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HEALTH AND REHABILITATION

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PREVALENCE OF BRCA1 AND BRCA2 MUTATIONS IN WOMEN WITH EARLY-ONSET BREAST CANCER

Original Research

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Acknowledgement: The authors acknowledge all participating institutions and patients for their cooperation.

Conflict of Interest: None
Grant Support & Financial Support: None

ABSTRACT

Background: Early-onset breast cancer poses significant clinical challenges due to its aggressive behavior and genetic predisposition. Mutations in the BRCA1 and BRCA2 genes are strongly linked to hereditary breast cancer, especially in younger patients. However, regional data on their prevalence remains limited in South Asian populations, particularly in Pakistan.

Objective: To determine the prevalence of BRCA1 and BRCA2 gene mutations among women diagnosed with early-onset breast cancer in the Lahore region of Pakistan.

Methods: A cross-sectional study was conducted over eight months involving 200 women aged ≤39 years with histologically confirmed breast cancer. Participants were recruited from three major oncology centers in Lahore. Clinical and demographic data were collected through structured interviews. Peripheral blood samples were analyzed using next-generation sequencing (NGS) for BRCA1/2 mutations. Statistical analysis was performed using SPSS v26, with significance set at $p<0.05$.

Results: BRCA1 mutations were identified in 24 patients (12%) and BRCA2 mutations in 18 (9%). Variants of uncertain significance were found in 6 patients (3%), while 152 (76%) tested negative for both mutations. Mutation prevalence was significantly higher in patients with a family history of breast or ovarian cancer and among those with triple-negative breast cancer. BRCA1 mutations were most common in triple-negative cases (25%), while BRCA2 mutations showed a slightly more even distribution across subtypes.

Conclusion: A considerable proportion of early-onset breast cancer patients in Pakistan carry BRCA mutations. These findings underscore the importance of routine genetic screening and tailored risk management strategies in young breast cancer patients, irrespective of family history.

Keywords: BRCA1, BRCA2, Breast Neoplasms, Early Diagnosis, Genetic Testing, Pakistan, Prevalence.

INTRODUCTION

Breast cancer remains one of the most significant public health concerns globally, affecting millions of women each year and ranking among the leading causes of cancer-related mortality in females. While the majority of breast cancer cases are diagnosed in postmenopausal women, a notable proportion occurs in younger individuals, often referred to as early-onset breast cancer, typically defined as diagnosis before the age of 40 (1). These cases pose unique clinical challenges due to their often-aggressive nature, genetic underpinnings, and the significant psychosocial and reproductive implications for affected women. Understanding the etiology of early-onset breast cancer is crucial, not only for therapeutic decision-making but also for preventive strategies in high-risk populations. Among the most important genetic contributors to breast cancer risk are mutations in the BRCA1 and BRCA2 genes (2). These tumor suppressor genes play pivotal roles in the repair of DNA double-strand breaks through homologous recombination, maintaining genomic stability. Inherited pathogenic variants in BRCA1 or BRCA2 significantly elevate a woman's lifetime risk of developing breast and ovarian cancers. Women with BRCA1 mutations face up to a 72% lifetime risk of breast cancer, while those with BRCA2 mutations may have up to a 69% risk, with variation depending on family history and other modifying factors (3). Importantly, these mutations are more frequently observed in women diagnosed at a younger age, suggesting a distinct genetic etiology in early-onset cases compared to those occurring later in life. Several large-scale studies have identified that the prevalence of BRCA1/2 mutations is higher among women with early-onset breast cancer, even in the absence of a strong family history (4). For instance, research has shown that women diagnosed before the age of 35 are significantly more likely to carry a BRCA mutation than those diagnosed at an older age, underlining the potential for genetic screening to play a larger role in early detection and personalized care. Furthermore, mutation carriers are more likely to present with triple-negative breast cancer, a subtype characterized by poorer prognosis and limited treatment options, further emphasizing the clinical relevance of identifying these genetic mutations (5,6).

