REVIEW

MECHANISMS IN ENDOCRINOLOGY

Primary HT and risk for breast cancer: a systematic review and meta-analysis

Anna G Angelousi, Valsamo K Anagnostou¹, Michael K Stamatakos², Georgios A Georgiopoulos³ and Konstantinos C Kontzoglou⁴

Department of Endocrinology, University Hospital of Nancy, 13 Rue de Stanislas, Nancy 54000, France, ¹Department of Internal Medicine, Yale New Haven Hospital, New Haven, Connecticut, USA, ²Department of Surgery, Athinaion Hospital, Athens, Greece, ³Vascular Laboratory, Department of Therapeutics, Alexandra Hospital, Athens University Medical School, Athens, Greece and ⁴2nd Department of Surgery, Athens Medical School, Laiko Hospital, Athens, Greece

(Correspondence should be addressed to A G Angelousi; Email: a.angelousi@gmail.com)

Abstract

Objective: The association between hypothyroidism and breast cancer has been described from very early on. Breast and thyroid tissue are interconnected on a molecular level mainly through activation of thyroid hormone receptors expressed on cells of the mammary gland as well as on the plasma membrane of breast cancer cells. Despite the experimental evidence the true value of hypothyroidism as a risk factor for breast cancer remains controversial.

Methods: We searched the PubMed database through February 2011 to identify studies that evaluated the association between hypothyroidism and risk for breast cancer as well as the effect of thyroid hormone replacement therapy on breast cancer incidence.

Results: A meta-analysis performed in 12 studies showed that hypothyroidism was not associated with risk for breast cancer (pooled risk ratio (RR)=1.06, 95% confidence intervals (CIs) 0.82–1.35, $P=0.672$). The effect of treatment was assessed in seven studies and no evidence for an association between thyroid hormone replacement and breast cancer was observed with an overall RR of 0.99 (95% CI 0.73–1.35, $P=0.965$).

Conclusions: Our meta-analysis showed that hypothyroidism is not associated with increased risk for breast cancer and thyroid hormone replacement therapy does not reduce breast cancer prevalence; however, the heterogeneity of the studies analyzed precludes firm conclusions.

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Introduction

Breast cancer is the most common type of cancer in women with a cumulative incidence of 182 460 new cases per year in the United States, 45 822 in the United Kingdom, and 21 200 in Canada (1, 2, 3). The association between breast cancer and thyroid gland function has been reported as early as 1896 when Beatson used thyroid extract as a potent treatment for breast cancer (4). In the 1950s, Loeser and Ellerker reported that breast cancer rarely occurred in hyperthyroid women whereas more frequently than expected in hypothyroid women (5, 6). Multiple studies have shown that hyperthyroidism may be protective against breast cancer (7, 8), while other studies have reported a strong relationship between antithyroid peroxidase autoantibodies (TPO Abs) with the risk for breast cancer (9, 10, 11).

The thyroid gland and the mammary gland share common physiology; both thyroid follicular and lactating breast cells store iodine by a membrane active transport

mechanism known as sodium–iodide symporter (NIS) mediated iodine uptake (11, 12, 13, 14, 15, 16, 17, 18) and iodine oxidation in the alveolar mammary cells is carried out by lactoperoxidase, which is immunologically similar to the thyroid gland's peroxidase (16). The crosstalk between the thyroid and the mammary gland mainly involves the triiodothyronine (T_3) pathway, and activation of thyroid hormone receptors (TR) of the mammary gland induces differentiation and lobular growth in an estrogen-like manner (19, 20).

Furthermore, iodine has been shown to play an antioxidant role and thus inhibit breast cancer progression (11, 17, 18). Overexpression of NIS has been found in malignant breast cells leading to an increased iodine uptake in the mammary gland, playing a protective role for malignant transformation (11). TR gene transcription deregulation has been implicated in breast carcinogenesis (19) and TR- α receptors have been shown to translocate from the nucleus to the cytoplasm of breast cancer cells, suggesting a possible role in the histological changes of the epithelium during

carcinogenesis (20). It has been shown that hypothyroidism may result in hypersensitization of the mammary glandular epithelium to prolactin and estrogen, thus promoting breast cancer growth (21). Moreover, estrogens as well as pregnancy increase thyroxine-binding globulin concentration that in turns increases serum concentration of total thyroxine (T_4), with a transient reduction of free T_4 , and an increase of thyrotropin (TSH) (22, 23).

