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Clinicopathological correlation of thyroid dysfunction with breast cancer prognostic panel

[1]Dr. Riya Shah, Junior Resident (Third Year), Department of Pathology, MGM Medical College & Hospital, Chhatrapati Sambhajinagar

[2]Dr. Reeta Kataruka, Professor, Department of Pathology, MGM Medical College & Hospital,Chhatrapati Sambhajinagar;

[3]Dr. Chandrashekhar P. Bhale, HOD and Professor, Department of Pathology, MGM Medical College & Hospital, Chhatrapati Sambhajinagar

Corresponding Author: Dr. Riya Shah, Junior Resident (Third Year), Department of Pathology, MGM Medical College & Hospital, Chhatrapati Sambhajinagar.

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Abstract

Introduction: According to recent data from World Health Organization (WHO) number of breast cancer (BC) patients has been increased to about 2.26 million, indicating breast cancer is progressing to become one of the commonest cancers around the world. Hypothyroidism has been identified as late effect of radiation therapy (RT) given to the lower neck and head cancer patients. Studies suggest a higher risk of hypothyroidism amongst breast cancer patients, even if they have taken radiotherapy or systemic therapies. Role of identifying comorbid conditions like hypothyroidism is essential to decrease morbidity in breast cancer. High thyroid hormone levels are also found to have oestrogen-like effects in several studies. Hence present study was undertaken in breast cancer patients to assess incidence of thyroid dysfunction & its association to prognostic panel of breast cancer i.e., ER, PR, Her2Neu and Ki-67

Materials and Methods: 60 female cases of breast cancer of all age groups diagnosed on histopathology with available thyroid profile (obtained retrospectively from medical data) were enrolled. After obtaining detailed clinical history breast cancer (BC) was staged according to AJCC staging and all breast cancer (BC) patients thyroid profile consisting Thyroid-stimulating hormone (TSH), free thyroxine (fT4), antithyroid peroxidase antibody (TPOAb) were retrieved from data.IHC profile results consisting of ER/PR, Her2/neuand Ki-67were noted. Data obtained were assessed for possible associations

Observations and Results: ≤40 year's cases were 4 (7 %) & all of which were euthyroid. 40 to 45 years cases

were 6 (10 %) & all of which were euthyroid. >45 years cases were 50 (83 %) amongst which 44 (73 %) were euthyroid, 4 (7 %) were hypothyroid & 2 (3 %) were hyperthyroid**.** Thyroid dysfunction was found in only postmenopausal cases i.e., 4 (7 %) cases with hypothyroidism & 2 (3 %) cases with hyperthyroidism**.** No Significant association found between Sub-types of breast cancer& incidence of thyroid dysfunction **(P=0.993).** Oestrogen receptor (ER) was found negative20 (31 %) cases. Amongst them 16 (27 %) were euthyroid, 2 (4 %) were hypothyroid & 0 (0 %) were hyperthyroid. Insignificant association found between type of thyroid dysfunction& incidence of oestrogen receptor (ER) negativity **(P=0.44).** progesterone receptor (PR)was found negative in26 (44 %) cases. Amongst them 24 (40 %) were euthyroid, 2 (4 %) were hypothyroid & 0 (0 %) were hyperthyroid. Insignificant association found between type of thyroid dysfunction& incidence of progesterone receptor (PR) negativity **(P=0.442).** HER2NEUwas found negative in28 (47 %) cases. Amongst them 24 (40 %) were euthyroid, 4 (7 %) were hypothyroid &0 (0 %) were hyperthyroid. Significant association found between type of thyroid dysfunction & HER2NEU negativity **(P=0.04).** Ki-67 index>20 % was found in 46 (79 %) cases. Amongst which 43 (72 %) were euthyroid, 4 (7 %) were hypothyroid &0 (0 %) were hyperthyroid. Significant association found between type of thyroid dysfunction &Ki-67 index **(P=0.015).**

Conclusion: To conclude, prevalence of hypothyroidism found was 7 % & hyperthyroidism as 3 % in breast cancer (BC) patients. HER2NEU & Ki-67 index showed statistically significant correlation with thyroid dysfunction. Breast cancer (BC) patients should be considered a risk group who should receive routine screening for thyroid dysfunction

Keywords: Thyroid Dysfunction**,** Euthyroid, Hypothyroid, Hyperthyroid, Breast Cancer

