

An analysis of infections incidence of multiple human papillomavirus (HPV) rising in cervical and genital samples

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Abstract

Background : Human papillomavirus (HPV) is associated with cervical cancer and genital condyloma, which is mainly transmitted through sexual contact. Cervical HPV infection in females and genital HPV infection in males can induce epithelial proliferation on both mucosal and cutaneous surfaces. HPV is divided into high-risk (HR) and low-risk (LR) types according to their oncogenic potential. The HR geneotypes are considered as etiological factors for invasive cervical cancer in females, and the LR geneotypes are correlated with hyperplastic lesions, including external genital warts, condyloma acuminata, and so on. The aim of this study was to investigate the prevalence of HPV infection and geneotype distribution among individuals in Xinjiang Province.

Methods A total of 1094 patients the etiology and species with characteristic of cervical and genital warty surface which mainly come from CA in dermatology and STD outpatient service of People's Hospital of Xinjiang Uygur Autonomous Region. Using a method of real-time fluorescence quantitative PCR for the detection of human papilloma virus HPV 23 typing.

Results The prevalence of HPV infection was 67.46%, the most common LR-HPV subtypes were HPV-6 (16.27%), HPV-11 (4.57%), HPV-42(1.19%) and HPV-43(1.19%), and HR-HPV subtypes were HPV-16 (1.65%) and HPV-58(0.91%). The prevalence of HPV infection with single subtype and multiple subtypes was 32.91% and 34.55%, respectively. Among the females infected with a single HPV subtype, 26.11% were infected with a HR-HPV subtype. Among the females infected with multiple HPV subtypes, 18.52% were infected with multiple HR-HPV subtypes. The prevalence and subtype distribution of HPV infection showed age differences ($P = 0.012$), and the prevalence peak of HPV infection was observed in females aged 20-29 years (292/404, 72.28%).

Conclusion The prevalence of multiple infection was higher than single infection, and the prevalence varied significantly with age while had little association with race and gender.

1. Background

As a small double-stranded DNA virus, human papillomavirus (HPV) can lead to epithelial proliferation on both mucosal and cutaneous surfaces and is mainly transmitted through sexual contact. Approximately 75% of sexually active adults have been infected with HPV in their lifetime, and 54% of these infections are cleared within two years^[1]. However, a small portion persist or progress to pre-neoplastic lesions and even to cancer^[2]. Approximately 5% of all cancers are attributable to HPV infection around the world. More than 200 HPV subtypes have been identified, and 40 subtypes can infect the ano-genital region and cause anal cancer with persistent infection among them^[3]. In addition, HPV infection is an acknowledged cause of cervical cancer^[4-5]. HPV is divided into high-risk (HR) and low-risk (LR) types according to their oncogenic potential^[6]. The HR subtypes, such as HPV-16,-18,-31,-33,-35 and - 82, infect human epithelial cells and are considered as etiological factors of invasive cervical cancer in females^[7-8], and HPV-16 and HPV-18 induce several cancers of the anogenital tract in males, including approximately 50% of penile

cancers^[9]. The LR subtypes, such as HPV-6, -11, -42 and - 81, have less oncogenic risk and are associated with hyperplastic lesions, including external genital warts, condyloma acuminata, and so on^[10-11]. However, some studies showed that infection with multiple HR-HPV and LR-HPV subtypes occurred in cervical and vulvar specimens with intraepithelial lesions^[12-13], and there were occasional reports of the presence of HR-HPV subtypes in vulvar specimens diagnosed as condyloma acuminatum^[14], and LR-HPV subtypes in high-grade cervical lesions, mainly HPV-6 and HPV-11, cause the majority of anogenital warts^[15].

