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Association of Breast Cancer with Thyroid Function and Autoimmunity in Yemeni Women

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Abstract:-

➢ ***Background.***

Breast cancer (BC) is one of Yemeni women's leading causes of cancer mortality. In BC patients, supraclavicular radiation exposure may result in thyroid dysfunction, including hypothyroidism (HT). This case-control study aimed to evaluate the association of BC with the levels of thyroid hormones and anti-TPO Ab in Yemeni women and the influence of obesity, menopause, and treatment as effect modifiers of this association.

➢ ***Methods.***

The serum levels of FT3, TSH, FT4, anti-TPO Ab, CEA, and CA 15-3 were measured in 147 BC females (59 pretreatment and 88 post-treatment) and 70 healthy controls.

➢ ***Results.***

The results showed that BC patients had a significantly higher level of TSH than healthy controls (*P* = 0.048). A considerably higher level of TSH and a lower level of FT3 in post-treatment compared to pretreatment BC patients were found and associated with increased BMI and age (*P* < 0.05) in postmenopausal patients and decreased FT4 levels. Positive anti-TPO Ab levels were significantly higher in the BC group and post-treatment subgroup compared to the healthy control (22.4% vs. 3.3%; 22.7% vs. 3.3%, *P* = 0.001, respectively). HT prevalence was considerably greater in post-treatment BC patients than pretreatment BC patients (26.1% vs. 10.2%, *P* = 0.017).

➢ ***Conclusion.***

This study found a strong link between breast cancer, and thyroid function, and autoimmunity in Yemeni women with breast cancer, especially those who had recently been treated. A significantly higher prevalence of HT, a higher level of TSH, and a lower level of FT3 in post-treatment compared to pretreatment BC patients were associated with increasing BMI and age in post-menopausal patients. Further studies with a large sample size in the future are recommended.

Keywords:- *Breast Cancer, Free Triiodothyronine, Free Thyroxin, Thyroid Stimulating Hormone, Anti-Thyroid Peroxidase Antibody.*

I. INTRODUCTION

Breast cancer (BC) is the most prevalent type of cancer and a significant cause of mortality in women worldwide, accounting for 2.3 million (11.7%) of the total new cancer cases and 685,000 (6.9%) of the total cancer deaths in 2020. [1], [2] In Yemen, BC is the top common diagnostic malignancy and the key reason why women die of cancer, accounting for 2,894 (31.1%) of the total new cancer cases and 1,638 (13.5%) of the total cancer deaths in 2020. [3] BC incidence is rapidly rising because of changes in dietary habits, reproductive risk factors, and life expectancy, especially in developing countries. [4] It becomes clear that all cancers have a genetic link, either through hereditary gene mutations or acquired mutations throughout life. Decades of research have identified several genetic variants associated with BC etiology. In addition to the genetic factors, various risk factors have been identified, including age, hormonal, reproductive, menstrual history, obesity, alcohol, and radiation. [5] The endocrine system and BC are closely linked. [6] The thyroid gland is an integral part of the endocrine system and secretes thyroid hormones that play important biological roles in controlling cellular metabolism, proliferation, and differentiation. [7] The increased thyroid enlargement rate among BC patients was also reported. [8] Previous studies have demonstrated that almost all types of autoimmune and nonautoimmune thyroid diseases may be connected to BC [9], and the higher incidence of thyroid-registered cases in BC patients than in the average population was recently reported. [10]

If there is too little or too much thyroid-stimulating hormone (TSH) in the blood, it can cause hyperthyroidism or hypothyroidism (HT). This can cause the thyroid hormones triiodothyronine (T3) and/or thyroxine (T4) to move up or down in production. Scientists measured TSH, free (F)T3, and FT4 levels to see how well the thyroid was working. They also measured anti-thyroid peroxidase antibody (Anti-TPO Ab) levels to see if the thyroid was producing too much of an immune system protein.

Additionally, thyroid hormones control several metabolic pathways that are important for resting energy expenditure and variations in body weight; hence, thyroid dysfunction may change with body mass index (BMI). [11] It is one of women's most common endocrine disorders and may interfere with menopause and aging. [12]

The thyroid gland, an important endocrine organ, is close to the supraclavicular nodal area, which is often part of the radiation field for locally advanced BC. The most dangerous side effect of ionizing radiation is its capacity to trigger biochemical alterations in cellular genetic integrity, which may result in cancer or other functional abnormalities in irradiated organs and tissues. An increased incidence of HT in BC patients, especially younger individuals, has been linked to radiotherapy in the supraclavicular area. [13, 14]

The thyroid gland is susceptible to radiation. The causal relationship between radiation and thyroid dysfunction is well known for late radiation toxicity in patients with head and neck cancer who have received neck radiation therapy. [15, 16] However, the effect of radiation therapy on breast regions (e.g., the supraclavicular region) in BC patients remains controversial.

Several case-control studies in different ethnic populations have been conducted to evaluate the link between BC and the risk of thyroid dysfunction and/or autoimmunity. [17-26] However, the outcomes from various studies were inconsistent. Patients' quality of life must be improved by anticipating the extent of radiation risk and looking for ways to lower the risk of HT following radiotherapy, particularly as survivorship problems in BC become more and more significant.

Therefore, this study aims to evaluate the association of BC with the levels of hormones (FT3, FT4, and TSH) and anti-TPO Ab in Yemeni women and examine obesity, menopause, and treatment as an effect modifier of this association in BC patients.

II. MATERIALS AND METHODS

➢ *Subjects and Study Design*

This case-control study was conducted at the Radiology and Outpatient Department of the National Oncology Center (NOC) in Sana'a, Yemen, between January 2021 and October 2021. A total of 217 females aged 20-75 years were recorded. Of these, 147 were BC patients, and 70 were age-matched healthy controls. BC patients were subdivided into 59 pretreatment patients at the initial BC diagnosis and 88 post-treatment patients who had undergone primary therapy, including surgery, chemotherapy, and radiotherapy. Females with other types of primary cancer, a history of thyroid problems, and pregnancy status were excluded from the study. All participants gave their oral informed consent.

➢ *Laboratory Data and Blood Collection*

Standard techniques were used to measure weight and height, and the BMI was determined by dividing the weight (kg) by the height (m^2) of all subjects. Obesity was measured using BMI cut-offs based on 2004 WHO guidelines for Asians: underweight (BMI <18.5 Kg/m^2), non-obese (normal weight) (18.5≤ BMI <25 Kg/m^2), and obese (BMI ≥25 Kg/m^2). Menopause was defined as amenorrhea lasting for a year or more; in addition, women over 55 years without information on menopause were considered postmenopausal.

A 5 ml sample of venous blood was taken from each female and put into a test tube that did not have an anticoagulant. This was done so that the biochemical levels of FT3, FT4, TSH, Anti-TPO Ab, CEA, and CA 15-3 could be found using the electrochemiluminescence immunoassay (ECLIA) in the COBAS e411 automated analyzer (ROCHE/Hitachi-Germany). The thyroid function and autoimmunity were assessed according to the reference range values as follows:

FT3 3.07-6.76 pmol/L, FT4 12.3-20.2 pmol/L, TSH 0,47-4.64 mIU/L, CEA 0-5 µg/L, CA15-3 up to 25 KU/L, and Anti-TPO Ab less than 35 KIU/L, whereas Anti-TPO Ab level more than 35 IU/mL was supportive for thyroid autoimmunity. High levels of TSH assessed the HT above the maximum laboratory range and low levels of FT3 and/or FT4 in serum below the minimum laboratory range.

