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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 hyperthyroidism or hypothyroidism increases the risk of subsequent breast cancer in an Asian population.

Design Nationwide population-based case–control study.

Setting All healthcare 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 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 hyperthyroidism or hypothyroidism prior to the diagnosis of breast cancer or the same index date was identified, age, histories of thyroid disease treatment, oestrogen 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 hyperthyroidism or hypothyroidism.

Results There was a significantly increased risk of breast cancer in women with hyperthyroidism under the 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 minimised 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 thyroid-stimulating hormone, thyroxine, triiodothyronine 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 oestrogen-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 using 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 oestrogen.[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 using the Taiwanese National Health Insurance Research Database (NHIRD), one of the largest administrative healthcare

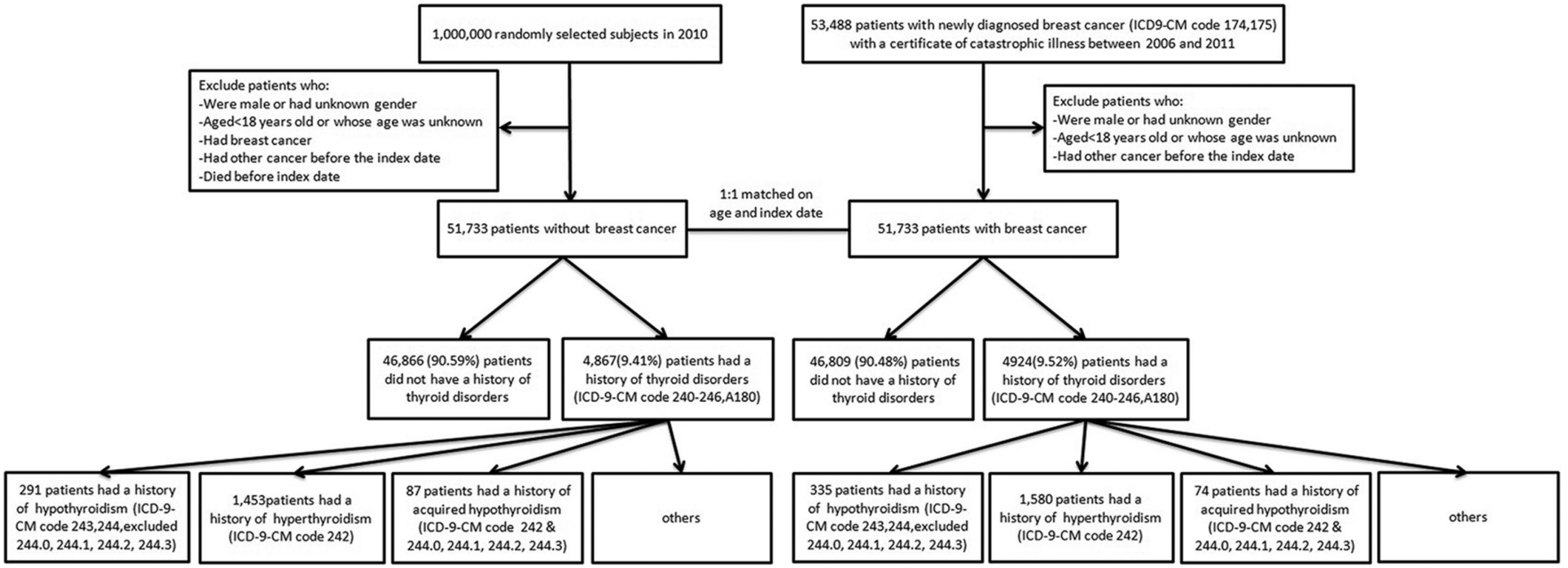

Figure 1 Flow diagram of participants selection and study design. ICD9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

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

METHODS

We designed a case–control study using the Taiwanese 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 NHIRD

The National Health Insurance programme was established in Taiwan in March 1995 and covers about 99% of the Taiwanese population. The 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, Ninth 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 oestrogen 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, oestrogen-containing products including oral forms, injection forms or external-use forms available on the market in Taiwan, and labelled them as ever-used versus never-used. We did not calculate the length of use in each woman since it is very difficult to know their compliance and effects between different products. We also identified women 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 analyse continuous variables and the X^2 test to analyse 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% CIs. All analyses were performed using SAS V.9.4.

