

BMJ Open Prevalence characteristics of cervical human papillomavirus (HPV) genotypes in the Taizhou area, China: a cross-sectional study of 37 967 women from the general population

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ABSTRACT

Objectives High-risk human papillomaviruses (hrHPVs) are highly prevalent worldwide, and HPV genotypes differ between geographical regions; however, sexually transmitted HPV may lead to cervical carcinogenesis. The objective of this cross-sectional study was to estimate the prevalence characteristics of cervical HPV genotypes in Taizhou, Southeast China.

Setting and participants A population-based sample of 37 967 eligible women (median age: 41.6; range: 15–90 years) visiting the Taizhou ENZE Medical Center in Taizhou (2012–2016) was analysed. HPV genotyping was performed on the collected specimens using a GP5+/bioGP6+-PCR/MPG assay by Luminex 200, which simultaneously identifies 27 different HPV genotypes and the β -globin gene (internal control).

Results The overall HPV infection rate was 22.8% in the Taizhou-based population, and the prevalence of high-risk HPV, low-risk HPV and mixed high-risk and low-risk HPV infection was 14.2%, 5.7% and 3.0%, respectively. The most prevalent genotypes were HPV52 (19.7%), 16 (11.9%), 58 (11.5%), 39 (7.2%), 18 (6.6%) and 56 (5.6%). The rate of multiple-type HPV infection was 5.7% in the whole population, and the HPV52+58, HPV16+52 and HPV16+18 mixed genotypes were most common in women with multiple infections. The age-specific HPV prevalence showed a bimodal curve, with a first peak below the age of 21 years (41.6%), followed by a second peak in the age group of 56–60 years (28.5%). Moreover, the HPV infection rate differed significantly between the outpatient and physical examination groups (24.0% vs 19.5%, $p < 0.0001$). Further data comparisons showed that the distribution of HPV genotypes varied markedly between the two groups.

Conclusions Data from this study could be valuable for HPV-based cervical cancer screening efforts in certain areas, support the local vaccination programme in the Taizhou region and facilitate future diagnosis and treatment of HPV diseases.

BACKGROUND

Cervical cancer is the second most commonly diagnosed cancer and the third leading cause

Article summary

Strengths and limitations of this study

- This human papillomavirus (HPV) study in the Taizhou Area is the first cross-sectional and large-scale study that aimed to estimate the prevalence characteristics of cervical HPV genotypes before HPV vaccines were approved in the Taizhou region.
- We conducted HPV surveillance among a large number of women attending primary cervical cancer screening, with HPV genotyping tests performed for 37 967 eligible women.
- The ultimate aim of the Taizhou Area HPV study is to establish a foundation for primary HPV screening and to support the local vaccination programme in Taizhou. We consider the implementation of only one screening round with HPV genotyping a limitation, in addition to follow-up based on cytology or histology; we will conduct a second round of screening for eligible women.

of cancer deaths among women in low-income countries.¹ Persistent infection of high-risk human papillomavirus (hrHPV) is necessary for the development of high-grade cervical intraepithelial neoplasia (CIN2/3) and invasive cervical cancer (ICC).² To date, more than 170 types of HPV can infect the anogenital epithelium, of which at least 12 are classified as ‘high risk’ because of their high carcinogenic potential; sexually transmitted HPV may lead to cervical carcinogenesis.³ HPV16/18 are well-known oncogenic genotypes; additionally, HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 are also closely associated with cervical cancer. All other HPV types are classified as ‘low-risk’ genotypes (lrHPV), as they are associated with benign or low-grade changes in cervical cells, such as genital warts.^{3–4} The hrHPV prevalence among women attending routine cervical

screening has been shown to correlate well with cervical cancer incidence rates based on independently obtained HPV prevalence data as well as findings on the worldwide cervical cancer burden.

The current hrHPV testing algorithm is designed to serve as an additional approach for triaging atypical squamous cells of unknown significance (ASCUS) results or cotesting with cervical cytology in clinical practice.^{5,6} Recently, the Food and Drug Administration (FDA) in America approved hrHPV testing as an option for primary screening, and these tests use HPV16 and HPV18 genotyping along with a cocktail test of 12 other hrHPV genotypes.⁷ Based on the results of clinical trials, the high negative predictive value of hrHPV testing is sufficient to reassure a woman of an extremely low risk of CIN3+ or cancer for 5 years.⁸ In addition to the HPV screening strategy, HPV vaccination has been shown to be an effective programme against HPV infection and has been recently implemented in most western countries. However, HPV vaccination programmes have not been implemented in the Taizhou region.

As high-risk HPV genotypes are highly prevalent worldwide, HPV genotypes differ by geographical region, and sexually transmitted HPV may lead to cervical carcinogenesis, we conducted this study to establish a foundation for HPV-based screening in a specific area to support the local vaccination programme in Taizhou. The objective of this cross-sectional study was to investigate the characteristics of the distribution of HPV genotypes among women living in Taizhou.

