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The risk of thyroid cancer and sex differences in Hashimoto's thyroiditis, a meta-analysis

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Abstract

Background and objective The prevalence of thyroid cancer (TC) has exhibited an upward trajectory in recent years. An accelerating amount of evidence shows a significant association between Hashimoto's thyroiditis (HT) and TC. The present study encompasses a meticulously designed systematic review and meta-analysis with the aim of scrutinizing the risk of TC and clarifying sex disparities in HT.

Methods A comprehensive search was conducted across reputable online databases, including PubMed, Cochrane Library, EMBASE, and Web of Science. English-language publications on the correlation between HT and TC were examined without temporal restrictions. Two authors independently screened the articles and extracted pertinent data. The collected data underwent statistical analysis using the STATA software, enabling the calculation of the pooled Odds Ratio (OR) and 95% confidence intervals (CI). Additionally, a supplementary analysis was conducted on studies incorporating sex-specific data to determine the OR (female vs. male) and the sex-based prevalence of TC in HT.

Results A total of 2,845 records were obtained, and 26 retrospective studies were included in this meta-analysis. The results indicated a significant role for HT in TC (OR: 2.22, 95% CI: 1.85–2.67). Supplementary analysis indicated that the prevalence of TC in HT patients was lower in women (0.31, 95% CI: 0.17–0.45) than in men (0.37, 95% CI: 0.21–0.53). However, the result was not statistically significant.

Conclusion This systematic review and meta-analysis provide evidence that HT is associated with increasing odds of TC. Regular review of HT patients holds positive clinical significance.

Keywords Hashimoto's thyroiditis, Thyroid cancer, Meta-analysis

Introduction

Hashimoto's thyroiditis, an autoimmune thyroiditis, is among the most common causes of hypothyroidism in regions abundant in iodine [1]. Evidence suggests that women are at a higher risk of HT compared to men [2, 3]. Activation of T helper cells that target thyroid antigens orchestrates an immune response against the thyroid, resulting in follicular destruction within the gland. Histologically, HT is characterized by diffuse lymphocytic infiltration, eosinophil metaplasia, interlobular fibrosis, and atrophy of the thyroid tissue. Clinically, it can manifest as varying degrees of thyroid dysfunction [4–6].

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Diagnosis of HT primarily relies on elevated levels of thyroid peroxidase antibodies. Thyroglobulin antibodies, as well as ultrasound imaging also have some value in diagnosis of HT [7, 8].

Thyroid cancer (TC) represents the most prevalent malignant neoplasm within the endocrine system, encompassing papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), anaplastic thyroid cancer (ATC), and medullary thyroid cancer (MTC). Among these, the former three arise from thyroid follicular cells, whereas MTC originates from thyroid parafollicular C cells. PTC accounts for approximately 80% of TC cases [9]. In recent years, the incidence rate of TC has increased worldwide. This phenomenon can be attributed to increased surveillance of thyroid diseases and advancements in diagnostic technology [10, 11]. Abundant evidence demonstrates a significantly higher incidence of TC in females compared to males [12, 13]. The 2020 Global Cancer Statistics report revealed a threefold higher TC incidence in women worldwide than in men [14]. Gul et al. [15] found that the prevalence of incidental TC discovered during surgery for benign thyroid conditions is higher in the presence of HT. Graceffa et al. [16] supported the notion that thyroid nodules in the presence of HT substantially increase the risk of TC. Other studies have indicated a higher prevalence of HT in women, with women affected by HT also showing an elevated susceptibility to TC [2, 17]. However, Meinhold et al. [18] reported that while the prevalence of TC is lower in men compared to women, men with benign thyroid disorders have a significantly increased risk of TC.

Does HT increase the odds of TC? Are women with HT more susceptible to developing TC? These questions have sparked debates, and this meta-analysis aims to explore the risk of TC in individuals with HT and assess the sex-specific risk of TC in HT. While HT and chronic lymphocytic thyroiditis (CLT) can be distinguished based on pathological criteria, such as the absence of Askanazy or Hürthle cells in CLT [19], most studies fail to make a strict differentiation between the two conditions. Therefore, this study collectively refers to both conditions as HT.

