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Cervical cancer screening: comparative study of human papillomavirus detection between cervical cytology and urine samples

Jinwei Song[1,2] and Jiandong Wang[1*]

Abstract

Objective To evaluate the efficacy of urine-based human papillomavirus detection in detecting high-grade cervical lesions (CIN2+) compared to cervical cytology examination.

Method The data of 458 patients with cytological abnormalities and/or positive human papillomavirus test results were retrospectively selected from December 1, 2017, to March 31, 2022, at the Beijing Obstetrics and Gynecology Hospital affiliated with Capital Medical University. Cervical cytology and urine samples were used to detect human papillomavirus status and analyze the correlation between the results and cervical biopsy results.

Results Among the selected 458 samples, 386 were positive for human papillomavirus through cervical cytology examination, with a detection rate of 84.3%. Out of 458 urine samples, 362 were positive, with a detection rate of 79.0%. The data shows a high consistency between cervical cytology and urine sample testing, with a kappa value of 0.637 ($P < 0.01$). The most prevalent subtypes in cervical samples included HPV16, HPV58, and HPV52, while the detection rates of HPV16 and HPV58 subtypes were relatively high in urine samples. The comparison of subtype distribution between cervical and urine samples showed that the positivity rate of HPV44 subtype was consistent, both at 3.9%. Among the five HPV subtypes corresponding to the HPV nine-valent vaccine, the kappa value of HPV16 in cervical and urine samples was 0.791 ($P < 0.05$), the kappa value of HPV52 was 0.766 ($P < 0.05$), HPV18 was 0.762 ($P < 0.05$), HPV33 was 0.539 ($P < 0.01$), and HPV31 was 0.458 ($P < 0.05$). Among 458 specimens, the sensitivity of human papillomavirus detection in cervical cytology was 96.7%, with a specificity of 20.2% ($P < 0.01$). The sensitivity of human papillomavirus detection in urine samples was 85.2%, with a specificity of 23.2% ($P < 0.01$).

Conclusion Urine human papillomavirus testing, as a non-invasive screening method, has significant application effects. The screening results are highly consistent with cervical cytology screening and may improve the compliance of women who do not want to undergo invasive gynecological examinations. This screening method simplifies the screening process and has great potential in screening cancer lesions and preventing cervical cancer.

Keywords Urine testing, Human papillomavirus, Cervical cell detection, Vaginal colposcopy biopsy

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Background

Cervical cancer remains a major global health issue, primarily caused by high-risk Human Papillomavirus (HPV) infection. Epidemiological studies [1] have shown that approximately 80% of sexually active women will be infected with the HPV at some point in their lives, with about 10% developing persistent infections that may lead to cervical precancerous lesions or cancer. Globally [2], cervical cancer is the fourth most common cancer among women, with reports showing 604,000 new cases and 342,000 deaths in 2020. In low- and middle-income countries, the number of new cases is higher due to the lack of national cervical cancer screening programs. The limited opportunities and ways of prevention have led to an increase in incidence rate and mortality, especially among young women [3]. Data research emphasizes the importance of cervical cancer screening, which is crucial to reduce the incidence rate and mortality of cervical cancer.

The main cause of cervical cancer is persistent infection with HPV, and effective detection of HPV can be an important way to screen for cervical cancer [4]. Traditional Pap cytology is the standard for cervical cancer screening, but its sensitivity for detecting high-grade cervical lesions (CIN2+) is only 65% [5]. Compared with it, the second-generation hybrid capture detection (HC2) shows strong screening performance, with a sensitivity of 96.0% and specificity of 90.5% for identifying HPV infection [6]. HPV types mainly include HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, and HPV59, which are closely related to the risk of cervical cancer [7]. The real-time fluorescence quantitative Polymerase Chain Reaction (PCR) technology used domestically to detect HPV DNA can accurately detect and distinguish different HPV genotypes, which is crucial for disease risk assessment and management of disease progression [8]. Multiple methods have been applied in HPV screening and genotyping to achieve significant therapeutic effects. However, some regions lack medical services and women lack awareness of disease screening, resulting in some women missing early diagnosis of cervical cancer, delaying treatment, and reducing treatment effectiveness. Therefore, adopting simple, convenient, and non-invasive testing methods is crucial for improving the early detection rate of cervical cancer precancerous lesions, obtaining timely treatment early, and improving disease prognosis.