As one of the most widespread sexually transmitted diseases induced by HPV^[16-17], condyloma acuminatum (CA) represents a momentous HPV disease burden around the world and brings about substantial healthcare costs. LU et al. reported that among 3288 CA patients with HPV infection, 61.98% were infected with a single HPV subtype, and 38.02% were infected with multiple HPV subtypes^[18]. There was an increased risk of anal cancer or cervical cancer for CA patients since they were more likely to acquire a HR-HPV subtype, such as 16, 18, 31 and 45^[19], and these subtypes were closely associated with cervical cancers. Wentzensen et al. also reported that most of invasive cervical cancer was correlated with different HPV subtypes^[20]. However, the role of multiple HPV genotypes in females with cervical and genital infection has been ignored in most of reported studies, there are limited estimates for the prevalence of multiple HPV genotypes. And in the present study, there are only several reports associated with the epidemiological characteristics of HPV infection in Xinjiang of China, and most of them focus on individuals with HR-HPV infection rather than individuals with LR-HPV or multiple infection. The prevalence and genotype distribution of HPV infection vary substantially with respect to certain factors, such as age, region, and so on^[21]. In this study, we investigated the prevalence of HPV infection and genotype distribution in females in Xinjiang.

2. Methods

2.1

Study population

This was a hospital-based study, which was permitted by the Ethical Committee of People's Hospital of Xinjiang Uygur Autonomous Region. Between December 2016 and December 2018, a total of 1094 patients the etiology and species with characteristic of cervical and genital warty surface which mainly come from CA in dermatology and STD outpatient service. They included 723 males and 371 females with an age ranging from 15 to 80 years old (average age: 34.10). Among them, 897 were Han; and 197 were ethnic minorities including 178 Uygurs, accounting for 90.35% (178/197). Cast-off cells were collected from cervix uteri and genitals, including the perianal, penis coronary sulcus, foreskin, glans penis and labium majus. All participants signed informed consent forms with an explanation of the purpose of this study.

2.2 DNA extraction

DNA was extracted from the cast-off cells from genitals and cervix uteri in all participants with the HybriBio mini DNA kit (HybriBio, ChaoZhou, China). The quality of the DNA was evaluated using PCR amplification of the housekeeping gene β -globin which was used as an internal control for ruling out possible PCR inhibition and assessing the quality of extracted DNA.

2.3 HPV genotyping

HPV genotyping was conducted with real-time fluorescence polymerase chain reaction. All the 1094 specimens were detected with the HPV Genotyping Real-time PCR kit (HybriBio, ChaoZhou, China) for 23 genotypes according to the manufacturer's instructions. The 23 genotypes included 16 HR-HPV genotypes (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68, -73 and -82) and 7 LR-HPV genotypes (HPV-6, -11, -42, -43, -44, -53 and -81). Four fluorescence detection channels were set for testing them (Table 1).

Table 1
Fluorescence detection channel Settings

Detector Name	Corresponding PCR MIX channel detection items						Reporter Dye	Quencher
	1	2	3	4	5	6		
FAM	6	35	52	66	42	81	FAM	none
HEX	18	39	56	68	43	73	HEX/JOE	none
ROX	31	45	58	6	44	82	ROX/Red610	none
Cy5	33	51	59	11	53	globin	Cy5	none

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HEX	18	39	56	68	43	73	HEX/JOE	none
ROX	31	45	58	6	44	82	ROX/Red610	none
Cy5	33	51	59	11	53	globin	Cy5	none

2.4 Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). Qualitative data were expressed as percentages or ratios (%) and compared with a χ^2 test, and significance was set at $P < 0.05$.

