

# Analysis and comparison of the prevalence and genotype distribution of human papillomavirus in two different areas of China: a cross-sectional study

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**Objectives:** This study investigated and compared the prevalence and distribution of high-risk human papillomavirus (HR-HPV) genotypes in Tongliao and Huidong regions of China. **Materials and methods:** A cross-sectional study of the results of cervical cancer screening was conducted between August 2017 and April 2018 in Tongliao, Inner Mongolia as well as Huidong, Sichuan Province, China. Totals of 2351 and 1583 women recruited in Tongliao and Huidong, respectively, who underwent cytology sampling, collected for thinprep cytologic tests (TCT) and PCR-based HPV genotyping tests. Participants whose HPV and TCT results met relevant indications were referred for colposcopy. **Results:** The overall prevalence in the Tongliao and Huidong cohorts were 19.35% and 10.4% ( $P < 0.05$ ), among which the five most common genotypes were HPV16 (3.91%), 52 (3.79%), 53 (2.42%), 68 (2.04%), and 51 (1.96%) in Tongliao and HPV52 (2.27%), 16 (1.58%), 58 (1.39%), 51 (1.39%), and 53 (0.95%) in Huidong. In both cohorts, single-type infections were more common than multiple-type infections. HPV16 was the most common genotype in high-grade squamous intraepithelial lesions. In the Tongliao cohort, HPV33, HPV52, and HPV58 showed a risk of carcinogenesis similar to HPV18. **Conclusions:** This study provides information on HPV prevalence and genotype distribution in Tongliao and Huidong. The HPV prevalence and genotype distribution were found to differ geographically. The HPV genotyping tests provided more details, which can be instructive and meaningful for both the prevention and management of HPV infection and cervical lesions.

## Keywords

Human papillomavirus; Prevalence; Genotypes; Cervical cancer; Cervical intraepithelial neoplasia

## 1. Introduction

Cervical cancer is one of the most common diseases in the world. It has been estimated that in 2018, approximately 570,000 new cases of cervical cancer and 311,000 deaths oc-

curred worldwide; in China, there were about 106,000 cases and 48000 deaths [1]. At first, cytology-based screening played a predominant role during primary screening. Persistent infection with high-risk human papillomavirus (HR-HPV) has been considered as the major cause of cervical cancer and precancerous lesions [2]. With increasing knowledge of HPV virology and the development of molecular HPV testing, HPV-based assays are playing an increasingly important role in the screening: the development moved from the triage for mild cytological abnormalities, to co-testing with cytology and HPV, and recently, to primary HPV screening. The HPV prevalence and genotype distribution in China varies geographically [3, 4]. Different types of HPV are linked to varying risks of carcinogenicity—with HPV16 and 18 being responsible for approximately 65% to 75% of cervical cancers, respectively [5, 6]. The HPV genotyping test provides more details about infections with different HPV genotypes, which may guide the treatment of the HPV infection more precisely according to the specific genotype. In addition, while an HPV vaccine has been introduced in China, it is not popular. It would be helpful to better assess the protective value of this particular vaccine if further knowledge of the epidemiology of each specific genotype were available.

The present study organized a free screening program in two different areas in China: one in northern China and one in southwestern China. The screened areas feature different climates, terrains, ethnicities, and lifestyles. The HPV prevalence and genotype distribution were analyzed and compared between both different areas, with the aim to identify similarities and differences between both cohorts. This data provides more information about the characteristics of different types of HPV.

## 2. Materials and methods

### 2.1 Study population and design

A cross-sectional study was conducted based on a population-based free cervical cancer screening program organized by Peking University People's Hospital and West China Second University Hospital, Sichuan University cooperating with the local hospital Inner Mongolia University for Nationalities and Huidong County People's Hospital. The latter two hospitals were responsible for the recruitment of subjects in Tongliao and Huidong, respectively. The participants were informed about the program either through online publications or the propaganda board displayed in the local hospital. The participants were not compensated in money or gifts, but they received free access to cervical cancer screening and acquired knowledge of cervical cancer screening. The inclusion criteria for the screening program were: (1) age  $\geq 25$  or  $\leq 65$ ; (2) active sexual life; (3) voluntarily participated in the study. The exclusion criteria included: (1) age  $< 25$  or  $> 65$ ; (2) confirmed HPV infection, precancerous lesions or cervical cancer; (3) subjects that underwent hysterectomy or excision procedure on their cervix; (4) subjects with a history of pelvic radiation therapy or chemotherapy; (5) pregnant or lactational subjects.

