Ibrahim Card Med J 2024; 14 (2): 37-44
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Diagnostic Accuracy of VIA, Conventional Cytology, HPV DNA Tests in Detecting Premalignant Cervical Lesions

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ABSTRACT

Background & objective: Cervical cancer is a leading cause of cancer-related mortality in women in Bangladesh and other developing countries. Early diagnosis and treatment of premalignant lesions are essential for prevention. This study aimed to evaluate and compare the diagnostic accuracy of three cervical cancer screening methods-Visual Inspection with Acetic Acid (VIA), Conventional Cytology (Pap smear), and Human Papillomavirus (HPV) DNA testing-to inform screening policies in a local setting.

Methods: This cross-sectional descriptive study was conducted from January to December 2022 at the Gynecological Oncology Department of National Institute of Cancer Research and Hospital (NICRH), Dhaka. A total of 100 women aged 25-65 with symptoms and signs suggestive of cervical pathology or suspicious cervical findings on naked eye examination were enrolled. All participants underwent screening with VIA, Pap smear, and HPV-DNA tests, with histopathology serving as the gold standard. Diagnostic accuracy measures, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy, were calculated. Cohen's Kappa statistic was used to assess the inter-rater reliability among the three tests.

Results: HPV-DNA testing demonstrated the highest overall diagnostic accuracy at 89%, with a sensitivity of 68.2% and a specificity of 94.9%. Pap's smear (conventional cytology) showed high specificity (98.7%) but poor sensitivity (31.8%), resulting in an overall accuracy of 84%. VIA had a moderate sensitivity (54.5%) but a low specificity (74.4%), with an overall accuracy of 70%. The inter-rater agreement between the three tests was found to be poor to fair, with Cohen's Kappa values of 0.290 (HPV-DNA vs. Pap), 0.202 (HPV-DNA vs. VIA), and 0.197 (VIA vs. Pap).

Conclusion: The findings suggest that HPV-DNA testing is the most accurate diagnostic tool for detecting premalignant cervical lesions. Its superior performance in sensitivity, specificity, and overall accuracy makes it the most effective screening modality. These results support a strategic shift towards an HPV-DNA-based national screening program in Bangladesh to improve early detection and reduce the burden of cervical cancer.

Key words: Diagnostic accuracy, VIA, conventional cytology, HPV-DNA, Premalignant cervical intraepithelial lesions, colposcopy, Biopsy, histopathology, Gold Standard.

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INTRODUCTION:

Cervical cancer presents a serious global health emergency, with a disproportionate impact on developing regions due to inadequate access to prevention methods. Less developed and developing countries account for the majority (87%) of cervical cancer-related deaths, underscoring ongoing healthcare disparities worldwide.[1] It is the fourth most common cancer among women globally, causing an estimated 604,000 new cases and 342,000 deaths each year. In Bangladesh, it is the second most prevalent female cancer, contributing substantially to national cancer-related morbidity and mortality.[2] Early diagnosis and treatment of cervical precursor lesions are crucial for significantly reducing its incidence and mortality.[3] Despite being largely preventable through effective screening, vaccination, and timely treatment, cervical cancer continues to cause a high burden, primarily due to infrastructural deficits, lack of awareness, and social barriers that impede early detection and intervention.[4-7] The World Health Organization (WHO) has set ambitious targets for controlling cervical cancer by 2030, encapsulated in the 90/70/90 goals: vaccinating 90% of adolescents against HPV, screening 70% of women at least twice with HPV-DNA testing in their lifetime, and ensuring that 90% of women with precancerous lesions or cancer receive effective treatment, including palliative care when necessary.[8] These goals underscore the critical role of screening in the early identification and management of precancerous lesions to reduce incidence and mortality.

