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Association between asymptomatic sexually transmitted infections and high-risk human papillomavirus in cervical lesions

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Abstract

Objective: This study aimed to determine the association of asymptomatic sexually transmitted infections (STIs), including *Ureaplasma urealyticum* (UU), *Mycoplasma hominis* (MH), *Mycoplasma genitalium*, *Chlamydia trachomatis*, and herpes simplex virus type 2, with high-risk human papillomavirus (hrHPV) in cervical intraepithelial lesions and neoplasms.

Methods: A total of 320 hrHPV-positive and 160 hrHPV-negative women were divided into high-grade squamous intraepithelial lesion (HSIL) + invasive cervical cancer and low-grade squamous intraepithelial lesion + normal subgroups, respectively, on the basis of pathological cervical lesions. Cervical brush specimens were amplified and hybridized using polymerase chain reaction kits.

Results: MH was associated with hrHPV infection, but not with specific hrHPV genotypes or with single or multiple genotypes. Coinfection of hrHPV and UU serotype 14 (Uup14) showed an increased risk of HSILs and cervical carcinoma (odds ratio [OR]: 12.541, 95% confidence interval [CI]: 3.625–43.390). *U. urealyticum* biovar (Uuu) and Uup1 infections showed a similar increased

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risk (OR: 11.646, 95% CI: 1.493–90.850; OR: 7.474, 95% CI: 1.140–49.015, respectively) without hrHPV.

Conclusions: Asymptomatic STIs are widespread. This study shows an association between UU subtypes and cervical cancer, providing new insight into cervical lesion etiology. Screening for MH, Uup14, Uup1, and Uuu is important under different hrHPV statuses.

Keywords

Asymptomatic sexually transmitted infection, cervical intraepithelial neoplasia, high-risk human papillomavirus, lower reproductive tract, uterine cervical neoplasm, lesion, *Ureaplasma urealyticum*

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Introduction

Cervical cancer (CC) is the fourth most common malignant tumor in women worldwide. The incidence of CC has remained high, with approximately 570,000 cases worldwide in 2018. Approximately 311,000 CC-related deaths occur globally each year.[1] Although the incidence of CC has decreased in recent decades, a huge burden remains, especially in low Human Development Index countries.

The most accepted cause of CC is persistent infection with the high-risk human papillomavirus (hrHPV), including human papillomavirus (HPV) genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, and 68. Women with cervical neoplastic lesions have HPV rates of 83.7% in China, 86% to 91% in Asia, and even almost 99% when using the most sensitive HPV detection methods.[2] Subtypes 16 and 18 are considered the most dangerous, and the HPV-16-positive rate is as high as 66% in all patients with CC and hrHPV. Among women in China, the most predominant genotypes are 16, 58, 18, and 52.[3]

Precancerous cervical lesions take a long time to progress to carcinoma. Persistent hrHPV infection and other cofactors can lead to cell transformation, development of low-grade squamous intraepithelial lesions (LSILs), progression to high-grade squamous intraepithelial lesions (HSILs), and even invasive cervical cancer (ICC). Multiple sexual partners, early sexual activity, poor sexual hygiene, and lower genital tract infections are important factors that can alter the vaginal microenvironment and accelerate hrHPV infection.[4] Asymptomatic infections are easily ignored by patients and doctors. Therefore, pathogens can coexist for a long time and cause chronic injury.[5] *Ureaplasma urealyticum* (UU), *Mycoplasma hominis* (MH), *Mycoplasma genitalium* (MG), *Chlamydia trachomatis* (CT), and herpes simplex virus type 2 (HSV-2) may cause sexually transmitted infections (STIs) without apparent symptoms. The associations between these pathogens, especially UU subtypes, and hrHPV infection are unclear. This study aimed to determine the association between non-hrHPV STIs of the lower reproductive tract and cervical lesions in women in Xi'an, China. We hoped to provide more evidence for preventing and treating precancerous lesions and uterine cervical neoplasms.