In this study, all participants firstly signed informed consent, then filled in a case report form, in which the following demographic data of participants was collected: name, age, ethnicity, education level, marital status, gravidity and parity, contraceptives, smoking history, screening history, age of first sexual intercourse, and number of sexual partners. Then, all participants underwent pelvic examination performed by a gynecologist. Cervical cells were collected from each participant using a thinprep cytological test (TCT) brush and were stored in Thinprep PreservCyt solution (20 mL). A total of 1–2 mL sample was separated for the HPV DNA genotyping test by Yaneng Biosciences (Shenzhen, China); then, the rest of the samples was transported and stored at room temperature in the cytologic laboratory of Peking University People's Hospital for cytological diagnosis. The testing was performed within two weeks after sample collection. Participants whose screening results meet the following criteria were referred to colposcopy examination: (1) atypical squamous cells that cannot exclude HSIL [ASC-H] or worse; (2) HPV 16/18 positivity; (3) ASCUS in combination with HPV positivity. A coloscopy directed biopsy was conducted. Considering the probable mis diagnosis of the subjective impression and the unsatisfactory access to screening of these participants, participants without obvious abnormality under the colposcope underwent a multi-point biopsy or endocervical curettage. Participants who neither had negative TCT and HPV results nor meet the criteria for referral to colposcopy were recommended to take a repeat TCT/HPV test one year later.

### 2.2 Human papillomavirus DNA detection and genotyping

HPV DNA genotyping was preformed using an L1 consensus primer-based PCR-reverse dot blot (PCR-RDB) assay kit (Yaneng Biosciences, Shenzhen, China). This kit can identify and distinguish 15 HPV genotypes including 13 high-risk (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and two likely high-risk (types 53 and 66) HPV types [7]. The experimental procedures, including DNA extraction, polymerase chain reaction (PCR), and reverse dot blot hybridization (RDB), were performed according to the manufacturer's instructions. The PCR amplification was started with an initial enzyme reaction at 50 °C for 15 min, followed by pre-denaturation at 95 °C for 10 min, 40 cycles of amplification including denaturation at 94 °C for 10 s, annealing at 46 °C for 1 min, and extension at 72 °C for 20 s. Then, a final extension was conducted at 72 °C for 5 min.

### 2.3 Cytology

Cervical samples were prepared using a liquid-based cytology method (Thinprep, Hologic) and the cytological results were categorized according to the 2001 Bethesda System [8] as summarized in the following: negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells cannot exclude HSIL(ASC-H), high-grade squamous intraepithelial lesion (HSIL), squamous cervical cancer (SCC), atypical glandular cells (AGC), and endocervical adenocarcinoma in situ (AIS).

### 2.4 Statistical analysis

The characteristics of participants were summarized at baseline and described by counts and percentages. Categorical variables were described by absolute frequencies, percentages, and  $\chi^2$  test while continuous variables were described by means and standard deviations (SD). *P* values below 0.05 were considered to indicate statistically significant differences. All statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM, Armonk, NY, USA).

