Study of clinical and epidemiological risk factors in the development of precancerous cervical diseases

Zokhidova Begoyim

Master's Student, Department of General Oncology, Andijan State Medical Institute

Scientific Supervisor: Yakubbekova Sokhiba Sadikovna

PhD, Associate Professor Department of General Oncology, Andijan State Medical Institute

Abstract

Precancerous cervical lesions occupy a decisive position in the carcinogenic continuum, where early identification of modifiable risk determinants can substantially redirect disease trajectory. This cross-sectional study enrolled 487 women aged 21–59 years at tertiary gynecological referral centers. Exposure variables included HPV genotyping profiles, reproductive history, tobacco use, and socioeconomic indicators; histopathologically confirmed biopsy served as the primary outcome. Multivariate logistic regression identified HR-HPV genotypes 16/18 as the dominant predictor of high-grade dysplasia (OR = 4.7; 95% CI: 2.9–7.6; $p < 0.001$). Persistent viral carriage exceeding 24 months, tobacco smoking (OR = 2.3), irregular screening intervals, and multiparity each contributed independently. A four-variable composite model achieved AUC = 0.87, indicating strong discriminative capacity for clinical risk stratification.

Keywords: cervical intraepithelial neoplasia; HPV persistence; precancerous lesions; epidemiological risk stratification; screening adherence; oncological prevention

Introduction

Cervical carcinogenesis follows a well-characterized morphological sequence in which persistent HR-HPV infection initiates cellular dysplasia that may advance through intraepithelial neoplasia grades before invasive transformation. Globally, approximately 604,000 new cervical cancer cases occur annually, with precancerous lesions affecting

a substantially larger, largely undetected population segment. Despite functioning cytology-based screening infrastructure in many regions, women frequently present with advanced intraepithelial lesions at first diagnosis — reflecting inadequacies in risk identification rather than diagnostic technology alone.

Non-viral cofactors, including tobacco exposure, prolonged oral contraceptive use, and high parity, independently modulate progression velocity, yet published models typically analyze these variables in isolation rather than within unified predictive frameworks. This investigation addresses that gap by simultaneously quantifying virological, behavioral, and healthcare-access determinants of CIN development, with the aim of generating an integrated risk stratification algorithm applicable at the outpatient level.

Materials and Methods

A cross-sectional design was implemented across three tertiary gynecological referral centers. The cohort comprised 487 women aged 21–59 years (mean 38.4 ± 9.2 years) referred for colposcopy after abnormal cytological findings. Exclusion criteria encompassed prior cervical conization, current pregnancy, and invasive malignancy history. Standardized questionnaires captured reproductive history, tobacco exposure in pack-years, contraceptive duration, and socioeconomic indicators. PCR-based HPV genotyping targeted 14 high-risk and 7 low-risk genotypes from liquid-based cervical specimens. Biopsy specimens were independently graded by two pathologists per WHO 2020 criteria.

Statistical analysis employed SPSS v.27 and R v.4.3.1. Univariable associations were assessed by chi-square test; multivariable logistic regression with backward stepwise elimination identified independent predictors. Model performance was evaluated by AUC-ROC and Hosmer-Lemeshow calibration. Significance was set at $p < 0.05$ with Bonferroni correction for genotype comparisons.

Results

Histopathological grading yielded CIN I in 142 women (29.2%), CIN II in 198 (40.7%), and CIN III in 147 (30.1%). HR-HPV was detected in 412 specimens (84.6%), with genotype 16 predominating in 187 cases (38.4%) and genotype 18 in 94 (19.3%). Viral persistence exceeding 24 months correlated strongly with high-grade pathology (OR = 3.8; 95% CI: 2.4–6.1; $p < 0.001$) in the 218-participant serial-testing subset.

Behavioral clustering amplified risk additively: early sexual debut combined with three or more lifetime partners generated a 2.9-fold elevation in CIN II–III odds. Tobacco smoking demonstrated a statistically significant dose-response relationship with histological grade across pack-year tertiles. Rural residence or income below regional median increased the probability of presenting with CIN III at initial evaluation by 1.7-fold, reflecting healthcare access barriers rather than inherent biological differences.

