Is Hashimoto thyroiditis associated with increasing risk of thyroid malignancies? A systematic review and meta-analysis

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Abstract
Background and purpose: Hashimoto thyroiditis (HT) is the most common inflammatory autoimmune thyroid disease and also the most common cause of hypothyroidism in developed countries. There is evidence of the role of HT in developing thyroid cancers (TCs). This study investigated the association between HT and different types of TCs.

Methods: Results of a comprehensive search in three major databases, as well as hand searching, were screened in title/abstract and full-text stages and the relevant data were extracted from the studies that met the inclusion criteria. Risk of bias (RoB) was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools and the meta-analysis was conducted with Comprehensive Meta-Analysis software.

Results: Out of 4785 records, 50 studies were included in the systematic review, and 27 of them met the criteria for quantitative synthesis. The results indicated a significant role for HT in developing papillary TC (OR: 1.65; 95% CI: 1.04 to 2.61), medullary TC (OR: 2.70; 95% CI: 1.20 to 6.07) and lymphoma (OR: 12.92; 95% CI: 2.15 to 77.63); but not anaplastic TC (OR: 1.92; 95% CI: 0.29 to 1.90) and follicular TC (OR: 0.73; 95% CI: 0.41 to 1.27). Also, this study found a significant association between HT and thyroid malignancies (OR: 1.36; 95% CI: 1.05 to 1.77).

Conclusion: Although we found a significant association between HT and some types of TCs, High RoB studies, high level of heterogeneity, and the limited number of well-designed prospective studies, suggested the need for more studies to reach more reliable evidence.

Keywords: Hashimoto Thyroiditis, Chronic autoimmune thyroiditis, Thyroid neoplasms, Systematic review, Meta-analysis

Introduction
Chronic lymphocytic thyroiditis also called “Hashimoto thyroiditis” (HT) is the most common inflammatory autoimmune thyroid disease and the most common cause of hypothyroidism in regions with adequate amounts of iodine [1]. HT was first delineated by Japanese surgeon Hakaru Hashimoto as an autoimmune disease [2]. HT is characterized by immune cells infiltration of the thyroid gland as a result of failure in immune tolerance. This condition frequently affects females (more than 10:1 ratio of females to males) [3]. The occurrence of HT has increased during the last decades. Thyroid cancer (TC) is the most common endocrine tumor and the occurrence of TC has increased rapidly worldwide. Papillary thyroid carcinoma (PTC) is the most common type of thyroid neoplasms and accounts for 80-90% of all thyroid cancers. It occurs more frequently in females.

Rudolf Virchow first described the link between chronic inflammation and cancer in 1893, which is now well determined [4]. The association between HT and PTC was first described by Dailey et al. in 1955 [5].

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Despite several retrospective and prospective studies performed, the relationship between them remains controversial. A recent meta-analysis of 64,628 patients in 36 studies reported a relation between HT and PTC and an association between HT and thyroid lymphoma [6]. Consistently with this finding, several studies have been performed and they reported that HT is associated with a greater probability of developing PTC [7]. Another meta-analysis revealed the correlation between HT and PTC and this systematic review only investigated the incidence of HT in TC patients and not the incidence of TC in HT patients [8]. In contrast with this finding, Jankovic et al. reported no significant association between HT and TC based on 8 fine-needle aspiration studies [9].

Given the selection bias and limitations of previous studies as well as new publications in this area, an updated systematic review is needed to better clarify the association between HT and TC. Therefore, we elaborated a new meta-analysis via a complete investigation of the literature aiming to evaluate the association between HT and TCs, and also the investigation of the role of HT in different subgroups of TC, based on current knowledge.

**Methods**

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

**Search**

After getting the approval of the study protocol, an electronic search was conducted in 3 major databases including Medline via PubMed, EMBASE, and Scopus, with ((Chronic autoimmune thyroiditis) OR Hashimoto) AND (thyroid neoplasm* OR thyroid carcinoma* OR thyroid cancer* OR thyroid adenoma* OR thyroid malignanc*) and related MeSH keywords on 23 February 2021.