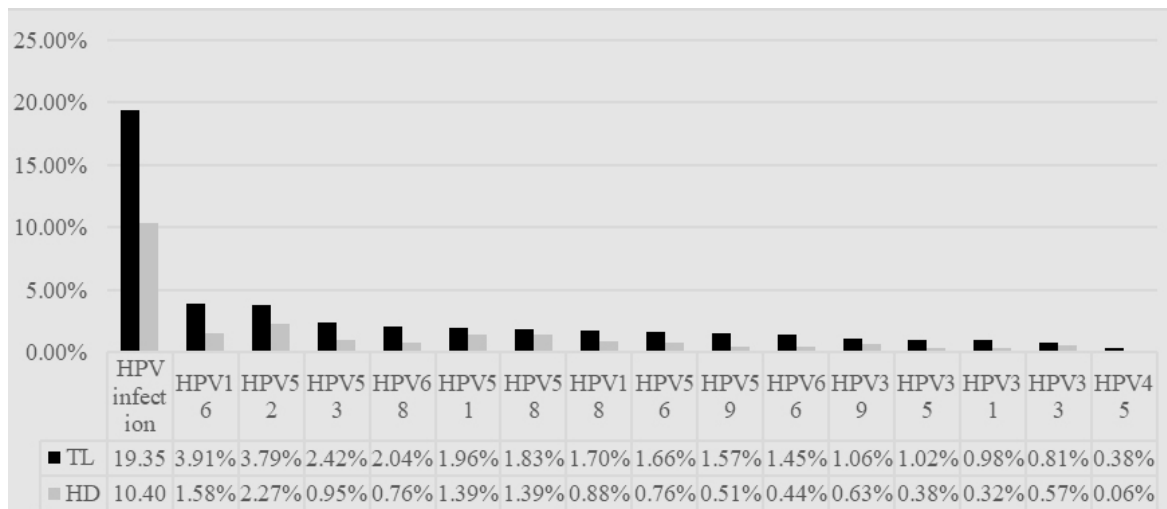
## 3. Results

A total of 2473 and 1583 women were recruited in Tongliao and Huidong. Of the 2473 participants in Tongliao, 122 women failed to undergo the screening. As a result, 2351 women in Tongliao and 1583 women in Huidong were included in the final analysis at the baseline. In the Tongliao cohort, 49.1% of participants were Han, 43.2% were Mongolian, and 7.7% were other minorities (including Manchu, Hui, Daur, Evenki, and Korean). In the Huidong cohort, 94.44% were Han and only 5.56% were minorities (including Yi, Miao, Tujia, Buyei, Manchu, Hui, Bai, and Lisu). The basic demographic characteristics of the participants of both cohorts are described in Table 1.

The overall rate of HR-HPV infection in Tongliao was 19.35% (455/2351), and the five most common genotypes were HPV16 (3.91%), HPV52 (3.79%), HPV53 (2.42%),

**Table 1. Basic demographic characteristics of the population in both cohorts.**

Characteristics	Tongliao	Huidong
	(n = 2351)	(n = 1583)
Age (mean ± SD, years)	44.41 ± 8.40	44.79 ± 9.00
Age of first intercourse (mean ± SD, years)	24.42 ± 2.33	22.11 ± 2.28
Ethnicity		
Han	51.34%	94.44%
Other minorities	48.66%	5.56%
Education level		
≤High school	65.0%	68.8%
>High school	35.0%	31.2%
Marital status		
Married	98.4%	96.5%
Others (never married, divorced, or widowed)	1.6%	3.5%
Pap test history		
Never	75.2%	79.2%
Ever	24.8%	20.8%
History of smoking		
No	96.0%	98.5%
Yes	4.0%	1.5%



**Fig. 1. Human papillomavirus (HPV) prevalence and genotype distribution in Tongliao (TL) and Huidong (HD) cohorts.**

HPV68 (2.04%), and HPV51 (1.96%). The prevalence of HR-HPV infection in Huidong was 10.4% (165/1583), and the five most common types of HR-HPV were HPV52 (2.27%), HPV16 (1.58%), HPV58 (1.39%), HPV51 (1.39%), and HPV53 (0.95%). The difference in the prevalence of HR-HPV infection between the two cohorts was significant ( $\chi^2 = 56.826$ ,  $P < 0.001$ ). Fig. 1 summarizes the prevalence and distribution of HPV genotypes in both cohorts. Among the HPV-positive participants in Tongliao and Huidong, HPV infections with single genotype and multiple genotypes in Tongliao and Huidong were 72.97% (332/455) vs 27.03% (123/455) and 82.42% (136/165) vs 17.58% (29/165), respectively.

