RESEARCH PAPER

Human papillomavirus genotypes and infection among women in Changzhou, China

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ABSTRACT

Human papillomavirus (HPV) infection is a major cause of cervical cancer. HPV vaccine has been shown to be highly effective in preventing HPV infection, and understanding the genotypes of HPV infection can guide the utilization of HPV vaccine. This epidemiological study aimed to investigate the genotype distribution of HPV in HPV-positive female patients in Changzhou. This study enrolled HPV-positive female patients admitted at the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University were enrolled in this study. HPV genotypes were identified via standard HPV DNA testing. The cohort comprised 5738 patients, that the predominant genotypes were HPV52 (13.4%), HPV16 (9.6%), HPV58 (8.8%), HPV81 (8.6%), and HPV53 (7.7%). HPV infection prevalence was the highest among those aged 41–45 y (16.6%), followed by those aged 31–35 y (15.1%) and 36–40 y (15.1%). In total, 46.8% of infections were found in women aged 31–45 y. The main genotypes of HPV infection upon physical examination or diagnosis of cervicitis and cervical cancer were HPV52, 16, 58, 81, and 53. HPV52, 16, 58, 81, and 53 are the most predominant genotypes of HPV infection. Further, HPV infection is most prevalent among women aged 31–45 y. Our findings provide experimental evidence for guiding HPV vaccination policy.

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Introduction

Human papillomavirus (HPV) is the most frequent reproductive tract infection. It shows high human tropism and can immortalize normal epithelial cells while reside stably in the nucleus.¹ Most HPV infections are asymptomatic and resolve spontaneously,² but persistent HPV infections can cause paralysis or precancerous lesions.³ The risk factors for persistent HPV infection include pregnancy, multiple sex partners, smoking, and aberrant immune function.⁴ Moreover, persistent HPV infections increase the risk cervical, vulvar, vaginal, penile, and throat cancers.^{5–8}

The primary modes of HPV transmission are sex and skin contact,⁵ and HPV infection is the primary causative factor in >96% of cervical cancer cases.^{9,10} Over 200 HPV genotypes have been identified,¹¹ but HPV is mainly divided into high-risk and low-risk genotypes according to their association with cancers.¹² At least 17 HPV genotypes (i.e., 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82) have been proven to cause >96% of cervical cancers and are thus considered as high-risk HPV genotypes.¹³ Meanwhile, there are at least 6 HPV genotypes (i.e., 6, 11, 42, 43, 81, and 83) that cause benign or low-grade changes and are thus considered as low-risk HPV genotypes. The rate and genotypes of HPV infections vary in different countries.⁶ HPV infection is prevalent in 11–12% of women without cervical abnormalities, while the prevalence rate in China, is 11.4–20.3%.¹⁰ Approximately 561,000 new cancer cases worldwide annually (5.2% of all new cancers) are attributable to HPV, making HPV one of the most important infectious causes of cancer.¹⁴

HPV vaccine is a major strategy for preventing HPV infection.¹⁵ China has approved bivalent (2vHPV), quadrivalent (4vHPV), and 9-valent (9vHPV) vaccines, with 9vHPV being the successor to 4vHPV vaccine. The 2vHPV vaccine prevents infection from HPV16 and 18 genotypes; 4vHPV from HPV6, 11, 16, and 18 genotypes; and 9vHPV from HPV6, 11, 16, 18, 31, 33, 45, 52, and 58 genotypes. Due to the lack of data on HPV genotypes, the rate of HPV vaccination is low and the incidence of HPV infection is increasing in China. Therefore, the detection of HPV genotypes in China will provide valuable information for guiding the development of HPV vaccination policies.

In this epidemiological study, we aimed to assess HPV DNA genotypes to determine the genotype distribution of HPV infection in HPV-positive female patients in China.