Introduction

According to recent data from World Health Organization (WHO) number of breast cancer (BC) patients has been increased to about 2.26 million, indicating breast cancer is progressing to become one of the commonest cancers around the world[1,2]. Identifying risk factors such as age, gender, estrogens level, family history, gene mutation, and unhealthy living habits for timely prevention of breast cancer (BC) is important[3].Thyroid and breast tissue have some common molecular markers. There is active involvement of breast tissues in iodine metabolism as indicated by high concentrations of sodium-iodide symporter, peroxidise, and deiodinase in breast tissues[4,5]. Thyroid hormone levels and their association with the development of breast cancers have been studied in the previous studies. High thyroid hormone levels are found to have oestrogen-like effects in several studies. Hypothyroidism has been identified as late effect of radiation therapy (RT) given to the lower neck and head cancer patients[6,7]. Studies suggests a higher risk of hypothyroidism amongst breast cancer patients, even if they have taken radiotherapy or systemic therapies[8,9,10,11]. Higher prevalence of hypothyroidism in patients with breast cancer as found in previous studies could be a result of hypothyroidism induced breast epithelial cells' sensitivity to prolactin and oestrogen[12,13,14,15]. Some studies on contrary have found that either hypothyroidism or hyperthyroidism has no association with breast cancer[16]. Over the recent years, breast cancer survival has been improved drastically due to their

earlier detection and improvedtherapies[17]. Almost about 90% of patients with early-stage breast cancer cases nowadays receive neo adjuvant therapy and 10-year life expectancy after diagnosis is about 75%[18]. Hence role of identifying comorbid conditions like hypothyroidism is essential to decrease morbidity in breast cancer. With this objective present study was undertaken in breast cancer patients to assess incidence of thyroid dysfunction& its association to prognostic panel of breast cancer i.e., ER, PR, Her2Neu and Ki-67

Aim

To assess the association of thyroid dysfunction with breast cancer and its prognosis

Objectives

1. To determine incidence of hyperthyroidism, hypothyroidism and euthyroidism in breast cancer patients.
2. To determine association of thyroid dysfunction with known prognostic panel of breast cancer i.e., ER, PR, Her2Neu and Ki-67.
3. To determine association of thyroid dysfunction and breast cancer with different age group
4. To determine association of thyroid dysfunction with histologic sub-types of breast cancers

Material and Methods

Present study is a cross sectional retrospective study conducted from duration January 2023 to June 2023. Institutional ethics committee permission was taken prior to commencement of present study. 60 women cases fulfilling inclusion and exclusion criteria were enrolled.

Inclusion Criteria

Any form of histopathologically proven cases of breast cancer in females irrespective of their age received in MGM Medical College and Hospital, Chhatrapati Sambhaji Nagar, Pathology department were included.

Exclusion Criteria

NIL

Procedure

Breast cancer (BC) was diagnosed and staged according to AJCC staging and managed according to standard guidelines and departmental protocols[19].All histopathologically proven breast cancer (BC)patients underwent assessment of their thyroid function. Thyroid-stimulating hormone (TSH), T3, and T4 were measured in the blood samples and cases categorized into euthyroid, hypothyroid & hyperthyroid. Personal clinical history of the patients was also recorded. IHC profile results of these patients consisting of ER/PR, Her2/neu and Ki67 were retrieved from the IHC registers.

ER/PR assay

ER/PR results were processed in the Department of Pathology, MGM Medical College, Chhatrapati Sambhajinagar. The ER assay clone used was SP1, the PR assay clone was SP2 and the detection system was a polymer. IHC staining for detection and localization of ER/PR done within sections from formalin-fixed, paraffin-embedded tissues.

Her2/neu assay

The clone used was a SP3 and the detection system used was a polymer. Performed in Department of Pathology, MGM Medical College, Chhatrapati Sambhajinagar.