Despite the promising nature of experimental data, hypothyroidism has been investigated as a potential predictor for breast cancer risk with conflicting results (18, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34). In this systematic review and meta-analysis we sought to determine the association between hypothyroidism and breast cancer as well as the role of standard replacement therapy in modifying the incidence of breast cancer.

Materials and methods

Data source and search strategy

We searched the PubMed database on February 20, 2011 to identify studies that evaluated the association of hypothyroidism and breast cancer using the following algorithm: ((hypothyroidism) OR (thyroid dysfunction) OR (thyroid)) AND ((breast cancer) OR (breast neoplasm) OR (breast carcinoma) OR (breast tumor)).

Our search was restricted to English and French literature. One reviewer (A G Angelousi) reviewed the title and abstract to identify studies likely to report associations between hypothyroidism and breast cancer and subsequently obtained the full texts. Additional relevant publications were identified from references of the initially retrieved articles.

Study selection

The selection of the eligible studies for inclusion in the review was based on the following criteria: retrospective or prospective cohort design or case-control studies with clearly defined source population, clear statement of primary hypothyroidism, statistical methodology including univariate or multivariate analysis and reporting of the resultant odd ratios (ORs) and their 95% confidence intervals (CIs). We excluded case reports, reviews, commentaries, letters, studies which studied drug-induced hypothyroidism as well as studies assessing thyroid dysfunction based on thyroid hormones measurement in women with breast disease with no previous history of hypothyroidism (Fig. 1).

Data extraction and quality assessment

Two investigators (A G Angelousi and V K Anagnostou) reviewed independently each eligible manuscript and

extracted data on general characteristics of the study including first author's name, institution and country of origin, year of publication, study design, sample size, demographics (age, ethnicity, menopausal status, parity, family history of breast cancer, and hormone replacement treatment), and follow-up period (Table 1). The primary outcome of the meta-analysis concerned the association between hypothyroidism and the breast cancer risk; the association between thyroid hormone replacement therapy and the risk for breast cancer was analyzed as a secondary endpoint. The compared groups, the clinical covariates incorporated in multivariable analysis and the outcomes studied are presented in Table 2.

Data synthesis and statistical analysis

Effect sizes and 95% CIs were estimated by pooling available data using the STATA (StataCorp, Texas, USA) version 10 Software (35). The heterogeneity among studies was analysed by using the Random effects meta-analysis of Der Simonian and Laird's method. ORs were presented as point estimates with 95% CI. An observed OR of more than 1 implied a higher risk for the test group relative to the reference group and was considered statistically significant if the 95% CI did not overlap with 1 ($P < 0.05$). Inter-study heterogeneity was assessed using the I^2 index (37).

This systematic review followed the Meta-analysis Of Observational Studies in Epidemiology guidelines for reporting meta-analyses of observational studies (38).

Figure 1 Flow diagram showing the selection process for the studies included in the meta-analysis.

Table 1 Demographic characteristic of the included populations.

