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Association of Thyroid Hormone Dysfunction with Breast Cancer and Its Effect on Tumor Behaviour

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***Abstract*:** *Both breast cancer and thyroid dysfunction are fairly common in the peri and post menopausal age group of females but whether this is an incidental or causal association is not properly known. Thus this study was undertaken to determine the association of thyroid dysfunction with breast cancer, if any and whether it can affect the tumor behaviour? All patients with chief complaints of breast lump were thoroughly examined and a detailed clinical history was taken. Age matched females for control group and Benign Breast Diseases (BBD) group were also included for comparison. Blood samples were collected from all for estimation of FT3, FT4 and TSH. All the cancer cases included underwent detailed histopathological and immunohistochemical (IHC) evaluation for ER, PR and Her 2neu of the surgical specimen. 54 controls, 58 BBD cases and 52 cases of breast cancer were included in this study. No significant association between thyroid dysfunction and breast cancer was seen as the number of euthyroid, hypothyroid and hyperthyroid cases were comparable in the control, BBD and cancer groups. Also no significant difference in the behaviour of tumour with respect to Modified Bloom Richardson (MBR) grade, lymphovascular invasion (LVI) and molecular typing based on IHC status was seen in the cancer cases with and without thyroid dysfunction. Hence, this study shows that there is no association between thyroid dysfunction and breast cancer nor does it alter the tumor behaviour.*

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I. Introduction

Both thyroid disorders & breast cancer are more prevalent in peri and postmenopausal women,[1,2] so a very pertinent question arises whether this is just a co-incidental finding or the association is causal [3]. The said association dates back to almost a century ago when Beatson undertook an attempt to cure breast cancer patients with an extract from the thyroid gland, unfortunately without great success. Since then, this issue has continued to intrigue scientists and many epidemiologic and experimental studies have been performed on this subject with highly inconsistent results .[4] [5-18] A very recently published study from Asia [19] has shown increased risk of breast cancer with both hyperthyroidism as well as hypothyroidism. There is no central hypothesis to explain the association, but a few theories have been postulated - early studies done on animal models stated iodine deficiency leading to breast malignancies due to excessive production of prolactin and estrogen in the epithelium of mammary glands; [20] recent studies done on breast tissue cell lines have demonstrated presence of Thyroid Receptors (TR's) and Thyroid Stimulating Hormone Receptors (TSHR's) which are said to affect both the normal breast cell differentiation as well as cancer cell proliferation; [21] also T3 has been supposed to activate the same signal transduction pathways as estradiol, regulate the gene expression of both ER and PR; [22] and the T3 response element [TRE] DNA sequence has been found to be identical to an ER response element (ERE) due to which ER-immunoreactive cells have been seen to increase dramatically following T3 treatment. [23]

Hence, this study was undertaken with the aim of assessing the nature of association between breast cancer and thyroid dysfunction if present, and also to assess if there is any significant difference between the tumour behaviour (on the basis of histological grading, lymphovascular invasion and molecular subclassification) in breast cancer cases with and without thyroid dysfunction.

II. Material and Method

This "case control - cross sectional" study was conducted jointly by the Departments of Pathology at M.L.N. Medical College and Kamla Nehru Hospital and the Department of Oncosurgery, Kamla Nehru Hospital, Prayagraj over a period of one year (September 2017-18).

Subject selection- The cases were the patients coming to department of Oncosurgery with chief complaints of breast lump/mass.

CRITERIA FOR INCLUSION- Newly diagnosed cases of breast cancer (either Mammogram/FNAC/ biopsy proven) , irrespective of age.

CRITERIA FOR EXCLUSION- Patient on thyroid drugs; past medical condition(s) predisposing to increased exposure to endogenous/exogenous estrogen such as nulliparity/ no or inadequate breast feeding/ Hormonal therapy; any history of prior exposure to chemotherapy/radiotherapy; history of breast cancer in first degree relative and patients in whom the breast cancer was not newly diagnosed(old cases).
Age matched females were included for comparison and were divided into two groups-
1. Control group (females with no breast problem) and
2. Benign breast diseases [BBD] group (females with breast diseases of benign nature).
Sample size- 54 controls, 58 benign breast diseases and 52 breast cancer cases were enrolled in the study.

