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ORIGINAL RESEARCH ARTICLE

Study of Significance and Expression of BRCA1 in Epithelial Ovarian Cancers and Association with Clinico-Pathological Parameters

Loitongbam Tappisana Chanu[1], Tanu Agrawal[2*], Surabhi Pandey[2]

ABSTRACT

Introduction: Epithelial ovarian carcinoma (EOC) remains the most fatal gynecological malignancy, largely due to late presentation and lack of effective screening markers. BRCA1, a tumor suppressor gene involved in homologous recombination repair, plays a crucial role in maintaining genomic stability. Loss of BRCA1 expression has been implicated in tumor aggressiveness, chemotherapy response, and prognostic stratification.

Immunohistochemistry (IHC) offers a practical approach to assessing BRCA1 protein status, particularly in resource-limited settings where molecular testing is not widely available. The aim is to evaluate BRCA1 expression in epithelial ovarian carcinomas and analyze its association with various clinicopathological parameters, including histological type, tumor grade, FIGO stage, and CA-125 levels.

Material and Methods: This prospective observational study included 35 histologically confirmed cases of epithelial ovarian carcinomas received as surgically resected salpingo-oophorectomy specimens over an 18-month period (May 2023–October 2024). BRCA1 expression was determined using immunohistochemistry and categorized as positive or negative based on cytoplasmic staining. Statistical analysis was performed using SPSS v21, with $p < 0.05$ considered significant.

Results: BRCA1 expression was negative in 54% and positive in 46% of cases. Serous carcinoma was the most common histological subtype (68.6%), and high-grade tumors accounted for 71.4%. A significant association was observed between BRCA1 loss and histological type ($p = 0.003$) and tumor grade ($p = 0.010$). Among serous carcinomas, high-grade tumors showed significant BRCA1 loss ($p = 0.027$). No significant correlation existed between BRCA1 expression and CA-125 levels ($p = 0.7817$) or FIGO stage ($p = 0.2034$).

Conclusion: BRCA1 loss is strongly associated with serous and high-grade epithelial ovarian carcinomas, supporting its role as a prognostic biomarker. Larger multicenter studies are required to validate its diagnostic utility.

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[1]Junior Resident, [2]Professor

Department of Pathology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India

***Corresponding Author:** Tanu Agrawal, Professor, Department of Pathology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India, e-mail: tanuagrawal510@yahoo.co.in

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INTRODUCTION

Epithelial ovarian carcinoma (EOC) is a complex gynecological malignancy arising from the ovarian surface epithelium and includes subtypes such as serous, mucinous, endometrioid, and clear cell carcinomas. BRCA1, a tumor suppressor gene, is integral for DNA repair through the homologous recombination pathway, ensuring genomic stability. Alterations or loss of BRCA1 function contribute to genetic instability and increased susceptibility to ovarian malignancy.[1]

BRCA1 protein expression has been studied to understand its role in tumor biology and its correlation with clinicopathological features. BRCA1 protein expression was evaluated in epithelial ovarian cancers, and loss of BRCA1 expression was observed in 33.7 % of cases, particularly in high-grade tumors, indicating its potential correlation with tumor aggressiveness and clinicopathological features.[2] In high-grade serous ovarian carcinoma, BRCA1 expression correlates with response to neoadjuvant chemotherapy and tumor aggressiveness, highlighting its clinical impact.[3]

In the Indian context, BRCA mutations show a variable prevalence among breast and ovarian cancer patients. Systematic reviews have emphasized the necessity of population-specific data to guide screening, risk assessment, and management strategies.[4] BRCA1 expression was observed in 61.2% of ovarian serous carcinoma cases, with a significant association between positive BRCA1 expression and higher tumor grade, advanced stage, and reduced disease-free and overall survival ($p < 0.05$).[5] Additionally, mRNA expression levels of BRCA1 and BRCA2 have been shown to influence therapy response and survival, supporting the clinical relevance of these biomarkers.[6]

