CLINICOPATHOLOGICAL AND GENETIC CHARACTERISTICS OF BREAST CANCER PATIENTS UNDERGOING MULTIGENE PANEL TESTING: A SINGLE-CENTER COHORT STUDY

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Abstract

Background: Breast cancer remains the leading malignancy among women worldwide, with a subset of cases linked to hereditary genetic mutations. Multigene panel testing plays an increasingly important role in identifying pathogenic variants and guiding management.
Methods: A retrospective cohort of 12 breast cancer patients who underwent genetic testing between 2022–2024 was analyzed. Clinical, pathological, and molecular data—including age, histology, grade, hormonal receptor profile, HER2 expression, and hereditary cancer gene mutations—were collected and evaluated.
Results: The mean age at diagnosis was 54 years. Invasive ductal carcinoma was the predominant subtype (≈75%). Grade 2 tumors represented the majority. Most patients were hormone receptor–positive (ER ≈80%, PR ≈70%), while HER2 positivity was observed in ~25% of cases. Two pathogenic variants were identified: BRCA2 (8.3%) and CHEK2 (8.3%). Ten patients (83.4%) tested negative.
Conclusion: The genetic mutation rate in this cohort was low, consistent with global data suggesting that most breast cancer cases are sporadic. Multigene testing remains essential for risk assessment and personalized therapy.

Keywords: breast cancer, genetic testing, BRCA2, CHEK2, hormone receptors, hereditary cancer.

Introduction

Breast cancer is the most frequently diagnosed cancer among women, representing a significant global health burden. While most breast cancer cases occur sporadically, approximately 5–10% are attributable to hereditary genetic mutations. The most well-established genes associated with hereditary breast cancer include BRCA1, BRCA2, and CHEK2.
The development of **multigene panel testing** has enabled simultaneous evaluation of multiple genes associated with increased cancer risk. This approach has significantly improved the ability to detect pathogenic variants beyond BRCA1/2.
In regions such as the Western Balkans, the prevalence and distribution of hereditary mutations have not been extensively documented. This study aims to evaluate the clinicopathological and genetic characteristics of breast cancer patients undergoing multigene testing at two oncology centers.

Materials and Methods

Study Design and Population

This retrospective study included **12 female patients** diagnosed with breast cancer between January 2022 and December 2024 at the Skopje oncology clinics. All patients met at least one criterion for hereditary cancer testing, including:

[1] early age at diagnosis
[2] bilateral breast cancer
[3] family history of breast/ovarian cancer
[4] triple-negative breast cancer
[5] or clinician referral based on suspicion

Data Collection

The following parameters were recorded:

1. **Age at diagnosis**
2. **Histological subtype** (ductal, lobular, NST)
3. **Tumor grade**
4. **Estrogen receptor (ER)** status
5. **Progesterone receptor (PR)** status
6. **HER2 expression**
7. **Genetic testing results**
8. Mutations in BRCA1, BRCA2, CHEK2, ATM, PALB2, and other genes included in standard multigene panels

Genetic Analysis

Testing was performed using commercial next-generation sequencing (NGS) multigene panels. Variants were classified according to ACMG guidelines into:

- pathogenic
- likely pathogenic
- variant of uncertain significance (VUS)
- benign

Statistical Methods

Descriptive statistics were used. Continuous variables were expressed as means, while categorical variables as percentages.

Results

Demographic and Clinical Characteristics

The mean age at diagnosis was **54 years** (range: 32–71). The majority had invasive ductal carcinoma (**~75%**), while lobular or NST subtypes represented the remainder.
Grade distribution indicated that **grade 2** tumors were the most prevalent.

Receptor Status

[1]. **ER-positive:** ~80%
[2]. **PR-positive:** ~70%
[3]. **HER2-positive:** ~25%

Most tumors belonged to **luminal-like molecular subtypes (A/B)**.

Genetic Findings

Pathogenic variants were found in:

- **BRCA2:** 1 patient (8.3%)
- **CHEK2:** 1 patient (8.3%)

No pathogenic variants were detected in **83.4%** of the cohort.

TABLE 1. Summary of Clinicopathological Characteristics

Variable	Value
Number of patients	12
Mean age	54 years
Invasive ductal carcinoma	75%
Lobular/NST	25%
Grade 2 tumors	Majority
Grade 3 tumors	Minority
ER positive	80%
PR positive	70%
HER2 positive	25%
BRCA2 mutation 1	8.3%
CHEK2 mutation 1	8.3%
Negative genetic results 10	83.4%

Discussion

The findings of this study are consistent with global epidemiological patterns, where invasive ductal carcinoma and luminal subtypes predominate. Hormone receptor positivity aligns with international data, reinforcing the relevance of endocrine therapy as a major component of treatment.
The identification of a **CHEK2 mutation**, a moderate-risk gene, is notable. CHEK2 carriers require enhanced screening due to elevated risk for contralateral breast cancer.

The relatively low prevalence of BRCA mutations indicates that most cases are sporadic, which is consistent with European data. Despite the low mutation yield, genetic testing still provides significant clinical value:

- identifies candidates for PARP inhibitors
- guides family counseling
- informs risk-reduction strategies

Conclusion

This study demonstrates that in our cohort, breast cancer is predominantly sporadic, with luminal subtype being most common. Genetic testing remains an essential component of personalized oncology care.
Further research with larger sample sizes is recommended to better understand hereditary breast cancer in the region.

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