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High Prevalence of Oncogenic Human Papillomavirus Types 16/18 in Negative Inflammatory Pap Smears Implies Masking Cervical Cancer

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Abstract

Purpose: Infection of high-risk HPV types 16/18 have been known to be the principal causative agents for the development of cervical cancer. The objective of the present study was to examine whether positive oncogenic HPV types 16/18 in a negative inflammatory Pap smear could be an indicator of cervical cancer risk in a symptomatic woman.

Methods: A total of 550 symptomatic women who attended the gynaecology outpatient department of the Mahavir Cancer Sansthan, Patna, for pap smear examinations were screened, and simultaneously cervical scrapes were taken for HPV DNA analysis. After evaluation of Pap smear reporting, an oncogenic HPV types 16/18 test using qRT PCR was conducted through preserved DNA, on 431 women with negative inflammatory smears and 75 women without inflammation negative Pap smears. A further 82 HPV positive women with negative inflammatory smears were randomly selected due to their highly clinical symptoms from the study population for colposcopy guided biopsy to correlate HPV positivity with negative inflammatory smears.

Results: The prevalence of oncogenic HPV types 16/18 positive cases in 431 with inflammatory smears was found to be 389. However, HPV type 18 was detected only in 7 women whereas in 21 out of 75 women without inflammatory negative smears, only HPV type 16 was detected. The association with HPV positivity was found to be statistically highly significant ($p<0.0001$). A biopsy of 82 patients revealed that 24 (29%) women had cervical cancer, of which 19 had a Squamous cell carcinoma and 05 had Adenocarcinoma, 20 women had cervicitis, 02 women had a dysplasia, 12 women had a benign tissue, 12 women had a haemorrhage, and 06 women were asked to repeat biopsy.

Conclusion: Thus, detection of high-risk HPV can be utilized to eliminate false negative Pap tests, especially in those with inflammation, as inflammatory smears have a greater risk of developing neoplasia.

Keywords: Pap smear; HPV; Cervical Cancer; Inflammation.

Introduction

Pap cytology has always been a major technique to screen for cervical cancer. Since Pap smears are a simple and cost-effective test, they are widely used for early detection programmes. Despite the fact that cervical cancer burden is still high & mortality rate is remaining steady [1]. Failure of a Pap smear-based screening program leading to cervical cancer [2,3]. The Pap smear-based technique has several limitations, as an error in the

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sample collection is a big issue because it is difficult to reach an adequate level of coverage for optimal collection of samples & lack of well-trained persons for drawing the sample. Apart from these problems, interpretation of cytology is very subjective, therefore frequent repeated screening is recommended. Thus, it fails to detect changes in cervical cells and gives a high rate of false negative results [4,5,6,7]. Limitations of Pap testing are further observed as a large number of Pap smear reports are being reported as negative with inflammation [8,9,10,11,12]. In India, it has been observed that a substantial number of Pap smears are being reported as negative for inflammation [8,13,14]. Interpretation of inflammatory negative Pap smear is controversial; hence, reporting negative inflammatory smears for moderate to severe inflammation in many cases may represent to the undetected precursor lesion [4].

It is well established through epidemiological, clinical and experimental studies that cervical cancer is initiated by the infection of the genital tract with the oncogenic type of human papillomavirus. Specifically, oncogenic types 16 and 18 are considered as causative agents for cervical cancer [15,16,17,18,19,20]. Studies show that women with inflammation and infected with oncogenic types 16 and 18 have a higher rate of developing malignancy, [21,22] thus, detection of oncogenic type HPV infection in women may play a key role in checking the development of precursor lesions. Therefore, HPV testing along with cytology may be a good strategy to identify women before developing invasive cancer despite negative inflammatory Pap smears. Colposcopy may be used as a secondary triaging method, but it is unable to detect viral infections and would be a costly affair for the patients.

Therefore, the present study was aimed at showing that the detection of high-risk HPV types 16 and 18 in symptomatic women with a negative inflammatory Pap smear should be treated as test-positive and led to further confirmation by histopathology.

