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Distribution of High-Risk Human Papillomavirus Genotypes among Women with Colposcopic Diagnosis of Cervical Intraepithelial Neoplasia in Bangladesh

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Abstract

Background: The incidence of cervical cancer is high in Bangladesh and there is a high prevalence of preinvasive lower genital tract disease among women of reproductive age. Persistent high-risk Human Papilloma Virus (HPV) infection is the main underlying cause of cervical cancer and its precursor, cervical intraepithelial neoplasia (CIN). **Objective:** The aim of the study was to identify the subtypes of high-risk HPV infection among women with the colposcopic diagnosis of cervical intraepithelial neoplasia in Bangladesh. **Methods:** This cross-sectional observational study was conducted in the colposcopy clinic of Dhaka Medical College Hospital over a six-month period. A total of 100 participants were enrolled. Married women, between 30 - 60 years of age with colposcopically diagnosed cervical intra epithelial neoplasia were enrolled. Women with chronic illness, pregnancy, and women unable to consent were excluded from this study. After counselling, colposcopically directed punch biopsies were taken from each CIN case concurrently with high-risk HPV testing by polymerase chain reaction (PCR). **Results:** The mean age of the patients was 38.69 (SD ±7.76) years. CIN 1 was diagnosed in 57% of participants, while 24% had CIN II and 19% had CIN III lesions. High-risk HPV was present in 52 patients. HPV 16 was the most common identified in 28 (53.84%) and HPV 18 was the second most common with 20 (38.46%) either singly or in combination with other high-risk subtypes. The

other HPV strains, HPV 31, 33, 35, 52, 56 and 58, were also detected either as mono or co-infections. Out of the 52 HPV positive cases, 29 (55.8%) had mono infection and 23 (44.2%) had co-infection with several subtypes. The highest incidence (50%) of oncogenic HPV infections was present among women aged 35 - 45 years. Risk factors associated with HPV positive cases were high parity ($P < 0.05$), early age at marriage ($P = 0.754$) and early age of first child. **Conclusion:** This study identified a high prevalence of HPV 16 and 18 genotypes. HPV vaccination with the current 9-valent HPV vaccine, which contains HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Will be an effective public health measure to eradicate cervical cancer in Bangladesh.

Keywords

Bangladesh, Cervical Cancer, Cervical Intraepithelial Neoplasia, Human Papillomavirus Infection, High-Risk HPV

1. Introduction

In 2020, there were at least 604,127 estimated new cases of cervical cancer, with over 88% occurring in the Global South, a five-year prevalence of 1.5 million cases, and 341,831 cervical cancer deaths [1]. There is no national cancer registry in Bangladesh and so the full incidence and prevalence are unknown [2]. Based on limited data from university hospitals [3], Globocan reports that about 8268 new cervical cases are diagnosed annually and is the second leading cause of female cancer in Bangladesh [4] [5].

Invasive cancer of cervix is a preventable condition, since it is associated with a long preinvasive phase referred to as cervical intraepithelial neoplasia (CIN) making it amenable to screening, treatment of preinvasive disease and prevention of cervical cancer [6] [7]. Colposcopic guided biopsies to identify both preinvasive disease and early cervical cancer in the evaluation of abnormal cervical cytology and/or positive HPV testing have been the standard of care for over forty years [8] [9]. Colposcopic evaluation has been effectively used at large teaching hospitals in Bangladesh [10].

Persistent HPV infection, defined as active infection without clearance for over two years, is the essential cause of cervical cancer and its precursor, cervical intraepithelial neoplasia [11]. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. Over 100 HPV genotypes have been isolated to date. Among these more than 40 have been shown to infect the genital tract. Chronic infection of the uterine cervix by one or more oncogenic Human Papilloma virus strains (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 70, 82) leads to precancerous lesions (CIN I, CIN II, CIN III) [12].

The prevalence of HPV infection has shown to vary by region, country and, within a country, by population sub-groups [13] [14] [15]. Type-specific distri-

bution of HPV infection also varies by geographic region [16] [17] [18] [19] [20]. Hospital-based studies in Bangladesh reported that 96.7% of cervical cancer cases and 83.3% of CIN 2/3 cases were HPV high-risk positive but there is little data on which subtypes are most prevalent [21].

Correlation between colposcopic diagnosis of CIN and high-risk HPV genotyping is important and will give support for efficacy of HPV vaccination programs in Bangladesh. The present study is aimed at detecting the type-specific distribution of high-risk HPV among patients with colposcopic diagnoses of cervical intraepithelial neoplasia. Colposcopic identification of CIN has been well described [22] [23] [24]. Lesions that have a sharp boundary, an irregular contour, acetowhite color, and a vascular pattern of punctation and/or mosaic pattern are suspicious for preinvasive disease. These lesions are usually biopsied for histopathologic confirmation of CIN or cancer. In resource-limited regions, where it is not financially or technically feasible to biopsy all lesions, visual identification of an acetowhite lesion alone leads to treatment by cryotherapy or loop electrosurgical excision (LEEP) [16] [25].

