COMPARISON OF CERVICAL CANCER SCREENING MODELS BASED ON PAP AND HPV TESTS IN TBILISI, GEORGIA

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SUMMARY

Objective: The objective of this study was to evaluate the effectiveness of human papillomavirus HPV test with HPV16/18 genotyping and liquid-based cytology (LBC) triage as a primary screening method for cervical cancer compared to conventional Pap test in women undergoing routine cervical cancer screening in Tbilisi.

Methods: Cross-sectional, prospective study was conducted, where 1,000 enrolled women aged 30–60 years during one visit underwent conventional Pap smear and Hr-HPV testing (Roche Cobas system). Women with any positive screening results were referred for further evaluation and remaining cells from the Cell Collection Medium vial were used for LBC. The study calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each screening method and receiver-operating characteristic (ROC) curve to evaluate the accuracy of each diagnostic method in identifying people with CIN2+ diseases.

Results: The HPV test with HPV16/18 genotyping and LBC triage demonstrated higher sensitivity (76.9%), specificity (71.6%), and PPV (34.5%) compared to conventional Pap tests ($p < 0.05$). NPV was also high with the HPV test (94.1%). The HPV test alone had the highest sensitivity (92.3%) and NPV (96.7%), but lower specificity (41.4%) and PPV (22.6%) than the HPV test with HPV16/18 genotyping and LBC triage ($p < 0.05$). Comparing the areas under the curve (AUCs), only the HPV with HPV16/18 genotyping and LBC triage showed a statistically significant difference when compared to conventional Pap (0.71 vs. 0.55, $p = 0.03$) and high figures of AUC 0.71 (95% CI: 0.58–0.85) suggesting that HPV test with HPV16/18 genotyping and LBC triage is a more reliable screening method for detecting CIN2+ disease and preventing cervical cancer, than other screening modality.

Conclusion: The results suggest that the HPV test with HPV16/18 genotyping and LBC triage is a more effective primary screening method compared to conventional Pap tests. This information should be the basis for transition from cytological screening to HPV testing in Georgia.

Key words: cervical cancer screening, HPV test, cytology

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https://doi.org/10.21101/cejph.a8014

INTRODUCTION

Cervical cancer (CC) is one of the most common cancers among women and a leading cause of female mortality worldwide, including Georgia. According to the GLOBOCAN/IARC 2020, the estimated number of cervical cancer cases was 604,127, with 341,831 deaths (1). In Georgia, cervical cancer is the fifth most common cancer among women, with approximately 280 new cases diagnosed each year. In 2021, the incidence and mortality rates of CC in Georgia were 14.6 and 7.8 per 100,000 women, respectively (2). This presents a significant health and financial burden for women and the government of the country. However, CC is one of the most preventable diseases through human papilomavirus (HPV) vaccination and screening, including accurate diagnosis and treatment of precancerous cervical lesions – cervical intraepithelial neoplasia grade 2 (CIN2) and worse CIN2+ (3).

For over 60 years, the Papanicolaou test (Pap test) has been used worldwide as the primary screening test for CC (4). Its introduction has decreased the incidence of CC by almost 70% in countries with well-organized screening programmes (5). However, the Pap test has several limitations:

- The pooled sensitivity and specificity of conventional cytology were 65.9% (54.9 to 75.3%) and 96.3% (94.7 to 97.4%), respectively (6). This leads to a high proportion of false negative results and subsequently missed cervical lesions. The low negative predictive value reflects the necessity of repeating the Pap test with a 3–5 years interval to catch CIN2+ (4).
- Cytology shows a high degree of subjectivity, and results depend on the quality of the smear and the skills of the cytopathologist. Therefore, only well-trained cytotechnicians-pathologists who follow regular quality assurance sessions can perform cervical cancer screening (4).

- A Pap test-based CC screening programme is successful if it is based on a call-and-recall model (7). However, due to the cost and implementation problems, this screening method has had only limited impact in low-resource countries where it is most needed.

In the last decade, new scientific discoveries and high-quality studies have shown that the high-risk HPV test is a highly accurate alternative for CC screening (8–11). The HPV test is easy to perform in clinical laboratories and has a high degree of reproducibility. The test has some advantages in comparison with cytology:

- High pooled sensitivity – 95.1% (89.5 to 97.8)) for the detection of CIN2+, which is 37% higher than that of cytology at the lowest cytological cut-off (ASC-US+) on average (6).
- High screening interval – 5–10 years (3).
- High objectivity of results due to the automated testing process (8).

