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Original Research Article

PREVALENCE AND CLINICOPATHOLOGICAL CORRELATES OF BRCA POSITIVITY IN HIGH-RISK BREAST CANCER PATIENTS

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ABSTRACT

Background: Germline BRCA1 and BRCA2 mutations contribute to 5–10% of breast cancer cases, with increased prevalence in high-risk groups such as early-onset breast cancer, triple-negative breast cancer (TNBC), and those with a strong family history. This study assessed BRCA mutation frequency and its association with clinicopathological factors in high-risk breast cancer patients. **Materials and Methods:** We prospectively enrolled breast cancer patients meeting at least one high-risk criterion: age <50, TNBC, or family history. BRCA1/2 genetic testing was performed on peripheral blood samples, and associations with clinical factors were analyzed statistically ($p<0.05$). **Result:** The median age was 45 years (range 28–70), with 75% <50 years. 57.5% had TNBC, and 12.5% had a family history. The overall BRCA positivity rate was 37.5% (15/40), with all detected mutations in BRCA1. BRCA positivity was 40% in patients <50 years, 60% in those with a family history, and 34.8% in TNBC cases. BRCA prevalence was slightly higher in advanced-stage tumors (41%) and high-grade tumors (22%), but these differences were not statistically significant ($p>0.05$). **Conclusion:** Over one-third of high-risk breast cancer patients carried BRCA mutations, all in BRCA1. These findings highlight the importance of genetic counseling and BRCA testing to guide PARP inhibitor therapy and preventive strategies.

INTRODUCTION

Hereditary breast cancer, primarily due to BRCA1/2 mutations, accounts for 5–10% of breast cancer cases.[1] BRCA mutations increase the risk of breast and ovarian cancer, with a general population prevalence of 1 in 300–500 women.[2] High-risk subgroups, such as triple-negative breast cancer (TNBC) and early-onset cases, show elevated BRCA mutation rates. For instance, 15–25% of TNBC patients harbor BRCA1/2 mutations.[3] Clinical guidelines recommend genetic testing for high-risk patients, including those with TNBC diagnosed at ≤50 years or early-onset breast cancer.[4]

This study examines BRCA mutation prevalence in high-risk breast cancer patients and correlates mutation status with clinico-pathological features. We hypothesize that BRCA mutation prevalence will be high in this cohort, with certain features (e.g., family history, TNBC) further increasing the likelihood of BRCA positivity.

MATERIALS AND METHODS

Study Design and Patients: This prospective study enrolled 40 high-risk breast cancer patients in a tertiary institution from June–August 2024.

Inclusion criteria

(1) age <50 at diagnosis, (2) TNBC, or (3) family history of breast cancer in a first- or second-degree relative. Patients with prior BRCA mutations were excluded.

Data Collection: Clinical and tumor characteristics (age, family history, tumor subtype, grade, stage) were recorded. Tumor receptor status (ER, PR, HER2) was determined by immunohistochemistry and/or FISH.

BRCA Testing: Germline BRCA1/2 testing was performed using the HELINI BRCA1 & BRCA2 Real-time PCR Kit 6. Peripheral blood samples were analyzed for three major pathogenic mutations: BRCA1 185delAG, BRCA1 5382insC, and BRCA2 6174delT. Mutation detection was based on fluorescence signal curves.

Statistical Analysis: Descriptive statistics summarized patient and tumor characteristics. BRCA mutation prevalence was calculated, and associations

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between mutation status and clinical factors (age, family history, tumor subtype, stage, grade) were examined using Chi-square and Fisher's exact tests. A p-value <0.05 was considered statistically significant.

Table 1: Basic Characteristics of Study Poppulation

Characteristic	Total(N-40)	Brca 1 Positive(N-15)	Brca Negative(N-25)
Age at Diagnosis (Years)			
Median (Range)	45(28-70)	43(28-60)	47(30-70)
<50 Years	30(75%)	12(40%)	18(60%)
>50years	10(25%)	3(30%)	7(70%)
Family History			
Yes	5(12.5%)	3(60%)	2(40%)
No	35(87.5%)	12(34.3%)	23(65.7%)
Tumor Subtype			
TNBC	23(57.5%)	8(34.8%)	15(65.2%)
Non-TNBC	17(42.5%)	7(41.2%)	10(58.8%)
Tumor Grade			
Grade I	1(3.3%)	0(0%)	1(100%)
Grade II	18(60%)	2(11.1%)	16(88.9%)
Grade III	11(36.7%)	2(18.2%)	9(81.8%)
Stage			
Stage I-II	13(32.5%)	4(30.8%)	9(69.2%)
Stage III	24(60%)	7(29.2%)	17(70.8%)
Stage IV	3(7.5%)	3(100%)	0(0%)

