

# HPV and HIV Infection in Women with Precancerous and Cancerous Lesions of Uterine Cervix

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## ABSTRACT

**Background:** Globally, 500,000 new cases of cancer of the uterine cervix are recorded annually, nearly 20% are from India. Numerous clinical and experimental studies have established an association between HPV and cervical cancer. Most immune responses are important in resolution of HPV infection; hence, women with HIV are more likely to have severe, frequent HPV disease. Considering the increasing incidence of HIV in India, an increase in cervical abnormalities and cervical cancer can be expected in the near future. This study was thus carried out to study the prevalence and association of HPV and HIV co-infection in women with precancerous and cancerous lesions of cervix.

**Design:** Cross-sectional study.

**Aims:** To study the prevalence and correlation of HPV and HIV infection in women with cervical intraepithelial neoplasia and cervical cancer.

**Materials and methods:** Sexually active women attending the Gynecology OPD and IPD with sign and symptoms suggestive of cervical pathology were subjected to cytology, colposcopy, and biopsy. Cervical samples for HPV detection and blood samples for HIV detection were taken.

**Statistical analysis:** Chi-square test for statistical significance.

**Results:** 254 women were enrolled based on signs and symptoms. 143 women returned for follow-up. 129 were subjected to cervical biopsy and HPV testing of cervical tissue. HPV positivity in low-grade squamous intra-epithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL) and cervical cancer was 60%, 100% and 93.1% respectively. None of the women tested were reactive for HIV.

**Conclusion:** For early detection and identification of high-risk population with precancerous lesions, there is a need for incorporation of HPV testing along with cytology to screen women. In view of the spreading HIV infection in India, we need to increase surveillance for HIV positive cases and increase awareness regarding prevention of HIV infection.

**Keywords:** Human papilloma virus, Human immunodeficiency virus, precancerous and cancerous cervical lesions.

## INTRODUCTION

Cervical cancer kills approximately 230,000 women annually, with the vast majority of deaths occurring in developing countries. Worldwide, cervical cancer is the fifth most common cancer related cause of death among women. In the developing world, it is the leading

cause of cancer deaths in women.<sup>1</sup> Globally, 500,000 new cases of cancer of the uterine cervix are recorded annually, nearly 26% of these are from China and 20% are from India.<sup>2</sup> Numerous clinical and experimental studies have established an association between high-risk Human Papilloma Virus (HPV) types and cervical

cancer.<sup>3-6</sup> However, infection with HPV alone may not be sufficient for development of cervical intraepithelial neoplasia (CIN) and the ability of the immune response to resist changes plays an important role in the development of cervical cancer. Prevalence of HPV infection among HIV-1 seropositive women is high due to similar epidemiological risk factors such as early age of sexual intercourse, multiple partners and presence of other sexually transmitted diseases. Large observational studies involving HIV positive women have shown a strong and consistent relation between co-infection with HIV and HPV and cervical intraepithelial neoplasia.<sup>7-9</sup> Various studies have reported prevalence ranging from 14.4% to 93% of oncogenic HPV types in HIV infected patients.<sup>10-12</sup> HIV positive women are more likely than HIV negative women to be infected with HPV types of high oncogenic risk including type 16 and 18 and to be infected with multiple HPV types.<sup>13</sup> Most immune responses are important in resolution of HPV infection; hence, women with HIV are more likely to have severe, frequent HPV disease.<sup>14</sup> According to studies, both CD-4 immunosuppression and presence of multiple HPV types were associated with persistence of HPV in HIV positive women.<sup>15</sup> An estimated 2.5 million people in the 15–49 year age range were living with HIV in 2006, as estimated by National AIDS Control Organization (NACO). Considering the rising HIV trend, an increase in cervical abnormalities and cervical cancer can be expected in the near future. This study was thus carried out to study the prevalence and association of HPV and HIV in women with precancerous and cancerous lesions of cervix.

## MATERIALS AND METHODS

### Study Design

This study was a cross-sectional study conducted in the Department of Obstetrics and Gynecology, Jawaharlal Nehru Medical College and Hospital (JNMCH), Aligarh and Institute of Cytology and Preventive Oncology (ICMR), Noida over a period of 2 years. All women included were sequentially tested for identifying patients with CIN and carcinoma cervix in the following order—specimen collection for cytology and HPV testing, colposcopic evaluation, directed biopsies in women with colposcopic abnormalities and sampling for HIV antibody detection.

### Study Population

This study included sexually active women attending the gynecology OPD and IPD of JNMCH. The patients with any of the following complaints were included in the study—history of pain lower abdomen, abnormal vaginal discharge, post-coital or post-menopausal bleeding or any patient attending OPD for other complaints but found to be having a clinically suspicious cervix. Antenatal and hysterectomized women were excluded from the study. Informed consent was obtained from all participants and they were then subjected to a detailed history and examination.

