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Thyroid Disorders and Breast Cancer Risk in Asian Population: A Nationwide Population-Based Study

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Key words: hyperthyroidism; hypothyroidism; breast cancer; cancer risk

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Abstract

Objective: To evaluate whether hyper- or hypothyroidism increases the risk of subsequent breast cancer in an Asian population.

Design: Nationwide population-based case-control study.

Setting: All health care facilities in Taiwan.

Participants: A total of 103,466 women (mean age 53.3 years) were enrolled.

Methods: 51,733 adult women with newly diagnosed with primary breast cancer without a previous cancer history between 2006 and 2011 were identified and included in our study. 51,733 women with no cancer diagnosis prior to the index date were age-matched as controls. Diagnosis of hyper- or hypothyroidism prior to the diagnosis of breast cancer or the same index date was identified, age, histories of thyroid disease treatment, estrogen use and radioactive-iodine treatment were adjusted.

Main outcome measures: To identify risk differences in developing breast cancer among patients with a medical history of hyper- or hypothyroidism.

Results: There was a significantly increased risk of breast cancer in women with hyperthyroidism under age of 55 years (age <45: OR 1.16, p=0.049; age 45-55: OR 1.15, p=0.019). Patients with hypothyroidism also showed an increased risk of breast cancer (OR 1.19, p=0.029) without statistical significance after stratification by age group (age <45, 45-55, >55 years). Treatment for thyroid disorders did not alter the association in subgroup analyses (p=0.857; 0.262 respectively).

Conclusions: Asian women under 55 years of age with history of hyperthyroidism have a significantly increased risk of breast cancer regardless of treatment. Women with history of hypothyroidism may also have an increased risk.

Strengths and limitations of this study

- This is the first study in an Asian population assessing the association between hyperthyroidism, hypothyroidism, breast cancer, and age.
- Asian women under 55 years of age with history of hyperthyroidism have a significantly increased risk of breast cancer regardless of treatment. Women with history of hypothyroidism may also have an increased risk.
- Treatment for hyper- or hypothyroidism did not alter this association.
- The most important limitation of this study is the characteristic of the database. Since it is a national health insurance claims database, detailed TSH, T4, T3 level, types and stages of breast cancer are not available for further stratification and analysis.

INTRODUCTION

One in eight women will develop breast cancer in their lifetime, a disease prevalence similar to the risk of thyroid disorders in this population.[1-3] Since high thyroid hormone levels are found to have estrogen-like effects in several *in vitro* studies, thyroid hormone levels and their relation to the development of breast and other cancers have been studied in the past with conflicting results and primarily in Caucasian populations.[4-14]

This is the first study conducted to assess the association between hyperthyroidism, hypothyroidism and breast cancer in an Asian population. We designed a nationwide population-based case-control study utilizing the Taiwanese National Health Insurance Research Database (NHIRD), one of the largest administrative health care databases in the world; our aim was to discover the relationship between hyper- or hypothyroidism and breast cancer from the epidemiological aspect.

METHODS

We designed a case-control study utilizing the Taiwanese National Health Insurance Research Database (NHIRD). Female patients with a new diagnosis of primary breast cancer and no previous cancer history were identified from the NHIRD (diagnosed between 2006 and 2011). Age-matched female individuals without a breast cancer diagnosis were randomly selected as controls. We then identified the status of thyroid disorders prior to the diagnosis of breast cancer in the case group or the same index date in the control group. We excluded those with a history of a thyroid malignancy. (Figure 1)

Taiwanese National Health Insurance Research Database (NHIRD)

The National Health Insurance program was established in Taiwan in March 1995 and covers about 99% of the Taiwanese population. The National Health Insurance Research Database (NHIRD), established by the National Health Research Institute (NHRI), is a claims database maintained by the Department of Health and the NHRI. There are several subset databases in the NHIRD including the Registry for Catastrophic Illness Patient Database (RCIPD). Breast cancer is defined as a catastrophic illness by the government. Thus, when patients are diagnosed with breast cancer, they will apply and register for the certificate of catastrophic illness.

The Longitudinal Health Insurance Database (LHID) is a database of one million randomly selected insurers from the NHIRD. We used the 2010 version of the LHID which included 1,000,000 individuals randomly selected from the total of 23,251,700 insured.

Breast cancer

In order to identify patients with newly diagnosed primary breast cancer, we searched the NHIRD by using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM) code 174 and 175, cross-linking these to the RCIPD. The identified patients all had newly diagnosed breast cancer between 2006 and 2011 and possessed a certificate of catastrophic illness. There were 53,488 total patients identified.

We then excluded male gender, age unknown, sex unknown, or age < 18 or >120 years old at the time of diagnosis. We excluded patients with diagnoses of other malignant diseases before the diagnosis of breast cancer. A total of 51,733 patients were identified from the NHIRD by the above criteria as cases.

Case-control match

We applied a one-to-one match for the control group, randomly matched for age, sex, and the same index date (the month and year of breast cancer diagnosis in the case group) from the LHID. We excluded male gender, age unknown, sex unknown, age < 18

or >120 years old at time of index date, or deceased before index date. We excluded patients with the diagnosis of breast cancer. Also excluded patients were those with diagnoses of other malignant diseases before the index date. A total of 51,733 women were selected as controls.

Hyperthyroidism and hypothyroidism

To identify patients with the diagnosis of hyperthyroidism, we used the ICD9-CM code 242 with additional criteria including the same diagnosis in at least three outpatient visits or one inpatient admission. We stipulated that the first diagnosis of hyperthyroidism had to occur before the date of first breast cancer diagnosis in the case group or the index date in the control group. We used the ICD9-CM codes 243 and 244 with the same additional criteria to identify patients with hypothyroidism. We also excluded patients with ICD9-CM codes 244.0, 244.1, 244.2, 244.3 in the hypothyroidism group since those are acquired hypothyroidism. We identified a specific group of patients with both hyperthyroidism (ICD9-CM 242) and hypothyroidism diagnoses (ICD9-CM 244.0, 244.1, 244.2, 244.3), which represents acquired hypothyroidism from hyperthyroidism treatments. We excluded those with a diagnosis of thyroid malignancy in our study.

Other adjustments

We adjusted for estrogen use or hormone replacement therapy, a history of radioactive iodine treatment, medication or surgical treatment for thyroid disease, and age. We identified the use of hyperthyroidism, hypothyroidism medications, estrogen-containing

products including oral forms, injection forms, or external-use forms available on the market in Taiwan, and labeled them as ever-used versus never-used. We did not calculate the length of use in each female since it is very difficult to know their compliance and effects between different products. We also identified females who have ever received radioactive iodine treatment and adjusted it in our analysis.

Statistical analysis

To examine the differences in clinical characteristics between breast cancer and control groups, we used the Student's t-test to analyze continuous variables and the chi-square test to analyze categorical variables. Conditional logistic regression analysis was applied to examine the effect of thyroid disorders, including hyperthyroidism, hypothyroidism, and acquired hypothyroidism, on the risk of developing breast cancer, and controlled for potential confounders. Logistic regression analysis was applied to examine the associations between treatments for hyperthyroidism or hypothyroidism and the risk of developing breast cancer in subgroup analysis. All statistical tests were two-sided, conducted at a significance level of 0.05, and reported using *p*-values and/or 95% confidence intervals (95% CI). All analyses were performed using Statistical Analytic System (SAS) software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 103,466 patients were enrolled in our study, 51,733 in each group. As for patient characteristics, the mean ages were 53.4 years and 53.3 years in the breast cancer and control groups, respectively (p=0.137). In the breast cancer group, 36.9% of the patients had ever used estrogen-containing medications; in the control group, 41.6% of patients had ever used estrogen-containing medications (p<0.001). Prior to the time of breast cancer diagnosis or the index date, 46 and 42 women received radioactive iodine treatment in the breast cancer and control groups, respectively (p=0.67). Significant differences in the proportions of thyroid disorders in the breast cancer group and control group were found (p=0.022). There were 335 patients (0.7%) with hypothyroidism in the breast cancer group and 291 patients (0.6%) in the control group. A total of 1580 patients (3.1%) had the diagnosis of hyperthyroidism in the breast cancer group and 1453 patients (2.8%) in the control group. (Table 1)

Table 1. Clinical characteristics of study subjects with and without breast cancer

Variable	Total (N=103,466)		Without breast cancer (N=51,733)		With breast cancer (N=51,733)		*p* value
	n	(%)	n	(%)	n	(%)	
Age, years (mean ± SD)	53.3±12.1		53.3±12.2		53.4±12.0		0.137[†]
Gender							—

Female	103466	(100.0)	51733	(100.0)	51733	(100.0)	
Male	0	(0.0)	0	(0.0)	0	(0.0)	
Thyroid disorders							0.022
No	93675	(91.0)	46866	(91.0)	46809	(90.9)	
With Hypothyroidism	626	(0.6)	291	(0.6)	335	(0.7)	
With Hyperthyroidism	3033	(2.9)	1453	(2.8)	1580	(3.1)	
With Acquired Hypothyroidism	161	(0.2)	87	(0.2)	74	(0.1)	
Others	5462	(5.3)	2782	(5.4)	2680	(5.2)	
History of estrogen use							<0.001
No	62834	(60.7)	30197	(58.4)	32637	(63.1)	
Yes	40632	(39.3)	21536	(41.6)	19096	(36.9)	
History of radioactive iodine treatment							0.670
No	103378	(99.9)	51691	(99.9)	51687	(99.9)	
Yes	88	(0.1)	42	(0.1)	46	(0.1)	
Medication treatment for thyroid disorder							0.510
No	100569	(97.2)	50302	(97.2)	50267	(97.2)	
Yes	2897	(2.8)	1431	(2.8)	1466	(2.8)	
Thyroidectomy							0.330
No	102307	(98.9)	51137	(98.8)	51170	(98.9)	
Yes	1159	(1.1)	596	(1.2)	563	(1.1)	

+ T test; chi-squared test for all other *p-values*.