Procedural methodology- The institutional ethical committee approval and informed consent from all the controls and cases was taken before enrolling them in the study. A detailed clinical history was taken from all the cancer cases followed by a thorough clinical examination.
Blood samples were collected from all the cancer cases, BBDs and controls in a plain vial for estimation of FT3, FT4 and TSH by .chemiluminiscence on Immulite 1000SR. Anti thyroid antibodies (anti-TPO/TG) estimation was done only in those subjects who showed deranged Thyroid Function Test results.
The breast cancer cases included in the study underwent detailed histopathological and immunohistochemical evaluation of the surgical specimen. However in cases where only biopsies were available, comment upon MBR grading and LymphoVascular Invasion could not be done for obvious reasons.
Sections taken were fixed in 10% (v/v) Neutral Buffered Formalin and processed routinely. 2-3 micron thick sections were taken and stained with:-
1) Hematoxylin and Eosin- For morphological evaluation with special emphasis on-
a) Modified Bloom Richardson (MBR) scoring and grading
b) Presence/absence of lymphatic and vascular invasion (LVI).
2) IHC for ER, PR and Her-2-neu (Bio SB, California, USA) with special emphasis on their scoring according to ASCO guidelines.
Statistical analysis – It was carried out using Graph Pad software. Student's unpaired *t*- test and chi square test was used for comparison. "P" value of <0.05 was considered statistically significant.

III. Result

Out of the 52 cancer cases, 31 cases were received as Modified Radical Mastectomy specimens (MRMs') and 21 as Excisional Biopsies (EBs'). All were of Invasive Ductal type (IDC-NOS) on histopathological examination.

Mean age in control group, BBD and breast carcinoma [BC] group was 44 ±10.2 years, 35±10.7 years and 44 ±11.1 years respectively. Mean age in BC cases who were euthyroid, hypothyroid and hyperthyroid was 44.4±8.5 yr, 45.0±15.2 yr and 43.0±10.6 yr respectively.

1.Comparison of thyroid status amongst control, BBD and breast cancer group :
The distribution of euthyroid, hypothyroid and hyperthyroid cases was almost similar amongst the controls, BBDs and BC cases with statistical insignificance (Table 1)

Table no. 1: Comparison of thyroid status amongst Control, Benign Breast Diseases[BBD] and Breast Cancer [BC] group

THYROID STATUS	CONTROL (N=54)	BBD (N=58)	BC (N=52)	P Value		
EUTHYROID	44	44	40	A Vs B	A Vs C	B Vs C
THYROID DYSFUNCTION	12	14	10	(NS)	(NS)	(NS)

*NS= Non Significant

2. Comparison of antithyroid antibodies (Anti- TPO and Anti TG) amongst control, BBD and breast cancer subgroup:

In control group and BBD group, Anti-TPO as well as Anti-TG was negative in all subjects with thyroid dysfunction. In breast cancer group, only 1 out of the 8 cases with hypothyroidism was Anti-TPO positive (12.5%). None of the cases showed Anti TG positivity. Hence no significant association was seen between anti thyroid antibodies and breast cancer.

