

# Evaluation of cytology as secondary triage in visual inspection after application of 4% acetic acid-based cervical cancer screening program

Gauravi A. Mishra, Sharmila A. Pimple, Subhadra D. Gupta

## Abstract

**Context (Background):** Visual-based screening techniques are low cost and have good sensitivity. Hence, they appear promising for primary screening in low-resource settings. However, to reduce referrals for diagnostic colposcopy, there is need to triage these screen-positive women with test with good specificity. **Aims:** The study aims to evaluate the performance of cytology as triage for visual inspection after application of 4% acetic acid (VIA) screen-positive women. **Settings and Design:** Community-based cervical cancer screening using VIA was implemented among socioeconomically disadvantaged women in Mumbai, India. **Methods:** Cytology was performed on screen-positive women. All primarily screen-positive women underwent colposcopy. Directed biopsies were obtained among women with positive findings on colposcopy. The gold standard used for final disease status was histopathology or negative colposcopy. **Statistical Analysis Used:** Test characteristics of cytology as triage test. **Results:** Among the 138,383 population, 16,424 eligible women were screened with VIA. 785 (4.78%) women were VIA positive and 580 women participated in triage with cytology. The sensitivity and specificity of cytology at threshold of atypical squamous cells of undetermined significance in detecting  $\geq$ cervical intraepithelial neoplasia (CIN) 2 were 75.0 and 94.7, respectively. The positive and negative predictive values of cytology as triage test were 23.1 and 99.4, respectively, and the false positivity and false negativity rates were 5.34 and 25.0, respectively. **Conclusion:** Cytology triage with VIA can reduce referrals for colposcopy to 4.97% of original referrals but may miss around 25%, of high-grade CIN. The substantial reduction in referrals has special implication for low-resource settings, wherein compliance to referral and availability of diagnostic facilities are poor.

**Key words:** Cytology, screening, triage, visual inspection after application of 4% acetic acid

## Introduction

Cervical cancer is the fourth most common cancer among women globally. India bears nearly one-fourth of the global cervical cancer burden. It is the second most common cancer among Indian women, being responsible for 132,314 new cases and 73,337 deaths annually. It accounts for 22.9% of all cancers among women in India.<sup>[1]</sup> Here, population-based screening services are almost nonexistent because of the logistics challenges of implementing cytology-based screening program. Hence, alternative strategies are being explored. Visual-based screening techniques, i.e., visual inspection after application of 4% acetic acid (VIA) and visual inspection after application of Lugol's iodine are low cost and have fairly good sensitivity<sup>[2,3]</sup> and thus appear promising for primary screening. The WHO has recommended visual-based techniques for primary screening of cervical cancers in countries with limited resources.<sup>[4,5]</sup> However, the specificity of visual-based tests is low, resulting in high false-positive rates.<sup>[2]</sup> Referral of all the screen positives (many of whom are false positives) for colposcopy will result in substantial costs for the health-care systems and may create unnecessary anxiety in the women and their families.<sup>[6]</sup> Colposcopy services are still available only to a limited extent, with most of these facilities concentrated in the urban areas. Hence, there is need to triage the women screened positive on visual-based techniques with test with higher specificity to reduce referrals for colposcopy.

Cytology for cervical cancer screening has low sensitivity but fairly good specificity.<sup>[2,7]</sup> It has reduced the incidence and mortality of cervical cancers in countries that implemented cytology-based screening over a period.<sup>[8-10]</sup> There is also good evidence from lot of cross-sectional studies about its usefulness as a primary screening tool.<sup>[11]</sup> However, for resource-poor countries, primary screening with cytology at population

level is still not feasible. Cytology can however be explored as a secondary triage test for women screened positive with visual-based tests. Only around one-fifth to one-tenth of the total eligible women will then have to undertake cytology. It will also limit the referrals for colposcopy as only women screened positive on primary and secondary screening tests will now have to be referred.

