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ORIGINAL ARTICLE

Complementary Procedures in Cervical Cancer Screening in Low Resource Settings

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Abstract
Objective To evaluate the efficacy of pap smear, HPV DNA testing and colposcopy and to determine the approach for cervical cancer screening in low resource settings.
Methods Eight hundred non pregnant married women above 30 years of age were studied and subjected to pap smear examination. Hysterectomised women were excluded from the study. Selected patients were followed by HPV DNA testing by Hybrid Capture II method, colposcopy and biopsy. Sensitivity, specificity, Positive predictive value (PPV), Negative predictive value (NPV), diagnostic accuracy and kappa value (k) were calculated for each screening test.
Result Out of eight hundred women with mean age 36.5 ± 5.94 years undergoing pap smear, ASCUS was found in 66(8.25%), ASC-H in 2(0.25%), LSIL in 48(6%), HSIL in 8(1%), inflammatory in 540(67.5%). Out of 260 women who underwent HPV DNA testing, 120 (46.15%) had abnormal cytology and/or positive HPV DNA test (Group I, $n = 120$) and 140(53.8%) had dual negative results (Group II, $n = 140$) HPV DNA test was found positive in 64 women (53.3%) in Group I. Sensitivity and specificity of pap smear was 69.2 and 63.72% while for HPV DNA testing was 92.3 and 84% respectively. PPV and NPV of pap smear, HPV DNA testing and colposcopy was 18, 40, 76.4% and 94.7, 98.9, 100% respectively. Diagnostic accuracy of pap smear ($k = 0.14$), HPV DNA test ($k = 0.70$) and colposcopy ($k = 0.81$) was 64.29, 84.9, and 96.8% respectively. Combining pap smear & HPV DNA testing ($k = 0.25$) increased the sensitivity and NPV to 100%.
Conclusion Sensitivity and diagnostic accuracy of HPV DNA test is more than that of pap smear and the test is not influenced by inflammatory conditions of vagina. In low resource settings, women with ASCUS and LSIL on cervical cytology should be subjected to HPV DNA test and only if found positive should be referred for colposcopy thereby reducing colposcopy referrals. Women with HSIL should be directly subjected to colposcopy guided biopsy. Using this approach, most of the preinvasive cervical lesion will be detected but few cases will still be missed among inflammatory smears, if HPV DNA testing is not supplemented.

Keywords HPV testing · Pap smear · Cervical cancer

Introduction

In developing countries, cancer cervix is the most common genital malignancy accounting for 80% of all world cases,

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16% cases are from India. Infection with high risk Human Papilloma virus (HR-HPV) is the major risk factor for the development of cervical cancer. HPV is highly prevalent among sexually active persons and traceable in its natural history with technology that can detect HPV DNA. HPV testing is being evaluated as a potential alternative or adjunctive to cervical cytology for early detection of cervical cancer precursors. This study was done to compare the diagnostic accuracy of pap smear, HPV DNA test by Hybrid Capture II method and colposcopy and to determine an approach for cervical cancer screening that can be used in low resource settings.

Material and Method

Eight hundred non pregnant married women above 30 years of age were enrolled in the study. A detailed history was taken followed by gynecological examination. Hysterctomised women were excluded from the study. Women with clinically apparent vaginitis were first treated and then subjected to study. Four hundred women were subjected to pap smear examination. Out of 800, 260 women underwent HPV DNA testing by HC-II method. Colposcopy was done in women with abnormal cytology and/or a positive high risk HPV DNA test and in a randomly selected sample of 10% women with negative findings on both test. Biopsy was done if colposcopy was found suspicious. Sensitivity, specificity, Positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy and kappa value (k) were calculated for each screening test.

Results

Out of eight hundred women with mean age 36.5 ± 5.94 years undergoing pap smear examination, 124 had abnormal cytology. ASCUS was found in 66(8.25%), ASC-H in 2 (0.25%), LSIL in 48(6%), HSIL in 8(1%) and inflammatory in 540 (67.5%) (Table 1). Fifty (6.25%) smears were reported as unsatisfactory. Out of 260 women who underwent HPV DNA testing, 120(46.15%) had abnormal cytology and/or positive HPV DNA test (Group I, $n = 120$) and 140(53.8%) had dual negative results (Group II, $n = 140$) (Table 2). HPV DNA test was found positive in 64 women (53.3%) in group I. Sensitivity and specificity of pap smear was 69.2 and 63.72% while for HPV DNA testing was 92.3 and 84% respectively. PPV of pap smear was low 18% as compared to 40% of HPV DNA testing. Negative predictive value of pap smear was 94.7% and that of HPV DNA test was 98.9%. Sensitivity and negative predictive value of combined pap smear and HPV DNA test increased to 100%. Biopsy results showed 4 cases of cervicitis, 10 cases of CIN1, 4 cases of CIN 3 and 2 cases of squamous cell carcinoma. The sensitivity of colposcopy was found to be highest 100%. The PPV and negative predictive value of colposcopy was 76.4 and 100% respectively. Diagnostic accuracy of pap smear was 64.29% and k was 0.14 which was in slight agreement with histology. Diagnostic accuracy of HPV DNA test was found to be 84.9% and its kappa value ($K = 0.70$) was in substantial agreement with histology. Diagnostic accuracy of colposcopy was found to be highest 96.8% and its kappa value ($k = 0.81$) was in perfect agreement with histology. Combining pap smear and HPV DNA testing increased the sensitivity and negative predictive value to 100% and its kappa value ($k = 0.25$) was in fair agreement with histology (Table 3).

