

# Evaluation of multiple screening methods for cervical cancers in rural areas of Xinjiang, China

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## Abstract

This study is to evaluate the screening methods of cervical cancers for rural females in Kash bachu, Xinjiang, China.

A total number of 3000 married females were surveyed, and subjected to the gynecological examination. In these subjects, 1993 females received the careHPV (human papillomavirus) test, while 1007 females underwent the visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI). The subjects positive for careHPV detection were subjected to Cervista, Cobas 4800, and Aptima HPV detection, and Thinprep Cytologic Test (TCT). The subjects positive for 1 detection only received colposcopy cervical biopsy.

A total of 569 subjects received the cervical biopsy, and the positive rate was 2.3% (69/3000), while the detection rate for CIN (cervical intraepithelial neoplasia) II and above levels was 1.13% (34/3000). Receiver operator characteristic (ROC) curve analysis showed that, the area under the curve (AUC) value for the careHPV test was 0.671, which was higher than the VIA/VILI (0.619), suggesting higher diagnostic value for the careHPV test. For the Cervista, Cobas 4800, Aptima HPV detection, and TCT methods, the highest AUC value was observed for the TCT method, indicating that the TCT method is the most valuable for the cervical cancer screening.

The diagnostic value of careHPV test is superior to the VIA/VILA detection method. The TCT method has the greatest value for the cervical cancer screening. The Cervista HPV detection method should be considered where the conditions are limited.

**Abbreviations:**  $\geq$ CIN II = Cervical Intraepithelial Neoplasia Grade 2 or Higher, AUC = area under the curve, CIN = cervical intraepithelial neoplasia, HPV = human papillomavirus, ROC = receiver operator characteristic curve, TCT = Thinprep Cytologic Test, VIA = visual inspection with acetic acid, VILI = visual inspection with Lugol's iodine.

**Keywords:** cervical cancer screening, high-risk HPV detection, TCT, VIA/VILI

## 1. Introduction

Cervical cancer is one of the main threats to the women's health, which not only brings great economic burden and psychological pressure to the involved individuals and families, but also increases the national medical financial expenditure. Fortunately,

the cause of cervical cancer has been clarified. Moreover, the available vaccines in the market would contribute to the efficient prevention of the cervical cancer.

The prevention and treatment level of cervical cancer is one of the indicators to reflect the fairness of public health service for a specific country, in which early screening method is one of the effective methods to reduce the disease incidence. Moreover, the prevention and early diagnosis of cervical cancer are strongly recommended by the World Health Organization. The early screening of diseases can significantly improve the curing rates, and reduce the economic burden due to the later treatment.<sup>[1,2]</sup> The thin-layer liquid-based cytology, that is Thinprep Cytologic Test (TCT), combined with the human papillomavirus (HPV) detection, significantly improves the screening sensitivity and specificity for cervical cancers, which is currently the most effective screening method for the disease. However, it is expensive and not suitable for the economically underdeveloped rural and marginal areas. Therefore, it is of great importance to find and/or develop a screening program that is low in cost and has certain sensitivity and specificity.

In this study, the careHPV test and VIA (visual inspection with acetic acid)/VILI (visual inspection with Lugol's iodine) primary screening methods were performed and compared. The cases positive for the careHPV test were further subjected to the Cervista, Cobas 4800, Aptima high-risk HPV detections, and TCT. The cases negative for the careHPV test were subjected to careHPV test at review after 3 years. The diagnostic outcomes of Cervista, Cobas 4800, Aptima high-risk HPV detections, and TCT were analyzed and compared.

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## 2. Materials and methods

### 2.1. Study subjects

Based on the cluster sampling method, from August 10, 2105 to September 20, 2105, in total 3000 Uighur females (with sexual life) were subjected to the questionnaire survey for the cervical cancer screening. They were local permanent residents in the Bachu County, Xinjiang, China (involving 4 small towns and 2 towns). Inclusion criteria were as follows: rural nonpregnant females aged 35–64 years old, with a history of sexual life, with no history of hysterectomy, pelvic radiation therapy, or chemotherapy, who did not take vaginal medication or have sexual life within 3 days before the examination. The exclusion criteria included: subjects with deafness or mental retardation, mental illness that was not suitable for the gynecological examination, or cervical insufficiency; subjects with no cervix; subjects with acute reproductive tract inflammation, or intolerance to examination due to severe internal and/or external diseases; subjects who did not finish the questionnaires; or subjects who should be excluded according to the gynecological examinations. Written informed consent was obtained from every patient and the study was approved by the local ethics review board.