References	Country	Study type	Follow-up or period during which cases were diagnosed	Total population	Age (mean $\pm$ S.D., or median (range)), years	Caucasian/ African/ Hispanic	Premen./ postmen.	Family history BC+/no family history BC	Parity +/no parity	Estrogen use +/ no estrogen use
(34)	Germany	Case-control	ND	143	ND	143/0/0	ND	ND	ND	ND
(18)	Canada	Cohort	Apr 1993–Dec 2003	179 462	74.9 $\pm$ 7	ND	0/179 462	ND	ND	1236/178 266
(33)	Netherlands	Cohort	1994–Jul 2003	2738	ND	2738/0/0	0/2738	350/2425	2157/618	2108/667
(32)	USA	Case-control	Jan 1997–Dec 2000	2224	51.6 $\pm$ 12.6	1714/245/165	803/1416	447/1707	1805/276	853/2194
(31)	USA	Case-control	Jul 1994–Apr 1998	9257	ND	5974/3283	4177/3953	1231/7666	4213/1695	3666/5586
(29)	Ireland	Case-control	ND	350	ND	ND	ND	ND	ND	ND
(30)	Ireland	Case-control	1988–1989	878 ^a	(57) vs (52); (36) vs (34)	ND	ND	ND	ND	ND
(28)	USA	Case-control	1925–1980	1039	(46.7)	ND	ND	ND	ND	ND
(27)	USA	Case-control	Jul 1973–May 1977	2612	ND	ND	ND	323/1523	ND	ND
(26)	UK	Case-control	Dec 1969–Sept 1980	2352	ND	ND	ND	ND	ND	ND
(25)	Sweden	Case-control	Oct 1975–Mar 1976	358	(64)	ND	ND	ND	ND	ND
(24)	USA	Case-control	Mar 1974–Dec 1974	5505	ND	ND	4533/971	ND	ND	ND

ND, no data; BC, breast cancer; Netherlands, The Netherlands; premen., premenopausal; postmen., postmenopausal.

^a200 women with breast cancer vs 200 controls and 354 women with benign breast disease vs 124 controls.

Results

Identified studies

A total of 2623 studies were retrieved: of these, 499 studies were selected for further evaluation. Studies evaluating thyroid dysfunction without separate analysis for hypothyroidism ($n=153$) and studies assessing thyroid dysfunction in terms of thyroid hormone serum levels in women with breast cancer without history of hypothyroidism ($n=333$) were excluded (Fig. 1).

Of the remaining 13 studies, one was excluded (7) as it was a sub-analysis of a larger study that met the inclusion criteria (28). Finally, 12 studies comprising cohort studies (18, 33), and ten case-control studies (24, 25, 26, 27, 28, 29, 30, 31, 32, 34) were selected for further analysis.

Patient demographics

Clinical characteristics incorporated in the studies included age, ethnicity, menopausal status, family history, parity, and prior hormone replacement therapy; patient characteristics are summarized in Table 1.

Four studies presented data about the ethnicity of their included population which was largely represented by Caucasian people (31, 32, 33, 34). The total population was represented by 9513 premenopausal vs 188 577 postmenopausal women – data available in five studies (18, 24, 31, 32, 33), and by 13 321 women without family history vs 2351 women with family history of breast cancer – data available in four studies (27, 31, 32, 33).

Estrogen replacement therapy was reported in four studies accounting for 4519 women that received hormone replacement therapy and 186 673 that did not (18, 31, 32, 33). Of note, in three of the above-mentioned studies hormone replacement treatment was significantly more frequent among the breast cancer group compared with controls (31, 32, 33).

Effective sample size ranged from 61 to 89 731 (total 97 477), with six studies including <200 patients (25, 28, 29, 30, 33, 34), four studies including 200–1500 individuals (24, 26, 27, 32), one including 4575 (31), and one including 89 731 individuals (18).

Studied outcome

Ten studies (18, 24, 25, 26, 27, 29, 30, 31, 32, 34) analyzed the incidence of hypothyroidism in women with breast cancer compared with matched healthy controls or women with benign breast disease (30, 34). Additional studied parameters included the breast cancer-specific mortality among women with treated vs untreated hypothyroidism (28), the ORs for the association between self-reported hypothyroidism (treated and untreated) and breast cancer (33) and

Table 2 Characteristics of the comparison groups and studied outcomes.