The present paper evaluates the test characteristics of cytology as a triage for VIA screen-positive women. The data for the present paper is from a service program on cervical cancer screening implemented in Mumbai, India.

## Methods

A community-based cervical cancer screening project was implemented in selected slum clusters in Mumbai, India, during 2010–2017. Eleven slum clusters, not previously covered by any cancer screening program were selected. Meetings were held with the local leaders in order to ensure their support for the program. The project staff comprising mainly of the medical social workers (MSWs) and female primary health workers (PHWs) were recruited. The MSWs were graduates and the PHWs were 10<sup>th</sup> grade educated. The MSWs received intensive training to conduct the project activities such as area mapping, conducting household surveys, obtaining informed consent, personal interviews of the eligible women, health education, counseling, and report preparation. PHWs were trained in insertion of speculum, preparation of 4% acetic acid, preparing the examination trolley, screening of cervical cancers by VIA, referral of screen-positive women, collection of cervical smears for cytology etc., Training to conduct VIA-based screening was offered to the PHWs using IARC manuals.<sup>[12]</sup>

The slum clusters were mapped to identify each and every lane and to identify every household. Surveys were conducted

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Department of Preventive Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India

**Correspondence to:** Dr. Gauravi A. Mishra,

E-mail: [mishraga@tmc.gov.in](mailto:mishraga@tmc.gov.in)

in each slum cluster to enlist all the population residing in the slums, list total members of each household and the eligible women for screening. Women between the age group of 30 and 65 years residing in the selected slum clusters and with no history of cancer were considered as eligible for cervical cancer screening. Community-based screening clinics were set up with participation from the local community. The eligible women were invited to the nearby screening clinic, where they were explained the program and informed consent was obtained from women who were willing to participate. Their sociodemographic and risk factor information was recorded on a predesigned questionnaire after personal interviews. Women then participated in health education program explaining the risk factors, signs and symptoms, methods of early detection, and prevention of cervical cancers, after which they were invited to participate in cervical cancer screening. The PHWs conducted screening of cervix using VIA. All the screen-positive women and 10% of the screen-negative women were independently reexamined by the medical officer at the camp place for quality assurance. The women screened negative were advised routine follow-up screening after 2 years at a nearby screening clinic. Cytology was offered to all VIA-positive women. The cervical smears were collected using small sterilized cotton swab stick. The smears were categorized as normal, inflammatory, atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion, and invasive cancer at the cytology laboratory of Tata Memorial Hospital according to the Bethesda system.<sup>[13,14]</sup>

All primarily screen-positive women by VIA were referred to the nodal hospital for diagnostic Colposcopy by trained physicians. Cervical punch biopsy was performed for all women with positive findings on colposcopy. The histopathology reporting of the biopsy specimens was conducted at the hospital using the cervical intraepithelial neoplasia (CIN) system.<sup>[15]</sup> The gold standard used for final disease status was histopathology report, whenever biopsy was performed or negative colposcopy. All women with cervical precancers and cancers received treatment at the nodal hospital according to the standard disease management guidelines. The project flowchart is represented in Figure 1.

The data was entered in IBM SPSS Statistics version 20 and then analyzed with STATA software version 10.0 (Stata Corp, College Station, TX, USA). The test characteristics of cytology as a secondary triage test, namely sensitivity, specificity, positive and negative predictive values, and false positive and false negative rates, were calculated with their 95% confidence intervals using  $2 \times 2$  tables and standard formulae.

## Results

The total population of the eleven slum clusters was 138,383. A total of 23,580 eligible women were enlisted from these clusters for cervical cancer screening, among which 21,422 (90.85%) eligible women could be contacted during the camp period and 16,424 (76.67%) women participated in cervical cancer screening by VIA at the screening camp. The sociodemographic profile of the participating women is as shown in Table 1.

