DOI: https://doi.org/10.53350/pjmhs2023175677

ORIGINAL ARTICLE

The Prevalence of BRCA1 and BRCA2 Mutations in Breast Cancer Patients

PIRYANKA GOINDANI[1], ABDUL REHMAN[2], AISHA SIDDIQA[3], BERKHA RANI[4], SONA DEVI[5], AAKASH RAMCHAND[6]
[1,2,5,6]*Postgraduate Trainee, Oncology Department, JPMC Karachi*
[3]*Clinical Oncologist, Atomic Energy Medical Centre, JPMC, Karachi*
[4]*Senior Registar, Oncology Department, JPMC, Karachi*
Corresponding author: Piryanka Goindani, Email: goindanipriyanka@gmail.com, Cell: 0336120047

ABSTRACT

Aim: Genetic mutations in BRCA1 and BRCA2 are crucial for breast cancer riskassessment and treatment planning.

Methods: This prospective observational study at Jinnah Postgraduate Medical Centre, Pakistan, involved female breast cancer patients aged 18 or older. The sample size calculation was based on a 3.4% prevalence rate of BRCA mutations, aiming for a 95% confidence level. Data on demographic, clinical characteristics, and genetic testing for BRCA mutations were collected and analyzed using SPSS version 23.

Results: Among the study participants, 10% exhibited BRCA1 or BRCA2 mutations. The majority were diagnosed at stage 3 tumor development, with invasive ductal carcinoma being the predominant histological type. No significant familial predisposition to breast cancer was noted among the majority. Educational status and ethnicity showed varying associations with BRCA mutation presence.

Conclusion: The study highlights a modest incidence of BRCA mutations among Pakistani breast cancer patients, underscoring the importance of genetic testing for risk assessment and targeted treatment. The findings support the need for comprehensive genetic screening programs in Pakistan, considering the diverse demographic and clinical characteristics of the population.

Keywords: BRCA mutations, breast cancer, genetic testing, Pakistan, risk assessment, targeted treatment.

INTRODUCTION

Breast cancer is a complex and heterogeneous disease that affects millions of women worldwide. Genetic abnormalities in the BRCA1 and BRCA2 genes have been linked to a higher risk of breast cancer, with carriers having a lifetime risk of up to 80% .[1,2] Finding those who have BRCA1 or BRCA2 mutations is essential for developing preventative, treatment, and risk assessment plans.

Previous research has demonstrated that different populations have different frequencies of BRCA1 and BRCA2 variants. [3,4] In Brazil, a study by Gomes et al. (2007) found an incidence of 5.3% and 1.6% for BRCA1 and BRCA2 genetic alterations, respectively, in a cohort of breast cancer patients.[5] However, there is limited data on the prevalence of these mutations in other populations, including in developing countries. Ferla and colleagues (2007) examined ancestral variations within the BRCA1 and BRCA2 genes within a community located in Southern Italy. Six distinct mutations were found by the scientists, three in BRCA1 and three in BRCA2, accounting for 69% of all mutations found. The authors concluded that the high frequency of these founder mutations in the Southern Italian population could facilitate the development of cost-effective genetic screening programs for HBOC in this region. [6,7] The study by De Leon Matsuda et al. (2002) investigated the frequency of variations in BRCA1 and BRCA2 within individuals affected by breast cancer in the Philippines. The study comprised 187 breast cancer patients who had undergone BRCA1 and BRCA2 mutation tests. The study discovered that 5 (2.7%) of the 187 women with breast cancer had a BRCA1 mutation, whereas 2 (1.1%) had a BRCA2 mutation.[8]

Baretta et al. (2016) used a systematic review and meta-analysis to explore the impact of BRCA germline mutations on breast cancer prognosis. The analysis included 33 studies involving 51,450 participants, including both BRCA1 and BRCA2 mutation carriers and non-carriers.[9]

The meta-analysis found that individuals with BRCA1 mutations had a hazard ratio (HR) of 1.44 (95% confidence interval [CI] 1.23-1.68), which was lower than the overall survival rate of patients without the mutation. Similarly, patients with BRCA2 mutations had a poorer overall survival rate than non-carriers, with an HR of 1.26 (95% confidence interval 1.03-1.54).

