Observational Study

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The crosstalk between benign thyroid disease and breast cancer

A single center study

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Abstract

This study aims to investigate the relationship between benign thyroid disease and breast cancer. The clinical study includes a total of 600 participants, divided into 2 groups: the control group (N = 300), which consists of individuals from the checkup population during the same periods, and the experimental group (N = 300), which consists of patients with breast cancer. General data of the participants, including age, tumor diameter, tumor staging, pathological classification, lymph node metastasis, and classification of benign thyroid disease, were collected and analyzed. The levels of TT3, TT4, FT3, FT4, TSH, TPOAb, and TgAb in blood samples from the experimental and control groups were determined using a radioimmune method. The levels of TPOAb, TgAb, and TSH in the experimental group were significantly higher than those in the control group, while the levels of TT3, TT4, FT3, and FT4 in the experimental group were significantly lower. The general data of the participants contributed to the appropriate sample size and allocation. Furthermore, benign thyroid disease contributes to the development of breast cancer by regulating the levels of TT3, TT4, FT3, FT4, TSH, TPOAb, and TgAb.

Keyword: anti-thyroid autoantibodies, benign thyroid disease, breast cancer

1. Introduction

This study aims to carry out research on the association between breast cancer and thyroid diseases. Breast cancer, the most prevalent malignant tumor among women worldwide, is renowned for its high occurrence and mortality rates.[1,2] Currently, breast cancer is categorized into 4 different pathological types: in situ cancer, early-stage invasive cancer, specialized invasive cancer, and nonspecific invasive cancer. With continuous advancements in early detection and clinical treatment strategies, the 5-year survival rate for breast cancer has significantly increased.[3,4] However, it is important to acknowledge that breast cancer remains a significant cause of mortality for women, with the second highest mortality rate among female cancers. In 2022, there were more than 2260,000 new cases of breast cancer diagnosed worldwide, resulting in over 500,000 reported deaths.[5] The main reason why breast cancer leads to death is the recurrence of cancer. The primary cause of recurrence is the spread of breast cancer cells, with triple-negative breast cancer cells being an aggressive and difficult-to-treat type of breast cancer associated with a poor prognosis.[6–8] Different changes in key genes and pathways are involved in the metastasis process of various types of breast cancer cell lines. Furthermore, deaths reported in previous studies can be attributed to drug resistance and breast cancer subtypes.[6,9,10] Some studies suggest that benign thyroid disease may be involved in the progression of breast cancer.[7] Related information remains limit.

Benign thyroid disease, which is also one of the most frequent diseases in women, known for a common disease of the endocrine system. Benign thyroid disease seriously endangers human health, and thyroid dysfunction caused by benign thyroid disease attracted widespread attention worldwide.[11–13] Thyroid diseases mainly consist of nontoxic goiter, hyperthyroidism, hypothyroidism, thyroiditis, and thyroid cancer. According to the GLOBOCAN database in 2022, it is estimated that 449,000 new cases of thyroid cancer were diagnosed in women in 2022.[14] Thyroid cancer is a life-threatening health problem worldwide. Additionally, benign thyroid diseases such as nontoxic goiter, hyperthyroidism, hypothyroidism,

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The ethic approval was reviewed and approved from the Ethic Committee of Zhejiang Provincial People Hospital, Hangzhou Medical College and informed written consent from all of the patients. All methods were carried out in accordance with relevant guidelines and regulations.