New international recommendations from the WHO, European and American organizations now recognize the HPV test as the preferred test for CC screening over cytology (3, 8, 12, 13). Some developed countries have already replaced cytological screening with HPV screening (12–16). In some developing countries where HPV screening technologies are being introduced, studies have been conducted to compare the results of Pap and HPV screenings to determine the benefits and drawbacks of using this model for a given country (17–19).

CC screening in Georgia is opportunistic and based on the conventional Pap test (using the Bethesda system 2014), targeting women between 25 and 60 years with a screening interval of three years. According to data from the Georgian National CC Screening Programme, 14–15% of participants have a positive Pap test. All women with positive results are referred to colposcopy, as per national guidelines. Despite further colposcopy and biopsy/histology showing that 65% of these women have no lesions, they still undergo follow-up after 6–12 months. This results in an increased load and cost for the screening programme, highlighting the importance of establishing the most efficient, accurate, and cost-effective model of cervical screening in Georgia.

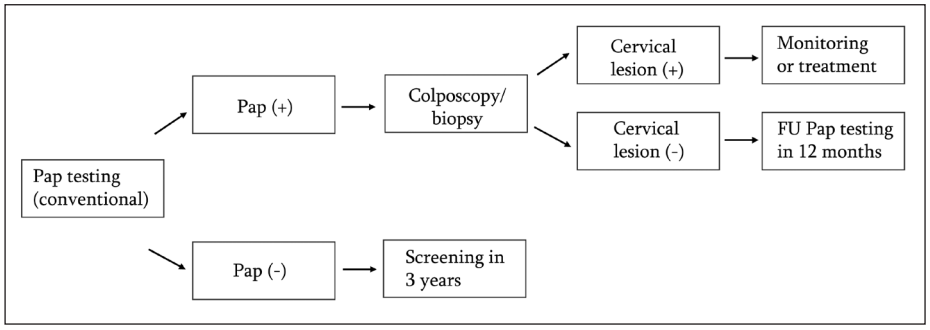
This study, conducted by the Georgian National Screening Centre (GNSC) in Tbilisi from October 2021 to May 2022, is the first to compare the results of HPV and conventional cytology-based screenings for CC in Georgia. The aim of the study was the comparison of the effectiveness of Pap test-based and HPV test-based cervical cancer screening models in detecting CIN2+ lesions in the population of Tbilisi.

MATERIALS AND METHODS

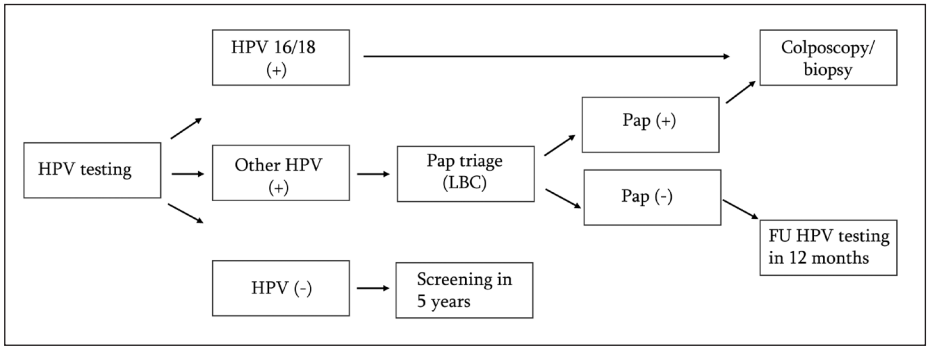
In this cross-sectional, prospective study, we compared two screening models, implemented in accordance with schemes 1 and 2. Participants were enrolled in the study at three different sites of the National Screening Centre located in geographically diverse locations of Tbilisi.

Scheme 1 utilizes a cytological screening approach, employing the conventional Pap test for screening followed by colposcopy confirmation in case of a positive test result. Scheme 2, on the other hand, utilizes molecular screening for high-risk HPV, followed by colposcopy confirmation in case of a positive test result for HPV 16/18, or for other HPV types, triaged with liquid-based cytology (LBC). Only women who test positive for other HPV types and were LBC positive were referred to colposcopy.

