


# BMJ Open Prevalence of human papillomavirus in Wenzhou, China: a cross-sectional study of 127 938 outpatient women

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## ABSTRACT

**Objectives** Understanding the prevalence and genotype distribution of human papillomavirus (HPV) is critical for managing HPV vaccination programmes. Using a retrospective cross-sectional study, we examined long-term trends of HPV prevalence in Wenzhou, a coastal city in China.

**Setting and participants** Cervical exfoliated cells were collected from 127 938 women who underwent cervical cancer screening at the gynaecology outpatient clinic of Wenzhou People's Hospital from January 2011 to December 2020. HPV infections and genotypes were determined. The HPV genotypes were 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 6, 11, 42, 43, 44 and 81. From 2011 to 2014, we used PCR and inflow hybridisation for typing assays. In 2015–2020, HPV genotyping was performed on the collected specimens using PCR and flow fluorescence hybridisation.

**Results** The overall prevalence of HPV infection was 17.8%. Across age groups, the prevalence fluctuated between 15.9% and 37.4%, with two peaks in the ≤20 and ≥51 year groups. The annual prevalence varied between 12.2% and 28.8%, with a significant decrease in 2011–2018 and a flat trend in 2018–2020. The five most common HPV genotypes were HPV52 (3.6%), 16 (3.0%), 58 (2.5%), 53 (1.9%) and 81 (1.3%). The prevalence of high-risk gene subtypes HPV56, 59 and the low-risk subtype HPV44 increased. Single HPV infection was the most common.

**Conclusion** The prevalence of HPV in Wenzhou is low to mid-range; however, the high-risk genetic subtypes HPV56 and 59 have increased in recent years. We need to promote HPV vaccination and increase education regarding safer sex.

## INTRODUCTION

Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women, with an estimated 604 000 new cases and 342 000 deaths worldwide in 2020.<sup>1</sup> Human papillomavirus (HPV) infection is a significant cause of cervical cancer.<sup>2</sup> Mucosal HPV types can be grouped into high-risk (HR) and low-risk (LR) HPV types depending on their association with cervical cancer and precursor lesions. Twenty-five serotypes are HR, according to

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study of human papillomavirus (HPV) in Wenzhou is the first large-scale cross-sectional, long-term sequence study to assess the epidemiological characteristics of cervical HPV genotypes.
- ⇒ We analysed the HPV genotyping results from 127 938 female outpatients from 2011 to 2020.
- ⇒ The purpose of HPV research in Wenzhou is to lay the foundation for HPV screening to support vaccination programmes.
- ⇒ A limitation is that the study population was outpatient women.

the International Agency for Research on Cancer (serotypes 16, 18, 26, 30, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, 85 and 97).<sup>3</sup> HR-HPV subtypes are responsible for almost all cervical carcinomas.<sup>4</sup> HPV screening and vaccines are the most effective measures for preventing HPV infection.<sup>5</sup> In recent years, large-scale vaccination projects have been undertaken in several countries, and the prevention of HPV-associated diseases has been confirmed.<sup>6 7</sup> In a region or city, it is helpful to understand the incidence and distribution of viral genotypes to determine whether the HPV vaccine needs to be updated.

More than 85% of cervical cancer cases worldwide occur in developing countries,<sup>8</sup> and China is no exception. The incidence among women is trending younger, and the disease burden is increasing; therefore, the current status of cervical cancer prevention and treatment is pessimistic.<sup>9</sup> Currently, China accounts for 11.9% of cervical cancer deaths and 12.3% of cervical cancer disability-adjusted life years worldwide.<sup>10</sup> There are many HPV subtypes; the cancer-causing ability of different types varies greatly and the distribution of HPV types infected across regions and populations varies widely.<sup>11 12</sup> The current cervical cancer vaccine does not fully meet public health needs.<sup>13</sup> Although studies

have been conducted to measure the prevalence and incidence of HPV genotypes in regions and cities, most are based on small samples and short durations.<sup>14–17</sup>

Wenzhou is one of China's first open coastal cities, with a resident population of approximately 9.5 million. A previous study showed that HPV infection in the region was at a moderate level.<sup>18</sup> Using a retrospective cross-sectional study, the primary purpose of this paper was to examine the long-time trend of HPV prevalence characteristics in Wenzhou, including population distribution, time trend and virus genotypes. We hope that the results of this study will help to understand the ecology of HPV-infected diseases and provide a scientific basis for vaccine development and promotion.

