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# Prevalence and Clinical Implications of *BRCA1* and *BRCA2* Mutations in Breast and Ovarian Cancer among Pakistani Women

Tahrim Zafar[1], Zeeshan Asghar[1], Urooj Liaqat[1], Saira Zafar[2], Areeba Khan[1], Muqadas Naseer Ahmed[3]

1. *BS MLT, University of Sialkot, Sialkot, Pakistan*
2. *BS MLT, Islam Medical and Dental College Sialkot, Sialkot, Pakistan*
3. *BS MLT, Imran Idrees Institute of Rehabilitation Sciences, Sialkot, Pakistan*
4. *Corresponding Author: Tahrim Zafar (tahreemzafar7@gmail.com)*

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## Abstract

*Introduction:* Major causes of hereditary breast and ovarian cancers are mutations in the *BRCA1* and *BRCA2* genes, especially affecting cancer type, onset, and prognosis.

*Objective:* To investigate the frequency and clinical correlations of *BRCA1* and *BRCA2* mutations among breast and ovarian cancer patients, as well as individuals with strong family histories, in a Pakistani population.

*Methodology:* This cross-sectional study was conducted at the Department of Medical Laboratory Technology, University of Sialkot, from January 2024 to December 2024. Using a practical sampling technique, 168 female participants—including those with a substantial family history and diagnosed breast and ovarian cancer sufferers—were gathered. Blood or tissue samples were first stripped of DNA, then subjected to PCR and sequencing to identify *BRCA1* and *BRCA2* mutations. SPSS version 25 was used to examine data; significance was defined at p 0.05.

*Results:* Among breast cancer patients, 17.65% had *BRCA1* and 11.76% had *BRCA2* mutations. In ovarian cancer patients (n=43), 25.58% had *BRCA1* and 18.60% had *BRCA2* mutations. *BRCA1* mutations were more frequent in younger age groups (25.00% in 18–30 years), and were significantly associated with triple-negative tumors (53.13%). *BRCA2* mutations were more often found in hormone receptor-positive tumors (50.00%). A strong family history of breast cancer was observed in over 60% of BRCA mutation carriers.

*Conclusion:* *BRCA1* and *BRCA2* mutations are prevalent in Pakistani breast and ovarian cancer patients and are closely linked to age at diagnosis, tumor subtype, and family history.

*Keywords:* *BRCA1*, *BRCA2*, breast cancer, ovarian cancer, genetic mutations, Pakistan, tumor subtypes, hereditary cancer.

## Introduction

Two of the most common and devastating diseases afflicting women worldwide still are breast and ovarian ones [1]. Although lifestyle and environmental elements help to shape them, a good number of malignant tumors have inherited genetic abnormalities [2]. Among the most investigated genetic causes are the *BRCA1* and *BRCA2* genes, whose changes have been strongly linked to raised sensitivity to both ovarian and breast malignancies [3]. Mostly by homologous recombination, these tumor suppressor genes repair double-stranded DNA breaks, hence preserving genomic stability [4]. Normal functioning *BRCA1* and *BRCA2* assist stop the accumulation of mutations that can cause tumors [5].

Mutations in *BRCA1* and *BRCA2* can throw off this protective mechanism, increasing early-onset cancer risk and usually affecting tumor aggressiveness and treatment responsiveness [6,7]. Genetic screening and counseling are therefore absolutely vital components of modern oncology since carriers of deleterious BRCA mutations have a far higher lifetime risk of getting breast and ovarian cancers than non-carriers. Recent years have seen developments in molecular biology and sequencing technology that have broadened our knowledge of how particular mutations in these genes affect cancer pathogenesis [9,10]. More individualized methods to cancer prevention, surveillance, and treatment—including preventative procedures and tailored medicines like PARP inhibitors—have been made possible by these discoveries [11].

Notwithstanding these developments, factors including mutation type, position within the gene, and interaction with other genetic or environmental modifiers continue to cause great variation in cancer risk among BRCA mutation carriers. Deeper research of the molecular activities, mutation patterns, and pathways affected by *BRCA1* and *BRCA2* mutations may help one to understand their biological and clinical repercussions. Refining risk assessment algorithms and enhancing results for people at high genetic risk depend on such knowledge.

### Research Objective

The objective of study was to investigate the molecular mechanisms by which *BRCA1* and *BRCA2* mutations contributed to the initiation and progression of breast and ovarian cancer, with an emphasis on genetic variability, mutation-specific effects, and implications for personalized medicine.

