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The prevalence and genotype distribution of human papilloma virus in cervical squamous intraepithelial lesion and squamous cell carcinoma in Taizhou, China

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Abstract

Human papillomavirus (HPV) infection is a common sexually transmitted disease worldwide and the leading cause of cervical cancer. Current vaccines do not cover all HPV genotypes whereas the distribution of HPV genotypes varies in different geographic regions. The study aimed to investigate the distribution of HPV genotypes in patients with cervical squamous intraepithelial lesion (SIL) and cervical squamous cell carcinoma (SCC) in Taizhou City of Jiangsu Province, China. A total of 940 patients including 489 cases with cervical low-grade squamous intraepithelial lesions (LSIL), 356 cases with cervical high-grade squamous intraepithelial lesions (HSIL), and 95 cases with cervical SCC, underwent a biopsy or surgery in Taizhou People's Hospital between January 2019 and December 2019. The HPV testing results were retrospectively analyzed. The overall prevalence of any, high-risk, and low-risk HPV was 83.83%, 81.91%, and 12.13%, respectively. The 5 most common HPV genotypes were HPV16 (35.64%), HPV52 (16.91%), HPV58 (13.94%), HPV33 (8.94%), and HPV18 (7.98%). The prevalence of any and HR-HPV in SCC was significantly higher than those in LSIL and HSIL, while the prevalence of LR-HPV in SCC was significantly lower than those in LSIL and HSIL ($P < .01$). Single and dual HPV infections were prevalent in SCC, LSIL, and HSIL. Furthermore, the prevalence of dual HPV infection in SCC was significantly higher than those in LSIL and HSIL ($P = .002$). The HPV prevalence varied by age, being highest among women with SCC, LSIL, and HSIL aged 40 to 49 years, 40 to 49 years, and 50 to 59 years, respectively. In conclusion, the findings revealed a very high prevalence of HPV in women with cervical lesions in Taizhou. Routine HPV tests must cover all common HPV genotypes in clinical practice.

Abbreviations: CIN = cervical intraepithelial neoplasia, HPV = human papillomavirus, HSIL = high-grade squamous intraepithelial neoplasia, LR = low risk, LSIL = low-grade squamous intraepithelial neoplasia, SCC = squamous cell carcinoma, SIL = squamous intraepithelial lesion.

Keywords: cervical cancer, cervical squamous intraepithelial lesion, human papillomavirus, vaccine

1. Introduction

Cervical cancer is one of the most common malignancies in women. Approximately 604,127 new cases were diagnosed, and 341,831 people die from cervical cancer in 2020 worldwide.[1] Cervical cancer ranks fourth for both incidence (13.1%) and mortality (6.9%) among women, and 85% of cases occurred in developing countries, with China and India together contributing to more than a third of all cases.[2] In China, there were 109,741 new cases of cervical cancer and 59,060 deaths caused by cervical

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RJ and XY contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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cancer in 2020, both which were lower than those in 2015.[3,4] Cervical cancer is still seen as a serious threat to the health and lives of Chinese women.

Human papillomavirus (HPV) infection is a common sexually transmitted disease worldwide, and approximately 75% of sexually active people will experience HPV infection in their lifetime.[5] HPV infection is the leading cause of cervical cancer, and about 90% of cervical carcinoma contain DNA sequences of specific HPV genotypes. The development of cervical cancer is a slow-evolving cellular change after HPV infection, and the persistent infection of high-risk HPV (HR-HPV) is the key and necessary pathogenic factor for cervical cancer.[6,7] Therefore, compared with many other cancers, cervical cancer is an avoidable disease that can be prevented, treated and eradicated due to its well-defined causes. HPV testing has been widely used in the world as a main method of the secondary prevention of cervical cancer, and the primary prevention can be achieved with a prophylactic HPV vaccine. Currently, 3 HPV vaccines are licensed against HPV infections internationally. The quadrivalent vaccine (4vHPV) targeting HPV6/11/16/18 was first licensed in 2006, bivalent vaccine (2vHPV) targeting HPV16/18 in 2007, and the nonavalent vaccine (9vHPV) targeting HPV6/11/16/18/31/33/45/52/58 in 2014.[8] However, the effect of prophylactic vaccines is type-specific. Above 3 licensed vaccines do not cover all HR-HPV genotypes associated with cervical cancer. In China, the first HPV vaccine was available in 2017, but only a small number of women at the right age have been vaccinated so far.[9] Although 3 kinds of imported HPV vaccines and domestic bivalent HPV vaccines are currently available in the Chinese mainland, but the HPV vaccines in China are self-paid vaccines and in short supply, China has not yet implemented mass vaccination. Multiple studies have shown that the prevalence and genotype distribution of HR-HPV vary by race, region, country, and even the most widely reported HPV genotypes may vary in the same country.[10–12] It is necessary to determine the HPV genotype distribution, especially in women with cervical lesions, in different regions of China before beginning a large vaccination to help improving cervical screening and vaccination. The identification of the most carcinogenic HPV genotypes will provide important knowledge for the development of HPV vaccines since it is impossible to investigate all HPV genotypes for routine screening and testing. The study was to investigate the clinical significance and the distribution of HPV genotypes in from 940 patients with cervical squamous intraepithelial lesion (SIL) and cervical squamous cell carcinoma in Taizhou.