## MATERIALS AND METHODS

### General information

Cervical exfoliated cells were collected from 127 938 female patients who underwent cervical cancer screening at the gynaecology outpatient clinic at Wenzhou People's Hospital from January 2011 to December 2020. The ages ranged from 16 to 97 years, with an average of  $38\pm 10.7$  years. The samples were divided into 10 age groups ( $\leq 20$ , 21–25, 26–30, 31–35, 36–40, 41–45, 46–50, 51–55, 56–60 and  $\geq 61$ ). The patients visited the outpatient clinic for various reasons, including physical examination, infertility, vaginitis, cervicitis, undiagnosed abdominal pain, irregular vaginal bleeding, genital warts, cervical intraepithelial neoplasia and pregnancy. HPV testing is a routine examination for HR patients. HPV-positive individuals were identified by PCR followed by HPV genotyping. The Ethics Committee of Wenzhou People's Hospital, Zhejiang Province, approved this retrospective study.

### Specimen collection and treatment

The specimen collection was as follows. First, the examiner uses a speculum or vaginal dilator to open the vagina and expose the cervix. Next, secretions from the cervix are wiped off with a cotton swab. Then, the examiner gently rotates the cervical brush close to the cervical orifice clockwise for 4–5 circles. Finally, the examiner places the cervical brush head into an elution tube containing cell preservation solution, tightens the tube cap, marks the specimen and keeps the elution tube upright. The samples are stored in 4°C refrigerators, and the detection is completed within 3 days. All these procedures were performed according to the kit instructions.

### DNA extraction and HPV genotyping

From 2011 to 2014, we used PCR and inflow hybridisation for HPV typing assays. The nucleic acid microarray detection system based on rapid flow hybridisation of nucleic acid molecules for 21 HPV types used was provided by Guangdong Kepu Biological Company. Of the 21 detectable HPV types, 15 were HR genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68) and six were LR genotypes (6, 11, 42, 43, 44, 81). In 2015–2020, HPV

genotyping was performed on specimens using PCR and flow fluorescence hybridisation. We used Touch Thermal Cycler with a 96-well module flow fluorescence detector-Luminex 200 (Hangzhou Bioer Technology Co) with HPV-DNA typing kit (Shanghai Toujing Life Technology Co) to detect 27 HPV genotypes at one time, including 17 HR genotypes (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 82) and 10 LR genotypes (6, 11, 40, 42, 43, 44, 55, 61, 81, 83). This study was a trend analysis over a long period; therefore, only 21 genotypes were selected for statistical analysis in the last interval to avoid bias in the overall prevalence.

### Statistical analysis

Count data were expressed as frequency or percentage. The  $\chi^2$  test was used to compare the positive rate of each group. The Bonferroni method was used to adjust the p-value in the paired comparison between the two groups. R language was used for statistical analysis. Time trend analysis was performed using Joinpoint Regression Programme V.4.8.0.1 (online supplemental file 1).

### Patient and public involvement

We obtained HPV test results from outpatients at Wenzhou People's Hospital from 2011 to 2020. This study is based on established data, does not involve interventions with patients and exemptions from informed patient consent were requested from the ethics committee. The data are anonymous; therefore, the requirement for informed consent was waived. Patients or the public were not involved in our research's design, conduct, reporting or dissemination plans.

## RESULTS

### Prevalence of HPV infection in different age groups

From 2011 to 2020, 22 766 positive samples were detected, for an overall prevalence of 17.8% (22 766/127 938). Among age groups, the prevalence fluctuated between 15.9% and 37.4% (table 1). The highest prevalence was in the  $\leq 20$  years group, followed by the  $\geq 61$  years group and the 56–60 years group. The prevalence varied across all age groups ( $\chi^2=7916.9$ ,  $p<0.001$ ). After Bonferroni correction, there were significant differences between the  $\leq 20$ ,  $\geq 61$  and 51–55 year groups and the other groups.

### Prevalence of HPV infection over time

The annual prevalence fluctuated between 12.2% and 28.8% (table 2). The  $\chi^2$  showed positive annual rates differed between years ( $\chi^2=1659.9$ ,  $p<0.001$ ). After Bonferroni correction, the positive rates of HPV in 2011, 2012 and 2013 were significantly different from the other years. Using Joinpoint time trend analysis, the annual percentage change (APC) was  $-10.8$  (95% CI:  $-13.7$  to  $-8.0$ ,  $p=0.001$ ) from 2011 to 2018 and  $21.8$  (95% CI:  $-3.8$  to  $54.2$ ,  $p=0.09$ ) from 2018 to 2020, indicating a significant decrease in the years 2011–2018. The trend was