➢ *Treatments*

Postoperative irradiation of patients with BC to the chest wall and supraclavicular with or without axilla lymph nodes. The radiation dose was 50 Gy divided into 25 fractions (2 Gy) per fraction per day and five fractions per week. All patients were treated using a two-dimensional (2D) conformal radiation approach. Patients were prone with a side arm of treatment extended overhead and immobilized with a breast board. The pathologist at Sana'a NOC diagnosed the cancerous diseases. A physician determined the treatment volume in the axillary and supraclavicular areas. All patients were treated with CT scans and manual contouring before receiving dosages. The supraclavicular area was treated with tangential fields. Treatment planning was performed using a simulator (Varian Medical System). The treatment machine was then delivered using this technique (Theratron Equinox Cobalt-60). The standard chemotherapy regimens carried out chemotherapy for BC.

➢ *Statistical Analyses*

All statistical analyses were performed using SPSS software (version 21) for Windows and GraphPad Prism (version 8.0.2). The Mann-Whitney U test was used for continuous variable analysis, and the Chi-square test was used for categorical analysis. Spearman correlation coefficients and the Spearman rank-order correlation coefficient employing the Graphpad prism were applied to investigate the correlation between thyroid laboratory parameters and tumor markers. The two-tailed *P* value was considered statistically significant at $P < 0.05$.

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III. RESULTS

➢ *Clinical Parameters of the Study Subjects*

Table 1 and Figure 1 summarize the clinical parameters of the study subjects as means ± standard deviation. The BC patients had a significantly higher level of TSH and a non-significantly higher level of anti-TPO Ab than the healthy control (*P = 0.048, P = 0.091*, respectively). However, there was no difference in FT3 and FT4 levels between BC patients and healthy controls (*P > 0.05*). According to the stratified analysis of BC patients by treatment status, the post-treatment subgroup had a significantly higher level of TSH (*P = 0.015*), a lower level of FT3 (*P = 0.016*), and a marginally more elevated level of anti-TPO Ab (*P = 0.054*) than that of the pretreatment subgroup. Additionally, the post-treatment subgroup had a significantly higher level of TSH and a non-significantly higher level of anti-TPO Ab than the healthy control (*P = 0.005, P = 0.597*, respectively). However, there was no difference in FT3 and FT4 levels between the post-treatment and the healthy control (*P* > 0.05*) (*Figures 1A, 1B, 1C, and 1D). Similarly, the pretreatment subgroup had a significantly higher Anti-TPO Ab level than the healthy control (*P = 0.005*). However, there was no difference in thyroid hormone levels between the pretreatment subgroup and the healthy control (*P > 0.05*) (Figure 1D).

The percentage of positive Anti-TPO Ab was significantly higher in the BC group and pre-and post-treatment subgroups compared to the control group (22.4 % vs. 3.3%, *P = 0.001*; 22% vs. 3.3%, *P = 0.002*; 22.7 % vs. 3.3%, *P = 0.001*, respectively), whereas it was non-significantly higher in post-treatment compared to the pretreatment subgroups (*P > 0.05*) (Figure 1E).

The mean values of carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA 15-3) were significantly higher in the BC group and pre- and post-treatment subgroups compared to the control group (CEA: *P*=0.000, *P*=0.001; *p*=0.000, CA153: *P*=0.008, *P*=0.039, *P*=0.013, respectively), whereas they were non-significantly lower in the post-treatment compared to pretreatment subgroup (*P*=0.958, *P*=0.757, respectively) (Figure 1F, 1G).

➢ *Stratified Analysis of Clinical Parameters According to Treatment, Menopausal, BMI Status, and Age*

The levels of thyroid hormones showed no difference between BC patients and healthy controls according to BMI and menopausal status, even though the postmenopausal subgroup had a significantly lower value of FT3 and FT4 levels (*P = 0.033 and 0.036*, respectively) and a non-significantly higher level of TSH than that in the premenopausal subgroup (*P > 0.05*). The level of anti-TPO Ab was significantly higher in BC patients than that in healthy controls for BMI ≥25 and age >35 (*P = 0.045 and 0.028*, respectively) (Table 2).

According to the stratified analysis of BC patients by treatment and menopausal status, the post-treatment subgroup had a significantly lower value of FT3 level (*P = 0.009*) and a non-significantly higher value of TSH level than that in the pretreatment subgroup for the postmenopausal patients. However, for premenopausal patients, the post-treatment subgroup had a significantly higher value of TSH and non-significantly higher anti-TPO Ab levels than that in the pretreatment subgroup (*P = 0.036; p = 0.153*, respectively), whereas the levels of FT3 and FT4 showed no differences between the two subgroups (*P > 0.05*). For the post-treatment patients, the postmenopausal subgroup had a significantly lower value of FT3 and FT4 levels (*P = 0.009; P = 0.041*, respectively) and a non-significantly higher value of TSH level than that in the premenopausal subgroup (*P > 0.05*). However, for pretreatment patients, there was no difference in thyroid parameters between the two subgroups (*P > 0.05*).

According to a stratified analysis by treatment and BMI status, the post-treatment subgroup had a significantly lower value of FT3 and anti-TPO Ab levels (*P = 0.025 and 0.024*, respectively) and a higher value of TSH level than that in the pretreatment subgroup (*P = 0.008) for* BMI ≥25 patients. However, for BMI <25 patients, there was no difference in thyroid parameters between the two subgroups (*P*>0.05). For pretreatment patients, the BMI ≥25 subgroup had a significantly lower value of FT4 than that of the BMI <25 subgroups (*P = 0.046*). However, for post-treatment patients, there was no difference in thyroid parameters between the two subgroups (*P > 0.05*). According to a stratified analysis by treatment and age status, the post-treatment subgroup had a significantly lower value of FT3 level and a higher value of TSH and anti-TPO Ab levels than the pretreatment subgroup (*P = 0.029, P = 0.020, and P = 0.030*, respectively) for age >35 patients. However, for patients aged ≤35, there was no difference in thyroid parameters between the two subgroups (*P > 0.05*) (Table 3).

According to a stratified analysis of BC patients by clinicopathological characteristics, the results showed that the CA15-3 level was significantly higher in the larger tumor size (T3-T4) than that in smaller tumor stage (T1-T2) of BC patients (*P = 0.023*). For BC metastases, the positive organ metastases had significantly higher CEA and CA153 levels than that in negative organ metastases (*P = 0.022; P = 0.026*, respectively), and the positive lymph node metastases had a significantly higher CEA level than those in the negative lymph node metastases (*P = 0.048*). However, there is no relation between thyroid hormones or anti-TPO Ab and the histopathological characteristics of the BC patients (*P > 0.05*) (data not showed).

➢ *Correlation Coefficient between Laboratory Parameters and Tumor Markers*

In pretreatment patients, CA 15-3 was significantly positively correlated with TSH and CEA (*r = 0.318, P = 0.014; r = 0.454, P = 0.000*, respectively) (Figure 2A and B). There was no apparent correlation between other thyroid laboratory parameters and CEA or CA 15-3 (*P > 0.05) (*Figures 2C, 2D, 2E, and 2F).

In post-treatment patients, FT4 had a strong positive relationship with CEA (*r = 0.295, P = 0.026*) (Figure 3A) and a strong negative relationship with both TSH and anti-TPO Ab (*r = -0.523, P = 0.000; r = -0.231, P = 0.031*, respectively) (Figures 3B and C). There was no apparent correlation between other thyroid laboratory parameters and CEA or CA 15-3 (*P > 0.05*) (Figure 3D, 3E, and 3F).

➢ *Prevalence of HT in BC Patients*

The overall prevalence of HT in BC patients was 19.9% (15.6% subclinical HT, 6.8% clinical HT), with a significantly higher prevalence in post-treatment BC patients than in pretreatment BC patients (26.1% vs. 10.2%, *P = 0.01*) (Table 4).