2. Materials and methods

2.1. Patients

This study was designed to retrospectively analyze the genotype distribution of HPV in 940 women with pathologically confirmed SIL and SCC who had undergone a biopsy or surgery in Taizhou People's Hospital between January 2019 and December 2019. The exclusion criteria were as follows:

1. patients without cervical lesions;
2. a history of systemic anticancer therapy including chemotherapy and radiotherapy before HPV testing.

A woman receiving multiple HPV testing during this period counted as 1 case. Furthermore, for women with different positive HPV results across different time points, the samples were detected repeatedly to verify the results. If the results were consistent with previous results, these detected HPV genotypes were considered as that women infected with. Cases were classified according to the 2014 WHO classification of female reproductive organ oncology. The samples in this study were classified as: low-grade SIL (LSIL), high-grade SIL (HSIL), and SCC. This study was approved by the Ethics Committee of Taizhou people's Hospital.

2.2. HPV detection

In this study, we used the PCR-RDB Yaneng HPV genotyping kit (Yaneng Biotech, Shenzhen, China) to detect 23 HPV genotypes, including 17 HR-HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82) and 6 low-risk HPV (LR-HPV) genotypes (6, 11, 42, 43, 81, and 83). DNA was extracted from formalin-fixed and parrffin-embedded specimens. Briefly, the tissue sections were put into 1.5 mL centrifuge tubes, and 150 μL of lysate was added into the tissue tube. Samples were mixed thoroughly by shaking the tube, followed by heating at 100°C for 10 minutes. The solution was then centrifuged immediately at 13,000 rpm for 5 minutes. The middle layer DNA solution was taken for further use. Fragments of 23 HPV genotypes were amplified from DNA extract according to the manufacturer's instructions. The amplified products were hybridized with HPV genotype probes, which were fixed on the membrane. The HPV genotypes was determined by the hybridization signals according to the manufacturer's introductions.

2.3. Statistical analyzes

All statistical analyses were performed by using SPSS V.23.0 (SPSS, Chicago, Illinois, USA). Differences between groups were examined using the Chi-Squared test and Fisher exact probability test. A P value $<.05$ was considered statistically significant.

3. Results

3.1. General characteristics

A total of 940 patients had undergone a biopsy or surgery in Taizhou People's Hospital between January 2019 and December 2019. The mean age was 45 years (range, 19–88 years). Of 940 patients, 489 had LSIL, 356 had HSIL and 95 had SCC. The mean age of patients with LSIL was 43 years (range, 19–70 years), those with HSIL was 45 years (range, 20–75 years), and those with SCC was 56 years (range, 28–88 years).

3.2. Prevalence and genotype distribution of HPV according to different cervical lesions

Of 940 patients, 788 were positive for HPV infection, with the infection rate of 83.83% (Table 1). The prevalence of HR-HPV and LR-HPV was 81.91% (770/940) and 12.13% (114/940), respectively. The 5 most common HPV genotypes were HR-HPV genotypes, including HPV16 (35.64%), HPV52 (16.91%), HPV58 (13.94%), HPV33 (8.94%), and HPV18 (7.98%). For the LR-HPV genotypes, HPV81 (4.47%) was the most common genotype, followed by HPV6 (2.87%), HPV43 (2.87%), and HPV42 (2.02%). The prevalence of any HPV in LSIL, HSIL, and SCC were 80.57% (394/489), 85.11% (303/356), and 95.79% (91/95), respectively. The prevalence of HR-HPV in LSIL, HSIL

Table 1

The prevalence and genotype distribution and of HPV in cervical lesions.