## Materials and Methods

### Study Design and Setting

This cross-sectional study was conducted at the Department of Medical Laboratory Technology, University of Sialkot, from January 2024 to December 2024. The study population consisted of female patients with histologically confirmed breast and/or ovarian cancer who were referred by oncologists from affiliated hospitals and outpatient oncology clinics within the Sialkot region. This was a single-center study. The University of Sialkot was chosen as the study setting due to its central role in the regional healthcare network and its access to a diverse patient population, reflecting the local burden of *BRCA1* and *BRCA2*-related hereditary cancers.

### Inclusion and Exclusion Criteria

Patients were included if they were female, aged 18 years or older, with a histologically confirmed diagnosis of primary breast and/or ovarian cancer based on pathology reports, and had a strong family history of cancer—defined as having at least two or more first-degree relatives (parents, siblings, or children) diagnosed with breast, ovarian, or other BRCA-associated cancers. Only patients of Pakistani ethnic background were included, due to the known regional variability in BRCA mutation prevalence. Pedigree analysis was performed to evaluate familial cancer history and to identify potential hereditary patterns of BRCA mutations. Exclusion criteria included patients with metastatic or recurrent disease, a prior history of other malignancies, incomplete medical or family history records, or those who did not provide informed consent**.**

### Sample Size

A total of 168 participants were recruited using a convenient sampling technique. The sample included both cancer patients and individuals with a significant family history of breast or ovarian cancer. The sample size was determined based on feasibility within the given study duration and available resources.

### Data Collection

Data collection involved retrieving clinical, pathological, and genetic data through structured face-to-face interviews conducted by trained medical technologists using a validated questionnaire, along with a review of hospital records. Information collected included demographic details, personal and family history of breast and ovarian cancer, reproductive history, lifestyle factors, and pedigree analysis to assess familial patterns of cancer. Tumor characteristics such as histological subtype, tumor grade, and receptor status (ER, PR, HER2) were confirmed via pathology reports. Genetic testing for *BRCA1* and *BRCA2* mutations involved amplification of known hotspot regions and commonly implicated exons using multiplex PCR, followed by Sanger sequencing. Variants of uncertain significance (VUS) were recorded but excluded from the primary mutation analysis.

### Statistical Analysis

SPSS version 25 was used for data analysis. Clinical and demographic traits were gathered using descriptive statistics. Calculated were the frequency of *BRCA1* and *BRCA2* mutations. Chi-square tests were used to evaluate relationships between mutation status and clinical characteristics—e.g., age at diagnosis, cancer type. Statistically significant p-value was <0.05.

### Ethical Approval

The study was approved by the Institutional Review Board (IRB) of the University of Sialkot IRB reference number: [1369/DMLT/UOS]. All participants provided written informed consent prior to enrollment. Genetic counseling was provided both before and after genetic testing to ensure participants understood the implications of testing, potential results, and available options. Data anonymization procedures were implemented to protect patient identity, and all genetic data were securely stored in compliance with institutional and ethical guidelines to ensure confidentiality and privacy.

## Results

Table 1 demonstrates the distribution of *BRCA1* and *BRCA2* mutations among persons with family history alone, ovarian cancer, and breast cancer. Of individuals with breast cancer, 70.59% had no alterations; 17.65% had *BRCA1* mutations and 11.76% had *BRCA2*. Of the forty-three cases of ovarian cancer, 25.58% had *BRCA1*, eighteen percent had *BRCA2*, and fifty-81% had no alterations. Of those with just a familial history (n=23), 78.26% showed no mutation; *BRCA1* and *BRCA2* mutations were discovered in 13.04% and 8.70% respectively.

**Table 1:** Distribution of Patients by Cancer Type and BRCA Mutation Status (n = 168)

| Cancer Type | *BRCA1* Mutation (n;%) | *BRCA2* Mutation (n;%) | No Mutation (n;%) |
|---|---|---|---|
| Breast Cancer | 18 (17.65%) | 12 (11.76%) | 72 (70.59%) |
| Ovarian Cancer | 11 (25.58%) | 8 (18.60%) | 24 (55.81%) |
| Family History | 3 (13.04%) | 2 (8.70%) | 18 (78.26%) |

| | | | |
|---|---|---|---|
| Only | | | |
| **Total** | **32 (19.05%)** | **22 (13.10%)** | **114 (67.86%)** |

Figure 1 shows BRCA mutation status broken out by age group. The 18–30 age group had the highest percentage of *BRCA1* mutations—25.00%; followed by 18.75% in the 31–45 age range, 17.65% in the 46–60 age range, and 16.00% in those over 60. Most often occurring in the >60 group (16.00%), followed by 14.06% in 31–45, 11.76% in 46–60, and 10.71% in the youngest group were *BRCA2* mutations. These numbers point to younger patients perhaps having more *BRCA1* mutations.