The characteristic of cervical epithelial tissue is that there is a thin layer of squamous cells that tend to continuously shed, and shedding accelerates after HPV infection. Exfoliated cells and cervical secretions accumulate around the vaginal opening and labia minora. During urination, the flow of urine washes away these cells and secretions, allowing for the detection of HPV in urine samples [9]. Research has shown [10] that there is high diagnostic consistency between urine samples and cervical samples, and urine testing has the advantage of non-invasive operation. When traditional screening methods are not ideal and invasive procedures are required, urine testing can be a more beneficial testing method. Urine samples can be collected by patients themselves, with simple operation and strong privacy. The sampling time and location are relatively flexible, which improves the compliance of patients in remote areas or areas with insufficient services for cervical cancer screening. Due to logistical constraints, traditional beliefs, and work schedules in these areas, population choices for healthcare may be limited [11]. With the development of digital health, household urine sampling has become a promising research direction for cervical cancer screening, strengthening patients' compliance with disease screening and enhancing their participation in early disease detection [12]. This study selected 458 women with cytological abnormalities and/or positive HPV test results, all of whom met the criteria for diagnostic colposcopy and biopsy, to evaluate the efficacy and relevance of urine-based HPV testing in screening and detecting CIN2+.

Methods

Research materials

This study collected cervical cell and urine samples from 458 women aged 20–60 years with an average age of (45.2 ± 10.6) years. These women underwent screening for suspected cervical precancerous lesions at the Beijing Obstetrics and Gynecology Hospital affiliated with Capital Medical University, and underwent vaginal colposcopy and HPV biopsy. According to their clinical manifestations, all participants showed indications for vaginal colposcopy biopsy. Ethical approval for this study was obtained from Capital Medical University. All experiments in this study were conducted in accordance with relevant guidelines and regulations, as well as the Declaration of Helsinki. Written informed consent was obtained from all patients.

Inclusion and exclusion criteria

Inclusion criteria: (A) The uterus and its appendages are intact; (B) Screening and testing show abnormal cervical cytology evidence or high-risk HPV positivity; (C) Having unexplained vaginal discharge and bleeding symptoms; (D) Normal mental state and cognitive function; (E) Meets the indications for vaginal colposcopy examination (cervical erosion like appearance, non-physiological erosion, symptoms cannot be improved after treatment), with contact bleeding, abnormal lesions in the cervix detected by naked eye, and growths in the vagina or cervix [13]; (F) The patient signed an informed

consent form and was able to comply with the research procedures.

Exclusion criteria: (A) Suspected pregnancy; (B) Previous history of cervical surgery or hysterectomy surgery; (C) Merge ureteral, bladder or kidney tumors; (D) Previously received pelvic radiotherapy treatment.

Research methods

Urine sample collection and HPV testing

Urine sampling: Patients are required to avoid sexual activity, vaginal lavage or medication treatment, and ensure no vaginal bleeding within 72 h before sample collection. Collect 10mL of the first morning urine or the first urine after 1 h of no urination using a sterile urine collection device containing 7mL of storage solution. Then, put the sample into the device for testing.

Urine sample preservation: Mix the collected urine thoroughly with buffer solution, filter, and centrifuge for 20 min to obtain a concentrated solution. Divide each patient's sample into three equal parts and store them at room temperature or at -20 °C. Randomly conduct preliminary experiments on these three aliquots to extract HPV DNA from urine using a centrifugal column method. Evaluate the sample qualification rate, achieving a success rate of 100%. Then, store the sample in a laboratory at -20 °C for further analysis.

HPV testing in urine samples: For HPV testing, first, use a centrifuge column to process the stored urine and remove the supernatant. Add 20 μl of proteinase K20 to 1mL of the sample and mix thoroughly. Then, add 200 μl of cell lysis buffer and mix it evenly by shaking. Incubate the sample solution in a 56℃ water bath for 15–20 min and add 200 μl anhydrous ethanol. The mixture is placed in a centrifuge tube on a silica gel column and centrifuged at 1000 rpm for 1 min. Abandon circulation and add 500 μl of cell lysis buffer W1, W2, and W2 sequentially into a silica gel column, centrifuging at the same speed and duration each time. After discarding the final circulating liquid, centrifuge the empty tube at 12,000 rpm for 3 min. Then, place the gel column in the test tube, open and air dry for 1–2 min, and elute with TE buffer. Centrifuge at 12,000 rpm for 2 min and let the column stand for 2–5 min. Discard the column and collect the elution solution containing HPV DNA from the tissue for analysis [11].