In high-grade serous ovarian carcinoma, the solid, pseudo-endometrioid, and transitional (SET) growth pattern was observed in 64.4% of cases, with BRCA1 loss detected in 35.5% of the tumors, highlighting the prevalence of altered BRCA1 expression in this histological subtype.[7] Systematic reviews have confirmed the reliability of IHC for detecting BRCA1/2 protein loss and its association with survival outcomes.[8] In epithelial ovarian cancers lacking germline BRCA1/2 mutations, immunohistochemical analysis can still reveal distinct protein expression patterns, emphasizing the value of IHC in characterizing tumor biology and assessing molecular alterations.[9] Furthermore, pathogenic or likely pathogenic BRCA1/2 variants influence tumor characteristics, recurrence risk, and therapy responsiveness across diverse populations.[10]

Given the high mortality of EOC and the scarcity of region-specific studies in India, evaluating BRCA1 expression through IHC is crucial to inform prognosis, optimize therapy, and generate local evidence. This establishes the rationale for the present study, which aims to evaluate the significance and expression of BRCA1 in epithelial ovarian carcinomas and its association with clinico-pathological parameters.

MATERIALS AND METHODS

This was a prospective observational study conducted in the Department of Pathology in collaboration with the Departments of Obstetrics & Gynecology and Radiation Oncology at SRMS Institute of Medical Sciences, Bareilly, India. The study was carried out over 18 months from 1st May 2023 to 31st October 2024. It included histologically confirmed cases of epithelial ovarian carcinoma, including fallopian tube and primary peritoneal serous carcinomas obtained from surgically resected salpingo-oophorectomy specimens.

Consecutive sampling was adopted, enrolling all eligible patients who met the inclusion criteria. A minimum sample size of 35 cases was determined by statistical calculation using the formula $n = Z^2_{1-\alpha/2} \times Sn\ (100 - Sn) / L^2 \times Prevalence$, where Z denotes the standard normal variate corresponding to the desired confidence level, Sn represents sensitivity, and L indicates the acceptable margin of error. Patients who underwent surgical resection of salpingo-oophorectomy specimens of confirmed epithelial ovarian carcinomas and fallopian tube carcinomas. Primary peritoneal serous carcinomas were included. Patients with non-neoplastic lesions, tumors other than epithelial ovarian carcinomas, small biopsies, recurrent or metastatic disease, and specimens lacking clinical information were excluded.

Procedure

Specimens were fixed in 10% neutral buffered formalin for 24 hours, grossed, and processed for paraffin embedding. Serial 5 μm sections were cut, mounted on adhesive-coated slides, and stained with hematoxylin and eosin (H&E) for histopathological evaluation according to the WHO classification and FIGO staging.

Immunohistochemistry

Sections (2–3 μm) were processed for BRCA1 IHC using GLK-2 clone antibody on Leica BOND-MAX. Antigen retrieval, primary and secondary antibody incubation, visualization with DAB, and hematoxylin counterstaining were performed following the manufacturer's protocols. Breast cancer tissue with a known BRCA1 mutation was used as a positive control. BRCA1 expression was evaluated based on cytoplasmic staining and categorized as positive or negative.

Statistical Analysis

Data were collected using a structured proforma capturing clinical and pathological variables such as age, tumor characteristics, invasion status, stage, lymph node involvement, ascitic fluid cytology, CA-125 levels, and BRCA1 expression. Entries were compiled in Microsoft Excel and analysed using SPSS v21 and Minitab, applying appropriate statistical tests with a significance threshold of $p < 0.05$.

Ethical Approval

Ethical approval was secured from the institutional ethics committee, and written informed consent was obtained from all participants, ensuring confidentiality and adherence to ethical research standards.

