Thyroid disease is associated with an increased risk of breast cancer: a systematic review and meta-analysis

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**Background:** This study investigated the relationship between thyroid diseases and the risk of breast cancer (BC). Clarifying this issue can help medical staff perform early prevention, diagnosis and treatment for breast cancer patients.

**Methods:** The meta-analysis combined data from cohort studies and case-control to obtain a comprehensive result of the relationship between thyroid diseases and risk of BC. We comprehensively searched PubMed, EMBase, Web of Science, and the Cochrane Library. The search period was from the establishment of the databases to August 2020. Literature was collected and screened individually by two reviewers. There was English language restriction on the search and unpublished literature was excluded. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the selected studies prior to data extraction. The data collected included country, author, year of publication, research type, and number of cases. In cases where the data and study heterogeneity permitted, meta-analyses were performed, and odd ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. Data were analyzed using the STATA 15.1 software.

**Results:** A total of 21 articles were included in this study. Hyperthyroidism, thyroid cancer, thyroglobulin antibody (TGAb) levels, and thyroid microsomal antibody (TPOAb) levels were all significantly associated with an increased risk of BC, while hypothyroidism was associated with a reduced risk of BC.

**Conclusions:** This study demonstrated that hyperthyroidism, autoimmune thyroiditis (AITD), and thyroid cancer are significantly associated with an increased risk of BC, while hypothyroidism is associated with a reduced risk of BC.

**Keywords:** Breast cancer (BC); thyroid disease; risk factor; meta-analysis

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**Introduction**

Breast cancer (BC) is the most common type of cancer in females, occurring in 20% of the female population worldwide, and is the main cause of tumor-related death in women (1). Studies have shown that BC is closely related to the endocrine system (2). The thyroid is an important part of the endocrine system and secretes thyroid hormone (TH), which plays a vital role in the growth, development, and
metabolism of cells and tissues (3,4). As pituitary hormones target both breast and thyroid tissues (5), there may be a correlation between BC and thyroid disorders. Hardefeldt et al. (6) found that there was significant evidence of an increased risk of BC in patients with presence of anti-thyroid antibodies, while they also found that there was no significant evidence of an increased risk of BC in patients with hypothyroidism and hyperthyroidism. But more high-quality prospective studies are needed to prove causality the relationship between benign thyroid disease and BC. However, the relationship between BC and thyroid diseases, such as hyperthyroidism, hypothyroidism, autoimmune thyroid disease (AITD) and thyroid cancer, is still not well understood.

Angelousi and colleagues demonstrated that TH promoted the proliferation of breast cancer cells in vitro, while hypothyroid function resulted in a lower incidence of lymph node metastases (7). Recent studies have suggested that TH may play a positive role in the cause and development of BC at a cellular level (8-11). However, Herebergs et al. found no evidence that TH causes BC in the clinical setting (12). Despite numerous studies having investigated the association between thyroid dysfunction and BC, the exact relationship and molecular mechanisms involved remain unclear. Further studies examining the prognostic role of TH in BC are thus warranted.

AITD is a disease whereby the body's own immune cells attack and damage the thyroid tissue. It is characterized by the presence of autoantigens such as thyroglobulin (Tg) and thyroid peroxidase (TPO). In patients with AITD, autoantibodies to the thyroid antigens can be detected in the blood. These autoantibodies include thyroglobulin antibody (TGAb), thyroid microsomal antibody (TPOAb), and thyroid-stimulating receptor antibody (TRAb). Furthermore, the immune system plays a complex role in BC and autoimmune factors are also crucial in the development of BC, so TGAb and TPOAb may have some correlation with BC. Several studies have shown an increased prevalence of AITD in patients with BC (13-15), while others have found no association (16). In fact, Tosovic and colleagues demonstrated that women with high levels of TPOAb had a relatively lower risk of BC (17).

