Low levels of thyroid hormone may reduce the risk of breast cancer: evidence from a meta-analysis

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Abstract

Background: At present, the relationship between hypothyroidism and the risk of breast cancer is still inconclusive. This meta-analysis was used to systematically assess the relationship between hypothyroidism and breast cancer risk, and to assess whether thyroid hormone replacement therapy can increase breast cancer risk.

Methods: The relevant articles about hypothyroidism and the risk of breast cancer were obtained on the electronic database platform. Relevant data were extracted, and odd ratios with corresponding 95% confidence intervals(95% CI) were merged using Stata SE 12.0 software. A total of 19 related studies were included in the meta-analysis, including 6 cohort studies and 13 case-control studies.

Result: The results show that hypothyroidism can reduce the risk of breast cancer(odd ratios= 0.90, 95% CI 0.77-1.03), but in Asian populations, patients with hypothyroidism have an increased risk of breast cancer(odd ratios=1.17, 95% CI 0.98-1.35). In addition, patients who received thyroid hormone replacement therapy had a lower risk of developing breast cancer(odd ratios=0.87, 95% CI 0.65-1.09).

Conclusion: Hypothyroidism and thyroid hormone replacement therapy reduces the risk of breast cancer, suggesting that low levels of thyroid hormone may be beneficial to breast cancer prevention. Due to the limited number of studies included more large-scale, high-quality, long-term prospective cohort studies are needed.

Background

As a global public health problem, breast cancer has an increasing incidence on a global scale[1]. According to the 2017 US cancer statistics, breast cancer has become the most common malignant tumour in women, with about 250,000 new cases each year, accounting for 30% of new malignant tumours in women[2]. Therefore, the identification of risk factors for breast cancer and the adoption of effective early prevention and intervention measures are of great significance for breast cancer prevention and treatment.

The physiology and pathology of the breast are closely related to the endocrine of the body[3]. As the largest endocrine organ in the human body, the thyroid gland has specific regulation effects on various hormone levels and cell growth and development in the body, which brings new enlightenment to the research of breast cancer[4–6]. In 1976, Kapdi et al. first proposed that hypothyroidism increases the risk of breast cancer and is a risk factor for breast cancer[7]. Since then, many scholars have studied the relationship between hypothyroidism and the risk of breast cancer. However, the relationship between the two diseases remains controversial. Some studies have shown that hypothyroidism increases the risk of breast cancer[7–9]. Some studies have shown that hypothyroidism reduces the risk of breast cancer[10]. Besides, some studies have found no correlation between thyroid disease and breast cancer[11]. Therefore, whether hypothyroidism can increase the risk of breast cancer is worthy of further study.

Two meta-analyses have previously been studied for hypothyroidism and breast cancer risk[11, 12]. Based on previous research, combined with the latest research, we have included more prospective studies and Asian population studies to assess the relationship between hypothyroidism and breast cancer risk systematically. In addition to this, explore the impact of thyroid hormone replacement therapy on breast cancer risk.

Methods

Search strategy

The Meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement[13]. Relevant clinical literature was extracted by systematic retrieval of PubMed(Medline), EMBASE, Springer, Web of Science, and Cochrane Library electronic databases up to date to October 2019. Our search strategy included terms for: “thyroid dysfunction” or “hypothyroidism” or “HT” and “thyroid diseases” or “breast cancer” or “BC” or “breast neoplasms” or “mammarmy cancer” and “risk” or“incidence.” At the same time, we manually screened out the relevant potential literature in the references extracted.

Inclusion and exclusion criteria

The inclusion criteria:

(1) Types of studies: Published studies exploring the relationship between hypothyroidism and breast cancer risk;

(2) Subject: Female;

(3) Exposure factors: Primary hypothyroidism, the diagnosis needs to be based on the detection of thyroid function;

(4) Outcome indicators: the occurrence of primary breast cancer.

The exclusion criteria:

(1) Non-primary hypothyroidism due to other causes;

(2) Non observational studies;

(3) Insufficient information was provided or no full-text;

(4) Unable to obtain full text or quality assessment of the literature;

(5) Only the research with higher methodological quality is maintained for the analysis with repeated publication or data overlap.

Data extraction and Quality Assessment

Two researchers separately conducted literature screening, data extraction, and literature quality evaluation, and any differences could be resolved through discussion or a third inspector. Information secured from the enrolled literature included: first author's surname, year of publication, country of the population, sample size, follow-up time, outcome index, and corresponding OR value.

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the study from three aspects: cohort selection, cohort comparability, and outcome evaluation[14]. NOS scores of at least six were considered high-quality literature. Higher NOS scores showed higher literature quality.

Statistical analysis

All data analysis was performed using Stata12.0 software. The included OR and 95%CI were treated with the combined effect size. After that, the heterogeneity test was conducted. When $p \geq 0.05$ or $I^2 < 50\%$ was performed, it meant that there was no apparent heterogeneity, and the fixed-effect model should be applied for a merger. When $p < 0.05$ or $I^2 \geq 50\%$ indicated high heterogeneity, the random-effect model was applied. Combined effect size, if OR > 1 indicates that hypothyroidism is an unfavorable factor for breast cancer.If OR < 1 is the opposite. Begg's funnel plot was used to research publication bias detection. If OR < 0.05 indicates obvious publication bias.

