

ROLE OF HUMAN PAPILLOMA VIRUS IN ETIOLOGY OF CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN) & CARCINOMA CERVIX BY PAP SMEARS

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ABSTRACT: The causal role of human papilloma virus in all cancers of uterine cervix has been confirmed. HPV infection of uterine cervix is associated with development of a spectrum of benign and malignant epithelial lesions. Morphological changes in the epithelial cells associated with HPV have been reported in up to 91% of women with invasive and intraepithelial neoplasia. With over 120 specific types described, type 16 and 18 are linked mainly to cervical neoplasia. Human papilloma virus although necessary but is not a sufficient cause. There are cofactors necessary for progression from cervical HIV infection to cancer. Long term use of hormonal contraceptives, high parity, socio-economic status, tobacco smoking, and young age at coitus has been identified as established cofactors. PAP smear has become a routine method of cervical cancer screening and its clinical utilization has certain limitations like false negative rate (Elovainio et al, 1999 reported 20%). Colposcopy (introduced in 1925 by Hans Hinselmann) as an adjunct to cytology possibly increases the accuracy of cervical cancer detection to almost 100%. It evaluates changes in terminal vascular network that reflects biochemical and metabolic changes in tissue that are earliest changes in development of cancer cervix. It is an O. P. D. procedure, no prior preparation or anesthesia required. Follow up of patients by HPV DNA detection can be used as an adjunctive to cytology preventing the requirement of unnecessary invasive interventions. Detection of Human Papilloma Virus by polymerase chain reaction along with screening by cytology can augment our ability to diagnose the cases in its early stage which will prove useful in preventing the cases of carcinoma cervix.

KEYWORDS: Human papilloma virus, Papsmear, HPV DNA-PCR, Cervical cancer.

INTRODUCTION: HPV infection of uterine cervix is associated with development of a spectrum of benign and malignant cervical epithelial lesions. Morphological changes in the epithelial cells associated with HPV have been reported in up to 91% of women with invasive and intraepithelial cervical neoplasia. Screening for cervical cancer is one of the most prevalent, cost effective and successful public health measures for the prevention of cancer. Early detection by screening methods are most effective in malignancies in which transit time from low grade to invasive carcinoma is more.^[1]

For detection of precancerous lesions among acceptors and non-acceptors of various family welfare methods, a scheme of PAP smear test has been approved by the government of India in a phased manner in a number of institutions.

That koilocytes in the cytological smear are pathognomic for an HPV infection was postulated.^[2]

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Concluded that regular PAP smear is cornerstone of women's preventive health care. The introduction of regular PAP smear as a screening tool for carcinoma cervix has markedly decreased number of deaths from cervical cancer.

Screening is normally done by cytological study of a PAP smear which detects only 50-80% of the abnormality found on histological examination of cervical biopsy. But if it is combined with identification of HPV-DNA, it augments our ability to identify women who are infected with HPV and are at high risk for CIN.^[3-6]

AIMS AND OBJECTIVES:

1. To study the usefulness of cervical cytology by Pap smear and their application in different preneoplastic and neoplastic lesions of cervix.
2. To evaluate the association between human papilloma virus in etiology of CIN and carcinoma cervix.
3. To assess the risk factors associated with cervical intraepithelial neoplasia.

MATERIAL AND METHODS: The present study was carried out on 74 women presenting to the cytology OPD in department of pathology over a period of approx. two years i.e; 1st January 2013 to October 2014, whose complaints or finding were of an unhealthy cervix warranting pap smear examination.

All women were subjected to the following protocol:

1. Detailed history.
2. Clinical examination.
3. Cervical cytology.
4. HPV DNA detection.

RESULTS: 1. Most of the cases were clinically diagnosed as chronic cervicitis with erosion i.e. 36(48.65%), followed by chronic cervicitis 26(35.14%).¹² cases were suspicious of malignancy. Maximum number of cases of cervical erosions are in 4th decade i.e. 41.85%. 82.43% cases had three or more children. Most of cases (83.78%) were from low socioeconomic status. 64.86% belonged to 15-21 age group at first coitus showing a direct relationship. Common complaints observed were vaginal discharge (55.41%), menstrual disturbances (17%), backache (9%), postcoital bleeding (5%) and dyspareunia.⁽²⁾ Mostly patients were non-contraceptive users (64.86%).