Refer- ences	Characteristics of population: n, disease	Compared groups		Studied parameters	Results		
		Case group (cancer) or (HT)	Control group (non- cancer) or (no HT)		Comparison of 'prevalence' or incidence of HT or BC between compared groups	Univariate analysis: statistical significance ORs (95% CI), <i>P</i>	Multivariate analysis: statistical significance ORs (95% CI), <i>P</i>
(34)	105 women with breast disease (65 with BC, 13 <i>in situ</i> , and 27 with benign breast disease)	65	78 (13 <i>in situ</i> , 27 with benign breast disease, and 38 healthy)	Prevalence of history of HT	7/65 (10%) vs 0/13, 5/27 (18.5%) and 3/38 (7.9%)	NS	ND
(18)	89 731 women with autoimmune HT	89 731	89 731	Incidence of BC (HRs)	1493/89 731 (1.7%) vs 1518/89 731 (1.64%)	HR=0.99 (0.92–1.07), <i>P</i> =0.8	HR ^a =0.99 (0.92–1.07), <i>P</i> =0.75
(33)	61 women with BC	61		Mortality among women with BC	ND	HR=0.87 (0.77–0.98), <i>P</i> <0.02	HR ^a =0.87 (0.77–0.98), <i>P</i> <0.02
				ORs for the association between self-reported HT (treated and untreated) and BC	ND	OR=3.8 (1.3–10.9), <i>P</i> =ND	OR ^b (for women with self-reported HT) =4.1 (1.4–12)
				ORs for thyroid medication and BC		OR=3.2 (1.0–10.7)	
(32)	1136 women with primary newly diagnosed BC	1136	1088	Prevalence of history of primary treated HT and ORs	80/1136 (7.0%) vs 162/1088 (14.9%)	OR=0.43 (0.33–0.57) <i>P</i> <0.001	OR ^c =0.44 (0.32–0.60), <i>P</i> <0.001
(31)	4575 women with newly diagnosed invasive BC	4575	4682	Prevalence of history of HT (treated and untreated) and ORs	465/4575 (10.2%) vs 530/4682 (11.3%)	NS	OR ^d =0.9 (0.8–1.02), <i>P</i> =NS
(29)	150 women with BC	150	200	Prevalence of history of HT	174/4502 (3.8%) vs 184/4604 (3.9%)	NS	NP
(30)	200 women with BC stage T0 (non palpable); T1 (<2.0 cm); T2 (2.0–5.0 cm); T3–T4 (>5.0 cm); 33	200	200	Prevalence of history of HT	5/150 (3.3%) vs 2/200 (1%)	NS	NP
(28)	157 deaths of women with history of HT	157	193	Prevalence of death from BC	6/157 (3.8%) vs 6/193 (3.1%)	NS	NP
(27)	1362 women with BC	1362	1250	Prevalence of history of non-treated HT and RRs	1/1362 (0.07%) vs 4/1250 (0.32%)	RR=0.23 (0.0–0.7), <i>P</i> =ND	RR ^e (for women with a history of HT (treated and untreated))=1.0 (0.8–1.2), <i>P</i> =ND
(26)	1176 women with newly diagnosed BC	1176	1176	Prevalence of history of treated HT and RRs	219/1362 (16%) vs 191/1250 (15.2%)	RR=1.04 (0.8–1.3), <i>P</i> =ND	NP
				Prevalence of history of HT	8/1176 (0.7%) vs 10/1176 (0.9%)	NS, <i>P</i> =ND	NP

Table 2 Continued

Compared groups				Results			
Refer- ences	Characteristics of population: <i>n</i> , disease	Case group (cancer) or (HT)	Control group (non- cancer) or (no HT)	Studied parameters	Comparison of	Multivariate analysis: statistical significance ORs (95% CI), <i>P</i>	
					'prevalence' or incidence of HT or BC between compared groups		
(25)	179 women with BC	179	179	Prevalence of history of treated HT	2/179 (1.1%) vs 2/179 (1.1%)	NS, <i>P</i> =ND	Correlation coefficient TSH 0.044, <i>T</i> ₃ − 0.091, <i>rT</i> ₃ −0.040, <i>T</i> ₄ −0.034 for age tumor diameter and TNM
(24)	635 women with treated HT	635	4870	Prevalence of BC	77/635 (12%) vs 303/4870 (6.2%)	<i>P</i> <0.005	NP

BC, breast cancer; HT, hypothyroidism; *n*, number; HR, hazard ratios; ORs, odd ratios; ND, no data; NS, non-significant; RR, relative risk; SMR (standardized mortality ratios, (95% CI)): observed/expected death from breast cancer; SIR, standardized incidence ratio: observed/expected cases; NP, not performed.

