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ORIGINAL ARTICLE

Is there an association between thyroid dysfunction and breast cancer?

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ABSTRACT

Objective: The association between thyroid disease and breast cancer risk remains unclear. A cross-sectional study was carried out to find the association between hypothyroidism, hyperthyroidism, and breast cancer.

Materials and Methods: The study included 71 diagnosed cases of breast cancer patients belonging to stage III of the disease. The mean age of controls and patients was 43-45 years. Their level of thyroid hormones was estimated. On the bases of high and low levels of thyroid hormone, women were divided into group one (hypothyroidism n= 56) and group two (hyperthyroidism n=15). Levels of neutrophils, lymphocytes, and hematocrit were estimated by the SWISS MAX analyzer. The level of thyroid hormones, TSH, 8OHG, Isoprostane, and 4-HNE was estimated by the technique of ELISA. The level of MDA was estimated spectrophotometrically.

Results: It was observed that body weight was high in hypothyroid females (group 1) Levels of neutrophils, lymphocytes, and monocytes were significantly higher in group 1 of the breast cancer afflicted women, as compared to the controls and group 2. The level of thyroid hormones FT3, FT4, and TSH was also higher in group 1. The level of MDA, isoprostane, and 4-HNE was significantly high in both women with hypo and hyperthyroidism as compared to controls.

Conclusions: We found an increased risk of breast cancer in women with hyporhyroidism and a slightly decreased risk in women with hyperthyroidism indicating an association between thyroid function level and breast cancer risk.

Key Words: breast cancer, hypo, and hyperthyroidism, MDA, HNE, and Isoprostane

INTRODUCTION

The risk of breast cancer(BC) development is 13.0% in women and it is, therefore, the most common cancer in women. Exogenous and endogenous sex hormones have a significant role in BC etiology. *In vitro*, estrogen-like effects are observed in high values of thyroid hormones that help in promoting the proliferation of BC cells and motivating angiogenesis[1,2]. Experimentally it is observed that high values of thyroid hormone bind with estrogen receptors and may encourage the development of BC [3,4].

Epidemiological proof related to thyroid disorders and BC risk is unclear. Some studies found that increased risks are related to hyperthyroidism,hypothyroidism[5,6], and thyroid autoimmune diseases[7], while others have found no association between them[8]. Hypothyroidism may decrease the BC risk in European people and no correlation was reported between hypothyroidism and breast cancer risk in non-European people. Women are 5-10 times are more at risk of developing hypo or hyperthyroidism as compared to men[9].

Asian women, younger than 55.0 years with a history of overactive thyroid had a 16.0 % higher risk of getting BC compared with women with no history of thyroid dysfunction[10]. However, it is found that 19% risk of development of BC in women with a history of the overactive thyroid gland and it is independent of age[5]. A meta-analysis study carried out 25000 women found that the risk of BC is not related to any type of thyroid dysfunction i.e. hypothyroidism or hyperthyroidism[11].

Besides the increased values of neutrophils, lymphocytes and hematocrit may be important markers of severity of disease and progress with inflammation and cancer[12]. Activation of neutrophils promotes the role of different types of cells that take part in acute or chronic inflammation and are related to cancer[13].

The redox imbalance can cause cancer and other chronic ailments by affecting the ROS in metabolic pathways including the thyroid metabolic pathways. Though some oxidants may have a role in abnormal growth and mutation, a high level of oxidative stress can sluggish cell proliferation and cancerous cells damage. Free radicals can harm lipid, DNA, and proteins[14]. Among the bases of DNA, guanine is easily oxidized, due to its low redox potential. Its oxidized form (8-oxy-deoxyguanosine) may be a marker of DNA damage in cells that experience oxidative stress and carcinogenesis. As 8-oxo-deoxyguanosine has mutagenic ability[15,16]. Increased values of isoprostane and 8-OH-deoxyguanosine shows inhibitory effects on enzyme related to inflammation and oxidative stress[17,18]. Malondialdehyde (MDA) is a creation of lipid peroxidation by reactive oxygen species and it is used to assess oxidative damage and oxidative stress. Reduction of MDA may increase the chances of hyperthyroidism[14].

HNE reacts with lipids, nucleic acids, vitamins, and signaling molecules. Excess of HNE impair the function of cell and signaling and thereby provoke many pathological issues like neurodegenerative complaints and cancers [19,20].

The link between thyroid dysfunction and BC has been studied previously and found controversial results. However, the relation between the overactive thyroid gland and the risk of breast cancer will shed light on the strong pathogenic links between thyroid dysfunction and breast cancer and may help in the clinical management of patients.

A cross-sectional study was carried out to find the association between hypothyroidism, hyperthyroidism, and risk of BC.

