

## **Anti-TPO antibody and thyroid hormone levels in Iranian female breast cancer patients and their association with prognostic factors: A case-control study**

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### **Abstract**

The aim of this study was to assess prevalence of anti-thyroid peroxidase (anti-TPO) antibody and thyroid hormones in Iranian female breast cancer patients, compare them to a control population, and investigate their association with prognostic factors. In this case-control study, breast cancer patients were selected from a surgery clinic in a tertiary hospital and control group participants were enrolled from those who had visited for mammography screening. Participants with any history of thyroid disease, or thyroid related medication were excluded from both groups. Groups were assessed for levels of thyroid stimulating hormone (TSH), T3, T4, and anti-TPO. In addition, the status of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) was determined for cancer patients. Overall 69 participants (39 cancer patients and 30 controls) were included. Difference in serum anti-TPO levels between the two groups was not statistically significant (p-value: 0.184). While a significant difference was observed for T4 and TSH levels between groups (p-value: 0.034 and <0.001, respectively), T3 levels did not reveal any significant difference (p-value: 0.177). In addition, ER, PR, and HER2 status were not correlated with anti-TPO levels. This results can serve as preliminary evidence that thyroid autoimmunity is not correlated with breast cancer incidence in Iranian female population.

**Key Words:** Breast neoplasms; anti-thyroid autoantibodies; thyroid hormones.

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**B**reast cancer is the most prevalent malignancy among women and it is the first cause of cancer related mortality in female population in most countries.<sup>1</sup> Breast tumors can be classified based on the expression of receptors such as estrogen (ER) and progesterone receptors (PR) and human epithelial growth factor receptor 2 (HER2), and each type leads to different prognosis. The incidence rate of breast cancer in Iran is approximately 33 cases per 100,000 people with a five-year overall survival of 72%.<sup>2</sup> Accordingly, identification of its risk factors is an important step for optimal preventing measures. Fat rich diets, obesity, oral contraceptive use, and postmenopausal hormone therapy are some of the most researched and established risk factors.<sup>3</sup> Over the years,

several studies have demonstrated an association between this cancer and thyroid autoimmunity, regardless of clinical manifestations.<sup>4-9</sup> However, the exact causal relation and the significance of this correlation is not determined. In contrast, there are studies that have reported no correlation or negative correlation between breast cancer and thyroid autoimmunity.<sup>10-13</sup>

The current controversy and discrepancy in literature justifies further investigation to determine the significance of thyroid examination in breast cancer prevention. In addition, to the best of our knowledge, no similar study has been carried in Iranian population. In this study we tried to compare the prevalence of anti-

**Table 1.** Demographic data of tumor staging and ER, PR and HER2.

		Number	Percentage
Stage	T1N0	5	12.8
	T1N1	3	7.7
	T2N0	15	38.5
	T2N1	2	5.1
	T3N0	4	10.3
	T3N2	4	10.3
	T4	1	2.6
	Missing data	5	12.8
ER	Positive	25	64.1
	Negative	12	30.8
	Missing data	2	5.1
PR	Positive	23	59.0
	Negative	13	33.3
	Missing data	3	7.7
HER-2	Positive (3+)	5	12.8
	Positive (2+)	6	15.4
	Positive (1+)	1	2.6
	Negative	24	61.5
	Missing data	3	7.7

ER: estrogen receptor; PR: progesterone receptor; HER-2: human epidermal growth factor 2.

thyroid peroxidase (anti-TPO) antibody, and thyroid hormones between breast cancer and control populations. Besides, the prevalence of anti-TPO antibody in different tumor stages and different tumor variants (based on hormone receptors and HER2 status) was investigated.

### Materials and Methods

This is a case-control study conducted in a tertiary hospital (affiliated with Semnan University of Medical Sciences) on patients with breast cancer as a case group. The study was conducted in concordance with the declaration of Helsinki and its later amendments. The local ethical committee approved the protocol, and all patients filled out informed consent before entering the study (IRSEMUMS.RFC.13990068). The patients were recruited from the hospital's surgery clinic in 2020 and 2021. We included consecutive patients who came to the surgery clinic with newly diagnosed breast cancer as our case group. Control group members were selected from those who came for screening mammography and had no abnormal findings. The serum levels of anti-TPO antibodies, TSH, T3, and T4 were assessed in participants of both groups. They were excluded from this study if they had any abnormality in these tests, had a history of thyroid dysfunction, or had a history of taking thyroid related medication. We gathered variables like age, and serum levels of TSH, T3, T4, and anti-thyroid peroxidase (anti-TPO) from both groups of subjects. Data on tumor staging, ER, PR, and HER-2 were also retrieved from the case group. We used IBM SPSS 25 to analyze the data (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). To assess the normality

of the data, we implemented the Shapiro-Wilk test. Numeric data were reported as frequency and percentage, and continuous data were described as mean and standard deviation. Parametric numeric data were compared using the  $\chi^2$  test. The independent sample t-test compared normally distributed continuous variables. To analyze the means of more than two variables, analysis of variances (ANOVA) was used. A *p-value* of less than 0.05 was considered statistically significant.

### Results

We included 69 participants in the study (39 breast cancer patients and 30 control subjects with normal mammography results). Mean age was 55.5 (SD: 9.5) year-old and 47.7 (SD: 15.0) year-old in the case and control groups, respectively; this difference was statistically significant (*p-value*: 0.016). As table 1 represents, most patients were ER and PR positive, while most of them were HER-2 negative. Regarding the tumor staging, 44.1 % of patients had the tumor score of two without any lymph node involvement or metastasis (T2N0M0). There was a significant difference between the two groups concerning serum T4 and TSH levels (*p-value*: 0.034 and <0.001, respectively). On the other hand, serum T3 levels did not significantly differ between the case and control groups (*p-value*: 0.177). The mean serum anti-TPO levels were 65.15 (SD: 179.74) IU/ml and 152.53 (SD: 317.30) IU/ml in the case and the control group, respectively. However, the difference in serum anti-TPO levels between the two groups was not statistically significant (*p-value*: 0.184).

