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Original Research Article

Pattern of high-risk human papilloma virus infection among women with cervical intraepithelial neoplasia

Mina Chowdhury[1]*, Rabeya Sultana Jolly[2], Rogina Amin[3], Ashfi Laila Elora[4], Mousumi Kader[4], Taslima Afrose[1]

[1]Department of Obstetrics and Gynecology, Saheed Suhrawardhy Medical College Hospital, Sher-E-Bangla Nagor, Dhaka, Bangladesh
[2]Department of Gynaecological Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka, Bangladesh
[3]Department of Obstetrics and Gynecology, Upazila Health Complex, Bhanga, Faridpur, Bangladesh
[4]Department of Obstetrics and Gynecology, Mugda Medical College Hospital, Dhaka, Bangladesh

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***Correspondence:**
Dr. Mina Chowdhury,
E-mail: minakarim1973@gmail.com

ABSTRACT

Background: Cervical cancer ranks as the fourth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths in women. The purpose of this study was to assess the pattern of high-risk human papillomavirus (HPV) infection in women diagnosed with cervical intraepithelial neoplasia (CIN). The aim of the study was to evaluate the pattern of high-risk human papillomavirus (HPV) infection among women with cervical intraepithelial neoplasia (CIN).
Methods: This descriptive observational study involved 100 patients diagnosed with cervical intraepithelial neoplasia (CIN) at the gynecological oncology unit, department of gynecology and obstetrics, Dhaka Medical College Hospital, Dhaka, Bangladesh, from January 1, 2020, to December 31, 2020. Inclusion criteria comprised married women aged 30 to 60 years with colposcopically diagnosed CIN. Socio-demographic data, medical history, and clinical findings were collected and analyzed using SPSS 22.0.
Results: The mean age of the patients was 39.26 years (±6.99), with most being housewives (87%) and a large proportion residing in Dhaka (29%). HPV strains were detected in 67% of histopathologically diagnosed CIN cases, with HPV 16 being the most common strain, found in 67.34% of HPV-positive cases. Additionally, mono-infection was more prevalent than co-infection among HPV-positive patients (61.22% versus 38.8%), with the difference being statistically significant ($p<0.05$).
Conclusions: HPV genotypes 16 and 18, being the most prevalent in this study, highlight the need for targeted HPV vaccines and screening programs tailored to the Bangladeshi population to effectively prevent cervical cancer.

Keywords: Cervical cancer, Cervical intraepithelial neoplasia, High-risk HPV, HPV infection, Women's health

INTRODUCTION

Cervical cancer ranks as the fourth most commonly diagnosed cancer and is the fourth leading cause of cancer-related deaths among women, with an estimated 604,000 new cases and 342,000 deaths globally in 2020.[1] The International Agency for Research on Cancer estimates that over 50 million women in Bangladesh are at risk, resulting in approximately 17,686 new cases and 10,362 deaths each year. Alarmingly, about 25% of women of reproductive age (15-49 years) die from cervical cancer in low-resource countries. In Bangladesh, a low-resource nation in southeast Asia, where women comprise nearly 50% of the population, the age-standardized incidence and

mortality rates of cervical cancer in 2018 were approximately 10.6 and 7.1 per 100,000 women, respectively. That same year, the country reported 8,068 new cases of cervical cancer and 5,214 deaths, making cervical cancer the second most common cancer among women and ranking second among women aged 15 to 44.[2] Despite this alarming situation, data on the HPV burden within the general population of Bangladesh remains scarce. In southern Asia, the region encompassing Bangladesh, it is estimated that about 4.4% of women harbor cervical HPV16/18 infections at any given time, with HPVs 16 or 18 accounting for 80.3% of invasive cervical cancers.[3]

