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Prevalence and Molecular Characterization of High-Risk Human Papillomavirus among Patients with Cervical Intraepithelial Neoplasia and Carcinoma

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Abstract

Background: Cervical carcinoma is closely linked to high-risk human papilloma virus (HPV) infection, underscoring its significance in research and public health efforts. Identifying HPV types and their distribution informs targeted prevention, including vaccination programs.

Aim of the study: This study aimed to investigate the prevalence and molecular characterization of high-risk HPV among patients with cervical intraepithelial neoplasia and carcinoma.

Methods: This cross-sectional descriptive study was conducted in the Rajshahi Medical College, along with Rajshahi Medical College Hospital in Bangladesh. A total of 310 VIA test-positive cases of cervical intraepithelial neoplasia and carcinoma through histopathological assessment were purposively enrolled as study subjects. MS Office tools were used for data analysis.

Results: Among participants, 77% exhibited high-risk human papillomavirus (HPV). In HPV-positive carcinoma cases (n=52), HPV-16 was the predominant single variant (32.7%), while HPV-16 & 18 coexisted in 17.3% of cases. For HPV-positive CIN-I cases (n=109), HPV-18 (39.4%) emerged as the primary single variant, and non-HPV-16/18 (6.4%) as multiple variants. HPV-16 (35.3%) prevailed in HPV-positive CIN-II cases (n=17), with HPV-16 & 18 in 17.6%. In HPV-positive CIN-III cases (n=62), HPV-16 (37.1%) and HPV-16 & 18 (12.9%) were most prevalent as single and multiple variants, respectively.

Conclusion: Among the three-fourths of VIA test-positive cases with cervical intraepithelial neoplasia and carcinoma, high-risk HPV is prevalent. In the Rajshahi region of Bangladesh, the most prevalent viral causes of single or multiple HPV infections are HPV-16 and HPV-18.

Keywords: Prevalence, High-risk human papillomavirus, HPV, Cervical carcinoma, CIN-III, Cancer

Introduction

Cervical cancer stands as the second most prevalent malignancy, contributing to the highest number of cancer-related deaths in women globally [1]. Developing countries bear a substantial burden, accounting for an estimated 86% of the total global incidence of the disease [2,3]. An additional study [4] reported that on a global scale, cervical cancer ranks as the third most frequent cancer and the fourth leading cause of cancer-related

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mortality in women. This results in approximately 530,000 new cases and nearly 275,000 deaths annually. The World Health Organization (WHO) highlighted invasive cervical cancer as the second most common cancer among women in Sri Lanka and estimated 1,395 new cases and nearly 814 deaths each year [5].

Persistent infection with high-risk human papillomavirus (HPV) is widely recognized as a significant factor in the development of cervical cancer [6-8]. The presence of HPV is pervasive in cervical cancer specimens, representing the leading causative agent for this major human cancer globally [7]. The prevalence of HPV in women with cervical cancer is reported to be as high as 99.7% worldwide [7] and approximately 90% in Asia [8]. Notably, HPV-16 and HPV-18 are the most commonly identified HPV types, responsible for about 70% of cervical cancer cases globally [9]. Utilizing cytological screening such as the Pap smear test and the early detection of HPV are crucial elements in the secondary prevention of cervical cancer, contributing to a reduction in HPV-associated mortality [6]. In lower and middle-income countries, including Sri Lanka, the absence of effective screening programs poses challenges in detecting cervical abnormalities, contributing to elevated mortality rates from cervical cancer in these regions [10]. However, recent advancements in molecular biological techniques, such as HPV-DNA testing, offer effective screening methods for HPV and have the potential to enhance the early detection of cervical cancer in developing areas [11].