### 2.2. Questionnaire survey

The included subjects were asked to complete the Cervical Cancer Screening Questionnaire. In order to ensure the personal privacy and the authenticity of the answers to the questionnaire, the interview questionnaire was conducted in a one-on-one and face-to-face manner.

### 2.3. Screening methods

These 3000 female subjects were divided into the HPV and VIA/VILI groups. Basic information was collected from the subjects who finished and completed the questionnaire. For the VIA/VILI group, the gynecological examination and sample collection were conducted by the trained gynecologists from the Maternal and Child Health Hospital of the Bachu County and the gynecologists from our hospital (with the titles of attending physicians or above). For the HPV group, the careHPV test samples were harvested with the careHPV sampler. After screening, the female subjects with positive result based on the careHPV test or VIA/VILI detection were further subjected to the colposcopy and the 4-quadrant biopsy. In the 1993 females subjected to screening, the cases positive for the HPV test results (in total 217 cases) and about 7% negative cases (except for Aptima), were further detected with the Cobas 4800 high-risk HPV detection, Cervista enzyme digestion signal amplification method, and Aptima HPV detection. For the suspicious lesions, the biopsy samples were collected. On the other hand, subjects with no suspicious lesions received the random 4-quadrant biopsy and endocervical curettage.

### 2.4. VIA detection

The surface of the cervix was smeared with 5% acetic acid. After 60 seconds, the changes related to the cervix were observed with the naked eye, especially the cervical transformation area. Initial diagnosis was obtained based on the thickness, extent, surface morphology, and turbidity of the white epithelium. Cervical abnormalities were suggested by the positive findings from the

acetic acid, as follows: after smearing with the acetic acid, the cervix exhibited thickened white lesions, which were opaque and oyster-like wax white, with irregular clear boundaries and nonsmooth surface, adjacent to the squamo-columnar junction; in the transformation area, the lesions appeared rapidly and lasted for relatively long period (2–3 min).

### 2.5. VILI detection

For the VILI detection, the cervix was evenly smeared with 5% iodine solution. The normal cervix epithelium would absorb the iodine and showed brown, while the abnormal cervical epithelium would not be colored and showed pale yellow or mustard yellow. Diagnosis was made based on the degree of coloration and the shape, edge, and size of the colored area, as well as its distance from the scale column. Cervical abnormalities were suggested by the positive results from the iodine staining, as follows: the cervix would not be stained by iodine (or uncolored) and showed mustard yellow, khaki, or banana yellow, with irregular clear boundaries, and the nonsmooth surface.

### 2.6. The careHPV test

In total 14 high-risk HPV subtypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 types) were detected with the commercially available kit (careHPV test kit; Qiagen, Hilden, Germany). To collect the samples, the Qiagen cervical brush (careBrush) was held against the cervical opening by the gynecologist, which was then rotated clockwise for 6 to 8 turns. The brush head was placed in the careHPV collection medium to collect the cervical epithelial cells, and the sample was collected and stored at  $-80^{\circ}\text{C}$ . The test was completed within 1 to 3 days after sample collection, and the careHPV test was completed on site. The test procedures mainly included: lysis, hybridization, capture, washing, luminescence, and detection. The whole process took 2.5 hours.

### 2.7. Cobas 4800 high-risk HPV detection

The Cobas 4800 HPV detection was performed with the same biological samples as TCT. The sample was obtained by rotating the sampling brush clockwise for 3 to 5 turns. The exfoliated cells at the junction of the cervical squamous column were effectively adhered, which were then placed in the PreservCyt cell preservation solution. The thin-layer cell images were obtained and analyzed with the equipment and typing test kits from the Kapude Technology Development Co, Ltd, Harbin, Heilongjiang, China.

### 2.8. Cervista enzyme digestion signal amplification

The Cervista sampling brush was placed into the cervical canal to the 1-cm depth, which was rotated clockwise for more than 3 turns. The sampling brush was then placed in the sealed bottle. The Cervista high-risk HPV laboratory reagents, consumables, and instruments were all provided by the Hologic Corporation, Waltham, MA.

### 2.9. Aptima HPV test

The Aptima HPV test was performed with the kit from the Hologic Corporation. The cervical sample cells stored in the

PreservCyt Solution from the NewPherson TCT cytology test would be used herein, as well as the cervical sample cells collected using a broom, brush, or squeegee sampler. To collect the TCT samples, the patient was set in the lithotomy position, and the sampling brush was rotated clockwise at the cervix opening for 6 to 8 turns. The brush head was then placed in the Thinprep fixative solution. The test was performed with 1 week of the sample collection.

