RESEARCH PAPER

Prevalence and genotype distribution of human papillomavirus among women with cervical lesions in Shenzhen city, China

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ABSTRACT

There is currently a lack of sufficient data on human papillomavirus (HPV)-attributable cervical carcinoma in China. Accordingly, we aimed to determine the prevalence and genotype distribution of HPV among women with cervical lesions in Shenzhen, in order to evaluate the potential benefit of HPV vaccination programs and inform cervical cancer control policies. We enrolled 5,255 patients who were admitted to the University of Chinese Academy of Sciences Shenzhen Hospital from January 2017 to December 2019. The HPV prevalence and genotype distribution were analyzed using the 21 HPV GenoArray diagnostic assay. A total of 937/5,255 patients showed HPV-positivity (prevalence rate 17.83%), of whom 85.81% (804/937) had high-risk HPV infection. HPV52 was the most prevalent genotype (4.72%, 248/5,255), followed by HPV58 (3.04%, 160/5,255), and HPV16 (2.72%, 143/5,255). The HPV prevalence rates among women with a normal cervix, low-grade intraepithelial lesions, high-grade intraepithelial lesions, invasive cervical cancer, and other characteristics were 15.63% (50/320), 58.65% (61/104), 80.00% (44/55), 88.57% (31/35), and 15.84% (751/4,741), respectively. HPV16, HPV18, and HPV52 accounted for the majority of cervical lesions, and the infection rates of HPV16 and HPV18 gradually increased with intraepithelial lesion progression (both $P < .001$). Our study found that HPV16, HPV52, and HPV18 played important roles in the occurrence and development of cervical lesions. This finding has the potential to guide the formulation of HPV screening and vaccination programs and preventive strategies for HPV-attributable cancer in this region.

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Introduction

Cervical cancer (CC) was the second most frequently occurring cancer among women in 2018, worldwide, with an estimated incidence of 570,000 cases, and the World Health Organization (WHO) reported a mortality value of 311,000 deaths, with China and India together contributing to more than a third of all such cases.¹ CC and its precursors are commonly caused by persistent human papillomavirus (HPV) infection.^{2,3} HPV is a small double-stranded DNA virus, which belongs to *Papillomaviridae*, a large family with a tropism for squamous epithelium. Till date, more than 200 HPV genotypes have been identified, and these have been clinically divided into high-risk and low-risk genotypes based on the degree of tissue infection.⁴ HPV16 and HPV18, the most commonly noted high-risk genotypes, were previously found to be responsible for almost three quarters of all CC cases, worldwide, with high-risk HPV genotypes HPV31, HPV45, and HPV52 accounting for the remaining cases.^{2,3}

HPV vaccines are effective against HPV16, HPV18, and some other high-risk genotypes, and are the optimal prevention strategies for the control of the prevalence of CC and other HPV-associated diseases in women.^{5,6} Currently, there are three HPV vaccines licensed against HPV infections. Bivalent HPV vaccine (2vHPV) and quadrivalent HPV vaccine (4vHPV) are

the first-generation HPV vaccines, and both of them protect against HPV16 and HPV18, while 4vHPV also protects against HPV6 and HPV11. The second-generation nonviral HPV vaccine (9vHPV), which addresses the four HPV types in 4vHPV plus five additional oncogenic types (HPV31, 33, 45, 52, and 58), was licensed by the Food and Drug Administration (FDA) of the United States in 2014 and has the potential to prevent up to 93% of cervical cancers.⁷ However, due to multiple factors, including the lack of comprehensive CC screening programs and treatment of lesions found on screening, absence of access to HPV vaccines due to the high costs, limited health-care services for the delivery of these vaccines, as well as the vaccine being considered low-priority, CC remains the most widespread form of cancer induced by HPV and the second most commonly observed type of malignancy affecting women.^{8–11} Although HPV vaccines have been on the national immunization schedule in 92 countries, the overall HPV prevalence is still 12% in women, globally, with a majority of these cases occurring in low to lower-middle-income countries.⁹

