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Prevalence and Genotyping of Human Papillomavirus Infections in Females and Males in Zhejiang, China

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Objective: This study aimed to investigate the infection rate, types of human papillomavirus (HPV), and the relationship between HPV types and host factors in Zhejiang and lay a foundation for developing a prophylactic HPV vaccine.

Methods: A retrospective analysis of the genotyping results of 27 hPV types using exfoliated cells from the cervix, vulva, perianal region, or oral mucosa of 28206 females, and exfoliated cells from the penis, perianal region or oral mucosa of 2923 male patients undergoing treatment between January 2016 and December 2021 at Zhejiang Provincial People's Hospital was performed.

Results: In females, the overall positive rate was 30.26%. The top five HPV types were HPV52, 58, 16, 6, and 53. In males, the overall positive rate was 31.85%. The top five HPV types were HPV6, 11, 16, 52, and 43. About 90.48% of patients with CINII+ were HR-HPV+. HPV33, 16 were the top two HPV types that increased CINII+ risks.

Conclusion: Currently, the bivalent (HPV16, 18), quadrivalent (HPV6, 11, 16, 18), and 9-valent (HPV6, 11, 16, 18, 31, 33, 45, 52, 58) HPV vaccines are marketed. Of these, the 9-valent HPV vaccines are more suitable for people in the Zhejiang province; however, it is still insufficient. Therefore, the 11-, 14-, and 15-valent vaccines being developed and marketed include more genotypes, and their outcomes are worth anticipating.

Keywords: human papillomavirus, genotype, cervical cancer, vaccine

Introduction

Globally, one of the most prevalent sexually transmitted viruses is human papillomavirus (HPV). Both females and males have an equal chance (50%) of contracting HPV at least once during their lifetime.[1] A meta-analysis of 1,016,719 women estimated global HPV prevalence was 11.7%.[2,3] The global prevalence of high-risk genital HPV in men is 21%.[4] The Chinese female prevalence of HPV infection was 18%.[5,6]

More than 200 hPV genotypes have been identified based on genomic differences, and most genotypes are harmless.[7] Based on its oncogenic potential, HPV is classified into high- and low-risk. Benign lesions on the mucous membranes and skin caused by infections due to HPV6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108 are deemed as low-risk HPV (LR-HPV). Moreover, HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82, etc., cause mucocutaneous malignancies are called high-risk HPV (HR-HPV).[8] The HPV genome can be integrated into the DNA of the region of the host cell that codes for the E6 and E7 cancer proteins. E6 binds to and degrades the p53 tumor suppressor protein and E7 interacts with and inactivates the retinoblastoma (Rb) tumor suppressor protein.[9,10] Persistent infections with high-risk HPV can lead to abnormal cellular changes, such as precancerous lesions, which may progress to cancer over time.[11] Some of these infections can persist for

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years, which could lead to cervical, anal, vaginal, oropharyngeal, and penile cancers. The prevalence of cervical cancer in China is also very serious. In 2020, the number of new cervical cancer cases in China is 109,741, and the number of deaths is 59,060.[12] Different types of HPV can cause different types of cervical cancer in females. In addition, studies have found that HPV is closely related to the development of female reproductive tract malignancies such as vulvar squamous cell carcinoma and high-grade vaginal intraepithelial neoplasia.[13,14] HPV-16 and HPV-18 are the most prevalent worldwide and are responsible for the majority of HPV-related cancers.[15] The persistence of human papillomavirus (HPV) infection is widely recognized as the most important causative factor in the development of cervical cancer.[16] In addition, previous studies have shown that multiple HPV infections may prolong persistent infection, thereby increasing cervical cancer risk in patients compared to patients with single HPV-type infections.[17,18]

