sciendo

252 ENDOCRINE REGULATIONS, Vol. 58, No. 4, 252–258, 2024

doi:10.2478/enr-2024-0030

The relationship between breast cancer and thyroid autoimmune disorders in southeast Iran: A case-control study

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Objective. To better understand the role of thyroid hormones in regulating the growth of breast epithelial cells and the estrogen-like effects of these hormones, the present study was conducted to investigate the relationship between breast cancer and thyroid autoimmune disorders in southeast Iran women.

Methods. In this case-control study, in the case group, all newly diagnosed breast cancer patients referred to the oncology clinics in Zahedan city in years 2021–2022 were studied. The number of participants in each group was represented by 40 breast cancer patients. The control group was represented by women without breast cancer. The sampling method was simple or available using the nonprobability method. The presence or absence of thyroid dysfunction was checked using thyroid-stimulating hormone (TSH), free thyroxin (FT4), free triiodothyronine (FT3), anti-thyroid peroxidase (TPO), and anti-thyroglobulin (Tg) tests.

Results. The mean age of participants was 47±11 years. The risk of subclinical hyperthyroidism was higher in subjects with breast cancer and about 8 times higher than in the healthy ones (OR=8.27). According to the value of OR=1, the risk of developing autoimmune thyroid disease was the same in individuals with breast cancer as in healthy individuals. The odds ratio of hypothyroidism could not be calculated because the value in the control group was zero.

Conclusion. The results of this study show that there are abnormal characteristics of the thyroid gland in breast cancer patients compared to the control group. The incidence of subclinical hyperthyroidism was significantly increased in the breast cancer patients. However, there was no difference in the incidence of autoimmune thyroid disease between the two groups.

Keywords: breast neoplasms, thyroid hormones, autoimmune diseases, estrogens

Today, breast cancer is the most prevalent type of cancer in women after non-melanoma skin cancer. More than 250,000 new cases of breast cancer have been diagnosed in the United States in 2017. It has been reported that 12% of women in the United States are diagnosed with breast cancer in their lifetimes (Antonelli et al. 2015). In 2012, close to 1.67 million cases were diagnosed and 250,000 passed away worldwide due to breast cancer (Stathatos 2019). In general, breast cancer is the most common cancer in Iran. According to the latest national databases, the standardized rate of breast cancer is 33.21 cases

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per 100,000 people. The age-standardized mortality rate is 14.2 per 100,000 people with an average age of 49.84 years. Invasive ductal carcinoma has been reported as the most prevalent type of breast cancer in Iran (Journy et al. 2017).

Two main target molecules have been recognized to be involved in the pathogenesis of breast cancer. One of them is the estrogen receptor alpha (ERα), which is expressed in approximately 70% of invasive breast cancers. Estrogen receptor alpha is a steroid hormone receptor and a transcription factor that when activated by estrogen, switches on the oncogene growth pathways in breast cancer cells. The expression of the receptor for steroid hormones like progesterone (PR) is an indicator of ERα signaling. Tumors are classified as hormone receptor (HR)-positive by expressing either estrogen or progesterone receptors in at least 1% of the tumor cells. The second main target molecule is epidermal growth factor 2 (ERbb2). Tyrosine kinase membrane receptor in the epidermal growth factor receptor family is amplified or overexpressed in approximately 20% of breast cancers and is associated with poor prognosis in the absence of systemic therapy (Journy et al. 2017).

