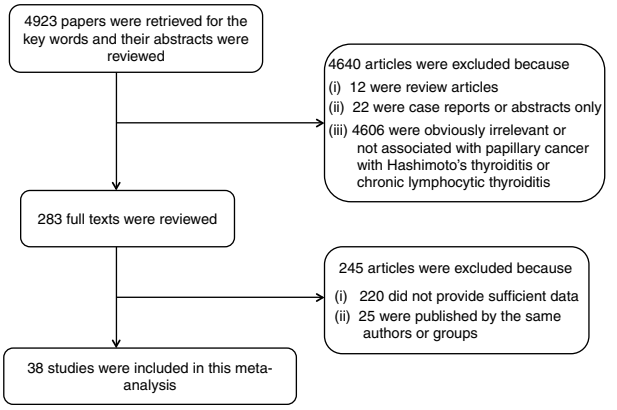

Figure 1 Flow diagram of article selection for this meta-analysis.

difference (WMD) with 95% confidence intervals (CIs). For studies without hazard ratios (HRs) for survival, we assessed HRs and CIs using a published approximation method (44). The ORs, WMDs, or HRs were combined using a random-effects model (DerSimonian–Laird method). For identifying and quantifying inter-study heterogeneity, Q statistics were calculated, which is an adaptation of the χ^2 goodness-of-fit test. $P<0.10$ was considered statistically significant. Sensitivity analyses according to study design (case–control vs cohort studies) were performed to examine the influence of each study on the pooled OR, WMD, or HR by serially omitting an individual study and pooling the remaining studies. Publication bias was examined by funnel plots and Egger's tests for the degree of asymmetry. $P<0.05$ was considered statistically significant. The pooled analysis was conducted using Comprehensive Meta-analysis software version 2.0 (Biostat, Englewood, NJ, USA).

Results

A total of 38 articles satisfied the eligibility criteria (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40). The eligible studies consisted of 37 case–control studies and one cohort study, all of which were hospital based. The eligible studies are summarized in Table 1. The number of patients in each study ranged from six to 1788, for a total of 10 648 PTC patients. Among the PTC patients, HT was present in 2471 (23.2%) cases.

PTC vs benign lesions

Eleven studies compared the occurrences of HT in PTCs and in benign thyroid diseases such as nodular hyperplasia and follicular adenoma (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13). HT was found in 938 (40.5%) of 2317 PTC patients, whereas it was found in 634 (21%) of 3019 benign thyroid diseases. The coexistence of HT was significantly associated with PTCs than benign lesions (OR = 2.766; 95% CI 1.947–3.929; $P<0.001$) (Fig. 2). Significant statistical heterogeneity was found among the studies (Q = 39.664, df = 10, $P<0.001$).

PTC vs other carcinomas

Sixteen studies investigated the frequencies of HT in PTCs and in other carcinomas such as follicular carcinoma and medullary carcinoma (3, 5, 8, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23). HT was present in 797 (17.1%) of 4664 PTC patients and in 57 (7.9%) of 725 other carcinoma patients. The coexistence of HT was more related to PTCs than other thyroid carcinomas (OR = 2.432; 95% CI 1.614–3.665; $P<0.001$) (Fig. 3). There was significant statistical heterogeneity among the studies (Q = 22.727, df = 15, $P=0.090$).

Clinicopathologic characteristics of PTCs with HT

Gender The incidence of HT in PTCs according to gender was compared in 23 studies (3, 4, 5, 6, 7, 14, 15, 19, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38). HT in PTCs was observed in 1677 of 7346 (23%) female patients and in 180 of 573 (11%) male patients. On the basis of this finding, there was a high association of HT in PTCs with females but not with males (OR = 2.678; 95% CI 1.755–4.087; $P<0.001$). Significant statistical heterogeneity was found among the studies (Q = 78.712, df = 22, $P<0.001$).