According to epidemiological statistics, the cumulative incidence of developing a second malignancy in a patient with thyroid cancer is 16 % at 25 years (18). Previous studies have shown that there is a unidirectional or bidirectional association between thyroid cancer, breast cancer and renal cell carcinoma (19,20). A unidirectional association is defined as a primary cancer that increases the relative risk of subsequent cancers, while a bidirectional association indicates that there is a two-way relationship or mutual relationship between two cancers, and has nothing to do with the subsequent occurrence. Thyroid cancer survivors have a high incidence of breast cancer, and breast cancer survivors have a high incidence of thyroid cancer (21,22).

This is the largest-scale meta-analysis, including 21 studies involving 67,049 female breast cancer patients to explore the correlation between thyroid diseases (benign and malignant) and the risk of breast cancer. Based on the data from cohort studies and case-control studies, this meta-analysis examined the relationship between thyroid diseases and the risk of BC, aiming of obtaining a comprehensive and comprehensive result. Understanding this relationship can aid in the early prevention, detection and treatment of patients with BC.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/gs-20-878).

**Methods**

**Search strategy**

The databases PubMed, EMBase, Web of Science, and the Cochrane Library were searched systematically. The search period was from the establishment of the databases to August 2020. All searches were performed using the combination of medical subject heading terms (MeSH), text words, and keywords. The search terms “breast neoplasms”, “breast cancer”, “breast cancer tumor”, “breast carcinoma”, “thyroid disease”, “thyroid cancer”, “hyperthyroidism”, “hypothyroidism”, “autoimmune thyroiditis”, “TGAb”, and “TPOAb”. There was English language restriction on the search, and unpublished literature was not included. Based on the references listed in the literature obtained in the initial search, a secondary search was performed and literature retrieval was expanded by manual retrieval.

**Literature inclusion and exclusion criteria**

Studies where the patients had a definite diagnosis of BC, hyperthyroidism, hypothyroidism, AITD, or thyroid cancer were included in this meta-analysis. Studies that reported a 95% confidence interval (CI) and odd ratio
(OR), or where the 95% CI and OR could be calculated from the data presented, were included. Non-English publications, duplicate publications, reviews, editorials, single case reports, studies without full text, and studies with incomplete information, or where the data could not be extracted, were all excluded. Studies of drug-induced thyroid disease, and literature including patients with irrelevant acute or chronic diseases were excluded. Any study that did not meet the inclusion criteria was also excluded.

Literature screening and data extraction

The literature search, screening, and information extraction were performed independently by two professionally trained researchers. Any discrepancies were resolved by discussion, and the final decisions were made by the corresponding author. The data was collated according to a standardized form, and included the country, author, year of publication, research type, number of cases, and clinical outcomes.

Literature quality assessment

Two researchers independently adopted the Newcastle-Ottawa Scale (NOS) to evaluate the quality of the literature (23). Any differences in opinions were resolved through discussion or consultation with a third party. NOS evaluates the quality of a study by assessing four items in the “Research Subject Selection” domain (4 points), one item in the “Comparability between Groups” domain (2 points), and three items in the “Result Measurement” domain (3 points). Each study can have a maximum of 9 possible points. Studies with 7 points or more are regarded as high-quality literature, and studies scoring less than 7 points are considered lower-quality literature.

Statistical methods

Odds ratio (OR) with 95% CI was used to evaluate whether each thyroid disease was an independent risk factor. The fixed effects model was used for analysis if the heterogeneity tests showed that $P \leq 0.1$ and $I^2 \leq 50\%$. The random effects model was used for combined analysis if the heterogeneity tests showed $P > 0.1$ and $I^2 > 50\%$. Sensitivity analyses and meta-regression analyses were used to examine the sources of heterogeneity when required. Symmetry on the funnel plot was used to determine publication bias. All data were analyzed using Stata software (version 15.1).

Results

Literature search results

A total of 1,642 articles were obtained by searching through PubMed, EMBase, Web of Science, and the Cochrane library. After excluding duplicate articles, there were 1,420 articles remaining. The abstracts of these publications were reviewed and 1,224 articles were selected. Reading the full text of the articles resulted in the selection of 21 publications suitable for this meta-analysis (Figure 1).