HPV	LSIL (n = 489)	HSIL (n = 356)	SCC (n = 95)	Total (n = 940)
HPV (-)	95 (19.43)	53 (14.89)	4 (4.21)	152 (16.17)
Any HPV	394 (80.57)	303 (85.11)	91 (95.79)	788 (83.83)
HR-HPV	379 (77.51)	299 (83.99)	91 (95.79)	769 (81.81)
16	104 (21.27)	153 (42.98)	78 (82.11)	335 (35.64)
18	42 (8.59)	20 (5.62)	13 (13.68)	75 (7.98)
31	18 (3.68)	30 (8.43)	6 (6.32)	54 (5.74)
33	23 (4.70)	43 (12.08)	18 (18.95)	84 (8.94)
35	10 (2.04)	18 (5.06)	0 (0.00)	28 (2.98)
39	13 (2.66)	2 (0.56)	0 (0.00)	15 (1.60)
45	3 (0.61)	3 (0.84)	1 (1.05)	7 (0.74)
51	41 (8.38)	12 (3.37)	0 (0.00)	53 (5.64)
52	73 (14.93)	74 (20.79)	12 (12.63)	159 (16.91)
53	55 (11.25)	18 (5.06)	0 (0.00)	73 (7.77)
56	47 (9.61)	16 (4.49)	3 (3.16)	66 (7.02)
58	58 (11.86)	58 (16.29)	15 (15.79)	131 (13.94)
59	18 (3.68)	7 (1.97)	0 (0.00)	25 (2.66)
66	18 (3.68)	6 (1.69)	3 (3.16)	27 (2.87)
68	34 (6.95)	16 (4.49)	4 (4.21)	54 (5.74)
73	5 (1.02)	1 (0.28)	1 (1.05)	7 (0.74)
82	1 (0.20)	0 (0.00)	0 (0.00)	1 (0.11)
LR-HPV	85 (17.38)	27 (7.58)	2 (2.11)	114 (12.13)
6	17 (3.48)	10 (2.81)	0 (0.00)	27 (2.87)
11	5 (1.02)	1 (0.28)	0 (0.00)	6 (0.64)
42	12 (2.45)	5 (1.40)	2 (2.11)	19 (2.02)
43	23 (4.70)	4 (1.12)	0 (0.00)	27 (2.87)
81	30 (6.13)	12 (3.37)	0 (0.00)	42 (4.47)
83	2 (0.41)	0 (0.00)	0 (0.00)	2 (0.21)

and SCC were 77.51% (379/489), 83.99% (299/356), and 95.79% (91/95), respectively. The prevalence of any HPV and HR-HPV in SCC was significantly higher than those in LSIL and HSIL, whereas the prevalence of LR-HPV in SCC was significantly lower than those in LSIL and HSIL ($P < .01$). HPV16 was the most prevalent genotype (21.27%) in LSIL, followed by HPV58 (11.86%), HPV53 (11.25%), and HPV56 (9.61%), whereas the 5 most prevalent HPV genotypes in HSIL were HPV16 (42.98%), HPV52 (20.79%), HPV58 (16.29%), HPV33 (12.08%) and HPV31 (8.43%). In SCC, the 5 most prevalent HPV genotypes were HPV16 (82.11%), HPV33 (18.95%), HPV58 (15.79%), HPV18 (13.68%), and HPV52 (12.63%). The prevalence of HPV16 in SCC was significantly higher than that in both HSIL and LSIL ($P < .001$). Furthermore, SCC had the highest prevalence of HPV18 (13.68%), whereas HSIL had the lowest prevalence of HPV18 (5.62%).