To be eligible for inclusion in the study, women had to be between 30–60 years of age, residents of Georgia, and scheduled for a screening round. They were required to confirm their willingness to participate in the study by signing an informed consent form. Women who were currently being followed up for



Scheme 1. *Cervical cancer screening model based on Pap test.*



Scheme 2. *Cervical cancer screening model based on HPV test.*

a cervical lesion, lacked a cervix, were pregnant, had a history of cervical cancer, or were unable to provide informed consent were excluded from the study.

One thousand women were systematically selected to participate in the study: every second woman who came to each facility of the Georgian National Screening Centre for a routine screening round and met inclusion criteria. Participants were fully informed about the study and signed written informed consent forms.

The study was conducted in accordance with ethical requirements set forth by the Institutional Review Board of the Infectious Diseases, AIDS, and Clinical Immunology Research Centre, and the 1964 Helsinki Declaration (OHRP # IRB00006106, N 20-001).

Study Procedure

During one visit all enrolled women after taking conventional Pap smear from the cervix with Ayre wood spatula and endocervical brush, took also additional scrape with new brush for HPV testing using the specially designed trident-shaped Cervex-Brush (Rovers Medical Devices, B.V. Oss, the Netherlands) according to the manufacturer's instructions. Samples were taken by a gynaecologist.

Cytology screening was performed according to the Georgian National Guidelines. Conventional Pap smears glasses for analysis were referred to GNSC Cytolab and results were reported according to Bethesda 2014 system: negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), atypical glandular cells (AGC), atypical squamous cells cannot exclude HSIL (ASC-H), high-grade squamous intraepithelial lesion (HSIL), cancer.

HPV tests were done by Cobas 4800 system (Roche Molecular Systems, Pleasanton, CA, USA) which is an automated qualitative *in vitro* test for the detection of human papillomavirus DNA in patient specimens. The test utilizes amplification of target DNA by the polymerase chain reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk (hr) HPV types in a single analysis. The test specifically identifies HPV16 and HPV18 while concurrently detecting the other high-risk types at clinically relevant infection levels. Cervical cell specimens were collected using Roche Cell Collection Medium vials (Roche Diagnostics GmbH, Mannheim, Germany) and was reported: HPV negative (−), HPV16 or HPV 18 positive (+), and hr-HPV positive (+).

The cytologists were not aware of the HPV DNA test results, nor were the molecular biologists of the cytology results. Women with negative both test (Pap test and/or HPV test) were referred for a further round of screening after 3 years according to the National Guidelines. Women with any positive screening results (Pap test and/or HPV test), or in case of suspicion of cervical cancer during visual examination of cervix were referred to colposcopy. During colposcopy was performed standard 5% acetic acid test and Schiller's test. The result of colposcopy examination was reported using the International Federation for Cervical Pathology and Colposcopy (IFCPC) 2011 nomenclature: normal colposcopic findings, miscellaneous findings, abnormal colposcopic findings – grade 1 (minor), grade 2 (major), and suspicious for invasion. In case of absence of abnormal colposcopy women were referred for follow up visit in 12 months.

Cervical punch biopsy was taken only in the case of abnormal colposcopy. Endocervical curettage was performed in cases of AGC at Pap result. Biopsy tissue was stained according to the standard protocol with Hematoxylin and Eosin (Bio-Optica, Milano, Italy) and was read by two pathologists without knowledge of each other's diagnoses. In case of discrepant results, the final diagnosis was made by consensus. Histology diagnoses were categorized following the CIN classification system as negative (unremarkable, inflammation/cervicitis, squamous metaplasia), cervical intraepithelial neoplasia grade 1, 2, or 3 (CIN1, CIN2 or CIN3), and cancer. If the biopsy revealed CIN1 lesions or less, the women were referred for follow up visit in 12 months. The final endpoint of the study was the histological diagnosis of CIN2 or worse CIN2+, and those women were advised treatment – large loop excision of transformation zone.

In all cases of positive tests (HPV or cytology) the rest cells from Roche Cell Collection Medium vials (Roche Diagnostics GmbH, Mannheim, Germany) were used for LBC cytology.

