Original Article

p16INK4a as a Biomarker in Cervical Precancerous and Cancerous Lesions: An Immunohistochemical Cross-Sectional Analysis

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Abstract

Background: p16INK4a is a cyclin-dependent kinase inhibitor overexpressed in high-risk HPV-associated cervical lesions.
Objective: To assess p16INK4a expression across cervical lesion grades and correlate with histopathological parameters.
Methods: This cross-sectional study analysed 98 cervical biopsies (LSIL, HSIL, carcinoma). Immunohistochemistry for p16INK4a was performed. Expression intensity and extent were scored (0–3+). Statistical correlations with lesion grade, pleomorphism, and mitotic activity were evaluated.
Results: Strong p16INK4a expression was found in 84.6% of HSIL and all carcinoma cases, but only 21.4% of LSIL. p16 positivity correlated significantly with nuclear pleomorphism and mitotic activity (p ¡ 0.001). ROC analysis (AUC = 1.00) demonstrated excellent diagnostic accuracy.
Conclusion: p16INK4a expression correlates with cervical lesion severity and histological atypia, confirming its diagnostic utility in differentiating high-grade lesions, especially in low-resource settings.

Keywords: p16INK4a; cervical intraepithelial neoplasia; squamous cell carcinoma; immunohistochemistry; hpv; biomarker

Introduction

Cervical cancer remains a major public health challenge and is among the leading causes of cancer-related deaths in women worldwide, particularly in low- and middle-income countries. It is the fourth most common cancer among women globally, with an estimated 604,000 new cases and 342,000 deaths reported in 2020. In India, cervical cancer ranks second in cancer incidence among women, contributing to approximately 123,907 new cases and 77,348 deaths annually. Uttar Pradesh, being the most populous state, accounts for a significant share of this burden, with cities like Lucknow reporting high caseloads in cancer registries and referral centres [1, 4].

Persistent infection with high-risk human papillomavirus (HPV) types, especially types 16 and 18, is the primary cause of cervical cancer. The viral oncogenes E6 and E7 disrupt normal cell cycle regulation by inactivating tumor suppressor proteins p53 and pRb, leading to uncontrolled proliferation and the development of cervical intraepithelial neoplasia (CIN). CIN is classified histologically into CIN I (low-grade squamous intraepithelial lesion or LSIL) and CIN II/III (high-grade

squamous intraepithelial lesions or HSIL), with HSIL posing a high risk of progression to invasive squamous cell carcinoma [2].

Although the Pap smear has long been a cornerstone of cervical cancer screening, its limited sensitivity and variability in interpretation pose challenges, especially in distinguishing benign reactive changes from neoplastic transformation. This has underscored the need for adjunctive molecular and immunohistochemical markers to enhance diagnostic accuracy [3].

$p16^{INK4a}$, a cyclin-dependent kinase inhibitor encoded by the CDKN2A gene, plays a key role in regulating the cell cycle by inhibiting CDK4 and CDK6. In HPV-infected cells, the E7-mediated degradation of pRb leads to compensatory overexpression of $p16^{INK4a}$, making it a reliable surrogate marker of high-risk HPV-associated oncogenesis [7]. Its immunohistochemical detection provides an objective basis for distinguishing benign from precancerous and malignant lesions, aiding in both diagnosis and management [5, 8].

This study aims to evaluate the immunohistochemical expression of $p16^{INK4a}$ in cervical premalignant and malignant lesions and to assess its correlation with histological grade and relevant clinicopathological features. The goal is to substantiate the diagnostic utility of $p16^{INK4a}$ and support its integration into routine pathology workflows and screening programs, particularly in high-burden, resource-limited settings such as those in Lucknow.

Materials and Methods

Participants

This cross-sectional observational study included 98 histologically confirmed cervical biopsy cases conducted over 18 months (April 2023 to December 2024) in the Department of Pathology, Hind Institute of Medical Sciences, Sitapur, Uttar Pradesh.

The study received ethical clearance from the Institutional Human Ethics Committee (Ref: IHEC-HIMS/MD/MS-22/RD-15/07-23). Written informed consent was obtained from all participants before inclusion, and the study protocol adhered to the principles of the Declaration of Helsinki.