Acquired Hypothyroidism: with diagnoses of hyperthyroidism + hypothyroidism.

Both hyperthyroidism and hypothyroidism were associated with an increased risk of developing breast cancer after adjusting for age, estrogen-containing medication use, and a history of radioactive iodine treatment. Hyperthyroidism in all age groups showed an overall increased risk by 12% in breast cancer development (OR 1.12, 95% CI 1.04-

1.20, *p*=0.003), while hypothyroidism in all age groups had a 19% increased risk (OR 1.19, 95% CI 1.02-1.40, *p*=0.029). No significant change in risk was found among those who had acquired hypothyroidism after treatment for hyperthyroidism (OR 0.88, 95% CI 0.64-1.22, *p*=0.453).

When we stratified by age group (age<45, age 45-55, age>55 years), patients with hyperthyroidism aged 55 or under showed a significantly increased breast cancer risk; this association disappeared in those aged 55 years and older. Among patients aged <45 years, there was a 16% increased risk in breast cancer (OR 1.16, 95% CI 1.00-1.34, *p*=0.049). In those aged 45-55 years there was a 15% increased risk (OR 1.15, 95% CI 1.02-1.29, *p*=0.019). The increased odds for breast cancer in patients with hypothyroidism did not reach statistical significance among those 3 age groups. (Table 2)

Table 2. Adjusted odds ratio of breast cancer associated with thyroid disorders

Variable	Adjusted OR	95% CI	*p* value
Overall			
Without Thyroid disorders	1.00	—	—
With Hypothyroidism	1.19	(1.02-1.40)	0.029
Without Thyroid disorders	1.00	—	—
With Hyperthyroidism	1.12	(1.04-1.20)	0.003
Without Thyroid disorders	1.00	—	—
With Acquired Hypothyroidism	0.88	(0.64-1.22)	0.453
Without Thyroid disorders	1.00	—	—
Others	0.99	(0.94-1.05)	0.806

Age < 45			
Without Thyroid disorders	1.00	—	—
With Hypothyroidism	1.07	(0.71-1.60)	0.757
Without Thyroid disorders	1.00	—	—
With Hyperthyroidism	1.16	(1.00-1.34)	0.049
Without Thyroid disorders	1.00	—	—
With Acquired Hypothyroidism	0.62	(0.29-1.32)	0.214
Without Thyroid disorders	1.00	—	—
Others	1.03	(0.91-1.16)	0.692
Age 45-55			
Without Thyroid disorders	1.00	—	—
With Hypothyroidism	1.18	(0.90-1.54)	0.226
Without Thyroid disorders	1.00	—	—
With Hyperthyroidism	1.15	(1.02-1.29)	0.019
Without Thyroid disorders	1.00	—	—
With Acquired Hypothyroidism	0.84	(0.50-1.43)	0.532
Without Thyroid disorders	1.00	—	—
Others	1.05	(0.96-1.15)	0.276
Age ≥ 56			
Without Thyroid disorders	1.00	—	—
With Hypothyroidism	1.23	(0.98-1.54)	0.070
Without Thyroid disorders	1.00	—	—
With Hyperthyroidism	1.05	(0.93-1.19)	0.454
Without Thyroid disorders	1.00	—	—
With Acquired Hypothyroidism	1.07	(0.65-1.76)	0.792
Without Thyroid disorders	1.00	—	—
Others	0.92	(0.84-1.00)	0.052

Adjusted OR was adjusted for age, estrogen use, and history of Iodine treatment by logistic regression analysis.

In the subgroup analysis, we examined whether medication and/or surgical treatment for hyper- or hypothyroidism would change the risk of having breast cancer. The

analysis showed no statistically significant differences between treatments for hyper- or hypothyroidism and the risk of developing breast cancer (OR 1.01, 95% CI 0.88-1.17, *p*=0.857; OR 0.80, 95% CI 0.54-1.18, *p*=0.262; respectively). (Table 3)

Table 3. Subgroup analysis for treatment - adjusted odds ratio of breast cancer associated with thyroid disorders (TD)

Variable	Adjusted OR	95% CI	*p* value
Subjects with Hypothyroidism			
Without TD medications	1.00	—	—
With TD medications[1]	0.80	(0.54-1.18)	0.262
Subjects with Hyperthyroidism			
Without TD medications and surgery	1.00	—	—
With TD medications[2] or surgery[3]	1.01	(0.88-1.17)	0.857
Subjects with Hyperthyroidism			
Without TD medications and surgery	1.00	—	—
With surgery[4]	0.97	(0.74-1.27)	0.825
With TD medications	1.02	(0.88-1.19)	0.789

Adjusted OR was adjusted for age, estrogen use, and history of Iodine treatment by logistic regression analysis.

[1] Hypothyroidism medication: levothyroxine.
[2] Hyperthyroidism medications: methimazole, propylthiouracil (did not include radioactive iodine treatment since it was adjusted separately).
[3] Surgery: thyroidectomy (partial or total).
[4] If the patient received both medication and surgical treatment, the patient would be classified as surgical patient in this subgroup.

DISCUSSION

This is the first study in an Asian population assessing the association between hyperthyroidism, hypothyroidism and breast cancer. Among a total of 103,466 women in our study, we found increased risks of developing breast cancer in patients with medical history of either hyperthyroidism or hypothyroidism despite treatment. The association is significant in patients under age 55 years old with hyperthyroidism.

We also performed a separate analysis for autoimmune thyroid disease- Hashimoto's thyroiditis and Graves' disease, to examine the association with breast cancer but found no statistical significance (OR 0.94, 95% CI 0.68-1.29, p=0.685 for Hashimoto; OR 1.20, 95% CI 0.96-1.50, p=0.109 for Graves').

Since Beaston first described using thyroid extract to treat metastatic breast cancer in the Lancet in 1896, many studies have investigated the relationship between thyroid hormone and cancers.[15 16] Specific alterations of thyroid hormone receptors (TR) have been found in different types of carcinomas, including breast cancer, and many studies observed associations between the expression of TRs and the regulation of oncogenes.[16-18] Several physiological similarities have been discovered between the thyroid gland and mammary gland. For one, both thyroid follicular cells and breast

lactating cells store iodine through natrium-iodine symporter (NIS)-mediated iodine uptake.[19-22] The oxidization of iodine in the alveolar mammary cells utilizes lactohyperoxidase, which is mechanistically similar to hyperoxidase in thyroid glands.[23]

Several *in vitro* studies have shown that high levels of thyroid hormones may possess estrogen-like effects and may promote breast cancer proliferation and angiogenesis.[5 13 16 18 24] It has also been shown that the activation of TR in mammary glands may induce the differentiation and lobular growth of breast tissues, an effect similar to that seen with estrogen.[16 17] Active triiodothyronine (T3) has been found to promote breast cancer cell proliferation and to increase the effect of 17beta-estradiol (E2)-mediated cell proliferation in some breast cancer cell lines.[13] In population-based studies, T3 levels have also been found to have a positive correlation with breast cancer tumor size and the risk of lymph node metastasis.[25]

Hypothyroidism may lead to hypersensitization of mammary glandular epithelium to estrogen and prolactin, possibly related to low circulating thyroid hormone.[26] Some studies have proposed that there could be different set points for thyroid function in women with higher risks of breast cancer; specifically, they may have lower free T4 and low-normal TSH levels without clinical symptoms.[6 27] The existence of a genetic predisposition for hypothyroidism and breast cancer has been hypothesized as well.[10]

In our study, the significantly increased risk of breast cancer among patients with the diagnosis of hyperthyroidism under 55 years of age is possibly related to higher levels of thyroid hormone in addition to the physiological level of estrogen. The increased risk drops from 15-16% to 5% with no statistical significance in hyperthyroidism patients >55 years of age. This is likely related to the menopausal status of these patients, an indicator of low estrogen levels. In the further subgroup analysis, we found that hyperthyroidism treatment with medications and/or surgery and thyroid replacement treatment for hypothyroidism did not alter the risk of having breast cancer in the future. While there is a 19% increased risk of breast cancer in hypothyroidism patients, the statistical significance disappears when we stratify these patients into the 3 age groups. Since there were only 335 patients with a diagnosis of hypothyroidism who developed breast cancer, dividing this group into 3 age cohorts led to a decrease in power. Based on our overall results, however, we can hypothesize that there is no protective effect of hypothyroidism in the development of breast cancer. Interestingly, the use of estrogen-containing products (which we controlled for) was not a contributing factor to an increased risk of breast cancer in this study.