Patients and methods

Study participants

From July 2017 to July 2018, participants were randomly recruited from thousands of outpatients, inpatients, and healthy check-up populations at the Department of Gynecology, the First Affiliated Hospital of Xi'an Jiaotong University. Histological biopsies were performed when necessary on the basis of results of a gynecological examination, laboratory testing, and cytology tests. The results were interpreted with a diagnosis as follows.

Results were considered normal as follows: when healthy women had no typical infectious symptoms or signs and no reason for a colposcopy examination; or patients whose biopsy results that were diagnosed by two doctors were "cervicitis" without a squamous intraepithelial lesion (SIL). LSIL was diagnosed when a woman's biopsy results showed cervical intraepithelial neoplasia (CIN) 2 and p16− or CIN 1. HSIL was diagnosed when a woman's biopsy results showed CIN 2 and p16+ or CIN 3. Women with cervical squamous cell carcinoma were diagnosed with ICC.

Women were excluded for any of the following reasons: no history of sexual activity or more than one sexual partner; pregnant or having a menstrual period at the time of the test; previous history of cervical surgery or physiotherapy; previous pelvic radiation therapy or chemotherapy; suffering from acquired immune deficiency syndrome or other immune disorders; a previous gynecological examination or sexual activity in the past 3 days; and medication, especially antibiotic use, in the past week.

Women were divided into an hrHPV-negative group and an hrHPV-positive group (Figure 1). No participants had apparent clinical symptoms of STIs. Our study was approved by the First Affiliated Hospital of Xi'an Jiaotong University

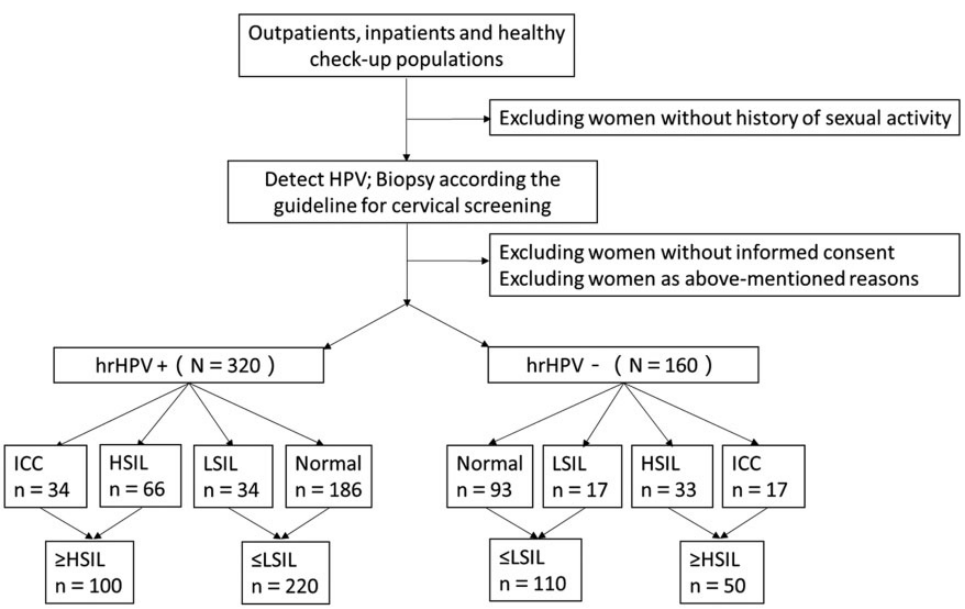

Figure 1. Procedure for choosing participants.

Institutional Review Board. Each participant signed their written informed consent, and case histories were reviewed in detail. All specimens were anonymized.

Detection of microorganisms

Specimens were sampled by professional gynecologists after standard training. After conventional vulvar disinfection, a sterile speculum without lubricant was used to expose the cervix. Cervical exfoliated cells and secretions were removed from the ectocervix using a cytobrush and preserved in buffer solution specialized for HPV-DNA testing immediately or within 10 days of storage at 4°C.

