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Original Research Article

Human papillomavirus genotype distribution among colposcopy diagnosed cervical precancerous lesions

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ABSTRACT

Background: Cervical cancer (CC) is one of the primary causes of gynaecological cancer death. Cervical cancer is the fourth most frequent cancer worldwide, and it is the second most common cancer in Bangladesh. The stage of cervical cancer at diagnosis has a significant impact on survival. Cervical cancer mortality is high in Bangladesh due to late detection and limited management facilities. The aim of the study was to determine the pattern of human papillomavirus (HPV) genotype among colposcopy diagnosed cervical precancerous lesions.
Methods: This cross-sectional study was conducted in the department of gynecological oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka. Total of 142 women attending the colposcopy clinic of BSMMU.
Results: The mean age was found 38.7±7.3 years with a range from 30 to 60 years. 10 (7.0%) patients were found HPV 16 positive followed by 1 (0.7%) HPV 18, another hr-HPV 3 (2.1%), HPV 16 and other hr-HPV 3 (2.1%) and HPV 16, HPV 18 and other hr-HPV 1 (0.7%). Regarding colposcopy reports 99 (69.7%) patients had CIN I, 33 (23.7%) had CIN II and 10 (7.0%) had CIN III identification by colposcopy reports. 61 (43.0%) patients had CIN I followed by 15 (10.6%) had CIN II, 11 (7.7%) had CIN III, 7 (4.9%) had CIS, and 48 (33.8%) had normal or squamous metaplasia by histopathological reports.
Conclusions: It can be concluded that among all the 14 hr-HPV genotype HPV 16 is more prevalent while HPV18 prevalence was very low in colposcopy diagnosed cervical precancer cases. The study revealed HPV16 was more common among high grade lesions.

Keywords: Cervical cancer, Hr- HPV genotype, Colposcopy, Cervical precancerous lesions

INTRODUCTION

Cancer ranks as a leading cause of death and a substantial barrier to life expectancy in every country of the world.[1] Cervical cancer (CC) is a growing and serious problem worldwide in women but is more acute in developing countries, especially in the Indian subcontinent. The primary causative agent for cervical cancer is the human papillomavirus (HPV), a sexually transmitted virus which is one of the most common viral infections of the reproductive tract.

CC is the fourth most frequent cancer in women, with an estimated 5,70,000 new cases in 2018, representing 6.6% of all female cancer.[1] It has been estimated that 311365 deaths worldwide were due to cervical cancer in 2018, with 90% occurring in low and middle-income countries.[2]

In Bangladesh, CC is the second most common cancer among women. It is estimated that 8068 new cases of CC are detected every year, and 5,214 women die of the disease, and CC constitutes about 12% of female cancer in this country.[1] The survival of CC patients is strongly determined by the stage they have been diagnosed in. Due to the late stage of diagnosis and inadequate management facilities, mortality rates from cancer cervix are high in Bangladesh. Incidence and mortality rates are disproportionately high in transitioning versus transitioned.[3] In developed countries, the incidence of CC has decreased over the last decades due to organized screening programs.

Oncogenic HPVs cause several human cancers, in particular CC. HPV is the causative agent of CC.[4] There are more than 220 HPV types and among them 12 are classified as oncogenic (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) and HPV 68 as probably carcinogenic. HPV 16 has the highest oncogenic potential followed by HPV 18.[5] Among over 200 different HPV genotypes, about 30 types of HPV infect the genital mucosa.[6] It has been categorized as low-risk HPV (6, 11, 42, 43, and 44), intermediate-risk HPV (31, 33, 35, 51, and 52) and high-risk (16, 18, 45, and 56).[7] Most women can clear the infection by natural immunity, but a small number of women cannot clear the infection. Persistent HPV infection causes neoplastic changes in the transformation zone.[8] Furthermore, persistent infection with hr-HPV is critical in the development of high-grade cervical lesions that can progress to invasive CC. Moreover, the progression of HPV infection to invasive cancer is associated with some co-factors like multi-parity, age of first full-term pregnancy, and use of the oral contraceptive pill.[9]