MATERIALS AND METHODS

Study population: The study included 71 BC females belonging to stage III. Their level of thyroid hormones was estimated. On the bases of high and low levels of thyroid hormone, women were divided into group one (hypothyroidism n= 56) and group two (hyperthyroidism n=15). Participants were recruited from clinical centers in the city of Lahore between October 2019-2020.50 age-matched women with no history of any disease were taken as controls. The study included middle-aged women who had no history of any cancer except BC. The study excluded women whose data was missing for specific exposures, women lost to follow-up or women with un-staged invasive BC, and women who used thyroid medication. Levels of neutrophils, lymphocytes, and hematocrit were estimated by the SWISS MAX analyzer. The level of thyroid hormones, TSH, 8OHG, Isoprostane, and 4-HNE were estimated ELISA. The level of MDA was estimated spectrophotometrically using the chemical method.

Statistical analysis: To compare the baseline characteristics between the groups of patients and controls subjects, we used student 't' test. P values <0.05 was considered statistically significant.

Table 1: Demographic and heamatological profile in breast cancer patients with suspected thyroid dysfunction

Variables	Control (n=50)	Hypothoiroid Subjects (n=56) (one)	Hyperthoiroid Subjects (n=15) (two)	P (≤0.05)
WEIGHT (Kg)	65.029±9.65	74.29±15.529	71.59±9.68	0.125
AGE (YRS)	43.23±7.148	45.29±4.29	43.99±6.58	0.145
SBP (mmHg)	120.25±4.589	99.35±7.59	133.44±8.59	0.0253
DBP (mmHg)	81.59±5.29	64.29±4.58	89.65±8.99	0.000
NEUTROPHILS	57.59±8.59	64.29±16..35	78.59±14.58	0.014
LYMPHOCYTES (% ages)	36.35±4.89	41.59±17.59	56.54±10.58	0.025
MONOCYTES (% ages	4.59±1.05	7.58±1.88	12.58±3.99	0.002
HEMATOCRIT (%ages)	43.29±7.58	31.59±6.58	37.259±5.29	0.001

Table 2: Predictive variables of diagnostic importance in breast cancer patients experiencing thyroid dysfunction

Variables	Control (n=50)	Hypothoiroid Subjects (n=56)	Hyperthoiroid Subjects (n=15)	P (≤0.05)
TSH (IU/L)	2.29±0.25	3.289±0.014	1.018±1.04	0.015
FT3 (pmol/L)	7.59±2.15	3.298±0.956	10.251±2.265	0.000
FT4 (pmol/L)	24.25±5.59	17.59±5.25	31.59±3.99	0.014
MDA (nmol/ml)	0.932±0.089	6.35±1.58	9.68±2.25	0.014
8HG (pmol/L)	0.591±0.018	1.59±0.089	2.185±0.85	0.018
IsoP (pmol/L) (isoprostane)	1.598±0.014	3.29±1.058	6.358±2.48	0.016
HNE (pmol/L (4-Hydroxynonenal)	0.048±0.0048	.8956±.0945	1.058±0.047	0.024

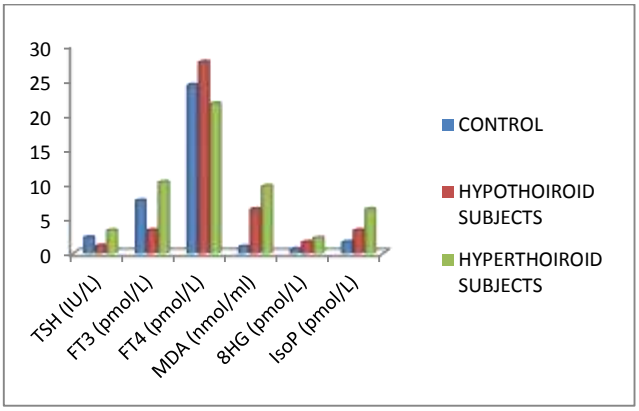

Figure 1:Predictive variables of diagnostic importance in bc patients experiencing thyroid dysfunction

RESULTS

Table 1 showed the demographic and hematological parameters in breast cancer women with suspected thyroid dysfunction. It is observed that body weight was high in-group women with hypothyroidism (group 1) than women with hyperthyroidism (group 2). The mean age of controls and patients was 43-45 years. The blood pressure of group one was low as compared to group 2 women and controls. Levels of neutrophils, lymphocytes, and monocytes were significantly higher in both the groups 1 and 2 BC women as compared to the controls. The values of neutrophils, lymphocytes, and monocytes were non-significantly high in group 1 as compared to control. However, the values of hematocrit were significantly low in both hype and hyperthyroidism as compared to controls.

Table 2 and Figure 1 showed that the level of thyroid hormones FT3, FT4, and TSH was high in group 2 but a significant difference was only observed with the values of FT3. The level of MDA, isoprostane, and 4-HNE was significantly high in both women with hypo and hyperthyroidism as compared to controls.

DISCUSSION

Results of our study showed that almost 78% of our study participants had hypothyroidism as compared to hyperthyroidism.A cohort study that followed females for 30-years showed an increased risk of developing BC in females with hyperthyroidism. However, in the same period, a lower risk of developing the disease was found in women with hypothyroidism[9].