3. Results

3.1 HPV infection and genotype distribution

Among the 1094 participants, the total prevalence of HPV infection was 67.46% (738/1094), the most common LR-HPV genotypes were HPV-6 (178/1094, 16.27%), HPV-11 (50/1094, 4.57%), HPV-42 (13/1094, 1.19%) and HPV-43 (13/1094, 1.19%), and the most common HR-HPV genotypes were HPV-16 (18/1094, 1.65%) and HPV-58 (10/1094, 0.91%). Among the infected individuals with HPV infection, 48.78% (360/738) had infection with a single HPV subtype, accounting for 32.91% (360/1094) of all participants. Among the individuals with a single HPV subtype infection, 73.89% (266/360) were infected with LR-HPV subtypes, and 26.11% (94/360) were infected with HR-HPV subtypes. 51.22% (378/738) of the infected individuals had infection with multiple HPV subtypes, accounting for 34.55% (378/1094) of all participants. Among the individuals infected with multiple HPV subtypes, 25.40% (96/378) were infected with multiple LR-LR HPV subtypes, of which 48.96% (47/96) were infected with a combination of HPV-6 and HPV-11; and 18.52% (70/378) were infected with multiple HR-HR HPV subtypes; and 56.08% (212/378) were infected with multiple LR-HR HPV subtypes (Table 2).

Table 2
HPV infection and genotype distribution

Infections	HPV genotypes	individuals	HPV infections (n = 738)	All samples (n = 1094)	
Single infections	HPV-6	178	24.12%	16.27%	
Low-risk	HPV-11	50	6.78%	4.57%	
	HPV-42	13	1.76%	1.19%	
	HPV-43	13	1.76%	1.19%	
	HPV-53	6	0.81%	0.55%	
	HPV-44	4	0.54%	0.37%	
	HPV-81	2	0.27%	0.18%	
	High-risk	HPV-16	18	2.44%	1.65%
HPV-58		10	1.36%	0.91%	
HPV-59		9	1.22%	0.82%	
HPV-73		9	1.22%	0.82%	
HPV-45		8	1.08%	0.73%	
HPV-66		7	0.95%	0.64%	
HPV-18		6	0.81%	0.55%	
HPV-56		6	0.81%	0.55%	
HPV-39		4	0.54%	0.37%	
HPV-68		4	0.54%	0.37%	
HPV-82		4	0.54%	0.37%	
HPV-31		3	0.41%	0.27%	
HPV-51		2	0.27%	0.18%	
HPV-1		1	0.14%	0.09%	
HPV-33		1	0.14%	0.09%	
HPV-35		1	0.14%	0.09%	
HPV-52		1	0.14%	0.09%	
Total			378	51.22%	34.55%

Infections	HPV genotypes	individuals	HPV infections (n = 738)	All samples (n = 1094)
Multiple infections	Low-low	96	13.01%	8.60%
	Low-high	212	28.73%	19.38%
	High-high	70	9.49%	6.40%
	Total	360	48.78%	32.91%

Table 2 HPV infection and genotype distribution

Infections	HPV genotypes	individuals	HPV infections (n = 738)	All samples (n = 1094)
Single infections	HPV-6	178	24.12%	16.27%
Low-risk	HPV-11	50	6.78%	4.57%
	HPV-42	13	1.76%	1.19%
	HPV-43	13	1.76%	1.19%
	HPV-53	6	0.81%	0.55%
	HPV-44	4	0.54%	0.37%
	HPV-81	2	0.27%	0.18%
	High-risk	HPV-16	18	2.44%
HPV-58		10	1.36%	0.91%
HPV-59		9	1.22%	0.82%
HPV-73		9	1.22%	0.82%
HPV-45		8	1.08%	0.73%
HPV-66		7	0.95%	0.64%
HPV-18		6	0.81%	0.55%
HPV-56		6	0.81%	0.55%
HPV-39		4	0.54%	0.37%
HPV-68		4	0.54%	0.37%
HPV-82		4	0.54%	0.37%
HPV-31		3	0.41%	0.27%
HPV-51		2	0.27%	0.18%

3.2 Gender and nationality distribution of HPV subtypes

The prevalence of HPV infection was 63.7% (461/723) and 74.66% (277/371), respectively for males and females, and 69.23% (621/897) and 89.85% (177/197), respectively for Han and ethnic minorities. The five most prevalent HPV subtypes were HPV-6, -11, -16, -42 and -58 in males, and HPV-6, -11, -43, -16 and -45 in females (Fig. 1A). The five most prevalent HPV subtypes were HPV-6, -11, -16, -42 and -43 in Han, and HPV-6, -11, -53, -16 and -58 in ethnic minorities (Fig. 1B). Among males, 52.49% were infected with a single HPV subtype and 47.51% with multiple HPV subtypes. Among females, 42.60% were infected with a single HPV subtype and 57.40% with multiple HPV subtypes. Among Han, 48.15% were infected with a single HPV subtype and 51.85% with multiple HPV subtypes, and 52.14% were infected with a single HPV subtype and 47.86% were infected with multiple HPV subtypes (Table 3).