Cervical intraepithelial neoplasia (CIN) is the abnormal growth of cells on the surface of the cervix that could potentially lead to CC. CIN is the precancerous transformation of the cell of the cervix. CIN is graded on a 1-3 scale, with 3 being the most abnormal. HPV infection is necessary to develop CIN, but not all with this infection develop CC. Many women with HPV infection never develop CIN or CC, in these cases, the HPV resolves on its own. However, those with an HPV infection that lasts more than one or two years have a higher risk of developing a higher grade of CIN. However, most CIN will spontaneously regress. Progression to invasive cancer occurs in approximately 1% of CIN 1, 5% of CIN2 and at least 12% of CIN3 cases.[10]

Colposcopy is an important tool for screening and diagnosing cervical precancerous lesions (cervical intraepithelial neoplasia). Visual inspection of the cervix with 3-5% acetic acid (VIA), referral for colposcopic evaluation, and offering curative treatment has been started in our country since the last decade as a national carcinoma cervix screening program. Population-based carcinoma cervix screening was started as a pilot project in Bangladesh in 2004 and as a national program in 2005.[11] Since 2010, for better patient compliance regarding diagnosis and treatment, women with high-grade precancerous lesions arebeing managed by loop electrosurgical excision procedure (LEEP) at the colposcopy clinic of BSMMU and several MCH.[12]

In Bangladesh, limited data are available that describe HPV genotype distribution for cervical precancerous lesions, especially in a reproductive age population that is mainly targeted for screening. This study aims to find out HPV genotype distribution among colposcopy-diagnosed CIN cases in a tertiary hospital.

METHODS

This cross-sectional study was carried out in the department of gynecological oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, during October 2021 to September 2022. A total of 142 patients were participated in the study. Total of 142 women attending the colposcopy clinic of BSMMU, who were colposcopy diagnosed CIN fulfilling the inclusion and exclusion criteria were included in this study. Then after proper counseling, an appointment was given 2 weeks later for cervical specimen collection for HPV genotyping. On the appointed day, the cervical specimen was collected for HPV genotype.

Statistical analysis

Data were collected using the structured questionnaire designed for interview, clinical examination, colposcopy, hr-HPV genotyping and histopathology report of the women. hr-HPV genotyping was performed by polymerase chain reaction. After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, observation. Statistical analyses of the results were obtained by using window-based Microsoft excel and statistical packages for social sciences (SPSS-24).

RESULTS

Table 1 shows age distribution of the study population, it was observed that, 47% were 30-34 years, 42% were 35-39 years, 24% were 40-44 years, 14% were 45-49 years, 8% were 50-54 years and 7% were 55-60 years respectively.

Table 2 shows that 48(33.8%) patients were married between the ages of 15-17 years, 48 (33.8%) were between 16-18 years during their first delivery, and 60 (42.3%) had 3-4 children.

Table 3 shows the HPV genotyping reports of the study population. According to HPV genotype reports the HPV 16, HPV 18, Other HR-HPV and HPV 16 and other HR-HPV were 7.0%, 0.7%, 2.1% and 2.1% respectively.

Table 1: Age distribution of the study population (n=142).

Age (years)	N	%
30-34	47	33.1
35-39	42	29.6
40-44	24	16.9
45-49	14	9.9
50-54	8	5.6
55-60	7	4.9
Mean±SD	38.7±7.3	

Table 2: Reproductive H/O of the study population (n=142).

Variables	N	%
Age at marriage (years)		
<15	43	30.3
15-17	48	33.8
18-20	35	24.6
>20	16	11.3
Age at first delivery (years)		
≤15	27	19.0
16-18	48	33.8
19-21	41	28.9
>21	26	18.3
Parity		
No child	1	0.7
1-2 children	27	19.0
3-4 children	60	42.3
>4 children	54	38.0

Table 3: HPV genotyping reports of the study population (n=142).

HPV genotype reports	N	%
HPV 16	10	7.0
HPV 18	1	0.7
Other HR-HPV	3	2.1
HPV 16-HPV 18 and other HR-HPV	1	0.7
HPV 16 and other HR-HPV	3	2.1
Negative	124	87.3

Figure 1 show the pie chart of HPV genotyping reports of study population where, HPV 18 were 1%, HPV 16 were 7%, other HR-HPV were 2%, HPV 16 and other HR-HPV were 2% and HPV 16-HPV 18 and other HR-HPV were 1%.