In 2016, it is estimated that 40,450 women may die of breast cancer in the U.S.[1] Current breast cancer screening guidelines published by the U.S. Preventive Services Task Force (USPSTF) recommend biennial screening mammography for women at average risk aged 50 to 74 years.[28] The American Cancer Society (ACS) recommends annual screening mammography for women at average risk aged 45 to 55 years then biennial screening after 55 years of age.[29] Our nationwide population-based study showed a

significantly increased breast cancer risk in women with hyperthyroidism under the age of 55 years and an increased risk or at least no protective effect of hypothyroidism. More large studies are needed to examine this association in different age groups.

Limitations

The findings from our study were derived from a large population-based dataset; this minimized selection bias. The case-control study design using an administrative claims database reduced the recall bias; however, the findings might be less accurate due to the lack of supporting laboratory data; this includes thyroid antibody, TSH and thyroid hormones levels as well as breast cancer stages and receptor status. In order to minimize bias, we only studied those with a diagnosis of hyper- or hypothyroidism who were documented as having these diagnoses in at least three outpatient visits or one inpatient admission. All breast cancer patients in this study had the diagnosis of breast cancer and possessed the certificate of catastrophic illness. To avoid false claims, the National Health Insurance Bureau (NHIB) randomly samples a fixed percentage of claims from each hospital every year to confirm diagnosis validity, and medical records were independently reviewed by professional experts. Since this study is based on administrative claims, the results may be underestimated or overestimated, as only patients who seek medical attention were evaluated and treated. Since thyroid disorders are often chronic diseases rather than acute onset, we thought that it might not be as useful to adjust the time lapse from the diagnosis of thyroid disorder to breast cancer.

Conclusion

Our nationwide Asian population-based study suggests that Asian women under the age of 55 years with medical history of hyperthyroidism have a significantly increased risk of developing breast cancer regardless of treatment. Women with a history of hypothyroidism may also have an increased risk. Further studies are needed to assess the association between age, hypothyroidism, and breast cancer risk.

Author contributions:

Concept of study: C-H Weng and T-H Lin

Study design: C-H Weng, X Luo, C-H Lin and T-H Lin

Statistical analysis: Y-H Chen and C-H Lin

Interpretation of results: C-H Weng, Y-H Chen, X Luo, and C-H Lin

Manuscript writing: C-H Weng

The other authors provided inputs, expertise, and critical review of the manuscript.

C-H Weng and T-H Lin contributed as co-senior authors to this article.

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Figure legend:

Figure 1. Flow Diagram of Participants Selection and Study Design

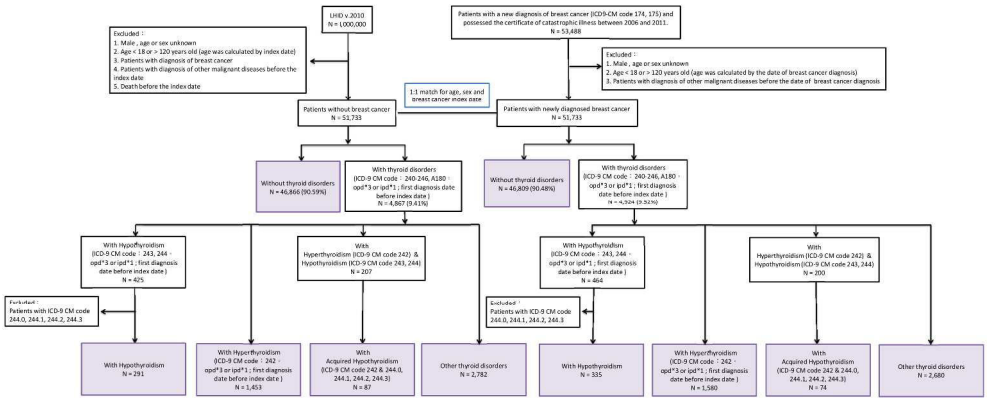

Figure 1. Flow Diagram of Participants Selection and Study Design

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Thyroid Disorders and Breast Cancer Risk in Asian Population: A Nationwide Population-Based Case-Control Study in Taiwan

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Thyroid Disorders and Breast Cancer Risk in Asian Population: A Nationwide Population-Based Case-Control Study in Taiwan

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Key words: hyperthyroidism; hypothyroidism; breast cancer; cancer risk

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Abstract

Objective: To evaluate whether hyper- or hypothyroidism increases the risk of subsequent breast cancer in an Asian population.

Design: Nationwide population-based case-control study.

Setting: All health care facilities in Taiwan.

Participants: A total of 103,466 women (mean age 53.3 years) were enrolled.

Methods: 51,733 adult women with newly diagnosed with primary breast cancer without a previous cancer history between 2006 and 2011 were identified and included in our study. 51,733 women with no cancer diagnosis prior to the index date were age-matched as controls. Diagnosis of hyper- or hypothyroidism prior to the diagnosis of breast cancer or the same index date was identified, age, histories of thyroid disease treatment, estrogen use and radioactive-iodine treatment were adjusted.

Main outcome measures: To identify risk differences in developing breast cancer among patients with a medical history of hyper- or hypothyroidism.

Results: There was a significantly increased risk of breast cancer in women with hyperthyroidism under age of 55 years (age <45: OR 1.16, p=0.049; age 45-55: OR 1.15, p=0.019). Patients with hypothyroidism also showed an increased risk of breast cancer (OR 1.19, p=0.029) without statistical significance after stratification by age group (age <45, 45-55, >55 years). Treatment for thyroid disorders did not alter the association in subgroup analyses (p=0.857; 0.262 respectively).

Conclusions: Asian women under 55 years of age with history of hyperthyroidism have a significantly increased risk of breast cancer regardless of treatment. Women with history of hypothyroidism may also have an increased risk.

Strengths and limitations of this study

- This is the first study in an Asian population assessing the association between hyperthyroidism, hypothyroidism, breast cancer, and age.
- The main strength of this study is the large population-based dataset which minimized the selection bias.
- The most important limitation of this study is the characteristic of the database. Since it is a national health insurance claims database, detailed TSH, T4, T3 level, types and stages of breast cancer are not available for further stratification and analysis.

INTRODUCTION

One in eight women will develop breast cancer in their lifetime, a disease prevalence similar to the risk of thyroid disorders in this population.[1-3] Since high thyroid hormone levels are found to have estrogen-like effects in several *in vitro* studies, thyroid hormone levels and their relation to the development of breast and other cancers have been studied in the past with conflicting results and primarily in Caucasian populations. Most of the literature published to date have relied on studies of relatively small sample sizes.[4-14] Sogaard *et al.* published a large study in 2016 utilizing the national registry in Denmark found an increased risk of breast cancer in those who had a medical history of hyperthyroidism without age stratification.[5]

Previous observational studies also showed a higher prevalence of hypothyroidism in patients with breast cancer.[15 16] Older studies proposed that hypothyroidism may induce the breast epithelial cells' sensitivity to prolactin and estrogen.[17 18] A recent systematic review and meta-analysis included 13 population-based studies with a total of 24,808 participants through June 2016 found that either hypothyroidism or hyperthyroidism has no related risk for breast cancer.[19]

We conducted the first study in an Asian population In order to assess the association between hyperthyroidism, hypothyroidism and breast cancer in different age groups. It is a nationwide population-based case-control study utilizing the Taiwanese National Health Insurance Research Database (NHIRD), one of the largest administrative health

care databases in the world; our aim was to discover the relationship between hyper- or hypothyroidism and breast cancer from the epidemiological aspect.

METHODS

We designed a case-control study utilizing the Taiwanese National Health Insurance Research Database (NHIRD). Female patients with a new diagnosis of primary breast cancer and no previous cancer history were identified from the NHIRD (diagnosed between 2006 and 2011). Age-matched female individuals without a breast cancer diagnosis were randomly selected as controls. We then identified the status of thyroid disorders prior to the diagnosis of breast cancer in the case group or the same index date in the control group. We excluded those with a history of a thyroid malignancy. (Figure 1)

Taiwanese National Health Insurance Research Database (NHIRD)

The National Health Insurance program was established in Taiwan in March 1995 and covers about 99% of the Taiwanese population. The National Health Insurance Research Database (NHIRD), established by the National Health Research Institute (NHRI), is a claims database maintained by the Department of Health and the NHRI. There are several subset databases in the NHIRD including the Registry for Catastrophic Illness Patient Database (RCIPD). Breast cancer is defined as a catastrophic illness by the government. Thus, when patients are diagnosed with breast cancer, they will apply and register for the certificate of catastrophic illness.

