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Unraveling P53 Expression In Surface Epithelial Ovarian Tumors: A Clinicopathological Insight From A Tertiary Care Center

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ABSTRACT

Introduction: Ovarian cancer remains a major health concern, ranking as the fifth leading cause of cancer-related deaths in women. Among its various histological types, surface epithelial ovarian tumors (SEOTs) account for approximately 90% of all ovarian malignancies. These tumors demonstrate diverse biological behaviours ranging from benign to borderline and malignant. The tumor suppressor gene p53, known for its role in cell cycle regulation and apoptosis, has been widely studied as a potential biomarker in ovarian cancer. Altered p53 expression is often associated with high-grade tumors, poor prognosis, and resistance to chemotherapy.

Objectives: This study aims to assess the immunohistochemical expression of p53 in various subtypes and grades of surface epithelial ovarian tumors and correlate its staining patterns with their histopathological classification.

Materials And Methods: A retrospective study was conducted over two years (January 2023 to December 2024) and included 30 histologically confirmed cases of surface epithelial ovarian tumors. These cases were categorized as benign, borderline, or malignant based on standard histopathological criteria. Immunohistochemistry (IHC) for p53 was performed on all cases, and expression was evaluated based on nuclear staining patterns, categorized as wild-type, overexpression, or null.

Results: Total of the 30 cases studied, 18 (60%) were benign, 5 (16.7%) borderline, and 7 (23.3%) malignant. Benign tumors showed wild-type p53 expression, indicating normal p53 function. Borderline tumors demonstrated partial or focal nuclear positivity, reflecting a potential transition toward malignancy. In contrast, malignant tumors displayed aberrant p53 expression, including both diffuse nuclear overexpression and complete absence (null pattern). Notably, all p53-positive malignant tumors were of serous subtype. Mucinous carcinomas did not exhibit p53 positivity. The most common clinical presentation was abdominal pain, with contributory risk factors including family history, late menopause, and tumor laterality.

Conclusion: This study highlights the diagnostic and prognostic significance of p53 expression in surface epithelial ovarian tumors. The progressive pattern—from wild-type in benign, to partial positivity in borderline, to aberrant expression in malignant tumors—emphasizes the importance of p53 as a molecular marker. Accurate interpretation of IHC staining is crucial for diagnosis, grading, and potential application in targeted therapies, especially in high-grade serous carcinomas

Keywords: *Surface epithelial ovarian tumor, p53 expression, immunohistochemistry, serous carcinoma, ovarian cancer biomarkers*

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1. INTRODUCTION

Ovarian cancer poses a substantial global health challenge, ranking as the fifth leading cause of cancer-related deaths among women worldwide[1]. Among its histological subtypes, surface epithelial ovarian tumors (SEOTs) comprise approximately 90% of all malignant ovarian neoplasms[2]

These tumors span a wide clinicopathologic and molecular spectrum — from benign cystic lesions through borderline neoplasms to frankly invasive carcinomas — and each point on this spectrum has distinct histology, behavior, and underlying genetics. Surface epithelial ovarian tumors (SEOTs) include serous, mucinous, endometrioid, and clear-cell types; importantly, different histotypes follow different pathogenetic routes. For instance, the low-grade serous neoplastic pathway typically evolves in a stepwise manner from serous cystadenoma to serous borderline tumor, culminating in low-grade serous carcinoma, and is characteristically underpinned by activating mutations within the RAS–RAF signaling cascade, whereas high-grade serous carcinoma (HGSOC) generally arises de novo from the fallopian tube/ovary and is characterized by early disruption of TP53. These contrasting developmental models explain the very different natural histories: borderline and many low-grade tumors behave indolently and have a favorable prognosis**.** Concurrently, high-grade serous ovarian carcinoma exhibits marked aggressiveness and is responsible for the majority of deaths attributable to ovarian cancer. [3]