3. Comparison of thyroid status with Modified Bloom Richardson Grading :

This could be done in 31 cases only where the specimen received was a MRM. Maximum cases in euthyroid, hypothyroid as well as hyperthyroid subgroups fell in Grade II. None of the cases with either hypo/hyperthyroidism presented in Grade I. No significant association between tumor grading with presence of thyroid dysfunction was seen.(Table 2)

Table no. 2: Comparison of Thyroid status with Modified Bloom Richardson[MBR] Grading in Breast Cancer cases

THYROID STATUS	GRADE I	GRADE II	GRADE III	Total cases(n)
EUTHYROID	5(20%)	15(60%)	5(20%)	25
HYPOTHYROID	0(0%)	3(60%)	2(40%)	5
HYPERTHYROID	0(0%)	1(100%)	0(0%)	1

4.Comparison of thyroid status with lymphovascular invasion(LVI) :

18(72%) out of the 25 cases who were euthyroid, 4(80%) out of the 5 cases with hypothyroidism and the single case with hyperthyroidism (100%) had lymphovascular invasion with no significant association between the tumor invasion and thyroid status. (Table 3)

Table no. 3: Comparison of Thyroid status with status of Lympho Vascular Invasion[LVI]

THYROID STATUS	LVI Present	LVI Absent	Total (n)
EUTHYROID	18(72%)	7(28%)	25
HYPOTHYROID	4(80%)	1(20%)	5
HYPERTHYROID	1(100%)	0(0%)	1

5.Comparison of Thyroid status with Immunohistochemical (IHC) status for ER, PR and Her 2 neu :

IHC for ER, PR and Her 2 neu was done on all the 52 cases. Out of these 8 cases were excluded from the final observation as these showed equivocal results for Her-2-neu. Amongst the rest 44 cases, the distribution of euthyroid, hypothyroid and hyperthyroid cases was 35, 6 and 3 respectively. The cases who were euthyroid showed mixed pattern. Maximum cases with hypothyroidism fell into triple negative class. None of the cases with hyperthyroidism were triple positive or triple negative/basal like. There was no significant association between the molecular status and the thyroid status (Table 4; Fig 1,2,3).

Table no. 4: Comparison of Thyroid status with Immunohistochemical [IHC]status for ER, PR and Her 2 neu

THYROID STATUS	Luminal A (ER,PR+ve, Her2 neu-ve)	Luminal B (ER+ve, PR-ve, Her 2neu-ve)	Luminal B (ER, PR+ve, Her2 neu+ve)	Non-luminal (ER,PR-ve, Her2 neu +ve)	Basal like (ER,PR –ve, Her 2 neu –ve)	Total n= 44
EUTHYROID	6(17%)	4(11%)	9(26%)	7(20%)	9(26%)	36
HYPOTHYROID	0(0%)	1(16.6%)	1(16.6%)	1(16.6%)	3(50%)	5
HYPERTHYROID	1(33.3%)	1(33.3%)	0(00%)	1(33.3%)	0(00%)	3