Infections	HPV genotypes	individuals	HPV infections (n = 738)	All samples (n = 1094)
	HPV-1	1	0.14%	0.09%
	HPV-33	1	0.14%	0.09%
	HPV-35	1	0.14%	0.09%
	HPV-52	1	0.14%	0.09%
	Total	378	51.22%	34.55%
Multiple infections	Low-low	96	13.01%	8.60%
	Low-high	212	28.73%	19.38%
	High-high	70	9.49%	6.40%
	Total	360	48.78%	32.91%

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Table 3 Frequency of single and multiple HPV Genotypes

HPV genotypes	Men	Women	Han	ethnic minorities
1 Type	242(52.49%)	118(42.60%)	299(48.15)	61(52.14%)
2 Types	133(28.85%)	68(24.55%)	160(25.76)	41(35.04%)
≥ 3 Types	86(18.66%)	91(32.85%)	162(26.09)	15(12.82%)
Total	461(100%)	277(100%)	621(100%)	117(100%)

3.3 Age distribution of HPV genotypes

The prevalence of HPV infection was 57.78% (26/45), 72.28% (292/404), 65.99% (227/344), 68.45% (141/206), 52.05% (38/73) and 63.64% (14/22), respectively for participants aged under 20 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years and over 60 years. The difference was significantly different among different age groups ($\chi^2 = 14.662$, $P = 0.012$). The peak prevalence of HPV infection (36.93%) was observed in the age group of 20–29 years. and the prevalence of infection with a single subtype and multiple subtypes in this age group was 31.44% and 40.84%, respectively. The peak prevalence of infection with a single subtype was observed in parti in 40–49 years old (Table 4).

Table 3
Frequency of single and multiple HPV Genotypes

HPV genotypes	Men	Women	Han	ethnic minorities
1 Type	242(52.49%)	118(42.60%)	299(48.15)	61(52.14%)
2 Types	133(28.85%)	68(24.55%)	160(25.76)	41(35.04%)
≥ 3 Types	86(18.66%)	91(32.85%)	162(26.09)	15(12.82%)
Total	461(100%)	277(100%)	621(100%)	117(100%)

Table 4 Frequency of HPV infection in different age groups

Age (year)	No.(%)	Single infection	Multiple infection	Total
≤20	45(4.11)	14(31.11)	12(26.67)	26(57.78)
20–29	404(36.93)	127(31.44)	165(40.84)	292(72.28)
30–39	344(31.44)	110(31.98)	117(34.01)	227(65.99)
40–49	206(18.83)	79(38.85)	62(30.10)	141(68.45)
50–59	73(6.67)	24(32.88)	14(19.18)	38(52.05)
≥60	22(2.01)	6(27.27)	8(36.36)	14(63.64)
Total	1094(100)	360(32.91)	378(34.55)	738(67.46)

Table 4
Frequency of HPV infection in different age groups

Age (year)	No.(%)	Single infection	Multiple infection	Total
≤20	45(4.11)	14(31.11)	12(26.67)	26(57.78)
20–29	404(36.93)	127(31.44)	165(40.84)	292(72.28)
30–39	344(31.44)	110(31.98)	117(34.01)	227(65.99)
40–49	206(18.83)	79(38.85)	62(30.10)	141(68.45)
50–59	73(6.67)	24(32.88)	14(19.18)	38(52.05)
≥60	22(2.01)	6(27.27)	8(36.36)	14(63.64)
Total	1094(100)	360(32.91)	378(34.55)	738(67.46)