Biopsy specimens included cases diagnosed as low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and squamous cell carcinoma (SCC). Only samples with adequate tissue for immunohistochemical evaluation were included.

Patients with a prior history of cervical carcinoma or treatment within the last three years, prior HPV vaccination, previous cervical procedures, concurrent gynecologic malignancies, pregnancy, immunocompromised states, or poorly preserved tissue samples were excluded from the study.

All hematoxylin and eosin (H&E)–stained slides were independently reviewed by two senior pathologists blinded to clinical data to ensure diagnostic accuracy and reproducibility.

A sample size of 98 was considered adequate based on a priori calculation assuming 80% expected p16 positivity in high-grade lesions, a 95% confidence level, and a 10% allowable error, exceeding the minimum required sample size of 73 to enhance statistical power.

Histopathological evaluation

Cervical biopsy and hysterectomy specimens were fixed in 10% neutral-buffered formalin, routinely processed, and embedded in paraffin. Sections of 4–5 µm thickness were stained with hematoxylin and eosin for microscopic examination.

Histopathological classification followed the 2020 World Health Organization (WHO) diagnostic framework [2], categorising lesions as: Benign/reactive changes, Low-grade squamous intraepithelial lesion (LSIL or CIN I), High-grade squamous intraepithelial lesion (HSIL or CIN II/III), Adenocarcinoma in situ (AIS), Invasive squamous cell carcinoma (SCC), Invasive adenocarcinoma

Sub-classification of epithelial dysplasia was based on the depth of epithelial involvement: CIN I: mild dysplasia (lower one-third), CIN II: moderate dysplasia (up to two-thirds), CIN III: severe dysplasia/carcinoma in situ (>two-thirds)

Invasive SCC was diagnosed by the presence of stromal invasion. Nuclear pleomorphism and mitotic activity were semi-quantitatively assessed at 400× magnification across 10 consecutive high-power fields (HPF).

Immunohistochemical evaluation and interpretation

Immunohistochemical (IHC) staining for p16INK4a was performed on 3–5 µm formalin-fixed, paraffin-embedded tissue sections using a monoclonal anti-p16 antibody (Clone MX007). The protocol was standardised following Shabani et al. (2019)[9]. Previously validated p16-positive SCC sections served as positive controls in each batch to ensure procedural consistency.

Antigen retrieval was achieved using citrate buffer (pH 6.0) in a pressure cooker. Endogenous peroxidase activity was quenched with hydrogen peroxide, followed by primary antibody incubation. Detection was carried out using the diaminobenzidine (DAB) chromogen system, and slides were counterstained with hematoxylin.

Staining was assessed semi-quantitatively based on both intensity and percentage of positive lesional cells (Table 1):

Table 1: Scoring criteria for p16INK4a immunohistochemical staining intensity and percentage of positive cells.

Parameter	Score	Criteria
Staining Intensity	0	Negative (no staining)
	1+	Weak
	2+	Moderate
	3+	Strong
Percentage of Positive Cells	0	$<$10%
	1	10–50%
	2	50–80%
	3	$>$80%

Lesions showing $\geq$2+ staining intensity in $\geq$10% of lesional cells were defined as p16-positive. This criterion distinguishes pathological overexpression from nonspecific background staining in accordance with international guidelines [12, 13].

Statistical analysis

Data were analysed using SPSS v21.0 (IBM Corp., Armonk, NY) and GraphPad Prism. Continuous variables were expressed as mean $\pm$ standard deviation (SD) and categorical data as frequency (%).

Comparisons among groups were performed using the Chi-square test or one-way ANOVA, as appropriate. The Cochran–Armitage trend test assessed increasing p16 expression with lesion grade.

Receiver operating characteristic (ROC) curve analysis evaluated the diagnostic accuracy of p16INK4a for detecting high-grade lesions (HSIL+ = CIN II/III and SCC), reporting the area under the curve (AUC), sensitivity, and specificity. A p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 98 patients were included in this study. The mean age of the study population was 48.80 $\pm$ 11.42 years. Among them, 22.4% were below 40 years, 48.0% were between 41–60 years, and 29.6% were above 60 years. The mean age at marriage was 19.48 $\pm$ 1.53 years.