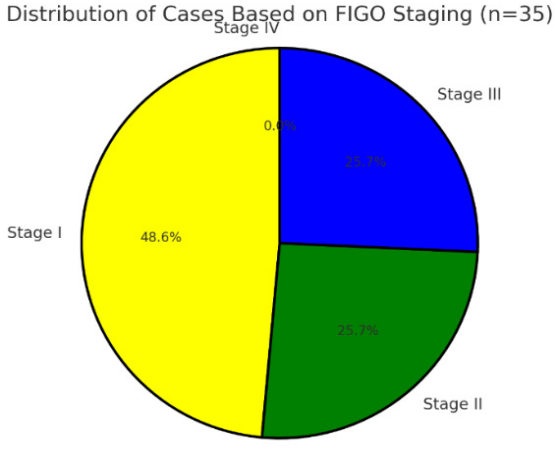

Figure 1: Distribution of cases based on FIGO staging

Table 1: Baseline clinicopathological characteristics of study participants (n = 35)

Parameter	*Category*	*Frequency*	*Percentage*
Age (years)	21–30	2	5.8
	31–40	4	11.4
	41–50	12	34.3
	51–60	11	31.5
	61–70	3	8.5
	70–80	3	8.5
Histological type	Serous carcinoma	24	68.6
	Mucinous carcinoma	6	17.2
	Endometrioid carcinoma	3	8.5
	Clear cell carcinoma	2	5.7
Tumor grade	High grade	25	71.4
	Low grade	10	28.6

Table 2: BRCA1 expression status and diagnostic performance metrics

Parameter	*Category/Description*	*Value*
BRCA1 expression status	Negative	19 (54%)
	Positive	16 (46%)
Total Cases		35 (100%)
Diagnostic Performance	Sensitivity (TP/TP + FN × 100)	53%
	Specificity (TN/TN + FP × 100)	40%
	Positive Predictive Value (TP/TP + FP × 100)	84%
	Negative Predictive Value (TN/TN + FN × 100)	12%

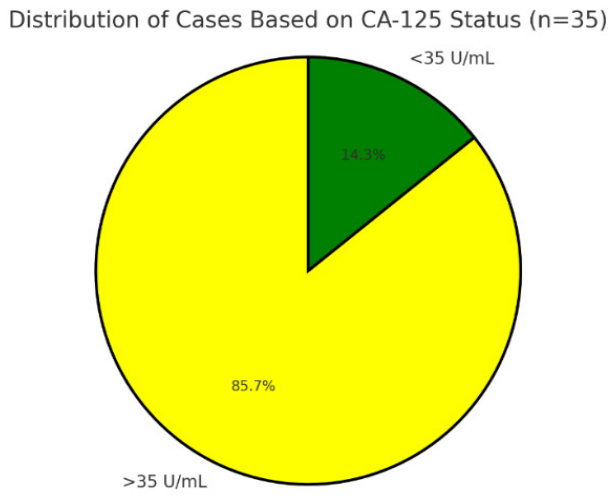

Figure 2: Distribution of cases based on CA-125 status

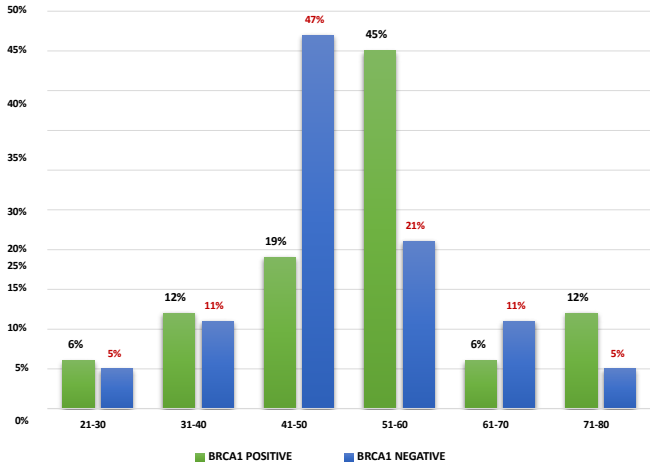

Figure 3: Association between BRCA1 Expression and Age in patients

Table 3: Association between BRCA1 expression and clinicopathological parameters (n = 35)

