

# HPV Testing Can Be Used as a Primary Screening Method for Cervical Lesions Among Women in Western China

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**Abstract: Objective:** The purpose of our study is to explore screening strategies suitable for cervical cancer and precancerous lesions in Western Chinese women. **Methods:** Between January 2010 and December 2020, a total of 7009 patients were diagnosed with high-grade squamous intraepithelial neoplasia (CIN2+) after HPV testing, cytology screening or a combination of both. **Results:** The positive rate of human papillomavirus (HPV) was 91.2% and the cytology was 75.1%. The negative rate of co-testing was 2%. 2453 (45.2%) cases were infection with HPV16, following HPV58 (1131, 20.8%), HPV52 (1043, 19.2%), HPV33 (566, 10.4%), HPV18 (294, 5.4%). HPV16/18-positive and cytology-negative infection rate was 54.5%, HPV52/58/33-positive and cytology-negative infection rate was 44.7%, the difference was 9.8%. 35-45 years old is the peak age for the incidence of CIN2+ patients. **Conclusion:** The common genotypes of HPV infection are HPV16, 58, 52, 33 and 18. Cytology negative patients with HPV52/58/33 positive are recommended to be referred for colposcopy as soon as possible. HPV testing is the primary method of cervical cancer or cervical lesions screening among women in western China, and HPV testing is more sensitive than cytology in predicting cervical lesions.

**Keywords:** Cervical Cancer; High-Grade Squamous Intraepithelial Lesions; Cervical Cancer Screening; HPV; Cytology

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## Introduction

According to the World Health Organization (WHO), In China, cervical cancer caused 106,430 new cases and 47,739 deaths in 2018<sup>[1]</sup>. Based on the epidemiological evidence available in Chinese mainland urban and rural areas, the annual number of new cases of cervical cancer will increase significantly without intervention, a possible increase of approximately 40-50% over 2010-2050<sup>[2]</sup>. HPV and cytology testing is the main strategy for secondary prevention of cervical cancer.

ASCCP proposed cytology screening for cervical cancer in 2001, HPV DNA testing as an adjunctive method for cytology screening for abnormal shunting in 2006. A combined HPV and cytology screening protocol was proposed in 2012 and HPV as a primary screening method for cervical cancer in the 2015 guidelines. Cervical cancer screening methods are constantly adjusted with the deepening of human cognition. HPV plays a very important role in the occurrence and development of cervical cancer, the status of HPV detection in the secondary prevention screening process of cervical cancer is also gradually increasing. Preliminary studies have been conducted on precancerous lesion and canceration caused by HPV infection in some areas of China<sup>[3-5]</sup>. This study will explore the impact of HPV infection on CIN2+ patients in western China.

## 1. Materials and Methods

### 1.1 Patient Selection

With Institutional Research Review Board approval, a retrospective study was performed to document CIN2+ patient reports. Between January 2010 and December 2020, In the Department of Gynecology of the First Affiliated Hospital of

Chongqing Medical University, a total of 7009 patients were diagnosed with CIN2+ (CIN2/3, Adenocarcinoma (AIS), squamous cell carcinoma (SCC) or adenocarcinoma (ADC)) after HPV test, cytology test or a combination of both. We collected the results of the cytology, HPV DNA, HPV E6/E7mRNA, colposcopy biopsy and pathological reports after cervical conization. Informed consent of all participants was obtained before sample collection.

## **1.2 Pap Test**

Sample of patients from 2010 to 2016 underwent ThinPrep (Hologic) and from 2017 to 2020 experienced Liqui-PREP™ (LGM International Inc., Melbourne, FL, USA). All Pap tests were screened, interpreted and reported by experienced pathologists.

## **1.3 HPV testing**

### **1.3.1 Real-time fluorescence quantitative PCR method**

HPV genotypes were determined using an HPV Geno-Array Test Kit (Chaozhou HybriBio Biotechnology Limited Corporation, Guangdong, China), according to the manufacturer's instructions. Geno-Array is capable of identifying 21 HPV genotypes, including 15 HR-HPV subtypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, and 68) and six LR-HPV subtypes (HPV6, 11, 42, 43, 44, CP8304).

### **1.3.2 HPV E6/E7 mRNA**

The kit used for HPV E6/E7mRNA is Aptima in 2018-2020, which is the world's first E6/E7 mRNA based HR-HPV kit approved by the FDA of the United States. Results: Copy number  $\geq 1$  copy / mL positive (+) and the opposite is negative (-). No data have been recorded for HPV E6/E7 mRNA from 2010-2017.

