

Evaluation of thyroid dysfunction in breast cancer before surgery.

Mohammad Reza Motie* , Reza Taheri, Faegheh Noorian

Surgical Oncology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Abstract

Introduction: Breast cancer is the most common malignancy in women and is one of the leading causes of death in women. Hence, the study of factors involved in the incidence and progression of disease is of great importance. In this study, the relationship between breast cancer and thyroid disorders will be discussed.

Methods: In a case-control study, 86 women with confirmed breast cancer and 50 age-matched healthy women as controls were studied for 12 months in the Cancer Research Center, Imam Reza hospital, Mashhad University of Medical Sciences, Iran. After examination of the thyroid, serum level of Thyrotropin (TSH), Thyroxine (T4), Triiodothyronine (T3) and Anti-Thyroid Peroxidase Antibody (anti-Tpo AB) were tested by radioimmunoassay. The results were compared between the two groups and different pathological subtypes of breast cancer.

Results: Mean serum TSH level was not significantly different between the two groups, but the mean serum levels of T4 and anti-Tpo AB was higher in patients ($p < 0.05$). Increased levels of TSH and T4 were observed in 5.8% and 2.3% of the patient and 12% and 8% of the control group, respectively. Also, decreased TSH and T4 levels were observed in 7% and 2.3% of the patient and 5% and 0% of the control group, respectively. As well, increased levels of T3 and anti-Tpo AB were observed in 0% and 20.9% of patients and in 4% and 8% of the control group, respectively.

Conclusion: Although there was a significant difference between the groups regarding the anti-Tpo AB level, but no obvious connection between thyroid function and breast cancer was found in this study. Therefore, studies with larger sample sizes are required to achieve more qualified results.

Keywords: Breast cancer, Thyroid disorder, Thyroid hormones.

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Introduction

Breast cancer is the most common cancer in women and the second leading cause of death from cancer [1]. It is shown that breast cancer is more common in societies with high prevalence of goitre disease and hypothyroidism than those with euthyroid or hyperthyroid [2,3]. Breast cancer is a hormone-dependent tumor. In addition, studies suggest that thyroid disease is more prevalent in women with breast cancer [4,5].

Findings show that almost all types of thyroid disorders, including nodular hyperplasia, hyperthyroidism and thyroid cancer may be connected to breast cancer [6]. Although the relationship between breast cancer and thyroid disorders is a controversial issue, findings show that the incidence of breast cancer is higher in patients with thyroid disorders [2,6]. Studies also show that the risk of breast cancer increases after thyroidectomy [7].

Evidences suggest that hypothyroidism may have a protective role against breast cancer [8]. As well, it is shown that the deficiency of circulating thyroid hormone may cause the

excessive production of prolactin and estrogen in the epithelium of mammary glands leading to breast cancer [9].

Hyperthyroidism is also associated with a reduced risk of breast cancer. Therefore, in patients with hyperthyroidism and non-operable breast cancer, the growth of tumors is rather slow [9].

Studies have also shown that hyperthyroidism is associated with the development of breast cancer in premenopausal women [10]. Currently, the role of thyroid hormones in the pathobiology of breast cancer is unknown [11]. If such association is confirmed, evaluation of the thyroid function can be used for screening the risk of breast cancer.

Since little researches have been conducted on the relationship between thyroid disease and breast cancer in Iranian patients, therefore, in this study thyroid function and serum levels of the thyrotropin (TSH), thyroxine (T4), triiodothyronine (T3) and anti-thyroid peroxidase antibody (anti-Tpo AB) were evaluated in patients with breast cancer prior to surgery to determine the possible association between thyroid disease and the incidence and progression of breast cancer.

Material and Methods

Sample collection

This case-control study was conducted from January 2013 to 2014 in the Cancer Research Center at Imam Reza hospital, Mashhad, Iran on patients with breast cancer who underwent simple or modified and conservative mastectomy and other patients without breast cancer as control groups. Patients in the control group had not been diagnosed with breast cancer, but had undergone surgery. According to the results of previous studies in which the prevalence anti-Tpo AB in women with breast cancer was 34% in comparison with 36% in control group, and also given that the allocation ratio is equal to 0.55, and considering the significance level of 5% and the power of at least 80% for this test, the minimum sample size for the control and experimental group was defined 50 and 86 participants, respectively. Before enrolment, informed consent was obtained from participants and the study was confirmed by the Ethical Committee.

Clinical evaluation

After primary medical examination and a day before surgery, serum level of TSH, T4, T3 and anti-Tpo AB were assessed in both groups by radioimmunoassay. The normal range considered for thyroid hormones were 0.5 to 4.5 mg/ml for TSH, 80 to 200 pg/ml for T3 and 4 to 12 ng/ml for T4. Also, the amount of anti-Tpo AB more than 40 units/ml was considered as positive.