Cervical intraepithelial neoplasia (CIN) is a premalignant lesion classified histologically as CIN1, CIN2, or CIN3. If untreated, high-grade lesions such as CIN2 or CIN3 can progress to cervical cancer. Thirteen distinct high-risk HPV genotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) have been identified as "carcinogenic", significantly increasing the risk of cervical cancer. These carcinogenic HPV types are detected in over 90% of cervical cancer specimens and more than 60% of CIN tissues.[4] Furthermore, more than 70% of sexually active individuals, including both women and men, will experience an HPV infection during their lives, with some individuals potentially facing multiple infections. The highest rates of HPV acquisition typically occur shortly after individuals become sexually active, although most infections clear spontaneously within a few months, with around 90% resolving within two years.[5]

Epidemiological studies indicate that the type-specific prevalence of HPV in cervical cancer varies by geographical region. For instance, HPV 16 is the predominant subtype, with prevalence rates ranging from 45.9% in Asia to 62.6% in North America and Australia. HPV 18, the second most prevalent subtype, is found in approximately 10-14% of cases. Globally, HPV types 45, 31, and 33 follow in frequency, with HPV 58 and 52 being more common in Asia.[6] Co-infection among different HPV types is common among women; however, the clinical significance of such co-infections remains controversial, and the epidemiology of HPV genotype combinations is unknown.[7] A study from India reported multiple genotypes in 23.41% of HPV-positive cases, noting that infections with multiple genotypes, excluding HPV 16 and 18, were associated with a higher risk of cervical cancer, with odds ratios of 5.3 and 2.5, respectively.[8]

Understanding HPV genotype distribution is crucial for developing HPV-based cervical cancer screening strategies, cost-effective HPV vaccination programs, and evaluating the efficacy of recently available vaccines. This study aims to evaluate the pattern of high-risk human papillomavirus (HPV) infection among women with cervical intraepithelial neoplasia (CIN), contributing valuable insights into the epidemiology of HPV in Bangladesh and informing future screening and vaccination strategies.

Objectives

The aim of the study was to evaluate the pattern of high-risk human papillomavirus (HPV) infection among women with cervical intraepithelial neoplasia (CIN).

METHODS

This descriptive observational study was conducted at the gynecological oncology unit, department of gynecology and obstetrics, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh, from January 1, 2020, to December 31, 2020. It included 100 patients diagnosed with cervical intraepithelial neoplasia (CIN) through colposcopy during this period. The sample size was calculated using a standard estimation formula, based on a reported prevalence of high-risk HPV in low-grade cervical lesions (23.1%), leading to an estimated total study population of 120 patients, with 100 ultimately included in the analysis.

Inclusion criteria

Married women aged 30 to 60 years with colposcopically diagnosed CIN.

Exclusion criteria

Women unable to understand written or oral information. Women mentally unable to provide informed consent. Women with chronic illnesses, including malignancies, heart disease, stroke, diabetes, or arthritis. Pregnant women or those with previous treatments for CIN. Women menstruating at the time of the study.

Informed consent was obtained from all participants, ensuring confidentiality and voluntary participation. A thorough history was taken, and each patient received counselling regarding the study. Colposcopy was performed, and guided punch biopsies were taken from the CIN lesions, with one biopsy sample sent for histopathological analysis and the second preserved for HPV DNA detection. Thirteen internationally recognized high-risk HPV genotypes were assessed using polymerase chain reaction (PCR) techniques.

Data collection involved a pre-designed questionnaire to gather socio-demographic details, medical history, examination findings, and investigation results. The data were analyzed using SPSS version 22.0, with quantitative data presented as mean and standard deviation (±SD) and qualitative data shown as frequency and percentage. Comparisons between HPV infection patterns and clinical findings were made using chi-square tests, and a p value <0.05 was considered statistically significant. The study was approved by the institutional review board (IRB) of DMCH, adhering to ethical guidelines and maintaining patient confidentiality throughout. The primary outcome

variables included the pattern of high-risk HPV genotypes and their association with socio-demographic, marital and childbirth-related, personal, and clinical factors.