### 2.10. Electronic colposcopy and biopsy

In this study, patients positive for the careHPV test or VIA/VILI test received the colposcopy and were diagnosed by the pathological biopsy. The electronic colposcope used a similar system with the inverted microscopy to enlarge the cervix for observation. With the light source and filter system, the fine structure of the cervix could be observed, to determine whether the cervix had abnormal or suspicious lesions.

### 2.11. Biopsy specimen processing

The biopsy specimen was appropriately flattened, and then placed in 10% neutral formalin for 24h. Then the samples were subjected to the embedding, sectioning, and related processing.

### 2.12. Statistical analysis

All the original data were checked and recorded in the EpiData 3.1 (CDC, Atlanta, GA). SPSS 18.0 software was used for statistical analysis. To describe the basic characteristics, the quantitative data were expressed as mean  $\pm$  SD. Qualitative data were expressed as frequency. The chi-square and rank sum test were used for the comparison of different individual characteristics. Receiver operator characteristic curve (ROC) analysis was performed and the area under curve (AUC) value was calculated.  $P < .05$  was considered as statistically significant.

## 3. Results

### 3.1. General information of study subjects

In total 3000 females completed the gynecological examinations and questionnaires, with an average age of  $44.95 \pm 6.66$  years. In these subjects, 77.87% had with the education level of junior high school and below. These subjects were randomly divided into the VIA/VILI ( $n=1007$ ) and careHPV test ( $n=1993$ ) groups, respectively. In the VIA/VILI group, there were 79 positive cases, with the positive rate of 7.85% (79/1007). On the other hand, in the careHPV test group, there were 217 positive cases, with the positive rate of 10.9%. Moreover, there were 569 patients receiving the cervical biopsy, and the detection rate for the CIN (cervical intraepithelial neoplasia) II and above levels was 1.133% (34/3000). In addition, based on the results from the VIA/VILI and careHPV tests, there were no significant differences in the distribution of the 12 related indicators, including the baseline characteristics and behavior information ( $P > .05$ ). Basic information of the subjects (age at screening, marital status, education level, family income and occupation, etc.) and behavioral factors (in total 12 indicators, including the menarche age, lover's partner, age of first sexual act, age at first marriage, number of live births, menopause, and breastfeeding) was analyzed.

### 3.2. Comparison of VIA and VILI screening methods

In the study, in total 1007 females participating in the survey underwent the VIA and VILI tests. The patients with positive results received the colposcopy and biopsy. The accuracy for the VIA and VILI detection was compared and summarized in Tables 1 and 2. As shown by the ROC analysis, the AUC values for the VIC and VILI detecting methods were 0.619 and 0.622, respectively, which were comparable (Fig. 1). Our results showed that there were no significant differences in the diagnostic value between the VIA and VILI methods ( $P > .05$ ).

### 3.3. Comparison of VIA/VILA and careHPV screening tests

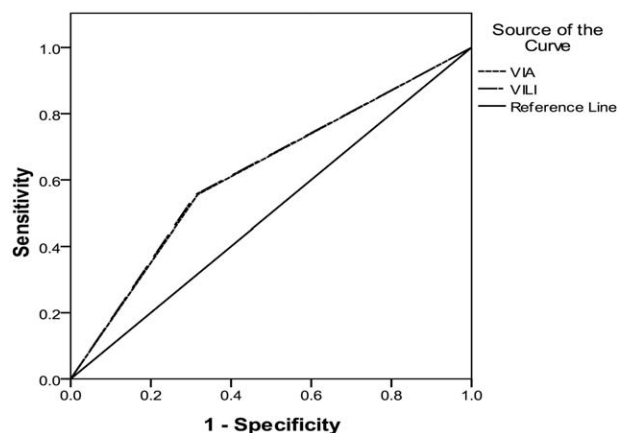
As shown in Tables 3 and 4, in the ROC analysis, the AUC values for the careHPV test and VIA/VILI were 0.671 and 0.619, respectively (Figs. 2 and 3). Moreover, the Kappa value for the careHPV test was higher than the VIA/VILI detection, indicating that the diagnostic value of careHPV test was superior to the VIA/VILI detection.

