Cytology compared with Hybrid Capture 2 human papilloma virus cervical cancer screening in HIV positive and HIV negative South African women

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ABSTRACT

Objectives: Cervical cancer is preventable and caused by persistent infection with oncogenic human papilloma virus (HPV) types. HPV screening is more sensitive and is the preferred screening test. HPV screening data are mainly from developed settings, and the purpose of this study was to investigate the performance of HPV screening in previously unscreened HIV positive and negative women.

Methods: In this cross sectional multicenter study, liquid based cytology and HPV testing were performed on women attending different clinics. Patients with positive screening tests had colposcopy and biopsy or large loop excision of the transformation zone. Some women with normal screening had colposcopy and biopsy. Data of women with histology results, and data of HIV positive and negative women were analyzed for comparison. For women without histology results, data were imputed using a statistical model.

Results: In 903 women with known HIV status, 683 (75.6%) had negative cytology, 202 women (22.4%) had abnormal cytology, and in 18 patients (2.0%) the results were uncertain. Mean age was 41.4 years (range 25–65). HPV tests were negative in 621 women (68.8%). In HIV positive women, 54.5% tested negative compared with 79.7% HIV negative women ($p<0.0001$). HPV screening had higher sensitivity (60.9%), but lower specificity (82.4%), compared with cytology (48.6% and 86.7%) for detection of cervical intraepithelial neoplasia (CIN) 2+ in all women. For detection of CIN 3+, HPV screening had higher sensitivity (70.4%) compared with cytology (62.9%), and specificity (75.5%) was lower compared with cytology at a threshold of atypical squamous cells of undetermined significance (ASCUS+) (82.4%).

Conclusion: HPV screening was more sensitive than cytology in HIV positive and HIV negative women, but specificity was lower. Although HPV screening should be the preferred screening test, cytology is a suitable screening test in HIV positive women in low resource settings.

Trial registration number: NCT02956031.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Human papilloma virus (HPV) is recommended as the primary screening test for cervical cancer because it has much higher sensitivity than cytology screening.

WHAT THIS STUDY ADDS

⇒ This study did not confirm the same sensitivity and other metrics of HPV as a primary screening test in women with HIV infection and a high prevalence of HPV infection, and different test metrics in the two HIV populations were found.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ More research is indicated in unscreened women from low resource settings. This study provides information on the screening test performance of HPV and cytology in different HIV populations.

INTRODUCTION

The incidence of cervical cancer varies in different regions of the world. The age standardized rate for newly diagnosed cervical cancer per 100 000 women worldwide is estimated to be 13.1.[1] The age standardized rate in South Africa is 22.92, making it the second most common cancer in women after breast cancer.[2] Sub-Saharan Africa has the largest burden of human papilloma virus (HPV) related disease.[1] Primary prevention with a vaccine against HPV 16 and 18 is effective in substantially reducing the risk of developing invasive cervical carcinoma.[3] Secondary prevention also substantially reduces the risk of developing cervical cancer, and the risk of death from cancer.[4]

It is widely accepted that cervical cytology screening is effective in reducing the incidence of cervical cancer.[5–7] The sensitivity of cervical cytology screening ranges from 30% to 78%, and specificity from 86% to 100%.[7] HPV screening for cervical cancer is a more effective strategy than cytology, providing 60–70% more protection against invasive carcinoma.[8] Although the reported sensitivity of HPV screening is much better than that of cytology at around 96%, specificity is poorer (about 90%).[9]

More than eight million people in South Africa are living with HIV.[10] The detrimental effects of HPV infections in HIV infected women are well known. Women living with HIV have more high risk HPV (hrHPV) types, and lower regression and higher progression rates of infection.[11] HPV screening studies in women living with HIV have shown similar sensitivity and specificity compared with HPV screening in HIV negative women.[12–15]

The current unimplemented screening policy in South Africa is liquid based cytology screening every 10 years in HIV negative women (ages 30, 40, and 50), and 3 yearly in women living with HIV after diagnosis.[16] The aim of this study was to investigate the sensitivity, specificity, positive predictive value, and negative predictive value of cytology and HPV DNA screening in

women living with HIV and HIV negative women. This might impact the cervical cancer screening policy in South Africa and other similar populations.

