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# Benign thyroid disease is associated with breast cancer: a meta-analysis

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**Abstract** The controversial relationship between benign thyroid diseases and breast cancer (BC) has been investigated for over 50 years. Despite extensive population studies, the results as a whole have been inconsistent. The purpose of this study was to collate and analyse available data, calculating a pooled odds ratio (OR) of the risk of BC in patients diagnosed with benign thyroid diseases. Studies were obtained from a database search of MEDLINE, EMBASE, PubMed, Current Contents Connect and Google Scholar with additional cross checking of reference lists. Inclusion criteria required a confirmed diagnosis of a benign thyroid disease, reporting of an OR or data to calculate an OR (and 95% confidence interval, CI) and the use of an internal control group as the comparator. Collated data was assessed for heterogeneity and a pooled OR calculated. 28 studies were included in the meta-analysis. There was significant evidence of an increased risk of BC in patients with autoimmune thyroiditis, evident in a pooled OR 2.92 (95% CI 2.13–4.01). In addition, the results supported an increased risk associated with the presence of anti-thyroid antibodies (OR 2.02, 95% CI 1.63–2.50) and goitre (OR 2.26, 95% CI 1.39–3.69). Subgroup analysis of antibody presence revealed increased risk associated with both anti-TPO (OR 2.64, 95% CI 1.82–3.83) and anti-TG (2.71, 95% CI 1.58–4.69). Quantitative analysis of hypothyroidism and hyperthyroidism was not significant. While these results indicate an association between thyroid auto-immunity and BC, further prospective studies are required to definitively prove causality.

**Keywords** Breast cancer · Autoimmune thyroiditis · Goitre · Thyroid antibody · Meta-analysis

**Abbreviations**

| | |
|---|---|
| BC | Breast cancer |
| AITD | Autoimmune thyroiditis |
| OR | Odds ratio |
| CC | Case–control study design |
| CO | Cohort study design |
| CS | Cross-sectional study design |

## Introduction

The controversial relationship between benign thyroid diseases and breast cancer (BC) has been investigated for over 50 years. Despite extensive population studies, the results as a whole have been inconsistent. To date a relationship between specific benign thyroid diseases and BC has not been quantified with the exception of autoimmune thyroiditis (AITD), which was investigated in a meta-analysis published in 2002 [1]. This study by Sarlis et al. [1] found no association between AITD and BC despite significant positive findings in an number of primary studies [2–5].

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The effect of hypothyroidism on BC incidence has also proved a point of contention. Cristofanilli et al. [6] found primary hypothyroidism reduced the risk of BC despite other studies reporting an increased risk of BC [7, 8] or no association at all [9–11]. This variation in results is also present when investigating the relationship between goitre and BC. Although numerous studies have reported an increased risk of BC associated with goitre [2, 11–13], other studies have failed to find a relationship between the two [9]. In regards to benign thyroid disease and BC, this disparity in results appears relatively commonly throughout the literature.

Despite numerous studies investigating the association between benign thyroid disease and BC, the exact mechanism behind any such relationship has not yet been identified. Hypotheses have focussed on common elements to both the thyroid and the breast such as the sodium–iodide symporter (NIS) [14] and the proliferative effects of thyroid hormones [15]. However, a reversal in the relationship with BC acting as the predecessor in triggering thyroid dysfunction has not been ruled out [16, 17].

The purpose of this study was to collate and analyse literature investigating the relationship between benign thyroid diseases and BC. In addition, we aimed to incorporate data from recent studies to re-assess the relationship between autoimmune thyroid disease and BC, offering an updated analysis, since that completed by Sarlis et al. in 2002, of whether the presence of autoimmune thyroid disease may indicate a higher risk of BC [1].