## **1.4 Statistical Analysis**

The chi-square test was used in our study. P-values $<0.05$  were considered to indicate statistical significance. Statistical analysis was performed using SPSS software (version 26.0; IBM Corp., Armonk, NY).

## **2. Results**

As shown in Figure 1, among 7009 patients, a total of 4797 patients were selected for cytology testing and 3603 patients positive (ASCUS and above), accounting for 75.1%. A total of 6064 patients were selected for HPV test and 5529 patients positive (including HPV DNA positive and HPV E6/E7 positive), accounting for 91.2%. There were 5429 (98.2%) HPV DNA positive cases and 100 (1.8%) HPV E6/E7 positive cases. A total of 4499 patients underwent both cytology and HPV testing. 3097 cases (68.8%) were positive for both methods. In the combined screening, the positive rate of HPV was 92.5% (4164/4499), the positive rate of cytology was 74.2% (3342/4499) and the negative rate of both screening methods was 90 (2%).

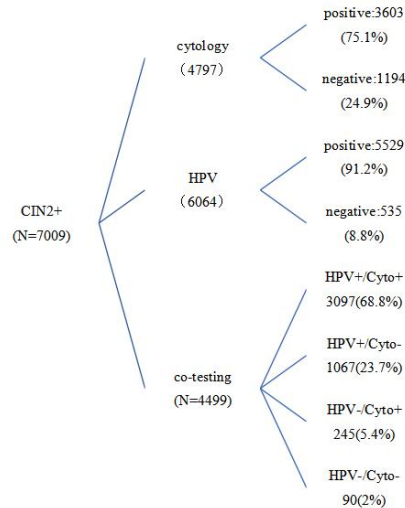


Figure 1: HPV and cytology screening results of 7009 patients with CIN2+. Cytology-positive, ASC-US or worse; HPV+/-, including HPV DNA+/- and HPV E6/E7 mRNA+/- and including either HR-HPV positive and/or LR-HPV positive results. HPV+, HPV-positive; HPV-, HPV-negative (including HPV DNA+/- and HPV E6/E7 mRNA+/-) ; Cyto+, cytology-positive; Cyto-, cytology-negative.

A total of 5429 of 7009 patients selected HPV genotypes, as shown in Table 1, 2453 (45.2%) cases were infection with HPV16, following HPV58 (1131, 20.8%), HPV52 (1043, 19.2%), HPV33 (566, 10.4%), HPV18 (294, 5.4%), HPV31 (239, 4.4%), HPV53 (169, 3.1%), HPV51 (168, 3.1%), HPV39 (114, 2.1%), HPV56 (108, 2%). All ten genotypes were HR-HPV infection.

	HPV type(n=5429)									
	16	18	31	33	39	52	53	56	58	51
positive	2453	293	239	566	114	1043	169	108	1131	168
	45.2%	5.4%	4.4%	10.4%	2.1%	19.2%	3.1%	2%	20.8%	3.1%

Table 1: The top ten most common types of HR-HPV are distributed in CIN2+.

Table 2 shows HPV infection in 1076 HPV-positive and cytology-negative patients, including single infection and multiple infection, of which 994 patients selected for HPV typing test. There were 466 HPV-positive patients, accounting for 46.9%, 52 type 21.1%, 58 type 15.9%, 33 type 7.7% and 18 type 7.6%. In the single infection of HPV, there were 322 HPV16 positive patients, accounting for 32.4%, 52 type 12.8%, 58 type 9.3%, 33 type 4.3% and 18 type 3.6%.

Cytology negative (n=1067)						
HPV type (n=994)	16	18	33	52	58	other
positive (%)	466 (46.9)	76 (7.6)	77 (7.7)	210 (21.1)	158 (15.9)	106 (10.7)

Cytology negative(n=1067)						
single HPV type (n=994)	16	18	33	52	58	other/Multiple infection
positive (%)	322 (32.4)	36 (3.6)	43 (4.3)	127 (12.8)	92 (9.3)	37 (37.6)

Table 2: Percentage of cytological negative patients who were positive different HPV types.

As shown in Figure 2, the peak age of HPV infection is 35-44 years for both HPV16/18 and non-HPV16/18. There were more HPV16/18 infections than non-HPV16/18 infections in 25-34 years old and more non-HPV16/18 infections in 45-54 years old than HPV16/18 infections.