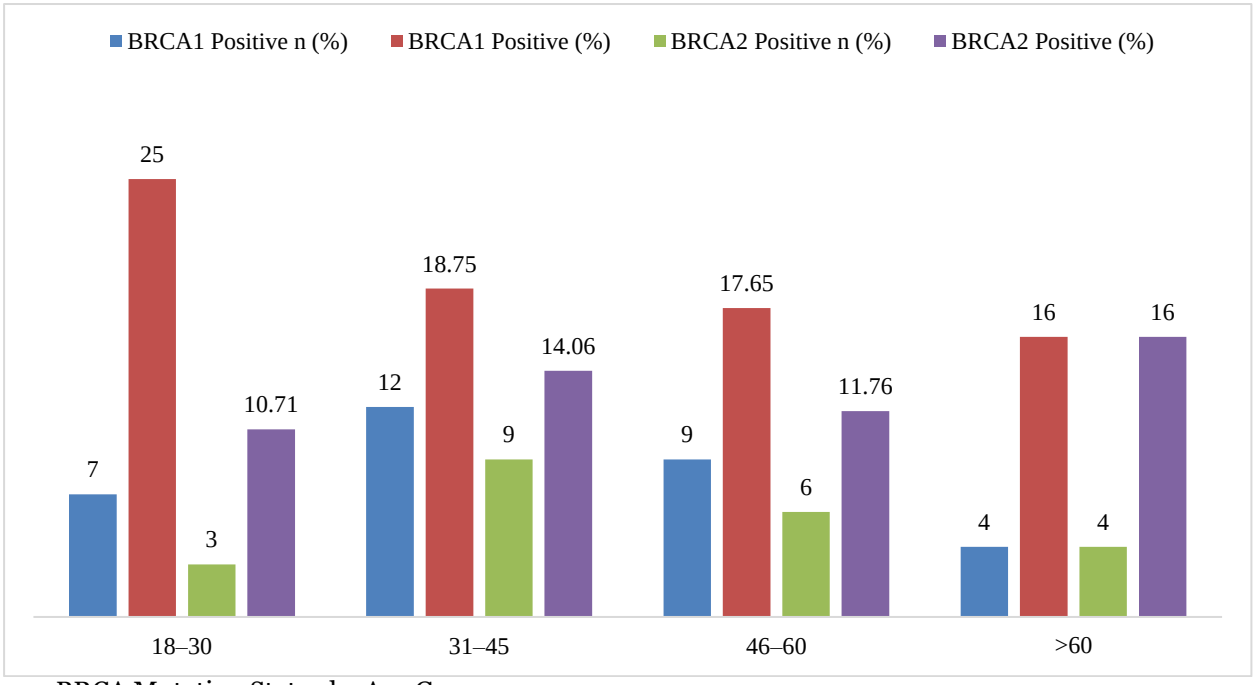


**Figure 1:** BRCA Mutation Status by Age Group

Figure 2 delineates tumor features in BRCA mutation-positive patients (n=54). In a cohort of *BRCA1* carriers (n=32), 53.13% exhibited triple-negative tumors, 25.00% were hormone receptor-positive, and 15.63% were HER2-positive. Among *BRCA2* carriers (n=22), 27.27% exhibited triple-negative tumors, 50.00% were hormone receptor-positive, and 13.64% were HER2-positive. This suggests that *BRCA1* mutations are more correlated with aggressive triple-negative tumors, whereas *BRCA2* mutations are more associated with hormone-sensitive variants.