## Methods

### Study protocol

One reviewer (PH) following the meta-analysis of Observational Studies in Epidemiology guidelines (MOOSE)[18] completed a database search. The databases, MEDLINE (from 1950), EMBASE (from 1949), PubMed (from 1946), Current Contents Connect (from 1998) and Google Scholar (from 1992), were searched using medical subject headings, text word and keyword searches wherever possible (Fig. 1). The search terms used were "thyroid disease" or "hyperthyroid" or "hypothyroid", "thyroiditis" or "graves" AND "breast disease", or "breast carcinoma", or "breast cancer" or "breast neoplasm". While there was no language restriction placed on the search, we did not search for unpublished literature. The reference lists of relevant studies were checked manually to locate any missing studies.

### Study selection

Studies which met the following inclusion criteria were included in the meta-analysis: (1) the risk point estimate was reported as an odds ratio (OR) or the OR could be calculated from the presented data; (2) the 95% confidence interval (CI) was reported or the CI could be calculated from the presented data; (3) an internal control group was used to calculate the OR and the internal control group had been diagnosed with neither breast disease nor thyroid disease; (4) the diagnosis of benign thyroid disease adhered to the criteria in Table 1. Any study that did not meet the above criteria was excluded from the meta-analysis.

### Data extraction

Data was extracted by a single reviewer (PH) and entered into a standardised data spread sheet (Table 2). For each article, data collected included publication date, timeframe for data collection, study type [cross section (CS), Cohort (CO) or case–control (CC)], sample size, mean age, country (geographical and economic status), OR, CI and adjusted variables. Where applicable, adjusted ORs were recorded. However, where no OR was given, an unadjusted OR and CI was calculated by the reviewer (PH). Where multiple ORs were given within the same study, i.e. from two different geographical locations [19], the data was entered as two separate ORs. Studies that did not define the specific type of benign thyroid disease were analysed as "non-specific thyroid disease".

### Statistical analysis

A random effects model was used to calculate a pooled OR for the effect of thyroid disease on the risk of developing BC. Heterogeneity was assessed using Cochran's $Q$ statistic with a $p$ value of $<0.10$ indicating significant heterogeneity. The extent of heterogeneity was further quantified using the $I^2$ statistic with results of 25, 50 and 75 % correlating with low, moderate and high levels of heterogeneity, respectively. Egger's regression model was used to calculate publication bias with the extent of bias documented using the "fail safe" method whereby the number of studies required to nullify our results was calculated. A fail safe ($n$) with a $p$ value $<0.05$ was considered significant. Data was analysed using Comprehensive meta-analysis (version 2.0).

## Results

### Autoimmune thyroiditis

14 studies were identified investigating the risk of BC in patients with AITD. Ten studies were excluded for failing to meet the inclusion criteria: Two studies were excluded for failing to confirm the diagnosis [20, 21], Four studies

