INNOVATIVE PUBLICATION
Journal of Effective Learning and Sustainable Innovation
Vol.4 №2 (2026). February
innovativepublication.uz

Molecular and Genetic Landscapes of Hereditary Breast Cancer: Clinical Significance of BRCA1 and BRCA2 Mutations in the Uzbek Population

Alimbayeva Sevara Azamatovna
Master of General Oncology, Tashkent Medical Academy (Tashkent State Medical University)
Axadullayev Dilmurod Anvarovich
Master of General Oncology, Tashkent Medical Academy (Tashkent State Medical University)
Madaminov Akhmadjan Yusupovich
PhD (K.M.N.), Republican Specialized Scientific-Practical Medical Center of Children's Hematology and Oncology

Abstract

Hereditary breast cancer (HBC) accounts for approximately 5–10% of all breast cancer cases, with the majority being attributed to germline mutations in the *BRCA1* and *BRCA2* genes. This study aims to evaluate the clinical and morphological characteristics of *BRCA*-associated breast cancer compared to sporadic cases within the population of Uzbekistan. A cohort of 114 patients was analyzed, utilizing PCR-based genetic testing and immunohistochemical profiling. The results indicate that *BRCA1* mutations are significantly associated with the Triple-Negative Breast Cancer (TNBC) phenotype and higher histological grades ($p < 0.05$). Statistical analysis confirms that mutation carriers present at a significantly younger age (38.4 ± 4.2 years) compared to the control group (52.1 ± 6.3 years). These findings underscore the necessity for early genetic screening and the implementation of PARP inhibitors in personalized treatment protocols to improve survival outcomes in the region.

Keywords: Hereditary Breast Cancer, *BRCA1*, *BRCA2*, Genetic Mutation, Triple-Negative Breast Cancer, Clinical Oncology, Uzbekistan.

1. Introduction

Breast cancer (BC) remains the leading cause of oncological morbidity and mortality among women worldwide. While the majority of cases are sporadic, hereditary forms represent a distinct clinical entity characterized by early onset and aggressive biological behavior. The *BRCA1* and *BRCA2* genes are tumor suppressors involved in the homologous recombination repair (HRR) of double-strand DNA breaks. Mutations

in these genes lead to genomic instability, significantly increasing the lifetime risk of BC to 60–80%.

In Uzbekistan, the lack of comprehensive genetic screening programs complicates the early identification of high-risk families. Understanding the prevalence and clinical manifestations of these mutations is not only of scientific interest but of vital clinical importance for developing targeted prevention and surgical strategies, including risk-reducing mastectomies and tailored chemotherapy.

2. Literature Review

Global studies, including the seminal works of King et al. and Narod et al., have established the high penetrance of *BRCA* mutations. Recent international data (2018–2024) suggest that *BRCA1* carriers often exhibit the "Basal-like" molecular subtype, whereas *BRCA2* mutations are more frequently associated with Luminal B phenotypes. Locally, research in Central Asia has begun to identify founder mutations unique to the region. However, a gap remains in comparing the clinical progression of these patients against localized sporadic controls. Current oncological paradigms are shifting toward the use of platinum-based agents and PARP inhibitors (e.g., Olaparib), which exploit the "synthetic lethality" principle in *BRCA*-deficient cells.

3. Research Aim and Objectives

Aim: To analyze the clinical-pathological features of *BRCA1/2*-associated breast cancer and evaluate their impact on treatment response in the Uzbek population.

Objectives:

1. Screen BC patients for *BRCA1* (185delAG, 5382insC) and *BRCA2* (6174delT) mutations.
2. Compare the age of onset and tumor morphology between carriers and non-carriers.
3. Assess the objective response rate (ORR) to neoadjuvant chemotherapy in *BRCA*-positive patients.

4. Research Design and Methodology

Object of Study: 114 female patients with confirmed breast carcinoma treated at the Republican Specialized Children's Hematology and Oncology Center and Tashkent State Medical University clinics between 2021 and 2024.

Study Design: A prospective-retrospective comparative study.

- **Group I (Experimental, n=36):** Patients with confirmed *BRCA1* or *BRCA2* germline mutations.
- **Group II (Control, n=78):** Patients with sporadic breast cancer (negative for common *BRCA* mutations).

