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THE POSSIBLE ASSOCIATION BETWEEN BREAST CANCER AND THYROID FUNCTION AND THE CONSEQUENCES OF TREATMENT ON THYROID FUNCTION AFTER CHEMORADIOTHERAPY

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ABSTRACT

Breast cancer (BC) is the most prevalent type of cancer in women worldwide. Chemotherapy and radiation can synergistically affect thyroid tissue and cause an inflammatory change in endothelial cells. The combination of chemotherapy and concurrent radiation therapy increases the thyroid susceptibility to the effects of the treatment, which increases the risk of thyroid damage and hypothyroidism (HT). This treatment method kills not only malignant breast cells but also harms healthy cells and inevitably irradiates the organs and tissues far from the treatment site. This means that radiation-induced thyroid toxicities after breast supraclavicular (SCV) radiotherapy with/without chemotherapy may impact thyroid dysfunction, such as HT, and the quality of life in cancer survivors. This review summarizes the available data on the possible association of BC with thyroid function and autoimmunity thyroid and the main focus on the consequences of SCV breast radiation on thyroid function with or without chemotherapy. Although the thyroid and breast are hormone-sensitive organs linked to endocrine dysfunction and glandular illness, understanding the mechanisms underlying the link between thyroid function and BC is still elusive. Additionally, the literature results revealed that thyroid function and TSH levels might alter in BC patients with decreased FT3 and FT4 levels after chemoradiotherapy. This review suggests an increasing probability of HT among breast cancer survivors, particularly in those who received radiation therapy to the SCV region together with/without chemotherapy. We recommend employing a more precise technique to lower thyroid dose in order to decrease the probability of HT. After breast cancer chemoradiotherapy, routine thyroid function monitoring with periodic TSH tests. A future prospective study should include high sample size and long-term follow-up.

KEYWORDS: breast cancer; thyroid function; radiotherapy; chemotherapy; supraclavicular; autoimmune thyroid disease.

INTRODUCTION

Breast Cancer (BC) is the most prevalent malignancy in women, accounting for 11.7% of all cancer occurrences globally, with an estimated 2.3 million new cases in 2020. It ranked as the fifth most common reason for cancer deaths worldwide, with an estimated 685,000 (6.9%) deaths of all cases.[1] BC is considered the first malignancy neoplasm in Yemeni women, with an estimated 2,894 (31.1%) new cases in 2020, and it is the first main cause of cancer mortality, with an estimated 1,638 (13.5 %) death of all cancers.[2] The incidence rates of BC in women vary globally, 88% higher in underdeveloped countries than in industrialized countries (55.9 vs. 29.7/100,000, respectively). However, compared to women in industrialized countries, the mortality rates for BC women in underdeveloped countries are 17% higher (15.0 vs. 12.8/100,000, respectively).[1] In Yemen, the incidence rate was raised over the last years, from 18.5 No distance between 2018 and the reference[3] 30.5% in 2020,[2] and the death rate increased from 12.1% in 2018[3] to 18.9% in 2020.[2]

Thyroid hormones play important biological roles in the growth, differentiation, metabolism, and physiological functions of almost all human tissues, including mammary glands.[4,5] The high levels of thyroid hormones have estrogen-like effects that increase BC cell proliferation.[6] and stimulate angiogenesis.[7] Physiologically, free thyroxin (FT4) is a growth factor that controls cancer progression, anti-apoptosis, and endothelial cell migration, while triiodothyronine (T3) promotes BC cell division.[8,9]