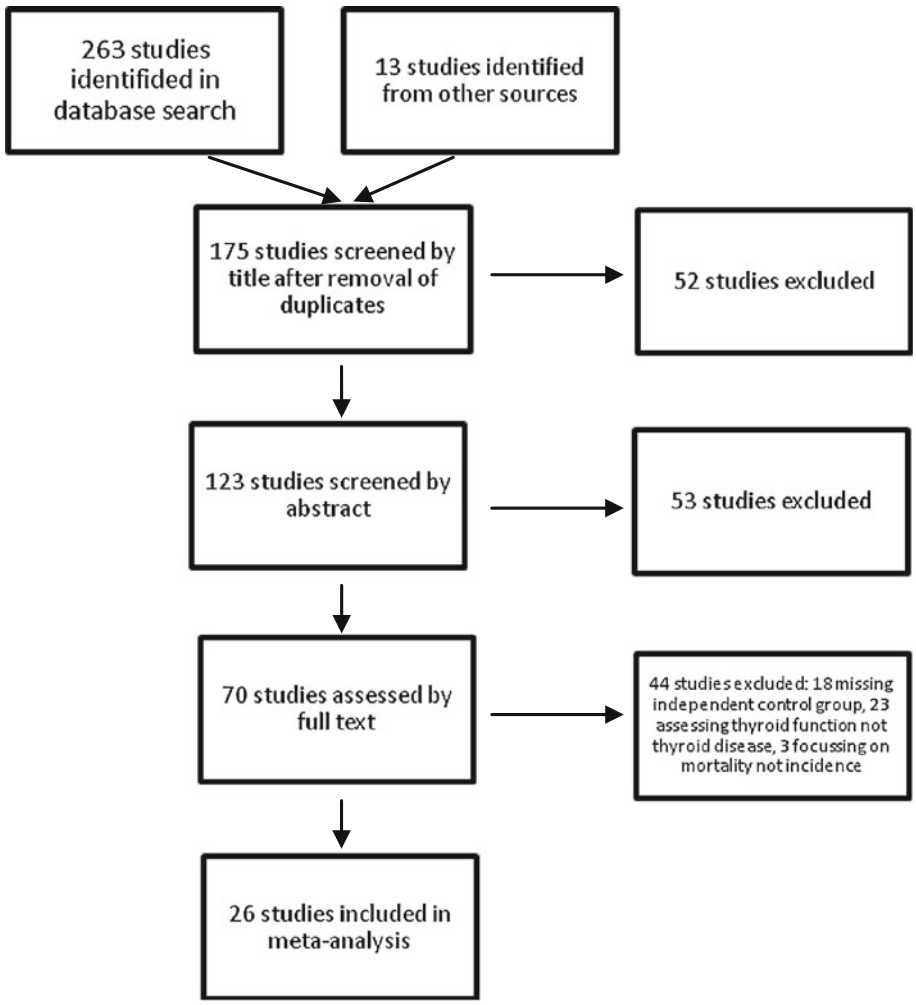


**Fig. 1** Results of the literature search

**Table 1** Diagnostic criteria for benign thyroid diseases

| Thyroid disease | Diagnostic criteria |
|---|---|
| Auto-immune thyroiditis | Positive serum antibody (anti-TPO, anti-TG or microsomal) and evidence of thyroid dysfunction (goitre, altered serum thyroid function tests) and/or histological confirmation of the diagnosis |
| Antibody presence | Presence of Anti-TPO, anti-Tg or microsomal antibodies in serum |
| Goitre | Increased thyroid volume on ultrasound, palpable goitre on clinical examination, or confirmation of diagnosis in medical record |
| Hyperthyroid | Thyroid function tests indicating thyrotoxicosis (i.e. decreased TSH and raised T3/T4) |
| Hypothyroid | Thyroid function tests indicating hypothyroidism (i.e. increased TSH and decreased T3/T4) |
| Graves Disease | Presence of TSH-receptor antibody and thyroid function tests indicating thyrotoxicosis |

were excluded for failing to include an internal control group diagnosed with neither breast nor thyroid diseases [22–25] and two studies were excluded for investigating mortality rather than incidence [26, 27]. Jiskra et al. [4] and Smyth et al. [11] were included, however, Jiskra et al. [5] and Smyth [28] were excluded as they appeared to use the same study population evident in the similar characteristics present in case and control groups and the identical study designs.

The four remaining studies [2–4, 13] were homogenous in their results, each reporting a statistically significant risk point estimate (Fig. 2). The pooled OR, 2.92 (95% CI 2.13–4.01), demonstrated an increased risk of BC in the AITD population. Minimal heterogeneity was present

