RESEARCH ARTICLE

Comparative analysis of HPV DNA and LBC for screening of cervical cancer in women with unhealthy cervix

Shreya Raj, Mala Srivastava

Corresponding author: Dr. Shreya Raj, Senior resident at Dr Baba Saheb Ambedkar Medical College and Hospital, New Delhi, India; Email : raj.shreya@yahoo.com

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ABSTRACT

Background: The cervical cancer is one of the leading cause of cancer death among women in developing and developed countries. Screening for cervical cancer is essential as the women are often asymptomatic and it also reduces both the incidence and mortality of the cancer cervix if detected in early stage. **Objectives:** We aimed to determine sensitivity and specificity of liquid based cytology (LBC) and HPV DNA to detect pre-neoplastic and neoplastic lesions of cervix. **Methods:** This was a prospective observational study including 506 women of reproductive, perimenopausal and postmenopausal age group who presented with abnormal vaginal discharge, post coital bleeding, abnormal uterine bleeding, postmenopausal bleeding or had unhealthy cervix on examination, who were subjected to screening by doing LBC and HPV DNA testing. The diagnosis of LBC and HPV DNA was compared against the gold standard of cervical biopsy. The data was entered in MS Excel and analysed using SPSS ver 21.0. A $p < 0.05$ was considered as significant. **Results:** The mean age of patients in the study was 43.36 years. The sensitivity and specificity of LBC was 76.47%, 43.85%, and that of HPV DNA was 88.23%, 57.89%. The co-testing of LBC and HPV-DNA had a sensitivity and specificity of 94.11% and 24.56%. Discriminatory power of LBC (AUC 0.6; 95% CI: 0.48 to 0.71) and HPV DNA (AUC 0.73; 95% CI: 0.61 to 0.83) was acceptable. Among all the parameters, HPV DNA was the best predictor of pre-invasive or invasive lesion with 73.00% chances of correctly predicting pre-invasive or invasive lesion. **Conclusion:** Though the early detection and treatment of pre-invasive and invasive lesion of cervix is required, it is important that the best and most sensitive diagnostic tools are used for the screening purposes. Overall HPV DNA was best predictor of pre-invasive or invasive lesion with significantly higher diagnostic accuracy as compared to co-testing.

Keywords: Cervical cancer, liquid based cytology, HPV DNA.

The cervical cancer is a leading cause of cancer death among women, resulting in major cause of mortality and morbidity¹. It is the second most common cancer in women of less developed countries with nearly 570,000 new cases in 2018 (84% of the new cases worldwide)². Cervical cancer screening has been advocated considering that it may reduce the mortality and morbidity associated with the cancer³⁻⁶. A plethora of screening techniques have been applied which include pap smear, liquid based cytology (LBC) and human papilloma virus (HPV) testing⁷. The variation in quality of the conventional pap smear is quite substantial and this might influence the detection rate of high grade CIN, hence,

LBC has been introduced. In addition, LBC carries the advantages of faster reporting, less missing out of cases and application of HPV testing from the remnant fluid⁷.

The history of LBC dates back to 1996, when Thin Prep® was first approved by US Food and Drug Administration (USFDA)⁸. Since then it has gained popularity in terms of clinical benefit/versatility and is now used in over 90% cases in USA;⁹ however, it also suffers from false negative results in a small proportion.

To further serve the purpose, HPV DNA testing (molecular based studies) have shown better sensitivity in identifying the risk of cervical cancer^{10,11}. The use of HPV

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testing as a primary screen has shown promise in developing countries but remains experimental due to its high cost ^{12,13}. High risk HPV screening is highly sensitive, but specificity depends on subsequent evaluation strategies and screening frequencies ¹¹⁻¹⁴.

The present study aims to evaluate and compare the efficacy of LBC and HPV as a screening modality in diagnosing the pre-invasive and invasive lesions of cervix. The study results may help guide the use of HPV DNA testing as an additive for cervical cancer screening.

