Original Article

DOI: 10.7860/IJARS/2022/56367.2830

Surgery Section

Karyotypic Analysis of Synchronous Breast Cancer and Thyroid Diseases: A Pilot Study at a Tertiary Care Centre

DEVENDRA CHOUDHARY[1], ARVIND RAI[2], SUDHIR PAL[3], KUNAL VAIDYA[4]

ABSTRACT

Introduction: The coincidence of thyroid disease and breast cancer is in controversy since long time. Current scientific evidence supports a strong association between the hormone oestrogen and breast cancer and also with thyroid diseases.

Aim: To study the karyotypic association between breast cancer and thyroid diseases.

Materials and Methods: This cross-sectional pilot study was conducted from October 2018 to August 2020 in Department of Surgery, Hamidia hospital, Bhopal, Madhya Pradesh, India. A total of 50 patients were included in the study with a division into two respective arms of patients with Carcinoma breast (Ca breast) and thyroid diseases. Each arm included 25 patients. All patients were subjected to detailed history and complete physical examination. Karyotyping of all patients was carried out by using fasting blood samples and standard staining techniques were applied to detect any chromosomal aberration. Statistical analysis done on the collected data, by Chi-square test and t-test by Statistical Analysis of the Social Sciences (SPSS) v23 (IBM Corp.).

Results: In a total of 50 patients with breast cancer (25) and thyroid disorders (25), most of these patients 24 (48%) were in the age group of 40-49 years. Amongst the 25 patients with breast cancer, thyroid diseases were present in 10 (40%), while no case of carcinoma breast was seen in patients with thyroid disorders. In seven patients, karyotype abnormality was observed in the form of co-existing deletions and micro deletions, and all of them had synchronous carcinoma breast and thyroid diseases, which is significant (p-value=0.0085), showing some definite association at the genetic level.

Conclusion: To summarise, the present study clearly shows that patients with breast cancer tend to have co-existing thyroid diseases, which can either be benign or malignant thus these individuals should be appropriately investigated to exclude the possibility of an underlying undiagnosed thyroid disease, which would also help in early diagnosis and treatment.

Keywords: Carcinoma breast, Karyotypic aberrations, Thyroidectomy

INTRODUCTION

The coincidence of thyroid disease and breast cancer is a matter of controversy since long time. Although associations with hyperthyroidism, hypothyroidism, thyroiditis and non toxic goitre have been reported in the literature, no convincing evidence exists for a causal role of overt thyroid disease in breast cancer [1]. Geographical variations in the incidence of breast cancer had been attributed to differences in dietary iodine intake. The effect of iodine on the breast has also been postulated [1]. The possible interactions between thyroid gland and breast tissue are based on the common property of the mammary and thyroid epithelial cells to concentrate iodine by a membrane active transport mechanism [2] as well as on the presence of Thyroid Stimulating Hormone (TSH) receptors in fatty tissue, which is abundant in mammary glands [3]. Additionally, some endocrine stimuli identified in thyroid products that exert a simultaneous action on the breast and the various thyroid antibodies, which could also interact with receptors on breast tumours, have been postulated to be responsible for the coincidence of mammary and thyroid gland disorders [4,5]. Current scientific evidence supports a strong association between the hormone oestrogen and breast cancer and also with thyroid diseases [6,7]. Identification of a causal or temporal relationship between breast cancer and thyroid diseases can thus help to reduce the burden on healthcare system as well as on the patients.

In addition to these hormonal and molecular correlations there exists some genetic correlation between these two entities as evidenced by occurrence of some hereditary cancer syndromes like Cowden syndrome, Ataxia telangiectasia syndrome and familial adenomatosis syndrome, which are associated with both carcinoma breast and carcinoma thyroid [8].

The present study aimed to study genetic association between breast cancer and thyroid diseases based on karyotypic aberrations which can be of prognostic significance and can be taken as screening tool for early detection of thyroid diseases in patients of carcinoma breast.