MATERIALS AND METHODS

Ethics statement

This study was approved by the Institutional Medical Ethics Review Board of Taizhou Hospital in Zhejiang Province. Informed consent was obtained from the participants. For participants aged younger than 18 years, consent forms were signed by parents. Confidentiality was ensured during the data collection process, which was completed by Taizhou Hospital. Data were analysed anonymously.

Study population

The current Taizhou Area HPV study is a cross-sectional and large-scale study of Taizhou women conducted from 2012 to 2016. Between December 2012 and February 2016, a total of 42 707 consecutive women ranging in age from 15 to 90 years underwent HPV testing in the Taizhou ENZE Medical Center, which includes Taizhou Hospital, Taizhou Maternity Hospital, Taizhou Central Hospital, Luqiao Hospital and a Health Management Center. The inclusion criteria for the study were as follows: women who were attending first-time cervical screening (first round of screening), were living in the selected Taizhou area, were not currently pregnant and had no history of total uterus or cervix resection. The exclusion criteria were the following: women who were in their second

round of screening or more (n=4178), were not living in the Taizhou area (n=129), were receiving cervical physical therapy (n=411) or had a history of cancer (n=22). A total of 37 967 eligible women (median age: 41.6; range: 15–90 years) were included; 27 899 were outpatients who complained of cervical erosion, itching, etc and were spontaneously visiting our gynaecological clinic, and 10 068 women were receiving a physical examination as part of a health check-up while visiting our Health Management Center.

Specimen collection

According to the accepted protocols of practice, cervical cell specimens were collected by a gynaecologist with a cytobrush and were then placed in a specimen transport medium and stored at 4°C. Subsequently, all specimens were shipped to the Medical Research Center of Taizhou Hospital for HPV genotyping within 24 hours.

HPV genotyping

HPV genotyping was performed on the collected specimens using a GP5+/bioGP6+PCR/MPG assay, which was approved by China's FDA (Certified No. (2014): 3400847). HPV genotyping was performed with the protocol as previously described.⁹ Briefly, this assay comprises GP5+/bioGP6+PCR, which uses sets of biotinylated amplimers and multiplex human papillomavirus genotyping (MPG) methods with bead-based Luminex suspension array technology. The biotin-labelled amplicons were captured by HPV type-specific probes attached to colour-coded beads; streptavidin-phycoerythrin was used as the reporter that bound to the target and the HPV genotypes were analysed using a Luminex 200 analyser.^{9,10} This assay could simultaneously identify 27 different HPV genotypes and the β -globin gene (internal control); in this study, the HPV genotypes defined as high-risk HPV types were 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.^{3,4,6,7}

Statistical analysis

All statistical analyses were performed using SPSS V.15.0 (SPSS, Chicago, Illinois, USA). Chi-squared tests were used to assess the statistical significance of any differences in prevalence and the 95% CIs. p Values were two-sided, and statistical significance was accepted if the p value was 0.05 or less.

RESULTS

Characteristics of the study population

In total, 42 707 women were screened. However, we obtained a final sample of 37 967 eligible women who had HPV genotyping results, of whom 27 899 were from the outpatient group from the gynaecological clinic and 10 068 were from the physical examination group from the Health Management Center in Taizhou ENZE Medical Center. The study population was divided into four age groups (<21, 21–29, 30–65 and >65 years) according to the American Cancer Society guidelines for cervical cancer screening.¹¹

Table 1 Baseline characteristics of the study population

Characteristics	Outpatients		Women receiving physical examinations	
	Number	% (95% CI)	Number	% (95% CI)
All participants	27 899	73.5 (73.0 to 73.9)	10 068	26.5 (26.1 to 27.0)
Age (years)				
Median, years (SD)	40.7 (10.1)		44.3 (9.3)	
Range	15–90		21–82	
Age group (years)*				
<21	264	0.9 (0.8 to 1.1)	0	0.0 (0.0 to 0.0)
21–29	4023	14.4 (14.0 to 14.8)	495	4.9 (4.5 to 5.3)
30–65	23 221	83.2 (82.8 to 83.7)	9427	93.6 (93.2 to 94.1)
>65	391	1.4 (1.3 to 1.5)	146	1.5 (1.2 to 1.7)
HPV				
High risk [†]	4278	15.3 (14.9 to 15.8)	1104	11.0 (10.4 to 11.6)
Low/undetermined risk [‡]	1527	5.5 (5.2 to 5.7)	622	6.2 (5.7 to 6.6)
Mixed types [§]	900	3.2 (3.0 to 3.4)	238	2.4 (2.1 to 2.7)
Multiple infection				
No	4946	17.7 (17.3 to 18.2)	1530	15.2 (14.5 to 15.9)
2 HPV types	1271	4.6 (4.3 to 4.8)	337	3.3 (3.0 to 3.7)
3 HPV types	360	1.3 (1.2 to 1.4)	66	0.7 (0.5 to 0.8)
4 HPV types	93	0.3 (0.3 to 0.4)	24	0.2 (0.1 to 0.3)
5 or more HPV types	35	0.1 (0.1 to 0.2)	7	0.1 (0.0 to 0.1)

*According to the 2012 American Cancer Society guidelines for cervical cancer screening.