Operational definition

1. **Hypothyroidism[20]:** Elevated TSH levels beyond the reference range (0.4-4.8μIU/mL) with subnormal T4 levels (4.4-12.5 ug/dl).
2. **Hyperthyroidism[20]:** Patients with TSH levels < 0.01 μIU/mL and with T3, T4 above the reference range were considered to have hyperthyroidism

3. ER/PR scoring system[21]

Proportion Score	Positive Cells, %	Intensity	Intensity Score
0	0	None	0
1	<1	Weak	1
2	1 to 10	Intermediate	2
3	11 to 33	Strong	3
4	34 to 66	-	-
5	≥67	-	-

4. Her2 scoring system[21]

Result	Criteria
Negative (Score 0)	No staining observed or Membrane stating that is incomplete and is faint/barely perceptible and within ≤10% of tumor cells
Negative (Score 1+)	Incomplete membrane staining that is faint/barely perceptible and within >10% of tumor cells*
Equivocal (Score 2+)	Weak to moderate complete membrane staining in >10% of tumor cells or Complete membrane staining that is intense but within ≤10% of tumor cells*
Positive (Score 3+)	Complete membrane staining that is intense and >10% of tumor cells

5. Ki-67 index[22]

a. 'low proliferative activity' as Ki-67 values <20%

b. 'high proliferation activity' as Ki-67 values >20%.

Statistical analysis

Statistical analysis was performed using medcalc software. Data were expressed as frequency with percentages N (%). $\chi 2$-test was used to study association between two variables and Statistical significance was assumed if P value less than 0.05.

Observation and Result

Table 1: Distribution of age

Sn.	Age group (Years)	Euthyroid N (%)	Hypothyroid N (%)	Hyperthyroid N (%)	Total N (%)	Chi square	P value
1	≤40	4 (7 %)	0 (0 %)	0 (0 %)	4 (7 %)	1.33	0.855 (NS)
2	40 to 45	6 (10 %)	0 (0 %)	0 (0 %)	6 (10 %)		
3	>45	44 (73 %)	4 (7 %)	2 (3 %)	50 (83 %)		
Total N (%)		54 (90 %)	4 (7 %)	2 (3 %)	60 (100 %)	-	-

As shown in **Table 1** ≤40 years cases were 4 (7 %) & all of which were euthyroid. 40 to 45 years cases were 6 (10 %) & all of which were euthyroid. >45 years cases were 50 (83 %) amongst which 44 (73 %) were euthyroid, 4 (7 %) were hypothyroid & 2 (3 %) were hyperthyroid**.** Thyroid dysfunction was found in only postmenopausal cases i.e., 4 (7 %) cases with hypothyroidism & 2 (3 %) cases with hyperthyroidism

Table 2: Distribution of Sub-types of breast cancer

Sn.	Sub-types of breast cancer	Euthyroid N (%)	Hypothyroid N (%)	Hyperthyroid N (%)	Total N (%)	Chi square	P value
1	No special type (NST/ NOS)	52 (86 %)	4 (7 %)	2 (3 %)	58 (96 %)	0.22	0.993 (NS)
2	Mucinous	1 (2 %)	0 (0 %)	0 (0 %)	1 (2 %)		
3	Medullary	1 (2 %)	0 (0 %)	0 (0 %)	1 (2 %)		
Total N (%)		54 (90 %)	4 (7 %)	2 (3 %)	60 (100 %)	-	-

As shown in **Table 2,** 1 (2 %) case had mucinous type of breast cancer who was Euthyroid. Similarly, 1 (2 %) case had medullary type of breast cancer who was also Euthyroid. No Significant association found between Sub-types of breast cancer& incidence of thyroid dysfunction **(P=0.993) (Graph 1)**