**Table 1** HPV infection rates across age groups

Age group (year)	Number of positive samples (cases)	Number of negative samples (cases)	Number of samples (cases)	Prevalence (%)
≤20	533	892	1425	37.4
21–25	2546	8893	11 439	22.3
26–30	3863	20 463	24 299	15.9
31–35	3639	19 214	22 853	15.9
36–40	3323	16 944	20 267	16.4
41–45	3015	15 364	18 379	16.4
46–50	2443	11 667	14 110	17.3
51–55	1481	6277	7758	19.1
56–60	896	2762	3658	24.5
≥61	1027	2723	3750	27.4
Total	22 766	105 172	127 938	17.8

HPV, human papillomavirus.

not statistically significant in 2018–2020 (online supplemental figure A).

### HPV gene subtypes

The prevalence and distribution of each HPV gene subtype are shown in table 3. There were 15 high-risk gene subtypes and six low-risk gene subtypes. The top five HR gene subtypes were HPV52, HPV16, HPV58, HPV53 and HPV39, while LR gene subtypes were HPV81, HPV6, HPV11, HPV43 and HPV44. The top five genotypes of prevalence were HPV52, HPV16, HPV58, HPV53 and HPV81, and the top four genotypes were all HR-HPV (table 3).

### Prevalence of single and mixed HPV infection

Single HPV genotype infection was the most common pattern (74.28%, 16 910/22 766) (table 4). Regardless of the year, single HPV infection was the most common, and the prevalence was much higher than the sum of multiple infections (online supplemental file 3).

**Table 2** HPV infection rates over time

Year	Number of positive samples (cases)	Number of negative samples (cases)	Number of samples (cases)	Prevalence (%)
2011	2227	5504	7731	28.8
2012	2190	6748	8938	24.5
2013	2077	7301	9378	22.1
2014	1928	8591	10 519	18.3
2015	2227	9916	12 143	18.3
2016	2378	11 539	13 917	17.1
2017	1846	12 328	14 174	13.0
2018	2077	14 980	17 057	12.2
2019	2972	15 172	18 144	16.4
2020	2844	13 093	15 937	17.8
Total	22 766	105 172	127 938	17.8

HPV, human papillomavirus.

**Table 3** Prevalence and distribution of each HPV gene subtype

HPV subtypes	Number of positive samples (cases)	Proportion among HPV-positive samples (%)	Prevalence in total samples (%)
HR-HPV	24 670	79.4	19.3
16	3788	12.2	3.0
18	1509	4.9	1.1
31	776	2.5	0.6
33	1189	3.8	0.9
35	483	1.6	0.4
39	1552	5.0	1.2
45	376	1.2	0.3
51	1115	3.6	0.9
52	4592	14.8	3.6
53	2458	7.9	1.9
56	961	3.1	0.8
58	3152	10.1	2.5
59	949	3.1	0.7
66	1000	3.2	0.8
68	770	2.5	0.6
LR-HPV	6420	20.6	5.0
6	1552	5.0	1.2
11	1344	4.3	1.1
42	278	0.9	0.2
43	777	2.5	0.6
44	746	2.4	0.6
81	1723	5.5	1.3

Prevalence of single and mixed HPV infection.  
LR-HPV, low-risk human papillomavirus.

### Trends of the prevalence of HPV infection across age groups

The time trend of the prevalence of age-specific HPV infection was analysed using Joinpoint (online supplemental file 4). The annual prevalence of HPV infection of the 26–30 years group (APC, 2.6; 95% CI: 1.5 to 3.7, p=0.001), 31–35 years old group (APC, 2.5; 95% CI: 1.1 to 4.0, p=0.004) and 51–55 years group (APC, 3.5; 95% CI: 0.1 to 6.9, p=0.045) increased over 2011–2020 (online supplemental figure B). The annual prevalence of HPV infection in the 36–40 years group (APC, -2.9; 95% CI:

**Table 4** Prevalence of single and multiple HPV infections

Genotype of HPV infection	Number of cases	Prevalence (%)	Percentage of positive samples (%)
Single*	16 910	13.2	74.28
Double	4455	3.48	19.57
Triple	1028	0.80	4.52
Quadruple	278	0.22	1.22
Quintet	65	0.05	0.29
Sextuple and more	30	0.02	0.13

\*The prevalence of a single HPV infection was higher than that of multiple HPV infections, p<0.001  
HPV, human papillomavirus.



-3.5 to -2.2,  $p < 0.001$ ), 41–45 years group (APC, -3.2; 95% CI: -4.0 to -2.4,  $p < 0.001$ ) and 46–50 years group (APC, -1.9; 95% CI: -2.9 to -1.0,  $p = 0.002$ ) decreased over 2011–2020 (online supplemental figure B). We compared data from different years for each age group and found no significant difference between years after the Bonferroni correction.