Results

Process of study selection and description of qualified studies

A total of 2415 studies were identified on our online databases.After exclusion of duplicate references,129 articles were considered. After screening the abstract and title, 102 articles were excluded. After careful review of the full texts, 8 studies have been excluded because 5 of them did not provide relevant data, and 3 articles did not have full-text. 19 articles published between 1978 and 2019 met the inclusion criteria (Fig. 1).

A total of 367416 samples from 19 studies involving were enrolled in this meta-analysis[4, 8–10, 15–29]. 6 cohort studies and 13 case-control studies were included in the study. Twelve articles were studied in the European population, five in the North American population, and two in the Asian population. All articles are of high quality because of NOS score no less than 6. The chief characteristics of the enrolled materials are detailed in Table 1.

Table 1
Main characteristics of the included studies in our-analysis

Study	Year	Region	Sample	Follow-up (years)	Median (Mean)Age (years)	NOS	Study design
Hoffman	1984	Swedish	1665	21.9	47.2	8	Cohort
Kuijpens	2005	Netherlands	2775	9	50.5	8	Cohort
Sandhu	2009	Canada	179462	10	74.9 ± 7	8	Cohort
Hellevik	2009	Norwegian	29691	9	≥ 20	7	Cohort
Søgaard	2016	Danish	61873	35	71	7	Cohort
Grani	2012	Italy	380	5	59	7	Case-control
Ditsch	2010	Germany	130	NA	58.6 ± 13.5	7	Case-control
Cristofanilli	2005	USA	2224	3	51.6 ± 12.6	6	Case-control
Simon	2002	USA	9257	4	NA	6	Case-control
Talamini	1997	Italy	5157	3	55	7	Case-control
Smyth	1996	Ireland	400	1	57.2 ± 1.4	7	Case-control
Shering	1996	Ireland	350	NA	NA	7	Case-control
Moseson	1993	Canada	1101	4	54	7	Case-control
Turken	2003	Prague	250	4	63	6	Case-control
Brinton	1984	USA	2612	4	NA	7	Case-control
Kalache	1982	UK	2352	11	NA	6	Case-control
Adami	1978	Sweden	358	1	64	7	Case-control
Weng	2018	USA	103466	NA	53.3	8	Case-control

Study	Year	Region	Sample	Follow-up	Median (Mean)Age	NOS	Study design
				(years)	(years)		
Kim	2019	Korea	67416	4	≥ 40	8	Cohort

Table 2
Stratiedanalysis of the relationship between hypothyroidism and breast cancer risk.

Variable	No.of studies	OR(95%CI)	P	Heterogeneity	
				I^2	P_h
Region					
Europe	12	0.93 (0.88–0.99)	< 0.001	0	0.877
North America	5	0.86 (0.60–1.11)	< 0.001	93.8%	0
Asia	2	1.17 (0.98–1.35)	< 0.001	0	0.319
Study design					
Case-control	13	0.85 (0.62–1.09)	< 0.001	80.4%	0
Cohort	6	0.96 (0.91–1.01)	< 0.001	0	0.517
Follow-up date					
> 4	7	0.96 (0.91-1.00)	< 0.001	0	0.435
≤ 4	9	0.80 (0.54–1.70)	0.015	81.0%	0

Relationship between hypothyroidism and breast cancer risk

There were 20 studies reported the relationship between hypothyroidism and breast cancer risk. With obvious heterogeneity (I^2 =78.2%, p = 0.000) among these studies, so a random effect model was used for assessment. The pooled analysis suggested that hypothyroidism can reduce the risk of breast cancer(OR 0.90, 95% CI 0.77–1.03; p < 0.001)((Fig. 2a).

Subgroup analysis of hypothyroidism and risk of breast cancer

To further explore the relationship between hypothyroidism and breast cancer risk, subgroup analysis was conducted from three aspects: study type, population distribution, and follow-up time. In the subgroups with a follow-up date of no more than four years, the case-control study, and the North American study, the results showed that the risk of breast cancer in patients with hypothyroidism decreased by 20%, 15%, and 14%, respectively(Fig. 3). But in Asian patients with hypothyroidism, the risk of breast cancer increases by 17% (OR 1.17, 95% CI 0.98–1.35; $p < 0.001$) (Fig. 3a).

Relationship between thyroid hormone replacement therapy and breast cancer risk

A total of 10 studies reported the relationship between the use of thyroid hormone replacement therapy and the risk of breast cancer[4, 8, 9, 16, 18, 22, 24, 26, 27]. As obvious heterogeneity observed, the fixed-effect model was used(I^2 =86.3%, p = 0.000). The pooled analysis suggested that patients who received thyroid hormone replacement therapy had a lower risk of developing breast cancer(OR = 0.87, 95% CI 0.65–1.09; $p < 0.001$) (Fig. 4a).