Patients and Methods

Study Subjects

A study was designed to conduct oncogenic HPV types 16 and18 tests on 431 women with negative inflammatory Pap test results and 75 women with negative Pap test results without "inflammation", who attended the gynaecology outpatient department of the Mahavir Cancer Sansthan and Research Centre, Patna, India. The histopathological examination was done on randomly selected 82 women (from those who had negative inflammatory Pap test results but detected oncogenic HPV type 16/18) as the reference standard to confirm the negative inflammatory Pap smear and positive oncogenic HPV types 16 and18 results. This study was conducted during the period of August 2022 to July 2023. Patients in the age group of 22- 75 years were included in the study, presenting with various symptoms like chronic vaginal discharge with a foul smell, pelvic pain, heavy menstrual bleeding, post-menopausal bleeding, and post coital bleeding.

Specimen Collection

Cervical scrapes were collected by scraping the ectocervix using an Ayre's spatula, for Pap smear examination and HPV testing from each of 550 women. After smearing the slides for a Pap test, the remaining scraped cervical cells along with the spatula were transferred to sterile vials containing 10 ml of normal saline and proceeded to DNA extraction.

Pap Test

A cervical smear was made with the help of an endocervical brush, an Ayre's spatula, and a cotton swab by the gynaecologist. Smears were fixed immediately in 95% isopropyl alcohol and stained with Papanicolaou stain for observation. Reporting of Pap smears was done based on the revised Bethesda system of 2014 by the pathology department of the Mahavir Cancer Sansthan & Research Centre.

DNA Extraction from Cervical Scrapes

DNA extraction was made using the MyLab Discovery solutions kit, which was based on silica membrane technology. The whole process involved the steps of sample lysis, DNA binding to the silica columns, and washing elution.

Quantification of DNA: Used the QuantiFluor® dsDNA protocol for quantification of DNA. A fluorometer was used to measure the DNA in the isolated specimen. In the present study, a 50ng to 85ng concentration of DNA was used for the PCR reaction.

Amplification of specific E6/E7 region of HPV types 16 and 18

The HPV test was done using the MyLab Discovery solutions kit. The test was based on real-time PCR-based technology, for the amplification of a specific conserved target sequence of the E6/E7 region of HPV 16 as well as 18 and detection by a target specific probe. The beta globin gene was also detected as a housekeeping gene to check for extraction efficiency and PCR inhibition. The assay principle wass based on Taqman technology which allows higher specificity and sensitivity.

Histopathological Examination

Randomly selected 84 women with negative inflammatory Pap smears and positive for HPV DNA were subjected to a punch biopsy with the help of colposcopy examination after the application of 5% acetic acid. The gynaecologist had taken the punch biopsy wherever it was necessary and sent it to the pathology department of the Mahavir Cancer Sansthan for histopathological examination.

Ethical Approval

Informed consent was obtained from all recruited participants, and the study was explained orally to all women. The study was reviewed and approved by the Institution's Ethics Committee of Mahavir Cancer Institute & Research Centre, Patna. (India) with IEC No. MCS/Admin/2018-19/1223dated 23/08/2018. The study was carried out in accordance with the guidelines and principles of the Helsinki Declaration.

Statistical Analysis

Statistical analysis of the association of HPV infection with Pap smear in the female population was done by using the Chi-square test/Fishers' exact test with prism software. Statistically significant was considered by getting a P value below 0.05.

Results

In the present study, an oncogenic HPV type 16/18 test was conducted on 431 women with negative inflammatory Pap test results and 75 women with negative Pap test results without "inflammation". The prevalence of oncogenic HPV type 16/18 positive cases as detected by qRT PCR in 431 negative with inflammatory smear women was found to be 389. However, HPV type 18 was detected only in 7 women, whereas in 21 out of 75 women without inflammatory negative smear, only HPV type 16 was detected. The association for HPV positivity was found to be statistically highly significant ($p< 0.0001$) (Table 1). The high prevalence of positive oncogenic types HPV 16/18 (389/431) detection in negative inflammatory smears was investigated in relation to the patients' age group and clinical symptoms.

The age of the women considered for the study ranged between 20 to 70 years, and the mean age of the women was 45 years (±5.6). It was observed that most of the HPV positive women (77.14%) belonged to the higher age group (40-70) whereas 22.85% belonged to the younger age group (20-39). It was found that (74.90%) patients had the symptoms of chronic vaginal discharge with foul odours and pelvic pain, heavy menstrual bleeding was seen in (19.92%) patients, post- menopausal bleeding in (3.12%) and post coital bleeding in (2.16%) patients (Table 2).

