BRIEF REPORT



Influence of COVID-19 pandemic on prevalence and genotype distribution of HPV in cervical cancer screening population

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Abstract

Background Human Papillomavirus (HPV) DNA screening was a crucial element in the fight against cervical cancer and had been adopted in many countries, including China. However, the onset of the COVID-19 pandemic in March 2020 disrupted this program significantly.

Methods The aim of this study is to investigate the prevalence and distribution of HPV genotypes among the population undergoing cervical cancer screening during the pandemic period. From January 2017 to December 2022, Peking Union Medical College Hospital gathered 45,496 cervical swabs from individuals undergoing cervical cancer screening. These samples were analyzed to detect fifteen high-risk HPV (HR-HPV) DNA types and a combination of two low-risk HPV (LR-HPV) types.

Results The study revealed an overall infection rate of 11.24% (5,114/45,496), with 11.06% (5,032/45,496) of individuals infected with HR-HPV. The number of HPV screening patients and the infection rates of HPV, HR-HPV, LR-HPV, multiple genotype HPV (M-HPV), and single genotype HPV (S-HPV) during the pandemic were lower than those observed before the pandemic. Moreover, the age group with the highest percentage of infected individuals was under 45–49 years, with HPV52, HPV58, HPV16, and HPV51 being the most prevalent genotypes. Notably, HPV66 emerged as the fifth most commonly detected genotype during the pandemic. Additionally, among the eleven age groups examined, women under 25 exhibited the highest detection rate, with HPV52 and HPV16 infection rates exceeding those observed in the pre-pandemic period.

Conclusions The findings of this study offer significant insights for shaping HPV prevention strategies and enhancing cervical cancer screening initiatives in China following the epidemic.

Keywords Human papillomavirus, HPV genotype, COVID-19

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Introduction

Oncogenic human papillomavirus (HPV) infection has been identified as a causative factor for cervical cancer, as well as other anogenital malignancies including cancers of the vulva, vagina, penis, anus, head and neck [1]. Cervical cancer ranks as the fourth most prevalent cancer among women globally and is the second most common cancer in women aged 15 to 44 years, with an estimated 604,127 new cases and 341,831 deaths reported in 2020 [2]. In China, the most populous nation, cervical cancer is the third leading cause of cancer related mortality among women in the 15 to 44 age group. Annually, it is estimated that 109,741 women are diagnosed with cervical cancer, and 59,060 (53.82%) of these women succumb to the disease, highlighting its substantial burden, particularly in associated with HPV [3]. To date, more than 200 HPV genotypes have been identified, with approximately 40 originating from the female genital tract. Persistent infection with HPV, particularly high-risk types, can lead to the development of cervical cancer [4]. Notably, HPV16 and HPV18 are responsible for nearly 70% of cervical cancers cases, while five other high-risk types (HPV31, HPV33, HPV45, HPV52, and HPV58) contribute to 15% [5]. Furthermore, substantial geographical variation exists in the prevalence and distribution of HPV infections [6]. The disease risk associated with HPV infection also varies significantly based on the genotype, persistence, and duration of the infection [7-9]. Consequently, identifying the genotype and monitoring the persistence of HPV infection are of considerable clinical importance.

In 2019, the World Health Organization initiated a Cervical Cancer Elimination Strategy aimed at decreasing the incidence of cervical cancer from approximately 15 cases per 100,000 women to fewer than 4 cases per 100,000 by the year 2030, leveraging effective cervical screening and HPV vaccination programs [9]. However, in China, cervical cancer screening coverage and vaccination rates remain low, primarily due to the country's large population and the uneven distribution of healthcare resources. However, the COVID-19 pandemic, declared in March 2020 following the outbreak of SARS-CoV-2 [10], has had a profound impact on global health systems, including the Cervical Cancer Elimination Strategy [11, 12]. In response to the outbreak, the Chinese government implemented stringent measures, such as physical distancing, cessation of non-essential activities and instituting quarantine protocols, which may have contributed to a reduction in HPV transmission. This article examines the effects of the pandemic on the prevalence and genotype distribution of HPV within the in cervical cancer screening population in China, aiming to provide empirical data to support for cervical cancer prevention and control efforts in the post-pandemic context.