Materials and methods

Study registration

This systematic review and meta-analysis were conducted following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [20]. The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration ID: CRD42022382557. Ethical approval was not required as this study is a systematic review.

Search strategy

A systematic search was conducted in PubMed, Cochrane Library, EMBASE, and Web of Science databases. Medical subject headings "Thyroid Neoplasms" and "Hashimoto Disease" were used in the search. The search included all English-language publications without temporal restrictions and without restrictions on countries or article types. Additionally, the reference lists of selected articles were independently screened to identify any additional relevant studies that may have been missed in the initial search. The detailed search terms used in PubMed are provided in Supplementary File 1.

Inclusion and exclusion criteria

Study inclusion criteria

The following inclusion criteria were applied: (1) studies investigating the risk of TC associated with HT; (2) the study focused on HT and TC as the subject matter; (3) only English-language articles were considered eligible for inclusion; (4) outcome indicators included the total number of cases, the number of TCs, the number of HTs, the number of TCs coexisting with HT, and corresponding counts for males and females.

The following exclusion criteria were applied: (1) non-research articles; (2) studies not related to TC risk; (3) animal experiments; (4) studies with low quality or insufficient outcome indicators; (5) research on TC related to the atomic bombing of Japan and the Chernobyl nuclear accident.

Quality assessment and data extraction

The Newcastle-Ottawa quality assessment Scale (NOS) was utilized to assess the quality and potential bias of case-control and cohort studies. The Joanna Briggs Institute (JBI) scale was used to evaluate the quality of cross-sectional studies (refer to Supplementary File 2). Two authors independently reviewed the titles and abstracts of the articles based on pre-established inclusion and exclusion criteria to determine eligibility. Subsequently, they individually assessed the full texts to determine the final articles to be included in the study. Any discrepancies were resolved through collaborative consultation between the two authors. The following information was independently extracted by the two authors: author, year of publication, enrollment period, country, study methodology, tumor type, and outcomes.

Statistical analysis

Statistical analysis was performed using "metan"of the STATA software (version 14.0, StataCorp, College Station, TX, USA) to analyze the data and assess heterogeneity. Given the expected heterogeneity among the included studies, a random-effects model (M-H heterogeneity) was employed for the meta-analysis and calculation of

the pooled odds ratio (OR) with 95% confidence intervals (Cl). Heterogeneity was evaluated using Cochran's Q statistic ($p<0.10$ indicating heterogeneity), and the I^2 statistic was used to quantify the degree of heterogeneity. In cases where $I^2>50\%$, subgroup analysis was conducted to explore potential sources of heterogeneity. Funnel plots were employed to detect possible publication bias, and Egger's test was performed to quantitatively assess reporting biases. Sensitivity analysis was conducted to evaluate the influence of each individual study on the overall assessment.

Results

Figure 1 illustrates the identification of 2,845 publications through multiple databases, with 26 studies ultimately included after the screening process [1, 3, 15, 16, 21–42]. Table 1 presents the characteristics of the studies included in the meta-analysis. All of the studies in this meta-study were retrospective in nature. Among them, there were 16 retrospective case-control studies, 6 retrospective cohort studies, and 4 retrospective cross-sectional studies. In 23 of the studies, patients underwent thyroidectomy for either TC or other benign diseases. The remaining 3 studies included selective thyroidectomy, where the procedure was performed if fine needle aspiration biopsy indicated malignancy. Among the 26 studies, 11 focused on the relationship between PTC and HT, 4 on DTC and HT, and 11 on TC and HT. The patients included in the study had various causes of benign thyroid disease, such as hyperthyroidism, goiter, and benign thyroid nodules. The prevalence of TC across the 26 studies ranged from 1 to 67%, while the prevalence of TC in HT patients ranged from 0.7 to 92%.