### Trends of the prevalence of type-specific HPV infection

Trends in the prevalence of type-specific HPV infection were assessed by year (online supplemental file 5). For the HR subtype, the prevalence of HPV56 (APC, 9.3; 95% CI: 2.8 to 16.2,  $p = 0.01$ ) and HPV59 (APC, 12.8; 95% CI: 4.2 to 22.0,  $p = 0.008$ ) increased over 2011–2020 (online supplemental figure C). The prevalence of HPV16 (APC, -13; 95% CI: -17.3 to -8.4,  $p < 0.001$ ), HPV18 (APC, -6.4; 95% CI: -11.2 to -1.2,  $p = 0.02$ ), HPV31 (APC, -17.8; 95% CI: -30.2 to -3.2,  $p = 0.025$ ), HPV33 (APC, -17.7; 95% CI: -22.1 to -13.0,  $p < 0.001$ ) and HPV58 (APC, -9.7; 95% CI: -12.9 to -6.4,  $p < 0.001$ ) decreased over 2011–2020 (online supplemental figure C).

For the LR subtype, the prevalence of HPV44 (APC, 17.8; 95% CI: 7.3 to 29.2,  $p = 0.004$ ) increased over 2011–2020, while HPV6 (APC, -8.2; 95% CI: -13.1 to -3.1,  $p = 0.007$ ) and HPV11 (APC, -15.5; 95% CI: -19.5 to -11.2,  $p < 0.001$ ) decreased over 2011–2020 (online supplemental figure D). We compared the data of each genotype in different years, and there was no significant difference between each year after the Bonferroni correction.

### DISCUSSION

The total prevalence of HPV in Wenzhou was 17.8% among 127 938 outpatient women over 10 years, at the lower middle level compared with similar studies in other regions in China and other countries.<sup>5 14–21</sup> The annual prevalence of Wenzhou fluctuated between 12.2% and 28.8%, decreasing from 2011 to 2018. One of the possible reasons is that the public's awareness of the HPV vaccine and willingness to vaccinate increased with the improvement in living conditions. Another reason is the increased publicity of cervical cancer prevention and treatment increases the screening population because individuals without cervical disease participate. This finding is consistent with a previous study in southern China, where the prevalence of HPV infection trended downward during 2012–2018.<sup>5</sup> However, a study in Shanghai showed that the prevalence of HPV infection increased from 2011 to 2019.<sup>19</sup> The reason might be the rapid economic development, expanding city size, sizeable foreign population and complex population composition in Shanghai.

The total prevalence of HPV infection in Wenzhou was the highest in the youngest group and second highest in the oldest group. This bimodal pattern is consistent with other studies in China and elsewhere.<sup>20 22–25</sup> This result might be related to earlier sexual activity and riskier sexual behaviours in younger age groups.<sup>26</sup> Older adults have difficulty recovering from HPV infection

because of the persistence or reactivation of latent HPV resulting from physiological and immune dysregulation that occurs during menopause.<sup>20 27</sup> The results suggest that more attention should be paid to preventing and controlling HPV infection in young and older women. Despite the HPV prevalence in the  $\leq 20$  age group being the highest, the sample proportion was not high, implying that HPV screening of cervical disease for women  $\leq 20$  years old is necessary and feasible. Younger Chinese women have earlier sexual debuts and engage in higher-risk sexual behaviour than older women, which may increase the probability of HPV infection.<sup>26</sup> HPV detection in women peaks immediately after the onset of sexual relations, usually from 15 years of age (primarily transient infections) which clear within 1 or 2 years.<sup>24</sup> The higher prevalence in women aged 56–60 may be associated with decreased oestrogen levels after perimenopause, decreased immune function, increased susceptibility to HPV and decreased clearance.<sup>28 29</sup> The introduction and promotion of the HPV vaccine in recent years have increased the attention to HPV infection among older women ( $\geq 56$  years) and increased the number of regular follow-up visits. This phenomenon may be due to the interaction between hormones and the life cycle, viral characteristics and host susceptibility of HPV, resulting in the reactivation of latent HPV before and after menopause.<sup>30 31</sup> Women  $\leq 25$  years old and  $\geq 56$  years old are HR groups for HPV in Wenzhou; therefore, targeted preventive and control measures are necessary. The HPV prevalence in the 26–30, 31–35 and 51–55 year groups increased over 2011–2020. The first reason may be the promotion of HPV screening, the number of people tested increased yearly, and occult infections were detected. Second, the proportion of outpatients aged 26–35 years is high. Women in this age group are becoming more health-conscious and are increasingly willing to undergo physician-recommended HPV testing. The HPV prevalence in the 36–40 years, 41–45 years and 46–50 year groups decreased over 2011–2020. The downward trend in HPV prevalence in the 36–50 age group, in addition to the fact that some of the population is vaccinated against HPV, may also be because HPV infection in younger women is temporary and has the potential to disappear within 1 to 2 years, with prevalence decreasing gradually with age.<sup>16</sup>

