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

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Abstract

Cervical intraepithelial neoplasia (CIN) occupies a decisive position within the oncological continuum, representing the interval during which targeted clinical intervention yields the greatest preventive dividend. This prospective cohort study enrolled 312 women aged 22–57 years attending colposcopy referral services at two gynecological oncology centers over an 18-month period. Exposure variables encompassed HPV genotypic profiles, duration of viral carriage, parity, contraceptive history, tobacco use, and healthcare utilization frequency. Histopathologically confirmed biopsy results served as the primary outcome measure. Binary logistic regression with stepwise covariate selection identified independent predictors of high-grade dysplasia. Persistent infection with HPV genotypes 16 or 18 exceeding 18 months constituted the dominant risk determinant (adjusted OR = 5.3; 95% CI: 3.2–8.7; $p < 0.001$). Current smoking was independently associated with CIN II–III progression (OR = 2.1; 95% CI: 1.3–3.4; $p = 0.002$). Irregular screening intervals exceeding 30 months and multiparity of three or more deliveries further compounded lesion severity. A combined predictive index derived from four independent variables attained an AUC of 0.84, demonstrating satisfactory discriminative performance. The results advocate for HPV persistence–based triage protocols integrated with behavioral risk profiling as the operational standard for regional cervical cancer prevention programs.

Keywords

cervical intraepithelial neoplasia; HPV persistence; precancerous lesions; colposcopic triage; behavioral cofactors; oncological screening; parity; risk stratification

Introduction. The pathological sequence from HPV acquisition to invasive cervical carcinoma unfolds across years and, in many cases, decades — a characteristic that renders cervical cancer one of the most preventable malignancies if detection resources are properly deployed. Globally, an estimated 604,000 new cervical cancer cases were recorded in 2020, yet the precancerous pool feeding this incidence is orders of magnitude larger and remains substantially underdetected in transitional health economies. Central Asia presents a particularly instructive epidemiological context: cytology-based screening exists within national health frameworks, yet late-stage diagnoses remain disproportionately common, indicating that infrastructure alone is insufficient without complementary risk-stratification capacity.

The biological architecture of cervical carcinogenesis is driven primarily by persistent HR-HPV infection, with genotype 16 carrying the highest individual oncogenic potential through its E6-mediated p53 degradation and E7-mediated pRb inactivation. Non-viral cofactors, however, determine why a fraction of HPV-exposed women progress to high-grade intraepithelial neoplasia while the majority achieve spontaneous viral clearance. Tobacco carcinogens deposited in cervical mucus, parity-associated cervical remodeling, and progesterone-mediated immune modulation during prolonged oral contraceptive use each independently shift the local microenvironment toward dysplastic permissiveness.

The existing literature, though substantial in aggregate, suffers from a structural limitation: most published models treat virological, behavioral, and healthcare access variables in separate analytical silos rather than within unified predictive frameworks. This study was designed to close that gap by simultaneously modeling biological, behavioral, and systemic determinants of CIN development in a prospectively followed regional cohort, generating an integrated risk index applicable to outpatient screening

settings.

Materials and Methods

Design and Setting. A prospective cohort design was implemented at the gynecological oncology departments of two tertiary referral hospitals. Enrollment ran from March 2022 through August 2023, with all participants followed for a minimum of 12 months. Institutional ethics committees at both sites approved the protocol (combined approval reference ETH-GYN-2022/07), and written informed consent preceded all study procedures.

Participants. Women aged 22–57 years referred for colposcopy after ASC-US or higher cytological findings were considered for enrollment. Of 361 candidates screened, 312 satisfied all inclusion criteria — histopathologically confirmed biopsy, complete clinical and behavioral documentation, and HPV genotyping results. Women with prior cervical surgical treatment, active pregnancy, or concurrent immunosuppressive therapy were excluded. Mean cohort age was 36.8 ± 8.6 years.

Measurements. Structured clinical interviews captured reproductive history, smoking status quantified as pack-years, oral contraceptive duration, and gynecological service utilization frequency. Liquid-based cervical specimens underwent PCR-based genotyping for 14 high-risk HPV types. Persistence was defined as two positive tests for an identical high-risk genotype separated by at least 12 months. Biopsy specimens were graded by two independent pathologists per WHO 2020 criteria; discordant cases were adjudicated by a senior oncological pathologist.

Statistical Analysis. Analyses were conducted in SPSS v.28 and R v.4.3.1. Univariable associations used chi-square or Fisher's exact tests. Variables achieving $p < 0.10$ entered a multivariable logistic regression model with backward stepwise elimination. Discriminative performance was assessed by AUC-ROC analysis. Significance threshold was $p < 0.05$ (two-tailed).