[†]Includes HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

[‡]Includes HPV types 6, 11, 26, 40, 42, 43, 44, 53, 55, 61, 73, 81, 82 and 83.

[§]Mixed high-risk and low-risk HPV infection.

HPV, human papillomavirus.

The average age of the outpatient group was 40.7 years (SD: 10.1, range: 15–90 years): most outpatients were aged 30–65 years (83.2%). Of the 6705 (24.0%) women with HPV infection analysed, a single HPV type was detected in 4946 (17.7%), and multiple types were observed in 1759 (6.3%). Moreover, women in the physical examination group had a median age of 44.3 years (SD: 9.3, range: 21–82 years), and most women were aged 30–65 years (93.6%). Of the 1964 (19.5%) women with an HPV infection, a single HPV type was detected in 1530 (15.2%), and multiple types were observed in 434 (4.4%). The baseline characteristics of the study population are shown in [table 1](#).

The total prevalence of HPV infection

The overall HPV infection rate was 22.8% (8669/37967, 95% CI 22.4% to 23.3%) in the Taizhou-based population. Between the outpatient group and the physical examination group, the HPV infection rate differed significantly (24.0% vs 19.5%, $p < 0.0001$). Among all HPV-positive women, the prevalence of hrHPV, lrHPV and mixed high-risk and low-risk HPV (defined ‘mixed HPV’) infections was 14.2% (5382/37967, 95% CI 13.8%

to 14.5%), 5.7% (2149/37967, 95% CI 5.4% to 5.9%) and 3.0% (1138/37967, 95% CI 2.8% to 3.2%), respectively.

Multiple HPV genotypes with high-risk and/or low-risk HPV genotypes were found in 5.7% (2193/37967, 95% CI 5.5% to 6.0%) of the overall population and 25.3% (2193/8669, 95% CI 24.4% to 26.2%) of the women with HPV infection. Of the women with multiple HPV infections, 843 (38.4%), 212 (9.7%) and 1138 (51.9%) were infected with hrHPV, lrHPV and mixed HPV genotypes, respectively. Moreover, 73.3% (1608/2193, 95% CI 71.5% to 75.2%) were infected with two types; the most common combinations were 52+58 (49 cases), 16+52 (33 cases) and 16+18 (29 cases). Additionally, 19.4% (426/2193, 95% CI 17.8% to 21.1%) of the infected women had three types, the most common combinations were 16+52+58 (seven cases) and 16+52+68 (five cases). Finally, 5.3% (117/2193, 95% CI 4.4% to 6.3%) had four types, and 1.9% (42/2193, 95% CI 1.3% to 2.5%) had more than five types of infection.

Among the 37967 women (age range from 15 to 90 years, mean age 41.6±10.0 years), we examined the HPV prevalence in 5-year periods to assess the age trends in relation to HPV infection in more detail. The age