Additionally, patients with BRCA1 mutations had a 1.43 (95% CI 1.19-1.71) higher risk of distant recurrence than non-carriers, according to the study, however patients with BRCA2 mutations did not have a statistically significant elevated risk of distant recurrence. The study's findings suggest that BRCA1 and BRCA2 mutations have a significant impact on breast cancer prognosis, with BRCA1 mutations associated with a worse overall survival and a higher risk ofdistant recurrence.[9]

This study protocol aims to investigate the clinical and demographic characteristics of carriers, as well as the frequency of BRCA1 and BRCA2 mutations in Pakistani breast cancer patients.

Research on breast cancer in Pakistan is scarce, despite the disease's high incidence. As a result, the study will examine how frequently patients having breast carcinoma had BRCA1 and BRCA2 mutations.

METHODS

The Department of Oncology at Jinnah Postgraduate Medical Centre in Pakistan undertook prospective observational research. The study was carried out for six months after obtaining clearance from JPMC's institutional review board. The sample size was determined using the BRCA gene mutation prevalence of 3.4% in breast cancer patients.[9] Using the chosen statistics software, a 95% confidence level, a 3.55% margin of error, and a sample size of 100 were calculated.

This study's patients were recruited using a deterministic convenience technique of sampling.

Female patients of age 18 years or older, diagnosed with breast cancer, were made part of this study and referred to the Department of Oncology at Jinnah Postgraduate Medical Center for treatment.

The data were acquired prospectively from the recruited patients. Enrollment of patients commenced following ethical approval from JPMC's Institutional Review Board. Before enrolling patients in the trial, their guardians were asked to provide written informed consent. A standardized proforma was utilized to collect population characteristics and medical records, such as age, family history of breast cancer, tumor stage, histological type, hormone receptor status, and previous treatment. Each patient gave blood samples for genetic examination for BRCA1 and BRCA2 variants.

The obtained data was analyzed using SPSS version 23 to assess the incidence of BRCA1 and BRCA2 variations in the study population. Measures of central tendency and variability, such as means and standard deviations, were utilized for continuous variables like age and disease duration. The categorical variables, such as sex, family history of breast and ovarian cancer, histological type, BRCA mutations, and outcome, were given in frequency and proportion. The study's effect modifiers were stratified and compared to the primary outcome, which was either age or gender, using the Chi-squared test. Statistical significance is determined using a two-sidedP-value of < 0.05.

RESULTS

The table below presents a demographic and clinical profile of breast cancer patients, reflecting a nearly balanced age distribution, with a slight majority being younger than 45 years.

Predominantly, participants are of Sindhi ethnicity, with a significant portion having achieved college-level education or higher. A minimal presence of a family history of breast cancer is noted. Clinically, the majority of patients are at stage 3 of tumor development, with invasive ductal carcinoma being the most common histological type.

Three patients (10%) out of the whole study population have BRCA1 or BRCA2 mutations; the other 27 patients (90%) do not have these mutations. This study focuses on patients with breast cancer. Regarding hormone receptor status, the distribution is as follows: ER-positive in 2 patients (6.7%), HER2-positive in 7 patients (23.3%), Triple-negative in 4 patients (13.3%), ER-

PR-HER2-Positive in 8 patients (26.7%), and ER-PR-positive in 9 patients (30%). This data highlights the genetic and molecular diversity within the breast cancer patient cohort, indicatingvaried therapeutic targets and prognostic implications.