The association between thyroid hormone levels and BC was investigated in many studies, but the results were controversial.[10-15] Some studies had approved this association,[11,12,15] whereas others did not.[10,13,14,16-18] Similarly, the association between BC and autoimmune thyroid disease was estimated in several studies. However, contradictory results were reported.[13,14,18-21] Many studies have shown that BC patients have a higher percentage of positive Anti-thyroid peroxidase antibody (anti-TPO Ab) than healthy controls.[13,14,19,22] However, no differences were found in other studies.[18,20,21] The thyroid is extremely sensitive to radiation, and the impacts of various BC therapies (e.g., radiotherapy and chemotherapy) on thyroid function and autoimmune disease have long been investigated in several studies. However, conflicting results were reported. Numerous studies have reported that BC patients receiving supraclavicular (SCV) radiation therapy have a higher risk of developing hypothyroidism (HT),[23-28] and this risk increases with increasing radiation dose.[24,26,29] However, no effect was reported in other studies.[25, 30] The thyroid gland, a crucial endocrine organ, is close to the SCV nodal region, frequently included in the radiation field for locally progressed 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 breast cancer patients, especially younger individuals, has been linked to radiotherapy in the SCV region.[31,32]

Furthermore, many studies have reported an increased incidence of HT,[33,34] and a decrease in thyroid hormones in patients receiving chemotherapy for BC.[35] Finally, within the conflicting results reported for the association between thyroid hormones/autoimmune thyroiditis and BC, we hypothesized that thyroid dysregulation, such as HT, would be diagnosed more often in BC patients after mastectomy and SCV radiation. 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 breast cancer become more and more significant.

This review summarizes the available data on the possible association of BC with thyroid function and autoimmunity. And the main focus is on the side effect of BC therapy on thyroid function after chemo-radiotherapy, especially SCV area radiation.

Thyroid

Definition

The thyroid gland is a two-lobed organ of the endocrine system in the neck region. Thyroid hormones are produced by thyroid follicular cells. Thyroid follicular cells are the most numerous cell population in the gland and comprise the thyroid follicles, spherical structures that store and control the release of thyroid hormones.[36]

Thyroid gland and hormones

The thyroid is a sizeable endocrine gland located in the neck that is made up of closely spaced follicles that are outwardly bounded by thyroid epithelial cells called thyrocytes and inside packed with proteinaceous colloids.[37] Many follicular cells in the thyroid gland store the thyroid hormones L-thyroxine (T4) and triiodothyronine (T3) in the thyroglobulin molecule until the body requires them. The main metabolic hormones, or thyroid hormones, affect almost every cell in the human body. Iodine and tyrosine are necessary for the synthesis and secretion of thyroid hormones, as is the development of the hypothalamic-pituitary-thyroid system.[38]

Actions of thyroid hormones

The thyroid hormone system starts in the hypothalamus, where the periventricular nucleus synthesizes and releases thyrotropin-releasing hormone (TRH). TRH promotes the production and release of thyroid-stimulating hormone (TSH) by binding to the anterior pituitary thyrotropin receptors. TRH binds to its receptor on the thyrotrophin of the anterior pituitary gland to stimulate the synthesis and secretion of thyrotropin or TSH. Then TSH binds to the TSH receptor on individual thyroid follicular cells, producing and releasing thyroid hormones into the blood.[39] In addition, the rough endoplasmic reticulum of thyroid follicular cells also makes the dimeric protein thyroglobulin, which is then discharged by exocytosis into the follicular colloid. Concurrently, the sodium iodide symporter pumping action moves iodide to thyroid follicular cells. Pendrin, at the apical membrane, is necessary to cross the cytoplasmic barrier and enter thyroid follicular cells. Thyroid peroxidase is an enzyme in the follicular colloid that catalyzes the iodination of thyroglobulin tyrosine residues. Thyroglobulin then re-enters thyroid follicular cells via endocytosis and is proteolyzed by various proteases, releasing T4 and T3. Specific membrane transporter proteins, such as monocarboxylate transporter 8 and 10,[40,41] facilitate the efflux of T4 and T3 from thyroid follicular cells to diverse target cells.[42] Previous studies have shown that circulating blood T4 and T3 are regulated by negative feedback loops mediated by the hypothalamus and pituitary thyroid.[43] (Figure 1).

