

Prevalence and genotype distribution of human papillomavirus: implications for cancer screening and vaccination in Henan province, China

Jun-Wei Zhao^[1], *Jing-Jing Xu*^[2], *Min Yan*^[3], *Xiao-Xu Sun*^[1],
Guang Shi^[1] and *Liang Ming*^[1]

[1]. Clinical Laboratory, The First Affiliated Hospital of Zhengzhou University, Key Clinical Laboratory of Henan Province, Department of Laboratory Medicine of Zhengzhou University, Zhengzhou, China. [2]. Department of pathology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China. [3]. Key Laboratory of Medical Immunology, Henan University of Traditional Chinese Medicine, Zhengzhou, China.

ABSTRACT

Introduction: To provide information for cervical cancer screening and vaccination in Henan province, China, the distribution of human papillomavirus (HPV) was analyzed. **Methods:** The HPV genotypes were detected using gene array and flow-through hybridization. **Results:** Overall, 38.1% (1,536/4,033) of the women were human papillomavirus deoxyribonucleic acid (HPV DNA) positive. The prevalence of high-risk HPV types was 32.4%. HPV 16 was the most prevalent genotype (8.9%), followed by HPV 52 (5.8%) and HPV 58 (4.4%). **Conclusions:** The data support close surveillance of women for cervical cancer screening, and HPV prophylactic vaccines including HPV16, HPV 52, and HPV 58 might offer greater protection in this area.

Keywords: Human papillomavirus. Prevalence. Henan. China.

Cervical cancer is the third most common cancer and fourth leading cause of mortality among women worldwide⁽¹⁾, with more than 85% of the cases occurring in developing countries such as China⁽²⁾. Evidence indicates that a large proportion of cervical cancer can be prevented through organized cervical screening⁽³⁾.

Because human papilloma virus (HPV) causes almost all cervical cancers⁽⁴⁾, human papillomavirus deoxyribonucleic acid (HPV DNA) testing would be appropriate to objectively screen cervical cancer, with high sensitivity and specificity. More than 200 different HPV genotypes have been identified to date, and approximately 40 oncogenic subtypes are associated with the majority of cases of cervical cancer⁽⁵⁾. Based on their association with cervical cancer, HPV genotypes can be classified into high-risk (HR) HPV (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) or low-risk (LR) HPV (HPV 6, 11, 40, 42, 43, and 44)⁽⁵⁾. In particular, HPV 16 and HPV 18 collectively account for 70% of cervical cancers worldwide⁽⁶⁾. To some extent, the detection of HR-HPV may reduce the risk of developing cervical cancer and associated deaths⁽⁷⁾, and understanding the HPV genotype distribution would aid with the design of HPV vaccines for cervical cancer prevention.

Here, we investigated cervical HPV infections in the general female population in Henan province, located in central China,

to determine the overall and type-specific HPV prevalences, using the commercially available HPV DNA Array.

From January 2014 to August 2014, 4,033 consecutive samples of exfoliated cervical cells from women attending the gynecological outpatient clinic were collected in the First Affiliated Hospital of Zhengzhou University, China. Eligible women included those who were not a virgin, were not presently pregnant, were not presently menstruating, had not had sexual intercourse within seven days, had not undergone a total hysterectomy, had not used vaginal medication in the previous 48 hours, had no history and associated symptoms of other HPV-related diseases, and were willing to undergo HPV testing. All participants agreed to participate in the present study, and the study project was approved by the ethical committee of the First Affiliated Hospital of Zhengzhou University.

Samples of exfoliated cervical cells were collected for HPV genoarray testing according to the manufacturer's instructions (Yaneng Biotechnology Corp., Shenzhen, China). All data were analyzed using Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Corp., Chicago, IL, USA). The χ^2 test was used to assess the statistical significance of any differences in prevalence. A significance level of 0.05 was used.

The median age of the participating women was 40 years (16-87 years). Of the 4,033 samples, no sample was lost, as the control was normal in all tests. Overall, 1,536 (38.1%) women were HPV-positive for any HPV DNA, 32.4% (1,308/4,033) had an HR-HPV infection, which was higher than the 12.6% (510/4,033) that had an LR-HPV infection (**Table 1**). HPV 16 was the most prevalent genotype (8.9%, 357/4,033), followed by HPV 52 (5.8%, 235/4,033) and HPV 58 (4.4%, 176/4,033)

Corresponding author: Dr. Liang Ming.

e-mail: mingliang3072@163.com

Received 13 June 2015

Accepted 17 August 2015

TABLE 1 - Overall prevalence of human papillomavirus, including specific types and categories (n = 4,033)*.