Publication bias

Figure 5A shows a funnel plot of the 20 articles included in this meta-analysis. The Begg test (Pr = 0.529) and the Egger test(P = 0.892) were used to detecting publication bias showed that there was no possibility of publication bias. As shown in Fig. 5B, there were no publication biases in the ten articles on the study of thyroid hormone replacement therapy. The Egger test was P = 0.672, and the Begg test (Pr = 0.858).

Sensitivity analysis

The results of sensitivity analysis are generally stable, and the primary source of heterogeneity is in the research of Cristofanilli et al[24]. (Fig. 6a). So we excluded the literature of Cristofanilli and analyzed the other studies. The results revealed that the hypothyroidism could reduce the risk of breast cancer (OR:0.96 95%CI:0.92 -1.00, $P < 0.001$), and there was no heterogeneity($I^2 = 0$, P = 0.577)(Fig. 2b).

As shown in Fig. 6b, we can see that the source of heterogeneity is the Cristofanilli and Sandhu articles[24, 26]. Therefore, we removed the two articles and re-executed the meta-analysis. With no obvious heterogeneity (I^2 =0, p = 0.922) among these studies, so a fixed-effect model was used for assessment. The results show that patients taking thyroid hormone replacement therapy have a lower risk of breast cancer(OR:0.96 95%CI:0.83–1.08, $P < 0.001$(Fig. 4b).

Discussion

In recent years, the incidence of breast cancer has been on the rise worldwide.,which has become a major public health problem in today's society. The prevention and treatment of breast cancer has become an important task in the prevention and treatment of malignant tumors. Therefore, understanding the risk factors of breast cancer and facilitating the implementation of effective prevention and early intervention, is of great significance for the effective prevention and treatment of breast cancer.

More than 100 years ago, Beatson et al. used thyroid extracts to treat patients with metastatic advanced breast cancer, and the condition was significantly alleviated, sparking interest in exploring the relationship between thyroid and breast cancer[30]. Subsequent, a prospective study enrolled 2,738 women, and 61 women with breast cancer during follow-up showed that low serum free thyroxine levels increased the risk of breast cancer[8]. In 2016, a prospective cohort study of 61,873 women with hypothyroidism and 80,343 hyperthyroidism found that hypothyroidism slightly reduced the risk of breast cancer[10]. However, a prospective cohort study of 89,731 women with autoimmune hypothyroidism and 89,731 women with normal thyroid function indicated that autoimmune hypothyroidism was not associated with breast cancer risk[26]. Besides, some animal experiments also reflect the relationship between the two[31, 32]. Animal experiments by López Fontana et al. found that hypothyroidism mice inhibit the development of breast cancer and promote the apoptosis of breast cancer cells due to the low expression of β-chain protein and activation of the apoptotic pathway on the tumour cell membrane[31]. Due to the inconsistency of the above conclusions, we performed a meta-analysis to evaluate the relationship between hypothyroidism and breast cancer risk.

Main Findings

A total of 19 studies were included in this meta-analysis, and the results showed that patients with hypothyroidism had a lower risk of breast cancer. However, there was significant heterogeneity among the included studies. After subgroup analysis and sensitivity analysis, we found that Cristofanilli's research may cause heterogeneity[24]. Cristofanilli's research is a retrospective study, and the diagnosis of hypothyroidism patients was based on the information recorded in the medical records, which may lead to the bias risk of misclassification and have a positive impact on the positive results of this study[24]. After excluding Cristofanilli's research, we found that patients with hypothyroidism had a lower risk of breast cancer. In the analysis of the Asian population, we came to the opposite conclusion, which we assumed might be related to different genetic background and environmental factors. However, only two studies were included in the subgroup analysis[9, 29]. Therefore, a large number of Asian population studies are still needed to determine the relationship between hypothyroidism and breast cancer risk. In addition, we evaluated the risk of breast cancer in thyroid hormone replacement therapy and show that thyroid hormone replacement therapy can prevent the occurrence of breast cancer. The results of the meta-analysis are inconsistent with the findings of Hardefeldt et al. and Angelousi et al. Perhaps because our study included more prospective studies and was included in the new Asian population cohort study.

Strengths

Normal mammary epithelial cells can express a large number of T3 receptors, and breast cancer cells have similar ability to bind to T3[33]. T3 has an estrogen-like effect that promotes the growth of mammary gland lobes and stimulates normal breast tissue differentiation[34, 35]. Therefore, T3 can mimic the effect of estrogen on the proliferation of breast cancer cells. When the concentration of T3 is low in vivo, it may inhibit the proliferation of breast cancer cells.