**Table 2** Summary of studies included in the meta-analysis

| Study | Year | Study design | Cases | Control | Diagnostic tests[e] | Summary of findings |
|---|---|---|---|---|---|---|
| Giani et al. [2] | 1996 | CS | 102 | 100 | TFT, ultrasound, TPO, TG, FNA | Increased prevalence of AITD associated with BC |
| Jiskra et al. [4] | 2007 | CS | 84 | 49 | TFT, ultrasound, TPO, TG | Increased prevalence of AITD associated with BC |
| Gogas et al. [3] | 2001 | CS | 310 | 190 | TFT, ultrasound, TPO, TG, FNA | Increased prevalence of AITD associated with BC |
| Turken et al. [13] | 2003 | CS | 150 | 100 | TFT, ultrasound, TPO, TG, FNA | Increased prevalence of AITD associated with BC |
| Mittra et al. [19][a] | 1976 | CS | 85 | 96 | Microsomal antibodies | No increased prevalence of microsomal antibodies in BC |
| Mittra et al. [19][b] | 1976 | CS | 277 | 211 | Microsomal antibodies | No increased prevalence of microsomal antibodies in BC |
| Kuijpens et al. [7] | 2005 | CO | 278 | 2738 | TFT, TPO | No relationship between incidence of BC and anti-TPO antibody presence |
| Kuijpens et al. [7] | 2005 | CS | 278 | 2497 | TFT, TPO | Increased prevalence of BC with presence of anti-TPO |
| Giustarini et al. [29] | 2006 | CS | 36 | 100 | TFT, TPO, TG, ultrasound | Increased prevalence of anti-thyroid antibodies in patients with BC |
| Rasmussen et al. [31] | 1987 | CS | 58 | 75 | TFT, TPO, TG, TSH-R | Increased prevalence of anti-thyroid antibodies in BC patients |
| Smyth et al. [30] | 1998 | CS | 356 | 194 | TFT, TPO, ultrasound | Increased prevalence of anti-TPO antibodies in BC patients |
| Adamopoulos et al. [12] | 1986 | CS | 97 | 60 | TFT, microsomal antibodies, ultrasound | Increased prevalence of goitre in BC patients |
| Smyth et al. [11] | 1996 | CS | 200 | 200 | TFT, ultrasound | Increased prevalence of goitre in patients with BC, no relationship between hypothyroidism or hyperthyroidism |
| Adami et al. [9] | 1978 | CC | 179 | 179 | TFT, medical record search | No relationship between presence of goitre, hypothyroidism or hyperthyroidism and BC |
| Singh et al. [8] | 1982 | CS | 34 | 40 | Radioactive iodine uptake | Increased prevalence of hypothyroidism in BC patients |
| Ditsch et al. [10] | 2010 | CS | 65 | 38 | TFT, antibodies | No relationship between BTD and BC |
| Cengez et al. [45] | 2004 | CS | 136 | 68 | Ultrasound, TFI, antibodies | Increased prevalence of goitre and BTD in BC |
| Purde [44][c] | 1990 | CC | 148 | 149 | Medical record search | No relationship between BTD and BC |
| Purde [44][d] | 1990 | CC | 216 | 160 | Medical record search | Increased risk of BC in patients with BTD |
| Brinton et al. [34] | 1984 | CC | 1552 | 1375 | Self reporting | No relationship between BTD and BC |
| Franceschi et al. [46] | 1990 | CC | 2663 | 2344 | Self reporting | No relationship between BTD and BC |
| Kalache et al. [42] | 1982 | CC | 1176 | 1176 | Self reporting | No relationship between BTD and BC |
| Moseson et al. [32] | 1993 | CC | 370 | 783 | Self reporting | No relationship between BTD and BC |
| Talamini et al. [33] | 1997 | CC | 2569 | 2588 | Self reporting | No relationship between BTD and BC |

**Table 2** continued

| Study | Year | Study design | Cases | Control | Diagnostic tests[e] | Summary of findings |
|---|---|---|---|---|---|---|
| Weiss et al. [50] | 1990 | CC | 2173 | 1990 | Self reporting | No relationship between BTD and BC in younger women |
| Simon et al. [21] | 2002 | CC | 4575 | 4682 | Self reporting | No relationship between BTD and BC |
| MacFarlane et al. [47] | 1980 | CS | 162 | 72 | TFT | No relationship between BTD and BC |
| Saraiva et al. [48] | 2005 | CS | 26 | 22 | TFT, antibodies | Increased prevalence of BTD in BC patients |
| Schottenfield [49] | 1968 | CC | 73 | 102 | Medical record search, TFT | No relationship between BTD and BC |

