Association between Hashimoto thyroiditis and clinical outcomes of papillary thyroid carcinoma: A meta-analysis

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Abstract

Objective
To assess association between Hashimoto thyroiditis (HT) and clinical outcomes of papillary thyroid carcinoma (PTC).

Methods
Databases including Pubmed, Embase, Cochrane Library, and Web of Science were searched. Weighed mean differences (WMDs) and odds ratios (ORs) were used to evaluate association between HT and clinical outcomes of PTC, and the effect size was represented by 95% confidence intervals (CIs). Heterogeneity test was performed for each indicator. If the heterogeneity statistic $I^2 \geq 50\%$, random-effects model analysis was carried out, otherwise, fixed-effect model analysis was performed. Sensitivity analysis was performed for all outcomes, and publication bias was tested by Begg’s test.

Results
Totally 47,237 patients in 65 articles were enrolled in this study, of which 12909 patients with HT and 34328 patients without HT. Our result indicated that PTC patients with HT tended to have lower risks of lymph node metastasis (OR: 0.787, 95%CI: 0.686–0.903, $P = 0.001$), distant metastasis (OR: 0.435, 95%CI: 0.279–0.676, $P < 0.001$), extrathyroidal extension (OR: 0.745, 95%CI: 0.657–0.845, $P < 0.001$), recurrence (OR: 0.627, 95%CI: 0.483–0.813, $P = 0.004$), and a better 20-year survival rate (OR: 1.396, 95%CI: 1.109–1.758, $P = 0.005$) while had higher risks of multifocality (OR: 1.245, 95%CI: 1.132–1.368, $P < 0.001$), perineural infiltration (OR: 1.922, 95%CI: 1.195–3.093, $P = 0.007$), and bilaterality (OR: 1.394, 95%CI: 1.118–1.739, $P = 0.003$).

Conclusions
PTC patients with HT may have favorable clinicopathologic characteristics, compared to PTCs without HT. More prospective studies are needed to further elucidate this relationship.
Background

Hashimoto thyroiditis (HT) is a chronic inflammation of the thyroid gland initially described over a century ago, which is now considered the most common autoimmune disease [1, 2]. An incidence is estimated to range from 0.3 to 1.5 cases per 1,000 people, with a prevalence of 5–10% in the overall population [3]. HT is characterized by hypothyroidism, the presence of serum antithyroglobulin and antiperoxidase antibodies, and widespread lymphocytic infiltration with depletion of follicular cells [4, 5]. Thyroid cancer (TC) is the most common malignancy of the endocrine system, with papillary thyroid carcinoma (PTC) being the most prevalent form that accounts for 80% of all diagnosed TCs [6]. The incidence of PTC and HT is rapidly increasing in many countries [7, 8]. The disease of PTC coexisted with HT presents an increasing trend year by year [9]. The coexistence of these two diseases has also been reported to range from 10% to 58% [10, 11], which has aroused great concern.

The relationship between HT and PTC was investigated in several studies. Coexistent HT has been reported to be significantly associated with the less aggressive clinicopathologic characteristics of PTC [10, 12]. Whereas several scholars observed HT is associated with a significantly increased risk of PTC [13]. Other studies have shown no connection between the presence of HT and PCT [14, 15]. Moreover, the association with prognosis between HT and PC remains unclear. It is uncertain whether coexisting with HT in PTC represents a good prognosis or is simply the concurrence of both diseases. It is therefore reasonable to further evaluate the association between HT and PTC.

Herein, we conducted a meta-analysis with a multitude of outcome assessments included to explore the association between HT and PTC prognosis.

Methods

Search strategy

Published literature search was performed on Pubmed, Embase, Cochrane Library, and Web of Science databases from inception to December 11, 2020. The search words were as follows: “Thyroid Cancer, Papillary” OR “Cancer, Papillary Thyroid” OR “Papillary Thyroid Cancer” AND “Hashimoto Disease” OR “Hashimoto Struma” OR “Hashimoto Thyroiditis” OR “Hashimoto Thyroiditides” OR “Autoimmune thyroid disease”. The detailed search terms from PubMed are listed in S1 File.

Inclusion and exclusion criteria

Inclusion criteria were: (1) studies with patients with PTC; (2) studies including patients with HT in the case group, and those without HT in the control group; (3) studies with the latest research results for the same studies by the same authors; (4) studies published in English; (5) cohort studies, case-control studies, and cross-sectional studies.

Exclusion criteria: (1) animal experiments; (2) studies in which data were incomplete; (3) reviews, meta-analyses, case reports, conference reports, editorial materials, and letters.

Quality assessment and data extraction

The Chinese version of the Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the literature in cohort studies and case-control studies. The total score of the scale was 10, with < 5 as low quality and ≥5 as high quality. Regarding quality evaluation of cross-sectional studies, the Business Integration (JBI) scale was adopted, with 1–14 as low quality and 15–20 as high quality.
For each study, the following information was extracted, including author, year, country, study design, group, the number of patients, gender, age, subtype, tumor size, extent of surgery, tumor node metastasis stage, follow up, quality, outcomes.

**Outcomes**

The association between HT and clinical outcomes of PTC was assessed by lymph node metastasis (including lymph node metastasis, central lymph node metastasis, lateral lymph node metastasis), distant metastasis, extrathyroidal extension, recurrence, multifocality, invasion (includes vascular invasion, capsular invasion, perineural infiltration), bilaterality, number of deaths, AMES stage and MACIS score.

**Statistical analysis**

Software Stata (version 15.1, Stata Corporation, College Station, TX, USA) was used for statistical analysis. Weighed mean differences (WMDs) were statistics for measurement data, odds ratios (ORs) were used as effect indicators for continuous variables and frequency of events, and effect sizes were represented by 95% confidence intervals (CIs). A heterogeneity test was performed for each indicator. If THE heterogeneity statistic $\hat{I}^2 \geq 50\%$, random-effects model analysis was carried out, otherwise, fixed-effects model analysis was performed. Each meta-analysis may create a false-positive or negative conclusion. Given this, TSA was conducted to reduce these statistical errors [16]. TSA is a methodology that combines an information size calculation (accumulated sample sizes of all included trials) to reduce type I error and type II error for a meta-analysis with the threshold of statistical significance (http://www.ctu.dk/tsa). TSA was used to quantify the statistical reliability of data in the cumulative meta-analyses by adjusting significance levels for sparse data and repetitive testing on accumulating data. Sensitivity analysis was performed for all outcomes, and publication bias was tested by Begg’s test. Given the age imbalance between the case group and control group, an age-based sensitivity analysis was also applied (S2 File). $P<0.05$ was considered statistically significant.