Appropriate cancer control strategies and HPV vaccination programs are formulated based on a comprehensive understanding of the HPV-attributable disease burden. However, the prevalence and genotype distribution of HPV infection vary

geographically in China, and the HPV-attributable cancer burden is still not well characterized.¹² Gaining an understanding of the behaviors of HPV type-specific infection can boost not only the implementation and evaluation of vaccination strategies, but also CC screening, and can provide useful data for the cost-effective evaluation of these intervention programs. We sought to perform a study (including 5,255 women) to identify the most prevalent genotypes of HPV and the correlation between HPV genotypes and cervical pathology status, as presented in Shenzhen city, with the aim of guiding the formulation of HPV screening and vaccination programs and preventive strategies for HPV-attributable cancer.

Materials and methods

Participants

A total of 5,255 outpatients treated for gynecological diseases, aged between 17 and 60 years (median age: 35.5 years), at the University of Chinese Academy of Sciences Shenzhen Hospital from January 2017 to December 2019 were included in this study. The subjects met the following requirements: long-term permanent resident of Shenzhen city, and more than 1 year of sexual history. Exclusion criteria were pregnancy, previous surgical procedures on cervix, systemic infection or autoimmune diseases, sexual activity, or receive surgery for uterine diseases within 3 days. This study was conducted in accordance with the Declaration of Helsinki and a protocol approved by the University of Chinese Academy of Sciences, Shenzhen Hospital (Guangming).

Histopathological diagnosis

All patients first underwent routine cervical exams. Patients with cervical lesions, or HPV infection or other morphologic abnormalities by cytological screening (ThinPrep cytological test, TCT), underwent histological (biopsy) and histopathological procedures for final diagnosis. The biopsy specimens obtained from these patients were fixed, embedded, and stained. Pathological identification was performed according to the 2014 WHO classification criteria (fourth Edition) and described as follows: a) Normal cervix: negative for malignancy, intraepithelial lesions, inflammation, and other benign lesions, b) Low-grade squamous intraepithelial lesion (LSIL) corresponding to cervical intraepithelial neoplasia grade (CIN) I (low dysplasia), c) High-grade squamous intraepithelial lesion (HSIL) corresponding to CIN II (moderate dysplasia) and CIN III (severe dysplasia), d) invasive cervical cancer (ICC), and e) Others, pertaining to the presence of inflammatory conditions, including cervical hypertrophy, hyperplasia, chronic cervicitis, bleeding, and erosion, or the use of surgery or hysteromyoma treatment, etc.

HPV genotype testing

HPV genotyping detection was performed using 21 HPV GenoArray Diagnostic Kit (Guangdong Kaipu Biotechnology Co., Ltd, China). The 21 HPV GenoArray Diagnostic Kit is

a qualitative polymerase chain reaction (PCR)-based test used for the detection and determination of 21 specific HPV DNAs in cervical specimens. The 21 HPV genotypes are divided into 15 high-risk genotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 and 68) and 6 low-risk genotypes (HPV 6,11,42,43,44, CP8304), and the specific detection steps were followed in strict adherence to instructions, as described previously.^{13,14} Briefly, the HPV DNA extracted from cervical samples was amplified using PCR, and then hybridized with specific HPV probes located inside the membrane strip, followed by the use of the enzyme immunoassay method to obtain colorimetric results. Positive results appeared as a clearly visible violet dot, and HPV genotypes were determined by the dot distribution of the membrane strip.

Statistical analysis

Analyses were performed using SPSS 25.0 statistical software (Chicago, USA). The infection rates were expressed as percentage and compared based on the disease group using a Chi-square test. An independent sample *F/t* test was used for comparisons among groups to evaluate the changes in the HPV prevalence; statistical significance was defined as $p < .05$.