*BTD* benign thyroid diseases, *BC* breast cancer, *AITD* autoimmune thyroiditis

[a] Japanese population

[b] British population

[c] Estonian population

[d] Slovakian population

[e] Diagnostic tests: serum thyroid function tests (TFT), immunoassay for anti-TPO antibodies (TPO), immunoassay for anti-TG antibodies (TG), fine needle aspiration (FNA)

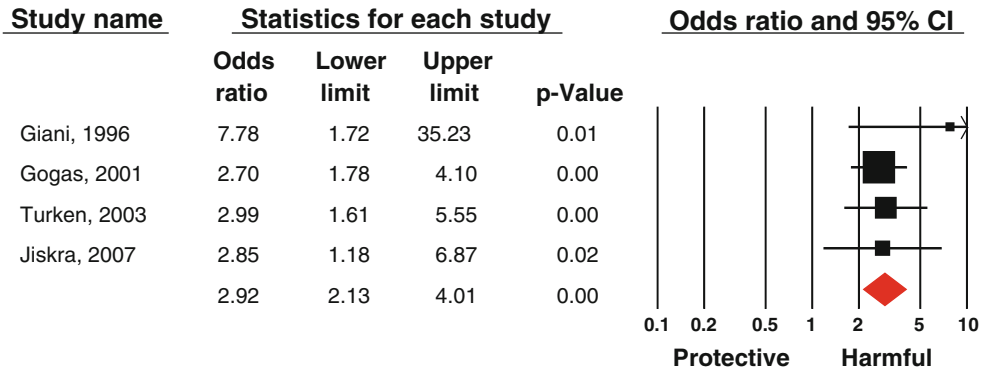


**Fig. 2** Autoimmune thyroiditis and breast cancer risk

($I^2 = 0\%$, $p = 0.15$) and, with a failsafe ($n$) of 41 ($p = 0.15$), there was no evidence of publication bias.

## Presence of anti-TPO, anti-TG or microsomal antibodies

Eight studies were found investigating the link between thyroid antibody presence and the risk of BC. Six of the eight studies reported a significant increase in the risk of BC. However, two studies [7, 19] reported an increased risk point estimate despite non-significant results (Fig. 3). All eight studies met the inclusion criteria, resulting in a pooled OR 2.02 (95% CI 1.63–2.50). Heterogeneity was moderate ($I^2 = 58.3$) and significant ($p = 0.08$).

We performed a subgroup analysis investigating the risk specific antibodies (anti-TG and anti-TPO) have on the development of BC. Five studies were identified investigating anti-TPO presence, with all studies meeting the inclusion criteria. Four studies supported an increased risk [2, 4, 29, 30], while one study found no significant results in its cohort study, and significant results in the cross-sectional study [7]. Anti-TPO was associated with an increased risk (2.64, 95% CI 1.82–3.83) in the pooled odds ratio. Minimal heterogeneity was present ($I^2 = 29.34$, $p = .22$) and, with a failsafe number of 56, publication bias was unlikely.

We identified four studies investigating anti-Tg presence and the associated risk of BC. Three studies showed an increases risk of BC with anti-Tg presence [4, 29, 31], while one study was not significant despite a protective risk point estimate [2]. Overall, an increased risk of BC was found (OR 2.72, 95% CI 1.58–4.69) further supporting the autoimmune link. Minimal heterogeneity was present ($I^2 = 18.10$, $p = 0.30$) and there was no evidence of publication bias ($n = 15$, $p = 0.17$).