MATERIALS AND METHODS

This cross-sectional pilot study was conducted on 50 patients from October 2018 to August 2020 admitted in the Department of Surgery, at Hamidia Hospital, Bhopal, Madhya Pradesh, India. The study was approved by the Ethical Clearance Committee of the hospital (letter no. 36148055/mc/IEC/2018 dated 16/11/18).

Inclusion criteria: The study included only female patients having carcinoma breast (any stage, and not had received any form of radiotherapy or chemotherapy), and thyroid diseases (biochemical or pathological, preoperative status, not had taken any form of radiotherapy or chemotherapy).

Exclusion criteria: Male patients with breast or thyroid diseases, female patients with history of mastectomy, chemo/radiotherapy or thyroidectomy were excluded from the study. Female patients with benign breast diseases, and female patients with biochemical thyroid diseases taking thyroxin or anti-thyroid drugs were also excluded.

In the present study only female patients were included as both carcinoma breast and thyroid diseases are common in female patients and hormonal factors especially oestrogen which is important in

pathogenesis of both the entities [9]. Since surgery or chemotherapy, may influence immune system (specially autoimmunity) and can trigger or worsen the autoimmune diseases hence only patients with newly diagnosed breast cancer or benign breast disease before surgery, chemotherapy, radiation or anti hormonal therapy were included in the study, which eliminates bias produced by these confounding factors [8,10-13].

Study Procedure

Patients were placed into two respective arms, patients with carcinoma breast and thyroid diseases. Each arm included 25 patients. All patients were subjected to detailed history and complete physical examination including general, systemic and locoregional examination. All breast cancer patients were examined for apparent or occult thyroid diseases (by using thyroid profile and ultrasound examination of the thyroid gland by the same radiologist, and core needle biopsy of any lesion found in clinical or radiological examination). All patients of thyroid diseases were examined for breast cancer by clinical examination and ultrasound of both breast and axilla by the very same radiologist, after taking informed consent.

Breast cancer was diagnosed by core needle biopsy of breast tumour (taken with cook's tru cut biopsy needle of 18 gauge, and analysed by the same pathologist in the Department of Pathology, Gandhi Medical college, Bhopal) and staged according to the Tumour, Nodes and Metastases (TNM) classification given by the American Joint Committee on Cancer (AJCC) 8th edition on tumour size, axillary lymph node status and metastatic status (as per findings of clinical and radiological examinations) [14]. Thyroid diseases were diagnosed using core needle biopsy of thyroid lesions (taken with 22F cook's tru cut biopsy needle and analysed by the same pathologist visible clinically or radiologically.

Thyroid profile of all the patients was performed using an automated immunoassay system based on electrochemiluminescence. TSH values >3.80 µU/mL were considered to indicate hypothyroidism, TSH values <0.44 µU/mL were considered to indicate hyperthyroidism. Karyotyping of all patients done by using fasting blood samples, standard staining techniques were applied to detect any chromosomal aberration.

STATISTICAL ANALYSIS

Statistical analysis done on the collected data, by Chi-square test and t-test by SPSS v23 (IBM Corp.). A p-value <0.05 were regarded as significant association.

RESULTS

In a total of 50 patients with breast cancer (25) and thyroid disorders (25), most of these patients 24 (48%) were in the age group of 40-49 years [Table/Fig-1].

Age (years)	Ca breast	Hyperthyroid	Hypothyroid	Ca thyroid	Total
<40	1	0	2	0	3
40-49	10	2	10	2	24
50-59	7	1	3	1	12
60-69	7	3	1	0	11
Total	25	6	16	3	50

[Table/Fig-1]: Age-wise distribution of cases with carcinoma breast and thyroid disorders.

The synchronicity between carcinoma breast and functional thyroid status of patients was studied and it was found that eight patients of carcinoma breast had hypothyroidism, two had hyperthyroidism (p-value <0.63) and 15 patients were euthyroid. Hypothyroidism was found significantly associated with Ca breast (p<0.024) [Table/Fig-2].

