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The Relationship Between Prognostic Factors of Breast Cancer and Thyroid Disorders in Turkish Women

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Background: Breast carcinoma is a frequent disease that affects the female population. As for other malignant diseases, several studies have been carried out in an attempt to identify its etiology, yet the etiological agent has not been clearly defined. The etiological relationship between thyroid disease and breast cancer is still being investigated. However, most of the studies in this field are conflicting and discussions on this relationship still continue.

Patients and Method: Our prospective open study was conducted on 136 consecutive patients operated for breast carcinoma. As a control group, 68 individuals with normal breast examination, who did not have any known malignancy and/or thyroid disease, living in the same geographical region and with matching socio-cultural and economical status, were included in the study. We aimed to identify the occurrence and frequency of thyroid pathologies in both groups to compare the clinical and the laboratory features of thyroid disease and breast carcinoma in an attempt to contribute to the studies investigating the relationship between these two entities.

Results: We found thyroid pathology in 77.9% of breast cancer patients while this was 47.1% in the control group. Breast cancer patients had higher levels of free-T3 and more frequent diffuse and nodular enlargement of thyroid gland in ultrasonography when compared to the control group. Furthermore, in the presence of thyroid disease, breast cancer patients had statistically significant increases in the number of metastatic lymph nodes, vascular invasion, and tumor size.

Conclusion: In conclusion, the frequency of thyroid pathology is higher in breast cancer patients compared to controls indicating a relationship between breast carcinoma and thyroid pathology. Our study shows that the presence of thyroid pathology in breast cancer patients can be influential on the spread of cancer and adversely affect its prognosis. We thought further studies are needed to confirm these findings and to explain the reason for co-occurrence of breast cancer and thyroid disease and furthermore to investigate the prognosis and survival of breast cancer patients in the presence of thyroid pathology.

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KEY WORDS: **breast cancer; thyroid disorders; vascular invasion; tumor size; metastatic lymph nodes**

INTRODUCTION

Breast cancer is the most commonly observed malignancy in females in both our country and in the world [1]. As it is the case for other malignancies, many factors have been suggested in the etiology of the disease, yet we are still far away from the real etiology.

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After the utilization of thyroid hormones for therapeutic purposes in breast cancer patients in 1896 and following the recommendation of Beatson about using thyroid hormones and performing oopherectomy in the patients with breast cancer, many studies were initiated in order to identify the relationship between thyroid disease and breast carcinoma [1,2]. In literature, some studies report higher incidence of breast cancer in women with thyroid disease compared to normal population [2–8]. These studies are numerous and diverse, and still we do not have any concrete clinical data or proof regarding the relationship of these two entities.

Thyroid hormones are vital for normal growth, development, differentiation, and metabolic regulation especially in developed organisms and their receptors are found in all of the cells [3,9]. These important hormones with a diverse spectrum of action may play a role in the carcinogenesis and may act as a cofactor in this process [3]. Studies conducted in animal models and culture environments demonstrated the effects of thyroid hormones on tumor formation, growth, metastasis, and neoplastic transformation [3,9,10]. The suspicions increased after understanding that thyroid hormones used C-erbA, which is a proto-oncogene product, as a receptor [9,11–16]. As a result, studies concentrated to reveal the relationship between thyroid hormone, thyroid diseases, and malignancies. One of the issues that are being investigated is breast cancer and its relationship with disorders of the thyroid.

In this study, we investigated the incidence of thyroid disorders in patients with breast cancer. We also investigated the clinical and laboratory features of the breast cancer and their relation to thyroid disorders.

PATIENTS AND METHODS

This prospective study was performed on 136 consecutive breast carcinoma patients who were operated in Ankara Numune Education and Research Hospital, 2nd Surgery Department in the 2-year period. Sixty eight patients stayed in hospital with any disorders with normal breast examinations and without any evidence of malignancy anywhere and/or thyroid disorders served as controls. They were living in same geographical region and had similar socio-cultural and economical status with the breast cancer patients. All participants gave their oral consents both for participating in the study and for the analysis of their thyroid functions.

Blood samples were obtained from groups; f-T3, f-T4, TSH, thyroglobulin levels, anti-thyroglobulin, and anti-M antibodies was assayed. Thyroid hormone levels were measured by luminometric immunoassay method with Liason model Byk-Sangtec Diagnostica Device (Germany), thyroid hormone levels were measured in the hormone laboratory by utilizing Brahms Dynotest anti TPOn, anti-TGn with RIA method.

