

Incidence of BRCA Positivity in Young Pakistani Women with Breast Cancer

Ayesha Ehsan, Vishal Farid Raza, Aun Jamal, Hassan Ahmad, Haroon Anjum*, Afroz Mushtaq Khattak

Department of Surgical Oncology, Shaukat Khanum Memorial Cancer Hospital, and Research Center, Lahore Pakistan, *Department of General Surgery, Bhatti International Teaching Hospital, Kasur Pakistan

ABSTRACT

Objective: To determine the incidence of BRCA positivity in young Pakistani women with Breast Cancer at our institution.

Study Design: Retrospective Chart Review.

Place and Duration of Study: Shaukat Khanum Memorial Cancer Hospital and Research Center, Pakistan from Jan 2014 to Jan 2024.

Methodology: Three hundred and forty-nine patients were included in this retrospective chart review. Frequency of BRCA positivity was enumerated across different age groups. Post-stratification chi-square analysis for BRCA positivity with family history, inflammatory breast cancer, grade of tumor, stage 4 at presentation, bilateral breast cancer and tumor biology was done.

Results: 31(8.9%) of patients were BRCA positive and the most common variant was c.3770_3771delAG BRCA 1 mutation in 4 (12.9%) of patients. BRCA positivity was greater in younger women aged 45 or less with 23 (6.59%) women. A positive family history ($P=0.003$) and bilateral breast cancer ($P=0.003$) was associated with BRCA positivity. 51.6% of BRCA positive patients had Triple-Negative Disease.

Conclusion: BRCA mutations in Pakistani women population may be the underlying cause of greater proportion of younger women presenting with cancer in the country. Genetic counseling, screening criteria and population-specific guidelines for breast cancer in light of this data is the need of the hour.

Keywords: BRCA; Breast Cancer; Pakistan; Early Breast Cancer; High Risk Group; Young women.

How to Cite This Article: Ehsan A, Raza VF, Jamal A, Ahmad H, Anjum H, Khattak AM. Incidence of BRCA Positivity in Young Pakistani Women with Breast Cancer. *Pak Armed Forces Med J* 2026; 76(5): 720-724. DOI: <https://doi.org/10.51253/pafmj.v76i5.12316>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

The prevalence of breast cancer is the highest in Asian countries like India and Pakistan. It has been reported that approximately 178,388 new breast cancer cases were registered in Pakistan in 2020.¹ BRCA1- and BRCA2-associated hereditary breast and ovarian cancer (HBOC) is characterized by an increased risk for female and male breast cancer, ovarian cancer (including fallopian tube and primary peritoneal cancers), and to a lesser extent other cancers such as prostate cancer, pancreatic cancer, and melanoma.² It is estimated that 55%–72% of women who inherit a harmful BRCA1 variant and 45%–69% of women who inherit a harmful BRCA2 variant will develop breast cancer by 70–80 years of age.^{3–5} Of all breast cancers only between 1–3% of breast cancers will be BRCA positive.⁶ Younger women may be at a higher risk for BRCA positivity thus routine testing is indicated in women younger than 35 years of age and one such study showed that out of 54 women 6 were BRCA positive i.e 11%.⁷ Similarly a web based survey found

that of women who were eligible for BRCA testing 26% had undergone testing and 24% of these were positive for a mutation.⁸ A case report from Pakistan found that a 15 year old girl was BRCA positive with stage 2 breast cancer that was clinically mimicking a Fibroadenoma.⁹ Studies done in Pakistan have pointed to estimates that upto 7% of cancers maybe BRCA positive which is higher than the expected international data and may account for the burden of disease in the region.¹⁰ This higher proportion of younger women diagnosed with breast cancer in South Asia is the rationale for conducting this study as it merits BRCA testing to assess whether the incidence is similar to the west or higher to fashion treatment and screening in this special population of women.

METHODOLOGY

This retrospective chart review was done from January 2014 till January 2024 after ethical approval was with Approval Number (EX-09-01-24-01). 349 patients tested for BRCA were enrolled by non-probability consecutive sampling technique. Minimum sample size estimate of 45 was calculated using OpenEpi and a 3%⁶ incidence of BRCA positive breast cancer.