High-risk HPV infection is responsible for nearly all cervical cancers, emphasizing HPV testing's critical role in screening. Most HPV infections are transient; only about 10% persist and may progress to CIN1, CIN2, CIN3, and ultimately malignancy.[9] Cervical carcinogenesis unfolds over approximately 10-12 years, providing a window for early detection. While CIN1 often regresses, CIN2 and CIN3 are high-grade lesions with a higher risk of progressing to invasive cancer.[10-14] Early diagnosis and treatment of these lesions are vital to reducing incidence and mortality. For over 60 years, Pap smear cytology has been the main screening tool, significantly reducing cervical cancer rates in developed nations.[5] However, its sensitivity is limited (55.4%), although specificity remains high (96.8%).[16] In resource-limited settings like Bangladesh, widespread Pap screening faces logistical challenges, leading to reliance on opportunistic screening. To address this, WHO recommends screening via Visual Inspection with Acetic Acid (VIA), which involves naked eye inspection after acetic acid application, with sensitivities of 50-96% and specificities of 44-97%-though false positives pose concerns.[8,17,18] In contrast, HPV-DNA testing offers higher sensitivity, negative predictive value, and feasibility for self-sampling, making it an increasingly global standard, especially in developed countries.

Despite the success of large-scale screening programs in reducing cervical cancer in many countries, debates persist regarding VIA's low specificity compared to HPV-DNA tests. The cost and infrastructure constraints limit Pap smears in Bangladesh, and detection in postmenopausal women remains challenging for VIA and cytology. HPV-DNA testing, though costly, provides superior sensitivity and reproducibility. A high-quality, widespread screening program could reduce cervical cancer incidence by up to 80%.[3] The key to elimination is maximizing coverage with the most accurate tests.

Given the current transition from opportunistic VIA screening to organized national programs, there is a pressing need to identify the most effective screening modality in the local context. However, limited data are available from Bangladesh to compare the diagnostic accuracy of VIA, conventional cytology, and HPV-DNA testing in detecting premalignant cervical lesions. This study aims to evaluate the diagnostic performance of these three screening methods in our setting, with the goal of informing policy and optimizing early detection strategies. By assessing the diagnostic accuracy of different methods, this study could play a pivotal role in shaping future cervical cancer screening programs in Bangladesh and similar settings.

METHODS:

Having obtained prior approval from the Ethical Review Committee, this cross-sectional descriptive study was conducted in the Department of Gynecological Oncology at the National Institute of Cancer Research & Hospital (NICRH), Dhaka, over a

Table A. The Swede Colposcopic Index

Swede score	0	1	2
Aceto uptake	Zero or transparent	Shady, milky neither transparent nor opaque	Distinct opaque
Margin/surface	Diffuse	Sharp but irregular, jagged, geographic satellite	Sharp, even difference in Surface level, includes cuffing
Vessels	Fine, irregular	Absent	Coarse or atypical
Lesion size	< 5 cm	5-15 cm or two quadrants	15 cm or 3-4 quadrant or undefined endocervically
Iodine staining	Brown	Faintly or patchy yellow	Distinct yellow

Table B. Overall Swede score colposcopic prediction of probable histology

Overall Swede score	Colposcopic prediction of probable histology
0-4	Low grade/normal, CIN 1
5-6	High grade/non-invasive cancer, CIN 2+
7-10	High grade/suspected invasive cancer, CIN 3

period of twelve months, from January 2022 to December 2022. The study population consisted of women aged 25 to 65 years who attended the Gynecology Outpatient Department (GOPD) for cervical cancer screening and presented with defined symptoms or exhibited suspicious cervix findings upon visual examination. A total of 100 such women were purposively recruited. Enrolment criteria encompassed women within the specified age range, presenting with symptoms such as post-coital bleeding, irregular vaginal bleeding, post-menopausal bleeding, or other clinical signs suggestive of cervical pathology, along with findings of a suspicious cervix on naked-eye examination. However, women with a known frank cervical growth, pregnant women or women in the immediate postpartum period, or those with active cervical infections, unmarried women, or individuals unwilling to participate in the study were excluded. Colposcopic evaluation was done and the result was interpreted with the help of Swede Colposcopic Index as follows:

Data collection was performed using a semi-structured questionnaire designed to capture variables of interest. The collected data were analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY). Descriptive statistics were employed to present qualitative data as frequencies and percentages, while quantitative data were summarized using means, standard deviations, and ranges. Diagnostic accuracy measures-including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)-were calculated. The level of agreement between different diagnostic modalities was evaluated using Cohen's Kappa statistic, a statistical measure of inter-rater reliability. It quantifies the agreement between two methods or raters, accounting for the possibility of agreement occurring by chance. A kappa-value of 1 indicates perfect agreement, while a value of 0 suggests agreement equivalent to chance. In between 0 and 1 the strength of agreement is classified as 0.1-0.2 poor, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial, 0.81-0.99 near perfect, and 1 perfect agreement. The level of significance was set at 5% and a p-value of less than 0.05 was considered statistically significant.

RESULTS:

Baseline characteristics

Socio-demographic characteristics of the study subjects are depicted in the Table I. The mean age was 39.3 ± 8.5 years. Over half (56%) of the subjects were in the range of 31-40 years followed by 41-50 years (25%), 30 or < 30 years (10%), 51-60 years (6%), and > 60 years (3%). Approximately three-quarters (74%) were rural residents, & the rest urban

residents. The majority (98%) was housekeepers and primary level educated (84%). The median income of the subjects was Taka 25000. The vast majority were nonsmokers (98%).

Reproductive and obstetric characteristics

Descriptive statistics (mean/median, SD, and ranges) for reproductive and obstetric characteristics shows that mean age at marriage was 16.4 ± 2.4 years and mean age at first child-birth was 18.3 ± 2.9 years. The median parity was 3. Over 80% of participants reported using oral contraceptive pills, and 17% did not adopt any method. The vast majority (95%) reported having a single sexual partner (Table II).

Presenting symptoms, signs & screening findings

The predominant symptom was vaginal discharge (95%) followed by chronic backache (85%) intermenstrual bleeding (59%), postcoital bleeding, persistent leucorrhoea (each 30%), and post-menopausal bleeding (10%) (Fig. 1). Vaginal speculum examination commonly revealed cervical hypertrophy (62%) and cervical erosion (58%) (Fig. 2). HPV-DNA testing was negative in 81% and positive in 19% of participants. Pap smear results showed high-grade cervical intraepithelial lesions (CIN2+) or malignancy in 8%; the remaining cases were normal or low-grade CIN1. About one-third (32%) of the participants were tested positive on VIA examination (Table III). Most (n=72) participants exhibited normal cervix on colposcopy and 28 had cervical intraepithelial lesions (20 CIN1 and 8 CIN2). Histopathologic findings of colposcopy-directed biopsy material taken from suspected cervical lesions revealed 78% with normal study, 16% with CIN 1 and 6% with CIN 2 (Table IV).

Accuracy of Different Screening Tests in Predicting CIN:

The accuracy of visual inspection under acetic acid (VIA), Pap's Smear, and HPV-DNA tests was assessed against the gold standard diagnostic modality, histopathology. The VIA test revealed that it was 54.5% sensitive to diagnose the cervical cancer correctly, while it showed 74.4% specificity to rule out the condition. The positive and negative predictive values of the test were 37.5%, 85.3% and respectively, while its overall diagnostic accuracy was found to be 70%. Pap's smear test demonstrated a very low sensitivity of 31.8%, although its specificity was appreciably high (98.7%) to exclude the condition. The PPV, NPV, and diagnostic accuracy of Pap's smear were found to be 87.5%, 83.7% and 84% respectively. The HPV-DNA test was moderately sensitive (68.2%) to diagnose the premalignant cervical lesions while its specificity was commendably high (94.9%). The PPV, and NPV of HPV-DNA were 78.9%, and 91.4% respectively with an overall diagnostic accuracy of 89%. These results suggest that HPV-DNA testing provides the best overall screening performance among the three tests (Table-V). Interrater reliability analysis evaluated agreement between HPV-DNA and Pap smear, VIA and Pap smear, and VIA and HPV-DNA using Cohen's kappa statistics. The agreement between HPV-DNA and Pap's test report demonstrated a kappa or k-value of 0.290, indicating a fair agreement (29%) between the two screening tests (p = 0.006). The consistency between HPV-DNA and VIA reports as well as between VIA and Pap's test were poor (k=0.202, p=0.053, and k=0.197 and p=0.012 respectively) (Table VI).