**Study selection**

Results of the electronic search were imported into EndNote 20 and after removing the duplicated studies, the remaining records were screened in two title/abstract and full-text stages. Two independent authors screened the studies and in case of any disagreements, a third author deemed the issue. For full coverage of any published studies, after selecting the final articles to be included in this systematic review, the reference lists of these articles and recently published reviews have been checked for possible inclusion in our study.

**Eligibility criteria**

We included the journal articles which assess the possible relation between HT and TC with both retrospective and prospective study designs. In case of lack of a control group, the study was included in our systematic review but excluded from the meta-analysis. We only selected the articles which have been written in English and animal studies, case reports, review articles, editorials, letters, conference abstracts, and withdrawn articles were excluded from our study.

**Data extraction**

Data extraction was conducted by two authors with an electronic table in Microsoft Word. The following data were extracted from each study: the name of the first author of the study, the year of study publication, the study design which could be retrospective or prospective, the setting of the study, the method for diagnosis of thyroid cancer, the sample size, the mean and standard deviation of ages, the number of female and male cases, the type of thyroid cancer and finally the rate of TC between HT cases and control group, or rate of HT between TC and control group.

**Risk of Bias assessment**

The risk of bias (RoB) in included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools for cohort or case-control studies based on the study design [11]. The checklist for case-control studies includes 10 questions and the cohort studies’ checklist includes 11 questions. These tools assess the similarity of case and control groups, using a standard and similar method for assessing the condition, appropriate dealing with cofounding factors, enough period of interest, and appropriate statistical analysis.

**Statistics**

All the statistical analyses were conducted using the second version of Comprehensive Meta-Analysis (CMA.2) software with 95% confidence intervals and a 0.05 level of significance. I² model was used for assessing the heterogeneity between the studies, and for outcomes with more than 50% level of heterogeneity, a random effect model was used. The number of events in case and control groups in both study designs and also the size of the group was imported into the CMA and the odds ratio (OR) was collected for each study. Then the results were then combined in both random and fixed effect models and the ORs for each subgroup (based on the type of thyroid cancer) as well as the overall result were calculated and presented by forest plot.

**Results**

Globally, 7141 records were identified through database searching, and after removing the duplicated studies, 4785 studies were screened. Finally, 50 studies were
selected for qualitative synthesis and 27 of them were included in the quantitative synthesis (Fig. 1). Among them, 23 studies found the rate of HT in TC cases; on the other hand, 29 of them assessed the rate of TC in HT cases, whereas 3 of them reported both of these findings. The characteristics of the included studies are summarized in Table 1. Figure 2 summarized the results of the meta-analysis.

Papillary thyroid cancer
45 of the included studies investigated the possible relation between HT and PTC. In these studies, the rate of HT in PTC cases was ranged between 4.75 to 38.4%, whereas the rate of PTC in HT ranged between 0.12 to 64.3%. The meta-analysis of 23 studies with an appropriate control group, found 1.65 OR (95% CI: 1.04 to 2.61; I² test for heterogeneity: 96.48%) and the difference between the groups was significant (p = 0.03).

Follicular thyroid cancer
13 studies assessed the possible association between HT and follicular thyroid cancer (FTC). In these studies, the rate of HT in the FTC group ranged between 2.08 to 9.62% and the rate of FTC in HT ranged between 0 to 9.2%. The meta-analysis of the 7 studies that met the proper inclusion criteria, reached 0.73 OR (95% CI: 0.41 to 1.27; I² test for heterogeneity: 0%) and the difference between the groups was not statistically significant (p = 0.26).