Cervical cell sample collection and HPV detection

Sample collection and preservation: Collect cervical cells using a cervical exfoliated cell collector at the bladder stone removal site and immediately place them in a cell preservation solution. If the sample is to be tested within two weeks, it should be stored at 4 °C. If tested within six months, it should be stored at -20 °C.

HPV testing of cervical samples: First, prepare for the test by centrifuging 2 ml of cervical exfoliated cell samples at 13,000 rpm for 1 min to separate the supernatant. Then, discard the supernatant. Add 0.5 ml of sample cell preservation solution and mix thoroughly, followed by centrifugation again at 13,000 rpm for 1 min. After discarding the supernatant, add 50 μl of cell lysate to the sample, shake, mix, and boil for 10 min. Centrifuge the sample at 13,000 rpm for 10 min to obtain the supernatant for analysis. Use a kit equipped with amplification reagents, and centrifuge the sample for 10 s at a speed of 8000 rpm. PCR reaction analysis: Mix 18 μl of amplification reagent with 2 μl of DNA sample in a reaction tube, and gently centrifuge. Then, transfer to a fluorescent PCR detection instrument for analysis [14]. Obtaining cervical samples is quite complex. Communication and exchange with the inspector should be carried out before the inspection, and the inspection process, cooperation matters, and precautions should be educated to ensure the smooth and accurate completion of the inspection.

Vaginal colposcopy tissue biopsy

Before obtaining the sample, inform the patient of the examination procedure and guide them to take the bladder lithotomy site. The examination items include the evaluation of secretions from the perianal area, external genitalia, vagina, and cervix. Use 3–5% acetic acid staining to identify damaged tissue. During vaginal colposcopy, use forceps to select the location of obvious lesions on the cervix for biopsy. If necessary, the diseased tissue in the cervical area can be scraped off, or additional samples can be obtained from external genital tissue. If no suspicious lesions are observed in the cervix, routine biopsies should be performed at the 3, 6, 9, and 12 o'clock positions of the cervix, and the specimens should be subjected to pathological examination. Informing the patient of the significance of conducting this examination before sample inspection is to enable them to clearly understand the importance of the examination, actively cooperate with the examination, inform the patient that their privacy will be protected according to regulations during the examination, and communicate the examination items in advance to improve cooperation [15].

Detection of various types of HPV in urine and cervical samples

PCR amplification is used to analyze various HPV types in HPV DNA samples from the cervix and urine. The types of detection include HPV16, HPV58, HPV52, HPV53, HPV56, HPV66, HPV18, HPV42, HPV81, HPV33, HPV51, HPV68, HPV59, HPV39, HPV44, HPV43, and HPV31.

Table 1 Consistency between cervical cell sample detection and urine sample detection

Project indicators	Detection method	Cervical cell specimen		*kappa*	*P*
		Positive	Negative		
Urine detection	Positive	362	0	0.637	$P<0.001$
	Negative	24	72		

Data statistics processing

SPSS software version 26.0 was used for data processing and analysis. The categorical data was represented by the number of cases (n) and the percentage (%). Chi square ($\chi 2$) test was used for inter group comparison. The diagnostic criteria were based on the results of HPV testing through cervical cell and vaginal colposcopy tissue biopsy. Histologically confirmed high-grade lesions (CIN2+) in cervical biopsies were used as the gold standard. Sensitivity, specificity, positive predictive value, and Negative Predictive Value (NPV) were calculated based on the positivity rate. Kappa analysis evaluates the consistency between the test results of urine samples, cervical cell samples, and vaginal colposcopy tissue biopsies. The explanation of the kappa number is as follows. Less than 0 indicates poor consistency, 0 to 0.20 indicates mild consistency, 0.21 to 0.40 indicates weak consistency, 0.41 to 0.60 indicates moderate consistency, 0.61 to 0.80 indicates strong consistency, and 0.81 to 1.00 indicates very strong consistency. A P value < 0.01 is considered statistically significant.

Results

Consistency analysis between cervical cell specimen detection and urine specimen detection

Among the selected 458 samples, 386 were positive for HPV through cervical cytology examination, with a detection rate of 84.28%. Out of 458 urine samples, 362 were positive, with a detection rate of 79.04%. The data shows a high consistency between cervical cytology and urine sample testing, with a kappa value of 0.637 ($P<0.01$), indicating that the two testing methods are consistent, as shown in Table 1.