Parameters	Hypothyroid	Hyperthyroid	Normal	Total
Ca breast	8	2	15	25

[Table/Fig-2]: Synchronicity between carcinoma breast and thyroid diseases.

Amongst the 25 patients with breast cancer, thyroid diseases were present in 10 (40%) of them, while no case of carcinoma breast was seen in patients with thyroid disorders. Thus thyroid disorders were significantly seen more among cases with carcinoma breast this was statistically significant (p=0.042) [Table/Fig-3].

Abnormal karyotype was seen in total seven patients and all of them were found to have thyroid diseases [Table/Fig-3]. All these patients had invasive ductal carcinoma, while in thyroid diseases two patients had diffuse goitre, two patients had nodular goitre and rest three patients had thyroid malignancy.

Karyotype	Thyroid disease present	% Thyroid disease present	Thyroid disease absent	% Thyroid disease absent	Total
Abnomal karyotype	7	100.0	0	0.0	7
Normal karyotype	28	65.1	15	34.9	43
Total	35	70	15	30	50

[Table/Fig-3]: Karyotypical abnormalities and thyroid disease.

Abnormal karyotype was seen in seven patients and all of them were found to have Ca breast. Thus total seven patients were having positive karyotype report.

All patients with positive karyotype report were having synchronous diseases which was statistically significant (p-value=0.0085) [Table/Fig-4].

Karyotype status	Ca breast present n (%)	Ca breast absent n (%)	Total
Abnormal karyotype	7 (100%)	0	7
Normal karyotype	18 (41.9%)	25 (58.1%)	43
Total	25 (50%)	25 (50%)	50

[Table/Fig-4]: Karyotypical abnormalities and breast diseases.

All three patients with positive karyotype report with thyroid cancer, were also having synchronous Ca breast and this association was statistically significant (p-value <0.0001) [Table/Fig-5]. Out of these three patients two had papillary carcinoma and one patient had follicular neoplasm. Out of total seven patients with abnormal karyotype four of patients had deletions of chromosome 16q which were seen either individually or with another chromosomal aberrations like 7q, 13p, 16p, 17p and 17q.

Karyotype	Ca thyroid present	%	Ca thyroid absent	%	Total
Abnormal	3	42.9	4	57.1	7
Normal	0	0.0	43	100.0	43
Total	3	6.0	47	94.0	50

[Table/Fig-5]: Abnormal karyotype and thyroid cancer.

Functional thyroid status in relation with tissue differentiation of Ca breast was studied. In patients with hypothyroidism eight had poorly differentiated Ca breast, three had moderately differentiated Ca breast and only one had well-differentiated Ca breast.

In hyperthyroid group, no patient had poorly differentiated Ca breast, one had moderately differentiated Ca breast and two patients had well-differentiated Ca breast. In euthyroid group of

patients hypothyroidism one had poorly differentiated Ca breast, two had moderately differentiated Ca breast and seven patients had well-differentiated Ca breast. So, in the present study significant number of patients (i.e.8/25=32%) with hypothyroidism had poorly differentiated Ca breast.

DISCUSSION

The present study had total 25 patients with carcinoma breast, out of these 25 patients, 10 (40%) had synchronous carcinoma breast and thyroid diseases. Giani C et al., also reported similar overall prevalence (46%) of synchronous diseases in their study [3]. Out of these, 10 patients with synchronous disease, 7 (28%) had benign thyroid diseases in the form of diffuse goitre (2/25 i.e.8%) and nodular goitre (5/25 i.e.20%) while 3 (12%) were having thyroid malignancy. In a study conducted by Turken OY et al., there was overall 58% occurrence of benign thyroid diseases with 8% incidence of diffuse goitre, and 50% incidence of nodular goitre [15]. Both Giani C et al., and Turken OY et al., reported <2% incidence of thyroid cancer in patients with carcinoma breast while in present study it is 12% that is significantly much higher which may be due to geographic variation in the incidence of thyroid malignancy [3,15].