Hence, HPV genotyping must be conducted to classify HPV+ females. Furthermore, the prevalence and HPV type-specific distribution may vary from country to country and within different regions of the same country. Hence,[19,20] to prevent HPV infection in the Zhejiang province of China, it is necessary to determine the prevalence and distribution of the type of HPV infection in women of different age groups. This will aid in developing and evaluating HPV screening tests, as well as determining the efficacy of HPV vaccines. Since HPV transmits through sexual contact, evaluating HPV infections in women alone could be insufficient. A high rate of HPV infection is observed in male partners of HPV-infected women, and the types of HPV infection in them are highly consistent.[21] Recently, HPV infections in males have attracted attention. However, only a few epidemiological studies have determined the status of HPV infection in males in Zhejiang, China. Further, it is still unclear if HPV vaccines available in the Chinese market could be used for males at high risk of HPV infection in Zhejiang, China. Therefore, it is necessary to determine the status and distribution of the type of HPV infection in males, as well as compare similarities and differences to the infection types in females. This could aid in preventing, treating, and designing HPV vaccines for males.

Therefore, in this study, we retrospectively analyzed the results of 27 hPV types genotyped using the exfoliated cells obtained from the cervix, vulva, perianal region, and oral mucosa of 28206 females and exfoliated cells from the penis, perianal region, and oral mucosa of 2923 males. These samples were obtained from patients who underwent HPV testing between January 2016 and December 2021 at Zhejiang Provincial People's Hospital.

Methods

Specimen Source

We obtained the results of 27 hPV types genotyped in 31,129 patients undergoing treatment at Zhejiang Provincial People's Hospital between January 1, 2016 and December 31, 2021. Female patients included those who had HPV testing for excessive leukorrhea, vaginitis, cervicitis, genital warts, cervical intraepithelial neoplasia, or physical examination. TCT (ThinPrep cytology test) and colposcopy were performed on HPV-positive patients who were clinically suspicious. Male patients who underwent HPV testing during their STD clinic visit were included. In addition, the electronic records of the clinical and pathological data like age at diagnosis, cytological, HPV genotyping, colposcopy, and histological results of patients were obtained. This study was approved by the ethics committee of the Zhejiang Provincial People's Hospital, and the reference number was QT2022281.

Specimen Collection

HPV Testing

In female patients, the cervical os was exposed using a vaginal dilator, and the cervical secretions were wiped with a cotton swab by medical staff. The HPV exfoliative cell detection brush was inserted into the cervical os and gently rotated clockwise closer to the cervical os 4–5 times. The exfoliated tissues from the skin and mucous membranes of the vulva, perianal region, or oral cavity were collected using the HPV Exfoliative cell detection brush. In males, the exfoliated tissues from the skin and mucous membranes of the penis, oral cavity, or perianal region were collected. The head of the brush was inserted into the elution tube containing a solution for preserving cells, and the tube cap was tightened. The samples were labeled, the elution tubes were kept upright, and stored at −20 °C for further evaluation.

ThinPrep Cytology Test (TCT)

The special TCT cell collection brush was inserted in the cervical canal and rotated clockwise or counterclockwise 5–6 times. Next, the cell collection brush was placed in a special vial for preservation and subsequent evaluation.

Cervical Histopathology

Colposcopy was used to perform a biopsy at the suspected sites of cervical lesions and 3, 6, 9, and 12 o'clock sites. The location of lesion in the cervix was marked. The specimens were fixed using formaldehyde and embedded in paraffin.

Specimen Testing

HPV Testing

The HPV nucleic acids were qualitatively detected using the HPV nucleic acid typing assay kit from Shanghai Tellgen Life Science and Technology Co., Ltd. The kit can detect 27 hPV types like HPV 16, 26, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 82, 6, 11, 40, 42, 43, 44, 55, 61, 81, 83. The samples were first treated with a nucleic acid-releasing agent derived from exfoliated cells of Shanghai Tellgen Life Science and Technology Co., Ltd. 15 μL PCR reaction mixture/tube was prepared in the reagent formulation room and amplified using a PCR machine (Eppendorf Mastercycler Gradient). Finally, the Luminex 200 multifunctional flow array instrument was used to detect hybridization. HPV type-specific probe signal >150 was considered positive; otherwise, the signal was negative.