The most common HR-HPV genotypes among gynaecological outpatients in Wenzhou were HPV52, followed by HPV16, 58, 53 and 39. The most common LR-HPV genotypes were HPV81 and 6, a finding different from other countries or regions. For example, in Vojvodina province, Serbia, the most common HR-HPV genotypes were HPV16, 31, 53, 51, and the most common LR-HPV genotype was HPV42.<sup>32</sup> In Taizhou (a city neighbouring Wenzhou), the most common HR-HPV genotypes in the outpatient group were HPV52, 16, 58, 39 and 53, and LR-HPV genotypes were HPV81, 61.<sup>21</sup> The prevalence of HR-HPV genotypes HPV56, 59, and the LR-HPV genotype HPV44 showed an increasing trend over 2011–2020.

These findings suggest that we should pay attention to these genotypes with increasing prevalence trends in addition to the common genotypes. Of course, some genotypes showed downward trends, such as HR-HPV genotypes HPV16, 18, 31, 33 and 58 and LR-HPV genotypes HPV6 and 11. The bivalent vaccine (Cervarix, HPV16, 18), quadrivalent vaccine (Gardasil; HPV6, 11, 16, 18) and nine-valent vaccine (Gardasil<sup>®</sup>9) were approved in China in 2016, 2017 and 2018, respectively. The bivalent vaccine developed independently in China and was marketed.<sup>33</sup> Among the approved vaccines, the nine-valent vaccine (Gardasil<sup>®</sup>9) covers the most genotypes, including HR HPV16, 18, 31, 33, 45, 52, 58 and LR HPV6 and 11.<sup>4</sup> The genotypes with decreasing HPV prevalence trends were all covered by the vaccine, while the genotypes with increasing trends were not covered. The effectiveness of the HPV vaccine was demonstrated by the significant reduction in the prevalence of these HPV subtypes targeted by the vaccine. The extensive data from this study demonstrate that although the nine-valent vaccine covers most subtypes, it does not cover HPV 53 and 81, which are common in Wenzhou. Therefore, targeted vaccine research and development could improve the cost-effectiveness of preventive vaccination for the Chinese population to a greater extent. From 2011 to 2020, the primary type of HPV infection in Wenzhou was the single type. Previous studies indicate that multiple types of mixed infections increase the risk of cervical cancer more than single-genotype infections.<sup>34</sup> Women infected with multiple HPV genotypes have a lower risk of developing HR cervical lesions than women infected with a single genotype and multiple genotype infections may trigger cross-protection.<sup>35</sup> The mechanisms and potential oncogenic effects of multiple infection genotypes require further study. The pessimistic outlook is because of the prevalence of some high-risk gene subtypes and mixed infections.

In summary, this study assessed HPV infection characteristics and the time trend among gynaecological outpatients in Wenzhou from 2011 to 2020 with a large sample size and a long-time series. There were some limitations. First, the sample only included women who had been to a gynaecological clinic, which might lead to higher results. We obtained only HPV test results and could not ascertain whether the patient was vaccinated for HPV. HPV vaccination has a significant impact on HPV test results. There was no information about risky behaviour. Second, recommendations for HPV are based on the patient's needs and economic level, and the voluntary nature might cause selection bias. Third, we do not have data on socioeconomic status; we will consider this in future studies. Finally, the lack of cervical cytology or histological results makes it impossible to correlate HPV infection and genotype distribution with different cervical abnormalities.

## CONCLUSIONS

The five most common HPV genotypes in Wenzhou were HPV 52, 16, 58, 53 and 81. The prevalence of HR genotypes HPV 56 and 59 and LR genotype HPV 44 showed a continuously increasing trend from 2011 to 2020. The findings have important implications for future cervical cancer screening and HPV vaccine development strategies in the study area.

**Contributors** GC and XD collected and analysed the data; YZ, MZ, ZW and HH contributed to the manuscript draft and provided revisions. Guarantor: YZ. All authors read and approved the final manuscript.

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