Some basic experiments support this theory.In 2002, Gonzalez-Sancho et al. studied the relationship between T3 and breast cancer[36]. It was found that there is an over-expressed T1 gene in human breast cancer cells, and T3 inhibits the proliferation of mammary epithelial cells by inhibiting the expression of cyclin D1 and T1, thereby inhibiting the proliferation of breast cancer cells[36]. After that, Martinez-Iglesias found that hypothyroidism can inhibit the growth of breast cancer cells[32]. In 2010, Tosovic conducted a prospective study of T3 levels associated with breast cancer risk and found that T3 levels in postmenopausal women were positively correlated with breast cancer risk in a dose-response manner[37]. Therefore, we suspect that low levels of thyroid hormone may reduce the incidence of breast cancer. Our meta-analysis results also confirm the above conjecture.

Limitations

There are still some deficiencies in the research. First, the studies that have been included do not adjust for important risk factors for breast cancer. Second, in subgroup analysis, for example, there are only two articles in Asian studies, and we should be cautious about the results of Asian analysis. Third, the results of this meta-analysis indicate that there is a large heterogeneity between studies. Fourth, Third, follow-up time at different endpoints cannot be uniform. Finally, publication bias cannot be avoided entirely.

Conclusion

Patients with hypothyroidism or thyroid hormone replacement therapy have a lower risk of breast cancer, suggesting that low levels of thyroid hormone may be beneficial to breast cancer prevention. It is necessary to conduct a large sample size, strictly controlled prospective study of hypothyroidism patients to further demonstrate the relationship between hypothyroidism and breast cancer risk.

Abbreviations

OR: odd ratios; CI: confidence intervals; NOS: Newcastle–Ottawa Scale

Declarations

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Further information
Not applicable

Authors' contributions

Conception and Design:BW; Extraction of Data:BW,TL,and YH; Quality assessment: BW and TL; Drafting the Article:BW; Revising It for Intellectual Content:YH; Final Approval of the Completed Article:YH. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interests.