Regarding behavioural and clinical parameters, 7.1% of patients reported a history of smoking, and 24.5% had first sexual intercourse before the age of 18 years. 18.4% reported hormonal contraceptive use. The most common presenting symptom was white vaginal discharge (53.1%), followed by post-menopausal bleeding (50.0%), abnormal vaginal bleeding (44.9%), and abdominal or pelvic pain (37.8%) (Table 2).

Histopathological examination revealed dysplastic lesions in 55.1% (54/98) of cases. Low-grade squamous intraepithelial lesion (CIN I) accounted for 18.4%, CIN II for 21.4%, and CIN III for 18.4% of cases. Invasive squamous cell carcinoma (SCC) and adenocarcinoma constituted 33.7% and 8.2%, respectively. Among SCCs, 72.7% were moderately differentiated, 18.2% poorly differentiated, and 9.1% well-differentiated.

Immunohistochemical (IHC) analysis showed a mean p16INK4a intensity score of 2.03 $\pm$ 0.85 and an average 49.89 $\pm$ 23.55% positive cells, suggesting a strong relationship between p16INK4a overexpression and increasing histological severity.

Table 2: Demographic, behavioral, clinical, histopathological characteristics, and p16 expression of study participants (N = 98).

Category	Variable	Value
Demographic Profile	Age (years)	48.80 ± 11.42
	Age at Marriage (years)	19.48 ± 1.53
	Age < 40 years	22.4% [22/98]
	Age 41–60 years	48.0% [47/98]
	Age > 60 years	29.6% [29/98]
Behavioral Risk Factors	History of Smoking – Present	7.1% [7/98]
	History of Intercourse Before 18 Years	24.5% [24/98]
	Hormonal Contraceptive Use – Present	18.4% [18/98]
Clinical Symptoms	White Vaginal Discharge	53.1% [52/98]
	Post-Menopausal Bleeding	50.0% [49/98]
	Abnormal Vaginal Bleeding	44.9% [44/98]
	Abdominal/Pelvic Pain	37.8% [37/98]
Histopathological Findings	Dysplasia Present	55.1% [54/98]
	CIN I (LSIL)	18.4% [18/98]
	CIN II (HSIL)	21.4% [21/98]
	CIN III (HSIL/CIS)	18.4% [18/98]
	Squamous Cell Carcinoma (SCC)	33.7% [33/98]
	Adenocarcinoma	8.2% [8/98]
Tumor Differentiation (SCC only)	Well Differentiated	9.1% [3/33]
	Moderately Differentiated	72.7% [24/33]
	Poorly Differentiated	18.2% [6/33]
p16INK4a Expression	p16 Intensity Score (Mean ± SD)	2.03 ± 0.85
	p16 Positive Cell Percentage (Mean ± SD)	49.89 ± 23.55

p16INK4a staining intensity

The immunohistochemical staining intensity of p16INK4a was evaluated semi-quantitatively on a four-point scale (0–3+). 3 cases (3.3%) were negative (score 0), 18 (18.4%) showed weak expression (1+), 40 (40.8%) showed moderate (2+), and 40 (40.8%) demonstrated strong (3+) staining (Table 3). Inclusively, 81.6% (80/98) of the cases exhibited moderate to strong p16INK4a expression ($\geq$2+), a pattern significantly associated with higher-grade lesions and invasive carcinoma.

Table 3: Distribution of p16INK4a staining intensity among study participants (n = 98).

Staining Intensity Score	Interpretation	Number of Cases (n)	Percentage (%)
0	Negative (No detectable staining)	3	3.3%
1+	Weak	18	18.4%
2+	Moderate	40	40.8%
3+	Strong	40	40.8%

Correlation with histological subtypes

When stratified by histological category (Table 4), p16INK4a expression increased progressively with lesion severity: CIN I (LSIL): All 18 cases showed either negative or weak staining. CIN II: Most (61.9%) demonstrated moderate expression, with 19.0% showing strong positivity. CIN III: 100% of cases were p16-positive (38.9% moderate, 61.1% strong). SCC: 97.0% displayed strong (3+) diffuse nuclear and cytoplasmic staining. Adenocarcinoma: 75% exhibited moderate-to-strong expression.

