Original Research

Breast Cancer; Clinical Spectrum and Genetic Abnormalities in Women of Reproductive Age: A Retrospective Study

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ABSTRACT

Objective: To examine the clinical spectrum of breast cancer, its symptoms, presentation, histologic types and different types of its genetic aberrations in the women of reproductive age.

Methodology: This Retrospective study was conducted at the Heavy Industries Taxila (HIT) Hospital, Taxila Cantt, from March 2022 to December 2022. The Temporal sampling technique was used to collect the data. We looked at the data of patients with breast cancer that were treated at the HIT hospital Taxila. The retrospective data was collected from the files of the patients who visited HIT Hospital, dated back from January 2011 to December 2020. The study included women of reproductive age with breast cancer symptoms, regardless of whether they had a family history of the disease. The women with metastatic breast lesions and breast trauma were excluded from the study. Age, hormone receptor status, axillary lymph node status, histologic grade and subtype, tumor size margin status, menopausal status, human epidermal growth factor receptor-2 (HER2)/neu status, and the entire genetic spectrum were all included in the charts. The clinical spectrum, staging, and genetic spectrum are all described in tables.

Results: The disease's genetic makeup was found to be quite diverse, with abnormalities in genes; ATM, BARD1, CDH1, and BRCA2 making up 2 (3%) each, 3 (4%) breast cancer gene 1 (BRCA1) and BRCA2 abnormalities making up 48 (67%) of the cases. Twelve (16%) of the patients had TP53 mutations, while two (2%) of the patients had NF1 and RECQL gene alterations.

Conclusions: This study identifies multiple genes that contribute to the development of breast cancer, including BRCA1, BRCA2, TP53, BARD1 and Cadherin 1 (CDH1) genes.

KEYWORDS:

Genes, BRCA1, BRCA2, TP53 gene, HER2 gene, Breast neoplasm

INTRODUCTION

The most common malignancy is breast cancer in both developed and developing countries, trailing only lung cancer.[1] The worldwide Cancer toll is anticipated by 2030, there will be 21.7 million cases and 13 million fatalities. Because of its varied nature, each patient is distinct. With the use of precision medicine, we can discover the illnesses genomic and genetic markers and reduce the disease burden through early detection, effective treatment, and a better prognosis.[2] In Asia, 0.65million new cases of breast cancer were recorded in 2012, with 0.23 million persons dying as a result.[3] Although the death rate from breast cancer has decreased significantly over the last two decades, the disease's incidence rate is fast growing in formerly low-risk nations. This necessitates good illness management.[4] The most frequent cancer among Pakistani women is Breast cancer. Cancer affects one out of every nine women. Pakistan has a 2.5-fold higher incidence of breast cancer than Iran and India.[5] Much research has been conducted on the genetic anomalies of breast cancer. Women who have hereditary BRCA 1 gene mutations have an 85 percent likelihood of developing breast cancer while those with mutations in the BRCA 2 gene have an 84 percent chance of developing breast cancer until the age of 70. Tumor Protein 53(TP53), Partner and localizer of BRCA 2 (PALB2), Cadherin 1(CDH1), Serine / Threonine Kinase 11 (STKII), Phosphatase and tensin

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homolog (PTEN), Checkpoint Kinase 2 (CHEK2), Ataxia telangiectasia mutated 14(ATM14), and RADIALIS (RAD5) are other genes whose germline mutations can cause breast cancer.[2]

Breast neoplasms vary in kind. Benign lesions outnumber malignant tumors. In terms of benign lesions, they often appear in the second decade of life. Lactating adenoma, phyllodes tumor, Fibro adenoma, and tubular adenoma are some of the most frequent benign breast tumors. Breast abscess and granulomatous mastitis are inflammatory conditions, but fibrocystic disease is a benign proliferating condition. Malignant breast lesions include ductal carcinoma, lobular carcinoma, and medullary carcinoma. [6] Mammograms are one of the most costly screening tests for breast lumps. Histopathological examination of the biopsy samples is a significantly less expensive approach for tissue diagnosis. It is both accessible and inexpensive.[7] Because Pakistan is a dynamic geographically changing country with people of many faiths and hierarchies, genetic research on patients with breast cancer should be conducted at the regional and ethnic levels. Breast cancer is associated with genetics, parity, family history, obesity, and ionizing radiation exposure, hence it is imperative to raise awareness and diagnose it sooner to prevent morbidity and death.[8]

This Retrospective study aims to examine the clinical spectrum of breast cancer and its genetic underpinnings in women of reproductive age who were treated for breast cancer from January 2011 till December 2020 at HIT Hospital Taxila.