Results

HPV infection genotypes

A total of 5738 HPV-positive female patients admitted at the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University were enrolled in this study. In total, 23 different HPV genotypes were detected, including 17 high-risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82) and 6 low-risk HPV genotypes (6, 11, 42, 43, 81, and 83). The primary genotypes were HPV52 (13.4%), HPV16 (9.6%), HPV58 (8.8%), HPV81 (8.6%), and HPV53 (7.7%) (Figure 1(a)). To analyze the genotype distribution of HPV infection in different types of patients, we

Figure 1. HPV genotype distribution in the HPV-positive patients and the physical examination group, the cervicitis group, and the cervical cancer group. (a) HPV52, HPV16, HPV58, HPV81, and HPV53 were the most predominant genotypes in the HPV-positive patients. (b) HPV52, HPV16, HPV58, HPV81, and HPV53 were the main type of HPV infections in all the three groups (the physical examination group, the cervicitis group, and the cervical cancer).

divided the HPV-positive patients into the voluntary physical examination group, cervicitis group, and cervical cancer group. The main genotypes of HPV infection in the physical examination group were HPV52 (19.5%), HPV58 (14.9%), HPV81 (12.5%), HPV16 (11.4%), and HPV53 (11.1%) patients. Similarly, HPV52 (20.3%), HPV81 (14.7%), HPV16 (13.8%), HPV58 (13.6%), and HPV53 (11.4%) were the main genotypes of HPV infections in cervicitis patients, although at a different distribution. Similarly, we found that HPV16 (22.7%), HPV52 (15.5%), HPV58 (14.6%), HPV81 (12.9%), and HPV53 (11.0%) were also the main genotypes of HPV infections in cervical cancer patients (Figure 1(b)). These results indicated that HPV52, 16, 58, 81, and 53 were the main genotypes of HPV infection in female patients in Changzhou, China.

Type of HPV infection

We analyzed the distribution of HPV infections in the physical examination group, the cervicitis group, and the cervical cancer group. As shown in Table 1, the proportion of high-risk HPV infection in the physical examination group, cervicitis group, and cervical cancer group was 76.7%, 79.9%, and 80.1%, respectively. Meanwhile, that the proportion of low-risk HPV infection in the physical examination group, cervicitis group, and cervical cancer group was 23.3%, 20.1%, and 19.9%, respectively. Regarding single and multiple genotype infection, the proportion of single HPV genotype infection in the physical examination, cervicitis group, and cervical cancer group was 65.2%, 61.6%, and 70.9%, respectively. Meanwhile, the proportion of multiple HPV genotype infection in the physical examination group, the cervicitis group, and the

Table 1. Genotype distribution of HPV infection in the physical examination group, the cervicitis group, and the cervical cancer group.

Type of HPV infection	Physical examination group	Cervical vaginitis group	Cervical cancer group	P value
High-risk HPV infection	76.7 (%)	79.9(%)	80.1(%)	0.0014
Low-risk HPV infection	23.3(%)	20.1 (%)	19.9 (%)	
Single HPV genotype infection	65.2(%)	61.6 (%)	70.9(%)	0.0275
Multiple HPV genotype infection	34.8(%)	38.4(%)	29.1(%)	

cervical cancer group was 34.8%, 38.4%, and 29.1%, respectively. These data suggested that high-risk HPV infection and single HPV infection were predominant in HPV-positive female patients ($p < .05$).

Age distribution of HPV infection

We also analyzed the age of prevalence for HPV infection in HPV-positive female patients and the age distribution of HPV-positive patients in the physical examination group, cervicitis group, and cervical cancer group. As shown in Table 2, the age of highest prevalence for HPV infection was 41–45 y (16.6%), and women aged 31–45 accounted for 46.9% of patients. The age of highest prevalence for female HPV infection in the physical examination group, the cervicitis group, and the cervical cancer group was 26–30 y (19.1%), 36–40 y (18.9%), and 41–45 y (27.9%), respectively. In addition, we found a linear positive association between age and HPV-positive cervicitis and between patient age and HPV-

Table 2. Age of prevalence for HPV-positive patients and in the physical examination group, the cervicitis group, and the cervical cancer group.

Age range, years	HPV-positive patients	Physical examination group	Cervical vaginitis group	Cervical cancer group
17–20	1.5%	1.7%	1.6%	0(%)
21–25	6.7%	9.3%	6.4%	1.6%
26–30	13.5%	19.2%	13.9%	5.5%
31–35	15.2%	14.6%	13.7%	9.1%
36–40	15.1%	14.8%	18.9%	14.3%
41–45	16.6%	17.0%	14.6%	27.9%
46–50	13.7%	12.8%	13.9%	16.2%
51–55	8.4%	4.4%	9.5%	9.1%
56–60	4.4%	3.0%	3.9%	8.2%
61–65	3.1%	2.9%	2.5%	3.6%
≥66	1.8%	0.3%	1.1%	4.5%

Figure 2. The association of ages between HPV-positive cervicitis and HPV-positive cervical cancer.

positive cervical cancer ($P < .05$; Figure 2). These results showed that the age of highest prevalence for female HPV infection was 31–45 y, and HPV-positive cervicitis increased the risk of cervical cancer.

