Prevalence of and risk factors for high-risk human papillomavirus infection: A population-based study from Hetian, Xinjiang, China

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ABSTRACT

Human papillomavirus (HPV) infection contributes to most cases of cervical cancer, and HPV genotypes exhibit different distributions according to geographic region. This study evaluates the prevalence of HPV infection in Hetian Prefecture, Xinjiang, and establishes risk factors associated with high-risk HPV (HR-HPV) genotypes in this region. In this cross-sectional, population-based study, 883 healthy women 15-54 years of age were enrolled. All participants completed a questionnaire regarding sociocultural and sexual activity characteristics. Visual inspections with acetic acid, colposcopies and biopsies were performed using the Preventive Oncology International microbiopsy protocol for pathological diagnosis. Cervical epithelial tissue specimens were collected and tested for HPV using linear array assays. According to the results of HR-HPV infection status, individuals infected with HR-HPV were classified into one group, and the remaining individuals were classified into the control group. The risk factors for HR-HPF infection were analyzed. The participants included 66 women (7.47%) with HR-HPV, 10 women (1.13%) with low-risk HPV, and 14 women (1.59%) with HPV of unknown risk. The five most prevalent types of HR-HPV were HPV-16 (0.31%), HPV-51 (0.08%), HPV-31 (0.07%), HPV-58 (0.07%), and HPV-39 (0.06%). Vulvovaginal ulcers and vulvovaginal inflammation were found in 190 participants (21.52%) and 256 participants (28.99%), respectively. The HR-HPV and control groups significantly differed with respect to age at first marriage, number of marriages, and the presence of vulvovaginal ulcers and vulvovaginal inflammation ($p<0.05$). Based on this study, an immunization strategy targeting HPV-16 should be prioritized in Hetian Prefecture. These findings contribute to the understanding of HPV infection.

KEY WORDS: High-risk HPV; prevalent, risk factors; genotype distribution; cervical cancer
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INTRODUCTION

Cervical cancer, which accounts for 9.8% of all cancer cases among women, is one of the most common malignancies among women worldwide [1]. The enormous burden of cervical cancer on patients is slightly increasing in developing countries, whereas the incidence and mortality of cervical cancer have substantially declined in Western countries in recent decades due to advances in screening and surveillance techniques [2-4].

Human papillomavirus (HPV) infection appears to be involved in the development of cervical cancer in more than 90% of cervical cancer cases. HPV is a DNA virus in the papillomavirus family. More than 170 types of HPV have been identified; these various forms of HPV are referred to by number [5]. Among the numerous members of the HPV family, 15 HPV genotypes (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) are associated with a high risk for cervical cancer; in particular, HPV-16 and HPV-18 account for 70% of all cervical cancer cases, and HPV-16 is the most common form of HPV [6, 7].

HPV exposure is critically dependent on risky sexual behavior, which is related to the age of first sexual intercourse, the selection of contraceptive methods, and, most importantly, the lifetime number of sexual partners [8]. In China, a recent study revealed an increasing prevalence of cervical cancer among young women and an increasing incidence of early-stage cervical cancer [9]. To date, numerous scholars have conducted studies on prevalent high-risk HPV (HR-HPV) genotypes in China, but the results of these studies remain controversial. A recent study conducted in Qujing of Yunnan Province, Southwest China, demonstrated that the five most prevalent HR-HPV genotypes in this region were HPV-16 (3.4%), HPV-56 (1.7%), HPV-58 (1.4%), HPV-33 (1.2%) and HPV-52 (0.88%) [10]. However, another study conducted on 600 patients with cervical intraepithelial neoplasm in

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Western China indicated that HPV-16 and HPV-58 were the most prevalent types of HPV, with prevalences of 37.8% and 21.8%, respectively, and that HPV-18 and HPV-45 were uncommon [11]. Considering that the distribution of HPV genotypes may greatly differ according to geographic region [11], large-scale investigations in different regions are still needed.

The goal of this study was to investigate the prevalence of HPV infection among women between 15 and 54 years of age in Hetian Prefecture in Xinjiang, China, to describe the epidemiological characteristics of HR-HPV genotypes and establish risk factors associated with these genotypes in this region. The results of this study may contribute to our understanding of cervical cancer and may provide useful data for the prevention and treatment of this condition.