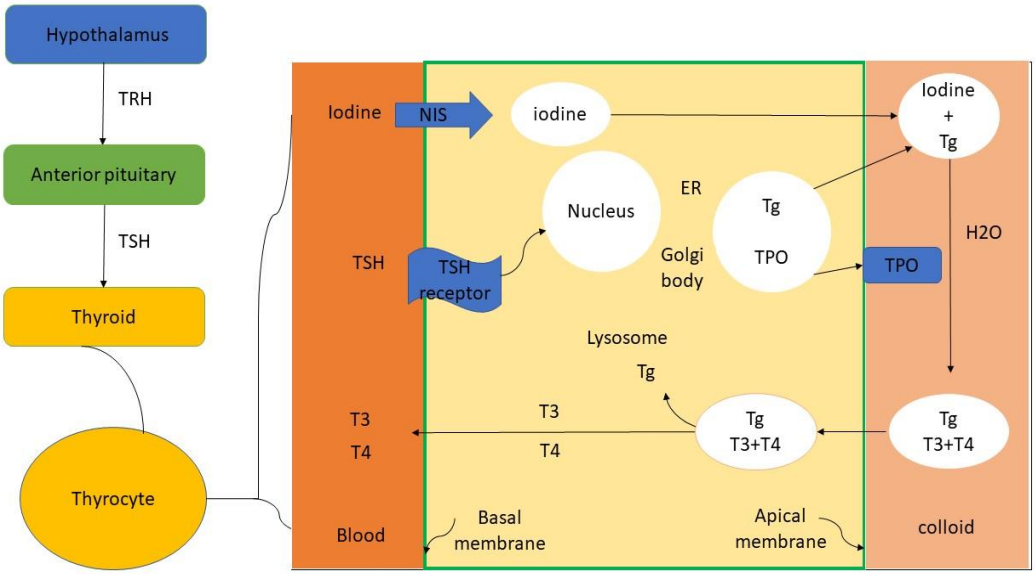

Figure 1: Thyroid function and structure. thyrotropin-releasing hormone (TRH); thyroid-stimulating hormone (TSH); thyroglobulin (Tg); hydrogen peroxide (H2O); thyroid peroxidase (TPO); endoplasmic reticulum (ER); thyroxine (T4) and triiodothyronine (T3)

Thyroid disorders

Despite the fact that the causes are still not fully understood, women are far more likely than males to get thyroid disease. Elevated levels of free thyroid hormones in the blood are the hallmark of hyperthyroidism. 0.2% of males and 2% of women are affected by it, respectively. The most common causes are Graves disease, which primarily affects younger women, and other thyroid disorders in older women. a deficiency in thyroid hormones is the hallmark of HT. It is a typical endocrine condition that can result after surgery, radioiodine therapy, iodine deficiency, or autoimmune thyroiditis (Hashimoto thyroiditis).[44]

Autoimmune thyroid diseases

Autoimmune thyroid diseases (AITDs) are caused by an immune attack on the thyroid gland due to a malfunctioning immune system. AITDs are T cell-mediated organ-specific autoimmune diseases[45,46] and are characterized by reactivity to self-thyroid antigens, which manifest as different inflammatory or anti-receptor autoimmune illnesses.[47,48] They are produced by interactions between genetic and environmental predisposing factors, leading to autoimmune dysfunction.[49,50] TPO Ab and thyroglobulin Ab are the most common AITD serum markers, and TPO Abs is found in 90% of AITD patients.[94]

Thyroid function and BC

Thyroid dysfunction and BC are common in women, so it is important to find a link between thyroid function and BC prognosis.[11] Some studies indicate that BC is more prevalent in women with thyroid disease,[12,18,51,52] many others have failed to show such a relationship[20,53,54] or even have established a reverse relationship,[55] and this discrepancy exists among various types of thyroid disorders including HT,[56,57] hyperthyroidism,[18,58,59] and AITDs.[60-62] In addition, Søgaard et al. and Glushakov et al. found that women with hyperthyroidism have an increased risk of BC, while those with HT had lower rates of BC.[52,63] Significant cohort research by Journey et al. reported that women with hyperthyroidism after 60 years of age were found to have an increased risk of BC mortality.[64]