Statistical Analysis

All data was analysed using SAS/STAT® software version 9.4. The performance of every test or combination of tests was assessed by the calculation of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) along with 95% CIs using Wilson score method. This analysis was performed for the disease threshold CIN2+ for the whole study population.

The ability of each diagnostic method to accurately identify people with CIN2+ diseases was evaluated by calculating the area under the receiver-operating characteristic (ROC) curve using logistic regression model. The model included CIN2+ disease based on morphology test as a dependent variable with four different diagnostic methods included as explanatory variables: HPV scheme 2, HPV alone, LBC Pap, and conventional Pap.

RESULTS

Of 1,000 women enrolled in the study the Roche Cell Collection Medium vials were damaged in two cases and were excluded from analysis. So finally study participants number was 998 women. The median age of study participants was 43.3 years.

From 998 women HPV testing revealed 113 positive cases (11.3%): 33 cases (3.3%) of positive HPV 16 and 18 alone or in combination with other types, and 80 cases (8.0%) of positive HPV other tests. In 872 women (87.4%) HPV test was negative and in 13 (1.3%) women test was inadequate.

Conventional cytology detected 110 abnormal results of 998 cases (11%): ASCUS-55/998 (5.5%), LSIL-44/998 (4.4%), AGC-5/998 (0.5%), and HSIL-6/998 (0.6%) cases.

Overall, 211 colposcopy and 87 biopsy procedures were performed identifying 71/998 (7.1%) cases of < CIN2 and 13/998 (1.3%) cases of CIN2+.

LBC was performed in 224 cases: 208 cases of positive results of conventional cytology or HPV test (95 cases of atypical conventional Pap, 98 of positive HPV cases, 15 cases of positive both conventional Pap and HPV results) and 16 cases of control group (cases with negative cytology and HPV tests). LBC detected 95/224 (42.2%) abnormal results: ASCUS-54/224 (24.1%), LSIL-37/224 (16.5%), ASC-H-2/224 (0.9%), and HSIL-2/224 (0.9%) cases (Table 1).

Table 1. *Results of conventional Pap test, HPV test, biopsy and LBC Pap test*

Conventional Pap test result			HPV test result			Biopsy result			LBC Pap test result		
Result interpretation	**Pap test result**	**n**	**Result interpretation**	**HPV test result**	**n**	**Result interpretation**	**Biopsy result**	**n**	**Result interpretation**	**LBC Test result**	**n**
Pap positive	HSIL (CIN2, CIN3, CIS)	6	HPV 16/18	HPV16	15	Non-disease (< CIN2)	CIN in the canal	1	LBC Pap positive	ASC-H	2
	AGUS	5		HPV16, HPV other	9		CIN1	40		ASCUS	54
	LSIL	44		HPV18	5		Keratosis	1		HSIL	2
	ASC-US	55		HPV18, HPV other	4		No dysplasia	29		LSIL	37
Pap negative	NILM	884	12 other HPV	HPV other	80	Disease (≥ CIN2)	CIN2	10	LBC Pap negative	NILM	112
Inadequate	Inadequate	4	HPV negative	HPV negative	872		CIN3	3	Inadequate	Inadequate	17
			Inadequate	Inadequate	13	Inadequate	Inadequate	3	Not done	Not done	774
						N/A (not done)	Not done	911			
Total	998			Total	998		Total	998		Total	998

Table 2. *Results of biopsy according to HPV test results and LBC Pap smear results*

HPV	LBC	Biopsy result		Total n (%)
		Negative (< CIN2) n (%)	Positive (≥ CIN2) n (%)	
HPV16/18	Pap negative	4 (4.8)	5 (6.0)	9 (10.7)
HPV16/18	Pap positive	3 (3.6)	3 (3.6)	6 (7.1)
Other	Inadequate	3 (3.6)	0 (0.0)	3 (3.6)
Other	Pap negative	19 (22.6)	2 (2.4)	21 (25.0)
Other	Pap positive	12 (14.3)	2 (2.4)	14 (16.7)
Negative	Inadequate	3 (3.6)	0 (0.0)	3 (3.6)
Negative	Pap negative	10 (11.9)	1 (1.2)	11 (13.1)
Negative	Not done	6 (7.1)	0 (0.0)	6 (7.1)
Negative	Pap positive	10 (11.9)	0 (0.0)	10 (11.9)
Inadequate	Pap positive	1 (1.2)	0 (0.0)	1 (1.2)
Total		71 (84.5)	13 (15.5)	84 (100.0)

Among 84 women with biopsy result, 72 had valid LBC Pap results (NILM, ≥ASC-US) and 83 had valid HPV test results and all had valid conventional Pap results.