The Longitudinal Health Insurance Database (LHID) is a database of one million randomly selected insurers from the NHIRD. We used the 2010 version of the LHID which included 1,000,000 individuals randomly selected from the total of 23,251,700 insured.

Breast cancer

In order to identify patients with newly diagnosed primary breast cancer, we searched the NHIRD by using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM) code 174 and 175, cross-linking these to the RCIPD. The identified patients all had newly diagnosed breast cancer between 2006 and 2011 and possessed a certificate of catastrophic illness. There were 53,488 total patients identified.

We then excluded male gender, age unknown, sex unknown, or age < 18 or >120 years old at the time of diagnosis. We excluded patients with diagnoses of other malignant diseases before the diagnosis of breast cancer. A total of 51,733 patients were identified from the NHIRD by the above criteria as cases.

Case-control match

We applied a one-to-one match for the control group, randomly matched for age, sex, and the same index date (the month and year of breast cancer diagnosis in the case group) from the LHID. We excluded male gender, age unknown, sex unknown, age < 18

or >120 years old at time of index date, or deceased before index date. We excluded patients with the diagnosis of breast cancer. Also excluded patients were those with diagnoses of other malignant diseases before the index date. A total of 51,733 women were selected as controls.

Hyperthyroidism and hypothyroidism

To identify patients with the diagnosis of hyperthyroidism, we used the ICD9-CM code 242 with additional criteria including the same diagnosis in at least three outpatient visits or one inpatient admission. We stipulated that the first diagnosis of hyperthyroidism had to occur before the date of first breast cancer diagnosis in the case group or the index date in the control group. We used the ICD9-CM codes 243 and 244 with the same additional criteria to identify patients with hypothyroidism. We also excluded patients with ICD9-CM codes 244.0, 244.1, 244.2, 244.3 in the hypothyroidism group since those are acquired hypothyroidism. We identified a specific group of patients with both hyperthyroidism (ICD9-CM 242) and hypothyroidism diagnoses (ICD9-CM 244.0, 244.1, 244.2, 244.3), which represents acquired hypothyroidism from hyperthyroidism treatments. We excluded those with a diagnosis of thyroid malignancy in our study.

Other adjustments

We adjusted for estrogen use or hormone replacement therapy, a history of radioactive iodine treatment, medication or surgical treatment for thyroid disease, and age. We identified the use of hyperthyroidism, hypothyroidism medications, estrogen-containing

products including oral forms, injection forms, or external-use forms available on the market in Taiwan, and labeled them as ever-used versus never-used. We did not calculate the length of use in each female since it is very difficult to know their compliance and effects between different products. We also identified females who have ever received radioactive iodine treatment and adjusted it in our analysis.

Statistical analysis

To examine the differences in clinical characteristics between breast cancer and control groups, we used the Student's t-test to analyze continuous variables and the chi-square test to analyze categorical variables. Conditional logistic regression analysis was applied to examine the effect of thyroid disorders, including hyperthyroidism, hypothyroidism, and acquired hypothyroidism, on the risk of developing breast cancer, and controlled for potential confounders. Logistic regression analysis was applied to examine the associations between treatments for hyperthyroidism or hypothyroidism and the risk of developing breast cancer in subgroup analysis. All statistical tests were two-sided, conducted at a significance level of 0.05, and reported using *p*-values and/or 95% confidence intervals (95% CI). All analyses were performed using Statistical Analytic System (SAS) software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 103,466 patients were enrolled in our study, 51,733 in each group. As for patient characteristics, the mean ages were 53.4 years and 53.3 years in the breast cancer and control groups, respectively (p=0.137). In the breast cancer group, 36.9% of the patients had ever used estrogen-containing medications; in the control group, 41.6% of patients had ever used estrogen-containing medications (p<0.001). Prior to the time of breast cancer diagnosis or the index date, 46 and 42 women received radioactive iodine treatment in the breast cancer and control groups, respectively (p=0.67). Significant differences in the proportions of thyroid disorders in the breast cancer group and control group were found (p=0.022). There were 335 patients (0.7%) with hypothyroidism in the breast cancer group and 291 patients (0.6%) in the control group. A total of 1580 patients (3.1%) had the diagnosis of hyperthyroidism in the breast cancer group and 1453 patients (2.8%) in the control group. (Table 1)

Table 1. Clinical characteristics of study subjects with and without breast cancer

Variable	Total (N=103,466)		Without breast cancer (N=51,733)		With breast cancer (N=51,733)		*p* value
	n	(%)	n	(%)	n	(%)	
Age, years (mean ± SD)	53.3±12.1		53.3±12.2		53.4±12.0		0.137[†]
Gender							—

Female	103466	(100.0)	51733	(100.0)	51733	(100.0)	
Male	0	(0.0)	0	(0.0)	0	(0.0)	
Thyroid disorders							0.022
No	93675	(91.0)	46866	(91.0)	46809	(90.9)	
With Hypothyroidism	626	(0.6)	291	(0.6)	335	(0.7)	
With Hyperthyroidism	3033	(2.9)	1453	(2.8)	1580	(3.1)	
With Acquired Hypothyroidism	161	(0.2)	87	(0.2)	74	(0.1)	
Others	5462	(5.3)	2782	(5.4)	2680	(5.2)	
History of estrogen use							<0.001
No	62834	(60.7)	30197	(58.4)	32637	(63.1)	
Yes	40632	(39.3)	21536	(41.6)	19096	(36.9)	
History of radioactive iodine treatment							0.670
No	103378	(99.9)	51691	(99.9)	51687	(99.9)	
Yes	88	(0.1)	42	(0.1)	46	(0.1)	
Medication treatment for thyroid disorder							0.510
No	100569	(97.2)	50302	(97.2)	50267	(97.2)	
Yes	2897	(2.8)	1431	(2.8)	1466	(2.8)	
Thyroidectomy							0.330
No	102307	(98.9)	51137	(98.8)	51170	(98.9)	
Yes	1159	(1.1)	596	(1.2)	563	(1.1)	

+ T test; chi-squared test for all other *p-values*.

Acquired Hypothyroidism: with diagnoses of hyperthyroidism + hypothyroidism.

Both hyperthyroidism and hypothyroidism were associated with an increased risk of developing breast cancer after adjusting for age, estrogen-containing medication use, and a history of radioactive iodine treatment. Hyperthyroidism in all age groups showed an overall increased risk by 12% in breast cancer development (OR 1.12, 95% CI 1.04-

1.20, *p*=0.003), while hypothyroidism in all age groups had a 19% increased risk (OR 1.19, 95% CI 1.02-1.40, *p*=0.029). No significant change in risk was found among those who had acquired hypothyroidism after treatment for hyperthyroidism (OR 0.88, 95% CI 0.64-1.22, *p*=0.453).

When we stratified by age group (age<45, age 45-55, age>55 years), patients with hyperthyroidism aged 55 or under showed a significantly increased breast cancer risk; this association disappeared in those aged 55 years and older. Among patients aged <45 years, there was a 16% increased risk in breast cancer (OR 1.16, 95% CI 1.00-1.34, *p*=0.049). In those aged 45-55 years there was a 15% increased risk (OR 1.15, 95% CI 1.02-1.29, *p*=0.019). The increased odds for breast cancer in patients with hypothyroidism did not reach statistical significance among those 3 age groups. (Table 2)

Table 2. Adjusted odds ratio of breast cancer associated with thyroid disorders

Variable	Adjusted OR	95% CI	*p* value
Overall			
Without Thyroid disorders	1.00	—	—
With Hypothyroidism	1.19	(1.02-1.40)	0.029
Without Thyroid disorders	1.00	—	—
With Hyperthyroidism	1.12	(1.04-1.20)	0.003
Without Thyroid disorders	1.00	—	—
With Acquired Hypothyroidism	0.88	(0.64-1.22)	0.453
Without Thyroid disorders	1.00	—	—
Others	0.99	(0.94-1.05)	0.806

Age < 45			
Without Thyroid disorders	1.00	—	—
With Hypothyroidism	1.07	(0.71-1.60)	0.757
Without Thyroid disorders	1.00	—	—
With Hyperthyroidism	1.16	(1.00-1.34)	0.049
Without Thyroid disorders	1.00	—	—
With Acquired Hypothyroidism	0.62	(0.29-1.32)	0.214
Without Thyroid disorders	1.00	—	—
Others	1.03	(0.91-1.16)	0.692
Age 45-55			
Without Thyroid disorders	1.00	—	—
With Hypothyroidism	1.18	(0.90-1.54)	0.226
Without Thyroid disorders	1.00	—	—
With Hyperthyroidism	1.15	(1.02-1.29)	0.019
Without Thyroid disorders	1.00	—	—
With Acquired Hypothyroidism	0.84	(0.50-1.43)	0.532
Without Thyroid disorders	1.00	—	—
Others	1.05	(0.96-1.15)	0.276
Age ≥ 56			
Without Thyroid disorders	1.00	—	—
With Hypothyroidism	1.23	(0.98-1.54)	0.070
Without Thyroid disorders	1.00	—	—
With Hyperthyroidism	1.05	(0.93-1.19)	0.454
Without Thyroid disorders	1.00	—	—
With Acquired Hypothyroidism	1.07	(0.65-1.76)	0.792
Without Thyroid disorders	1.00	—	—
Others	0.92	(0.84-1.00)	0.052

Adjusted OR was adjusted for age, estrogen use, and history of Iodine treatment by logistic regression analysis.