Table 1: Demographics of participants

Variable	N (%)
Age	
< 45 years	16 (53.3%)
> 45 years	14 (46.7%)
Ethnicity	
Sindhi	6 (20.0%)
Urdu Speaking	23 (76.7%)
Punjabi	1 (3.3%)
Education	
Less than high school	14 (46.7%)
Higher Schol Graduate	11 (36.7%)
College	4 (13.3%)
College Graduate	1 (3.3%)
Family History	
Yes	3 (10%)
No	27 (90%)

Table 2: Clinical information of participants

Variable	N (%)
Tumor Stage	
Stage 2	7 (23.3%)
Stage 3	17 (56.7%)
Stage 4	6 (20%)
Histological Type	
Ductal carcinoma	5 (16.7%)
Invasive ductal carcinoma	21 (70%)
Invasive lobular carcinoma	4 (13.3%)
Hormone Receptor Status	
ER-positive	2 (6.7%)
HER2-positive	7 (23.3%)
Triple-negative	4 (13.3%)
ER-PR-HER2-Positive	8 (26.7%)
ER-PR-positive	9 (30.0%)

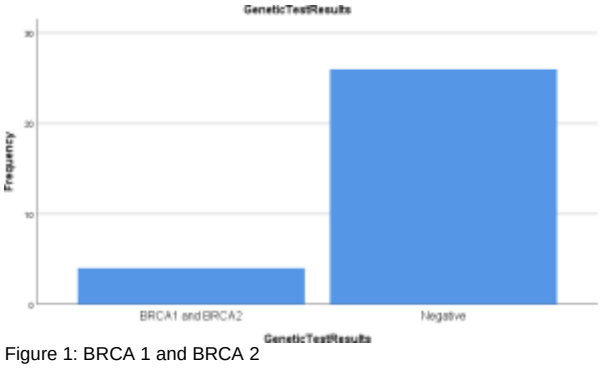

Figure 1: BRCA 1 and BRCA 2

For age groups, the OR was 4.333 (p=0.209) for individuals aged 26-45 years. Educational status showed varying ORs, with a significant association in college graduates (OR: 5.821, p=0.000). Family history demonstrated no significant association (p=0.433). Ethnicity revealed significant associations for Urdu Speaking (OR: 2.106, p=0.020), Sindhi (OR: 4.747, p=0.097), and Punjabi (OR: 3.508, p=0.005) groups (Table 3).

Table 3: Association of demographic variable with BRCA1 and BRCA2 mutations

Variables	BRCA1 & BRCA2		OR (95% CI)	P-Value
	Positive (n=5)	Negative (n=25)		
Age Group				
26 – 45 years	4 (25.0)	12 (75.0)	4.333 (0.423---44.428)	0.209
>45 years	1 (7.1)	13 (92.9)		
Educational Status				
Less than high school	1 (7.1)	13 (92.9)	2.889 (0.226---36.868)	0.414
Higher Schol Graduate	2 (18.2)	9 (81.8)	0.346 (0.027---4.418)	0.396
College	1 (25.0)	3 (75.0)	0.231 (0.011---4.838)	0.345
College Graduate	1 (100.0)	0 (0.0)	5.821 (2.77---12.20)	0.000
Family History				
Yes	1 (33.3)	2 (66.7)	2.875 (0.208---39.680)	0.433
No	4 (14.8)	23 (85.2)		
Ethnicity				
Urdu Speaking	5 (21.7)	18 (78.3)	2.106 (0.000---21.362)	0.020
Sindhi	0 (0.0)	6 (100.0)	4.747 (0.000---17.213)	0.097
Punjabi	0 (0.0.)	1 (100.0)	3.508 (1.508---35.082)	0.005

Values are presented as frequency (%)
C.I. (Class Interval), OR (Odd Ratio)

There were significant associations in Stage 2 (OR: 1.208, p=0.000), Stage 3 (OR: 8.272, p=0.096), and Stage 4 (OR: 1.103, p=0.220). Histological type showed significant associations with Ductal Carcinoma (OR: 1.546, p=0.023), Invasive Lobular Carcinoma (OR: 4.202, p=0.739), and Invasive Ductal Carcinoma (OR: 6.468, p=0.013). Hormone receptor status associations were observed in ER-Positive (OR: 6.108, p=0.178) and HER2-Positive (OR: 2.00, p=0.433). Additionally, ER-Positive (OR: 3.274, p=0.000) and HER2-Positive (OR: 2.368, p=0.796) status exhibited associations (Table 4).