Thyroid hormones and BC

The thyroid hormones control various bodily processes, including metabolism, sexual development, and neurodevelopment.[65] The thyroid and the breast are hormone-sensitive organs correlated to endocrine dysfunction and glandular disease.[66] Estrogens are considered important in the development of BC.[67] However, the correlation between thyroid function and BC is uncertain. Several studies reported that thyroid hormones could affect normal breast cell differentiation[68] and/or BC cell proliferation.[6,21] In addition, the BC process has been demonstrated to be regulated by both T4 and T3. T4 appears to interact only with hormone receptors on the cell surface, whereas T3 can activate phosphatidylinositol 3-kinase through a cytoplasmic or integrin αvβ3-dependent pathway.[4] Furthermore, thyroid hormones in BC stimulate human BC cell proliferation by phosphorylating estrogen at Ser-118 by activating the extracellular signal-regulated kinase1/2 mitogen-activated protein pathway.[69,70] T4 and T3 stimulate cell proliferation in the human breast cell line Michigan Cancer Foundation-7 and T47D in a dose-dependent manner.[6,71,72] Moreover, thyroid hormones at high levels have estrogen-like effects on breast tumor cells in vitro, suggesting that they may stimulate BC development via binding to the estrogen receptor.[6,73]

Association between BC and thyroid function

Thyroid function in BC patients was evaluated based on serum levels of hormones such as free triiodothyronine (FT3), FT4, and TSH. The link between thyroid hormone levels and BC has been the subject of numerous investigations. In the case of women with BC and benign tumor tissues and the control group, Szychta et al. reported no differences in the thyroid hormone profile.[18] Certain research findings also suggested that the amount of FT4 and/ or TSH is related to the incidence of BC.[12,56,59] Low levels of TPO Ab and high levels of FT4 were linked to an increased risk of BC, according to Brandt et al.[74] Also found by several cross-sectional research is the fact that T3 levels are positively correlated with the risk of developing BC.[68,75,76] A case-control study showed an association between higher serum total T4 and BC in both premenopausal and postmenopausal women, whereas a negative association was demonstrated between total T3 and BC.[77] Similarly, according to Huang et al., patients with newly diagnosed BC had higher FT4 and lowered T3 levels than those with benign breast tumors.[55] Recently, a cohort study reported that BC patients had a significantly higher value of FT4 level and a lower ratio of FT3/FT4 than that in benign breast disease. However, the value of the TSH level showed no difference between the two groups.[78] Likewise, Angelousi et al. reported that patients with BC had a higher FT4 level than that in benign breast disease and control groups. However, the FT3 and TSH values were not different between the two groups.[21] However, Rose et al. research show a higher TSH level in BC with advanced cancer.[79] Another study found no connection between TSH level and tumor stage.[80] As an illustration, Hellevik et al. research. They have found no association between TSH and BC.[59] Also, the same results were obtained by other researchers.[12,58,81]

Thyroid autoimmunity and BC

Many similarities between the thyroid and neoplastic breast tissues, which could stimulate a shared immune system responsible for such a link, suggest the relationship between thyroid autoimmunity and BC.[54] A rising number of results indicating an increased prevalence of AITDs, specifically TPO Ab, among BC patients suggests that AITDs may act as a risk factor for BC.[61,82] Anti-thyroid autoantibodies, particularly ant - TPO Ab, are more common in patients with BC than in healthy controls.[16,56,83-86] whereas this has not been confirmed in finding studies.[87,88] Additionally, compared to healthy controls, BC patients were assessed to have a prevalence of TPO Ab of 15-36% versus 8-19%.[56,83,89] Furthermore, several studies reported the possible correlation between BC and autoimmune thyroiditis.[14,15,90,91] However, different meta-analyses have reached different conclusions on the relationship between autoimmune thyroid disease and BC.[61,92] The 2002 study found no evidence of this association,[92] whereas a meta-analysis conducted in 2012 found evidence of the association.[61]