Positive cases of human papillomavirus analysis with different types of cervical markers

Different subtypes of HPV were analyzed in 458 cervical cell specimens, and the most prevalent subtypes in cervical samples included HPV16, HPV58, and HPV52, reflecting the expected distribution of subtypes in China. For HPV16 and HPV58, as well as some other high-risk subtypes, the detection rates of these subtypes in urine samples were usually slightly higher, highlighting the sensitivity of urine-based detection (Fig. 1). The comparable distribution of subtypes between cervical and urine samples showed that HPV44 maintained a consistent positivity rate of 3.9% in both methods, indicating that urine testing effectively reflected the subtype distribution observed in cervical cytology, supporting its potential utility in non-invasive HPV screening, as shown in Table 2.

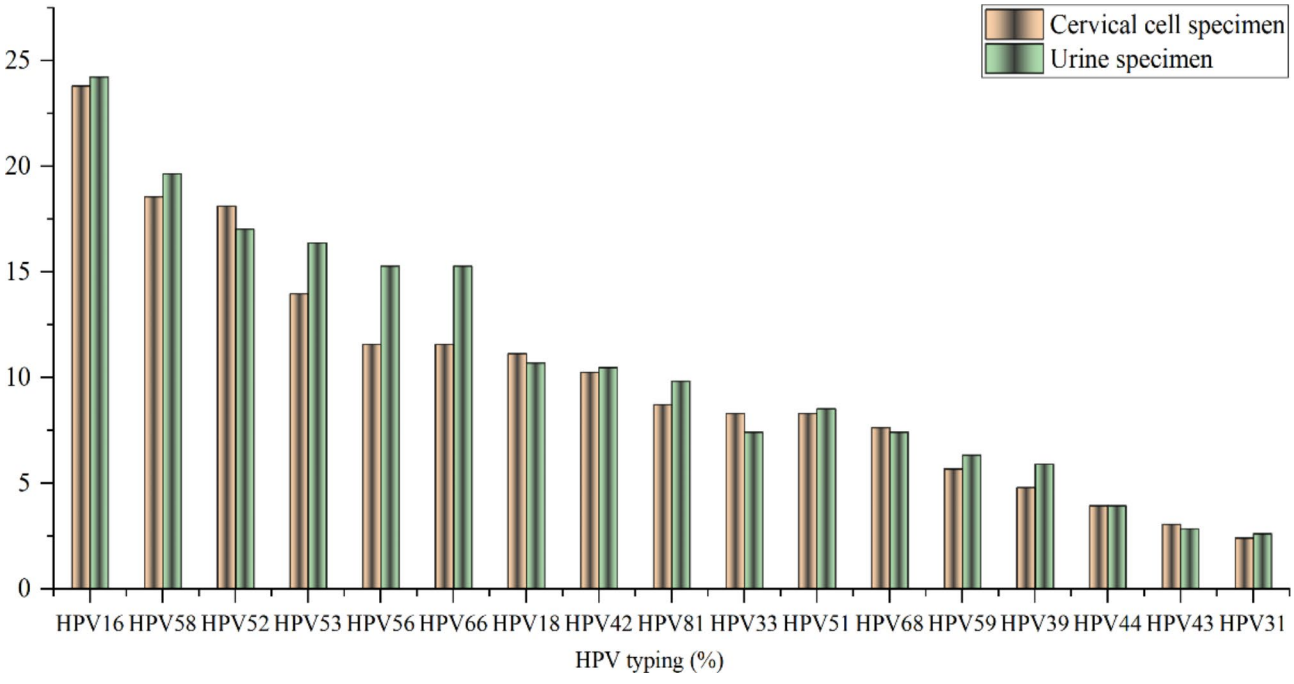

Fig. 1 Positive distribution of different types of HPV in cervical cell samples and urine samples

Table 2 Positive distribution of different types of HPV in cervical cell samples and urine samples (n, %)

Subtypes of HPV	Positive cases of cervical cell specimens (*n*)	Positive rate (%)	HPV positive cases in urine samples (*n*)	Positive rate(%)
HPV16	109	23.8	111	24.2
HPV58	85	18.6	90	19.7
HPV52	83	18.1	78	17.0
HPV53	64	14.0	75	16.4
HPV56	53	11.6	70	15.3
HPV66	53	11.6	46	15.3
HPV18	51	11.1	49	10.7
HPV42	47	10.3	48	10.9
HPV81	40	8.7	45	9.8
HPV33	38	8.3	34	7.4
HPV51	38	8.3	39	8.5
HPV68	35	7.6	34	7.4
HPV59	26	5.7	29	6.3
HPV39	22	4.8	27	5.9
HPV44	18	3.9	18	3.9
HPV43	14	3.1	13	2.8
HPV31	11	2.4	12	2.6