Seven hundred and eighty-five (4.78%) women were VIA positive and were offered cytology. Five hundred and

**Table 1: Distribution by important sociodemographic and risk factor variables among the participating women**

Variables	Participant women (%)
Total	16,424
Age groups (%)	
30-34	3628 (22.09)
35-39	3681 (22.41)
40-44	3117 (18.98)
45-49	2641 (16.08)
50-54	1579 (9.62)
55-59	1065 (6.48)
60-64	713 (4.34)
Mean age (years)	
Mean (SD)	41.95 (8.46)
Range	30-64
Education (%)	
Literate without formal education	965 (5.88)
Illiterate	3573 (21.75)
School	10,526 (64.09)
High school	809 (4.93)
Sr. college	378 (2.30)
Graduates and above	173 (1.05)
Monthly family income (Rs.) (%)	
<2000	188 (1.14)
2001-5000	5763 (35.09)
5001-10,000	9633 (58.65)
10,001-15,000	675 (4.11)
Above 15,000	165 (1.01)
Occupation (%)	
Homemaker	13,105 (79.79)
Manual labor	2224 (13.54)
Service (White Collar)	656 (3.99)
Self-employed	438 (2.67)
Others	1 (0.01)
Religion (%)	
Hindu	12,858 (78.29)
Muslim	1902 (11.58)
Others	1664 (10.13)
Language (%)	
Marathi	12,094 (73.64)
Hindi	2986 (18.18)
Others	1344 (8.18)
Marital status (%)	
Unmarried	6 (0.04)
Married	14,405 (87.71)
Divorced	58 (0.35)
Widowed	1781 (10.84)
Separated	174 (1.06)
Menstrual status (%)	
Premenopausal	10,792 (65.71)
Perimenopausal	1173 (7.14)
Postmenopausal	4459 (27.15)
Mean age at menarche (years)	
n	16,424
Range	10-22
Mean (SD)	13.84 (1.04)
Mean age at menopause (years)	
n	4459
Range	16-56
Mean (SD)	44.68 (3.92)

Contd...

**Table 1: Contd...**

Variables	Participant women (%)
Mean age at marriage (years)	
<i>n</i>	16,418
Range	5-42
Mean (SD)	18.63 (3.98)
Mean age at first childbirth (years)	
<i>n</i>	16,007
Range	12-43
Mean (SD)	20.94 (3.75)
Average number of children	
<i>n</i>	15,867
Range	1-13
Mean (SD)	2.83 (1.30)
Tobacco use (%)	
Yes	7558 (46.02)
No	8866 (53.98)
History of cancer screening (%)	
Yes	226 (1.38)
No	16,198 (98.62)

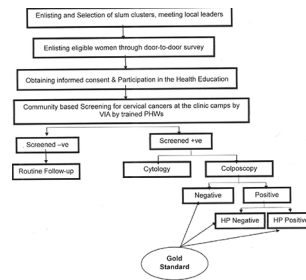
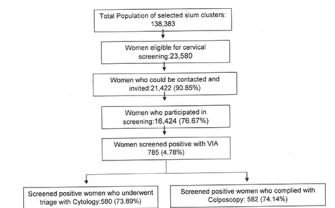
SD: Standard deviation

eighty screen-positive women complied with cytology (conventional PAP smears) and 582 screen-positive women complied to diagnostic colposcopy. Figure 2 shows the outcome of the screening program.

In six cases, the cytology was reported as inadequate and were excluded from the analysis. Conventional cytology was reported as normal in 535 women, ASCUS in 25 women, Low Grade Squamous Intraepithelial Lesion (LGSIL) in 6 women, and High Grade Squamous Intraepithelial Lesion (HGSIL) in 8 women. No case of carcinoma was reported on cytology. On histopathological examination of the cervical biopsy samples, 507 were reported as benign, 14 atypia/HPV changes, 49 CIN 1, 6 CIN 2, and 6 CIN 3. No case of cervical cancer was reported on histopathology. Table 2 shows the agreement between cytology and histopathology reports.

Final disease status by screening test result for the women positive on VIA and who had simultaneously undergone cytology, at the threshold of ASCUS and LSIL is as shown in Table 3.

