Original Article

Cervical Cancer Screening in Low Resource Settings: Cytology versus HPV Triage for VIA Positive Women

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Abstract

Background: The objective of the study is to comparatively evaluate performance of human papillomavirus (HPV) hybrid capture 2 (HC2) and cytology as triage tests among visual inspection after application of 3–5% acetic acid (VIA) screen positive women, thus aiming to reduce the referral burden. **Methods:** The community-based cross sectional cervical cancer screening with VIA was conducted among women aged between 30 and 65, residing in selected low socio-economic areas of Mumbai, India, during October 2010–March 2017. After obtaining informed consent, delivering health education and collecting socio-demographic data, participants were offered VIA screening by trained primary health workers. The VIA screen positive women underwent cytology, HPV HC2 and diagnostic colposcopy at nodal hospital. Women with positive colposcopy underwent cervical biopsies. **Results:** 231 VIA positive women underwent cytology and HPV HC2 test, followed by colposcopy. Cervical biopsies were obtained in 83 cases. The sensitivity and specificity in detecting ≥ CIN 2 were 77.8 and 92.3 for HC2 and 66.7 and 98.2 for cytology. The false positivity and negativity rates were 7.7 and 22.2 for HC2 and 1.8 and 33.3 for cytology. **Conclusions:** HPV HC2 reduces referrals to larger extent and misses fewer cases compared to cytology, thus appearing a better triage test among VIA positive women.

Keywords: *Cell biology, human papillomavirus DNA tests, mass screening, triage*

Introduction

Cervical cancer, though the fourth most common cancer among women globally, remains the predominant cancer affecting women in the less developed world. 85% of the global burden of cervical cancer cases amounting to nearly 445,000 cases and 230,000 deaths annually, occur in the less developed world. The disease burden can be reduced with well-organized screening programs enrolling the target population, systematic recalls, diagnostic investigations, treatment and follow-up care of women with abnormalities on screening combined with quality assurance, data maintenance and monitoring and evaluation of the program. It is the second most common cancer among women of the less developed regions but does not feature even in the top ten cancers among women belonging to the more developed world.[1] Worldwide cytology has been used as a screening test for cervical cancer screening since several decades. However, it is still not feasible to offer even once in a lifetime screen to all women in India with cytology-based screening. Organized and quality assured cytology-based cervical cancer screening programs supported by timely and appropriate management of the cervical pre-cancers and cancers, led to a decrease in the incidence and mortality due to cervical cancers in the more developed regions.[2] Population level cytology-based screening necessitates trained human resources, high-quality cytology laboratories, good quality assurance, other logistics and repeat screening at regular intervals, all of which are still not feasible in most less developed regions.[3] Hence, other options are being explored. Screening tests are an important component of the entire program, though the program can be successful only when all the constituents are effectively implemented.

Two large randomized controlled trials, both from India, demonstrated significant reduction in mortality due to cervical cancers with use of visual inspection after application of 4–5% acetic acid (VIA).[4,5] VIA has several advantages: it is less expensive, does not require laboratories, can be performed in any community-based clinic wherever

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privacy for examination and availability of good light source can be ensured, does not require qualified technicians/pathologist to perform/interpret the test – nurses/primary health workers/paramedics can be trained to perform the test and the results are available immediately. Hence, screen and treat protocol remains an option.[6] In a RCT in South India, trained nurses offered single round of VIA screening. Whenever necessary, the women were also treated in the same visit. This led to a significant 25% reduction in incidence and a significant 35% reduction in mortality due to cervical cancers at the end of 7 years of follow-up.[4] In another RCT in Mumbai, India, four rounds of cervical cancer screening were offered by trained primary health workers (PHWs) at 24 months interval. The trial demonstrated a significant 31% reduction in cervical cancer mortality at the end of 12 years of follow-up.[5] These trials also show that VIA-based screening is acceptable, feasible and implementable at population level in low resource settings. Several cross-sectional studies carried out in India and Africa using VIA have demonstrated fairly good sensitivity but lesser specificity and high false positive rates.[7]

The referral of all screen positives of primary VIA screening for colposcopy would burden the already scarce health resources available in the less developed regions. A secondary triage of all the VIA screen positives with a test with good specificity will help to reduce the referrals. However, this may lead to missing of some true positive cases. Hence, the secondary triage test has to be well chosen.