Baseline characteristics and quality assessment of the included studies

The baseline characteristics and quality assessment of the included studies are shown in Table 1.

Meta-analysis results

The meta-analysis results demonstrated that patients with hyperthyroidism had a significantly increased risk of BC. The six studies (3,24-28) showed low heterogeneity (OR = 1.12, 95% CI: 1.08–1.16, $P=0.000$; $I^2=34.9\%$; Figure 2). Contrary to hyperthyroidism, hypothyroidism was significantly correlated with a reduced risk of BC, with no heterogeneity (OR = 0.95, 95% CI: 0.91–1.00, $P=0.042$; $I^2=0.0\%$; Figure 3) observed in the eight studies (17, 24-27,29-31). Moreover, analysis of five studies (32-36) demonstrated that patients with thyroid cancer had a 1.3-fold increased risk of BC, with no heterogeneity observed (OR = 1.28, 95% CI: 1.15–1.42, $P=0.000$; $I^2=0.0\%$; Figure 4).

To examine the effect ofAITD on the risk of BC, the relationship between TGAbs or TPOAbs and risk of BC was investigated. Analysis of four studies (14,15,37,38) demonstrated that patients with elevated TGAb levels were 2.6 times more likely to develop BC, and low heterogeneity was observed (OR = 2.57, 95% CI: 1.58–4.18, $P=0.000$; $I^2=0.9\%$; Figure 5). The analysis of five studies (14,15,38-40) showed that elevated TPOAb levels were also significantly correlated with an increased risk of BC (OR = 2.83, 95% CI: 2.03–3.94, $P=0.000$; $I^2=0.0\%$; Figure 5).

Sensitivity analysis

Sensitivity analyses were performed to evaluate whether
individual studies had an excessive impact on the results of the entire meta-analysis. During sensitivity analyses, the included studies was eliminated one by one, and then the OR value of the remaining studies was calculated. The results demonstrated that none of the studies had an excessive impact on the results of the meta-analysis (Figures S1–S5), indicating that the results of this meta-analysis were stable and reliable.

**Publication bias**

Funnel plot analysis was used to assess publication bias. As shown in the Figure 6, the funnel plot was asymmetric, indicating potential publication bias in the results of this meta-analysis.

**Discussion**

To our knowledge, this is the largest meta-analysis examining the correlation between thyroid diseases (both benign and malignant) and the risk of BC. A total of 21 studies, involving 67,049 female patients with BC, were analyzed. Our meta-analysis results demonstrated that hyperthyroidism, hypothyroidism, thyroid cancer, and AITD were significantly associated with an increased risk of BC.

The causes of BC are complex. Its occurrence has been closely associated with various factors such as genetic, environmental, social, and behavioral factors, as well as the use of hormones and drugs (41,42). The endocrine system plays a crucial role in the physiology and pathology of the breast. The thyroid, being the largest endocrine organ in the human body, plays a major role in the growth and development of cells through regulating the levels of various hormones in the body. Therefore, understanding the relationship between thyroid diseases and the risk of BC is of vital importance.

In 2009, a study by Sandhu et al. (31) found no significant association between hypothyroidism and the risk of BC. This contrasted with a prospective cohort study by Søgaard et al. The latter study, involving 61,873 women with hypothyroidism and 80,343 women with hyperthyroidism (27), demonstrated that patients with hypothyroidism had a slightly reduced risk of BC, while patients with hyperthyroidism had an increased risk of BC. In agreement with Søgaard and colleagues, this...
current meta-analysis demonstrated that patients with hypothyroidism had a reduced risk of BC. It is evident that the relationship between thyroid function and the risk of BC requires further investigation.

