Research Article

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HPV Testing Can Be Used As a Primary Screening Method for Cervical Lesions among Women in Western China

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Citation: Li X, Wu Y, Wu J, Duan Z, Li S, et al. (2022) HPV Testing Can Be Used As a Primary Screening Method for Cervical Lesions among Women in Western China. Ann Case Report. 7: 1011. DOI: 10.29011/2574-7754.101011

Received Date: 22 October 2022; Accepted Date: 26 October 2022; Published Date: 28 October 2022

Abstract

Objective: Cervical cancer screening has gradually changed from single cytology to diversification, and HPV testing has steadily become a primary screening method. 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 mean age of these patients was 40±1 years, the positive rate of human papillomavirus (HPV) was 91.2% and the cytology was 75.1%. The positive rate and negative rate of co-testing were 68.8% and 2% respectively. The positive rate of HPV16/18 was 50.6% and that of HPV52/58/33 was 50.4%, the difference was 0.2%. 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%. **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

Background

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Cervical cancer remains one of the most common malignancies among women worldwide, causing 300,000 women to die each year, affecting nearly 600,000 women [1, 2]. In May 2018, WHO announced "the launch of the Global Strategy to Accelerate the Elimination of Cervical Cancer" [3], which aims to achieve the "90-70-90" goal by 2030. Which will put all countries in the world on the path to eliminating cervical cancer, namely 90% of girls complete full HPV vaccination by the age of 15, 70% of girls receive high-quality screening at age 35 and 45, and 90% of women diagnosed with cervical cancer receive treatment (90% of precancerous patients are treated and 90% of cases of invasive cancer are managed) [4, 5].

According to the World Health Organization (WHO), In China, cervical cancer caused 106,430 new cases and 47,739 deaths in 2018. 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 [6]. In 1951, Pap smear was introduced into China to promote the early screening of cervical cancer. In 2001, TCT was introduced to replace Pap smear in China to improve the accuracy of cervical cancer screening [4]. In 2004, China launched the "*Population-based Epidemiological Survey of HPV infection and cervical cancer in Chinese Women*", which is the first large population, multi-center study of HPV infection in China. 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 [7-9]. This study will explore the impact of HPV infection on CIN2+ patients in western China.

Materials and Methods

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. Most patients were from Chongqing province and other adjacent areas, including Sichuan and Guizhou, Yunnan, Gansu and Xinjiang province. We collected their age, the results of the cytology, HPV DNA, HPV E6/E7mRNA, colposcopy biopsy results and pathological reports after cervical conization. The Ethics Committee approved this study of the first affiliated Hospital of Chongqing Medical University under the Helsinki Declaration of 1975 of the World Medical Association. Informed consent of all participants was obtained before sample collection. The requirement for written informed consent was waived by the IRB.

Pap test

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Sample of patients from 2010 to 2016 underwent ThinPrep (Hologic) and from 2017 to 2020 experienced Liqui-PREPTM (LGM International Inc., Melbourne, FL, USA). All Pap tests were screened, interpreted and reported by experienced pathologists who read 60-80 slides per day and the results based on Bethesda system 11 in 2001 [10], divided into negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells cannot exclude a high-grade squamous intraepithelial lesion or worse (HSIL+). The specimens for Pap and HPV tests were collected in two separate vials.

HPV testing

Real-time fluorescence quantitative PCR method

HPV genotypes were determined using an HPV Geno-Array Test Kit (Chaozhou Hybribio Biotechnology Limited Corporation, Guangdong, China) [11] in 2010-2014, 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). The test was conducted in four steps as follows: (a) HPV DNA extraction, (b) PCR amplification, (c) flow-through hybridization [12], and (d) result interpretation. Positive test results appeared as bluish violet dots. The performance and technical parameters of 21 HPV Geno-Array Diagnostic Kit remains the same from 2010-2014. The testing methods and reagents used in our study are completely consistent and the sensitivity and specificity of the reagent remained the same in this period.

Cell samples were collected in 2.5 ml of cell preserve solution (Tellgen Corporation, Shanghai, China) [13] for HPV DNA testing in 2015-2020. The TellgenplexTM HPV DNA Test was performed using a Luminex-based suspension beads array to identify HPV types. The experimental protocol includes DNA extraction, PCR amplification, bead-coated hybridization, and digital signal processing. The TellgenplexTM HPV DNA Test can identify 27 HPV types, including 14 HR-HPV (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Final results are expressed as the number of cycles (Ct) of the amplification reaction. The corresponding type was positive according to the analysis software.

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 ≥ 1 copy / mL positive (+) and the opposite is negative (-). No data have been recorded for HPV E6/E7 mRNA from 2010-2017.

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).

Result

The mean age of these patients was 40 ± 1 years. Some patients had previous Pap smears and HPV results that had been processed and reported at other facilities, these outside results were included in this study. The average time interval between cervical sampling and histopathologic diagnoses was 0.5 months (range,

0.1-5 months). As shown in (Table 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%).



Table 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.