Graph 1: Distribution of Sub-types of breast cancer

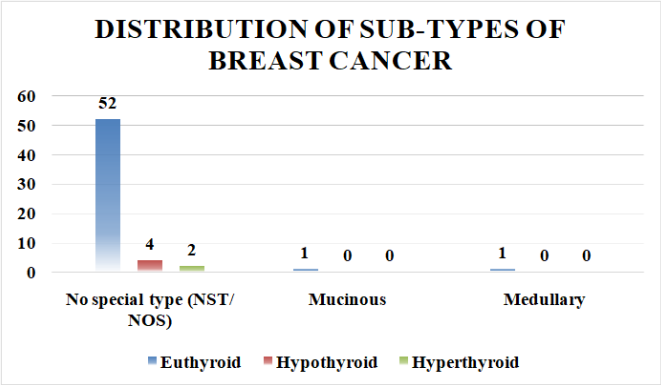

Table 3: Distribution of IHC markers of breast cancer

Sn.	IHC Markers Of Breast Cancer	Euthyroid N (%)	Hypothyroid N (%)	Hyperthyroid N (%)	Total N (%)	Chi square	P value
1	ER a. Positive b. Negative	 38 (63 %) 16 (27 %)	 2 (3 %) 2 (4 %)	 2 (3 %) 0 (0 %)	 42 (69 %) 20 (31 %)	1.62	0.44 (NS)
2	PR a. Positive b. Negative	 30 (50 %) 24 (40 %)	 2 (3 %) 2 (4 %)	 2 (3 %) 0 (0 %)	 34 (56 %) 26 (44 %)	1.629	0.442 (NS)
3	HER2NEU a. Positive b. Negative	 30 (50 %) 24 (40 %)	 0 (0 %) 4 (7 %)	 2 (3 %) 0 (0 %)	 32 (53 %) 28 (47 %)	6.42	0.04 (S)
Total N (%)		54 (90 %)	4 (7 %)	2 (3 %)	60 (100 %)	-	-

As shown in **Table 3,** oestrogen receptor (ER) was found negative20 (31 %) cases. Amongst them 16 (27 %) were euthyroid, 2 (4 %) were hypothyroid &0 (0 %) were hyperthyroid. Insignificant association found between type of thyroid dysfunction& incidence of oestrogen receptor (ER) negativity **(P=0.44).** progesterone receptor (PR)was found negativein26 (44 %) cases. Amongst them 24 (40 %) were euthyroid, 2 (4 %) were hypothyroid &0 (0 %) were hyperthyroid. Insignificant association found between type of thyroid dysfunction& incidence of progesterone receptor (PR) negativity **(P=0.442).** HER2NEUwas found negative in28 (47 %) cases. Amongst them 24 (40 %) were euthyroid, 4 (7 %) were hypothyroid &0 (0 %) were hyperthyroid. Significant association found between type of thyroid dysfunction & HER2NEU negativity **(P=0.04).**Amongst thyroid dysfunction casesall hypothyroid cases i.e., 4 (7 %) showed HER2NEU negative result which suggested bad prognosis **(Graph 2)**

Graph 2: Distribution ofIHC markers of breast cancer

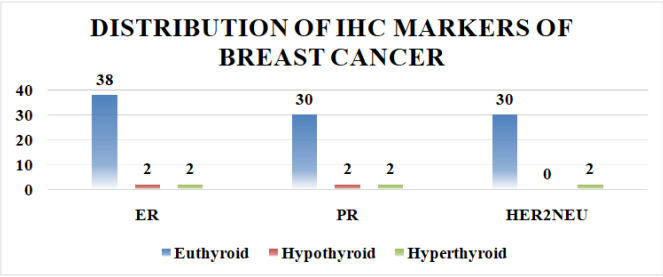

Table 4: Distribution of Ki-67 index

Sn.	Ki-67 index	Euthyroid N (%)	Hypothyroid N (%)	Hyperthyroid N (%)	Total N (%)	Chi square	P value
1	≤20 %	11(18 %)	0 (0 %)	2 (3 %)	13 (21 %)		
2	>20 %	43 (72 %)	4 (7 %)	0 (0 %)	46 (79 %)	8.39	0.015 (S)
Total N (%)		54 (90 %)	4 (7 %)	2 (3 %)	60 (100 %)	-	-

As shown in **Table 4,** Ki-67 index>20 % was found in 46 (79 %) cases. Amongst which 43 (72 %) were euthyroid, 4 (7 %) were hypothyroid &0 (0 %) were hyperthyroid. Significant association found between type of thyroid dysfunction &Ki-67 index **(P=0.015).** Amongst thyroid dysfunction cases all hypothyroid cases i.e., 4 (7 %) showed Ki-67 index>20 % which suggested bad prognosis

Discussion

Thyroid cancer (TC) and breast cancer (BC), which rank first and seventh, respectively, are two of the most often diagnosed cancers in women[23]. Many researchers have acknowledged and assessed the connection between the two cancers since the late 19th century[24,25]. The first investigation in this area to employ epidemiological techniques was released in 1984[26]. In present Study60 female cases of breast cancer of all age groups diagnosed on histopathology with available thyroid profile (obtained retrospectively from medical data) were enrolled. IHC profile results consisting of ER/PR and Her2/neu were noted. Data obtained were assessed for possible associations. In present study ≤40 years cases were 4 (7 %) & all of which were euthyroid. 40 to 45 years cases were 6 (10 %) & all of which were euthyroid. >45 years cases were 50 (83 %) amongst which 44 (73 %) were euthyroid, 4 (7 %) were hypothyroid & 2 (3 %) were hyperthyroid**.** Thyroid dysfunction was found in only postmenopausal cases i.e., 4 (7 %) cases with hypothyroidism & 2 (3 %) cases with hyperthyroidism **(Table 1).** In similar study by **Handan Kumar Jha et al (2020)**[20]they found