Table 4 shows the accuracy estimates for different disease status for the women found positive on VIA and who had simultaneously undergone cytology for the outcome  $\geq$  CIN 1 and  $\geq$  CIN 2, using ASCUS and LSIL as threshold. The sensitivity of cytology as a triage test using ASCUS and LSIL as thresholds for the outcomes  $\geq$  CIN 1 is 25.9 and 13.8 and for  $\geq$  CIN 2 is 75.0 and 50.0, respectively. The specificity of cytology as a triage test using ASCUS and LSIL as threshold for the outcomes  $\geq$  CIN 1 is 95.3 and 98.8 and for the outcome  $\geq$  CIN 2 is 94.7 and 98.6, respectively. The positive and negative predictive values of cytology as triage test with ASCUS as threshold for the outcomes  $\geq$  CIN 1 are 38.5 and 92.0 and for the outcomes  $\geq$  CIN 2 are 23.1 and 99.4, respectively. The same with LSIL as threshold for the outcomes  $\geq$  CIN 1 and CIN 2 are 57.1 and 91.1 and 42.9 and 98.9, respectively. The false-positive and false-negative rates of cytology as triage test are 4.65 and 74.14 and 5.34 and 25.0 with ASCUS as threshold for the outcomes  $\geq$  CIN 1 and  $\geq$  CIN 2, while with LSIL as threshold, they are 1.16 and 86.21 and 1.42 and 50.0, respectively.

**Figure 1: Project schema****Figure 2: Flowchart of project activities and outcomes**

## Discussion

A triage test is a test that is applied to primarily screen-positive individuals, before a diagnostic test, to further shortlist the probably diseased individuals. Most low-resource settings may not have easily accessible health-care facilities providing colposcopy for all primary screen-positive women. A triage test, in such settings, reduces the number of women that need to get back for repeat testing. An ideal cervical cancer screening strategy using triage test should be able to identify women needing colposcopic referral and separate the rest of the women who are at low risk of cervical cancer.<sup>[16]</sup>

In a cancer screening project, there is a loss of participation of women at many levels during the program. In the present program, 76.67% women participated in VIA-based cervical cancer screening conducted in local community-based camps. In an earlier community-based cervical cancer screening study in Mumbai, 71.5% women participated in the first round.<sup>[17]</sup>

Among those who participated in the present program, 79.56% were below 50 years, 21.75% were illiterates, 93.74% had monthly family income between Indian rupee 2000/- and 10,000/-, 79.79% were homemakers, 78.29% belonged to Hindu religion, 73.64% were Marathi speaking, 87.71% were married, 65.71% were premenopausal, 46.02% used tobacco, and 1.38% had undertaken cancer screening in the past. The mean age at menarche, menopause, marriage, and first childbirth were 13.84, 44.68, 18.63, and 20.94, respectively, and the average number of children born was 2.83.

In the present program, 74% of the VIA-positive women complied for cytology and colposcopy. The compliance of VIA positives to referral was 68% in the Kenyan study.<sup>[18]</sup> Of the 574 VIA-positive women who complied to cytology and had adequate cells in the present program, 39 women had findings ASCUS and above on cytology and 58 women had findings CIN 1 and above on histopathology.

In the present study, using positive histology or negative colposcopy as the gold standard, the sensitivity of cytology triage is extremely poor for the outcome CIN 1, at the threshold of LSIL (13.8). It remains poor even with the threshold of ASCUS (25.9). The sensitivity of cytology as triage test is best for outcome  $\geq$  CIN 2 with ASCUS threshold (75.0) followed by LSIL as threshold (50.0). In a study from Kenya, the sensitivity of cervical cytology as a triage test on VIA-positive women was 62% and 80% with CIN 1+ and CIN 2+ as disease outcomes, respectively.<sup>[18]</sup> In one of the Indian studies, the sensitivity of sequential testing of VIA followed by PAP was 75.8.<sup>[19]</sup> An earlier Mumbai study reported sensitivity of 67.9%, 62.3%, and 57.4% of cytology at the threshold of ASCUS+, LGSIL+, and HGSIL, respectively, with CIN 2+ histopathology as the gold standard on all VIA-positive women.<sup>[20]</sup>



