Original Article

Immunoexpression of P53, KRAS, BRAF, PTEN and PIK3CA in ovarian epithelial carcinomas

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Abstract

Background: Epithelial ovarian carcinomas (EOCs) constitute the majority of ovarian malignancies and display distinct molecular profiles based on histologic subtype. The dualistic model classifies EOCs into Type I and Type II tumors, based on differing morphologic and molecular characteristics. While TP53 mutations predominate in Type II tumors, Type I tumors frequently harbor alterations in genes such as KRAS, BRAF, PTEN, and PIK3CA. Immunohistochemistry (IHC) serves as a cost-effective and accessible surrogate for detecting underlying molecular abnormalities This is study to evaluate the immunohistochemical expression of P53, KRAS, BRAF, PTEN, and PIK3CA across major histological subtypes of ovarian epithelial carcinomas and assess their correlation with tumor type and known mutation frequencies.. **Materials and Methods:** This prospective cross-sectional study included 52 histologically confirmed cases of epithelial ovarian carcinoma. Immunohistochemistry was performed on 73 tumor samples (including bilateral cases) using standard protocols. Marker expression was evaluated and classified based on established IHC scoring criteria. Tumors were categorized into Type I (P53 wild-type) and Type II (P53 mutant) according to the dualistic model. Statistical analysis was performed using Chi-square test. **Results:** High-grade serous carcinoma (HGSC) was the most common subtype (65.4%), followed by low-grade serous, mucinous, and endometrioid carcinomas. Mutant P53 expression was seen in 70.8% of HGSC, validating its utility as a surrogate marker for TP53 mutation. KRAS was positive in a majority of Type I and Type II tumors (62.2% and 69.4%, respectively). BRAF expression was limited to Type I tumors, with 40% positivity in low-grade serous carcinoma. PTEN loss was more frequent in Type I tumors (59.5%) compared to Type II (41.7%). PIK3CA expression was significantly higher in Type I tumors (67.6%) compared to Type II (47.2%) ($p = 0.042$). Discordant immunoexpression was observed in some bilateral tumors. **Conclusion:** The study supports the dualistic model of ovarian carcinogenesis, with distinct immunoprofiles observed between Type I and Type II tumors. PIK3CA showed significant discriminatory value and may be useful alongside P53 for molecular classification. However, discrepancies with known mutation frequencies highlight the need for further standardization of IHC protocols and validation with molecular studies.

Keywords: Ovarian epithelial carcinoma; P53; KRAS; BRAF; PTEN; PIK3CA; Immunohistochemistry; Dualistic model; High-grade serous carcinoma; Molecular classification.

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Introduction

Ovarian cancer ranks as the eighth most common malignancy among women worldwide and remains the leading cause of death from gynecological cancers.[1,2] Among its various forms, epithelial ovarian carcinomas (EOCs) account for approximately 90% of all cases. According to the World Health Organization (WHO) classification, EOCs are histologically categorized into five major subtypes: high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), endometrioid carcinoma (EC), clear cell carcinoma (CCC), and mucinous carcinoma (MC). These subtypes are further stratified based on the dualistic model of ovarian carcinogenesis into two distinct categories: Type I tumors: which include LGSC, EC, MC, and malignant Brenner tumors, are typically slow-growing, often arise from benign or borderline precursors, and are characterized by genomic stability. These tumors frequently harbor mutations in genes such as KRAS, BRAF, PTEN, ARID1A, PIK3CA, and also demonstrate microsatellite instability. Type II tumors: such as HGSC, carcinosarcomas, and undifferentiated carcinomas, are highly aggressive, lack identifiable precursor lesions, and display marked genomic instability with near-universal mutations in the TP53 gene.[3,4] With the increasing understanding of the molecular

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pathogenesis of EOCs, there is growing emphasis on the importance of molecular characterization to inform targeted therapeutic strategies. Immunohistochemistry (IHC) serves as a practical and accessible technique for evaluating protein expression and can act as a surrogate marker for underlying genetic alterations. For example, aberrant P53 immunoexpression has been well established as a reliable proxy for TP53 mutations.[5,6]

In this context, the present study aims to evaluate the immunohistochemical expression of KRAS, BRAF, PTEN, and PIK3CA in ovarian epithelial carcinomas, alongside P53. Furthermore, the study attempts to correlate these immunoexpression patterns with known molecular alterations reported in the literature, thereby contributing to the understanding of subtype-specific tumorigenesis and potential implications for precision oncology in ovarian cancer.