prevalence of thyroid dysfunction as 29.8%. **Weng C-H et al (2018)**[27]in their study foundmean ages as 53.4 years in the breast Cancer**.** There were 0.7% patients with hypothyroidism and 3.1 % hyperthyroidism. **Anne Mette Falstie-Jensen et al (2020)**[28]in their study foundincidence of hypothyroidism as1.8% (95%CI = 1.7 to 1.9). **Kikawa Y et al (2017)**[29]in their study found prevalence of HT as 2.4%. In present study 1 (2 %) case had mucinous type of breast cancer who was Euthyroid. Similarly, 1 (2 %) case had medullary type of breast cancer who was also Euthyroid. No Significant association found between Sub-types of breast cancer& incidence of thyroid dysfunction **(P=0.993) (Table 2).** In similar study by **Adedayo A. Onitilo et al**[21] they identified 24 cases of medullary type of breast cancer representing 3.09% of all 766 invasive breast cancers. In present study oestrogen receptor (ER) was found negative 20 (31 %) cases. Amongst them 16 (27 %) were euthyroid, 2 (4 %) were hypothyroid & 0 (0 %) were hyperthyroid. Insignificant association found between type of thyroid dysfunction & incidence of oestrogen receptor (ER) negativity **(P=0.44).** Progesterone receptor (PR) was found negative in 26 (44 %) cases. Amongst them 24 (40 %) were euthyroid, 2 (4 %) were hypothyroid & 0 (0 %) were hyperthyroid. Insignificant association found between type of thyroid dysfunction & incidence of progesterone receptor (PR) negativity **(P=0.442).** HER2NEUwas found negative in 28 (47 %) cases. Amongst them 24 (40 %) were euthyroid, 4 (7 %) were hypothyroid & 0 (0 %) were hyperthyroid. Significant association found between type of thyroid dysfunction &HER2NEU negativity **(P=0.04).** Amongst thyroid dysfunction cases all hypothyroid cases i.e., 4 (7 %) showed HER2NEU negative result which suggested bad prognosis**.** Ki-67 index>20 % was found in 46 (79 %) cases. Amongst which 43 (72 %) were euthyroid, 4 (7 %) were hypothyroid & 0 (0 %) were hyperthyroid. Significant association found between type of thyroid dysfunction &Ki-67 index**(P=0.015).** Amongst thyroid dysfunction cases all hypothyroid cases i.e., 4 (7 %) showed Ki-67 index>20 % which suggested bad prognosis**.(Table 3, Table 4).** In similar study by**Adedayo A. Onitilo et al**[21]theyfoundER status positive in 77.9 %, PR status positive in 59.1 % & Her2 status positive in 17.7 %. **Tran T-V et al (2021)**[30]found no statistically significant association between hypothyroidism and breast cancer risk, overall (HR=0.93, 95%CI 0.84–1.02). **Michał Piotr Budzik et al (2021)**[31]found ER status positive 70.8 %, PR status positive in 62.5 % & Her2 status positive in 16.7 %. In present study amongst IHC markers i.e., ER, PR & HER2NEU, only HER2NEU showed statistically significant correlation with thyroid dysfunction. It was found positive in 3 % hyperthyroid cases. Ki67 Index however found abnormal more in hypothyroid cases 7%. Possible mechanism is hypothyroidism may trigger hypersensitisation of mammary glandular epithelium to oestrogen and prolactin, possibly related to low circulating thyroid hormone which further leads to mammary dysplasia[27]

Conclusion

To conclude, prevalence of hypothyroidism found was 7 % & hyperthyroidism as 3 % in breast cancer (BC) patients. Amongst various prognostic markers i.e., ER, PR, HER2NEU& Ki-67 index only HER2NEU& Ki-67 index showed statistically significant correlation with thyroid dysfunction. Breast cancer (BC) patients should be considered a risk group who should receive routine screening for thyroid dysfunction.

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