RESULTS

The distribution of patients by demographic features is shown in Table 1. Nearly half of the patients were in the 36-45 years age group (42%). The mean age of the patients was 39.26 years (±6.99). Most of the patients were housewives (87%), while 12% were employed. More than one-third of the patients (37%) had no formal education. Around one-fifth (21%) had attained primary level education, and exactly one-fourth (25%) had completed secondary level education. The remaining 17% had completed either SSC or HSC level education. The majority of the patients (84%) were Muslims.

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

Variables		Frequency	Percentage
Age group (range 30-60) (years)	30-35	39	39
	36-45	42	42
	46-60	19	19
Occupation	Housewife	87	87
	Service	12	12
	Tailor	1	1
Level of education	Illiterate	37	37
	Primary	21	21
	Secondary	25	25
	SSC	3	3
	HSC and above	14	14
Religion	Muslims	84	84
	Hindus	16	16

Table 2: Distribution of patients by district of residence (n=100).

Districts of residence	Frequency	Percentage
Dhaka	29	29
Narayangonj	10	10
Shariatpur	6	6
Narsingdi	5	5
Chandpur	4	4
Faridpur	4	4
Comilla	3	3
Gazipur	3	3
Madaripur	3	3
Tangail	3	3
Chuadanga	2	2
Gopalgonj	2	2
Laxmipur	2	2
Munshigonj	2	2
Mymensingh	2	2
Netrokona	2	2
Noakhali	2	2
Other districts	16	16

The distribution of patients by district of residence is presented in Table 2. The largest proportion of patients (29%) were from Dhaka district, while 10 patients (10%) were from neighboring Narayanganj district. Six patients (6%) were from Shariatpur, and five (5%) were from Narsingdi districts.

The Figure 1 shows that, among the 73 histopathologically diagnosed CIN cases, HPV strains were detected in 49 cases (67%). No HPV infection was found in 24 cases (33%).

Table 3: Distribution of patients by high-risk HPV strain (n=49).

HPV strain	Histopathology			Total
	CIN-I	CIN-II	CIN-III	
Present:16	14	5	2	21
Present:16, 18	2	0	1	3
Present:16, 31	1	0	0	1
Present:16, 35	0	1	1	2
Present:16, 58	2	0	0	2
Present:18	4	1	0	5
Present:18, 16	0	1	1	2
Present:18, 33	2	0	0	2
Present:18, 35	0	3	0	3
Present:31	1	1	0	2
Present: 33	1	0	1	2
Present: 33, 35	0	0	1	1
Present: 52, 16	0	1	0	1
Present: 52, 16, 56	1	0	0	1
Present: 56, 18	0	1	0	1
Total	28	14	7	49

Table 4: Association of high-risk HPV infection with different grades of CIN (n=73).

Histopathology	HPV infection		χ^2 test	P value
	Present	Absent		
	n (%)	n (%)		
CIN-I (n=46)	27 (58.7)	19 (41.3)	5.345	0.069
CIN-II (n=18)	16 (88.9)	2 (11.11)		
CIN-III (n=9)	6 (66.67)	3 (33.3)		

Table 5: Distribution of study subjects according to mono- and co-infection (n=49).

Pattern of infection	Present	Absent	χ^2 test	P value
	N (%)	N (%)		
Mono infection	30 (61.22)	19 (38.8)	4.9388	0.026
Co-infection	19 (38.8)	30 (61.22)		
Total	49 (100.0)	49 (100.0)		

Among the 49 HPV-positive cases, HPV strain 16 was the most common, occurring in 33 cases (67.34%), while HPV 18 was the second most common, occurring in 32.65% of cases. Other HPV strains, including HPV 31, 33, 35, 52, 56, and 58, were also present (Table 3).

