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Distribution of High-Risk Human Papillomavirus Genotypes Among Histopathologically Diagnosed Cervical Intraepithelial Neoplasia

Lubna Yasmin[1*], Ashrafunnessa[2], Asma Akter Sonia[3], Amatus Salam Nimmi[4], Tahsin Zaman[5], Snigdha Chakraborty [6], Rajia Sultana[7], Sadia Nusrat Alamgir[8]

[1]Medical Officer, Department of Obstetrics and Gynecology, Dhaka Medical College Hospital, Dhaka, Bangladesh.

[2]Professor, Department of Gynaecological Oncology, Bangladesh Medical University, Dhaka, Bangladesh,

[3]Assistant Professor, Department of Obstetrics and Gynecology, Khwaja Yunus Ali Medical College & Hospital, Sirajganj, Bangladesh.

[4]Junior Consultant, Department of Obstetrics and Gynecology, Kuwait Bangladesh Friendship Govt. Hospital, Dhaka, Bangladesh.

[5]OSD, Directorate General of Health Services (DGHS), Dhaka, Bangladesh.

[6]RMO, Upazila Health Complex & Hospital, Mehendiganj, Barishal, Bangladesh.

[7]Department of Gynaecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

[8]Consultant, Department of Obstetrics and Gynecology, Directorate General of Health Services (DGHS), Dhaka, Bangladesh

Corresponding Author: Lubna Yasmin, MO, Department of Obstetrics and Gynecology, Dhaka Medical College Hospital, Dhaka, Bangladesh.

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KEYWORDS

Cervical intraepithelial neoplasia, HPV genotype, HPV 16, cervical precancer, cervical cancer

ABSTRACT:

Background: Cervical intraepithelial neoplasia (CIN) is a precursor of cervical carcinoma, predominantly caused by high-risk human papillomavirus (hr-HPV) infection. Genotype-specific data are essential for optimizing screening and vaccination strategies in resource-limited settings. This study aimed to determine the distribution of hr-HPV genotypes in histopathologically diagnosed CIN cases in Bangladeshi women.

Methods: A hospital-based cross-sectional study was conducted at the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from April 2022 to March 2023. A total of 100 women aged 30–60 years with histopathologically confirmed CIN were enrolled. Cervical specimens were collected and analyzed using the Cobas 4800 PCR system to detect HPV 16, 18, and other hr-HPV types. Associations between HPV genotype, age group, and CIN grade were analyzed using the chi-square test.

Results: The mean age of the participants was 39.9 ± 7.2 years. HPV 16 was detected in 17%, HPV 18 in 3%, and other hr-HPV in 3% of women; two participants had mixed infections. Among the 76 CIN I cases, only one (1.3%) was hr-HPV-positive, whereas all CIN II (n = 11) and CIN III (n = 13) cases were hr-HPV-positive. The association between genotype and histopathological grade was statistically significant ($P < 0.001$).

Conclusion: HPV 16 is the most prevalent genotype in cervical precancerous lesions, particularly in high-grade CIN. Incorporating HPV genotyping into routine screening can enhance risk stratification and inform targeted vaccination policies for Bangladesh.

Introduction

Cervical cancer remains a major public health burden globally, particularly in low- and middle-income countries where organized screening and vaccination programs are limited [1]. According to GLOBOCAN 2020 estimates, approximately 604,127 new cases and 341,831 deaths were reported worldwide, with nearly 83% occurring in developing regions. Carcinoma of the cervix is the second most frequent malignancy among women in Bangladesh, accounting for over 8,000 new cases annually [2]. Persistent infection with high-risk human papillomavirus (hr-HPV) types is the primary etiological factor responsible for cervical carcinogenesis [3].

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Human papillomaviruses (HPVs) are small, double-stranded DNA viruses belonging to the Papillomaviridae family. To date, more than 200 genotypes have been identified, of which approximately 14 are classified as high-risk or oncogenic. Among these, HPV 16 and HPV 18 possess the highest oncogenic potential, together accounting for about 70% of all cervical cancers worldwide [4]. HPV infects the basal epithelial cells of the cervix, usually at the squamocolumnar junction, and can cause cellular changes leading to cervical intraepithelial neoplasia (CIN). CIN is a precancerous lesion graded as CIN I, II, and III based on histopathological severity, ranging from mild dysplasia to carcinoma in situ [5]. Persistent HR-HPV infection disrupts the normal epithelial cell cycle, mediated primarily by the viral oncoproteins E6 and E7, which inactivate tumor suppressor proteins p53 and Rb, promoting uncontrolled cellular proliferation [6].

