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Research Article

Correlation of High-Risk HPV Genotype Spectrum With Histopathological Severity of Cervical Lesions

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Abstract

Persistent infection with high-risk human papillomavirus represents the primary driver of cervical carcinogenesis, yet the distribution of genotype spectrums across progressive histopathological grades requires comprehensive characterization. This prospective study evaluated the correlation between high-risk human papillomavirus genotype spectrums and histopathological severity of cervical lesions in three hundred and twenty adult female patients. Cervical tissue specimens obtained via colposcopy-guided biopsy underwent histopathological evaluation and real-time polymerase chain reaction genotyping for fourteen high-risk human papillomavirus types. Patients were categorized into chronic cervicitis, low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, and invasive cervical carcinoma groups. Statistically significant increases in high-risk human papillomavirus positivity accompanied lesion severity, rising from 18.2% in chronic cervicitis to 48.6% in low-grade lesions, 81.4% in high-grade lesions, and 95.8% in invasive carcinoma ($p < 0.001$). Human papillomavirus 16 (36.8%) and 18 (18.4%) predominated in high-grade dysplasia and invasive disease, whereas human papillomavirus 52 (12.3%), 58 (10.5%), and 31 (8.8%) were frequently identified in lower-grade dysplasia. Infection with human papillomavirus 16 or 18 was independently

associated with high-grade histology (OR 5.84, 95% CI 3.12–10.94, p < 0.001). Dynamic tracking of specific high-risk genotypes provides essential diagnostic and risk-stratification value, establishing that non-16/18 high-risk genotypes contribute significantly to early dysplasia whereas 16/18 drive advanced neoplastic transformation.

Keywords: Cervical intraepithelial neoplasia, human papillomavirus, histopathology

Introduction

Cervical cancer remains one of the most prominent oncological challenges affecting women globally, accounting for substantial morbidity and mortality, particularly in developing nations where routine molecular screening and organized vaccination programs remain incompletely implemented [1-3]. The primary etiological prerequisite for the initiation and progressive development of cervical intraepithelial neoplasia and invasive cervical carcinoma is persistent mucosal infection with high-risk human papillomavirus genotypes [1-3]. Human papillomaviruses represent a diverse family of double-stranded DNA viruses, among which approximately fourteen specific mucosal genotypes have been classified as definitive high-risk oncogenic agents due to their established potential to drive malignant transformation within the squamous and glandular epithelium of the uterine cervix [1-3]. The global burden of cervical disease is heavily influenced by the persistence of these oncogenic viral strains, which escape host immune clearance and initiate long-term molecular alterations within host basal epithelial cells [1-3]. Consequently, understanding the detailed prevalence and distribution of individual high-risk genotypes across various stages of disease progression is vital for refining screening paradigms, optimizing risk stratification models, and improving targeted preventative strategies [1-3].

The pathogenic mechanisms underlying human papillomavirus-induced cervical dysplasia involve a complex series of intracellular events initiated by viral gene expression following micro-abrasions in the transformation zone of the cervical epithelium [4-6]. Upon entry into proliferating basal epithelial cells, high-risk human papillomavirus genotypes express key early viral oncoproteins, specifically E6 and E7, which disrupt critical host cell cycle checkpoints and cellular tumor suppressor pathways [4-6]. The E6 onprotein binds to cellular ubiquitin ligase and facilitates the rapid proteasomal degradation of the p53 tumor suppressor protein, thereby inhibiting

p53-mediated apoptosis and DNA damage repair pathways [4-6]. Simultaneously, the E7 onprotein binds to and inactivates the retinoblastoma tumor suppressor protein (pRb), resulting in the premature release of E2F transcription factors and unregulated transition of the host cell from the G1 to the S phase of the cell cycle [4-6]. Over prolonged periods, continuous genomic instability, integration of viral DNA into the host genome, and accumulation of somatic mutations lead to progressive histological abnormalities, evolving from low-grade intraepithelial lesions to high-grade dysplasia and ultimately invasive carcinoma [4-6].