Methods

This prospective observational study was conducted for duration of 18 months. A total of 506 women of reproductive, perimenopausal, and postmenopausal age group with unhealthy cervix and who presented with the complaints of abnormal vaginal discharge, postcoital bleeding, abnormal uterine bleeding, and postmenopausal bleeding were included after obtaining an informed consent. Pregnant women and hysterectomized patients were excluded from the study.

A detailed history of the women including age, age at first sex and marriage, family history, socioeconomic history and personal history (hygiene and addictions to drugs), presenting complaints, obstetric outcome, marital history/ number of sexual partners, use of contraceptives were taken.

After obtaining the history, a general physical examination and systemic examination was carried out. Per speculum examination was performed to note any abnormality on direct visual inspection of the cervix without magnification. For each women, LBC and HPV DNA testing was done.

LBC reporting was done by modified Bethesda system (2001). Cytology was considered positive if it revealed any of the following lesions - atypical squamous cells of undetermined significance (ASCUS) and ASC-H, low grade squamous intraepithelial lesions (LSIL), high grade squamous intraepithelial lesions (HSIL) or cells suspicious of malignancy. Negative smears included those with normal and inflammatory report.

HPV DNA testing was done by hybrid capture testing (principle of chemiluminescence). Sure path hybrid capture II technique was used for detection for high risk HPV DNA (16,18, 31, 33, 35, 39, 45, 51, 52, 56,58,59,68). Clinical interpretation of HPV results was done on the basis of relative light units (RLU).¹⁴ The report was expressed as negative HPV- RLU/ cut off ratio <1.0; positive HPV- RLU/ cut off >1.0; 1RLU= 5000 copies of DNA. Histopathology/cervical biopsy was taken as the gold

standard for cervical cancer for comparison of the findings of LBC and HPV DNA.

Statistical analysis: Categorical variables were presented in number and percentage (%). Qualitative variables were associated using Chi-Square test/Fisher Exact test. Diagnostic accuracy was compared using Chi square test. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spread sheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Table 1 shows the sociodemographic profile of the patients. Majority of the patients (22.10%) were 36-40 years of age, followed by 20.80% patients each in age groups 41-45 and 46-50 years. Most of the patients were para 2 (50.60%), followed by para 3 (28.50%), and para 1 (9.90%).

Table 1: Distribution of socio-demographic characteristics.

Socio demographic characteristics	Number	Percentage
Age		
22-25 years	3	0.60%
26-30 years	25	4.90%
31-35 years	63	12.50%
36-40 years	112	22.10%
41-45 years	105	20.80%
46-50 years	105	20.80%
>50 years	93	18.40%
Parity		
P0	2	0.40%
P1	50	9.90%
P2	256	50.60%
P3	144	28.50%
P4	48	9.50%
P5	4	0.80%
P6	2	0.40%
Class		
I	2	0.40%
II	11	2.20%
III	75	14.80%
IV	223	44.10%
V	195	38.50%
Age at marriage		
17-20 years	130	25.70%
21-25 years	332	65.60%
26-30 years	44	8.70%
31-35 years	0	0.00%
>35 years	0	0.00%
Method		
None	214	42.30%
Barrier	112	22.10%
Ligation	111	21.90%
Intra uterine contraceptive device	36	7.10%
Oral contraceptive pill	33	6.50%
Vasectomy	0	0%

65.6% patients were 21-25 years of age at the time of marriage (table 1). Method of contraception was barrier in 22.10% patients, ligation in 21.90%, intrauterine

contraceptive device in 7.10%, and oral contraceptive pill in 6.50% patients.

Table 2: Distribution of clinical examination findings.

Clinical examination findings	Number	Percentage
Clinical sign		
Cervical ectropion	131	25.88%
Hypertrophy	427	84.38%
Nabothian follicles	25	4.94%
Cervical polyp	10	1.97%
Ulcer	0	0
Leukoplakia	0	0
Growth over cervix	2	0.39%
P/V examination		
Normal	55	10.86%
Multiparous size	336	66.40%
Uterus 8- 10 weeks size	99	19.56%
Uterus 10-12 weeks size	3	0.59%
Uterus 12-14 weeks size	7	1.38%
Uterus > 14 weeks size	6	1.18%

Table 3: Distribution of diagnosis findings.