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

Variable	Total (N=103 466) n (%)	Without breast cancer (N=51 733) n (%)	With breast cancer (N=51 733) n (%)	P value
Age, years (mean±SD)	53.3±12.1	53.3±12.2	53.4±12.0	0.137*
Gender				–
Female	103 466 (100.0)	51 733 (100.0)	51 733 (100.0)	
Male	0 (0.0)	0 (0.0)	0 (0.0)	
Thyroid disorders				0.022
No	93 675 (91.0)	46 866 (91.0)	46 809 (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 oestrogen use				<0.001
No	62 834 (60.7)	30 197 (58.4)	32 637 (63.1)	
Yes	40 632 (39.3)	21 536 (41.6)	19 096 (36.9)	
History of radioactive iodine treatment				0.670
No	103 378 (99.9)	51 691 (99.9)	51 687 (99.9)	
Yes	88 (0.1)	42 (0.1)	46 (0.1)	
Medication treatment for thyroid disorder				0.510
No	100 569 (97.2)	50 302 (97.2)	50 267 (97.2)	
Yes	2897 (2.8)	1431 (2.8)	1466 (2.8)	
Thyroidectomy				0.330
No	102 307 (98.9)	51 137 (98.8)	51 170 (98.9)	
Yes	1159 (1.1)	596 (1.2)	563 (1.1)	

Acquired hypothyroidism, with diagnoses of hyperthyroidism + hypothyroidism.
*Student 's t-test; X^2 test for all other P values.

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 oestrogen-containing medications; in the control group, 41.6% of patients had ever used oestrogen-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).

Both hyperthyroidism and hypothyroidism were associated with an increased risk of developing breast cancer after adjusting for age, oestrogen-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 to 1.20, P=0.003), while hypothyroidism in all age groups had a 19% increased risk (OR 1.19, 95% CI 1.02 to 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 to 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 to 1.34, P=0.049). In those aged 45–55 years, there was a 15% increased risk (OR 1.15, 95% CI 1.02 to 1.29, P=0.019). The increased odds for breast cancer in patients with hypothyroidism did not reach statistical significance among those three age groups (table 2).

In the subgroup analysis, we examined whether medication and/or surgical treatment for hyperthyroidism or hypothyroidism would change the risk of having breast cancer. The analysis showed no statistically significant

Table 2 Adjusted OR 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 to 1.40	0.029
Without thyroid disorders	1.00	–	–
With hyperthyroidism	1.12	1.04 to 1.20	0.003
Without thyroid disorders	1.00	–	–
With acquired hypothyroidism	0.88	0.64 to 1.22	0.453
Without thyroid disorders	1.00	–	–
Others	0.99	0.94 to 1.05	0.806
Age <45 years			
Without thyroid disorders	1.00	–	–
With hypothyroidism	1.07	0.71 to 1.60	0.757
Without thyroid disorders	1.00	–	–
With hyperthyroidism	1.16	1.00 to 1.34	0.049
Without thyroid disorders	1.00	–	–
With acquired hypothyroidism	0.62	0.29 to 1.32	0.214
Without thyroid disorders	1.00	–	–
Others	1.03	0.91 to 1.16	0.692
Age 45–55 years			
Without thyroid disorders	1.00	–	–
With hypothyroidism	1.18	0.90 to 1.54	0.226
Without thyroid disorders	1.00	–	–
With hyperthyroidism	1.15	1.02 to 1.29	0.019
Without thyroid disorders	1.00	–	–
With acquired hypothyroidism	0.84	0.50 to 1.43	0.532
Without thyroid disorders	1.00	–	–
Others	1.05	0.96 to 1.15	0.276
Age ≥56 years			
Without thyroid disorders	1.00	–	–
With hypothyroidism	1.23	0.98 to 1.54	0.070
Without thyroid disorders	1.00	–	–
With hyperthyroidism	1.05	0.93 to 1.19	0.454
Without thyroid disorders	1.00	–	–
With acquired hypothyroidism	1.07	0.65 to 1.76	0.792
Without thyroid disorders	1.00	–	–
Others	0.92	0.84 to 1.00	0.052