At the molecular echelon, p53 (encoded by TP53) is a central guardian of genomic integrity. As a sequence-specific transcription factor, wild-type p53 induces cell-cycle arrest (via p21), apoptosis (via BAX, PUMA, and others), senescence, and DNA-repair programs in response to genotoxic stress; it is tightly regulated by negative feedback (e.g., MDM2). Loss or alteration of p53 abolishes these fail-safe responses and predisposes cells to accumulate DNA damage and chromosomal instability. [4]

TP53 is one of the most commonly mutated genes in human cancer, and ovarian carcinoma illustrates the functional consequences clearly. In HGSOC, TP53 mutation is essentially ubiquitous (reported in >95% of cases in large genomic series), making p53 disruption an early and defining molecular event in this subtype. Mutations are heterogeneous: missense substitutions in the DNA-binding domain are frequent and commonly produce a stable, dysfunctional p53 protein that accumulates in the nucleus (detectable as strong, diffuse nuclear immunostaining); by contrast, nonsense, frameshift or splice-site mutations can produce truncated proteins and an absent ("null") immunostaining pattern. These molecular and IHC patterns have diagnostic utility: an abnormal p53 IHC pattern (diffuse overexpression or complete absence) supports a TP53-mutant HGSOC phenotype and helps separate high- from low-grade serous lesions and other histotypes. [5,6]

Functionally, TP53 mutations promote genomic instability, allowing additional driver events (copy-number alterations, homologous recombination defects, etc.) to accumulate — a hallmark of aggressive disease biology in HGSOC. Some TP53 missense mutants also exert dominant-negative or gain-of-function effects that can enhance proliferation, invasion and resistance to apoptosis, and these mutant-specific activities likely influence clinical behavior and therapy response. Nevertheless, the prognostic value of TP53 status by itself is inconsistent across studies and appears to be context-dependent (histotype, coexisting genomic alterations, treatment modalities).[5,6]

Clinically, p53 assessment is most useful today as part of integrated histopathologic and molecular classification rather than as a stand-alone prognostic biomarker. p53 immunohistochemistry is a practical surrogate for TP53 mutation in routine diagnostic practice and helps refine tumor classification. Therapeutic strategies that directly target mutant p53 or exploit downstream vulnerabilities are under investigation, but they remain largely experimental. Meanwhile, therapeutic decisions in ovarian cancer are more commonly directed by histotype and other molecular features (e.g., BRCA/HRD status) that influence response to platinum chemotherapy and PARP inhibitors.

2. AIMS & OBJECTIVES

This study aims to assess the immunohistochemical expression of p53 in various subtypes and grades of surface epithelial ovarian tumors and correlate its staining patterns with their histopathological classification.

Inclusion Criteria

The study encompassed all cases of surface epithelial ovarian tumors with a definitive histopathological diagnosis, irrespective of patient age**.**

Exclusion Criteria

Cases were excluded if they met any of the following conditions:

1. Incomplete surgical specimens.
2. Poorly preserved or inadequately processed tissue samples.
3. Non-compliance with study protocols or follow-up requirements.

4. Tumor-like ovarian lesions, including oophoritis, ovarian tuberculosis, pregnancy luteoma, and polycystic ovarian syndrome.

3. MATERIALS AND METHODS

This retrospective study involved the examination of 30 epithelial ovarian tumor specimens submitted to the Department of Pathology over a duration of two years. Prior to initiation, Approval for the study was granted by the Institutional Ethics Committee.

All collected specimens underwent meticulous gross and histopathological examination. Relevant clinical information was retrieved from medical records using a standardized proforma. Tumors were classified according to the WHO 2017 classification following evaluation of hematoxylin and eosin–stained slides.