Table 4: Association of clinical variable with BRCA1 and BRCA2 mutations

Variables	BRCA1 & BRCA2		OR (95% CI)	P-Value
	Positive (n=5)	Negative (n=25)		
Tumor Stage				
Stage 2	0 (0.0)	7 (100.0)	1.208 (0.371---10.658)	0.000
Stage 3	2 (11.8)	15 (88.2)	8.272 (8.272---16.356)	0.096
Stage 4	3 (50.0)	3 (50.0)	1.103 (0.013---11.935)	0.220
Histological Type				
Ductal Carcinoma	0 (0.0)	5 (100.0)	1.546 (0.000---12.163)	0.023
Invasive Lobular Carcinoma	5 (23.8)	16 (76.2)	4.202 (0.261---6.150)	0.739
Invasive Ductal Carcinoma	0 (0.0)	4 (100.0)	6.468 (0.000---13.852)	0.013
Harmone Receptor Status				
ER-Positive	1 (33.3)	2 (66.7)	6.108 (0.073---25.658)	0.178
HER2-Psoitive	4 (14.8)	23 (85.2)	2.00 (0.181---22.056)	0.433
ER-Positive	1 (33.3)	2 (66.7)	3.274 (0.296---36.109)	0.000
HER2-Psoitive	4 (14.8)	23 (85.2)	2.368 (0.000---24.149)	0.796
ER-Positive	1 (33.3)	2 (66.7)	1.637 (0.359---16.286)	0.178

Values are presented as frequency (%)
C.I. (Class Interval), OR (Odd Ratio)

DISCUSSION

In this prospective observational research, we sought to determine the occurrence of BRCA1 and BRCA2 mutations in the Pakistani populace. The main findings of the study indicate the detection of BRCA1 and BRCA2 amongst three individuals, making up 10% of the study population. The remaining 27 patients (90%) did not exhibit these mutations. From a clinical perspective, plenty of patients are detected at stage 3 of tumor development (56.7%), and invasive ductal carcinoma is the most common histological

type (70%). The findings of our study reveal that the majority of the patients (90%), did not have any familial predisposition of developing breast cancer.

A systematic review gave a thorough assessment of the global incidence of BRCA mutations among patients suffering from breast cancer, encompassing diverse populations globally.

Prevalence exhibited considerable variation across essential clinical and demographic subcategories as well as among different countries. Within triple-negative breast cancer (TNBC) cohorts, the incidence of germline BRCA variations varied between 9.3% and 15.4%, while among individuals with advanced breast carcinoma, it varied between 2.7% and 4.3%.[10] A second comprehensive review was carried out to look into the variety of BRCA1 and BRCA2 gene mutations found in female South Asian breast cancer patients. The South Asian population exhibits diverse genetic alterations in BRCA1 and BRCA2, varying across countries and ethnicities.[11]

Correspondingly, Jai Min Ryu et al conducted a study on Korean women which found that a total 131 Korean patients (13.1%) were found to have BRCA1/2 mutations, with 97 (9.7%) in BRCA1 and 35 (3.5%) in BRCA2. Recommendations indicated that Korean women diagnosed with triple-negative breast cancer (TNBC) at or before 60 years of age should undergo testing for BRCA1/2 mutations.[12]

According to a study in Pakistan on the incidence of BRCA1 and BRCA2 mutations in Pakistani population suffering from ovarian and breast cancer in 2006 revealed that among 176 patients, 30 (17%) were identified with deleterious germline mutations, containing seven in BRCA2 and 23 in BRCA1.[13] M Usman Rashid et al. carried out a thorough investigation in a different study to determine the frequency and range of BRCA1/2 germline mutations in the Pakistani population.[14] They came to the conclusion that, of 539 families, 133 (24.7%) had harmful mutations found in them, 110 of which were in BRCA1 and 23 of which were in BRCA2.