The 21 HPV GenoArray Diagnostic Kit (HBGA-21PKG; HybriBio, Ltd., Chaozhou, China) with the Rapid Capture System uses an HPV genotyping macroarray for human papillomavirus identification. This kit detects fifteen hrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 53, and 66) and six low-risk HPV types (not mentioned in our study). We used this kit by following the manufacturer's instructions and analyzed the results after cell lysis, DNA extraction, polymerase chain reaction (PCR) amplification, and hybridization.

A nucleic acid test kit (HBRT-STD6; HybriBio Ltd.) was used to simultaneously detect STIs, such as UU, MH, MG, CT, and HSV-2. (This kit can also detect *Neisseria gonorrhoeae,* but it was not evaluated in our study.) The UU subtypes, including *U. parvum* serotypes 1, 3, 6, and 14 (Uup1, 3, 6, and 14) and the other biovar *U. urealyticum* (Uuu), were detected. Using the real-time PCR fluorescent probe method, five microorganisms that are responsible for sexually transmitted diseases were quantitatively detected in a single reaction. This method is applicable to single and mixed infections.

Statistical analysis

Data were analyzed using SPSS 18.0 software (SPSS, Inc., Chicago, IL, USA). Normality tests and Student's t-test were used for statistical evaluations between groups. The prevalence of infection was calculated, and the differences were examined via the chi-squared test, continuity correction, and Fisher's exact test. Logistic regression was used for multivariate analysis. Statistical tests were considered significant if the P value was ≤ 0.05.

Results

There were 160 women in the hrHPV-negative group, which included 93 normal cases, 17 LSIL cases, 33 HSIL cases, and 17 ICC cases. There were 320 women in the hrHPV-positive group, which included 186, 34, 66, and 34 cases in the same four cervical lesion stages, respectively (Figure 1). Women in the hrHPV-positive group were aged 21 to 76 years (mean, 44.23 ± 11.492 years) and those in the hrHPV-negative group were aged 20 to 71 years (mean, 42.62 ± 10.731 years). Age was not significantly different between the two groups ($P = 0.519$).

The overall infection rate (positive for at least one non-hrHPV pathogen) was not significantly different between the groups (Table 1). UU was the most common pathogen. Among the UU subtypes, the rates of *U. parvum* were 42.8% and 42.5% in the positive and negative groups, respectively, and these rates were significantly higher than those of *U. urealyticum* at 12.2% and 10.6%, respectively (both $P < 0.001$). For *U. parvum,* Uup3 was the most prevalent, followed by Uup6. Only Uup14 and MH infections were significantly different between the hrHPV-positive and hrHPV-negative groups ($P = 0.003$ and $P = 0.005$, respectively), which indicated that these pathogens may be related to hrHPV

infection. However, further analysis showed that the prevalence of Uup14 and MH infections was not significantly different among the different hrHPV genotype subgroups (the four most common HPV types [16/18/52/58] in Chinese women, as well as the other high-risk subtypes) or in the single and multiple genotype groups (Tables 2 and 3).

To compare differences in infection based on age group, participants were grouped into reproductive age (≤49 years) and non-reproductive age (>49 years) groups (Table 4a). The reproductive age group included 224 cases with hrHPV and 118 cases without hrHPV. Uup14 was negatively associated with hrHPV (P = 0.020), while MH was positively associated with hrHPV (P = 0.001) in the reproductive age group. However, no significant differences in infection were observed in women in the non-reproductive age group.

The 2016 American College of Obstetricians and Gynecologists CC screening clinical guidance recommends that women aged younger than 30 years should be tested for only HPV-DNA. Therefore, we further grouped reproductive-aged women into ≤29 and 30 to 49 years (Table 4b). The overall and UU infection rates of women aged ≤29 years were significantly higher in the hrHPV-positive group than in the hrHPV-negative group (P = 0.009 and P = 0.031, respectively). In 30- to 49-year-old participants, only the

Table 1. General characteristics of each group.