Materials and methods Study subject

Clinical specimens from 45,496 healthy female individuals, aged 19 to 86 years, were collected at the Physical Examination Center of Peking Union Medical College Hospital (PUMCH) between January 2017 and December 2022. The inclusion criteria for participation were as follows: (1) age 18 years or older; (2) good physical and mental health; (3) not pregnant; (4) no history of a total hysterectomy or cervicectomy. This study received approval from the Ethics Committee (I-23PJ1016).

Sample collection and DNA extraction

Exfoliated cells were collected by rotating a sample brush clockwise three to five times in the cervical region. The cells were subsequently transferred to sterile sample tubes containing a cell preservation solution and stored at 4 °C. In accordance with the manufacturer's protocol, DNA was extracted from the cervical cells utilizing a DNA extraction kit on an automated nucleic acid extraction workstation (Liferiver Biotechnology Co., Ltd., Shanghai, China).

HPV DNA genotype testing

The HPV genotyping Real-time PCR kit (Liferiver Biotechnology Co., Ltd., Shanghai, China) was employed for the detection of HPV DNA genotypes. Approximately 4 µL of the extracted DNA was subjected to amplification using the SLAN 96P Real-time PCR system (Hongshi Medical Technology Co., Ltd., Shanghai, China) in accordance with the manufacturer's protocol. The thermal cycling conditions were as follows: an initial heating step at 94 °C for 2 min, followed by 40 cycles of denaturation at 93 °C for 10 s and annealing at 62 °C for 31 s, with subsequent single-point fluorescence detection. Fifteen HR-HPV DNA types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 82) and a combination of two LR-HPV types (6/11) were identified. The presence of any of the 17 HPV DNA types was confirm in samples reported as HPV positive. Positive and negative controls were employed throughout the experiment to ensure quality control.

Statistical analysis

The prevalence rates of HPV infection, both overall and type-specific, were determined by calculating the percentage of cases that tested positive for HPV among all tested cases. Participants were stratified into nine age groups (<25, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, and >70 years). Differences between these groups were assessed using contingency tables and the chi-square test (χ^2). For all statistical analyses, *p*-values were two-sided, and a *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using R software, version 4.1.1.

Results

Overall HPV infection in healthy females

A total of 45,496 female participants were in the study to detect HPV DNA. The age range of the participants varied from 19 to 86 years, with a mean age of 45.61 years. The majority of the participants were aged 45 to 49 years (15.91%, 7,237/45,496), followed by those aged 50 to 54 years (14.60%, 6,643/45,496) (Fig. 1A). Among the 45,496 participants, 5,114 women tested positive for HPV, resulting in an overall infection rate of 11.24%. The number of participants who tested positive for HPV prior to the pandemic (January 2017 - December 2019) was 3,818, accounting for approximately 11.70% of the total participants. In contrast, during the pandemic period (January 2020 - December 2022), there were 1,296 cases of HPV positivity, representing approximately 9.88% of the total participants (P < 0.05, Table S1). Compared to the same period in 2017-2019, HPV infection rates showed a significant decline during 2020-2022 (Fig. 1B). A statistically significant difference in HPV infection prevalence was observed among healthy females from 2017 to 2022 (P < 0.05) (Fig. 2A). When examining prevalence across age groups, HPV infection rates varied significantly. The highest overall prevalence of HPV infections was observed in individuals under 25 years of age, at 21.87% (75/343) (Fig. 2B).