TCT

A liquid-based thin-section cytology technique was used for performing cytological evaluation on cervical samples. The Bethesda System describes a specimen as negative for intraepithelial lesion or malignancy (NILM) by the presence of normal and inflammatory. Squamous cell abnormalities include squamous intraepithelial lesion (SIL) like both low- and high-grade SILs, atypical squamous cells (ASC) including ACS of undetermined significance and high-grade SILs, and squamous cell carcinoma. The glandular cell abnormalities consist of atypical glandular cells as well as adenocarcinoma.

Histopathological Examination of the Cervix

The histology was examined and classified as follows: normal, cervical intraepithelial neoplasia (CIN) grade 1 (CIN 1), grade 2 (CIN 2), grade 3 (CIN 3) and cervical cancer. Vaginal intraepithelial neoplasia (VAIN) is an abnormal growth of epithelial cells similar to cervical intraepithelial neoplasia in the vaginal area.

Statistical Analysis

Statistical analysis was performed using SPSS 25.0 software. The enumeration data were represented as the number of cases and percentage (%). The positive rates of all types of HPV across groups were compared using the $\chi 2$ test. $P < 0.05$ (two-sided) was considered statistically significant. The incidence of CINII + in each HPV type was calculated based on the cervical histopathological examination, which is the gold standard for diagnosis.

Results

Overall Status of HPV Infection

Of the 28206 female patients, 8535 patients were HPV+, and the overall positive rate was 30.26%. HPV52, 58, 16, 6, and 53 were the top five HPV types with high infection rates. HPV6 was the low-risk HPV type. Of 2923 male patients, 931 were HPV+, and the overall positive rate was 31.85%. In males, HPV6, 11, 16, 52, and 43 were the top five HPV types with high infection rates, and HPV6, 11, and 43 were the low-risk HPV types (Figure 1). In both males and females, HPV 6, 16, 52 were the top five HPV types with infection rates, and the probability of high-risk HPV infection in women was significantly higher than that in men ($P < 0.001$) (Figure 1).

Age-Specific Distribution of HPV Infection

Depending on their age, 27716 females were divided into seven groups. The HPV infection rates were 61.85% (≤20 years), 38.72% (21–30 years), 26.99% (31–40 years), 25.64% (41–50 years), 30.60% (51–60 years), 33.40% (61–70

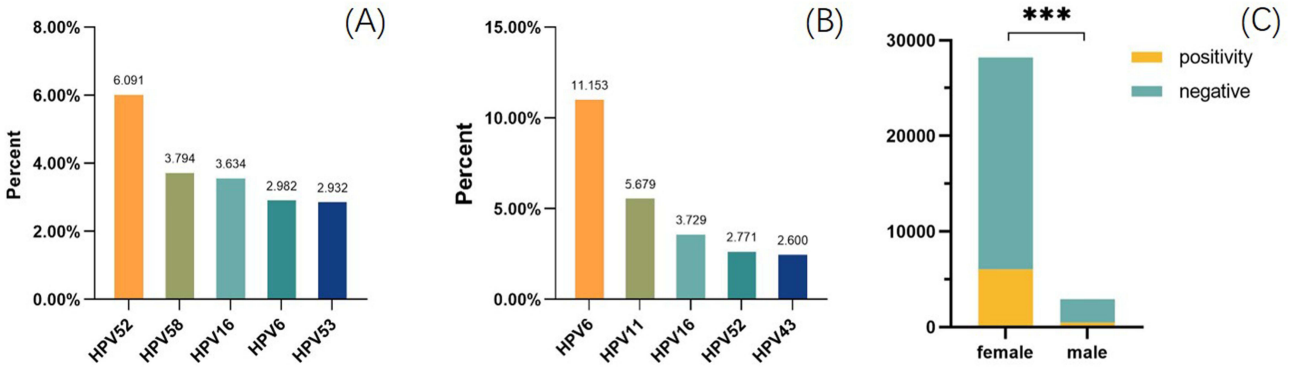

Figure 1 (**A**) The top five types of HPV in female patients. (**B**) The top five types of HPV in male patients. (**C**) Statistically different between the male and female groups in high-risk infections (***, P < 0.001).

years), and 19.30% (≥71 years). A significant difference (χ^2=544.904, P ≤ 0.001) was observed in the infection rates in patients in the seven groups. Further, 2921 males were divided into seven age groups, and the results showed that the HPV infection rates varied with age. The infection rates were 40.37% (≤20 years), 31.55% (21–30 years), 29.75% (31–40 years), 32.27% (41–50 years), 37.61% (51–60 years), 47.37% (61–70 years), and 35.71% (≥71 years). The HPV infection rate was the highest in patients in the 61–70-year age group and the lowest in the 31–40-year age group, with a significant difference (χ^2=5.372, P < 0.05) (Table 1).