Immunohistochemistry (IHC) for p53 was performed on all 30 cases using the heat-induced epitope retrieval method and a ready-to-use PATHINSITU mouse monoclonal antibody, capable of detecting both wild-type and mutant p53 expression. For the initial antibody run, FALLOPIAN TUBE carcinoma served as positive controls as per the manufacturer's datasheet. In subsequent runs, previously confirmed p53-positive cases were retained as additional positive controls. Negative controls included sections processed without the primary antibody and IHC-performed controls. Each tumor was evaluated for p53 expression and staining pattern.

The study assessed a range of clinical and histomorphological parameters, including patient age, tumor laterality, presence of ascites, tumor size, capsular rupture, metastasis, stage at diagnosis, and tumor grade. Patients who had undergone radiotherapy or neoadjuvant chemotherapy before surgery were excluded to avoid potential alterations in IHC results.

Interpretation of Staining:

Nuclear staining for p53 was assessed and recorded as a percentage of tumor cells showing positivity. Two distinct aberrant staining patterns were considered positive:

(a) Diffuse strong nuclear positivity in more than 70% of tumor cells, typically indicative of a p53 missense mutation. (b) Complete absence of nuclear staining (null pattern), suggestive of a p53 nonsense mutation.

Cases showing patchy nuclear staining in 1–70% of tumor cells were interpreted as wild-type p53 expression. The percentage score reflected the proportion of tumor cells positive for p53.A double-blind assessment was employed to evaluate p53 expression.

4. STATISTICAL ANALYSIS

Data were entered into a Microsoft Excel spreadsheet and analyzed using SPSS software (version 22) and Epi-Info software (version 7.2.1, CDC, Atlanta). Categorical variables were expressed as frequencies and proportions. A p-value <0.05 was considered statistically significant, per the assumptions underlying the applied statistical tests.

The Chi-square test was employed to assess the significance of associations in qualitative data. Continuous variables were presented as mean ± standard deviation. The normality of continuous data distribution was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk tests.

5. RESULT

Among the 30 cases evaluated, 18 (60%) were identified as benign, 5 (16.7%) as borderline, and 7 (23.3%) as malignant tumors.

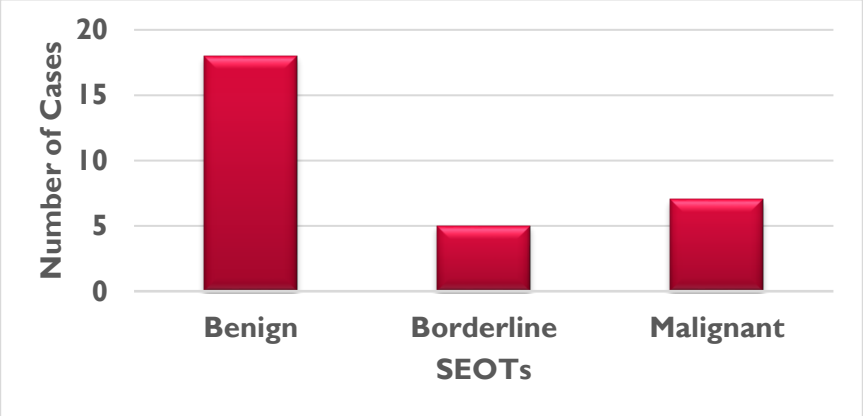

Figure 1: Distribution of cases in SEOTs

Table 1: Age-wise distribution of cases

AGE	Number of Cases	%
<30 years	6	20.0%
31 to 40 years	4	13.3%
41 to 50 years	11	36.7%
51 to 60 years	8	26.7%
>60 years	1	3.3%
Total	30	100.0%

Table 2: Distribution of clinical features

Clinical features	Count	%
Abdominal pain	15	50.0 %
Bleeding per vagina	5	16.7 %
Menstrual abnormality	4	13.3 %
Abdominal lump	3	10.0 %
Infertility	3	10.0 %
Asymptomatic	3	10.0 %
Loss of weight	2	6.7 %
GI disturbances	2	6.7 %
Ascites	1	3.3 %

Abdominal pain was the most frequent clinical presentation, occurring in 50% of patients. This was followed by bleeding per vagina (16.7%) and menstrual abnormalities (13.3%). Abdominal lump, infertility, and asymptomatic presentation were each observed in 10% of cases. Less common features included loss of weight and gastrointestinal disturbances (6.7% each), while ascites was the rarest finding, present in 3.3% of patients.