METHODOLOGY

This Retrospective study was conducted at the Heavy Industries Taxila (HIT) Hospital, Taxila Cantt Department of Surgery, from March 2022 to December 2022. The study was approved by the Institutional Review Board (IRB) of Heavy Industries Taxila Education City- Institute of Medical Sciences (HITEC-IMS) under approval number HITEC-IRB-02-2022. The Temporal sampling technique was used to collect the data.

We looked at the data of patients with breast cancer who were treated at the HIT hospital Taxila Department of Surgery. The retrospective data was collected from the files (accessed from the record room of HIT Hospital) of the patients who visited HIT Hospital, dated back from January 2011 to December 2020. The study included women of reproductive age with breast cancer symptoms, regardless of whether they had a family history of the disease. The women with metastatic breast lesions and breast trauma were excluded from the study.

The data of a total of 300 patients with breast cancer treated at the Heavy Industries Taxila Hospital, Taxila Cantt from 2011 to 2020 were examined and only 72 cases were found following the inclusion criteria, remaining 228 with the history of metastatic breast lesions and breast trauma and the one who failed to get genetic analysis due to various reasons were excluded from the study following the exclusion criteria**.** Patients of reproductive age with breast cancer symptoms, with or without a history of breast cancer in the family, and status or gene analysis were included in the study. SPSS 28 was used to analyze the data, Age, hormone receptor status, axillary lymph node status, histologic grade and subtype, tumor size margin status, menopausal status, HER2/neu status, and the entire genetic spectrum were all investigated in the charts.

Table 1: TNM Staging of Breast Cancer (n=72)

Pathologic Stage 0	**T Stage Score**	**N Stage Score**	**M Stage Score**
0	Tis	N0	M0
Pathologic Stage I	**T Stage Score**	**N Stage Score**	**M Stage Score**
IA	T1	N0	M0
IB	T0	N1mi	M0
IB	T1	N1mi	M0
Pathologic Stage II	**T Stage Score**	**N Stage Score**	**M Stage Score**
IIA	T0	N1	M0
IIA	T1	N1	M0
IIA	T2	N0	M0
IIB	T2	N1	M0
IIB	T3	N0	M0
Pathologic Stage III	**T Stage Score**	**N Stage Score**	**M Stage Score**
IIIA	T0	N2	M0
IIIA	T1	N2	M0

The data were provided as mean standard deviation and to identify prognostic factors, Chi-square testing and multivariate analyses were used. To evaluate statistical significance, a P value of 0.05 was employed. Tables provide descriptive factors related to the clinical spectrum, TNM staging

(Table 1), and genetic spectrum. The histologic categories employed are based on Wargotz's meta-plastic breast cancer classification: spindle cell carcinoma, carcinosarcoma, matrix-producing carcinoma, ductal squamous cell carcinoma, and metaplastic carcinoma with osteoclastic large cells.[9]

RESULTS

We found 72 cases following the inclusion criteria, and all of them were women. At the time of the first presentation, there were no signs of distant meta-stases in any of the patients. Resection of the main malignancy and axillary lymph nodes was performed on all patients. Fifty-two cases (82%)

Table 2: Clinical spectrum of Breast cancer (n=72)

Age	
<50	23(31%)
>50	49(69%)
Reproductive status	
Pre-Menopause	24(32%)
Post Menopause	37(53%)
unknown	10(13%)
Size of Tumor	
<5cm	48(66%)
>5cm	24(34%)
Status of Axillary nodes	
Positive	27(37%)
Negative	44(63%)
Estrogen Receptor status	
Positive	58(81%)
Negative	7(09%)
Not Known	7(09%)
HER2/neu overexpression	
Positive	0
Negative	27(37%)
Unknown	44(63%)
TNM stage	
One (I)	10(13%)
Two (II)	41(56%)
Three (III)	21(28%)
Histologic Subtype	
Matrix producing carcinoma	7(10%)
Spindle-cell carcinoma	21(29%)
Squamous cell carcinoma of ductal origin	24(33%)
Carcinosarcoma	7(10%)
Metaplastic carcinoma with osteoclastic giant cells.	4(5%)
Unknown	17(24%)

had proven negative pathologic margins. The remaining patients' margin status remained unknown, how-ever, all were presumed to have received thorough excisions. (Table 2) shows the clinical range and features of the patients. The age (Average & Median) ranged from 33 to 82 years with a mean age and SD of 54± 5. Median size of the tumor was 4.1 cm, with a mean of 4.72 cm (range, 1.3 – 13.0 cm). Positive axillary lymph nodes were seen in 27 individuals (37%). In terms of TNM staging, 10 (13 %) of patients were stage I, 41 (56 %) were stage II, and 20 (28 %) were stage III. Table 2 shows the histologic subtypes identified by Wargotz and Norris. The genetic spectrum of the illness was discovered to be highly broad, as shown in (Table 3), with 48 (67 percent) having BRCA1 and BRCA2 abnormalities, and abnormalities of ATM, BARD1, CDH1, and CDEK2 were 2(3 percent), 3(4 percent), 3 (4 percent) in charts, respectively.