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

Table 3 Subgroup analysis for treatment-adjusted OR 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*	0.80	0.54 to 1.18	0.262
Subjects with hyperthyroidism			
Without TD medications and surgery	1.00	–	–
With TD medications† or surgery‡	1.01	0.88 to 1.17	0.857
Subjects with hyperthyroidism			
Without TD medications and surgery	1.00	–	–
With surgery§	0.97	0.74 to 1.27	0.825
With TD medications	1.02	0.88 to 1.19	0.789

Adjusted OR was adjusted for age, oestrogen use and history of Iodine treatment by logistic regression analysis.
*Hypothyroidism medication: levothyroxine.
†Hyperthyroidism medications: methimazole, propylthiouracil (did not include radioactive iodine treatment since it was adjusted separately).
‡Surgery: thyroidectomy (partial or total).
§If the patient received both medication and surgical treatment, the patient would be classified as surgical patient in this subgroup.

differences between treatments for hyperthyroidism or hypothyroidism and the risk of developing breast cancer (OR 1.01, 95% CI 0.88 to 1.17, P=0.857; OR 0.80, 95% CI 0.54 to 1.18, P=0.262, respectively) (table 3).

A separate analysis for autoimmune thyroid disease (AITD) to examine the association with breast cancer showed no statistical significance (OR 0.94, 95% CI 0.68 to 1.29, P=0.685 for Hashimoto's disease; OR 1.20, 95% CI 0.96 to 1.50, P=0.109 for Graves' disease). 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 to 1.21, P=0.002), while hypothyroidism in all age groups had an 18% increased risk (adjusted OR 1.18, 95% CI 1.01 to 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 the age of 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 (TRs) 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-mediated iodine uptake.[25–28] The oxidation of iodine in the alveolar mammary cells uses lactoperoxidase, which is mechanistically similar to peroxidase in thyroid glands.[29]

Several in vitro studies have shown that high levels of thyroid hormones may possess oestrogen-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 oestrogen.[22 23] Active triiodothyronine (T3) has been found to promote breast cancer cell proliferation and to increase the effect of 17beta-oestradiol-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 tumour size and the risk of lymph node metastasis.[31]

Hypothyroidism may trigger hypersensitisation of mammary glandular epithelium to oestrogen 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 hyperprolactinaemia did not carry significant health risks, and thus treatment was not required in postmenopausal women.[35] The existence of a genetic predisposition for hypothyroidism and breast cancer has been hypothesised as well.[6 10]

We did not find a statistically significant association between 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 oestrogen. The increased risk drops from 15%–16% to 5% with no statistical significance in patients with hyperthyroidism >55 years of age. This is likely related to the menopausal status of these patients, an indicator of low oestrogen 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 patients with hypothyroidism, the statistical significance disappears when we stratify these patients into the three age groups. Since there were only 335 patients with a diagnosis of hypothyroidism who developed breast cancer, dividing this group into three age cohorts led to a decrease in power. Based on our overall results, however, we can hypothesise that there is no protective effect of hypothyroidism in the development of breast cancer. Interestingly, the use of oestrogen-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 USA[1] Current breast cancer screening guidelines published by the US Preventive Services Task Force recommend biennial screening mammography for women at average risk aged 50–74 years.[37] The American Cancer Society recommends annual screening mammography for women at average risk aged 45–55 years and 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 minimised 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, thyroid-stimulating hormone and thyroid hormones levels as well as breast cancer stages and receptor status. In order to minimise bias, we only studied those with a diagnosis of hyperthyroidism or hypothyroidism who were documented as having these diagnoses in at least three outpatient visits or one inpatient admission. All patients with breast cancer 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 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.

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