^aMultivariate analysis adjusting for income quintile, number of hospital visits, number of primary care visits, number of specialist visits, urban residence, and Charlson score.

^bMultivariate analysis adjusting for alcohol use, smoking, parity > 1, estrogen use, menarche, and positive family history for breast cancer.

^cMultivariate analysis adjusting for family history of breast carcinoma, history of pregnancy, menopausal status, age, and hormone replacement treatment (OR (95% CI): 0.44 (0.32–0.60)).

^dMultivariate analysis adjusted for age, ethnicity and study setting.

^eMultivariate analysis adjusted for age of first use of thyroid supplements, years of use, years since initial use, and last use, age of menarche, weight parity status, family history of breast cancer, or benign breast disease.

BC, breast cancer; HT, hypothyroidism; n, number; HR, hazard ratios; ORs, odds ratios; ND, no data; NS, non-significant; RR, relative risk; SMR (standardized mortality ratios, (95% CI)): observed/expected death from breast cancer; SIR, standardized incidence ratio: observed/expected cases; NP, not performed.

^aMultivariate analysis adjusting for income quintile, number of hospital visits, number of primary care visits, number of specialist visits, urban residence, and Charlson score.

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^cMultivariate analysis adjusting for family history of breast carcinoma, history of pregnancy, menopausal status, age, and hormone replacement treatment (OR (95% CI): 0.44 (0.32–0.60)).

^dMultivariate analysis adjusted for age, ethnicity and study setting.

^eMultivariate analysis adjusted for age of first use of thyroid supplements, years of use, age of menarche, weight parity status, family history of breast cancer, or benign breast disease.

also the survival outcomes for breast cancer in women with hypothyroidism (18) as they presented in Table 2.

Key question 1: does hypothyroidism increase the risk for breast cancer? Eight (18, 25, 26, 28, 29, 30, 31, 34) studies showed that there is no significant association between primary hypothyroidism and breast cancer. Two of those studies (18, 31) incorporated multivariate analysis adjusting for clinical characteristics. Four studies (24, 27, 32, 33) identified a significant association between hypothyroidism and breast cancer in univariate analysis that was subsequently confirmed by multivariate analysis in three of them (27, 32, 33). Interestingly, one study (33) showed that hypothyroidism was significantly associated with an increased risk for breast cancer as opposed to another study (32) that demonstrated that primary hypothyroidism was a strong protective factor against breast cancer after adjusting for clinical parameters including thyroid hormone replacement therapy. In one study (27), the untreated hypothyroidism was correlated with a significantly lower risk for breast cancer although the incidence of treated hypothyroidism was similar between the women with breast cancer and the women with no breast disease.

Our meta-analysis incorporated all 12 studies; pooled overall risk ratios are shown in Fig. 2. There was a 6% increase in risk for breast cancer among women with primary hypothyroidism (RR 1.06, 95% CI 0.82–1.35, $P=0.672$); however, the effect did not reach statistical significance due to study heterogeneity. I^2 values were calculated to quantify heterogeneity between studies, an I^2 value of 85.2% ($P<0.001$) indicated high inter-study heterogeneity. We found no publication bias as indicated by Egger ($P=0.642$) and Harbord ($P=0.771$) tests (Fig. 3).

We subsequently conducted two separate analyses stratifying patients by country of origin. In the European group (including six studies with a total population of 6819, of which 1831 women had breast cancer), a trend toward a significant association between hypothyroidism and higher risk for breast cancer was observed (pooled risk ratio=1.46, 95% CI 0.91–2.34, $P=0.12$). I^2 was 8% indicating low inter-study heterogeneity ($P=0.365$). In the US and Canada groups (including six studies with a total population of 200 099, from which 7073 women had breast cancer and 90 523 women had hypothyroidism) no association was identified between hypothyroidism and breast cancer (pooled risk ratio=0.97, 95% CI 0.73–1.29, $P=0.837$); a high inter-study heterogeneity was observed (I^2 92.4%, $P<0.001$).