Table 3 Consistency of cervical cell sample and urine detection for five human papillomavirus subtypes corresponding to the nine valent vaccine

Subtypes of HPV	Detection method			*Kappa*	*P*
	Urine	Cervical			
		Positive	Negative		
HPV16	Positive	100	11	0.791	$P<0.001$
	Negative	9	338		
HPV52	Positive	72	6	0.766	$P<0.001$
	Negative	11	369		
HPV18	Positive	40	9	0.762	$P<0.001$
	Negative	11	398		
HPV33	Positive	26	8	0.539	$P<0.001$
	Negative	12	412		
HPV31	Positive	2	10	0.458	$P<0.001$
	Negative	9	437		

Consistency of cervical cell sample and urine detection for five human papillomavirus subtypes corresponding to the nine valent vaccine

The consistency of cervical cell sample testing and urine testing for five HPV subtypes corresponding to the HPV virus nine valent vaccine was analyzed to evaluate the consistency of the two testing methods. The kappa value of HPV16 was 0.791 ($P<0.01$), HPV52 was 0.766 ($P<0.01$), HPV18 was 0.762 ($P<0.01$), HPV33 was 0.539 ($P<0.01$), and HPV31 was 0.458 ($P<0.01$). The detailed findings listed in Table 3 demonstrated significant consistency between urine and cervical cytology HPV testing, validating the use of urine testing for HPV detection.

Cervical tissue biopsy CIN2 + and HPV detection in cervical tissue samples and urine samples

Among 458 specimens, the HPV positivity rate in cervical cytology was 84.3% (386/458), with a sensitivity of 96.7%, specificity of 20.2%, positive predictive value of 30.6%, and negative predictive value (NPV) of 94.4% ($P<0.01$). The HPV positivity rate in urine samples was 79.0% (362/458), with a sensitivity of 85.2%, specificity of 23.2%, positive predictive value of 28.7%, and negative predictive value (NPV) of 81.2% ($P<0.01$), as shown in Table 4.

Discussion

The role of HPV detection in detecting CIN2 + in urine samples

Cervical cancer ranks as the fourth most common malignancy among women worldwide, posing a significant public health challenge. Persistent infection with high-risk human papillomavirus (HPV) is the primary etiological factor for cervical cancer, leading to the development of cervical intraepithelial neoplasia (CIN) and its progression to invasive cancer. CIN is categorized into three stages (CIN1, CIN2, and CIN3) based on the degree of epithelial dysplasia. The risk of progression to cervical cancer varies with different HPV types, with high-risk subtypes being the predominant contributors. Importantly, studies have highlighted that HPV viral load may serve as a key indicator of the likelihood of persistent

Table 4 Cervical tissue biopsy CIN2 + and HPV detection in cervical tissue samples and urine samples

Indicators	Testing method	CIN2+		Sensitivity	Specificity	Positive predictive value	Negative predictive value (NPV)	*P*
		Positive	Negative					
Cervical HPV	Positive	118	268	96.7%	20.2%	84.3%	94.4%	$P<0.001$
	Negative	4	68					
Indicators	**Testing method**	**CIN2+**		**Sensitivity**	**Specificity**	**Positive predictive value**	**Negative predictive value (NPV)**	***P***
		Positive	**Negative**					
Cervical HPV	Positive	104	258	85.2%	23.2%	79.0%	81.2%	$P<0.001$
	Negative	18	78					

infection and progression to precancerous or cancerous lesions [16].

The application of HPV detection in cervical cancer screening plays a crucial role in identifying precancerous lesions in developing high-risk diseases. HPV testing is a recognized component of cervical cancer screening research. Traditional screening and clinical doctors often use brushes to collect cervical cell tissue when obtaining tissue samples. This method is invasive and can cause discomfort or embarrassment to the examiner, which can reduce their compliance with the disease screening plan [17]. In addition, for remote areas, transportation and complex screening procedures further hinder the active participation of examiners, especially for women who lack awareness of the risk of cervical cancer [18, 19].