The burden of cervical cancers has been reduced in the developed countries, that introduced cytology-based screening several decades ago.[2] Cytology has poor sensitivity but fairly good specificity and thus can be considered to triage the VIA screen positive women. The Osmanabad district RCT in India demonstrated a significant 48% reduction in cervical cancer mortality with a single round of human papillomavirus (HPV)-based screening after 7 years of follow-up.[8] HPV DNA test has good sensitivity and specificity and a very good negative predictive value and hence is another good test to be considered to triage the VIA positive women.[9]

The aim of the present program is to comparatively evaluate the test characteristics of cytology and HPV HC2 as secondary triage test for all VIA screen positive women.

Methods

The program, a community-based cross sectional cervical cancer screening program with VIA, was implemented during October 2010–March 2017 in selected low socio-economic areas of Mumbai, India, which were previously not exposed to any cancer health education or cancer screening program. Sample selection was based on survey sampling technique, wherein geographical selection of population was done based on their residence in particular locality. Women between the age group of 30 and 65 years, with no history of cancer, residing in the selected clusters for more than a year were considered as eligible for cervical cancer screening.

The project activity was initiated by meeting the local leaders and local health authorities to ensure their support throughout service program. Intricate mapping of the selected clusters was done by the medical social workers (MSWs) of the project to facilitate easy location of participants. They went door to door and explained the project to the eligible community women and invited them to participate in the screening at the camp setting. Health education program was delivered by the MSWs to the eligible women explaining the risk factors, signs and symptoms, methods of early detection and management of uterine cervix pre-cancers and cancers. Thereafter, a discussion on the subject was held and queries related to the project were answered. The MSWs then introduced the informed consent form and enrolled the eligible women in the project after completing the necessary documentation. This was a community-based service programme and not a research protocol. The informed consent form was explained to each and every participant woman. The women were screened only after obtaining the written informed consent. This was done in a similar manner to the nodal hospital-based screening clinic, wherein, each and every woman is explained the screening procedure and an informed consent is obtained, though they may not be part of any research protocol. Personal interviews were further conducted by MSWs to obtain socio-demographic and risk factor history from the women.

The project PHWs received training to perform VIA using IARC charts and manuals.[10] Trained PHWs offered VIA screening to women in community-based temporarily set-up clinics. VIA screen positive women were referred to the nodal hospital for cytology, HPV DNA test and colposcopy. Training was provided to the technicians to collect process and test cytology and HPV HC2 specimens. Periodic refresher training was repeated to all staff involved. The medical officers too received intensive training to perform Colposcopy, obtain cervical biopsies and manage cervical pre-cancers with cryotherapy and loop electrosurgical excision procedure.[11]

At the nodal hospital, cytology and HPV specimens were collected for the referred women. A Cusco's speculum was inserted and the sample for cytology was collected using a swab stick with small cotton tip. Next, the digene HC2 high-risk HPV test by Qiagen was used for VIA screen positive women. It is the most widely used HPV Test for early detection of cervical cancer and disease. The digene HC2 high-risk HPV DNA test is FDA-approved and CE-IVD marked for testing for high-risk types of HPV. It

detects 13 high-risk and 5 low-risk HPV types and uses full genome probes for detection. The HPV collection brush was removed from the sealed packet and inserted through the speculum, such that the tip was inside the os and the back of the brush was touching the external part of the cervix. The brush was rotated three and half times in anti-clock wise direction. The tip of the brush collected cells from inside the os and the back of the brush collected cells from outside the os. The brush was then removed and inserted in the collection media and stirred. The extra portion of the tip was broken and the bottle was closed and sent to the lab. The digene HC2 HPV DNA test is an *in vitro* microplate assay based on signal-amplified nucleic acid hybridization that uses chemiluminescence for the qualitative detection of 18 types of HPV DNA in cervical specimens.

Colposcopy was performed by trained medical officers. Colposcopy directed cervical biopsies were obtained in women with positive colposcopy findings. Histopathology reports among women in whom biopsies were performed and negative colposcopy findings in others were treated as gold standard. Women with diagnosed pre-cancer or cancer received appropriate management as per the institutional evidence-based management protocol.[12] Cytology was reported using the Bethesda system[13,14] and histopathology was reported using the CIN system.[15] The flow chart of the project activities is shown in Figure 1.

The data was computerized in MySQL and then error checks were conducted in Stata 8.2. The sensitivity, specificity, false positive rates, false negative rates, positive predictive value and negative predictive values of cytology and HPV HC2 as secondary triage test were calculated at 95% confidence interval using Stata software. The ethics committee approval was not needed as this data was collected as part of service program and not a research setting.