Correspondence: Dr Vishal Farid Raza, Department of Surgical Oncology, SKMCH, and Research Center, Lahore Pakistan
Received: 05 Jun 2024; revision received: 21 Jul 2024; accepted: 22 Jul 2024

Inclusion Criteria: Female patients of any age with breast cancer treated at Shaukat Khanum hospital and tested for BRCA gene mutations.

Exclusion Criteria: Patients with incomplete charts were excluded.

Data was analyzed by using IBM Statistical Package for Social Sciences version 24.0. Counts with percentages were given for baseline characteristics and BRCA mutations and positivity. Counts and percentages were given of women who were BRCA positive stratified by age into 4 groups i.e women aged less 35 years, 36 to 39 years, 40 to 45 years and above 45 years. Pearson Chi Square test was applied to explore inferential statistics. The p -value of ≤ 0.05 was set as the cut-off value for significance. Risk ratios were reported for women in each age strata to develop BRCA positive breast cancer.

RESULTS

Three hundred and forty nine ($n=349$) women tested for BRCA had their charts reviewed for the current study. 81(23.2%) of respondents had a family history of cancer of which 128(36.7%) had a family history of breast cancer. Patients identified between 1 to 4 first or second-degree relatives who had breast cancer which was a mean 0.52 ± 0.81 relatives with breast cancer. Shapiro-Wilk test was used to assess normality of data and was found to be not normally distributed ($p=0.001$.) Figure-1 shows the distribution of BRCA positive versus BRCA negative patients with a positive family history of breast cancer. BRCA positive patients relatively had a denser family history of breast cancer.

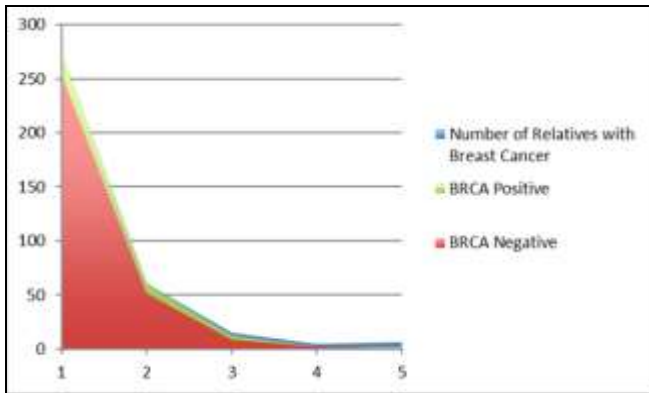


Figure-1: Distribution of Family History of Breast Cancer Between BRCA Positive and Negative Participants

Patients were identified who had a personal history of cancer besides breast cancer. 1(0.3%) had

uterine cancer, 1(0.3%) had leukemia and 6(1.7%) had ovarian cancer. None of these patients were BRCA positive. Of the patients 337(96.6%) had invasive ductal carcinoma while 12(3.4%) has invasive lobular carcinoma. 18(5.2%) patients had inflammatory breast carcinoma. 140(40.1%) of tumors were grade 2 while 208(59.6%) were grade 3. 36(10.3%) had bilateral breast cancer and 23(6.6%) had metastatic or stage 4 disease at presentation. 60(17.2%) had stage 3 disease at presentation, 243(69.6%) had stage 2 disease and 23(6.6%) had stage 1 disease. 61(17.5%) patients had Her2Neu positive disease disease, 128(36.7%) had PR positivity and 180(51.6%) had ER positivity. 137(39.3%) had Luminal A disease, 49(14%) had luminal B disease, 35(10%) had Her2Neu enriched disease and 128(36.7%) had triple negative disease. 10(2.9%) of patients had a recurrence on follow up. Frequencies of BRCA positivity and mutant variants identified in each subject are enumerated in Table-I.

Table-I: Frequency of BRCA Positivity And BRCA Variants Identified ($n=31$)

Variables	Frequency (%)
BRCA Positive	31(8.9%)
BRCA 1	31(8.9%)
c.3770_3771delAG	4(12.9%)
3598C>T	2(6.45%)
c.4485-1G>A	3(9.67%)
Exon 1-2 deletion	2(6.45%)
c.685deT	2(6.45%)
c.66dupA	1(3.22%)
c.57703771	2(6.45%)
c.5503c>T	2(6.45%)
c.5278-1G>C	2(6.45%)
c.5074+1G>A	1(3.22%)
c.4508CA	1(3.22%)
5035de1c	1(3.22%)
c.1793T>G	3(9.67%)
c.2269de1G	3(9.67%)
c.2340-2343	1(3.22%)
c.35980>5	1(3.22%)

BRCA positivity was tested to find association with different risk factors shown in Table-II.