Parameter	*Category*	*BRCA1 Positive (n = 16)*	*BRCA1 Negative (n = 19)*	*Total (n = 35)*	*p-value*	*Significance*
Histological type	Serous carcinoma	7 (44%)	17 (90%)	24 (68.6%)	0.003	Significant
	Non-serous (Total)	9 (56%)	2 (10%)	11 (31.4%)		
	- Mucinous	5 (32%)	1 (5%)	6 (17.2%)		
	- Endometrioid	2 (12%)	1 (5%)	3 (8.5%)		
	- Clear cell	2 (12%)	0 (0%)	2 (5.7%)		
Tumor grade	High Grade	8 (50%)	17 (90%)	25 (71.4%)	0.010	Significant
	Low Grade	8 (50%)	2 (10%)	10 (28.6%)		
Serous carcinoma grading only	High Grade Serous	4 (57%)	16 (94%)	20 (83%)	0.0271	Significant
	Low Grade Serous	3 (43%)	1 (6%)	4 (17%)		

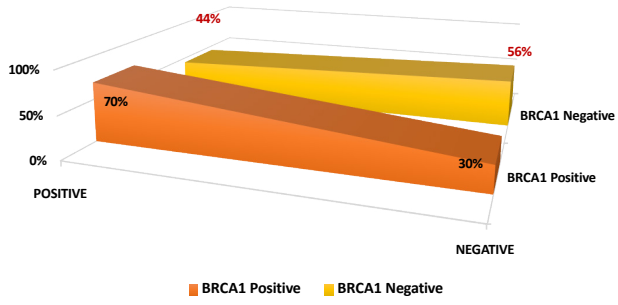

Figure 4: Association of BRCA1 expression with peritoneal/ascitic fluid status

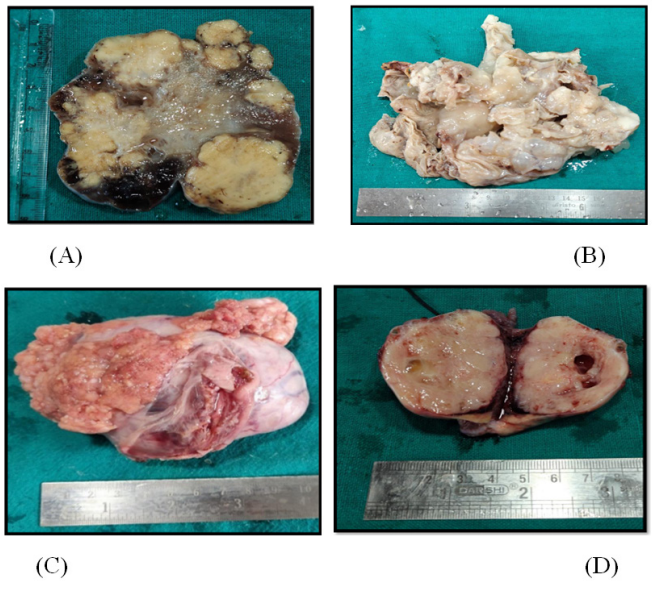

Figure 5: (A) Cut surface of high-grade serous carcinoma with solid cystic area, papillary-like growth, (B) Cut surface of mucinous carcinoma ovary showing solid cystic areas with no discrete nodularity, (C) Endometrioid carcinoma outer surface with solid cystic component and areas of hemorrhage, (D) Cut surface of clear cell carcinoma ovary with solid cystic areas

RESULTS

In the present study, 35 cases of epithelial ovarian carcinoma were evaluated. The baseline clinicopathological characteristics are shown in Table 1, where the majority of patients belonged to the 41 to 50-year age group, serous carcinoma was the predominant histological subtype (68.6%), and high-grade tumors constituted 71.4% of cases. Table 2 demonstrates BRCA1 expression status, showing loss of BRCA1 expression in 54% of cases and retained expression in 46%, along with diagnostic performance values: sensitivity 53%, specificity 40%, PPV 84%, and NPV 12%.

The distribution of FIGO staging is illustrated in Figure 1, and CA-125 status is represented in Figure 2.