Table I. Socio-demographic characteristics of respondents (n = 100)

Socio-demographic characteristics	Frequency	Percentage	Mean/ Median ± SD
Age group (years)			
≤ 30	10	10.0	--
31-40	56	56.0	--
41-50	25	25.0	--
51-60	6	6.0	--
> 60	3	3.0	--
Mean ± SD	--	--	39.3 ± 8.5
Residence			
Rural	74	74.0	--
Urban	26	26.0	--
Occupation			
Housekeeper	98	98.0	--
Service	2	2.0	--
Education			
Primary	84	84.0	--
Secondary	14	14.0	--
Higher secondary	2	2.0	--
Monthly income (median)	--	--	25000 ±7730
Smoking			
Smoker	2	2.0	--
Non smoker	98	98.0	--

Table II. Reproductive and obstetric characteristics of the subjects (n = 100)

Reproductive and obstetric characteristics	Frequency	Percentage	Mean/ Median ± SD	Range
Age at marriage	---	---	16.4 ± 2.4	12 – 25
Age at first child	---	---	18.3 ± 2.9	15 – 30
Parity	---	---	3	1 – 7
Contraceptives Used	---	---	16.4 ± 2.4	12 – 25
OCP	81	81.0	---	---
Condom	2	2.0	---	---
No method	17	17.0	---	---
Sexual Partner	---	---	16.4 ± 2.4	12 – 25
Single	95	95.0	---	---
Multiple	5	5.0	---	---

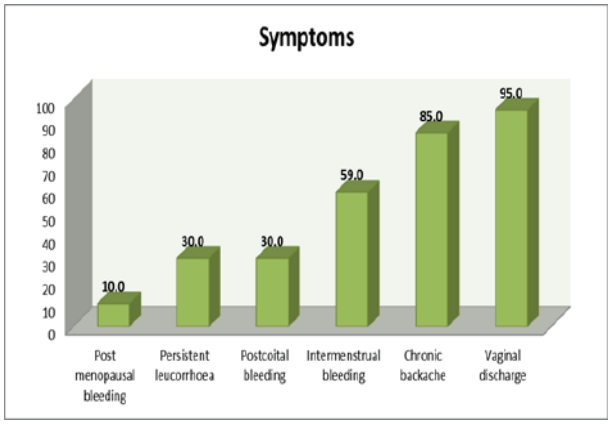

Figure 1: Distribution of the respondents by symptoms

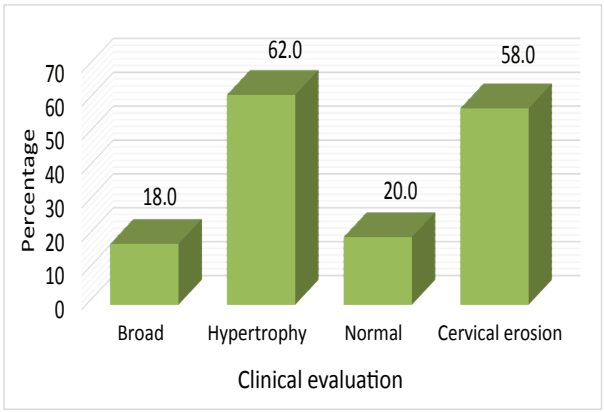

Figure 2: Clinical evaluation of cervix on per speculum examination

Table III. Distribution of study subjects by different screening tests

Screening tests	Frequency	Percentage
HPV-DNA (+ve)	19	19.0
Pap's Smear (+ve)	08	62.0
VIA (+ve)	32	32.0

Table IV. Participants stratified by colposcopic histopathlogic findings (n=100)