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and thyroiditis also have a high incidence globally. Currently, numerous treatments[15] for benign thyroid disease such as surgical treatment, antithyroid drug have been used to treat benign thyroid disease and these methods have protective effect in preventing the development of benign thyroid disease.[16,17] However, the therapeutic effect of these treatment methods in benign thyroid disease still do not meet requirement of patients. In addition, benign thyroid disease has associated with other diseases process such as breast cancer. The possible interactions between thyroid gland and breast tissue may be based on the common property of both epithelial tissues to concentrate iodine by means of a sodium/iodine symporter, as well as on the presence of TSH receptors in fatty tissue, which is abundant in mammary glands.[18] The breast and thyroid are both hormone responsive organs. The changes in endocrine function are closely related to the occurrence of glandular diseases. Thyroid hormone can regulate the growth of the body and cell proliferation, and its insufficient or excessive content can change the metabolism of hormones and chemical carcinogens in the anterior pituitary and target organs.[19] Therefore, it is believed that the progression of breast cancer may be affected by different levels of thyroid hormone content. The effect of thyroid hormone on breast cancer is still unknown, which may be both a promoting factor for tumor cell formation and a protective factor against tumor cell formation and growth. Clinically, breast cancer patients may be accompanied by changes in thyroid morphology, such as thyroid dysfunction, Hashimoto thyroiditis which is one of the most common chronic autoimmune diseases, multiple nodules, and benign and malignant thyroid tumors. However, the detailed correlation of benign thyroid disease and breast cancer is still unclear, it is urgent to investigate the effect of benign thyroid disease in development of breast cancer.

Previous studies have suggested that benign thyroid disease can influence the development of breast cancer.[18,20,21] Based on these findings described in previous studies, we hypothesized that benign thyroid disease is correlated with development of breast cancer. This study aims to carry out research on the association between breast cancer and thyroid diseases, in order to assess any possible association in terms of clinical presentation, management, and breast cancer, then analyze the difference of the incidence rate of various thyroid diseases between breast cancer patients and the general population, detect the changes of biological indicators of breast cancer patients with thyroid diseases, judge the impact of thyroid diseases on the prognosis of breast cancer patients. These outcomes will provide important clinical implications in treating breast cancer and benign thyroid disease.

2. Methods

2.1. Study design and participants

To account for bias and confounding factors, we carried out a single-center, prospective, non-randomized controlled trial. From January 2021 to June 2022, we enrolled a total of 300 breast cancer patients from our hospitals. The sample size was determined using PASS software. All these patients were assigned to the experimental group (N = 300). We also selected a control group of 300 individuals who underwent checkups during the same time period, matched on a 1:1 basis., and these participants in experimental group and control group who receive ultrasound diagnostic apparatus detection. In addition, all participants also receive thyroid ultrasound imaging, thyroid antibody levels detection, thyroid function detection. The hospital ethics committee have approved all protocols used for this study and written informed consent forms are obtained from all patients with breast cancer.

Inclusion criteria for breast cancer patients: Chinese women aged between 18 and 65; breast cancer patients with an Eastern Cooperative Oncology Group performance status of 0 to 2; patients with non-metastatic, unilateral, initially treated, pathologically confirmed clinical stage I, II, or stage III primary invasive breast cancer; no contraindications for taking aspirin, such as no allergy to aspirin, no history of grade 4 hypertension, no history of atrial fibrillation or myocardial infarction, no history of thrombosis, no history of cerebrovascular accidents, no history of gastrointestinal bleeding, and currently no history of gastric/duodenal ulcers; no surgical treatment within 30 days before breast cancer diagnosis; written informed consent signed by the patient or their guardians.

Exclusion criteria for breast cancer patients: Disease progression or serious complications during the treatment process; patient request to withdraw from the study; no signed written informed consent.

Inclusion criteria for the control group: Chinese women aged between 18 and 65; all participants in the control group undergo thyroid ultrasound imaging, thyroid antibody levels detection, and thyroid function detection; written informed consent signed by all participants.

The exclusion criteria for the control group are as follows: participants who do not undergo thyroid ultrasound imaging, thyroid antibody level detection, and thyroid function detection; participants who have not signed the written informed consent.

2.2. Collection for clinical material from patients

Upon admission of patients in the experimental group to the hospital, various factors such as age, tumor size, tumor stage, pathology, lymph node involvement, and classification of benign thyroid diseases are collected and analyzed. Both the control group and the experimental group undergo thyroid ultrasound imaging, detection of thyroid antibody levels and thyroid function, and simultaneous collection of blood samples from both groups. These blood samples are then used for further experimental analysis.