4. Discussion

Investigations on the prevalence and subtype distribution of HPV infection in Xinjiang are seldom, especially in individuals infected with multiple HPV subtypes. CA represents a momentous HPV disease burden around the world, which is associated with anal cancer, cervical cancer, penile cancer, vulva cancer and other genital cancers^[22]. The samples in our study were mainly from patients with CA. Many investigations have demonstrated that HPV infection is more widespread than expected, particularly in individuals infected with multiple HPV subtypes. The prevalence and genotype distribution of HPV infection are significantly different in different regions. Investigating these differences will be helpful for the prevention and treatment of HPV infection and development of HPV vaccine.

In this study, we investigated the prevalence and subtype distribution of HPV infection in cervical and genital samples in Xinjiang. The prevalence of HPV infection was 67.46%. Among them, 36.04% were infected with a single low-risk single subtype, 12.74% with a single high-risk single subtype, and 51.22% with multiple subtypes. These results showed that the prevalence of HPV infection with multiple subtypes was higher than that with a single subtype, which was consistent with previous studies^[23]. It has been reported that HPV infection with multiple subtypes has greatly increased from 4–15.7% during the past two decades. Lee et al.^[24] demonstrated that the risk of cervical cancer induced by HPV infection with multiple subtypes was higher than that induced by HPV infection with a single subtype. Ho et al.^[25] believed that HPV infection with multiple subtype can induce persistent infection to a greater extent, while persistent infection is more likely to induce cervical cancer.

The distribution of HPV subtypes also exhibited regional differences. Recent studies have showed that the HR subtypes, including HPV-16, -18, -35, -45, -58 and -59, were closely associated with cervical cancer, and the LR types, including HPV-6 and -11, were main cause of genital condynoma^[26–27]. In our study, the most common HPV subtypes were HPV-6, -11, -16, -42, -43 and -58 in Xinjiang, which

demonstrated a different genotype distribution compared with other regions. Certainly, this study was not a random sampling investigation based on the entire population in Xinjiang, which was a main limitation. Studies show that CA patients have increased risk of genital cancer except for cervical cancer in females^[28], and males infected by HPV were at risk of genital warts^[29]. In this study, there were no differences in the prevalence and genotype distribution of HPV infection between Han and other ethnicities in Xinjiang. However, the differences were found among different ethnic groups in Yunnan Province^[30], it was perhaps because Yunnan Province had more diversified nationalities than Xinjiang where ethnics were mainly Uygur. Additionally, the distribution of HPV subtypes also exhibited age-related differences. The peak prevalence of HPV infection was observed in the age group of 20–29 years, followed by the age group of 30–39 and 40–49 years in our study. Previous investigations have shown that high HPV prevalence was observed in the age group of below 20 years in Europe and the United States^[31], and in the age group of 30–44 years in India^[32], while in the age group of 40–49 years in China^[33] which was possibly associated with relatively weak immunity in the elderly. In conclusion, HPV-6, HPV-11, HPV-16, HPV-43, HPV-42 and HPV-58 were the primary subtypes in females with HPV infection in Xinjiang, the prevalence of multiple infection was higher than single infection, and the prevalence varied significantly with age while had little association with race and gender.

Abbreviations

HPV: Human papillomavirus; CA: Condyloma acuminatum; HR-HPV: High-risk human papillomavirus; LR-HPV: Low-risk human papillomavirus; PCR: Polymerase chain reaction

Declarations

Ethics approval and consent to participate

All procedures performed in this study involving human were approved by the Committee on the Ethics of People's Hospital of Xinjinag Uygur Autonomous Region, and informed consent signed was obtained from all participants included under 16 years old from their parents or guardians in this study.

Consent for publication

Informed consent was obtained from all individual participants included in the study, and once accepted, we all can consent for publication.