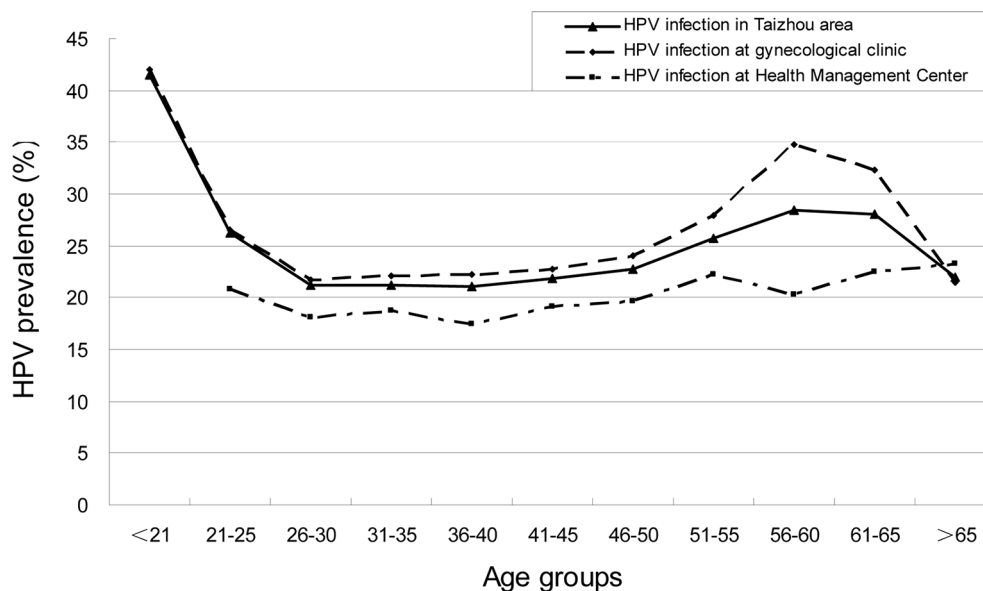


Figure 1 HPV prevalence in 5-year age groups. HPV, human papillomavirus.

distribution of HPV infection showed a bimodal curve in overall HPV prevalence, as shown in [figure 1](#). The prevalence of total HPV exhibited its first peak below the age of 21 years (41.6%, 95% CI 35.7% to 47.5%) and decreased thereafter until the age of 56 years (28.5%, 95% CI 26.5% to 30.5%), where it peaked a second time. Notably, outpatients in the older age group (56–60 years) presented the highest HPV infection rate (34.7%, 95% CI 31.9% to 37.5%).

Distribution characteristics of HPV genotypes

Overall, HPV52 was the most prevalent genotype (19.7%, 95% CI 18.8% to 20.5%), both alone and in combination with other types, followed by HPV16 (11.9%, 95% CI 11.2% to 12.6%), HPV58 (11.5%, 95% CI 10.8% to 12.2%), HPV39 (7.2%, 95% CI 6.6% to 7.7%), HPV18 (6.6%, 95% CI 6.0% to 7.1%) and HPV56 (5.6%, 95% CI 5.1% to 6.1%). For low-risk/undetermined-risk HPV genotypes, HPV53 was the most common type, with an overall prevalence of 7.8% (95% CI 7.2% to 8.4%), followed by HPV81 (7.5%, 95% CI 6.8% to 8.3%), HPV61 (7.0%, 95% CI 6.5% to 7.6%), HPV43 (5.9%, 95% CI 5.2% to 6.6%), HPV06 (4.0%, 95% CI 3.6% to 4.4%) and HPV44 (3.8%, 95% CI 3.4% to 4.2%). The prevalences of HPV genotypes in the overall population, outpatients and women receiving a physical examination are shown in [table 2](#).

Regarding the population-based distribution of hrHPV, the top six genotypes were analysed in both outpatients and women receiving a physical examination. HPV52 was the most frequent high-risk type (20.3%) in the outpatient population, followed by 16 (13.0%), 58 (11.8%), 39 (7.0%), 18 (6.7%) and 56 (5.9%). However, six different types were the most common in the physical examination population: HPV52 (17.4%), 58 (10.4%), 16 (8.2%), 39 (7.7%), 18 (6.1%) and 51 (4.9%). For low-risk/undetermined-risk HPV genotypes, HPV81 (7.2%) was the most

common genotype in outpatients, followed by 53 (7.0%), 61 (6.8%), 43 (5.8%), 06 (4.2%) and 44 (3.5%), whereas HPV53 (10.3%) was the most frequent genotype in the physical examination population, followed by 81 (8.3%), 61 (7.9%), 43 (6.2%), 55 (5.0%) and 44 (4.8%).

The distribution of the top three HPV genotypes was also determined on the basis of age ([table 3](#)). For hrHPV, HPV16, 52 and 58 were the most prevalent among all of the age groups in outpatients and in the physical examination population, with the exception of the age group of 21–29 years, in which HPV52, 39 and 18 were the most common genotypes. For low-risk/undetermined-risk HPV genotypes, HPV06 was the leading genotype in younger age groups (ie, age groups <21 and 21–29 years), while in the older group (ie, 46–65 years), HPV53, 61 and 81 were the most prevalent lrHPV type. The presence of any HPV genotype was also significantly more frequently identified in younger rather than older women ($p < 0.001$).

DISCUSSION

This article described a cross-sectional and large-scale study on the prevalence of HPV genotypes in Taizhou, Zhejiang Province, Southeast China. To date, to the best of our knowledge, there has been very little research on the population-based epidemiology of high-risk and low-risk HPV in different female age groups from both outpatients and women receiving physical examinations. HPV detection is currently an effective way to screen for cervical cancer. Knowledge of the distribution of HPV genotypes in population-based women will enable the evaluation of the potential efficacy of next-generation HPV prophylactic vaccines. All of the study specimens were collected before the approval of HPV vaccines in Taizhou.