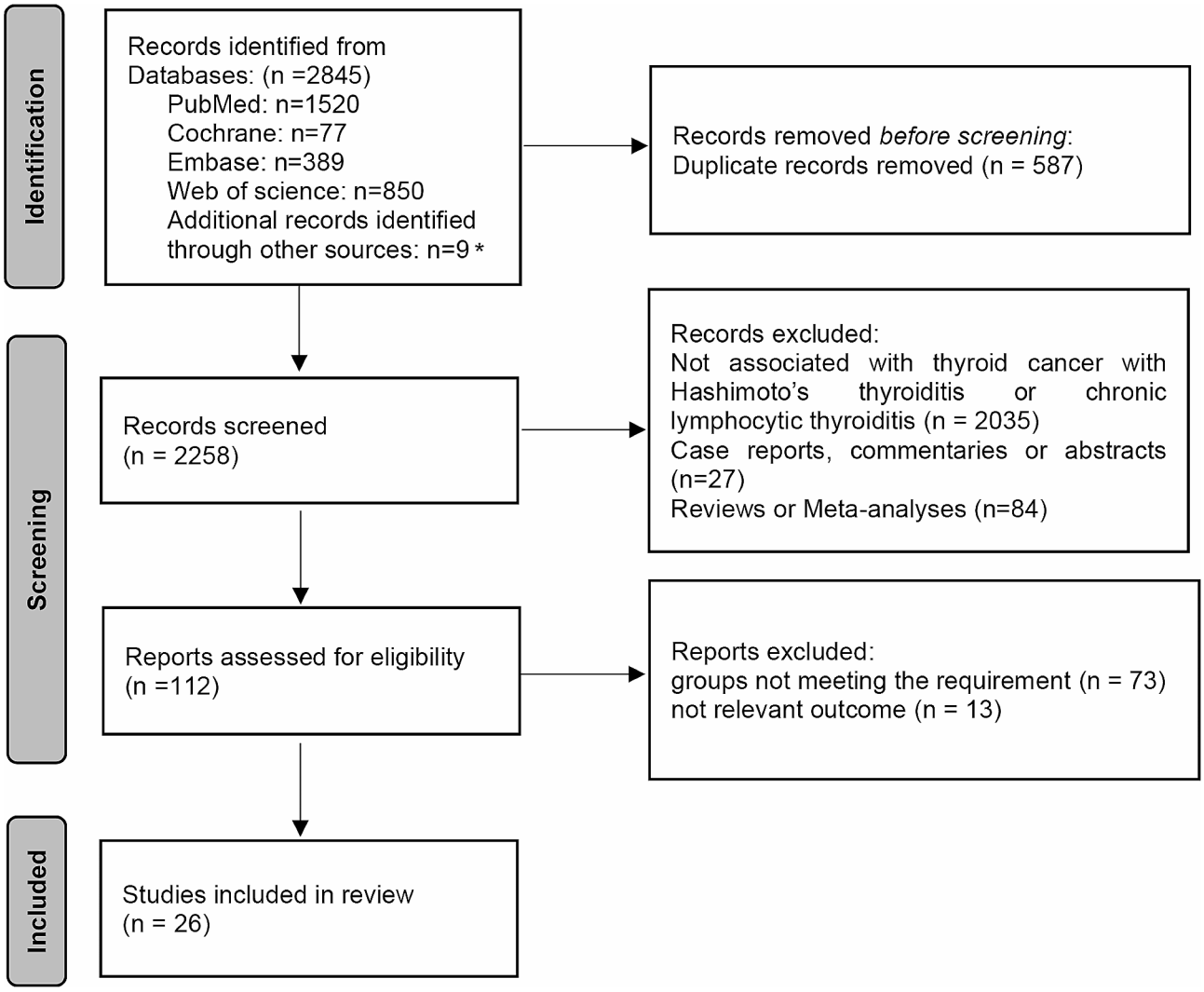

Fig. 1 Flow diagram of study selection process. (* Checking the references of accepted articles.)