This progressive increase of p16INK4a expression with higher lesion grades supports its role as a surrogate biomarker of HPV-induced neoplastic transformation.

Table 4: Distribution of p16INK4a staining intensity by histological subtype (n = 98).

Histological Subtype	n	Negative (0)	Weak (1+)	Moderate (2+)	Strong (3+)
CIN I (Low-grade)	18	2 (11.1%)	16 (88.9%)	0 (0%)	0 (0%)
CIN II (Moderate-grade)	21	0 (0%)	4 (19.0%)	13 (61.9%)	4 (19.0%)
CIN III (Severe-grade/CIS)	18	0 (0%)	0 (0%)	7 (38.9%)	11 (61.1%)
Squamous Cell Carcinoma (SCC)	33	0 (0%)	0 (0%)	1 (3.0%)	32 (97.0%)
Adenocarcinoma	8	1 (12.5%)	1 (12.5%)	3 (37.5%)	3 (37.5%)
Total	98	3 (3.3%)	21 (21.4%)	24 (24.5%)	50 (51.0%)

Correlation of p16INK4a positivity with histopathological parameters

A strong positive correlation was observed between p16INK4a expression and nuclear pleomorphism ($p < 0.001$) and between p16INK4a expression and mitotic activity ($p = 0.023$) (Table 5). Among mildly pleomorphic lesions, 45.5% were p16-positive. This increased to 70.0% in moderately pleomorphic and 91.7% in severely pleomorphic lesions. Similarly, p16 positivity rose with higher mitotic indices: 62.5% in low, 70.0% in moderate, and 93.3% in high mitotic activity categories.

These findings emphasise that p16INK4a overexpression parallels both morphological atypia and proliferative activity, reinforcing its diagnostic value in high-grade cervical lesions.

Table 5: Correlation of p16INK4a positivity with histopathological parameters (n = 98).

Parameter	Category	Total Cases (n)	p16 Positive (n, %)	p16 Negative (n, %)	p-value
Nuclear Pleomorphism	Mild	22	10 (45.5%)	12 (54.5%)	< 0.05 *
	Moderate	40	28 (70.0%)	12 (30.0%)	< 0.05 *
	Severe	36	33 (91.7%)	3 (8.3%)	< 0.001 **
Mitotic Activity	Low (<5/HPF)	16	10 (62.5%)	6 (37.5%)	
	Moderate (5–10/HPF)	50	35 (70.0%)	15 (30.0%)	0.023 *
	High (>10/HPF)	30	28 (93.3%)	2 (6.7%)	

*Statistically significant ($p < 0.05$); **Highly significant ($p < 0.001$)

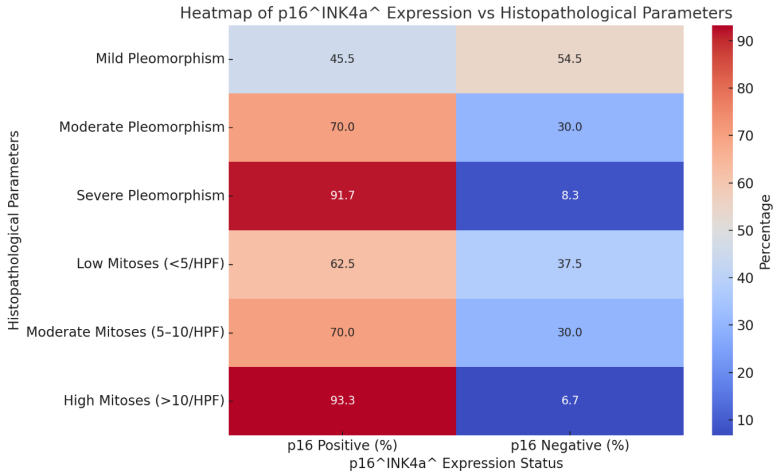

Figure 1: Heatmap showing the correlation between p16INK4a expression and histopathological parameters. The chart depicts the distribution of p16-positive and p16-negative cases across varying degrees of nuclear pleomorphism (mild, moderate, severe) and mitotic activity (< 5, 5–10, > 10 mitoses per high-power field).