In the subgroup analysis, we examined whether medication and/or surgical treatment for hyper- or hypothyroidism would change the risk of having breast cancer. The

analysis showed no statistically significant differences between treatments for hyper- or hypothyroidism and the risk of developing breast cancer (OR 1.01, 95% CI 0.88-1.17, *p*=0.857; OR 0.80, 95% CI 0.54-1.18, *p*=0.262; respectively). (Table 3)

Table 3. Subgroup analysis for treatment - adjusted odds ratio of breast cancer associated with thyroid disorders (TD)

Variable	Adjusted OR	95% CI	*p* value
Subjects with Hypothyroidism			
Without TD medications	1.00	—	—
With TD medications[1]	0.80	(0.54-1.18)	0.262
Subjects with Hyperthyroidism			
Without TD medications and surgery	1.00	—	—
With TD medications[2] or surgery[3]	1.01	(0.88-1.17)	0.857
Subjects with Hyperthyroidism			
Without TD medications and surgery	1.00	—	—
With surgery[4]	0.97	(0.74-1.27)	0.825
With TD medications	1.02	(0.88-1.19)	0.789

Adjusted OR was adjusted for age, estrogen use, and history of Iodine treatment by logistic regression analysis.

[1] Hypothyroidism medication: levothyroxine.
[2] Hyperthyroidism medications: methimazole, propylthiouracil (did not include radioactive iodine treatment since it was adjusted separately).
[3] Surgery: thyroidectomy (partial or total).
[4] If the patient received both medication and surgical treatment, the patient would be classified as surgical patient in this subgroup.

A separate analysis for autoimmune thyroid disease to examine the association with breast cancer showed no statistical significance (OR 0.94, 95% CI 0.68-1.29, p=0.685 for Hashimoto; OR 1.20, 95% CI 0.96-1.50, p=0.109 for Graves'). We also performed an additional analysis with the exclusion of those who only had a 'one-time' diagnosis of thyroid disorder during an inpatient admission to eliminate possible inpatient admission bias. In the breast cancer group, there were 22 patients with only one-time hypothyroidism diagnosis and 77 patients with only one-time hyperthyroidism diagnosis out of 335 and 1580 patients respectively; while in the control group, 17 patients with only one-time hypothyroidism diagnosis out of 291 and 82 patients with only one-time hyperthyroidism diagnosis out of 1453 patients. After excluding those with only one-time diagnosis of hyperthyroidism or hypothyroidism, the results showed similar associations as above. Hyperthyroidism in all age groups showed an overall increased risk by 13% in breast cancer development (adjusted OR 1.13, 95% CI 1.05-1.21, p=0.002), while hypothyroidism in all age groups had an 18% increased risk (adjusted OR 1.18, 95% CI 1.01-1.39, p=0.043).

DISCUSSION

This is the first study in an Asian population assessing the association between hyperthyroidism, hypothyroidism and breast cancer. Among a total of 103,466 women in our study, we found increased risks of developing breast cancer in patients with medical history of either hyperthyroidism or hypothyroidism despite treatment. The association is significant in patients under age 55 years old with hyperthyroidism.

Since Beaston first described using thyroid extract to treat metastatic breast cancer in the Lancet in 1896, many studies have investigated the relationship between thyroid hormone and cancers.[20 21] Specific alterations of thyroid hormone receptors (TR) have been found in different types of carcinomas, including breast cancer, and many studies observed associations between the expression of TRs and the regulation of oncogenes.[21-23] Several physiological similarities have been discovered between the thyroid gland and mammary gland. For one, both thyroid follicular cells and breast lactating cells store iodine through natrium-iodine symporter (NIS)-mediated iodine uptake.[24-27] The oxidization of iodine in the alveolar mammary cells utilizes lactohyperoxidase, which is mechanistically similar to peroxidase in thyroid glands.[28]

Several *in vitro* studies have shown that high levels of thyroid hormones may possess estrogen-like effects and may promote breast cancer proliferation and angiogenesis.[5 13 21 23 29] It has also been shown that the activation of TR in mammary glands may induce the differentiation and lobular growth of breast tissues, an effect similar to that seen with estrogen.[21 22] Active triiodothyronine (T3) has been found to promote breast cancer cell proliferation and to increase the effect of 17beta-estradiol (E2)-mediated cell proliferation in some breast cancer cell lines.[13] In population-based studies, T3 levels have also been found to have a positive correlation with breast cancer tumor size and the risk of lymph node metastasis.[30]

Hypothyroidism may trigger hypersensitization of mammary glandular epithelium to estrogen and prolactin, possibly related to low circulating thyroid hormone, and further lead to mammary dysplasia and neoplasia of the breast.[17 18 31] Previous studies showed a positive correlation between elevated serum prolactin level and an increased risk of breast cancer,[32 33] while other study also found that mild hyperprolactinemia did not carry significant health risks and thus treatment was not required in post-menopausal women.[34] The existence of a genetic predisposition for hypothyroidism and breast cancer has been hypothesized as well.[6 10]

We did not find a statistically significant association between autoimmune thyroid disease (AITD) and breast cancer risk in this study. However, several studies have shown that there may be a possible association between AITD and breast cancer, but

controversial in AITD and breast cancer survival. A study by Jiskra *et al.* found a higher prevalence of euthyroid AITD in women with breast cancer and no prognostic impact from AITD on breast cancer survival.[35]

In our study, the significantly increased risk of breast cancer among patients with the diagnosis of hyperthyroidism under 55 years of age is possibly related to higher levels of thyroid hormone in addition to the physiological level of estrogen. The increased risk drops from 15-16% to 5% with no statistical significance in hyperthyroidism patients >55 years of age. This is likely related to the menopausal status of these patients, an indicator of low estrogen levels. In the further subgroup analysis, we found that hyperthyroidism treatment with medications and/or surgery and thyroid replacement treatment for hypothyroidism did not alter the risk of having breast cancer in the future. While there is a 19% increased risk of breast cancer in hypothyroidism patients, the statistical significance disappears when we stratify these patients into the 3 age groups. Since there were only 335 patients with a diagnosis of hypothyroidism who developed breast cancer, dividing this group into 3 age cohorts led to a decrease in power. Based on our overall results, however, we can hypothesize that there is no protective effect of hypothyroidism in the development of breast cancer. Interestingly, the use of estrogen-containing products (which we controlled for) was not a contributing factor to an increased risk of breast cancer in this study.

In 2017, it is estimated that 40,610 women may die of breast cancer in the U.S.[1] Current breast cancer screening guidelines published by the U.S. Preventive Services Task Force (USPSTF) recommend biennial screening mammography for women at average risk aged 50 to 74 years.[36] The American Cancer Society (ACS) recommends annual screening mammography for women at average risk aged 45 to 55 years then biennial screening after 55 years of age.[37] Our nationwide population-based study showed a significantly increased breast cancer risk in Asian women with medical history of hyperthyroidism under the age of 55 years and an increased risk or at least no protective effect of hypothyroidism. More studies are needed to examine this association in different age groups.

Limitations

The findings from our study were derived from a large population-based dataset; this minimized selection bias. The case-control study design using an administrative claims database reduced the recall bias; however, the findings might be less accurate due to the lack of supporting laboratory data; this includes thyroid antibody, TSH and thyroid hormones levels as well as breast cancer stages and receptor status. In order to minimize bias, we only studied those with a diagnosis of hyper- or hypothyroidism who were documented as having these diagnoses in at least three outpatient visits or one inpatient admission. All breast cancer patients in this study had the diagnosis of breast cancer and possessed the certificate of catastrophic illness. To avoid false claims, the National Health Insurance Bureau (NHIB) randomly samples a fixed percentage of claims from each hospital every year to confirm diagnosis validity, and medical records

were independently reviewed by professional experts. Since this study is based on administrative claims, the results may be underestimated or overestimated, as only patients who seek medical attention were evaluated and treated. Since thyroid disorders are often chronic diseases rather than acute onset, we thought that it might not be as useful to adjust the time lapse from the diagnosis of thyroid disorder to breast cancer.

Conclusion

Our nationwide Asian population-based study suggests that Asian women under the age of 55 years with medical history of hyperthyroidism have a significantly increased risk of developing breast cancer regardless of treatment. Women with a history of hypothyroidism may also have an increased risk. Further studies are needed to assess the association between age, hypothyroidism, and breast cancer risk.

Author contributions:

Concept of study: C-H Weng and T-H Lin

Study design: C-H Weng, X Luo, C-H Lin and T-H Lin

Statistical analysis: Y-H Chen and C-H Lin

Interpretation of results: C-H Weng, Y-H Chen, X Luo, and C-H Lin

Manuscript writing: C-H Weng

The other authors provided inputs, expertise, and critical review of the manuscript.