Key question 2: does thyroid hormone replacement therapy affect the risk for breast cancer? Seven studies assessed the association between thyroid hormone replacement treatment and breast cancer

Figure 2 Forest plot. Overall risk ratio for breast cancer in women with primary hypothyroidism in a meta-analysis of 12 studies and separate risk ratios for European studies and USA/Canada studies (subtotal effect size). A fixed effects meta-analysis (Mantel-Haenszel method) was performed in the European studies and a random effects meta-analysis in the USA/Canada studies.

risk (18, 24, 25, 27, 31, 32, 34). Of those, five studies failed to identify a difference in risk for breast cancer among women that received thyroid hormone replacement (18, 24, 25, 27, 31). One study (34) showed that women who received thyroid hormone replacement treatment were at higher risk for breast cancer; however, results might have been confounded by absence of appropriate matching between the breast cancer and control groups. These findings were consistent with another study (24) that demonstrated that women with treated hypothyroidism had significantly increased risk for breast cancer compared with healthy controls.

We conducted a separate meta-analysis of these seven studies to identify the effect of thyroid replacement therapy on breast cancer risk (18, 24, 25, 27, 31, 32, 34). No statistically significant association between thyroid hormone replacement treatment and breast cancer risk was found (overall pooled risk ratio=0.99, 95% CI 0.73–1.35, $P=0.965$); however, high inter-study heterogeneity was observed ($I^2=90.7\%$, $P<0.001$). We found no publication bias as indicated by Egger ($P=0.979$) and Harbord ($P=0.910$) tests. Results are summarized in Figs 4 and 5.

Discussion

Our meta-analysis failed to show a statistically significant association between hypothyroidism and risk for breast cancer with a significant heterogeneity observed among studies. Subgroup analysis by country of origin revealed a trend toward increased risk for breast cancer in hypothyroid women in the

European group. Of note, inter-study heterogeneity in the meta-analysis of the six studies of the European group was minimal. We subsequently investigated the potential of thyroid hormone replacement treatment in modifying the risk for breast cancer; the meta-analysis on seven eligible studies failed to reveal a statistically significant effect.

Our findings are not in keeping with a large volume of experimental studies that suggest a strong association between hypothyroidism and breast cancer. Use of elemental iodine (I_2) has been shown to result in a significant reduction of the growth and number of mammary tumors in experimental animals (17, 39, 40). Interestingly, altered expression of the TRb and TRa genes that encode the TRs has been observed in breast cancer patients suggesting that deregulation of thyroid hormone target genes may be involved in breast carcinogenesis (41).

We observed a high inter-study heterogeneity: study design, retrospective nature, and control study group mismatch are major factors that account for the discrepancies seen since the diagnosis of hypothyroidism and replacement treatment specifics were based on patient recall or medical archives, increasing the possibility of misclassification bias. Another contributing factor to the high overall inter-study heterogeneity is the lack of multivariate analysis in seven of the 12 studies (18, 24, 26, 28, 29, 30, 34), as well as the variability of clinical parameters used for adjustment in those studies that performed multivariate analysis. The use of estrogen treatment – a well-known risk factor for breast cancer – was included in a multivariate analysis in only two studies (32, 33), as well as the adjustment for family history of breast cancer which was performed in three studies (31, 32, 33).

Figure 3 Funnel plot for publication bias of the meta-analysis studying the association of primary hypothyroidism with the risk for breast cancer. Egger (P value=0.642) and Harbord (P value=0.771) tests revealed no publication bias.

Figure 4 Forest plot. Overall risk ratio for breast cancer in women with thyroid replacement treatment in a meta-analysis of seven studies.

Moreover, few studies incorporated breast cancer stage in subsequent analysis; this is an important limitation since patients with more indolent *in situ* disease are grouped together with invasive breast cancer. In particular, five studies included data on breast cancer staging (25, 30, 32, 33, 34). One of them (32) found that women with primary hypothyroidism were more likely to have localized disease (95.0 vs 85.9% clinical T1 or T2 disease, respectively, $P=0.02$) and no lymph node involvement (62.8 vs 54.4%, $P=0.15$) compared with euthyroid women. These findings were not consistent with the study of Ditsch *et al.* (34) which observed that the history of hypothyroidism was more frequent although not statistically different in women with breast cancer compared with patients with Tis stage and benign breast disease. Three studies evaluated the association of thyroid hormones circulating levels or thyroid volume with stage at the time of diagnosis independent of the history of hypothyroidism (25, 30, 33).