Compared with region-based data on the Chinese population, the hrHPV-positive rate (17.2%) found in

Table 2 Prevalence of HPV genotypes in outpatients, women receiving physical examinations and the overall population (Taizhou, Zhejiang)

HPV genotypes*	Overall population (n=37967)				Outpatients (n=27899)				Women receiving physical examinations (n=10068)			
	Single infection (n=6476)	Multiple infections (n=2193)	Overall infections (n=8669)	Single infection (n=4946)	Multiple infections (n=1759)	Overall infections (n=6705)	Single infection (n=1530)	Multiple infections (n=434)	Overall infections (n=1964)			
High-risk HPV												
52	1082 (12.5)	623 (7.2)	1705 (19.7)	850 (12.7)	513 (7.7)	1363 (20.3)	232 (11.8)	110 (5.6)	342 (17.4)			
16	659 (7.6)	372 (4.3)	1031 (11.9)	559 (8.3)	311 (4.6)	870 (13.0)	100 (5.1)	61 (3.1)	161 (8.2)			
58	605 (7.0)	393 (4.5)	998 (11.5)	469 (7.0)	325 (4.8)	794 (11.8)	136 (6.9)	68 (3.5)	204 (10.4)			
39	366 (4.2)	255 (2.9)	621 (7.2)	277 (4.1)	193 (2.9)	470 (7.0)	89 (4.5)	62 (3.2)	151 (7.7)			
18	306 (3.5)	262 (3.0)	568 (6.6)	225 (3.4)	224 (3.3)	449 (6.7)	81 (4.1)	38 (1.9)	119 (6.1)			
56	240 (2.8)	247 (2.8)	487 (5.6)	184 (2.7)	210 (3.1)	394 (5.9)	56 (2.9)	37 (1.9)	93 (4.7)			
51	234 (2.7)	197 (2.3)	431 (5.0)	179 (2.7)	156 (2.3)	335 (5.0)	55 (2.8)	41 (2.1)	96 (4.9)			
33	200 (2.3)	208 (2.4)	408 (4.7)	167 (2.5)	173 (2.6)	340 (5.1)	33 (1.7)	35 (1.8)	68 (3.5)			
59	201 (2.3)	182 (2.1)	383 (4.4)	160 (2.4)	150 (2.2)	310 (4.6)	41 (2.1)	32 (1.6)	73 (3.7)			
68	182 (2.1)	190 (2.2)	372 (4.3)	137 (2.0)	146 (2.2)	283 (4.2)	45 (2.3)	44 (2.2)	89 (4.5)			
66	166 (1.9)	155 (1.8)	321 (3.7)	131 (2.0)	132 (2.0)	263 (3.9)	35 (1.8)	23 (1.2)	58 (3.0)			
31	144 (1.7)	115 (1.3)	259 (3.0)	119 (1.8)	102 (1.5)	221 (3.3)	25 (1.3)	13 (0.7)	38 (1.9)			
35	88 (1.0)	96 (1.1)	184 (2.1)	70 (1.0)	80 (1.2)	150 (2.2)	18 (0.9)	16 (0.8)	34 (1.7)			
45	66 (0.8)	72 (0.8)	138 (1.6)	48 (0.7)	54 (0.8)	102 (1.5)	18 (0.9)	18 (0.9)	36 (1.8)			
Low-risk/undetermined-risk HPV												
53	366 (4.2)	309 (3.6)	675 (7.8)	247 (3.7)	225 (3.4)	472 (7.0)	119 (6.1)	84 (4.3)	203 (10.3)			
81†	185 (3.9)	172 (3.6)	357 (7.5)	116 (3.4)	126 (3.7)	242 (7.2)	69 (5.0)	46 (3.3)	115 (8.3)			
61	330 (3.8)	281 (3.2)	611 (7.0)	229 (3.4)	226 (3.4)	455 (6.8)	101 (5.1)	55 (2.8)	156 (7.9)			
43†	121 (2.5)	160 (3.4)	281 (5.9)	76 (2.3)	120 (3.6)	196 (5.8)	45 (3.3)	40 (2.9)	85 (6.2)			
06	188 (2.2)	156 (1.8)	344 (4.0)	155 (2.3)	129 (1.9)	284 (4.2)	33 (1.7)	27 (1.4)	60 (3.1)			
44	187 (2.2)	144 (1.7)	331 (3.8)	130 (1.9)	107 (1.6)	237 (3.5)	57 (2.9)	37 (1.9)	94 (4.8)			
55	139 (1.6)	171 (2.0)	310 (3.6)	85 (1.3)	121 (1.9)	211 (3.1)	54 (2.7)	45 (2.3)	99 (5.0)			
11	99 (1.1)	114 (1.3)	213 (2.5)	82 (1.2)	104 (1.6)	186 (2.8)	17 (0.9)	10 (0.5)	27 (1.4)			
42	96 (1.1)	102 (1.2)	198 (2.3)	70 (1.0)	85 (1.3)	155 (2.3)	26 (1.3)	17 (0.9)	43 (2.2)			
82	111 (1.3)	85 (1.0)	196 (2.3)	92 (1.4)	70 (1.0)	162 (2.4)	19 (1.0)	15 (0.8)	34 (1.7)			
40	62 (0.7)	69 (0.8)	131 (1.5)	48 (0.7)	52 (0.8)	100 (1.5)	14 (0.7)	17 (0.9)	31 (1.6)			
83	42 (0.5)	43 (0.5)	85 (1.0)	30 (0.4)	35 (0.5)	65 (1.0)	12 (0.6)	8 (0.4)	20 (1.0)			
26	8 (0.1)	7 (0.1)	15 (0.2)	8 (0.1)	7 (0.1)	15 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)			