Diagnosis findings	Number	Percentage
Cytological diagnosis		
Normal	211	41.69%
Inflammatory	246	48.61%
ASCUS	25	4.94%
ASC-H	4	0.79%
LSIL	6	1.18%
HSIL	6	1.18%
AGUS	2	0.39%
Endometrial cell	4	0.79%
Cancer	2	0.39%
Result		
hrHPV DNA positive	39	7.70%
hrHPV DNA negative	467	92.29%
Appearance		
Normal	23	31.08%
Acetowhite area	45	60.81%
Mosaic/ Punctuation	3	4.05%
Abnormal vessels	4	5.40%
Rolled margins	0	0.00%
Iodine negative area	40	54.05%
unsatisfactory	4	5.40%
Microscopic observation		
Normal	0	0.00%
Chronic cervicitis	57	77.02%
CIN – I	6	8.10%
CIN – II	2	2.70%
CIN – III	3	4.05%
Carcinoma in situ	1	1.35%
Invasive cancer	5	6.75%

ASCUS - Atypical squamous cells of undetermined significance, ASC-H - Atypical squamous cells – high grade, LSIL - Low grade squamous intraepithelial lesions, HSIL - high grade squamous intraepithelial lesions, CIN – Cervical intraepithelial neoplasia.

The presenting symptoms included discharge per vaginam in 43.87% patients, low back pain/pain in lower abdomen in 43.67% patients, and AUB in 35.37% patients

(figure 1). On clinical examination, hypertrophy, cervical ectropion, nabothian follicles, cervical polyp, and growth over cervix were present in 84.38%, 25.88%, 4.94%, 1.97%, and 0.39% patients, respectively. Per vaginal examination revealed uterus was multiparous size in 66.40%, 8- 10 weeks size in 19.56%, 10-12 weeks size in 0.59%, 12-14 weeks size in 1.38%, and > 14 weeks size in 1.18% patients (table 2).

Figure 1: Distribution of presenting symptoms

On LBC, out of 461 negative reports 211 were reported as normal and 246 as inflammatory and 4 as endometrial cells. Among 45 abnormal reports, 4.94% were ASCUS, 1.18% were LSIL, 1.18% were HSIL, 0.79% were ASC-H, 0.39% were AGUS, and 0.39% were found to have cancer. HPV DNA was negative in majority of the cases (92.29%) and only 39 (7.7%) were found to be HPV DNA positive.

Colposcopy was performed in 74 women who presented with persistent vaginal discharge, or post coital bleeding or were positive on LBC or HPV DNA or both. Normal findings were reported in 23 (31.08%) and rest were abnormal, most common abnormality being acetowhite area (60.81%) and iodine negative area (54.05%). Maximum number of women (77.02%) had chronic cervicitis. CIN I was reported in 8.10%, CIN II in 2.70%, CIN III in 4.05% women. There was 1 patient (1.35%) with carcinoma in situ and 5 women (6.75%) with invasive carcinoma (table 3).

There was a significant association between LBC and HPV. Compared to HPV negative cases, HPV positive cases had significantly less cases that were normal/inflammatory (13 vs. 444, $p < 0.0001$) and low grade (15 vs. 16, $p < 0.0001$); but significantly more cases with high grade cervical lesions (8 vs. 2, $p < 0.0001$) and cancer (2 vs. 0, $p = 0.006$) (table 4).

There was a significant association between microscopic observation and HPV. Compared to HPV negative cases, HPV positive cases had significantly less chronic cervicitis cases (24 vs. 33, $P < 0.0001$), but significantly more CIN I cases (5 vs. 1, $p < 0.0001$), CIN-II (5 vs. 0, $p < 0.0001$), and cancer (5 vs. 1, $p < 0.0001$) (table 5).