## Goitre

We found 13 studies investigating the link between goitre and BC. Eight studies were excluded for failing to meet the

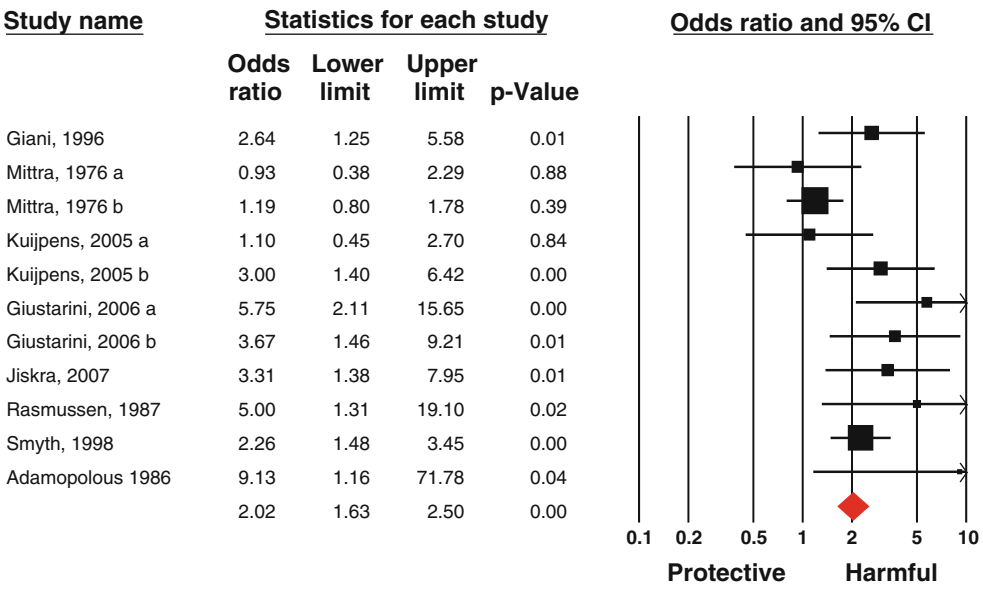


**Fig. 3** Antibody and BC risk. Kuijpens a = cohort, Kuijpens b = cross section, Guistarini a = anti-TPO antibodies, Giustarini b = anti-TG antibodies, Mittra a = Japanese population, Mittra b = British population

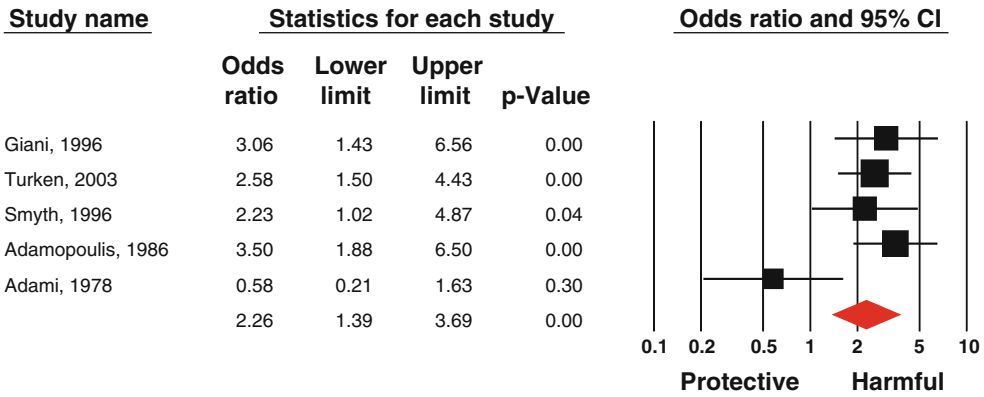


**Fig. 4** Goitre and BC risk

inclusion criteria, predominantly due to a reliance on self-reporting without confirming either the initial diagnosis or the type of goitre present [21, 32–34]. Two studies were excluded for failing to include an internal control group [35–37] and one study was excluded for investigating mortality rather than incidence [38].

The remaining five studies were included in the meta-analysis. Four of the five studies were homogenous in their findings of an increased risk of BC [2, 11–13], while one study found no evidence of a relationship [9] (Fig. 4). The goitre was diagnosed by clinical examination alone in one study [12], by clinical examination confirmed by ultrasound in three studies [2, 11, 13] and by self-reporting with confirmation from the medical record in the final study [9]. The pooled OR demonstrated an increased risk associated with goitre, evident in an OR of 2.26 (95% CI 1.39–3.69). Moderate and significant heterogeneity was present ($I^2 = 56.52$, $p = 0.06$) despite no evidence of publication bias ($n = 28$, $p = 0.15$).