Continued

Table 2 Continued

HPV genotypes*	Overall population (n=37967)			Outpatients (n=27899)			Women receiving physical examinations (n=10068)		
	Single infection (n=6476)	Multiple infections (n=2193)	Overall infections (n=8669)	Single infection (n=4946)	Multiple infections (n=1759)	Overall infections (n=6705)	Single infection (n=1530)	Multiple infections (n=434)	Overall infections (n=1964)
73 [†]	3 (0.1)	3 (0.1)	6 (0.2)	3 (0.1)	3 (0.1)	6 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

*Women with multiple HPV infections are counted for each type and are therefore counted more than once.

[†]19905 women detected with HPV43 and 81, including 12981 outpatients and 6924 women receiving physical examinations; 4754 women had an HPV infection, including 3373 outpatients and 1381 women receiving physical examinations.

[‡]18062 women detected with HPV73, including 14918 outpatients and 3144 women receiving physical examinations; 3915 women had an HPV infection, including 3332 outpatients and 583 women receiving physical examinations.
HPV, human papillomavirus.

the present study was lower than the rates reported in a meta-analysis that summarised Chinese data for Haikou (31.9%), Guangdong (20.0%), Chongqing (27.3%), Jinan (25.7%) and Shanghai (22.6%), but was similar to the rates in Hangzhou (19.9%) and Nanchang (18.4%), which is another region in Southeast China.¹² In China, the prevalence of hrHPV varied from 9.9% in Beijing¹³ to 31.9% in Haikou¹² because of the different economic conditions, cultural diversity, genetic variations, HPV vaccine awareness and different lifestyles.^{13–15} Notably, the rate of awareness of HPV vaccination was only 16.0% in China,¹⁵ but was found to range from 67.1% to 71.3% in Western countries.^{14 16} The Advisory Committee on Immunization Practices (ACIP) recommends bivalent HPV vaccines, quadrivalent HPV vaccines and 9-valent HPV vaccines (9vHPV) for routine vaccination.¹⁷ In China, the most urgent public health issue is increasing HPV vaccination coverage and improving completion of the vaccination schedule.

Consistent with the data generated by Chinese population-based investigations,^{14 15} HPV16, 52 and 58 were found to be the predominant hrHPV types, but these results differed from those of a meta-analysis that summarised global reports,¹⁸ in which HPV16, 18 and 45; HPV16, 18 and 33 and HPV16, 18 and 58 were most commonly detected. In our population, HPV52 and 58 accounted for 31.2% of the infections, representing common types among Asian populations, and this rate was markedly higher than the global rate of 14.0%.¹⁸ We found that the rate of HPV52+58 infection was significantly increased in outpatients compared with women receiving physical examinations (32.1% vs 27.8%, $p < 0.001$). The relatively high contribution of HPV52 and 58 to high-grade cervical lesions in East Asia has been previously reported,^{18–21} but HPV18, with an infection rate of 6.6%, is less common.²² Compared with women receiving physical examinations, the HPV16, 31, 33 and 52 infection rates were significantly increased in outpatients ($p < 0.05$). These findings indicated that in addition to HPV16 and HPV18, an HPV vaccine in Taizhou should include HPV31, 33, 52 and 58 genotypes. Notably, the ACIP has recommended 9vHPV,^{17 23} which contains HPV6, 11, 16, 18, 31, 33, 45, 52 and 58 virus-like particles and is suitable for the Taizhou population.