2. Methods

This was a descriptive cross-sectional type of observational study carried out in the colposcopy clinic of obstetrics and gynecology department and microbiology department of Dhaka Medical College, Dhaka, Bangladesh during the period from July 2019 to December 2019. Approval and ethical clearance from the Ethics committee of Dhaka Medical College were obtained.

One hundred consecutive women with colposcopically diagnosed CIN were included in this study. Sample size was established based on resources available. Married women, between 30 - 60 years of age, having colposcopically diagnosed cervical intra epithelial neoplasia were enrolled. Women with chronic illness, pregnancy, and women unable to consent were excluded from this study. Grading of CIN was done by Swede scoring [26]. Written informed consent was obtained from patients before taking biopsies. Colposcopically guided cervical punch biopsies were taken for CIN cases and sent to the Department of Microbiology, Dhaka Medical College for the detection of high-risk HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 70, 82 by Polymerase Chain Reaction (PCR) [27]. Variables examined included HPV subtypes, histopathological analysis of directed biopsies, and the characteristics of participants including age, income, and education. Chi-squared test was used examine clinical variables and evaluation of the independence of pairs of variables.

3. Results

One hundred women were recruited for the study. **Table 1** shows the distribution of demographic characteristics. The ages of the majority of patients were from 35 - 45 years (50%). The mean age of patients was 38.69 (±7.76) years. Most of the patients were housewives (93%). Fifty-three percent of them had

Table 1. Distribution of patients by demographic features (n = 100).

Variables	Frequency	Percentage
Age Group		
<35 years	30	30
35 - 45 years	50	50
>45 years	20	20
Occupation		
Housewife	93	93
Service	5	5
Student	1	1
Tailor	1	1
Level of education		
Illiterate	16	16
Primary	53	53
Secondary	23	23
HSC or above	8	8
Religion		
Muslim	91	91
Hindu	9	9
Monthly Family Income (Tk)		
<10,000	26	26
10,000 - 15,000	33	33
15,000 - 20,000	23	23
20,000 - 25,000	23	23
>25,000	6	6

completed primary education. Around 91% respondents were Muslim. Most of them were from lower socioeconomic status. Figure 1 shows the distribution of preinvasive lesions.

CIN 1 was diagnosed in 57% of participants, while 24% had CIN II and 19% had CIN III lesions. High-risk HPV was present in 52 patients. Figure 2 and Table 2 show the distribution of HPV subtypes. HPV 16 was the most common subtype in 28 women (53.84%) and HPV 18 was the second most common subtype in 20 women (38.46%) either singly or in combination with other high-risk subtypes. The other HPV strains, HPV 31, 33, 35, 52, 56 and 58, were also detected either as mono or co-infections.

Out of the 52 HPV positive cases, 29 (55.8%) had a single subtype infection and 23 (44.2%) had co-infection with several subtypes: 20 (38.5%) had two subtypes, two (3.95) were infected with three subtypes and one (1.9%) had four concurrent subtype HPV infections. Table 3 summarizes the breakdown of infections. Cross-tabulation between HR-HPV infection and colposcopic findings is presented in Table 4. Twenty-four (46.2%) women who were infected with

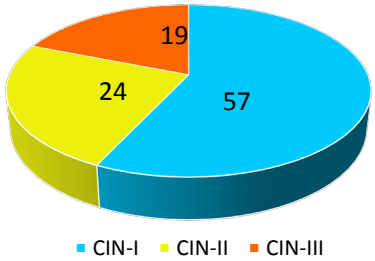

Figure 1. Colposcopic grading among Cervical Intraepithelial Neoplasia (CIN) among respondents (n = 100).

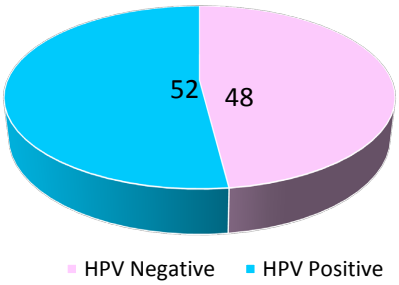

Figure 2. Detection of HR-HPV strains among patients (n = 100).

Table 2. Distribution of patients by HPV strain either as a single or with combination.