### 3.4. Baseline analysis for subjects in careHPV group

In total 1933 females received the careHPV, the Cobas 4800, Cervista, and Aptima HPV detection methods to analyze the basic information and behavioral factors of these involved females. Our results showed that there were no significant differences in the 8 indicators (such as basic characteristics and behavior factors) between these 3 groups ( $P > .05$ ). The basic information of females (the age at screening, occupation, marital status, and education level) and behavioral factors (in total 8 indicators, including the menarche age, first sexual behavior age, and number of live births) was analyzed (Table 5).

### 3.5. Comparison for careHPV groups with different ages

As shown in Table 6 and Figure 4, the females with the highest positive rate of HPV screening were mainly aged 60 to 64 years (15.1%), followed by the 40 to 44 year age group. Moreover, the highest detection rate of CIN II<sup>+</sup> lesions was observed in the 50 to 54 year age group. Our results showed that there was no



**Figure 1.** ROC analysis for the VIA/VILI screening method. ROC= receiver operator characteristic curve, VIA=visual inspection with acetic acid, VILI = visual inspection with Lugol's iodine.

**Table 1**  
Evaluation of VIA and VILI screening methods.

	Chronic cervicitis	Pathological outcome			Total
		CIN I	CIN II	CIN III	
VIA					
Positive	61	2	0	5	68
Negative	131	5	1	3	140
VILI					
Positive	60	2	0	5	67
Negative	132	5	1	3	141
Total	192	7	1	8	208

CIN = cervical intraepithelial neoplasia, VIA = visual inspection with acetic acid, VILI = visual inspection with Lugol's iodine.

**Table 2**  
ROC analysis of VIA/VILI screening methods.

	Sensitivity%	Specificity%	Positive predictive value%	Negative predictive value%	AUC	SE	P	95% CI	Kappa
VIA	55.6	68.3	7.4	97.1	0.619	0.099	.226	0.426–0.813	0.058
VILI	55.6	68.8	7.5	97.2	0.622	0.099	.216	0.429–0.815	0.060

AUC = area under the curve, CI = confidence interval, ROC = receiver operator characteristic curve, SE = standard error, VIA = visual inspection with acetic acid, VILI = visual inspection with Lugol's iodine.

significant difference in the positive rate of HPV screening, or in the detection rate of CIN II<sup>+</sup> lesions, between different age groups ( $P > .05$ ).

### 3.6. Valuation of TCT, and cervista, cobas 4800, and aptima high-risk HPV detection methods

As shown in Tables 7 and 8 and Figure 5, for these 4 methods, TCT had the highest AUC value (0.802) in the ROC analysis, with the sensitivity and specificity of 64% and 96.4%, respectively. Moreover, for the Cervista, the AUC value was 0.747, with the sensitivity and specificity of 84% and 65.5%, respectively. Furthermore, for the Cobas 4800, the AUC value was 0.723, with the sensitivity and specificity of 92% and 52.7%, respectively. In addition, for the Aptima, the AUC value in the

ROC analysis was 0.679, with the sensitivity and specificity of 95.7% and 40.2%. The Kappa value was 0.572, suggesting satisfactory consistency with the careHPV screening method.

## 4. Discussion

In the rural and marginal areas of Xinjiang, the females could not receive appropriate screening service due to the insufficiency of staff, funds, materials, and equipment, as well as the inconvenient transportation and low technical capability. In this study, several methods were used in the screening of cervical cancer in Xinjiang, China, to find a screening method suitable for these females in the marginal areas, at reasonable price and with high accuracy.

Xinjiang, in general, southern Xinjiang, in particular, is one of the areas with high incidence of cervical cancer. In this study, in total 3000 females were screened with the careHPV test and VIA/VILI detection, and the incidence for the cases with CIN II and above levels was 1.13% (34/3000). The detection rates of CIN II and above levels differ from country to country. Our results showed that the incidence herein was lower than the UK (2%) as indicated by previous studies,<sup>[3,4]</sup> higher than the results from a previous Finnish study (0.55%),<sup>[5]</sup> lower than the incidence in East China (the incidence of cervical precancerous lesions and cervical cancer is 10.3%) and Shanxi, China, where the incidence of cervical cancer is about 4.6%.<sup>[6]</sup> Moreover, the incidence obtained herein was also lower than the incidences from the early diagnosis and treatment program in Moyu, Hetian, in 2013 (1.33%), and the screening of cervical cancer in rural females in

