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Original Research Article

Assessment of cervicovaginal smear and HPV DNA co-test for cervical cancer screening: implications for diagnosis and follow-up strategies

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ABSTRACT

Background: Cancer of the cervix, despite being a preventable disease, continues to be a significant public health problem in females. In recent years, much new development has taken place in the field of screening, diagnosis and management of cervical intraepithelial neoplasia.
Methods: A total of 980 patients aged between 20 to 60 years were included in the study. All the patients have gone through Pap test, RT-PCR for HPV test and colposcopy biopsy. Then the sensitivity and specificity are calculated. Retrospectively selected Pap specimens with RT-PCR HPV testing results obtained from the Department of Pathology of Sheikh Fozilatunnessa Mujib Memorial KPJ Specialized Hospital, Gazipur, Bangladesh from July 2022 to July 2024 followed by the result is correlated with Colposcopy guided biopsy.
Results: We found 250 cases of human papilloma virus RT-PCR positive, 433 cases of Pap test positive result and 399 cases of positive colposcopy biopsy result. So, The HPV test was demonstrated to be more sensitive (75%) than specific (55%) and was more sensitive than colposcopy for detecting CIN changes (75% vs. 73%).
Conclusion: HPV tests showed a higher sensitivity than colposcopy, but colposcopy results presented higher specificity. Combining HPV testing and colposcopy proved to be the most efficient method for detecting CIN lesions.

Keywords: Real-time polymerase chain reaction, Human papillomavirus, Cervical intraepithelial neoplasm, Atypical squamous cells of undetermined significance

INTRODUCTION

Cancer of the cervix, despite being a preventable disease, continues to be a significant public health problem in females.[1] In Bangladesh, each year an estimated thirteen thousand women are diagnosed with cervical cancer and about six thousand die from the disease.[2] To decrease the burden of this cancer, cervical intraepithelial lesions must be timely diagnosed and treated. In recent years much new development has taken place in the field of screening, diagnosis and management of cervical intraepithelial neoplasia. Primary cervical cancer screening by cytological examination of cervical cells with a Pap smear has reduced the incidence of cervical cancer in countries with organized screening programs. However, several studies have shown that cytology has limited sensitivity for detecting high-grade CIN.[3,4] Several cross-sectional studies have reported that HPV-

DNA testing is more sensitive than cytology in detecting high-grade CIN.[4,5] On the other hand, several trials have raised concern about the lower specificity of HPV-DNA testing.[4,6]

Despite the introduction of the HPV prophylactic vaccine, the various screening programs for carcinoma cervix will have to continue.[7] The present study was therefore undertaken to evaluate and correlate the various methods of screening cervical intraepithelial neoplasia (CIN I, II, III) including Pap smear, colposcopy and HPV-DNA detection. We also utilized this opportunity to counsel patients and create awareness regarding cervical cancer screening and its prevention. Various screening methods for evaluation of cervical intraepithelial lesions are complementary to each other and need to be carried out depending on the clinical findings, patient's convenience and compliance, facilities and set-up available.

In this study, we selected a group of patients who attended a colposcopy clinic and had abnormal cytology results to compare the diagnostic validity of two screening tests, namely, colposcopy examination and DNA HPV testing with genotyping to detect low and high-grade dysplasia (CIN) and cervical cancer. We discuss the best combination of these methods to identify women with abnormal cytology who are at a high risk of developing cervical cancer.

The present study was therefore undertaken to evaluate and correlate the various methods of screening of cervical intraepithelial neoplasia including Pap smear, colposcopy and RT-PCR for HPV testing and compare the results to find out efficacy and sensitivity.

METHODS

Study area

Patients from the gynecological outpatient department of Sheikh Fozilatunessa Mujib Memorial KPJ specialized hospital, Gazipur.

Study duration

The study duration was about 2 years from July 2022 to July 2024.