Statistical analysis

After data collection and initial processing, the data were analyzed by SPSS v.19 statistical software. Initially the Kolmogorov-Smirnov test was used to evaluate the normality of the data, and then the Student t-test for two independent groups (in the case of normal data) and the nonparametric equivalent of Student t-tests such as the Mann-Whitney was used for data analysis. For comparing the chi-square test and Fisher's exact test group also was used in contingency tables. The chi-square test and Fisher's exact test were also used in contingency tables for comparison of the rate in the groups. The significant level was considered as $p < 0.05$.

Results

Demographic data

Studied participants included 86 patients with verified breast cancer and other 50 patients without breast cancer as experimental and control group, respectively. The average age of study participants was 46.5 ± 10.93 y. The age range of participants varied from 18-74 y in patients group mean 46.6 ± 11.27 y and 22-71 y in mean 46.5 ± 10.44 y in the control group, but the difference in the two groups was not significant ($p=0.957$).

Thyroid function test

The mean values for T3, T4, TSH and anti-Tpo AB are shown in Table 1. Results showed that the difference between the amount of TSH in the patient and control groups was not statistically significant ($p=0.166$). While a significant difference in the mean T4 ($p=0.001$), T3 ($p<0.001$) and anti-Tpo AB ($p=0.011$) was observed between the two groups. Chi-square test or Fisher's exact test was used in contingency tables for a comparison between the two groups regarding the number of decreased, increased and normal variables, and the results showed that the difference between the two groups concerning T3 ($p=0.028$) and anti-Tpo AB ($p=0.048$) was significant. However, the difference in the amount of TSH ($p=0.337$) and T4 ($p=0.173$) within normal or abnormal range was not significant.

Table 1. Demographic data of study population.

| | | Breast group N=86 | cancer Control group N=50 | P value |
|--------------------|------------|----------------------|------------------------------|---------|
| Age (y) | | 46.6 ± 11.27 | 46.5 ± 10.44 | 0.957 |
| TSH (Mlu/ml) | | 2.59 ± 1.85 | 3.18 ± 2.48 | 0.0166 |
| T4 (ng/ml) | | 7.39 ± 2/05 | 8.73 ± 2.25 | 0.001 |
| T3 (Pg/ml) | | 105.28 ± 25.86 | 132.66 ± 34.29 | <0.001 |
| Anti-Tpo AB (lu/m) | | 34.52 ± 53.94 | 17.66 ± 19.05 | 0.011 |
| TSH | Increase d | 5 (5.8%) | 6 (12%) | 0.337 |
| | Decrease d | 6 (7%) | 5 (10%) | |
| | Normal | 75 (87.2%) | 39 (78%) | |
| T4 | Increase d | 2 (2.3%) | 4 (8%) | 0.173 |
| | Decrease d | 2 (2.3%) | 0 (0%) | |
| | Normal | 82 (95.3%) | 46 (92%) | |
| T3 | Increase d | 0 (0%) | 2 (4%) | 0.028 |
| | Decrease d | 10 (11.6%) | 1 (2%) | |
| | Normal | 76 (88.6%) | 47 (94%) | |
| Anti-Tpo AB | Positive | 18 (20.9%) | 4 (8%) | 0.048 |
| | Negative | 68 (79.1%) | 46 (92%) | |

Histopathological examination

Histopathological analysis showed that of 86 patients with breast cancer, 62 patients (72.1%) are with invasive ductal carcinoma, 23 (26.7%) with ductal carcinoma *in situ* and one (1.2%) with lobular carcinoma, and any of these patients were not positive for estrogen or progesterone receptor. The age

range of patients in *in-situ* invasive carcinoma and ductal carcinoma *in situ* was 18-74 y (mean 46.09 ± 11.55 y) and 23-71 y (mean 47.86 ± 10.86 y), respectively, which showed no significant difference between the average ages in the groups (p=0.525).

As shown in Table 2, the average amount of TSH, T4, T3 and anti-Tpo AB in the two groups of invasive ductal carcinoma

and ductal carcinoma *in situ* were not significantly different (p>0.05). The results of the data survey regarding the percentage of decreased, increased and normal variables in each group are shown in Table 2. As shown, the difference between the two groups were not significant for any of the variables (p=0.884, p=0.302, p=0.824 and p=0.500 for TSH, T4, T3 and anti-Tpo AB, respectively) (Table 3).

Table 2. Comparison of the variables in patients with breast cancer based on histopathological diagnosis.

