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ORIGINAL ARTICLE

Insinuation of Extrapolative Factors of Diagnostic Importance in Breast Cancer Patients Experiencing Thyroid Dysfunction

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ABSTRACT

Background: Breast cancer (BC) is the most common malignancy in women and now regarded as the commonest cancer overall. Over 2 million new cases were diagnosed in 2018, accounting for almost 25% of cancer cases among women. The main objective of the study is to find the insinuation of extrapolative factors of diagnostic importance in breast cancer patients experiencing thyroid dysfunction.

Materials and methods: This correlational study was conducted on Jinnah Hospital patients with the permission of ethical committee of the hospital and consent of the patients. The data was collected from 88 cases and 50 controls. All the patients who had a definite diagnosis of BC along with, hyperthyroidism, hypothyroidism, autoimmune thyroid disease (AITD), or thyroid cancer were included in this study. The study population was divided into three comparative groups: (1) controls (n = 50), (2) BC cases with hypothyroidism (n = 27), and (3) BC cases with hyperthyroidism (n = 61).

Results: The mean age was 47.325±4.59 years for controls, 51.59±8.59 years for the hypothyroid cases, and 50.59±5.58 years for the hyperthyroid cases. The mean systolic blood pressure (SBP) for controls, hypothyroid and hyperthyroid was 121.25±6.58 mmHg, 98.259±8.59 mmHg and 129.65±7.59 mmHg respectively. The P-values less than 0.05 were considered to be significant (table 01). The demographic and hematological data of control, hypothyroid and hyperthyroid groups was tabulated. A positive correlation of breast cancer in women with hyperthyroidism and a slightly negative correlation in women with hypothyroidism was found.

Conclusion: There appears to be an association between the thyroid function level and breast cancer risk. It can be extrapolated that anxiety associated with hyperthyroidism may play a role in stress induced BC. Therefore, thyroid function should be monitored in patients at risk of BC.

Keyword: Breast cancer, Thyroid, Dysfunction, Hypothyroidism, Hyperthyroidism, Anxiety.

INTRODUCTION

Breast cancer (BC) is the most common malignancy in women and the now the most common cancer overall overtaking the lung cancer according to World Health Organization's 2021 statistics [1, 2]. Over 2 million new cases were diagnosed in 2018, accounting for almost 25% of cancer cases among women. Although hereditary and genetic factors account for 5–10% of BC cases [3], nonhereditary factors are more commonly involved in geographical and ethnic differences in incidence [4]. The relationship of BC with thyroid disease (TD) has been widely investigated. However, data are still controversial and, although almost every form of TD, including autoimmunity disorders and thyroid cancer, has been identified in association with BC, no convincing evidence exists of a causal role for TD in BC [5].

Hypothyroidism is the most common hormone deficiency. The severity of hypothyroidism varies significantly, and it has a variety of end organ effects. Because of both the nonspecific symptoms of hypothyroidism and the similar symptoms and morbidities associated with malignancies and their treatment, hypothyroidism can often go undiagnosed and untreated in patients with cancer [6]. Failure to adequately manage both overt and subclinical hypothyroidism can have serious consequences, hence the recognition of its presence is crucial for the successful treatment of cancer patients. Hypothyroidism is commonly noted in older women because of the prevalence of autoimmune thyroiditis [7]. Younger women and men are now being diagnosed secondary to other important causes, including previous thyroid, brain, and spinal cord surgery and irradiation and medications. Hypothyroidism is easily treated with thyroxine (T4) replacement. Unfortunately, suboptimal dosing is common [8].

Breast cancer (BC) is the most common type of cancer in females, occurring in 20% of the female population world-wide, and is the main cause of tumor-related death in women. Studies have shown that BC is closely related to the endocrine system [9]. The thyroid is an important part of the endocrine system and secretes thyroid hormone (TH), which plays a vital role in the growth, development, and metabolism of cells and tissues. As pituitary hormones target both breast and thyroid tissues, there may be a correlation between BC and thyroid disorders [10].

Hardefeldt et al. found that there was significant evidence of an increased risk of BC in patients with presence of anti-thyroid antibodies, while they also found that there was no significant evidence of an increased risk of BC in patients with hypothyroidism and hyperthyroidism [11]. But more high-quality prospective studies are needed to prove causal relationship between benign thyroid disease and BC. However, the relationship between BC and thyroid diseases, such as hyperthyroidism, hypothyroidism, autoimmune thyroid disease (AITD) and thyroid cancer, is still not well understood [12].