Table 1 Distribution of women according to cytology

Cytology	Number	Percentage
Normal	86	10.75
Inflammatory	540	67.5
ASCUS	66	8.25
ASC-H	2	0.25
LSIL	48	6
HSIL	8	1
Unsatisfactory	50	6.25
Total	800	100

Discussion

The present study showed the sensitivity of HPV DNA test for diagnosing CIN was 92.3%, specificity 84% and high negative predictive value of 98.9%. Lin et al. [1] and Clavel et al. [2] showed the sensitivity of HPV DNA test to be 100%. Petry et al. [3] calculated test characteristics of HPV DNA test for histologically confirmed CIN3 only and found 100% negative predictive value. Kappa value calculated for HPV DNA test was 0.70 in the present study which is similar to that of the study of Kumar et al. [5] who found kappa value to be 0.67. Ratnam et al. [4] found sensitivity of pap smear 45% and specificity 64% which is similar to present study. Clavel et al. [2] and Kumar et al. [5] found sensitivity of combined pap and HPV DNA test 93.3% and negative predictive value of combined test to be 98.8% which is similar to our study. HPV testing in conjunction with cytology improves the screening efficacy of cytology alone and may allow for a more effective and safe primary screening programme with increased screening interval.

Table 2 Distribution of women in groups according to pap smear and HPV DNA test results and their follow up by colposcopy and biopsy

Colposcopic impression							Biopsy			
Study Group	Negative	CIN 1	CIN 2	CIN 3	Malignancy	Cervicitis	CIN 1	CIN 2	CIN 3	SCC
IA Pap +ve and HPV +ve										
ASCUS	16	–	2	–	–	–	–	2	–	–
ASC-H	–	–	–	2	–	–	–	–	2	–
LSIL	10	2	6	2	–	4	–	6	–	–
HSIL	2	–	2	2	2	–	–	2	2	2
IB Pap +ve and HPV −ve										
ASCUS	34	–	–	–	–	–	–	–	–	–
ASC-H	–	–	–	–	–	–	–	–	–	–
LSIL	14	4	–	–	–	2	2	–	–	–
HSIL	–	–	–	–	–	–	–	–	–	–
IC Pap −ve and HPV +ve										
Inflammatory	2	8	2	–	–	2	6	2	–	–
Total	78	14	12	6	2	8	8	12	4	2

Table 3 Test characteristics of cytology, HPV testing, colposcopy and combined cytology-HPV testing

Test diagnostic	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	*k*
Pap smear	69.2	63.72	18	94.7	64.29	0.14
HPV DNA test	92.3	84	40	98.9	84.9	0.70
Colposcopy	100	96.4	76.4	100	96.8	0.81
Combined cytology + HPV DNA test	100	61.9	23.2	100	65.8	0.25

Conclusion

Pap smear, HPV DNA testing and colposcopy are complementary to each other for detecting preinvasive cervical cancer. Sensitivity and negative predictive value of HPV DNA test is more than that of pap smear and the test is not influenced by inflammatory conditions of vagina. Women with preinvasive cervical cancer which are not diagnosed by pap smear are detected by HPV DNA test with accuracy. Diagnostic accuracy of HPV DNA test is quite high 84.9% and kappa value is in substantial agreement with histology ($k = 0.70$). HPV DNA test should be used in conjunction with pap smear test wherever feasible and affordable. Pap's smear is a cost effective screening method in low resource settings. Women with ASCUS and LSIL on cervical cytology should be subjected to HPV DNA test and if found positive should be referred for colposcopy thereby reducing colposcopic referrals. Women with HSIL should be directly subjected to colposcopic guided biopsy. Using this approach most of the preinvasive cervical lesion will be detected but few cases will still be missed among inflammatory smears, in case where HPV DNA testing is not supplemented.

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