Inclusion criteria:

Women with complaints of postcoital bleeding, lower abdominal pain, intermenstrual bleeding, low backache, persistent vaginal discharge, vulval itching or burning, persistent dysuria, menstrual irregularities, or other complaints. Women with cervical erosions or unhealthy cervix on per speculum examination. Women with a history of infertility, abortions, STD/ HIV, HSV or vulval warts. Immunocompromised patients. Patients with poor personal hygiene and very poor socioeconomic status. Patients were briefed about the purpose of the tests to be done on them and written well-informed consent was obtained. These patients were subjected to Pap smear, HPV-DNA detection by RT PCR, colposcopy and directed cervical biopsy if required. If hysterectomy was performed, histopathological examination was done. The various screening methods were correlated and evaluated by standard statistical methods.

Laboratory procedures

All cervical smears were obtained with a cytological brush, collected in 1 ml of lysis buffer and stored at 4˚C until HPV testing could be conducted in the laboratory. The DNA was isolated using the tissue DNA purification kit nucleic acid extraction kit (Magnetic Bead Method) made by Zybio Inc. is highly recommended to make extraction and preparation of viral DNA, automatic processes are available for sample preparation, loading specimen 200 µl/well. Nucleic acid extraction is simultaneously conducted on the Negative Control and the Positive Control in this kit. The DNA samples were stored at -20˚C, according to the manufacturer's instructions.

The commercial Zybio-detection kit was used as recommended to detect HPV DNA by standard PCR and determine the virus types. Viral DNA sample preparation (conducted in sample processing zone) nucleic acid extraction kit (magnetic bead method) loading specimen 200 µl/well. Nucleic acid extraction is simultaneously conducted on the negative control and the positive control in this kit.

PCR reagent preparation (conducted in the reagent preparation zone) removes the HPV reaction solution and HPV primer probe from the kit, mixes well and centrifuges briefly for a few seconds. According to the number of samples to be amplified, prepare the HPV amplification reagent as HPV reaction solution 18 µl/test, HPV primer probe 2 µl/test. After mixing, 20 µl/tube is dispensed into the PCR reaction tube, and the reaction tube containing the HPV amplification reagent is transferred to the sample processing area.

Sampling (carried out in the sample processing area) Using a nozzle with a filter element to add 20µl nucleic acid template separately, close the tube cover tightly, and transfer to the amplification detection area after a short period. PCR amplification parameters as UNG enzyme reaction 50˚C for 2 min 1 cycle. Pre-denaturation 95˚C for 5 min, 1 cycle, denaturation 95˚C 10 sec, 5 cycle, amplification 60˚C 20 sec for 5 cycle, denaturation 95˚C 5 sec, 335 cycle amplification and flurencence detection 58˚C 30 sec 35 cycle quality control procedure, positive control.[3,5] The test results of FAM, ROX and Cy5 fluorescent channels were all positive (Ct<32). Negative control. The test results of FAM, ROX, and Cy5 fluorescent channels were all negative (Ct=35 or no value), and the VIC channel was positive (Ct<32). All the

above must be met in the test, otherwise the results are invalid.

Result analysis

The instrument software automatically analyzes and obtains the DNA test results of each sample.

Statistical analysis

The performance characteristics sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of the HPV test, colposcopy and both tests together in detecting CIN II and CIN II changes were calculated for all patients with abnormal cytology results. The reference method used for obtaining the final diagnosis of patients with abnormal Pap smear results as well as for the assessment of HPV testing and colposcopy characteristics was histology.

For determining the sensitivity and specificity of colposcopy, positive colposcopy results in patients with a positive final diagnosis (histology) were considered as true positives positive colposcopy results in patients with negative histology results were considered as false positives negative colposcopy results in patients with negative histology results were considered as true negatives and negative colposcopy results in patients with positive histology results were considered as false negatives.

Unsatisfactory colposcopy results were excluded from the analysis. For determining the sensitivity and specificity of HPV testing, positive HPV results in patients with positive final diagnosis (histology) were considered as true positives; positive HPV results in patients with negative histology results were considered as false positives; negative HPV results in patients with negative histology results were considered as true negatives; and negative HPV results in patients with positive histology results were considered as false negatives. Both high-risk and low-risk HPV testing results were included in the analysis.