DISCUSSION

BRCA 1 and 2 mutations may occur either as germline or somatic.¹¹⁻¹³ Studies have shown that breast cancer in younger women that is aged less than forty belies between 10 to 13%.¹⁴ Some series however show a much higher rate with upto 31% of cases occurring in younger women in South Asia.^{12,15} Similarly, a study comparing breast cancer in women aged less than 40 in Pakistani to the U.S found that 5%

of younger women are diagnosed with breast cancer in the U.S while upto 27% of younger women receive the diagnosis in Pakistan.¹³ A meta-analysis found that germline mutations of BRCA 1 may have an incidence of 7.8% in breast cancer, 5.7% for BRCA 2 and for somatic mutations the incidence was 3.4% and 2.7% for BRCA 1 and BRCA 216. Similarly it was found in one systematic review that BRCA 1 mutations were present in 10% of women and it was associated with the risk of developing triple negative breast cancer i.e 30% of women with BRCA 1 positivity had TNBC. However, this association was not seen with BRCA 2 positivity.¹⁷ In our study we found a similar rate of BRCA 1 positivity and interestingly more than 50% of women in our cohort who were BRCA positive had triple negative disease thus strengthening the association shown in this systematic review. Studies have found different incidences of BRCA positivity in young women however it is uniform that the age of diagnosis of Breast cancer occurs at a younger age with the mutation which was also seen in our study where more than 2/3rd of patients were younger women. A study in Mexican women found that out of 190 women 23.2% were BRCA positive. Of these only one had a BRCA 2 mutation the rest were all BRCA 1. For women diagnosed before age 40 30.3% had BRCA positivity while older women had 18.3% positivity. This is also reflected in our study where older women were less likely to be carrying a mutation. Women with BRCA mutations had a mean age of diagnosis of 38 as compared to 41 years for non-carriers. In our population however mean age of diagnosis for BRCA carriers was 43 as compared to 38.4 for non-carriers ($p=0.01$). 89% of the women had recurrent mutations that is present in the family tree-similarly 45% of women with BRCA mutations had a positive family history.¹⁸ This is similar to our study where 61.2% of women with BRCA mutations had a positive family history of breast cancer however none of our BRCA mutation carriers had a personal history of ovarian or any other carcinoma which may be a reflection of germline BRCA testing only in our study and not of somatic mutations.⁸ Women who had a history of any other cancer were BRCA negative. However, in contrast; pooled data has shown that women aged younger than 40 are more likely to not have a family history of breast cancer in upto 89% of cases nor germline mutations in 95% of cases-thus the significance of BRCA positivity incidence in younger women remains to be determined.¹⁹ Another study conducted in women aged less than 40 with triple

negative breast cancer found that 11% were BRCA positive with one woman harbouring a BRCA 2 gene mutation. In our study 16 women out of 31 who were BRCA positive had triple negative subtype which is significant. Thus the literature continually shows that younger age and certain aggressive sub-types of breast cancer may be more likely to present with BRCA mutations even without significant family history.⁷ In a study of Korean women with breast cancer at age less than 40 years 15% were found to be BRCA positive.¹⁴ A meta-analysis done to find the BRCA positivity incidence in South Asian women found interesting results especially since the peak of breast cancer among this diaspora is at the age of 40 as compared to 60 years in Western counterparts. In Bangladesh 4.6% and 9.3% women were identified with BRCA 1 and 2 mutations. In India BRCA 1 mutations were identified in different studies varying from 2% to 52% however most studies identified incidence of positivity for BRCA in the range of 20-35%. For BRCA 2 incidence in India it ranged from 4% to 43% between different studies. In Pakistan the BRCA positivity ranged from 6.7% to 15% which is similar to our 8.9% incidence. In Sri Lankan female upto 23% of women with breast cancer were identified with BRCA mutations. The most comprehensive data was available from Indian authors. South Asian women with early onset breast cancer have ranges of BRCA positivity from 8% to 32%. This is interesting data as it reflects the higher BRCA positivity present in this diaspora including a higher percentage of younger onset breast cancer which may be associated.¹⁵ One of the limitations of our study was the lack of somatic BRCA mutation testing which may in part be able to explain the higher number of early-onset breast cancers with a larger proportion of triple negative disease in South Asian Women as was seen in our Pakistani women population. Another limitation of our study would be that as it is a high volume center for breast cancer with free of cost treatment from funding- stringent guidelines are in place as to the stage of disease accepted; thus a large cohort of our patients are younger women with early stage breast cancer. A reflective incidence of BRCA positivity in women with breast cancer in Pakistan can not be conferred from our data which can inherently be seen in our age distribution where more than two-thirds of the women are younger than 45 years of age. Thus our data can only reflect the incidence of BRCA positivity in younger women in Pakistan aged 45 or less. Data from Pakistan is lacking in terms of large