The relationship between breast cancer and benign thyroid disorders, especially autoimmune thyroid disorders, has been the subject of controversy for decades. Considering the role of thyroid hormones in regulating the growth of breast epithelial cells and the estrogen-like effects of these hormones, there seems to be a relationship between thyroid disease and breast cancer. Some studies have shown higher levels of thyroid peroxidase antibodies, a hallmark of thyroid autoimmunity, among breast cancer patients compared to the general population (Dobrinja et al. 2019). Nevertheless, conflicting results have been reported by the studies that have investigated the association between thyroid hormone levels and the progression of breast cancer, and as yet the main mechanism of this potential link has remained elusive. Previous studies have shown an increase in the prevalence of autoimmune and non-autoimmune thyroid diseases in breast cancer patients (Lopes et al. 2020; Muller and Barrett-Lee 2020). Some studies suggested a higher incidence of breast cancer in women with thyroid disease, while several other studies have not shown such an association or even indicated an inverse correlation (Jia et al. 2024; Jin et al. 2024). Several small independent studies have shown a link between positive antibodies and a better prognosis of breast cancer, although such observations were not confirmed by subsequent retrospective studies conducted in larger groups (Baxevanis et al. 2021; Chai et al. 2024; Ouyang et al. 2024).

Therefore, due to the contradiction in different reports on the relationship between thyroid disease and breast cancer and the lack of regional information, the present study was designed to investigate thyroid autoimmune disorder in women who have recently been diagnosed with breast cancer in the southeast of Iran.

Materials and Methods

Design and participants. The present case-control study was conducted on 40 breast cancer patients who were diagnosed recently and referred to the oncology clinics of Zahedan City and 40 healthy participants in the southeast of Iran from 10 February 2021 to 10 March 2022. The participants in the control group were healthy women.

The inclusion criteria for the case group were included: having new cases of breast cancer, resident of Sistan and Baluchistan province, being willing to participate in the study having no history of chronic diseases including kidney failure and COPD and having no history of another type of cancers and drugs which impacted the thyroid function. The inclusion criteria for the control group were included same as the case-control group except they were healthy women aged more than 40 years.

The exclusion criteria for both groups included a diagnosis of another type of cancer, a history of diabetes and acute infection and unwillingness to participate in the study.

Based on the similar study of Fadavi et al. (2020) and using the below formula, the sample size for each group was determined 40 participants and a total of 80 participants.

$$n_1 = \kappa n_2$$

$$n_2 = \frac{(z_{\alpha/2} + z_{\beta})^2}{\varepsilon^2} \left[\frac{p_1(1-p_1)}{\kappa} + p_2(1-p_2) \right]$$

The values of parameters in the formula were: α=0.05, β=0.20, κ=1, and ε=0.25 and the power of study was 80%.

The participants in two groups were selected using the consecutive sampling method based on eligibility criteria. Two groups matched in terms of age and gender.

Ethical consideration. The protocol of the study was approved by the ethics committee of Zahedan University of Medical Sciences with the code IR.ZAUMS.REC.1400.264. In addition to obtaining a written consent form following a complete explanation of the study and also controlling the

symptoms and complications of the study and paying attention to the fact that the method used in the study is a standard method.

Tools. Data were collected using a researcher-made questionnaire with the variables included: age, diagnosis of breast cancer (yes/no) based on pathology results, thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Tg) antibodies.

Data collection. After the approval of the proposal by the Ethics Committee of Zahedan University of Medical Sciences and obtaining permission to collect information related to the research, the researcher went to the oncology clinics of Zahedan City. First, the necessary arrangements were made with the clinic doctor and the research objectives were explained. In addition, it was emphasized that the patients' information remains completely confidential and will be used only for this research. Patients with a new diagnosis of breast cancer and no previous history of cancer were identified from the respective clinics. The studied population included two groups: Case group, which includes patients who have recently been diagnosed with breast cancer and are in the stage before any medical cancer treatment such as chemotherapy, radiotherapy or hormone therapy and Control group. The number of the case group was selected from acquaintances (other than relatives) of referring patients and companions of patients hospitalized in other departments of the hospital who had no history of breast cancer, any other type of cancer, or thyroid disorders.

Peripheral blood samples were taken from all the studied subjects to evaluate the following thyroid tests and the measurement results were recorded: FT4, FT3, TSH, anti-TPO, anti-Tg. After receiving the results of the tests, the results were entered into the Excel form.