METHODS

Women recruited for this study were part of the larger Diagnostic Vaccine and Cervical Cancer Screen (DiaVACCS) initiative, investigating different screening and triage strategies for women who do not have the advantage of population based cervical cancer screening. Patients attending various clinics at Steve Biko Academic Hospital and Kalafong Provincial Tertiary Hospital in the Gauteng Province, and Tygerberg Academic Hospital in the Western Cape Province of South Africa, were recruited to the study. The detailed methods section has been published and will be summarized below.[17]

Women with negative HIV or unknown status were recruited from the general population. Women living with HIV were recruited from clinics providing dedicated antiretroviral treatment. Informed consent was obtained from all participants after counseling. Women aged ≥25 and ≤ 65 years, requiring cervical cancer screening were recruited. Exclusion criteria included current pregnancy, hysterectomy, current or previous cervical cancer treatment, and known cervical cancer screen result in the previous 5 years.

Cervical samples were collected during speculum examination with cervical collecting brushes. Liquid based cytology was performed on all specimens. All specimens were tested for the presence of high risk HPV DNA using the digene Hybrid Capture 2 (HC2) HPV DNA test (QIAGEN, Germantown, USA). HC2 qualitatively detects 13 oncogenic HPV types (ie, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) through cross hybridization of a specific HPV RNA probe with the HPV DNA.[18] HC2 is widely considered the preferred screening test against which other HPV DNA tests are measured.[19, 20] The assay is automated and performed on the Rapid Capture system.[21]

Patients who had abnormal cytology (atypical squamous cells of undetermined significance, ASCUS+), and those who tested positive with HC2, were referred for colposcopy and punch biopsy or large loop excision of the transformation zone according to the unit protocol. A sample of screen negative women underwent colposcopy examination and punch biopsy regardless of colposcopy findings to comprise a negative control group. Histology results were available to healthcare providers providing treatment according to the respective unit protocols to these women.

Data from all women with histology results, as well as data from women living with HIV and HIV negative women, were analysed separately for comparison. Means were compared using the unpaired t test. The $\chi 2$ test was used to compare proportions. Results were stratified according to CD4 count results. The performances of cervical cytology and HC2 results were evaluated against the final histology results. The total number of tests conducted and percentage positive tests were calculated as descriptive statistics for test performance. For patients who did not have histology reports, results were imputed using a statistical model which maintained the underlying distribution of the available results, to allow calculation of the test performance for the total screening population compared with histology results. For each screening test (cytology and HC2) sensitivity, specificity, and positive and negative

predictive values using histological outcome of cervical intraepithelial neoplasia (CIN) 2+ were calculated for the whole population making use of the statistical prediction model described above. Sample size, prevalence, specificity, 1–specificity (for the receiver operating characteristic curves), sensitivity, positive predictive value, negative predictive value, and percentage agreement were the test metrics used to compare each test with the chosen gold standard.

RESULTS

Data were available for 909 women. Mean age of the study population was 41.4 years (standard deviation (SD) 9.8, range 25–65). The HIV status of six women (0.7%) was unknown and these women were excluded from the analysis. A total of 512 women (56.3%) were HIV negative and 391 (43.0%) women were HIV infected. Mean age of the HIV negative study population was 41.8 years (SD 10.8, range 25–65) and 41.0 (SD 8.3, range 25–64) for women living with HIV (p=0.2).