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Figures

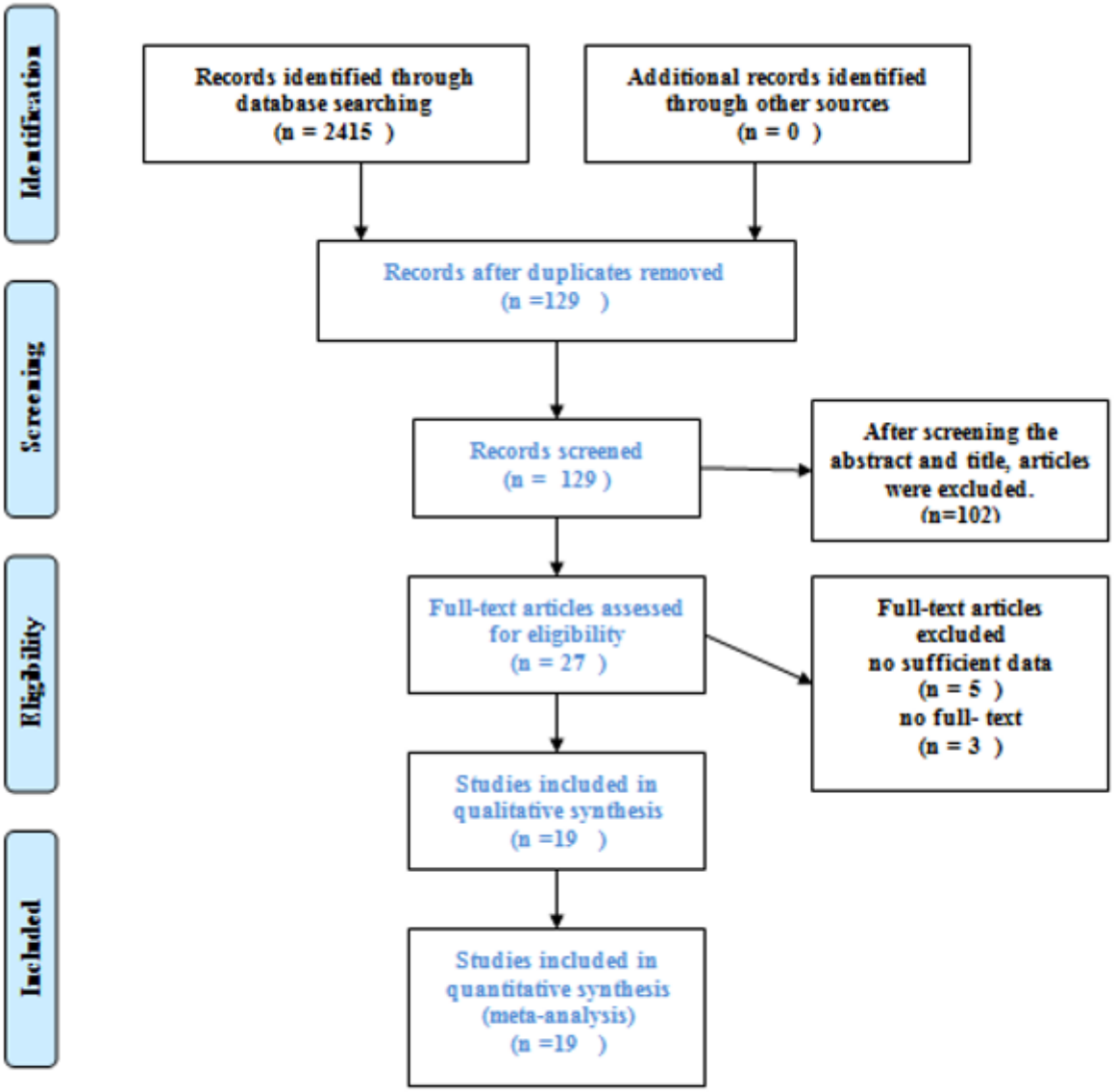


Figure 1

Flow chart of search strategy and study selection

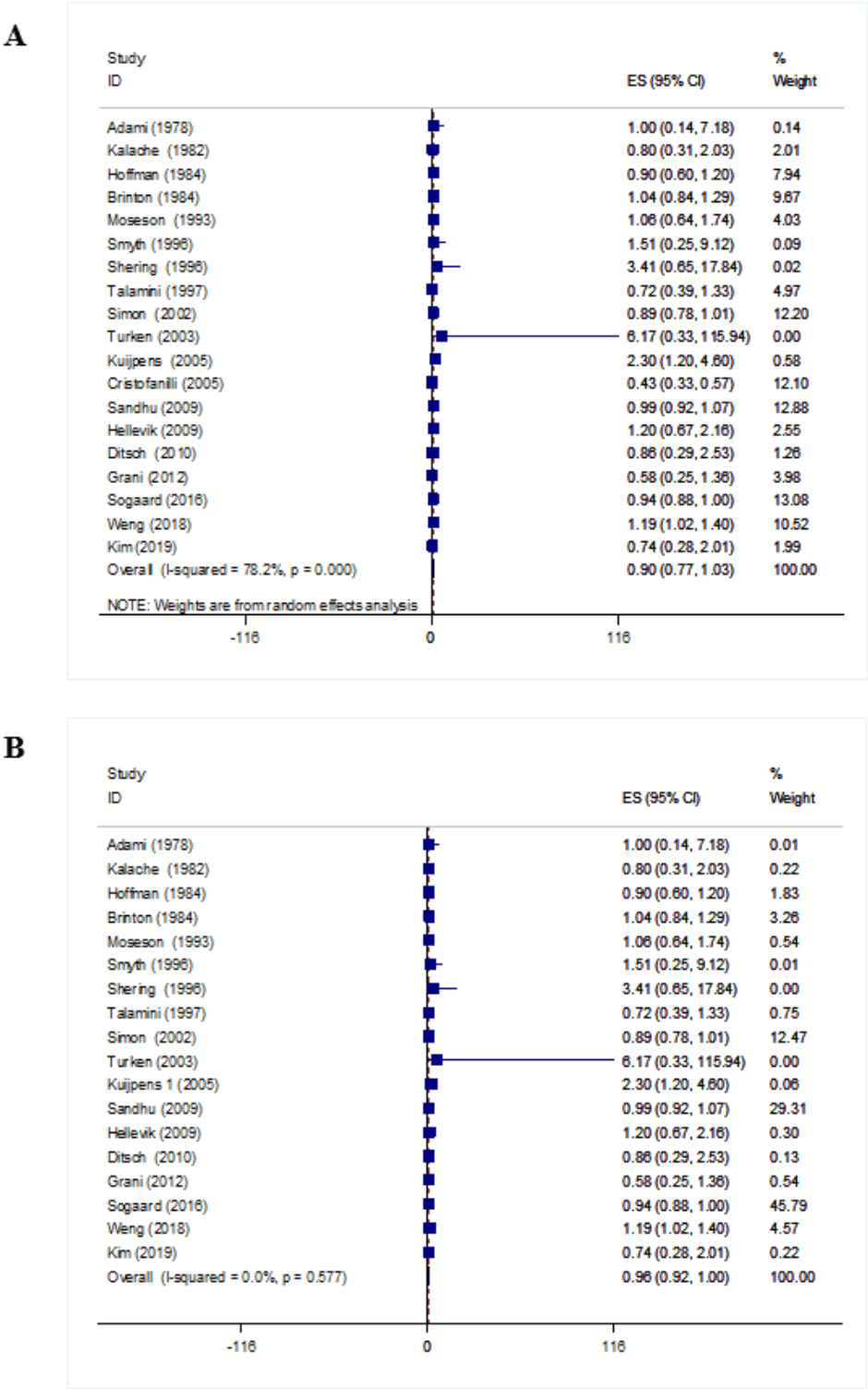
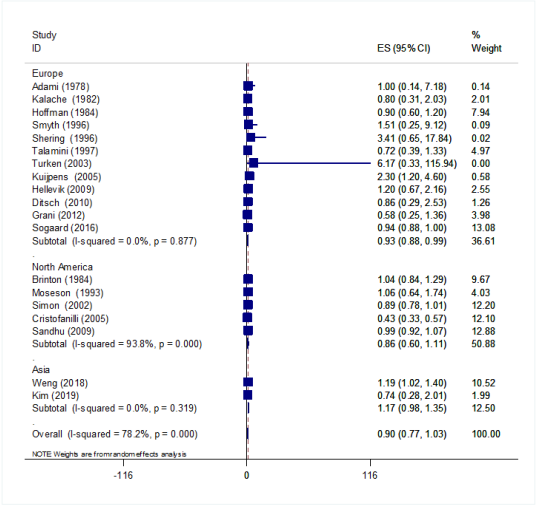