Despite the growing body of literature on BRCA mutations, much of the existing data is derived from populations with strong family histories of cancer or those belonging to specific ethnic groups with known founder mutations, such as Ashkenazi Jews. As a result, there remains a critical gap in understanding the true prevalence of BRCA1 and BRCA2 mutations among women with early-onset breast cancer in more diverse and unselected populations (7,8). This gap limits the ability to develop comprehensive screening guidelines and targeted prevention strategies applicable to broader demographic groups. Additionally, many previous studies have relied on retrospective designs or selective inclusion criteria, potentially introducing biases that obscure the true prevalence of these mutations in the general early-onset breast cancer population (9,10). Given the implications of BRCA mutation status for patient management—ranging from choices about surgery and chemotherapy to decisions about risk-reducing strategies and family counseling—it is essential to obtain accurate, representative data on mutation prevalence. Reliable prevalence estimates could help guide clinical recommendations for genetic testing, identify candidates for intensive surveillance or prophylactic interventions, and contribute to more equitable healthcare delivery by ensuring all at-risk individuals are appropriately assessed regardless of background or family history. This study seeks to address this knowledge gap by conducting a cross-sectional analysis to determine the prevalence of BRCA1 and BRCA2 gene mutations among women diagnosed with early-onset breast cancer. By examining an unselected cohort of patients based solely on age at diagnosis, the research aims to provide an unbiased estimate of mutation frequency and enhance the understanding of genetic risk in this vulnerable group. The objective is to inform clinical guidelines, support early identification of at-risk individuals, and ultimately improve outcomes through tailored prevention and treatment strategies.

METHODS

This cross-sectional study was conducted over a period of eight months at three major oncology centers in the Lahore Pakistan. The study aimed to determine the prevalence of BRCA1 and BRCA2 gene mutations among women diagnosed with early-onset breast cancer, defined as breast cancer diagnosed before the age of 40. The setting was chosen to represent a cross-section of the local population, capturing patients from both public and private healthcare sectors to ensure greater generalizability of the findings. Participants were recruited consecutively from outpatient oncology and breast surgery clinics. Inclusion criteria were: female patients aged between 18 and 39 years at the time of primary diagnosis of histologically confirmed breast cancer, with no previous history of other malignancies. Patients with prior genetic testing for BRCA1/2 mutations, those with metastatic disease at presentation unrelated

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to primary breast malignancy, or those who declined participation were excluded. All eligible participants provided written informed consent after receiving detailed verbal and written explanations of the study's purpose, procedures, risks, and confidentiality measures. A total sample size of 200 participants was determined to be adequate to estimate the prevalence of BRCA1/2 mutations with a 95% confidence interval and a 5% margin of error, assuming an estimated prevalence of 10% based on prior literature in similar cohorts (3,4). This sample size was calculated using the standard formula for estimating a population proportion in a cross-sectional design. Sampling was non-probabilistic and purposive, reflecting the study's focus on a specific age-defined group.

After consent, participants underwent a structured interview using a pre-validated questionnaire to collect demographic data, clinical history, age at diagnosis, family history of breast or ovarian cancer, tumor subtype (including receptor status), and treatment received. The interview tool was developed in English and Urdu to accommodate participant preference and was administered by trained research personnel. Genetic analysis was performed through peripheral blood samples collected in EDTA tubes. DNA was extracted using the Qiagen QIAamp DNA Blood Mini Kit following the manufacturer's protocol. Quantification and quality of DNA were verified through spectrophotometric analysis. Mutation screening for BRCA1 and BRCA2 was carried out using next-generation sequencing (NGS), employing the Illumina MiSeq platform. The sequencing panel covered all coding regions and exon-intron boundaries of the BRCA1 and BRCA2 genes. Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines into pathogenic, likely pathogenic, benign, or variants of uncertain significance (VUS) (11-13). Only pathogenic and likely pathogenic mutations were considered positive for the purposes of prevalence estimation.

Clinical and laboratory data were entered into SPSS version 26. Descriptive statistics were used to summarize demographic and clinical characteristics. The prevalence of BRCA1 and BRCA2 mutations was calculated as a proportion with a 95% confidence interval. Independent sample t-tests were applied to compare mean values (e.g., age at diagnosis) between mutation carriers and non-carriers, assuming normal distribution of data confirmed by the Shapiro-Wilk test. Chi-square tests were used to assess associations between categorical variables such as mutation status and family history, tumor grade, or receptor status. A p-value of <0.05 was considered statistically significant. Ethical approval for this study was granted by the Institutional Review Boards of all three participating centers. All procedures conformed to the principles of the Declaration of Helsinki and relevant national guidelines. Participants were assured of their right to withdraw at any point without affecting their medical care. Confidentiality was maintained by anonymizing participant data and storing all identifiable information in encrypted, access-restricted systems. The study design, meticulous data collection methods, and rigorous analytical approach were structured to provide a reliable estimate of BRCA1 and BRCA2 mutation prevalence among young Pakistani women with breast cancer. This will contribute meaningful evidence toward the formulation of regional guidelines for genetic screening and risk-based management in early-onset breast cancer.