Data analysis. After collecting the data, the raw data were entered into the statistical software SPSS version 22. The Kolmogorov-Smirnov test was used to check the normality of the data, and frequency distribution tables were used to describe the qualitative data. Also, to describe quantitative data, common central indices (mean and median) and dispersion indices (standard deviation) were used. An independent t-test was used to compare the average age variable between the two groups, according to the assumptions of parametric tests. The chi-square test and Fisher's exact test were used to compare the ratio between groups (checking the relationship). Also, to determine the relationship between independent qualitative variables with breast cancer, the Odds Ratio (OR) index was used. In all analyses, $p<0.05$ was considered as the significance level.

Results

In the present study, a total of 80 people were participated and divided into two groups, case and control, for further assessments. All participants were fully involved in the study and the response rate was 100%. Most of the participants in the control group were under 50 years of age. In the case group, most of the participants (85%) were in the early stage of the disease (Table 1).

In terms of the number of patients with hyperthyroidism, 8 cases with subclinical hyperthyroidism

Table 1
Demographic characteristics of participants

Variable		Case group n (%)	Control group n (%)
Age (years)	≥50	17	20
	<50	23	20
Early stage		–	34 (85.0)
Advanced stage		–	6 (15.0)
Triple-negative		–	8 (20.0)
Luminal A		–	8 (20.0)
Luminal B HER2+		–	13 (32.5)
Luminal B HER2-		–	7 (17.5)
ER&PR – HER2+		–	4 (10.0)
Autoimmune thyroid disease		6 (15.0)	6 (15.0)
Subclinical hyperthyroidism		1 (2.5)	7 (17.5)

Table 2
Comparison of the prevalence of hyperthyroidism, hypothyroidism and the frequency of thyroid autoimmune disorders in case and control groups

Variable	Breast cancer (Case group) n (%)	Healthy women (Control group) n (%)
Hyperthyroidism		
No	33 (82.5)	39 (97.5)
Yes	0	0
Clinical range	7 (17.5)	1 (2.5)
Hypothyroidism		
No	37 (92.5)	40 (100.0)
Yes	1 (2.5)	0
Clinical range	2 (5.0)	0
Frequency of thyroid autoimmune disorders		
No	34 (85.0)	34 (85.0)
Yes	6 (15.0)	6 (15.0)
Clinical range	0	0

were detected, of which 7 cases were in the breast cancer group. Fisher's exact test results showed a significant difference in the frequency of cases with subclinical hyperthyroidism between the breast cancer patients and the control groups [OR=8, 95% CI for OR (0.968, 70.734); p=0.05]. In terms of hypothyroidism and subclinical hypothyroidism, one case and two cases, respectively were observed in the breast cancer group. The odds ratio of hypothyroidism with zero value in the control group could not be calculated. Regarding the frequency of autoimmune thyroid disorders, 6 patients were diagnosed in each group. The results of the chi-square test showed no substantial difference in the frequency of autoimmune thyroid disorders between breast cancer patients and the control groups. According to OR=1, the chance of developing thyroid autoimmune disorders in breast cancer patients was equal to healthy individuals (Table 2).

The results of the study showed no significant (p>0.05) relationship between autoimmune thyroid disorders and breast cancer subtypes including ER^{χ}-PR, HER2, and metastasis in the studied patients (Table 3).

The results of the study on the relationship between hyperthyroidism and breast cancer subtypes showed that there is no statistically significant relationship between hyperthyroidism and ER-PR status and the presence of metastasis. However, there is a statistically significant (p=0.01) relationship between hyperthyroidism and HER2 status (Table 4).

Table 3
The results of determining the relationship between thyroid autoimmune disorders and estrogen receptor-progesterone receptor (ER-PR) status in the case group

Thyroid autoimmune disorders	Total n (%)	ER^{χ}-PR	
		Negative n (%)	Positive n (%)
Negative	34 (100)	11 (32.4)	23 (67.6)
Positive	6 (100)	1 (16.7)	5 (83.3)
Total	40 (100)	12 (30)	28 (70)
		HER2	
Negative	34 (100)	21 (61.8)	13 (38.2)
Positive	6 (100)	2 (33.3)	4 (66.7)
Total	40 (100)	23 (57.5)	17 (42.5)
		Existence of metastases	
Negative	34 (100)	29 (85.3)	5 (14.7)
Positive	6 (100)	5 (83.3)	1 (16.7)
Total	40 (100)	34 (85)	6 (15)