Thyroid ultrasonographies were performed in the radio diagnostics unit to calculate thyroid volume and to identify any nodule formation. Thyroid ultrasonography was carried out by Hitachi EUB-420 7.5 MHz device with a linear probe. The solid and cystic nodules equal to or greater than 5 mm were recorded. Thyroid volume was calculated by the following formula after measuring all dimensions = width $\times$ height $\times$ depth $\times$ 0.479. Values above 18 ml were evaluated as pathological for every lobe [4]. The same tests were employed in the control group in regard to the thyroid gland.

Fifteen patients had a history of previous thyroid surgery due to any reason. Mean thyroid volume of these patients was calculated separately and this parameter was excluded from the statistical analysis for this subgroup of patients.

Pathological results in any of thyroid function tests, autoantibody levels, or thyroid ultrasonography parameters were regarded as pathology in the thyroid gland. The patients with thyroid pathologies were treated with appropriate medical and/or surgical techniques according to their hypo- or hyperthyroid status. FNACs were obtained from the patients with thyroid nodules depending on the dimensions of the nodule and/or risk factors. They were either followed-up, medically treated, or operated on.

Weights and heights of all the patients were measured and recorded. The information regarding Estrogen and progesterone receptor status, size of the tumor, presence of lymphatic invasion, number of metastatic lymph nodes, and presence of vascular invasion, stage and grade of the tumor was recorded. The estrogen and progesterone receptors were identified by immunohistochemical staining of the specimens. The relationship of all these parameters with thyroid functions and thyroid disorders were investigated.

The subjects in the control group were compared with the patients in the study group in terms of their menopausal status, body weight, height, and age, the incidence of thyroid disorder, thyroid volume, and changes in hormone and antibody levels.

"SPSS for Windows Release 10, 0, SPSS Inc. USA" Computer Program was utilized for statistical analysis. Chi-square tests, logistic regression, and one way ANOVA tests were employed. $P < 0.05$ was regarded as statistically significant.

RESULTS

One hundred and six of the breast cancer patients had radical mastectomy whereas 27 underwent conservative breast surgery. As they were in an advanced stage,

TABLE I. Comparison Between Breast Cancer Group and Control Group

Parameter	Breast cancer group mean ± SD	Control group mean ± SD	P[a]
Age	50.56 ± 12.69	50.91 ± 13.2	0.079
Height (cm)	159.84 ± 5.54	160.33 ± 5.2	0.134
Weight (kg)	69.54 ± 12.55	64.269 ± 9.8	0.022
Anti-M (0–60 U/ml)	92.07 ± 212.7	24.58 ± 7.9	0.233
Anti-thyroglobulin (0–60 U/ml)	99.74 ± 248.15	30.17 ± 20.05	0.707
Thyroglobulin (0.0–25 ng/ml)	42.28 ± 85.11	27.22 ± 29.3	0.852
Thyroid disorders (+)	106 (77.9%)	32 (47.1%)	0.00035[a]
Thyroid disorders (−)	30 (21.1%)	36 (52.9%)	
f-T3 (1.4–4.1 pg/ml)	3.21 ± 1.73	2.44 ± 0.7	0.012[a]
f-T4 (0.7–2.3 ng/ml)	1.64 ± 1.94	1.39 ± 0.3	0.451
TSH (0.2–3.8 mIU/L)	2.07 ± 3.64	1.84 ± 1.58	0.721
Pathologic number of f-T_3	27 (21.1%)	0	0.00335[a]
Pathologic number of f-T_4	5 (39%)	0	0.241
Pathologic number of TSH	21 (16.4%)	12 (18.2%)	0.852
Thyroid USG normal (n = 51)	30 (28.8%)	42 (61.8%)	0.00151[a]
Thyroid USG diffuse (n = 18)	17 (16.3%)	2 (2.9%)	0.0530[a]
Thyroid USG nodular (n = 69)	57 (54.8%)	24 (35.3%)	0.0392[a]
Thyroid volume (ml)	17.02 ± 16.13	16.44 ± 11.04	0.844
Number of metastatic lymph nodes	3.97 ± 7.95		

[a]Statistically significant "P" values ($P < 0.05$).
Mean ± SD: mean ± standard deviation. f-T_3: free-T_3. f-T_4: free-T_4. TSH: thyroid stimulating hormone.

three patients had only biopsies to identify the tumor histopathology.