Previous in vivo experiments in hypothyroid mice demonstrated that low levels of β-catenin expression and activation of the apoptosis pathway on the tumor cell membrane inhibited the growth of BC cells in the mice (43). Additionally, in vitro studies using BC cell lines, showed that triiodothyronine (T3), a TH secreted by the thyroid gland, promoted the proliferation of tumor cells and enhanced the cell proliferation effects of estradiol (E2) (44). Hence, it is possible that TH promotes the occurrence of BC, and patients with hypothyroidism may have a reduced risk of BC due to lower TH levels. Conversely, hyperthyroidism may lead to an increased risk of BC, as shown in this meta-analysis (OR =1.12, 95% CI: 1.08–1.16, P=0.00, T²=34.9%; Figure 2). The low heterogeneity may be due to differences in thyroid hormone measurement instruments in different literatures, differences in the inclusion and exclusion criteria of experimental subjects. However, Hercbergs et al. (12) found no evidence that TH causes BC in the clinical setting (12), despite numerous studies having investigated the association between thyroid dysfunction and BC. That may due to limited clinical and preclinical studies to assess.

An awareness of the relationship between hyperthyroidism and BC is important in improving the clinical detection

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Research type</th>
<th>Number of cases (n)</th>
<th>Total sample size (n)</th>
<th>Age (year)</th>
<th>Mean follow-up (year)</th>
<th>NOS score</th>
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<tr>
<td>Brinton 1984</td>
<td>USA</td>
<td>Case-control</td>
<td>1,362</td>
<td>2,612</td>
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<td>–</td>
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<td>Denmark</td>
<td>Case-control</td>
<td>10</td>
<td>58</td>
<td>56 (27–80)</td>
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<tr>
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<td>USA</td>
<td>Case-control</td>
<td>354</td>
<td>1,101</td>
<td>22–86</td>
<td>2.3</td>
<td>7</td>
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<tr>
<td>Giani 1996</td>
<td>Italy</td>
<td>Cohort</td>
<td>17</td>
<td>102</td>
<td>54.3±11.25</td>
<td>–</td>
<td>8</td>
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<td>Talamini 1997</td>
<td>Italy</td>
<td>Case-control</td>
<td>2,569</td>
<td>5,157</td>
<td>55 (23–74)</td>
<td>–</td>
<td>7</td>
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<tr>
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<td>Ireland</td>
<td>Case-control</td>
<td>356</td>
<td>550</td>
<td>57 (32–81)</td>
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<td>7</td>
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<tr>
<td>Adjadj 2003</td>
<td>France</td>
<td>Case-control</td>
<td>48</td>
<td>2,413</td>
<td>39 (15–64)</td>
<td>13</td>
<td>8</td>
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<td>Israel</td>
<td>Cohort</td>
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<td>4,981</td>
<td>–</td>
<td>9.4</td>
<td>7</td>
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<tr>
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<td>France, Italy, Sweden</td>
<td>Cohort</td>
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<td>6,841</td>
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<td>13</td>
<td>8</td>
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<tr>
<td>Berthe 2004</td>
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<td>Cohort</td>
<td>12</td>
<td>875</td>
<td>–</td>
<td>8</td>
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<td>Brazil</td>
<td>Case-control</td>
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<tr>
<td>Giustarini 2006</td>
<td>Italy</td>
<td>Case-control</td>
<td>36</td>
<td>136</td>
<td>52.8±10.2</td>
<td>–</td>
<td>8</td>
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<tr>
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<td>Czech Republic</td>
<td>Case-control</td>
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<td>64.7±11.4</td>
<td>11.3</td>
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<td>9.8</td>
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<td>Cohort</td>
<td>370</td>
<td>29,691</td>
<td>–</td>
<td>9</td>
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<td>Sweden</td>
<td>Cohort</td>
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<td>1,356</td>
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<td>Chen 2013</td>
<td>China</td>
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<td>174</td>
<td>615</td>
<td>41.7±13.8</td>
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<tr>
<td>Lu 2013</td>
<td>China</td>
<td>Cohort</td>
<td>102</td>
<td>19,068</td>
<td>59.30±14.41</td>
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<td>970</td>
<td>61,873</td>
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<td>9.5</td>
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<tr>
<td>Chan 2017</td>
<td>Australia</td>
<td>Cohort</td>
<td>100</td>
<td>3,649</td>
<td>51.5±15.5</td>
<td>20</td>
<td>7</td>
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<tr>
<td>Weng 2018</td>
<td>China</td>
<td>Case-control</td>
<td>51,733</td>
<td>103,466</td>
<td>53.4±12.0</td>
<td>–</td>
<td>8</td>
</tr>
</tbody>
</table>
Figure 2  The association between hyperthyroidism and the risk of breast cancer. Patients with hyperthyroidism have a significantly increased risk of breast cancer with low heterogeneity being observed [OR = 1.12, 95% CI: 1.08–1.16, P=0.000; I^2=34.9%; enrolling 6 studies (3,24-28)].