2.3. Ultrasound diagnostic apparatus detection

An ultrasound diagnostic instrument (Philips HDllXE, USA) with a linear array broadband probe and a frequency of 7.5 to 12 MHz was used to detect benign thyroid diseases in both the control group and the experimental group. The participants were positioned in a supine position, with the anterior cervical area exposed. If necessary, the patients were instructed to tilt their heads to the opposite side while scanning one side of the thyroid using the ultrasound diagnostic instrument. The transverse and longitudinal sections of both sides and the isthmus of the thyroid gland were thoroughly scanned, ensuring not to miss the conical lobe. The ultrasound diagnostic results are presented in Figure 1.

2.4. The detection of blood samples by a radioimmune method

To clear the TT3, TT4, FT3, FT4, TSH, TPOAb, and TgAb level in blood samples from experimental group and control group, radioimmune method is used to measure TT3, TT4, FT3, FT4, TSH, TPOAb, and TgAb level. The blood samples are ground and lysed using cell lysate, and then we centrifuged these samples at 4°C, 10,000 rpm for 10 minutes, and the supernatant is then collected. An appropriate amount of supernatant is collected for protein quantification and a radioimmune method. The ELISA kit which is used to detect TT3, TT4, FT3, FT4, TSH, TPOAb, and TgAb level in blood samples from experimental group and control group according to protocol provided by manufacture.

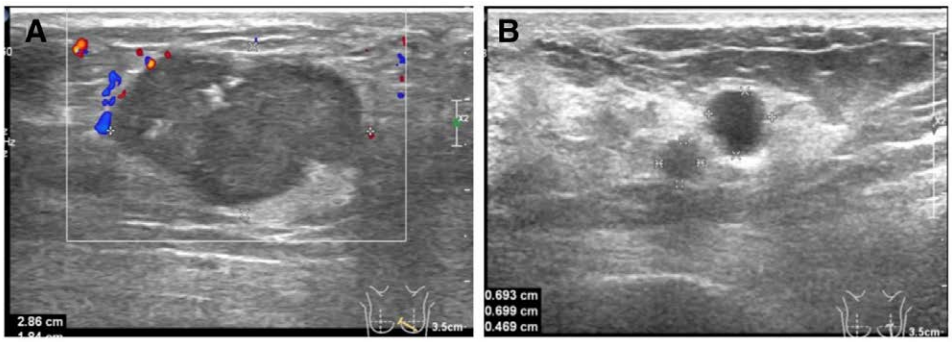

Figure 1. Ultrasound diagnostic apparatus results, A represent the ultrasound results of control group and B represent the ultrasound results of experimental group.

Table 1

Demographic, participants general data.

Variable		Experimental group	Control group	*P*
Age	≥55 yr-old	185	190	>.05
	<55 yr-old	115	110	
Tumor diameter	≥3 cm	181	—	—
	<3 cm	119	—	
Tumor staging	staging I– II	201	—	—
	staging III–IV	99	—	
Lymph node metastasis	Yes	102	—	—
	No	198	—	—
Benign thyroid disease				
	Thyroid dysfunction	55 (18.3%)	25 (8.3%)	<.05
	Hashimoto thyroiditis	41 (13.7%)	19 (6.3%)	<.05
	Multiple nodules	32 (10.7%)	15 (5%)	<.05
	Benign and malignant thyroid tumors	30 (10%)	5 (1.7%)	<.05

A Chi-square test is performed for evaluation of descriptive data.

2.5. Statistical analysis

Statistical analysis was conducted using SPSS 20.0 software. Descriptive data were presented as n (%) and measurement data were expressed as mean ± standard deviation (x ± s). The descriptive data were evaluated using a chi-square test, while a t-test was used to compare the measurement data between 2 groups. A significant difference was indicated by $P < .05$.