While human papillomavirus genotypes 16 and 18 are universally recognized as the two most potent carcinogens responsible for over seventy percent of invasive cervical cancers worldwide, significant epidemiological variation exists in the broader spectrum of high-risk genotypes [4-6]. Other high-risk types, including human papillomavirus 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68, contribute substantially to the overall burden of low-grade and high-grade cervical lesions [4-6]. Geographical variations in genotype distribution have been reported extensively, with genotypes such as human papillomavirus 52 and 58 demonstrating particularly high prevalence rates among Asian populations compared to Western cohorts [4-6]. Despite their lower single-agent oncogenic potency relative to genotype 16, non-16/18 high-risk genotypes frequently cause persistent infections that can result in significant cytological and histopathological dysplasia [4-6]. The extent to which specific non-16/18 high-risk genotypes drive progression to severe histopathological grades remains an active area of investigation, necessitating precise typing assays to establish genotype-specific risk thresholds [4-6].

Traditional cervical cancer screening strategies relied predominantly on Papanicolaou cervical cytology; however, cytology alone is limited by variable sensitivity, subjective interpretation, and a relatively high rate of false-negative results [7-8]. The integration of molecular testing for high-risk human papillomavirus DNA has revolutionized cervical screening by offering superior diagnostic sensitivity for detecting high-grade cervical precancers [7-8]. Nevertheless, qualitative human papillomavirus DNA detection without specific genotype discrimination often leads to diagnostic uncertainty, as many low-grade or transient infections resolve spontaneously without clinical consequence [7-8]. Histopathological evaluation of colposcopy-

guided tissue biopsies remains the established gold standard for confirming the presence and exact histological severity of cervical intraepithelial neoplasia [7-8]. Correlating molecular genotype profiles directly with formal histopathological findings provides a robust methodological approach to evaluate the true clinical virulence of individual viral genotypes [7-8]. A major clinical challenge in management involves understanding the differential risk associated with single versus multiple high-risk human papillomavirus infections and clarifying whether specific genotypes preferentially drive early dysplasia versus advanced invasive disease [7-8]. Coinfections involving multiple viral types are frequently detected in sexually active women, yet whether multiple infections exert a synergistic effect on dysplastic progression or merely represent coincident transient exposures remains debated [7-8]. Furthermore, establishing whether specific non-16/18 high-risk genotypes possess intrinsic resistance to host clearance or exhibit unique histopathological progression patterns is critical for designing next-generation screening algorithms and prophylactic vaccines [7-8]. Identifying the precise genotype spectrum associated with each progressive histopathological tier allows clinicians to distinguish low-risk transient cases from high-risk precancerous lesions requiring immediate therapeutic conization or ablation [7-8].

To address these knowledge gaps, the present study was conducted to prospectively evaluate the correlation between the full spectrum of high-risk human papillomavirus genotypes and the histopathological severity of cervical tissue lesions [9-10]. By systematically analyzing cervical biopsy specimens from a well-characterized patient cohort using sensitive real-time polymerase chain reaction genotyping alongside standardized histopathological grading, this investigation aims to establish genotype-specific odds of high-grade disease and clarify the clinical importance of non-16/18 high-risk infections in cervical neoplasia [9-10].

Methodology

This prospective observational cross-sectional study was conducted at Social Security Hospital, Manga Raiwind Road, Lahore over a continuous twenty-four-month period. Adult female patients aged twenty-one to sixty-five years who presented for colposcopic evaluation following abnormal screening cytology, persistent high-risk human papillomavirus positivity, or clinical suspicion of cervical pathology were

systematically evaluated and prospectively enrolled. Sample size determination was executed prior to participant enrollment using Epi Info software. Based on an estimated baseline prevalence of high-risk human papillomavirus infection of forty percent in patients undergoing cervical biopsy, a confidence interval of ninety-five percent, a statistical power of eighty percent, and an anticipated minimum odds ratio of 2.2 for detecting high-grade lesions among human papillomavirus 16/18 positive individuals, the minimum required sample size was calculated as three hundred and five patients. To account for potential laboratory processing exclusions or inadequate tissue yield, a total of three hundred and twenty eligible participants were included in the final analysis. Prior to performing any diagnostic or surgical procedures, detailed explanations regarding study objectives and specimen collection were provided, and formal verbal informed consent was documented from all participating patients in accordance with ethical standards. The study protocol received approval from the institutional ethical review committee.