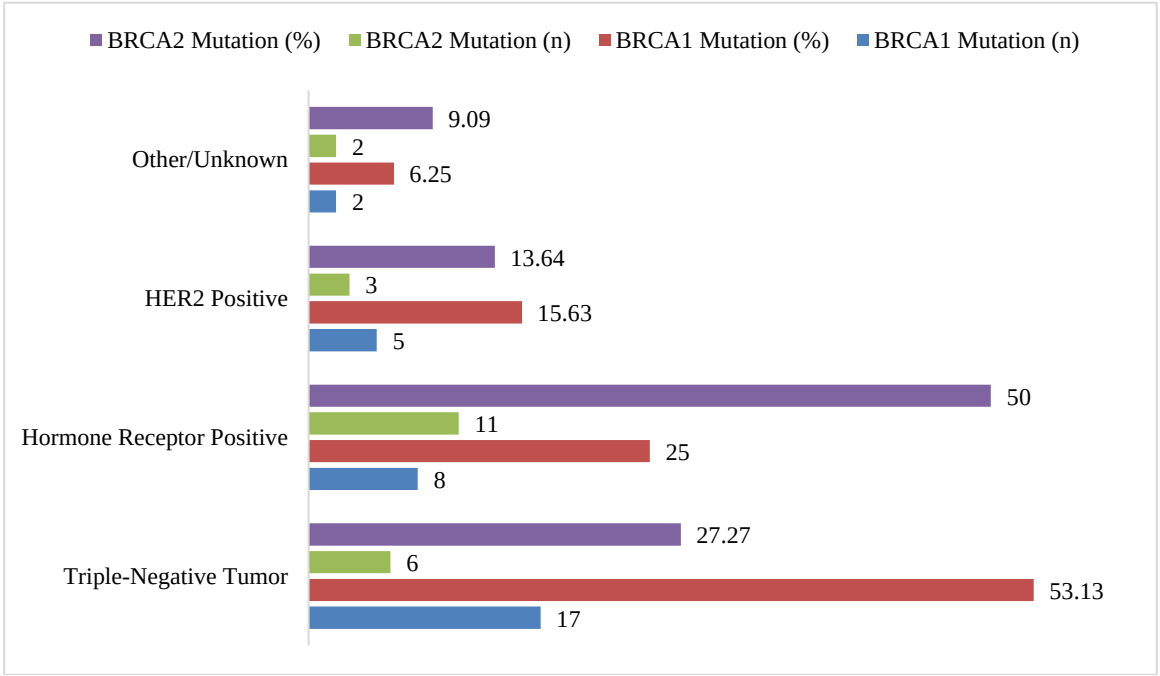


**Figure 2:** Tumor Characteristics in BRCA Mutation-Positive Patients (n = 54)

Family history among BRCA mutation carriers is shown in Table 2. Of *BRCA1*-positive individuals, 62.50% had a first-degree relative with breast cancer, 28.13% with ovarian cancer, 6.25% with both, and 3.13% had no known family history. Comparably, 63.64% of *BRCA2* carriers had a family history of breast cancer, 22.73% of ovarian cancer, 9.09% of both, and 4.55% of none. This supports the significant genetic connection of these mutations to ovarian and breast malignancies.

**Table 2:** Family History among BRCA Mutation Carriers (n = 54)

| Family History of Cancer | *BRCA1* Positive (n = 32) | *BRCA2* Positive (n = 22) |
|---|---|---|
| Breast Cancer (First-degree) | 20 (62.50%) | 14 (63.64%) |
| Ovarian Cancer (First-degree) | 9 (28.13%) | 5 (22.73%) |
| Both Breast and Ovarian | 2 (6.25%) | 2 (9.09%) |
| No Documented Family History | 1 (3.13%) | 1 (4.55%) |

Table 3 lists correlations between clinical characteristics and BRCA mutation status. With important p-values (0.025 and 0.045), *BRCA1* mutations were more common in ovarian cancer (25.58%) than in breast cancer (17.65%). Younger patients (18–30) had a p-value of 0.010. Their *BRCA1* mutation rates were 25.00%. While hormone receptor-positive tumors were more common in *BRCA2* carriers (50.00%), triple-negative tumors were substantially more common in those who had *BRCA1* (53.13%, p=0.011). These results draw attention to important clinical linkages involving mutation status.

**Table 3:** Associations between Mutation Status and Clinical Features (n = 168)

| Clinical Feature | | *BRCA1* Mutation (n;%) | *BRCA2* Mutation (n;%) | No Mutation (n;%) | Chi-Square Value | p-Value |
|---|---|---|---|---|---|---|
| Cancer Type | Breast Cancer | 18 (17.65%) | 12 (11.76%) | 72 (70.59%) | 6.256 | 0.045 |
| | Ovarian Cancer | 11 (25.58%) | 8 (18.60%) | 24 (55.81%) | 5.042 | 0.025 |
| Age at Diagnosis | 18–30 Years | 7 (25.00%) | 3 (10.71%) | 22 (64.71%) | 6.972 | 0.010 |
| | 31–45 Years | 12 (18.75%) | 9 (14.06%) | 24 (48.98%) | 5.024 | 0.030 |
| | 46–60 Years | 9 (17.65%) | 6 (11.76%) | 24 (47.06%) | 5.136 | 0.045 |
| | >60 Years | 4 (16.00%) | 4 (16.00%) | 14 (56.00%) | 2.392 | 0.300 |
| Tumor Characteristics | Triple-Negative | 17 (53.13%) | 6 (27.27%) | 9 (19.05%) | 8.713 | 0.011 |
| | HRP | 8 (25.00%) | 11 (50.00%) | 19 (40.43%) | 3.513 | 0.054 |
| | HER2 Positive | 5 (15.63%) | 3 (13.64%) | 11 (23.40%) | 1.797 | 0.201 |