Prevalence of type-specific HPV

An analysis of the distribution of HPV genotypes revealed that 9.82% of the population was infected with HR-HPV during pandemic, which was lower than the infection rate observed in the pre-pandemic period (P<0.05, Table S1 and Fig. 2A). Compared to the pre-pandemic period, the detection rates of HPV16, 52, 59, and 68 significantly decreased (P < 0.05), whereas the detection rates of HPV18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 66, and 82 did not show significant changes (Table S1). During both the pre-pandemic and pandemic periods, the prevalence of HPV genotypes was observed in descending order, with HPV52 being the most prevalent, followed by HPV58 (Fig. 3). Among individuals who tested positive for HPV during the pandemic, the prevalence of the genotypes targeted by the bivalent HPV vaccine (HPV16/18) was found to be 16.59% (215/1,296). Furthermore, the prevalence of genotypes targeted by the quadrivalent HPV vaccine (HPV6/11/16/18) was 18.06% (234/1,296), while the prevalence of genotypes included in the 9-valent HPV vaccine (HPV16/18/52/58) was 57.57% (746/1,296). Importantly, the prevalence of genotypes targeted by the bivalent, quadrivalent, and 9-valent vaccines was significantly lower compared to the pre-pandemic period (P<0.05, Fig. 2A).

Distribution of single genotype infection and multiple genotype infections

An HPV DNA screening indicated that the infection rate for single genotype infections was 82.26%, which was significantly higher than the prevalence of multiple infections (P < 0.05) (Fig. 4A). The incidence of multiple infections in this study included double HPV infections (14.27%, 730/5,114), triple HPV infections (2.74%, 140/5,114), and quadruple HPV infections (0.55%, 28/5,114) as illustrated in Fig. 4A. Further analysis of multiple infections identified HPV52/58, HPV16/52, and HPV51/52 as the three most prevalent co-infection types, as detailed in Supplement Table 2. During the pre-pandemic period, HPV16/52 type was identified as the most prevalent type, whereas during the pandemic period, HPV56/66 emerged as the predominant type. This investigation of the pre-pandemic period revealed an increase in the prevalence of single HPV infections, rising from 81.98% prior to the pandemic to 83.10% during the pandemic (Fig. 4B and C).

Age-specific infection rate of HPV

The prevalence of HPV infection demonstrated statistically significant variation across different age groups, with single infections exhibiting markedly higher rates of HPV infection compared to multiple infections across all eleven age groups (P < 0.01). The distribution of HPV infection by age demonstrated a bimodal pattern for genotypes such as HPV16, HPV52, HPV58, and HPV59 (Supplement Fig. 1). Notably, women under the age of 25 had significantly higher rates of both single and multiple infections compared to other age groups in both the prepandemic and pandemic periods (Fig. 5A). Furthermore, there was notable variation in the prevalence of different HPV type among women across various age groups, both prior to and during the pandemic. Specifically, HPV16 and HPV52 exhibited significantly elevated infection rates among women under 25 years of age in comparison to other genotypes during this period. Similarly, HPV52 and HPV16 displayed considerably higher infection rates among women under 70 years of age relative to other genotypes, both prior to and during the pandemic. Additionally, HPV52 emerged as the predominant genotype across the remaining five age groups before and during the pandemic (Fig. 5B).

Discussion

HPV infection is a leading cause of cervical cancer, making cervical screening and HPV vaccination widely accepted as the most effective methods for early detection and preventing cervical cancer progression [13].



Fig. 1 Characteristics of HPV infection in women. (A) Age distribution of women across the entire study population. (B) Overall trend in years HPV screening visits and infection rates. HPV+, human papillomavirus infection; HR-HPV, high-risk HPV infection; LR-HPV, Low-risk HPV infection; M-HPV, multiple genotype HPV infection; S-HPV, single genotype HPV infection; 2-valent, genotypes targeted by the bivalent vaccines HPV infection; 4-valent, genotypes targeted by the quadrivalent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection



Fig. 2 Changes in infection rates and population prevalence before and after the pandemic. (A) HPV infection rates of pre-pandemic and the pandemic period. (B) Prevalence of HPV infection by age groups. HPV+, human papillomavirus infection; HR-HPV, high-risk HPV infection; LR-HPV, Low-risk HPV infection; M-HPV, multiple genotype HPV infection; S-HPV, single genotype HPV infection; 2-valent, genotypes targeted by the bivalent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-valent, genotypes targeted by the 9-valent vaccines HPV infection; 9-vale