Cervical intraepithelial neoplasia is a pivotal stage in the natural history of cervical cancer, as progression to invasive carcinoma typically takes several years, offering a significant window for detection and intervention [7]. Although most HPV infections are transient and cleared by the host immune system, persistent hr-HPV infection—especially with genotypes 16, 18, 31, 33, and 45—is strongly associated with high-grade CIN and cervical cancer [8]. The estimated risk of progression to invasive carcinoma is approximately 1% for CIN I, 5% for CIN II, and at least 12% for CIN III [9].

Globally, various screening approaches such as Pap cytology, HPV DNA testing, and visual inspection with acetic acid (VIA) are employed to detect precancerous lesions [10]. Bangladesh adopted VIA as a low-cost, community-based screening program in 2004, expanding colposcopy and loop electrosurgical excision procedures (LEEP) in tertiary centers [11]. However, VIA's limited specificity often results in false positives and overtreatment, emphasizing the need for more accurate HPV-based testing. The World Health Organization (WHO) has recently recommended HPV DNA detection as the preferred screening method due to its superior sensitivity and predictive value [12].

Despite significant advancements in global HPV vaccination and screening, data on genotype distribution in Bangladesh remain sparse. Understanding the genotype prevalence among histopathologically confirmed CIN cases is essential for optimizing national vaccination strategies and for assessing the performance of existing screening programs.

This study was conducted to determine the distribution of hr-HPV genotypes among histopathologically diagnosed CIN lesions in Bangladeshi women attending a tertiary care colposcopy clinic. By correlating genotype distribution with CIN grades and age groups, the study aims to provide locally relevant evidence that could guide national screening, vaccination, and treatment strategies.

Methodology & Materials

A hospital-based cross-sectional analytical study was carried out in the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from April 2022 to March 2023. The study included 100 women aged 30–60 years who attended the Colposcopy Clinic and met the inclusion criteria.

Inclusion criteria:

- Women aged 30–60 years.
- Histopathologically diagnosed as cervical intraepithelial neoplasia (CIN I–III).
- Women who provided informed written consent.

Exclusion criteria:

- Women with frank cervical malignancy.
- Pregnant or within the immediate postpartum period.
- Presence of acute cervical infection.
- Unmarried women.
- Prior treatment for CIN lesions.

Study Procedure

After approval from the Institutional Review Board (IRB) of BSMMU, women attending the Colposcopy Clinic with a positive VIA test were evaluated for possible inclusion. Each participant received an explanation of the study's purpose, procedures, potential benefits, and their right to withdraw at any time. After obtaining informed written consent, data were collected using a pre-tested semi-structured questionnaire. Socio-demographic information, reproductive history, and

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contraceptive practices were recorded through face-to-face interviews.

Clinical examination was performed with the patient in the lithotomy position. The cervix was visualized using a sterile Cusco's speculum, and secretions were gently removed with a cotton swab. Cervical samples were collected using a cytobrush; the central bristle was inserted into the endocervical canal and rotated five times in a clockwise direction to ensure contact with the entire transformation zone. The brush head was then rinsed in Cobas PCR media and discarded. Specimens were transported to the National Screening Centre's PCR Laboratory and stored at −20°C until analysis.

HPV DNA detection and genotyping were performed using the Cobas 4800 system, which employs real-time PCR technology for simultaneous detection of HPV 16, HPV 18, and pooled other hr-HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Each assay included β-globin as an internal control for sample adequacy. After sample collection, the cervix was evaluated using 5% acetic acid for VIA positivity, followed by colposcopy. Acetowhite lesions and vascular changes were recorded, and targeted punch biopsies were taken from suspicious sites. The biopsy specimens were fixed in 10% formalin and examined histopathologically to confirm CIN grade. Laboratory personnel were blinded to clinical data to ensure objectivity.

Ethical Considerations

The study followed the ethical principles of the Helsinki Declaration (1964). Institutional Review Board (IRB) approval was obtained from BSMMU. Participants' confidentiality was strictly maintained; all data were anonymized using unique identification codes. Informed written consent was taken before enrollment, ensuring voluntary participation.

Statistical Analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 23.0. Descriptive statistics summarized baseline characteristics, while categorical data were presented as frequencies and percentages. Associations between HR-HPV genotypes, age groups, and histopathological grades were evaluated using the Chi-square test. A p-value of less than 0.05 was considered statistically significant.