**Table 2.** Sub-group analysis of serum anti-TPO levels.

		Mean ±SD	<i>p</i> -value
<b>Stage</b>	T1N0	133.2±278.8	
	T1N1	185.3±264.0	
	T2N0	12.0±14.6	0.343
	T2N1	10.0±0.00	
	T3N0	38.1±41.6	
	T3N2	15.9±7.4	
	T4	10.0±0	
<b>ER</b>	Positive	39.9±124.1	0.373
	Negative	55.3±139.1	
<b>PR</b>	Positive	41.9±129.5	0.808
	Negative	53.0±133.5	
<b>HER-2</b>	Positive (3+)	112.0±210.6	
	Positive (2+)	122.0±250.5	0.179
	Positive (1+)	10.0±0	
	Negative	14.5±21.3	

ER: estrogen receptor; PR: progesterone receptor; HER-2: human epidermal growth factor 2.

Subgroup analysis revealed that there is no significant difference between different stages of breast cancer in respect to anti-TPO levels (*p*-value: 0.343). Likewise, prognostic factors (ER, PR, HER-2) had no significant relationship with anti-TPO levels (Table 2).

## Discussion

There has been a long debate over causal relationship between thyroid autoimmunity and breast cancer, and no consensus has been reached.

In this case-control study, thyroid hormones and anti-TPO antibody were compared between the groups. Significantly higher levels of TSH and T4 were observed in breast cancer group. In contrast, we did not find any significant correlation between anti-TPO or T3 levels, and breast cancer incidence. However, the large numerical difference of anti-TPO levels between study groups may indicate insufficient sample size for determination of significance. Consequently, it can be inferred that while thyroid hormone imbalance is more common in breast cancer population, higher anti-TPO antibody levels is not correlated with breast cancer incidence. Several articles have reported similar results, finding no association between thyroid autoimmunity or disorders and breast cancer. In a recent meta-analysis by Wang et al. (2020), by reviewing 19 studies, it was demonstrated that hypothyroidism was not related to a higher risk of breast cancer and moreover, in European subgroup, it may decrease this risk.<sup>14</sup> Similarly, a 2012 article by Angelousi et al., reviewed 12 studies and found no significant association in this regard.<sup>15</sup> A meta-analysis by Fang et al. has also shown that neither of hyper- or hypothyroidism were related to the risk of

breast cancer.<sup>16</sup> On the contrary, some small sample studies have highlighted a relation between thyroid autoimmunity and breast cancer.<sup>9,17,18</sup> A large scale study with 103 466 participants has also revealed that hyper- and hypothyroidism have a significantly increased risk of breast cancer regardless of treatment.<sup>6</sup> Another 2012 meta-analysis by Hardefeldt et al. found significant evidence for increased risk of breast cancer in autoimmune hypothyroid population.<sup>19</sup> Furthermore, analysis did not reveal any significant association between anti-TPO antibody levels and different cancer stages, different hormone receptor expressions, and HER2 status.

This was similar to the results of a study where by analyzing 143 breast cancer patients, no relationship between ER and PR status, and the presence of serum thyroid autoantibodies was observed.<sup>13</sup> Interestingly, in another study where ER status and thyroid autoantibodies (anti-TPO and anti-thyroglobulin antibodies) had no association, it was demonstrated that ER positivity and higher levels thyroid autoantibodies were correlated with better survival.<sup>20</sup> In contrast, a large scale study did not find any prognostic value for anti-TPO antibodies in breast cancer patients.<sup>21</sup>

On the other hand, in a case-control study, Saraiva et al. found significantly higher concentrations of TSH in premenopausal breast cancer patients. Menopausal patients were diagnosed with higher levels of free T4 and lower TSH, consistent with subclinical hyperthyroidism in this study.<sup>22</sup> Some studies have also reported higher T4,<sup>23</sup> or T3 and T4.<sup>24</sup> levels in breast cancer patients, while finding no significant difference for TSH. On the

other hand, some studies have found that low T4 might be associated with higher risk of breast cancer.<sup>8</sup>

The main shortcoming of this study was small sample size which might limit the generalizability of our results. Implementation of age matching in control group selection could have omitted age difference as a confounding factor. Classification of samples into pre- and postmenopausal groups was considered initially but due to the limited sample size it was not carried out in order to maintain study power. Additional multicentric multiethnic studies with greater sample size are needed to draw more precise conclusions.

In conclusion, this case-control study, which was carried for the first time in Iranian population, it was demonstrated that while breast cancer was not associated with T3 and anti-TPO levels, T4 and TSH levels were higher in patient group. This can serve as preliminary evidence that thyroid autoimmunity is not correlated with breast cancer. However, additional studies with larger sample sizes are required for more conclusive evidence.

### List of acronyms

anti-TPO - anti-thyroid peroxidase

ER - estrogen receptors

HER2 -human epidermal growth factor receptor 2

PR - progesterone receptors

TSH - thyroid stimulating hormone

### Contributions of Authors

SE contributed in the conception of the work, conducting the study, revising the draft. SF contributed in analysis, or interpretation of data, drafting the work and revising it critically for important intellectual content. SAT contributed in draft and critical revision for important intellectual content. ZR contributed substantially to the conception, design and drafting the work. All authors read and approved the final edited typescript.

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### Conflict of Interest

The authors declare no conflict of interests.

### Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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