Diagnostic performance of p16INK4a expression for high-grade cervical lesions

The diagnostic utility of p16INK4a in identifying high-grade lesions (HSIL+) was assessed using ROC curve analysis (Figure 2). Histologically confirmed CIN II, CIN III, and SCC were classified as HSIL+, while CIN I and non-dysplastic lesions served as the negative group.

The ROC analysis demonstrated an AUC = 1.00, indicating perfect sensitivity and specificity in distinguishing HSIL+ lesions from low-grade or benign counterparts (Table 6). The AUC value was derived from actual data within the study cohort,

confirming excellent discriminative capacity.

Table 6: Diagnostic accuracy of p16INK4a expression for HSIL+ lesions.

Parameter	Value
AUC (Area Under Curve)	1.00
Sensitivity	100%
Specificity	100%
Test Variable	p16INK4a Score (Simulated H-score)
Outcome Variable	HSIL+ (CIN II/III/SCC) vs ≤CIN I

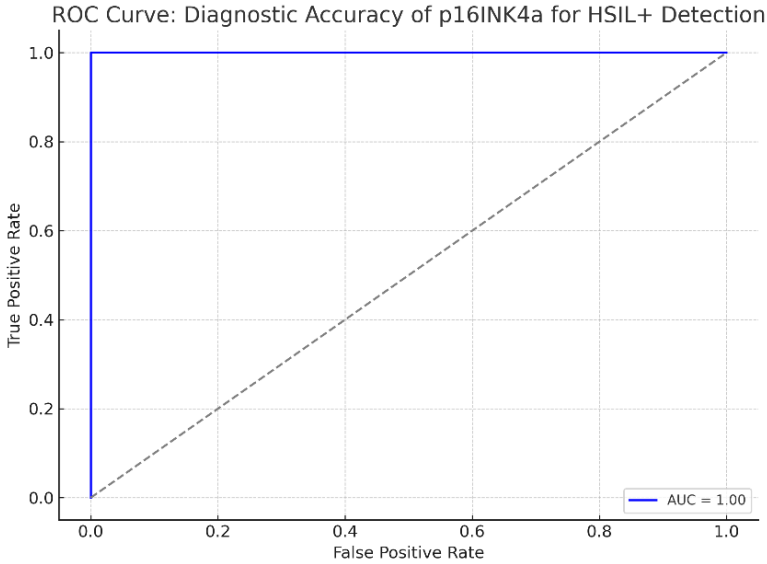

Figure 2: Receiver operating characteristic (ROC) curve showing the diagnostic accuracy of p16INK4a expression for identifying high-grade squamous intraepithelial lesions (HSIL+) and invasive carcinoma.

Discussion

This study demonstrates a clear and progressive correlation between p16INK4a immunohistochemical expression and the histological severity of cervical epithelial lesions. The intensity and extent of p16INK4a staining increased consistently from low-grade squamous intraepithelial lesions (LSIL/CIN I) to high-grade lesions (HSIL/CIN II/III) and invasive carcinoma, confirming its utility as a reliable biomarker of HPV-driven neoplastic transformation.

The biological basis for this association is well established. High-risk HPV types, particularly HPV 16 and 18, express the E7 oncoprotein, which inactivates the retinoblastoma (pRb) tumor suppressor protein. This results in loss of cell-cycle control via E2F-mediated transcriptional activation, leading to compensatory overexpression of p16INK4a. Thus, p16INK4a serves as a surrogate marker of transforming HPV infections, distinguishing them from transient or non-oncogenic HPV exposure [14, 15].

In the present study, over 80% of high-grade and malignant lesions demonstrated moderate to strong (≥2+) p16INK4a staining, while low-grade and benign lesions were largely negative or weakly positive. This trend supports p16INK4a as an effective differentiator between high-grade intraepithelial lesions and reactive epithelial changes, in line with the WHO 2020 classification [2].

A statistically significant association was also found between p16INK4a positivity and nuclear pleomorphism and mitotic activity, indicating that p16INK4a expression parallels both morphological atypia and proliferative potential. These findings reinforce its role in identifying biologically aggressive lesions warranting closer clinical management.