Discussion

HPV is the most common sexually transmitted virus, and approximately 75% of sexually active women and men will acquire HPV infection in their lifetime.¹⁶ Worldwide, approximately 20 million women have HPV infection.¹⁷ HPV infection is an epitheliotropic infection.^{18,19} Most infections are subclinical and will cause no physical symptoms, but some cases of subclinical infections progress to clinical infections and may cause benign papillomas (such as warts or squamous cell papilloma) or cancers.^{11,20,21} The HPV infection rate and genotypes vary between countries.²² In our epidemiological study, we investigated the prevalence and genotype distribution of HPV infection in HPV-positive female patients admitted at the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University. We found that HPV52, 16, 58, 81, and 53 were the most predominant genotypes in this population. Previous studies have shown that HPV16, 52, 58, 18, and 81 and HPV16, 58, and 52 are the main infectious genotypes in Guangdong and Xinjiang, China, respectively.^{23,24} We

found that HPV53 was also the main HPV genotype in Changzhou, which could support the development of strategies to promote vaccination and help identify the specific vaccine valence needed in this area.

HPV vaccination is widely recommended as an effective strategy against HPV infection and has been recently implemented in most Western countries. The 2vHPV and 4vHPV vaccines are known to prevent most cervical cancers caused by HPV16/18 infection.²⁵ In China, three HPV vaccines are currently available; these are 2vHPV vaccine, 4vHPV vaccine, and 9vHPV vaccine. According to our epidemiological survey, HPV18 is not the main type of HPV infection, but HPV53 is the main type of HPV infection, in Changzhou, China. Therefore, our research can effectively guide local governments to develop HPV vaccination programs for targeted vaccination.

Persistent infection with high-risk HPV genotypes is the primary risk factor for cervical cancer.^{26,27} Previous studies have shown that the proportion of HPV16 and HPV18 infection is closely related with the incidence of cervical cancer.⁹ In a Swedish cohort of cervical cancer patients, HPV16, 18, 31, 45, and 33 were the most frequently detected genotypes.²⁸ In this epidemiological study, we found that HPV16 (22.7%), HPV52 (15.5%), HPV58 (14.6%), HPV81 (12.9%), and HPV53 (11.0%) were the common genotypes of HPV infections in HPV-positive cervical cancer patients. Further, our epidemiological study showed that HPV53 accounted for a high proportion of infection in both HPV-positive female patients and HPV-positive cervical cancer patients. Given that HPV vaccines currently do not prevent HPV53 genotype infection, high-risk HPV vaccines should be developed.

A total of 70% of HPV infections are eliminated via autoimmunity within 2 y. However, the persisting infection can induce inflammation and further lead to malignancy. We found that the age of highest prevalence for HPV infection is 41–45 y (16.6%), and women aged 31–45 y accounted for 46.9% of patients. These results may be due to the diverse lifestyle of women at this age and because the rate of HPV screening was higher among women aged 31–45 y. In addition, there was a linear positive association between age and HPV-positive cervicitis and between age and HPV-positive cervical cancer. The findings of our epidemiological study are consistent with the fact that long-term persistent HPV infection can induce inflammation and malignant tumors.

This study also has some limitations. The collected samples were mainly from Changzhou, and the sample size was inadequate to be representative of the entire country. Further, we only detected the expression of 23 HPV genotypes, including 17 high-risk HPV genotypes and 6 low-risk HPV genotypes, which may lead to overestimation of the high-risk HPV genotype in the HPV-positive female patients. In addition, although we found that HPV53 accounted for a high proportion of infection in both HPV-positive female patients and HPV-positive cervical cancer patients, we only detected the expression of 23 HPV genotypes, including 17 high-risk HPV genotypes and 6 low-risk HPV genotypes, and this may have led to overestimation of the high-risk HPV genotype in the HPV-positive female patients. Further research focus on these aspects is needed to confirm these

association and develop an effective vaccination policy for HPV infection.