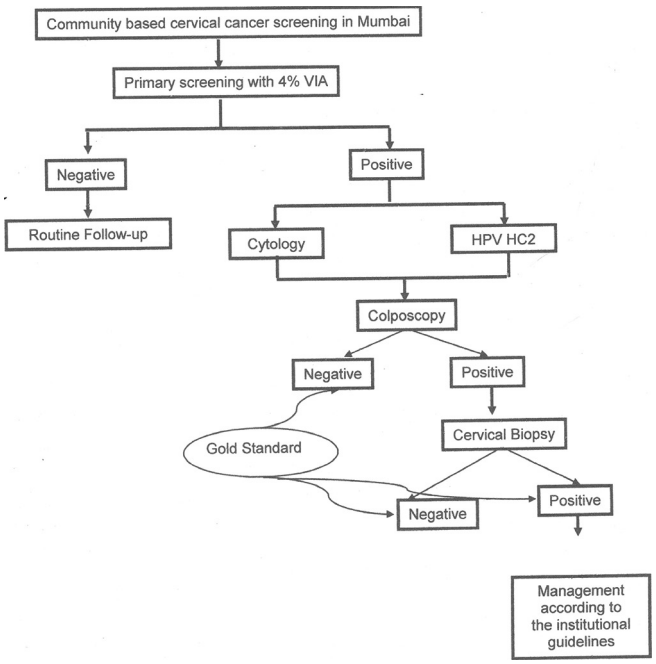

Figure 1: Flow chart of project activities

Results

231 VIA screened positive women were evaluated with cytology and HPV HC2 as secondary triage test. The sociodemographic profile of the VIA positive women is as shown in Table 1.

All VIA positive women underwent colposcopy. Colposcopy was negative in 147 cases and this was considered as the gold standard. Colposcopy was positive in 85 cases and cervical biopsies were obtained in 83 cases amongst which 54 were positive on histopathology. A biopsy was considered positive if it was reported as CIN 1, CIN 2 or CIN 3 or if it was an invasive carcinoma. Histopathology was used as the gold standard in all the cases where cervical biopsies were obtained except in ten cases wherein cervical biopsy was reported as inadequate sample. The final disease status with histopathology or negative colposcopy as gold standard in VIA screen positive women is as shown in Table 2. This is compared with cytology at the threshold of ASCUS and HPV HC2 as triage test.

Two cytology samples were reported as inadequate and were excluded from the analysis. The test characteristics of cytology and HPV HC2 when used as secondary triage test among VIA positive women is as shown in Table 3.

When cytology is used as secondary triage test among VIA positive women, the sensitivity is 22.2% and 66.7%, specificity is 89.1% and 98.2%, false positive rate is 10.9% and 1.8%, false negative rate is 77.8% and 33.3%, positive predictive value is 38.7% and 60% and negative predictive value is 78.8% and 98.6% for the outcomes ≥CIN 1 and ≥CIN 2, respectively. While with the use of HPV HC2 as secondary triage test among VIA positive women, the sensitivity is 18.5% and 77.8%, specificity is 92.0% and 92.3%, false positive rate is 8.0% and 7.7%, false negative rate is 81.5% and 22.2%, positive predictive value is 41.7% and 29.2% and negative predictive value is 78.5% and 99% for the outcomes ≥CIN 1 and ≥CIN 2, respectively.

The VIA positive women underwent secondary screening with cytology. About 13.54% of VIA positive women were also positive on cytology and hence required to undergo further diagnostic evaluation. While, when these women underwent secondary screening with HPV HC2, 10.48% of these women were positive on HPV HC2. Thus secondary screening with HPV HC2 reduces referrals to larger extent as compared to secondary screening with cytology. The false negative rate with cytology as secondary triage was 33.3% for the outcomes ≥CIN 2, while it was 22.2% with HPV HC2 as secondary triage test. Thus, it appears that HPV HC2 misses fewer cases compared to cytology. Hence, HPV may act as a better secondary triage test compared to cytology among VIA positive women.