HPV type	Number	Overall prevalence (%)
Any type	1536	38.1
High-risk types	1308	32.4
HPV 16	357	8.9
HPV 18	86	2.1
HPV 31	51	1.3
HPV 33	86	2.1
HPV 35	32	0.8
HPV 39	47	1.2
HPV 45	24	0.6
HPV 51	127	3.1
HPV 52	235	5.8
HPV 53	161	4.0
HPV 56	116	2.9
HPV 58	176	4.4
HPV 59	103	2.6
HPV 66	73	1.8
HPV 68	125	3.1
HPV 73	15	0.4
HPV 82	14	0.3
HPV 83	8	0.2
Low-risk types	510	12.6
HPV 6	139	3.4
HPV 11	107	2.7
HPV 42	107	2.7
HPV 43	66	1.6
HPV 81	142	3.5

HPV: human papillomavirus. *Both single and multiple types of infections were included in the prevalence for each type or category.

(Table 1). As shown in Figure 1, there were two peaks of HPV infection based on age: the first was for women aged <21 years, of whom 55.6% were infected, and the second was for women aged 66-70 years, of whom 48% were infected (p = 0.003). Similar patterns of two peaks were also observed for HR-HPV infections (p = 0.028) and LR-HPV infections (p < 0.001), with the first peaks for both types of infection for women aged <21 years (48.1% and 29.6%, respectively). However, the second peak for HR-HPV infection was for women aged 56-60 years, of whom 42.5% were infected, and the second peak for LR-HPV infection was for women aged 61-65 years, of whom 25% were infected. The prevalences of multiple types of HPV infections were significantly different among the age groups

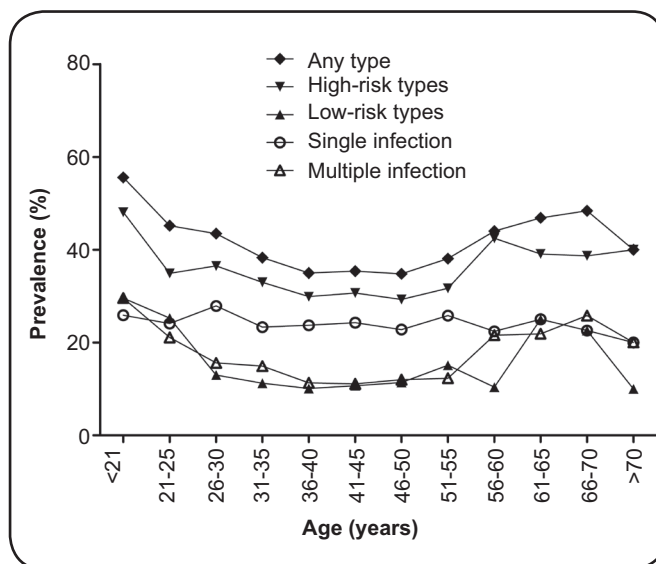


FIGURE 1 - Age-specific prevalence of human papillomavirus infection.

(p < 0.001), while the prevalences of a single type of HPV infection were relatively constant across the age groups (p = 0.930) (Figure 1). Among the women infected with multiple types of HPV, the first peak (29.6%) was for those aged <21 years old, and the second peak (25.8%) was for those aged 66-70 years (p < 0.001). The prevalence of HPV 16 or HPV 18 did not differ across the age groups (data not shown).

A single type of HPV infection was detected in 24.2% (977/4,033) of the entire sample, and multiple types of HPV infections were detected in 13.9% (559/4,033) of the entire sample (Table 2). In the group of women with a single type of infection-, HPV 16 was the most prevalent (18.9%, 185/977), followed by HPV 52 (10.3%, 101/977), HPV 58 (8.1%, 79/977), HPV 53 (6.7%, 65/977), and HPV 6 (5.9%, 58/977). In the group of women with multiple types of infection-, the most prevalent genotype was HPV 16 (30.8%, 172/559), followed by HPV 52 (24%, 134/559), HPV 58 (17.4%, 97/559), HPV 53 (17.2%, 96/559), and HPV 81 (16.1%, 90/559) (Table 2).

In the present study, the most prevalent HPV genotype was HPV 16, followed by HPV 52 and HPV 58 (Table 1), which was similar to the findings of a previous study of the prevalence of HPV infection in Henan province⁽⁸⁾. However, in another study conducted in this area, the most prevalent HPV genotype was HPV 16 (9.2%, 53/578), followed by HPV 52 (7.8%, 45/578) and HPV 6 (6.9%, 40/578)⁽⁹⁾. As the biggest hospital in the center of China, clinical data from the First Affiliated Hospital of Zhengzhou University might be more representative of the population. In other areas, such as in the North⁽¹⁰⁾, South⁽¹¹⁾, and Southeast⁽¹²⁾ of China, the most commonly detected HPV types were also different. These differences may be due to the geographical and biological interplay between HPV types or variants and host immunogenic factors, as previously described⁽¹³⁾.