Results

Table I: Socio-demographic characteristics of the study population (N=100)

Characteristics	Number of patients	Percentage
Age (years)		
30-40	62	62.0
41-50	28	28.0
>50	10	10.0
Mean±SD	39.92±7.21	
Educational status		
No formal education	30	30.0
Primary	54	54.0
Secondary and above	16	15.0
Higher Secondary	1	1.0
Family monthly income		
≤10000 Tk	4	4.0
10001-20000 Tk	86	86.0
> 20000 Tk	10	10.0
Service holder	47	47.0
Husband's occupation		
Business	19	19.0
Farmer	15	15.0
Expatriate	9	9.0
Other	10	10.0

The mean age of the women was 39.92±7.21 years, with a range from 30 to 60 years. Half (54.0%) of the women completed primary education, and 86(86.0%) came from a 10001–20000-taka monthly income range.

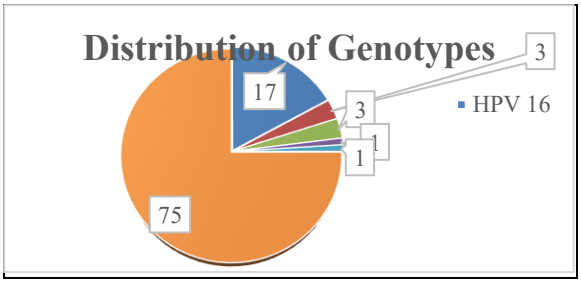

Figure 1: Showing HPV genotyping of the study population

Figure 1 shows that 17(17.0%) women were found HPV 16 positive, 3(3.0%) women were positive for HPV 18 and 3(3.0%) women were positive for other hr-HPV. Among 100 women, 2 women had mixed infection, of which one had HPV 16 with other hr- HPV and one had HPV 18 with other hr-HPV. Overall,75(75.0%) women were negative for hr-HPV genotype.

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Table II: Histopathology reports of the study population (N=100)

Histopathology reports	Number of patients	Percentage
CIN I	76	76.0
CIN II	11	11.0
CIN III	13	13.0

Histopathology report showed that 76(76.0%) women had CIN I, 11(11.0%) women had CIN II and 13(13.0%) women had CIN III.

Table III: Distribution of hr-HPV genotypes in different age groups (N=100)

HPV genotype reports	Age (years)			Total	P value
	30-40 (n=62)	41-50 (n=28)	> 50 (n=10)		
HPV 16	10	6	1	17	0.88
HPV 18	2	1	0	3	
Other HR-HPV	2	2	1	5	
HPV 18 with others	0	1	0	1	
HPV 16 with others	1	0	0	1	
Negative	48	19	8	75	

HPV 16 was most frequent among the age group of 30-40 years. Of the 62 women who belonged to the 30-40 years age group, 10 cases were HPV 16, among the 41-50 age group, 6 cases were hr-HPV 16 positive, and only one HPV16 positive case was found above the age of 50 years. However, the distribution of hr-HPV in histopathology-proven CIN with different age groups was not statistically significant (p>0.88).

Table IV: Distribution of hr-HPV in different histopathological grades of CIN (N=100)

HPV genotype reports	Histopathology reports						P value
	CIN I (n=76)		CIN II (n=11)		CIN III (n=13)		
	N	%	N	%	N	%	
Positive							
HPV 16	1	1.32	8	72.73	8	61.54	0.001
HPV 18	0	0	1	9.09	2	15.38	
Other hr-HPV	0	0	1	9.09	2	15.38	
HPV 18 with others	0	0	0	0	1	7.69	
HPV 16 with others	0	0	1	9.09	0	0	
Negative	75	98.68	0	0	0	0	0.001

Among the 76(76%) histology-proven CIN I cases, only 1(1.32%) was hr-HPV positive. All 11(11%) cases of CIN II and 13(13%) cases of CIN III were hr-HPV DNA positive. HPV 16 was more prevalent both in CINII (9.09%) and CINIII (13%). Other hr-HPV was present in 9.09% in CINII and 15.38% in CINIII. High-risk HPV was distributed significantly in CINII and CINIII.

Discussion

The present study explored the distribution of high-risk human papillomavirus (hr-HPV) genotypes among histopathologically diagnosed cervical intraepithelial neoplasia (CIN) in Bangladeshi women. The findings reaffirmed that HPV 16 is the most prevalent genotype associated with high-grade cervical precancers, while HPV 18 and other hr-HPV types contributed to a smaller proportion of lesions. These observations are consistent with global and regional evidence underscoring HPV 16 as the dominant carcinogenic type implicated in cervical neoplasia.

The mean age of participants was 39.9 ± 7.2 years, comparable to the findings of Shahida et al., who reported a mean age of 38.7 ± 7.8 years among Bangladeshi women with CIN [13]. The concentration of cases within the 30–40-year age group corresponds with the epidemiological pattern of hr-HPV persistence, which typically manifests in middle-aged women rather than younger age groups where transient infections predominate [8]. Although this study found no significant association between age and hr-HPV positivity, the observed clustering of HPV 16 infection in the 30–40-year range may indicate that viral persistence rather than new acquisition plays a central role in the development of CIN at this age.