| | | Invasive ductal carcinoma (N=62) | Ductal carcinoma in situ (N=23) | P |
|------------------------------------|-----------|-------------------------------------|------------------------------------|-------|
| Age | | 46.09 ± 11.55 | 47.86 ± 10.86 | 0.525 |
| TSH (Mlu/ml) | | 2.65 ± 2.00 | 2.39 ± 1.40 | 0.572 |
| T4 (ng/ml) | | 9.53 ± 12.23 | 7.44 ± 1.96 | 0.225 |
| T3 (pg/ml) | | 103.61 ± 25.33 | 108.70 ± 27.52 | 0.424 |
| Anti-Tpo AB (lu/ml) | | 35.41 ± 61.06 | 31.91 ± 29.91 | 0.425 |
| TSH | Increased | 4 (6.5 %) | 1 (4.3%) | 0.884 |
| | Decreased | 4 (6.5 %) | 2 (8.7 %) | |
| | Normal | 54 (87.1 %) | 20 (87 %) | |
| T4 | Increased | 4 (6.5 %) | 0 (0 %) | 0.302 |
| | Decreased | 2 (3.2 %) | 0 (0%) | |
| | Normal | 56 (90.3 %) | 23 (100 %) | |
| T3 | Increased | 0 (0%) | 0 (0%) | 0.824 |
| | Decreased | 7 (11.3 %) | 3 (13 %) | |
| | Normal | 55 (88.7 %) | 20 (87 %) | |
| Anti-Tpo AB | Positive | 12 (19.4 %) | 6 (26.1 %) | 0.5 |
| | Negative | 50 (80.6 %) | 17 (73.9 %) | |
| The number of involved lymph nodes | | 3.29 ± 4.22 | 1.65 ± 3.43 | 0.018 |

The comparison of the two groups regarding the number of involved lymph nodes showed that the mean number of lymph nodes involved in invasive ductal carcinoma and ductal carcinoma *in situ* groups were 3.29 and 1.65, respectively, indicating the significance of the difference between the two groups (p=0.018).

Table 3. Associations between thyroid tests in two groups of case and control.

| | Odd ratio | 95% confidence interval |
|---------------------|-----------|-------------------------|
| Thyroid dysfunction | 1.107 | 0.54-2.28 |
| T3 dysfunction | 2.061 | 0.54-7.87 |
| T4 dysfunction | 0.561 | 0.13-2.35 |
| TSH dysfunction | 0.52 | 0.21-1.31 |

| | | |
|----------------------|-------|-----------|
| Anti TPO dysfunction | 0.329 | 0.10-1.03 |
|----------------------|-------|-----------|

Discussion

The results of some studies have shown that thyroid disease is more common among women with breast cancer. In some studies, the relationship between various types of thyroid disease, including nodular hyperplasia, hyperthyroidism and thyroid carcinoma with breast cancer have been identified [6,12]. Also, various studies have shown that the incidence of Autoimmune Thyroid Disorders (AITD) is more common among patients with breast cancer [13,14]. Several studies on the relationship between serum levels of anti-Tpo AB, thyroid volume, amount of FT3, FT4, TSH, and estradiol with breast cancer have shown that anti-Tpo AB is significantly higher in women with breast cancer, and these results demonstrated a possible association between breast cancer and autoimmune thyroid disorders [13,15-18]. In addition, along with the increasing prevalence of anti-Tpo AB in women with breast

cancer, it was found that a significant correlation may exist between breast cancer and autoimmune and non-autoimmune thyroid disease [6,19]. In consistent with some studies, in the present study, the average amount of anti-Tpo AB ($p=0.011$) and T4 ($p=0.001$) were significantly higher in patients with breast cancer than those in the control group [16,20]. Moreover, in our study, the average amount of T3 ($p=0.001$) and TSH ($p=0.166$) in patients with breast cancer were significantly lower than those in the control group, and these results were consistent with the results of similar studies in this area [21-24].

Laboratory findings have shown that thyroid hormones can have estrogen-like effect on breast cancer. As well, it has been shown that receptors of thyroid hormones may have an effect on the proliferation and differentiation of breast cancer cells [25]. Fierabracci et al. reported a strong relationship between thyroid autoimmune disorder and breast cancer [13]. The ratio of Free T3/Free T4 is also introduced as an indicator of breast carcinoma, so that this ratio may increase in patients with breast cancer [18]. As well, the findings show that any alterations in the level of T4 may be associated with increased risk of breast cancer. While, patients with high anti-Tpo AB are at lower risk of breast cancer. As well, serum level of T3, total T4 and free T4 were higher in patients with breast carcinoma [20,26,27]. Studies have also shown that thyroid diseases are associated with tumor grade in women with breast cancer, and the thyroid disorders increase with increasing the tumor grade [28]. But, several studies could not find any significant association between enlargement of the thyroid gland or other thyroid disorders with breast cancer [19,22].

Several reasons such as differences in the studied sample size, evaluation methods of thyroid diseases as well as the accuracy and sensitivity of laboratory methods may cause differences in the results of various studies. Another important factor is the racial differences and their impact on the incidence of thyroid diseases. The results of this study do not approve the relationship between thyroid disease and breast cancer, but to reach conclusive findings in this regard, further research is recommended in similar centers.

Conclusion

Although there was a significant difference between the groups regarding the anti-Tpo AB, T3 and T4 level, but the results of this study do not support correlation between thyroid function and the incidence or exacerbation of breast cancer. Therefore, to achieve more qualified results further studies with larger sample sizes and appropriate study design are required.

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***Correspondence to**

Mohammad Reza Motie
Surgical Oncology Research Center
Mashhad University of Medical Sciences
Mashhad
Iran