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

Study	Year of Publication	Period of enrolment	Country	Study design	Study method	Tumor type	Total cases	F: M
Osorio [3]	2020	2008–2018	Colombia	retrospective cross-section	Thyroidectomy	PTC	1136	1047:89
Cappellacci [1]	2022	2016–2019	Italy	retrospective cohort	Thyroidectomy	DTC	839	610:229
Graceffa [16]	2019	2006–2016	Italy	retrospective case-control	Thyroidectomy	PTC	268	206:62
Gul [15]	2010	2005–2008	Turkey	retrospective case-control	Thyroidectomy	TC	613	496:117
Büyükaşık [21]	2011	1999–2006	Turkey	retrospective case-control	Thyroidectomy	TC	917	743:174
Zhang L [22]	2012	N/A	China	retrospective cross-section	Thyroidectomy	PTC	5115	3821:1294
Mazokopakis [23]	2010	2005–2009	Greece	retrospective case-control	Thyroidectomy	PTC	140	121:19
Liu [24]	2014	2008–2013	China	retrospective cohort	Thyroidectomy	TC	6432	5059:1373
Zhang Y [25]	2014	2004–2011	China	retrospective case-control	Thyroidectomy	TC	647	N/A
Ye [26]	2013	2006–2008	China	retrospective case-control	Thyroidectomy	TC	2052	1645:407
Lun [27]	2013	2004–2012	China	retrospective case-control	Thyroidectomy	PTC	2478	1954:524
Paparodis [28]	2014	1994–2013	US	retrospective case-control	Thyroidectomy	DTC	2718	2122:596
Larson [29]	2007	1987–2002	US	retrospective case-control	Thyroidectomy	TC	812	N/A
Repplinger [30]	2008	1994–2007	US	retrospective case-control	Thyroidectomy	TC	1198	922:276
Zeng [31]	2018	2004–2017	China	retrospective cross-section	Thyroidectomy	PTC	258	216:42
Consorti [32]	2010	1995–2008	Italy	retrospective cohort	Thyroidectomy	PTC	404	326:78
Kurukahvecioglu [33]	2007	2001–2005	Turkey	retrospective case-control	Thyroidectomy	PTC	888	721:167
Ohmori [34]	2007	1998–2002	Japan	retrospective case-control	Selective thyroidectomy	PTC	2167	1897:270
Tamimi [35]	2002	1985–2000	Saudi Arabia	retrospective case-control	Thyroidectomy	DTC	117	N/A
Mukasa [36]	2011	2006	Japan	retrospective cohort	Selective thyroidectomy	TC	3688	N/A
Isik [37]	2010	2005–2009	Turkey	retrospective cohort	Selective thyroidectomy	TC	500	400:100
Konturek [38]	2012	2002–2010	Poland	retrospective cohort	Thyroidectomy	PTC	7545	6831:714
Alcantara-Jones [39]	2015	2011	Brazil	retrospective, case-control	Thyroidectomy	PTC	49	41:8
Zayed [40]	2015	2000–2012	Jordan	retrospective cross-section	Thyroidectomy	TC	863	689:174
Gabalec [41]	2016	1991–2014	Czech Republic	retrospective, case-control	Thyroidectomy	DTC	1603	N/A
Uhliarova [42]	2018	2005–2014	Slovakia	retrospective, case-control	Thyroidectomy	TC	2117	1739:378

N/A: not available; F: female; M: male

PTC: papillary thyroid cancer; DTC: differentiated thyroid cancer; TC: thyroid cancer

The odds of TC in HT

Among the 26 eligible studies, a total of 45,564 patients were included, consisting of 8,300 HT patients, 11,168 TC patients, and 2,553 patients with coexisting TC and HT. A random effects model was used for meta-analysis. The results revealed that patients with HT had a significantly higher odds of developing TC compared to those without HT (pooled OR: 2.22, 95% CI: 1.85–2.67, I^2=85.3%, p<0.001) (Fig. 2A). The I^2 value of 85.3% indicated substantial heterogeneity among the included studies.