Table 1: Socio-demographic and risk factor characteristics of the women with VIA test result positive on cervical cancer screening

Variables		Distribution	(%)
Total		231	
Age groups (%)	30-34	89	38.5
	35-39	65	28.1
	40-44	37	16.0
	45-49	30	13.0
	50-54	7	3.0
	55-59	1	0.4
	60-65	2	0.9
Mean age (in years) (SD/range)		37.5; 6.3 (30-64)	
Education (%)	Literate without formal education	15	6.5
	Illiterate	22	9.5
	School	172	74.5
	High school and graduates	22	9.5
Income (%)	Less than Rs. 5000	65	28.1
	Rs. 5001-10000	157	68.0
	Over Rs. 10000	9	3.9
Occupation (%)	Housewife	193	83.6
	Manual labour	23	10.0
	Service (white collar)	12	5.2
	Self-employed	3	1.3
Religion (%)	Hindu	200	86.6
	Muslim	14	6.1
	Others	17	7.4
Language (%)	Marathi	195	84.4
	Hindi	27	11.7
	Others	9	3.9
Marital status (%)	Unmarried	0	0
	Married	216	93.5
	Widowed	11	4.8
	Separated	4	1.7
	Divorced	0	0
Menstrual status (%)	Premenopausal	202	87.5
	Perimenopausal	18	7.8
	Postmenopausal	11	4.8
Mean age at marriage (yrs.) (SD/range)		19.0; 3.7 (7-31)	
Mean age at first child birth (yrs.)		21.2; 3.5 (13-32)	
Average number of children		2.4; 1.0 (1-7)	
History of tobacco use (%)	Yes	103	44.6
	No	128	55.4
History of post-coital bleeding (%)	Yes	2	0.9
	No	229	99.1
History of post-menopausal bleeding (%)	Yes	2	18.2
	No	9	81.8
History of intermenstrual bleeding (%)	Yes	0	0
	No	220	100
Previous consultation for Gynaec-related complaints (%)	Yes	8	3.5
	No	223	96.5

Discussion

In this study, though both cytology and HPV test perform poorly as secondary triage tests at the threshold of CIN 1, both tests show good sensitivity and specificity at the threshold of CIN 2, with HPV having more sensitivity (77.8%) and cytology having more specificity (98.2%). The high negative predictive values (98.6% for cytology and 99% for HPV HC2) safely allows to increase the screening

Table 2: Comparison of final disease status with gold standard as histopathology or negative colposcopy for various primary and secondary screening tests

Screening tests	Benign	CIN I	≥CIN II	Total
VIA				
Positive	175 (76.4%)	45 (19.7%)	9 (3.9%)	229
Cytology				
Negative	156 (78.79%)	40 (20.20%)	2 (1.01%)	198 (86.46%)
Positive	19 (61%)	5 (16%)	7 (23%)	31 (13.54%)
HPV HC2 test				
Negative	161 (78.5%)	42 (20.5%)	2 (1.0%)	205 (89.52%)
Positive	14 (58%)	3 (13%)	7 (29%)	24 (10.48%)

VIA=Visual inspection after application of 3-5% acetic acid; CIN=Cervical intraepithelial neoplasia; HPV HC2=Human papillomavirus hybrid capture 2 test

Table 3: Test characteristics of cytology and HPV HC2 as secondary triage among VIA screen positive women with cut off of ≥CIN I and ≥CIN 2

Test characteristics	Triage test			
	Cytology (≥ CIN I)	Cytology (≥ CIN 2)	HPV HC2 (≥ CIN I)	HPV HC2 (≥ CIN 2)
Sensitivity (95% CI)	22.2% (12-35.6%)	66.7% (29.9-92.5%)	18.5% (9.25-31.4%)	77.8% (40.0-97.2%)
Specificity (95% CI)	89.1% (83.6-93.3%)	98.2% (95.5-99.5%)	92.0% (86.9-95.6%)	92.3% (87.9-95.4%)
Positive predictive value (95% CI)	38.7% (21.8-57.8%)	60% (26.2-87.8%)	41.7% (22.1-63.4%)	29.2% (12.6-51.1%)
Negative predictive value (95% CI)	78.8% (72.4-84.3%)	98.6% (96.0-99.7%)	78.5% (72.3-84.0%)	99% (96.5-99.9%)
False positive rates	10.9%	1.8%	8.0%	7.7%
False negative rates	77.8%	33.3%	81.5%	22.2%

CIN=Cervical intraepithelial neoplasia; HPV HC2=Human papillomavirus hybrid capture 2 test

intervals. Overall, in this study, HPV as a secondary triage test appears to perform better than cytology among VIA positive women in cervical cancer screening.

WHO,[16] NCCP[17] and several well researched scientific groups[18,19] have advised primary screening for cervical cancer using VIA for resource poor countries like India, for women 30 years and older because of their higher risk of cervical cancer. The outcome of VIA is available immediately, thus being a realtime screening test. Hence, further diagnostic confirmation and further "See and Treat" management can be conducted during the same visit.