Angelousi and colleagues demonstrated that TH promoted the proliferation of breast cancer cells in vitro, while hypothyroid function resulted in a lower incidence of lymph node metastases. Recent studies have suggested that TH may play a positive role in the cause and development of BC at a cellular level. However, Hercbergs et al. found no evidence that TH causes BC in the clinical setting. Despite numerous studies having investigated the association between thyroid dysfunction and BC, the exact relationship and molecular mechanisms involved remain unclear. Further studies examining the prognostic role of TH in BC are thus warranted [13-14].

According to epidemiological statistics, the cumulative incidence of developing a second malignancy in a patient with thyroid cancer is 16% at 25 years. Previous studies have shown that there is a unidirectional or bidirectional association between thyroid cancer, breast cancer and renal cell carcinoma [15]. A unidirectional association is defined as a primary cancer that increases the relative risk of subsequent cancers, while a bidirectional association indicates that there is a two-way relationship or mutual relationship between two cancers, and has nothing to do with the subsequent occurrence. Thyroid cancer survivors have a high incidence of breast cancer, and breast cancer survivors have a high incidence of thyroid cancer [16].

The main objective of the study is to find the insinuation of extrapolative factors of diagnostic importance in breast cancer patients experiencing thyroid dysfunction.

MATERIALS AND METHODS

This study was conducted in Jinnah Hospital Lahore during the period of January, 2022-June, 2022 and Institute of Molecular Biology and Biotechnology (IMBB), the University of Lahore with the permission of ethical committees of both the institutes. The data was collected from eighty eight (88) cases and Fifty (50) healthy controls. All the patients who had a definite diagnosis of breast cancer along with, hyperthyroidism and hypothyroidism were included in this study. The study population was divided into three comparative groups: (1) controls (n = 50), (2) BC cases with hypothyroidism (n = 27), and (3) BC cases with hyperthyroidism (n = 61).

All the disease related data including age, weight, blood pressure, neutrophils, lymphocytes and hematocrit was recorded in the study population. Blood sample was drawn for serum based analysis of cases and controls. All the predictive variables of diagnostic importance in breast cancer patients developing thyroid dysfunction were calculated. One-way ANOVA was performed among the variables using SPSS version 24. Results of the performed variables were expressed as (Mean±SD) where p value ($p \geq 0.05$) remained significant.

RESULTS

The mean age was 47.325±4.59 years for controls, 51.59±8.59 years for the hypothyroid cases, and 50.59±5.58 years for the hyperthyroid cases. The mean systolic blood pressure (SBP) for controls, hypothyroid and hyperthyroid was 121.25±6.58 mmHg, 98.259±8.59 mmHg and 129.65±7.59 mmHg respectively. The P-values less than 0.05 were considered to be significant (table 01). Demographic and hematological data of control, hypothyroid and hyperthyroid groups was tabulated. A positive correlation of breast cancer in women with hyperthyroidism and a slightly negative correlation in women with hypothyroidism was found.

Table 1: Demographic And Heamatological Profile In Breast Cancer Patients Developing Thyroid Dysfunction

Variables	Control (n=50)	Hypothyroidism subjects (n=27)	Hyperthyroidism subjects (n=61)	P (≤0.05)
Weight (kg)	61.58±7.59	70.259±10.59	60.58±6.258	0.214
Age (yrs)	47.325±4.59	51.59±8.59	50.59±5.58	0.152
Sbp (mmhg)	121.25±6.58	98.259±8.59	129.65±7.59	0.005
Dbp (mmhg)	83.29±6.58	64.99±6.59	74.59±7.59	0.019
Neutrophils	47.59±8.59	71.59±10.59	78.59±14.58	0.011
Lymphocytes	31.25±5.29	51.59±7.59	51.55±7.59	0.025
Monocytes	5.59±1.58	6.35±2.59	10.25±1.59	0.000
Hematocrit	47.59±4.58	41.59±4.58	40.59±6.259	.0001

Table 2: Predictive Variables Of Diagnogtioc Importance In Breast Cancer Patients Developing Thyroid Dysfuntion

Variables	Control (n=50)	Hypothyroidism subjects (n=27)	Hyperthyroidism subjects (n=61)	P (≤0.05)
TSH (IU/L)	1.25±0.085	3.28±1.07	2.01458±0.158	0.015
FT3 (pmol/L)	6.358±3.259	4.258±1.65	9.68±1.35	0.014
FT4 (pmol/L)	25.29±6.35	19.68±4.58	28.59±6.35	0.032
MDA (nmol/ml)	0.759±0.077	4.59±1.08	7.359±1.59	0.001
8HG (pmol/L)	0.921±0.033	1.55±0.077	3.259±0.78	0.000
IsoP (pmol/L)	1.651±0.035	2.598±0.158	3.259±1.08	0.024
HNE (pmol/L)	0.033±0.0084	.652±.0456	1.055±0.033	0.018

