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Original Research Article

HPV-DNA testing for detecting precancerous lesions of cervix: how effective?

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ABSTRACT

Background: Human Papilloma Virus has been found to be associated with cervical squamous cell carcinoma. Studies and reviews indicate that HPV testing is more sensitive than Pap smear for identifying cervical cancer and its precursors in population screening. Hybrid capture 2 assays detect high oncogenic risk viruses and can be used as primary screening tool for women older than 30 years.
Methods: A detailed history followed by a thorough clinical and gynecological examination was carried out for women attending the gynecological O.P.D. HPV-DNA (HCT) samples were collected using a cytobrush. Suspicious lesions of the cervix were further subjected to colposcopy directed loop electrosurgical excision procedure (LEEP) and sent for histopathological examination in formalin. The results of HPV-DNA (HCT) and histopatholgical report were then correlated.
Results: In this study, one hundred and sixty women were screened for HPV-DNA. Thirty-two women were found to be positive for HPV-DNA. They were further subjected to colposcopy directed large loop electrosurgical procedure. The positive patients were found to have either low-grade or high-grade cervical intraepithelial neoplasia.
Conclusions: The use of HPV-DNA test may make it a viable alternative to cytological screening especially as a less frequent screening.

Keywords: CIN, HPV DNA, Human papilloma virus

INTRODUCTION

The link between genital HPV infection and cervical cancer was first demonstrated in the early 1980s by Harold Zur Hausen. HPV has been implicated in 99.7% of cervical cancers.[1] 30 subtypes of HPV have been identified. Of these types 16 accounts for half the cases, while type 18, 31, and 45 account for 30% of cases.[2] Transmission of HPV occurs by sexual activity. The age is an important determinant of risk of HPV infection.[3] Most cervical cancers occur at squamo-columnar junction of the cervix. The greatest risk of HPV infection coincides with the greatest metaplastic activity occurring at the squamo-columnar junction. Greatest metaplastic activity occurs at puberty and first pregnancy and declines after menopause. The infection is very common in sexually active young women with a sharp decrease after 30 years of age.

However cervical cancer is more common in women after 35 years suggesting infection at a young age and slow progression to cancer. Persistence of infection is more common with high-risk HPV types and is an important determinant in development of cervical cancer. The HPV infection leads to a gradual progression to more severe disease. CINI indicates a self-limiting sexually

transmitted lesion. Whereas HPV infection, CIN II and CIN III (high grade lesions) are the due cervical cancer precursors.[4]

Early detection of these lesions can lead to several preventative strategies. HPV-DNA testing by hybrid capture assay (HC2) detects 13 high risk types of HPV using signal amplification. It is developed by Digene Corporation and was granted USFDA approval in 1995.

METHODS

This prospective study was carried out in Sassoon General Hospitals, Pune for women attending the OPD of Department of Obstetrics and Gynecology.

Inclusion criteria

- Women with complaints of white p/v discharge, post-coital bleeding, blood stained discharge, irregular menses, menometrorhagia, and offensive discharge
- Apparently healthy sexually active women

Exclusion criteria

- Diagnosed cases of cancer cervix
- HIV positive infection
- Patient who have taken HPV-vaccines

A detailed history followed by a thorough clinical and gynecological examination was carried out. HPV-DNA (HCT) samples were collected using a cytobrush. Suspicious lesions of the cervix were further subjected to colposcopy directed loop electrosurgical excision procedure (LEEP) and sent for histopathological examination in formalin. The results of HPV-DNA (HCT) and histopatholgical report were then correlated.

RESULTS

The total number of women undergoing this test was one hundred and sixty. The average age of patients was thirty -nine years (Table 1).

Table 1: Age of the patients.

Age-group	No. of patiens
30-35	36
36-41	66
42-47	41
48-53	1

The mean age of sexual debut for these women was also calculated to be eighteen years (Table 2). Of the total 160 patients undergoing the HPV-DNA test, one hundred twelve patients had varied complaints like white p/v discharge, post-coital bleeding, blood stained discharge, irregular menses, menometrorhagia, offensive discharge.

Table 2: Age at sexual debut.