Results

HPV prevalence and genotypes

A total of 5,255 female patients were enrolled in this study, and the overall prevalence of HPV infection was 17.83% (937/5255). Of the 937 patients, 85.81% (804/937) were identified as having the high-risk HPV genotypes. HPV52 was the most commonly observed genotype (4.72%, 248/5255), followed by HPV58 (3.04%, 160/5255), HPV16 (2.72%, 143/5255), HPV51 (1.67%, 88/5255), and HPV53 (1.50%, 79/5255) (Table 1).

Twenty-one HPV genotypes were detected a total of 1,253 times in 937 HPV-positive patients. Of all the infections, single genotype infection was the most commonly observed, with a prevalence rate of 74.28% (696/937). The single low-risk HPV and high-risk HPV infection rates were 12.17% (114/937) and 62.11% (582/937), respectively, while the prevalence of multiple infections (≥ 2 genotypes) was 25.72% (241/937) and that of double infection was 19.21% (162/937) (Table 2).

HPV genotypes in relation to the severity of cervical lesions

Of the 5,255 patients, 6.09% (320/5,255) had a normal cervix, 1.98% (104/5,255) had LSIL, 1.05% (55/5,255) had HSIL, 0.67% (35/5,255) had ICC. Moreover, 90.22% (4741/5,255) had other characteristics typically involved chronic cervicitis, cervical erosion, cervical hypertrophy, bleeding, nabothian cysts, cervical polyp, cervical hypertrophy, and erosion (Table S1). Our results showed HPV infection prevalence rates of 15.63% (50/320), 58.65% (61/104), 80.00% (44/55), 88.57% (31/35), and 15.84% (751/4,741), respectively, among those with a normal cervix, LSIL, HSIL, ICC, and others

Table 1. Distribution of human papillomavirus genotypes according to the final diagnoses among the 5,255 patients.

Genotype	All cases(%)	Normal Cervix(%)	LSIL(%)	HSIL(%)	ICC(%)	Others(%)	χ^2 value	p value
Number of cases	4318 (82.17)	320	104	55	35	4741	-	-
HPV-positive	937 (17.83)	50 (15.63)	61 (58.65)	44 (80.00)	31 (88.57)	751 (15.84)	396.810	0
Low-risk HPV								
HPV6	64 (1.22)	1 (0.31)	2 (1.92)			61 (1.29)	2.855	0.452
HPV11	40 (0.76)		1 (0.96)		1 (2.86)	38 (0.80)	5.305	0.171
HPV42	5 (0.10)					5 (0.11)	3.640	1
HPV43	11 (0.21)		2 (1.92)			9 (0.19)	9.002	0.074
HPV44	19 (0.36)	2 (0.63)				17 (0.36)	1.690	0.673
CP8304	73 (1.39)	4 (1.25)	3 (2.88)	1 (1.82)		65 (1.37)	2.422	0.538
High-risk HPV								
HPV16	143 (2.72)	3 (0.94)	21 (20.19)	27 (49.09)	21 (60.00)	71 (1.50)	318.072	0
HPV18	39 (0.74)		7 (6.73)	6 (10.91)	4 (11.43)	22 (0.46)	70.063	0
HPV31	19 (0.36)	3 (0.94)	2 (1.92)		1 (2.86)	13 (0.27)	13.862	0.007
HPV33	29 (0.55)	7 (2.19)	1 (0.96)			21 (0.44)	12.308	0.011
HPV35	10 (0.19)	2 (0.63)			1 (2.86)	7 (0.15)	10.726	0.034
HPV39	71 (1.35)	4 (1.25)	3 (2.88)	2 (3.64)		62 (1.31)	4.612	0.253
HPV45	20 (0.38)	3 (0.94)	2 (1.92)			15 (0.32)	8.756	0.063
HPV51	88 (1.67)	5 (1.56)	4 (3.85)	2 (3.64)		77 (1.62)	4.769	0.243
HPV52	248 (4.72)	13 (4.06)	18 (17.31)	8 (14.55)	5 (14.29)	204 (4.30)	40.142	0
HPV53	79 (1.50)	4 (1.25)	4 (3.85)	1 (1.82)		70 (1.48)	3.933	0.314
HPV56	32 (0.61)	2 (0.63)	2 (1.92)			28 (0.59)	3.286	0.380
HPV58	160 (3.04)	10 (3.13)	9 (8.65)	3 (5.45)	1 (2.86)	137 (2.89)	10.473	0.023
HPV59	26 (0.49)	1 (0.31)				25 (0.53)	0.262	1
HPV66	41 (0.78)	1 (0.31)	2 (1.92)			38 (0.80)	2.589	0.498
HPV68	36 (0.69)	2 (0.63)	1 (0.96)			33 (0.70)	0.615	0.818

HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; ICC, invasive cervical carcinoma

Table 2. Single and multiple infection status in patients with HPV infection.

HPV infection	N	%
Single infection	696	74.28
Single low-risk infection	114	12.17
Single high-risk infection	582	62.11
Multiple infection	241	25.72
Double infection	180	19.21
Triple infection	47	5.02
Quadruple or five infection	14	1.49

(Table 1). The most commonly observed HPV genotypes in patients with a normal cervix (normal cervix group) were HPV52 (4.06%, 13/320), HPV58 (3.11%, 10/320), and HPV33 (2.19%, 7/320). However, the most prevalent HPV genotypes were HPV16 (20.19%, 21/104), and HPV52 (17.34%, 18/104) in patients with LSIL, and HPV16 (49.09%, 27/55), HPV 52 (14.55%, 8/55) and HPV18 (10.91%, 6/55) in those with HSIL. In the 35 patients with ICC, HPV16, HPV52, and HPV18 were also the most prevalent HPV genotypes, with prevalence rates of 60.00% (21/35), 14.59% (5/35), and 11.43% (4/35), respectively.

Moreover, although HPV52 and HPV58 were the most prevalent subtypes in the 5,255 cases, their prevalence rates decreased with the severity of intraepithelial lesions, from 17.31% to 8.65% in patients with LSIL to 14.29% and 2.86% in those with ICC, respectively (Table 1). However, HPV16, HPV18, and HPV52 accounted for the majority of cases with severe cervical lesions (74.55% in HSIL patients and 85.71% in ICC patients) (Figure 1). The majority of HSIL cases were attributed to HPV16 (49.09%), followed by HPV52 (14.55%) and HPV18 (10.91%). HPV16 also accounted for most of the ICC cases, with a prevalence rate of 60.00%, followed by HPV52 (14.29%) and HPV18 (11.43%). Interestingly, with

Figure 1. Distribution of the five most prevalent HPV genotypes according to diagnosis. HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; ICC, invasive cervical carcinoma.

intraepithelial lesion progression, the infection rates of HPV16 and HPV18 gradually increased (both $p < .001$).

HPV infection in different age groups

The total rate of HPV infection in women aged <25 years was 23.77% (87/366), which was significantly higher than that observed in the age of 25–45 years group (714/4,137, 17.26%) and >45 years group (136/752, 18.08%) ($\chi^2 = 9.938$, $p = .007$). However, as shown in Figure 2, the rates of high-risk HPV infection in women aged <25 years, 25–45 years, and >45 years were 14.75% (54/366), 13.58% (562/4137), and

Figure 2. Rate of total and high-risk HPV infection across all age groups among 5,255 gynecology outpatients in Shenzhen city, China. HPV, human papillomavirus.

17.29% (130/752), respectively, and the difference between the three groups was statistically significant ($\chi^2 = 7.262$, $p = .026$).