Medullary thyroid cancer
The possible role of HT in developing medullary thyroid cancer (MTC) was investigated in 6 studies. All of these studies assessed the rate of MTC in the HT group and it
| Study            | Study design | Setting  | Study method | Sample size | Mean age ± SD | Female: Male | Thyroid cancer type | Rate of Hashimoto's thyroiditis (in percent) |
|------------------|--------------|----------|--------------|-------------|---------------|--------------|-------------------|-----------------------------------------------|
| Alcântara-Jones 2015 [12] | Retrospective | Brazil | Thyroidectomy | 49          | 48.5 ± 30.3 | 30.3         | Papillary         | 27.27 (9/33) |
| Zeng 2016 [13] | Retrospective | China | Thyroidectomy | 619         | 45.9 ± 484.135 | 34.7         | Papillary         | 35.86 (222/619) |
| Campos 2012 [1] | Retrospective | Brazil | Thyroidectomy | 315         | 44.9 ± 34.7 | 34.7         | Papillary         | 26.83 (11/41) |
| Ye 2013 [14]   | Retrospective | China | Thyroidectomy | 2052        | – ± 828.176 | 34.7         | Papillary         | 18.63 (187/1004) |
| Cipolla 2005 [15] | Retrospective | Italy | Thyroidectomy | 178         | – ± 68.21 | 34.7         | Papillary         | 26.76 (19/71) |
| Kim 2011 [16]  | Retrospective | Korea | Thyroidectomy | 1329        | 47.5 ± 821.207 | 34.7 | Papillary         | 29.86 (307/1028) |
| Ahn 2011 [17]  | Retrospective | Korea | Thyroidectomy | 303         | 42.8 ± 225.44 | 34.7 | Papillary         | 21.56 (58/269) |
| Huang 2011 [18] | Retrospective | China | Thyroidectomy | 1997        | 39.9 ± 1450.338 | 34.7 | Papillary         | 4.75 (85/1788) |
| Lun 2013 [19]  | Retrospective | China | Thyroidectomy | 2478        | 41.3 ± 538.138 | 34.7 | Papillary         | 18.79 (127/676) |
| Moshynska 2008 [20] | Retrospective | Canada | Thyroidectomy | 20          | – ± – | 34.7 | Lymphoma         | 60 (12/20) |
| Singh 1999 [21] | Retrospective | United States | Thyroidectomy | 453         | 41 ± 267.121 | 34.7 | Papillary         | 14.69 (57/388) |
| Zhang 2014 [22] | Retrospective | China | Thyroidectomy | 8524        | 43.1 ± – | 34.7 | Papillary         | 28.46 (592/2080) |
| Nemetz 2011 [23] | Retrospective | Brazil | Thyroidectomy | 52          | 51.3 ± 48.4 | 34.7 | Papillary         | 32.69 (17/52) |
| Jeong 2012 [24] | Retrospective | Korea | Thyroidectomy | 1357        | 44.5 ± 1176.181 | 34.7 | Papillary         | 26.46 (359/1357) |
| Kashima 1998 [25] | Retrospective | Japan | Thyroidectomy | 1533        | 42.6 ± 1402.131 | 34.7 | Papillary         | 18.33 (281/1533) |
| Kebebew 2001 [26] | Retrospective | United States | Thyroidectomy | 136         | 45.5 ± 95.41 | 34.7 | Papillary         | 30.15 (41/136) |
| Yoon 2012 [27]  | Retrospective | Korea | Thyroidectomy | 195         | 45.9 ± 166.29 | 34.7 | Papillary         | 28.72 (56/195) |
| Graceffa 2019 [28] | Retrospective | Italy | Thyroidectomy | 305         | 50.6 ± 258.47 | 34.7 | Papillary         | 28.6 (36/126) |
| Selek 2016 [29] | Retrospective | Turkey | Thyroidectomy | 870         | 47 ± 47.12 | 34.7 | Papillary         | 30 (172/577) |
| Topaloglu 2016 [30] | Retrospective | Turkey | Thyroidectomy | 427         | 47.78 ± 34.186 | 34.7 | Papillary         | 38.4 (73/190) |
| Zeng 2018 [31]  | Retrospective | China | Thyroidectomy | 258         | 17.3 ± 212.46 | 34.7 | Papillary         | 17.8 (23/129) |
| Study                          | Study design | Setting          | Study method | Sample size | Mean age ± SD | Female: Male | Thyroid cancer type | Rate of Hashimoto's thyroiditis (in percent) |
|-------------------------------|--------------|------------------|--------------|-------------|---------------|--------------|---------------------|--------------------------------------------|
| Osorio 2019 [7]              | Retrospective| Colombia         | Thyroidectomy | 1136        | 47.5 ± 14.3   | 1047: 89     | Papillary           | 24 (44/183) 13.11 (125/953)                  |
| Youssef Mohamed 2020 [32]    | Retrospective| Egypt            | Thyroidectomy | 80          | –             | 22: 58       | Papillary           | 20 (16/80)                                 |
| JNawaratna 2018 [33]         | Retrospective| Sri Lanka        | Thyroidectomy | 684         | 48 ± 12.5     | 611: 73      | Papillary           | OR: 0.867 (0.25-2.99)                      |
| Repplinger 2008 [34]         | Retrospective| United States    | Thyroidectomy | 1198        | 215.77        | Papillary    | 29.03 (63/217) 23.34 (229/981)                  |
| Paparodis 2014 [35]          | Retrospective| United States    | Thyroidectomy | 2718        | Papillary     | 42.68 (242/567) 26.27 (565/2151)                  |
| Anil 2010 [36]               | Prospective  | Turkey           | FNA          | 715          | Papillary     | 1.76 (10/567) 2.14 (46/2151)                     |
| Konturek 2013 [37]           | Retrospective| Poland           | Thyroidectomy | 7545        | 53.5          | Papillary    | 23.45 (106/452) 7.47 (530/7093)                  |
| Mukasa 2011 [38]             | Retrospective| Japan            | FNA          | 2036        | Papillary     | 1.77 (36/2036) Lymphoma 0.10 (2/2036) 2.72 (227/8352) |
| Matesa-Anic 2009 [39]        | Retrospective| Croatia          | FNA          | 10,508      | 50            | Papillary    | 1.95 (42/2156) 2.72 (227/8352)                  |
| Dailey 1955 [5]              | Prospective  | United States    | Thyroidectomy | 2336        | 37.5          | Papillary    | 10.43 (29/278)     |
| Larson 2007 [40]             | Retrospective| United States    | Thyroidectomy | 812         | 41            | Papillary    | 34.7 (34/98) (34/98) 20.4 (145/710) |
| Zayed 2015 [41]              | Retrospective| Jordan           | Thyroidectomy | 180         | 51.3          | Papillary    | 3.85 (3/78) 1.53 (12/785)                      |
| Gul 2010 [42]                | Retrospective| Turkey           | Thyroidectomy | 613         | 43            | Papillary    | 43.48 (40/92) 25.14 (131/521)                  |
| Mazokopakis 2010 [43]        | Retrospective| Greece           | Thyroidectomy | 140         | 49.3          | Papillary    | 10.9 (1/92) 0.96 (5/521)                      |