**Table 2: Agreement between cytology and colposcopy-directed biopsy**

Histopathology	Cytology						Total
	Benign	HPV	ASCUS	LGSIL	HGSIL	Invasive cancer	
Benign	478	0	18	5	1	0	502
Atypia or HPV	14	0	0	0	0	0	14
CIN 1	40	0	4	1	1	0	46
CIN 2	3	0	2	0	1	0	6
CIN 3	0	0	1	0	5	0	6
Invasive cancer	0	0	0	0	0	0	0
Total	535	0	25	6	8	0	574

ASCUS: Atypical cells of undetermined significance, CIN: Cervical intraepithelial neoplasia, HPV: Human papillomavirus, LGSIL: Low grade squamous intraepithelial lesion, HGSIL: High grade squamous intraepithelial lesion

**Table 3: Final disease status by screening test result for the women found positive on visual inspection with acetic acid and who had simultaneously undergone cytology**

Final diagnosis	Cytology					
	Using ASCUS threshold			Using LSIL threshold		
	Negative	Positive	Total	Negative	Positive	Total
Normal	492	24	516	510	6	516
CIN 1	40	6	46	44	2	46
CIN 2	3	3	6	5	1	6
CIN 3	0	6	6	1	5	6
Total	535	39	574	560	14	574

ASCUS: Atypical cells of undetermined significance, CIN: Cervical intraepithelial neoplasia, LSIL: Low-grade squamous intraepithelial lesion

**Table 4: Test characteristics of visual inspection with acetic acid as primary screening test and cytology as a triage test, using positive histology or negative colposcopy as the gold standard**

Parameter	Cytology as triage							
	Disease status $\geq$ CIN 1				Disease status $\geq$ CIN 2			
	$\geq$ ASCUS		$\geq$ LSIL		$\geq$ ASCUS		$\geq$ LSIL	
	Percentage	95% CI	Percentage	95% CI	Percentage	95% CI	Percentage	95% CI
Sensitivity	25.9	15.3-39	13.8	6.15-25.4	75.0	42.8-94.5	50.0	21.1-78.9
Specificity	95.3	93.2-97	98.8	97.5-99.6	94.7	92.5-96.4	98.6	97.2-99.4
PPV	38.5	23.4-55.4	57.1	28.9-82.3	23.1	11.1-39.3	42.9	17.7-71.1
NPV	92.0	89.3-94.1	91.1	88.4-93.3	99.4	98.4-99.9	98.9	97.7-99.6
FPR	4.65		1.16		5.34		1.42	
FNR	74.14		86.21		25.0		50.0	

ASCUS: Atypical cells of undetermined significance, CIN: Cervical intraepithelial neoplasia, LSIL: Low-grade squamous intraepithelial lesions, NPV: Negative predictive value, PPV: Positive predictive value, FPR: False-positive rates, FNR: False-negative rates, CI: Confidence interval

In the present study, the specificity of cytology as a triage test was best with LSIL threshold both for the outcomes  $\geq$  CIN 1 (98.8) and  $\geq$  CIN 2 (98.6), while it was comparatively lesser using ASCUS threshold both for the outcomes  $\geq$  CIN 1 (95.3) and  $\geq$  CIN 2 (94.7). In the African study from Kenya, the specificity of cervical cytology as a triage test on VIA-positive women was poor for CIN 2+ outcome (48%) and for CIN 1+ outcome (50%).<sup>[18]</sup> The specificity of cytology as a triage test was 83.0 in an Indian study.<sup>[19]</sup> In the Mumbai study, the specificity of pap as triage test was 99.4%, 98.0%, and 96.8% to detect HGSIL+, LGSIL+, and ASCUS+ with histopathology CIN 2+ as the gold standard on VIA-positive women.<sup>[20]</sup>