**Results**

Initially, 1992 studies were searched according to the search strategy, and after duplicated removed, 1331 records were identified. With 174 full-text articles eligible for screening, 65 articles [5, 8, 9, 12, 13, 17–76] were finally included in this meta-analysis, including 32 case-control studies, 27 cohort studies, and 6 cross-sectional studies. The flow chart depicting the study selection process is shown in Fig 1. Totally 47,237 patients were enrolled in this study, of which 12909 patients with HT and 34328 patients without HT. The characteristics of included studies are presented in Table 1.

**Lymph node metastasis**

**Lymph node metastasis.** Lymph node metastasis was assessed in 44 studies including 11254 patients. The heterogeneity test results were statistically significant ($\hat{I}^2 = 75.9\%$), so the random-effects model was adopted. The result showed that HT group had a lower risk of lymph node metastasis than non-HT group (OR: 0.787, 95%CI: 0.686–0.903, $P = 0.001$) (Table 2, Fig 2A).

**Central lymph node metastasis.** Seventeen studies involving 7328 patients were identified to assess central lymph node metastasis. The random-effect model result indicated that PTC patients with HT had a lower risk of developing central lymph node metastasis than those without ($\hat{I}^2 = 86.4\%$, OR: 0.796, 95%CI: 0.636–0.995, $P = 0.045$) (Table 2, Fig 2B).
Lateral lymph node metastasis. A total of 11 studies consisting of 1362 patients provided data to assess lateral lymph node metastasis. The heterogeneity test results were not statistically significant ($I^2 = 43.3\%$), so the fixed-effect model was adopted. It was shown that HT was associated with a decreasing risk of lateral lymph node metastasis in PTC patients (OR: 0.845, 95% CI: 0.733–0.973, $P = 0.02$) (Table 2, Fig 2C).

Distant metastasis

Distant metastasis was assessed in 11 studies comprising 151 patients. The fixed-effects model result showed that the HT group was at a lower risk of distant metastasis than the non-HT group (OR: 0.435, 95% CI: 0.279–0.676, $P<0.001$) (Table 2, Fig 3).
### Table 1. Basic characteristics of included studies.

| Author       | Year | Country | Study design | Group      | Diagnosis of HT | No | Sex (female/ male) | Age | Subtype of PTC | Tumor size (cm) | Extent of surgery | TNM stage | Follow up (months) | QA | Outcomes |
|--------------|------|---------|--------------|------------|-----------------|----|--------------------|-----|-----------------|-----------------|-------------------|-----------|---------------------|----|----------|
| Ahn          | 2011 | Korea   | retrospective cohort | PTC only | -               | 211 | 179/41             | 48.52 ±14.4 | conventional 203, follicular variant 7, tall cell variant 1 | 1.80±1.5 | TT 178, thyroid lobectomy with isthmusectomy 33 | I 127, III/ IV 84 | 62.8±27.0 | 9 | ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ |
| Dobrinja     | 2016 | Italy   | retrospective cohort | PTC + HT | diffuse lymphocytic and plasma cell infiltration, lymphoid follicle formation with germinal centres, varying degree of fibrosis, paracortical atrophy, and the presence of large follicular cells with abundant eosinophilic cell changes | 58 | 55/3 | 42.8±12.7 | conventional 75, follicular variant 2, tall cell variant 1 | 1.60±1.0 | TT 47, thyroid lobectomy with isthmusectomy 11 | I 35, III/ IV 23 | 59.0±28.4 | 7 | ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ |
| Cortesi      | 2010 | Italy   | retrospective cohort | PTC only | -               | 105 | 81/24             | 51.06 ±13.07 | papillary 70, FVPC 27, follicular 8 | - < 0.558 | - | - | - | - | 5 | ☐ ☐ |
| Cai          | 2015 | China   | retrospective case-control | PTC only | -               | 823 | 827/223 | 46.2±11.4 | - | 1.10±0.8 | TT or lobectomy with prophylactic CLND and/or therapeutic LLND | II/ II, III/ IV 298 | - | 5 | ☐ ☐ |
| Cai          | 2015 | China   | retrospective case-control | PTC + HT | diffuse lymphocytic and plasma cell infiltration, lymphoid follicle formation with germinal centres, paracortical atrophy with eosinophilic changes, and variable amounts of stromal fibrosis throughout the thyroid gland | 67 | 62/5 | papillary 95, FVPC 27, follicular 2 | - < 0.558 | - | - | - | - | 5 | ☐ ☐ |
| Cai          | 2015 | China   | retrospective case-control | PTC + HT | diffuse lymphocytic and plasma cell infiltration, lymphoid follicle formation with germinal centres, paracortical atrophy with eosinophilic changes, and variable amounts of stromal fibrosis throughout the thyroid gland | 229 | - | - | - | 1.10±0.8 | - | - | - | - | 5 | ☐ ☐ |
| Caralho      | 2017 | Brazil  | prospective cohort | PTC only | -               | 442 | 367/95 | median 46 (14–78) | - | ≤2.132, 2.4–228, >4.82 | TT 83 | T4N0, thyroid lobectomy + TT or lobectomy with prophylactic CLND and/or therapeutic LLND | 86 (24–120) | 8 | ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ |
| Consolini    | 2010 | Italy   | retrospective case-control | PTC only | -               | 76 | 57/19             | 56.27 ±12.79 | - | 1.26±1.203 | TT 101 | I 57, II, III/ IV 16 | - | 6 | ☐ ☐ |
| Dohranja     | 2016 | Italy   | retrospective cohort | PTC only | -               | 90 | 56/34             | 54 (12–84) | - | 2.51±2.09 | - | TT 115 | I 40, II, III/ IV 8 | 96 (82–140) | 7 | ☐ ☐ |
| Dohranja     | 2016 | Italy   | retrospective cohort | PTC + HT | diffuse lymphocytic and plasma cell infiltration, lymphoid follicle formation with germinal centres, paracortical atrophy with eosinophilic cell changes | 70 | 63/7 | 45.8±13.2 | - | 1.56±1.30 | TT 85, lobectomy + TT or lobectomy with prophylactic CLND and/or therapeutic LLND | I 50, II, III/ IV 11 | 39 (18–343) | 8 | ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ |

(Continued)
Table 1. (Continued)

| Author          | Year | Country       | Study design | Group         | No Sex (female/male) | Age | Subtype of PTC | Tumor size (cm) | Exstent of surgery | TNN stage | Follow up (months) | QA | Outcomes |
|-----------------|------|---------------|--------------|---------------|----------------------|-----|----------------|------------------|------------------|-----------|-------------------|----|----------|
| Dvorak 2013     | Israel| retrospective cohort | PTC only | - | 98 | 80/8 | 50.5±15 | - | TT 196 | - | - | 1.95±1.3 | 10 | 8 | (Continued) |
| Girardi 2015    | Brazil| retrospective cohort | PTC + HT | patient’s history of lymphadenitis with positive antithyroid antibodies or when there was a diffuse lymphocytic infiltration bilaterally on the pathology report | 98 | 91/7 | 50.5±15 | - | - | 1.78±1.2 | 10 | 5, 9, II, III 24, IV 8 | (Continued) |
| Jara 2013       | USA | retrospective cohort | PTC only | - | 554 | 405/149 | 30.6±13.1 | classic: 312, tall cell 73, follicular 80, mixed form 79, other 10 | - | - | 1.91±1.7 | 10 | 0 | (Continued) |
| Ieni 2017       | Italy| retrospective cohort | PTC only | - | 893 | 817/122 | 54±14 | papillary 410, papillary/follicular 120 | 2.12±1.62 | TT 1380 | 14 | 4 | 1.68±1.53 | 10 | 0 | (Continued) |
| Giagnetta 2014  | Greece| retrospective cohort | PTC + HT | dense or diffuse lymphocytic and plasma cell infiltration, oxyphilic cells, and formation of lymphoid follicles in the tissue of both lobes | 441 | 379/62 | 42±10 | papillary 282, papillary/follicular 159 | 1.83±1.53 | TT 1380 | 14 | 10 | 1.3±1.53 | 10 | 0 | (Continued) |
| Garaveli 2015   | Brazil| retrospective cohort | PTC only | - | 209 | 205/66 | 47.15±14.14 | - | TT 289 | 102 | 10 | 1.91±1.70 | 10 | 0 | (Continued) |
| Han 2019        | China | case-control | PTC only | - | 89 | 65/28 | 42.3±12.3 | papillary/follicular variant 148, follicular variant 32, conventional 150, papillary/follicular 99, papillary 110, follicular 66, papillary/follicular 159 | 1.2±0.7 | - | 1.91±1.70 | 10 | 0 | (Continued) |
| Huang 2011      | China| retrospective cohort | PTC only | - | 1703 | 1386/337 | 40.8±14.4 | - | TT 431 | LND/radical neck dissection 1292 | 1.15 | 4 | 1.2±0.7 | 10 | 0 | (Continued) |
| Jenni 2017      | Italy | retrospective case-control | PTC only | - | 357 | 253/94 | 47.2±11.78 | classic: variant 140, follicular variant 118, sclerosing 23, tall cell 4, Warthin-like 3, hobnail/microglandular 6, cebroïdent 1 | 1.2±0.971 | - | 1.91±1.70 | 10 | 0 | (Continued) |
| Jara 2013       | USA | retrospective case-control | PTC only | - | 259 | 192/77 | medium 47(11–86) | conventional: 205, follicular variant 48, papillary/follicular variant 37, tall cell variant 18, trabecular variant 18, Warthin-like 3, follicular 110, papillary/follicular 110, trabecular variant 18, follicular variant 37, Warthin-like 3, follicular 110, papillary 110, papillary/follicular 110 | 2.0±1.0–2.5 | TT 127 | LND/radical neck dissection 12 | 1.69 | 4 | 1.4±1.0–2.5 | 10 | 0 | (Continued) |
| Jeong 2012      | Korea | retrospective cohort | PTC only | - | 402 | 312/90 | 48±8 | medium: 47(11–86) | conventional: 140, follicular variant 118, sclerosing 23, tall cell variant 18, trabecular variant 18, Warthin-like 3, follicular 110, papillary/follicular 110, trabecular variant 18, follicular variant 37, Warthin-like 3, follicular 110, papillary 110, papillary/follicular 110 | 1.5±1.0–2.0 | TT 127 | LND/radical neck dissection 12 | 1.69 | 4 | 1.4±1.0–2.5 | 10 | 0 | (Continued) |
| Kashima 1998    | Japan | case-control | PTC only | - | 2352 | 1325/129 | 48.6 | - | TT 402 | 102 | 10 | 1.12±0.77 | 10 | 0 | (Continued) |

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(Continued)
| Author       | Year | Country | Study design | Group         | Diagnosis of HT                                                                 | No | Sex (female/male) | Age | Subtype of PTC | Tumor size (cm) | Extent of surgery | TNM stage | Follow up (months) | QA | Outcomes |
|--------------|------|---------|--------------|---------------|--------------------------------------------------------------------------------|----|------------------|-----|----------------|-----------------|------------------|-----------|-------------------|----|----------|
| Kebebew      | 2001 | USA     | retrospective cohort | PTC only      | diffusely lymphoplasmyctotic infiltrate, oxyphilic cells, formation of lymphoid follicles with germinal centers and atrophic changes in the area of normal thyroid tissue | 95 | 62/34            | 54  | -              | ≤1, 1.5–4       | TT/near TT 64, subtotal thyroidectomy 3, lobectomy 20 | 1, 11 II, 12, III, IV | 52.8            | 8 | 官方认证 |
| Kim          | 2009 | Korea   | case-control | PTC only      | diffusely lymphoplasmyctotic infiltrate, oxyphilic cells, formation of lymphoid follicles with germinal centers and atrophic changes in the area of normal thyroid tissue | 64 | 54/10            | 44.1±13.4       | -   | ≤1, 1.5–4       | TT/near TT 64, subtotal thyroidectomy 4, lobectomy 11 | 1, 11 II, 12, III, IV | - | 官方认证 |
| Kim          | 2010 | Korea   | case-control | PTMC only     | heavy infiltration of lymphocytes with varying degrees (including germinal centers) in thyroid tissue, the presence of Hurthle cells and varying degree of acinar atrophy | 218 | 174/44          | <45  | -              | 0.8–1          | TT 128            | -           | - | 官方认证 |
| Kim          | 2011 | Korea   | case-control | PTC only      | any 1 of the following criteria: (1) positive for anti-TPO antibody, (2) positive for antithyroglobulin antibody, (3) pathologic confirmation of Hashimoto's thyroiditis | 721 | 527/194         | 46.0±12.1       | -   | 1.24±0.96       | III/IV 132       | - | 官方认证 |
| Kim          | 2013 | Korea   | retrospective cohort | PTC only      | diffusely lymphoplasmyctotic infiltrations with germinal centers, oxyphilic cells, formation of lymphoid follicles with germinal centers and atrophic changes in the area of normal thyroid tissue | 931 | 778/153         | 46.8±11.01      | -   | 0.9±0.3         | lobectomy 106, TT-MRND 294 | -           | - | 官方认证 |
| Kim          | 2014 | Korea   | retrospective cohort | PTC only      | diffusely lymphoplasmyctotic infiltrates, oxyphilic cells, formation of lymphoid follicles, fibrosis, and follicular cell atrophy | 125 | 114/11          | 44.6±25–75      | -   | 0.9±0.2         | TT 144           | - | 官方认证 |
| Kim          | 2016 | Korea   | case-control | PTC only      | diffusely lymphoplasmyctotic infiltrates, oxyphilic cells, formation of lymphoid follicles, fibrosis, and follicular cell atrophy | 1576 | 1289/287       | 47.2±12.0       | -   | 0.9±0.5         | TT 1406, ≤TT 110 | II, III/IV 619 | - | 官方认证 |
| Kim          | 2016 | Korea   | case-control | PTC only      | diffusely lymphoplasmyctotic infiltrates, oxyphilic cells, formation of lymphoid follicles, fibrosis, and follicular cell atrophy | 204 | 198/8           | 44.8±11.9       | -   | 0.8±0.5         | TT 190, ≤TT 14 | II, III/IV 619 | - | 官方认证 |
| Kim          | 2016 | Korea   | case-control | PTC only      | diffuse parenchymal infiltration by lymphocytes (particularly plasma B-cells), a germinal center formation, follicular cell destruction, Hurthle cell change and variable amounts of stromal fibrosis throughout the thyroid gland | 1006 | 912/94          | 46.0±11.4       | -   | 1.1±0.7         | TT-bilateral CND 3332 | -           | - | 官方认证 |