Table 2: BRCA mutation prevalence by risk factors

Risk Factor	Number Of Patients	BRCA Positive(N-15)	Prevalence	P Value
Age<50 Years	30	12	40%	0.30
Tnbc	23	8	34.8%.	0.67
Family History	5	3	60%	O.29
Stage Iv Disease	3	3	100%	0.07

RESULTS

Patient Characteristics: A total of 40 high-risk breast cancer patients were included in the analysis as shown in [Table 1]. All patients were female, with a median age of 45 years (range: 28–70). By design, 75% (30/40) were <50 years at diagnosis, and 30% (12/40) were <40 years. Family history of breast cancer was reported in 12.5% (5/40) of patients, with four cases involving a first-degree relative (mother or sister) and one involving a second-degree relative (aunt). No patient reported a family history of ovarian cancer, though one had a personal history of ovarian cancer.

Tumor Pathology: Most tumors were invasive ductal carcinoma (IDC) (92.5%, 37/40). Other histologies included mixed invasive ductal and lobular carcinoma (2.5%, 1/40), pure mucinous carcinoma (2.5%, 1/40), and metaplastic carcinoma (2.5%, 1/40). Tumor grade was reported for 30 patients: grade I (3.3%, 1/30), grade II (60%, 18/30), and grade III (36.7%, 11/30). In ten cases, grade was not documented due to neoadjuvant treatment or biopsy-only assessments.

Receptor Status and Tumor Subtypes: Triple-negative breast cancer (TNBC) accounted for 57.5% (23/40) of cases, while 42.5% (17/40) had at least one positive receptor. Among non-TNBC cases, the most common subtype was ER-positive/PR-positive/HER2-negative (25%, 10/40). HER2-positive tumors were rare (5%, 2/40).

Disease Stage at Diagnosis: Disease stages at presentation were: stage I–II (32.5%, 13/40), stage III (60%, 24/40), and stage IV (7.5%, 3/40). All three stage IV cases had aggressive features: two were TNBC, and one had hormone receptor-positive disease with visceral metastases.

BRCA Mutation Prevalence: BRCA mutations were detected in 37.5% (15/40) of patients, all in BRCA1. No BRCA2 mutations were found. Specific mutations included

- BRCA1 185delAG: 14 heterozygous cases, 1 homozygous case.
- BRCA1 5382insC: 3 heterozygous cases.
- BRCA2 6174delT: Not detected.

The remaining 62.5% (25/40) tested negative for BRCA mutations. These patients may have sporadic disease or other genetic predispositions not captured by BRCA testing.

Correlation of BRCA Status with Clinical Factor: We examined associations between BRCA mutation status and key clinical factors as shown in Table 2. Although no association reached statistical significance, several trends were observed:

1. Age: BRCA positivity was higher in patients <50 (40%, 12/30) vs. ≥50 (30%, 3/10), though the difference was not significant (p=0.30). Two of the three patients aged ≥50 with mutations had additional risk factors (TNBC or strong family history).

2. Family History: Patients with a family history of breast cancer showed the highest BRCA positivity (60%, 3/5) vs. those without (34.3%, 12/35). Although the difference was not significant (p=0.29), the trend aligns with prior studies.

3.Tumor Subtype (TNBC Status): BRCA positivity was similar in TNBC (34.8%, 8/23) and non-TNBC

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(41.2%, 7/17) patients (p=0.67). This suggests that TNBC alone is not the sole predictor of BRCA mutations, as many non-TNBC patients were tested due to early age or family history.

4. Stage: BRCA positivity was observed in 30.8% (4/13) of stage I–II patients, 35.0% (7/20) of stage III patients, and 100% (3/3) of stage IV patients. The 100% mutation rate in stage IV cases may reflect the aggressive nature of BRCA1-associated tumors, though the small sample size limits conclusions (p=0.07).