MATERIALS AND METHODS

Study population

This cross-sectional, population-based study was performed in Hetian Prefecture of Xinjiang Province in September 2006. Given that HPV is sexually transmitted and that most girls get married at the age of 15 years in this region, the subjects were required to be married women 15-54 years of age. Women who were not pregnant, had no history of pelvic radiation, hysterectomy, or prior treatment for cervical cancer and reported seronegativity for HIV were asked to participate in this research project.

Local health staff organized by the Hetian Maternal & Child Health Hospital traveled throughout the village to recruit women who satisfied the aforementioned criteria and explained the benefits and potential risks of the study. According to the survey manual, 125 subjects should be recruited per age group (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54 years), such that the total number of subjects would be up to 1,000. Participants who failed to satisfy additional criteria were excluded from further analysis. The flow diagram of subject selection is shown in Figure 1.

All subjects underwent gynecological examination by a chief physician who was blinded to the objectives of this study (http://dce.cicams.ac.cn/main.html#3). Female study staff used standardized questionnaires in interviews to collect demographic data, information regarding behavioral risk factors, and medical history data relevant to HPV and related diseases. All interview staff were trained in standardized methods and data collection procedures, and laboratory staff were trained in laboratory techniques.

This study was approved by the institutional review board of the Xinjiang Uygur Autonomous Region People's Hospital. Informed consent was obtained from all participants and from the parents of subjects younger than 18 years of age.

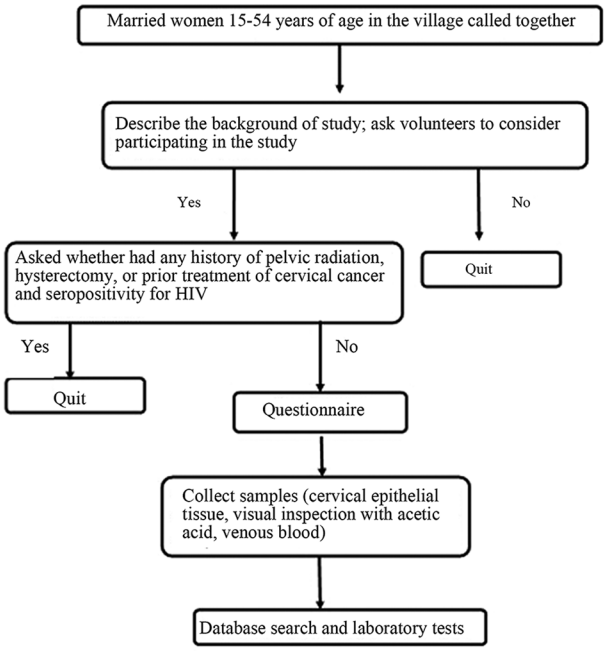

FIGURE 1. Flow diagram of subject selection

Sample collection and HPV genotyping

Cervical epithelial tissue specimens were collected onto swabs for HPV genotyping. In accordance with the manufacturer's instructions, Roche kits were used to amplify the L1 gene using biotinylated PGMY09/11 consensus primers. This approach is capable of detecting 37 HPV genotypes. Briefly, DNA was amplified via PCR in a PerkinElmer GeneAmp Polymerase Chain Reaction (PCR) System 9700 thermal cycler. The denatured PCR products were then hybridized to an array strip containing immobilized oligonucleotide probes. Using the reference guide, the results were interpreted by reading down the length of the strip to match the observed bands to individual types of HPV.

Pathological diagnosis

All women underwent visual inspection with acetic acid (VIA). For subjects whose endocervical specimens tested positive for HR-HPV and for subjects with abnormal VIA results, colposcopies and biopsies were performed using the Preventive Oncology International (POI) microbiopsy protocol for pathological diagnosis.

Statistical analysis

Age-stratified sampling was performed to group participants into the following age strata: 15-24 years, 25-34 years, 35-44 years, and 45-54 years. The study participants were also stratified according to other factors. To determine the factors related to HR-HPV infection, univariate statistical analyses were performed to assess relevant factors by comparing data from the HR-HPV group with data from the control

group. Chi-square tests (X^2) were used to determine whether there were significant differences between these groups. Subsequently, a stepwise logistic regression model was used to identify risk factors via multivariate analysis. HR-HPV infection status was used as the dependent variable in the stepwise logistic regression model, and all variables found to be significantly associated with HR-HPV infection ($p<0.05$) based on Chi-square tests were included as independent variables. Variables were entered and eliminated from the model in a stepwise manner with $p<0.05$ for entry and exit.