Analysis of Single and Multiple HPV Infections

In HPV+ female patients, 65.55% patients had a single HPV infection, and 34.45% had multiple HPV infections. Of these, 22.59% of patients had double infections, 7.72% had triple infections, and 4.14% had quadruple or more infections. In patients from different age groups, the multiple infection rates were highest in females ≤20 years (62.90%), followed by 42.61% in patients aged 61–70 years, 40.88% in patients aged 21–30-year group, 36.89% in patients aged 51–60 years, 31.82% in patients aged ≥71 years, 28.37% in patients aged 31–40 years, and 26.18% in patients in the 41–50-year age group (Table 1). A significant difference (χ^2=243.954, P ≤ 0.001) was observed in the infection rates in patients in seven groups. Moreover, we compared the positive rate of pathological results in female patients with single and multiple infections. The results revealed that 16.08% of patients with a single infection had positive pathological results, and 12.63% of patients with multiple infections had positive pathological results, with no significant difference (χ^2=2.729, P > 0.05). In HPV+ male patients, the single infection rate was 63.91%, and the multiple infection rate was 36.09%. Of these, 22.13% of patients had double infections, 7.95% of patients had triple infections, and 1.92% of patients had quadruple or more infections. The multiple infection rates were highest in patients who were ≤20 years and 61–70 years. The infection rates were 54.55% in patients aged ≤20 years and 50.00% in patients in the

Table 1 [HPV Infection in Different Age Groups]

Age	Female		Male	
	HPV Positivity n (% ±95% CI)	Multi-Infection n (% ±95% CI)	HPV Positivity n (% ±95% CI)	Multi-Infection n (% ±95% CI)
≤20	248(61.85±4.75)	156(62.90±6.01)	44(40.37±9.21)	24 (54.55±14.71)
21–30	2566(38.72±1.17)	1049(40.88±1.90)	418(31.55±2.50)	151 (36.12±4.60)
31–40	2379(26.99±0.93)	675(28.37±1.81)	299(29.75±2.83)	103 (34.45±5.39)
41–50	1837(25.64±1.01)	481(26.18±2.01)	101(32.27±5.18)	35 (34.65±9.28)
51–60	1049(30.6±1.54)	387(36.89±2.92)	44(37.61±8.78)	12 (27.27±13.16)
61–70	352(33.40±2.85)	150(42.61±5.17)	18(47.37±15.88)	9 (50.00±23.10)
≥71	44(19.30±5.12)	14(31.82±13.76)	5(35.71±25.10)	2 (40.00±42.94)
Total	8475	2912	2921	336

Table 2 [Positive Analysis of Single and Multiple HPV Infections in Different Gender]

	Female (n, %)	Male (n, %)	Total (n)	χ2	P
Single infection	5595 (65.55)	595 (63.91)	6190	1.002	0.317
Dual infection	1928 (22.59)	206 (22.13)	2134	0.103	0.748
Triple infection	659 (7.72)	74 (7.95)	733	0.061	0.805
Four or more infections	353 (4.14)	56 (6.02)	409	7.170	0.007

61–70-year age group. No significant difference (χ^2=9.952, P > 0.05) in infection rates was observed in patients in the seven groups. Next, we compared the infection rates in males and females. The results revealed that the quadruple and above HPV infection rates were significantly higher (P < 0.05) in males compared to females. No significant difference was observed between other types of infection (Table 2).