**Table 3**  
Evaluation of initial screening tests of VIA/VILA and careHPV.

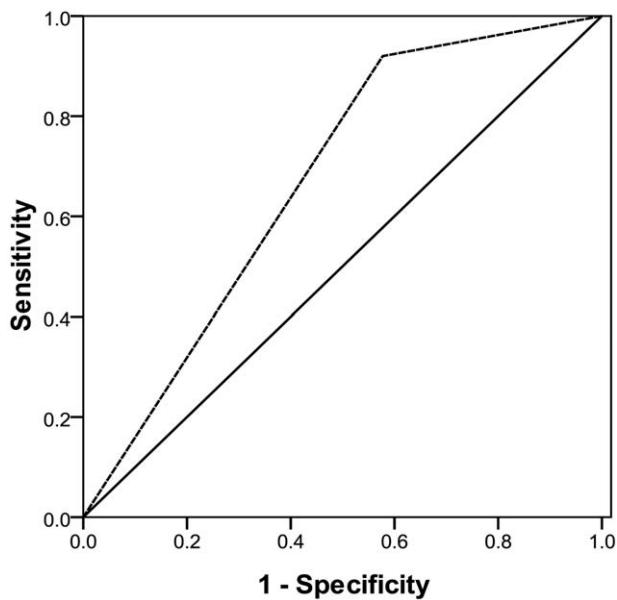
Detection results	Pathological outcome		Total
	Positive	Negative	
careHPV screening			
Positive	23	194	217
Negative	2	142	144
VIA/VILA screening			
Positive	5	63	68
Negative	4	136	140

HPV = human papillomavirus, VIA = visual inspection with acetic acid, VILI = visual inspection with Lugol's iodine.

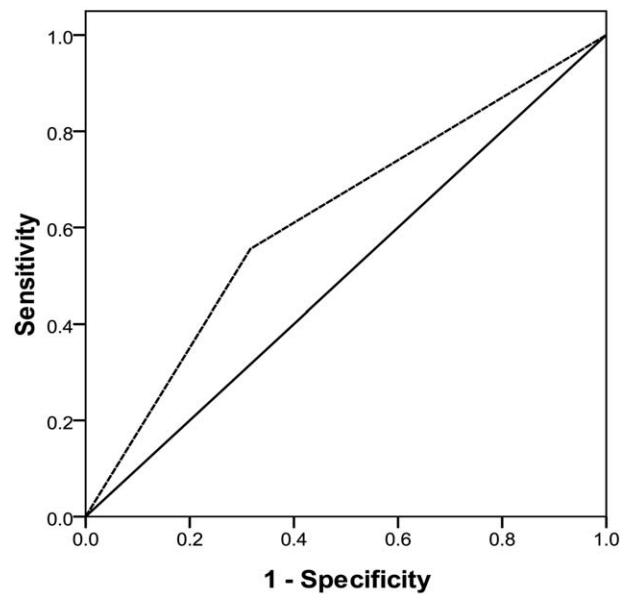
**Table 4**  
ROC analysis of VIA/VILA and careHPV primary screening methods.

	Sensitivity%	Specificity%	Positive predictive value%	Negative predictive value%	AUC	SE	P	95% CI	Kappa
careHPV	92.0	42.3	10.6	98.6	0.671	0.046	.004	0.581–0.762	0.075
VIA/VILA	55.6	68.3	7.4	97.1	0.619	0.099	.226	0.426–0.813	0.058

AUC = area under the curve, CI = confidence interval, HPV = human papillomavirus, ROC = receiver operator characteristic curve, SE = standard error, VIA = visual inspection with acetic acid, VILI = visual inspection with Lugol's iodine.



**Figure 2.** ROC analysis of careHPV screening method. HPV=human papillomavirus, ROC=receiver operator characteristic curve.



**Figure 3.** ROC analysis for the VIA/VILI screening method. ROC=receiver operator characteristic curve, VIA=visual inspection with acetic acid, VILI=visual inspection with Lugol's iodine.