The PPV of cytology as triage test is best with LSIL as threshold for the outcome  $\geq$  CIN 1 (57.1) and  $\geq$  CIN 2 (42.9). It is much lesser with ASCUS threshold both for outcome  $\geq$  CIN 1 (38.5) and outcome  $\geq$  CIN 2 (23.1). The negative predictive value of cytology as triage is best for outcome  $\geq$  CIN 2 (99.4) with ASCUS threshold, followed by LSIL threshold (98.9). For the outcome  $\geq$  CIN 1, the NPV is much lesser (92.0) for ASCUS threshold and LSIL threshold (91.1). The PPV and NPV of cytology triage in the Kenyan study were 36% and 75%, respectively,<sup>[18]</sup> and in the Indian study were 50 and 93.9, respectively.<sup>[19]</sup> The PPV and

NPV of cytology triage in the Mumbai cross-sectional study were 89.4% and 96.2%, respectively, for HGSIL to detect CIN2+ lesions.<sup>[20]</sup> The PPV and NPV of cytology in the African study were 12% and 97%, respectively.<sup>[18]</sup>

The huge referral burden of false-positive cases resulting from low specificity is the major limitation of VIA-based screening.<sup>[21]</sup> When cytology was used as triage test in the present study, the referral burden was reduced from 785 to 39, i.e., only 4.97% of the original referrals. However, even after combining all VIA-positive cases with cytology, some cases still remained false positives. The false-positive rate of cytology triage was much lesser with LSIL as threshold for the outcomes  $\geq$  CIN 1 (1.16) and outcomes  $\geq$  CIN 2 (1.42) as compared to ASCUS as threshold for the outcomes  $\geq$  CIN 1 (4.65) and  $\geq$  CIN 2 (5.34), respectively. It is important to limit the number of false positives in a screening program, since these women may undergo lot of psychological distress associated with long-term sequelae of unnecessary investigations and overtreatment.<sup>[22]</sup>

The major negative aspect of triaging is missing of the true cases or the false negativity. In the present study, the false-negative rates of cytology triage were 74.14 and 25.0 with ASCUS as threshold and 86.21 and 50.0 with LSIL as

threshold, for the outcomes  $\geq$  CIN 1 and  $\geq$  CIN 2, respectively. The Mumbai study had a false-negative rate of 42.6% cytology triage.<sup>[20]</sup>

Compliance to diagnostic referral of screen-positive women may remain poor in many low-resource settings, wherein the diagnostic centers may be situated at far off distances and there may be other sociocultural and logistic barriers for good compliance. Hence, if the screen positives also receive a triage test at the community level, the number of women needed to be referred to higher centers will reduce, without loss of diagnostic accuracy. Further, there is a loss of compliance at the level of diagnosed cases complying with the treatment. All this can be prevented if treatment is also provided in the same sitting, at the community level. This can be achieved by the use of “see and treat” strategy. However, if all VIA-positive women are to be treated, it will lead to overtreatment, since VIA has a high false-positive rate and many women will get unnecessarily treated. However, overtreatment will be several times less if only VIA and cytology positive women are treated with “see and treat” strategy in the subsequent visit.

The limitation of cytology triage is that it requires laboratory services and skilled cytologists and also does not provide immediate results. Hence, it necessitates revisits by patients for further management, which remains a challenge for implementing cervical cancer screening program in low-resource settings. Meticulous quality control practices for cytology need to be maintained even when it is serving as a triage test.

## Conclusion

To conclude, the test characteristics of cytology triage are much better with CIN 2+ as the gold standard compared to CIN 1+. Cytology triage of VIA-positive cases reduces the referral burden to only 5% of the original referrals. However, this also leads to missing of some precancer cases. The loss is much lesser (25%) with CIN 2+ as the gold standard and ASCUS+ as cutoff. The study findings have special implication for low-resource settings, wherein compliance to referral and availability of diagnostic facilities are poor.

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## Conflicts of interest

There are no conflicts of interest.

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