(Continued)
| Author      | Year | Country | Study design | Group       | Diagnosis of HT | No | Sex (Female/Male) | Age | Subtype of PTC | Tumor size (cm) | Extant of surgery | TNM stage | Follow up (months) | QA | Outcomes |
|-------------|------|---------|--------------|-------------|-----------------|----|-----------------|-----|----------------|----------------|-----------------|-----------|-------------------|----|----------|
| Kim        | 2018 | Korea   | retrospective case-control | PTC only | diffuse lymphatic and plasma cell infiltration, neoplastic cells and the formation of lymphoid follicles or reactive germinal centers in the area of normal thyroid tissue | 124 | 107/17 | 50.38 ± 11.51 | - | 0.92 ± 0.73 | T1 272 | I 117, II 40, IV 13 | - | 6 |
| Konturek   | 2014 | Poland  | retrospective cohort | PTC + HT (1) high anti-thyroid peroxidase antibodies titer (anti-TPO), (2) lesions visualized by ultrasonography showing a hypochogenic or hypodense, nodular pattern at least 5 mm in diameter, identification of a perinodular hypochogenic or hypechogenic halo and presence of an anechoic lesion with a well-defined posterior wall, (3) histology: presence of a diffuse lymphocytic infiltrate in the thyroid parenchyma and stroma with reactive follicles and lymphoid follicles, presence of small follicles with a decreased colloid volume, focal of fibrosis and epithelial cells containing cells | 643 | 574/69 | < 45.27 ± 45.56 | - | 0.94 ± 0.69 | TT + CLND, subtotal bilateral lobectomy | T1a 191, T1b 77, T2 79, T3 108 | - | 7 |
| Kurnakovcingslu | 2007 | Turkey  | retrospective case-control | PTC only | diffuse mononuclear cell infiltration with fibrosis, occasional well-developed germinal centers, and enlarged follicular cells with abundant eosinophilic, granular cytoplasms | 162 | - | 46.6 ± 13.5 | follicular variant 37 | < 1.18 ± 1.14 | TT 199 | - | 6 |
| Kwon       | 2015 | Korea   | retrospective cohort | PTC + HT (1) pathological diagnosis included chronic lymphocytic infiltration | 1493 | 1187/308 | 46.12 ± 11.13 | classical follicular variant 94, cystic 14, oncocytic 4, others 22 | 0.95 ± 0.67 | thyroid lobectomy or TT with cervical LND 1945 | I 164, II 9, III 736, IV 100 | 279 ± 55 |
| Kwon       | 2014 | Korea   | cohort | PTC + HT (1) pathological diagnosis included chronic lymphocytic infiltration | 86 | 72/14 | 48.8 ± 12.2 | conventional follicular variant 79, variants 7 | 0.003 | T1a 191, T1b 77, T2 79, T3 108 | I 229, II 38, III 10, IV 16 | - |
| Kwon       | 2016 | Korea   | retrospective cohort | PTC + HT (1) pathological diagnosis included chronic lymphocytic infiltration | 473 | 350/123 | 48.4 ± 10.5 | - | 1.23 ± 0.93 | TT + CLND 435 | 40 ± 23.5 |
| Lee        | 2018 | Korea   | case-control | PTC + HT histological diagnosis | 215 | 200/15 | 46.9 ± 10.4 | - | 1.11 ± 0.96 | TT + CLND 198 | - | - |
| Lee        | 2020 | Korea   | retrospective cohort | PTC + HT pathological reports or chronic lymphocytic thyroiditis | 563 | 528/35 | 46.4 ± 11.3 | - | 0.83 ± 0.55 | - | - |
| Liang      | 2017 | China   | retrospective cohort | PTC + HT lymphocytic infiltration of germinal centers and the presence of large follicular cells with abundant granular eosinophilic cytoplasms on histologic examination | 1174 | 1082/92 | 45.5 ± 10.32 | - | 0.96 ± 0.71 | TT 822, 90 ± 0.2 | T1 118, T2 46, T3 109, T4 21 | 24 (1–90) |
| Liang      | 2017 | China   | retrospective cohort | PTC + HT diffuse lymphocytic infiltration, germinal centers and enlarged epithelial cells with large nuclei and eosinophilic cytoplasms | 1055 | 789/266 | 41.34 ± 11.63 | - | 1.34 ± 1.1 | thyroid lobectomy with inhomogeneity 520, TT 972, CLND without LLND 785, comprehensive neck dissection 409 | I 164, II 9, III 175, IV 165 | 38.4 ± (5.1–129.3) |