In the present cohort of 30 surface epithelial ovarian tumors, laterality analysis revealed a marginal predominance of right ovarian involvement (**n = 13; 43.3%**), closely approximated by left-sided lesions (**n = 12; 40.0%**). Bilateral ovarian disease was documented in **3 cases (10.0%)**, whereas **2 cases (6.7%)** exhibited primary localization within the endometrium. This laterality profile highlights a subtle right-sided predilection, with synchronous bilateral and extraovarian presentations accounting for a minority of cases.

P53 Staining Pattern	Count	%
Negative	19	63.3%
Moderate	3	10.0%
Mutant Pattern	4	13.3%
Overexpression	3	10.0%
Wild	1	3.3%
Total	30	100.0%

Table 3: P53 staining pattern

In the present study table 3 , immunohistochemical evaluation of P53 staining pattern was performed across 30 cases of surface epithelial ovarian tumors. The predominant staining pattern was negative, identified in 19 cases (63.3%). Mutant expression was observed in 4 cases (13.3%), while both overexpression and moderate expression were noted in 3 cases each (10.0% apiece). A wild-type staining pattern was documented in only a single case (3.3%). The high prevalence of negative staining is suggestive of complete loss of P53 protein expression, likely attributable to null mutations or biallelic inactivation of the TP53 gene. Aberrant staining patterns, encompassing both mutant and overexpression phenotypes, accounted for nearly one-quarter of the cohort, underscoring the central role of TP53 dysregulation in ovarian tumorigenesis. These findings align with prior literature, wherein TP53 alterations are recognized as a defining molecular hallmark of surface epithelial ovarian tumors, particularly high-grade serous carcinomas.

p53 expression was negative in the majority (66.7%), indicating the absence of detectable overexpression in most tumors. Positive expression was noted in 23.3% of cases, suggesting a subset with marked p53 protein accumulation, while moderate expression was the least common pattern, observed in 10% of cases. This distribution highlights that loss of p53 expression predominated over partial or strong positivity in the study cohort.

In the analysis of p53 immunoreactivity, 18 out of 30 cases (60.0%) demonstrated complete absence of positive tumor cell staining. The remaining 12 cases (40.0%) showed varying degrees of p53 positivity, ranging from as few as 2 positive cells (3.3%) to over 51 positive cells (3.3%). Specifically, isolated cases (each representing 3.3% of the cohort) exhibited 2, 10, 16, 18, 20, 30, or 40 positive cells. Two cases (6.7%) demonstrated 50 positive cells, and single cases each (3.3%) displayed staining patterns exceeding 50 cells, exactly 51 cells, or more than 51 cells. These findings indicate that while the majority of tumors lacked p53 expression, a subset exhibited a broad spectrum of positive cell counts, suggestive of heterogeneous expression patterns within the cohort.

Tumor Type	P53 Staining Intensity	Number of Cases
Benign (n=18)		
Serous Cystadenoma	Weak (1+)	6 (20%)
Mucinous Cystadenoma	Negative	5
Serous Cystadenofibroma	Weak (1+)	3
Seromucinous Cystadenoma	Weak (1+)	1
Brenner Tumor	Weak (1+)	1
Borderline (n=5)		
Borderline Serous Papillary Tumor	Moderate (2+)	1
Borderline Serous Tumor	Strong (3+)	2
Borderline Mucinous Tumor	Negative	2
Malignant (n=7)		
Malignant Neoplasm	Strong (3+)	1
High Grade Serous Carcinoma	Strong (3+)	1
Seromucinous Carcinoma	Strong (3+)	1
Mucinous Cystadenocarcinoma	Moderate (2+)	1
Serous Papillary Cystadenocarcinoma	Strong (3+)	1
High Grade Endometrioid Carcinoma	Strong (3+)	2
Total Cases		30