Materials and Methods

Study Design and Duration: This was a prospective cross-sectional study conducted over a period of one and a half years at a tertiary care center. The study was approved by the institutional ethics committee.

Inclusion Criteria: All surgically resected cases histologically diagnosed as ovarian epithelial carcinomas.

Exclusion Criteria: Tumors diagnosed solely on core needle biopsies or samples deemed insufficient for analysis.

Clinical and Histopathological Assessment

Relevant clinical data including patient age and tumor laterality were recorded.

Tissue specimens were formalin-fixed and paraffin-embedded (FFPE), and hematoxylin and eosin (H&E) staining was performed for histopathological evaluation. Tumors were subtyped according to the World Health Organization (WHO) classification of ovarian epithelial tumors. Histologic grading of endometrioid and mucinous carcinomas was carried out based on the three-tier FIGO grading system.[7]

Molecular Classification

Based on P53 immunohistochemical (IHC) expression, tumors were classified in line with the dualistic model of Kurman and Shih:[3,4] Type I tumors: P53 wild-type pattern; Type II tumors: P53 mutant-type pattern

Immunohistochemistry (IHC)

It was done by manual staining. Heat induced antigen retrieval was done in pressure cooker with TRIS EDTA buffer pH 9. Interpretation of markers: KRAS (rabbit polyclonal, Medaysis) and BRAF (rabbit monoclonal antibody, clone RM8, BioSB) were considered positive if there was cytoplasmic positivity of any intensity in greater than 10% of the tumour cells.[8] PTEN (mouse monoclonal antibody, clone 6H2.1, Master diagnostica) was interpreted as lost when there was none or weaker staining in the tumour cells compared to stromal cells.[9,10] PIK3CA (rabbit monoclonal antibody, clone SP139, Zytomed systems) was considered positive if there was membranous positivity of any intensity in greater than 10% of tumour cells.[11] Immunopositivity for KRAS, BRAF, PIK3CA and loss of expression for PTEN indicate possible mutation of the respective genes. P53 (mouse monoclonal, clone DO7, Biogenex) was interpreted as mutant type if there was nuclear positivity in greater than 60% tumour cells (overexpression) or no staining at all (null) and as wild type when less than 60% tumour cells were positive.[5]

Statistical Analysis

Categorical variables were expressed as counts and percentages; continuous variables as means. Chi-square test was applied, and p-values <0.05 were considered statistically significant. Analysis was done using SPSS version 26.

Results

A total of 52 patients were diagnosed with epithelial ovarian carcinoma. Patient ages ranged from 30 to 78 years, with a mean age of 53.6 years. The largest age group was 51–60 years (34.6%).

Histopathologic Subtypes

- HGSC: 34 cases (65.4%)
- LGSC: 9 cases (17.3%)
- MC: 6 cases (11.5%)
- EC: 3 cases (5.8%), including one high-grade EC

Laterality and Sample Size

Bilateral ovarian involvement was observed in 25 cases, and IHC was performed on both sides, giving a total of 77 samples. Four samples were excluded due to tissue depletion in deeper sections. Thus, 73 samples were analyzed.

PTEN IHC could not be performed in 7 samples due to unavailability of the reagent. These included 4 HGSC, 2 MC, and 1 high-grade EC.

Final Sample Distribution

- HGSC: 48 samples (65.8%)
- LGSC: 15 samples (20.5%)
- MC: 7 samples (9.6%)
- EC: 3 samples (4.1%)

Bilateral tumors in each case showed identical morphology and grade.