We agreed with a study that found a high BMI of BC women with hypothyroidism as compared to a group of women with hyperthyroidism[8]. A study carried out in Mexico, reported that about 14.50% of middle-aged women with thyroid dysfunction were found to suffer from other illnesses, especially BC. The study stated that thyroid dysfunction may be changed with BMI because of the role of thyroid hormones in the regulation of many metabolic pathways[21]. However, a study found no confounding effect by comorbidities was observed, except hypertension observed only in scarce cases[8].

Levels of neutrophils, lymphocytes, and monocytes were significantly high in group 2 breast cancer women as compared to the controls. The values of neutrophils, lymphocytes, and monocytes were also high in group 1 as compared to control. However, the values of hematocrit were significantly low in both hype and hyperthyroidism as compared to controls. Several studies found that hematological indices are predictors for the prognosis of tumors[22,23]. Low values of hematocrit were also observed by a study. It is reported that Pre-treatment low HCT is independently related to poor prognosis in BC patients and may be a predictor of mortality in breast cancer women[24].

According to our study, the level of thyroid hormones FT3, FT4 and TSH were high in BC women with hypethyroidism as compared to controls but a significant difference was only observed with the values of FT3. The level of MDA, isoprostane, and 4-HNE was significantly high in both subgroups of women with hypo and hyperthyroidism as compared to controls.

Several studies were carried out to find the link between thyroid dysfunction and the development of BC. We agreed with cohort studies that found a good association between risk of breast cancervand thyroid dysfunction[25,26].

However, a meta-analysis of twelve studies found no association between the risk of BC and hypothyroidism. Levels of thyroid hormones and thyroid autoantibodies were estimated in 97 Greek females with primary BC . The study found no associations between history of thyroid disease and BC. In a subgroup examination, it is observed that BC women with hypothyroidism had a significantly lower frequency of lymph node metastases compared with breast cancer women without any thyroid problem. The study confirmed the proliferative effect of thyroid hormones on cells of the breast[27].

A cohort study was carried out in 35463 women with BC. The study observed that 1272 women afflicted with BC developed hyperthyroidism and 860 developed hypothyroidism on follow-up. A study including 5810 BC afflicted females found that hypothyroidism is not related to the recurrence or relapse of BC[6]. However, in 2021 a review based on 21 types of the research reported that hyperthyroidism, hypothyroidism, thyroid cancer, and thyroid-related antibodies were significantly related to increased risk of BC[28].

Another study was carried out in UK on 239,437 females. Among these women, 3,227 or 1.3% and 20,762 or almost 8.7% women had hyper and hypothyroidism respectively. During a follow-up of 7.10 years, about 5,326 or 2.2% of women developed BC. The study found no link between hypothyroidism and risk of BC but the study found a reduced risk > 10 years after the diagnosis of hypothyroidism. The study concluded that the risk of BC was decreased long after diagnosis of hypothyroidism, but the risk was increased among women who treated their thyroid dysfunction[8].

Several biological processes may show the associations of thyroid diseases with the risk of BC. A proliferative effect of hormone T3 is reported in the cells of the breast[29]. It is proposed that T_3 binds to nuclear receptors and persuades transcription of mark genes to take part in energy homeostasis and proliferation of cells. An important role of the nuclear receptor in the development of breast cancer is suggested[30,31]. It is reported that T3 along with the estrogen-stimulated proliferation of the breast cancer cell line[32].

The association between thyroid hormone and cancers has been investigated in many *in vivo* and *in vitro* studies[5,10,33]. Alterations of thyroid hormone receptors are observed in many types of cancers, plus BC and a link are observed expression thyroid hormone receptor and regulation of oncogene[34]. Mammary and thyroid glands share some similarities. T3 can affect the mammary gland via the activation of thyroid receptor mammary glands and may persuade differentiation and lobular growth of breast tissues, estrogen also shows this effect[35].

It is suggested that hypothyroidism results in high sensitization of mammary glandular epithelium to hormones estrogen and prolactin secondary to very low thyroid hormone[9]. However, a study proposed a genetic tendency for both hypothyroidism and breast cancer[36].

The increased values of MDA showed the increasing oxidative condition in mild stage toward advanced stages[14]. Redox imbalance causes increased production of the reactive oxygen species and reactive nitrogen species resulting in oxidative stress. This redox imbalance can be related to oncogenic motivation. It is proposed that 8-hydroxy-2-deoxyguanosine, 4-hydroxy-2-nonenal (4-HNE), malondialdehyde (MDA), and isoprostane, by-products of oxidative damage, have the mutagenic ability. Increased levels of these oxidative stress messengers have been reported in plasma and tissues of the lung, colon, gastric, and BCs. DNA damage plays an important role in the initiation of cancer and the production of 8-OH-G, a strong biomarker for carcinogenesis[37,38,39].

CONCLUSION

Hyporthyroidism in addition to stress markers / DNA damage markers was more related to BC as compared to hyperthyroidism. However further studies are needed on a large number of women to find the exact relationship of thyroid dysfunction with BC. There is a need that women with thyroid dysfunction should have close contact with their clinician and follow screening BC regularly.

Limitations: We are unable to find the duration and severity of hyper- or hypothyroidism or medication compliance, factors that help in the development of BC. The sample size is small.

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