IV. DISCUSSION

Although TSH and other thyroid laboratory parameters were within normal limits in our study, the BC patients had a significantly higher level of TSH than healthy controls. However, there was no difference between BC patients and controls in FT3 and FT4 levels. According to a stratified analysis by treatment status, the post-treatment BC patients had a significantly higher level of TSH than pretreatment BC patients or healthy controls. These results were consistent with the previous studies. [14, 17, 27-29] In pretreatment BC patients, TSH was significantly positively correlated with CA15-3. However, there was no difference between pretreatment patients and healthy controls in TSH level, which is consistent with previous studies. [18, 19]

FT3 was significantly lower in post-treatment than pretreatment BC patients, which was consistent with the previous studies of Shi et al. (2017) [10] and de Groot et al. (2015). [29] FT4 was significantly positively correlated with FT3 and CEA and negatively correlated with TSH and anti-TPO Ab. However, there were no differences in FT3 and FT4 levels between pre- or post-treatment BC patients and healthy controls, which is also consistent with research. [20] The elevated levels of TSH and lower FT3 in this study suggested that chemotherapy and/or radiotherapy may affect the function and regulation of the thyroid gland in post-treatment BC patients, resulting in an increased level of TSH. Chemotherapy and radiation can change how the thyroid works and how it controls hormones in women with BC [30], and it was reported that the effects of chemicals and radiation on thyroid tissue work together. [31] Chemotherapy, one of the most successful systemic cancer treatments, kills malignant cells and injures normal cells. Therefore, chemotherapy may cause thyroid dysfunction in BC patients, and thyroid hormone levels decrease after BC chemotherapy. [32] When combined with radiation therapy, chemotherapy makes the thyroid more vulnerable to its effects. This makes the two treatments a major risk factor for thyroid damage and HT. [33] Additionally, Radiation therapy also changes the inflammatory state of endothelial cells [34], which can damage the parenchyma directly or affect blood vessels through fibrosis [35] and cause thyroid dysfunction [14]. Due to conventional radiation therapy for breast, head, and neck malignancies, thyroid hormone levels decreased and respiratory rates increased significantly. [36] Although the radiation field of the supraclavicular radiation field in breast cancer only partially includes the thyroid compared with the head and neck cancer cases, the effect was so significant because of the broad penumbra profile of the Cobalt-60 source of the teletherapy machine as well as insufficient shielding during radiation therapy. [36] Furthermore, the effect of thyroid radiation depends on thyroid gland size and radiation dose in the case of cancer, the field distribution, the planning technique used, the type of radiation equipment, and the age and gender of the patient. [14, 27, 37] Moreover, chemotherapy is thought to induce HT by inhibiting the release of thyroglobulin in the liver [38] and the function of the hypothalamic-pituitary-thyroid axis. [39]

In our study, BC patients had a non-significantly higher level of anti-TPO Ab than healthy controls. Nevertheless, the percentage of positive anti-TPO Ab was significantly higher in BC patients than in healthy controls, especially in the post-treatment subgroup. In addition, the level of anti-TPO Ab was substantially more remarkable in the pretreatment subgroup than the control group and marginally higher in post-treatment than in pretreatment subgroups. These results were consistent with research from previous studies [21, 22], and a meta-analysis by Pan et al. (2020) [23], which confirmed the relationship between anti-TPO Ab and BC. The high percentage of positive anti-TPO Ab in BC patients may be due to a different geographical iodine intake, potentially affecting the pathogenesis of both thyroid autoimmune and breast diseases. [30] A recent study by Muller et al. (2020), reported that both the thyroid and mammary glands express the sodium iodide symporter. One of the most important thyroid autoantigens, thyroid peroxidase, is found in breast tissue. This is a key antigen link between thyroid autoimmunity and BC. Lactoperoxidase (LPO), an enzyme in the same family as thyroid peroxidase and with a structure similar to thyroid peroxidase, is found in breast cancer cells that are not healthy and reacts with some autoantibodies that are meant to attack thyroid peroxidase. [31] Many studies have found that BC has higher TPO-Abs. [24] This is likely because of a common antigen that makes TPO and LPO react normally in the breast. [40] Cross-reactivity of TPO-Abs with LPO may help explain why there are more TPO-Abs in patients with BC. Also, higher levels of TPO gene expression in BC cells may be another reason for the higher levels of TPO-Abs in patients with BC. [9, 41] Several studies reported that surgery or chemotherapy could affect the autoimmune system and cause or worsen autoimmune thyroid disease. [41, 42] Although the relationship between irradiation and thyroid autoimmune disease is still debated, irradiation can induce or exacerbate thyroid autoimmunity with clinical or experimental evidence [43, 44], and thyroid dysfunction has already been reported as a side effect of radiotherapy for head and neck cancer. [35, 45] Primary HT and autoimmune thyroiditis are more common following radiotherapy in BC patients. [46, 47] The radiotherapy may cause thyroid gland inflammation and damage and trigger the production of TPO Ab and thyroglobulin antibodies. The high levels of these antibodies will block the formation of thyroid hormones, dropping FT4 and enhancing TSH levels. [48] The present results call

attention to the usefulness of examination for anti-TPO Ab during follow-up of BC patients who received surgery, radiotherapy, and chemotherapy.

According to menopausal status, the results showed that postmenopausal BC patients had a significantly lower value of FT3 and FT4 levels and a non-significantly higher value of TSH than that of premenopausal BC patients. Postmenopausal status is primarily associated with advanced age, and the age-related changes in thyroid physiology include decreased thyroid iodine absorption, synthesis of FT4 and FT3, and catabolism of FT4, whereas increased reverse T3 and TSH levels remain normal, sometimes with a trend toward a higher limit. [12] Even without evident disease, the endocrine system changes with age. Thus, age-related decreased T4 activity and reduced thyroid responsiveness to TSH may lead to increased TSH secretion. [49] The level of FT3 was significantly lower in the post-treatment subgroup of postmenopausal BC patients whose BMI went up, while the level of FT4 was not significantly lowe. In contrast, the level of TSH was boosted considerably in the post-treatment subgroup with increasing BMI. These results were consistent with previous studies. [50, 51] The reduction of thyroid function was associated with chemotherapy progress, particularly in postmenopausal women. [51] However, for premenopausal patients, the TSH level was significantly higher in post-treatment subgroup than pretreatment subgroup. The hormone estrogen may play a part in thyroid problems, and estrogen receptors and their different forms on thyroid cells may also play a role, mainly by raising the risk of cancer. [52, 53] Estrogen binding to thyroglobulin is the most common mechanism of thyroid dysfunction in postmenopausal women. Inhibiting thyroxine from entering cells causes bound thyroxine levels to rise and free thyroid hormone availability to decline. [54] Therefore, further studies on BMI and menopausal status are needed to understand the association of thyroid hormones with BC after treatment.

The overall prevalence of HT in BC patients was 19.9%, with a significantly higher prevalence post-treatment than in pretreatment BC patients (26.1% and 10.2%, respectively). These results were consistent with those of previous researchers. [20, 55, 56] They reported that HT is a common side effect of both chemotherapy and radiotherapy, and that there may be strong links between the two treatments and HT in BC caused by thyroid damage. [47, 57] Recent studies from Danish and China reported that the risk of HT was elevated in patients with BC after being treated with radiation therapy to supraclavicular lymph nodes and chemotherapy. [13, 58] The high rate of HT in BC patients who have finished treatment has been linked to the multimodality therapy used to treat cancer [47] These treatments may influence the development of thyroid dysfunction via auto-immunologic reactions. [42, 59] Even though the thyroid gland is exposed to secondary beams during radiotherapy of BC patients, the dose absorbed by the thyroid is the most essential factor in developing HT. Many studies showed that BC patients receiving ≥30 Gy or ≥36 Gy and V20-40 significantly affect the development of HT. [27, 60] In addition, a significant association between increased thyroid absorbed dose and thyroid hormone changes in BC patients was reported. [61] Also, damage to thyroid parenchymal cells and capsular contracture after radiation have been suggested as possible causes of HT. Small thyroid vessel damage and large vessel atherosclerosis may also be caused by radiation. [15, 62] So, this study showed that chemotherapy and radiotherapy with high radiation doses may have an effect on the thyroid function of BC patients and may even cause HT.