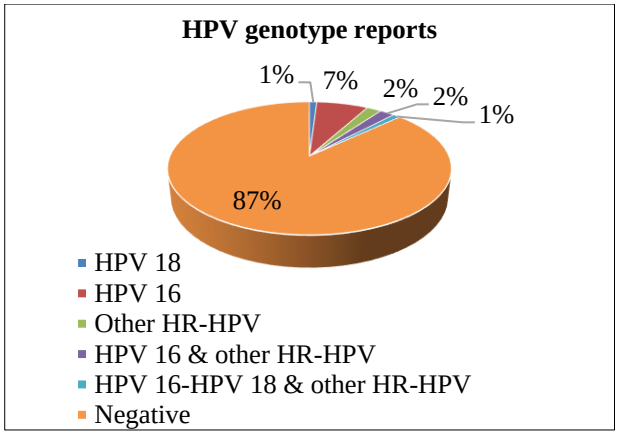

Figure 1: HPV genotyping reports of study population.

Table 4 shows that 99 (69.7%) patients had CIN I, 33 (23.7%) had CIN II and 10 (7.0%) had CIN III identification by colposcopy reports.

Table 4: Colposcopy reports of the study population (n=142).

Colposcopy reports	N	%
CIN I	99	69.7
CIN II	33	23.2
CIN III	10	7.0

Table 5 shows that 61 (43.0%) patients had CIN I followed by 15 (10.6%) had CIN II, 11 (7.7%) had CIN III, 7 (4.9%) had CIS and 48 (33.8%) had normal/squamous metaplasia by histopathological reports.

Table 5: Histopathological reports of the study population (n=142).

Histopathological reports	N	%
CIN I	61	43.0
CIN II	15	10.0
CIN III	11	7.7
CIS	7	4.9
Normal/squamous metaplasia	48	33.8

Table 6 shows that 47 patients belonged to age 30-34 years among them 1 case in HPV 16, 1 in HPV 18, 1 in other HR-HPV and 44 in negative HPV genotype. The difference was not statistically significant (p>0.05) among six groups.

Table 7 shows that 47 patients belonged to age 30-34 years among them 21 cases in CIN I, 4 in CIN II, 2 in CIN III and 20 in normal/squamous metaplasia by histopathological reports. The difference was not statistically significant (p>0.05) among the six groups.

Table 6: Relationship between age and HPV genotype reports (n=142).

HPV genotype reports	Age (years)						P value
	30-34 (n=47)	35-39 (n=42)	40-44 (n=24)	45-49 (n=14)	50-54 (n=8)	55-60 (n=7)	
HPV 16	1	1	3	3	0	2	0.158[ns]
HPV 18	1	0	0	0	0	0	
Other HR-HPV	1	1	0	0	0	1	
HPV 16-HPV 18 and other HR-HPV	0	1	0	0	0	0	
HPV 16 and other HR-HPV	0	2	0	0	1	0	
Negative	44	37	21	11	7	4	

ns=not significant.

Table 7: Relationship between age and histopathological reports (n=142).

Histopathological reports	Age (years)						P value
	30-34 (n=47)	35-39 (n=42)	40-44 (n=24)	45-49 (n=14)	50-54 (n=8)	55-60 (n=7)	
CIN I	21	20	9	4	4	3	0.306[ns]
CIN II	4	4	3	3	1	0	
CIN III	2	3	3	1	1	1	
CIS	0	1	3	1	0	2	
Normal/squamous metaplasia	20	14	6	5	2	1	

ns=not significant.

DISCUSSION

HPV infection is a necessary factor for CC. Information about genital HPV infection in Bangladesh is not available. CC has a prolonged precancerous condition that is caused by HPV infection. If we detect precancerous conditions along with hr-HPV infection and treat the patient accordingly, then we can reduce the incidence of CC.