Age at sexual debut (Years)	No. of patiens
16	9
17	13
18	48
19	29
20	36
> 21	25

The highest frequency was that of discharge per vaginum followed by post coital bleeding (Table 3).

Table 3: Frequency of complaints.

Complaints of the women	No.of women
White discharge p/v	43
Post-coital bleeding	19
Blood-stained discharge	14
Offensive discharge	14
Irregular menses	9
Menometrorrhagia	13
Total	112

HPV DNA was reported positive in 32 women. Symptomatic 29 patients who tested HPV positive underwent LEEP biopsy. They had following findings.

- Two patients were found to have microinvasive squamous cell carcinoma
- Twenty-one women had high grade lesions, which include both CIN-3 and CIN-2. These were distinct dysplasia with increased mitotic figures and nuclear abnormality.
- Six patients had low grade lesions showing koilocytic changes, with good maturation and dysplasia confined to lower third of the cervical epithelium

Forty-eight patients had no apparent complaints but were still tested for HPV-DNA of these patients. Of these three patients were found to be HPV-DNA positive and are in follow-up regularly (Table 4).

Table 4: HPV DNA positivity.

Women tested (N =160)	HPV Positive (%) 32 (20%)
Women having some symptoms N=112	9 (25.9%)
No symptoms N=48	3 (6.3%)

DISCUSSION

Epidemiological studies have identified a number of risk factors that contribute to the development of cervical cancer precursors and cervical cancer. These include persistent infection with high oncogenic HPV-DNA,

sexual intercourse at an early age, infection co-existing with HPV like *Chlamydia Trachomatis* HPV-DNA tasting as a primary screening tool has an important role to play.[5] Good sensitivity (i.e. ability to detect the condition of interest in all women who have it) has to be balanced against its specificity.

Particularly in cervical cancer screening because the screening involves large number of otherwise healthy women. A woman with positive result needs further evaluation with its economic, social and emotional consequences. The sensitivity of HPV-DNA testing is 27% higher than cytology and specificity is 8.4% lower.[6] However the performance of HPV-DNA testing in women older than 30 years is significantly better. The negative predictive value of HPV-DNA is also very high at 91.7%.[7] The high NPV has important implications for screening programs. Thus, screening intervals can be increased in women older than 30 years.[8] Women who test negative for high risk HPV-DNA (HCT) are almost at negligible risk for developing CIN.[3]

In present study HPV DNA test gave a good yield of 14.4% women having either micro-invasive cancer or CIN. This made it possible to treat the patients with micro-invasive cancer immediately and get rid of the disease totally in patients who otherwise would have been detected late with gloomy survival. Other women having CIN received treatment with excision halting their progression to cancer. This can be considered a good achievement.

Prevalence of HPV in normal women in Thailand is 9-20%, but HPV testing has not been used on any systematic basis to date.[8] In India, in a large study of screening 142,701 women aged 30-59 years in Osmanabad District, test positivity rates were found to be 10.3% for HPV. The detection rate of high-grade lesions was 0.9% for HPV testing.[9] In present study HPV positivity is similar i.e. 20% (Table 4) and high risk lesion (CIN 2+) detection rate is 13.1%. This high detection rate in present study is due to HPV DNA testing of symptomatic women coming to the hospital. This implies that symptom-wise HPV screening would be more yielding and will prove economical for low resource settings.

HPV testing in low resource settings have an important role to play. In countries with limited funds for disease prevention cancer screening programs compete with other health needs. All cervical cancer screening programmed face common challenges to successful implementation. Barriers such at logistic and infrastructure support, cost concerns, poor follow-up and socio-cultural constraints need to be considered. Effective HPV testing programs must develop clinical protocols based on natural history of HPV. HPV infection in older women is associated with CIN II on CIN III persistent infection along with other co-injections and early age of sexual debut are other incriminating factors. Molecular diagnostic techniques for detecting HPV may provide feasible alternative to large scale cytological screening if it is shown to be cost effective, feasible to implement and broadly acceptable.

CONCLUSION

In conclusion, HPV DNA testing of symptomatic women coming to hospital has high detection rate for precancerous lesions and will prove economical for low resource settings.

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