The demographic data of the control and the study groups are presented in Table I. Seventy two patients were in menopausal period and 64 were in the premenopausal period. There was no difference of statistical significance between the groups in terms of average weight, height, and average age.

Of 136 breast cancer patients, 106 had thyroid pathology (77.9%), while 30 (22.1%) did not have any thyroid pathology. When breast carcinoma patients were compared with the control group, thyroid pathology were found to be significantly high in patients with breast cancer ($P = 0$, 00035, Table I).

When f-T3, f-T4, and TSH levels of the breast cancer patients and the controls were compared, the levels of f-T3 in the breast carcinoma patients were significantly higher than that of the controls (t-test = 0.012), although f-T3 levels were found to be within normal ranges (1.4–4.1 pg/ml). There was no statistically significant difference between the two groups with respect to f-T4 and TSH levels ($P = 0.451$, $P = 0.721$, Table I).

When the pathological changes in f-T3, f-T4, and TSH levels were compared between the two groups, 27 patients in the breast cancer group (21.1%) had pathological f-T3 levels (hypothyroidism or hyperthyroidism) whereas the control group did not have any pathological f-T3 level ($P = 0.00335$, chi square test). However, there was no statistically significant relationship for f-T4 or TSH levels ($P = 0.241$, $P = 0.852$, Table I).

The changes that have been identified with thyroid ultrasonography in breast cancer and the control groups are summarized in Table I. When patients were categorized into three groups as nodular, diffuse enlargement, and normal thyroid gland; normal ultrasonographic findings were significantly higher in control groups compared to breast cancer patients ($P = 0.00151$). Two breast cancer patients had ultrasonographical findings suggesting thyroiditis. These two patients were excluded from statistical analysis because of the small sample size of this pathology. Nodular and diffuse thyroid pathologies were significantly higher in the breast cancer group when compared to the control group (chi-square test, $P = 0.0530$ for diffuse enlargement, $P = 0.0392$ for nodular formation). The nodular pathology were not dominating diffuse ones or vice versa ($P = 0.209$).

In breast cancer patients with thyroid pathology, the number of metastatic lymph nodes were significantly more compared to the patients without thyroid disease ($P = 0.005$, Table II). When patients with positive lymph nodes were examined as a subgroup, in case of coexisting thyroid pathology, average number of metastatic lymph nodes were 7 whereas in the absence of thyroid pathology the average number of metastatic lymph nodes were 3 (t-test, $P = 0.005$).

Breast cancer patients with thyroid pathology had statistically significant bigger tumor volumes ($P = 0.023$, Table II).

Vascular invasion was more frequent in breast cancer patients with thyroid pathology and this result was

TABLE II. Significant Parameters in Breast Cancer Patients With or Without Thyroid Disorders

Parameters	Thyroid disorders (+) (n = 93)	Thyroid disorders (−) (n = 28)	*P*
Metastatic lymph nodes	4.64 ± 8.84	1.71 ± 2.74	0.005*
Tumor size (cm)	3.36 ± 2.23	2.39 ± 1.16	0.023*
Vascular invasion (+)	28 (33.7%)	1 (4.2%)	0.00410*
Vascular invasion (−)	55 (55%)	23 (95.8%)	

*Statistically significant "*P*" values ($P < 0.05$).

statistically significant in chi-square test ($P = 0.0041$, Table II).

There was no relationship of statistical significance between the changes in thyroglobulin, anti-thyroglobulin, anti-M levels, and breast cancer.

There was no significant relationship between the clinical stages of the breast cancer patients and the presence of thyroid pathology, however, *t*-value is close to the limit of significance ($P = 0.068$). As seen in the Table III, there was no thyroid pathology in the majority of stage I breast cancer patients, however in the majority of breast cancer patients at stage III, there were thyroid pathology. This raises the suspicion that there might be a relationship between the presence of thyroid pathology and the stage of the disease (Table III, $P = 0.068$). In breast cancer patients, there was no relationship between the histopathological grade and the presence of thyroid pathology ($P = 0.818$).

When the relationship between the menopausal status of breast carcinoma patients and the presence of thyroid pathology was investigated, we could not find any relationship of statistical significance; however, *P* value was close to the limit of statistical significance ($P = 0.086$).