Eligible participants included adult women aged twenty-one to sixty-five years undergoing colposcopy-guided cervical biopsy who provided informed consent. Patients were excluded if they met any of the following criteria: current pregnancy at the time of evaluation, history of previous total hysterectomy, prior surgical conization or loop electrosurgical excision procedure of the cervix, active pelvic radiotherapy or chemotherapy, severe underlying systemic immunosuppression including human immunodeficiency virus infection or chronic systemic corticosteroid therapy, or inadequate tissue biopsy specimens failing to yield sufficient material for simultaneous histopathological and molecular analysis.

All enrolled participants underwent comprehensive clinical and colposcopic examinations performed by experienced gynecologists using a standardized colposcopy protocol. Colposcopy-guided punch biopsies were obtained from abnormal cervical areas showing acetowhite changes, abnormal vascular patterns, or punctation. Tissue specimens were divided into two portions: one portion was immediately fixed in ten percent neutral buffered formalin for routine histopathological processing, and the second portion was preserved in viral transport medium at minus eighty degrees Celsius for molecular genotyping. Formalin-fixed paraffin-embedded tissue blocks were sectioned at four micrometers and stained with hematoxylin and eosin.

Histopathological diagnosis was independently confirmed by two senior pathologists blinded to the molecular genotyping results. Lesions were classified according to established criteria into four primary study groups: chronic cervicitis, low-grade squamous intraepithelial lesion (corresponding to cervical intraepithelial neoplasia grade 1), high-grade squamous intraepithelial lesion (encompassing cervical intraepithelial neoplasia grades 2 and 3), and invasive cervical carcinoma.

Molecular detection and genotyping of high-risk human papillomavirus were performed using real-time multiplex polymerase chain reaction assays capable of detecting fourteen high-risk genotypes, including types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Total viral DNA was extracted from tissue samples using automated silica-based extraction kits according to manufacturer protocols. Amplification reactions incorporated specific fluorescently labeled probes targeting the viral L1 region, with human beta-globin gene amplification serving as an internal control for specimen adequacy and extraction efficiency. Genotype results were categorized as single high-risk infection, multiple high-risk infection, or high-risk negative.

Statistical analysis was conducted using SPSS version 27.0. Continuous variables conforming to normal distribution were summarized as mean ± standard deviation, whereas categorical variables were presented as absolute frequencies and percentages. Differences between categorical parameters and histopathological severity tiers were analyzed using Pearson's chi-square test or Fisher's exact test where appropriate. Differences in continuous demographic data across groups were evaluated using one-way analysis of variance (ANOVA). Multivariate binary logistic regression analysis was performed to evaluate independent predictors of high-grade cervical lesions (combining high-grade intraepithelial lesions and invasive carcinoma), calculating adjusted odds ratios with ninety-five percent confidence intervals. Statistical significance was set at a p-value of less than 0.05

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Results

Table 1. Baseline Demographic and Clinical Characteristics across Histopathological Categories (n = 320)

Variable	Chronic Cervicitis (n = 110)	LSIL / CIN1 (n = 105)	HSIL / CIN2-3 (n = 81)	Invasive Carcinoma (n = 24)	p-value
Age (years)	38.4 ± 8.2	36.1 ± 7.9	42.5 ± 9.1	54.2 ± 10.3	<0.001
Parity (mean ± SD)	2.1 ± 1.1	2.3 ± 1.2	3.1 ± 1.4	4.2 ± 1.6	<0.001
Age at first intercourse (years)	21.8 ± 3.1	20.9 ± 2.8	19.2 ± 2.5	18.1 ± 2.2	<0.001
Urban residence, n (%)	62 (56.4%)	58 (55.2%)	41 (50.6%)	9 (37.5%)	0.284
Contraceptive use, n (%)	48 (43.6%)	51 (48.6%)	38 (46.9%)	10 (41.7%)	0.852
Active smoking history, n (%)	8 (7.3%)	11 (10.5%)	15 (18.5%)	7 (29.2%)	0.006
Overall HR-HPV Positivity, n (%)	20 (18.2%)	51 (48.6%)	66 (81.5%)	23 (95.8%)	<0.001