RESULTS

A total of 883 females who were 15-54 years of age (mean age: 37.25 years) were enrolled in this study. More than half of the enrolled women (65.1%) had their first menstruation prior to 15 years of age; 95.7% of the study subjects were married prior to 20 years of age; 76.1% of the study subjects underwent their first childbirth prior to 20 years of age; 74.1% of the study subjects had experienced more than one live birth; 95.9% of the study subjects had their first sexual intercourse prior to 20 years of age; 65.6% of the study subjects had only one sexual partner; 74.1% of the study subjects did not shower before sex; and 95.7% of the study subjects showered after sex (Table 1).

A total of 66 samples (7.5%) tested positive for HR-HPV genotypes; 10 samples (1.1%) tested positive for LR-HPV genotypes; and 14 samples (1.6%) tested positive for HPV genotypes of unknown risk. The 66 HR-HPV samples included 12 high-risk genotypes: HPV-16, HPV-31, HPV-33, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV 59, HPV-68 and HPV-82. The 10 LR-HPV samples included the HPV-6, HPV-42, HPV-54 and HPV-83 genotypes, and the samples of unknown risk included the HPV-40, HPV-53, HPV-62, HPV-66, HPV-84 and hcp6108 genotypes. The study results demonstrated that the five most prevalent HR-HPV genotypes were HPV-16 (0.3%), HPV-51 (0.1%), HPV-31 (0.1%), HPV-58 (0.1%), and HPV-39 (0.1%); no cases of HPV-18 were detected (Table 2).

Based on visual inspection, colposcopy and biopsy, 190 participants (21.5%) were diagnosed with vulvovaginal ulcers, and 256 participants (29.0%) were diagnosed with vulvovaginal inflammation.

Chi-square results demonstrated that the HR-HPV and control groups significantly differed ($p<0.05$) with respect to several factors, including age at first marriage (in years) ($p=0.0005$), number of marriages ($p=0.002$), and the presence of vulvovaginal ulcers ($p=0.008$) and vulvovaginal inflammation ($p=0.02$) (Table 3).

Next, a stepwise logistic regression model was constructed to analyze the aforementioned factors. The logistic regression

TABLE 1. Participant characteristics

Variable	Status	Cases (*n*)	Percentage
Age (yr)	15-24	147	16.65
	25-34	251	28.43
	35-44	251	28.43
	45-54	234	26.50
Age at first menstruation (yr)	≤15	575	65.12
	>15	308	34.88
Age at first marriage (yr)	<20	845	95.70
	20-25	32	3.62
	≥25	6	0.68
Number of marriages	1	590	66.82
	2	205	23.22
	≥3	88	9.97
Age at first childbirth (yr)	≤20	672	76.10
	20-30	199	22.54
	≥30	12	1.36
Number of live births	0	35	3.96
	1	194	21.97
	≥2	654	74.07
Age at first sexual intercourse (yr)	>20	36	4.08
	≤20	847	95.92
Number of sexual partners	1	579	65.57
	2	203	22.99
	≥3	101	11.44
Consistent condom use	No	652	73.84
	Yes	231	26.16
Shower before sex	No	654	74.07
	Yes	229	25.93
Shower after sex	No	38	4.30
	Yes	845	95.70
Vulvovaginal ulcers	No	693	78.48
	Yes	190	21.52
Vulvovaginal inflammation	No	627	71.01
	Yes	256	28.99

TABLE 2. Genotyping results for the 90 HPV-positive samples

HPV type	*N*	Percentage
High-risk		
HPV-16	28	0.31
HPV-31	6	0.07
HPV-33	3	0.03
HPV-39	5	0.06
HPV-45	2	0.02
HPV-51	7	0.08
HPV-52	2	0.02
HPV-56	2	0.02
HPV-58	6	0.07
HPV-59	1	0.01
HPV-68	3	0.03
HPV-82	1	0.01
Low-risk		
HPV-6	2	0.02
HPV-42	4	0.04
HPV -54	3	0.03
HPV-83	1	0.01
Unknown risk		
HPV-40	1	0.01
HPV-53	5	0.06
HPV-62	2	0.02
HPV-66	4	0.04
HPV-84	1	0.01
hcp6108	1	0.01