Discussion

In the present study, we reported on the correlation between HPV genotypes and cervical pathology status among women with cervical lesions presenting in Shenzhen city and found that the overall prevalence of HPV infection was 17.83%, with 85.81% of these cases showing the high-risk genotypes. HPV52, HPV16, and HPV58 were the three subtypes with the highest prevalence, whereas HPV16 was the most commonly observed carcinogenic HPV subtype in patients with intraepithelial lesions, followed by HPV52 and HPV18. Moreover, HPV16 and HPV18 were associated with premalignant lesion severity in the cervix. This study would demonstrate the understanding of the prevalence and distribution of the HPV genotypes in the female population with cervical lesions presenting in Shenzhen, China, and will assist in developing the formulation of preventive strategies for cervical carcinoma and HPV vaccination programs.

Persistent high-risk HPV infection is considered a driving factor for the progression of precancerous lesions to ICC. Early detection, prevention, and treatment are key to reducing the associated morbidity and mortality. In our study, the overall HPV prevalence rate was 17.83% (937/5,255) in Shenzhen city. However, HPV infection rates are known to vary across different regions in China (7.3% in Guangdong,¹⁵ 9.9% in Beijing,¹⁶ 10.3% in Liaoning,¹⁷ 18.7% in Shaanxi,¹⁸ and 24.7% in Xinjiang¹⁹), and across different countries (8.0% to 27.3%).^{9,20-22} Demographic factors such as ethnicity, socioeconomic status, health conditions, and education level may contribute to the uneven distribution of HPV incidence.²³ A total of 21 HPV genotypes including 15 high-risk types and six low-risk types were detected in this study. The most prevalent HPV subtypes were HPV52, HPV58, and HPV16, which supported the viewpoint that HPV52 and HPV58 are highly prevalent among individuals in eastern Asia.²⁴ Similar to our results, another study also found that HPV-52 was the most prevalent HPV genotype in women in Guangdong province.²⁵ However, our results are inconsistent

with those of a worldwide retrospective cross-sectional study, in which the top eight HPV genotypes related to ICC were HPV16, 18, 31, 33, 35, 45, 52 and 58 in America, Europe, and Africa.²⁴ Therefore, current knowledge on the distribution of HPV subtypes in a given region remains to be further verified through studies with large sample sizes; this may have great value in the formulation of screening, treatment, prevention, and vaccine development strategies for HPV-attributable diseases.

Previous studies have demonstrated that the pathogenic ability of HPV differs across its genotypes and that HPV16 and HPV18 are the two most commonly observed genotypes associated with intraepithelial lesion severity.^{26,27} For better preparedness against future precancerous lesions and ICC, virological HPV screening was recommended by the International Agency for Research on Cancer in 2017.²⁸ In addition, according to the American Congress of Obstetricians and Gynecologists and American Society for Colposcopy and Cervical Pathology guidelines, patients with HPV16 and HPV18 infection should be examined by colposcopy even if the cytology is negative for malignancy.²⁹ In the present study, the prevalence rates of HPV16, HPV18, and HPV52 infections in cases with a normal cervix were significantly lower than those observed in cases with intraepithelial lesions, consistent with several previous studies from China and western countries.^{3,26,27,30} As the most commonly occurring genotype among all grades of cervical lesions,^{24,27,31} the prevalence of HPV16 significantly increased with intraepithelial lesion severity, from 20.19% in LSIL patients to 60.00% in patients with ICC. This suggests that HPV16 is the subtype with the strongest carcinogenic potential in Shenzhen city and that its prevalence increases with intraepithelial lesion severity. Comparatively, although HPV18 was not the most prevalent genotype, it was the third most commonly observed genotype in patients with cervical intraepithelial changes following HPV16 and HPV52. Previous reports have indicated that HPV16 is highly correlated to both adenocarcinoma and squamous-cell carcinoma, whereas HPV18 is predominantly a risk factor for the development of adenocarcinoma.³² Further investigation is required to confirm the relationship between the types of CC and HPV genotypes. Inconsistent with the results observed in western countries,^{20,24} we demonstrated that HPV52 occurred commonly in Chinese women with or without cervical lesions.^{12,25,26} However, no significant differences in the rates of HPV52 infection between cases with LSIL, HSIL, and ICC were found. This result illustrates that, while HPV52 may be associated with cervical intraepithelial lesions, its contribution to the carcinogenesis from LSIL to ICC is small.