C-H Weng and T-H Lin contributed as co-senior authors to this article.

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This study has been approved by the Institutional Review Board of Taichung Veterans General Hospital, Taichung, Taiwan (IRB # CE13151B-3). The study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not

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Data sharing: Extra data is available by emailing the Corresponding author (jth.lin@gmail.com).

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Figure legend:

Figure 1. Flow Diagram of Participants Selection and Study Design

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12x4mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Nationwide population-based study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4	Findings and Interpretation
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6	Paragraph 1-2
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6	Paragraph 3
Methods				
Study design	4	Present key elements of study design early in the paper	7	Paragraph 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7	Paragraph 1
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls ***Cross-sectional study***—Give the eligibility criteria, and the sources and methods of selection of participants	8-9	Breast cancer Case-control match Hyperthyroidism and hypothyroidism
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed ***Case-control study***—For matched studies, give matching criteria and the number of controls per case	8-9	Case-control match
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10	NHIRD & RCIPD & LHID Hyper-/hypothyroidism, breast cancer
Bias	9	Describe any efforts to address potential sources of bias	26	Limitations of study

Study size	10	Explain how the study size was arrived at	8-9	51,733 patients in each group

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10	Statistical analysis paragraph
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10	
		(*b*) Describe any methods used to examine subgroups and interactions	10	
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8-9	Case-control match paragraph
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-9 & Fig 1	
		(b) Give reasons for non-participation at each stage	7-9 & Fig 1	
		(c) Consider use of a flow diagram	Fig 1	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11	Paragraph 1 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	N/A	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	12-16	
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-15	
		(*b*) Report category boundaries when continuous variables were categorized	12-15	Paragraphs and Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-16 and Table 2	
Discussion				
Key results	18	Summarise key results with reference to study objectives	17	Paragraph 1
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-20	Paragraph 2-6
Generalisability	21	Discuss the generalisability (external validity) of the study results	19-20	
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23	Acknowledgement

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Thyroid Disorders and Breast Cancer Risk in Asian Population: A Nationwide Population-Based Case-Control Study in Taiwan

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Abstract

Objective: To evaluate whether hyper- or hypothyroidism increases the risk of subsequent breast cancer in an Asian population.

Design: Nationwide population-based case-control study.

Setting: All health care facilities in Taiwan.

Participants: A total of 103,466 women (mean age 53.3 years) were enrolled.

Methods: 51,733 adult women with newly diagnosed with primary breast cancer without a previous cancer history between 2006 and 2011 were identified and included in our study. 51,733 women with no cancer diagnosis prior to the index date were age-matched as controls. Diagnosis of hyper- or hypothyroidism prior to the diagnosis of breast cancer or the same index date was identified, age, histories of thyroid disease treatment, estrogen use and radioactive-iodine treatment were adjusted.

Main outcome measures: To identify risk differences in developing breast cancer among patients with a medical history of hyper- or hypothyroidism.

Results: There was a significantly increased risk of breast cancer in women with hyperthyroidism under age of 55 years (age <45: OR 1.16, p=0.049; age 45-55: OR 1.15, p=0.019). Patients with hypothyroidism also showed an increased risk of breast cancer (OR 1.19, p=0.029) without statistical significance after stratification by age group (age <45, 45-55, >55 years). Treatment for thyroid disorders did not alter the association in subgroup analyses (p=0.857; 0.262 respectively).

Conclusions: Asian women under 55 years of age with history of hyperthyroidism have a significantly increased risk of breast cancer regardless of treatment. Women with history of hypothyroidism may also have an increased risk.

Strengths and limitations of this study

- This is the first study in an Asian population assessing the association between hyperthyroidism, hypothyroidism, breast cancer, and age.
- The main strength of this study is the large population-based dataset which minimized the selection bias.
- The most important limitation of this study is the characteristic of the database. Since it is a national health insurance claims database, detailed TSH, T4, T3 level, types and stages of breast cancer are not available for further stratification and analysis.

INTRODUCTION

One in eight women will develop breast cancer in their lifetime, a disease prevalence similar to the risk of thyroid disorders in this population.[1-3] Since high thyroid hormone levels are found to have estrogen-like effects in several *in vitro* studies, thyroid hormone levels and their relation to the development of breast and other cancers have been studied in the past with conflicting results and primarily in Caucasian populations. Most of the literature published to date have relied on studies of relatively small sample sizes.[4-14] Sogaard *et al.* published a large study in 2016 utilizing the national registry in Denmark found an increased risk of breast cancer in those who had a medical history of hyperthyroidism without age stratification.[5]

Previous observational studies also showed a higher prevalence of hypothyroidism in patients with breast cancer.[15 16] Older studies proposed that hypothyroidism may induce the breast epithelial cells' sensitivity to prolactin and estrogen.[17 18] A recent systematic review and meta-analysis included 13 population-based studies with a total of 24,808 participants through June 2016 found that either hypothyroidism or hyperthyroidism has no related risk for breast cancer.[19]

We conducted the first study in an Asian population In order to assess the association between hyperthyroidism, hypothyroidism and breast cancer in different age groups. It is a nationwide population-based case-control study utilizing the Taiwanese National Health Insurance Research Database (NHIRD), one of the largest administrative health

care databases in the world; our aim was to discover the relationship between hyper- or hypothyroidism and breast cancer from the epidemiological aspect.

METHODS

We designed a case-control study utilizing the Taiwanese National Health Insurance Research Database (NHIRD). Female patients with a new diagnosis of primary breast cancer and no previous cancer history were identified from the NHIRD (diagnosed between 2006 and 2011). Age-matched female individuals without a breast cancer diagnosis were randomly selected as controls. We then identified the status of thyroid disorders prior to the diagnosis of breast cancer in the case group or the same index date in the control group. We excluded those with a history of a thyroid malignancy. (Figure 1)

Taiwanese National Health Insurance Research Database (NHIRD)

The National Health Insurance program was established in Taiwan in March 1995 and covers about 99% of the Taiwanese population. The National Health Insurance Research Database (NHIRD), established by the National Health Research Institute (NHRI), is a claims database maintained by the Department of Health and the NHRI. There are several subset databases in the NHIRD including the Registry for Catastrophic Illness Patient Database (RCIPD). Breast cancer is defined as a catastrophic illness by the government. Thus, when patients are diagnosed with breast cancer, they will apply and register for the certificate of catastrophic illness.

The Longitudinal Health Insurance Database (LHID) is a database of one million randomly selected insurers from the NHIRD. We used the 2010 version of the LHID which included 1,000,000 individuals randomly selected from the total of 23,251,700 insured.

Breast cancer

In order to identify patients with newly diagnosed primary breast cancer, we searched the NHIRD by using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM) code 174 and 175, cross-linking these to the RCIPD. The identified patients all had newly diagnosed breast cancer between 2006 and 2011 and possessed a certificate of catastrophic illness. There were 53,488 total patients identified.

We then excluded male gender, age unknown, sex unknown, or age < 18 or >120 years old at the time of diagnosis. We excluded patients with diagnoses of other malignant diseases before the diagnosis of breast cancer. A total of 51,733 patients were identified from the NHIRD by the above criteria as cases.

Case-control match

We applied a one-to-one match for the control group, randomly matched for age, sex, and the same index date (the month and year of breast cancer diagnosis in the case group) from the LHID. We excluded male gender, age unknown, sex unknown, age < 18

or >120 years old at time of index date, or deceased before index date. We excluded patients with the diagnosis of breast cancer. Also excluded patients were those with diagnoses of other malignant diseases before the index date. A total of 51,733 women were selected as controls.

Hyperthyroidism and hypothyroidism

To identify patients with the diagnosis of hyperthyroidism, we used the ICD9-CM code 242 with additional criteria including the same diagnosis in at least three outpatient visits or one inpatient admission. We stipulated that the first diagnosis of hyperthyroidism had to occur before the date of first breast cancer diagnosis in the case group or the index date in the control group. We used the ICD9-CM codes 243 and 244 with the same additional criteria to identify patients with hypothyroidism. We also excluded patients with ICD9-CM codes 244.0, 244.1, 244.2, 244.3 in the hypothyroidism group since those are acquired hypothyroidism. We identified a specific group of patients with both hyperthyroidism (ICD9-CM 242) and hypothyroidism diagnoses (ICD9-CM 244.0, 244.1, 244.2, 244.3), which represents acquired hypothyroidism from hyperthyroidism treatments. We excluded those with a diagnosis of thyroid malignancy in our study since strong evidences have shown an increased risk of developing breast cancer among thyroid cancer survivors.[20]

Other adjustments

We adjusted for estrogen use or hormone replacement therapy, a history of radioactive iodine treatment, medication or surgical treatment for thyroid disease, and age. We identified the use of hyperthyroidism, hypothyroidism medications, estrogen-containing products including oral forms, injection forms, or external-use forms available on the market in Taiwan, and labeled them as ever-used versus never-used. We did not calculate the length of use in each female since it is very difficult to know their compliance and effects between different products. We also identified females who have ever received radioactive iodine treatment and adjusted it in our analysis.