To minimize heterogeneity we performed subgroup analysis by country of origin, which revealed a marginal association between hypothyroidism and increased risk for breast cancer in the European group compared with the USA and Canada group. To note that the two groups differ significantly in sample size, with a total population of 6819 vs 200 099 for the European and the US groups respectively, in the number of women with treated hypothyroidism (11 vs 2042 for the European and the US groups respectively) as well as in the performance of the multivariate analysis (one study (33) vs four studies (18, 27, 31, 32) performed multivariate analysis in the European and the US groups respectively). Additional meta-regression analysis and comparison of demographics (ethnicity, family history of breast cancer, parity, estrogen replacement treatment, and menopausal status) between the two groups was not feasible since relevant data were not available.

Interestingly, the high inter-study heterogeneity observed was largely caused by two studies (24, 32);

when these studies were excluded overall heterogeneity was minimized (data not shown). One of them (32) was the only study reporting a statistically significant protective role for hypothyroidism with an objective risk for breast cancer of 0.43; these findings were not replicated in subsequent trials. With respect to the other study (24), the generalizability of its results may be limited by inappropriate matching of the compared groups since the control group (women with no thyroid disease and no thyroid treatment) largely consists of premenopausal (4533 vs 971) and nulliparous women (4349 nulliparous vs 1156 parous) compared with the hypothyroid group.

In this meta-analysis we did not manage to study separately the association of autoimmune hypothyroidism with the risk for breast cancer although it is largely presented in the literature (9, 10, 11, 15) due to the lack of information concerning the thyroid function of the patients with known Hashimoto's thyroiditis or positive TPO Abs. However, it is worth presenting that two of the studies (29, 33) included in the meta-analysis showed that the presence of high levels of TPO Abs were related to an increased risk for breast cancer although in one of them (33) this relationship was not confirmed in the follow-up. To the contrary, three other included studies (18, 31, 34) found no association between autoimmune hypothyroidism (18) or Hashimoto's thyroiditis (31) or high levels of TPO Abs (34) with the risk for breast cancer. To note that in one study (28), women with Hashimoto's thyroiditis who died from breast cancer had the lowest percent of deaths due to breast cancer in the group with thyroid diseases with no further statistical analysis.

Lastly, our meta-analysis failed to demonstrate a statistically significant role of thyroid hormone replacement therapy in modifying the risk for breast cancer. This finding is in agreement with previous studies (18, 40, 42, 43) showing that thyroid hormone replacement therapy did not affect the risk for breast cancer.

Figure 5 Funnel plot. Publication bias of the meta-analysis of studies presented the association between thyroid hormone replacement treatment and the risk for breast cancer. Egger (P value = 0.979) and Harbord (P value = 0.91) tests reveal no publication bias.

Conclusions

Our meta-analysis failed to demonstrate an association between hypothyroidism and risk for breast cancer; our study was limited by significant inter-study heterogeneity introduced by retrospective study design, inappropriately matched control groups, and absence of multivariate analysis in the majority of studies analyzed. Yet, we can equally postulate that hypothyroid women receiving replacement therapy might benefit from tighter health control and lifestyle modifications that could result in early diagnosis and diminution in risk of breast cancer. Thus, we believe that larger prospective studies should be performed in hypothyroid women to clarify a potential association between hypothyroidism and breast cancer.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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Author contribution statement

A G Angelousi had the editorship of the manuscript, performed most of the statistical analysis and edited most of the manuscript. V K Anagnostou edited most of the manuscript. M K Stamatakis performed part of the literature search and edited part of the manuscript. G A Georgiopoulos edited part of the statistical analysis. K C Kontzoglou had the original idea for this article and edited part of the manuscript. All authors have read and approved the final manuscript.

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