Biological and epidemiological investigations have shown that population type and age may impact the rate of HPV infection and genotype distribution.^{9,15,24} Young, sexually active women show the highest rates of HPV infection, and HPV vaccination provides the best preventive effect in women who are not yet sexually active.²⁸ According to the present study, the rate of HPV infection was the highest among women aged between 25 and 45 years, with the highest rate noted among those aged <25 years; this may be related to the small number of people included in the <25 years old age group. In addition, the rapid development of the economy, changes in sexual concept, and participation in unsafe sexual

behaviors may have resulted in younger age at first sexual activity and high levels of sexual activity among women in Shenzhen city, increasing the risk of infection.^{33,34} Consistent with previous studies,^{27,35} the rate of high-risk HPV infection in women aged >45 years was statistically significant higher than that among those aged <25 years and 25–45 years. A previous study showed that the incidence of HPV infection has steadily increased with age in China, and the incidence of CC peaked in the 45–54 years group.³⁶ Nonetheless, early detection and active prevention are still important principles in CC prevention and treatment.

The HPV vaccine is a prophylactic vaccine that prevents HPV infection, and the WHO recommends its administration to girls aged 9 to 14 years as the most cost-effective public health measure against cervical cancer and other HPV-associated diseases.²⁸ As of 2019, the HPV vaccine has been on the national immunization schedules in 92 countries, globally, showing outstanding results in some countries.^{5,6} Since 2008, the rate of immunization using 2vHPV vaccines for girls aged 12 to 13 years has exceeded 90% in Scotland, and the prevalence of HPV infection has decreased by 89%.⁶ The Australian federal government started providing free HPV vaccination for girls aged 12 to 13 years in 2007, and this was expanded to boys in 2013, resulting in a major decrease in the HPV infection rate, from 22.7% in 2005 to 1.1% in 2015.⁵ In China, 2vHPV, 4vHPV, and 9vHPV vaccines were approved by the China Food and Drug Administration for marketing in July 2016, May 2017, and April 2018, respectively. However, previous studies showed that the coverage rates of HPV vaccines among young women in China were still low,^{37–40} and the main reasons for this may be related to confusion about the choice of vaccine type, optimal age for vaccination, insufficient vaccine supply, as well as vaccination procedures and cost. In addition, women's levels of awareness and attitudes toward the etiology of cervical lesions, and HPV and its vaccines greatly influence the rate of vaccination and participation in screening.^{40,41} Our study showed that HPV16, HPV52, and HPV18 played important roles in the occurrence and development of intraepithelial lesions in Shenzhen city; infection with all these subtypes can only be prevented with the use of the 9vHPV vaccine. However, insufficient vaccine supply and the high cost seriously limit the promotion and application of the 9vHPV vaccine. Clarifying the infection rates and epidemiological patterns of HPV is of great significance for the prevention and control of HPV-attributable cancer, and useful for the design of vaccination policies in order to improve vaccine coverage.

There are several limitations in this study, one of which is the absence of behavioral information. Previous studies showed that behavioral information, including smoking, sexual activity, and dietary patterns, plays key roles in the development of HPV infection and cervical cancer.^{27,42–44} In our further research, a study about the correlation between behavioral information and cervical cancer will be performed. Moreover, in consideration of the selected women mostly with gynecological diseases, our findings cannot be generalized to the entire female population in Shenzhen, which may limit the use of the current data for epidemiological purposes. Further large sample population-based surveys based on the entire female population are in demand.

In conclusion, our study yielded extensive results on the prevalence and distribution of the HPV genotypes in the female population of Shenzhen city, China, and found that HPV16, HPV52, and HPV18 played important roles in the occurrence and development of intraepithelial lesions. Our results may offer guidance for the establishment of HPV vaccination programs and preventive strategies for cervical carcinoma in this region.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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