Original Article

Study on the prevalence and subtypes of human papillomavirus infection among women in the Xuhui District, Shanghai City, China

Han Liu[1#], Chao Zeng[2#], Mingming Jiang[1], Yue Dai[1], Minyi Xu[1], Fangfang Zhou[1], Yaling Wang[1], Alessandra Pulliero[3], Tomasz Sobierajski[4], Whitney Nesser[5], Motoki Matsuura[6], Lei Wang[1], Jiaying Wu[2], Muyuan Ji[7,8]

[1]Department of Clinical Laboratory, Shanghai Eighth People's Hospital, Shanghai, China; [2]Department of Laboratory Medicine, Jiading Branch of Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [3]Department of Health Sciences, University of Genoa, Genoa, Italy; [4]The Center of Sociomedical Research, Faculty of Applied Social Sciences and Resocialization, University of Warsaw, Warsaw, Poland; [5]Department of Applied Clinical and Educational Sciences, Indiana State University, Terre Haute, IN, USA; [6]Department of Obstetrics and Gynecology, Sapporo Medical University, Sapporo, Japan; [7]Department of Hematology and Oncology, Children's Hospital Affiliated to Shandong University, Jinan, China; [8]Department of Hematology and Oncology, Jinan Children's Hospital, Jinan, China

Contributions: (I) Conception and design: H Liu, L Wang, C Zeng; (II) Administrative support: L Wang, M Ji; (III) Provision of study materials or patients: H Liu, J Wu, Y Wang; (IV) Collection and assembly of data: M Jiang, Y Dai, M Xu; (V) Data analysis and interpretation: H Liu, F Zhou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Lei Wang, MMed. Department of Clinical Laboratory, Shanghai No. 8 People's Hospital, No. 8 Caobao Road, Xuhui District, Shanghai 200235, China. Email: wolei6610@126.com; Jiaying Wu, MB. Department of Laboratory Medicine, Jiading Branch of Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, No. 800 Huangjia Garden Road, Shanghai 201803, China. Email: 364578151@qq.com; Muyuan Ji, MMed. Department of Hematology and Oncology, Children's Hospital Affiliated to Shandong University, Jinan, China; Department of Hematology and Oncology, Jinan Children's Hospital, No. 23976 Jingshi Road, Jinan 250000, China. Email: jimuyuan@126.com.

Background: Human papillomavirus (HPV) can cause various gynecological diseases, create a long-term inflammatory immune microenvironment, and induce the occurrence of cervical tumors. However, the prevalence of HPV is species-specific in different eras or in different countries and regions. This paper aimed to investigate the characteristics of HPV infection in the Xuhui District, Shanghai City, China.

Methods: We collected HPV data from 6,760 female testers, focusing on the younger population for data analysis. We focused more on the HPV subtypes to which young women were susceptible, performed t-Distributed Stochastic Neighbor Embedding (TSNE) analysis to screen for characteristic subtypes, and compared the prevalent subtypes lacking effective vaccine protection.

Results: HPV infection exhibited a trend of affecting a younger population, and eight subtypes were more likely to occur in young people. HPV43, 51, 53, and 59 showed a higher incidence and lacked vaccine protection. We performed TSNE dimensionality reduction analysis to organize the HPV data. The results indicated that HPV16, 18, and 51 are characteristic subtypes in the younger population. The Thinprep cytologic test (TCT) also revealed that the infection with HPV43, 51, 53, and 59 also triggers significant pathological phenotypes.

Conclusions: HPV51 is a subtype that occurs more frequently in young women, can induce a variety of significant pathological features, and lacks effective vaccine protection. This study inspires us to take measures to deal with HPV rejuvenation and conduct research on vaccines for specific HPV subtypes.

Keywords: Human papillomavirus (HPV); vaccine; t-Distributed Stochastic Neighbor Embedding (TSNE)

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Introduction

According to the World Health Organization (WHO), human papillomavirus (HPV) is responsible for nearly all cases of cervical cancer, which seriously endangers women's health (1). As well as a significant number of cases of other types of cancer, such as anal cancer, oropharyngeal cancer, and genital cancer in both men and women (2-7). In addition to cancer, some types of HPV can cause genital warts, which can be a sign of infection with a more high-risk strain of HPV that could potentially lead to cancer (8-11). The commonest types of HPV in women from Mainland China were HPV16, 52, 58, 18, and 33. Central China had the highest overall HPV prevalence. HPV16 was the commonest type in all the regions except in South China and East China (12). Due to its large population, China accounted for 11.9% of cervical cancer deaths, and 12.3% of global cervical cancer disability-adjusted life-years (DALYs) in 2017 (13).