Table 4
The results of determining the relationship between hyperthyroidism and estrogen receptor-progesterone receptor (ER-PR) status in the case group

ER-PR	Total n (%)	Hyperthyroidism	
		Negative n (%)	Clinical n (%)
Negative	12 (100)	11 (91.7)	1 (8.3)
Positive	28 (100)	22 (78.6)	6 (21.4)
Total	40 (100)	33 (82.5)	7 (17.5)
		HER2	
Negative	23(100)	22 (95.7)	1 (4.3)
Positive	17(100)	11 (64.7)	6 (35.3)
Total	40(100)	33 (82.5)	7 (17.5)
		Existence of metastases	
Negative	34 (100)	27 (79.4)	7 (20.6)
Positive	6 (100)	6 (100)	0
Total	40 (100)	33 (82.5)	7 (17.5)

Discussion

Our main objective in designing this study was to determine the relationship between thyroid autoimmune disorders and breast cancer. The results of the study showed that the chance of developing subclinical hyperthyroidism was 8-fold higher in people with breast cancer compared to healthy people. One case of hypothyroidism and 2 cases of subclinical hypothyroidism were observed in the breast cancer group. In addition, the results of this study showed that the chances of developing autoimmune thyroid disorders in people with breast cancer were equal to those of healthy people.

The coincidence of thyroid disease and breast cancer has long been debated. Although the association of hyperthyroidism, hypothyroidism, thyroiditis, and non-toxic goiter with breast cancer has been reported in several articles, there is no convincing evidence regarding the cause of thyroid disease manifestation in breast cancer. According to the study conducted by Smyth (2016) in Ireland, the geographical variation in the incidence of breast cancer has been attributed to differences in dietary iodine intake, and the reason for this has been hypothesized to be the effect of iodine on the breast tissue (Smyth 2016). In another study conducted in Austria, Frohlich and Wahl (2017) showed that the possible interactions between the thyroid gland and the breast tissue are based on the common feature of breast and thyroid epithelial cells for iodine condensation through an active membrane transport mechanism as well as the presence of TSH receptors in the adipose tissue of the mammary gland. In addition, some endocrine stimulants have been identified in

thyroid secretions that have simultaneous effects on the breast and various thyroid antibodies and can interact with receptors on breast tumors, hence they are assumed to be responsible for the co-occurrence of mammary and thyroid gland disorders (Frohlich and Wahl 2017).

The present study showed higher rates of hyperthyroidism in breast cancer patients. A meta-analysis conducted by Cordel and colleagues (2018) in France showed that the association between hyperthyroidism and breast cancer has been reported in numerous papers and that women with hyperthyroidism had an increased risk of breast cancer compared to the general population. This finding was more pronounced among people who were diagnosed with toxic goiter nodular at a younger age. Hyperthyroidism was also associated with predictive risk factors for breast cancer such as body mass index (BMI), age at the time of first delivery, and duration of breastfeeding. The link between mammographic results (density) and hyperthyroidism has only been observed in women who were diagnosed with toxic goiter-nodular. Moreover, having hyperthyroidism with a high Polygenic Risk Score (PRS) was associated with breast cancer, in particular, ER-positive breast cancer (Fang et al. 2017; Cordel et al. 2018.)

Several biological pathways may explain the link between hyperthyroidism and breast cancer development. The activation of phosphatidylinositol 3-kinases (PI3K) pathways is mediated by T3 through αvβ3 integrin, leading to increased invasion of breast cancer cells. Additionally, thyroxine (T4) induces mitogen-activated protein kinases (MAPK)-mediated nuclear phosphorylation of ERα and promotes cell proliferation to a degree comparable to the effect of estradiol. The effect of this hormone can be inhibited by a T4 analogue known as Tetrac (Fang et al. 2017). Furthermore, some studies have demonstrated that hyperthyroidism may lead to increased levels of the estrogen hormone, which promotes the growth of breast cancer (Saxena et al. 2022).