3.3. Prevalence of single, dual, and multiple HPV infections in cervical lesions

As shown in Table 2, the prevalence of single, dual, and multiple HPV infections was 45.21% (425/940), 25.96% (244/940), and 12.66% (119/940), respectively. The maximum multiple infections were 7 genotypes, where the most common multiple infections were 3 infections. In SCC, the prevalence of single, dual, and multiple HPV infections was 41.05% (39/95), 41.05% (39/95), and 13.68% (13/95), respectively. In LSIL and HSIL, single infection was the most common infection form. The prevalence of HPV in LSIL and HSIL was 44.17% (216/489) and 47.75% (170/356), respectively, whereas the dual infection rates were 24.34% (119/489) and 24.16% (86/356), respectively, and the multiple infection rates were 12.07% (59/489) and 13.20% (47/356), respectively. There was no statistical difference in single infection rate of HPV between different cervical lesions ($P = .406$), but the dual infection rates of HPV in SCC were significantly higher than those in both LSIL and HSIL ($P = .002$).

Table 2

The prevalence of single and multiple HPV infections in cervical lesions.

HPV infection	LSIL n (%)	HSIL n (%)	SCC n (%)	Total n (%)
Any type	394 (80.57)	303 (85.11)	91 (95.79)	788 (83.83)
Single infection	216 (44.17)	170 (47.75)	39 (41.05)	425 (45.21)
Dual infections	119 (24.34)	86 (24.16)	39 (41.05)	244 (25.96)
Three infections	43 (8.79)	28 (7.87)	13 (13.68)	84 (8.94)
Four infections	11 (2.25)	15 (4.21)	0 (0.00)	26 (2.77)
Five infections	5 (1.02)	2 (0.56)	0 (0.00)	7 (0.74)
Six infections	0 (0.00)	1 (0.28)	0 (0.00)	1 (0.11)
Seven infections	0 (0.00)	1 (0.28)	0 (0.00)	1 (0.11)
Multiple infections	59 (12.07)	47 (13.20)	13 (13.68)	119 (12.66)

3.4. HPV infection and genotype distribution among different ages

All women were divided into 5 age groups: ≤29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, and ≥60 years. The prevalence of HPV reached a peak in patients between 50 and 59 years (46.32%), which was older than the peak in patients with LSIL and HSIL lesions (Fig. 1). Among patients with LSIL and HSIL, the highest prevalence of HPV occurred among those aged 40 to 49 years, with the infection rates of 31.70% (155/489), and 33.43% (119/356), respectively, whereas the second highest in those aged 30 to 39 years, and the third highest in those aged 50 to 59 years. HPV16 was the most common genotype in all age groups and HPV52 was the second most common genotype in patients aged ≥ 30 years and the third most common genotype in those aged ≤29 years (Table 3). Furthermore, HPV58 and HPV33 were one of the most common genotypes in patients aged ≥30 years, whereas HPV53 was one of the 5 most common genotypes in age groups of ≤29 years, 40 to 49 years, and 50 to 59 years.

The 5 most common HPV genotypes in different age groups were also analyzed in patients with different cervical lesions (Table 4). Among patients with LSIL aged 40 to 49 years, the 5 most common HPV genotypes were HPV16 (19.35%), HPV52 (16.77%), HPV58 (15.48%), HPV53 (10.32%), HPV56 (9.68%), and HPV68 (9.68%). Among patients with HSIL aged 40–49 years, the 5 most common HPV genotypes were HPV16 (42.02%), 52 (24.37%), HPV58 (19.33%), HPV33 (10.08%), and HPV53 (7.56%). Among patients with SCC aged 50 to 59 years, the 5 most common HPV genotypes were HPV16 (86.36%), HPV33 (18.18%), HPV18 (15.91%), HPV58 (15.91%), and HPV52 (9.09%). HPV16 was the first most common genotype in almost all age groups in patients with different cervical lesions except the age group of 50 to 59 years in LSIL in which it ranked the second most common genotype. Moreover, the prevalence of HPV16 in SCC was 100.00% in patients younger than 30 years, but the sample size was too small