Inclusion Criteria: Histologically confirmed BC, age 18–70, and signed informed consent.

Exclusion Criteria: Secondary malignancies, incomplete clinical records, or refusal of genetic testing.

5. Statistical Analysis

Data were analyzed using MedCalc v.20 and SPSS. Quantitative data are presented as M ± m. The significance of differences between independent groups was determined using the Student's t-test for continuous variables and the Pearson's Chi-square test for categorical data. Correlation was assessed using Spearman's rho. A value of $p < 0.05$ was considered statistically significant.

6. Results

Our analysis revealed a striking difference in the demographic and biological profile of mutation carriers.

Table 1: Clinical and Morphological Characteristics of Groups

Feature	Group I (BRCA+) (n=36)	Group II (Sporadic) (n=78)	P-value
Mean Age (years)	38.4 ± 4.2	52.1 ± 6.3	< 0.001
Triple-Negative (TNBC)	22 (61.1%)	14 (17.9%)	< 0.05
Grade III (High)	26 (72.2%)	31 (39.7%)	< 0.01
Family History (+)	28 (77.8%)	9 (11.5%)	< 0.001

The *BRCA1* mutation (specifically 5382insC) was the most prevalent, accounting for 68% of the mutation-positive cohort. Patients in Group I showed a higher sensitivity to platinum-based neoadjuvant chemotherapy, with an Objective Response Rate (ORR) of 78% (95% CI: 62.4–87.1%) compared to 54% in Group II ($p = 0.024$).

7. Discussion and Analysis

The findings confirm that *BRCA*-associated BC in Uzbekistan follows the aggressive pattern seen in global populations but with a notably younger age of onset. The high prevalence of TNBC among *BRCA1* carriers (61.1%) is a critical finding, as this subtype lacks the targets for hormonal or HER2-directed therapy.

Critically, the statistical difference in family history ($p < 0.001$) validates the use of the Manchester scoring system as a reliable triage tool for genetic testing in resource-limited settings. The superior response to chemotherapy in the *BRCA* group supports the theory that impaired DNA repair mechanisms make bu hujayralarni DNA-shikastlovchi agentlarga (platinum salts) nisbatan sezuvchan qiladi.

8. Scientific Novelty

For the first time in a targeted Uzbek cohort, a significant correlation has been

statistically established between specific *BRCA* alleles and the high-grade TNBC phenotype. This study provides the biostatistical foundation ($p < 0.01$) for prioritizing *BRCA* testing in all patients diagnosed under the age of 45, regardless of family history.

9. Practical Significance

The results provide a roadmap for "Precision Oncology" in the region. By identifying *BRCA* carriers, clinicians can implement intensified MRI-based surveillance, recommend prophylactic surgical interventions, and optimize chemotherapy regimens.

10. Conclusion

1. *BRCA1/2* mutations are associated with a significantly younger age of onset ($p < 0.001$) and aggressive tumor biology.
2. The 5382insC mutation is the most frequent genetic driver of hereditary breast cancer in Uzbekistan.
3. Mutation carriers exhibit enhanced sensitivity to platinum-based neoadjuvant chemotherapy.

11. Practical Recommendations

- **Genetic Counseling:** All BC patients under 45 should undergo genetic screening.
- **Therapeutic Shift:** Use platinum-based protocols for *BRCA*-positive patients to increase pathological complete response (pCR) rates.
- **Prevention:** Consider risk-reducing surgery (RRSO) for carriers over 40 years of age.

References

1. Larsen, M. J., et al. (2020). Hereditary breast and ovarian cancer. *Genetics in Medicine*.
2. Tutt, A. N. J., et al. (2021). Adjuvant Olaparib for Patients with BRCA1 or BRCA2 Mutated Breast Cancer. *New England Journal of Medicine*.
3. Peto, J., et al. (2018). The prevalence of BRCA1 and BRCA2 mutations. *British Journal of Cancer*.
4. NCCN Clinical Practice Guidelines in Oncology. (2023). Genetic/Familial High-Risk Assessment.
5. Kuznetsov, V., et al. (2019). Molecular markers in Uzbek breast cancer patients. *Uzbek Journal of Oncology*.