observational studies from which conclusions can be extrapolated. Our study is to the best of our knowledge the first of its kind from Pakistan with the largest cohort of women studied where BRCA positivity incidence and the different variant mutations have been identified and reported.

Table-II: Analysis of Risk Factors and Association With BRCA Positivity (n=31)

Risk Factor		BRCA		p-value
		Positive (n=31)	Negative (n=318)	
Family History	Positive	19(61.2%)	109(34.2%)	0.003*
	Negative	12(38.7%)	209(65.7%)	
Inflammatory Breast Cancer	Yes	2(6.5%)	16(5.0%)	0.73
	No	29(93.5%)	302(95.0%)	
Grade of Tumor	Grade 2	9(29.0%)	131(41.1%)	0.18
	Grade 3	22 (71.0%)	186(58.4%)	
Stage of Tumor	Stage 4	0(0.0%)	23(7.3%)	0.12
	All Other Stages	31(100.0%)	295(92.7%)	
Bilateral Breast Cancer	Yes	8(25.8%)	28(8.9%)	0.003*
	No	23(74.2%)	290(91.1%)	
Luminal A	Yes	10(32.3%)	127(39.9%)	0.40
	No	21(67.7%)	191(60.1%)	
Luminal B	Yes	1(3.2%)	48(15.1%)	0.06
	No	30(96.8%)	270(84.9%)	
Her2Neu Enriched	Yes	4(12.9%)	31(9.7%)	0.57
	No	27(87.1%)	287(90.3%)	
Triple Negative	Yes	16(51.6%)	112(35.2%)	0.07
	No	15(48.4%)	206(64.8%)	
Recurrence	Yes	1(3.2%)	9(2.8%)	0.95
	No	30 (96.8%)	309 (97.2%)	

LIMITATION OF STUDY

The retrospective nature of the study is a potential for introduction of bias along with non-inclusion of incomplete charts. This study focused on women aged 45 or younger however data of older women who had been tested for BRCA was included. However, due to limited resources the institution rarely tests for BRCA in women older than 45 unless there is a very strong family history thus older women may have been excluded who potentially carry the mutation. As only germline BRCA mutations were tested women carrying somatic mutations would have been missed from the study population. Variables such as environmental factors, lifestyle and detailed family history were not extensively controlled or analysed which may influence the conclusions that can be drawn. The study was conducted in a high-volume center with stringent guidelines preferring acceptance of early breast cancer in younger women due to treatment funding policies, potentially skewing the patient population towards younger women with early-stage breast cancer. Family testing of index patients was not done, limiting the ability to understand hereditary patterns and the impact of BRCA mutations within families. Although covering a decade, the study might still miss long-term trends or late-onset effects associated with BRCA mutations

as each patient was not followed for the same amount of time. While data stratification was performed, the limited sample size and retrospective nature might affect the robustness of post-stratification chi-square analyses.

CONCLUSION

BRCA mutations in Pakistani women population may be the underlying cause of greater proportion of younger women presenting with cancer in the country. Studies on somatic mutations in younger women in Pakistan are needed to strengthen this association. Luminal A and triple-negative breast cancer are the most common tumor biology seen in younger women with breast cancer and triple-negative breast cancer is more likely to be found with BRCA positive women in Pakistan. Genetic counseling, screening criteria and population-specific guidelines for breast cancer in Pakistani women in light of this data should be reformed.

Conflict of Interest: None.