In 903 women with known HIV status, 683 (75.6%) had negative cytology, 202 (22.4%) had abnormal cytology, and in 18 patients (2.0%) the results were uncertain due to the absence of sufficient epithelial cells. In 885 women, HIV status was known and cytology results were classifiable. In 126 women living with HIV (33.2%), cytology was abnormal, compared with 76 (15.0%) HIV negative women. HC2 HPV test results were available for 903 women. The differences between cytology and HPV tests were highly statistically significant, with cytology reporting a higher proportion of normal smears in women living with HIV as well as HIV negative women. These results are shown in Table 1.

Table 1 Cytology results and human papilloma virus test results

	Cytology (n=885)		HIV positive (n=380)		HIV negative (n=505)		
	No	%	No	%	No	%	P value
NILM	683	77.2	254	66.8	429	85.0	<0.0001
ASCUS	52	5.9	17	4.5	35	6.9	0.1
ASC-H	24	2.7	12	3.2	12	2.4	0.5
LSIL/CIN 1	34	3.8	25	6.6	9	1.8	0.0002
HSIL/CIN 2/3/AGUS	83	9.4	63	16.6	20	4.0	<0.0001
Malignancy	9	1.0	9	2.4	0	0	0.005
HPV test (n=903)			(n=391)		(n=512)		
Negative	621	68.8	213	54.5	408	79.7	<0.0001
Positive	282	31.1	178	45.5	104	20.3	

AGUS, atypical glandular cells; ASC-H, atypical squamous cells, cannot exclude HSIL; ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; HSIL, high grade squamous intraepithelial lesion; LSIL, low grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion.

Cytology, HPV test results, and histology results were available for 568 women. In this group, 285 women (50.2%) were HIV negative, 280 (49.3%) were HIV positive, and the status of three patients (0.5%) was unknown. Mean age of women living with HIV was 40.8 years, and 40.9 years for HIV negative women (p=0.8).

The unadjusted cytology and HC2 screening results for this subgroup (excluding 10 women with uncertain cytology) as well as the HIV groups are shown in Table 2. Less women living

with HIV had normal cytology results compared with HIV uninfected women. HIV negative women had more ASCUS, while women living with HIV had more low grade and high grade squamous intraepithelial lesions. The proportion of women with normal cytology was significantly higher for the whole population (77.2%) compared with the population of women with histology results (65.5%) ($p<0.0001$). Due to verification bias, differences in negative HPV test results between the study population and the subset of women with histology results (68.8% vs 55.1%; $p<0.0001$) were statistically significant.

Table 2 Unadjusted cytology results of women with histology

Women with histology			HIV positive (n=280)		HIV negative (n=285)		
Cytology (n=568)	No	%	No	%	No	%	P value
NILM	372	65.5	159	56.8	212	74.4	<0.0001
ASCUS	48	8.5	15	5.4	32	11.2	0.01
ASC-H	24	4.2	11	3.9	12	4.2	0.9
LSIL/CIN 1	33	5.8	24	8.6	9	3.2	0.006
HSIL/AGUS/CIN 2/3	82	14.4	62	22.1	20	7.0	<0.0001
Malignancy	9	1.6	9	3.2	0	0	0.002
HPV test (n=568)							
Negative	313	55.1	120	42.9	191	67.0	<0.0001
Positive	255	44.9	160	57.1	94	33.0	<0.0001

AGUS, atypical glandular cells; ASC-H, atypical squamous cells, cannot exclude HSIL; ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; HSIL, high grade squamous intraepithelial lesion; LSIL, low grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion.

The unadjusted histology results of the study population with the HIV group comparisons are shown in Table 3. Although HIV negative women had more CIN 1, women living with HIV had significantly more CIN 3 compared with HIV negative women.