3. Results

3.1. Participants general data

Table 1 presents the clinical medical data of participants in the experimental group and control group. The age, tumor diameter, tumor staging, and lymph node metastasis of both groups are displayed in Table 1. The occurrence and analysis of benign thyroid diseases, such as thyroid dysfunction, Hashimoto thyroiditis, multiple nodules, and benign and malignant thyroid tumors, were recorded. The analysis revealed no significant differences in patient general data, including age, tumor diameter, tumor staging, and lymph node metastasis, between the experimental group and control group. However, the number of cases with thyroid dysfunction, Hashimoto thyroiditis, multiple nodules, and benign and malignant thyroid tumors was significantly higher in the experimental group compared to the control group.

3.2. Comparison of TPOAb level, TgAb level

The radioimmune method was used to calculate the TPOAb level and TgAb level in the experimental group and control group. According to Figure 2, the TPOAb value in the control group was 11.6 ± 3.5 IU/mL, while in the experimental group it was 41.3 ± 10.6 IU/mL. The TgAb value in the control group was 14.8 ± 3.8 IU/mL, and in the experimental group it was 86.5 ± 15.1 IU/mL. The TPOAb level in the experimental group showed a significant increase, with a significant statistical difference ($P < .05$). Similarly, the TgAb level in the experimental group also showed a significant increase, with a significant statistical difference ($P < .05$). These findings suggest that an up-regulated TPOAb level and TgAb level can promote the development process of breast cancer.

3.3. Comparison of TT3, TT4, FT3, FT4, TSH between 2 groups

The levels of TT3, TT4, FT3, FT4, and TSH were determined using the radioimmune method and are presented in Figure 3. The results from the radioimmune method indicated that the experimental group exhibited low expression of TT3, TT4, FT3, and FT4 levels, while the control group showed low expression of TSH levels. There was a significant difference in the levels of TT3, TT4, FT3, FT4, and TSH between the 2 groups. These findings suggest that up-regulation of TSH levels and down-regulation of TT3, TT4, FT3, and FT4 levels may promote the development of breast cancer. Regression analysis was performed to evaluate the association between breast cancer and the levels of TT3, TT4, FT3, FT4, TSH, TPOAb, and TgAb (shown in Table 2). The results revealed a negative association between breast cancer and the levels of TT3, TT4, FT3, and FT4, while a positive association

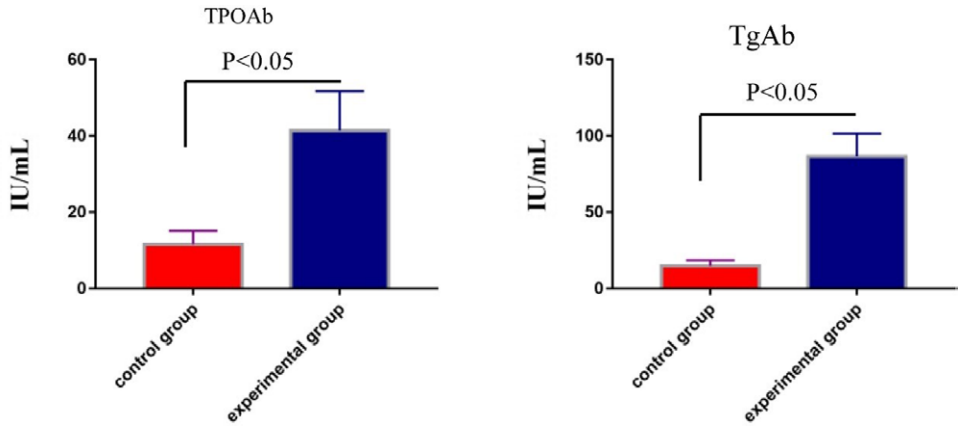

Figure 2. The levels of TPOAb level, TgAb level. The TPOAb level, TgAb level in blood samples from control group and experimental group are determined by radioimmune method, and these results are presented in Figure 2. The value is presented as means ± standard deviation and measurement data was compared using *t* test. **P* < .05 versus control group and shows the difference is statistical differences.