Figure 4: p53 result on intensity score

In this series of 30 cases, the negative p53 staining pattern was overwhelmingly predominant, identified in 63.3% of tumors. The mutant pattern was documented in 13.3% of cases, whereas both moderate expression and overexpression were each discerned in 10% of cases. The wild-type pattern constituted the rarest finding, occurring in merely 3.3% of cases. Collectively, these observations elucidate that the complete absence of p53 immunoreactivity represented the most prevalent staining profile, while aberrant expression patterns—most notably the mutant and overexpression phenotypes—were distinctly less frequent within the studied cohort.

The percentage of predominance of specimens (60%) exhibited a complete absence of p53-positive cells. Minimal

immunoreactivity, ranging from 2 to 40 positive cells, was observed sporadically, each category accounting for 3.3% of cases. A modest elevation in expression, represented by 50 positive cells, was identified in 6.7% of cases. Markedly elevated p53 positivity—exceeding 50 cells—was distinctly uncommon, with only isolated instances (3.3% each) demonstrating counts of >50 cells, exactly 51 cells, or >51 cells. Collectively, these findings underscore a prevailing absence of p53 expression within the study population, with robust overexpression constituting a rare event.

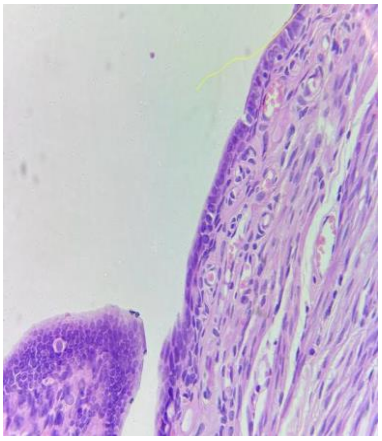

Figure 2a: Benign serous cystadenoma

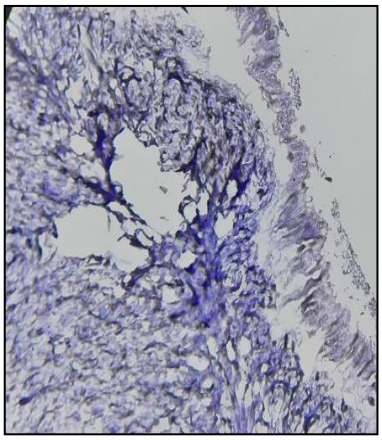

Figure 2b: P53 Negative

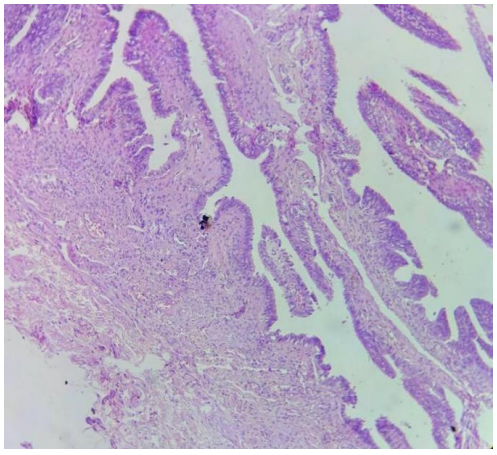

Figure 3a: Benign serous cystadenofibroma

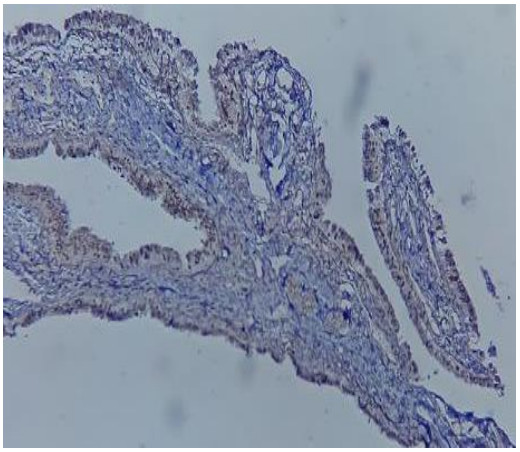