Statistical analysis

To examine the differences in clinical characteristics between breast cancer and control groups, we used the Student's t-test to analyze continuous variables and the chi-square test to analyze categorical variables. Conditional logistic regression analysis was applied to examine the effect of thyroid disorders, including hyperthyroidism, hypothyroidism, and acquired hypothyroidism, on the risk of developing breast cancer, and controlled for potential confounders. Logistic regression analysis was applied to examine the associations between treatments for hyperthyroidism or hypothyroidism and the risk of developing breast cancer in subgroup analysis. All statistical tests were two-sided, conducted at a significance level of 0.05, and reported using *p*-values and/or 95% confidence intervals (95% CI). All analyses were performed using Statistical Analytic System (SAS) software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 103,466 patients were enrolled in our study, 51,733 in each group. As for patient characteristics, the mean ages were 53.4 years and 53.3 years in the breast cancer and control groups, respectively (p=0.137). In the breast cancer group, 36.9% of the patients had ever used estrogen-containing medications; in the control group, 41.6% of patients had ever used estrogen-containing medications (p<0.001). Prior to the time of breast cancer diagnosis or the index date, 46 and 42 women received radioactive iodine treatment in the breast cancer and control groups, respectively (p=0.67). Significant differences in the proportions of thyroid disorders in the breast cancer group and control group were found (p=0.022). There were 335 patients (0.7%) with hypothyroidism in the breast cancer group and 291 patients (0.6%) in the control group. A total of 1580 patients (3.1%) had the diagnosis of hyperthyroidism in the breast cancer group and 1453 patients (2.8%) in the control group. (Table 1)

Table 1. Clinical characteristics of study subjects with and without breast cancer

Variable	Total (N=103,466)		Without breast cancer (N=51,733)		With breast cancer (N=51,733)		*p* value
	n	(%)	n	(%)	n	(%)	

Age, years (mean ± SD)	53.3±12.1		53.3±12.2		53.4±12.0		0.137[+]
Gender							—
Female	103466	(100.0)	51733	(100.0)	51733	(100.0)	
Male	0	(0.0)	0	(0.0)	0	(0.0)	
Thyroid disorders							0.022
No	93675	(91.0)	46866	(91.0)	46809	(90.9)	
With Hypothyroidism	626	(0.6)	291	(0.6)	335	(0.7)	
With Hyperthyroidism	3033	(2.9)	1453	(2.8)	1580	(3.1)	
With Acquired Hypothyroidism	161	(0.2)	87	(0.2)	74	(0.1)	
Others	5462	(5.3)	2782	(5.4)	2680	(5.2)	
History of estrogen use							<0.001
No	62834	(60.7)	30197	(58.4)	32637	(63.1)	
Yes	40632	(39.3)	21536	(41.6)	19096	(36.9)	
History of radioactive iodine treatment							0.670
No	103378	(99.9)	51691	(99.9)	51687	(99.9)	
Yes	88	(0.1)	42	(0.1)	46	(0.1)	
Medication treatment for thyroid disorder							0.510
No	100569	(97.2)	50302	(97.2)	50267	(97.2)	
Yes	2897	(2.8)	1431	(2.8)	1466	(2.8)	
Thyroidectomy							0.330
No	102307	(98.9)	51137	(98.8)	51170	(98.9)	
Yes	1159	(1.1)	596	(1.2)	563	(1.1)	

[+] T test; chi-squared test for all other *p-values*.

Acquired Hypothyroidism: with diagnoses of hyperthyroidism + hypothyroidism.

Both hyperthyroidism and hypothyroidism were associated with an increased risk of developing breast cancer after adjusting for age, estrogen-containing medication use,

and a history of radioactive iodine treatment. Hyperthyroidism in all age groups showed an overall increased risk by 12% in breast cancer development (OR 1.12, 95% CI 1.04-1.20, *p*=0.003), while hypothyroidism in all age groups had a 19% increased risk (OR 1.19, 95% CI 1.02-1.40, *p*=0.029). No significant change in risk was found among those who had acquired hypothyroidism after treatment for hyperthyroidism (OR 0.88, 95% CI 0.64-1.22, *p*=0.453).

When we stratified by age group (age<45, age 45-55, age>55 years), patients with hyperthyroidism aged 55 or under showed a significantly increased breast cancer risk; this association disappeared in those aged 55 years and older. Among patients aged <45 years, there was a 16% increased risk in breast cancer (OR 1.16, 95% CI 1.00-1.34, *p*=0.049). In those aged 45-55 years there was a 15% increased risk (OR 1.15, 95% CI 1.02-1.29, *p*=0.019). The increased odds for breast cancer in patients with hypothyroidism did not reach statistical significance among those 3 age groups. (Table 2)

Table 2. Adjusted odds ratio of breast cancer associated with thyroid disorders

Variable	Adjusted OR	95% CI	*p* value
Overall			
Without Thyroid disorders	1.00	—	—
With Hypothyroidism	1.19	(1.02-1.40)	0.029
Without Thyroid disorders	1.00	—	—
With Hyperthyroidism	1.12	(1.04-1.20)	0.003
Without Thyroid disorders	1.00	—	—

With Acquired Hypothyroidism	0.88	(0.64-1.22)	0.453
Without Thyroid disorders	1.00	—	—
Others	0.99	(0.94-1.05)	0.806
Age < 45			
Without Thyroid disorders	1.00	—	—
With Hypothyroidism	1.07	(0.71-1.60)	0.757
Without Thyroid disorders	1.00	—	—
With Hyperthyroidism	1.16	(1.00-1.34)	0.049
Without Thyroid disorders	1.00	—	—
With Acquired Hypothyroidism	0.62	(0.29-1.32)	0.214
Without Thyroid disorders	1.00	—	—
Others	1.03	(0.91-1.16)	0.692
Age 45-55			
Without Thyroid disorders	1.00	—	—
With Hypothyroidism	1.18	(0.90-1.54)	0.226
Without Thyroid disorders	1.00	—	—
With Hyperthyroidism	1.15	(1.02-1.29)	0.019
Without Thyroid disorders	1.00	—	—
With Acquired Hypothyroidism	0.84	(0.50-1.43)	0.532
Without Thyroid disorders	1.00	—	—
Others	1.05	(0.96-1.15)	0.276
Age ≥ 56			
Without Thyroid disorders	1.00	—	—
With Hypothyroidism	1.23	(0.98-1.54)	0.070
Without Thyroid disorders	1.00	—	—
With Hyperthyroidism	1.05	(0.93-1.19)	0.454
Without Thyroid disorders	1.00	—	—
With Acquired Hypothyroidism	1.07	(0.65-1.76)	0.792
Without Thyroid disorders	1.00	—	—
Others	0.92	(0.84-1.00)	0.052

Adjusted OR was adjusted for age, estrogen use, and history of Iodine treatment by logistic regression analysis.

In the subgroup analysis, we examined whether medication and/or surgical treatment for hyper- or hypothyroidism would change the risk of having breast cancer. The analysis showed no statistically significant differences between treatments for hyper- or hypothyroidism and the risk of developing breast cancer (OR 1.01, 95% CI 0.88-1.17, *p*=0.857; OR 0.80, 95% CI 0.54-1.18, *p*=0.262; respectively). (Table 3)

Table 3. Subgroup analysis for treatment - adjusted odds ratio of breast cancer associated with thyroid disorders (TD)

Variable	Adjusted OR	95% CI	*p* value
Subjects with Hypothyroidism			
Without TD medications	1.00	—	—
With TD medications[1]	0.80	(0.54-1.18)	0.262
Subjects with Hyperthyroidism			
Without TD medications and surgery	1.00	—	—
With TD medications[2] or surgery[3]	1.01	(0.88-1.17)	0.857
Subjects with Hyperthyroidism			
Without TD medications and surgery	1.00	—	—
With surgery[4]	0.97	(0.74-1.27)	0.825
With TD medications	1.02	(0.88-1.19)	0.789

Adjusted OR was adjusted for age, estrogen use, and history of Iodine treatment by logistic regression analysis.

[1] Hypothyroidism medication: levothyroxine.
[2] Hyperthyroidism medications: methimazole, propylthiouracil (did not include radioactive iodine treatment since it was adjusted separately).
[3] Surgery: thyroidectomy (partial or total).
[4] If the patient received both medication and surgical treatment, the patient would be classified as surgical patient in this subgroup.