Immunoexpression in histological subtypes:

The comparative analysis of immunohistochemical marker expression between Type I and Type II ovarian epithelial carcinomas revealed important molecular distinctions that align with the dualistic model of ovarian tumorigenesis [Table 1]. KRAS expression was observed in a high proportion of both Type I (62.2%) and Type II tumors (69.4%), though this difference was not statistically significant ($p = 0.406$). While KRAS mutations are characteristically associated with Type I tumors particularly low-grade serous and mucinous carcinomas the relatively high frequency in Type II tumors suggests potential alternative pathways or overexpression without mutation in high-grade carcinomas, warranting further molecular correlation.

BRAF expression followed a similar pattern, with 27% of Type I and 22.2% of Type II tumors showing positivity, again without a statistically significant difference ($p = 0.583$). BRAF mutations are well-documented in Type I tumors, particularly low-grade serous carcinoma, but their low expression levels across subtypes in this study reflect the rarity of BRAF alterations in high-grade disease.

Interestingly, PTEN loss was more frequently observed in Type I tumors (59.5%) compared to Type II tumors (41.7%), although this trend did not reach statistical significance (p = 0.0825). These findings support previous evidence that PI3K/AKT pathway dysregulation, often via PTEN loss, is a common event in endometrioid and clear cell carcinomas classified as Type I.

The most notable and statistically significant finding was with PIK3CA expression, where 67.6% of Type I tumors were positive compared to only 47.2% of Type II tumors (p = 0.042). This reinforces the role of PIK3CA activation in the pathogenesis of Type I tumors, particularly endometrioid and mucinous subtypes. The difference highlights the potential of PIK3CA as a biomarker and therapeutic target in Type I ovarian cancers.

Overall, while KRAS, BRAF, and PTEN showed expected trends aligning with known molecular profiles of Type I and II tumors, only PIK3CA expression demonstrated a statistically significant association, underscoring its relevance in molecular classification and its potential for targeted therapy development.

Table 1: Association of Immunoexpression of KRAS, BRAF, PTEN, and PIK3CA with Type I and Type II Tumors

IHC Marker	IHC Expression	Type I (n = 37)	Type II (n = 36)	Total	p-value
KRAS	Positive	23 (62.2%)	25 (69.4%)	48	0.406
	Negative	14 (37.8%)	11 (30.6%)	25	
BRAF	Positive	10 (27.0%)	08 (22.2%)	18	0.583
	Negative	27 (73.0%)	28 (77.8%)	55	
PTEN	Retained	11 (29.7%)	18 (50.0%)	29	0.0825
	Lost	22 (59.5%)	15 (41.7%)	37	
	Not Done	04 (10.8%)	03 (8.3%)	07	
PIK3CA	Positive	25 (67.6%)	17 (47.2%)	42	0.042
	Negative	12 (32.4%)	19 (52.8%)	31	

Note: Type I tumors include LGSC, MC, EC; Type II tumors include HGSC and related high-grade subtypes; Statistical test used: Chi-square test of independence; Significance threshold: $p < 0.05$.

Comparison of Immunoexpression

[Table 2] provides a comparative overview of the immunoexpression results from the current study against the documented frequencies of molecular alterations (Mol.Alt.) from published literature across the major histologic subtypes of epithelial ovarian carcinoma: high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), mucinous carcinoma (MC), and endometrioid carcinoma (EC).

P53

In HGSC, the present study found mutant P53 expression in 70.8%, which is consistent with the high frequency of TP53 mutations (~96%) reported in TCGA and other genomic studies. This validates P53 IHC as a robust surrogate marker in HGSC. Conversely, P53 mutations were rare or absent in LGSC and MC in both our study and the literature, supporting their classification as Type I tumors, typically not driven by TP53 alterations. In EC, 1 of 3 cases (33.3%) showed mutant P53, which may correspond to high-grade endometrioid tumors where TP53 mutations are more frequently encountered.