Further, the high prevalence of HPV positive women with negative inflammatory Pap smear reports was confirmed through histopathological examination. Thus, 82 patients were randomly selected from among these 389 (HPV positive and Pap negative with inflammation) patients for colposcopy guided biopsy. It was found that 24 (29%) women had cervical cancer, in which 19 had a Squamous cell carcinoma and 05 had an adenocarcinoma. 20 women had cervicitis, 02 women had dysplasia, 12 women had benign tissue, and 12 women had haemorrhages. And 06 women were asked to repeat biopsy (Table - 3).

A case of Pap smear slide was showed which was reported negative for intraepithelial lesion or malignancy (NILM) with inflammation (Figure 1) that was missed in screening, but after biopsy, it was found to be non Keratinising squamous cell carcinoma grade – I (Figure 2).

Table 1: HPV positivity in negative with or without inflammatory Pap smear

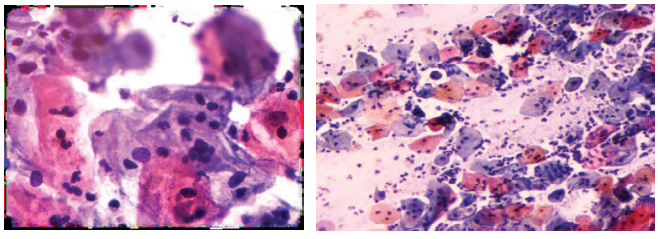
Pap Report	(n) 506	HPV 16	HPV 18	HPV16/18	P
		Positive	Positive	Positive	Value
Negative with INFLAMMATION	431	382	7	389 (90.25%)	
Negative without INFLAMMATION	75	21	0	21 (28%)	< 0.0001 Highly significant

Table 2: Clinical symptoms with HPV infection in women with negative with inflammatory Pap smear

Symptoms	n = 431 Negative inflammatory smear	HPV positive patients n = 389
Vaginal discharge with foul smelling and pelvic pain	319	292 (91.53%)
Heavy menstrual Bleeding	67	58 (86.56%)
Post-menopausal Bleeding	33	29 (87.87%)
Post coital Bleeding	10	10 (100%)

Table 3: Biopsy report in women with negative inflammatory smear and HPV positive.

Biopsy report	Number of subjects	Percentage
Cervical Cancer	24	(29.26%)
Benign tissue	12	(14.63%)
Cervicitis 20 (24.39%)	20	(24.39%)
Dysplastic 02 (2.43%)	2	(2.43%)
Haemorrhage 14 (17.07%)	14	(17.07%)
Repeat Biopsy 10 (12.19%)	10	(12.19%)



10x 40x

Figure 1: Smear showing superficial, intrermediate and parabasal cells with atrophic changes. In the background inflammatory cells are seen at 10x and 40x (Inflammatory smear)

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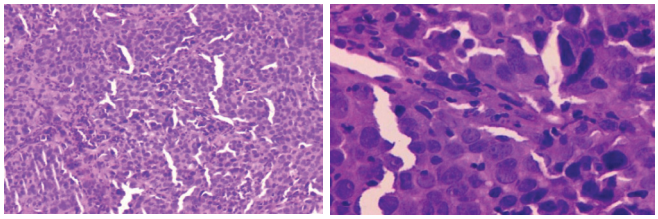

10x 40x

Figure 2: Showing Non Keratinising Squamous Cell Carcinoma grade – I at 10x and 40

Discussion

It was observed in our study that more than 70% of the patients came with the most common complaint of chronic per vaginal discharge with foul odour and pain in the pelvic area. The second most common problem was with heavy menstrual bleeding and post-menopausal bleeding, and there was the least problem with post coital bleeding. It was also observed that all patients were referred to a cancer centre to rule out cervical malignancy as their primary screening was already done at local level, despite the fact that 95.47% of smears were reported as Negative for Intraepithelial Lesion (NILM) with inflammation in our cancer centre. The highest incidence of vaginal discharge cases in our study population was reported as an inflammatory smear, but since lesions were not observed by a cytologist, they were reported as Negative for Intraepithelial Lesion or Malignancy (NILM).