In this study, among 142 colposcopy diagnosed cervical precancerous lesions 18 (12.7%) cases were hr-HPV positive. A Chinese study showed the prevalence of hr-HPV among cervical precancerous lesions of the Chinese population was 15.2% (194/1274).[13] Another Chinese study reported the overall prevalence of HPV among cervical precancerous lesions was 17.83% (937/5255).[14] Therefore, hr-HPV prevalence in cervical precancerous lesions in this study is similar to in China. A study was carried out in MMCH, Bangladesh, on high-grade CIN and cervical cancer patients; the study observed the prevalence of hr-HPV is 56.3%.[15] This result does not correlate with the present study, probably due to this study including both high-grade CIN and cervical cancer. In a Thai study, the prevalence of hr-HPV with cervical precancerous lesions varies from 40.3% in grade I CIN to 70.3% in CIN II-III.[16]

This hospital-based study showed that the distribution of HPV 16(7.0%) was more prevalent among the study population followed by another hr-HPV (2.1%), HPV 16 and other hr-HPV (2.1%), HPV 18 (0.7%), and all hr-HPV (0.7%). However, in a Chinese study, HPV 52 (21.7%) was the most common hr-HPV genotype among the Chinese population.[13] Another study also identified HPV 52 (4.72%) as the most commonly observed genotype, followed by HPV 58 (3.04%) among the Chinese population.[14] But similarity was found in a Bangladeshi study by Nahar in a population-based study where HPV 16 (1.2%) was the most common hr-HPV.[17]

This study showed that about two-thirds of 99 (69.7%) colposcopy diagnosed cervical precancerous lesions had CIN I, 33 (23.7%) had CIN II, and 10 (7.0%) had CIN III identified by colposcopy. Nessa reported a large number of cervical precancerous had low-grade lesions (CIN I) (36.7%), (10.6%) women had high-grade lesions (9.5% CIN II and 1.1% CIN III), and (7.1%) had carcinoma of the cervix.[18] Nessa, also observed cervical precancerous lesions among VIA-positive women throughout the country, 26773 (29.1%) attended the colposcopy clinic of BSMMU of which 11501 (44.0%) had colposcopy diagnosed precancerous and 1897 (7.0%) had cervical cancer.

Colposcopy is considered a subjective procedure, and the result depends on the clinician's assessment. Many factors can bias diagnosis, such as knowing cytology results, HPV subtypes and transformation zone types.[19] Therefore, the colposcopy-directed cervical biopsy reports in the present study showed that nearly half, 61 (43.0%) of the patients had CIN l followed by 15 (10.6%) had CIN II, 11 (7.7%) had CIN III, 7 (4.9%) had CIS and 48 (33.8%) had normal/squamous metaplasia by histopathological reports. Dray et al in their study, revealed that 77 (40.7%) biopsies had a high grade squamous intraepithelial lesion (CIN 2-3), 27 (14.3%) showed a low grade squamous

intraepithelial lesion (CIN 1) and 85 (45%) showed arrange of non-dysplastic (inflammatory or reactive) changes.[20]

In this study, a majority (33.1%) of the respondents were between 30-34 years of age followed by (29.6%) patients of 35-39 years. The average age was 38.7±7.3 years, with the range of 30 to 60 years. This age group was close to the study of Agorastos, which has shown the average age of the women was 39.9 years (SD 9.01).[6] According to Kang et al the average age was 39.9 years. Globally around 20% of all CCs were diagnosed between the ages of 15-39 years. An almost similar number of women were identified positively in all age groups and there was no significant association between age and hr-HPV genotype. Therefore, the current study showed that any women between 30-60 years of age are susceptible to hr-HPV infection.

HPV genotyping in colposcopy diagnosed cervical precancerous lesions helps to achieve the WHO target to eliminate CC by 2030. HPV genotyping is currently being discussed for better risk stratification and the identification of women at high risk who will require more intensive monitoring along with women who are at risk of developing CC within 3 to 10 years. Implementation of HPV test with genotype along with colposcopy will improve the CC elimination program of WHO in low and middle-income countries.

Limitations

The present study was conducted in a very short period due to time constraints and funding limitations. The small sample size was also a limitation of the present study.

CONCLUSION

It can be concluded that among all the 14 hr-HPV genotype HPV 16 is more prevalent while HPV 18 prevalence was very low in colposcopy diagnosed cervical precancer cases. The study revealed HPV 16 was more common among high grade lesions. HPV genotyping can be performed to appropriately manage colposcopy diagnosed precancerous lesions of the cervix to avoid over or under treatment.

Recommendations

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

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