TABLE 3. Univariate analysis of risk factors for HR-HPV infection

Factors	Status	Cases (*N*)	HR-HPV cases (%)	χ^2 value	*p*
Age at first marriage (yr)	<20	845	58 (6.9)	-	0.005*
	20~	38	8 (21.1)		
Number of marriages	1	590	34 (5.8)	7.54	0.006
	≥2	293	32 (10.9)		
Presence of vulvovaginal ulcers	No	693	60 (8.7)	6.52	0.01
	Yes	190	6 (3.2)		
Presence of vulvovaginal inflammation	No	627	55 (8.8)	5.26	0.02
	Yes	256	11 (4.3)		
Age at first childbirth (yr)	≤20	672	44 (6.5)	-	0.136*
	20-30	199	21 (10.6)		
	≥30	12	1 (8.3)		
Number of live births	0	35	3 (8.6)	-	0.725*
	1	194	17 (8.8)		
	≥2	654	46 (7.0)		
History of smoking	No	821	61 (7.4)	-	0.855*
	Yes	62	5 (8.1)		
Shower before sex	No	654	45 (6.9)	1.286	0.257
	Yes	229	21 (9.2)		
Shower after sex	No	38	2 (5.3)	-	0.596*
	Yes	845	64 (7.6)		
History of contraceptive drug use	No	632	43 (6.8)	2.728	0.099
	Yes	225	23 (7.7)		
Consistent condom use	No	652	52 (8.1)	1.011	0.315
	Yes	231	14 (6.1)		

*This *p* value was obtained using Fisher's exact test

TABLE 4. Stepwise logistic regression-based analysis of risk factors for HR-HPV infection

Factors	Status	β	SE	Wald	*p*	OR	95% CI
Age at first marriage (yr)	<20	0.774	0.268	8.334	0.004	2.169	1.282-3.669
	20~						
Number of marriages	1	0.917	0.270	11.489	0.001	2.501	1.472-4.249
	≥2						
Presence of vulvovaginal ulcers	No	–0.747	0.287	6.765	0.009	0.474	0.270-0.832
	Yes						

results indicated that HR-HPV infection was significantly associated with age at first marriage (OR: 2.2; CI: 1.3-3.7), number of marriages (OR: 2.5; CI: 1.5-4.3) and the presence of vulvovaginal ulcers (OR: 0.5; CI: 0.3-0.8) (Table 4).

DISCUSSION

HPV, particularly high-risk genotypes of HPV, is a key cause of cervical cancer [12]. However, HPV genotypes may exhibit differing distributions according to geographic region. In this study, we investigated the prevalence of HPV infection in Hetian Prefecture in Xinjiang, China, and established risk factors associated with infection with HR-HPV genotypes.

HR-HPV genotypes (7.47%), LR-HPV genotypes (1.13%) and HPV genotypes of unknown risk (1.59%) were detected in the study population. The overall prevalence of HPV infection was 10.19%, which was higher than the reported HPV prevalences of 8.3% (494/5936) in Qujing in Yunnan Province, Southwest China [10], and 6.7% in Beijing, China [13]. In studies conducted in developing countries, the prevalence of HR-HPV infection was 9.0% in a population-based study conducted in Ho Chi Minh City, Vietnam [14], and in urban Tunis, the most frequent HPV type among women 18-69 years of age was HPV-16 (3.27%) [15], which was far higher than the prevalence of HPV-16 infection in Hetian (0.3%). The above studies and this study revealed that HPV-16 was the most frequent HPV type in these districts.

One study has suggested that cervical cancer screening should be performed by implementing primary HPV testing via genotyping and reflex cytology for women over the age of 25 years [16,17]. To explore HR-HPV infection with respect to the adoption of cervical screening and HPV vaccination in the general population, the third British National Survey of Sexual Attitudes and Lifestyles surveyed men and women 16-74 years of age. In the present study, married women ranging from 15 to 54 years of age were recruited for HPV screening.