RESULT

We have a total study population of 980. The median age of the patients was 35.8 years (range=18-65 years). Among them, 18(1.8%) smoked cigarettes, 680 (69%) were taking contraceptive pills and 520 (53%) had a history of vaginal infections. In all the cases we do cytological tests. We found 433 cases of positive cytological lesions. Colposcopy biopsy and RT-PCR HPV genotyping were done in all the cytologically positive (433) cases. We found 399 cases of positive lesions in histopathology and 265 cases in RT-PCR HPV typing. In cyto-pathologically positive cases we found HSIL=26, LSIL=150, ASC-H=10, ASCUS=244 and AGUS=4. In histopathology, we found CIN I=312, CIN II=60, CIN III=23 and carcinoma=4 cases. Among the RT-PCR HPV test positive cases we found HSIL=22, LSIL=81, ASC-H=6, ASCUS=68 and NILM=84 again in biopsy we found CIN I=82, CINII=43, CIN III=18 and carcinoma=4 cases, which shows in table 1. So, in the RT-PCR HPV negative cases, we found HSIL=4, LSIL=69, ASC-H=4, ASCUS=176 AGUS=0 and CIN I= 230, CIN II=17 and CIN III=5 and no carcinoma, all shown in figure 3.

The distribution of HPV infections in the different cytological groups is shown in table 1. Among all of the HPV-positive patients, single genotypes were most frequently detected, We found 100 (37%) cases infected with the high-risk variant HPV 18, 43 (16%) cases infected with the high-risk variant HPV 16 and 36 (13.5%) cases showing combined infection with both high-risk variant, that was total 179 (67.5%) cases among 265 positive HPV test, Rest 66 (25%) cases are infected with low-risk variant HPV 30,31 and 32. Multiple infections (double or triple) were identified in 20 (7.5%) cases, these HPV distributions are shown in figure 2.

Considering the different cytology groups, the high-risk genotypes were the most frequent among patients with HSIL, LSIL and ASC-H and were detected in 100%,75%, and 50% of such patients, respectively. Low-risk genotypes were most common in patients with an ASCUS cytology result and comprised 29% of the positive HPV cases. The distribution of colposcopy and HPV virus and its genotype in women according to their cytological smear results is shown in table 1.

HPV infections were most common in women in the age group 18-29 and 30-39 years, in whom the virus was detected in 39% and 37% respectively of the patients. The lowest number of infections (3% of patients) was observed in the group aged over 60 years. The frequency of HPV infection according to the age group is shown in figure 3. The overall distribution of 5 different HPV genotypes concerning a cytological diagnosis is shown in table 1.[18,16,30-32]

Among the RT-PCR HPV-positive cases were diagnosed with 82 CIN I, 18 with CIN III and 43 with CIN II. Only 1 patient with LSIL cytology had cervical cancer as their final diagnosis. The distribution of the final result according to the cytological diagnosis is presented in table 1. Among the 18 patients with a diagnosis of CIN III, we found all are infected with high-risk HPV mostly HPV genotype 18. Of the 43 patients with CIN II, we diagnosed 33(76%) infected with high-risk HPV and 10(24%) low-risk HPV.

In the 82 cases of CIN I group, 50(61%) women had high-risk HPV infection, 26 (32%) had low-risk HPV. Among 4 cases of cervical cancer was found in a patient with other high-risk types both type that is HPV 16 and 18. Comparison of efficacy of DNA HPV testing and colposcopy. The reference method for the assessment of DNA HPV testing and colposcopy efficacy was

histology. The distribution of colposcopy and HPV infection results, according to final diagnosis (histology) are presented in table 2. The screening efficacy of both tests, including the combination of colposcopy and HPV testing for CIN, is shown in figure 2.

Table 1: Distribution of colposcopy and cytology smear results among the RT- HPV positive cases.