The age-specific HPV distribution presents a bimodal curve, with the first peak below the age of 21 years (just after sexual debut), a lower prevalence plateau at middle ages and a variable rebound at older ages (≥ 56 years). Figure 1 shows high infection rates (41.6%) in younger age groups and a gradual decline to a plateau in middle-aged women, which reflects the natural history of HPV infections. The detection of HPV in women has been found to start consistently with a peak immediately after the onset of sexual relations, usually from 15 years of age, and to reach a prevalence of up to 80% among younger women, mostly transient infections that can be cleared within 1 or 2 years.²⁴ In our population, we observed a less steep second peak in the older age group of those

Table 3 HPV infection, hrHPV genotypes and multi-infections by age subgroups

HPV status	Outpatients						Women receiving physical examinations								
	<21 y			30-65 y			>65 y			30-65 y			>65 y		
	n=264	21-29 y n=4023	30-45 y n=15108	46-65 y n=8113	>65 y n=391	21-29 y n=495	30-45 y n=5178	46-65 y n=4249	>65 y n=146						
HPV+	111 (42.0)	937 (23.3)	3384 (22.4)	2189 (27.0)	84 (21.5)	89 (18.0)	959 (18.5)	882 (20.8)	34 (23.3)						
Multiple	49 (18.6)	301 (7.5)	746 (4.9)	627 (7.7)	36 (9.2)	17 (3.4)	187 (3.6)	213 (5.0)	15 (10.3)						
hrHPV	77 (29.2)	743 (18.5)	2572 (17.0)	1723 (21.2)	69 (17.6)	66 (13.3)	640 (12.4)	606 (14.3)	29 (19.9)						
High-risk HPV*															
52	18 (16.2)	208 (22.2)	683 (20.2)	435 (19.9)	19 (22.6)	17 (19.1)	165 (17.2)	152 (17.2)	8 (23.5)						
16	16 (14.4)	127 (13.6)	421 (12.4)	288 (13.2)	18 (21.4)	7 (7.9)	83 (8.7)	69 (7.8)	2 (5.9)						
58	17 (15.3)	97 (10.4)	354 (10.5)	312 (14.3)	14 (16.7)	5 (5.6)	85 (8.9)	108 (12.2)	6 (17.6)						
39	12 (10.8)	79 (8.4)	230 (6.8)	147 (6.7)	2 (2.4)	11 (12.4)	75 (7.8)	61 (6.9)	4 (11.8)						
18	12 (10.8)	71 (7.6)	215 (6.4)	143 (6.5)	8 (9.5)	8 (9.0)	50 (5.2)	60 (6.8)	1 (2.9)						
56	8 (7.2)	46 (4.9)	182 (5.4)	148 (6.8)	10 (11.9)	8 (9.0)	46 (4.8)	36 (4.1)	3 (8.8)						
51	6 (5.4)	71 (7.6)	156 (4.6)	99 (4.5)	3 (3.6)	6 (6.7)	49 (5.1)	39 (4.4)	2 (5.9)						
33	8 (7.2)	51 (5.4)	155 (4.6)	119 (5.4)	7 (8.3)	1 (1.1)	32 (3.3)	33 (3.7)	2 (5.9)						
59	8 (7.2)	55 (5.9)	145 (4.3)	99 (4.5)	3 (3.6)	1 (1.1)	34 (3.5)	35 (4.0)	3 (8.8)						
68	5 (4.5)	38 (4.1)	126 (3.7)	108 (4.9)	6 (7.1)	3 (3.4)	38 (4.0)	45 (5.1)	3 (8.8)						
66	8 (7.2)	40 (4.3)	127 (3.8)	82 (3.7)	6 (7.1)	1 (1.1)	26 (2.7)	29 (3.3)	2 (5.9)						
31	3 (2.7)	29 (3.1)	103 (3.0)	77 (3.5)	9 (10.7)	1 (1.1)	19 (2.0)	17 (1.9)	1 (2.9)						
35	3 (2.7)	17 (1.8)	71 (2.1)	55 (2.5)	4 (4.8)	1 (1.1)	10 (1.0)	19 (2.2)	4 (11.8)						
45	3 (2.7)	16 (1.7)	55 (1.6)	26 (1.2)	2 (2.4)	0 (0.0)	15 (1.6)	19 (2.2)	2 (5.9)						
Low-risk/undetermined-risk HPV*															
53	8 (7.2)	59 (6.3)	232 (6.9)	168 (7.7)	5 (6.0)	8 (9.0)	104 (10.8)	88 (10.0)	3 (8.8)						
81†	4 (7.7)	34 (7.4)	111 (6.6)	91 (8.0)	2 (4.5)	7 (10.8)	56 (8.1)	50 (8.3)	2 (11.1)						
61	6 (5.4)	48 (5.1)	218 (6.4)	176 (8.0)	7 (8.3)	4 (4.5)	61 (6.4)	90 (10.2)	1 (2.9)						
43†	5 (9.6)	27 (5.9)	88 (5.2)	72 (6.3)	4 (9.1)	3 (4.6)	48 (6.9)	32 (5.3)	2 (11.1)						
06	23 (20.7)	63 (6.7)	128 (3.8)	66 (3.0)	3 (3.6)	4 (4.5)	34 (3.5)	22 (2.5)	1 (2.9)						
44	6 (5.4)	29 (3.1)	131 (3.9)	68 (3.1)	3 (3.6)	3 (3.4)	44 (4.6)	47 (5.3)	0 (0.0)						
55	4 (3.6)	18 (1.9)	100 (3.0)	87 (4.0)	2 (2.4)	2 (2.2)	46 (4.8)	50 (5.7)	1 (2.9)						
11	11 (9.9)	45 (4.8)	75 (2.2)	51 (2.3)	4 (4.8)	2 (2.2)	14 (1.5)	10 (1.1)	1 (2.9)						
42	5 (4.5)	12 (1.3)	72 (2.1)	66 (3.0)	0 (0.0)	2 (2.2)	23 (2.4)	18 (2.0)	0 (0.0)						