Distribution of Cytological and Histological Diagnosis of HPV

TCTs were performed on 2087 HPV+ patients between 2020 and 2021 (Figure 2). Colposcopies were performed in 1192 women who had undergone TCTs. Among them, 199 (16.69%) patients were diagnosed with CINI, 175 (14.68%) were diagnosed with CINII+ (Figure 3). The pathological tissues were positive in 11.59% of patients aged ≤30 years and 16.08% of patients aged ≥30 years, and the difference was statistically significant (χ^2=4.108, P < 0.05). Furthermore, 90.48% (171/189) of INII+ patients with pathological findings were positive for HR-HPV. The CINII+ risk for all HPV

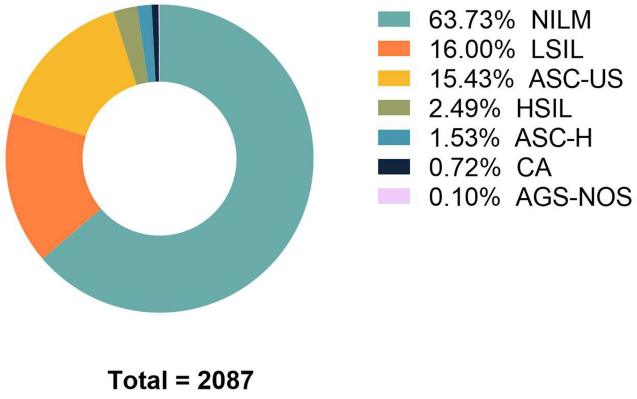

Figure 2 TCT results of female HPV positive patients.

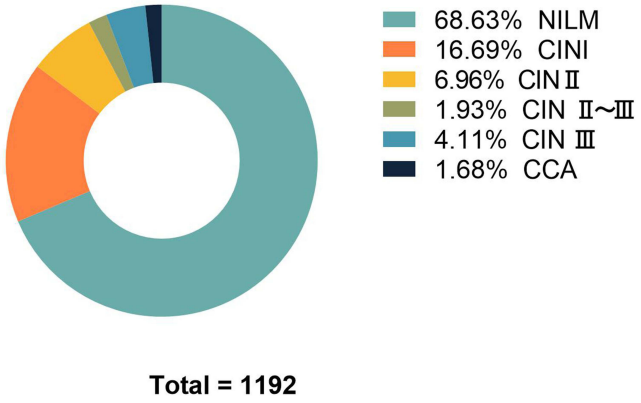

Figure 3 Pathology of female HPV positive patients.

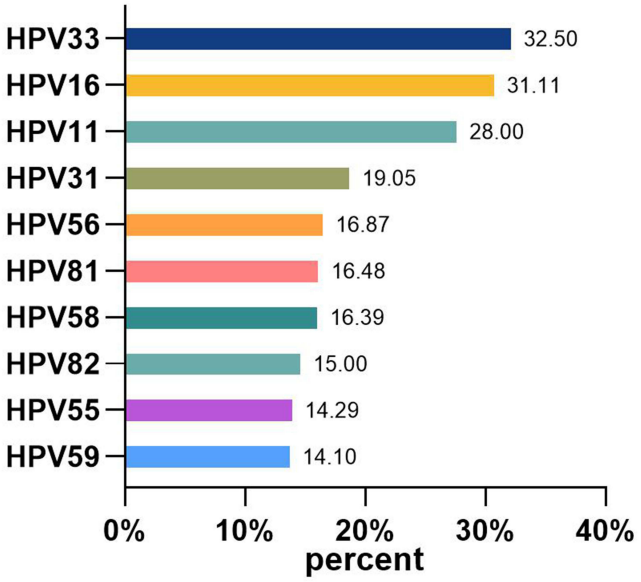

Figure 4 The risk of CINII+ for different HPV types.

types was assessed. In HPV+ females, the CINII+ risk was 32.50% (95% CI: 27.82%~37.18%) for patients with HPV33, 31.11% (95% CI: 26.43%~35.79%) for patients with HPV16, 28.00% (95% CI: 23.32%~32.68%) for patients with HPV11, 19.05% (95% CI: 14.37%~18.14%) for patients with HPV31, and 16.87% (95% CI: 12.19%~21.55%) for patients with HPV56 (Figure 4).