Conclusions

Our epidemiological study showed that HPV52, 16, 58, 81, and 53 were the main genotypes of HPV infection in Changzhou. Further, the age of highest prevalence for HPV infection was 41–45 y, and majority of patients were aged 31–45 y. Moreover, the age of highest prevalence for female HPV infection in patients who undergo physical examination, those with cervicitis, and those with cervical cancer was 26–30 y, 36–40 y, and 41–45 y. These findings will be valuable in developing strategies to promote HPV vaccination in different regions according to population characteristics.

Methods

Study subjects

This study enrolled HPV-positive female patients admitted at the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University. The inclusion criteria were as follows: (1) aged from 17–80 y; (2) no previous HPV test, and (3) no history of vaginal drug use, no sexual intercourse 3 d before sample collection, or no previous HPV infection. The patients were divided into 3 groups as follows: the physical examination group comprised the healthy population who had normal physical examination findings; the HPV-positive group comprised patients diagnosed with cervicitis after gynecological examination, white blood cell examination, pathogen test, cervical scraping, and biopsy; and the cervical cancer group comprised HPV-positive patients diagnosed with cervical cancer via cervical smear cytology, cervical iodine test, colposcopy, cervical biopsy, cervical surgery, and pathological screening. This epidemiological study was approved by the Human Ethics Committees of the Affiliated Changzhou No. 2 People's Hospital, Nanjing Medical University, and written informed consent was obtained from all the patients.

Specimen collection and storage

The cervical epithelial cells were collected using Cervix Epithelial cell Extraction Kit (Yaneng BioScience Co., Ltd. Shenzhen, China). Briefly, specimens were collected by inserting a speculum into the endocervical canal and rotating it unidirectionally four times. The exfoliated cervical epithelial cells then adhere to the flat sides of the bristles. The tip of the cervix brush is then placed into a vial containing transport medium and stored at 4°C.

DNA extraction

DNA from exfoliated cervical cells was collected using a DNA Extraction Kit (Yaneng BioScience Co., Ltd. Shenzhen, China) as per the manufacturer's instructions. The cervical brush was fully eluted and transferred to a 1.5 ml centrifuge tube and then centrifuged at 13000 rpm for 10 min. After, the

supernatant was discarded, and 50 µL of the lysate was added to suspend the pellet. This was then heated in a boiling water bath for 10 min and centrifuged again at 13000 for 10 min.

HPV DNA genotype testing

HPV DNA genotype testing was performed using HPV DNA testing Kit (Yaneng BioScience Co., Ltd. Shenzhen, China) following the manufacturer's instructions.

The amplification system comprised 5 µL HPV-DNA and 20 µL reaction system (Yaneng BioScience Co., Ltd. Shenzhen, China). HPV was amplified using Roche LightCycler 480 instrument (Roche, USA) following the manufacturer's guidelines as follows: 50°C for 15 min; 95°C, 10 min; 94°C, 30 sec; 42°C, 90 sec; 72°C, 30 sec (40 cycles); and 72°C, 5 min. HPV genotyping was performed via flow-through hybridization and using gene-chips that contained type-specific oligonucleotides (Yaneng BioScience Co., Ltd. Shenzhen, China). The gene-chip includes 23 type-specific oligonucleotides designed to detect 17 high-risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82) and 6 low-risk HPV genotypes (6, 11, 42, 43, 81, and 83). The final results were determined according to colorimetric change on the chip under direct visualization. Quality controls were performed throughout the experiments, including DNA extracting, amplification, and hybridization by applying positive and negative quality control products as control groups for PCR amplification.

Data analysis

Single and multiple HPV infections were defined as infection with one and with two or more subtypes of HPV infections, respectively. The proportion of women in different age groups with single and multiple infections was then analyzed. Data were compared using Pearson χ^2 or Fisher exact tests. Descriptive and inferential statistical analysis were conducted using Statistical Package for the Social Sciences version 22 (SPSS Inc., Illinois, USA), and $P < .05$ was considered to be statistically significant.

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Disclosure of potential conflicts of interest

The authors declare that there is no conflict of interest.

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