Table 3 Unadjusted and verification bias adjusted histology results

Unadjusted study population n=575			HIV positive (n=287)		HIV negative (n=285)		
	No	%	No	%	No	%	P value
NILM	205	35.7	91	31.7	113	39.7	0.05
CIN 1	155	27.0	64	22.3	90	31.6	0.01
CIN 2	108	18.8	61	21.3	47	16.5	0.2
CIN 3	93	16.2	62	21.6	30	10.5	0.0005
ICC	11	1.9	7	2.4	4	1.4	0.4
Other	3	0.5	2	0.7	1	0.4	0.6
Verification biased adjusted study population			**HIV positive**		**HIV negative**		
	n=903	%	n=391	%	n=512	%	P value
NILM	352	39.0	134	34.3	218	42.6	0.01
CIN 1	263	29.1	95	24.3	168	32.8	0.005
CIN 2	152	16.8	76	19.4	76	14.8	0.07
CIN 3	114	12.6	72	18.4	42	8.2	<0.0001
ICC	18	2.0	11	2.8	7	1.4	0.1
Other	4	0.4	3	0.8	1	0.2	0.2

CIN, cervical intraepithelial neoplasia; ICC, invasive cervical cancer; NILM, negative for intraepithelial lesion.

Of the 391 HIV positive women, CD4 count information was available for 351 (89.8%) women. The CD4 count was <200 cells/mm^3 in 32 (9.1%) women, 200–500 cells/mm^3 in 143 (40.7%) women, and >500 cells/mm^3 in 176 (50.1%) women. Cytology results for 345 women and

histology results for 264 women with CD4 count information are shown per CD4 count category in Table 4.

Table 4 Cytology and histology results per CD4 (cells/mm^3) categories

CD4 count	<200		201–500		>500	
Cytology (n=351)	**n=32**	**%**	**n=143**	**%**	**n=176**	**%**
NILM	8	25.0	91	63.6	128	72.7
ASCUS	2	6.3	8	5.6	7	4.0
ASC-H	1	3.1	5	3.5	5	2.8
LSIL/CIN 1	8	25.0	7	4.9	6	3.4
HSIL/AGUS/CIN 2/3	11	34.4	26	18.2	23	13.1
Malignancy	2	6.3	4	2.8	3	1.7
Cytology uncertain			2	1.4	4	2.3
Histology (n=264)	**n=30**	**%**	**n=109**	**%**	**n=125**	**%**
NILM	5	16.7	34	31.2	44	35.8
CIN 1	3	10.0	25	22.9	32	27.0
CIN 2	10	33.3	22	20.2	21	17.1
CIN 3	11	36.7	24	22.0	22	17.9
ICC	1	3.3	3	2.8	3	2.4
Other	–	–	1	0.9	1	0.8

AGUS, atypical glandular cells; ASC-H, atypical squamous cells cannot exclude HSIL; ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HSIL, high grade squamous intraepithelial lesion; ICC, invasive cervical cancer; LSIL, low grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion.

Fewer women with <200 cells/mm^3 had normal smears compared with women with 201–500 cells/mm^3 (p=0.0001) and women with >500 cells/mm^3 (p<0.0001). The difference between women with 201–500 cells/mm^3 and >500 cells/mm^3 was not significant (p=0.11). Women with a CD4 count of >500 cells/mm^3 had significantly more CIN I and significantly less CIN 2 and CIN 3 compared with women with a CD4 count of <200 cells/mm^3 (p=0.048). Between 2% and 4% of women in each group were diagnosed with invasive cancer.

For detection of CIN 3+in women of all ages, HPV screening had higher sensitivity compared with cytology for ASCUS+, but specificity was lower in both women living with HIV and HIV negative women. The sensitivity of HPV screening in women living with HIV was higher than that of HIV negative women, and the specificity was better in HIV negative women. (Table 5).

The sensitivity of HC2 in women living with HIV was better than in HIV negative women, while specificity was better in HIV negative women of ≤40 years of age. Cytology and HPV screening performance for 456 women aged 40 years or younger using CIN 3+ is shown in Table 5. The performance of HC2 HPV screening was similar in this group compared with women of all ages.