** HRP: Hormone Receptor Positive; statistically significant at p < 0.05.*

## Discussion

Revealing mutation frequencies of 19.05% and 13.10%, respectively, this study underlines the crucial part of *BRCA1* and *BRCA2* mutations in the development of breast and ovarian malignancies among Pakistani women. *BRCA1* mutations were found in 17.65% and *BRCA2* mutations in 11.76% of cases among breast cancer patients, in line with past research showing BRCA mutation frequencies between 10% and 20% in breast cancer cohorts [12,13]. Furthermore supporting the results of our investigation are reported mutation rates of 16.3% for *BRCA1* and 8.5% for *BRCA2* among patients with high risk of breast cancer [14]. With *BRCA1* mutations in 25.58% and *BRCA2* in 18.60%, our ovarian cancer group (n=43) notably had higher mutation rates, in line with global statistics implying stronger links of BRCA mutations with ovarian cancer [15].

The 18–30 age group had the highest proportion of *BRCA1* mutations (25.00%), followed by the 31–45 age group at 18.75%. Age-specific analysis. This tendency points to a predilection for early-onset cancer among mutation carriers, therefore supporting earlier results showing that BRCA mutation carriers typically get cancer a decade earlier than non-carriers [16]. By contrast, patients over 60 (16.00%) had more common *BRCA2* mutations, suggesting possible age-related phenotypic variation between the two genes.

Unlike *BRCA2* carriers, where 50.00% of tumors were hormone receptor-positive, tumor subtype analysis found a startling association between *BRCA1* mutations and triple-negative breast cancers (53.13%). This is consistent with past studies showing more aggressive tumor biology reflected in over 50% of *BRCA1*-associated cancers being triple-negative [17]. The different tumor characteristics highlight the need of mutation-specific pathology in directing therapy plans, including chemotherapy courses and PARP inhibitors use.

Data on family histories showed that 63.64% of *BRCA2* carriers and 62.50% of *BRCA1* carriers had a first-degree

relative with breast cancer. As observed in previous studies showing first-degree relatives of BRCA mutation carriers had a notably increased cancer risk [18], this genetic pattern supports the function of familial predisposition in BRCA-driven malignancies.

The noted variations in tumor features, age distribution, and mutation frequency support the necessity of region-specific genetic screening plans. Variability in studies could be a reflection of variations in sample size, population genetics, and detection techniques, therefore highlighting the need of ongoing molecular research in many ethnic populations.

### Strengths and Limitations

This study's primary merit is its concentrated examination of *BRCA1* and *BRCA2* mutations in breast and ovarian cancer patients within a Pakistani population, which is underrepresented in global genetic research. The application of PCR and sequencing yielded precise molecular data, whereas stratification by age, tumor subtype, and familial history for a thorough examination of clinical correlates. The inclusion of individuals with robust family histories, even without present malignancies, offered insights into hereditary cancer risk beyond afflicted patients. Nonetheless, the study possesses certain drawbacks. The sample size (n=168), while adequate for a single-center investigation, may restrict the generalizability of the results. Employing convenience sampling may result in selection bias, and the absence of categorization for variations of unknown significance (VUS) could have omitted significant genetic information. The cross-sectional design prevents the evaluation of long-term outcomes or survival data in mutation carriers.

## Conclusion

This study underscores the critical involvement of *BRCA1* and *BRCA2* mutations in the etiology of breast and ovarian cancers among Pakistani women, with *BRCA1* exhibiting a stronger correlation with triple-negative and early-onset cancers, whereas *BRCA2* was predominantly found in hormone receptor-positive tumors and older individuals. The documented mutation rates—19.05% for *BRCA1* and 13.10% for *BRCA2*—highlight the significance of genetic screening, especially for those with a robust family history or early-onset illness. The results endorse the adoption of individualized risk evaluation and focused treatment approaches in clinical practice, including the application of PARP inhibitors and preventive measures. These findings provide significant regional data to the worldwide comprehension of BRCA-related cancers and underscore the necessity for expanded access to genetic counseling and testing in resource-constrained environments.

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