The causal relationship between BC and thyroid function has not been well established. Nevertheless, HT appears to be a significant clinical problem associated with BC. Based on these results, chemotherapy, radiation technique, radiation dose, and the way radiation fields are spread out in the supraclavicular and axillary areas may all play a part in BC patients getting HT after treatment. Therefore, we suggest regular thyroid hormone screening and anti-TPO Ab levels should be included in the evaluation of BC patients periodically, especially after supraclavicular radiotherapy. This will allow us to identify the patients who require thyroxine replacement therapy, thereby avoiding the complications of HT seen in post-treatment mastectomy patients.

V. CONCLUSION

The present study concluded that the TSH level was significantly higher in BC patients compared to healthy controls; it was considerably higher in post-treatment than pretreatment BC patients, associated with increasing BMI and advanced age. However, the FT3 level was significantly lower in post-treatment compared to pretreatment BC patients, associated with increasing BMI and advanced age in postmenopausal BC patients. The percentage of positive anti-TPO Ab was substantially higher in BC patients compared to healthy controls, especially post-treatment. The prevalence of HT was significantly increased in BC patients; it was significantly higher in post-treatment compared to pretreatment BC patients. Our study supports the association of BC with thyroid dysfunction and autoimmunity. The study is the first to evaluate thyroid function and autoimmunity in Yemeni BC women. Further studies with large sample sizes in the future are recommended.

ABBREVIATIONS

BC: Breast cancer, HT: Hypothyroidism, TSH: Thyroid stimulating hormone, FT3: Free Triiodothyronine, FT4: Free Thyroxin, Anti-TPO Ab: Anti-thyroid peroxidase antibody, BMI: Body mass index, NOC: National Oncology Center, ECLIA: Electrochemiluminescence immunoassay, CEA: Carcinoembryonic antigen, CA15-3: Carbohydrate antigen 15-3, LPO: Lactoperoxidase.

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Table 1 Clinical Parameters of the Study Subjects.

Parameters	BC	BC		Healthy Controls (n = 70)	P^a	P^b	P^c	P^d
	BC (n = 147)	Pre-treatment (n = 59)	Post-treatment (n = 88)					
Age	44.8±10.7	44.5±11.2	45±10.4	44±12.8	0.459	0.746	0.378	0.454
FT3 [pmol/L]	5.33±1.76	5.70±1.86	5.07±1.63	5.27±1.22	0.565	0.324	0.109	0.016
FT4 [pmol/L]	15.45±3.34	15.46±3.5	15.44±3.25	15.38±2.65	0.762	0.828	0.766	0.972
TSH [mIU/L]	3.36±3.22	2.42±1.66	3.99±3.82	2.22±1.19	0.048	0.830	0.005	0.015
Anti-TPOAb [KIU/L]	33.78±29.9	33.41±26.13	34.04±32.3	23.30±5.9	0.091	0.005	0.597	0.054
Positive Anti-TPOAb	33/147 (22.4%)	13/59 (22%)	20/88 (22.7%)	2/60 (3.3%)	0.001	0.002	0.001	0.921
CEA [µg/L]	3.9±5.15	4.17±5.45	3.63±4.86	1.43±0.92	0.000	0.001	0.000	0.958
CA15-3 [KU/L]	15.49±19.3	18.83±24.28	12.08±11.24	8.3±3.43	0.008	0.039	0.013	0.757

Data of clinical parameters are expressed as means±SD. P^a breast cancer (BC) compared to healthy control; P^b pretreatment BC patients compared to control; P^c post-treatment BC patients compared to controls; P^d post-treatment BC patients compared to pretreatment BC patients; FT3: Free Triiodothyronine, FT4: Free Thyroxin; TSH: Thyroid stimulating hormone; Anti-TPO Ab: Anti-thyroid peroxidase antibodies; CEA: Carcinoembryonic antigen; and CA15-3: Carbohydrate antigen 15-3.

Table 2 Clinical Parameters of Study Subjects According to Menopausal, BMI, and Age.

Parameters			N (cases/controls)	BC	Controls	*P*
FT3	menopausal	premenopausal	136 (92/44)	5.93±1.71	5.14±1.19	0.408
		postmenopausal	81 (55/26)	5.01±1.79	5.45±1.25	0.038
		P		0.033	0.368	
	Age group	≤35	53 (31/22)	5.27±1.76	5.17±1.31	0.807
		>35	164 (116/48)	5.34±1.75	5.31±1.17	0.550
		P		0.683		
	BMI	<25	130 (92/38)	5.50±1.96	5.49±1.32	0.369
		≥25	87 (55/32)	5.04±1.31	4.99±1.02	0.972
FT4	menopausal	premenopausal	136 (92/44)	15.82±3.44	15.49±2.91	0.915
		postmenopausal	81 (55/26)	14.66±3.66	15.22±2.19	0.537
		P		0.036	0.226	
	Age group	≤35	53 (31/22)	15.89±3.38	16.26±2.27	0.279
		>35	164 (116/48)	15.42±3.09	15.24±1.83	0.766
		P		0.657		
	BMI	<25	130 (92/38)	15.96±3.43	15.48±2.14	0.577
		≥25	87 (55/32)	14.78±2.47	15.66±1.89	0.151
TSH	menopausal	premenopausal	136 (92/44)	3.01±2.8	2.27±1.18	0.267
		postmenopausal	81 (55/26)	3.94±3.79	2.14±1.23	0.077
		P		0.469	0.662	
	Age group	≤35	53 (31/22)	2.35±1.51	2.06±1.18	0.665
		>35	164 (116/48)	3.63±3.5	2.29±1.2	0.069
		P		0.092		
	BMI	<25	130 (92/38)	3.3±3.25	2.17±1.1	0.129
		≥25	87 (55/32)	3.46±3.2	2.27±1.22	0.199
Anti-TPO Ab	menopausal	premenopausal	136 (92/44)	36.29±35.18	23.85±5.72	0.306
		postmenopausal	81 (55/26)	29.58±17.34	21.81±6.29	0.082
		P		0.965	0.263	
	Age group	≤35	53 (31/22)	30.770±29.3	24.67±5.5	0.718
		>35	154 (116/38)	34.59±30.12	22.51±6.05	0.028
		P		0.268		
	BMI	<25	130 (92/38)	35.89±35.21	23.85±35.32	0.636
		≥25	87 (55/32)	30.26±17.48	22.79±6.44	0.045

BC patients, FT3: Free Triiodothyronine; FT4: Free Thyroxin; TSH: Thyroid stimulating hormone; Anti-TPO Ab: Anti-thyroid peroxidase antibodies; BMI: Body mass index.

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Table 3 Effect of the Interaction between Menopausal, BMI, and Treatment Status on Thyroid Hormones Levels in BC Patients.