Several types of HPV therapeutic vaccines are under evaluation in both preclinical and clinical trials, encompassing live vector, protein or peptide, nucleic acid, and cell-based vaccines [12]. Currently, three HPV vaccines are included in vaccination programs in various countries: Cervarix (bivalent vaccine targeting HPV 16, 18), Gardasil (quadrivalent vaccine covering HPV 6, 11, 16, 18), and the nine-valent vaccine (addressing HPV 6, 11, 16, 18, 31, 33, 45, 52, 58). These vaccines are designed to target between 2 and 7 oncogenic HPV serotypes [13]. Over the long term (30-50 years), they hold the potential to reduce the incidence of diseases associated with the targeted HPV vaccine types [14].

A recent systematic review and meta-analysis affirmed the safety, tolerability, and efficacy of these vaccines against the vaccine-HPV types responsible for persistent infection and cervical disease in young women [15]. In Bangladesh, study on CIN and cervical carcinoma are very limited. Most of the study restricted mainly in Dhaka. Prevalence of CIN and cervical carcinoma in Rajshahi region was assessed in our previous study [16]. Molecular characterization is essential for further advancement in implementation of vaccination programme. So, the objective of this study was to investigate the prevalence and molecular characterization of high-risk HPV among patients with cervical intraepithelial neoplasia and carcinoma in a tertiary care hospital at Rajshahi, Bangladesh.

Methodology

This cross-sectional descriptive study was carried out at the Department of Pathology, Rajshahi Medical College, and the Department of Gynecology & Obstetrics, Rajshahi Medical College Hospital, Rajshahi, Bangladesh, spanning from July 2019 to June 2022. A total of 310 cases, identified as positive through the visual inspection with acetic acid (VIA) test, followed by histopathological examination were purposively enrolled as study subjects which were reported in our previous study [16]. The focus of the study was on CIN and carcinoma identified through histopathological assessment.

Cervical swab sample collection:

Cervical swab samples were collected by using commercially available digene HC2 DNA collection device and Kept at -20°C until HPV DNA detection were performed according to manufacturer`s instructions.

DNA extraction:

Extraction of DNA from cervical swab was performed by using QIA amp®DNA mini kit (QIAGEN Germany) according to the manufacturer's instructions. For further analysis the DNA samples were stored in AE buffer at -20°C.

Detection of HPV DNA Typing:

Geno typing of HPV DNA was done in real time PCR test by using QlAscreen HPV PCR test kit (QIAGEN, Germany) which targets a conserved region within the E7 gene. This test kit separately detects HPV-16, HPV-18 and the 13 other high-risk types as a pool. Subsequently, the DNA samples underwent analysis using MS Office tools.

Results

In this study, out of the total 310 participants in Figure-1, 17% had histopathologically diagnosed cases of cervical carcinoma. Additionally, patients with CIN-I, CIN-II, and CIN-III constituted 53%, 7%, and 23% of the total cases, respectively. Figure-2 showed among the total participants, HPV DNA was positive in 77% (n=240) of cases. In Figure-3 among cervical carcinoma patients, HPV DNA was detected in 98.1% (n=52) of cases. Conversely, among patients with CIN-I, CIN-II, and CIN-III, HPV DNA was present in 66.5% (n=109), 77.3% (n=17), and 87.3% (n=62) of cases, respectively. Figure-4(A) showed in HPV-positive carcinoma cases (n=52), HPV-16 was present in the highest proportion (32.7%) as both a single variant and in combination with HPV-18, found in 17.3% of cases. In Figure-4(B) we saw the highest proportion of HPV-positive CIN-I cases (n=109),

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other than HPV-16/18 was found as a single variant (39.4%), and as multiple variants, HPV-18 and other than HPV-16/18 (6.4%) were observed. In the highest proportion of HPV-positive CIN-II cases (n=17), HPV-16 was observed as a single variant (35.3%), and as multiple variants, HPV-16 & 18 (17.6%) were found in Figure-4(C) Similarly, in the highest proportion of HPV-positive CIN-III cases (n=62), HPV-16 was observed as a single variant (37.1%), and as multiple variants, HPV-16 & 18 (12.9%) were found in Figure-4(D).