Furthermore, the HPV positivity rate were analyzed by participants' age and ethnicity. No significant difference was found in the HPV prevalence between different ethnicity

both Tongliao ( $\chi^2 = 1.069$ ,  $P = 0.586$ ) and Huidong ( $\chi^2 = 0.149$ ,  $P = 0.700$ ) cohorts. The participants were divided into four groups by age (25–34, 35–44, 45–54, and 55–65). No significant differences were found in the HPV positivity rate in Tongliao ( $\chi^2 = 1.855$ ,  $P = 0.603$ ) and Huidong ( $\chi^2 = 5.467$ ,  $P = 0.141$ ).

Among all 2351 participants included in Tongliao, 12 samples had invalid or unsatisfactory cytology, 2215 (95.22%) were identified as NILM, and only 124 (5.27%) were diagnosed with cytology abnormalities. Of these, 94 were ASCUS, 12 were LSIL, six were ASC-H, and four were HSIL. Moreover, one sample was diagnosed as ASC-H and AGC. The proportion of HPV positivity in the NILM group was 17.02% (377/2215), while that in cytology abnormalities was 58.87% (74/124): 54.26% (51/94) in ASCUS, 100% (12/12) in

**Table 2. Distribution of high-risk human papillomavirus (HR-HPV) infections among women of different cytology.**

HPV genotypes	Tongliao				Huidong			
	NILM	ASCUS	>ASCUS*	AGC	NILM	ASCUS	>ASCUS	AGC
	(n = 2215)	(n = 94)	(n = 23)	(n = 7)	(n = 1511)	(n = 49)	(n = 9)	(n = 4)
Single-/Multiple-	280/97	38/13	11/12	0/1	104/18	22/8	6/3	3/0
HPV16	36/31	10/4	2/5	0/1	4/3	8/4	5/1	0/0
HPV18	19/12	3/2	1/3	0/0	6/1	5/1	0/0	1/0
HPV31	12/4	3/1	2/0	0/1	2/2	0/0	0/0	1/0
HPV33	5/7	2/3	0/2	0/0	7/1	0/1	0/0	0/0
HPV35	9/10	1/2	0/2	0/0	1/2	2/0	0/1	0/0
HPV39	5/12	3/2	1/1	0/0	7/3	0/0	0/0	0/0
HPV45	3/6	0/0	0/0	0/0	0/0	1/0	0/0	0/0
HPV51	26/16	1/1	0/2	0/0	12/6	1/2	0/1	0/0
HPV52	47/28	6/4	1/2	0/0	23/7	1/3	1/1	0/0
HPV53	34/13	2/4	1/3	0/0	9/4	0/1	0/1	0/0
HPV56	15/19	1/0	1/2	0/0	4/4	2/1	0/1	0/0
HPV58	17/15	3/3	1/2	0/0	12/6	1/1	0/0	1/0
HPV59	21/10	0/1	1/3	0/1	3/2	1/2	0/0	0/0
HPV66	10/18	2/2	0/2	0/0	6/0	0/1	0/0	0/0
HPV68	21/25	1/0	0/1	0/0	8/3	0/1	0/1	0/0

\* Three samples whose TCT showed ASC-H and AGC were included in the cytology group '>ASCUS', but were excluded from the group 'AGC'.

LSIL, 100% (7/7) in ASC-H, and 100% (4/4) in HSIL, while only one of seven AGC cases was HPV positive.

In Huidong, 10 of 1583 samples had valid cytology, 1511 of 1583 samples (95.45%) were identified as NILM for cytology while only 62 (3.92%) had abnormal cytology, including 49 ASCUS, one LSIL, two ASC-H, three HSIL, one SCC, and four AGC. Moreover, two samples were diagnosed as ASC-H and AGC. The HPV positivity proportion in the NILM group was 8.07% (122/1511), while that in the abnormal group was 67.74% (42/62) and 61.22% (30/49) in ASCUS, 100% (1/1) in LSIL, 100% (4/4) in ASC-H, 100% (4/4) in HSIL, and 83.3% (5/6) in AGC. As shown, there was no significant difference between the rate of cytological abnormalities of both cohorts ( $\chi^2 = 3.841, P = 0.05$ ). Moreover, in both cohorts, an increased rate of HPV infection was found with increasing severity of cytology. Table 2 shows the detailed HPV prevalence and genotype distribution of different cytological results.