However, VIA has high false positive rate, 76.4% in the present study, resulting in several women being falsely labelled as positive and referred for colposcopic evaluation. Hence, secondary triage with highly specific test like cytology; specificity of 98.2% for ≥CIN 2 or HPV HC2; specificity of 92.3% for ≥CIN 2, as seen in the present study, have been comparatively evaluated.

In the current study the sensitivity of cytology as a triage test was 22.2% and 66.7% at the threshold of CIN I and CIN 2, respectively, while the sensitivity was 80% for CIN2+ among Kenyan women.[20]

In the current study, 13.5% VIA positive women had positive cytology at the threshold of ASCUS and above, whereas in Kenya, 54% VIA positive women were positive on cytology.[20] 10.5% of VIA positive women were positive for HPV HC2 in the present study, while Pimple *et al*.[21] reported HPV HC2 positivity rate of 11% among VIA positive women.

The sensitivity, specificity, PPV and NPV of cytology as triage among VIA positive women with outcome ≥CIN 1 were 22.2%, 89.1%, 38.7% and 78.8%, respectively in the present study with ASCUS as threshold as compared to 62%, 50%, 36% and 75%, respectively in the study from Kenya.[20] The similar values for outcome ≥CIN 2 were 66.7%, 98.2%, 60% and 98.6%, respectively, in the present study as compared to 80%, 48%, 12% and 97%, respectively in the Kenyan study. The discrepancy in the test characteristics between the two studies may be due to the fact that after an expert pathologist reviewed the cytology and the histopathology slides in the Kenyan study, only a slight agreement between the in country and the expert readers was reported for both cytology as well as histopathology.[20]

The sensitivity, specificity, PPV and NPV of HPV HC2 as triage among VIA positive women with outcome ≥CIN1 and ≥CIN 2 were 18.5% and 77.8%, 92% and 92.3%, 41.7% and 29.2%, 78.5 and 99%, respectively, in the present study. The earlier Mumbai study using HPV HC2 as secondary test to triage VIA positives found sensitivity, specificity, PPV and NPV for detecting CIN1+ lesion as 40%, 100%, 62% and 99%, respectively and for detecting CIN2+ lesions as 61%, 99%, 44% and 100%, respectively.[21] In both studies the PPV is much higher at the threshold of CIN 1+ as compared to CIN 2+. Bhatla

et al.[22] reported specificity of 90.4%, for VIA followed by HPV test which was comparable to HPV HC2 on physician collected sample followed by Pap.

The basis of incorporating a triage test in a screening algorithm is to increase the specificity and efficiency, thus reducing the number of more expensive and invasive tests. Sequential testing of VIA followed by cytology or VIA followed by HPV and thereafter colposcopies and directed biopsy for diagnosis, combines economic viability with high scientific fidelity. The high specificity and NPV results in minimal referrals, recall visits and follow-up screenings. The choice of triage test (cytology or HPV HC2) will also be determined by the availability of infrastructure and expertise in different LMICs.[23]

In the present study, both cytology and HPV test perform poorly as secondary triage tests at the threshold of CIN 1. However, both these tests show good sensitivity and specificity at the threshold of CIN 2, with HPV having more sensitivity and cytology having more specificity. The positive predictive value is much higher for cytology whereas the negative predictive values when used as triage tests are high (98.6% for cytology and 99% for HPV HC2) for both the tests, thus safely allowing to increase the screening intervals. The false negative rates are also much lower for HPV HC2 as compared to cytology. Thus when cytology is used as a secondary triage test in VIA positive women the referrals for colposcopy are reduced to 13.5% of the original referrals, however 33.3% of the CIN 2 and above lesions are missed whereas when HPV is used as a secondary triage test in VIA positive women the referrals for colposcopy are reduced to 10.5% and 22.2% of the CIN 2 and above lesions are missed.

The limitation of the study is that the program incorporated only a single one time screen at the community-based camp setting. All the HPV and cytology negative participants were asked to come for subsequent follow-up screening after 5 years at the nodal hospital. There was no provision for follow-up screening at the community level and compliance to follow-up screening was entirely dependent on the participant, though the importance of this was emphasized during the Health education that was offered to all participants.

Conclusions

Human papillomavirus as a secondary triage test appears to perform better than cytology among VIA positive women. Further if HPV HC2 test becomes available at substantially lower cost and if the results can be immediately obtained as with fast HPV Kits or GeneXpert test, this approach would be economically viable and can be combined with see and treat strategies.

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Conflicts of interest

There are no conflicts of interest.

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