Bachu County in 2014 (1.66%). These differences in the disease incidence from different countries and regions might be caused by the differences in the following factors: screening subjects (sociodemographic characteristics), geographical location, popularity of cervical cancer screening, investigation protocols and methods, sample size, economic status, and propaganda intensity. In addition, some of the subjects participated in the early diagnosis and screening of these 2 cancers in Bachu, Hetian in 2014, indicating that the incidence of CIN in the area with high screening frequency is significantly lower than the area with relatively lower frequency. The VIA/VILI visual observation method is the basic program for screening of cervical cancer in underdeveloped areas in China. The reports of VIA and VILI screening programs abroad mainly came from the developing countries and regions, such as India and Africa. It has been shown that the visual observation could help effectively prevent the occurrence of cervical cancer, thereby reducing the disease incidence and mortality. In 2015, 21,806 cases in 4 pilot counties in Hunan, China, were subjected to the careHPV test, whose false negativity rate was significantly lower than the cervical cytology and the VIA/VILI detection, also with higher sensitivity.<sup>[7]</sup> In this study, our results showed that the diagnostic value of the careHPV test was superior to the VIA/VILI detection. The sensitivity and specificity of the VIA/VILI detection method was relatively low, accompanied by certain misdiagnosis and missed diagnosis rates. In addition, considering the cost, a VIA/VILI test would cost about 10 Yuan, while the careHPV test would cost 30 Yuan. Although the cost of the careHPV test is relatively higher than the VIA/VILI test, the careHPV test could provide the screening results in relatively short time. Furthermore, the careHPV test needs only simple equipment, and is easier to operate. Therefore, the careHPV test is suitable for the hospitals in the rural township, especially for those less developed regions where it is difficult to use cytology as the first choice for primary screening due to the limitations of the technology, equipment, and economic development.

There are differences in the HPV infection rates in different regions and populations, and the HPV infection rates are also different for the patients with different degrees of cervical lesions. In this study, the positive detection rate of the careHPV test was 10.9%, which was lower than the reported HPV infection rate in China (16.8%)<sup>[8]</sup>. Reports on the HPV infection rates in different populations in other countries and areas also show different findings. The HPV infection rate herein was lower than the rates reported from a screening survey of house holding females in Concordia, Argentina (16.6%)<sup>[9]</sup> and another HPV screening of females with normal TCT in Colombia (14.9%).<sup>[10]</sup> Compared with these previous findings, the relatively lower HPV infection rates in the rural females in Xinjiang, China, might be due to the differences in ethnicity, lifestyle, habits, and sexual behavior. HPV infection is affected by various social and economic factors. Moreover, there are also differences in the HPV infection rates between different age groups. Therefore, it is of great significance to investigate the epidemiological characteristics of HPV infection in females from different regions and with different ages for the prevention and treatment of cervical precancerous lesions and cervical cancers. However, differential findings about the onset age of cervical cancers are obtained from previous studies. A previous study has shown that there were 2 age-related peaks in the HPV infection incidence, that is, younger than 20 years old and older than 55 years old.<sup>[11]</sup> However, in China, the incidence of cervical cancer in the females younger than 30 years old is at relatively low level, which is increased over the age of 30–44 years old (rapidly being increased after 35 years old), peaking between 45 and 59 years old.<sup>[12]</sup>

In this study, the highest positive HPV screening rate was observed for the women aged 60–64 years old (15.1%), and the highest detection rate for CIN II+ lesions was observed in the 50–54 age group (11.1%). These findings were in contrary with the results from the screening in Bachu county in 2014,<sup>[13]</sup> which has shown that the subjects aged 60–65 years old had the lowest positive rate for the VIA/VILI detection (3.7%). This discrepancy