Figure 1: Molecular distribution of euthyroid cases

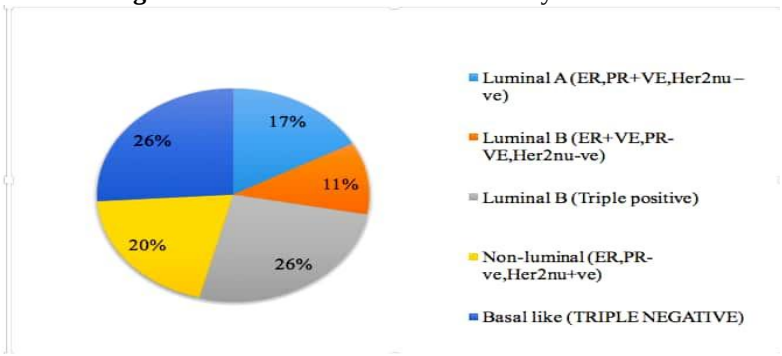


Figure 2: Molecular distribution of Hypothyroid cases

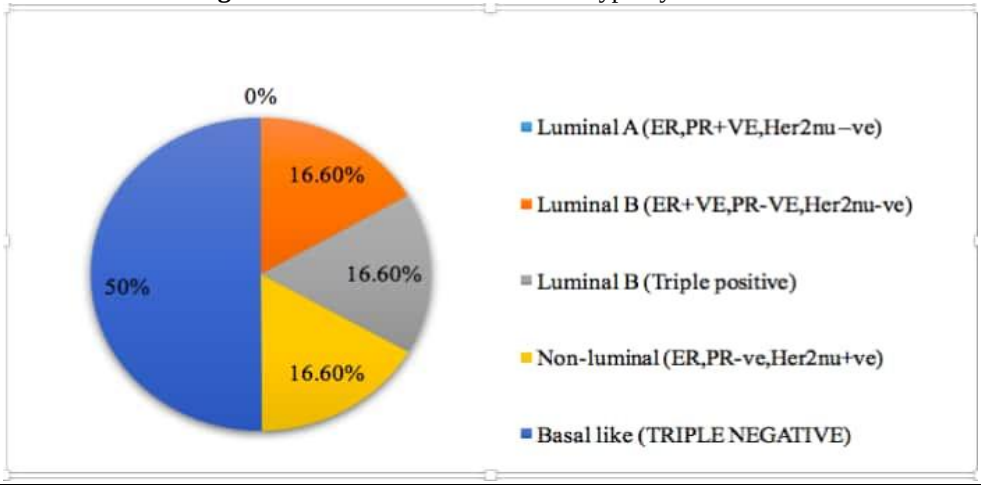
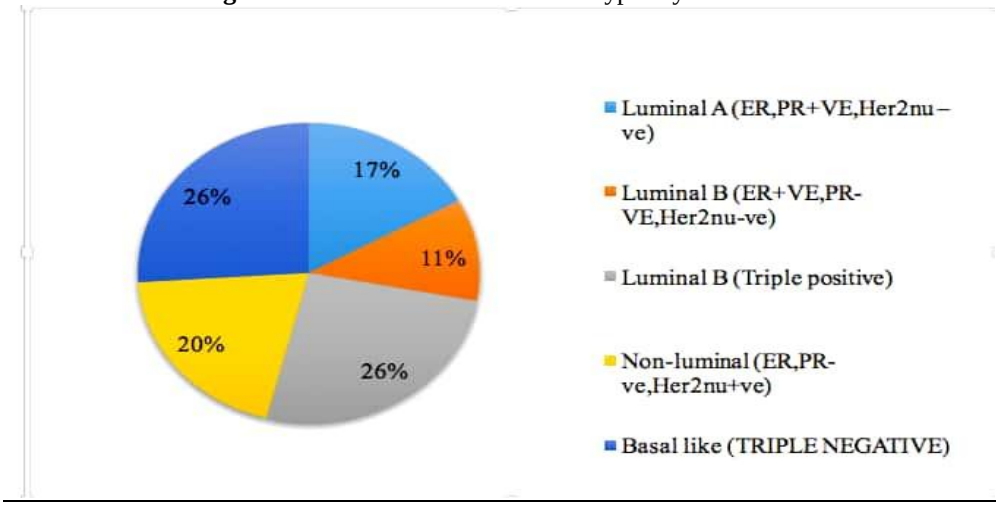


Figure 3: Molecular distribution of Hyperthyroid cases



IV. Discussion

Breast cancer is the most common cancer affecting women in the western part of the world, while in India it ranks second to cervical cancer.[2] Multiple etiological factors contribute to breast cancer risk like age at menarche and menopause, parity, duration of breast feeding done, hormonal therapy, and genetic factors such as presence of BRCA-1/ BRCA-2 mutations.[3]

The association of thyroid disorders and breast cancer dates back to almost a century ago when in 1896 Beatson undertook an attempt to cure breast cancer patients with an extract from the thyroid gland, unfortunately without great success.[4]

Since years the speculated relationship between breast cancer and thyroid diseases has been a matter of controversy. While most of the studies done in 70's and 80's reported breast cancer to occur more frequently in hypothyroid women,[24] studies done in the recent years have shown highly mixed results with some of them having found no such association,[5-10] whereas many proposing an association with thyroid dysfunction, some with hypothyroidism and some with hyperthyroidism.[11-18] Interestingly all of these studies were conducted in the western part of the world. Only one study till date has been done from Asia[19] which showed an increased risk of breast cancer with both hyperthyroidism and hypothyroidism.