Subgroup analysis

Considering the variations in study design and patient inclusion criteria among the 26 studies, we conducted a subgroup analysis based on tumor type. The effect size was expressed as the OR, and the pooled OR was 2.34 in the PTC group (95% CI: 1.66–3.29, I^2=86.9%, p<0.001), 2.1 in the DTC group (95% CI: 1.54–2.87, I^2=65.9%, p=0.03), and 2.1 in the TC group (95% CI: 1.55–2.83, I^2=86.6%, p<0.001). Heterogeneity analysis between subgroups showed no significant difference in the pooled results (p=0.88) (Fig. 2B).

Sensitivity analysis and publication bias

Sensitivity analysis indicated that none of the individual studies had a significant impact on the overall assessment (Supplementary File 3). Publication bias was assessed using funnel plots, which demonstrated a symmetrical distribution. Additionally, quantitative analysis using Egger's test showed no evidence of publication bias (p=0.99) (Fig. 3).

The prevalence of TC in HT by sex

Among the 26 studies, 10 studies provided data on the prevalence of TC in HT patients stratified by sex, totaling 2,541 patients (2,309 females and 232 males). Using a random effects model, we calculated the prevalence of

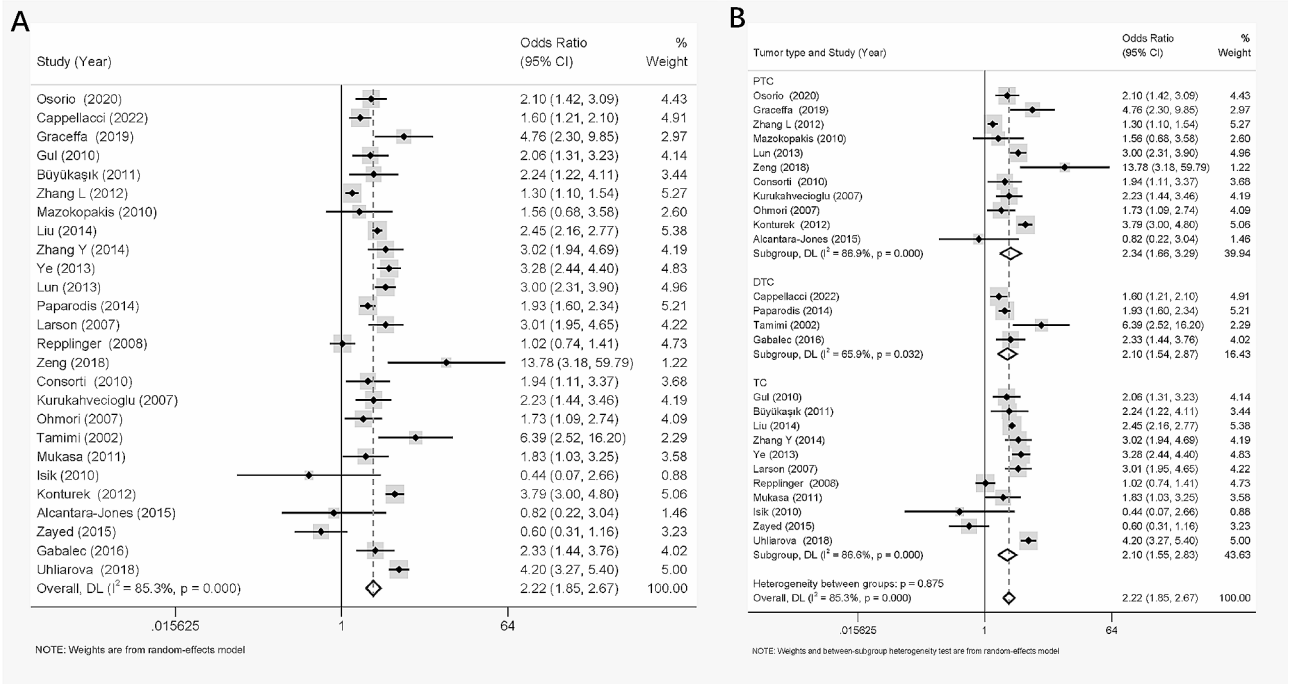

Fig. 2 Forest plot (**A**) Forest plot of odds of TC between HT group and non-HT group. (**B**) Subgroup analysis using tumor type