We performed a subgroup analysis investigating the effect diffuse and nodular goitres have on the risk of BC. Of the five studies investigating goitre, three studies presented data on diffuse goitre [3, 12, 13]. The studies were homogenous in reporting a significantly increased risk of BC. This increased risk was confirmed in a pooled OR 2.84 (95% CI 1.53–5.27) and the absence of heterogeneity ($I^2 = 0$, $p = 0.72$).

The presence of nodular goitre was also associated with BC. Five studies provided data investigating BC risk and nodular goitre [2, 3, 12, 13, 28]; four studies were homogenous in their support of an increased risk [2, 3, 13, 28]; while one study found non-significant results [12]. The pooled OR supported an increased risk (OR 3.77, 95% CI 2.30–6.17) with moderate and significant heterogeneity ($I^2 = 62.6$, $p = 0.03$).

## Hypothyroidism

The database search identified 15 studies investigating hypothyroidism and BC. Nine studies failed to meet the inclusion criteria due the absence of a control group

[39, 40], use of mortality as primary outcome [38] or failure to confirm the benign thyroid diagnosis [25, 32–34, 41, 42].

The remaining six studies were included in the meta-analysis. There was a degree of heterogeneity in the results with two studies reporting an increased risk [7, 8], with one study finding hypothyroidism to be protective [6] and three studies finding no connection between the two [9–11]. The quantitative synthesis did not support a relationship between hypothyroidism and BC evident in a non-significant pooled OR 1.79 (95% CI 0.65–4.97) and high heterogeneity ($I^2 = 85.43$, $p = 0.001$). Publication bias was significant ($n = 0$, $p = 0.04$,).

### Hyperthyroidism

13 studies investigating the risk of BC associated with hyperthyroidism were identified in our literature search. Nine studies were excluded for failing to meet the inclusion criteria: six for failing to confirm the thyroid diagnosis [25, 32–34, 41, 42]; two for the absence of an internal control group [23, 40] and one for the investigation of mortality rather than incidence [26].

The remaining four studies were included in the meta-analysis. The four studies were homogenous in their finding of no relationship between hyperthyroidism and BC [8, 9, 11, 13]. This was confirmed in a non-significant pooled OR 1.53 (95% CI 0.77–3.04) devoid of heterogeneity ($I^2 = 0$, $p = 0.59$). Publication bias was not significant ($p = 0.32$).

### Graves disease

The database search identified four studies investigating the association between Graves disease and BC [2, 10, 21, 43]. Three of the four studies failed to meet the inclusion criteria: two for failing to include an internal control group [10, 43] and one for failing to confirm the diagnosis of Graves disease [21]. The only remaining study did not find a relationship between Grave's disease and BC [2].

### Non-specific thyroid disease

Studies that investigated benign thyroid disease as a whole, without subclassification, were identified and collated to calculate a pooled OR. 14 studies were included in the meta-analysis [2, 10, 21, 32–34, 42, 44–50] resulting in an OR 1.28 (95% CI 1.08–1.53). Heterogeneity was high ($I^2 = 80$) and significant ($p = 0.001$).

## Discussion

The ORs associated with AITD, goitre and anti-thyroid antibody support the increased risk of BC associated with thyroid auto-immunity. This finding is a direct contradiction to the findings of Sarlis et al. [1]. Our study differed from the study of Sarlis in two major areas: (1) the inclusion of eight recently published studies and (2) the use of more specific inclusion criteria in regards to the diagnosis of AITD.