A meta-analysis of HPV infection among 157,879 females without cervical lesions (by cytological diagnosis) in six regions of the world indicated that the prevalence of HPV infection was approximately 10.4% [17]; this finding is similar

to our results. However, a markedly lower prevalence of HPV infection was observed in our study (10.19%) than in another study conducted in Urumqi, a different region of Xinjiang (20.27%) [18]. Although both Hetian and Urumqi are in Xinjiang, these locations are separated by approximately 1400 kilometers. In Hetian, the Uigur and Han nationalities account for 96.4% and 3.4%, of the population, respectively; in Urumqi, the Han nationality accounts for 74.91% of the population. As children, men of the Uigur nationality undergo circumcision, which reduces the relative risk of cervical cancer among their sexual partners. A population-based quantitative survey in Panama revealed significant knowledge gaps and behavioral factors related to HPV infection and cervical cancer screening [19].

In this study, the results indicated that 66/883 (7.5%) samples tested positive for HR-HPV genotypes. The three major HR-HPV types observed in the examined samples were HPV-16, HPV-31 and HPV-51; no cases of HPV-18 were detected. The aforementioned study conducted in Urumqi, Xinjiang, found that the HR-HPV genotypes HPV-16, HPV-58, HPV-52 and HPV-18 accounted for 6.03, 2.56, 1.23 and 1.05% of all cases, respectively [18]. Another investigation, performed in Yunnan, China, revealed that the five most prevalent HR-HPV genotypes were HPV-16 (3.4%), HPV-56 (1.7%), HPV-58 (1.4%), HPV-33 (1.2%) and HPV-52 (0.88%), with an HPV-18 prevalence of 0.8% [11]. In both of these prior studies, the HPV-82 genotype was also detected; in our study, only one sample infected with the HPV-82 genotype was found. Therefore, in China, the prevalence and subtype distribution of HPV differs according to geographic region. This phenomenon may be caused by local customs and habits or by different immunities to HPV across various populations. In the US, 40,901 women of at least 25 years of age were screened, and HPV-16 infection was detected at prevalences ranging from 3.5% for women 25-29 years of age to 0.8% for women at least 50 years of age; the next most prevalent HPV genotypes were HPV-52, HPV-31 and HPV-18 [20].

Our logistic regression results indicated that early marriage may be a risk factor for HR-HPV infection, although the reason for this phenomenon is unclear. Girls may be forced to marry at a young age due to poverty, which may be associated with an increased risk of HR-HPV infection. Young couples may also be likely to thoughtlessly engage in unprotected sexual behaviors. A prior study found that early age at marriage, multiple sexual partners, multiple pregnancies, poor genital hygiene, malnutrition, the use of oral contraceptives, and a lack of HPV awareness were epidemiological risk factors for HPV infection [21].

There were several limitations to this study. First, all participants were from the Hetian Prefecture of Xinjiang Province; this selection bias may limit the generalizability of the study results. A comparative study across multiple distinct regions would provide more generalizable findings. Second, considering that the primary mediator of HPV is sexual transmission and that most girls in Hetian Prefecture got married at the age of 15 years, we chose married women from 15 to 54 years of age as the study population; women younger than this age were excluded from this study. This strategy may cause another form of selection bias. Third, this cross-sectional study could neither indicate the course of HR-HPV infection nor determine and compare the outcomes of participants infected with different types of HR-HPV. Fourth, the selection criteria used in this study excluded women older than 54 years of age and less than 15 years of age; these exclusions could have influenced the study results.

CONCLUSION

This study showed that the five most prevalent types of HR-HPV were HPV-16, HPV-51, HPV-31, HPV-58, and HPV-39 in Hetian Prefecture, Xinjiang, China. This result greatly differs from the genotypes reported in other regions of China. Therefore, the selection of HPV vaccines in this region should fully consider these differences. In addition, age at first marriage, number of marriages, and the presence of vulvovaginal ulcers and vulvovaginal inflammation were associated with HR-HPV infection. In the future, a cohort or experimental study may be conducted to further confirm the risk factors for HR-HPV infection in this region.

DECLARATION OF INTERESTS

The authors declare no conflicts of interest.

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