The thyroid volumes of breast cancer patients and the control group did not differ significantly ($P = 0.844$). There was no relationship between the thyroid gland volumes and clinical stages of breast cancer patients ($P = 0.190$). When breast cancer patients were compared with respect to their thyroid status as euthyroid, hypothyroid, and hyperthyroid there were no relationship ($P = 0.904$). The relation between estrogen and progesterone receptor positivity and thyroid pathology was not significant also ($P = 0.539$ for ER, $P = 0.990$ for PR). The status of estrogen and progesterone receptors which might be of prognostic importance for breast cancer patients, the presence of vascular and lymphatic invasion, menopausal state, clinical stage, and histological grade where not significantly correlated to hyperthyroidism or hypothyroidism. However, the number of patients with hypothyroidism and hyperthyroidism were small to reach any meaningful conclusion.

When the relationship between the presence of lymphatic invasion and thyroid pathology was analyzed in breast cancer patients, no relationship of statistical significance was found ($P = 0.0480$).

In logistic regression analysis and unvaried analysis; menopause, the number of metastatic lymph nodes, the presence of vascular invasion, and the dimension of the tumor were the factors discriminating the breast cancer patients with and without thyroid pathology. These variables were included into an analysis in order to identify their ability to predict the presence of thyroid pathology. In the equation driven out of this analysis, we concluded that postmenopausal status and the presence of vascular invasion were determinants for the occurrence of thyroid pathologies in breast cancer population. When the variance of thyroid pathology occurrence was analyzed, it was related up to 19% with the absence or presence of vascular invasion and 17% with the fact that the patients were postmenopausal or not. The occurrence of thyroid pathology in postmenopausal breast carcinoma patients was 3, fourfold higher than the premenopausal patients. Similarly, the occurrence of thyroid pathology in breast cancer patients with vascular invasion was 14, fourfold higher than the ones without vascular invasion (Table IV).

DISCUSSION

The studies investigating the relationship between breast carcinoma and thyroid disorders are not new. The results of these studies are conflicting, and an etiological relationship has not been proven [2,17–19]. The rates of

TABLE III. The Relationship Between Clinical Stage and Thyroid Disorders

Clinical stage	Thyroid disorders (−) (n = 30)	Thyroid disorders (+) (n = 104)	*P* (Chi-square)
Stage I (n = 22)*	9 (30%)	13 (12.5%)	$P = 0.068$
Stage II (n = 83)	18 (60%)	65 (62.5%)	
Stage III (n = 24)*	2 (6.7%)	22 (21.2%)	
Stage IV (n = 5)	1 (3.3%)	4 (3.8%)	

TABLE IV. The Prediction Equation at Breast Cancer Patients Having Thyroid Disorders

Variable	B	SE	Wald	Df	Sig.	R[a]	Exp (B)[b]
Menopause	1.2364	0.5271	5.5023	1	0.190	0.1774	3.4433
Vascular invasion	2.6723	1.0605	6.3502	1	0.0117	0.1977	14.4733
Stable	0.2517	0.3288	0.5857	1	0.4441		

[a]R: demonstrates the explained variance for the dependent variable (the possibility of predicting the presence of thyroid disease).
[b]Exp (B): demonstrates the risk of having thyroid pathology in patients with or without positive variables.

detecting thyroid pathology in breast cancer patients change 7.8–46% in literature whereas in our study it was 77.9% [2,6,17,20]. On the other hand, some studies did not find a statistically significant relationship between breast cancer and thyroid pathology [21–23]. The discrepancies in the results of these studies may be due to different criteria used in the evaluation of thyroid pathology [24–30]. We evaluated thyroid pathology by measuring f-T3, f-T4, TSH, thyroglobulin, thyroid auto antibodies, and performing thyroid ultrasonography. However, in certain studies, instead of objective methods, subjective methods like palpation or limited numerical parameters have been used in the analysis, and it was concluded that there was no relationship between the thyroid disorders and breast cancer [41]. Another important dimension is the difference brought forward by the geographical features [2]. Unlike the study of Report, in our study, the patients and the controls were chosen from similar geographical regions.

In our study, we found a significant correlation between the presence of thyroid pathology and breast cancer; however, having the high percentage of thyroid disorders in our study might be related to the fact that Turkey is an endemic region for thyroid problems.