In India, there is a high prevalence of vaginal discharge cases in upfront patients that are associated with inflammatory smears. It is presumed that bacterial and fungal infections are the reasons for inflammation in patients. The majority of such patients are treated with antibiotics and followed up with Pap screening but the study of viral infection of inflammation has been completely ignored. However, human papillomavirus (HPV) has been shown to be the causative agent for cervical cancer [23]. Similarly, in our study population, a high percentage of HPV positivity (91.53%) was observed in patients with complaints of vaginal discharge. In the lack of an HPV test patients were treated with antibiotics for vaginal discharge, but symptoms continued hence they were referred to a cancer centre. Negative Pap test results with inflammation in such patients in cancer centre may be a barrier to detecting cervical neoplasia.

There is a strong relationship between chronic inflammation and cancer [24,25,26], in which autocrine and paracrine signals are arbitrated by oncogenic activity, which gives rise to changes in somatic cells with the impact of epigenetic factors or the microbial genome. Among the infectious agents that are responsible for cancer, the role of the human papillomavirus is well established. Fernandes et al [27] observed in their study that the human papillomavirus is responsible as an invading agent for inflammatory responses, which activate stimulus for the release of cytokines and chemokines. These mediators act together to employ the effector cells on the wound for healing and remove the stimulus to disable inflammation. Even so, if the stimulus continues, inflammation changes to chronic and is strongly linked with the development of cervical cancer. Deivandran et al [28] and Hemmat et al [29] have also observed in their studies that human papillomavirus (HPV) is responsible for the acceleration of inflammation and changes in the chronic inflammation involved in the process of cervical cancer. Moreover, it was observed that the occurrence of HSIL is highly associated with inflammation in HPV infected females. This strengthens the theory that inflammation caused by HPV infection may be an important cofactor for developing HSIL [30,31].

In the present investigation, the correlation between negative inflammatory smears and HPV positivity was found to be highly significant. The high prevalence of HPV positivity in women with a negative Pap smear report was confirmed through colposcopy guided biopsy in 82 randomly selected patients. It was observed that 24 (29.26%) of the patients were clearly reported to have cervical Cancer and the biopsy report in the remaining patients also suggested progression to cervical cancer. Based on positive report of HPV, 29.26% clear cut cervical cancer was detected through biopsy which was missed by cytology. In the present investigation, detection of cervical cancer in negative with inflammatory smear cytology suggested that inflammatory smear should be treated as a test positive, which agrees with Sadoul et al [32] who suggested that persistent inflammatory smear should not be considered as negative and lead to further investigation. Sandmire et al. [33] observed severe lesions in 36% of patients who initially had inflammatory smears and in 25 patients with persistent inflammatory smears who had cervical cancer after histopathological examination, which is in support of my present study. Studies by Kohan et al. [34] and Reiter et al. [35] showed that after histopathological examination of inflammatory Pap smear cases, 30% of intraepithelial neoplasia after a single inflammatory smear and 70% of intraepithelial neoplasia in cases of persistent inflammation, which is a fair level of agreement with my study.

It is, therefore, proposed that high risk HPV positive cases with simultaneously negative inflammatory Pap smears should lead to further investigation as inflammatory smears have a greater risk of developing neoplasia. Thus, detection of high-risk HPV can be utilized to eliminate false negative Pap tests, specially in those with inflammation.

In conclusion, it has been observed from the present study and various above-mentioned studies that negative inflammatory Pap test results in symptomatic women fail

to detect cervical cancer, even in follow - up women. The investigation done on Pap test results of symptomatic women revealed that the interpretation of the smear by the cytopathologist is quite crucial. Microbiological and epigenetic factors are responsible for making changes in cervical cells, and HPV is a proven causative agent for the development of cervical cancer. Therefore, the HPV status of the patients will be very helpful for the cytopathologist in interpreting the changes in cervical cells. Along with this, at the time of smear examination, the cytopathologist must know the clinical history of the patient with regard to evaluating changes in the cell. In our study, data revealed that cervical cancer cases were confirmed after biopsy in those women who had previously reported inflammatory smears. If the cytopathologists knew the HPV status and clinical history of the patients, and whether the patients had antibiotics before coming to the cancer centre, then the interpretation of the smear would have been conclusive. Thus, we delineate in this study a novel perspective for interpreting Pap smears in light of the clinical history of the Patients and their HPV status to identify underlying squamous intraepithelial lesions in women.

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Disclosure

The authors declare that they have no conflicts of interest in regard to this study.

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