KRAS

KRAS positivity in our cohort showed notable expression across all subtypes, particularly in LGSC (73.3%), MC (71.4%), and EC (100%), aligning with literature reports that document KRAS mutations in 26–64% of LGSC and MC cases. Interestingly, HGSC also showed a 60.4% KRAS positivity rate in IHC, despite literature indicating mutation rates as low as 11%. This suggests that while KRAS protein may be expressed, it may not necessarily indicate mutation in HGSC, underlining the limitation of IHC as a mutation surrogate in this context.

BRAF

Our study found low BRAF expression in HGSC (22.9%), aligning with the extremely low mutation rate (~0.5%) reported in the literature. In LGSC, 40% BRAF positivity was observed, consistent with published mutation frequencies of 38%, reinforcing the role of BRAF in the pathogenesis of LGSC. In MC and EC, BRAF positivity was absent or low in both the current study and previous studies, supporting its limited role outside of LGSC.

PTEN

PTEN loss was frequently observed in LGSC (66.7%) and HGSC (52.3%), which contrasts with the low mutation frequencies reported in the literature (7% for HGSC). This discrepancy may suggest alternative mechanisms of PTEN inactivation, such as promoter methylation or post-translational degradation, which are not always mutation-driven. In EC, PTEN loss was observed in all tested cases, consistent with the well-established role of PTEN loss in EC as documented in literature (~33.3%).

PIK3CA

The most striking observation was the high frequency of PIK3CA immunoexpression in MC (85.7%), LGSC (73.3%), and EC (66.7%), compared to literature mutation frequencies ranging from 11% to 13.5%. This suggests that PIK3CA protein overexpression may not always correlate with gene mutation but may still indicate activation of the PI3K/AKT/mTOR pathway. Even in HGSC, where literature reports only 18% mutation frequency, our study found 47.9% PIK3CA positivity, possibly reflecting pathway up regulation via mechanisms other than mutation (e.g., upstream receptor tyrosine kinase activation). Overall, the IHC findings in this study largely mirror the molecular alteration profiles reported in literature, particularly for P53 in HGSC, KRAS and BRAF in LGSC and MC, and PTEN in EC. However, discrepancies especially in PIK3CA and PTEN expression highlight the complexity of correlating protein expression with underlying genetic alterations. This underscores the importance of integrating IHC with molecular diagnostics for a comprehensive understanding

of tumor biology, especially in guiding targeted therapeutic strategies.

Table 2: Comparison of Immunoexpression in Present Study with Reported Molecular Alteration Frequencies across Histologic Subtypes

Marker	HGSC Our Study	HGSC Mol.Alt.[15]	LGSC Our Study	LGSC Mol.Alt.[16,22]	MC Our Study	MC Mol.Alt.[25–27]	EC Our Study	EC Mol.Alt.[26,28,30]
P53 (Mutant)	34 (70.8%)	~96%	1 (6.7%)	0%[16]	0	~56.8%[26]	1 (33.3%)	–
KRAS (+)	29 (60.4%)	~11%	11 (73.3%)	~26.7%[16]	5 (71.4%)	~64%[27]	3 (100%)	~42%[28]
BRAF (+)	11 (22.9%)	~0.5%	6 (40.0%)	~38%[22]	0	~0–5%[25,26]	2 (66.7%)	~24%[29]
PTEN (Loss)	23 (52.3%)	~7%	10 (66.7%)	–	2 (40.0%)	~2.7%[26]	2 (100%)	~33.3%[28]
PIK3CA (+)	23 (47.9%)	~18%	11 (73.3%)	~11%[22]	6 (85.7%)	~13.5%[26]	2 (66.7%)	~12%[30]

Abbreviations: HGSC = High-Grade Serous Carcinoma; LGSC = Low-Grade Serous Carcinoma; MC = Mucinous Carcinoma; EC = Endometrioid Carcinoma Mol.Alt. = Molecular Alteration; (+) = Positive Expression; (Mutant) = Mutant Pattern; (Loss) = Loss of Expression.