Variables	CIN-I	CIN-II	CIN-III	Total
HPV-16	5	6	3	14
HPV-16, 18	1	4	2	7
HPV-16, 31	1	0	0	1
HPV-16, 33	0	1	0	1
HPV-16, 35	0	0	1	1
HPV-16, 52	1	0	0	1
HPV-16, 56	1	0	0	1
HPV-16, 35, 52	0	0	1	1
HPV-16, 35, 52, 56	0	0	1	1
HPV-18	8	2	3	13
HPV-18, 33	2	1	0	3
HPV-18, 35	1	0	1	2
HPV-18, 58	1	0	0	1
HPV-18, 35, 56	0	0	1	1
HPV-31	2	0	0	2
HPV-33, 35	1	0	1	2
Total	24	14	14	52

HR-HPV developed CIN-I, fourteen (26.9%) had developed CIN-II and fourteen (26.9%) had developed CIN-III. HPV infection correlated significantly with preinvasive cervical disease ($P < 0.05$).

Table 3. Distribution of HR-HPV positive cases according to infection with number of high-risk HPV genotypes (n = 52).

Infection with number of subtypes of High-risk Human Papillomavirus (HR-HPV)	Frequency	Percentage
Single infection (n = 29)	29	55.8%
Co-infection (n = 23)		
Two Subtypes HR-HPV	20	38.5%
Three subtypes HR-HPV	2	3.9%
Four subtypes HR-HPV	1	1.9%
TOTAL	52	100%

Table 4. Comparison between colposcopic findings and HR-HPV infection.

Colposcopic findings	HR-HPV Positive		HR-HPV Negative		X^2 test	p-value
	Frequency	Percentage	Frequency	Percentage		
CIN-I	24	46.2	33	68.8	6.2008	0.045
CIN-II	14	26.9	10	20.8		
CIN-III	14	26.9	5	10.4		
Total	52	100	48	100		

Table 5 summarizes the distribution of HPV positive cases according to age group. HPV infections were most frequent in women in the 35 - 45 age group (50%), followed by those less than 35 years old. Prevalence was lowest in the age group > 45 years.

The results of Table 6 illustrate that there was significant relationship between high parity and HR-HPV infections. Risk factors associated with HPV positive cases were high parity ($P < 0.05$). There was less association with early age at marriage ($P = 0.754$) and early age of first child ($P = 0.134$).

4. Discussion

The present study was carried out to detect prevalence of high-risk HPV subtypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 70 and 82 among the patients with colposcopically diagnosed cervical intraepithelial neoplasia in the gynecologic outpatient department of Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh. DMCH is the largest tertiary hospital of Bangladesh. Patients attending the DMCH are from all the districts of Bangladesh.

The mean age of the colposcopic diagnosed CIN cases of our study was 38.69 (SD ±7.76) years and most (50%) of our study population were between 35 - 45 years. These findings are substantiated by observations made by a population-based study on prevalence of cervical precancers in different districts of Bangladesh, that women, ages 35 to 39 years, have strong association with cervical precancers [28]. This age group of women should get priority in the national cervical cancer screening program [29]. The majority (69%) of the study

Table 5. Distribution of HR-HPV positive cases according to age group.

Age in years	Positive		Negative		X^2 test	p-value
	Frequency	Percentage	Frequency	Percentage		
<35 years	16	30.8	14	29.2	0.0534	0.974
35 - 45 years	26	50	24	50		
>45 years	10	19.23	10	20.3		
Total	52	100	48	100		

Table 6. Risk factors associated with HR-HPV positive cases.

Variables	Positive		Negative		X^2 test	p-value
	Frequency	Percentage	Frequency	Percentage		
High Parity (4 and above)	24	46.2	28	53.8	4.8478	0.028
Early age of marriage (<18 years)	33	53.2	29	46.8	0.0982	0.754
Early age of first child (<18 years)	25	61	16	39	2.2429	0.134

population had education levels up to primary school or below that. Fifty-nine percent of families had monthly income less than 15000 taka per month ($138.00 US Dollars), representing the poorest section of the society: low education, low income and higher [30] [31] [32]. Poverty is associated with increased cervical and vaginal cancer incidence rate. The low-income group may also be related to high incidence of early marriage, high parity, low attendance to physicians, which compounds this group's vulnerability to the development of cervical cancer.

Out of 100 colposcopic diagnoses of CIN, 57% were LSIL and 43% were HSIL in the current study. This result is in contrast with studies done at Faridpur Medical College Hospital and at Khulna Medical College Hospital, Bangladesh. They reported 30% cases of HSIL [33] [34]. Dhaka Medical College hospital is the largest referral hospital of Bangladesh and may receive a greater number of HSIL cases from both government and private hospitals.

In this study, the prevalence of high-risk HPV was found in 52% of cases. Our result does not correlate the study by other countries like Norway (92%) [35], Australia (90%) [36], and China (83%) [37]. The result of the current study has shown the lower HPV prevalence because this study included only colposcopically diagnosed CIN cases to observe the types of HR-HPV among them. Colposcopists were blinded to the results of the tests, where the histopathological grading of cervical neoplasia was the gold standard for CIN diagnosis.