Rate of thyroid cancer (in percent)

Hashimoto's thyroiditis

Control group
Table 1 (continued)

| Study design | Setting | Study method | Sample size | Mean age ± SD | Female: Male | Thyroid cancer type | Rate of Hashimoto's thyroiditis (in percent) |
|--------------|---------|--------------|-------------|---------------|--------------|---------------------|-------------------------------------------|
| Retrospective United States | Thyroidectomy | 48 | 51.7 | | | Papillary | 12.5 (6/48) |
| Retrospective United States | Thyroidectomy | 757 | | | | Papillary | 2.60 (2/777) |
| Retrospective | China | Thyroidectomy | 647 | 43.3 | | Papillary | 37.96 (41/108) |
| Retrospective United States | Thyroidectomy | 2/108 | | | | Papillary | 37.25 (93/539) |
| Retrospective | China | Thyroidectomy | 108 | 43.3 | | Papillary | (41/108) |
| Retrospective United States | Thyroidectomy | 8263: 1588 | | | | Papillary | 15.4 (1105/7200) |
| Retrospective United States | Thyroidectomy | 15 (8/52) | | | | Papillary | 15 (8/52) |
| Retrospective Turkey | Thyroidectomy | 300 | 12.1 ± 3.1 | 238.62 | | Papillary | 0.66 (2/300) |
| Retrospective China | Thyroidectomy | 927 | 46 ± 0 | 706.221 | | Papillary | 1.1 (10/904) |
| Prospective United States | Thyroidectomy | 9851 | 52.2 ± 15 | 8263: 1588 | | Undefined | 22.8 (606/2651) |
| Prospective United States | Thyroidectomy | 15 (8/52) | | | | Thyroid cancer | 37 (19/52) |
| Retrospective United States | Thyroidectomy | 89 | 11.1 ± 3.7 | 76.13 | | Papillary | 7.9 (7/89) |
| Retrospective Turkey | Thyroidectomy | 645 | | | | Thyroidectomy | 28.9 (44/152) |
| Retrospective Czech republic | Thyroidectomy | 4947 | | | | Thyroidectomy | 29.5 (26/88) |
| Retrospective Turkey | Thyroidectomy | 917 | adult | 743.7/14 | | All Cancer Types | 19.4 (15/77) |
| Retrospective Turkey | Thyroidectomy | 14.2 (85/592) | | | | Papillary | 9.8 (82/840) |