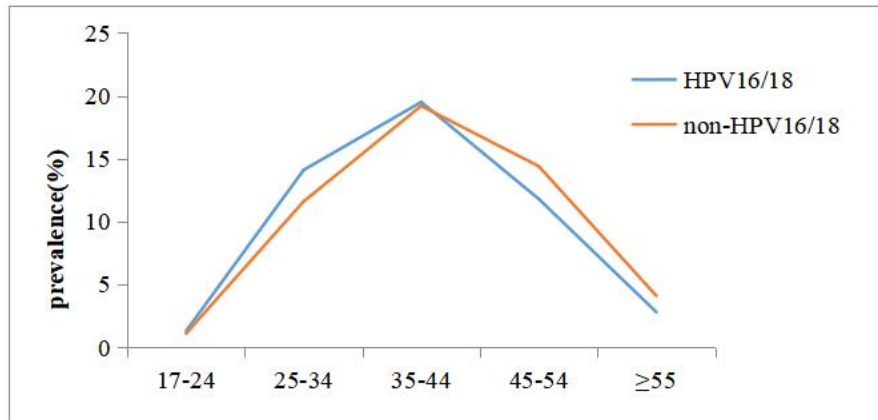


Figure 2: Prevalence of HPV16/18 and non-HPV16/18 in different age groups in patients with CIN2+.

### 3. Discussion

HPV testing is based on molecular biology to determine etiology, while cytology testing relies on exfoliated cells to determine pathology<sup>[6]</sup>. Due to the vast territory of western China, the backward economic development and uneven distribution of healthcare resources between rural and urban areas compared with the eastern coastal areas<sup>[7-8]</sup>. Convenient, private, efficient and accurate sampling of HPV test is in line with the characteristics of social development in the region. The “self-sampling HPV test” model introduced in 2017 is not restricted by region, the test samples are easily available and analyzed by laboratory tests, which further promotes the popularization of cervical cancer screening in China and makes cervical cancer screening easily available to women in areas with poor health resources<sup>[9-10]</sup>.

It is undeniable that positive rate of combined test is slightly higher than of single HPV test (6.8%). At the same time, the test cost increases significantly, which is twice that of single test, greatly increasing the financial burden of patients and also a waste of social resources. Therefore, single HPV test has excellent cost performance and it can be used as a primary screening program for cervical cancer in western China. In a Dutch study<sup>[11]</sup>, it is expected that five years after the introduction of the HPV test as a primary screening test for cervical cancer, the cost of screening will be lower and the screening time will be shorter.

Different types of HPV infection can lead to cervical cancer, with types 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 66 and 68 considered high-risk<sup>[12]</sup>. In our study, the top 5 most common HPV genotypes in western China were HPV16, 58, 52, 33 and 18. In 5429 patients who selected HPV genotype test, the positive infection rate of HPV16/18 was 50.6% and that of HPV52/58/33 was 50.4%, the difference between the two was only 0.2%. It can be said that the risk of CIN2+ in HPV52/58/33 positive patient is the same as that in HPV16/18 positive patients. Among cytology-negative and HPV-positive patients, the infection rate of HPV16/18 positive patients is 54.5% and that of HPV52/58/33 positive patients is 44.7%. Therefore, we should pay more attention to patients with HPV52/58/33 positive infection, while the current guidelines only recommend referral to colposcopy for patients with HPV16/18 positive<sup>[12]</sup>. We recommend that HPV52/58/33-positive and cytology-negative patients also be referred for colposcopy.

In the current guidelines, HPV-based screening strategies have been used as primary screening for cervical cancer<sup>[13-15]</sup>. Furthermore, 35-45 years old is the peak age for the incidence of CIN2+ patients. Standardized cervical cancer screening during this period can effectively detect precancerous lesions of cervical cancer, early detection and treatment, in order to achieve the goal of eliminating cervical cancer<sup>[16-17]</sup>. This study provides strong evidence for HPV testing as a primary screening program for cervical cancer in western China.

### 4. Conclusion

The results of this study indicate that Patients with negative cytology should also attach attention to HPV testing.

Cytology negative patients with HPV52/58/33 positive are recommended to be referred for colposcopy as soon as possible. Moreover, HPV testing is more sensitive than cytology in predicting cervical lesions. Therefore, HPV testing can be used as a primary screening method for cervical cancer in women in western China.

## Disclosure Statement

We have no conflicts of interest to disclose.

## Funding

The study was sponsored by the Chongqing Medical Scientific Research Project (Joint project of Chongqing Health Commission and Science and Technology Bureau)(2021MSXM332) and the Municipal Graduate Student Research Innovation Project of Chongqing (CYS21219).

## Author contributions

Xiaoge Li, Writing-original draft preparation. Yutong Wu, Zhaoning Duan and Jin Wu, Data curation. Sijing Li, Methodology. Ying Jia, Supervision, writing-review.

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