Histopathological analysis revealed that 76% of women had CIN I, 11% had CIN II, and 13% had CIN III, mirroring the natural gradient of precancerous lesions observed in population-based studies. The strong,

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statistically significant association between HPV genotype and histopathological grade ($p < 0.001$) reinforces the biological gradient between viral oncogenicity and disease severity. The predominance of HPV 16 in both CIN II and CIN III aligns with reports by Akter et al. and Zhao et al., who demonstrated similar genotype-specific clustering in high-grade lesions [14,15]. In contrast, only 1.3% of CIN I cases in the present study were hr-HPV positive, suggesting that most low-grade lesions may either represent transient low-risk infections or reactive epithelial atypia rather than persistent oncogenic infection.

Comparative data from other Asian regions show variation in genotype distribution, reflecting geographical heterogeneity. Studies from Japan have documented higher proportions of HPV 52 and HPV 58 in CIN II–III, while HPV 16 remains the leading type worldwide [16]. These differences underscore the necessity of country-specific genotype surveillance to guide vaccine selection and screening algorithms. Bangladesh currently uses bivalent and quadrivalent HPV vaccines targeting types 16 and 18; however, the inclusion of genotypes 31, 33, 45, 52, and 58 in the nonvalent vaccine could provide broader coverage, particularly if regional data confirm their circulation [17].

The overall hr-HPV positivity rate (25%) in this cohort was lower than that reported in other South-East Asian studies, where rates range from 35% to 70% among histopathologically confirmed CIN lesions [11]. Several factors may explain this difference: limited sensitivity of VIA-based screening in identifying high-risk lesions, the predominance of low-grade CIN in this sample, and potential under-representation of rural women with advanced disease who may not access tertiary facilities. Nevertheless, the presence of hr-HPV in all CIN II and CIN III cases confirms its essential causal role in cervical carcinogenesis and supports integrating HPV testing as a triage tool following VIA screening.

Globally, HPV 16 exhibits unique biological properties that enhance viral persistence and oncogenic potential. Its E6 and E7 oncoproteins have stronger binding affinity to tumor-suppressor proteins p53 and Rb compared with other genotypes, leading to rapid genomic instability and cellular transformation [6]. The predominance of HPV 16 in this study may thus reflect its greater ability to evade immune clearance. Moreover, environmental cofactors such as multiparity, prolonged oral contraceptive use, and low socioeconomic status—common in the studied population—are known to enhance viral persistence and lesion progression [18,19].

The absence of a statistically significant age association suggests that hr-HPV infection remains relevant throughout the reproductive lifespan of Bangladeshi women. Screening programs limited to younger women may therefore miss a substantial portion of persistent infections in women aged 40 years and above. The data reinforce WHO recommendations advocating HPV testing at ages 35 and 45 years as part of a lifetime screening strategy [12].

From a public-health perspective, the study provides baseline molecular evidence that can inform national cervical-cancer-control efforts. Incorporating HPV genotyping in tertiary centers like BSMMU could improve patient management by distinguishing women who require immediate treatment (those positive for HPV 16/18 with CIN II/III) from those suitable for surveillance (CIN I with negative hr-HPV).

Limitations of the study

This study was conducted in a single tertiary hospital with 100 participants, limiting external validity. As a cross-sectional analysis, temporal relationships between HPV infection and CIN progression could not be determined. The study was restricted to women attending a colposcopy clinic, introducing selection bias toward symptomatic or VIA-positive cases. Genotyping was limited to HPV 16, 18, and a pooled group of other hr-HPV types, precluding analysis of less common genotypes such as 31, 33, 45, 52, and 58.

Conclusion

The study shows HPV 16 is the predominant high-risk genotype associated with histopathologically confirmed cervical intraepithelial neoplasia in Bangladeshi women, followed by HPV 18 and other hr-HPV types. All CIN II and CIN III lesions were hr-HPV positive, underscoring the virus's role in cervical precancer pathogenesis. These findings highlight the utility of HPV genotyping in complementing histopathological assessment to improve diagnostic accuracy, guide management, and support evidence-based screening and vaccination strategies. Integrating molecular testing into national cervical-

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cancer-prevention programs could accelerate Bangladesh's progress toward the WHO's 2030 elimination targets.

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Conflicts of interest

There are no conflicts of interest.

Ethical approval

The study was approved by the Institutional Ethics Committee.

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