The patients recruited in the study were subjected to following investigations:

#### 1. Cytology

Cytology sampling was done by Pap smear technique. The slides were stained using the Papanicolaou stain. After staining, the slides were screened by a pathologist who used the Bethesda system for grading the slides.

#### 2. Colposcopy

Colposcopy was performed using a video colposcope. The images were stored in the video colposcope and used for retrieval later. Colposcopic classification used was according to the International Federation for Cervical Pathology and Colposcopy, 2002.

#### 3. Cervical Biopsy

Histological confirmation was taken as the reference standard. Biopsy samples were obtained by use of either of the following techniques:

- Punch biopsy
- Loop electrosurgical excision procedure (LEEP)

#### 4. HPV Detection

All the women in the study group were subjected to HPV detection irrespective of their cytology and histopathology report using PCR technique.

Sample collection, transport and storage was done by the following methods:

- i. *Dry paper smear method*: Scraped cervical cells were obtained using an Ayre's spatula. These were smeared onto a 3 mm Whatman paper cut to size of 5 cm × 5 cm. The paper slides were air dried and put into

individual autoseal polythene bags and stored at room temperature.

- ii. *Wet method:* Tumor biopsies obtained were put in a 15 mL collection vial containing 5 mL PBS. These were stored at  $-70^{\circ}\text{C}$ .

These samples were transported to ICPO, Noida for detection of total HPV as well as typing for high-risk HPV types 16 and 18 using consensus and type-specific primers.

### 5. HIV Detection

HIV detection was done by taking blood samples after proper counseling for detection of antiHIV antibodies using ELISA. Confirmation of positive cases was done using PCR.

### Statistical Analysis

Statistical analysis was carried out using Chi-square test to detect statistical significance. Sensitivity, specificity and predictive values were calculated using  $2 \times 2$  tables and standard formula.

## RESULT

A total of 254 patients were screened for precancerous and cancerous lesions based on signs and symptoms. 143 women turned for follow-up and were included in the study (**Table 1**). Of these women, 129 consented for biopsy. Histopathological analysis (**Table 2**) showed 3 were normal, 52 (40.3%) had chronic cervicitis, 13 (10.07%) had precancerous lesion and 58 (44.9%) had malignancy. Out of the 58 cases positive for malignancy all were of squamous cell carcinoma and only 1 case was of adenocarcinoma. The mean age of women with carcinoma cervix was 48.3 years. Precancerous lesions occurred at a mean age of 31.9 years.

Of 129 patients included in study 88 women consented to and were subjected to HIV antibody testing by ELISA. 40 of these cases were of cervical cancer, 21 had precancerous lesions and 27 had chronic cervicitis. None of them was found to be reactive for HIV.

All 129 women were subjected to HPV testing of the cervical tissue by PCR technique. 77 (59.68%) patients tested positive for HPV, 49 (37.98%) women tested negative and in 3 women HPV reporting could not be done due to improper sampling. Out of the cases found

**Table 1**

Pap smear analysis

N = 143

	Normal	Inflammatory	AS-CUS/AGUS	LSIL	HSIL	CA
No. of Cases	8	47	2	19	13	50

Inadequate smear—4

**Table 2**

Histopathological analysis

N = 129

	Normal	Chronic Cervicitis	LSIL	HSIL	Malignant
No. of Cases	3	52	10	3	58

Inadequate biopsy—4

positive, 75 (97.4%) were positive for HPV type 16 and 2 (2.59%) were found positive for HPV type 18. HPV positivity was higher in age > 40 years, same age group as having higher number of malignancy cases.

In women with precancerous lesions, 9 (69.2%) were HPV positive while 4 (30.7%) were HPV negative. 54 (93.1%) of malignant cases were HPV positive (**Table 3**).

In women with cytomorphologically normal smears, HPV positivity was 61.1% in age group of 20–30 years as compared to 43.4% in the age group of 31–40 years. HPV positivity in the age group of 61–70 years and 51–60 years was 88.8% and 76.4% respectively (**Table 4**).

For HPV testing along with clinical assessment as a screening tool for precancerous and cancerous lesion of cervix, sensitivity was 88% and specificity was 74.5%, Predictive value of a positive test was 81.8% and predictive value of a negative test was 83.6%.

## DISCUSSION

In our study, the mean age of women with carcinoma was 48.3 years while it was 31.9 years for women with precancerous lesions. This supports the fact that precancerous lesions may take several years (10–15 years) to progress to the stage of invasive cervical cancer.<sup>16</sup>

54 cases (93.1%) of cervical cancer cases were positive for HPV. 75 (97%) HPV positive cases were of type 16 and only 2 (3%) cases were positive for HPV type 18.