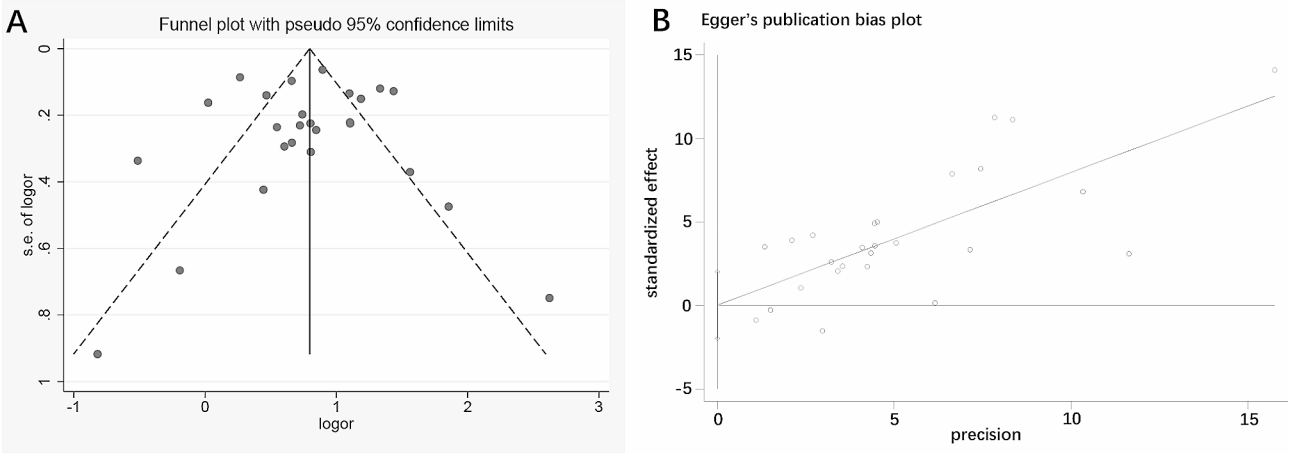

Fig. 3 Publication bias (**A**) Funnel plot (**B**) Egger's test

TC by sex in HT patients. The prevalence of TC in female HT patients was approximately 0.31 (95% CI: 0.17–0.45, I^2=98.6%, p<0.001), while the prevalence of TC in male HT patients was approximately 0.37 (95% CI: 0.21–0.53, I^2=88.4%, p<0.001) (Supplementary File 3). The female-to-male prevalence ratio was 0.84:1, with an OR of 0.9 (95% CI: 0.66–1.24, I^2=0, p=0.51). The Z-test indicated that the results were not statistically significant (p=0.52) (Fig. 4).

Discussion

This meta-analysis provides compelling evidence that the prevalence of TC is significantly higher in patients with HT compared to those without HT, indicating that HT may serve as a risk factor for TC. Subgroup analysis based on tumor type demonstrates a strong association between HT and PTC, DTC, and overall TC. Importantly, there were no significant differences observed between the subgroups, suggesting consistent associations across different tumor types.

This conclusion aligns with previous research indicating that HT is associated with an increased odds of TC. Evidence suggests that chronic inflammation resulting