Despite evidence that the HPV vaccine can protect against up to 90% of cervical cancer cases, vaccination coverage in low- and middle-income countries often falls short of the 80–100% target, largely due to the high cost of the vaccines. Moreover, vaccination of women already infected with HPV did not cause HPV elimination [14]. Consequently, screening remains the only feasible method for preventing infection. However, COVID-19 caused greater disruptions to cervical cancer screening programs than some of the most damaging natural



Fig. 3 Distribution of HPV genotypes over the period from 2017 to 2022

disasters [15]. There is little published data from low- and middle-income countries, and this study is a rare study exploration of HPV prevalence and genotype distribution in a cervical cancer screening population during COVID-19 pandemic in China. Prior to the pandemic, the prevalence of HPV and HR-HPV infections in the healthy population at PUMCH was recorded at 12.18% and 11.78%, respectively [16]. However, these figures declined to 9.88% and 9.82%, respectively, during the pandemic. This suggests that the implementation of lockdown measures in China significantly impacted the reduction of HPV transmission.

During the pandemic period, although the infection rates of HPV52, 16, 58, and 51 decreased, these types remained the most prevalent genotypes among both single and multiple infections in the healthy women analyzed. Notably, HPV52 was the most frequently detected type across various regions of China, with detection rates ranging from 4.23% to 5.64% [17–20]. However, the significance of this observation remains uncertain. A study by Yang et al. noted that HPV52 positivity decreased with the progression of cervical lesions, while individuals with invasive cervical cancer exhibited a higher positivity rate compared to those with a normal cervix [20]. In the present study, HPV52 was the most frequently detected genotype in both single and multiple HPV infections. Furthermore, HPV52 exhibited a bimodal age distribution, which aligns with previous research indicating the



Fig. 4 Human papilloma virus (HPV) infection types in healthy women. (A) High-risk human papilloma virus (HR-HPV) infection rates in 45,496 cases of healthy women from 2017 to 2022. (B) High-risk human papilloma virus (HR-HPV) infection rates in 32,375 cases of healthy women from 2017 to 2019. (C) High-risk human papilloma virus (HR-HPV) infection rates in 13,121 cases of healthy women from 2020 to 2022



Fig. 5 The prevalence of different types of HPV infections by age group. (A) The prevalence of single and multiple HPV types infection across different age groups. (B) The prevalence of HPV16, 51, 52, 56, 58 and 66 in different age groups

highest rate of HR-HPV infection in individuals aged 30-39 and the highest incidence of cervical cancer in women aged 50-59 [21-23]. HPV66 has been previously suggested as a genotype characteristic of Northern China [24]. Prior to the pandemic, HPV66 ranked seventh among healthy women [16], but during the pandemic, it rose to the fifth position in our study. Additionally, HPV56/66 emerged as the most prevalent genotypic combinations in cases of multiple HPV infection during the pandemic period, whereras, HPV16/52 type were the most prevalent during the pre-pandemic period. In contrast to HPV52, the rate of HPV66 infection exhibited an upward trend after the age of 25-29 and remained stable at 20% until the 55–59 age group. Numerous studies have reported the prevalence of HPV66 to range from 4.6 to 36.5%, primarily in premalignant lesions that do not progress to cancer [25-28]. This variability may be attributed to the rapid clearance of HPV66 infections following initial contact, which could reduce its potential for carcinogenesis [29]. Consequently, further investigation is warranted to explore the implications of HPV66 in terms of persistent and progressive cancer.