According to their findings, BRCA1 and BRCA2 variations are responsible for 12.5% of early- onset breast cancer cases in Pakistan, 20% of breast cancer cases are that of males, and 25% of instances of hereditary breast/ovarian cancer in Pakistan. According to the study, genetic testing, particularly a comprehensive panel covering 21 recurrent BRCA1/2 mutations, should be carried out on correctly chosen individuals and their families in Pakistan. Similar studies were found to show similar association and the need to conduct gene testing. [15,16,17]

Uzma Shamsi et al, conducted a study on the frequency and length of delays in seeking medical consultation which concluded with similar results to our study with stage III of BC being the most common stage at diagnosis and the majority of the cases were histopathologically identifiedas invasive ductal carcinoma (80%).[18]

The study's strength lies in its contribution to the limited existing research, providing valuable insights with a focus on the local context. However, the study's shortcomings include the fact that the patients were enrolled at a single tertiary care centre in Karachi, which may have resulted in selection bias. It is worth noting that families from Sindhi ethnic groups are overrepresented, which may lead to an overabundance of mutations in these groups.

Our recommendation is to investigate the clinical and demographic characteristics of BC carriers, as it is critical to improve our understanding of the scope of BRCA1/BRCA2 mutations, which will aid medical professionals provide accurate familial counseling with efficient cancer surveillance to women who have been afflicted with or are in a greater danger of getting breast cancer. More extensive, widely documented epidemiological investigations of BRCA prevalencein the local setting are required.

CONCLUSION

Our investigation into the incidence of BRCA1 and BRCA2 mutations among Pakistanis suffering from breast carcinoma highlights a lower mutation incidence compared to global averages. This finding underscores the potential variability in genetic predisposition to breast cancer across different populations and suggests the need for region-specific genetic screening strategies. Despite the small sample size, the presence of BRCA mutations in 10% of patients emphasizes the critical importance of genetic testing in the clinical management and risk assessment of breast carcinoma in Pakistan. It also points to the necessity of broader genetic studies to fully understand the diversity of mutations that contribute to breast cancer in this region. The subsequent research should involve a broader and more diverse cohort to offer a more complete genetic landscape of breast cancer in Pakistan. This study contributes valuable data to the limited research on breast carcinoma genetics in Pakistan, offering a foundation for more thorough studies as well as informing clinical practices and healthcare policies tailored to the genetic profiles of the Pakistani population.