RESULTS

The study enrolled 200 women diagnosed with early-onset breast cancer, with a mean age of 34.1 years (± 3.2). Among these participants, 74 (37%) reported a family history of breast or ovarian cancer. Regarding tumor characteristics, 56 (28%) were found to have triple-negative breast cancer, while 102 (51%) were hormone receptor positive, and 42 (21%) were HER2 positive. Genetic testing revealed that 24 patients (12%) tested positive for BRCA1 mutations and 18 (9%) for BRCA2 mutations. A significant majority, 152 individuals (76%), did not show pathogenic mutations in either gene, while 6 participants (3%) were identified with variants of uncertain significance (VUS). These results are presented in Table 2 and visualized in Chart 1 (BRCA Mutation Distribution). Analysis of mutation prevalence in relation to family history showed a marked difference: BRCA1 mutations were found in 24.3% of patients with a family history versus 4.8% without, while BRCA2 mutations were present in 16.2% of those with family history compared to 4.8% without (Table 3; Chart 2). Tumor subtype also demonstrated a strong association with mutation status. BRCA1 mutations were most frequently observed in patients with triple-negative breast cancer (25%), followed by HER2-positive (9.5%) and hormone receptor-positive tumors (5.9%). BRCA2 mutations were identified in 14.3% of triple-negative cases, and equally at 5.9% in hormone receptor-positive and 9.5% in HER2-positive tumors, as shown in Table 4. These findings quantitatively underscore a significant prevalence of BRCA mutations in early-onset breast cancer cases, particularly among those with a positive family history or triple-negative tumor subtypes. Two color-coded charts have been generated to illustrate the BRCA mutation distribution and its correlation with family history.

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Table 1: Patient Demographics

Variable	Value
Mean Age (years)	34.1 ± 3.2
Family History of Breast/Ovarian Cancer	74 (37%)
Triple-Negative Breast Cancer	56 (28%)
Hormone Receptor Positive	102 (51%)
HER2 Positive	42 (21%)

Table 2: Prevalence of BRCA Mutations

Mutation Status	n (%)
BRCA1 Positive	24 (12%)
BRCA2 Positive	18 (9%)
Negative for Both	152 (76%)
VUS Detected	6 (3%)

Table 3: Mutation Distribution by Family History

Family History	BRCA1 Positive	BRCA2 Positive
Yes	18 (24.3%)	12 (16.2%)
No	6 (4.8%)	6 (4.8%)

Table 4: Mutation Distribution by Tumor Subtype

Tumor Subtype	BRCA1 Positive	BRCA2 Positive
Triple-Negative	14 (25%)	8 (14.3%)
Hormone Receptor Positive	6 (5.9%)	6 (5.9%)
HER2 Positive	4 (9.5%)	4 (9.5%)