Table 3: Genetic spectrum of Breast cancer (n=72)

Gene	n (%)
BRCA1 & BRCA2	48(67%)
ATM	2(3%)
BARD1	3(4%)
CDH1	3(4%)
CHEK2	3(4%)
TP53	12(16%)
NF1	1(2%)
RECQL	1(2%)

TP53 mutations were found in 12 (16%) of patients, and NF1 and RECQL gene mutations were found in 1 (2%) of patients.

DISCUSSION

Although BRCA1/2 pathogenic variations are the most commonly connected with hereditary breast cancer, germline mutations in other genes may also be involved. As a result, multi-gene panels frequently include breast cancer genes with high and moderate penetrability.[11–13] Our method identified 49 distinct illnesses as being related to breast cancer susceptibility genes (BCSGs). With the exception of BARD1 and RecQ Like Helicase (RECQL), which were only linked to breast cancer, each BCSG was linked to at least three disorders. BARD1 is structurally similar to BRCA1 and is engaged in the cellular DNA repair process.[14] A relationship between breast cancer and BARD1 gene alterations was established in a large casecontrol study of 65,057 breast cancer patients conducted in USA where the incidence of BARD1 mutations was 0.18 percent, significantly higher

than in controls.11 In 201, two distinct research groups reveled RECQL as a novel breast cancer susceptibility gene.[15,16]

Bogdanova et al. determined that the RECQL* c.1667 1667 + 3delAGTA allele may represent a moderate-risk breast cancer susceptibility allele.[17] According to a recent study, African American women with the RECQL mutation had a moderate chance of developing breast cancer. [18] RECQL is also connected to hereditary breast cancer in ClinGen. However, no high-quality penetrance study for disorders other than breast cancer has established statistical significance. Though in our Study it is responsible for only 2% of the cases. The BCSGs are thought to influence female breast cancer risk in general, but some are associated to male breast cancer risk as well (MBC).

Jin et al. investigated six trustworthy genetic resources paired with a literature analysis using NLP to delineate the illness spectrum for the twelve BCSGs. Finally, 49 distinct disorders were identified as being linked to the twelve BCSGs. [19] Breast cancer has different histopathological and clinical features. The advanced stage of presentation is one of the clinical hallmarks of this illness and the proclivity for local recurrence. [20]

We noticed that the clinical and genetic range of breast cancer is extensive in our study, and the genes responsible for the disease are linked to other diseases. There is also a time lag between the onset of symptoms and reporting to the hospital for treatment, indicating a lack of awareness among patients about the disease.

Limitation: The study was conducted at only one tertiary care facility; further research in other parts of the country is needed to find the genetic spectrum of breast cancer.

CONCLUSION

This study identifies multiple genes that contribute to the development of breast cancer, including BRCA1, BRCA2, TP53, BARD1, RECQL and CDH1 genes.

Significance of Study: The study highlights the complexity of the disease and the wide range of symptoms and clinical features that can be associated with it. The identification of these additional genes may lead to more accurate diagnostic tools and targeted treatments, emphasizing the importance of genetic testing as part of the diagnostic process for breast cancer.

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Author's Contribution	
Dr. Syed Muhammad Ali Haider	Study design, acquisition of data and manuscript writing. Revised and approved the articles.
Dr. Najeeba Harim	Data acquisition, manuscript writing, Reviewed and approved the manuscript.
Dr. Noor ul Ain	Study design, data analysis and interpretation and write up of results Revising manuscript critically for important intellectual content.
Dr. Warda Altaf	Study design, Data collection Contributed to review the article and approved it.
Dr. Tayyaba Mumtaz	Study design, acquisition of data and manuscript writing. Revised and approved the articles.
Dr. Saad Farukh	Data acquisition, manuscript writing, Reviewed and approved the manuscript.
Dr. Syeda Aiman Hussain	Study design, data analysis and interpretation and write up of results Revising manuscript critically for important intellectual content.
Dr. Hassan Mumtaz	Study design, Data collection Contributed to review the article and approved it.
All authors are responsible for the integrity of the data and the accuracy of the data analysis.	
**Data availability statement:* All the data is provided in this manuscript	

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