A statistically significant association was identified between BRCA1 loss and histological type, as well

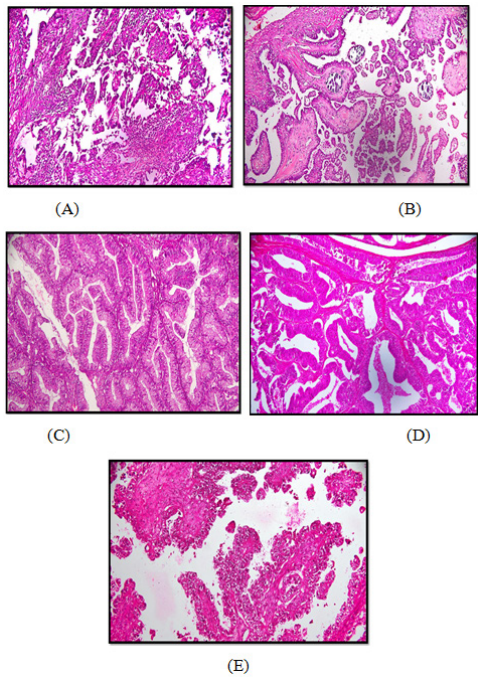

Figure 6: (A) H&E stain of high-grade serous carcinoma showing solid masses of columnar to cuboidal cells with slit-like spaces. Significant nuclear atypia and nuclear pleomorphism, (B) H&E stain of low-grade serous carcinoma in micropapillary pattern showing monotonous to moderately pleomorphic cells, (C) H&E stain of mucinous carcinoma with back to back intestinal type glands, (D) H&E stain of endometrioid carcinoma in confluent (back to back) gland arrangement, (E) H&E stain of clear cell carcinoma in papillary architecture showing polyhedral to hobnail cells with uniform nuclear atypia and clear to pale eosinophilic cytoplasm

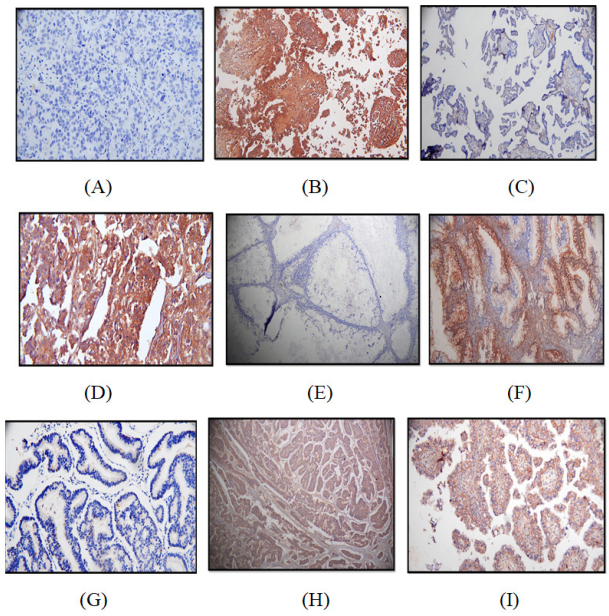

Figure 7: (A) IHC of High-grade serous carcinoma showing loss of BRCA1 expression, (B) IHC of high-grade serous carcinoma showing positive BRCA1 expression, (C) IHC of low-grade carcinoma showing BRCA1 loss of expression, (D) IHC of low-grade carcinoma showing positive BRCA1 expression, (E) IHC of mucinous carcinoma showing loss of BRCA1 expression, (F) IHC of mucinous carcinoma showing positive BRCA1 expression, (G) IHC of endometrioid carcinoma with loss of BRCA1 expression, (H) IHC of endometrioid carcinoma showing positive BRCA1 expression, (I) IHC of clear cell carcinoma showing positive BRCA1 expression.

as tumor grade, detailed in Table 3 (p = 0.003 and p = 0.010, respectively). When evaluated exclusively in serous carcinoma, BRCA1 loss demonstrated significant correlation with high-grade tumors (p = 0.0271).

Additional graphical representation of relationships between BRCA1 and clinicopathological parameters is presented in Figure 3 (BRCA1 and age) and Figure 4 (BRCA1 and ascitic cytology), both showing statistically insignificant associations. These findings indicate that BRCA1 loss is strongly associated with aggressive tumor phenotype, particularly high-grade serous carcinoma, supporting its role as a potential prognostic biomarker.