Compared with Shenzhen and Shanghai City (13.8% and 30.2%, respectively)^{(11) (13)}, a higher (38.1%) prevalence

TABLE 2 - Distribution of human papillomavirus infections (n = 4033).

HPV genotype	Samples (n)	Single infection (n = 977)		Multiple infections (n = 559)		Double infection (n = 372)		Triple infection (n = 123)		At least a quadruple infection (n = 64)	
		n	%	n	%	n	%	n	%	n	%
HPV 16	357	185	18.9	172	30.8	96	25.8	48	39.0	28	43.8
HPV 18	86	35	3.6	51	9.1	27	7.3	14	11.4	10	15.6
HPV 31	51	18	1.8	33	5.9	18	4.8	9	7.3	6	9.4
HPV 33	86	29	3.0	57	10.2	27	7.3	16	13.0	14	21.9
HPV 35	32	11	1.1	21	3.8	14	3.8	4	3.3	3	4.7
HPV 39	47	18	1.8	29	5.2	12	3.2	9	7.3	8	12.5
HPV 45	24	7	0.7	17	3.0	10	2.7	3	2.4	4	6.3
HPV 51	127	52	5.3	75	13.4	47	12.6	11	8.9	17	26.6
HPV 52	235	101	10.3	134	24.0	81	21.8	33	26.8	20	31.3
HPV 53	161	65	6.7	96	17.2	42	11.3	32	26.0	22	34.4
HPV 56	116	38	3.9	78	14.0	40	10.8	20	16.3	18	28.1
HPV 58	176	79	8.1	97	17.4	49	13.2	25	20.3	23	36.0
HPV 59	103	37	3.8	66	11.8	33	8.9	12	9.8	21	32.8
HPV 66	73	22	2.3	51	9.1	25	6.7	12	9.8	14	21.9
HPV 68	125	53	5.4	72	12.9	46	12.4	13	10.6	13	20.3
HPV 73	15	3	0.3	12	2.1	4	1.1	3	2.4	5	7.8
HPV 82	14	8	0.8	6	1.1	4	1.1	1	0.8	1	1.7
HPV 83	8	3	0.3	5	0.9	2	0.5	0	0.0	3	4.7
HPV 6	139	58	5.9	81	14.5	38	10.2	20	16.3	23	36.0
HPV 11	107	54	5.5	53	9.5	24	6.5	19	15.4	10	15.6
HPV 42	107	37	3.8	70	12.5	36	9.7	20	16.3	14	21.9
HPV 43	66	12	1.2	54	9.7	31	8.3	11	8.9	12	18.8
HPV 81	142	52	5.3	90	16.1	45	12.1	27	22.0	18	28.8

HPV: human papillomavirus.

of HPV infection was observed in the present study. The first peak of HPV infection occurred for women aged <21 years (55.6%), which might be related with a lack of adaptive immune responses and susceptibility to HPV infection⁽¹²⁾. The second peak was observed for women aged 66-70 years (48.4%); this age group also had the most cervical cancer patients (data not shown). It is possible that latent HPV in the body was reactivated owing to physiologic and immunologic dysregulation caused by hormonal fluctuations during the transition to menopause⁽¹³⁾ (**Figure 1**). However, the reasons for the decrease in HPV infection prevalence in women aged >70 years requires further investigation.

Most HPV infections are transient and might resolve spontaneously; however, persistent infections with a subset of HPV genotypes are necessary to develop cervical cancer and

its precursors. In the present study, the different peaks of HPV infection were observed in those aged 50-70 years; therefore, women who are first infected with HR-HPV at 56-60 years of age and do not receive appropriate treatment might become infected with LR-HPV at 61-65 years and finally develop multiple types of HPV infection at 66-70 years (**Figure 1**). When compared with women with a single infection, women infected with multiple types of HPV are at a significantly higher risk of both cervical intraepithelial neoplasia grade 2 and high-grade squamous intraepithelial lesions⁽¹⁴⁾. Unfortunately, in the present study, cervical cytology and cancer state were missing for the samples. Therefore, further analysis is needed.

