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Relationship between breast cancer and thyroid disorders

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SUMMARY

Background: The relationship between breast cancer and benign thyroid disease is controversial and the results of published studies have been conflicting. This study aimed at evaluating the prevalence of thyroid disease in patients with breast cancer and comparing the results with individuals without cancer.

Methods: In this retrospective case-control study, the demographic factors, basic characteristics of the tumor and thyroid function tests (T3, T4, TSH) and a number of patients with thyroid disorders, hypothyroidism and hyperthyroidism were measured in 100 breast cancer patients and 100 control individuals and the results were compared between the two groups.

Results: According to our results, there was no significant difference between the two groups in terms of demographic factors. Also, thyroid dysfunction was found in 15% of patients and 19% of the controls, and hypothyroidism and hyperthyroidism were 6% versus 8% and 9% versus 11% in cancer patients and control patients, respectively. The difference was not statistically significant.

Conclusion: Our prospective study did not show any significant difference in the prevalence of thyroid disorders between patients with breast cancer and individuals without cancer.

Key words: breast, cancer, thyroid dysfunction

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INTRODUCTION

Breast cancer is the most common malignancy and the most commonly diagnosed cancer in women, with an estimated 1.67 million cases and 520,000 deaths worldwide in 2012 [1]. Apart from familial aptitude, occupational, reproductive and hormonal factors, no clinical risk factors for breast cancer have been identified [2]. The link between thyroid disease and the risk of breast cancer is supported by studies that demonstrate the role of thyroid hormones in regulating breast epithelial cell growth [3]. A higher percentage of positive thyroid peroxidase antibodies are seen in women with breast cancer in comparison to healthy controls. Because high levels of thyroid hormones have estrogen-like effects in several laboratory studies, thyroid hormone levels and their association with the progression of breast cancer and other cancers have been studied in the past with inconsistent results. Recent studies have shown that elevated serum levels of Thyroid Stimulating Hormone (TSH), with subclinical or apparent hypothyroidism in is seen in 10.0%-19.7% of breast cancer patients [4]. Furthermore, T4 has been shown to increase cell proliferation through the αvβ3 integrin receptor in the plasma membrane of cells. In contrast, the effect of T3 on cell proliferation is not well established because it varies with the type of cell line used [5, 6].

The exact mechanism of such a potential relationship is not known. Some studies have suggested that the deregulation of thyroid hormone target genes might have a role in the initiation of this malignancy. Previous studies have demonstrated an increased prevalence of autoimmune and non-autoimmune thyroid disease in patients with breast cancer [7, 8].

Most of the literature published to date has relied on studies of relatively small sample sizes. Some studies indicate that breast cancer is more prevalent in women with thyroid disease [9-12] many others have failed to show such a relationship [4, 13], or even have shown a reverse relationship [14, 15], and this discrepancy exists among various types of thyroid disorders including goiter [16, 17], hypothyroidism [18, 19], hyperthyroidism [9, 20], thyroid autoimmune diseases [2, 21, 22] and thyroid malignancy [23-25]. In addition, some studies do not differentiate between hypothyroidism and hyperthyroidism despite their conflicting hormonal profiles [11, 26].

Therefore, due to differences in various reports about the relationship of thyroid disorders and breast cancer, in this

retrospective study, we aimed to assess the prevalence of thyroid disease in patients with breast cancer in Iran.

MATERIALS AND METHODS

In this retrospective case-control study, female patients with a new diagnosis of breast cancer and no previous cancer history were identified from Shohadaye 7 Tir hospital, Tehran, Iran during 2017-2018 were studied. Inclusion criteria included all patients with complete information in the file as well as consent to participate in the study. Exclusion criteria were also patients with impaired renal function, liver disease, other cancers and patients who received drugs that interfere with thyroid function.

Patients with breast cancer, women with benign tumors, and healthy controls provided written consent to participate in the study.

The study population consisted of two groups: The case group included 100 patients who were newly diagnosed with invasive breast cancer and had undergone breast surgery, before initiation of any other cancer treatment such as chemotherapy, radiotherapy or hormone therapy. The control group included 100 individuals who were chosen among the patients' relatives who came to the hospital with no history of breast cancer and any other malignancy and/or thyroid disorders. The control group patients were matched to cases based on age and demographic data. At first, demographic data of patients including age and sex were evaluated and then, patients were questioned for a detailed history of thyroid disease and related therapies. Peripheral blood samples were then taken to evaluate the thyroid tests: free thyroxine (FT4), free tri-iodothyroxine (FT3) and Thyrotrophin (TSH).

In the case group, the characteristics of the tumor and disease stage were determined by vacuum biopsy and pathological tests. The blood sampling for thyroid hormones was performed one month after breast surgery, before the initiation of any oncologic therapy.

Free T3 levels between 2.3 and 4.2 pg/mL, free T4 levels between 0.8 and 1.8 ng/dL, and TSH levels between 0.5 and 4.70 μIU/mL were considered to be within normal limits.

RESULTS

The demographic factors and basic characteristics of the two groups are shown in (Table 1). There was no significant difference in age, sex and Menopausal status between the two groups.

The results of thyroid function tests in the two groups are shown in (Table 2). According to our results, although the mean T3 level in the case group was higher than the control group, it was not statistically significant. It was also found that the mean T4 and TSH levels were not statistically different between the two groups.

Evaluation of patients with thyroid dysfunction, hypothyroidism and hyperthyroidism also showed that there was no significant difference between the two groups (Table 2).