DISCUSSION

Ovarian carcinoma is a major global health burden and remains the most lethal among gynecological malignancies due to its asymptomatic onset and delayed diagnosis. Epithelial ovarian carcinoma (EOC) constitutes approximately 95% of all ovarian cancers, and growing evidence supports the association of BRCA1 dysfunction with tumor behavior, therapeutic response, and patient outcomes. Immunohistochemistry (IHC) serves as an inexpensive and accessible initial tool for evaluating BRCA1 protein expression and may be useful in predicting prognosis and guiding individualized therapy, especially in settings where molecular testing remains limited (Figures 5 to 7).

In the present study, 35 histologically confirmed cases of epithelial ovarian carcinoma were evaluated to determine the significance of BRCA1 expression and its association with clinicopathological parameters. The majority of cases occurred in the 41 to 50 year age group, with a mean age of 51 years, consistent with findings from Okecha *et al*.[2] and Manchana *et al*.,[11] who reported mean ages of 52.7 and 48.7 years, respectively. Histologically, serous carcinoma was the most common subtype (68.6%), followed by mucinous (17.2%), endometrioid (8.5%), and clear cell carcinoma (5.7%). This aligns with previous studies by McCluggage *et al*.[12] and Gaona-Luviano *et al*.,[13] who similarly documented serous carcinoma as the predominant epithelial subtype worldwide.

High-grade tumors accounted for 71.4% of cases in the current study, reinforcing the aggressive biological behavior of EOC, which frequently presents with advanced differentiation. Comparable findings were reported by Manchana *et al*.,[11] where high-grade serous carcinoma represented the majority of cases. In this study, BRCA1 expression was negative in 54% of cases and positive in 46%, supporting earlier results by Okecha *et al*.,[2] who reported altered BRCA1 expression in 34% of tumors, and Amin *et al*., who documented BRCA1 retention in 60% of EOCs.

A statistically significant association was identified between BRCA1 loss and histological type (p = 0.003), with serous carcinoma demonstrating BRCA1 negativity in 90% of cases. This significant association is consistent with studies by Teixeira *et al*.[8] and Thrall *et al*.[14] who noted higher BRCA1 loss among serous tumors. BRCA1 loss was also significantly correlated with high tumour grade (p = 0.010), and when analysis was restricted to serous carcinoma alone, high-grade serous tumors demonstrated a significant association with BRCA1 loss (p = 0.027). These findings support work by Amin *et al*.,[5] who observed similar correlations, and reflect the biological aggressiveness of BRCA1-deficient tumors.

Although CA-125 levels were elevated in 86% of cases, no significant association was found between BRCA1 expression and CA-125 status (p = 0.7817), suggesting that serum markers do not reliably reflect underlying BRCA1 alterations. Similarly, FIGO staging did not show a significant relationship with BRCA1 expression (p = 0.2034), implying that BRCA1 loss may be an early molecular event rather than a parameter linked to clinical stage. These findings concur with study results from Shawky *et al*.,[15] who also reported no correlation between stage and BRCA1 expression.

Overall, the results of this study indicate that BRCA1 loss plays a critical role in tumor biology, particularly in high-grade and serous epithelial ovarian carcinomas, and may serve as a valuable prognostic biomarker. However, its role as a screening tool is limited due to low sensitivity and specificity, and therefore, it may be best used in combination with other diagnostic modalities.

LIMITATIONS

Single-center study and limited sample size.

CONCLUSION

BRCA1 loss of expression was observed in more than half of epithelial ovarian carcinoma cases, showing a significant association with serous histology and high-grade tumors. These findings highlight the potential role of BRCA1 as an important prognostic biomarker in EOC. However, no significant correlation was found between BRCA1 expression and CA-125 levels or FIGO stage. Although BRCA1 IHC may support risk stratification and treatment planning, its limited diagnostic accuracy indicates the need for larger multicenter studies and combined biomarker approaches to enhance early detection and patient outcomes.

ETHICAL APPROVAL

Obtained.

CONSENT

Written consent secured.

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