*1. Because of the diversity of cervical cancer screening methods in China, some patients have only cytological results, some have only HPV testing results, and some have both. 2. Some of the samples were taken simultaneously, others were sampled multiple times, and the specimens for Pap and HPV testing were collected in two separate vials.

(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%, and 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%, and 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.

*The sum of the percentages of each HPV type is not necessarily equal to 100%, because a result may be counted more than once where the sampled lesion contained multiple HPV type.

A total of 5429 of 7009 patients selected HPV genotypes, as shown in (Table 3), 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)									
Desitives	16	18	31	33	39	52	53	56	58	51
Positive	2453	293	239	566	114	1043	169	108	1131	168
	45.20%	5.40%	4.40%	10.40%	2.10%	19.20%	3.10%	2%	20.80%	3.10%

Table 3: The top ten most common types of HR-HPV are distributed in CIN2+

As shown in (Table 4), the top five types of HPV infection were HPV16, 58, 52, 33, 18. Among single infections, the proportion of HPV16/18 was 46.9%, non-HPV16/18 was 53.1%, HPV58/52/33 was 42.3% and HPV16/18/58/52/33 was 89.4%. Among the multiple infections, the proportion of HPV16/18 was 42.8%, non-HPV16/18 was 64.9%, HPV58/52/33 was 51.8% and HPV16/18/58/52/33 was 94.7%.

	HPV16	HPV18	HPV33	HPV52	HPV58	HPV other	Total
Single infection	1754	140	355	621	733	441	4044
Multiple infection	699	154	211	422	398	106	1990

Table 4: Distribution of single and multiple HPV infections in CIN2+ lesions.

*The sum of the percentages of each HPV type is not necessarily equal to 100%, because a result may be counted more than once where the sampled lesion contained multiple HPV type.

In (Figure 1), in total infection, the proportion of HPV16/18 infection was 34.9% (1894/5429), non-HPV16/18 was 39.6% (2150/5429). The proportion of HPV58/52/33 was 31.4% (1709/5429) and that of HPV16/18/58/52/33 was 66.4% (3603/5429). Mixed infection accounted for 36.7% (1990/5429), the proportion of HPV16/18 infection was 15.7% (853/5429), and non-HPV16/18 was 20.9% (1137/5429). The proportion of HPV58/52/33 was 19% (1031/5429) and that of HPV16/18/58/52/33 was 34.7% (1884/5429).

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Figure 1: Distribution of single and multiple HPV infections in patients with CIN2+.

*The sum of the percentages of each HPV type is not necessarily equal to 100% because a result may be counted more than once where the sampled lesion contained multiple HPV type.

The age range of those patients was 17-80 years, with an average age of 40 ± 1 years. 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+.

*The sum of the percentages of each HPV type is not necessarily equal to 100% because a result may be counted more than once where the sampled lesion contained multiple HPV type.

Discussion

HPV testing is based on molecular biology to determine etiology, while cytology testing relies on exfoliated cells to determine pathology [14]. In western China, HPV and cytology samples are collected in two separate vials, the sequence of samples can affect the results. Cytology tests require wellsampled samples and experienced pathologists [14], which are more demanding than HPV tests. 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 [11, 15, 16]. Convenient, private, efficient and accurate sampling of HPV test is in line with the characteristics of social development in the region. The "selfsampling 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 [17, 18].

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 [19], 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 [20]. The most common HPV infection genotypes were 16, 52, 31, 33 and 58 in Qingdao 8, 16, 58, 52, 31 and 51 in Beijing [21].

The most common HPV infection genotypes in Ganzhou 9 were 16, 52, 58, 33 and 18. 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. Non-HPV16/18 positive patients need to be evaluated for colposcopy after cytological shunt [20]. In accordance with the above screening recommendations, we will miss 44.7% of cytology-negative and HPV-positive CIN2+ patients. Therefore, 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 [22, 23, 24]. HPV testing can be effective in preventing future precancerous lesions and invasive cancers and can quickly predict treatment failure [1, 25]. Hausen found that HPV infection causes cervical cancer, making it the only cancer with a clear cause, the only one that can be prevented early and the only one that can be completely eradicated [26].

WHO has announced a goal of "90-70-90" by 2030, requiring 70% of girls to receive high-quality screening by the age of 35 and 45 respectively [3]? 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 [27, 28]. Standardized and effective screening strategies are the basis for the elimination of cervical cancer. This study provides strong evidence for HPV testing as a primary screening program for cervical cancer in western China.

Conclusion

The results of this study indicate that HPV testing can be used as a primary screening method for cervical cancer in women in western China. Moreover, HPV testing is more sensitive than cytology in predicting cervical lesions. Given the geographical limitations of the collected data, the conclusions obtained may be somewhat differentiated. Extensive studies are still needed to confirm the feasibility of HPV detection alone as a primary screening method for cervical cancer or cervical lesions.

Disclosure Statement: We have no conflicts of interest to disclose.

Author contributions: Xiaoge Li: Writing-original draft preparation. Yutong Wu, Zhaoning Duan, Jin Wu: Data curation. Sijing Li: Methodology. Ying Ji: Supervision, writing-review.

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