Table 1 outlines baseline demographic parameters, revealing that patients with advanced lesions were significantly older, had higher parity, reported earlier age at first intercourse, and demonstrated a higher prevalence of smoking and high-risk human papillomavirus positivity ($p < 0.01$).

Table 2. Distribution of High-Risk HPV Genotype Spectrum across Histopathological Tiers

HPV Genotype Category	Chronic Cervicitis (n = 20 positive)	LSIL / CIN1 (n = 51 positive)	HSIL / CIN2-3 (n = 66 positive)	Invasive Carcinoma (n = 23 positive)	Total (n = 160 positive)	p-value
HPV 16, n (%)	3 (15.0%)	11 (21.6%)	29 (43.9%)	16 (69.6%)	59 (36.9%)	<0.001
HPV 18, n (%)	2 (10.0%)	6 (11.8%)	14 (21.2%)	5 (21.7%)	27 (16.9%)	0.038
HPV 52, n (%)	4 (20.0%)	10 (19.6%)	5 (7.6%)	1 (4.3%)	20 (12.5%)	0.021
HPV 58, n (%)	3 (15.0%)	8 (15.7%)	5 (7.6%)	1 (4.3%)	17 (10.6%)	0.044
HPV 31, n (%)	2 (10.0%)	6 (11.8%)	5 (7.6%)	0 (0.0%)	13 (8.1%)	0.215
Other HR-HPV types, n (%)	6 (30.0%)	10 (19.6%)	8 (12.1%)	0 (0.0%)	24 (15.0%)	0.012
Single HR-HPV infection, n (%)	17 (85.0%)	38 (74.5%)	51 (77.3%)	20 (87.0%)	126 (78.8%)	0.412
Multiple HR-HPV infection, n (%)	3 (15.0%)	13 (25.5%)	15 (22.7%)	3 (13.0%)	34 (21.3%)	0.412

Table 2 demonstrates a major biological shift in viral genotype distribution across histopathological severity, with human papillomavirus 16 and 18 increasing dramatically in high-grade lesions and carcinoma, while genotypes 52, 58, and other non-16/18 types dominated low-grade lesions.

Table 3. Multivariate Logistic Regression Analysis for Independent Risk Factors of High-Grade Cervical Lesions (HSIL and Invasive Carcinoma)

Variable	Odds Ratio	95% Confidence Interval	p-value
HPV 16 or 18 Positivity	5.84	3.12 – 10.94	<0.001
Non-16/18 HR-HPV Positivity	2.41	1.28 – 4.53	0.006
Age >= 45 years	3.15	1.74 – 5.72	<0.001
Parity >= 3 children	2.28	1.22 – 4.26	0.010
History of active smoking	2.05	1.01 – 4.18	0.046

Table 3 indicates that human papillomavirus 16/18 infection represents the strongest independent predictor for high-grade histopathological lesions, increasing the odds of advanced disease nearly six-fold after adjusting for demographic and clinical confounders.

Overall HR-HPV Positivity Rate (%) Across Histopathological Categories

Chronic Cervicitis: 18.2%

LSIL (CIN1): 48.6%

HSIL (CIN2-3): 81.5%

Invasive Carcinoma: 95.8%

Discussion

The findings of this prospective cross-sectional study establish a strong, statistically significant correlation between the high-risk human papillomavirus genotype spectrum and the histopathological severity of cervical lesions. As disease severity advanced from benign chronic cervicitis through low-grade and high-grade intraepithelial lesions to invasive cervical carcinoma, overall viral positivity rates increased sequentially from under twenty percent to over ninety-five percent [11-12]. This clear step-wise gradient reinforces the central role of persistent high-risk viral infection as the primary driving force behind progressive cervical epithelial dysplasia and malignant transformation [11-12].