**Table 5**  
Basic characteristics of women participating in careHPV test screening.

	N	Cobas 4800 HPV test (+), N (%)	Cervista HPV test (+), N (%)	Aptima HPV test (+), N (%)
N	1993	182	137	138
Average age, years	44.82 ± 6.83	45.53 ± 7.35	45.99 ± 7.24	45.59 ± 7.09
Age				
35–39 y	513	41 (8.0%)	26 (5.1%)	32 (69.6%)
40–44 y	534	52 (9.7%)	40 (7.5%)	34 (49.3%)
45–49 y	445	35 (7.9%)	30 (6.7%)	31 (72.1%)
50–54 y	286	28 (9.8%)	19 (6.6%)	22 (71%)
55–59 y	142	15 (10.6%)	13 (9.2%)	13 (76.5%)
60–64 y	73	11 (15.1%)	9 (12.3%)	6 (54.5%)
Occupation				
Farmer	1777	170 (9.6%)	128 (7.2%)	130 (65.7%)
Staff + medical staff	114	4 (3.5%)	3 (2.6%)	2 (25%)
Unemployed	66	4 (6.1%)	2 (3%)	2 (40%)
Others (worker 3+freelance 33%)	36	4 (11.1%)	4 (11.1%)	4 (66.7%)
Education level				
Illiteracy	501	43 (8.6%)	32 (6.4%)	35 (68.6%)
Junior high school and below	1366	133 (9.7%)	102 (7.5%)	100 (64.5%)
High school and above	126	6 (4.8%)	3 (2.4%)	3 (27.3%)
Average age of first delivery, years	18.33 ± 3.04	18.14 ± 2.74	18.08 ± 2.87	17.96 ± 2.83
Age of first delivery				
≤ 14 y	25	3 (12%)	3 (12%)	3 (100%)
15–16 y	493	42 (8.5%)	37 (7.5%)	36 (70.6%)
17–18 y	791	81 (10.2%)	55 (7%)	62 (65.3%)
≥ 19 y	684	56 (8.2%)	42 (6.1%)	37 (54.4%)
Average number of live birth, N	3.53 ± 1.72	1.78 ± 0.42	3.36 ± 1.54	3.43 ± 1.5
Number of live birth,				
0–2 times	446	40 (9%)	33 (7.4%)	30 (66.7%)
≥ 3 times	1525	138 (9%)	102 (6.7%)	104 (62.3%)
Breast feeding				
Yes	1924	5 (9.8%)	4 (7.8%)	2 (28.6%)
No	51	173 (9%)	131 (6.8%)	132 (64.4%)
Menopause situation				
Perimenopause	145	16 (11%)	12 (8.3%)	15 (83.3%)
Premenopause	1219	101 (8.3%)	76 (6.2%)	74 (60.7%)
Menopause	629	65 (10.3%)	49 (7.8%)	49 (63.6%)
Average age of first sexual behavior, years	16.39 ± 2.34	16.09 ± 1.97	15.93 ± 1.92	15.96 ± 1.96
Age of first sexual behavior, years				
≤ 14 y	346	35 (10.1%)	29 (8.4%)	28 (75.7%)
15–16 y	879	80 (9.1%)	60 (6.8%)	64 (63.4%)
17–18 y	541	53 (9.8%)	40 (7.4%)	36 (63.2%)
≥ 19 y	227	14 (6.2%)	8 (3.5%)	10 (45.5%)

HPV = human papillomavirus.

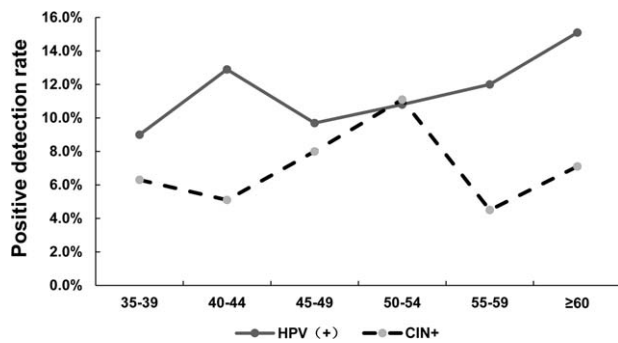
would be explained by the following reasons: first, considering that women of this age are mostly in menopause, the changes in the progesterone levels would affect the metaplasia of cervical epithelium, which accelerates the replication of HPV. Second, the

gradual decline of women's immune function at this age level also leads to a gradual decrease in the body's ability to clear the HPV in the body, which is more likely to cause the HPV infection. Third, the increased HPV infection rate in women of this age may

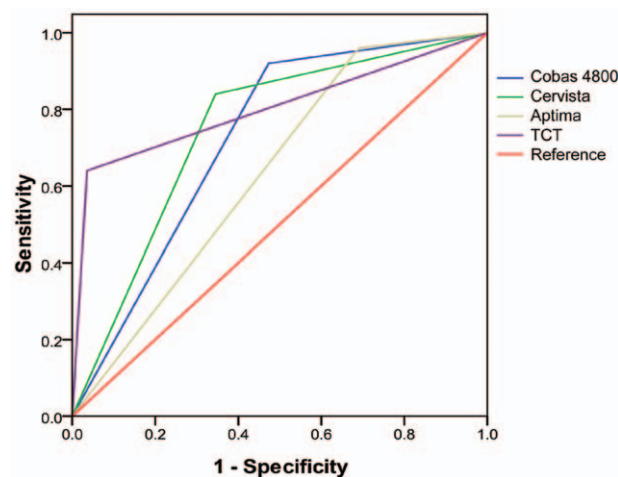
**Table 6**  
Comparison of careHPV test screening in different age groups.