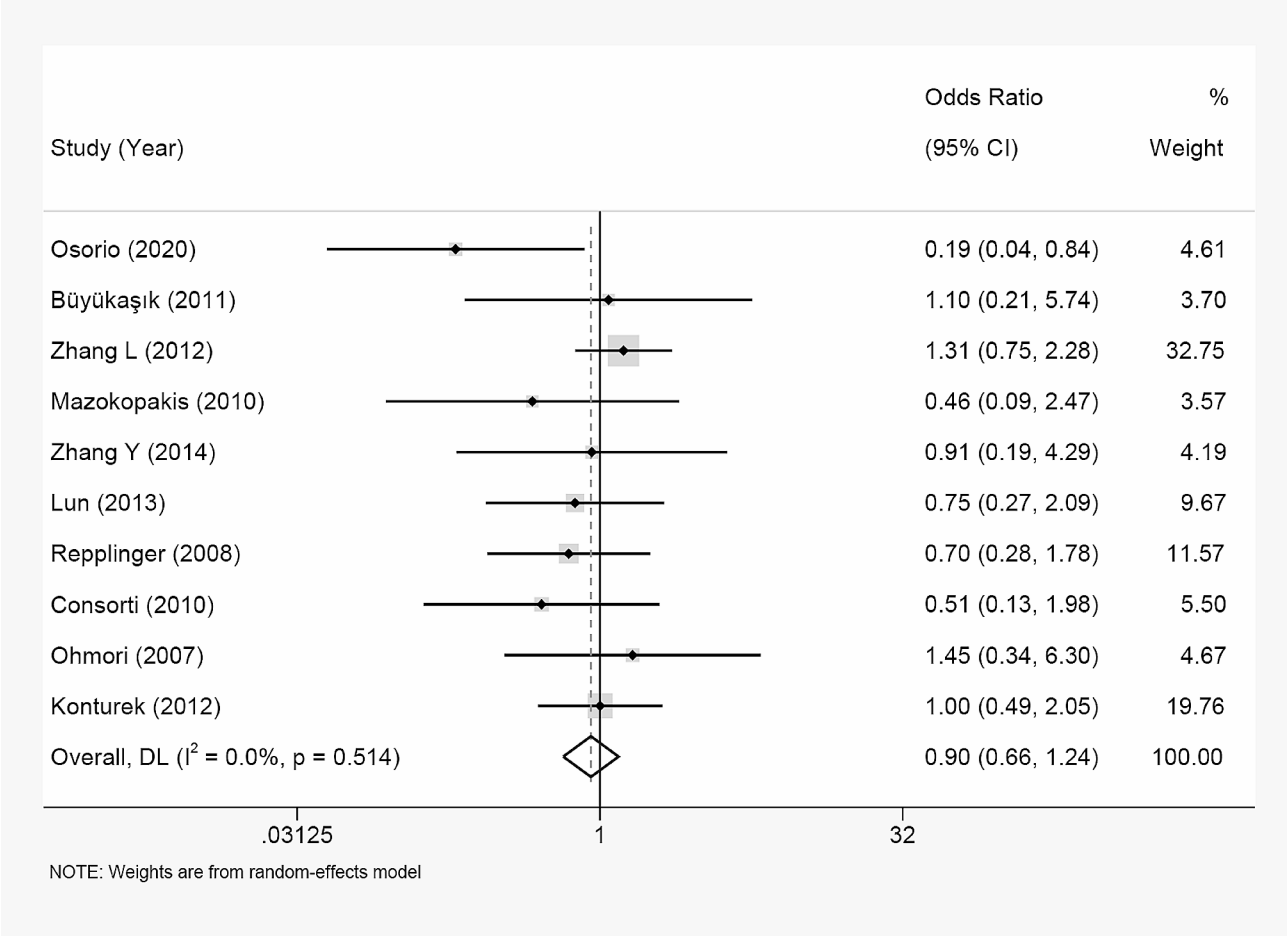

Fig. 4 Forest plot of odds of TC between women and men in HT

from HT is linked to the development of thyroid malignancies, with HT considered a precancerous condition for TC [43, 44]. A study conducted by Nicolson et al. [45] demonstrated a robust correlation between the infiltration of immune cells and dysregulation of DNA repair genes in thyroid cells. Autoimmune thyroiditis may act as a risk factor for TC, with the inflammatory processes of HT playing a significant role in TC development [46]. Furthermore, studies have revealed that the hypoxic conditions induced by inflammation can cause DNA damage and trigger tumorigenic factors, while the infiltration of immune cells can facilitate tumor progression through various mechanisms, including the secretion of cytokines, chemokines, cytotoxic mediators, and reactive oxygen species [47, 48].