(Continued)
Table 1. (Continued)

| Author       | Year | Country        | Study design       | Group | Diagnosis of HT                | No. | Sex | Age | Subtype of PTC | Tumor size (cm) | Extent of surgery | TNN stage | Follow up (months) | QA | Outcomes |
|--------------|------|----------------|--------------------|-------|-------------------------------|-----|-----|-----|---------------|----------------|------------------|-----------|-------------------|----|---------|
| Lim 2013     | Korea| retrospective case-control | PTC + HT | - | pathology reports | 964 | 873/3/1 | median 43 | - | - | 0.79 | III/IVA 3.11 | - | 4 | (Continued) |
| Liu 2014     | China| retrospective case-control | PTC + HT | - | diffuse lymphocytic infiltration with the formation of lymphoid follicles and reactive germinal centers | 1141 | 840/1/10 | 45.23 | - | - | 1.392 | 10.04/21 | - | - | 6 | (Continued) |
| Liu 2016     | China| retrospective case-control | PTC only | - | - | 179 | 77/42 | 46.35 | 113.23 | - | 0.07/0.22 | - | - | 5 | (Continued) |
| Lu 2020      | China| case-control | PTC only | - | - | 89 | 65/28 | 42.81/24 | - | - | 1.11/0.7 | - | III/IV 1, III/IV 2 | - | 4 | (Continued) |
| Lu 2013      | China| case-control | PTC only | - | - | 549 | 45/130 | 44.81/38 | - | - | 2.24/1.38 | - | III/IV 10 | - | 6 | (Continued) |
| Ma 2018      | China| case-control | PTC + HT | - | diffuse lymphocytic infiltration, germinal centers, enlarged epithelial cells with large nuclei and eosinophilic cytoplasm (Askanazy or Hurthle cells), and variable amounts of stromal fibrosis throughout the thyroid gland | 127 | 114/9 | 41.3/12.5 | - | - | 1.84/0.93 | III/IV 8 | - | (Continued) |
| Molnar 2019  | Hungary| case-control | PTC only | - | - | 49 | 47/4 | 56.513.1 | - | 0.84/0.44 | - | - | (Continued) |
| Mohamed 2020 | Egypt| cross-sectional | PTC only | - | - | 54 | 50/14 | 50.2 | - | - | 0.84/0.44 | - | III/IV 10 | - | 6 | (Continued) |
| Mohr 2019    | Hungary| case-control | PTC only | - | - | 173 | 155/40 | 57.25/61 | - | 1.3 | (Continued) |
| Nam 2016     | Korea| retrospective cohort | PTC only | - | - | 15 | 10/5 | 47.1 | 13.04 | - | 1.51/1.4 | 0.7–4.0 | TT + unilateral/bilateral CLND 57 | 15, II, III, IV 3 | 51.81/0.35 | 8 | (Continued) |
| Park 2015    | Korea| retrospective case-control | PTC only | - | - | 489 | 48/38 | 43.82 | 13.92 | - | 0.875 | 0.398 | TT 38, lobectomy 38, subtotal thyroidectomy 1 | Tia 279, Tia 59, Tia 71, Tia 70, Tia 70 | - | 6 | (Continued) |
Table 1. (Continued)

| Author       | Year | Country | Study design | Group | Diagnosis of HT | No | Sex (female/ male) | Age | Subtype of PTC | Tumor size (cm) | Extent of surgery | TNM stage | Follow up (months) | QA | Outcomes |
|--------------|------|---------|--------------|-------|-----------------|----|-------------------|-----|---------------|----------------|-----------------|-----------|-------------------|----|----------|
| Paulsen 2012 | USA  | historical cohort | PTC only | - | diffuse lymphocytomarcous infiltrate, epithelial cells, formation of lymphoid follicles with germinal centers and atrophic changes in the area of normal thyroid tissue | 78 | 57/21 | 45.6 | classic 65, follicular variant 12, other 1 | 2.8 | TT + CLND 139 | - | - | 8 | 

Pilk 2018 Italy retrospective cohort | PTC + HT | a rich lymphocytic infiltrate diffuse throughout the thyroid gland, commonly organized in follicles with a germinal center. | 75 | 68/7 | 45.7±14.5 | 

Qa 2016 China retrospective cohort | PTC + HT | any one of the following criteria: (1) positive for anti-thyroid peroxidase (TPO) antibody, (2) positive for antithyroglobulin antibody, (3) pathologic confirmation of HT | 300 | 209/91 | 45.1±18.9 | - | - | TT 375 | - | 75.36 ±50.32 | 7 | 

Ryu 2020 Korea retrospective cohort | PTC + HT | diffuse lymphocytic infiltration in the area of the normal thyroid tissue irrespective of the presence of anti-thyroid antibodies | 364 | 320/44 | 44.3±10.5 | - | - | TT 54, non-TT 802 | TI 782, T3 83, T4 21 | 85.7±18.6 | 8 | 

Singh 1999 USA retrospective cohort | PTC only | diffuse lymphocytic and plasma cell infiltrate, epithelial cells, and the formation of lymphoid follicles and reactive germinal centers | 331 | 222/109 | median 43 | - | median 2 | total 158, 26±31 | median 3 | 43.6 | 8 | 

Song 2018 Korea retrospective cohort | PTC only | bilaterally diffuse lymphocytic infiltrates and lymphoid follicles with germinal centers in the area of normal thyroid tissue | 1064 | 854/210 | median 49.0 | - | median 1.2 | TT + CLND 1389 | - | 98 | 8 | 

Wang 2018 China retrospective case-control | PTC only | diffuse lymphocytic infiltration in the thyroid parenchyma and stroma, with formation of reactive germinal centers and lymphoid nodules and presence of oxyphilic cells | 119 | 91/28 | <45 70, ≥45 60 | - | 1.924 ±0.93 | bilateral thyroidectomies 206 | I/II 86, III/IV 14, IV 6 | 4 | 

Yang 2016 China case-control | PTC only | diffuse lymphocytic and plasma cell infiltration, epithelial cells, and lymphoid follicles with reactive germinal centers | 87 | 81/6 | <45 70, ≥45 51 | 1.518 ±1.01 | I/II 11, III/IV 16 | - | 6 | 

Ye 2013 China retrospective case-control | PTC only | diffuse lymphocytic infiltrate and lymphoid follicles with germinal centers | 817 | 648/171 | <30 65, 30–44 362, 45–59 291, ≥60 69 | - | 1.498, 1–4 50, 5–9 17 | I/II 66, III/IV 35 | - | 6 | 

Yoon 2012 Korea case-control | PTC only | lymphoid follicles with germinal centers and atrophic changes in the area of normal thyroid parenchyma | 139 | 112/27 | 40.6±11.3 | - | 0.951±0.60 | TT + bilateral CLND 195 | - | - | 4 | 

Zong 2016 China retrospective case-control | PTC only | diffuse lymphocytomarcous infiltrate with germinal centers, parenchymatous atrophy with oncocytic changes, and variable amounts of stromal fibrosis throughout the thyroid gland | 222 | 195/27 | 45.9±12.1 | 1.431±0.86 | I/II 140, III/IV 81 | - | 14 | 