When clinical evaluations concerning the functional states of the patients have been evaluated different and controversial results have been obtained. Some researchers did not find any relationship between thyroid hormones and breast cancer; some authors found differences in levels of f-T3 and/or f-T4 and/or TSH [3,17,23,31]. The important point in our study was that f-T3 levels were at the upper limit of normal. Although f-T3 levels were within normal limits, it was statistically high in patients with breast cancer whereas no pathological result was found in the control group; this shows us that f-T3 which is the active form of the thyroid hormones can support the existing pathology in breast cancer patients. The reason for this increase is not clearly known, however, this condition may be related to incomplete explanation of hormonal balance at the level of hypothalamo-pituitary balance and their different interactions. Similarly, thyroid hormones are thought to influence breast tissue directly or indirectly together with TSH, PRL, estrogens and androgens; however, the physiopathology cannot be explained in detail [32–36]. In addition to this interaction at different levels, geographical changes, dietary factors, psychosomatic condition, menopausal status, and changes in hormonal state in correlation with such might result in obtaining different results.

Rose and Davis reported a study on thyroid disease and the distribution of breast cancer in 1978 [37]. However, other authors have not validated their results [33,38]. In our study, if breast cancer patients had accompanying thyroid pathology, the number of metastatic lymph nodes and the extension of the disease were greater when compared to breast cancer patients without thyroid pathology. This finding might bring the idea that concurrent thyroid pathology might influence the dissemination of the disease, and in this respect our findings are in correlation with the findings of Rose and Davis [33,37].

The information concerning the increase of vascular endothelial growth factor (VEGF) in thyroid pathology is not new. VEGF exerts its effects on lymph angiogenesis, angiogenesis, and intralymphatic tumor growth and these are mitogenic effects. As a result of such effects, lymphatic and vascular invasion occurs [9,11–16]. This factor also increases in patients with breast carcinoma. In our study, 33 (7%) of the patients with vascular invasion had thyroid pathology, which was of significance. The possible reason behind increased vascular invasion in the presence of thyroid pathology might be the over expression of VEGF [12,15]. However, we have not come across any study investigating the coexistence of breast cancer, thyroid disorders, and VEGF.

The size of the tumor and the number of involved lymph nodes were significantly related to thyroid pathology in our study, yet this condition did not influence clinical staging. Although this might seem as a contradiction, presence of thyroid pathology is not the only parameter influencing clinical staging in these patients. According to the results in the study of Smyth and Shering [39,40], together with tumor size, TNM stage and the thyroid volume had a positive correlation. We could not find any significant relationship between these parameters. The research by Lemaire et al. also support our findings about clinical stage and thyroid hormones concentration [31].

In our breast cancer patients, the status of estrogen and progesterone receptors, clinical and histopatholocigal grade, functional status and volume of thyroid gland, level of thyroglobulin and anti-thyroid antibodies did not demonstrate any difference of significant with the presence of thyroid pathology. There are numerous conflicting data trying to explain these issues in the literature but these are still controversial [6,13,14,24,34,38,41].

In breast cancer patients, the identification rates of nodular and diffuse hyperplasic structures by thyroid USG was higher when compared to controls which has also been demonstrated by several other researchers [17,40]. The possible explanation for this finding might be the expression of EGF, which is influencing thyroid nodule generation mechanism in breast cancer cells as well [42]. Hormones such as thyroid hormones, estrogens, progesterone, androgens are also making use of EGFR family and exerting endocrine, paracrine, and autocrine effects and these effects are exerted through tyrosine kinase [7]. This common pathway might be ending by over expression of a by-product at a certain step thereby stimulating both thyroid and breast cells. In an experimental study, it was shown that the regulation of EGFR levels in normal breast tissue and spontaneously developing breast tumors was closely related to the condition of thyroid gland [43]. Similarly, the members of the EGFR family that are influential on breast carcinoma and thyroid tissue (EGF, C-erbB2, VerbA etc) are stimulating growth through a common pathway by utilizing tyrosine kinase activity. This might result from molecular mechanisms aiming at explaining the relationship between breast carcinoma and the nodular enlargement and volume increase of the thyroid gland.

In conclusion, the incidence of thyroid pathology are higher in-patients with breast carcinoma compared to the controls, this suggests a relationship between breast carcinoma and thyroid pathology. However, we do not know how this relationship develops. In our study, in breast cancer patients with thyroid pathology, there were significant increases in the number of metastatic lymph nodes, vascular invasion, and tumor size. We might consider that the presence of thyroid pathology in breast cancer patients might influence the dissemination of the disease and adversely affect the prognosis. Especially in breast cancer patients at menopause, this relationship was more significant. However, we still need further studies to clarify the subject more. We hope our effort will be a contribution to the studies aiming to explain the relationship between thyroid pathology and breast cancer.

In order to contribute to the clarification of the relationship between prognosis and survival in breast cancer patients with thyroid disorders, we will continue to follow our patients.

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