Discussion

HPV infection is widespread, and the prevalence and distribution of various HPV genotypes differ drastically across geographical locations and ethnic groups. Our results show that the HPV-positive rate in 28206 female patients was 30.26%, higher compared to Beijing city (19.1%) and Jiangsu province (26.92%) but lower compared to Henan province (44.5%) and Qingdao city (32.2%).[22–25] Compared with neighbouring countries, it was lower than Kazakhstan (42.1%) and India (90%) and higher than South Korea (16.71%).[26–28] These variations in positive rates could be attributed to the differences in inclusion criteria set by these study groups, economic conditions, cultural habits, population distribution, detection methods, and HPV vaccination. Our results show that in females, the top five HPV types with infection rates were HPV52, 58, 16, 6, and 53. The HPV types identified in our study differ from the most common HR-HPV genotypes, such as HPV16, 18, detected globally.[3,26,29,30] Studies have shown that HPV 52 and 58 are more common HPV types detected in the Asian population, and the infection rates of HPV 52, 58, and 16 were higher in China, consistent with our results.[31,32]

In addition to regions, HPV infection differs in women according to age.[33] Our results show that the HPV infection rate was the highest in females ≤20 years. Additionally, the multiple HPV infection rates were the highest in females ≤20 years, which could be attributed to their premature sexual debut and poor immune function in females in this age group.[34,35] At the same time, males ≤20 years are also one of the peak groups of HPV infection, and the sexual activity within this age group is likely contributing to the increase in HPV transmission, leading to a peak in infections among the population ≤20 years. Although the rate of persistent infection and its progression in adolescent women is low, they are still at risk of developing a persistent infection as well as cervical cancers.[36] Hence, HPV vaccine should be administered to adolescent women at an early age.[37] Our analysis shows a high rate of HPV infection in females between 40 and 70 years, which could be due to low resistance and estrogen secretion in women. Therefore, we recommend that women over the age of 40 get an annual HPV test to check for high-risk HPV infection.

Numerous studies have shown that chronic HR-HPV infection in the reproductive tract increases the incidence of CIN and cervical cancers.[38] Cervical cancer is the most common gynecological malignancy, posing a severe threat to the lives and health of women.[39] Furthermore, over 85% of cervical cancer cases are diagnosed in developing countries, and the incidence

of cervical cancer in China constantly increases yearly, specifically in the younger population.[40] However, HR-HPV testing could be used for screening for cervical cancer.[41] Our results show that 90.48% of patients with CINII+ were HR-HPV+, thereby indicating the significance of HR-HPV screening while testing for cervical cancers. Different from previous studies, our results show no significant difference in pathological positivity in patients with single and multiple infections. Hence, the correlation between multiple infections and cervical lesions should be further investigated.[17,18] Furthermore, we analyzed CINII+ risks in patients infected with different HPV types, and HPV33, 16, 11, 31, and 56 were the top five HPV types that increased CINII+ risks. Our results showed that HPV11 increased the risk of CINII+, despite being categorized as LR-HPV type. However, in our study, all patients with CINII+ infected with HPV11 were infected with HPV16. On the contrary, previous studies have shown that HPV16 and 18 increase cervical lesion risk.[42,43] HPV types also vary between regions and ethnic groups.[44] According to earlier studies, the top 5 subtypes of high-risk HPV infection in CINII+ patients in different regions of China are HPV16 and 58, as well as HPV18, 31, 33, 52, 53, 56, and 59.[45] Immunization is one of the most crucial strategies for reducing the incidence of cervical cancer. Vaccines should be distributed effectively and reasonably based on the epidemiological characteristics of HPV. Among the bivalent (HPV16, 18) and quadrivalent (HPV6, 11, 16, 18), and 9-valent HPV (HPV6, 11, 16, 18, 31, 33, 45, 52, 58) vaccines, it is obvious that 9-valent HPV vaccines could be more appropriate for people in China. However, this could still be insufficient. It is worth noting that HR-HPV56 has a certain infection rate in the Chinese population and is closely related to the occurrence of CIN2, which is not covered by the current vaccine. Therefore, the 11-valent, 14-valent, and 15-valent vaccines being developed and marketed include more genotypes, and the outcomes are worth anticipating.