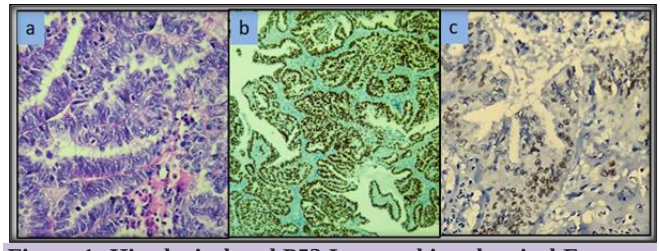

Figure 1: Histological and P53 Immunohistochemical Features of High-Grade Serous Carcinoma (HGSC)

(a) Hematoxylin and eosin (H&E) stained section showing papillary and micropapillary architecture with marked nuclear atypia, prominent nucleoli, and high mitotic activity, consistent with high-grade serous carcinoma (×200).
(b) Immunohistochemical staining for P53 showing diffuse and strong nuclear overexpression in nearly all tumor cells, representing the mutant (missense) pattern typically seen in HGSC (×200).
(c) Another case of HGSC showing heterogeneous and scattered P53 nuclear staining, indicative of a wild-type expression pattern (×400). This pattern suggests functional TP53 and is rarely encountered in morphologically high-grade tumors.

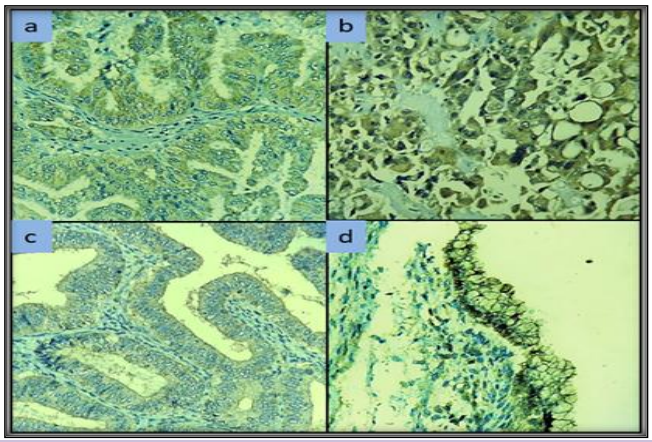

Figure 2: KRAS Immunopositivity in Histologic Subtypes of Ovarian Epithelial Carcinomas (×400)

a) High-grade serous carcinoma (HGSC) showing diffuse moderate cytoplasmic immunopositivity for KRAS in tumor cells.
b) Low-grade serous carcinoma (LGSC) demonstrating strong granular cytoplasmic KRAS staining, consistent with frequent KRAS pathway activation in Type I tumors.
c) Endometrioid carcinoma (EC) with diffuse cytoplasmic KRAS positivity in malignant glands.
d) Mucinous carcinoma (MC) showing strong cytoplasmic KRAS expression along the lining epithelium and underlying tumor cells.

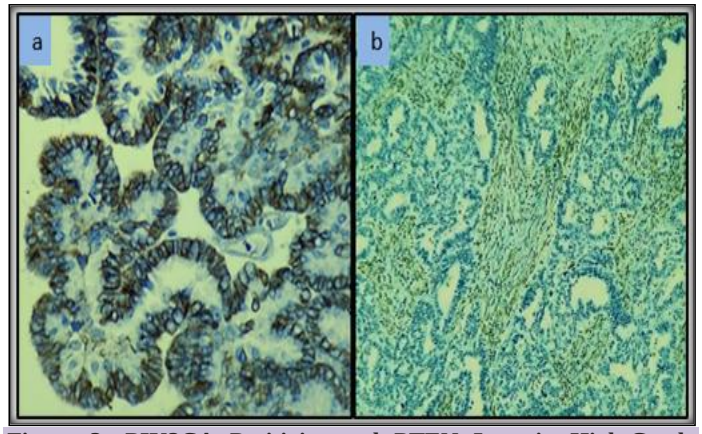

Figure 3: PIK3CA Positivity and PTEN Loss in High-Grade Serous Carcinoma (HGSC)

a) PIK3CA immunostaining showing strong membranous and cytoplasmic positivity in tumor cells of HGSC (×400), indicating activation of the PI3K/AKT/mTOR signaling pathway.
b) Loss of PTEN expression in tumor cells with preserved stromal staining (internal positive control) in another case of HGSC (×200), consistent with PI3K pathway dysregulation.