This study included 52 cases of breast cancer, 54 controls and 58 cases of benign breast diseases. Mean age in our cases of breast cancer was 44±11.1 yr which was quite similar to that reported in two studies.[9,10] The latter study had a comment that there was no significant difference in the age distribution between the

cancer cases who were euthyroid, hypothyroid and hyperthyroid. [10] Likewise in our study too, no such age difference was seen between these three groups.

No significant association of breast cancer with thyroid dysfunction was noted in our study and the distribution of cancer cases amongst the euthyroid, hypothyroid and hyperthyroid was somewhat similar to that observed in other researches,[8,9,10] but were in contradiction to few other studies as mentioned above that documented a significant association of breast cancer with hypothyroidism/ hyperthyroidism.[11-18]

Out of 8 cases of breast cancer with hypothyroidism only one case (12.5%) showed positive anti-TPO. Similar to ours, a low prevalence rate for TPO antibodies in the breast cancer patients with no significant differences between cancer patients, BBDs and controls have been documented by few other authors as well.[15,18] In contrast to these, however quite a few papers have reported increased prevalence of TPO-Ab in breast cancer[9,11,25] and proposed that this association might be due to the presence of common antigen which is able to trigger a common immunoreactivity between Thyroid Peroxidase in thyroid and Lactoperoxidase in breast.[26]

None of the cases were positive for anti-TG in our study. Although a few studies have reported the mean values for serum anti TG antibodies higher in breast cancer groups with respect to control group, it was statistically insignificant in all of them.[5,18] Thyroglobulin is said to show high false positivity in many conditions hence it is not a very reliable marker.[28]

The MBR grading analysis in the breast cancer patients did not reveal any statistically significant association with the presence/absence of thyroid dysfunction in our study that was similar to the observations of a few papers that in all the histological grades, maximum breast cancer patients were euthyroid.[9,18] However some authors have stated that the thyroid disorders do affect the tumor grade.[16,21,24]

There was no significant association between lymphovascular invasion and thyroid status in our study. Similar to ours, Muller et al and Angelouise et al too did not get any significant association in theirs,[9,18] though the latter observed that the BC cases with lymph node infiltration presented with lower mean TSH levels and higher fT4 levels compared to those without lymphatic invasion. However, many studies have reported quite contrary- in one study it was shown that hypothyroidism had an enhancing effect on invasiveness[29] whereas another study stated that hypothyroidism was associated with more localized form of disease.[4] TPO-Ab levels as well as the presence of nuclear TR-α receptors in breast cancer cells in vitro were said to inversely correlate with lymph nodes metastases in a study[11] whereas another study observed that the LVI rates were higher in patients with accompanying autoimmune thyroiditis.[27] A positive association between higher T_3 and presence of lymph node metastasis has also been reported.[16]

On IHC analysis for ER, PR and Her 2neu, we did not find any significant difference between thyroid status and molecular subtype of breast cancer. Similar to ours, there are studies where a similar distribution of euthyroid cases and cases with thyroid dysfunction has been shown amongst various molecular classes .[9,18]

However, enhanced ER positivity in hyperthyroid cases and with autoimmune thyroiditis has also been seen.[14,21,30] This could be because of the stimulation of ER-β dependent genes via a combination of ER-β TR-α_1 or via TR interaction with ERE. In contrast to these, Tosovic et al have observed an inverse association between T_3 and ER/PR status.

V. Conclusion

Studies from Asia exploring the association between thyroid dysfunction and breast cancer are scarce and to the best of our knowledge and research, this is the first study from India which has attempted so. This study showed that no significant association is seen between thyroid dysfunction and breast cancer neither does the thyroid status have any potential to alter the tumour behaviour. Hence screening of these patients for thyroid dysfunction might be of no diagnostic or therapeutic utility.

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