Figure 3b: P53 Negative

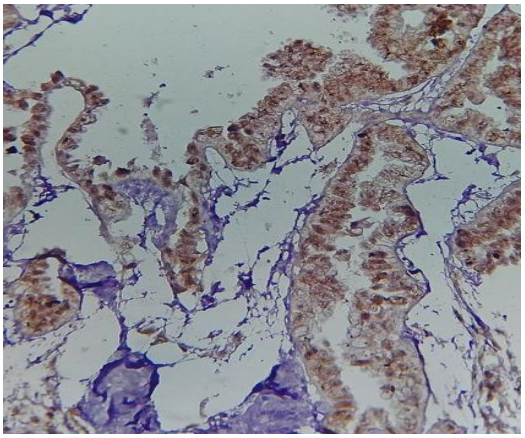

Figure 4a: Serous Boderline tumor

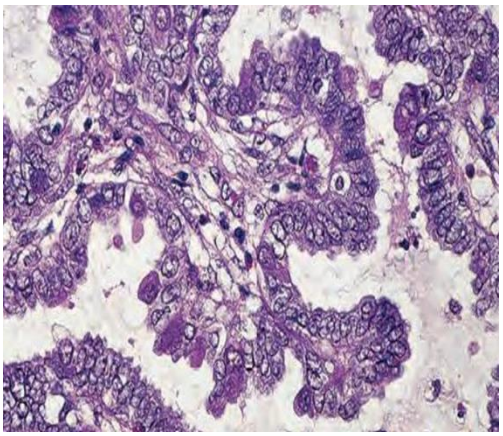

Figure 4b: Partial P53 -Positive

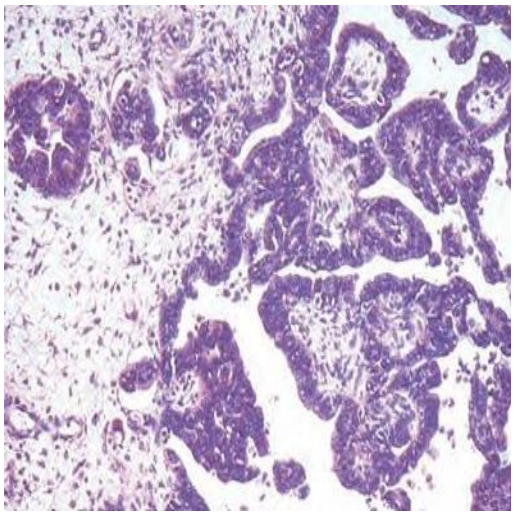

Figure 5a: High-grade serous carcinoma

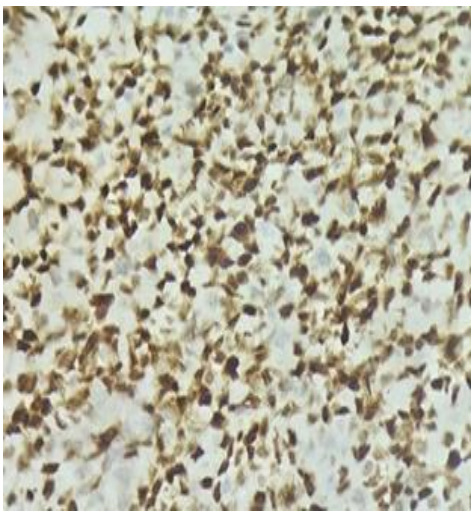

Figure 5b: P53- Positive

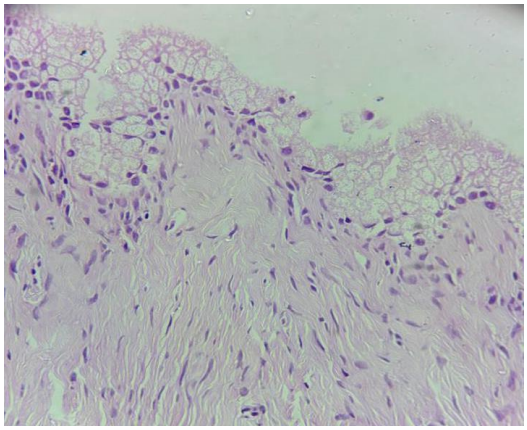

Figure 6a: Benign Mucinous cystadenoma

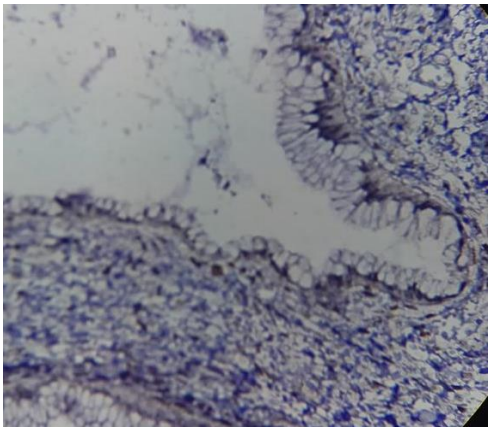

Figure 6b: P53 Negative

6. DISCUSSION

The term ovarian cancer encompasses a morphologically and molecularly heterogeneous spectrum of neoplasms, of which surface epithelial ovarian tumors (SEOTs)—including serous, mucinous, endometrioid, clear cell, transitional, and mixed epithelial subtypes—account for approximately 90% of cases.[7]

In the present cohort, p53 immunohistochemical (IHC) expression demonstrated striking histotype-specific concordance: all malignant neoplasms exhibiting aberrant p53 immunoreactivity were identified as serous carcinomas, whereas all endometrioid carcinomas uniformly retained wild-type staining patterns. This distribution is congruent with the extensive body of molecular evidence establishing that high-grade serous ovarian carcinomas (HGSOCs) almost invariably harbor pathogenic TP53 mutations, whereas low-grade serous and endometrioid tumors generally preserve wild-type TP53 function.[8]