Table 2 (A): Pearsons' Correlation Coefficients Matrix In Breast Cancer Patients Developing Hyperthyroidism Dysfuntion

Variables	Variables of hyperthoiroid dysfuntion in breast cancer						
	TSH	FT3	FT4	MDA	8HG	IsoP	HNE
TSH	1.00	0.756	.658	.425	-.785	-.652	.453
FT3		1.00	-.658	-.654	-.425	-.625	-.754
FT4			1.00	-.529	-.456	-.625	-.548
MDA				1.00	-.658	-.658	-.548
8HG					1.00	.589	-.658
IsoP						1.00	.511
HNE							1.00

The clinico-pathological features of the BC patients and its correlation with and without thyroid dysfunction and autoimmunity are summarized in table 03.

Table 3: Pearson S' Correlation Coefficients Matrix In Breast Cancer Patients Developing Hypothoiroid Dysfuntion

Variables	Variables of hypothyroidism dysfuntion in breast cancer						
	TSH	FT3	FT4	MDA	8HG	IsoP	HNE
TSH	1.00	-.148	-.568	-.359	.567	.148	.659
FT3		1.00	.596	.259	.458	.658	.658
FT4			1.00	-.458	.568	.658	.458
MDA				1.00	.625	.258	.659
8HG					1.00	.568	.562
IsoP						1.00	.759
HNE							1.00

Table 02 shows predictive variables of diagnostic importance in all breast cancer patients in which thyroid dysfunction is developed. Overall, hyperthyroidism was associated with an increased risk of breast cancer while hypothyroidism was associated with a slightly decreased risk of breast cancer. Breast cancer risk in women with hyperthyroidism was unaffected by censoring at IsoP (3.259±1.08 pmol/L) and HNE (1.055±0.033 pmol/L).

DISCUSSION

The current study shows that in comparison to Euthyroid-status, the prevalence of overall hypothyroidism (subclinical and clinical)

and hyperthyroidism in BC patients, although the prevalence of clinical hyperthyroidism remained significantly high. Both hyperthyroidism and BC are highly prevalent among females; also, the occurrence of both diseases increases with age, making it difficult to establish a real correlation between them [17]. Additionally, the BC prevalence might have been overestimated due to a higher rate of medical consults and visits in the group of thyroid patients than in the general population [18].

The higher incidence of hyperthyroidism compared with hypothyroidism is in agreement with previous studies, as is the increased incidence of thyroid disease over time. One contributing factor to the higher incidence in hyperthyroidism is the fact that before 1995 only inpatient diagnosis were recorded in the Danish National Patient Registry (DNPR), and hyperthyroidism is more likely than hypothyroidism to be diagnosed and treated in an inpatient setting as also shown in our study [19]. However, a sensitivity analysis restricted to patients diagnosed from 1995 onward and stratified by inpatient vs outpatient diagnoses, yielded similar findings. A limitation of our study was the lack of laboratory data [20]. We were therefore unable to distinguish between clinical and subclinical thyroid disease, as we were also unable to link the hormone levels at time of diagnosis to breast cancer risk. Of note, the exposure window in hyperthyroidism is short, as the hyperthyroid state is rapidly diagnosed, and ensuing treatment normalizes thyroid levels within a few weeks [21]. Finally, the observed association between hyperthyroidism and breast cancer risk may have been underestimated due to incompletely ascertained (and therefore not adjusted for) lifestyle risk factors for breast cancer, such as obesity and alcohol consumption, both of which are associated with a reduced risk of hyperthyroidism but an increased risk of breast cancer [22]. We stratified our analyses by hospital diagnoses of obesity and alcohol-related illness, however, these diagnoses are likely to capture only the most severe cases. Smoking has been associated with an increased risk of Graves' disease, but has no consistent association with breast cancer risk, and exclusion of patients with Graves' disease did not change our estimates. Finally, we did not address the role of hormonal treatment in the observed association [23-24]. The role of treatment should be explored in further studies.

CONCLUSION

It is concluded that an increased risk of breast cancer in women with hyperthyroidism and a slightly decreased risk in women with hypothyroidism suggesting an association between the thyroid function and breast cancer. Women diagnosed with hyperthyroidism may have an increased risk of breast cancer and should undergo screening of the major predictors for breast cancer, like Thyroid Stimulating Hormone (TSH), Free Tri-iodothyronine (FT3), Free Tetra-iodothyronine (FT4), Malondialdehyde (MDA) and (4-hydroxynonenal (HNE).

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