Among 100 colposcopically diagnosed CIN cases, eight different HR-HPV subtypes could be identified in the present study. Another study done in Northern Xinjiang, China identified seventeen different HR-HPV subtypes [38]. This

underestimation of HPV prevalence in this study is most likely due to the study methodologies. The prevalent genotypes of HPV among CIN cases of current study were HPV 16, 18, 31, 33, 35, 52, 56 and 58 either as single or multiple infections. A prospective study from Varnasi and adjoining areas of India reported that HR HPV 16, 18, 31, 33, 35, 45, 58, 86 were observed among CIN cases and cervical cancer cases [39]. In Pakistan, the prevalent genotypes in cervical cancer were HPV 16, 18, 45, 56, 73. Meta analysis from World Cancer Research Center indicated that HPV 16, 31, 51 and 53 were the most prevalent HPV genotypes [18] [19].

The present study identified HPV 16 as the most common subtype (53.84%). HPV 18 was the second most common strain (38.46%) in this study. Our results are consistent with the findings from several other university centers in Bangladesh [40] [41]. We found the less prevalent HPV 56 and 58 were detected but the more prevalent HPV 45 was not detected. There are geographic variations to high-risk HPV subtypes. A study in Yugoslav women showed that HPV 31 was the most common oncogenic type of HPV [42]. In South Korea, HR type HPV 58 was the second most prevalent type [43]. In Xinjiang, China, the second most prevalent type was HPV 53 (28.9%) which may be attributable to the regional and racial differences or relatively poor sanitation conditions [38].

According to ICO/IARC HPV information center summary report, 2022 reported HPV 16 and 18 causes 41% to 67% of high-grade cervical lesions and 16 to 32% of low-grade cervical lesions ICO. After HPV 16/18, the six most common HPV types are the same in all world regions, namely 31, 33, 35, 45, 52 and 58, which is consistent with the findings of this study [16].

In our study, among the 52 HPV positive cases, single subtype infections were found in 55.8% of cases and co-infection was found in 44.2% of cases. Although many reports indicated that multiple HPV infections are associated with cervical cancer, there are some controversial conclusions in other reports [44]. A report from South Africa could not correlate the presence of multiple HPV infections with the severity level of cervical cancer and didn't increase the incidence of cervical cancer [45].

Regarding association of HPV infection with grade of colposcopic diagnosis of CIN, previous investigations showed that 75% - 95% of high-grade CIN lesions and 25% - 40% of low-grade CIN lesions are associated with a positive HPV test [46]. This finding does not correlate the observation of current study where 54% HR-HPV were detected from high grade CIN lesions and 46% HR-HPV were detected from low grade CIN lesions. The study done in rural Gambia, West Africa could not detect 87% from high grade CIN lesions [47]. This may be due to integration of viral DNA into their genomic DNA and the consequent deletion of the target site for the consensus PCR primers causing failure of detecting HPV genotypes in high grade CIN.

In terms of age distribution, highest percentage (50%) of oncogenic HPV was found among women aged 35 - 45 years and lowest prevalence was in the age group > 45 years. Though statistically no significant result was observed, these

findings correlate the observation from a recent large population based multi-centered survey of HPV prevalence in China where they concluded the prevalence of oncogenic HPV was higher among women aged 20 - 25 and again in women aged 40 - 45 years [48]. Observation from another study conducted at Kazakhstan, found highest prevalence of HR-HPV infections was in the age group of 26 - 35 and 36 - 45 years old and lowest prevalence was in the age group more than 45 years [49].

In this study, risk factors associated with HPV positive cases were high parity ($P < 0.05$), early age at marriage ($P = 0.754$) and early age of first child ($P = 0.134$). Though some risk factors including age at first intercourse, smoking and number of sexual partners of patient or her husband increase the risk of HPV infection exposure, we were not able to obtain this information due to cultural norms [50]. The present study adds to the existing knowledge of the burden of high-risk HPV infections among a selected female population referred to our tertiary care hospital in Dhaka, Bangladesh. Limitations of this study include this being a single center-based study with a small sample size due to time and budget constraints. The limitations also include small numbers and a single point in time for the participants.

5. Conclusion and Recommendations

Data is not yet available on the HPV burden in the general population of Bangladesh. In this study, HPV-16 and HPV-18 are the most prevalent HPV genotypes. In addition, current study also detected other high risk HPV genotypes including HPV 31, 33, 35, 52 and 56 among colposcopically diagnosed cervical intraepithelial neoplasia. Based on these results, it can be concluded that there are various high risk HPV types involved in the development of cervical precancers depending on geographic distribution. HPV genotype distribution also provides basic knowledge for HPV-based cervical cancer screening, cost-effective prophylactic HPV vaccine and assessment of vaccination against specific HPV infection in each geographic area.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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