Table 5 Cytology, Hybrid Capture 2 human papilloma virus screening, and human papilloma virus with reflex cytology in women living with HIV and HIV negative women of all ages, and in women ≤40 years, for detection of cervical intraepithelial neoplasia 3+

	Prevalence of CIN 3+ (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Agreement (%)
HIV negative women all ages						
Cytology ASCUS+	9.6	51.0	87.5	30.1	94.4	84.0
Cytology CIN I+	9.6	28.6	96.8	48.3	92.8	90.2
HC2 HPV	9.6	59.2	83.8	27.9	95.1	81.5
Combo	9.6	44.9	94.2	44.9	94.2	89.5
HIV positive all ages						
Cytology ASCUS+	21.2	69.9	74.4	42.3	90.2	73.4
Cytology CIN I+	21.2	62.7	85.4	53.6	89.5	80.6
HC2 HPV	21.2	77.1	63.0	36.0	91.1	66.0
Combo	21.2	66.3	83.1	51.4	90.1	79.5
HIV negative women ≤40 years						
Cytology ASCUS+	12.0	56.7	88.2	39.5	93.7	84.4
Cytology CIN I+	12.0	30.0	95.9	50.0	91.0	88.0
HC2 HPV	12.0	76.7	75.9	30.3	96.0	76.0
HIV positive ≤40 years						
Cytology ASCUS+	22.3	76.1	69.4	41.7	91.0	70.9
Cytology CIN I+	22.3	69.6	79.4	49.2	90.1	77.2
HC2 HPV	22.3	82.6	53.8	33.9	91.5	60.2

AGUS, atypical glandular cells; ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; Combo, HC2 and reflex cytology ASCUS+; HC2, Hybrid Capture 2; HPV, human papilloma virus; NPV, negative predictive value; PPV, positive predictive value.

DISCUSSION

Summary of Main Results

The performance of primary HPV screening in previously unscreened women with high rates of HPV as well as HIV infection was significantly different from that reported in the published literature. The mean age of the study group as well as the two HIV groups was within the ideal age group for cervical cancer screening. The age distribution of the study population as well as the HIV cohorts were representative of women eligible for screening.

Results in the Context of Published Literature

Although South Africa has a screening policy, population based screening does not exist and screening is largely opportunistic. The proportion of women negative for intraepithelial lesion cytology and negative HPV tests was significantly higher compared with the population of women with histology results. This finding validates the need to adjust the results of the histology group for verification bias. Because the test results differed significantly between women living with HIV and HIV negative cohorts, the prevalence of HIV infection among the screened population is critical to enable further comparison. This difference is more profound for women living with HIV for both histologic thresholds. In line with other reports of HPV test performance, the specificity of cytology for CIN 2+ and CIN 3+ was higher than that of HC2 in both HIV groups, and better in HIV negative women where the prevalence of HPV is lower.

HC2 is a more sensitive test than cytology to detect CIN 2+ and CIN 3+ in women living with HIV and in HIV negative women. In HIV negative women, the sensitivity of HC2 for detection of CIN 2+ was 42.4% compared with 38.4%, for cytology ASCUS+, and specificity was 86.8% compared with 91.0% for cytology ASCUS+ to detect CIN 3+. For detection of CIN 3+ in women living with HIV, the sensitivity of HC2 was 77.1% compared with 69.9%, and specificity was 63.0% compared with 74.4%.

In women aged ≤40 years, HC2 had higher sensitivity and lower specificity compared with its performance in women of all age groups. HC2 screening can be used in women ≤40 years in the general population with unknown HIV status. Although HPV screening performs better than cytology and should be the preferred screening test, cytology screening using ASCUS+ as cut-off can also be considered as a screening test in women living with HIV who regularly attend follow-up for antiretroviral treatment in settings without access to HPV screening.