(Continued)
Table 1. (Continued)

| Author      | Year | Country   | Study design | Group | Diagnosis of HT | No  | Sex (female/ male) | Age | Subtype of PTC | Tumor size (cm) | Extent of surgery | TNM stage | Follow up (months) | QA | Outcomes |
|-------------|------|-----------|--------------|-------|-----------------|-----|--------------------|-----|----------------|----------------|-------------------|-----------|-------------------|----|----------|
| Zeng        | 2018 | China     | cross- sectional | PTC only | pathological diagnosis | 46  | 30/10             | < 45 25, ≥ 45 21 | -               | -                 | thyroidectomy 129 | I 190, II 8 | -                  | 10 | ☐☐☐☐☐ |
| Zhu         | 2016 | China     | retrospective cohort | PTC only | - | 180 85/23     | < 15 16, 15–20 52 | - | < 2 25, ≥ 2 80 | thyroidectomy 129 | I 190, II 8 | -                  | 10 | ☐☐☐☐☐ |

Notes: QA, Quality assessment; HT, Hashimoto thyroiditis; CLT, chronic lymphocytic thyroiditis; PTC, papillary thyroid cancer; PTMC, papillary thyroid microcarcinoma; FVPC, follicular variant of papillary cancer; ETE, extrathyroidal extension; TT, total thyroidectomy; LND, lymph node dissection; CLND, central-compartment lymph node dissection; MRND, modified radical neck dissection; TgAb, antithyroglobulin antibodies; MACIS, multifocality; Bilaterality; Invasion; Deaths; AMES stage.

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**Extrathyroidal extension.** Totally 41 studies covering 13940 patients identified the association between HT and clinical outcome of PTC. The heterogeneity test results were statistically significant ($I^2 = 74.1\%$), so the random-effect model was utilized. The result revealed that the risk of extrathyroidal extension in the HT group was lower than that in the non-HT group (OR: 0.718, 95%CI: 0.572–0.901, $P<0.001$) (Table 2, Fig 4).

**Recurrent.** Sixteen studies containing 577 patients have assessed the recurrence. The result of fixed-effects model demonstrated that HT could decrease the risk of recurrence in PCT (OR: 0.627, 95%CI: 0.483–0.813, $P<0.001$) (Table 2, Fig 5).

**Multifocality.** Multifocality referred to two or more foci found in the same lobe of the gland. A total of 44 studies embracing 10320 were included to evaluate multifocality. The heterogeneity test results were statistically significant ($I^2 = 61.3\%$), so the random-effects model was used. The result illustrated that the HT group had a higher risk of multifocality than the non-HT group (OR: 1.245, 95%CI: 1.132–1.368, $P<0.001$) (Table 2).

**Invasion.**

**Vascular invasion.** Totally 17 studies embodying 1837 patients probed into the vascular invasion. The result demonstrated that PTC patients with HT had a lower risk of vascular invasion than those without (OR: 0.718, 95%CI: 0.572–0.901, $P = 0.004$) (Table 2, Fig 6).

**Capsular invasion.** Nine studies including 2273 patients assessed the capsular invasion. No difference was found between the HT and non-HT groups in capsular invasion (OR: 1.234, 95%CI: 0.829–1.835, $P = 0.300$).

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**PLOS ONE**

Association between Hashimoto thyroiditis and clinical outcomes of papillary thyroid carcinoma

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| Variables | OR/WMD (95%CI) | P   | I² |
|-----------|----------------|-----|----|
| **Lymph node metastasis** | | | |
| Overall | 0.787(0.686,0.903) | 0.001 | 75.9 |
| Sensitivity analysis | 0.787(0.686,0.903) | | |
| Publication bias | Z = 0.86 | 0.39 | |
| **Central lymph node metastasis** | | | |
| Overall | 0.796(0.636,0.995) | 0.045 | 86.4 |
| Sensitivity analysis | 0.796(0.636,0.995) | | |
| Publication bias | Z = 1.52 | 0.127 | |
| **Lateral lymph node metastasis** | | | |
| Overall | 0.845(0.733,0.973) | 0.02 | 43.3 |
| Sensitivity analysis | 0.845(0.733,0.973) | | |
| Publication bias | Z = 0.78 | 0.436 | |
| **Distant metastasis** | | | |
| overall | 0.435(0.279,0.676) | <0.001 | 0 |
| Sensitivity analysis | 0.435(0.279,0.676) | | |
| Publication bias | Z = 0.08 | 0.938 | |
| **Extrathyroidal extension** | | | |
| Overall | 0.745(0.657,0.845) | <0.001 | 74.1 |
| Sensitivity analysis | 0.745(0.657,0.845) | | |
| Publication bias | Z = 0.82 | 0.412 | |
| **Recurrence** | | | |
| Overall | 0.627(0.483,0.813) | <0.001 | 16.4 |
| Sensitivity analysis | 0.627(0.483,0.813) | | |
| Publication bias | Z = 0.32 | 0.753 | |
| **Multifocality** | | | |
| Overall | 1.245(1.132,1.368) | <0.001 | 61.3 |
| Sensitivity analysis | 1.245(1.132,1.368) | | |
| Publication bias | Z = 1.16 | 0.245 | |
| **Invasion** | | | |
| vascular invasion | | | |
| Overall | 0.718(0.572,0.901) | 0.004 | 62 |
| Sensitivity analysis | 0.718(0.572,0.901) | | |
| Publication bias | Z = 0.29 | 0.773 | |
| Capsular invasion | | | |
| Overall | 1.234(0.829,1.835) | 0.3 | 88.5 |
| Sensitivity analysis | 1.234(0.829,1.835) | | |
| Publication bias | Z = 0.73 | 0.466 | |
| **Perineural infiltration** | | | |
| Overall | 1.922(1.195,3.093) | 0.007 | 0 |
| Sensitivity analysis | 1.922(1.195,3.093) | | |
| **Bilaterality** | | | |
| Overall | 1.394(1.118,1.739) | 0.003 | 78.9 |
| Sensitivity analysis | 1.394(1.118,1.739) | | |
| Publication bias | Z = 2.20 | 0.028 | |
| **Deaths** | | | |
| Overall | 0.827(0.386,1.773) | 0.626 | 16.8 |
| Sensitivity analysis | 0.827(0.386,1.773) | | |

(Continued)
Perineural infiltration. Two studies comprising 132 patients assessed the perineural infiltration. The perineural infiltration risk of the HT group was higher than that of the non-HT group (OR: 1.922, 95%CI: 1.195–3.093, \( P = 0.007 \)) (Table 2).

