Patterns and Prevalence of Pathogenic Germline Mutations Among Patients with Invasive Lobular Breast Cancer

Hikmat Abdel-Razeq[1,2], Faris Tamimi[1], Baha' Sharaf[1], Sarah Abdel-Razeq[2], Osama El Kahtib[1], Ahmad Sharaf[1], Hira Bani Hani[1], Areej Al-Atary[1], Lulwa El Saket[1], Yazan Talab[1], Hanan Khalil[1], Mohamad Harb[1], Seef Addin Yousef[1], Amani Nofal[1], Ahmad Alghrabli[1]

1 King Hussein Cancer Center, 2 School of Medicine, The University of Jordan

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Abstract

- Invasive lobular carcinoma (ILC) is the second most common breast cancer subtype, yet germline data in Arab patients are limited.[1,2]
- We reviewed 6,539 breast-cancer cases at King Hussein Cancer Center (2016–2024) and identified 477 with pure ILC who underwent germline testing.
- Pathogenic/likely pathogenic variants were found in 9.9 %—mainly *BRCA2* (53 %) and *BRCA1* (2 %)—and were associated with younger age and first-degree family history.
- These findings highlight the need for expanded genetic testing and counseling in high-risk ILC populations

Introduction

- Breast cancer is the second most common cancer worldwide and the leading cancer among women. Invasive lobular carcinoma (ILC) represents 10–15% of all breast cancers, typically presenting at an older age and showing higher rates of multifocality, multicentricity, bilaterality, ER/PR positivity, and lower HER2 expression.[1,2]
- Approximately 5–10% of breast cancers are hereditary, mainly due to *BRCA1/2* mutations. [2,3] However, the frequency of germline pathogenic variants in ILC is lower (≈5–7%), most often involving *ATM*, *BRCA2*, *CDH1*, *CHEK2*, and *PALB2*.[4] Some, such as *CDH1*, are linked to hereditary cancer syndromes.[5]
- Objective: To describe the prevalence and spectrum of germline pathogenic variants among Arab patients with ILC treated at King Hussein Cancer Center (KHCC).

Distribution of Pathogenic germline Mutations

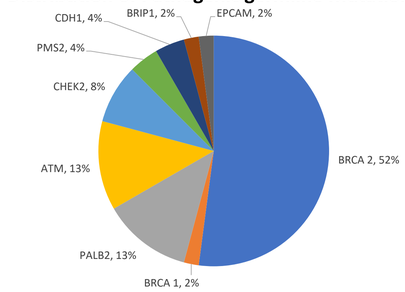


Figure 1. Distribution of Pathogenic germline mutation among patients with ILC (N=48)

Methods and Materials

- Design: Retrospective observational study (Jan 2016 – May 2024).
- Setting: King Hussein Cancer Center, Amman.
- Population: Histologically confirmed pure ILC cases that underwent germline testing using restricted or expanded gene panels.
- Analyses: Descriptive statistics; categorical data summarized as percentages.
- Comparisons: Chi-square and Fisher's exact tests used to compare variables between mutation-positive and mutation-negative patients, and between *BRCA* and *non-BRCA* carriers.

Characteristic	Overall (N=477)	
Gender	Female	475 (99.6%)
Age at Diagnosis	Median	49
	Range	19.0 - 89.0
Age Distribution	< 40	47 (9.9%)
	40 - 64	368 (77.1%)
	>64	62 (13%)
Nationality	Jordanian	452 (94.8%)
	Arab non-Jordanian	25 (5.2%)
Stage at diagnosis	Not metastatic	387 (81.1%)
Grade	1-2	407 (65.3%)
	3	70 (14.7%)
ER	Positive	454 (95.2%)
PR	Positive	439 (92.0%)
HER-2 Neu	Negative	433 (90.8%)
Unicentric vs Multicentric	Unicentric	270 (56.6%)
Breast cancer side	Left	201 (42.1%)
	Right	211 (44.2%)
	Bilateral	65 (13.6%)
Other type of malignancy	Breast	44 (9.2%)
	Others	17 (3.6%)
	None	416 (87.2%)
Family Hx of malignancy	Positive	406 (85.1%)