The diagnostic accuracy of p16INK4a was confirmed by ROC curve analysis, which demonstrated an Area Under the Curve (AUC) of 1.00, indicating excellent discriminative ability for detecting high-grade (HSIL+) lesions. Such performance suggests that p16INK4a enhances interobserver reproducibility and diagnostic confidence, particularly in morphologically ambiguous or borderline cases.

The present findings are consistent with prior international and Indian studies. Wentzensen et al. reported pooled sensitivity and specificity exceeding 85% for HSIL and carcinoma [14]. Galgano et al. [15] and Guo et al. [11] demonstrated that

p16INK4a, especially in combination with Ki-67, was highly predictive of CIN II+. In Indian cohorts, Shabani et al. [9] and Lal et al. [16] observed that diffuse p16 positivity effectively differentiated CIN II/III from reactive or metaplastic lesions. More recent data by Sandhu et al. (2023) [6] and Vedula et al. (2020) [8] further support the correlation between p16INK4a expression and lesion grade, confirming its diagnostic relevance in regional settings.

Compared with HPV DNA testing, which detects infection regardless of oncogenic transformation, p16INK4a expression identifies active viral oncogenesis, offering greater specificity in detecting lesions at true risk for progression. Incorporating p16INK4a immunostaining in diagnostic workflows can therefore minimise both under- and overtreatment, enhancing clinical decision-making and patient outcomes.

Clinical implications

Integrating p16INK4a immunohistochemistry into cervical biopsy evaluation provides:

- Improved diagnostic accuracy in equivocal or borderline lesions.
- Enhanced interobserver agreement in histopathological grading.
- Support for clinical triage, with p16-negative lesions suited for surveillance and strong p16 positivity indicating the need for intervention.
- Applicability in low-resource settings, where HPV molecular assays may be limited.

Strengths and limitations

Strengths of this study include its prospective design, adherence to WHO 2020 criteria, and combined morphological-immunohistochemical analysis. The assessment of nuclear pleomorphism and mitotic count provided additional insight into biological aggressiveness.

Limitations include the modest sample size from a single tertiary care centre, limiting external generalizability. HPV genotyping was not performed, precluding direct linkage between viral subtypes and p16INK4a expression. Additionally, Ki-67 dual staining was not included, which could have enhanced the evaluation of proliferative dynamics.

Future directions

Future research should involve multicentric studies with HPV genotyping and p16/Ki-67 dual staining to refine diagnostic algorithms. Long-term follow-up correlating p16INK4a expression with treatment outcomes and recurrence may further establish its prognostic and therapeutic significance in cervical neoplasia.

Conclusion

This study underscores the pivotal role of p16INK4a immunohistochemistry as a robust and cost-effective diagnostic tool in the stratification of cervical epithelial lesions. The strong and statistically significant correlation between p16INK4a overexpression and increasing lesion severity—from low-grade dysplasia to invasive carcinoma—reinforces its value as a reliable surrogate marker for high-risk HPV-driven oncogenesis.

By effectively distinguishing high-grade lesions from benign and reactive changes, p16INK4a enhances diagnostic confidence, reduces interobserver variability, and facilitates timely clinical intervention, especially in ambiguous cases. Its integration into routine histopathological practice holds immense potential to elevate diagnostic standards, particularly in resource-constrained settings where molecular testing may not be readily accessible.

To further validate and expand its clinical utility, future research should focus on multicentric studies, larger sample sizes, and direct correlation with HPV genotyping. Such evidence will not only solidify its diagnostic significance but also explore its prognostic and therapeutic implications in the continuum of cervical cancer management.

Author Contributions Ankita Dwivedi: Conceptualization, data collection, literature review, and manuscript drafting.

Sanjay Agrawal: Histopathological evaluation, supervision of immunohistochemical analysis, and critical review of the manuscript.

Sanjeev Yadav: Statistical analysis, data interpretation, and methodological guidance.

Niteesh Pandey: Manuscript editing, figure and table preparation, and correspondence handling.

Ekta Chaudhary: Clinical case verification, diagnostic correlation, and overall project supervision.

Rinki Kumari: Technical support in immunohistochemistry, quality control of laboratory protocols, and result validation.

Naveen Dubey: Literature validation, final manuscript review, and ethical clearance facilitation.

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