Discussion

This study aimed to evaluate the immunohistochemical expression of five key molecular markers P53, KRAS, BRAF, PTEN, and PIK3CA across the major histologic subtypes of

epithelial ovarian carcinomas (EOCs). Our findings provide insight into the molecular heterogeneity of ovarian tumors and support the dualistic model of ovarian carcinogenesis. Where applicable, findings were compared to prior studies and known mutation frequencies to assess concordance between immunohistochemical (IHC) expression and molecular alterations.

Clinicopathological Features and Histologic Subtypes

The age distribution in our cohort, with a mean age of 53.6 years and most patients between 51–60 years, aligns with previous studies such as those by Jindal D et al. (52.1 years),[12] Saini SK et al. (55.98 years),[13] and Akakpo PK et al. (50.1 years).[14] As in prior reports, serous carcinoma was the most frequent histologic subtype, followed by mucinous and endometrioid carcinomas.[12–14]

Bilateral tumors were noted in 48.7% of cases, slightly lower than the 56.4% reported by Saini SK et al.[13] In cases of bilateral ovarian tumors, IHC was performed on both sides, yielding a sample size of 73 for analysis, enhancing the robustness of our immunoprofiling data.

P53 Immunoexpression and Dualistic Tumor Classification

In the present study, 70.8% of high-grade serous carcinoma (HGSC) samples showed a mutant P53 expression pattern, in agreement with mutation rates reported by TCGA (~96%),[15] and studies using IHC such as Yemelyanova A et al. (94%).[5] A higher proportion of P53 wild-type HGSCs (29.2%) in our cohort may reflect intratumoral heterogeneity or sampling limitations, as highlighted by Kobel M et al., who reported 5.3% wild-type expression in HGSC.[6]

In contrast, 93.3% of low-grade serous carcinomas (LGSC) and all mucinous and low-grade endometrioid carcinomas were P53 wild-type, in line with their Type I classification and previous findings.[16,17] One endometrioid carcinoma showing null P53 pattern corresponded to a grade 3 tumor, consistent with the known association between high-grade morphology and TP53 mutation.

KRAS Immunoexpression across Subtypes

KRAS positivity was observed in a majority of tumors, including 69.4% of Type II tumors, which is significantly higher than molecular mutation rates reported for HGSC (~11%).[15] In contrast, expression in LGSC (73.3%), mucinous carcinoma (71.4%), and endometrioid carcinoma (100%) aligns well with the mutation frequencies reported in the literature (26–64%).[16,27,28]

Interestingly, there is limited literature on KRAS IHC in ovarian carcinomas. In our study, we observed KRAS protein overexpression, particularly in Type II tumors, where KRAS mutations are rare. This suggests that protein overexpression may not directly equate to mutational status, and IHC may reflect alternative activation mechanisms or upstream signaling events.[19]

BRAF Expression in LGSC and Other Subtypes

In our cohort, 77.08% of HGSC samples were BRAF-negative, consistent with findings from Bosmuller H et al. (100% negative) by both IHC and mutation analysis.[20] LGSC showed 40% BRAF positivity, similar to the 38% mutation frequency reported by Jones S et al,[22] although other IHC-based studies have reported lower frequencies.[20,21]

The absence of BRAF expression in mucinous carcinomas and the limited expression in endometrioid tumors (66.7%) also mirror mutation frequencies reported in the literature (0–5%).[25,26] Differences across studies may be attributable to technical variability in IHC staining and interpretation criteria.

PTEN Loss and PIK3CA Overexpression

PTEN loss was identified in 52.3% of HGSCs, which is higher than the ~7% mutation rate reported in literature,[15] but consistent with IHC findings from Bakkar RM et al. (42%),[10] and Chen S et al. (38%).[23] Both low-grade endometrioid carcinomas in our study showed PTEN loss, in line with the ~33% mutation frequency reported for EC.[28]

PIK3CA positivity was seen in 47.9% of HGSCs, 73.3% of LGSCs, and 66.7% of ECs, which is comparable to the findings of Abubaker J et al., who reported PIK3CA expression in ~55% of serous and ~58% of endometrioid carcinomas.[24] The high rate of expression suggests PI3K/AKT pathway activation even in the absence of gene mutations, likely due to post-translational modifications or upstream receptor activation.