Table 4: Association of LBC and HPV

LBC	Number of HPV positive cases (N=39)	Number of HPV negative cases	P value
Normal/Inflammatory	13	444	<.0001
Low grade	15	16	<.0001
High grade	8	2	<.0001
Cancer	2	0	0.006
Endometrial cells	1	5	0.383

Discriminatory power of LBC (AUC 0.6; 95% CI: 0.48 to 0.71) and HPV DNA (AUC 0.73; 95% CI: 0.61 to 0.83) was acceptable. Among all the parameters, HPV DNA was the best predictor of pre-invasive or invasive lesion with 73.00% chances of correctly predicting pre-invasive or invasive lesion.

Table 5: Association of microscopic observation and HPV

Microscopic observation	No. of HPV positive cases	No. of HPV negative cases	P value
Chronic cervicitis	24	33	<.0001
CIN I	5	1	<.0001
CIN – II	5	0	<.0001
Cancer	5	1	<.0001

Table 6: Sensitivity, specificity, NPV and PPV of LBC, HPV DNA and co-testing to predict pre-invasive or invasive lesion and comparison of their diagnostic accuracy.

Parameters	LBC	HPV DNA	Co-testing (LBC and HPV DNA)
Sensitivity (95% CI)	76.47% (50.10% to 93.19%)	88.24% (63.56% to 98.54%)	94.12% (71.31% to 99.85%)
Specificity (95% CI)	43.86% (30.74% to 57.64%)	57.89% (44.08% to 70.86%)	24.56% (14.13% to 37.76%)
AUC(95% CI)	0.6 (0.48 to 0.71)	0.73 (0.61 to 0.83)	0.59 (0.47 to 0.71)
Positive Predictive Value (95% CI)	28.89% (16.37% to 44.31%)	38.46% (23.36% to 55.38%)	27.12% (16.36% to 40.27%)
Negative Predictive Value (95% CI)	86.21% (68.34% to 96.11%)	94.29% (80.84% to 99.30%)	93.33% (68.05% to 99.83%)
Diagnostic accuracy	51.35%	64.86%	40.54%
LBC vs HPV DNA	0.134		
LBC vs Co-testing	0.248		
HPV DNA vs Co-testing	0.005		

Co-testing (LBC and HPV DNA) had sensitivity of 94.12% followed by HPV DNA (88.24%), LBC (76.47%). In prediction of pre-invasive or invasive lesion, LBC had lowest sensitivity of 76.47%. On the other hand, HPV DNA had specificity of 57.89% followed by LBC (43.86%), and co-testing (24.56%). In prediction of pre-invasive or invasive lesion, co-testing had lowest specificity of 24.56%.

The positive predictive value (38.46%) and negative predictive value (94.29%) was highest for HPV DNA testing. There is always a trade-off between sensitivity and specificity (any increase in sensitivity will be accompanied by a decrease in specificity). So we choose that variable as best in which combination of sensitivity and specificity gives

the maximum predictive value i.e. maximum diagnostic accuracy. So overall HPV DNA was best predictor of pre-invasive or invasive lesion with significantly higher diagnostic accuracy as compared to co-testing (table 6).

Discussion

The application of screening programs has brought down the incidence and mortality of cervical cancer in some developed countries^{15, 16}. However among developing countries, reports have been conflicting¹⁷⁻¹⁹. On evaluating performance of screening programs for cervical cancer in various countries, it became evident that the service capability of health care facilities in different regions, laboratory test conditions, the number of cytological readers, and acceptance as well as satisfaction of population with screening methods influence the efficacy of large scale screening of population¹⁹⁻²².

LBC has been developed to address the sampling problems of conventional pap smear²³. A high false negative rate has increased the problems inherent in cytological screening. Molecular techniques have been required to reduce the false negative rate, identify the earlier stages of infection and thus, improve follow up because most infections are not microscopically evident²⁴. The widely used alternative for cervical cancer screening is HPV DNA

testing which identifies women with papilloma virus infections. The present study was conducted to compare HPV DNA and LBC for screening of cervical cancer in women with unhealthy cervix.

Median age of screened population in present study was 43.36 years, which co-related well with the study of Karimi Zarchi et al²⁵ and Ronco et al²⁶ where median age was 42 and 45 years respectively.