A multitude of studies have demonstrated that chronic inflammation is implicated in the development of various types of tumors [49], such as gastric cancer [50], colon cancer [51], skin cancer [52], liver cancer [53], breast cancer [54], lung cancer [48] and head and neck cancer [55].

It is commonly understood that the prevalence of TC is higher in women compared to men [14], and the same trend is observed for HT [56]. Davies et al. [12] claims that the prevalence of TC is greater in women than in men, attributing the recent increase in TC incidence to changes in diagnostic criteria and enhanced screening practices. LeClair et al. [13] suggested that women exhibit higher compliance, leading to more frequent follow-up among female patients with thyroid disease, thereby resulting in a higher detection rate of TC in women. However, a study conducted by Kim et al. [57] indicated that both men and individuals with HT have an increased risk of PTC. This study aimed to examine whether there are differences in the prevalence of TC between women and men among HT patients. An analysis of individual group rates revealed that the prevalence of TC in HT patients was approximately 0.31 in women and 0.37 in men. Pooled risk estimates for TC odds in HT patients were calculated based on sex, with an odds ratio (female versus male) of 0.9. However, these results did not achieve statistical significance.

Considerable heterogeneity was observed among the studies included in this meta-analysis (I^2=85.3%, p<0.001). The variations in research methods likely

contributed to this heterogeneity. For instance, there were discrepancies in the diagnostic criteria for HT, with some studies relying on histological changes as the basis for diagnosis [1, 3, 15, 21, 22, 26], while others utilized positive thyroid autoantibodies [16]. Furthermore, the inclusion criteria for the control group differed, with some studies not explicitly mentioning the exclusion of Graves' disease, family history of TC, or history of radiation exposure [58]. It was also unclear whether patients with hyperthyroidism were excluded from the control group in certain studies. The study population varied in terms of region, ethnicity, and lifestyle. Among the 26 studies included in the meta-analysis, some focused on the relationship between PTC and HT, some examined the association between DTC and HT, and others explored the connection between malignant tumors in the thyroid gland and HT. These factors may contribute to the observed heterogeneity.

The strength of this study lies in its examination of the odds of HT in TC, as well as the association between sex and TC in HT patients. It emphasizes the importance of regular follow-up and examinations for HT patients to promptly detect potential malignant lesions. However, due to limited detailed sex data in some of the included studies, not all 26 studies could be included in the sex-related analysis. Furthermore, our research predominantly relied on retrospective studies involving patients who underwent thyroidectomy. Anil et al. [59] have argued that retrospective studies often include patients who undergo thyroidectomy, a procedure typically reserved for individuals with a heightened risk of malignancy. The suspicion of malignancy is one of the primary reasons why HT patients opt for surgical resection, which introduces a potential selection bias in these studies [60, 61]. The intricate relationship between TC and HT encompasses aspects of inflammation and immunity. Moreover, retrospective studies are prone to selective biases in their data. Therefore, a prospective study with a large sample size is crucial to uncover the underlying and intrinsic connection between HT and TC [62].

Conclusions

In conclusion, our meta-analysis findings demonstrate a substantial elevation in the prevalence of TC among HT patients compared to non-HT patients, indicating an increased odds of TC associated with HT. Additionally, our analysis reveals no significant disparity in TC prevalence between female and male HT patients. Nonetheless, it is essential to conduct large-scale, high-quality prospective studies for further investigation. In summary, we consider that there is an association between HT and TC. HT increases the odds of TC. Regular reviews play a vital role in facilitating early detection of potential TC lesions in HT patients, thus holding significant clinical relevance.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-024-01670-w.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Author contributions

P.Z. and Y.L. designed the meta. Y.L. and X.G. developed and conducted the search strategy. Y.L. and C.G. screened studies and extract data. P.Z. and Y.L. conducted data analyses and wrote the main manuscript text.

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Data availability

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate

Since this is a meta-analysis, ethics approval and informed consent is not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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