Note: The numbers in parentheses represent the number of cases out of the total sample size.
ranged between 0 to 20%. The meta-analysis of 5 studies with an appropriate control group, reached 2.70 OR for this outcome (95% CI: 1.20 to 6.07; I² test for heterogeneity: 0%) and the difference between the groups was significant (p = 0.01).

Lymphoma
6 studies investigated the relation between HT and lymphoma and the rate of HT in the lymphoma group was 5.88 and 60% in two studies. The range of lymphoma in HT was between 0.1 to 1.09%. The meta-analysis of 3 studies concerning this outcome reached 12.93 OR (95% CI: 2.15 to 77.63; I² test for heterogeneity: 0%) and the difference between these groups was significant (p = 0.01).

Anaplastic thyroid cancer
Only two studies assessed the relation between anaplastic thyroid cancer (ATC) and HT and the rate of TC in the HT group was 0 and 1.02% in these studies. The meta-analysis reached 1.92 OR (95% CI: 1.90 to 0.29; I² test for heterogeneity: 0%) and the difference between groups was not statistically significant (p = 0.05).

All cancer types
Twenty seven studies had an appropriate control group which allowed us to calculate the OR and include them in the meta-analysis. The results showed 1.36 OR (95% CI: 1.05 to 1.77; I² test for heterogeneity: 93.66%) and there was a significant difference between case and control groups in terms of incidence of TCs (p = 0.01).

**Risk of Bias**
The RoB assessment based on the JBI checklist is presented in Fig. 3. Based on our assessment, appropriately dealing with confounding factors was the most prevalent source of bias in included studies. The appropriate and complete follow-up period was the other source of bias in these studies. Generally, there is a concerning risk of bias in these studies which can affect these outcomes. The details of the RoB assessment are presented in Supplementary material 1.

**Discussion**
This study investigated the possible relationship between HT and different types of TCs. The results indicated a significant correlation between HT and thyroid malignancies in particular with PTC, MTC, lymphoma but not with ATC and FTC. Also, this study found a significant association between HT and thyroid malignancies.

As the most common cause of hypothyroidism in developed countries [59], the role of HT in developing thyroid malignancies, should be considered by the clinicians. As fine needle aspiration (FNA) has poor accuracy in the diagnosis of TCs in patients with thyroiditis, diagnosis of TC in the presence of HT is challenging. Previous studies have found a better prognosis for TC in case of coexistence of HT, because of earlier diagnosis based