Diagnostic Modalities	Frequency	Percentage
CIN-1	20	20.0
CIN-2	08	08.0
Normal	72	72.0
HP Findings		
CIN-1	16	16.0
CIN-2	06	06.0
Normal	78	78.0

Table V. Accuracy of ECG parameters in detecting PH in children with CHD

Screening Tests	HP Diagnosis		Components of Accuracy				
	Positive (n = 60)	Negative (n = 23)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA (%)
VIA							
Positive	12	20	54.5	74.4	37.5	85.3	70
Negative	10	58					
Pap's Test							
Positive	7	1	31.8	98.7	87.5	83.7	84
Negative	15	77					
HPV-DNA							
Positive	15	4	68.2	94.9	78.9	91.4	89
Negative	7	74					

PPV = Positive predictive value, NPV = Negative predictive value, DA = Diagnostic accuracy

Table VI. Agreement between different screening tests

Screening Tests		Agreement between Tests	
		k-statistics	p-value
HPV-DNA	Pap's Smear	0.290	0.006
HPV-DNA	VIA	0.202	0.053
VIA	Pap's Smear	0.197	0.012

DISCUSSION

This study aimed to evaluate the diagnostic performance of three cervical cancer screening methods—Visual Inspection with Acetic Acid (VIA), Conventional Cytology (Pap smear), and Human Papillomavirus (HPV) DNA testing—in the setting of Bangladesh. The findings provide crucial insights into the most effective strategy for early detection of premalignant cervical lesions, a key step in preventing cervical cancer.

Comparison of Diagnostic Accuracies

The present study revealed significant differences in the diagnostic accuracy of the three screening methods, with HPV-DNA test demonstrating the best

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overall performance. The HPV-DNA test showed a sensitivity of 68.2% and an impressive specificity of 94.9% which aligns with other studies as well.[19,20]

This high specificity, coupled with a high negative predictive value (NPV) of 91.4%, means that a negative HPV test result reliably rules out the presence of precancerous lesions, which is particularly valuable for extending screening intervals and reducing unnecessary follow-ups. The high positive predictive value (PPV) of 78.9% also indicates a high probability that a positive result corresponds to a true lesion. This strong performance, reflected in an overall diagnostic accuracy of 89%, aligns with numerous global studies that have established HPV-DNA testing as the gold standard for cervical cancer screening.[21] The high prevalence of high-risk HPV infection as the cause of cervical cancer underpins the effectiveness of this test.

In contrast, VIA had a low sensitivity (54.5%) with a moderate specificity (74.4%). The extremely lower sensitivity of VIA was identified in detail in different studies.[21,22] Although its sensitivity is better than that of the Pap smear, its moderate specificity leads to a significant number of false-positive results. This can cause unnecessary anxiety for patients and strain healthcare resources by leading to an increased number of follow-up procedures like colposcopies, which are often invasive and costly. Despite these drawbacks, VIA's high NPV of 85.3% is a redeeming feature. Given its low cost and ease of implementation in resource-limited settings, VIA remains a viable option for primary screening, particularly in "screen-and-treat" programs where immediate treatment is provided for positive cases.[23,24]

The Conventional Cytology (Pap smear) performed poorly in terms of sensitivity (31.8%), though it had the highest specificity (98.7%) among the three tests. This high specificity means a positive Pap smear result is highly reliable for indicating a lesion (PPV of 87.5%), but its low sensitivity means it misses a large proportion of existing precancerous lesions. The limitations of Pap smears, including their dependence on the quality of specimen collection, slide preparation, and the subjective interpretation by a trained cytologist, are well-documented.[25] These factors contribute to its variable performance and lower sensitivity in comparison to objective molecular tests like HPV-DNA.