Parameters			N (pre-/Post-treatment)	Pretreatment	Post-treatment	*P*
FT3	menopausal	premenopausal	92 (40/52)	5.68±1.85	5.37±1.60	0.384
		postmenopausal	55 (19/36)	5.70±1.96	4.64±1.59	0.009
		P		0.922	0.009	
	Age group	≤35	31 (13/18)	5.69±2.11	4.96±1.43	0.230
		>35	116 (46/70)	5.70±1.82	5.08±1.69	0.029
		P		0.609	0.967	
	BMI	<25	92 (29/63)	6.16±2.43	5.19±1.63	0.095
		≥25	55 (25/30)	5.25±0.91	4.79±1.65	0.025
		P		0.417	0.160	
FT4	menopausal	premenopausal	92 (40/52)	15.86±3.49	15.98±2.84	0.506
		postmenopausal	55 (19/36)	15.16±1.61	14.66±3.66	0.391
		P		0.470	0.041	
	Age group	≤35	31 (13/18)	15.86±4.63	15.91±2.26	0.230
		>35	116 (46/70)	15.56±2.45	15.32±3.46	0.580
		P		0.534	0.411	
	BMI	<25	92 (29/63)	16.48±3.72	15.72±3.29	0.396
		≥25	55 (25/30)	14.81±1.85	14.74±3.1	0.833
		P		0.046	0.355	
TSH	menopausal	premenopausal	92 (40/52)	2.39±1.74	3.49±3.34	0.036
		postmenopausal	55 (19/36)	2.48±1.526	4.7±4.38	0.167
		P		0.667	0.550	
	Age group	≤35	31 (13/18)	1.95±0.9	2.65±1.80	0.400
		>35	116 (46/70)	2.56±1.8	4.33±4.13	0.020
		P		0.437	0.119	
	BMI	<25	92 (29/63)	2.56±1.82	3.64±3.7	0.265
		≥25	55 (25/30)	2.28±1.52	4.85±4.1	0.008
		P		0.682	0.125	
Anti-TPO Ab	menopausal	premenopausal	92 (40/52)	33.94±28.83	38.1±39.55	0.153
		postmenopausal	55 (19/36)	32.29±19.9	28.16±15.95	0.111
		P		0.615	0.905	
	Age group	≤35	31 (13/18)	34.36±42.71	28.17±14.41	0.857
		>35	116 (46/70)	33.13±19.82	35.54±35.4	0.030
		P		0.055	0.824	
	BMI	<25	92 (29/63)	34.63±32.87	36.47±36.47	0.528
		≥25	55 (25/30)	32.23±17.86	27.91±17.08	0.024
		P		0.214	0.592	

FT3: Free Triiodothyronine; FT4: Free Thyroxin; TSH: Thyroid stimulating hormone; Anti-TPO Ab: Anti-thyroid peroxidase antibodies; BMI: Body mass index.

Table 4 Prevalence of HT.

BC patients				*P**
	Total	Pretreatment	Post-treatment	
HT	29/147 (19.9 %)	6/59 (10.2%)	23/88 (26.1%)	0.017
Clinical HT	6/147 (6.8%)	0 (0%)	6/88 (6.8%)	
Subclinical HT	23/147 (15.6%)	6/59 (10.2%)	17/88 (19.3%)	0.134

Prevalence of hypothyroidism (HT) (clinical HT and subclinical HT) in breast cancer (BC) patients, with pretreatment and post-treatment patients. * *P* was derived from the Chi-square test.

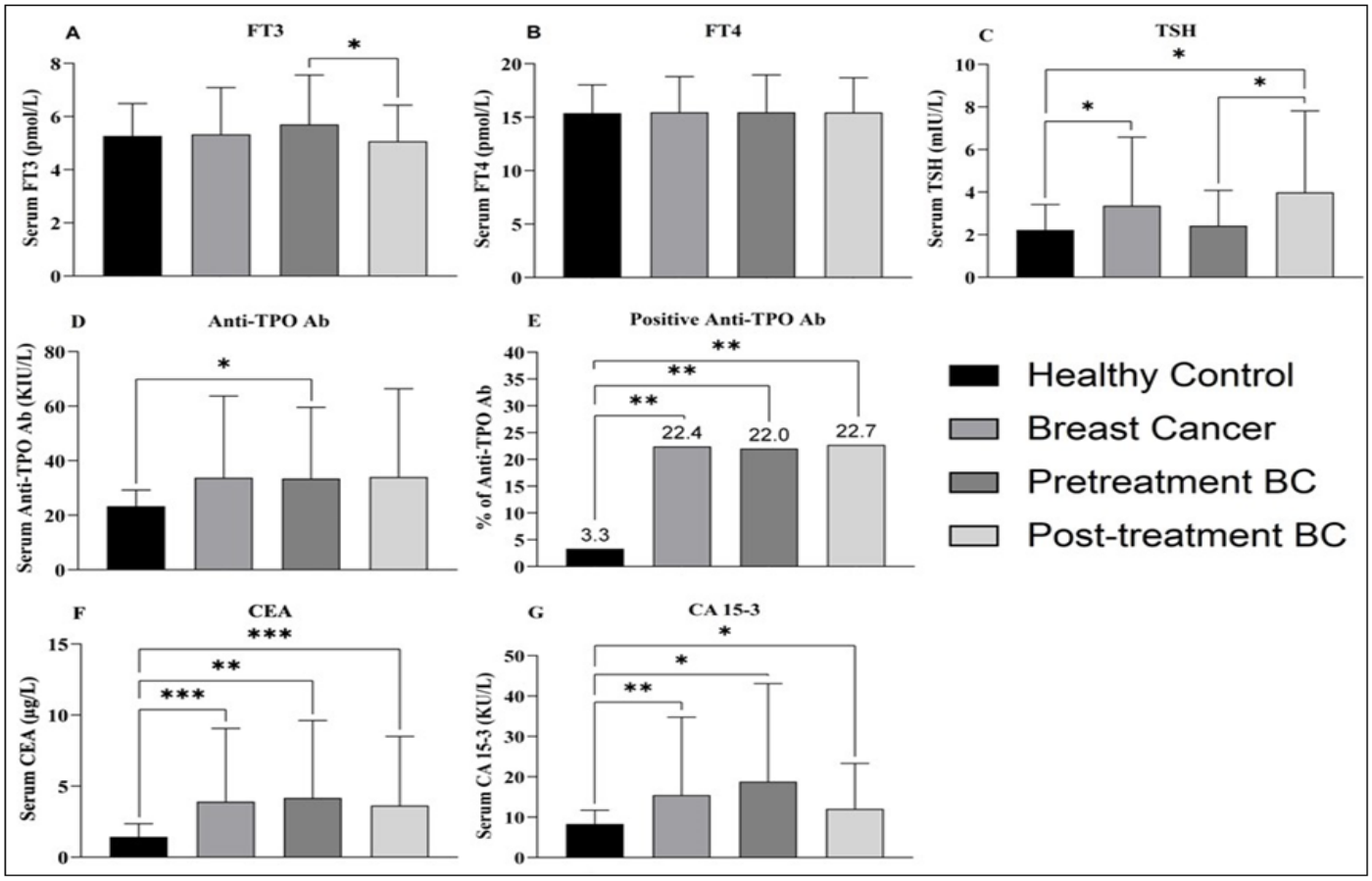

Fig 1 The Mean Levels of Clinical Parameters in Patients with BC, Pretreatment Patients, Post-Treatment Patients, and Controls. The Mean of (A) FT3, (B) FT4, (C) TSH, (D) Anti -TPO, (E) the Percentage of Positive Anti -TPO, (F) CEA, and (G) CA 15-3. *P<0.05, **P<0.01, ***P<0.001.