Currently, the information on the epidemiology of HPV in men is less focused. However, male HPV infection is an important risk factor for condyloma, penile cancer, anal cancer and other diseases.[46] Our analysis shows that HPV positive rate in 2923 male patients was 31.85%, which was significantly higher than the infection rate in Hangzhou from 2003 to 2004 (13.8%).[47] The increase of infection rate may be closely related to the development of social economy. The global pooled prevalence was 31% for any HPV and 21% (18–24) for HR-HPV.[4] Our analysis shows that the prevalence of HPV infection in males is relatively lower compared to western countries,[48,49] possibly due to the low homosexual population and sexual openness in China compared to the USA and western countries. The infection rate was highest in males between 61 and 70 years, followed by males ≤20 years. The high rate of HPV infection in males between 61 and 70 years could be attributed to decreased resistance. Additionally, a higher prevalence of HPV in males ≤20 years could be due to increased sexual activity and a high risk of HPV exposure. Our analysis showed that the infection rates in males and females were similar; however, the HPV types with higher infection rates and prevalence of these genotypes were slightly different in males. This could be attributed to the fact that these patients were not partners and the differences in susceptibility to HPV types in males and females. Consistent with our study, HPV16 and HPV6 were the most common infection types in men worldwide.[4] Generally, the HPV infection rate in male partners of female patients infected with HPV is high. However, there is a lack of efforts to treat couples with HPV infection in China. One partner often fails to visit the doctor in a timely manner after infection, thereby raising the risk of HPV cross-infection and clinical recurrence. Therefore, it is recommended that the sexual partners of patients with HPV participate in the examination and treatment. Furthermore, the risk of cancers caused by HPV in males and females is comparable; hence, immunization of males could greatly reduce the risk of HPV-related diseases and lead to herd immunity.[50,51] As a result, it is recommended that HPV vaccination be included in the national male vaccination program.

Our study reported the prevalence and types of HPV, the age distribution of HPV infection, and the correlation between HPV types and the severity of pathological cervical lesions in Zhejiang, China, which would provide useful information for the development of cervical cancer screening and vaccination. In addition, male subjects were rarely included in the study to show the infection rate and type of HPV in males. Gender differences were analyzed from different research perspectives to explore the impact of gender on HPV infection, so as to promote the development of male HPV screening and vaccination. However, our study still has a few limitations. First, no distinctions between transient and persistent HPV infection were made. Future studies should investigate the natural history of HPV infection in detail. Second, males and females were not sexual partners; hence, HPV infection in both partners was not assessed. Sexual partners of HPV-infected patients should be encouraged to participate in the examination and treatment. Third, the correlation between HPV infection and other potential risk factors was not evaluated; hence, future studies should focus on collecting more sample information for further investigation.

Conclusion

In summary, this article analyzed the prevalence and types of HPV infection, the age distribution of HPV infection, and the correlation between HPV types and the severity of pathological cervical lesions in Zhejiang Province, China, which would provide useful information for the development of cervical cancer screening and vaccination. The study synthesis results will be useful for the development of public health policy. We believe the 9-valent HPV vaccines are more suitable for people in the Zhejiang province. It is necessary to carry out regular cervical cancer screening such as HPV in middle-aged and elderly females.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics Statement

This study was approved by the ethics committee of the Zhejiang Provincial People's Hospital, and the reference number was QT2022281. And this study complied with the Declaration of Helsinki. Written informed consent from the patients was waived due to the retrospective nature of the study. The study confirmed that the data was anonymized or maintained with confidentiality.

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Author Contributions

WYC and WJT analysed the study data and wrote the initial draft. WJM and GQ collected and managed the study data. LW, TXH, and QW provided resources and clinical oversight, and edited the report. WYC presented data visualization. TY worked on the study design, project administration, critical review and revision. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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