Multiparity is a known risk factor of cervical cancer which may be attributable to nutritional and hormonal changes occurring in pregnancy, immune suppression in pregnancy, and cervical trauma during vaginal delivery²⁷. In present study, majority were multiparous, mean parity being

2.40, which co-related well with the study of Suguna M et al²⁸ as most of the patients were multiparous.

There is a definite co-relation between early age at intercourse and cervical carcinogenesis as evident in a meta-analysis²⁹. In our study maximum number of patients 332 (65.60%) had their marriage (i.e first sexual debut) between 21-25 years of age. Findings of present study were in accordance with the study of Zhao H et al³⁰ with respect to the mean age at marriage (21.77 years).

In present study, maximum number of patients (42.3%) did not use any method of contraception, 22.1% patients were using barrier method, and 21.9% were ligated. Ashmita D et al³¹ also showed that maximum numbers of patients were not using any contraceptive and 6.5% were on OCP.

Women with cervical cancer may be asymptomatic or they may present with symptoms like excessive vaginal discharge, foul smelling discharge, irregular or inter menstrual bleeding, post coital bleeding or postmenopausal bleeding. Majority of the patients (43.87%) presented with discharge per vaginum followed by 43.67% with low backache and pain lower abdomen. Suguna M et al²⁸ and Gopal N et al²⁷ reported similar findings as white discharge as their major symptom. Other common symptoms were irregular bleeding and postcoital bleeding.

Shankaranarayana et al³² stated that visual inspection of the cervix is an art, neglected in the recent years in reference to cytological screening, which will reveal characteristic signs of early lesions of dysplasia. In present study, 84.38% patients had hypertrophied cervix followed by 25.88% with cervical ectropion. Shankaranarayana et al³² found that cervicitis was the most common finding and Gopal N et al²⁷ reported that maximum number of patients had ectropion.

Between the two common methods of screening of cervical cancer (LBC and HPV DNA), American Society for Colposcopy and Cervical Pathology (ASCCP) recommends combination screening rather than use of either alone³³. Thereby we assessed and compared the individual methods along with the combination of methods to find the better accuracy among them.

In the present study, 91.10% patients were negative on cytology, 4.94% had ASCUS, 1.18 % had LSIL, 1.18% had HSIL, 0.79% had ASC-H, and 0.39% had AGUS. These findings are in accordance with Junyangdikul P et al²⁴ where 87.96% patients were negative on cytology, 4.80% had ASCUS, 1.07 % had HSIL, and 0.77% had ASC-H. Similarly, Agorastos T et al³⁴ found negative on cytology in 94.7% patients, 1.9% had LSIL, and 0.4% patients had AGUS.

In the present study, 7.70% women tested positive for high risk HPV as tested by DNA hybrid capture II technique. Present study co-related well with the study of Ronco et al²⁶, Ogilvie GS et al³⁵ and Zhao FH et al³⁰ with respect to the prevalence of HPV DNA infection.

In the present study, 74 patients underwent colposcopic examination. Screen-positive subjects and screen-negative patients with persistent vaginal discharge and postcoital bleeding were subjected to colposcopic evaluation. About 31.08% patients had normal colposcopy, aceto-white area was found in 60.81%, and iodine negative area in 54.05% patients. There was more than one colposcopic finding in some of the patients. Present study was comparable to the study of Ramesh G et al³⁶ with respect to the colposcopic findings. Maximum number of patients had aceto-white area as an abnormal finding on colposcopy.

Present study co-related well with the study of Gopal N et al²⁷ where CIN I was present in 8.10%, and CIN II and CIN III in 2.70% and 4.05% respectively. Present study was also in accordance with the study of Suguna et al²⁸ and Pravin S et al³⁷ with respect to histopathological diagnosis of invasive cancer which in our study was 6.75%.