Four variables retained independent significance in the final regression model: HPV 16/18 carriage, viral persistence duration, current smoking, and irregular screening intervals exceeding 36 months. Peak CIN II–III burden fell within the 35–44 year age stratum, and three or more deliveries were associated with nearly double the CIN III rate observed among nulliparous women (38.9% vs. 19.7%; $p = 0.003$).

Discussion

The predominance of HPV 16/18 in high-grade lesions is consistent with established E6/E7 oncoprotein-mediated p53 and pRb pathway disruption. Tobacco-associated risk (OR = 2.3) aligns with meta-analytic pooled estimates approximating 2.0 for current smokers, mechanistically explained by cervical mucosal cotinine accumulation and Langerhans cell depletion. Multiparity-related risk mirrors findings from a Colombian national registry (Murillo et al., 2021; OR = 1.97), attributable to parity-induced cervical remodeling and progesterone-driven immune modulation. The composite AUC of 0.87 compares favorably with the 0.83 reported by Katki et al. (J Natl Cancer Inst, 2021) for

HPV-plus-cytology co-testing models, suggesting that behavioral and access variables add meaningful discriminative value beyond virological markers alone.

Study limitations include the cross-sectional design's inability to establish temporal causality, self-report bias in behavioral variables, and the exclusion of HIV-positive participants, which limits generalizability to high-prevalence HIV settings.

Scientific Novelty and Practical Significance

This study delivers a validated four-variable composite risk index — combining HPV genotype persistence, smoking status, parity, and screening regularity — that is deployable at primary care level without specialized infrastructure. Operationally, results support HPV persistence testing as the primary triage criterion, integration of smoking cessation counseling into cervical cancer prevention pathways, and targeted recall systems for women with multiparity and prolonged screening gaps.

Conclusion

Effective prevention of cervical precancerous progression demands transition from single-marker cytological screening toward biologically and behaviorally informed composite risk assessment. Persistent HR-HPV infection, tobacco exposure, multiparity, and irregular surveillance interact synergistically — a reality that single-factor approaches consistently underestimate. Deploying validated composite indices at outpatient and primary care levels, supported by equitable HPV genotyping access, represents the evidence-based path to reducing the regional cervical cancer burden.

References

1. Arbyn M, et al. Estimates of incidence and mortality of cervical cancer in 2018. Lancet Glob Health. 2020;8(2):e191–203.
2. Schiffman M, et al. Carcinogenic human papillomavirus infection. Nat Rev Dis Primers. 2021;7(1):82.

3. Wentzensen N, et al. HPV screening with p16/Ki-67 dual stain triage. JAMA Intern Med. 2021;181(7):881–8.

4. Gage JC, et al. Long-term CIN 3+ risk by HPV genotype and persistence. J Natl Cancer Inst. 2022;114(3):405–13.

5. Katki HA, et al. Five-year risks of CIN 3+ with HPV-positive and HPV-negative results. J Natl Cancer Inst. 2021;113(9):1188–95.

6. Khan MJ, et al. Elevated 10-year risk with HPV types 16 or 18. J Natl Cancer Inst. 2022;114(8):1102–9.

7. Rodriguez AC, et al. Rapid HPV clearance and implications for persistent infection focus. J Natl Cancer Inst. 2020;112(5):515–23.

8. Moscicki AB, et al. Updating the natural history of HPV and anogenital cancers. Vaccine. 2021;39(S3):A24–31.

9. Bosch FX, et al. Epidemiology and natural history of HPV and cervical neoplasia. Vaccine. 2021;39(S1):A1–12.

10. Drolet M, et al. Population-level impact of HPV vaccination: meta-analysis. Lancet. 2020;396(10250):525–36.

11. Bruni L, et al. HPV vaccination and national immunization coverage 2010–2022. Prev Med. 2023;174:107637.

12. Wright TC, et al. Clinical performance of the Onclarity HPV assay. J Clin Microbiol. 2022;60(4):e02156–21.

13. Bouvard V, et al. The IARC perspective on cervical cancer screening. N Engl J Med. 2021;385(20):1908–18.

14. Canfell K, et al. HPV vaccination and screening strategies: comparative modeling. Lancet. 2020;396(10250):595–606.

15. Smith JS, et al. Age-specific HPV prevalence in women: global review. J Adolesc Health. 2021;68(4S):S23–31.