	hrHPV+ (n = 320)		hrHPV− (n = 160)			
	n	%	n	%	χ^2	P
Overall[a]	203	63.4	95	59.4	0.748	0.387
UU	164	51.3	84	52.5	0.067	0.796
Uuu	39	12.2	17	10.6	0.253	0.615
Uup1	35	10.9	17	10.6	0.011	0.917
Uup3	58	18.1	38	23.8	2.109	0.146
Uup6	46	14.4	24	15.0	0.033	0.855
Uup14	21	6.6	24	15.0	8.938	0.003
MH	77	24.1	21	13.1	7.853	0.005
MG	7	2.2	0	0	2.193	0.139
CT	16	5	4	2.5	1.670	0.196
HSV-2	3	0.9	0	0	0.377	0.539

[a]Positive for any STD-causing microorganisms, including multiple infections. hrHPV: high-risk human papillomavirus; UU: *Ureaplasma urealyticum*; Uuu: *Ureaplasma urealyticum* biovar; Uup: *Ureaplasma parvum* serotype; MH: *Mycoplasma hominis*; MG: *Mycoplasma genitalium*; CT: *Chlamydia trachomatis*; HSV-2: herpes simplex virus type 2.

Table 3. Different infections in participants with single and multiple hrHPV genotypes.

	Single hrHPV genotype (n=228)		Multiple hrHPV genotypes (n=92)			
	n	%	n	%	χ^2	P
Uup14	16	7.0	5	5.4	0.268	0.605
MH	58	25.4	19	20.7	0.822	0.365

hrHPV: high-risk human papillomavirus.

Table 2. Different infections by hrHPV genotype.

	Overall (n = 320)	HPV-16 (n = 109)			HPV-18 (n = 32)			HPV-52 (n = 49)			HPV-58 (n = 64)			Other genotypes (n = 99)		
	n	n	χ^2	P*	n	χ^2	P*	n	χ^2	P*	n	χ^2	P*	n	χ^2	P*
Uup14	21	10	0.827	0.363	3	0.055	0.815	2	0.124	0.725	6	0.287	0.592	3	1.747	0.186
MH	77	25	0.057	0.811	5	1.159	0.282	12	0.384	0.535	15	0.011	0.915	24	0.001	0.971

Compared with the overall infection rate in different hrHPV genotype groups, adjusted P = 0.05/5 = 0.01. hrHPV: high-risk human papillomavirus; HPV: human papillomavirus.

Table 4a. STIs between reproductive age and non-reproductive age groups.

	Reproductive age (≤49)				Non-reproductive age (>50)			
	HPV+ (n=224)	HPV− (n=118)			HPV+ (n=96)	HPV− (n=42)		
	n	n	χ^2	P	n	n	χ^2	P
Overall	159	72	3.501	0.061	44	23	0.932	0.334
UU	134	64	0.989	0.320	30	20	3.388	0.066
Uuu	27	14	0.003	0.959	12	3	0.401	0.527
Uup1	32	14	0.389	0.533	3	3	0.373	0.541
Uup3	51	30	0.302	0.583	7	8	3.043	0.081
Uup6	37	16	0.517	0.472	9	8	2.531	0.112
Uup14	15	17	5.417	0.020	6	7	2.595	0.107
MH	60	14	10.149	0.001	17	7	0.022	0.882
MG	3	0	0.426	0.514	4	0	0.626	0.429
CT	13	3	1.843	0.175	3	1	0.000	1.000
HSV-2	1	0	1.000	0.655	2	0	–	1.000

STIs: sexually transmitted infections; HPV: human papillomavirus; UU: *Ureaplasma urealyticum*; Uuu: *Ureaplasma urealyticum* biovar; Uup: *Ureaplasma parvum* serotype; MH: *Mycoplasma hominis*; MG: *Mycoplasma genitalium*; CT: *Chlamydia trachomatis*; HSV-2: herpes simplex virus type 2.

Table 4b. STIs between the age groups of ≤29 and 30 to 49 years.