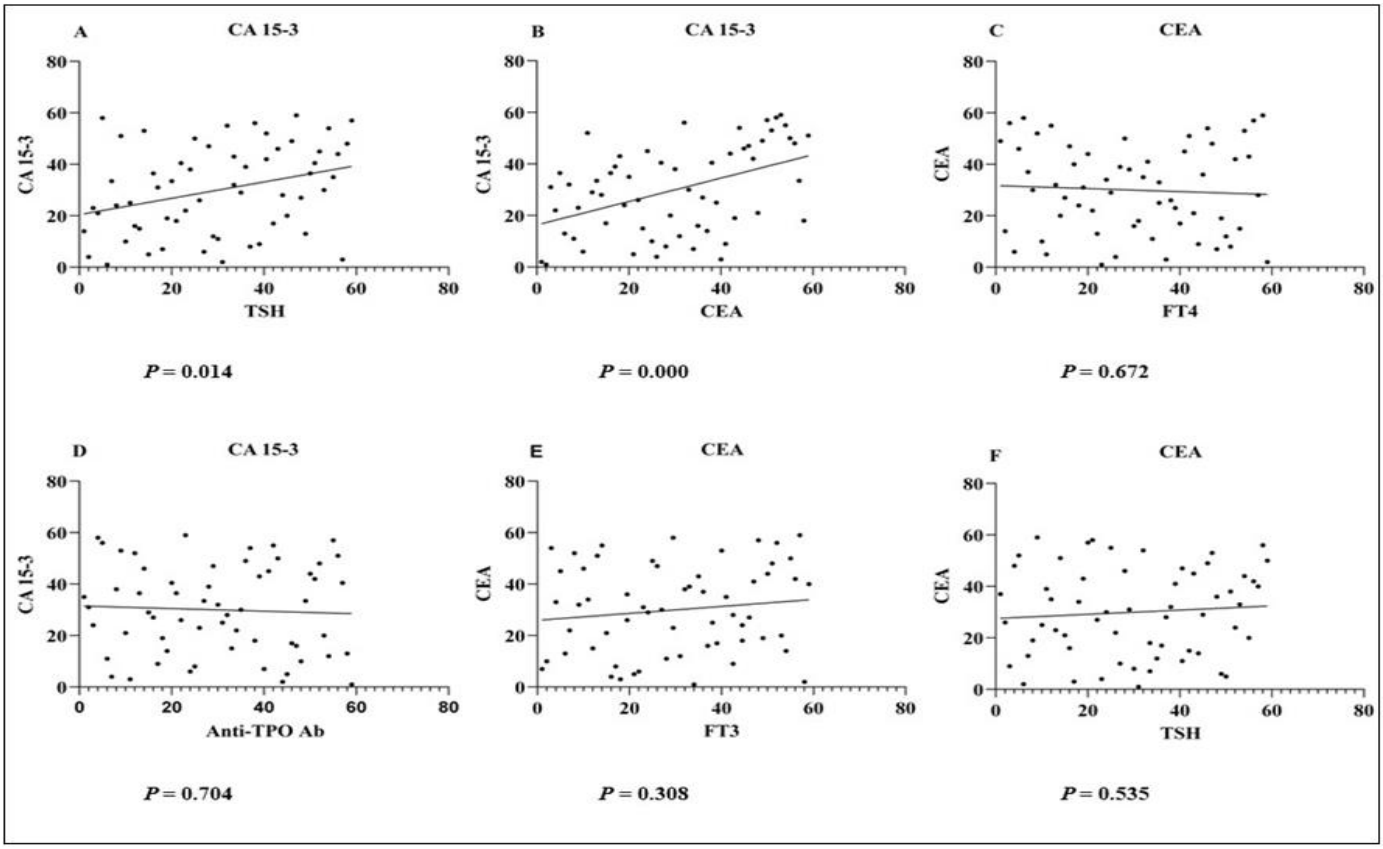

Fig 2 Correlation of Thyroid Parameters with CEA and CA 15-3 in Pretreatment Patients.

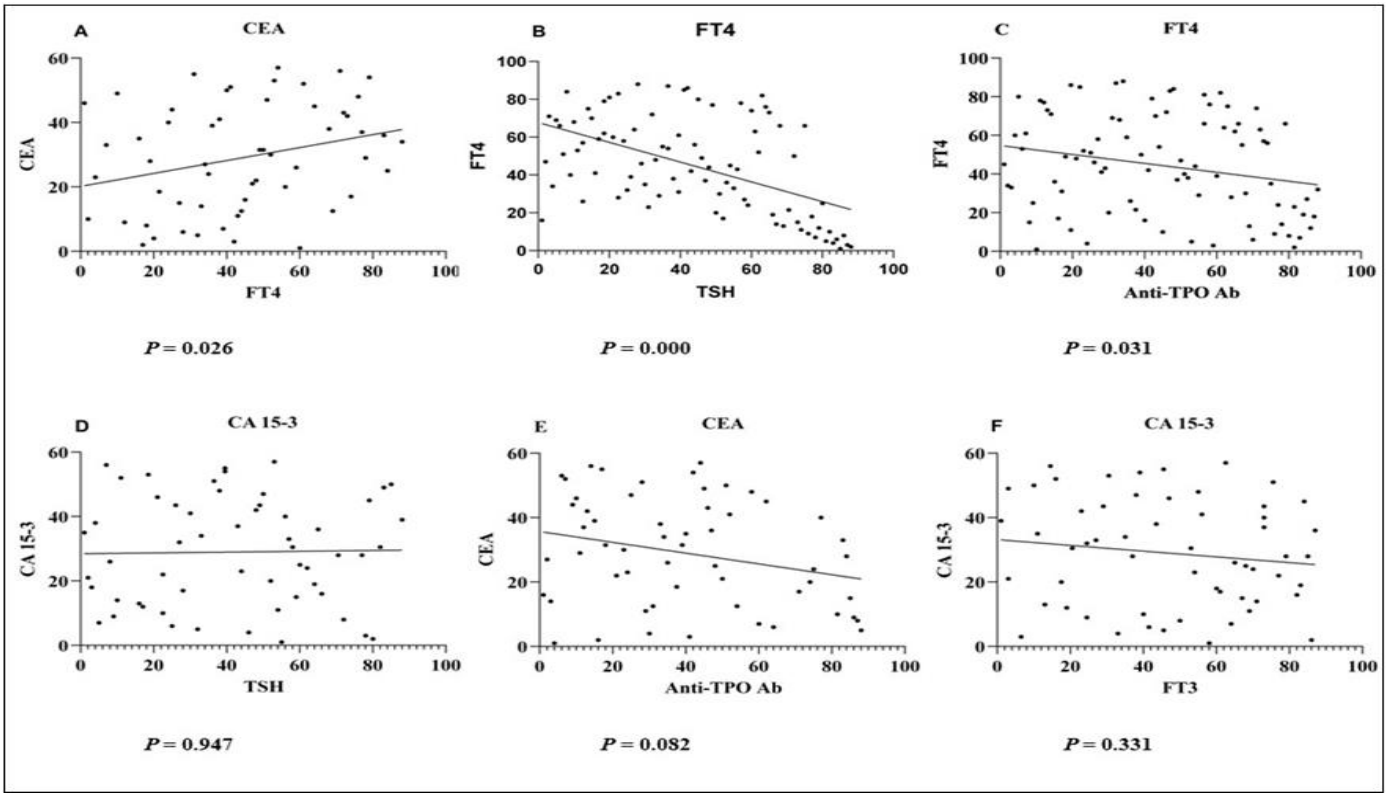

Fig 3 Correlation of Thyroid Parameters with CEA and CA 15-3 in Post-Treatment Patients.

REFERENCES

[1]. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; 69: 7-34. 2019/01/09. DOI: 10.3322/caac.21551.

[2]. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; 71: 209-249. 2021/02/05. DOI: 10.3322/caac.21660.

[3]. World Health Organization/International Agency for Research on Cancer (WHO/IARC) published the World Cancer Report 2020. https://gco.iarc.fr/today/ fact-sheets-populations. Accessed 20 April 2021.

[4]. Babu GR, Lakshmi SB and Thiyagarajan JA. Epidemiological correlates of breast cancer in South India. *Asian Pac J Cancer Prev* 2013; 14: 5077-5083. 2013/11/02. DOI: 10.7314/apjcp.2013.14.9.5077.

[5]. Yang JD, Lee JW, Kim WW, et al. Oncoplastic surgical techniques for personalized breast conserving surgery in breast cancer patient with small to moderate sized breast. *J Breast Cancer* 2011; 14: 253-261. 2012/02/11. DOI: 10.4048/jbc.2011.14.4.253.

[6]. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. *J Clin Oncol* 2014; 32: 2255-2269. 2014/05/29. DOI: 10.1200/jco.2013.54.2258.

[7]. Meng R, Tang HY, Westfall J, et al. Crosstalk between integrin αvβ3 and estrogen receptor-α is involved in thyroid hormone-induced proliferation in human lung carcinoma cells. *PLoS One* 2011; 6: e27547. 2011/12/02. DOI: 10.1371/journal.pone.0027547.