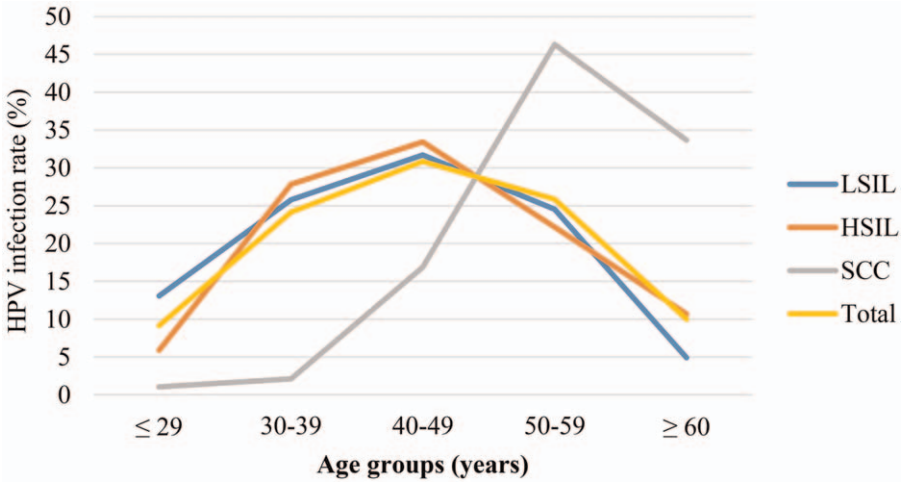

Figure 1. The prevalence of HPV in different age groups of different cervical lesions.

(n = 1). HPV18 was not among the 5 most common detected HPV genotypes in all age groups in patients with HSIL, and those with LSIL aged 30 to 59 years.

4. Discussion

Persistent infection of HPV is crucial for the development, maintenance, and progression of cervical cancer. To date, more than 220 HPV genotypes of have been identified, of which at least 40 genotypes infect the genital tract.[7,13] HPV genotypes can be classified as HR-HPV or LR-HPV based on their carcinogenic potential. HR-HPV is associated with HSIL and cervical cancer, including genotypes HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV53, HPV56, HPV58, HPV59, HPV66, HPV68, HPV73, and HPV82. LR-HPV is associated with genital warts and LSIL, including genotypes

Table 3

The prevalence and genotype distribution and of HPV according to age.

	Age groups (years)				
HPV	**≤29 (%) (n = 86)**	**30–39 (%) (n = 227)**	**40–49 (%) (n = 290)**	**50–59 (%) (n = 243)**	**≥60 (%) (n = 94)**
Any HPV	73 (84.88)	192 (84.58)	245 (84.48)	198 (81.48)	80 (85.11)
HR-HPV	71 (82.56)	186 (81.94)	238 (82.07)	194 (79.84)	80 (85.11)
16	29 (33.72)	75 (33.04)	93 (32.07)	93 (38.27)	45 (47.87)
18	11 (12.79)	22 (9.69)	18 (6.21)	17 (7.00)	7 (7.45)
31	2 (2.33)	24 (10.57)	13 (4.48)	11 (4.53)	4 (4.26)
33	3 (3.49)	20 (8.81)	24 (8.28)	28 (11.52)	9 (9.57)
35	1 (1.16)	3 (1.32)	9 (3.10)	9 (3.70)	6 (6.38)
39	4 (4.65)	2 (0.88)	7 (2.41)	2 (0.82)	0 (0.00)
45	0 (0.00)	2 (0.88)	0 (0.00)	5 (2.06)	0 (0.00)
51	11 (12.79)	15 (6.61)	14 (4.83)	8 (3.29)	5 (5.32)
52	11 (12.79)	34 (14.98)	58 (20.00)	38 (15.64)	18 (19.15)
53	12 (13.95)	17 (7.49)	25 (8.62)	17 (7.00)	2 (2.13)
56	6 (6.98)	20 (8.81)	15 (5.17)	16 (6.58)	9 (9.57)
58	7 (8.14)	26 (11.45)	49 (16.90)	36 (14.81)	13 (13.83)
59	6 (6.98)	3 (1.32)	9 (3.10)	6 (2.47)	1 (1.06)
66	3 (3.49)	8 (3.52)	7 (2.41)	8 (3.29)	1 (1.06)
68	7 (8.14)	8 (3.52)	20 (6.90)	14 (5.76)	5 (5.32)
73	2 (2.33)	0 (0.00)	1 (0.34)	3 (1.23)	1 (1.06)
82	1 (1.16)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
LR-HPV	13 (15.12)	25 (11.01)	39 (13.45)	30 (12.35)	7 (7.45)
6	6 (6.98)	3 (1.32)	10 (3.45)	8 (3.29)	0 (0.00)
11	1 (1.16)	1 (0.44)	0 (0.00)	4 (1.65)	0 (0.00)
42	3 (3.49)	1 (0.44)	7 (2.41)	5 (2.06)	3 (3.19)
43	2 (2.33)	7 (3.08)	9 (3.10)	7 (2.88)	2 (2.13)
81	2 (2.33)	13 (5.73)	15 (5.17)	8 (3.29)	4 (4.26)
83	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.41)	1 (1.06)

Table 4

The 5 most common HPV genotypes in different age groups.