Results

- 477 patients were enrolled.
- Median age at diagnosis was 49 years and only 13% were ≥ 65 years. Except for 2, all were female. Most patients (95%) were ER-positive, 92% PR-positive and 91% HER2 negative. Multicentric disease was observed in 43% of patients, bilateral disease in 14%, and 19% presented with metastatic disease.
- A family history of breast cancer was reported in 39% of patients, including 25% who had a first-degree relative with the disease.
- The most common additional malignancy observed in these patients were breast cancer (9.2%), with colorectal and endometrial cancers each at 0.8%, and ovarian cancer in only one patient.
- Regarding genetic testing, 12.6% had limited gene panels and 87.4% had extended panels.
- Overall, 48 (10%) carried a P/LP variant, most frequently in *BRCA2* (n=25, 53.2%), followed by *ATM* and *PALB2* (n=6 each, 12.8%). *BRCA1* pathogenic variant was detected in only one patient. *BRCA1/2* mutations were significantly more common in patients younger than 40 years; 17.0% compared to only 4.2% in older patients, p<0.001.
- Patients with P/LP variants presented at younger ages, had more frequent first-degree breast cancer family history (p<0.001), and were more likely to undergo risk-reduction surgery (p<0.001).
  Both male patients also carried P/LP variants.

Discussion

- Our study revealed a germline pathogenic variant prevalence of ~10%, aligning with global reports (5–11%).[1]
- The clinicopathologic profile mirrored classic ILC features—strong ER/PR positivity (~95%), low HER2 expression (~9%), and frequent multifocal/bilateral presentation—confirming biological similarity to global cohorts.[2]
- *BRCA2* was the most common mutated gene (over half of carriers), consistent with international data identifying *BRCA2* as the major susceptibility gene in ILC.[4]
- *BRCA1* mutations were rare, whereas *ATM* and *PALB2* contributed notably, in line with their established association with lobular histology. [4]
- Both male ILC patients harbored germline variants, emphasizing the strong genetic component in male breast cancer.
- Younger patients (<40 years) had higher mutation rates (17%), supporting early genetic testing in this subgroup.
- This retrospective, single-center study with referral bias may overestimate germline mutation rates and limit broader population-level generalizability.

Significant Associations with Pathogenic/Likely pathogenic variants

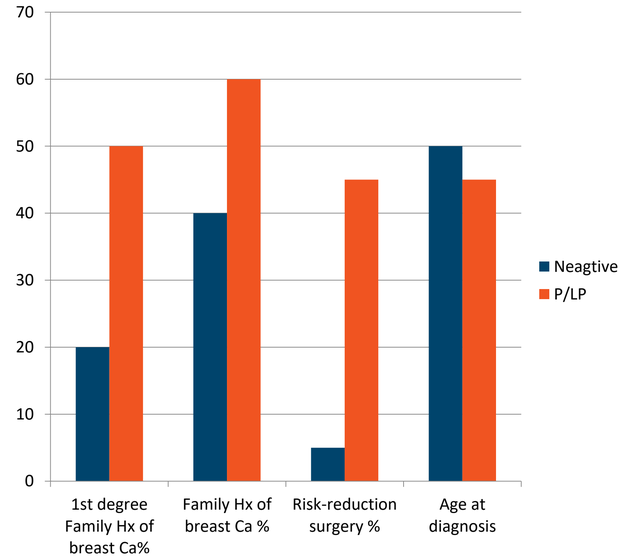


Figure 2. Variables significantly associated with pathogenic/likely pathogenic mutations.

Conclusions

- We found that many Jordanian patients with invasive lobular breast cancer had germline mutations, especially in *BRCA2*.
- Younger age at diagnosis and having a first-degree relative with breast cancer, were linked to a higher chance of having a pathogenic mutation.
- These results show the importance of genetic testing to guide preventive measures and personalize treatment.
- Larger future studies are needed to improve genetic testing guidelines and outcomes for these patients.

Contact

Hikmat Abdel Razeq M.D.
King Hussein Cancer Center
Email habdelrazeq@KHCC.JO
Tel + 962 6 530 0460 Ext : 1000
Mobile +962 79 643 3993

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