[8]. Smyth PP, Smith DF, McDermott EW, et al. A direct relationship between thyroid enlargement and breast cancer. *J Clin Endocrinol Metab* 1996; 81: 937-941. 1996/03/01. DOI: 10.1210/jcem.81.3.8772554.

[9]. Turken O, NarIn Y, DemIrbas S, et al. Breast cancer in association with thyroid disorders. *Breast Cancer Res* 2003; 5: R110-113. 2003/08/21. DOI: 10.1186/bcr609.

[10]. Shi Y, Li X, Ran L, et al. Study on the status of thyroid function and thyroid nodules in chinese breast cancer patients. *Oncotarget* 2017; 8: 80820-80825. 2017/11/09. DOI: 10.18632/oncotarget.20542.

[11]. Longhi S and Radetti G. Thyroid function and obesity. *J Clin Res Pediatr Endocrinol* 2013; 5: 40-44. 2012/11/15. DOI: 10.4274/jcrpe.856.

[12]. del Ghianda S, Tonacchera M and Vitti P. Thyroid and menopause. *Climacteric* 2014; 17: 225-234. 2013/09/04. DOI: 10.3109/13697137.2013.838554.

[13]. Choi SH, Chang JS, Byun HK, et al. Risk of Hypothyroidism in Women After Radiation Therapy for Breast Cancer. *Int J Radiat Oncol Biol Phys* 2021; 110: 462-472. 2021/01/08. DOI: 10.1016/j.ijrobp.2020. 12.047.

[14]. Darvish L, Ghorbani M, Teshnizi SH, et al. Evaluation of thyroid gland as an organ at risk after breast cancer radiotherapy: a systematic review and meta-analysis. *Clin Transl Oncol* 2018; 20: 1430-1438. 2018/05/16. DOI: 10.1007/s12094-018-1875-7.

[15]. Jereczek-Fossa BA, Alterio D, Jassem J, et al. Radiotherapy-induced thyroid disorders. *Cancer Treat Rev* 2004; 30: 369-384. 2004/05/18. DOI: 10.1016/ j.ctrv.2003.12.003.

[16]. Alterio D, Jereczek-Fossa BA, Franchi B, et al. Thyroid disorders in patients treated with radiotherapy for head-and-neck cancer: a retrospective analysis of seventy-three patients. *Int J Radiat Oncol Biol Phys* 2007; 67: 144-150. 2006/11/07. DOI: 10.1016/j.ijrobp.2006.08.051.
[17]. Jarari AM, AlJarari M H N, Rao Peela J, et al. Serum Thyroid Hormone Profile in Breast Cancer Patients. *JEMDS* 2018; 7: 719-723. DOI: 10.14260/jemds/2018/163.
[18]. Angelousi A, Diamanti-Kandarakis E, Zapanti E, et al. Is there an association between thyroid function abnormalities and breast cancer? *Arch Endocrinol Metab* 2017; 61: 54-61. 2017/03/09. DOI: 10.1590/2359-3997000000191.
[19]. Fadavi P, Jafari F, Najafi M, et al. Relationship between Breast cancer and Thyroid disorders. *Oncol Radiother* 2020; 14: 14-17.
[20]. Jha CK, Mishra A, Yadav SB, et al. Thyroid dysfunctions and autoimmunity in breast cancer patients: a prospective case-control study. *Arch Endocrinol Metab* 2021; 64: 743-750. 2021/05/26. DOI: 10.20945/2359-3997000000284.
[21]. Kedari G and Hareesh G. Relationship between levels of thyroid hormones and thyroid antibodies in breast cancer. *ijcrr* 2012; 04: 63-68.
[22]. Valizadeh N, Delpak A and Eishi Oskuie A. Is there any association between thyroid autoimmunity and breast cancer? *Iran J Blood Cancer* 2015; 7: 175-178.
[23]. Pan XF, Ma YJ, Tang Y, et al. Breast cancer populations may have an increased prevalence of thyroglobulin antibody and thyroid peroxidase antibody: a systematic review and meta-analysis. *Breast Cancer* 2020; 27: 828-836. 2020/04/13. DOI: 10.1007/s12282-020-01078-z.
[24]. Brandt J, Borgquist S, Almquist M, et al. Thyroid function and survival following breast cancer. *Br J Surg* 2016; 103: 1649-1657. 2016/11/02. DOI: 10.1002/bjs.10284.
[25]. Ortega-Olvera C, Ulloa-Aguirre A, Ángeles-Llerenas A, et al. Thyroid hormones and breast cancer association according to menopausal status and body mass index. *Breast Cancer Res* 2018; 20: 94. 2018/08/11. DOI: 10.1186/s13058-018-1017-8.
[26]. Shi XZ, Jin X, Xu P, et al. Relationship between breast cancer and levels of serum thyroid hormones and antibodies: a meta-analysis. *Asian Pac J Cancer Prev* 2014; 15: 6643-6647. 2014/08/30. DOI: 10.7314/apjcp.2014.15.16.6643.
[27]. Akyurek S, Babalioglu I, Kenan K, et al. Thyroid dysfunction following supraclavicular irradiation in the management of carcinoma of the breast. *Int J of Hema Oncol* 2014; 24: 139-144. DOI: 10.4999/uhod.14234.
[28]. Alhosainy A, Mohamed A and Elattar AJLSJ. The impact of supraclavicular irradiation on thyroid function and size in postoperative breast cancer patients by comparing 2D versus 3D-CRT. *Life Sci J* 2015; 12: 57-62. DOI: 10.7537/marslsj1205s15.7.
[29]. de Groot S, Janssen LG, Charehbili A, et al. Thyroid function alters during neoadjuvant chemotherapy in breast cancer patients: results from the NEOZOTAC trial (BOOG 2010-01). *Breast Cancer Res Treat* 2015; 149: 461-466. Clinical Trial, Phase III; Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't. DOI: 10.1007/s10549-014-3256-4.
[30]. Jiskra J, Límanová Z, Barkmanová J, et al. Autoimmune thyroid diseases in women with breast cancer and colorectal cancer. *Physiol Res* 2004; 53: 693-702. 2004/12/14.
[31]. Muller I and Barrett-Lee PJ. The antigenic link between thyroid autoimmunity and breast cancer. *Semin Cancer Biol* 2020; 64: 122-134. 2019/05/28. DOI: 10.1016/j.semcancer.2019.05.013.
[32]. Mortezaee K, Ahmadi A, Haghi-Aminjan H, et al. Thyroid function following breast cancer chemotherapy: A systematic review. *J Cell Biochem* 2019; 120: 12101-12107. 2019/04/26. DOI: 10.1002/jcb.28771.
[33]. Hancock SL, Cox RS and McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. *N Engl J Med* 1991; 325: 599-605. 1991/08/29. DOI: 10.1056/nejm199108293250902.
[34]. Mentzel T, Schildhaus HU, Palmedo G, et al. Postradiation cutaneous angiosarcoma after treatment of breast carcinoma is characterized by MYC amplification in contrast to atypical vascular lesions after radiotherapy and control cases: clinicopathological, immunohistochemical and molecular analysis of 66 cases. *Mod Pathol* 2012; 25: 75-85. DOI: 10.1038/modpathol.2011.134.
[35]. Alkan S, Baylancicek S, Ciftçic M, et al. Thyroid dysfunction after combined therapy for laryngeal cancer: a prospective study. *Otolaryngol Head Neck Surg* 2008; 139: 787-791. 2008/12/02. DOI: 10.1016/j.otohns.2008.09.011.
[36]. Omer MAA, Alsayyari AA, Aldokhail AM, et al. Estimation of Thyroid Hormones Levels & Lung Function in Conventional Radiotherapy of Breast, Head and Neck Cancer's. *Open J Radiol* 2019; 9: 194-205.
[37]. Johansen S, Reinertsen KV, Knutstad K, et al. Dose distribution in the thyroid gland following radiation therapy of breast cancer--a retrospective study. *Radiat Oncol* 2011; 6: 68. 2011/06/10. DOI: 10.1186/1748-717x-6-68.
[38]. Kano T, Kojima T, Takahashi T, et al. Serum thyroid hormone levels in patients with fulminant hepatitis: usefulness of rT3 and the rT3/T3 ratio as prognostic indices. *Gastroenterol Jpn* 1987; 22: 344-353. 1987/06/01. DOI: 10.1007/bf02774261.
[39]. Majkowska-Młynarczyk A, Kinalski M and Zaczek-Kucharska E. The thyroid gland function assessment in women after mastectomy and chemotherapy during breast cancer therapy. *Endokrynologia Pol* 2007; 58: 397-402.