A significant association was observed between LBC and HPV as among normal/inflammatory cases, 2.84% (13/457) were HPV positive; in low grade, 48.39% (15/31) were HPV positive; among High grade, 20% (2/10) were HPV positive; 2 cancer cases were HPV positive; and out of 6 Endometrial cells, 1 was HPV positive and 5 HPV negative. A significant association was also found between microscopic observation and HPV as in chronic cervicitis cases, 42.1% (24/57) were HPV positive; in 6 CIN I cases, 5 were HPV positive; all 5 CIN – II cases were HPV positive; and among 6 cancer cases, 5 were HPV positive and 1 HPV negative. Ma Y et al,¹⁹ included total 9,972 cases with cervical cancer and found that the overall prevalence of positive results by HPV and LBC was 7.5% and 3.1%, respectively. There were statistically significant differences in the total detection rate of CIN2+ between LBC and HPV groups (P = 0.007). In study by Wang J et al,³⁸ positive result was shown by LBC in 32.9% and HPV in 37.8% cases. Total 1178 patients had cervicitis or other benign lesion; LBC and HPV showed positive results in 9.4% and 13.4% cases, respectively. LBC and HPV showed positive results in 64.9% and 71.9% cases, respectively in total 473 cases of CIN1, in 81.8% and 89.8% cases, respectively in total 137 cases of CIN2, in 92.9% and 95.2% cases, respectively in total 84 cases of CIN3, and all 12 cases of cervical carcinoma were positive on LBC and

HPV. There was a significant association between LBC and HPV.

In the present study, sensitivity, specificity, AUC, PPV, NPV, and diagnostic accuracy for LBC were 76.47%, 43.86%, 0.6, 28.89%, 86.21%, and 51.35%; for HPV DNA were 88.24%, 57.89%, 0.73, 38.46%, 94.29%, and 64.86%; and for co-testing (LBC and HPV DNA) were 94.12%, 24.56%, 0.59, 27.12%, 93.33% and 40.54%. The sensitivity and specificity of HPV test was higher compared to that of LBC and with the combination of both sensitivity was increased but specificity was much reduced. Among other studies, Wang J et al,³⁸ found that sensitivity, specificity, AUC, PPV, NPV, and diagnostic accuracy for LBC were 86.7%, 74.7%, 0.807, 32.6%, 97.5%, and 74.7%; for HPV DNA were 92.3%, 69.8%, 0.810, 30.2%, 98.5%, and 72.6%; and for co-testing (LBC and HPV DNA) were 98.7%, 60.8%, 0.797, 65.4%, 26.2% and 99.7%. The sensitivity of HPV test was higher compared to that of LBC; however, specificity was lesser than that of LBC. This implies that HPV test was better in detecting cervical lesions, but the false positive rate might be greater compared to that of LBC, which was in agreement with the current screening experiences at home as well as abroad.³⁹ Their study also showed that sensitivity of combination of LBC plus HPV was moderate 80.7%, but the specificity and accuracy (83.5% and 83.1%) were the highest in comparison to LBC and HPV; similar results being reported in a meta-analysis by Lim KM et al.⁴⁰ This creates an enigma about the use of combination of LBC plus HPV. And also the use of both the tests for screening may entail more economic burden on the society.³³ However, future researches are warranted for the same.

One of the limitations of the study was that patients included in the study had higher risk of cervical cancer compared to the general population, due to which it was unable to assess overdiagnosis of cervical precancers or probabilities of their progression.

Conclusion

The addition of high risk HPV DNA improved the sensitivity of LBC significantly. Co-testing was found to have the highest sensitivity (98.80%) in predicting preinvasive and invasive lesion of cervix but the specificity was much reduced. Though the early detection and treatment of preinvasive and invasive lesion of cervix is required, it is important that the best and most sensitive diagnostic tools are used for the screening purposes. Overall HPV DNA was best predictor of pre-invasive or invasive lesion with

significantly higher diagnostic accuracy as compared to co-testing.

Conflict of interest: None. **Disclaimer:** Nil.

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Shreya Raj¹, Mala Srivastava²

¹ Senior resident at Dr Baba Saheb Ambedkar Medical College and Hospital, New Delhi, India; ² Senior Consultant, Department Of Obstetrics and Gynaecology, Sir Ganga Ram Hospital, New Delhi, India.