First, the HPV prevalence and genotype distribution were analyzed in participants diagnosed as HSILs and worse. In the Tongliao cohort, 187 participants needed referral to colposcopy. Eventually, 152 patients underwent colposcopy-directed biopsy, including 33 high-grade squamous intraepithelial lesions (HSILs) (17 CINIII and 16 CINII), 67 low-grade squamous intraepithelial lesions (LSILs/CINI), and 52 chronic cervicitis. Of the 33 HSILs, 17 were single-type infections and 16 were multiple-type infections. The detailed distribution of specific genotypes is shown in Fig. 2. Twenty-one of 33 (63.6%) HSILs had infection with HPV16 and all CIN3s with multiple HPV infections were HPV16 co-infections with other types.

In the Huidong cohort, 56 participants met the criteria for colposcopy. Thirty-five participants finally underwent colposcopy and had a biopsy examination, including two with cervical cancer, 12 HSILs (11 CINIII and 1 CINII), four LSILs, and 17 chronic cervicitis. Eight of 12 (66.7%) HSILs had infection with HPV16. The HPV infection of two cervical cancers were single infections with HPV16 and co-infection of HPV16 and HPV56, respectively.

The detailed HPV genotype distributions in HSILs or worse lesions in Tongliao and Huidong cohorts are shown in Figs. 2,3.

#### 4. Discussion

Persistent infection with HR-HPV is a leading cause of cervical cancer. The epidemiology of HPV shows great geographic variation [5, 6]. Having a good knowledge of the prevalence and distribution of the HPV genotype is helpful to develop more reasonable strategies for the prevention and management of cervical lesions. In the available studies, there was no absolute comparability in the overall HPV prevalence between different areas because of the different study backgrounds and populations as well as the different HPV genotypes the utilized HPV assays could detect.

A free screening program was conducted in two different areas of China using the same inclusion and exclusion criteria of the target population as well as the same study design and HPV genotyping test kits. This study explored and compared the HPV prevalence in women residing in Tongliao and Huidong. In this study, the HPV prevalence was significantly higher in Tongliao than in Huidong (19.35% vs 10.4%, respectively,  $P < 0.001$ ). The overall frequency of