PAP	No. (%)	Colposcopy biopsy results					Distribution of HPV types			Other bacterial infection %
		CIN II (%)	CIN III (%)	CIN I (%)	Negative colposcopy findings (%)	Sq. cell carcinoma or Adenocarcinoma (%)	High risk (%) 18HPV variant =100 16HPV variant =43 combined=36	Low risk (%)	Co-infection (%) Both high-risk and low-risk	
HSIL	22 (8.5)	10 (45)	6 (27)	3 (14.5)	1 (4.5)	2 (9)	22 (100)	0	0	22 (100)
LSIL	81 (32)	18 (22)	10 (13)	49 (60)	3 (3.5)	1 (1.5)	61 (75)	20 (25)	0	75 (93)
ASC-H	6 (02)	2 (34)	0	3 (50)	1 (16)	0	3 (50)	2 (33)	0	6 (100)
ASC-US	68 (26)	13 (19)	0	15 (22)	40 (59)	0	41 (60)	20 (29)	7 (10)	40 (59)
AGUS	4 (1.5)	0	2 (50)	0	1 (25)	1 (25)	3 (75)	0	1 (25)	4 (100)
NILM	84 (32)	0	0	12 (14)	72 (86)	0	48 (57)	24 (28)	12 (14)	74 (88)
Total	265 (27)						179 (68)	66 (25)	20 (8)	221 (83)

Table 2: Comparison between RT PCR for HPV test and colposcopy biopsy.

Test	Sensitivity %		Specificity %		PPV%		NPV%	
Lesion	**CIN I**	**CIN II**	**CIN I**	**CIN II**	**CIN I**	**CIN II**	**CIN I**	**CIN II**
RT-PCR HPV typing	75	80	55	52	48	20	88	86
Colposcopy biopsy	69	75	88	89	78	40	88	96
RT-PCR HPV and Colposcopy biopsy same time	92	94	82	67	77	45	92	96

Among 4 cancers and 18 cases of CIN III, all are HPV positive. So, the more dysplasia the more positive cases of HPV are found and decreasing dysplasia increases false negative cases that is about 25%. So, this decreases the specificity of RT-PCR HPV testing.

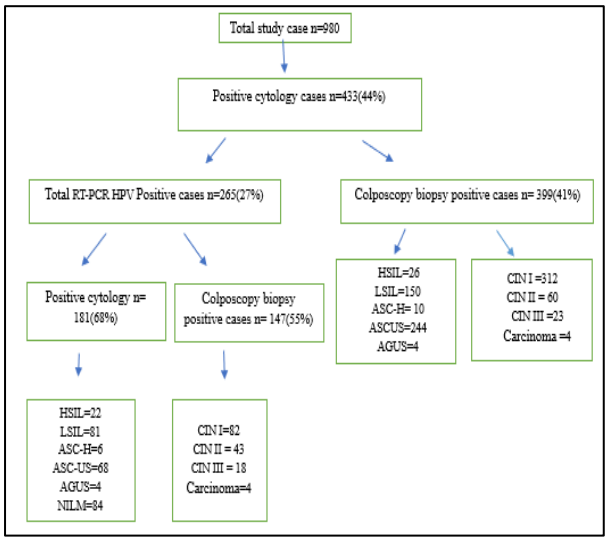

Figure 1: Flow chart of the study.

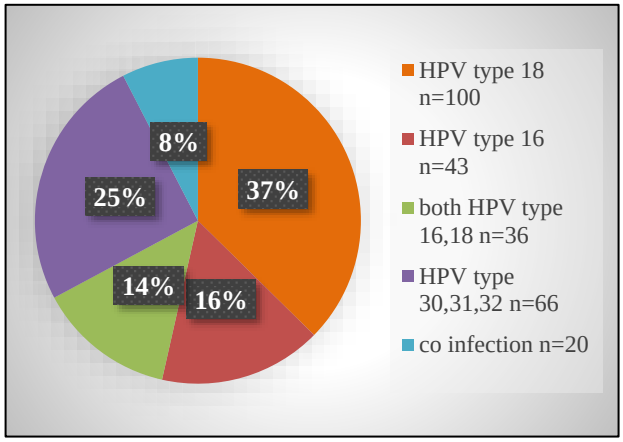

Figure 2: Distribution of the type of HPV infection in patients RT-PCR positive cases.

We determined that the HPV test is more sensitive than colposcopy for detecting CIN I cases, with values positive HPV of 75% for the HPV test and 26% negative HPV test, these are false negative but colposcopy shows and patients with CIN II lesions RT-PCR HPV test is positive 80% and 20% are negative HPV which is false negative.