Tumor Heterogeneity in Bilateral Tumors

Our study observed differences in IHC expression between bilateral tumors from the same patient. To our knowledge, no previous studies have systematically evaluated this, making this an important observation that raises the possibility of intrapatient molecular heterogeneity, which may have therapeutic implications and warrants further study.

Immunoexpression and the Dualistic Model

Consistent with the Kurman and Shih dualistic model,[3,4] Type I tumors (P53 wild-type) variably expressed KRAS, BRAF, PTEN, and PIK3CA, while Type II tumors (P53 mutant), predominantly HGSC, demonstrated high-grade morphology and were largely negative for BRAF and PIK3CA, with partial PTEN retention.

Interestingly, KRAS positivity was noted in the majority of Type II tumors (69.4%), and PTEN loss and PIK3CA expression were found in ~40%, although only PIK3CA expression showed a statistically significant difference ($p = 0.042$) between Type I and Type II tumors. These findings emphasize the overlap and complexity in the molecular profiles of EOCs and the need for combined morphological and molecular assessment.

Concordance and Discrepancies with Molecular Studies

Our IHC findings were largely in concordance with known molecular alteration frequencies, especially for:

- P53 in HGSC
- BRAF in LGSC and MC
- KRAS in MC
- PTEN in EC

However, the frequency of positive IHC expression was generally higher than mutation rates reported in molecular studies,[15,16,22,25–30] indicating IHC may overestimate functional pathway activation. Conversely, mucinous carcinomas were P53 wild-type by IHC, whereas up to 56.8% mutation frequency has been reported.[26] These discordances highlight the limitations of IHC as a standalone surrogate and underscore the need for standardization of antibodies, scoring systems, and cutoff values.

Limitations of the Study

Small Sample Size: The study included only 52 patients and 73 tissue samples, which limits the statistical power, especially for less common histological subtypes such as endometrioid and mucinous carcinomas. This may affect the generalizability of the findings.

Lack of Molecular Correlation: Immunohistochemical (IHC) expression was not validated with confirmatory molecular techniques such as PCR, Sanger sequencing, or next-generation sequencing (NGS). As a result, the correlation between protein expression and underlying gene mutations remains unconfirmed.

Potential IHC Interpretation Bias: IHC interpretation is semi-quantitative and may vary depending on antibody sensitivity, staining protocols, and inter-observer variability. This could impact the reproducibility and accuracy of results, particularly for markers like KRAS and PTEN.

Tumor Heterogeneity Not Fully Addressed: The study identified discordant immunoexpression in bilateral tumors from the same patient but did not perform clonal or molecular analysis to evaluate intra-patient heterogeneity in detail.

Limited Representation of Certain Subtypes: Subtypes such as clear cell carcinoma and high-grade endometrioid carcinoma were either underrepresented or absent, restricting conclusions on the full spectrum of epithelial ovarian carcinomas.

Lack of Clinical Outcome Correlation: The study did not assess correlations between marker expression and clinical parameters such as stage, response to therapy, or patient survival, limiting the prognostic and therapeutic implications of the findings.

Conclusion

The current study reinforces the utility of immunohistochemistry in profiling molecular markers of epithelial ovarian carcinomas and supports its role in tumor classification, prognostication, and therapeutic decision-making. While IHC findings generally mirrored molecular alterations, discordance between expression and mutation frequencies was observed, particularly for KRAS, PTEN, and PIK3CA. This underscores the importance of integrating IHC with molecular diagnostic techniques for accurate tumor characterization. Furthermore, heterogeneity in bilateral tumors and overlapping expression patterns challenge the rigidity of the dualistic model and point to the need for individualized tumor profiling in ovarian cancer management.

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Conflicts of interest

There are no conflicts of interest.

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