	LSIL		HSIL		SCC	
Age groups (years)	HPV+	n (%)	HPV+	n (%)	HPV+	n (%)
≤29	16	19 (29.69)	16	9 (42.86)	16	1 (100.00)
	18	10 (15.63)	52	4 (19.05)		
	53	10 (15.63)	6	3 (14.29)		
	51	9 (14.06)	51, 53, 58, 81	2 (9.52)		
	52	7 (10.94)	68	1 (4.76)		
30–39	16	28 (22.22)	16	45 (45.45)	16	2 (100.00)
	53	16 (12.70)	52	23 (23.23)	18	1 (50.00)
	56	15 (11.90)	31	16 (16.16)		
	58	14 (11.11)	33	14 (14.14)		
	51	13 (10.32)	58	12 (12.12)		
40–49	16	30 (19.35)	16	50 (42.02)	16	13 (81.25)
	52	26 (16.77)	52	29 (24.37)	33	4 (25.00)
	58	24 (15.48)	58	23 (19.33)	52	3 (18.75)
	53	16 (10.32)	33	12 (10.08)	18, 31, 58	2 (12.50)
	56, 68	15 (9.68)	53	9 (7.56)	42	1 (6.25)
50–59	52	24 (20.00)	16	34 (43.04)	16	38 (86.36)
	16	21 (17.50)	58	17 (21.52)	33	8 (18.18)
	58	12 (10.00)	33	15 (18.99)	18	7 (15.91)
	53	12 (10.00)	52	10 (12.66)	58	7 (15.91)
	56	10 (8.33)	31, 35, 53, 56	5 (6.33)	52	4 (9.09)
≥60	16	6 (25.00)	16	15 (39.47)	16	24 (75.00)
	52	5 (20.83)	52	8 (21.05)	33	6 (18.75)
	58	3 (12.50)	35	5 (13.16)	58	6 (18.75)
	18	3 (12.50)	56	5 (13.16)	52	5 (15.63)
	56	2 (8.33)	58	4 (10.53)	18	3 (9.38)

HPV6, HPV11, HPV42, HPV43, HPV81, and HPV83.[14] In Europe, HPV16, HPV18, HPV31, HPV33, and HPV58 are the most common genotypes; while HPV16, HPV52, HPV58, HPV18, and HPV56 are the most common genotypes in Asia.[15] In China, previous studies have revealed that the most common HPV genotypes are HPV16, HPV52, and HPV33 in Yunnan,[16] HPV16, HPV58, and HPV52 in Beijing,[17] HPV16, HPV52, and HPV58 in Xinjiang,[9] HPV52, HPV16, and HPV58 in Jiangsu,[18] and HPV52, HPV58, and HPV16 in Sichuan.[19] In the present study, we investigated the prevalence of HPV in 940 patients with LSIL, HSIL and SCC in Taizhou. The prevalence of any HPV, HR-HPV, and LR-HPV was 83.83%, 81.91%, and 12.13%, respectively. The most common HR-HPV genotypes were HPV16, HPV52, HPV58, HPV33, HPV18, and HPV53, which was consistent with the results in the overall populations in Mainland China but inconsistent with those in women with cervical lesions in a previous meta-analysis by Li et al.[20]. Furthermore, the prevalence and genotypes of HPV in women who had undergone a biopsy or surgery are obvious different from those who underwent HPV testing and cervical cytology.[21] The findings show that HPV infection is the most important risk factor for the cervical lesions in Taizhou, indicating that it is necessary to strengthen efforts to increase HPV screening coverage in Taizhou.