5. Tumor Grade: BRCA positivity was observed in 22.2% (2/9) of grade III tumors and 16.7% (2/12) of grade II tumors. The single grade I tumor was BRCA-negative. Many BRCA-positive cases (11/15) lacked grade data due to neoadjuvant treatment (p>0.05).

6. Histological Type: All BRCA-mutated tumors were IDC. The few non-IDC histologies (lobular, mucinous, metaplastic) did not harbor mutations. One BRCA1-positive case was a mucinous carcinoma, an uncommon subtype for BRCA1-associated tumors, likely explained by the patient's young age and strong family history (p>0.05).

DISCUSSION

Our study found a 37.5% BRCA1 mutation prevalence in high-risk breast cancer patients, significantly higher than the 5–10% reported in unselected populations. This elevated prevalence underscores the effectiveness of using clinical criteria (e.g., early age at diagnosis, TNBC, family history) to identify patients who are likely to carry BRCA mutation1. The absence of BRCA2 mutations in our cohort contrasts with prior reports, which suggest that BRCA2 mutations account for 5–10% of high-risk cases.[2] This discrepancy may reflect regional genetic variations or the specific risk profile of our cohort, which was enriched for BRCA1-associated phenotypes (e.g., young age, TNBC).[3] It also raises the possibility that our population may have fewer BRCA2 founder mutations, a hypothesis that warrants further investigation in larger, ethnically diverse cohorts.[4]

Family History and BRCA Positivity: Patients with a family history of breast cancer showed the highest BRCA positivity (60%), consistent with prior studies. Although the difference was not statistically significant (p=0.29), the trend aligns with the known association between family history and BRCA mutations. This underscores the importance of family history in identifying hereditary cancer syndromes, particularly in populations with limited access to comprehensive genetic testing.[5,6] Interestingly, the two family-history patients who tested negative both had only a single relative affected at an older age, suggesting a lower likelihood of a hereditary syndrome in those cases. This finding is consistent with prior research indicating that the number of affected relatives and their age at diagnosis are important predictors of BRCA mutation status.[7]

TNBC and BRCA Mutations: Surprisingly, TNBC status alone did not significantly predict BRCA positivity (p=0.67). While 34.8% of TNBC patients were BRCA-positive, 41.2% of non-TNBC patients also carried mutations. This counterintuitive finding may reflect the cohort's enrichment for other risk factors, such as early age or family history, which themselves are associated with BRCA mutations.[8] For example, most BRCA-positive non-TNBC cases in our series had significant family histories. This suggests that while TNBC is a useful criterion, it is not the sole predictor of BRCA mutations. Patients beyond TNBC who meet other high-risk criteria (e.g., early onset, family history) also have substantial mutation rates.[9] This finding has important implications for clinical practice, as it highlights the need to consider multiple risk factors when selecting patients for genetic testing.

Advanced Disease and BRCA1

All three metastatic cases in our cohort were BRCA1-positive, supporting the aggressive nature of BRCA1-associated tumors.[10] Although the small number of stage IV cases limits definitive conclusions (p=0.07), this finding aligns with studies indicating that BRCA1-driven breast cancers tend to have high proliferation rates and a greater tendency for visceral metastases.[11] This highlights the need for early genetic testing in advanced cases, as BRCA status may influence treatment decisions and prognosis.[12] For example, BRCA1-positive patients with metastatic disease may benefit from PARP inhibitors, which have shown significant efficacy in this population.[13]

Age and BRCA Positivity

Younger patients (<50 years) had a higher BRCA positivity rate (40%) compared to older patients (30%), though the difference was not statistically significant (p=0.30). This trend is consistent with prior studies showing that early-onset breast cancer is strongly associated with BRCA mmutations,[14] Notably, two of the three patients aged ≥50 with mutations also had other risk factors (TNBC or strong family history), further emphasizing the importance of considering multiple risk factors in genetic testing decisions.[15] This finding has important implications for clinical practice, as it suggests that age alone should not be the sole criterion for genetic testing. Instead, a comprehensive assessment of all risk factors (e.g., age, family history, tumor subtype) should be used to identify patients who are likely to benefit from genetic testing.