We did not consider nodular goitre, antibody presence or reduced thyroid function alone to be indicative of AITD. Instead, our inclusion criteria required a combination of two or more clinical parameters in confirming the diagnosis. In addition, we considered the presence of a diffuse goitre more indicative than nodular in the diagnosis of AITD [51]. At the time of diagnosis AITD is typically associated with hypothyroidism. Interestingly, our results did not demonstrate an increased risk of BC associated with hypothyroidism. A possible explanation for these findings lies in our inability to differentiate between primary hypothyroidism and iatrogenic hypothyroidism secondary to the treatment of thyrotoxicosis.

Sandhu et al. [20] published one study of note excluded from our meta-analysis. Despite its large population size ($n = 178{,}186$) the study did not meet our inclusion criteria. The study relied on the linking of a pharmaceutical database with a BC registry to identify BC patients who had previously been prescribed thyroxin. A diagnosis of AITD in this population was assumed without confirmation. This failure to confirm the diagnosis using conventional methods led to its exclusion from our study.

The increased risk associated with both diffuse and nodular goitre has proven difficult to interpret. While diffuse goitre fits in with the autoimmune model, mechanisms linking nodular goitre to BC are unknown. We cannot exclude the possibility that the increased screening and follow-up treatment of BC patients has resulted in an increase in the detection of thyroid dysfunction.

The lack of longitudinal studies forms the basis of the main limitation in our analysis. The majority of studies investigating thyroid autoimmunity were cross-sectional in their study design. Furthermore, the few longitudinal studies were predominantly large population studies with poor differentiation between types of benign thyroid disease and a reliance on self-reporting. Thus, despite demonstrating a relationship between BC and thyroid autoimmunity, we are unable to definitively prove causality.

Strengths of this study include a broad literature search, no restrictions on language and the use of precise inclusion criteria. A comprehensive database search was undertaken with no restrictions on language in place. Furthermore, the use of specific diagnostic criteria in defining the type of thyroid disease and the requirement for an internal control group improved the quality of our quantitative analysis.

Our results have demonstrated a strong relationship between thyroid autoimmunity and BC. These results have

implications in not only screening but also the development of new prognostic markers and treatment regimes. Recent studies in BC have shown significantly better prognosis associated with the presence of thyroid antibodies. Smyth et al. [30] found the presence of thyroid antibodies to be as relevant as tumour size and lymph node involvement in predicting disease free and overall survival [30]. Cengez et al. [45], however, did not confirm this finding in a study published in 2004.

While exact mechanisms linking benign thyroid disease and BC have not yet been identified, a number of hypotheses have been suggested. The presence of the NIS in both breast and thyroid tissue led to the hypothesis that the uptake and oxidation of iodine may play a role in the development of BC [52]. Tazebay et al. [53] found increased expression of the NIS in BC tissue when compared to surrounding breast tissue and tissue from healthy, non-lactating controls. The presence of the NIS in breast tissue also has implications in the development of future therapies. The up-regulation of the NIS in BC may allow use of radioiodine to specifically target carcinogenic cells [14]. This model has been investigated in prostate cancer cell lines with a significant reduction in tumour size achieved [54]. While research into extra thyroidal use of radioiodine therapy is only in the early stages, it has been used extensively and successfully in the treatment of thyroid cancer and thyrotoxicosis.

A reversal in the relationship with BC acting as a predisposing factor to the development of thyroid disease is an alternate theory into the mechanism linking the two diseases. Oestrogen receptors have been identified in the cytosol of abnormal thyroid tissue while receptors were not present in normal tissue [16, 17]. Receptors for progesterone were also found exclusively in thyroid tissue containing either neoplastic or benign lesions. Despite the majority of studies focusing on thyroid disease as the predisposing factor, we cannot exclude a reversal in the relationship with the oestrogen profile associated with BC triggering thyroid dysfunction.

## Conclusions

We have confirmed a relationship between AITD and BC. In addition, we found increased risk associated with a diagnosis of goitre or the presence of serum thyroid autoantibodies. We recommend further high-quality prospective studies to prove causality in addition to ongoing investigations into the prognostic and therapeutic benefits of a relationship between benign thyroid disease and BC.

**Conflict of interest** The authors declare that they have no competing interests.

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