Number of colposcopy referrals in case of scheme 1 was 110 (all cases of abnormal conventional Pap tests results) and in case of scheme 2 – 68 (all cases with positive HPV16 and 18 (33) plus positive HPV other tests with abnormal LBC Pap results) (Table 2).

Separately for conventional Pap test (scheme 1), HPV test with HPV 16/18 genotyping and reflex to LBC Pap (scheme 2), HPV test alone and LBC Pap test were calculated sensitivity, specificity, PPV, and NPV along with 95% CIs using Wilson score method (Table 3).

The study compared the diagnostic performance of four different screening modalities for detecting cervical cancer. When looking at sensitivity, the HPV test alone had the highest sensitivity (92.3%), followed by the HPV test with HPV16/18 genotyping and LBC triage (76.9%), while the conventional Pap test had the lowest sensitivity (30.8%). Besides, the HPV test with HPV16/18 genotyping and LBC triage (scheme 2) had the highest specificity (71.6%), while the HPV test alone had the lowest specificity (41.4%). When considering PPV, the highest PPV was observed with the HPV test with HPV16/18 genotyping and LBC triage (scheme 2) (34.5%), while the conventional Pap test had the lowest PPV (11.8%). For NPV, the HPV test alone had the highest NPV (96.7%), while the LBC Pap test had the lowest NPV (80.5%).

Receiver Operating Characteristic Curve Analysis

The area under the curve (AUC) with 95% confidence intervals (CI) was calculated to determine the predictive ability of each method for accurately diagnosing CIN2+ disease. The results showed that the AUC remained above the 0.5 cut-off only for the HPV-based diagnostic methods. Specifically, the AUC for HPV scheme 2 was 0.7 (95% CI: 0.6–0.8), and the AUC for HPV alone was 0.6 (95% CI: 0.5–0.7), indicating a good predictive ability of these methods. In contrast, the AUC for both Pap and LBC methods was the same – 0.5 (95% CI: 0.4–0.7), with their lower

Table 3. *Sensitivity, specificity, PPV and NPV for each of the testing schemes and methods*

	Scheme 1 (conventional Pap test)			Scheme 2 (HPV 16/18 genotyping with reflex to LBC Pap test)			HPV test alone			LBC Pap test		
	Biopsy result			Biopsy result			Biopsy result			Biopsy result		
	Non-disease (< CIN2)	Disease (≥ CIN2)	Total	Non-disease (< CIN2)	Disease (≥ CIN2)	Total	Non-disease (< CIN2)	Disease (≥ CIN2)	Total	Non-disease (< CIN2)	Disease (≥ CIN2)	Total
Negative	41	9	50	48	3	51	29	1	30	33	8	41
Positive	30	4	34	19	10	29	41	12	53	26	5	31
Total	71	13	84	67	13	80	70	13	83	59	13	72
Sensitivity (95% CI)	30.8 (12.7–57.6)			76.9 (49.7–91.8)			92.3 (66.7–98.6)			38.5 (12.0–64.9)		
Specificity (95% CI)	57.8 (46.2–68.6)			71.6 (59.9–81.0)			41.4 (30.6–53.1)			55.9 (43.3–68.6)		
PPV (95% CI)	11.8 (4.7–26.6)			34.5 (19.9–52.6)			22.6 (13.4–35.5)			16.1 (3.2–29.1)		
NPV (95% CI)	82.0 (69.2–90.2)			94.1 (84.1–98.0)			96.7 (83.3–99.4)			80.5 (68.4–92.6)		

Wilson score method was used for calculation.

95% confidence bounds dropping below 0.5, suggesting lower accuracy compared to HPV-based methods.