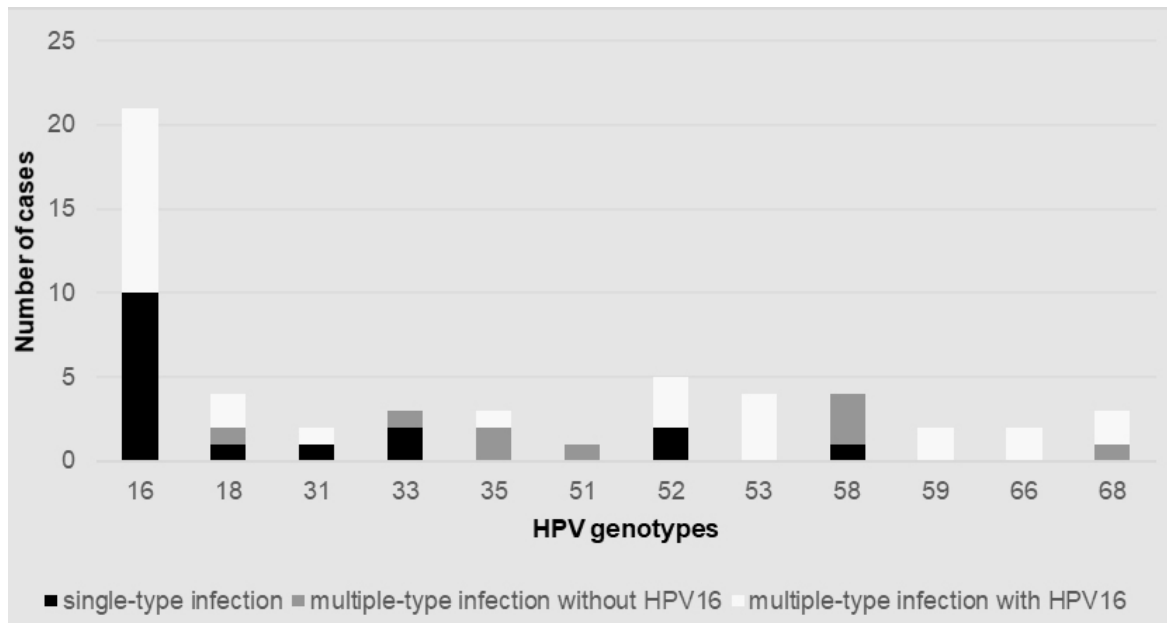


Fig. 2. Distribution of HPV genotypes in 33 cases of high-grade lesions in Tongliao.

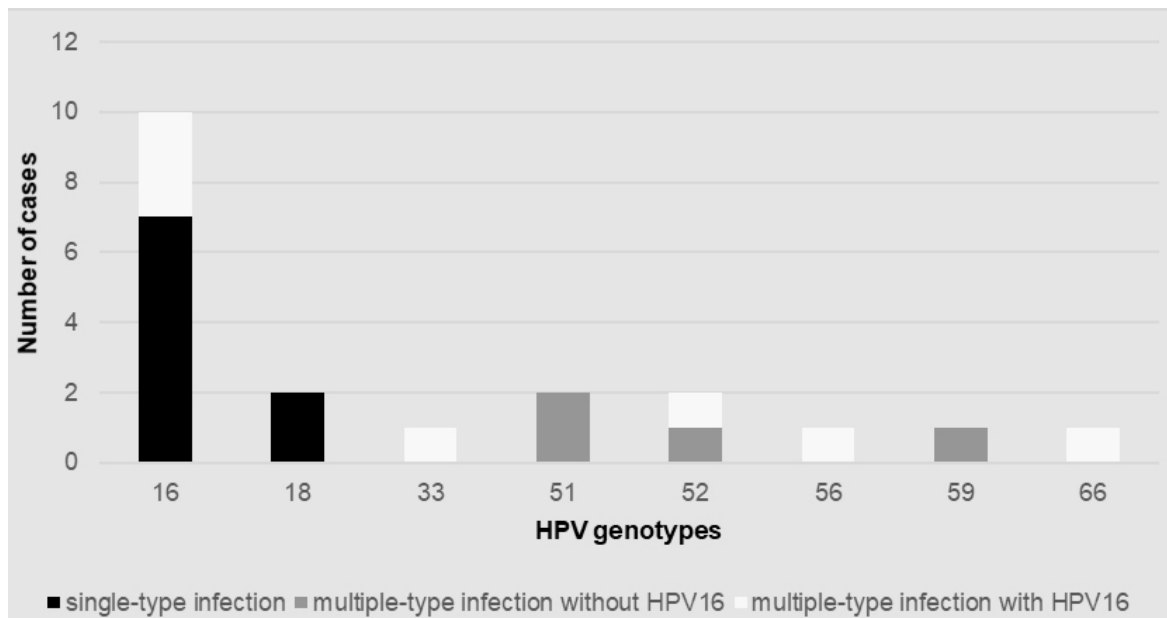


Fig. 3. Distribution of HPV genotypes in 14 cases of high-grade or worse lesions in Huidong.

HR-HPV in Inner Mongolia was also higher than the frequency of HPV infection reported before [7]. The prevalence of HPV in Huidong, Sichuan, was similar to the result of a cross-sectional study that explored the distribution of HPV in asymptomatic women in Sichuan conducted by He *et al.* [9]. In their study, the overall rate of HR-HPV infection was 12.6% (including HPV26 and HPV82 infections). Tongliao is a mining area with many migrant workers, while most participants in Huidong work in the primary industry. Therefore, this suggests that to some extent, the higher HPV prevalence in Tongliao may be correlated with the higher mobility of workers. The most common HPV genotypes in In-

ner Mongolia and Sichuan were HPV16 and HPV52, respectively, which is consistent with previously published findings [7, 9]. In both cohorts, the prevalence of HPV18 was not among the top five most common infected HPV genotypes, which has also been reported previously [9–11].