Funding Source: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

AE & VFR: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AJ & HA: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

HA & AMK: Data acquisition, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Khan S, Jalees S, Jabeen Z, Khan M, Qadri RH, Adnan H, et al. Myths and Misconceptions of Breast Cancer in the Pakistani Population. *Cureus* 2023 ;15(6): 40086. <https://doi.org/10.7759/cureus.40086>
2. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. *GeneReviews*;1998.
3. Kuchenbaecker KB, Hopper JL, Barnes DR. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA* 2017; 317(23): 2402-2416. <https://doi.org/10.1001/jama.2017.7112>
4. Antoniou A, Pharoah PDP, Narod S. 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 Human Gen* 2003; 72(5): 1117-1130. <https://doi.org/10.1086/375033>
5. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol* 2007; 25(11): 1329-1333. <https://doi.org/10.1200/JCO.2006.09.1066>
6. Balmana J, Diez O, Rubio IT, Cardoso F. BRCA in breast cancer: ESMO Clinical Practice Guidelines. *Ann Oncol* 2011; 22: vi31-34. <https://doi.org/10.1093/annonc/mdr373>

7. Young S, Pilarski RT, Donenberg T. The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. *BMC Cancer* 2009; 9: 86. <https://doi.org/10.1186/1471-2407-9-86>
8. Ruddy KJ, Gelber S, Shin J, Garber JE, Rosenberg R, Przypysny M, et al. Genetic testing in young women with breast cancer: results from a Web-based survey. *Ann Oncol* 2010; 21(4): 741-747. <https://doi.org/10.1093/annonc/mdp355>
9. Vohra LM, Ali D, Hashmi SA, Angez M. Breast cancer in a teenage girl with BRCA mutation: a case report from a low middle-income country. *Int J Surg Case Rep* 2022; 98: 107513. <https://doi.org/10.1016/j.ijscr.2022.107513>
10. Liede A, Malik IA, Aziz Z, De los Rios P, Kwan E, et al. Contribution of BRCA1 and BRCA2 mutations to breast and ovarian cancer in Pakistan. *Am J Human Gene* 2002; 71(3): 595-606. <https://doi.org/10.1086/342506>
11. Bonadio RC, Moreira OA, Testa L. Breast cancer trends in women younger than 40 years in Brazil. *Cancer Epidemiol* 2022 ;78: 102139. <https://doi.org/10.1016/j.canep.2022.102139>
12. Thangjam S, Laishram RS, Debnath K. Breast carcinoma in young females below the age of 40 years: A histopathological perspective. *S Asian J Cancer* 2014; 3(02): 97-100. <https://doi.org/10.4103/2278-330X.130441>
13. Zeeshan S, Ali B, Ahmad K, Chagpar AB, Sattar AK. Clinicopathological features of young versus older patients with breast cancer at a single Pakistani institution and a comparison with a national US database. *J Glob Oncol* 2019; 5: 1-6. <https://doi.org/10.1200/JGO.18.00208>
14. Choi DH, Lee MH, Bale AE, Carter D, Haffty BG. Incidence of BRCA1 and BRCA2 mutations in young Korean breast cancer patients. *J Clin Oncol* 2004; 22(9): 1638-1645. <https://doi.org/10.1200/JCO.2004.04.179>
15. 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; 50(1): 03000605211070757. <https://doi.org/10.1177/03000605211070757>
16. Shao C, Wan J, Lam FC, Tang H, Marley AR, Song Y et al. A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. *Environment Molecul Mutagenesis* 2022; 63(6): 308-816. <https://doi.org/10.1002/em.22505>
17. Tun NM, Villani GM, Ong K. Risk of having BRCA mutations in women with triple-negative breast cancer: A systematic review and meta-analysis. *J Clin Oncol* 2011; 29(27_suppl): 160-. <https://doi.org/10.1111/cge.12270>
18. Villarreal-Garza C, Weitzel JN, Llacuachqui M, Sifuentes E, Magallanes-Hoyos MC, Gallardo L, Alvarez-Gómez RM, Herzog J, Castillo D, Royer R, Akbari M. The prevalence of BRCA1 and BRCA2 mutations among young Mexican women with triple-negative breast cancer. *Breast Cancer Res Treat* 2015; 150: 389-94. <https://doi.org/10.1007/s10549-015-3312-8>
19. Gao Y, Samreen N, Heller SL. Non-BRCA early-onset breast cancer in young women. *Radiographics* 2022; 42(1): 5-22. <https://doi.org/10.1148/rg.210109>