However, when comparing the AUCs, only the HPV scheme 2 showed a statistically significant difference when compared to conventional Pap (0.7 vs. 0.5, p = 0.03). No statistically significant differences were found between HPV alone vs. conventional Pap and LBC Pap vs. conventional Pap (Fig. 1). Furthermore, there were no statistically significant differences between HPV scheme 2 (AUC 0.7) and HPV alone (AUC 0.6).

DISCUSSION

In this study we compared the effectiveness of two screening models of cervical cancer, namely, primary Pap-test and HPV test. Our study provides strong evidence that HPV testing is a more reliable screening method than cytology for detecting CIN2+ cases. Our results demonstrated that CIN2+ detection was 3 times higher with HPV test alone and 2.5 times higher with HPV test with HPV16/18 genotyping and LBC triage (corresponding 12 and 10 CIN2+ cases) compared to conventional Pap smear (4 cases of CIN2+). Our study also found that out of 13 cases of CIN2+, the conventional Pap test missed 9 cases of CIN2+, and the HPV test alone missed only one case of CIN2+. The HPV test with HPV16/18 genotyping and LBC triage (scheme 2) missed only two cases of CIN2.

Since the discovery that HPV infection is the main cause of CC (20), there have been significant advances in the early diagnosis of precancerous lesions. Initially, the HPV test was used as a triage test for ASCUS and LSIL atypia in cytological screening. Later, it became a test for confirming the absence of HPV after

Method	AUC (95% CI)	Difference in AUC vs. PAP (95% CI)	p-value
HPV scheme 2	0.7 (0.6; 0.8)	0.2 (0.01; 0.3)	0.03
HPV alone	0.6 (0.5; 0.7)	0.1 (-0.1; 0.1)	0.27
LBC	0.5 (0.4; 0.7)	-0.02 (-0.2; 0.2)	0.86
PAP	0.5 (0.4; 0.7)		

Fig. 1. *ROC curves for comparison of scheme 1 (conventional Pap test), scheme 2 (HPV 16/18 genotyping with reflex to LBC Pap test), HPV alone, and LBC Pap test.*

surgical treatment, and now HPV testing is a proven and accurate methodology for primary cervical cancer screening. However, the main disadvantage of the HPV test is that it can detect HPV infections that are transient and do not result in disease ("false positive" HPV test results) (21).

To address this, HPV (+) cases require further triage to identify women at a particularly high risk of developing cervical cancer. One evidence-based option is cytology, where only cases with abnormal cytology are referred to colposcopy. This algorithm is used in the national guidelines of several countries, including Turkey, Australia and the Netherlands (14–16). Another option is HPV genotyping, as women infected with HPV16 and/or HPV18 are more likely to develop CIN2+ lesions than those infected with other high-risk genotypes. One suggestion is that women with infection by the most high-risk types (such as HPV 16 or 18) could be referred immediately to colposcopy, and others recalled at regular screening intervals (22, 23).

Overall, HPV testing has revolutionized cervical cancer screening and has the potential to greatly reduce cervical cancer incidence and mortality. However, there is still a need for continued research to optimize screening algorithms, including triage strategies for HPV-positive women, to ensure that the benefits of screening are maximized while minimizing the harms of unnecessary diagnostic procedures.

In April 2014, the Cobas HPV test by the Roche Molecular Systems, Incorporated, Pleasanton, California, was approved by the US Food and Drug Administration (FDA) as a stand-alone method for cervical cancer screening. The sensitivity of the Cobas 4800 HPV test for detecting CIN2+ diseases ranges from 88% to 100%, according to various studies (24–29).

Our study found a sensitivity of 92.3%. However, the specificity of the HPV test alone as part of diagnostic modality in our study (41.4%) was lower than that reported in other studies (23–30). This lower specificity suggests that the HPV test alone may yield a high number of false-positive results and lead to unnecessary medical interventions. The specificity of the HPV test with HPV16/18 genotyping and LBC triage in our study was 71.6%, which is encouraging and means that it is better suited to identify healthy women and results in fewer overdiagnoses. We suggest that the lower specificity results in our study may have been affected by the quality of the sample. In our study, the HPV test was performed after a cytological scraping, which could potentially cause bleeding, particularly in the presence of vaginal infection and cervicitis, and this could have reduced the accuracy of the HPV test. Another factor that could have contributed to the different performance characteristics of the HPV test is the fact that colposcopy was not performed in our programme in a cytologically normal and HPV-negative population, and in cases of normal colposcopy findings, we did not perform a random biopsy. This could have led to partial underdiagnosis of lesions. It is known that the subjectivity of colposcopy may affect colposcopy diagnosis and biopsy sampling (31).