**Table 3**

HPV in relation to histopathology

N = 129

	Normal	Chronic cervicitis	LSIL	HSIL	CA
HPV+ve	–	14 (26.9%)	6 (60%)	3 (100%)	54 (93.1%)
HPV-ve	3 (100%)	38 (73.0%)	4 (40%)	–	4 (6.89%)

Inadequate - 3

**Table 4**

HPV in relation to age

N = 129

Age (Year)	HPV+ve (%)	HPV-ve (%)
20–30 (n = 18)	11 (61.11)	7 (38.88)
31–40 (n = 46)	20 (43.47)	26 (56.52)
41–50 (n = 36)	25 (69.44)	11 (30.55)
51–60 (n = 17)	13 (76.47)	4 (23.52)
61–70 (n = 9)	8 (88.88)	1 (11.11)

Inadequate — 3

This correlates well with other studies in India which show 98% HPV positivity in invasive cancer cases with HPV types 16 as the predominant type (90%).<sup>17–22</sup> Even in cases of adenocarcinoma HPV 16 was more frequent than HPV 18.<sup>23</sup> The prevalence of HPV type 18 has been found to be rather low in India,<sup>24</sup> as is also the case in our study.

In this study, HPV positivity in mild and moderate dysplasia was 60% and 100%. Other studies have reported similar high prevalence of HPV in the range of 70–80% in low-grade cervical dysplasia and approximating to 90% in high-grade cervical dysplasia or invasive cervical cancer.<sup>4,25</sup>

Studies have shown HPV infection to be strongly related to the age of population. The highest rates are reported in the early 20s, the same age at which low grade CIN is most prevalent. According to Rohan et al, HPV-16 or 18 positivity by general primer PCR peaks at 8–10% between 20 and 24 years of age. After the age of 35 years, only 1–2% are positive for these types.<sup>26</sup> These results are similar to our study in which higher HPV positivity is seen in 20–30 year age group as compared to 30–40 year age group. The high HPV positivity in age > 50 years is the result of larger number of women having precancerous and cancerous lesions of the cervix.

HPV infection in older women is more likely to represent persistent HPV infection.

The use of HPV along with clinical assessment as a screening method had sensitivity and specificity of 88% and 74.5% respectively in this study. The reported sensitivity and specificity of HPV testing as a primary screening tool were 88.4–89.4% and 81.9–93.9% respectively.<sup>27</sup> It was earlier suggested that incorporation of HPV testing in routine screening in India was not possible because of the high costs involved, lack of trained manpower, etc.<sup>28</sup> But, now that specific high-risk HPVs have been recognized as the principal causal agent for development of cervical cancer and since there has been an enormous improvement and simplification in virus detection techniques, incorporation of HPV testing along with cytology needs to be stressed.

A total of 88 patients were subjected to HIV testing by ELISA. None of them was found to be reactive. The reasons for this may be:

- Aligarh district is a low prevalence area where HIV prevalence is < 5% in high-risk group and < 1% among antenatal patients. According to NACO 2006 estimates, National adult female HIV prevalence is 0.29%. HIV prevalence is highest in the north eastern states and southern states (Andhra Pradesh, Karnataka, Maharashtra, and Tamil Nadu).
- Secondly, our study group did not have high-risk behavior seen to be associated with high HIV prevalence. Only two women gave history of having more than one sexual partner. None of the women gave history of IV drug abuse, or any history suggestive of STD in either partner. History of blood transfusion was positive for only 4 women. A similar study conducted in areas with higher prevalence or in women with high-risk behavior may have yielded better results. Most studies studying the impact of HIV status on cervical cancer have been undertaken in countries/areas where HIV prevalence is high.

According to Volkow, et al. HPV detection in HIV positive women was 69% as compared to 29% in HIV negative women. The relative risk for HPV infection was 5.5.<sup>29</sup> A South African study, found HPV positivity of 68% in HIV positive women as compared to 31% in HIV negative women.<sup>30</sup>

A study conducted at National AIDS Research Institute, Pune has found HPV-16/18 prevalence in HIV positive women to be 33%.<sup>31</sup> In a study from East India, HPV 16/18 was present in 62.9% of sex workers and HIV-16 alone was present in 30% of the women attending a STD clinic in North India.<sup>32</sup>

## CONCLUSION

The study of symptomatic women visiting the Gynecology OPD of Jawaharlal Nehru Medical College and Hospital, Aligarh, revealed that the prevalence of cervical cancer is high in this population. Organized screening programmes do not exist in our country and in areas where they exist, have also not been able to detect the disease in its early stages. The prevalence of high-risk HPV type 16 and 18 in histologically normal women was 25.4%, 69.2% in precancerous lesions and 93.1% in cervical carcinoma. The study showed an exclusively high prevalence of HPV type 16 in the Indian population with 97.4% case being positive for type 16 and only 2.5% cases positive for type 18. This high prevalence of HPV indicates the need to incorporate HPV testing along with cytology to screen women for cervical cancer. For early detection and identification of high-risk population with precancerous lesions, there is a need for incorporation of HPV testing along with cytology to screen women. This would be a step forward in decreasing the mortality and morbidity associated with cervical cancer. In view of the emerging AIDS epidemic in the country, we need to increase surveillance for HIV positive cases and increase awareness regarding prevention of HIV infection.

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