Thyroid and mammary glands share antigenic similarities

TPO Ab cross-reactivity with lactoperoxidase

The 712-residue single-chain monomeric human lactoperoxidase (LPO) protein is abundantly expressed in breast tissue.[93] Compared to BC, normal mammary glands have very little or no expression of the LPO protein.[94-96] Because TPO and LPO are both active enzymes, they have the potential to induce oxidative stress in breast tissue and play a role in the etiology of BC.[96] TPO Ab comes in several variations, some reacting with LPO and others not. TPO Ab is more common in BC patients, which may be due to cross-reactivity with LPO.[16,56,60,83-85,91]

TPO expression in BC

TPO is one of the most prevalent thyroid autoantigens, and it's also expressed in breast tissue; thus, it's a crucial link between thyroid autoimmunity and cancer.[97] Muller et al. and Godlewska et al. showed that TPO was expressed in both breast and thyroid tissues, and the antigenicity of the immunodominant regions in breast TPO was similar to that of thyroid TPO.[98,99] Other cells, besides thyrocytes, also express the TPO gene in the orbital tissue, such as fibroblasts and fat cells.[100] Expressing TPO genes in BC cells could be another reason for the rise of TPO Ab in BC patients.[16,56,60,85,91] Adipocytes, active cells present in BC and expressing TPO, may assist in the growth of tumors.[101] Similar immunological and biochemical properties of TPO expressed by thyroid and breast tissues were observed.[96,99,102] Some studies suggested a better prognosis for BC patients if they have TPO Ab.[98,103]

The relationship between anti-TPO Ab and BC

The association between thyroid diseases, especially thyroid autoimmunity, and BC has been widely studied. Several studies reported that the anti-TPO Ab level was significantly higher in BC patients,[14,16,85,91,104] and a meta-analyze study from China.[66] However, many studies reported no difference in anti-TPO levels between BC and control.[22,105] In addition, numerous independent small-scale investigations have found that patients with serum anti-TPO Ab had a better prognosis for BC than those without these antibodies, particularly in terms of long-term (often 5-year) disease-free and/or overall survival.[62,85,106] Furthermore, Dülger et al. and Bata et al. found that BC patients had greater anti-TPO Ab levels than controls, whereas thyroid hormone levels were similar in the two groups.[17,107] Moreover, Brandt et al. showed that low prediagnostic TPO Ab levels had been linked to an increased risk of BC.[74] However, Tosovic et al. showed that high TPO Ab levels were inversely related to BC risk.[12]

Thyroid function and treatments of BC

Chemo-radiotherapy, hormone therapy, and surgery are some of the therapeutic options for BC patients.[108] The selection of these modalities is influenced by many variables, including the patients age, menopausal state,