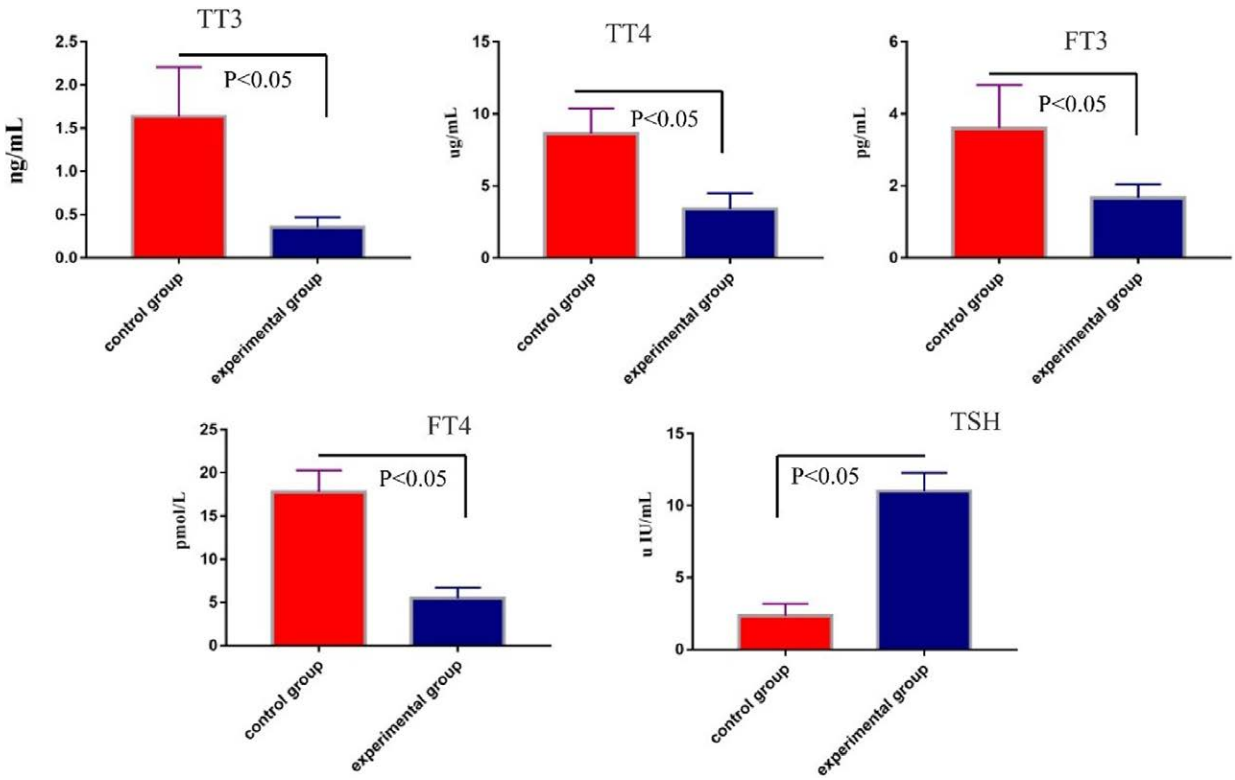

Figure 3. The relative levels of TT3, TT4, FT3, FT4, TSH. The TT3 level, TT4 level, FT3 level, FT4 level, TSH level in the blood samples from control group and experimental group are determined by radioimmune method, and these results are presented in Figure 3. The value is presented as means ± standard deviation and measurement data was compared using *t* test. **P* < .05 versus control group and shows the difference is significant statistical.

was observed between breast cancer and the levels of TSH, TPOAb, and TgAb.

4. Discussion

Results of this study supported the original hypothesis, indicating benign thyroid disease contributes to the breast cancer process. To clarify the detailed correlation between breast cancer and benign thyroid disease, we conduct this study to record the participants' clinical material data. TT3, TT4, FT3, FT4, TSH, TPOAb, and TgAb level in blood samples from experimental group and control group are detected. Our results show that the general material between 2 groups is no significant difference. Compared to number of patients with benign thyroid disease in control group, number of patients with benign thyroid disease in experimental group is clearly increased. TSH, TPOAb, and TgAb level in blood samples in control group are significantly decreased compared to those in experimental group, and TT3, TT4, FT3, and FT4 level in experimental group is clearly decreased compared to those in control group. These outcomes suggest that TT3, TT4, FT3, and FT4 level negatively correlated with breast cancer progression, while TSH, TPOAb, and TgAb level positively correlated with the development of breast cancer.