Figure 2

Relationship between hypothyroidism and breast cancer risk

A



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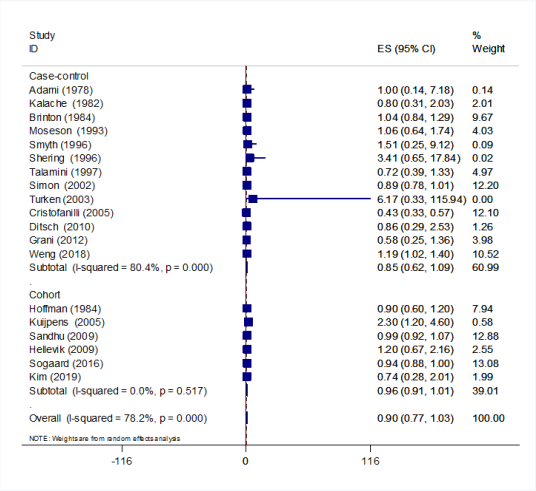

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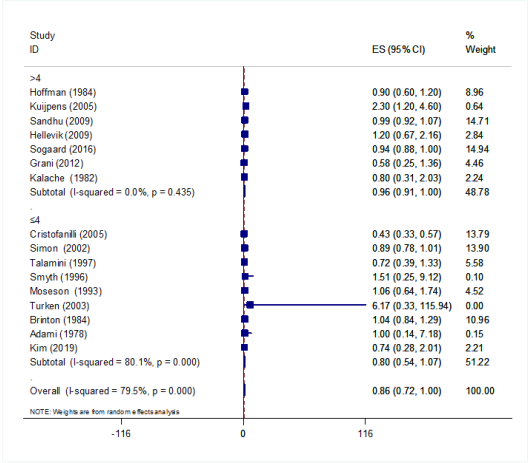
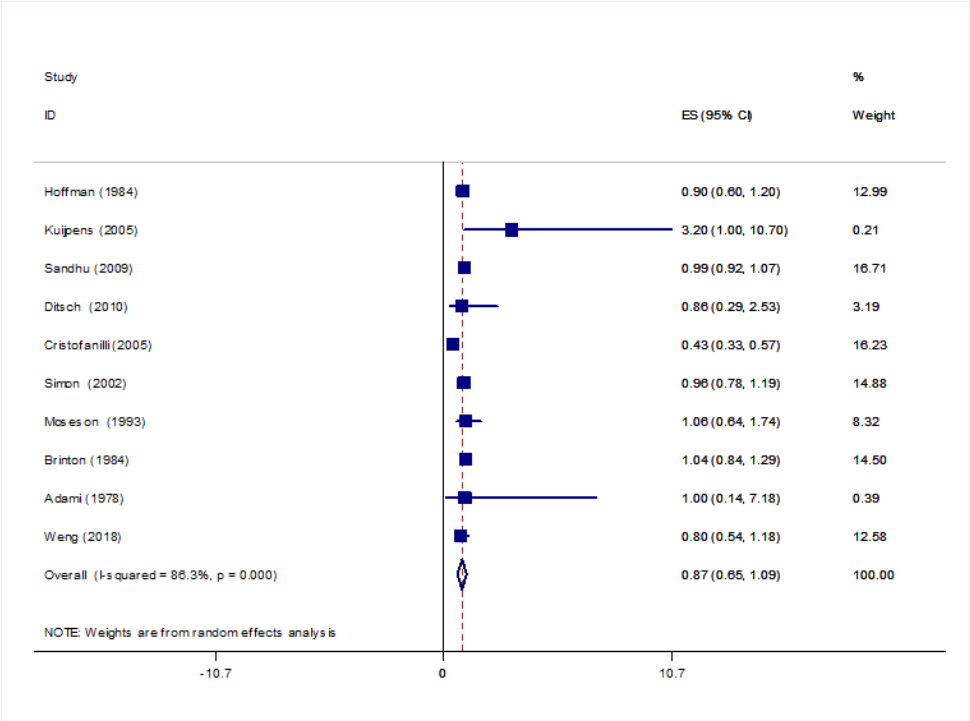