Reflex cytology in women testing positive on HC2 resulted in lower sensitivity and higher specificity. In the study population described here, 282 women had a positive HPV test, and 122 of these women (43.3%) had negative cytology. Reflex cytology of positive HPV tests would result in a significant reduction in patients referred for colposcopy, provided women with HC2 positive tests can be followed up. Ideally, in a screening program, lower sensitivity is compensated for by follow-up testing in women who screened positive on HC2. The sensitivity of cytology at a threshold of CIN 1+ for detection of CIN 3 among HIV negative women (28.6%) is too low for clinical use, and therefore all women with ASCUS+ should be referred for further testing in a cytology based screening program.

The differences in cytology screening results between women living with HIV and HIV negative women confirmed the available data, suggesting that these women have higher rates of HPV infection and lower rates of HPV clearance.[22] This difference was also clearly demonstrated in the HPV test results and confirms the findings of similar studies in the rural Eastern Cape and elsewhere in Africa.[23, 24] Prevalence rates of HPV and abnormal cytology exceeded the expected rates in HIV negative women compared with other studies.[25]

The finding that HIV negative women had a higher prevalence of CIN 1 compared with women living with HIV was unexpected, while the higher prevalence of HSIL in this group confirmed the lower clearance of HPV infection. This finding was similar to that of a systematic global review, reporting a threefold increase in squamous intraepithelial lesions in women living with HIV compared with HIV negative women.[26]

It is possible that early initiation with antiretroviral therapy can lower the incidence and progression of premalignant lesions.[27] This study confirmed the findings of other studies that have shown different prevalence distributions in women with different CD4 Original research count categories, despite the small number of patients with CD4 counts of <200 cells/mm^3 in this study.[28, 29]

HC2 was the first HPV test validated in randomized controlled trials for cervical cancer screening.[30–32] The test performances reported here for cytology and HC2 HPV screening in women living with HIV were comparable with those reported by Kelly et al.[33] They reported sensitivity, specificity, and positive predictive value for detection of CIN 3+ in this group of

patients for HC2 HPV at different relative light units. Sensitivity ranged between 86.4% (≥1 relative light units) to 75.8% (≥20 relative light units), with specificity of 51.3% and 67.2%, respectively. Kuhn et al reported sensitivity of 88.4% and specificity of 81.9% using HC2 screening for CIN 3+ in an unscreened general population in Cape Town.[34] Sensitivity ranging between 91% and 94% and specificity between 60% and 68% have been reported in women living with HIV in Cape Town using GeneXpert.[35]

Strength and Weaknesses

This is the largest study investigating the effect of HIV infection on HPV screening for cervical cancer. This is the first study reporting on the test performance of HC2 using imputed data derived from women with histology. The relatively small numbers for a screening study with no long term follow-up data available are the main limitations of this study.

Implications for Practice and Further Research

This study highlighted the performance of HPV screening in previously unscreened and untreated women with a high prevalence of HPV infection. The effect of HIV status was clearly demonstrated in this study. The study also confirmed that cytology remains a reasonable primary screening strategy in HIV infected women. Future research should include longitudinal follow-up data for women undergoing primary HPV screening.

CONCLUSION

Cervical cancer screening using HC2 testing performed relatively well in the population as a whole, in women living with HIV as well as in HIV negative women, but not as good as reported in other populations. Reflex cytology following positive HC2 screening will substantially reduce referrals for colposcopy. Liquid based cytology using ASCUS+ is an acceptable screening test for women living with HIV who regularly attend follow-up in settings without access to HPV screening.

Contributors: LCS: study design, investigator, analysis and data interpretation, and drafting manuscript. KLR: virology laboratory support, study design, and revising manuscript. AL: virology laboratory support, study design, and revising manuscript. GeD: statistical support, data analysis and interpretation, and revising manuscript. MHB: study design and concept, project leader Western Cape province, and revising manuscript. HvdM: study design, investigator Western Cape Province, and revising manuscript. CV: investigator, data collector, data analysis, and manuscript writing and revising. GrD: study concept, planning design, principal investigator and project coordinator, revising manuscript, and responsible for the overall content as guarantor.

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