A separate analysis for autoimmune thyroid disease to examine the association with breast cancer showed no statistical significance (OR 0.94, 95% CI 0.68-1.29, p=0.685 for Hashimoto; OR 1.20, 95% CI 0.96-1.50, p=0.109 for Graves'). We also performed an additional analysis with the exclusion of those who only had a 'one-time' diagnosis of thyroid disorder during an inpatient admission to eliminate possible inpatient admission bias. In the breast cancer group, there were 22 patients with only one-time hypothyroidism diagnosis and 77 patients with only one-time hyperthyroidism diagnosis out of 335 and 1580 patients respectively; while in the control group, 17 patients with only one-time hypothyroidism diagnosis out of 291 and 82 patients with only one-time hyperthyroidism diagnosis out of 1453 patients. After excluding those with only one-time diagnosis of hyperthyroidism or hypothyroidism, the results showed similar associations as above. Hyperthyroidism in all age groups showed an overall increased risk by 13% in breast cancer development (adjusted OR 1.13, 95% CI 1.05-1.21, p=0.002), while hypothyroidism in all age groups had an 18% increased risk (adjusted OR 1.18, 95% CI 1.01-1.39, p=0.043).

DISCUSSION

This is the first study in an Asian population assessing the association between hyperthyroidism, hypothyroidism and breast cancer. Among a total of 103,466 women in our study, we found increased risks of developing breast cancer in patients with medical history of either hyperthyroidism or hypothyroidism despite treatment. The association is significant in patients under age 55 years old with hyperthyroidism.

Since Beaston first described using thyroid extract to treat metastatic breast cancer in the Lancet in 1896, many studies have investigated the relationship between thyroid hormone and cancers.[21 22] Specific alterations of thyroid hormone receptors (TR) have been found in different types of carcinomas, including breast cancer, and many studies observed associations between the expression of TRs and the regulation of oncogenes.[22-24] Several physiological similarities have been discovered between the thyroid gland and mammary gland. For one, both thyroid follicular cells and breast lactating cells store iodine through natrium-iodine symporter (NIS)-mediated iodine uptake.[25-28] The oxidization of iodine in the alveolar mammary cells utilizes lactohyperoxidase, which is mechanistically similar to peroxidase in thyroid glands.[29]

Several *in vitro* studies have shown that high levels of thyroid hormones may possess estrogen-like effects and may promote breast cancer proliferation and angiogenesis.[5 13 22 24 30] It has also been shown that the activation of TR in mammary glands may induce the differentiation and lobular growth of breast tissues, an effect similar to that seen with estrogen.[22 23] Active triiodothyronine (T3) has been found to promote breast cancer cell proliferation and to increase the effect of 17beta-estradiol (E2)-mediated cell proliferation in some breast cancer cell lines.[13] In population-based studies, T3 levels have also been found to have a positive correlation with breast cancer tumor size and the risk of lymph node metastasis.[31]

Hypothyroidism may trigger hypersensitization of mammary glandular epithelium to estrogen and prolactin, possibly related to low circulating thyroid hormone, and further lead to mammary dysplasia and neoplasia of the breast.[17 18 32] Previous studies showed a positive correlation between elevated serum prolactin level and an increased risk of breast cancer,[33 34] while other study also found that mild hyperprolactinemia did not carry significant health risks and thus treatment was not required in post-menopausal women.[35] The existence of a genetic predisposition for hypothyroidism and breast cancer has been hypothesized as well.[6 10]

We did not find a statistically significant association between autoimmune thyroid disease (AITD) and breast cancer risk in this study. However, several studies have

shown that there may be a possible association between AITD and breast cancer, but controversial in AITD and breast cancer survival. A study by Jiskra *et al.* found a higher prevalence of euthyroid AITD in women with breast cancer and no prognostic impact from AITD on breast cancer survival.[36]

In our study, the significantly increased risk of breast cancer among patients with the diagnosis of hyperthyroidism under 55 years of age is possibly related to higher levels of thyroid hormone in addition to the physiological level of estrogen. The increased risk drops from 15-16% to 5% with no statistical significance in hyperthyroidism patients >55 years of age. This is likely related to the menopausal status of these patients, an indicator of low estrogen levels. In the further subgroup analysis, we found that hyperthyroidism treatment with medications and/or surgery and thyroid replacement treatment for hypothyroidism did not alter the risk of having breast cancer in the future. While there is a 19% increased risk of breast cancer in hypothyroidism patients, the statistical significance disappears when we stratify these patients into the 3 age groups. Since there were only 335 patients with a diagnosis of hypothyroidism who developed breast cancer, dividing this group into 3 age cohorts led to a decrease in power. Based on our overall results, however, we can hypothesize that there is no protective effect of hypothyroidism in the development of breast cancer. Interestingly, the use of estrogen-containing products (which we controlled for) was not a contributing factor to an increased risk of breast cancer in this study.

In 2017, it is estimated that 40,610 women may die of breast cancer in the U.S.[1] Current breast cancer screening guidelines published by the U.S. Preventive Services Task Force (USPSTF) recommend biennial screening mammography for women at average risk aged 50 to 74 years.[37] The American Cancer Society (ACS) recommends annual screening mammography for women at average risk aged 45 to 55 years then biennial screening after 55 years of age.[38] Our nationwide population-based study showed a significantly increased breast cancer risk in Asian women with medical history of hyperthyroidism under the age of 55 years and an increased risk or at least no protective effect of hypothyroidism. More studies are needed to examine this association in different age groups.

Limitations

The findings from our study were derived from a large population-based dataset; this minimized selection bias. The case-control study design using an administrative claims database reduced the recall bias; however, the findings might be less accurate due to the lack of supporting laboratory data; this includes thyroid antibody, TSH and thyroid hormones levels as well as breast cancer stages and receptor status. In order to minimize bias, we only studied those with a diagnosis of hyper- or hypothyroidism who were documented as having these diagnoses in at least three outpatient visits or one inpatient admission. All breast cancer patients in this study had the diagnosis of breast cancer and possessed the certificate of catastrophic illness. To avoid false claims, the National Health Insurance Bureau (NHIB) randomly samples a fixed percentage of claims from each hospital every year to confirm diagnosis validity, and medical records

were independently reviewed by professional experts. Since this study is based on administrative claims, the results may be underestimated or overestimated, as only patients who seek medical attention were evaluated and treated. Since thyroid disorders are often chronic diseases rather than acute onset, we thought that it might not be as useful to adjust the time lapse from the diagnosis of thyroid disorder to breast cancer.

Conclusion

Our nationwide Asian population-based study suggests that Asian women under the age of 55 years with medical history of hyperthyroidism have a significantly increased risk of developing breast cancer regardless of treatment. Women with a history of hypothyroidism may also have an increased risk. Further studies are needed to assess the association between age, hypothyroidism, and breast cancer risk.

Author contributions:

Concept of study: C-H Weng and T-H Lin

Study design: C-H Weng, X Luo, C-H Lin and T-H Lin

Statistical analysis: Y-H Chen and C-H Lin

Interpretation of results: C-H Weng, Y-H Chen, X Luo, and C-H Lin

Manuscript writing: C-H Weng

The other authors provided inputs, expertise, and critical review of the manuscript.

C-H Weng and T-H Lin contributed as co-senior authors to this article.

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The preliminary results from this study have been presented in part at the 86th Annual Meeting of the American Thyroid Association in Denver, CO by Chien-Hsiang Weng, MD, MPH, September 21-25, 2016. Authors thank all the comments and advices from the conference.

This study has been approved by the Institutional Review Board of Taichung Veterans General Hospital, Taichung, Taiwan (IRB # CE13151B-3). The study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not

represent those of National Health Insurance Administration, Department of Health or National Health Research Institutes.

Declaration of interest: The authors declare no potential conflicts of interest.

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Data sharing: Extra data is available by emailing the Corresponding author (jth.lin@gmail.com).

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Figure legend:

Figure 1. Flow Diagram of Participants Selection and Study Design

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12x4mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Nationwide population-based study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4	Findings and Interpretation
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6	Paragraph 1-2
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6	Paragraph 3
Methods				
Study design	4	Present key elements of study design early in the paper	7	Paragraph 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7	Paragraph 1
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls ***Cross-sectional study***—Give the eligibility criteria, and the sources and methods of selection of participants	8-9	Breast cancer Case-control match Hyperthyroidism and hypothyroidism
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed ***Case-control study***—For matched studies, give matching criteria and the number of controls per case	8-9	Case-control match
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10	NHIRD & RCIPD & LHID Hyper-/hypothyroidism, breast cancer
Bias	9	Describe any efforts to address potential sources of bias	2-6	Limitations of study

Study size	10	Explain how the study size was arrived at	8-9	51,733 patients in each group

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10	Statistical analysis paragraph
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10	
		(*b*) Describe any methods used to examine subgroups and interactions	10	
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8-9	Case-control match paragraph
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-9 & Fig 1	
		(b) Give reasons for non-participation at each stage	7-9 & Fig 1	
		(c) Consider use of a flow diagram	Fig 1	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11	Paragraph 1 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	N/A	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	12-16	
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-15	
		(*b*) Report category boundaries when continuous variables were categorized	12-15	Paragraphs and Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-16 and Table 2	
Discussion				
Key results	18	Summarise key results with reference to study objectives	17	Paragraph 1
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-20	Paragraph 2-6
Generalisability	21	Discuss the generalisability (external validity) of the study results	19-20	
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23	Acknowledgement

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.