	≤29 years				30 to 49 years			
	HPV+ (n=36)	HPV− (n=25)			HPV+ (n=188)	HPV− (n=93)		
	n	n	χ^2	P	n	n	χ^2	P
Overall	31	14	6.913	0.009	128	58	0.910	0.340
UU	27	12	4.665	0.031	107	52	0.025	0.873
Uuu	4	2	<0.001	1.000	23	12	0.026	0.873
Uup1	7	3	0.177	0.674	25	11	0.120	0.729
Uup3	11	7	0.046	0.830	40	23	0.427	0.514
Uup6	5	1	0.703	0.402	32	15	0.036	0.850
Uup14	2	4	0.828	0.363	13	13	1.764	0.184
MH	8	1	2.581	0.108	52	13	6.550	0.010
MG	1	0	–	1.000	2	0	–	1.000
CT	2	2	<0.001	1.000	11	1	0.036	0.850
HSV-2	1	0	–	1.000	0	0	–	1.000

STIs: sexually transmitted infections; HPV: human papillomavirus; UU: *Ureaplasma urealyticum*; Uuu: *Ureaplasma urealyticum* biovar; Uup: *Ureaplasma parvum* serotype; MH: *Mycoplasma hominis*; MG: *Mycoplasma genitalium*; CT: *Chlamydia trachomatis*; HSV-2: herpes simplex virus type 2.

MH infection rate was significantly different between the hrHPV-positive and hrHPV-negative groups ($P = 0.010$). There were no significant differences in UU subtype infection between the age groups. Differences in the prevalence of MG, CT, and HSV-2 were considered meaningless because of the low infection rates.

In the hrHPV-positive and hrHPV-negative groups, summing the frequencies of normal + LSIL and HSIL + ICC improved statistical accuracy and showed more obvious differences of STIs for benign diseases (≤LSIL) and cervical neoplastic lesions (≥HSIL). Table 5a shows that in the hrHPV-positive group, only women with Uup14 showed an increased risk for HSIL + ICC (odds ratio [OR]: 12.541, 95% confidence interval [CI]: 3.625–43.390, P<0.001) after adjustment by the potential confounder of age. None of the other infections (including P = 0.050 for CT) were significantly different between the ≤LSIL and ≥HSIL subgroups. In the hrHPV-negative group (Table 5b), there was an increased risk for HSIL + ICC in women with Uuu (OR: 11.646, 95% CI: 1.493–90.850, P = 0.019) and Uup1 (OR: 7.474, 95% CI: 1.140–49.015, P = 0.036) between the two subgroups. However, the other pathogens were not significantly different between the subgroups after being adjusted by age. No patient was infected with MG or HSV-2 in the hrHPV-negative group.

Discussion

In low Human Development Index regions, CC is still a heavy burden in women.[1] Current emphasis on reproductive tract infections and cancer of reproductive organs has increased. Our study investigated the prevalence of female asymptomatic STIs and their association with cervical lesions in women in Xi'an, northwest China. In studying the etiology of CC, we examined lower genital tract infections, which often lead to asymptomatic chronic cervicitis and vaginitis. A previous study showed that cervicitis increased the risk of developing CC.[6] *Neisseria gonorrhoeae* and CT are considered the main pathogens leading to cervicitis. Some scholars believe that MG is the only pathogen related to cervicitis among *Mycoplasmas*.[7] Common

Table 5a. Different microorganism infections between cervical lesions in hrHPV-positive women.

	≤LSIL (n=220)	≥HSIL (n=100)			
	n	n	P	OR	95% CI
Age	–	–	0.017	1.030	1.005–1.056
Overall	135	68	0.705	0.798	0.248–2.571
UU	108	56	0.823	1.200	0.243–5.915
Uuu	24	15	0.408	1.702	0.483–5.996
Uup1	22	13	0.864	1.131	0.278–4.608
Uup3	40	18	0.586	0.698	0.191–2.547
Uup6	32	14	0.833	1.170	0.273–5.019
Uup14	5	16	<0.001	12.541	3.625–43.390
MH	47	30	0.104	1.883	0.878–4.037
MG	3	4	0.178	3.360	0.576–19.605
CT	15	1	0.050	0.116	0.013–1.000
HSV-2	1	2	0.126	8.185	0.553–121.097

hrHPV: high-risk human papillomavirus; LSIL; low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; OR: odds ratio; CI: confidence interval; UU: *Ureaplasma urealyticum*; Uuu: *Ureaplasma urealyticum* biovar; Uup: *Ureaplasma parvum* serotype; MH: *Mycoplasma hominis*; MG: *Mycoplasma genitalium*; CT: *Chlamydia trachomatis*; HSV-2: herpes simplex virus type 2.