The distribution of HPV genotypes varies across different areas in China, but similarly, either HPV16 [11–17] or HPV52 [18–21] are the most common genotypes in almost every area in China according to the data available at present. Moreover, HPV53, HPV51, HPV58, HPV68, HPV56, and HPV18 are also common genotypes in China. In both cohorts, the rate of single-genotype infection was much higher

than that of multiple-genotype infection, which was consistent with the results of previous studies [18, 19]. The correlation of multiple-type infections with the severity of lesions has been debated. While it has been suggested that multiple-type infections increase the likelihood of abnormal cytology [9, 13, 22], others held different opinions [21, 23]. The present study showed that in samples with abnormal cytology or biopsy-confirmed HSILs, the proportion of infection with multiple genotypes was much higher than that in the whole cohort. However, it cannot be ignored that nearly half of the multiple-type infections were co-infections with HPV16; therefore, more evidence is needed to explore whether multiple-type infections increase the risk of more severe lesions and the underlying mechanism.

The rate of abnormal cytology in Tongliao was also higher than in Huidong; however, there was no significant difference (5.27% vs 3.92%,  $P = 0.05$ ). Surprisingly, although the Tongliao cohort showed a nearly two-fold higher HPV infection rate than the Huidong cohort, and the cases of HSILs detected in the Tongliao cohort were also much more than in the Huidong cohort, the only two cervical cancers found in the screening program were both in Huidong. This also reflects the different epidemic characteristics of different areas of China. Different ethnicities, environments, and lifestyles may lead to these differences. Moreover, Huidong is a poor county in Sichuan with limited medical resources. Many women have no access to physical examinations and have never participated in screening, which may cause the failure of early detection.

The HPV genotype distribution in HSILs in both cohorts showed both similarities and differences. HPV16 was the most common genotype in HSILs and cervical cancer in both cohorts. Totals of 63.6% (21/33) and 71.4% (10/14) of HSILs or carcinomas in Tongliao and Huidong were attributed to HPV16 infection, highlighting the overwhelming predominant role of HPV16 infection in the carcinogenesis. In the Tongliao cohort, there were also a number of cases of HSILs caused by single-type infection with HPV31, HPV33, HPV52, and HPV58. It seems that other HR-HPVs, such as HPV33, HPV52, and HPV58, are also at a relatively high risk of carcinogenesis. This was also mentioned by previous studies [13, 24–26]. The different risks of HPV genotypes should be included in the management of cervical lesions. In the Huidong cohort, only two cases of HSILs were non-HPV16 and non-HPV18 infections.

HPV16 and HPV18 accounted for 85.7% of HSILs in Huidong and 75.8% of HSILs in Tongliao. While nine-valent human papillomavirus vaccine (9vHPV; HPV6, 11, 16, 18, 31, 33, 45, 52, and 58) has covered more than 90% of HSILs in this study. However, the number of HSILs or worse was smaller in this study; therefore, there is a demand for further studies with larger sample size to determine the characteristics of different genotypes in the carcinogenesis of different areas in China.

## 5. Conclusions

In conclusion, this study first explored and compared the characteristics of HPV prevalence, and genotype distribution in two different areas of China. The same inclusion and exclusion criteria for the target population were applied and the same study design and HPV genotyping test kits were utilized. The HPV genotyping tests provided more details and are helpful for the management of the HPV infection and cervical lesions. It is of great significance to conduct more real-world studies that explore the epidemiology of HPV infection to obtain a better grasp of the characteristics of infection with different HPV genotypes and their association with cervical lesions.

## Author contributions

QL, YW, RY and LW designed the study. QF analyzed the data and wrote the manuscript. YW contributed to the analysis and revision of the manuscript. KB, PS, PZ, ML, CZ, NW and JL participated in the implementation of the research and acquisition of data. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Signed patient consents were obtained from each participant before study. This study was approved by the Institutional Ethic Committee of Peking University People's Hospital (Protocol Number 2016PHB206).

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## Conflict of interest

The authors declare no conflict of interest.

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