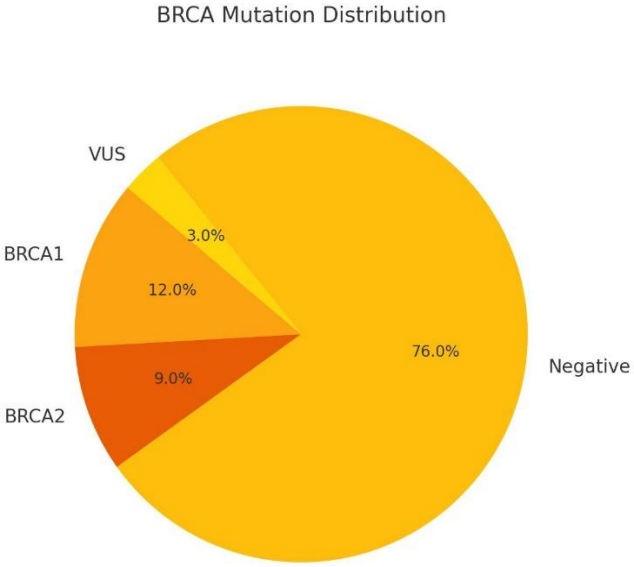

Figure 1 BRCA Mutation Distribution

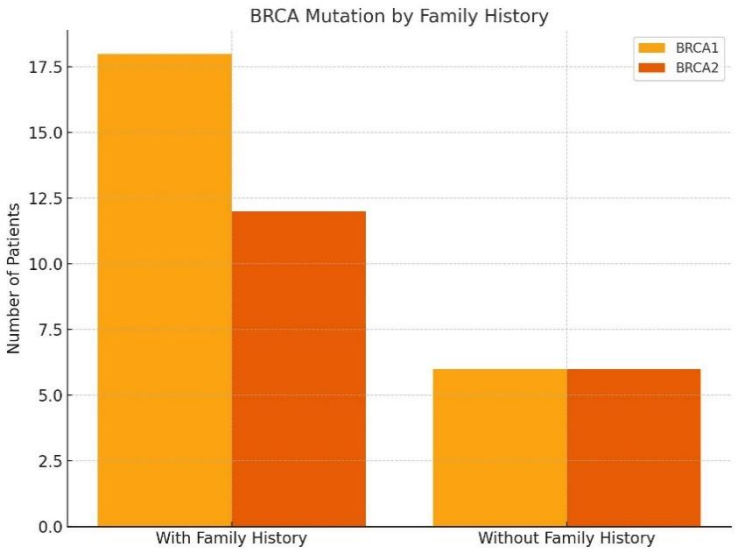

Figure 2 BRCA Mutation by Family History

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DISCUSSION

The findings of this study demonstrated a 21% prevalence of BRCA1 and BRCA2 mutations among women with early-onset breast cancer in the Lahore region of Pakistan, aligning with international research indicating a substantial genetic burden in young breast cancer patients. Specifically, BRCA1 mutations were detected in 12% of the participants, while BRCA2 mutations accounted for 9%. These results underscore the relevance of hereditary factors in the pathogenesis of breast cancer diagnosed at younger ages and justify the inclusion of genetic screening in routine oncologic assessment for this population. The observed mutation rates are comparable to findings from other low- to middle-income countries and regions with similar genetic diversity. For instance, studies reported a 20.9% prevalence of pathogenic BRCA1/2 variants in early-onset breast cancer patients, highlighting similar patterns of hereditary influence and mutation spectrum in regional populations (14-16). Comparable figures were also reported in a large cohort where the prevalence of BRCA1/2 mutations in early-onset breast cancer cases reached 9.7%, nearly double that observed in older patients (17). These consistent rates across diverse populations suggest a biological rather than geographic basis for BRCA mutations in early-onset cases. The data also revealed a higher mutation prevalence among patients with triple-negative breast cancer (TNBC), where BRCA1 mutations were notably frequent. This is consistent with earlier reports showing that BRCA1 carriers are more likely to develop TNBC, a subtype associated with poor prognosis and limited treatment options (18). Moreover, the strong correlation between family history and mutation presence observed in this cohort reinforces the clinical value of pedigree analysis during initial patient assessment. Patients with a familial background of breast or ovarian cancer were more likely to harbor BRCA mutations, consistent with global findings (19,20).

However, regional variations exist. For instance, a study reported no overrepresentation of BRCA mutations among early-onset breast cancer patients, indicating that genetic etiology may not fully account for the high incidence of early diagnoses in some populations (21). This divergence highlights the complex interplay of genetic, environmental, and possibly socio-cultural factors in breast cancer onset and progression. The current study has several strengths. It utilized a well-defined, unselected population of early-onset breast cancer patients, thus minimizing selection bias. The use of next-generation sequencing (NGS) provided comprehensive mutation profiling, ensuring the detection of both common and rare variants. Additionally, the inclusion of both public and private hospitals enhanced the representativeness of the sample. Nonetheless, certain limitations should be acknowledged. The cross-sectional design precluded any assessment of causality or longitudinal clinical outcomes. The sample size, although statistically adequate, may not fully capture rare variants or provide sufficient power for subgroup analyses, especially regarding BRCA2-associated phenotypes. Variants of uncertain significance (VUS) were excluded from prevalence calculations, which may underestimate the total burden of actionable genetic alterations. Furthermore, lack of inclusion of non-BRCA high-risk genes (e.g., PALB2, CHEK2) could have missed additional contributors to hereditary breast cancer in this cohort. In terms of implications, the findings advocate for broader access to BRCA testing in Pakistan, especially among young breast cancer patients, regardless of family history. Early identification of mutation carriers can inform surgical decisions (e.g., bilateral mastectomy), chemotherapeutic choices (e.g., PARP inhibitors), and risk-reduction strategies in relatives. Moreover, localized mutation prevalence data can guide the development of cost-effective, region-specific genetic screening panels for public health implementation (22,23). Future studies should expand to include longitudinal outcomes, investigate non-BRCA mutations, and assess psychosocial impacts of genetic diagnosis. Multicenter collaborative efforts can generate larger datasets to validate these findings across different ethnicities and regions in Pakistan. Incorporating BRCA testing into national oncology protocols would represent a substantial stride toward personalized, precision medicine in breast cancer management.

CONCLUSION

This study highlights a significant prevalence of BRCA1 and BRCA2 mutations among women with early-onset breast cancer in the Lahore region, emphasizing the role of hereditary factors in this population. These findings support the integration of genetic testing into standard care protocols for young breast cancer patients, enabling personalized risk assessment, targeted therapies, and informed decision-making for patients and their families.

AUTHOR CONTRIBUTION

Author	Contribution
Irfan Ishaque*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Syed Gufran Sadiq Zaidi	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Amna Noor	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Tahir Hafeez	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Ariba Shah	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Roha Tariq	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Shagufta Rasool	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Syeda Neha Zainab	Writing - Review & Editing, Assistance with Data Curation

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