estrogen or progesterone receptors, lymph node status, and unfavorable side effects of the chosen modality.[109,110] The results of differences in BC therapies on thyroid function and autoimmune disease have been discussed for years, with conflicting findings. In some situations, the ipsilateral thyroid lobe might be irradiated along with the internal mammary, supra-, and infraclavicular node in BC patients, resulting in HT.[111-113] One of the most clinically beneficial procedures for treating BC is surgery. However, after surgery, residual tumor disease deposits may be local or distant.[114,115] Therefore, radiotherapy is important in the local deposit of BC. Although radiation therapy greatly reduces the appearance of local deposit.[116,117] it has adverse effects on other organs, especially sensitive ones, including the thyroid.[118,119] Radiation therapy has been widely used to treat post-mastectomy patients with BC, especially those with locally advanced BC, ipsilateral chest wall, axillary, SCV, or intramammary lymph nodes.[120] Numerous studies have shown radiotherapy-induced thyroid diseases such as HT, Graves disease, and thyroid cancer.[25,119,121-123] However, Dorri et al. and Ansari et al. demonstrated no association between thyroid hormone levels before and after radiotherapy in BC patients.[124, 125] On the one hand, HT is a common late complication after curative radiotherapy to the lower neck in patients with head and neck cancer and Hodgkin lymphomas.[121,126-128] In these patients, the radiotherapy portal usually spans the entire thyroid, and the incidence of HT after radiotherapy treatment ranges from 30% to 50%.[119,121,129-131] On the other hand, although the treatment field with locoregional radiotherapy in patients with BC included only part of the thyroid gland,[23-25,132] the overall prevalence of HT in BC patients who received SCV radiotherapy with or without chemotherapy varied from 6% to 21%.[24,26,27,29,133,134] Chemotherapy, One of the most efficient cancer treatments available now. However, thyroid dysfunction can result from chemotherapy medication treatment in BC patients,[135] Chemotherapy has two treatment options: adjuvant and neoadjuvant. For many early-stage BC patients who are at a higher risk, adjuvant chemotherapy is the cornerstone of treatment.[136,137] Neoadjuvant chemotherapy is also known as preoperative or primary chemotherapy and is generally indicated for BC patients in two situations: locally advanced disease or downstaging of inflammatory BC; because it qualifies for surgery (typically a lumpectomy) or shrinking the size of the breast lesions to preserve the breast.[138] The only observed effect of chemotherapeutic medicines on thyroid function in all cancer patients taking those medications was a late effect, primarily manifested as HT.[139,140] However, cancer patients taking chemotherapeutic medicines had no alterations in thyroid function.[55] Chemotherapeutics are highly effective in treating various cancers, but their clinical use is restricted because of a wide range of unfavorable side effects on normal cells.[141,142] Furthermore, BC patients are more likely to develop HT, not just those who have had radiation therapy but also those who have had systemic treatment.[24,26,29,30,34,133,143,144] However, thyroid dysfunction was subclinical HT followed by clinical HT,[26,27,90] and thyroid function changes were manifested within 3 to 6 months after radiotherapy.[27,111,145] Bruning et al. and Reinertsen et al. reported that HT was significantly more common in BC patients after SCV radiation.[24, 146] Recent studies suggest that treating BC-induced thyroid dysfunction, such as HT.[147, 148] Falstie-Jensen et al. reported that BC survivors had a higher risk of HT than controls, especially those who received nodal radiation with chemotherapy.[147] Jha et al. found that BC patients after receiving chemo-radiation therapy, had a considerably greater prevalence of clinical HT than healthy controls.[148] A systematic review by Mortezaee et al. concluded that thyroid function and TSH levels may alter in BC patients after various chemotherapy regimens, with decreased FT3 and FT4 levels in patients after chemotherapy.[135]

A recent retrospective study by John Roberson et al. showed that after 6 months of regional nodal irradiation for breast cancer, the thyroid volume might vary due to radiation-induced thyroid atrophy in BC patients who had SCV-directed radiation. Clinical HT was found to be (18.0%), and subclinical HT was found to be (9.8%).[149] The results of Huang et al. showed that 37 out of 192 BC patients (19.3%) with SCV-directed radiation developed HT after a median follow-up of 25 months (range: 2–83 months).[150] A cohort study conducted on the Korean population by Park et al. showed that BC patients who received radiotherapy after having their breasts removed in Korea tended to have a higher risk of developing HT (HR = 1.248; 95% CI, 0.977-1.595) than those who received no radiotherapy for their breast cancer.[151] Another study by Choi et al.[152] reported that the risk of HT is highest for BC patients receiving chemotherapy and radiation therapy to the lymph nodes.

TSH /thyroid hormones and treatments of BC

The link between thyroid hormones and autoimmunity in BC is still being debated. Bruning et al. reported that TSH level was considerably higher in patients with BC who had received radiotherapy to the SCV field than in non-irradiated BC patients.[146] Akurek et al. showed that the mean TSH level in BC patients who received SCV radiotherapy was significantly higher after six months of radiotherapy completion than in BC patients before treatment[27] and after two years by Wolny- Rokicka et al. research.[29] Additionally, Kim et al.[153] and Joensuu et al.[113] reported a significantly higher serum TSH level in BC patients who received radiotherapy than those who did not. However, several studies showed no difference in TSH levels between BC patients before treatment and control.[17,18,21,60,74] On the other hand, many studies reported that the serum of FT3 and/or FT4 levels was significantly higher in BC patients before any treatment than in healthy control.[20,21,68,74,154] A meta-analyze study by Shi et al. reported that the serum FT3 and FT4 levels were considerably higher in BC patients than in the control group.[66] However, several studies reported no