This investigation advances the discourse on P53 dysregulation in surface epithelial ovarian tumors by transcending the conventional focus on high-grade serous carcinoma and incorporating the full morphologic continuum, including benign and borderline counterparts. In contrast to earlier studies that largely dichotomize immunoreactivity into wild-type and aberrant patterns, our analysis delineates nuanced gradations of expression and highlights patchy, intermediate staining profiles in borderline neoplasms, thereby substantiating their transitional molecular phenotype. The demonstration of a predominance of null/negative staining and the exploration of laterality trends within an Indian cohort provide population-specific insights that have hitherto remained underexplored in the global literature. Collectively, these observations refine the current paradigm of P53 immunoprofiling in ovarian tumorigenesis and furnish a platform for future biomarker standardization across diverse populations.[9]

Although Lassus et al. and Sylvia et al. reported slightly lower positivity rates, their findings are broadly concordant with those of Havrilesky et al., Leitao et al., and Chiesa et al., thereby reinforcing the overall consistency of p53 expression trends across studies.[12-16]

The present study was designed to evaluate the spectrum of P53 immunoexpression across surface epithelial ovarian tumors (SEOTs) and to compare these findings with existing international literature. Previous investigations have primarily concentrated on high-grade serous carcinoma (HGSOC), where TP53 mutations and aberrant P53 immunophenotypes are considered nearly universal [17,18]. In contrast, our analysis encompassed the full morphologic continuum—benign, borderline, and malignant lesions—allowing a more integrative appraisal of P53 dysregulation in ovarian tumorigenesis.