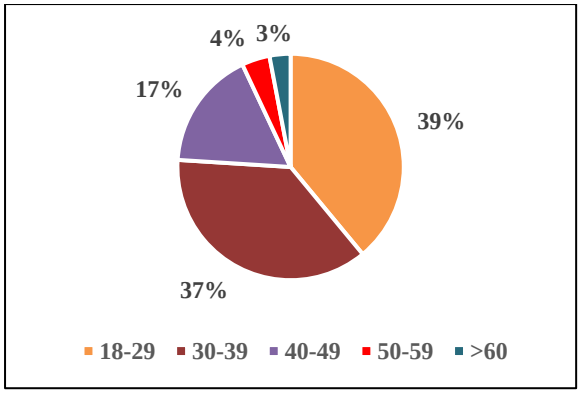

Figure 3: Distribution of HPV infections according to age group.

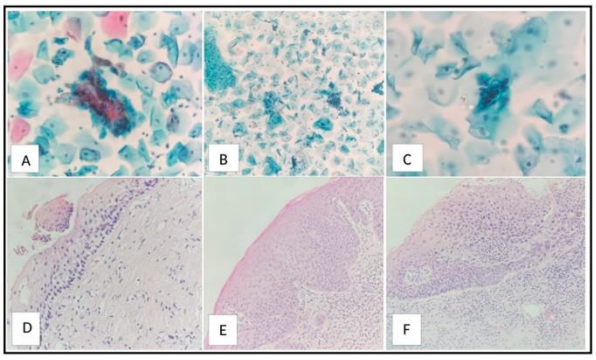

Figure 4: Microscopic photo of a case diagnosed as ASCUS by PAP smear (PAP stain,×400) (A), and CIN1/LSIL by cervical colposcopic biopsy (hematoxylin and eosin stain,×200) (D). Photomicrograph of a case diagnosed as CIN1/LSIL by PAP smear (PAP stain,×200) (B), and CIN2/HSIL by cervical colposcopic biopsy (hematoxylin and eosin stain, ×200) (E). Photomicrograph of a case diagnosed as CIN3/HSIL by PAP smear (PAP stain,×200) (C), and CIN3/HSIL by cervical colposcopic biopsy (hematoxylin and eosin stain,×200) (F).

DISCUSSION

One major finding of this study was that the highest positive and negative predictive values of the HPV test and colposcopy examination were attained when the tests were performed together. When comparing each test completed alone, the PPV was higher for the colposcopy examination (78%) compared to the HPV test (48%) in detecting any dysplasia (CIN I). Our results are similar to those reported in previous studies and even higher than those reported in a study from Germany, in which the PPV for the HPV test was 36% it was 38% for colposcopy.[8-11] The explanation for this finding may be that a high percentage of the female population acquires latent HPV infection at some point in their lives but most eliminate the virus before cervical dysplasia changes appear. A total of 31 % of patients with positive HPV tests were ultimately classified as healthy at the end of the study. The high PPV of colposcopy was obtained because when using this method, we observed changes in the cervix in real-time. The coupled tests performed together resulted in the best PPV for detecting CINI cases (77%). These methods should be recommended for diagnostic procedures in cases of abnormal cytology as the best approach for assessing the risk of development of cervical dysplasia. This statement is consistent with recommendations noted in many other studies.[11-13] We achieved the same NPV of 88% when conducting each test separately to detect CIN I.

The negative results of both tests were primarily observed with the CIN I cases thus, the NPV was 86% for detecting CIN II for the HPV tests and 96.0% for colposcopy. The reason is that we often observed the elimination of dysplasia after some time or even HPV disappearance from the cell, if the infection had been acquired a long time previously. Nevertheless, the HPV test is not recommended for patients with HSIL (NPV of 60%), in contrast to colposcopy, where 100% of cases with a negative colposcopy were confirmed at final diagnosis. The impressive negative predictive values of 92% for CIN I and 96% for CIN II were obtained for both tests performed together. The same result was found in a Greek publication, and a very high NPV of 99.8% was reported in a study from Spain.[13,14] However, we believe that colposcopy performed after a negative DNA HPV test has no application in routine diagnosis because of the additional psychological stress for the patient and the higher cost of diagnosis.