differences in FT3 and/or FT4 levels between BC patients before or after chemo-radiotherapy and healthy control.[13-15,17,18,85,90,107] Similarly, Wolny- Rokicka et al. reported no difference in thyroid hormones levels in BC patients who had received radiotherapy to chest wall/breast with SCV and the axillary areas.[29] Furthermore, there are several studies reported that the mean FT4 and/ or FT3 levels in BC patients were significantly lower in BC patients after treatment with radiotherapy or chemotherapy compared with BC patients before treatment.[27,55,155] However, many studies have found no difference in thyroid hormone levels in BC patients after radiotherapy compared with BC patients before treatment.[124,125,133] Moreover, there are several previous studies reported the percentage of positive Anti-TPO Abs level was a significantly higher in BC patients before treatment.[13,14,19,22,84,91] or after chemo-radiotherapy treatment compared to healthy control.[24,85] However, no difference between anti-TPO Ab BC patients before and after treatment.[148]

Finally, we conducted a cross-section study about thyroid function and autoimmunity in Yemeni BC women through (FT3, FT4, TSH, and Anti-TPO Ab levels) before and after chemoradiotherapy. It included 217 women (59 were pretreatment, 88 were post-treatments (chemotherapy, radiotherapy, and surgery had been performed, and 70 were healthy controls). Our results revealed the overall prevalence of HT in BC patients was 19.9% (15.6% subclinical HT, 6.8% clinical HT), significantly higher in the post-treatment patients than in the pretreatment BC patients (26.1 % vs.10.2%). The mean of TSH and positive anti-TPO Ab were significantly higher in BC patients and post-treatment than in healthy control and pretreatment BC patients. FT3 level was significantly lower in the post-treatment BC patients than pretreatment BC patients. However, no difference in FT4 between the groups (under review).

CONCLUSION

Breast cancer is the most prevalent type of cancer in women worldwide and one of the reasons so many people die from cancer in numerous countries. Although the thyroid and breast are hormone-sensitive organs linked to endocrine dysfunction and glandular illness, the link between thyroid function and BC remains unclear. In addition, anti-thyroid autoantibodies, notably anti-TPO Ab, are more common in patients with BC, suggesting the relationship between BC and thyroid autoimmunity due to the similarities between the thyroid and neoplastic breast tissues, which may activate a shared immune system accountable for such an association. In our opinion, it can be politely concluded that BC has a significant association with thyroid function and autoimmunity. However, understanding the mechanisms underlying the connection is still difficult despite abundant research and the results of meta-analyses.

Chemoradiotherapy and surgery are some of the therapeutic options for BC patients. The thyroid axis denotes a possible, unknown target for the therapy of BC. BC patients who received a comprehensive treatment plan during their illness, including chemotherapy and radiation therapy, had a higher chance of surviving, but at the cost of increased thyroid toxicity. Chemotherapy and radiation can synergistically affect thyroid tissue and cause an inflammatory change in endothelial cells, often leading to thyroid dysfunction, such as HT. The literature results revealed that thyroid function and TSH levels may alter in BC patients with decreased FT3 and FT4 levels after chemoradiotherapy. This review suggests an increasing probability of HT among breast cancer survivors, particularly in those who received radiation therapy to the SCV region together with/without chemotherapy. As a result of the common incidence of HT after treatment and the possible consequences of leaving this untreated, we recommend routine thyroid function monitoring with periodic TSH tests after chemoradiotherapy to breast cancer, particularly in the SCV region. The dose to the ipsilateral node regions of breast cancer should be kept to a minimum during intensity-modulated radiation to lower the incidence of HT. A future prospective study should include high sample size and long-term follow-up.

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