The correlation between multiple infections and the onset of cervical cancer, compared to single infections, remains inconclusive. Some studies propose that the simultaneous presence of multiple types of HPV infections may collectively contribute to the development of cervical cancer [30, 31]. Conversely, other studies suggest that these infections may occur randomly and independently, potentially leading to cervical disease without a discernible cumulative effect. Furthermore, the influence of multiple infections on the risk of high-grade squamous intraepithelial lesions does not seem to surpass the additive effect [32, 33]. A single high-risk HPV infection is prevalent throughout the female genital tract, although the viral load tends to be lower compared to cases involving multiple high-risk HPV infections [34]. Similar to the previous study, single infection were much more prevalent than multiple infection during both pre-pandemic and pandemic stages in present study. Further analysis is required to investigate the association between infection types and cervical carcinogenesis.

In agreement with the result observed before the pandemic, a significant peak in HPV prevalence was observed below the age of 25. This was followed by a discernible moderation in middle-aged groups, with a fluctuating rise observed in individuals over 45 years old. One potential explanation for the elevated prevalence of HPV in young women could be attributed to their frequent sexual activity and the higher number of childbirths, which can lead to increased risk of cervical injuries and, consequently, a higher likelihood of HPV infection [35–37]. It is worth noting that HPV infection rate below the age of 25 increased by 5.74% compared

to the pre-pandemic stage. This rise includes both single and multiple infections, with HPV16 and HPV52 exhibiting significantly higher infection rates in women under 25 years compared to other demographic groups. Thus, there is an urgent need for HPV vaccination campaigns and the dissemination of information and education regarding HPV infection. Due to COVID-19 outbreak, the HPV vaccination rate among adolescents significantly decreased during the pandemic [38, 39]. In our study, the detection rate of HPV genotypes covered by both bivalent (HPV16/18) and quadrivalent (HPV6/11/16/18) decreased to 16.59% and 18.06%, respectively, compared to the pre-pandemic stage. This decrease is closely related to the overall reduction in HPV infection rates observed during the pandemic. However, the detection rate of HPV16/18/52/58 was 57.56%, representing a 2.77% increase compared to the pre-pandemic period. These findings highlight the importance of restoring HPV vaccination coverage and preventing potential longterm consequences in the post-epidemic era.

The present study had several limitations. Firstly, it was conducted at a single center, which was a single hospital and was retrospective in nature. To enhance the validity of the findings, a multicenter study should be conducted to validate the results. Secondly, the study solely focused on examining the impact of COVID-19 on the prevalence and distribution of HPV genotypes among healthy women. It did not include patients from obstetrics, gynecology, or dermatology departments.

Conclusion

The present study provides insights into the impact of the COVID-19 pandemic on the HPV infections epidemiology among healthy women in Beijing, China. Our findings indicate a decrease in overall HPV infection rates, including HR-HPV, LR-HPV, M-HPV, S-HPV, HPV bivalent vaccine targeting HPV16/18, HPV quadrivalent vaccine targeting HPV6/11/16/18, and 9-valent HPV vaccine targeting HPV16/18/52/58 compared to the prepandemic period. Additionally, our results reveal that HPV52, 16, 58, and 51 remain the most prevalent genotypes among single and multiple infections in healthy women, with HPV66 showing an increased prevalence. Furthermore, it is noteworthy that the prevalence of HPV infection is particularly pronounced among females aged under 25 years, with a simultaneous rise in HPV52 and HPV16 incidence rates. The findings have significant implications for developing effective strategies to prevent HPV transmission and for implementing cervical cancer screening initiatives in China following the epidemic.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12985-024-02497-6.

Supplementary Material 1: Supplemental Fig. 1. Analysis of the infection rates of HPV subtypes in different age groups.

Supplementary Material 2: Supplement Table S1. Distribution of HPV types among the 45,496 healthy females.

Author contributions

J.Y. conceptualized and designed this study; X.L., and B.C., analyzed data; J.Y., X.L., H.Z., Z.Y., R.G., and S.L. collected and drafted the manuscript; J.Y., Y.X., and J.W. critically revised the manuscript. All authors read and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The protocol of this study was reviewed and approved by the Ethics Committee of the PUMCH (Approval Number: I-23PJ1016).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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