Age Fourteen studies addressed the frequency of HT in PTCs according to patients' mean age (3, 4, 5, 14, 24,

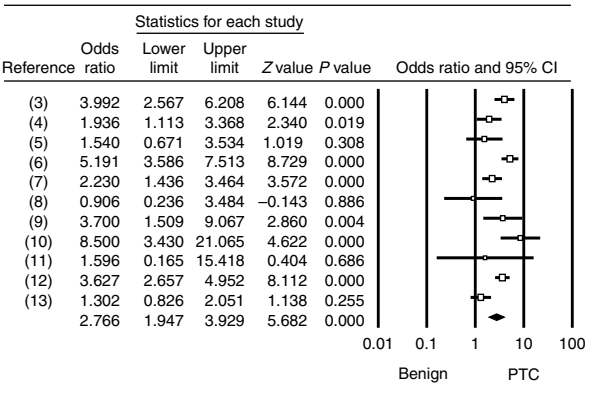

Figure 2 Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) of individual studies and pooled data for the association of Hashimoto's thyroiditis (HT) with papillary thyroid cancer (PTC), compared with benign thyroid lesions. Forest plot demonstrates the effect sizes and 95% CIs for each study and overall.

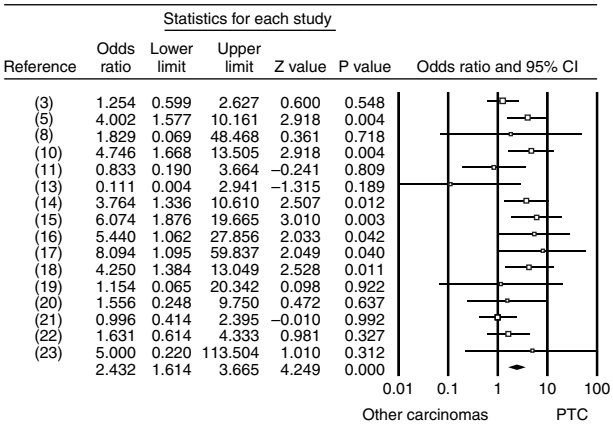

Figure 3 Pooled estimates for the frequencies of HT between PTC and other carcinomas.

28, 29, 30, 32, 33, 36, 37, 38, 39). The mean ages of PTC patients with HT ranged from 39.5 to 69.0 years, whereas the mean ages of PTC patients without HT ranged from 38.2 to 56.3 years. There was no association between the mean age of PTC patients and the incidence of HT in PTC (WMD = −0.081; 95% CI, −0.024 to 0.042; $P=0.195$). Statistical heterogeneity was detected among the studies (Q = 22.788, df = 13, $P=0.044$).

Tumor size Eleven studies identified the prevalence of HT in PTCs according to average tumor size (3, 4, 14, 24, 28, 32, 33, 36, 37, 38, 39). The mean tumor sizes of PTCs with HT ranged from 0.6 to 4.8 cm, whereas those of PTCs without HT ranged from 0.6 to 3.0 cm. The tumor size was not related to the frequency of HT in PTC (WMD = −0.355; 95% CI, −1.224 to 0.514; $P=0.424$). There was statistical heterogeneity among the studies (Q = 998.329, df = 10, $P<0.001$).

Tumor extension Eleven studies presented 4128 PTCs without extrathyroidal extension and 2897 PTCs with extrathyroidal involvement (3, 14, 19, 24, 27, 28, 29, 35, 38, 39, 40). HT was found in 722 (17.5%) of 4128 PTCs without extrathyroidal extension and in 500 (17.2%) of 2897 PTCs with extrathyroidal extension. The coexistence of HT in PTCs was associated with no extrathyroidal involvement of PTC (OR = 1.295; 95% CI 1.098–1.527; $P=0.002$). No significant statistical heterogeneity was detected among the studies (Q = 11.656, df = 10, $P=0.309$).

Lymph node metastasis Sixteen studies reported 4185 PTC patients without lymph node metastasis and 3462 patients with lymph node metastasis (3, 4, 7, 14, 19, 24, 25, 27, 28, 29, 30, 35, 37, 38, 39, 40). HT was seen in 746 (17.8%) of 4185 PTC cases without lymph node metastasis and in 622 (17.9%) of 3462 cases with lymph node metastasis. PTCs with HT were related to the absence of lymph node metastasis (OR = 1.287; 95% CI 1.010–1.639; $P=0.041$). There was significant statistical heterogeneity among the studies (Q = 29.899, df = 15, $P=0.012$).