Sl. No.	CYTOLOGICAL DIAGNOSIS	No. of Cases	Percentage
1.	Normal	7	9.46
2.	Inflammatory	30	40.54
3.	LSIL (CIN I)	15	20.29
4.	HSIL (CIN II & CIN III)	4	5.37
5.	Koilocytosis	13	17.58
6.	Carcinoma cervix	2	2.70
7.	Unsatisfactory	3	4.06
8.	Total	74	100

Table 1: DISTRIBUTION OF CASES ACCORDING TO CYTOLOGICAL DIAGNOSIS

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2. According to cytological findings, maximum number 30(35.14) cases had inflammatory picture on cytology. This group includes nonspecific, trichomonal and monileal infection. 13(18.93%) cases show koilocytosis suggestive of HPV infection. Total premalignant and malignant cases detected by cytology were 21(28.3%) while 3(4.06%) cases show unsatisfactory smear.

3. In this study, the cytological examination of patients revealed a prevalence of 17.58% for HPV infection. Cytological diagnosis was established on the basis of classical signs suggestive of HPV infection and the results were then compared with that of polymerase chain reaction which was taken as the gold standard diagnostic test but no significant statistical correlation could be established (p value- 0.89).

Cytology Class	No. of Cases	HPV DNA +cases		HPV DNA - cases	
		Number	Percentage	Number	Percentage
Normal	7	0	0	7	100
Inflammatory	30	1	3.33	29	96.67
LSIL (CIN I)	15	9	60	6	40
HSIL (CIN II AND CIN III)	4	2	50	2	50
Koilocytosis	13	3	23	10	77
CA	2	1	50	1	50
Unsatisfactory	3	0	0	3	100

Table 2: PREVALENCE OF HPV IN DIFFERENT CYTOLOGY CLASS

χ^2 -22.99 p value—0.0001 (highly significant).

DISCUSSION: In the present study, 74 cases were randomly selected from women whose history or clinical finding was suggestive of an unhealthy cervix. Cytological and HPV DNA testing by PCR method was performed in all patients in a subsequent manner.^[7]

Our findings are in accordance with previous studies done by Iyer and Shah, in London study in which 78% cases were above the age of 30 years. Number of cases recorded between 26-30 years was 19(25.74%). Similarly earlier authors found that early stages of cancer cervix occur at younger age group, the peak incidence of cervical intraepithelial neoplasia being 25-30 years. Our study proves the fact that etiology of carcinoma cervix is multifactorial. Other factors like coital habits, environment. Social status and assault on the cervix due to repeated childbirth are also responsible for the causation of carcinoma cervix.^[8]

Most of the cases 62(83.78%) in our study belonged to low socio-economic status as documented previously that cancer is commoner in low socio-economic class in whom the component of poverty, overcrowding, inadequate food and clothing, housing, hypothermia and poor personal hygiene are contributing factors to infection and malignancy.^[9]

In present study, the mean age at first coitus for cervical lesion was 21.22±4.03 years as seen in the study among patients who began coitus between the age of 15 to 17 years, twice as many had cervical cancer than control group.^[10] It was shown that the period of early squamous metaplasia is the most critical time for the development of cervical cancer. Squamous metaplasia is most frequent during puberty, early adolescence and during first pregnancy. Therefore women who begins sexual

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activities at an early age, when the squamous metaplastic process is most active would have a greater chance of developing cervical cancer.^[10]

In this study, the cytological examination of patients revealed a prevalence of 17.58% for HPV infection. Cytological diagnosis was established on the basis of classical signs suggestive of HPV infection and the results were then compared with that of polymerase chain reaction which was taken as the gold standard diagnostic test but no significant statistical correlation could be established (p value-0.89).^[11,12]

3.33% inflammatory smears were found to be HPV positive. 60% of LSIL, 50% of HSIL and 50% of carcinoma in situ cases were actually harboring HPV infection. None of the normal smear showed HPV DNA positivity. There was a statistically significant association between HPV DNA positive and cytologically detected premalignant and malignant lesions of the cervix.^[13]

CONCLUSION: Thus it was concluded from this study that HPV infection is sexually transmitted disease acting like an agent in the development of preneoplastic and neoplastic lesions of the cervix.

Thus follow up of patients by HPV DNA detection can be used as an adjunctive to cytology preventing the requirement of unnecessary invasive interventions. Detection of Human Papilloma Virus by polymerase chain reaction along with screening by cytology can augment our ability to diagnose the cases in its early stage which will prove useful in preventing the cases of carcinoma cervix.^[14]

Moreover, HPV can play a role in management of CIN II or CIN III. If decision has to be taken between surgical and conservative management, HPV DNA detection can help in solving this dilemma as the chance of developing higher grade cervical lesion are more in high risk HPV positive cases.^[15]

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