Recent studies have emphasized the urine-based HPV testing method, which has high potential as a non-invasive approach for early screening of cervical cancer and can address some obstacles in obstetrics and gynecology examinations. Van Keer S et al. reported [20] that when using morning urine samples and taking appropriate precautions during DNA testing collection, urine HPV testing may provide sensitivity and specificity comparable to traditional cervical cytology results. In addition, John J H et al. [21] selected urine and vaginal samples from pregnant women for testing. The results showed high consistency between the two methods in HPV detection. The research results were validated by a large number of kappa numbers. The above study found that HPV testing in urine samples may be an effective screening tool for cervical cancer screening, which not only reduces discomfort and embarrassment caused by invasive procedures, but also improves compliance, ensuring widespread participation of women in disease screening programs in some areas. The detection of HPV in urine samples has great potential in strengthening the screening of cervical precancerous lesions, helping to reduce the incidence rate and mortality of cervical cancer, and playing an important role in disease prevention and timely treatment.

Consistency between urine HPV and cervical cytology detection

The results of 458 samples showed that 383 (83.6%) were positive for HPV in cervical cytology, while 362 (79.0%) were positive for HPV in urine samples. The results showed a high degree of consistency between the two detection methods, with a kappa value of 0.764 ($P < 0.01$), indicating a strong correlation between the two detection methods. Especially for HPV subtypes targeted by the nine valent vaccine, this significant comparison is particularly important for preventing the onset, development, and treatment of cervical cancer. Previous studies by Hantre-Justino M et al. [22] reported similar results, showing a high degree of consistency between morning urine sample testing and cervical cytology testing in HPV positive patients. The above research indicates that urine samples have high potential in detecting HPV virus positivity. It is not only a screening tool for diseases, but also an easily accepted and non-invasive monitoring method. Especially when applied in traditional cervical screening, it has a significant effect on populations with low compliance. The non-invasive operation of urine sampling can significantly improve patients' compliance with the examination and increase coverage in some areas, especially in women who hesitate to undergo invasive procedures. In addition, women can collect urine samples on their own according to the doctor's advice, which enhances the flexibility and accessibility of screening programs. Considering that the progression of HPV infection is influenced by intrinsic factors such as immune response, widespread disease screening and improving disease screening coverage can promote early identification and management of high-risk cases of cervical cancer, thereby effectively preventing the occurrence and development of cervical cancer.

Comparison of the efficacy of HPV detection and cervical tissue biopsy in urine samples and cervical cytology samples

Taking cervical tissue biopsy as the diagnostic criterion, this study analyzed the diagnostic efficacy of urine samples and cervical cell samples. Among 458 specimens, 122 cases (26.6%) had CIN2 + in cervical tissue biopsy. There were 104 positive cases of HPV in urine samples, with a diagnostic sensitivity of 85.2% and specificity of 23.2%. However, when analyzing high-risk HPV types such as HPV16, HPV52, and HPV18, there was no statistically significant difference in sensitivity and specificity between urine samples and cervical cell samples ($P > 0.05$), indicating that the two types of tests had comparable effectiveness. Punyashthira A et al. [23] proposed that self-collecting urine samples for HPV testing was an effective alternative method, especially when HPV vaccination affected the incidence rate. Torre M D L et al. [24] analyzed the evolution of cervical lesions related to HPV infection after vaccination. After vaccination, the incidence rate of squamous cervical cell carcinoma showed a downward trend, and the incidence rate of adenocarcinoma was stable in the region, but the incidence rate of grade 2–3 cervical intraepithelial neoplasia increased, indicating that the vaccine was effective in preventing cancer containing serotypes, and the incidence rate of cervical cancer decreased. At the same time, it is important to verify the importance of age diagnosis. The vaccine does not include the effect on CIN2-3 precursor infections in disease prevention.

Conclusion

HPV testing serves as a valuable complement to cervical cytology screening, particularly by addressing the limitations of invasive procedures. While the sensitivity of HPV detection in urine samples is slightly lower than that of cervical samples, it remains a practical and effective method for early cervical cancer screening. The non-invasive nature of urine testing greatly enhances patient acceptance and compliance, broadening the reach and impact of HPV screening programs. Integrating urine-based HPV testing into existing cervical cancer prevention strategies can substantially increase screening rates, thereby improving the overall effectiveness of cervical cancer prevention and management efforts.

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Author contributions
JS and JW participated the draft and design, supervision, and editing, and resources, writing of original draft, experimental implementation, and data statistics and analysis. All authors read and approved final manuscript.

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Data availability
All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
The ethical approval for this study was obtained from the Capital Medical University. All the experiments of this study were conducted in accordance to the relevant guidelines and regulations or in accordance to the Declaration of Helsinki. Written informed consent was obtained from the patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
None.

Clinical trial number
Not applicable.

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