Table 5b. Different microorganism infections between cervical lesions in hrHPV-negative women.

	≤LSIL (n=110)	≥HSIL (n=50)			
	n	n	P	OR	95% CI
Age	–	–	0.047	1.037	1.000–1.074
Overall	66	29	0.331	0.343	0.040–2.966
UU	58	26	0.561	0.447	0.030–6.734
Uuu	8	9	0.019	11.646	1.493–90.850
Uup1	11	6	0.036	7.474	1.140–49.015
Uup3	28	10	0.123	3.984	0.687–23.123
Uup6	17	7	0.137	3.615	0.664–19.696
Uup14	19	5	0.209	0.374	0.081–1.731
MH	13	8	0.513	1.593	0.395–6.419
MG	0	0	–	–	–
CT	2	2	0.292	4.430	0.279–70.454
HSV-2	0	0	–	–	–

hrHPV: high-risk human papillomavirus; LSIL; low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; OR: odds ratio; CI: confidence interval; UU: *Ureaplasma urealyticum*; Uuu: *Ureaplasma urealyticum* biovar; Uup: *Ureaplasma parvum* serotype; MH: *Mycoplasma hominis*; MG: *Mycoplasma genitalium*; CT: *Chlamydia trachomatis*; HSV-2: herpes simplex virus type 2.

apparent infections, such as bacterial infections, *Trichomonas,* and candidal vaginitis, promote development of CC.[8,9] Whether other non-hrHPV sexually transmitted pathogens, such as UU, CT, MH, MG, and HSV-2, are associated with CC is controversial.

Our study showed that the prevalence of overall non-hrHPV infection was as high as 63.4% in the hrHPV-positive group and 59.4% in the hrHPV-negative group. UU, MH, and MG belong to the *Mycoplasmataceae* family, and their rate of infection has successively declined. UU is an opportunistic pathogen in the female lower reproductive tract and it infects hosts silently in most cases. UU was not previously considered a clinical pathogen, but it causes urethritis, infertility, and preterm delivery. In our study, the rate of UU infection was the highest among non-HPV pathogens, which is similar to data reported by Xu et al. in Shanghai and Beijing, China.[10,11] Such high rates indicate that these silent infections require earlier diagnosis and specific treatment to prevent adverse outcomes. Condom use and healthy sexual habits are important to reduce the chance of transmission.

UU can be classified into different biovars and serotypes via PCR. *U. parvum* (biovar 1), including Uup1, 3, 6, and 14, and biovar 2, also called Uuu, were both detected in our study. Biovar 1 was the most common in UU and Uup3 was the most common in biovar 1. The pathogenicity of these biovars was considered different in previous studies. Domingues et al. showed that biovar 2 was more strongly associated than biovar 1 with the loss of lactobacilli and genital–urinary tract infections.[12] Our study showed that Uup14 infection was closely associated with development of hrHPV-positive CC, though it appeared to be negatively associated with hrHPV infection. Moreover, Uuu and Uup1 showed a higher risk for HSIL + ICC than normal + LSIL in the hrHPV-negative group. To the best of our knowledge, our study is the first to describe the association

between cervical lesions and the prevalence of UU biovars and serotypes in a population of Chinese women. Consequently, Uup14 may be a risk cofactor for hrHPV-related CC and a biomarker for cervical neoplasia screening. However, upon further analysis, the HPV genotypes (16/18/52/58 and the other subtypes) and the presence of single or multiple genotypes did not affect Uup14. Apart from hrHPV, Uuu and Uup1 may be potential risk factors for promoting carcinogenesis and cancer progression in CC, but this possibility requires further study.