According to histopathology reports, 58.7% of patients with HPV infection had CIN I lesions. Notably, 88.9% of patients with HPV infection had CIN II lesions, and 66.6% had CIN III lesions. This suggests an association between the grade of CIN and HPV infection, although it was not statistically significant ($p>0.05$).

Among the 49 HPV-positive patients, mono-infection was found in 30 cases (61.22%), while co-infection was present in 19 cases (38.8%). This indicates a higher prevalence of mono-infection. The difference was statistically significant ($p<0.05$).

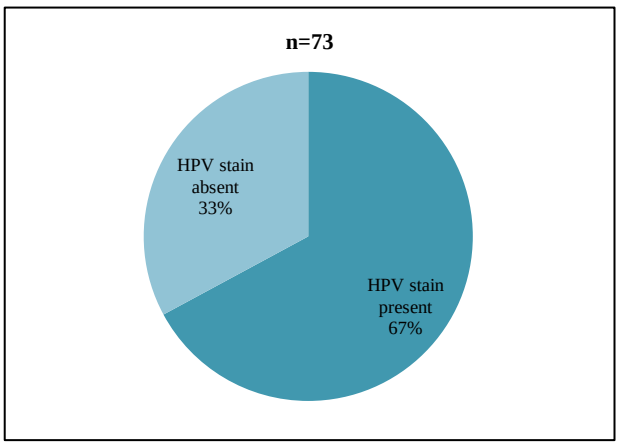

Figure 1: Detection of HPV strains among histopathologically diagnosed CIN cases (n=73).

DISCUSSION

Human papillomavirus (HPV) is one of the most prevalent causes of sexually transmitted diseases in both men and women worldwide. It is associated with a range of clinical conditions, from harmless lesions to various forms of cancer. The connection between genital HPV infections and cervical cancer was first established in the early 1980s by German virologist Harold zur Hausen. Since then, the relationship between HPV and cervical squamous cell carcinoma has been well documented. In fact, the association between HPV and cervical carcinoma is stronger than that between smoking and lung cancer.

In our study, a descriptive observational analysis was conducted to observe the pattern of high-risk HPV as a cause for CIN. The mean age of the patients was 39.26 years (SD±6.99), with an age range from 30 to 58 years. In comparison, a previous study done at BSMMU in collaboration with the department of pathology, Women and Infants Hospital/Alpert Medical School of Brown University, Providence, RI, USA, and Physicians Reference Laboratory, Overland Park, KS, USA, reported an age range of 25 to 70 years, with a mean of 48.38 years and a median of 50 years (SD±10.175).[9]

In our study, 87% of the patients were housewives and had typical educational backgrounds, similar to other Bangladeshi women. Most of the patients were from Dhaka (29%) and neighboring Narayanganj districts (10%). HPV DNA detection was performed, and HPV strains were identified in 49% of cases. The detected genotypes were HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV 52, HPV 56, and HPV 58. Another observational study conducted at the Mahavir Institute of Medical Sciences, Vikarabad, Telangana, India, found overall oncogenic activities of HPV 16, 18, 31, 35, 51, 52b, and 45 in 37.6% of respondents.[10] Our findings are consistent with that study.

A study in Beijing, China, investigated the prevalence of high-risk HPV (HR-HPV) genotypes among Han women with high-grade cervical lesions, detecting HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 in 90.1% of women (2537/2817).[11] Another study from Seoul, Korea, found HR-HPV types 16, 52, 58, 53, 51, 56, 68, 18, 39, and 31 in 97.4% of cases.[12] In Pune, India, a study detected HPV 16, 56, 18, 39, 35, 51, 31, 59, 33, 58, 68, 45, and 52 in 52.5% of cases (146/278).[13] All studies show a general similarity in HR-HPV infectivity, though some regional variations in type specificity exist.