Tumor Grade and Histology

High histologic grade is a common feature of BRCA1-associated breast cancers, which are often rapidly proliferative. In our data, 22.2% of grade III tumors were BRCA-positive, compared to 16.7% of grade II tumors. The single grade I tumor was BRCA-negative. Many BRCA-positive cancers (11/15) did not have grade reported, often because several mutation carriers received neoadjuvant chemotherapy and only residual disease was assessed. Thus, while a majority of BRCA1-mutated

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tumors were high-grade, our sample was too limited to draw conclusions on grade correlation ($p>0.05$). Similarly, all BRCA-mutated tumors were invasive ductal carcinomas (IDC), while the few non-IDC histologies (lobular, mucinous, metaplastic) did not harbor mutations. One BRCA1-positive case was a mucinous carcinoma, an uncommon subtype for BRCA1-associated tumors, likely explained by the patient's young age and strong family history.

Clinical Implications

Identifying BRCA mutations has critical therapeutic and preventive implications. BRCA-positive patients may benefit from PARP inhibitors, such as olaparib and talazoparib, which exploit defective homologous recombination repair mechanisms. These agents have shown significant efficacy in BRCA-mutated breast cancers, particularly in advanced or metastatic disease. Additionally, BRCA mutation carriers may opt for risk-reducing surgeries, such as bilateral mastectomy or prophylactic oophorectomy, to mitigate the risk of future malignancy. Our findings reinforce the importance of integrating BRCA testing into routine clinical practice for high-risk patients, particularly in resource-limited settings where comprehensive multigene testing may not be feasible.

Limitations

The small sample size and single-center design limit generalizability. Additionally, the absence of BRCA2 mutations may reflect regional genetic variations, warranting further investigation in larger, ethnically diverse populations. The lack of statistical significance for some associations (e.g., family history, TNBC status) may be due to the modest sample size and overlapping risk factors in many patients. Future studies with larger cohorts and multigene panel testing could provide more robust insights into the genetic landscape of high-risk breast cancer patients.

Future Directions

Larger, multicenter studies are needed to confirm our findings and explore potential regional genetic variations. Additionally, prospective studies evaluating the impact of BRCA testing on treatment decisions and patient outcomes could provide valuable insights into the clinical utility of genetic testing in high-risk populations. Long-term follow-up studies are also needed to assess the survival benefits of PARP inhibitors and risk-reducing surgeries in BRCA-positive patients. Finally, the integration of multigene panel testing into routine clinical practice could help identify additional genetic predispositions beyond BRCA1/2, further refining risk assessment and treatment strategies.

CONCLUSION

This study confirms a high prevalence of BRCA1 mutations (37.5%) in high-risk breast cancer patients, particularly those with triple-negative breast cancer (TNBC) or a family history of breast cancer. The absence of BRCA2 mutations in our cohort suggests potential regional genetic variations or population-specific factors, warranting further investigation in larger, ethnically diverse populations. Our findings underscore the importance of using clinical criteria (e.g., early age at diagnosis, TNBC, family history) to identify patients who are likely to benefit from genetic testing. While TNBC is a well-known indicator of BRCA positivity, our results highlight that other factors, such as family history and early-onset disease, are equally strong predictors. This has important implications for clinical practice, as it suggests that a comprehensive assessment of all risk factors should be used to guide genetic testing decisions.

The 100% BRCA positivity rate in metastatic cases reinforces the aggressive nature of BRCA1-associated tumors and the need for early genetic testing in advanced disease. Identifying BRCA mutations in these patients has critical therapeutic implications, as they may benefit from PARP inhibitors, such as olaparib and talazoparib, which have shown significant efficacy in BRCA-mutated breast cancers. Additionally, BRCA mutation carriers may opt for risk-reducing surgeries, such as bilateral mastectomy or prophylactic oophorectomy, to mitigate the risk of future malignancy. These interventions can significantly improve survival and quality of life for BRCA-positive patients, highlighting the importance of integrating genetic testing into routine clinical practice.

Our study also highlights the need for larger, multicentre studies to confirm these findings and explore potential regional genetic variations. The integration of **multigene panel testing** into routine clinical practice could help identify additional genetic predispositions beyond BRCA1/2, further refining risk assessment and treatment strategies.

In conclusion, our findings reinforce the importance of integrating BRCA testing into the routine clinical workup for high-risk breast cancer patients. Given the therapeutic and preventive implications of BRCA status, genetic counselling and testing should be routinely offered to high-risk patients, particularly in resource-limited settings where comprehensive multigene testing may not be feasible.

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