REFERENCES

1. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science.1994;266(5182):66-71.
2. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995;378(6559):789-92.
3. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1- mutation carriers. Breast Cancer Linkage Consortium. Lancet. 1994;343(8899):692-5.
4. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72(5):1117-30.
5. Gomes MC, Costa MM, Borojevic R, Monteiro AN, Vieira R, Koifman S, et al. Prevalence of BRCA1 and BRCA2 mutations in breast cancer patients from Brazil. Breast Cancer Res Treat. 2007;103(3):349-53.
6. Ferla R, Calò V, Cascio S, Rinaldi G, Badalamenti G, Carreca I, et al. Founder mutations in BRCA1 and BRCA2 genes. Ann Oncol. 2007;18 Suppl 6:vi93-8.
7. Molina-Montes E, Pérez-Nevot B, Pollán M, Sánchez-Cantalejo E, Espín J, Sánchez MJ. Cumulative risk of second primary contralateral breast cancer in BRCA1/BRCA2 mutation carriers with a first breast cancer: a systematic review and meta-analysis. The Breast. 2014 Dec 1;23(6):721-42.
8. De Leon Matsuda ML, Liede A, Kwan E, Mapua CA, Cutiongco EM, Tan A, Borg Å, Narod SA. BRCA1 and BRCA2 mutations among breast cancer patients from the Philippines. International journal of cancer. 2002 Apr 1;98(4):596-603.
9. Baretta Z, Mocellin S, Goldin E, Olopade OI, Huo D. Effect of BRCA germline mutations on breast cancer prognosis: A systematic review and meta-analysis. Medicine (Baltimore). 2016 Oct;95(40):e4975. doi: 10.1097/MD.0000000000004975. PMID: 27749552; PMCID: PMC5059054.
10. Armstrong N, Ryder S, Forbes C, Ross J, Quek RG. A systematic review of the international prevalence of BRCA mutation in breast cancer. Clinical epidemiology. 2019Jul 11:543-61.
11. Kharel S, Shrestha S, Yadav S, Shakya P, Baidya S, Hirachan S. BRCA1/BRCA2 mutation spectrum analysis in South Asia: a systematic review. J Int Med Res. 2022 Jan;50(1):3000605211070757. doi: 10.1177/03000605211070757. PMID: 35000471;PMCID: PMC8753086.
12. Ryu JM, Choi HJ, Kim I, Nam SJ, Kim SW, Yu J, Lee SK, Choi DH, Park YH, Kim JW, Seo JS. Prevalence and oncologic outcomes of BRCA 1/2 mutations in unselected triple- negative breast cancer patients in Korea. Breast Cancer Research and Treatment. 2019 Jan 30;173:385-95.
13. Rashid MU, Zaidi A, Torres D, Sultan F, Benner A, Naqvi B, Shakoori AR, Seidel Renkert A, Farooq H, Narod S, Amin A. Prevalence of BRCA1 and BRCA2 mutations in Pakistani breast and ovarian cancer patients. International journal of cancer.2006 Dec 15;119(12):2832-9.
14. Rashid MU, Muhammad N, Naeemi H, Khan FA, Hassan M, Faisal S, Gull S, Amin A, Loya A, Hamann U. Spectrum and prevalence of BRCA1/2 germline mutations in Pakistani breast cancer patients: results from a large comprehensive study. Hereditary cancer in clinical practice. 2019 Dec;17:1-3.
15. Akter H, Sultana N, Martuza N, Siddiqua A, Dity NJ, Rahaman MA, Samara B, Sayeed A, Basiruzzaman M, Rahman MM, Rashidul Hoq

M. Novel mutations in actionable breast cancer genes by targeted sequencing in an ethnically homogenous cohort. BMC medical genetics. 2019 Dec;20:1-8.

16. Lee DS, Yoon SY, Looi LM, Kang P, Kang IN, Sivanandan K, Ariffin H, Thong MK, Chin KF, Mohd Taib NA, Yip CH. Comparable frequency of BRCA1, BRCA2 and TP53 germline mutations in a multi-ethnic Asian cohort suggests TP53 screening should be offered together with BRCA1/2 screening to early-onset breast cancer patients. Breast Cancer Research. 2012 Apr;14(2):1-8.
17. Jakimovska M, Maleva Kostovska I, Popovska-Jankovic K, Kubelka-Sabit K, Karadjozov M, Stojanovska L, Arsovski A, Smichkoska S, Lazarova E, Jakimovska Dimitrovska M, Plaseska-Karanfilska D. BRCA1 and BRCA2 germline variants in breast cancer patients from the Republic of Macedonia. Breast Cancer Research and Treatment. 2018 Apr;168:745-53.
18. Shamsi U, Khan S, Azam I, Usman S, Maqbool A, Gill T, Iqbal R, Callen D. Patient delay in breast cancer diagnosis in two hospitals in Karachi, Pakistan: preventive and life-saving measures needed. JCO Global Oncology. 2020 Jun;6:873-83.