The other diagnostic parameters that we compared in the study were the sensitivity and specificity of the tests for detecting cases with any dysplasia. The specificity of the HPV test (55% for CIN I and 52% for CIN II) results from the detection of a large number of latent HPV infections that disappear after several years and do not cause any abnormal changes. This finding explains why HPV tests are more sensitive (75% for CIN I and 80% for CIN II) than specific: they detect most HPV infections, including those that are not clinically relevant. Previous studies have shown sensitivities ranging from 78% to 93% and specificities from 63% to 81%.[8,11,13-15]

The variance stems from the different HPV tests applied and the detection of different numbers of HPV genotypes. The colposcopy test in our study was more specific (88%) than sensitive (69%) only for detecting CIN I cases because the test detects cervical changes that already exist and demonstrates cervical neoplasia disease. A patient's colposcopy shows a higher sensitivity (75%) than specificity (89%) for finding CIN II lesions. Other studies have reported divergent results of very low sensitivity, e.g., 13%, and a specificity of 99% for detecting CIN II/313 and inverse values of high sensitivity (94%) and limited specificity (50%) for CIN cases.[14] In summary, the HPV test with molecular typing combined with colposcopy proved to be the most efficient combination, increasing the sensitivity to 94% and NPV to 96% in CIN II cases and the PPV to 77% in

CIN I diagnosis, values that are in agreement with other studies.[12,14] These findings also suggest that the screening intervals could be safely made longer for women with a negative HPV test. This is confirmed by other publications showing that primary HPV screening could be the most efficient test in detecting patients at high risk of dysplasia or may be a method to lengthen screen intervals for women with an HPV-negative result.[11,13,16-19]

In the studied population, the overall HPV prevalence was 53.2%. This finding is consistent with the results of previous studies on HPV infection and genotype distribution.[20] The prevalence of HPV in abnormal cytology in Poland is 65.7%, and in some European countries, it is 53.2%.[21,22] This contrasts with a finding from a study in Italy that showed a lower prevalence of 33.8%.23 Among the positive samples, oncogenic genotypes were found in 64.6% of the patients, non-oncogenic types were observed in 19.2% and multiple infections were detected in 16.2% of cases. These findings are similar to the results from studies in the Italian population.[24]

The high-risk types were most frequently observed in patients with LSIL (71.4%) and ASC-H (66.7%), rather than among patients with HSIL (50%). In contrast, studies from the US indicated the following distribution of oncogenic types 50% in patients with ASCUS, 54% in patients with LSIL, and 85% in patients with HSIL.[25,26] However, the positive HPV test correlates well with the end-of-study results, with 78% of patients with CIN III having a high-risk HPV infection and 55.5% being of the HPV 18 type. Concerning the diagnosis of CIN II, we detected 71% of women with HPV infection, mostly of high-risk types. This finding is not consistent with the other published studies that demonstrated that HPV 16 and other high-risk genotypes had the greatest association with CIN 2/3 dysplasia/lesion or cervical carcinoma.[1,25]

HPV 18 was the most prevalent genotype (37%), followed by the oncogenic genotypes HPV 16 (16%) combined infection with both HPV type 18, and 16 (13.5%) and the low-risk types 30, 31and 32 which was 25%. Only 7.5% of cases show infection with both high-risk and low-risk variants and that is mostly seen in CIN II and CIN II groups. Our results were not consistent with those from previous studies in Poland, in which HPV 16 was found to be the most common genotype and HPV 18 was less common.[27-29] A similar HPV distribution has been reported in other European countries, including Italy, Greece, Denmark, Estonia and Latvia.[23,30-33]

CONCLUSION

The efficacy of both colposcopy and the HPV test performed together provides the best diagnostic values for the PPV, NPV and sensitivity, which makes this coupled method highly effective and accurate in detecting mild and severe CIN lesions. Moreover, the HPV test itself, when negative, might improve the identification of healthy women and allow a lengthening of the screening interval in cervical cancer prevention programs. Additionally, we found that HPV 16 was the most prevalent genotype, followed by HPV types 31, 33 and 30. These results are unusual, given the results of previous studies. Further research on a larger scale is required.

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