| Study design | Setting | Study method | Sample size | Mean age ± SD | Female: Male | Thyroid cancer type | Rate of Hashimoto’s thyroiditis (in percent) |
|-------------|---------|--------------|-------------|---------------|--------------|-------------------|---------------------------------------|
| Chen 2013 [57] | prospective | Taiwan | 7605 | adult | 6845:755 | | Follicular | 6.6 (1/15) | Medullary | 20.0 (3/15) | Papillary | 27.6 (13/47) | Papillary | 14.24 (247/839) |
| Cipolla 2005 [15] | Retrospective | Italy | Thyroidectomy | 178 | – | 68.21 | Papillary | 27.6 (13/47) | Papillary | 28.83 (47/163) | Papillary | 14.24 (247/839) |
| Zhang 2014 [22] | Retrospective | China | Thyroidectomy | 8524 | 43.1 | – | Papillary | 14.24 (247/839) | Papillary | 28.83 (47/163) | Papillary | 14.24 (247/839) |
| Uhliarova 2017 [58] | prospective | Slovakia | Thyroidectomy | 2117 | 11.1 ± 3.7 | 1738:379 | All cancer types | 83.64% (266/318) |
on routine medical follow-up [18]. Moreover, a less aggressive form of malignancy in PTC patients in the top of HT has been reported, though but this conclusion was associated with controversies in an endemic area of iodine deficiency goiter [60].

Despite multiple hypotheses in this regard, the underlying mechanism of developing malignancies in HT patients is not fully understood [61, 62]. One of these mechanisms may rely on the inflammatory process in HT. Inflammatory reactions create free radical oxygen, resulting in DNA damage and mutations that finally cause the development of PTC [9]. Another hypothesis states that malignant transformation is caused by increased levels of TSH that stimulate thyroid tissue epithelial proliferation [61]. A recently published study assessed the prognostic value of FOXP3 in PTC and the difference in its expression in concomitant HT. FOXP3 is a PTC-related marker and its expression by HT infiltrating lymphocytes suggested a relationship between HT and PTC [32].

Despite the historical discussion about the possible role of HT in developing TCs, current guidelines didn't accept HT as a risk factor for developing thyroid malignancies [63]. Some experts believe that a good prognosis of TCs and particularly PTC, as the most incident thyroid malignancy, leads to a decrease in allocation of resources toward designing and conducting well-designed studies to identify predictive factors and improving the management of outcomes [64]. The controversial outcomes of the studies highlighted a need for more prospective studies with appropriate control groups and considering
the possible cofounding factors to reach more reliable evidence. Our meta-analysis as the most reliable evidence in this regard found a significant association between HT and MTC based on 5 published studies. This finding is obtained based on a retrospective point of view and only 11 cases of MTC were reported in 526 investigated cases of HT in our included studies. MTC is the third most common TC that originates from the parafollicular cells with an unfavorable prognosis [65, 66]. Previously the reports of this relation were limited to case reports [67–72]. One of the suggested pathophysiological bases for this relation is the occurrence of HT in response to MTC, so future prospective studies can give better insight in this regard. Also, the results of Zayed et al. only found such an association only in female patients [41], which should be more investigated in future studies.

One of the limitations of this study was the high level of heterogeneity between different studies. These differences can arise from multiple sources. Differences in pathological interpretation of HT, genetic factors, diagnostic methods for thyroid malignancies including the FNA and total thyroidectomy can cause variations in the reported rate of coexistence of HT and TC in our included studies. Besides, the variation in OR can arise from differences in defining the control groups.

A comprehensive search in three major databases and the adding of hand searching results was one of the strengths of this study that led to full coverage of published studies that met our inclusion. Besides, carefully selecting and extracting the data, was the other strength of this systematic review. Unlike previous studies, we conducted our meta-analysis based on OR, therefore, the studies without an appropriate control group were excluded from our meta-analysis. This made the findings of our study more practical and obvious.

**Conclusion**

Based on the current knowledge, HT is associated with developing thyroid malignancies, particularly PTC, MTC, lymphoma but not with ATC and FTC. Studies with high RoB, the high level of heterogeneity between different studies, and the limited number of well-designed prospective studies make the available evidence uncertain, so there is a need for more studies to reach more reliable conclusions.

**Abbreviations**

HT: Hashimoto thyroiditis; TC: Thyroid cancer; PTC: Papillary thyroid carcinoma; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RoB: Risk of bias; JBI: Joanna Briggs Institute; CMA: Comprehensive Meta-Analysis; OR: Odds ratio; FTC: Follicular thyroid cancer; MTC: Medullary thyroid cancer; ATC: Anaplastic thyroid cancer.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s13044-021-00117-x.

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**Conflict of interest**

None.
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