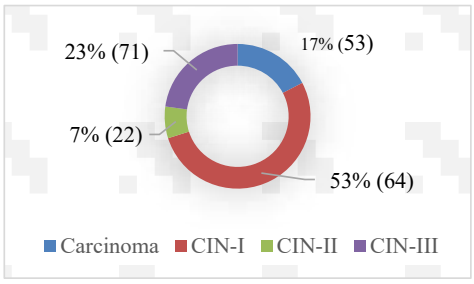

Figure 1: Distribution of histopathologically diagnosed cases of cervical intraepithelial neoplasia and carcinoma (N=310)

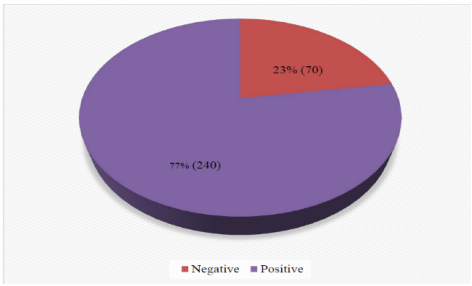

Figure 2: Frequency of HPV DNA

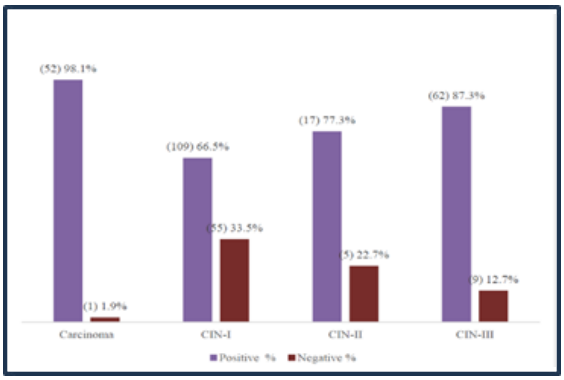

Figure 3: Distribution of HPV DNA (N=310)

Discussion

In this study, among a total of 310 participants, 17% were diagnosed with cervical carcinoma. The prevalence of HPV DNA was found to be positive in 77% (n=240) of total cases. A similar study [17] reported an HPV prevalence of 84.7%

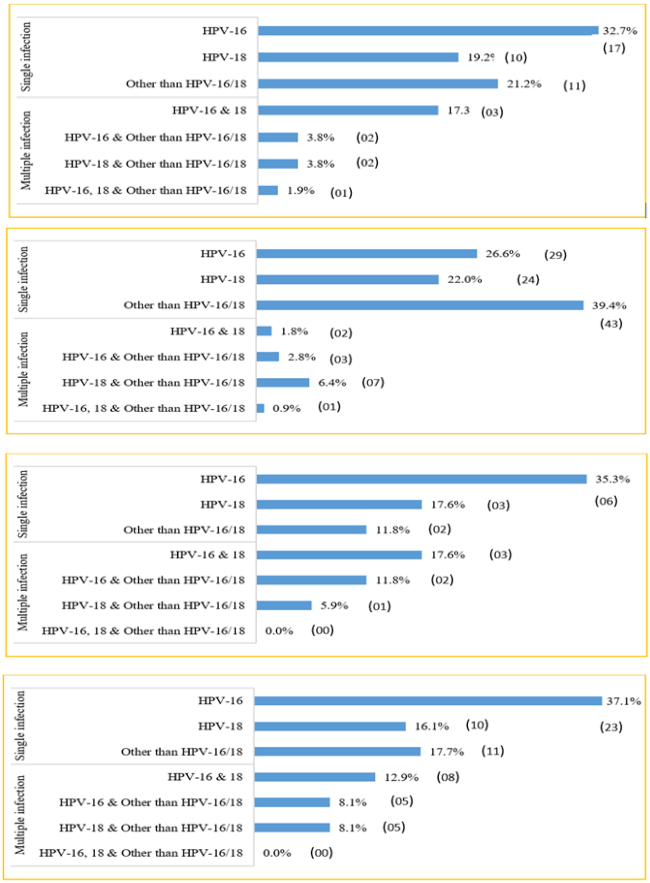

Figure 4: Characterization of high-risk HPV among HPV positive carcinoma n=52 (A), CIN-I n=109 (B), CIN-II n=17 (C) and CIN-III n=62 (D)