Bilaterality

Bilaterality referred to the presence of PTC in both thyroid lobes. Totally 18 studies involving 3421 were enrolled to assess bilaterality. Because the heterogeneity test results were statistically significant (\( I^2 = 78.9\% \)), the random-effects model was adopted. The result showed that HT increased the risk of bilaterality in PTC patients (OR: 1.394, 95%CI: 1.118–1.739, \( P = 0.003 \)) (Table 2).

Deaths

Deaths. Death was identified in 6 studies containing 42 patients. There was no statistically significant in death between HT and non-HT groups (OR: 0.827, 95%CI: 0.386–1.773, \( P = 0.626 \)).

Disease-specific death. Two studies including 82 patients were included to assess disease-specific death. The result of fixed-effects model demonstrated that HT was not associated with disease-specific death in PTC (OR: 0.305, 95%CI: 0.059–1.585, \( P = 0.158 \)).

Table 2. (Continued)

| Variables                  | OR/WMD (95%CI)         | \( P \)  | \( I^2 \) |
|----------------------------|------------------------|--------|--------|
| Disease-specific death     |                        |        |        |
| Overall                    | 0.305 (0.059, 1.585)   | 0.158  | 0      |
| Sensitivity analysis       | 0.305 (0.059, 1.585)   |        |        |
| AMES stage                 |                        |        |        |
| Low risk                   |                        |        |        |
| Overall                    | 1.396 (1.109, 1.758)   | 0.005  | 0      |
| Sensitivity analysis       | 1.396 (1.109, 1.758)   |        |        |
| MACIS score                |                        |        |        |
| overall                    | -0.221 (-0.306, -0.137)| <0.001 | 37.8   |
| Sensitivity analysis       | -0.221 (-0.306, -0.137)|        |        |
| <6                         |                        |        |        |
| Overall                    | 1.568 (0.930, 2.645)   | 0.092  | 56.7   |
| Sensitivity analysis       | 1.568 (0.930, 2.645)   |        |        |

Notes: OR: odds ratio; WMD: weighed mean difference.

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**Perineural infiltration.** Two studies comprising 132 patients assessed the perineural infiltration. The perineural infiltration risk of the HT group was higher than that of the non-HT group (OR: 1.922, 95%CI: 1.195–3.093, \( P = 0.007 \)) (Table 2).

**Bilaterality**

Bilaterality referred to the presence of PTC in both thyroid lobes. Totally 18 studies involving 3421 were enrolled to assess bilaterality. Because the heterogeneity test results were statistically significant (\( I^2 = 78.9\% \)), the random-effects model was adopted. The result showed that HT increased the risk of bilaterality in PTC patients (OR: 1.394, 95%CI: 1.118–1.739, \( P = 0.003 \)) (Table 2).

**Deaths**

**Deaths.** Death was identified in 6 studies containing 42 patients. There was no statistically significant in death between HT and non-HT groups (OR: 0.827, 95%CI: 0.386–1.773, \( P = 0.626 \)).

**Disease-specific death.** Two studies including 82 patients were included to assess disease-specific death. The result of fixed-effects model demonstrated that HT was not associated with disease-specific death in PTC (OR: 0.305, 95%CI: 0.059–1.585, \( P = 0.158 \)).
AMES stage-low risk

A total of 4 studies embracing 1874 patients were enrolled to assess AMES stage-low risk. The heterogeneity test results showed that the differences were not statistically significant ($I^2 = 0.0\%$), so the fixed-effects model was used for analysis. The low risk in the AMES stage represents a 20-year survival rate of 99%. The HT group had an advantage over the non-HT group in improving 20-year survival (OR: 1.396, 95%CI: 1.109–1.758, $P = 0.005$) (Table 2, Fig 7).

MACIS score

MACIS score. The higher the MACIS score, the worse the survival. Four studies involving 2733 patients were included to assess the MACIS score. The result uncovered that the the HT group had an advantage over the non-HT group in improving 20-year survival (WMD: -0.221, 95%CI: -0.306–-0.137, $P<0.001$) (Table 2, Fig 8).

MACIS score <6. MACIS score <6 was assessed in 3 studies including 2321 patients. When MACIS score was <6, there was no difference in 20-year survival between HT and non-HT groups (OR: 1.568, 95%CI: 0.930–2.645, $P = 0.092$).

Publication bias

Begg’s test was used for the assessment of publication bias. The result showed that there was no publication bias for lymph node metastasis ($Z = 0.86, P = 0.39$), central lymph node metastasis ($Z = 1.52, P = 0.127$), lateral lymph node metastasis ($Z = 0.78, P = 0.436$), distant metastasis ($Z = 0.08, P = 0.938$), extrathyroidal extension ($Z = 0.82, P = 0.412$), recurrence ($Z = 0.32, P = 0.753$), multifocality ($Z = 1.16, P = 0.245$), vascular invasion ($Z = 0.29, P = 0.773$), capsular invasion ($Z = 0.73, P = 0.466$) (Table 2). However, there was a publication bias for bilaterality ($Z = 2.20, P = 0.028$) (Table 2). The trim and fill method was applied to adjust data for
Fig 4. The forest plot of extrathyroidal extension between HT group and non-HT group.

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Fig 5. The forest plot of recurrence between HT group and non-HT group.

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publication bias. The OR value of the random effects model before the trim and fill method was 1.394 (95% CI: 1.118–1.739). The random effects model was used to estimate the number of missing studies after 7 iterations, and the meta-analysis of all studies was conducted again. The OR value of the random-effects model after the trim and fill method was 2.858 (95% CI: 1.999–3.718), there was no significant change before and after the results, indicating that publication bias had little influence and the conclusions in the literature were relatively robust.

**TSA**

Lymph node metastasis. A total of 44 articles were included, with a total sample size of 28,813 cases. The required information size (RIS) was 34,021. The estimation of RIS was based
on the following variables: Type I error of 0.05, Type II error of 0.2, Power of 80%, Relative Risk Reduction of 20%, and Incidence in Control arm of 10%. The TSA results showed that the cumulative Z curve crossed the traditional boundary line and intersected the TSA boundary line, but did not reach the RIS line, indicating that although the expected sample size was not reached, the positive results were obtained in advance, which further verified that the HT group was better in the low risk of lymph node metastasis than the HT group.

Central lymph node metastasis. Seventeen articles with a total sample size of 15947 cases were included, the RIS was 61030 cases, and the RIS was estimated based on the following variables: Type I error of 0.05, Type II error of 0.2, Power of 80%, Relative Risk Reduction of 20%, Incidence in Control arm of 10%. The TSA results showed that the cumulative Z curve crossed the traditional boundary line, but did not reach the TSA boundary line and the RIS line, revealing that the expected sample size was not reached. In the future, more experiments are needed to verify the risk of central lymph node metastasis in the HT group versus the non-HT group.