Groups	N	Positive for HPV primary screening		Positive for CIN II+ detection N (%)	95% CI
		N (%)	95% CI		
35–39 y old	513	46 (9.0%)		5 (6.3%)	
40–44 y old	534	69 (12.9%)	0.095–8.14	6 (5.1%)	1.015–2.235
45–49 y old	445	43 (9.7%)	0.078–6.301	6 (8.0%)	0.702–1.68
50–54 y old	286	31 (10.8%)	0.125–10.186	6 (11.1%)	0.763–1.995
55–59 y old	142	17 (12.0%)	0.179–14.723	1 (4.5%)	0.765–2.491
60–64 y old	73	11 (15.1%)	0.036–10.775	1 (7.1%)	0.886–3.661

CIN = cervical intraepithelial neoplasia, HPV = human papillomavirus.



**Figure 4.** Positive rates of careHPV screening and CIN II+ detection rates for different age groups. CIN=cervical intraepithelial neoplasia, HPV=human papillomavirus.



**Figure 5.** ROC analysis for TCT and HPV detection screening methods. HPV=human papillomavirus, ROC=receiver operator characteristic curve, TCT=Thinprep cytologic test.

be due to the fact that the postmenopausal HPV infection will tend to be single-type, increasing the monoclonal replication of integrated virus, which also contributes to the malignant transformation of cells. In addition, the lowest and highest levels of HPV infection were observed in the 35–39- and 40–44-year-old age groups, respectively. However, the CIN II+ detection rate was relatively low, which might be related to the immunity of the body to clear the HPV infection. Therefore, the detection of HPV infection should be strengthened for the females with the age greater than 45–65 years old, and the early diagnosis and treatment of the cervical lesions could prevent the occurrence and development of cancers.

**Table 7**  
Evaluation of the detection results of four HPV screening methods.

Detection results	Pathological outcome		Total
	Positive	Negative	
TCT			
Positive	16	12	28
Negative	9	324	333
Cobas 4800			
Positive	23	159	182
Negative	2	177	179
Cervista			
Positive	21	116	137
Negative	4	220	224
Aptima			
Positive	22	116	138
Negative	1	78	79

TCT=Thinprep Cytologic Test.

Clinical studies have shown that the combination of TCT and high-risk HPV detection (from the cellular morphological and molecular biological respects, respectively) could significantly improve the screening rate for the precancerous lesions and the diagnostic accuracy for the cervical cancer, which is of great value in the clinical screening for the diseases. It has been shown that, compared with the TCT and high-risk HPV screening method alone, the combination of these 2 screening methods could significantly improve the accuracy, sensitivity, and specificity of cervical cancer screening, contributing to the improved clinical diagnostic rate, suggesting great clinical value.<sup>[14,15]</sup> In this study, TCT was used as the method for the careHPV detection, and the AUC value was 0.802. Compared with these three high-risk HPV detection tests, it had higher AUC value, suggesting that the diagnostic value of the TCT method was higher than the other 3 high-risk HPV detection methods. Although the sensitivity was not high, the specificity and the AUC value were relatively high, again suggesting that the TCT detection had high diagnostic value for the CIN and cervical cancers. It can be used as the first choice for the cervical cancer screening in the developed areas.

In conclusion, our results showed that, for the 3 high-risk HPV screening methods, the TCT method had the highest value for the screening of cervical cancers. Our findings suggest that the Cervista HPV detection method can be used as a sensitive method for the cervical cancer screening in underdeveloped and/or rural areas. When the condition for TCT is limited, the Cervista HPV screening method could be considered. According to the technological simplicity and practicality, appropriate screening strategies and methods should be chosen based on the actual conditions.

**Table 8**  
ROC analysis of TCT, and Cervista, Cobas 4800, and Aptima methods.

	Sensitivity%	Specificity%	Positive predictive value%	Negative predictive value%	AUC	SE	P	95% CI	Kappa
TCT	64.0	96.4	57.1	97.3	0.802	0.059	<.001	0.686–0.918	0.572
Cervista	84.0	65.5	15.3	95.2	0.747	0.046	<.001	0.657–0.838	0.161
Cobas	92.0	52.7	12.6	98.9	0.723	0.042	<.001	0.640–0.806	0.114
Aptima	95.7	40.2	15.9	98.7	0.679	0.048	<.001	0.586–0.773	0.112

AUC=area under the curve, CI=confidence interval, ROC=receiver operator characteristic curve, SE=standard error, TCT=Thinprep Cytologic Test.

## Author contributions

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**Writing – original draft:** Gulimire Naizhaer.

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