Agreement between Screening Methods

The study also assessed the agreement between the different screening tests using Cohen's Kappa statistic. The results indicate a generally poor to fair agreement between the methods. The agreement between HPV-DNA and Pap smear was fair (k=0.290), while the consistency between HPV-DNA and VIA (k=0.202) and between VIA and Pap smear (k=0.197) was poor bearing consistency with findings of Vedantham et al.[22] This lack of strong agreement highlights that the tests are often identifying different subsets of women with cervical pathology, reinforcing the idea that they are not interchangeable. HPV-DNA tests detect the presence of the causative agent, whereas cytology and VIA identify the cellular and visual changes that may result from a persistent infection. This difference in what each test is designed to detect explains the limited agreement between them.

Implications for a National Screening Program in Bangladesh

Based on our findings, a structured HPV-DNA-based screening program would be the most effective strategy for Bangladesh. While the initial costs of HPV-DNA testing are higher compared to VIA and Pap smears, its superior diagnostic accuracy, especially its high NPV, allows for longer screening intervals. This could ultimately reduce the total number of screening visits and associated costs over a woman's lifetime, making it a potentially cost-effective solution in the long run. The high specificity of the HPV-DNA test also reduces the burden on the healthcare system by minimizing unnecessary referrals for colposcopy and biopsy.

The study population's characteristics, such as the mean age of 39.3 years and a median parity of 3, are typical for the target demographic in Bangladesh. The high prevalence of vaginal discharge (95%) and other symptoms underscores the need for an accurate screening method that can effectively differentiate between benign conditions and actual premalignal lesions. The finding of a sizable number of CIN1 (16%) and CIN2 (6%) cases on histopathology emphasizes the importance of early detection and intervention.

While our study's findings strongly support the adoption of HPV-DNA testing, VIA should not be entirely discarded, particularly in settings with limited resources. It can still serve as a valuable tool in a tiered approach, where a positive VIA result leads to immediate treatment or referral for confirmatory testing. However, given the limitations of VIA (low specificity) and Pap smears (low sensitivity), a shift towards more accurate and reliable methods like HPV-DNA testing is essential to align with WHO's cervical cancer elimination strategy[26] and to significantly reduce the morbidity and mortality associated with this preventable disease in Bangladesh. The findings of this study can serve as a strong basis for guiding policy-makers to design an effective and sustainable national screening program.

CONCLUSION:

Based on the comprehensive analysis, this study concludes that HPV-DNA testing is the most effective screening modality for detecting premalignant cervical lesions in Bangladesh. The superior diagnostic accuracy of HPV-DNA testing, particularly its high sensitivity and specificity, makes it the ideal choice for a national cervical cancer screening program. In contrast, both conventional cytology (Pap smear) and Visual Inspection with Acetic Acid (VIA) demonstrated significant limitations in accuracy, making them less suitable for widespread implementation. The study recommends that policymakers in Bangladesh prioritize an HPV-DNA-based screening program. Although initial costs may be a factor, its superior performance and ability to allow for longer screening intervals make it a more cost-effective and clinically sound strategy in the long term, aligning with global efforts to reduce the burden of cervical cancer.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136(5): E359-E386.
2. GLOBOCAN. Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2020. 2020.
3. IARC. Working Group on Cervical Cancer Screening. Summary Chapter. In: Hakama M, Miller AB, Day NE, eds. Screening for cancer of the uterine cervix. IARC Scientific Publications No. 76. Lyon: *IntAgen Res Cancer*;1986:133–42.
4. Poole DN, Tracy JK, Levitz L, Rochas M, Sangare K, Yekta S, et al. A cross-sectional study to assess HPV knowledge and HPV vaccine acceptability in Mali. *PLoS One* 2013;8(2): e56402. doi:10.1371/journal.pone.0056402
5. Denny L. The prevention of cervical cancer in developing countries. *BJOG* 2005;112(9):1204–1212.
6. Leyva M, Byrd T, Tarwater P. Attitudes towards cervical cancer screening: a study of beliefs among women in Mexico. *Californian J Health Promot* 2006;4(2):13–24.
7. Markovic M, Kesic V, Topic L, Matejic B. Barriers to cervical cancer screening: a qualitative study with women in Serbia. *Soc Sci Med* 2005;61(12):2528–2535. doi:10.1016/j.socscimed.2005.05.001
8. Canfel K. Towards the global elimination of cervical cancer. *Papillomavirus Res* 2019;8:100170.
9. Snijders PJ, Steenbergen RD, Heideman DA, Meijer CJ. HPV-mediated cervical carcinogenesis: concepts and clinical implications. *J Pathol* 2006;208(2):152-64. doi: 10.1002/path.1866. PMID: 16362994.
10. Wallin KL, Wiklund F, Angström T, Bergman F, Stendahl U, Wadell G, Hallmans G, Dillner J. Type-specific persistence of human papillomavirus DNA before the development of invasive cervical cancer. *N Engl J Med* 1999;341(22): 1633-8. doi: 10.1056/NEJM199911253412201.
11. Zielinski GD, Snijders PJ, Rozendaal L, Voorhorst FJ, van der Linden HC, Runsink AP, de Schipper FA, Meijer CJ. HPV presence precedes abnormal cytology in women developing cervical cancer and signals false negative smears. *Br J Cancer* 2001;85(3):398-404. doi: 10.1054/bjoc.2001.1926
12. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol* 1993;12: 186-192.
13. Castle PE, Adcock R, Cuzick J, Wentzensen N, Torrez-Martinez NE, Torres SM, et al. Relationships of p16 immunohistochemistry and other biomarkers with diagnoses of cervical abnormalities: implications for LAST terminology. *Arch Pathol Lab Med* 2020;144(6):725–734.
14. Arends MJ, Buckles CH, Wells M. Etiology, pathogenesis, & pathology of cervical neoplasia. *J Clin Pathol* 1998; 51:96–103.
15. Hakama M, Chamberlain J, Day NE, Miller AB, Prorok PC. Evaluation of screening programmes for gynecological cancer. *Br J Cancer* 1985;52:669–673.
16. Mayrand MH, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, et al. Human papilloma virus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med* 2007;357:1579–1588.
17. Schiffman M, Solomon D. Cervical cancer screening with human papilloma virus testing and cytology contesting. *N Engl J Med* 2013;369:2324–2331.
18. Schiffman M. Integration of human papilloma virus vaccination, cytology and human papilloma virus testing. *Cancer* 2007;111(3):145–153.
19. Li N, Shi JF, Franceschi S, Zhang WH, Dai M, et al. Different cervical cancer screening approaches in a Chinese multicentre study. *Br J Cancer* 2009;100:532–537.

20. Arbyn M, Sankaranarayanan R, Muwonge R, Keita N, Dolo A, et al. Pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India. *Int J Cancer* 2008;123:153–160.

21. Gravitt PE, Paul P, Katki HA, Vendantham H, Ramakrishna G, Sudula M, et al. Effectiveness of VIA, Pap, and HPV DNA testing in a cervical cancer screening program in a peri-urban community in Andhra Pradesh, India. *PLoS One* 2010;5(10):e13711. doi:10.1371/journal.pone.0013711

22. Vedantham H, Silver MI, Kalpana B, Rekha C, Karuna BP, et al. Determinants of VIA (Visual Inspection of the Cervix After Acetic Acid Application) positivity in cervical cancer screening of women in a peri-urban area in Andhra Pradesh, India. *Cancer Epidemiol Biomarkers Prev* 2010;19: 1373–1380.

23. World Health Organization (WHO). *WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention.* Geneva: WHO; 2013. Available from:http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf (accessed 10 January 2020).

24. Cubie HA, Campbell C. Cervical cancer screening – the challenges of complete pathways of care in low-income countries: focus on Malawi. *Womens Health (Lond)* 2020;16:1745506520914804.doi:10.1177/1745506520914804

25. Safaeian M, Solomon D, Castle PE. Cervical cancer prevention-cervical screening: science in evolution. *Obstet Gynecol Clin North Am* 2007;34(4):739–760. doi:10.1016/j.ogc.2007.09.004

26. World Health Organization (WHO). Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem. Geneva: WHO; 2020.