Extrathyroidal extension
Forty-one articles were included, with a total sample size of 35,547 cases, and the RIS was 34,408 cases. It was shown that the cumulative Z curve crossed the traditional boundary line, but did not reach the TSA boundary line and the RIS line, indicating that the expected sample size was not reached. More trials are needed in the future to verify the reliability of the conclusion that the HT group has a lower risk of central lymph node metastasis than the non-HT group.

Recurrence
Sixteen studies were included, with a total sample size of 15,856 cases, and the RIS was 8,342 cases. TSA results demonstrated that the cumulative Z curve crossed the traditional boundary line, intersected the TSA boundary line, and reached the RIS line, indicating that the expected sample size had been reached, and the result was true positive, further verifying that the HT group had a lower risk of recurrence than the non-HT group.
Multifocality
Concerning multifocality, 44 articles with 34,235 cases were included. The RIS was 20,849 cases. The TSA results illustrated that the cumulative Z-curve crossed the traditional threshold line, intersected with the TSA threshold line, and reached the RIS line, indicating that the expected sample size had been reached. The result was positive, further verifying that the HT group had a higher multifocality risk than the non-HT group.

Vascular invasion
Seventeen studies were included for vascular invasion, with 14,105 cases sample size, and the RIS was 24,373 cases. The TSA results showed that the cumulative Z-curve crossed the traditional threshold line and intersected with the TSA threshold line, but did not reach the RIS line, indicating that although the expected sample size was not reached, positive results were obtained in advance, further verifying that the risk of vascular invasion in the HT group was lower than that in the non-HT group.

Bilaterality
Eighteen studies were included to evaluate bilaterality, with a total sample size of 12783 cases, and the RIS was 42465 cases. The TSA results showed that the cumulative Z-curve did not reach the TSA threshold line and RIS line, indicating that the expected sample size was not reached. In the future, required to validate the reliability of the conclusion that the risk of bilaterality is higher in the HT group than that in the non-HT group.

Discussion
No consensus exists on the association between PTC and HT. To resolve this controversy, this study was performed to evaluate the relationship between the two conditions using a meta-analysis. Our analysis revealed that HT was associated with improvements in the clinicopathological characteristics and better prognosis of patients with PTC with lower risk of extrathyroidal extension, lower risk of distant metastasis, lower risk of lymph node metastasis, lower risk of vascular invasion, lower risk of recurrence rate, and a higher 20-year survival rate. Multifocal and bilaterality were positively correlated with HT. Since multifocal and bilaterality are thought to be features associated with PTC development, rather than with its deterioration, these findings are consistent with previous reports of a positive association between HT and PTC development and a protective effect of HT on PTC development [48]. Besides, PTC with HT had a risk of perineural infiltration.

There have been a number of proposed hypotheses to explain the linkage between HT and PTC. From a histological perspective, Tamimi et al. [77] assessed the prevalence and severity of thyroiditis among three types of surgically resected thyroid tumors and found a significantly higher rate of lymphocytic infiltration in patients with PTC. Nevertheless, PTC with concurrent HT is associated with less aggressive disease, less frequent capsular invasion, and less nodal metastasis [22]. Our result supported the result that HT may decrease the risk of lymph node metastasis and vascular invasion in patients with PTC. Similarly, Yoon et al. [70] and Donangelo et al. [78] reported that PTC with HT was significantly associated with a lower incidence of lymph node metastasis.

Furthermore, our findings showed that PTC patients with HT were also less likely to develop recurrence and have a higher 20-year survival rate, which were in agreement with prior studies [41, 66]. Although we did not find the presence of HT indicates lower disease-specific deaths, a recent study by Hu et al. reported that patients with HT had lower rates of...
tumor recurrence, and lower disease-related mortality compared with patients without HT [79]. Kashima et al. [13] reported a 0.7% cancer specific mortality and a 95% relapse-free 10-year survival rate in patients with HT compared to a 5% mortality and 85% relapse-free 10-year survival rate without chronic thyroiditis. The lymphocytic infiltration of HT may be an immunological response with a cancer-retarding effect, contributing to a favorable outcome of PTC versus other thyroid cancers [80].

Hypotheses about the mechanism of a better prognosis in PTC patients with HT have been evaluated in different ways [17]. HT is a kind of autoimmune disease that leads to the destruction of thyroid follicles through an immune response to a thyroid specific antigen. As PTC cells originating from the follicular cells would express the thyroid specific antigen, auto-antibodies from coexisting HT might destroy the tumor cells in much the same way as in HT alone [81]. Additionally, the infiltrated lymphocytes in patients with PTC are likely to be cytotoxic T cells acting as carcinoma cell killers, secreting interleukin-1 that inhibits thyroid cancer cell growth [82]. In a study on BRAF$^{V600E}$, Xing et al. reported a significantly lower prevalence of BRAF$^{V600E}$ mutation in patients with PTC and HT, suggesting that HT is less likely to be associated with poor prognostic outcomes [83].

Interestingly, we observed that PTC patients with HT were younger than PTC patients without HT. We found that the results among age-balanced were similar to our original outcomes. Nevertheless, in the age-imbalanced groups, there were no differences in lateral lymph node metastasis, extrathyroidal extension, extrathyroidal extension, recurrence, multifocality, and bilaterality between PTC patients with HT and PTC alone. A study by Lun et al. also demonstrated that patients with PTC and HT were younger [56]. Zhang et al. reported older age is a risk factors for BRAF mutation in PTC patients, especially in those without HT [84]. This result suggests that age may be one of the potential sources of bias. More studies are needed in the future with a larger sample size and rigorous design to confirm our findings.

The strengths of the current study need to be mentioned. This was an updated meta-analysis including more studies and more outcomes. There was no apparent publication bias, leading to the research results being more reliable and convincing. Besides, we used TSA to further validate our findings. However, residual confounding variables were a problem. Uncontrolled or unmeasured confounding factors have the potential for bias, and the possibility that residual confounders influenced the results cannot be ruled out. Our analysis was largely limited by the retrospective nature of most of the included studies where clinical details were usually not available. More prospective studies with longer follow-ups are needed to further elucidate this relationship.

Conclusions
This meta-analysis shows a clinical relationship between two disease entities. PTC patients with HT may have lower incidence of extrathyroidal extension, distant metastasis, lymph node metastasis, vascular invasion, and better prognosis than patients with PTC alone.

Supporting information
S1 Checklist.
(DOCX)

S1 File.
(DOCX)

S2 File.
(DOCX)
Author Contributions
Conceptualization: Qizhi Tang.
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Methodology: Qizhi Tang, Weiyu Pan, Liangyue Peng.
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Writing – review & editing: Qizhi Tang.

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