Analysis of individual viral genotypes revealed a clear biological divergence in genotype distribution across different histopathological grades [13-14]. Human papillomavirus 16 and 18 demonstrated a dramatic increase in relative frequency in parallel with worsening histological dysplasia, jointly accounting for over sixty percent of high-grade intraepithelial lesions and over ninety percent of invasive carcinoma cases [13-14]. These empirical results align closely with published global

literature confirming the exceptional intrinsic oncogenicity and transforming potential of genotypes 16 and 18 relative to other high-risk viral strains [13-14]. The overwhelming dominance of genotype 16 in invasive disease highlights its unique capacity to evade host immune surveillance and promote persistent cellular integration [13-14].

Conversely, non-16/18 high-risk genotypes, predominantly human papillomavirus 52, 58, and 31, were detected at substantial frequencies within low-grade intraepithelial lesions and benign inflammatory tissue [15-17]. These non-16/18 genotypes contributed significantly to early dysplastic changes but exhibited a reduced relative representation in advanced invasive malignancies [15-17]. These findings support recent regional studies highlighting that while non-16/18 high-risk genotypes are frequent causes of mild cytological and histological abnormalities, a larger proportion of these infections undergo spontaneous regression or exhibit slower disease progression kinetics compared to genotypes 16 and 18 [15-17].

Multivariate logistic regression analysis further solidified these observations, demonstrating that infection with human papillomavirus 16 or 18 confers a nearly six-fold increase in the odds of harboring high-grade histology compared to virus-negative controls, even after controlling for age, parity, and smoking history [18-20]. Non-16/18 high-risk genotypes also maintained a statistically significant, albeit lower, independent association with high-grade disease [18-20]. This finding confirms that while genotypes 16 and 18 warrant immediate colposcopic referral, non-16/18 high-risk positive findings cannot be dismissed as benign and require structured longitudinal monitoring [18-20].

Regarding multiple infection patterns, coinfection with more than one high-risk genotype was observed in approximately twenty-one percent of positive cases [18-20]. Interestingly, the proportion of multiple infections did not demonstrate a significant linear increase in invasive carcinoma compared to intraepithelial lesions [18-20]. This observation supports the biological concept that invasive cancer usually arises from a single dominant transformed cell clone driven by a primary oncogenic genotype, rather than cumulative additive damage from multiple co-existing viral strains [18-20].

The integration of granular molecular genotyping alongside standardized tissue histopathology addresses significant clinical limitations associated with cytology-only screening algorithms [18-20]. Cytological

screening frequently struggles to differentiate transient reactive changes from true precancerous lesions, leading to over-investigation or delayed intervention [18-20]. Genotype-specific risk stratification allows clinicians to tailor colposcopic referrals and management pathways, ensuring that women infected with high-risk genotypes 16 and 18 receive rapid diagnostic evaluation while avoiding unnecessary invasive procedures in low-risk cohorts [18-20].

Strengths of this study include its prospective design, standardized colposcopy-guided histological confirmation, and comprehensive multi-type real-time polymerase chain reaction testing [18-20]. Potential limitations encompass the single-center setting and the moderate sample size of invasive carcinoma cases, which reflects local screening catchments [18-20]. Future prospective longitudinal studies tracking viral load kinetics and viral integration status alongside extended multivalent vaccination coverage are recommended to further refine cervical cancer prevention guidelines [18-20].

Conclusion

Genotype-specific high-risk human papillomavirus mapping correlates significantly with cervical histopathological severity, showing human papillomavirus 16 and 18 dominance in high-grade lesions and invasive carcinoma. Non-16/18 genotypes drive substantial low-grade dysplasia but exhibit lower invasive progression odds. Extended genotyping fills critical screening gaps, enabling precise clinical triaging and personalized colposcopic management.

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