In the present study, the infection rates of any HPV and HR-HPV increased with increasing cervical lesion severity, which indicated that HPV infection is closely related to the occurrence and development of SIL and cervical cancer. However, the prevalence of any HPV in LSIL (80.57%) and HSIL (85.11%) were lower than those of the previous study (90.9% and 93.06%, respectively).[22] This inconsistency may be explained by the fact that hospital population-based surveys are opportunistic screenings with a selection bias. In the present study, the top 5 HPV genotypes in SCC were HPV16 (82.11%), HPV33 (18.95%), HPV58 (15.79%), HPV18 (13.68%), and HPV52 (12.63%). HPV16 was the most common genotype in different cervical lesions, which was consistent with that of previous studies.[23–25] HPV18 ranked fourth in SCC, but was not among the top 5 HPV genotypes in LSIL and HSIL. HPV 31 was the sixth common genotype in SCC, while HPV59 accounted for 0.00% in SCC. Previous studies had shown that the pathogenicity of HPV varies according to its genotype, and HPV16 and HPV18 are the 2 most common genotypes associated with the severity of intraepithelial lesion.[26] A study by Chen et al[27] revealed that HPV16 (76.7%) and HPV18 (7.8%) infections were most common genotype in SCC, followed by HPV31 (3.2%), HPV52 (2.2%), HPV58 (2.2%), and HPV33 (1.0%). Gong et al[28] reported that HPV16 and HPV18 were also the 2 most common genotype, accounting for 67.73% and 12.21% in SCC, respectively, followed by HPV33, HPV58, HPV59, HPV31, and HPV52. In addition, the prevalence of HPV16 and HPV18 in this study was higher than those in the above studies, and these differences may confirm the regional differences in HPV prevalence.

Prospective studies have shown that infection with multiple HPVs plays a synergistic role in the development of cervical cancer.[29] In addition, cervical cancer patients with multiple HPV infections have a higher risk of the treatment failure than that of those with a single HPV infection.[30] Therefore, it is necessary to investigate multiple HPV infections for the prevention and treatment of cervical cancer. Previous studies have shown that the prevalence of multiple HPV infections among HPV positive women is approximately 25% (ranging

from 18.5% to 46%).[31–33] In the present study, the positive rates of multiple HPV infections (including dual infection) were 38.62%, which was also consistent with the results of previous studies in China.[17,34] Wang et al[33] reported that the highest prevalence of multiple HPV was observed in inflammatory cervical cases, followed by cervical cancer, cervical intraepithelial neoplasia (CIN) 1, and CIN 2/3 in Xinjiang. In Jiangsu,[28] the highest prevalence of multiple HPV was found in the CIN 3, followed by the CIN 2, SCC, and CIN 1; In Beijing,[17] the highest incidence was in LSIL, followed by HSIL, normal. However, the present study showed that multiple infection rates of HPV in SCC were significantly higher than those in LSIL and HSIL. The inconsistencies may be due to geographical environment and the selection criteria for the samples. Furthermore, the study only retrospectively analyzed the results of HPV testing of women with cervical lesions in 2019 and thus the further studies with large samples are warranted to validate the findings.

Age is one of the most important risk factors for HPV infection. Similar to previous studies,[17,28] the prevalence of HPV in HSIL reached a peak in patients between 40 to 49 years of age in this study. In SCC, the peak age of HPV infection was 50 to 59 years, which was about 10 years older than that in previous studies,[28,34] probably due to different regions in China and the effectiveness of the increasing emphasis on cervical cancer prevention over the past few decades. HPV16 was the most common genotype in almost all age groups in patients with different cervical lesions except the age group of 50 to 59 years in LSIL in which ranked the second most common genotype in this study. HPV18 was not the one of the most common HPV genotypes in all age groups of all women, but was more prevalent in SCC. HPV53 was one of the top 5 HPV genotypes in patients with HSIL aged $\leq$29 years, 40 to 49 years, and 50 to 59 years, and HPV56 ranked the fourth in the age group of $\geq$60 years. HPV53 also ranked in the top 5 common HPV genotypes in the cervical cancer group in Hangzhou,[35] and HPV56 was among the top 5 HPV genotypes at the age of 31 to 40 years, $\geq$61 years in cervical cancer patients in Fujian.[36] These results indicated that HPV53 and HPV56 had relatively high infection rates in China. Therefore, the development of new HPV vaccines may need to take into account the prevalence and distribution of HPV in Chinese women.

In summary, the findings revealed a very high prevalence of HPV in women with cervical lesions, indicating that more than 95% of cervical cancers in Taizhou may be caused by HPV. HPV infection is an important factor for cervical lesions. As a routine cervical screening test, HPV tests should focus not only on HPV16 and HPV18 but also on HPV52, HPV58, HPV33, HPV56, and so on.

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