HPV vaccination could decrease the incidence of HPV-related cancers, as well as reduce the burden associated with the treatment of HPV-related benign lesions⁽¹⁵⁾. Our findings

indicate that the trivalent vaccine (targeted at HPV 16, HPV 52, and HPV 58) would provide good efficacy in the central area of China, because the three most prevalent HPV genotypes in this area were HPV 16, HPV 52, and HPV 58 (**Table 1**).

In summary, increasing women's awareness of the relationship between HPV infection and cervical cancer is the most important recommendation. The prevalence of HPV infection in the central area of China was 38.1%, and the most common genotypes were HPV 16 (18.9%), HPV 52 (10.3%), and HPV 58 (8.1%). Our data support close surveillance of women aged <21 years or >55 years for cervical cancer screening. Furthermore, our findings support the hypothesis that the next-generation HPV prophylactic vaccines that include HPV 52 and HPV 58 might offer greater protection for women in this area.

ACKNOWLEDGMENTS

The authors are grateful to Doctor Wen-Wen Wang from Department of Gynecology, The First Affiliated Hospital of Zhengzhou University, and associate professor Zhi-Guang Ping from the School of Public Health, Zhengzhou University, Zhengzhou, China for their assistances during this study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FINANCIAL SUPPORT

This study was supported by the National Natural Science Foundation of China (grant number 81501715), the Youth Innovation Fund of the First Affiliated Hospital of Zhengzhou University, China (grant number 2014001-042) and the Key Project on Science and Technology Research of Henan Province, China (grant number 152102410067; grant number 2013A310622).

REFERENCES

- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; 61:69-90.
- Li J, Huang R, Schmidt JE, Qiao YL. Epidemiological features of human papillomavirus (HPV) infection among women living in Mainland China. *Asian Pac J Cancer Prev* 2013; 14:4015-4023.
- Khorasanizadeh F, Hassanloo J, Khaksar N, Taheri SM, Marzaban M, Rashidi BH, et al. Epidemiology of cervical cancer and human papilloma virus infection among Iranian women - Analyses of national data and systematic review of the literature. *Gynecol Oncol* 2013; 128:277-281.
- Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; 127:2893-2917.
- Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003; 348:518-527.
- Tracy L, Gaff HD, Burgess C, Sow S, Gravitt PE, Tracy JK. Estimating the impact of human papillomavirus (HPV) vaccination on HPV prevalence and cervical cancer incidence in Mali. *Clin Infect Dis* 2011; 52:641-645.
- Levin CE, Sellors J, Shi JF, Ma L, Qiao YL, Ortendahl J, et al. Cost-effectiveness analysis of cervical cancer prevention based on a rapid human papillomavirus screening test in a high-risk region of China. *Int J Cancer* 2010; 127:1404-1411.
- Shen Y, Gong JM, Li YQ, Gong YM, Lei DM, Cheng GM, et al. Epidemiology and genotype distribution of human papillomavirus (HPV) in women of Henan Province, China. *Clin Chim Acta* 2013; 415:297-301.
- Wang XC, Sun LQ, Ma L, Li HX, Wang XL, Wang X, et al. Prevalence and genotype distribution of human papillomavirus among women from Henan, China. *Asian Pac J Cancer Prev* 2014; 15:7333-7336.
- Hou R, Xu C, Zhang S, Wu M, Zhang W. Distribution of human papillomavirus genotype and cervical neoplasia among women with abnormal cytology in Beijing, China. *Int J Gynaecol Obstet* 2012; 119:257-261.
- Wang YY, Li L, Wei S, Peng J, Yuan SX, Xie JS, et al. human papillomavirus (HPV) infection in women participating in cervical cancer screening from 2006 to 2010 in Shenzhen City, South China. *Asian Pac J Cancer Prev* 2013; 14:7483-7487.
- Ye J, Cheng X, Chen X, Ye F, Lu W, Xie X. Prevalence and risk profile of cervical human papillomavirus infection in Zhejiang Province, southeast China: a population-based study. *Virology* 2010; 7:66.
- Xue Y, Zhang W, Chen M, Han L, Luo M. "U" shape of age-specific prevalence of high-risk human papillomavirus infection in women attending hospitals in Shanghai, China. *Eur J Obstet Gynecol Reprod Biol* 2009; 145:214-218.
- Dickson EL, Vogel RI, Geller MA, Downs Jr LS. Cervical cytology and multiple type HPV infection: a study of 8182 women ages 31-65. *Gynecol Oncol* 2014; 133:405-408.
- Goldie SJ, O'Shea M, Campos NG, Diaz M, Sweet S, Kim SY. Health and economic outcomes of HPV 16,18 vaccination in 72 GAVI-eligible countries. *Vaccine* 2008; 26:4080-4093.