Multifocality Twelve studies addressed the frequencies of HT in single and multifocal PTCs (3, 4, 7, 24, 26, 28, 33, 34, 36, 37, 39, 40). The studies included 1378 cases with multifocal PTC and 2549 cases with single PTC. HT was present in 359 (26%) of 1378 multifocal PTCs and in 541 (21%) of 2549 single PTCs. HT was more often observed in multifocal PTCs than in single PTCs (OR = 1.467; 95% CI 1.096–1.964; $P=0.010$) (Fig. 4). Significant statistical heterogeneity was found among the studies (Q = 23.514, df = 11, $P=0.015$).

Survival analysis Four studies including 616 patients of PTC with HT and 4241 of PTC without HT presented recurrence-free survival outcomes (14, 28, 35, 38). The estimated unadjusted HRs ranged from 0.547 to 0.781. The presence of HT in PTCs was significantly associated with a long duration of recurrence-free survival (HR = 0.576; 95% CI 0.421–0.790; $P=0.001$) (Fig. 5). There was no significant statistical heterogeneity among the studies (Q = 0.303, df = 3, $P=0.960$).

Sensitivity analysis and publication bias

The sensitivity analyses revealed that all studies or case–control studies did not affect the pooled ORs and HR with CIs. However, seven studies influenced the result of lymph node metastasis (4, 7, 14, 29, 30, 37, 40). In the funnel plots and the Egger's regression tests, there was no evidence of publication bias (Fig. 6).

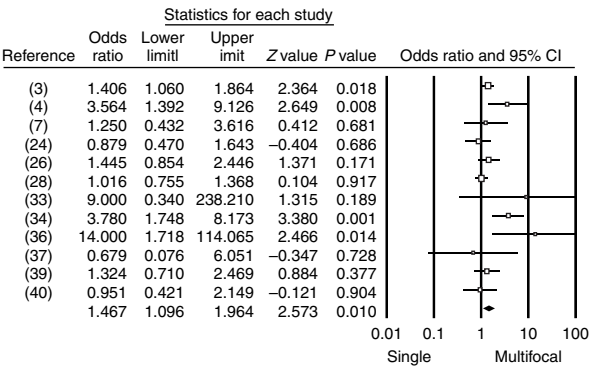

Figure 4 Pooled estimates for the frequencies of HT between single and multifocal PTCs.

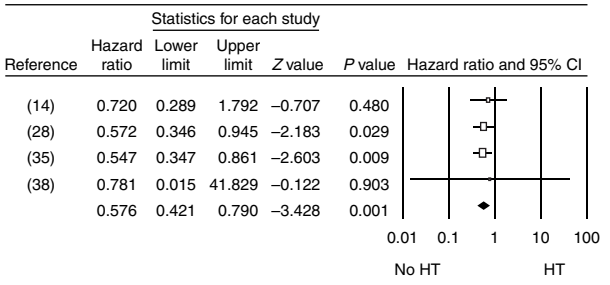

Figure 5 Hazard ratios with corresponding 95% CIs of individual studies and the pooled data for recurrence-free survival rates of PTC patients according to the presence or absence of HT.

Discussion

This meta-analysis showed that pathologically confirmed HT is more often found in PTC than in benign thyroid diseases and other carcinomas. Moreover, this analysis revealed that PTCs with coexisting HT are associated with female, multifocal involvement, the absence of extrathyroidal extension, no lymph node metastasis, and high recurrence-free survival rates.

Our pooled analysis indicates that the frequency of HT in PTCs was about 23%, ranging from 5 to 85%. The varying incidence rates of HT in PTC may be due to several factors such as different diagnostic criteria for HT, various surgical procedures, and heterogeneous patient characteristics. Most studies presented the incidence of HT in surgically resected PTC cases. In cytology specimens of HT patients, follicular cells often exhibit nuclear elongation, nuclear grooves, and even intranuclear inclusions, leading to a misdiagnosis of PTC (45, 46). Therefore, the current meta-analysis included only the studies that presented cases of HT confirmed by histopathologic diagnosis.