Figure 3  The association between hypothyroidism and the risk of breast cancer. Patients with hypothyroidism have a significantly reduced risk of breast cancer with no heterogeneity being observed [OR = 0.95, 95% CI: 0.91–1.00, P=0.042; I^2=0.0%; enrolling 8 studies (17,24-27,29-31)].
and prevention of BC in patients with thyroid disease. Additionally, active treatment of hyperthyroidism may reduce the risk of BC.

The results of this meta-analysis demonstrated that in patients with AITD, increased levels of TGAb and TPOAb were associated with an increased risk of BC. This is a summary of the current controversy about whether thyroid auto-antibodies are a risk factor or a protective factor for BC. A causal relationship between AITD and BC has not yet been discovered. Some hypotheses may explain this problem: one possibility is that the immune response to BC and thyroid can be regulated in the same way. Another possibility is that both thyroid and BC express common antigens such as sodium/iodide symporter (NIS) and TPO antibody (45). Our research results suggest that in the future, it is important for us to dig deeper into the causal relationship between auto-antibodies and the increased risk of BC.

This meta-analysis also demonstrated that patients with thyroid cancer were associated with an increased risk of BC. Early screening for BC should be performed for patients with thyroid disease to reduce the prevalence of BC as a secondary malignancy.

There were a few limitations to this meta-analysis. Firstly, several of the included studies adjusted for confounding factors, and as the adjusted variables were not identical in each study, residual confounding factors may still exist. Secondly, since the variables of the study included fewer than 10 articles, the study did not pass the Egger’s test for publication bias. Hence, a subjective determination of publication bias was used. The results of the funnel plot analysis suggested more studies are required in future meta-analyses to eliminate publication bias.

**Conclusions**

This research demonstrated that hyperthyroidism, AITD, and thyroid cancer are significantly associated with an increased risk of BC, while hypothyroidism can reduce the risk of BC.
Figure 5 The association between the levels of (A) TGAb and (B) TPOAb, and the risk of breast cancer. Elevating TGAb values are related to an almost 2.6-time increase in the risks for breast cancer with low heterogeneity being observed [OR =2.57, 95% CI: 1.58–4.18, P=0.000; I²=0.9%; enrolling 4 studies (14,15,37,38)], and TPOAb shows greater correlation with breast cancer risk [OR =2.83, 95% CI: 2.03–3.94, P=0.000; I²=0.0%; enrolling 5 studies (14,15,38-40)] TGAb, thyroglobulin antibody; TPOAb, thyroid microsomal antibody.
Acknowledgments

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gs-20-878). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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(English Language Editors: J. Teoh and J. Gray)

Supplementary

Figure S1 sensitivity analysis of the association between hyperthyroidism and risk of breast cancer.

Figure S2 sensitivity analysis of the association between hypothyroidism and risk of breast cancer.
Figure S3 sensitivity analysis of the association between thyroid cancer and risk of breast cancer.

Figure S4 sensitivity analysis of the association between TGAb and risk of breast cancer.
Figure S5 sensitivity analysis of the association between TPOAb and risk of breast cancer.