Availability of data and materials

All relevant data are within the paper. The data underlying this study are available and researchers may submit data requests to the the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Author contributions

Wen Hu and De-zhi Zhang conceived and designed the experiments. Wen Hu and Xin-mei Liu performed the experiments. Wen Hu and Meng-meng Guan analyzed the data. Wen Hu wrote and submitted the article. Xiao-jing Kang managed the paper. All authors have read and approved the final manuscript.

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Figures

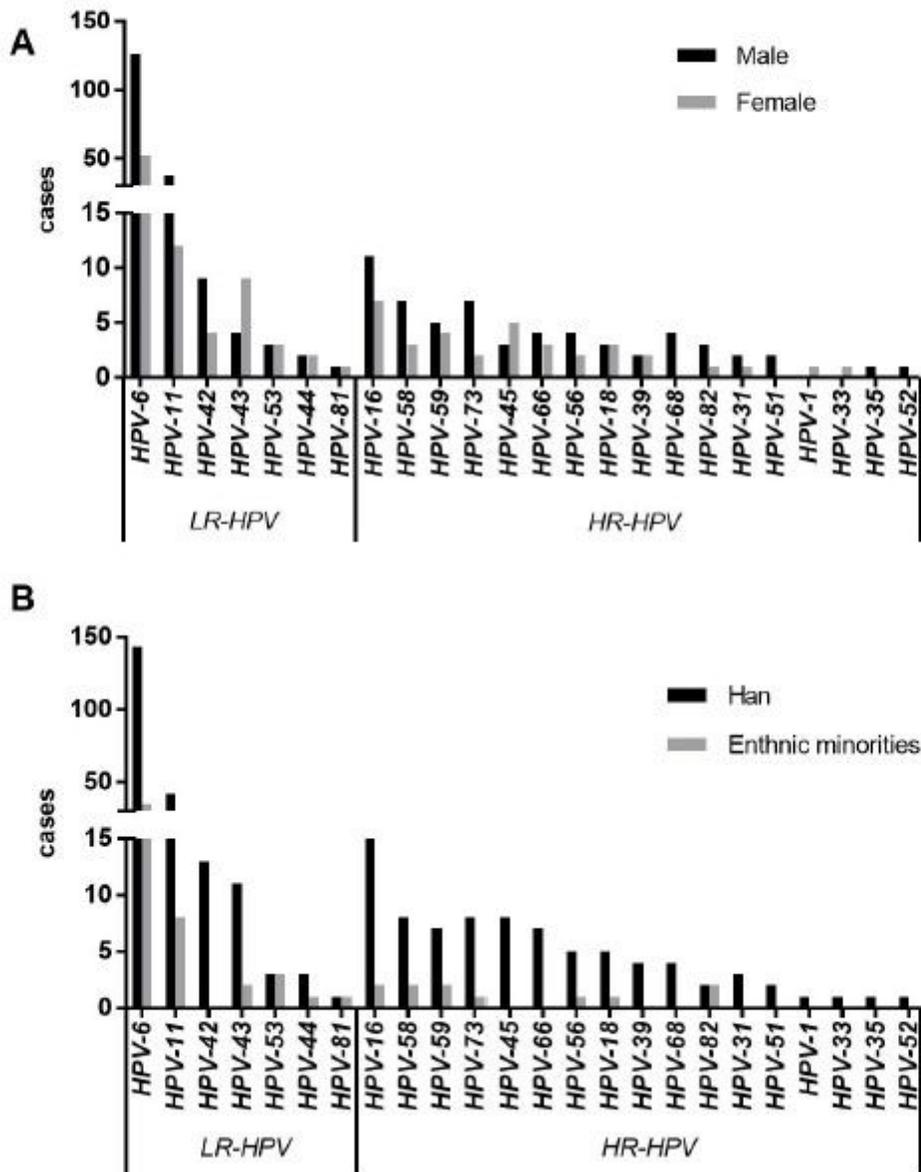


Figure 1

A. The overall distribution of HPV infected individuals in 461 men and 277 women. B. The overall distribution of HPV infected individuals in 621 Han and 177 ethnic minorities.

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