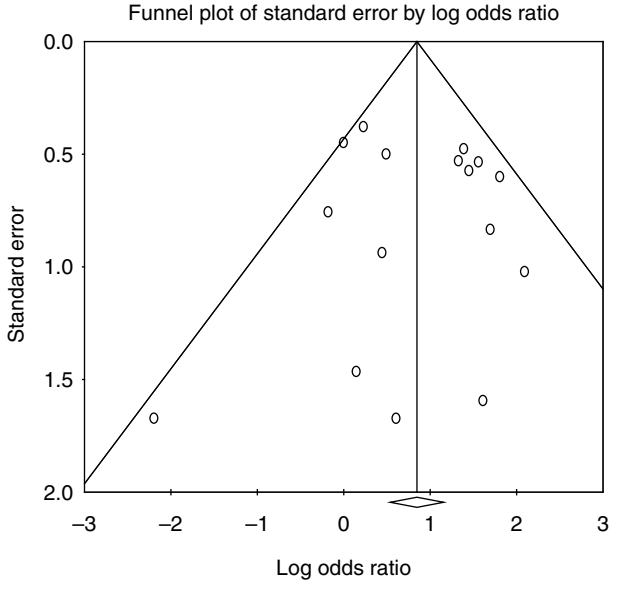

Figure 6 Funnel plot for publication bias in the incidence of HT between PTCs and other thyroid carcinomas. Individual studies are represented by small circles.

Our meta-analysis showed that the occurrence rate of HT in PTC patients was 2.8 times higher than HT patients in benign thyroid diseases. In addition, the incidence of HT in patients with PTC was 2.4 times higher than in those patients with other types of thyroid carcinoma. This result was similar to a previous result of another meta-analysis (19). In addition, some studies supported the tight association between HT and PTC, based on the fact that RET/PTC rearrangements were found in about 90% of HT cases (47) and transgenic mice expressing RET/PTC developed HT and PTCs (48).

Interestingly, this meta-analysis revealed that PTC patients with coexisting HT had distinctive clinicopathologic characteristics such as female gender, multifocality, no extrathyroidal extension, no lymph node metastasis, and long recurrence-free survival. Considerable controversy exists concerning the prognostic significance of HT in PTC patients. Loh *et al.* (18) and Yoon *et al.* (24) reported that PTC with HT was significantly associated with females and a lower incidence of extrathyroidal invasion and lymph node metastasis. Several studies found that PTC with HT had a tendency for multifocal involvement (3, 4, 26, 34). In contrast, other studies failed to present any significant clinicopathologic characteristics in PTC with HT (5, 25, 40).

This pooled analysis identified a paradoxical role of HT in the development and progression of PTC. The meta-analysis suggests a possible tight link between HT and the development of PTC rather than a chance occurrence of two relatively common diseases. Paradoxically, HT in PTC patients appears to play a role in impeding cancer progression. Therefore, the cross-link of these two conditions may represent a cause and effect relationship or a predisposing factor. It is hypothesized that PTC is induced or facilitated by a pre-existing lymphocytic infiltration. Conversely, lymphocytic infiltration of HT may be due to autoimmune thyroiditis and/or immune reaction to tumor-specific antigens from a pre-existing PTC (1).

Conclusions

Our pooled study indicates a close relationship between HT and PTC. As the incidence of HT is increased in PTC patients, careful clinical monitoring for the patients with HT and meticulous histopathologic examination of surgical specimens from these patients are required. The PTCs with HT are characterized by female predominance, multifocality, no extrathyroidal extension, no lymph node metastasis, and better recurrence-free survival outcomes.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

J-H Lee performed statistical analyses and wrote the manuscript draft. Y Kim and J-W Choi performed the literature search and data collection. Y-S Kim designed this study and edited the manuscript.

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