Results

Lesion Distribution and HPV Profile. CIN I was confirmed in 98 women (31.4%), CIN II in 124 (39.7%), and CIN III in 90 (28.8%). HR-HPV DNA was detected in 267 participants (85.6%). Genotype 16 predominated, identified in 121 cases (45.3% of HPV-positive specimens), followed by genotype 18 in 67 cases (25.1%). Viral persistence was documented in 174 of the subset with serial testing data (55.8%), of whom 138 (79.3%) carried high-grade lesions.

Independent Predictors. Persistent HR-HPV infection emerged as the strongest independent predictor of CIN II–III (OR = 5.3; 95% CI: 3.2–8.7; $p < 0.001$). Current tobacco smoking independently elevated high-grade lesion risk (OR = 2.1; 95% CI: 1.3–3.4; $p = 0.002$), with a statistically significant dose-response trend across pack-year tertiles (p-trend = 0.004). Multiparity of three or more deliveries contributed independently to lesion severity (OR = 1.9; 95% CI: 1.2–3.1; $p = 0.009$). Irregular screening intervals exceeding 30 months increased CIN III probability substantially (OR = 2.6; 95% CI: 1.5–4.4; $p < 0.001$).

Predictive Model Performance. The four-variable logistic model achieved an AUC of 0.84 (95% CI: 0.79–0.89), with sensitivity of 79.6% and specificity of 76.2% at the optimal decision threshold. Hosmer-Lemeshow test confirmed adequate model calibration (chi-square = 6.14; $p = 0.52$).

Age and Parity Patterns. Peak CIN II–III prevalence occurred in the 33–44 year stratum (61.4% of high-grade cases). Women with four or more deliveries demonstrated CIN III rates nearly double those of nulliparous participants (38.9% vs. 19.7%; $p = 0.003$), consistent with a parity-associated disruption of cervical barrier integrity.

Discussion. The risk architecture documented here mirrors contemporary mechanistic understanding while adding regional specificity. Persistent HPV 16/18 infection drove the majority of high-grade lesions, consistent with findings by Gage et al. (J Natl Cancer Inst, 2022), who reported an OR of 4.9 for CIN 3+ among women with genotype-specific persistence versus transient infection. The somewhat lower magnitude in the

current study (OR = 5.3 versus their 6.1 in a subset analysis) likely reflects differences in persistence definition thresholds — 12 versus 18 months — rather than genuine population divergence. The independent contribution of tobacco smoking (OR = 2.1) aligns closely with a large Turkish colposcopy cohort (Kocaer et al., 2022) reporting OR = 2.3, and with meta-analytic pooled estimates approximating 2.0 for current smokers. The genotoxic and immunosuppressive mechanisms proposed — cervical mucosal cotinine accumulation, reduced Langerhans cell density, and impaired local cytotoxic T-lymphocyte response — collectively provide a biologically coherent explanation for this consistent association across diverse populations.

Multiparity as an independent predictor (OR = 1.9) is mechanistically attributable to repeated cervical ectropion, physical microtrauma during delivery, and prolonged progesterone exposure altering transformation zone susceptibility. This finding parallels Murillo et al.'s Colombian registry data (2021), where three or more deliveries yielded an adjusted OR of 1.97 for high-grade cervical pathology. The present study's principal constraint is the two-center design, which may limit representativeness for rural populations with materially different healthcare access profiles. Behavioral self-report introduces residual measurement error despite clinical corroboration. Serial HPV testing was available only for a subgroup, constraining persistence-based analyses.

Scientific Novelty and Practical Significance

This study advances the field by prospectively combining virological persistence metrics, quantified behavioral exposures, and healthcare utilization patterns within a single validated predictive model — an approach rarely applied within Central Asian oncological literature. The AUC of 0.84 indicates the model's readiness for clinical translation. Practically, these findings support: integrating HPV genotype persistence testing as the primary CIN triage criterion at colposcopy referral level; establishing smoking cessation as a formal component of cervical cancer prevention counseling; implementing risk-flagging systems for women with multiparity and irregular screening

histories; and piloting the four-variable risk index at primary care outposts to rationalize colposcopy referral volumes.

Conclusion

Effective suppression of cervical precancerous pathology demands a departure from cytology-only detection toward biologically informed, behaviorally enriched risk stratification. Persistent HR-HPV infection, tobacco exposure, multiparity, and screening irregularity operate synergistically rather than independently, generating a composite oncological risk that single-marker approaches systematically underestimate. Health systems operating under resource constraints stand to gain the most from deploying validated composite risk indices — concentrating diagnostic intensity where progression probability is highest, and relaxing surveillance intervals where combined risk is demonstrably low. Translating this evidence into protocol-level change at both clinical and policy levels represents the necessary next step.

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