Regarding the cytology test performance, both conventional and LBC Pap tests showed low sensitivity rates of 30.8% and 38.5%, respectively. The accuracy of the Pap test greatly depends on the training and expertise of the providers, as well as the workplace infrastructure. The specificity of the cytology tests in our study also differs from the findings of other authors, with rates of 57.8% and 55.9% for conventional and LBC Pap tests, respectively. The pooled specificity of the conventional Pap test based on 16 studies is 96.3%, and for LBC Pap (based on 15 studies) is 91.8% in the systematic literature review (6). The low specificity results of our study could be explained by a high proportion of false positive Pap results, especially ASCUS and LSIL.

It is important to note that the accuracy of both HPV testing and cytology testing can be influenced by various factors, including the quality of the sample obtained, the expertise of the healthcare provider, and the diagnostic criteria used. Therefore, it is crucial to interpret the results of these tests in the context of other clinical and histological findings, and to ensure that quality assurance measures are in place to minimize the risk of false positive and false negative test results.

PPV indicates that a positive test result is more likely to indicate the presence of the disease, which can help avoid unnecessary diagnostic tests or treatments for false positive results. From this point of view, in our study, the HPV test with HPV16/18 genotype and LBC triage (scheme 2) has priority over other screening tests (34.5%).

Another important characteristic of a screening test is its NPV, which indicates that a negative test result is more likely to indicate the absence of the disease. In our study, the NPV for detecting CIN2+ using the HPV test alone was 96.7%, NPV using HPV test with HPV16/18 genotyping and LBC triage was 94.1%, NPV of conventional cytology in our study was 82.0%, which is lower than that obtained by other authors (28–30).

Although our NPV results were not as high as those reported by some other studies, they still indicate that a negative test result is generally reliable and can provide reassurance to patients and healthcare providers. Overall, our findings suggest that the HPV test with HPV16/18 genotype and LBC triage (scheme 2) may be the most effective screening option, as it had a high PPV and a moderate NPV, and was more effective than other screening options tested in our study.

While the specific figures for sensitivity, specificity, PPV, and NPV of our study's various screening schemes differed from those reported by other researchers, our findings are consistent with the trend that HPV screening is superior to cytological screening.

The same conclusion was reached by analysing ROC curves, which showed that only HPV scheme 2 had a statistically significant difference when compared to conventional Pap (0.7 vs. 0.5, $p = 0.03$) and had high figures of AUC 0.7 (95% CI: 0.6–0.8) suggesting that HPV with HPV16/18 genotyping and LBC triage (scheme 2) is a highly reliable screening method for detecting CIN2+ disease and in this way further prevent cervical cancer. Therefore, it should be considered as an alternative to cytology-based screening for cervical cancer prevention.

CONCLUSIONS

The study findings demonstrated that, similar to other countries, HPV testing is a more accurate screening modality than cytology and has a higher detection rate for CIN2+ lesions in the context of Georgia. These results support the use of HPV testing as the initial screening method, incorporating HPV16/18 genotyping and reflex LBC cytology (ASCUS threshold) for HPV16/18 negative but other high-risk HPV positive women. This information is critical for screening authorities and the government to consider

gradual transition from cytological screening to HPV testing. To further evaluate the implementation of this new screening model in clinical practice, a large longitudinal pilot study on a city or regional scale should be planned.

Acknowledgements

We thank all members of the Georgian National Screening Centre for active participation in the study. We also gratefully acknowledge the participation of 1,000 women volunteers who have made this project possible.

Conflicts of Interest

None declared

Funding

The Cobas HPV test kits and consumables for this study were provided by the Roche Diagnostics (http://molecular.roche.com). There were no other funding sources or sources of support. All the necessary work for the study performed by physicians, cytologists, pathologists and technicians was incorporated in their routine daily practice and was covered by the Georgian National Screening Programme.

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Received August 16, 2023
Accepted in revised form August 7, 2024