In addition to the known link between thyroid hormones and the risk of breast cancer development, there is a hypothesis that treating hyperthyroidism with I-131 (radioactive iodine) may also increase the risk of breast cancer. However, most of the studies found no significant association between I-131 treatment and breast cancer development. After surgery or treatment with radioiodine, patients with hyperthyroidism may subsequently develop hypothyroidism and therefore be prescribed thyroid replacement drugs (e.g. levothyroxine). In this regard, a meta-analysis study conducted by Kim (2022) in the UK showed no substantial increase in the risk of breast cancer in patients who developed hypothyroidism as a result of I-131 radiotherapy and underwent levothyroxine treatment. It should be noted that the observed association between hyperthyroidism and breast cancer in our study cannot be attributed to the effect of treatment because no previous history of thyroid dysfunction had been identified in patients before participation in this study and patients received no treatment. The results of our study showed no significant increase in the risk of hypothyroidism in breast cancer patients. However, previous studies have shown that hypothyroidism is relatively common in older patients with breast cancer. In a study by Smith et al. (2008) in the United States, the risk of hypothyroidism in people with breast cancer, regardless of whether or not patients received radiation to the neck area, was higher than in women without cancer in the general population.

The findings of the present study showed no meaningful correlation between an increased risk of thyroid autoimmune disorders and breast cancer. However, the association between autoimmune thyroid disorders and breast cancer has been reported in several articles and in these studies, increased serum levels of thyroid antibodies have been identified. A study by Godlewska and Banga (2019) in London also indicated the increased levels of anti-TPO as a good prognostic factor among patients with breast cancer. It has been suggested that the immune response may be directed by both tumor and thyroid tissue because the tumor and thyroid tissue share common characteristics such as expressing TPO and the NIS genes. Although high TPO levels have been indicated as an important factor in antibody-dependent cytotoxicity in the thyroid, and there may be a possible correlation between autoimmune thyroiditis and the immune system, there is no agreement on the importance of its association with breast cancer.

The relationship between thyroiditis and prognostic factors such as ER and the stage of the disease has been investigated. In one study, a higher prevalence of thyroiditis was reported in the more advanced stages of breast cancer (Godlewska and Banga 2019). In another study conducted by Dos Santos Valsecchi et al. (2024) in Italy, the increased prevalence of autoimmune thyroid disorders, especially Hashimoto's thyroiditis, was reported in patients with breast cancer, but no association was found between the status of ER and PR and the presence of serum thyroid antibodies. In the studies conducted by Godlewska and Banga (2019) and

Baldini et al. (2022), it was reported that the odds ratio for breast cancer patients increased in both antibody-positive and negative thyroid patients. Also, the odds ratio was significantly lower for autoantibody-positive thyroid patients compared to those who were negative for autoantibodies (Baldini et al. 2022).

Limitations of the study. The non-cooperation of patients during the implementation of the plan was one of the problems, and to solve this problem, the consent of the patients for cooperation was obtained by discussing and providing full explanations about the implementation method of the plan. Inadequate accuracy of tests was another limitation of this design, which was minimized by measuring in a precise way in one day by one person and one type of kit. Another limitation was the small sample size of the study, which may limit the generalization of the results to people in the community, so it is better to do it in the community with a larger statistical volume.

Conclusions

In this study, the frequency of thyroid disorders in breast cancer patients and the control group was studied. The results of this study demonstrated abnormal features of the thyroid gland in breast cancer patients compared to the control group. Moreover, the incidence of subclinical hyperthyroidism was significantly increased in breast cancer patients. However, autoimmune thyroid disorders showed no substantial difference between the two groups. To confirm the presence or absence of this association, more research is needed. Given the possible relationship between thyroid disease and breast cancer, screening of the patients for the co-occurrence of these diseases is recommended.

Conflict of interest: *The authors declared no conflict of interest.*

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