The association between carcinoma breast and thyroid dysfunction in the form of hypo or hyperthyroidism was also studied. Total 10 patients of carcinoma breast were having thyroid dysfunction out of patients which 08 patients of carcinoma breast had hypothyroidism, 2 had hyperthyroidism (p-value <0.63) and 15 patients were euthyroid. Hypothyroidism was found significantly associated with Ca breast (p<0.024) [Table/Fig-2]. Jiskra J et al., 2007 showed increased TSH serum levels and hypothyroidism in almost 20% of breast cancer patients [16].

Recently Rajoriya S et al., proposed that oestrogen and hypoxia are interlinked in thyroid cancer and can equally modulate epithelial-endothelial cell interactions by mediating key cellular, metabolic and molecular processes of thyroid cancer progression [17]. Kumar A and Klinge concluded that E2-mediated thyroid cancer cell proliferation involves ER alpha and ER beta transcriptional and non genomic signalling events [18]. In the present study relationship between tissue differentiation, and functional thyroid status of carcinoma breast patients was assessed and it was found that patients with hypothyroidism had poor tissue differentiation, but unfortunately authors could not found any study correlating these two variables so they postulated a possible role of hypothyroidism in development of high grade breast cancers, and suggested further studies for such correlation.

The present study aimed to study genetic association between carcinoma breast and thyroid disorders. Authors found a total seven patients karyotype abnormality in the form of deletions and micro deletions, and all of these seven patients had synchronous carcinoma breast and thyroid diseases, which is significant (p-value=0.0085), which showed some definite association at the genetic level.

Out of seven patients four patients had deletion in chromosome 16 q, interestingly all three patients with synchronous Ca breast and Ca thyroid had deletion in short arm of chromosome 16, so it was postulated that there may be some locus in this chromosome that is responsible for occurrence of both the malignancies while one patient had deletion in 16 p also. Rest three patients in the present study had deletion in chromosome number 7q, 13q and 17q, and all these three patients were having Ca breast along with benign thyroid diseases. In 1984 Rodgers C et al., studied nine cases of untreated Ca breast using direct chromosome preparation, and reported several chromosomal abnormalities [19]. They reported abnormalities in chromosome 1,8,16,6,12,13,17 in descending order.

There is no study in the literature that as studied chromosomal aberrations in patients with synchronous breast and thyroid diseases, so probably we are the first to study such association.

Limitation(s)

Small sample size and being a cross-sectional study authors can not strongly say there is some definite association but they suggest further study with a larger cohort and long follow-up to confirm or refute the present study.

CONCLUSION(S)

Patients with breast cancer tend to have co-existing thyroid diseases, which can either be benign or malignant thus these individuals should be appropriately investigated to exclude the possibility of an underlying undiagnosed thyroid disease, which would also help in early diagnosis and treatment. Chromosomal analysis should be offered to patients with breast cancer as malignant thyroid pathology has been found to develop in those individuals with alterations in chromosome 16 as well as 13 and 17. This will help to reduce the morbidity and mortality associated with thyroid diseases especially carcinoma of thyroid.