Benign thyroid disease, as a disease of the endocrine system, the changes in endocrine function in patients with benign

Table 2

Association between breast cancer and TT3 or TT4 or FT3 or FT4 or TSH or TPOAb or TgAb.

	Breast cancer	
	OR	95% CI
TPOAb	4.36	2.88–9.65
TgAb	3.67	2.55–4.68
TSH	3.31	2.31–4.12
TT3	0.14	0.12–0.21
TT4	0.04	0.02–0.08
FT3	0.07	0.05–0.17
FT4	0.12	0.08–0.19

CI = confidence interval, OR = odds ratio.

thyroid disease contribute to numerous diseases by controlling cell biological processes. Breast and thyroid are both hormone responsive organs, and benign thyroid disease is closely to breast diseases. Both TPOAb and TgAb are common antithyroid autoantibodies, and the changes of TPOAb level and TgAb level have associated with numerous disease such as breast cancer. A clinical study provided by Muller[22] pointed that relative expression level of TPOAb have association with the development of breast of cancer. In addition, a meta-analysis study by Pan[23] have reported that up-regulation of TgAb level have an increased prevalence of breast cancer. But the information about TPOAb level and TgAb level in breast cancer remains limit. Therefore, we conduct this trial to investigate the relationship between TPOAb level, TgAb level and breast cancer. Our results show that the changes of TPOAb level, TgAb level can influence the breast cancer process and up-regulation of TPOAb level, TgAb level can contribute the development of breast cancer. These results are consistent with those in previous studies. We can see that TPOAb, TgAb are promising targets for patients with breast cancer.

To further clarify the relationship between benign thyroid disease and breast cancer. We also investigate the relationship between TT3, TT4, FT3, FT4, and TSH level and breast cancer. TT3, TT4, FT3, FT4, TSH are important hormones which are secreted by thyroid, and participate in numerous diseases progression. Some trials have pointed out that the changes of TT3 level, TT4 level, FT3 level, FT4 level, TSH level participate in development process of breast cancer by controlling tumor microenvironment. A clinical trial by Ortega-Olvera[24] have reported that down-regulation of TT3 level, TT4 level in serum can promote the development of breast cancer. In addition, a study by Meirovitz[25] has described that high expression of TT3 level, TT4 level also promote breast cancer process by controlling the proliferative activity. These outcomes in our study suggested that low expression of TT3, TT4, FT3, FT4 level can promote the breast cancer process. And these outcomes hints at potential mechanisms by which thyroid dysfunction might influence breast cancer, indicating potential mechanisms of TT3, TT4, FT3, FT4, TSH, TPOAb, and TgAb regulating the tumor microenvironment in breast cancer.[5,6]

There are some limitations in our study. Firstly, this study has a single-center design and is non-randomized control. In the future, a multi-center design and randomized control study will be conducted. Secondly, the main limitation is the small sample size, and a larger sample study is needed. Moreover, all participants enrolled in this study are Chinese, so further investigation is needed to examine these results in the white and black population. In addition, 1 patient demonstrated poor compliance in the experimental group, which contributed to bias. However, the noncompliance rate was within 10%. Finally, this study only indicates an association between thyroid disease and breast cancer.

5. Conclusion

We can conclude that there is a correlation between benign thyroid disease and the development of breast cancer. This correlation is mediated by the regulation of TPOAb, TgAb, TT3, TT4, FT3, FT4, and TSH levels. These biomolecule levels are also associated with both benign thyroid disease and breast cancer, and can be utilized to predict treatment response and survival in patients with these conditions.

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Writing – review & editing: Yajuan Zheng, Hongchao Tang, Jun Wu, Dandan Guan, Qiuping Mo, Qinghui Zheng.

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