Figure 3

Subgroup analysis of hypothyroidism and risk of breast cancer

A



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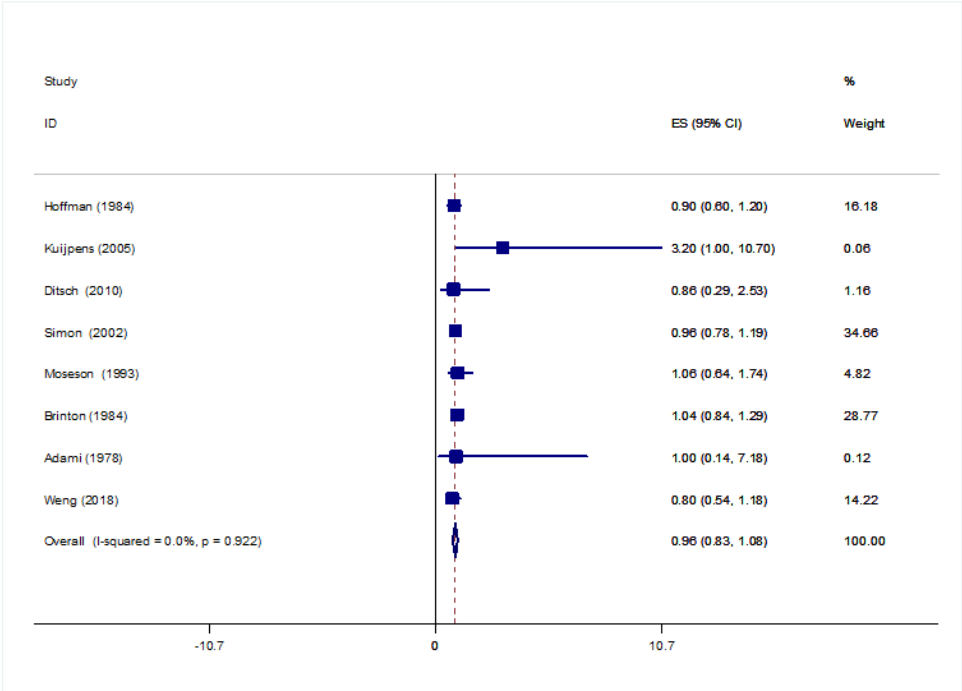