(83/98). Another study [18] found a prevalence of 93%, this rate was higher than our findings. It is speculated that the previous study [18] utilized archival cervical tissue samples and was retrospective, which may explain the variation in results compared to our study. Specifically, among cervical carcinoma patients (n=53) in our study, HPV DNA was detected in 98.1% of cases. Among patients with CIN-I, CIN-II, and CIN-III, HPV DNA was present in 66.5%, 77.3%, and 87.3% of cases, respectively. In HPV-positive carcinoma cases, HPV-16 was present in 32.1% as a single variant, and a combination with HPV-18 was found in 17% of cases. In HPV-positive CIN-I cases, variants other than HPV-16/18 were found in 39.4% as a single variant, and as multiple variants, HPV-18 and other than HPV-16/18 (6.4%) were observed. For HPV-positive CIN-II cases, HPV-16 was detected in 35.3% as a single variant, and as multiple variants, HPV-16 and 18 (17.6%) were found. Similarly, in HPV-positive CIN-III cases, HPV-16 was observed in 37.1% as a single variant, and as multiple variants, HPV-16 & 18 (12.9%) were detected. A study [19] conducted in China reported that HPV-16 and HPV-33 have a stronger positive correlation with cervical lesion development than other

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variants, which was nearly similar to our findings. However, for limitation of our DNA detection kit design, we did not specify an association with HPV-33. Some other studies [20,21] have also reported that HPV16, 58, 52, and 33 are the most common types among women with persistent HR-HPV infections in China. Similarly, in a Bangladeshi study [22], HPV 16 was the most commonly identified in 28 (53.84%) cases, and HPV 18 was the second most common with 20 (38.46%) cases, either singly or in combination with other high-risk subtypes. A prospective study in India reported that HR HPV 16, 18, 31, 33, 35, 45, 58, and 86 were observed among CIN cases and cervical cancer cases [23]. A meta-analysis from the World Cancer Research Center indicated that HPV 16, 31, 51, and 53 were the most prevalent HPV genotypes [24,25]. Differences between our findings and the findings of these studies may be due to variations in diagnostic procedures and geographic locations. The high prevalence of HPV-16 and HPV-18 among our participants was also supported by additional studies [26,27] conducted in Bangladesh.

Conclusion

In the Rajshahi region of Bangladesh, a significant prevalence of high-risk human papillomavirus (HPV) is identified in CIN and carcinoma cases. Specifically, HPV-16 and HPV-18 emerge as the most prevalent viral causes of single or multiple HPV infections in the region. These findings underscore the critical role of HPV in cervical cancer development and highlight the importance of targeted interventions, including HPV vaccination and enhanced screening strategies, to mitigate the burden of cervical carcinoma in this particular geographical context. Comprehensive efforts focusing on the prevention and early detection of HPV infections are crucial for improving women's health outcomes in the Rajshahi region of Bangladesh.

Ethical approval and concent

Institutional review board (IRB) clearance was granted & the Ethical clearance Committee of Institute of Biological science (IBSC) Rajshahi University also approved all protocols. Written consent was obtained from all participants before sample collection.

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Conflict of interest: The authors declare that they have no conflicts of interest.

Limitation: For DNA detection we used commercial kits those gave specific curve for type 16 and type 18 but for other high-risk types, it gave single curve as a pool. So we could not identify other high risk types of HPV separately.

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