[40]. Muller I, Giani C, Zhang L, et al. Rosellini 363 V, Funel N, Campani D, Giustarini E, Lewis MD, Bakhsh AD, Roncella M, Ghilli M, Vitti P, 364 Dayan CM, Ludgate ME: Does thyroid peroxidase provide an antigenic link between thyroid 365 autoimmunity and breast cancer. *Int J Cancer* 2014; 134: 1706-1714.
[41]. Giustarini E, Pinchera A, Fierabracci P, et al. Thyroid autoimmunity in patients with malignant and benign breast diseases before surgery. *Eur J Endocrinol* 2006; 154: 645-649. 2006/04/29. DOI: 10.1530/eje.1.02108.
[42]. Strieder TG, Prummel MF, Tijssen JG, et al. Risk factors for and prevalence of thyroid disorders in a cross-sectional study among healthy female relatives of patients with autoimmune thyroid disease. *Clin Endocrinol* 2003; 59: 396-401. 2003/08/16. DOI: 10.1046/j.1365-2265.2003.01862.x.
[43]. Pacini F, Vorontsova T, Molinaro E, et al. Prevalence of thyroid autoantibodies in children and adolescents from Belarus exposed to the Chernobyl radioactive fallout. *Lancet* 1998; 352: 763-766. 1998/09/16. DOI: 10.1016/s0140-6736(97)11397-6.
[44]. Nagayama Y, Kaminoda K, Mizutori Y, et al. Exacerbation of autoimmune thyroiditis by a single low dose of whole-body irradiation in non-obese diabetic-H2h4 mice. *Int J Radiat Biol* 2008; 84: 761-769. 2008/09/30. DOI: 10.1080/09553000802345910.
[45]. Lin Z, Wu VW, Lin J, et al. A longitudinal study on the radiation-induced thyroid gland changes after external beam radiotherapy of nasopharyngeal carcinoma. *Thyroid : official journal of the American Thyroid Association* 2011; 21: 19-23. 2010/11/09. DOI: 10.1089/thy.2010.0229.
[46]. Reinertsen KV, Cvancarova M, Wist E, et al. Thyroid function in women after multimodal treatment for breast cancer stage II/III: comparison with controls from a population sample. *Int J Radiat Oncol Biol Phys* 2009; 75: 764-770. 2009/03/17. DOI: 10.1016/j.ijrobp.2008.11.037.
[47]. Cutuli B, Quentin P, Rodier JF, et al. Severe hypothyroidism after chemotherapy and locoregional irradiation for breast cancer. *Radiother Oncol* 2000; 57: 103-105. 2001/02/24. DOI: 10.1016/s0167-8140(00)00183-3.
[48]. Lin Z, Chen L, Fang Y, et al. Longitudinal study on the correlations of thyroid antibody and thyroid hormone levels after radiotherapy in patients with nasopharyngeal carcinoma with radiation-induced hypothyroidism. *Head Neck* 2014; 36: 171-175. 2013/04/06. DOI: 10.1002/hed.23285.
[49]. Brabant G, Prank K, Ranft U, et al. Physiological Regulation of Circadian and Pulsatile Thyrotropin Secretion in Normal Man and Woman. *J Clin Endocrinol Metab* 1990; 70: 403-409. DOI: 10.1210/jcem-70-2-403.
[50]. Bruning P, Bonfrèr J, De Jong-Bakker M, et al. Primary hypothyroidism in breast cancer patients with irradiated supraclavicular lymph nodes. *Br J Cancer* 1985; 51: 659-663. 1985/05/01. DOI: 10.1038/bjc.1985.99.
[51]. Khan MA, Bhurani D and Agarwal NB. Alteration of Thyroid Function in Indian HER 2-Negative Breast Cancer Patients Undergoing Chemotherapy. *Asian Pac J Cancer Prev* 2015; 16: 7701-7705. 2015/12/03. DOI: 10.7314/apjcp.2015.16.17.7701.
[52]. Santin AP and Furlanetto TW. Role of estrogen in thyroid function and growth regulation. *J Thyroid Res* 2011; 2011: 875125. 2011/06/21. DOI: 10.4061/2011/875125.
[53]. Xu S, Chen G, Peng W, et al. Oestrogen action on thyroid progenitor cells: relevant for the pathogenesis of thyroid nodules? *J Endocrinol* 2013; 218: 125-133. 2013/05/07. DOI: 10.1530/joe-13-0029.
[54]. Mazer NA. Interaction of estrogen therapy and thyroid hormone replacement in postmenopausal women. *Thyroid* 2004; 14: S27-34. 2004/05/15. DOI: 10.1089/105072504323024561.
[55]. Laway BA, Shafi KM, Majid S, et al. Incidence of primary hypothyroidism in patients exposed to therapeutic external beam radiation, where radiation portals include a part or whole of the thyroid gland. *Indian J Endocrinol Metab* 2012; 16: S329-331. 2013/04/09. DOI: 10.4103/2230-8210.104078.
[56]. Kanyilmaz G, Aktan M, Koc M, et al. Radiation-induced hypothyroidism in patients with breast cancer: a retrospective analysis of 243 cases. *Med Dosim* 2017; 42: 190-196. 2017/05/16. DOI: 10.1016/j.meddos.2017.03.003.
[57]. Huang J, Jin L, Ji G, et al. Implication from thyroid function decreasing during chemotherapy in breast cancer patients: chemosensitization role of triiodothyronine. *BMC Cancer* 2013; 13: 334. 2013/07/09. DOI: 10.1186/1471-2407-13-334.
[58]. Falstie-Jensen AM, Esen B, Kjærsgaard A, et al. Incidence of hypothyroidism after treatment for breast cancer-a Danish matched cohort study. *Breast Cancer Res* 2020; 22: 106. 2020/10/15. DOI: 10.1186/s13058-020-01337-z.
[59]. Barbesino G and Chiovato L. The genetics of Hashimoto's disease. *Endocrinol Metab Clin North Am* 2000; 29: 357-374. 2000/06/30. DOI: 10.1016/s0889-8529(05)70136-5.
[60]. Tunio MA, Al Asiri M, Bayoumi Y, et al. Is thyroid gland an organ at risk in breast cancer patients treated with locoregional radiotherapy? Results of a pilot study. *J Cancer Res Ther* 2015; 11: 684-689. 2016/02/18. DOI: 10.4103/0973-1482.167613.
[61]. Ansari L, Nasiri N, Aminolroayaei F, et al. The Measurement of Thyroid Absorbed dose by Gafchromic™ EBT2 Film and Changes in Thyroid Hormone Levels Following Radiotherapy in Patients with Breast Cancer. *J Med Signals Sens* 2020; 10: 42-47. 2020/03/14. DOI: 10.4103/jmss.JMSS_10_19.
[62]. Monnier A. Late effects of ionizing radiations on the thyroid gland. *Cancer Radiother* 1997; 1: 717-731. 1997/01/01. DOI: 10.1016/s1278-3218(97)82948-4.