REFERENCES

[1] Maria C, Edwards B, Shin HR, Hans S, Ferlay J, Heanue M, et al. Cancer incidence in Five Continents. 2008; Vol IX.
[2] Mittra I, Perrin J, Kumaoka S. Thyroid and other autoantibodies in British and Japanese women: An epidemiological study of breast cancer. BMJ. 1976;1(6004):257-59.
[3] Giani C, Fierabracci P, Bonacci R, Gigliotti A, Campani D, De Negri F, et al. Relationship between breast cancer and thyroid disease: Relevance of autoimmune thyroid disorders in breast malignancy. The Journal of Clinical Endocrinology & Metabolism. 1996;81(3):990-94.
[4] Davies T. The thyrotropin receptors spread themselves around. Journal of Clinical Endocrinology and Metabolism. 1994;79(5):1232-33.
[5] Ron E, Curtis R, Hoffman D, Flannery J. Multiple primary breast and thyroid cancer. Br J Cancer. 1984;49(1):87-92.
[6] Dumont J, Maenhaut C, Pirson I, Baptist M, Roger P. Growth factors controlling the thyroid gland. Baillière's Clinical Endocrinology and Metabolism. 1991;5(4):727-54.
[7] Chen GG, Vlantis AC, Zeng Q, Van Hasselt CA. Regulation of cell growth by Oestrogen signaling and potential targets in thyroid cancer. Current Cancer Drug Targets. 2008; 8(5):367-77.
[8] Sotoca Covaleda A, van den Berg H, Vervoort J, van der Saag P, Strom A, Gustafsson J, et al. Influence of cellular ERα/ERβ ratio on the ERα-Agonist induced proliferation of human T47D breast cancer cells. Toxicological Sciences. 2008;105(2):303-11.
[9] Giustarini E, Pinchera A, Fierabracci P, Roncella M, Fustaino L, Mammoli C, et al. Thyroid autoimmunity in patients with malignant and benign breast diseases before surgery. Eur J Endocrinol. 2006;54(5):645-49.
[10] Barbesino G, Chiovato L. The genetics of Hashimoto's disease. Endocrinol Metabol Clin North Am. 2000;29:357-74.
[11] Strieder TG, Prummel MF, Tijessen JG, Endert E, Wiersinga WM. Risk factors for and prevalence of thyroid disorders in a cross-sectional study among healthy female relatives of patients with autoimmune thyroid disease. Clin Endocrinol 2003;59: 396-401.
[12] Dayan CM, Daniels GH. Chronic autoimmune thyroiditis. N Engl J Med. 1996;335:99-107.
[13] Forsen T, Eriksson JG, Toumilehto J, Osmond C, Barker DJ. Growth in utero and during childhood among women who develop coronary heart disease: Longitudinal study. BM J. 1999;319:1403-07.
[14] Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, et al. Breast cancer-major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(4):290-303.
[15] Turken OY, Demlrbas S, Onde M, Sayan O, Kandemlr E, Yaylacl M, et al. Breast cancer in association with thyroid disorders. Breast Cancer Res. 2003;5:R110-13.
[16] Jiskra J, Barkmanova J, Limanova Z. Thyroid autoimmunity occurs more frequently in women with breast cancer compared to women with colorectal cancer and controls but it has no impact on relapse-free and overall survival. Oncology Reports. 2007;18:1603-11.
[17] Rajoria S, Hanly E, Nicolini A, George A, Geliebter J, Shin E, et al. Interlinking of hypoxia and estrogen in thyroid cancer [rogression. CMC. 2014;21(11):1351-60.

[18] Kumar A, Klinge. Estradiol-induced proliferation of papillary and follicular thyroid cancer cells is mediated by estrogen receptors alpha and beta. Int J Oncol. 2010;36(5)1067-80.

[19] Rodgers CS, Hil SM, Hulten MA. Cytogenetic analysis in human breast carcinoma. Nine cases in the diploid range investigated using direct preparations. Cancer Genet Cytogenet. 1984;13:95-119.

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Surgery, Gandhi Medical College and Associated Hamidia Hospital, Bhopal, Madhya Pradesh, India.
2. Professor and Head, Department of Surgery, Gandhi Medical College and Associated Hamidia Hospital, Bhopal, Madhya Pradesh, India.
3. Professor, Department of Surgery, Gandhi Medical College and Associated Hamidia Hospital, Bhopal, Madhya Pradesh, India.
4. Senior Resident, Department of Surgery, Gandhi Medical College and Associated Hamidia Hospital, Bhopal, Madhya Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Kunal Vaidya,
Department of Surgery, Hamidia Hospital, Bhopal, Madhya Pradesh, India.
E-mail: drkunalvaidya@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 28, 2022
- Manual Googling: May 31, 2022
- iThenticate Software: Jun 06, 2022 (14%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval Obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 15, 2022**
Date of Peer Review: **Apr 27, 2022**
Date of Acceptance: **Jun 01, 2022**
Date of Publishing: **Oct 01, 2022**