Figure 4

Relationship between thyroid hormone replacement therapy and breast cancer risk

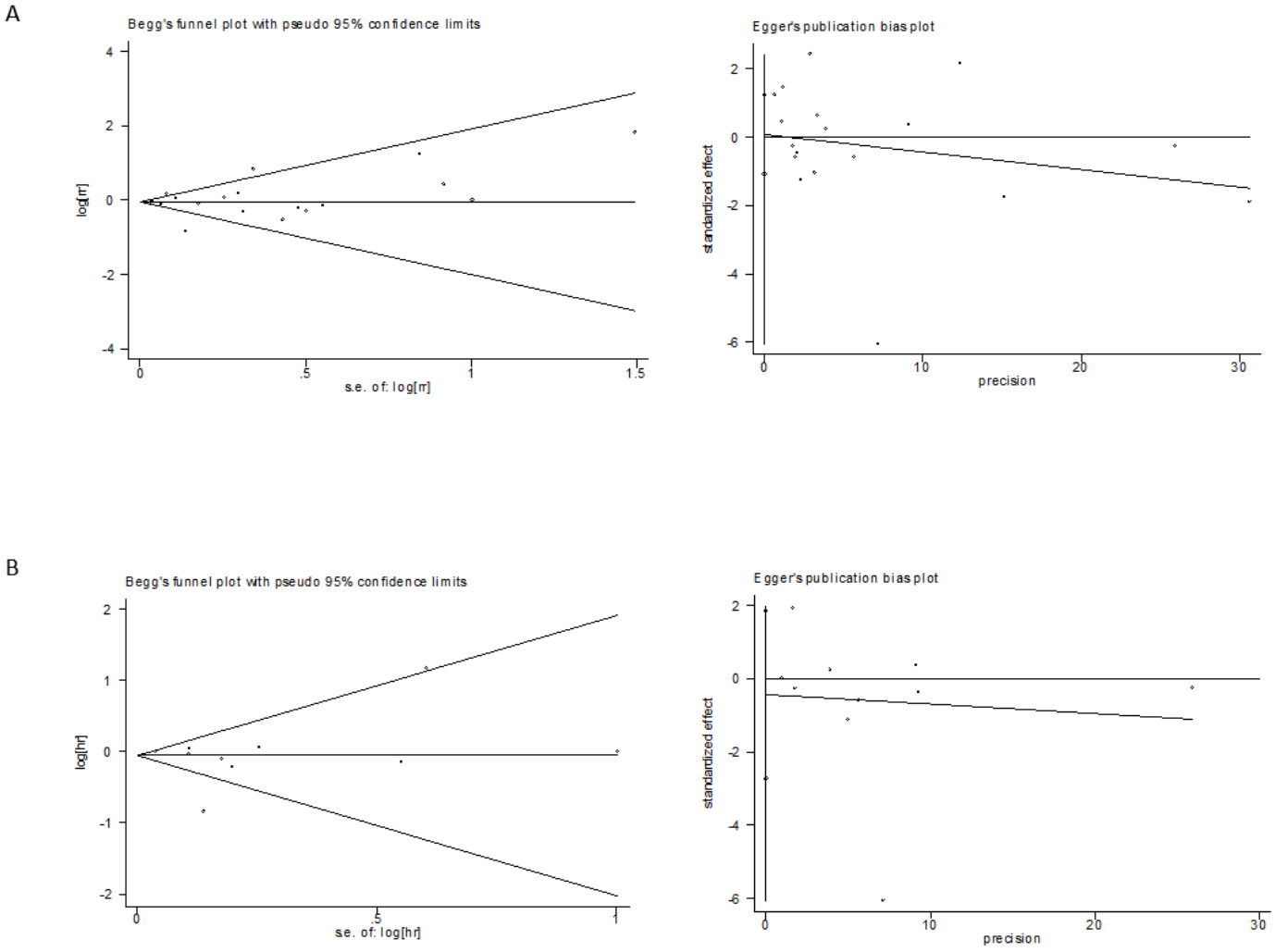

Figure 5

Publication bias assessment

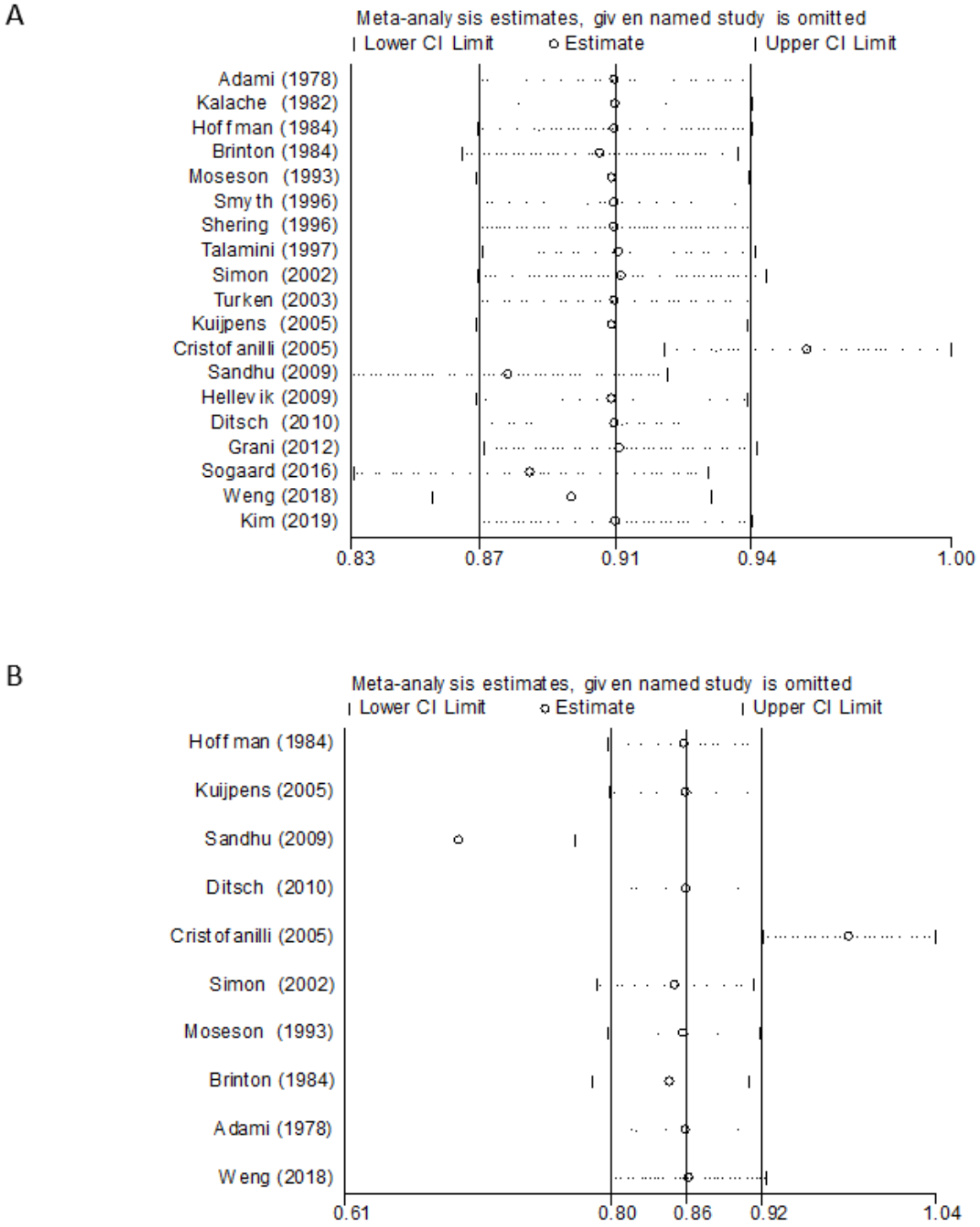

Figure 6

Sensitivity analysis