In our study, HPV strain 16 was the most commonly occurring infection, followed by HPV 18. In contrast, a retrospective study from Shanxi Medical University, Taiwan, China, found that the most commonly detected genotypes were HPV 16 (59.3%), HPV 58 (14.4%), HPV 33 (10%), and HPV 18 (6%).[10] A retrospective collaborative pilot study at the Department of Pathology, Women and Infants Hospital/Alpert Medical School of Brown University, Providence, RI, USA, in conjunction with BSM Medical University (BSMMU), Dhaka, Bangladesh, and Physicians Reference Laboratory, Overland Park, KS, USA, reported that 38 of 39 cases (97.4%) were HPV 16, either alone or in combination with HPV 18 (25.6%). Rare subtypes HPV 52 and HPV 45 were identified in only 2.5% of cases, with the rest being HPV 45 alone.[9] A study conducted in the department of gynecology and obstetrics at Bangabandhu Sheikh Mujib Medical University and another in Goiania, Brazil, showed a strong correlation between CIN II or CIN III and positivity for HPV DNA when compared to women with only CIN I or a normal cervix.[14,15] However, our study does not correlate with those findings.

In our study, 27 patients infected with HPV had CIN I, 16 patients had CIN II, and 6 patients had CIN III. This suggests an association between CIN and HPV, though the grading of CIN did not show higher positivity. In this study, the comparison between HPV type and histopathological findings revealed no statistical difference ($p>0.069$). A retrospective study conducted at the National Cancer Center in North China reported that the prevalence of HPV infection for histopathologically diagnosed CIN II and CIN III was 90.8%, significantly higher than for CIN I (78.4%).[16] Another retrospective study at the Department of Gynecology at Wenzhou People's Hospital, China, found that the prevalence of persistent HPV infection increased with the severity of cervical lesions.[17] According to the histopathology reports in our study, 27 (58.8%) patients with HPV infection (regardless of type) had CIN I lesions, 16 (88.8%) had CIN II lesions, and 6 (66.6%) had CIN III lesions. Therefore, it can be concluded that there is a relationship between HPV infectivity and CIN, though our study did not show that HPV infectivity increased with the severity of cervical lesions, and these differences were statistically insignificant.

In our recent study, among the 49 HPV-positive cases, monoinfection was found in 30 (61.22%) cases, and coinfection was found in 19 (38.77%) cases, which was statistically significant ($p<0.05$). A study from Shanxi Medical University reported that 91.9% (1274/1389) of patients with CIN were HPV-positive, with 71% having single infections and 29% having coinfections. This finding correlates with our observations.[18]

All studies show that the prevalence of HPV types is relatively consistent within similar geographical regions, though the pattern of HPV strain coinfection seems to be evolving. Further studies are necessary to establish this hypothesis. Some studies have shown that coinfection increases cervical cancer risk and that the presence of multiple HPV types is associated with a lower response and survival rate in patients receiving radiotherapy for cervical cancer. However, other authors found no evidence of synergy for high-grade squamous intraepithelial lesions and even observed viral antagonism during coinfection,

suggesting competitive integration of HPV 16 and 18 into the host genome when coinfected.

The current study had the following limitations: the cross-sectional design limits the study's ability to establish a clear cause-and-effect relationship between HPV infection types and CIN. The sample size was relatively small. The study was conducted at a single center, which reduces its generalizability to a broader population.

CONCLUSION

HPV genotypes 16, 18, 31, 33, 35, 52, 56, and 58 were detected in the current study, with HPV 16 being the most common strain, followed by HPV 18. This suggests that genotypes HPV 16 and 18 are of significant public health concern due to their high prevalence and potential to contribute to cervical carcinogenesis in the Bangladeshi population. The study highlights regional differences in the occurrence of HPV types and indicates that HPV prophylactic vaccines may need to target different HPV types based on the specific needs of various countries or regions.

Data on HPV type-specific prevalence and co-infections could provide valuable baseline information for predicting which genotype-specific HPV vaccines would be most effective and how HPV-based screening could influence cervical cancer prevention in Bangladesh.

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