In our cohort, the predominant staining profile was negative/null expression (63.3%), a finding that diverges from the classic aberrant (overexpression or complete absence) patterns described in landmark series. Köbel et al. [17] reported abnormal P53 expression in more than 90% of HGSOCs, with high concordance to underlying TP53 mutations. The divergence in our results may be attributable to deliberate inclusion of borderline and benign tumors, as well as population-specific molecular variations within Indian patients. This underscores the importance of interpreting immunohistochemical data in the context of histological subtype and demographic background (Table 1).

A secondary objective was to delineate P53 expression in borderline tumors, a group that remains underrepresented in earlier literature. We observed patchy and moderate nuclear staining in these lesions, which does not align with the rigid dichotomy of wild-type versus aberrant expression. This supports the concept of borderline tumors as molecular intermediates, bridging the spectrum between benign cystadenomas and frankly invasive carcinomas. Such nuanced expression patterns have diagnostic implications and may help refine risk stratification in clinical practice [19].

Additionally, we noted a right-sided predominance (43.3%), a clinicopathological observation seldom emphasized in the literature. While the biological basis of this laterality remains unclear, its recognition enriches the epidemiological profile of SEOTs in Indian patients and warrants further exploration in larger cohorts [20].

When compared with seminal series (Table 2), the novelty of our study lies in four domains: (i) inclusion of the entire histological spectrum of SEOTs rather than restriction to HGSOC, (ii) use of quantitative, cell-based scoring of immunopositivity, (iii) identification of borderline tumors as morpho-molecular intermediates, and (iv) provision of Indian population-specific data to a literature base that remains predominantly Western-centric.

Collectively, these findings contribute to refining the paradigm of P53 immunoprofiling in ovarian neoplasia, moving beyond binary interpretative frameworks, and laying the foundation for future studies on biomarker validation and diagnostic standardization across diverse patient populations.

Overall, 23.3% of malignant tumors in this Indian series exhibited abnormal p53 IHC profiles, manifesting as either diffuse, strong nuclear overexpression or complete absence of staining (the “null” phenotype). These staining paradigms are well-recognized correlates of underlying TP53 mutation subtypes—missense mutations yielding protein overaccumulation, and truncating or nonsense mutations producing null expression[10]. The reproducibility of this relationship underscores the clinical utility of p53 IHC as a robust, cost-effective surrogate for TP53 mutational analysis in diagnostic practice.[11]

7. CONCLUSION

P53 remains a molecular fulcrum at the interface of tumor suppression and oncogenesis, directing pivotal pathways in the initiation and progression of surface epithelial ovarian tumors (SEOTs). The present analysis delineates a histotype-specific spectrum of immunoexpression: aberrant patterns were confined to malignant serous carcinomas, wild-type staining predominated in endometrioid and benign lesions, and borderline tumors exhibited patchy, intermediate nuclear reactivity—substantiating their role as biologic intermediates within the neoplastic continuum.

The predominance of null/negative immunoprofiles and the recognition of right-sided laterality within this Indian cohort introduce population-specific insights that enrich and, in part, diverge from established Western data. These findings reinforce the diagnostic and prognostic value of p53 immunohistochemistry as a robust surrogate for TP53 mutational analysis, while also illuminating its potential translational relevance as a therapeutic target. Taken together, this study advances the paradigm of p53 profiling beyond binary interpretive models, laying the groundwork for biomarker standardization and precision-driven management strategies in ovarian carcinoma.

Future directions should include multi-institutional studies with larger, demographically diverse cohorts, integrated molecular validation, and exploration of p53-targeted therapeutic strategies. Collectively, these findings refine the paradigm of p53 immunoprofiling, highlight the morpho-molecular heterogeneity of ovarian tumorigenesis, and provide a foundation for biomarker standardization and precision oncology in diverse populations.

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Conflicts of interest: The authors declare no conflicts of interest.

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