Continued

Table 3 Continued

HPV status	Outpatients					Women receiving physical examinations				
	<21 y n=264	30–65 y		>65 y n=391	Total n=8113	21–29 y n=4023	30–65 y		>65 y n=146	Total n=4249
		30–45 y n=15108	46–65 y n=8113				30–45 y n=5178	46–65 y n=4249		
82	3 (2.7)	85 (2.5)	38 (1.7)	3 (3.6)	2 (2.2)	19 (2.0)	11 (1.2)	2 (5.9)	2 (5.9)	
40	4 (3.6)	44 (1.3)	30 (1.4)	1 (1.2)	1 (1.1)	13 (1.4)	18 (2.0)	0 (0.0)	0 (0.0)	
83	0 (0.0)	27 (0.8)	27 (1.2)	0 (0.0)	0 (0.0)	10 (1.0)	10 (1.1)	0 (0.0)	0 (0.0)	
26	1 (0.9)	6 (0.2)	8 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
73 [†]	0 (0.0)	2 (0.1)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

*Women with multiple HPV infections are counted for each type and are therefore counted more than once.

[†]For HPV43 and 81, 3373 outpatients had an HPV infection, including 52 cases aged <21 y, 461 cases aged 21–29 y, 1679 cases 30–45 y, 1137 cases aged 46–65 y and 44 cases aged >65 y. Additionally, 1381 women receiving physical examinations had an HPV infection, including 65 cases aged 21–29 y, 692 cases 30–45 y, 606 cases aged 46–65 y and 18 cases aged >65 y.

[‡]For HPV73, 3915 outpatients had an HPV infection, including 59 cases aged <21 y, 476 cases aged 21–29 y, 1705 cases 30–45 y, 1052 cases aged 46–65 y and 40 cases aged >65 y. Additionally, 583 women receiving physical examinations had an HPV infection, including 24 cases aged 21–29 y, 267 cases 30–45 y, 276 cases aged 46–65 y and 16 cases aged >65 y. HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; y, years.

aged 56–60 years (28.5%), which is a similar trend to those observed in Central America, Southeastern Asia and Western Africa.²⁴ The slight increase in the HPV infection rate in older women (aged ≥46 years) might reflect the persistence of HPV or the reactivation of latent HPV around menopause,²⁵ resulting from hormonal interactions with the HPV life cycle, viral characteristics and host susceptibility.²⁶

In the present study, multiple HPV infections were detected in 26.2% of the outpatients and were more frequent in younger women (aged <21 years). These findings are consistent with the results of Mejlhede *et al*²⁷ and support the fact that greater sexual activity in younger women may be associated with the transmission of multiple HPV types. We also found that the rate of multiple HPV infections increased in the older age group (aged >65 years). The most common two-type combinations were HPV52+58 (49 cases), HPV16+52 (33 cases) and HPV16+18 (29 cases). It is still controversial that coinfection increases the risk of progression to cancer.²⁸ Recently, Salazar *et al*²⁹ reported that women infected with multiple HPV infections were at a lower risk of high-risk cervical lesions compared with their single-genotype infection counterparts, suggesting a possible cross-protection triggered by multiple infections.³⁰ In contrast, Chaturvedi *et al*³¹ reported that women infected with multiple HPV infections were at significantly increased risk of CIN2+ when compared with those with single-genotype infections.

In addition to carcinogenesis, anogenital warts are a global public health problem that affects young men and young women and are mainly caused by two hrHPV types, HPV06 and 11.³² In our outpatients, the HPV06 (20.7%) and 11 (9.9%) infection rates significantly increased in younger women (<21 years). This highlights the importance of considering HPV6-related and HPV11-related diseases (genital warts) when assessing the potential benefits of preventive interventions such as HPV vaccination programmes.

In summary, the HPV prevalence and distribution of HPV type varied significantly in different female age groups between outpatients and women receiving physical examinations. The data from this study could be valuable for HPV-based cervical cancer screening efforts and could aid in the future vaccination, screening, diagnosis and treatment of HPV diseases.

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