Some serotypes of UU are considered to be associated with cervical lesions. Scholars have suggested that 15% to 30% of women who are ultimately diagnosed with CC have inflammation caused by UU.[13] Biernat-Sudolska et al.[14] found that more patients with CC had UU than did patients without CC, and HPV was significantly associated with detection of UU. The probability of being infected with Uup and Uuu was reported to be six-fold higher in HPV-positive women than in HPV-negative women ($P = 0.0016$).[15] The pathogenic mechanism of UU infection to cervical lesions is unclear. Zhang et al.[16] reported that mycoplasma infection alters gene expression in cervical epithelial cells, which may contribute to cervical oncogenesis and metastasis and enhance invasiveness. Verteramo et al.[17] found that asymptomatic chronic cervicitis caused by mycoplasma affects the immune function of host cells and generates free radicals, thus increasing susceptibility to HPV and altering HPV persistence. Inflammation may disrupt homeostasis in the lower genital tract, thus facilitating entry of virions.[18] Some studies have shown that only HPV and high-load UU are significantly associated.[17,19,20] However, we did not find a similar result because of the indefinite load.

Comparison of the hrHPV-positive and hrHPV-negative groups among women of different ages showed that MH was more prevalent in reproductive-aged women than in non-reproductive-aged women with hrHPV. For women aged 20 to 29 years (<30 years), the chance of being infected with overall pathogens or UU was higher in the presence of hrHPV, as was the chance for MH infection in women aged 30 to 49 years. The reason for these findings may be that more frequent sexual activity and less healthy habits increase the chance of disease transmission. In conclusion, women of childbearing age are more sensitive to interaction of hrHPV with other pathogens. Different screening strategies for women in different stages are good for earlier diagnosis of disease and cost saving for medical resources. In our study, only MH showed a significant positive association with hrHPV, as previously described,[21,22] although these previous studies could not rule out reverse causation. We did not find that MH infection was related to cervical carcinogenesis. In contrast to our results, previous studies showed that mixed infections with MH and UU were significantly associated with LSIL.[23]

The association between MG and hrHPV was insufficient for determining statistical significance. Some studies have suggested that MG is not significantly associated with abnormal cervical cytology,[5,20] but UU and MG are associated with an increased risk of hrHPV infection.[24]

CT is one of the most common sexually transmitted pathogens globally.[5] In our study, although the prevalence of CT infection was slightly higher in HPV-DNA-positive cases, no significant association was observed between CT and hrHPV and cervical lesions. In the hrHPV-positive group, CT infection tended to be different between the ≤LSIL and ≥HSIL groups ($P = 0.050$). The prevalence of CT appeared to be unassociated with a particular age group. Golijow et al.[25,26] also concluded

that CT positivity was unassociated with a higher risk of CC, but was associated with LSIL and HSIL. Nonetheless, some studies have shown a significant association between CT and HPV infection[17,19,27] and intraepithelial lesions.[28] A meta-analysis showed that individuals infected with CT had a higher risk of CC.[29] HSV-2 was discovered to increase the risk of abnormal cervical cytology when coinfected with HPV by promoting malignant cell transformation, not by participating in synergistic action in progression of cervical lesions.[5] Some scholars have suggested that HSV-2 serves as an independent predictor and cofactor for CC.[30,31] Unfortunately, from the perspective of analysis, only two participants in our study were infected with HSV-2, and thus we did not obtain a significant result. Cross-sectional measurement of infection cannot determine natural causation.

In conclusion, there are some significant differences in asymptomatic STIs and cervical lesions among women in Xi'an, China. Uup14 appears to cooperate with hrHPV infection to increase the risk of cancer progression. Uuu and Uup1 are associated with HSIL and neoplasms, and thus may be potential risk factors in CC. The widespread prevalence of MH is strongly positively associated with hrHPV, but unassociated with development of neoplasms.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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