Tab. 1. Characteristics of the two groups

Parameter		Case group (n=100)	Control group (n=100)	p -value
Age (years)	≥ 50	57	40	NS
	<50	43	60	
sex	female	100	59	NS
	male	0	41	
Menopausal status	pre	54	44	NS
	post	46	15	
Infiltrating ductal carcinoma		91	-	-
Infiltrating lobular carcinoma		9	-	-
Breast-conserving surgery		60	-	-
Modified radical mastectomy		40	-	-
Early-stage		53	-	-
Advanced stage		47	-	-
Triple-Negative		17	-	-
Luminal A		50	-	-
Luminal B		33	-	-
Lymph Node positive		71	-	-
Lymph Node Negative		29	-	-

Tab. 2. Results of thyroid function tests

Variable	Case group	Control group	p-value
Mean T3 level (pg/mL)	1.42 ± 0.50	1.28 ± 0.44	NS
Mean T4 level (ng/dl)	1.3 ± 0.47	1.4 ± 0.37	NS
Mean TSH level (μIU/mL)	2.15 ± 1.99	2.26 ± 1.87	NS
Thyroid dysfunction (number of cases)	15 (15%)	19 (19%)	NS
Hypothyroidism (number of cases)	6 (6%)	8 (8%)	NS
Hyperthyroidism (number of cases)	9 (9%)	11 (11%)	NS

DISCUSSION

The association between thyroid dysfunction and the risk of breast cancer is unclear. Thyroid hormones increase gene expression by binding to Thyroid Hormone Receptors (TRS). However, the non-genetic function of the thyroid hormone has also been proven. Epidemiological studies have yielded inconsistent results, with some indicating an association of hyperthyroidism or hypothyroidism with the risk of breast cancer, and others have reported no correlation [27].

The predominantly negative results of this study corroborate the results of many reports in the literature and provide more confidence that neither thyroid disorders nor the treatment of these conditions significantly alters the risk of breast cancer in women.

Thyroid hormones are involved in differentiation, growth, metabolism, and physiological function of almost all mammalian tissues, including breasts [28, 29]. Triiodothyronine (T3) has been shown to have proliferative effects in different types of cancer. In

breast cancer cell lines, T3 may stimulate tumor proliferation and play a role in the development and progression of breast cancer [30]. Smyth et al. Suggested that regional variations in the incidence of breast cancer may be attributed to differences in dietary iodine consumption and the effects of iodine on breast tissue cells [31]. Funahashi et al. fed rats with dimethylbenzanthracene-induced cancer with iodine-rich algae, which inhibited breast cancer progression, verifying that iodine had an antitumor effect; they speculated that this effect might be due to up-regulated expression of Transforming Growth Factor (TGF) β in tumor cells, which induced tumor cell apoptosis. Thus, iodine may play significant roles in the pathogenesis of breast cancer [32].

In our study, thyroid dysfunction was found in 15% of the case group while in other studies a wide range between 7% and 39% have been reported [16, 33]. This difference could be due to nutritional, racial and geographical factors. Our study did not show any significant differences in the prevalence of thyroid disorders between the two groups.

Even though there is in vitro evidence for the effect of thyroid hormones on breast epithelial proliferation [2, 22, 34], but epidemiological studies have little support for the association between thyroid disorders and breast cancer risk. Data from a hospital-based case-control study showed a small protective effect for thyroid adenoma in premenopausal women or among women <35 years [35]. In another report, there was a relationship between hyperthyroidism and the risk of breast cancer, but this was done in only 17 cases and 19 controls, and this finding is subject to further investigation due to the small sample size [36].

Some studies suggested that a family history of breast cancer would increase the risk of breast cancer, which might influence the results [37-39].

Prospective trial of Nina Ditsch et al. showed significantly higher mean levels of fT4 and fT3 (although within the normal limits) in breast cancer patients compared to the control group [4].

Mette Søgaard et al. examined breast cancer risk in individuals with hypothyroidism and hyperthyroidism. After a Median follow-up of 4.9 years, they found an increased risk of breast cancer in women with hyperthyroidism and a slightly decreased risk in women with hypothyroidism [12]. Adili et al. [26] in their study on 400 Iranian cases (200 patients with breast cancer and 200 controls) reported significantly higher mean values of anti-thyroid peroxidase antibodies in breast cancer patients. Besides, the incidences of autoimmune and non-autoimmune thyroid diseases were also higher in breast cancer patients than in control individuals (34% versus 12%, p=0.001; 21% versus 7%, p=0.001, respectively). Their study showed a higher prevalence of autoimmune and non-autoimmune thyroid diseases in breast cancer patients. Results of a meta-analysis in 2012 suggested a correlation between autoimmune thyroid disease and breast cancer but failed to show an increased risk of breast cancer in patients with hypothyroidism [21].

Another meta-analysis performed on 12 studies in 2012 showed that hypothyroidism was not associated with an increased risk of breast cancer. Furthermore, they showed that thyroid hormone replacement therapy had no effect on reducing the prevalence of breast cancer [13].

A prospective study on 2,696 women with the mean follow up of 19.3 years demonstrated that T3 levels in postmenopausal women were positively associated with the risk of breast cancer in a dose-response manner [20].

Overall, the relationship between thyroid dysfunction and breast cancer may reflect the influence of shared hormonal or genetic factors and should be studied further. Although there is laboratory evidence that thyroid hormones, insulin, and other growth factors can affect the growth and regulation of breast epithelial cells *in vivo*, there is no evidence of a positive association between breast cancer risk and thyroid disease or its treatment among women.

CONCLUSION

Although still controversial, there seems to be no relationship between the incidence of breast cancer and thyroid disorders. More population-based prospective studies are needed to clarify this issue.

CONFLICT OF INTEREST

None

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