International Agency for Research on Cancer, identifies 15 genotypes as high-risk oncogenic (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82) (14), and low-risk HPV types: 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108 (these subtypes are less likely to cause cancer but can cause benign warts and lesions) (15-17). HPV16 and HPV18 are the types most frequently associated with cervical lesions. More than 50% of cervical neoplasms are caused by HPV16 infection and about 20% by HPV18 (18).

HPV infections are common globally, but the prevalence and distribution of HPV types can vary by region and population. HPV16 and 18 are being more common in North America and Europe, while HPV52 and 58 are more common in Asia (19-21). This can be attributed to cultural and socioeconomic factors, differences in sexual behavior and HPV vaccination rates (22-25).

Highlight box

Key findings

- Human papillomavirus (HPV) subtypes, age, gender, HPV model, Thinprep cytologic test results. This study found that HPV51 is a subtype that occurs more frequently in young women.

What is known and what is new?

- HPV is high-risk and easy to cause cervical cancer.
- Currently, the vaccine does not cover HPV models that are prevalent in younger populations.

What is the implication, and what should change now?

- HPV51 should be urgently targeted by next-generation vaccines.

Several studies have shown that certain HPV subtypes are inversely associated with age, meaning that they are more commonly found in younger populations and their prevalence decreases with age (26-29). The reasons behind the inverse association between certain HPV subtypes and age are not fully understood, but from a sociological perspective, it is believed that differences in sexual behavior, immune function, and exposure to other types of HPV may play a role (30).

Studies have also reported that teenagers in developed regions may tend to be more open and casual than teenagers in developing regions (31,32). Therefore, a report on HPV dynamics focusing on teenagers in large cities will offer great guiding significance for future medical policy formulation.

This study also found that the most common types of HPV in China were HPV16, 52, 58 (33). Since to implement the most effective health policies and planning tasks for preventive health care—the need for research on HPV subtypes is very high, an analysis of HPV detection data in Shanghai, which is one of the biggest and most famous cities in China, was conducted. Research on HPV prevalence in this region has a certain guiding significance for China and even Asia. The study's main objective was to check how specific HPV subtypes vary according to the age of the women included in the study. We present this article in accordance with the MDAR reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1491/rc).

Methods

Study design

From December 31, 2020, to June 4, 2022, we collected detection results from 6,760 female testers in Jiading District, Shanghai. HPV genotyping, t-Distributed Stochastic Neighbor Embedding (TSNE) clustering and Thinprep cytologic test (TCT) information were used for data analysis.

HPV genotyping

HPV genotyping was determined using reverse transcription polymerase chain reaction (PCR). The experiments were carried out in X-level laboratories using Human Papillomavirus Genotyping Kits (Yaneng, Shenzhen, China), and the Automatic Nucleic Acid Molecular Hybridization Instrument (YN-H18) (Yaneng) was used for detection.

TSNE clustering

The first column of the chart was set to the sample number and the first row to age and HPV subtypes. Next, the TSNE R package was used to perform dimensionality reduction analysis on the table, and the k_{means} R package was applied to cluster the dimensionality reduction results (infection is 1, and non-infection is 0). The analysis was performed using the latest version of R (4.2.0).

TCT information

Some HPV testers were detected by TCT. The TCT results we collected were provided by the Department of Pathology. The processing of pathological tissue complied with the ethical rules of the hospital. All detection results were kept strictly confidential. We grouped the population by type of infection and the ages of those tested.

Statistical analysis

The statistical significance of the data was calculated using Prism 8.0 (GraphPad). We applied the unpaired two-tailed Mann-Whitney *U* test (nonparametric) to compare the significance of differences between different groups. P value <0.05 was considered as to be statistically significant.

Ethical considerations

The researchers who analyzed the data were informed of the purpose of the study and were bound by confidentiality. The published data does not contain any sensitive information that would identify the individuals from whom the samples came. All analyses are aggregate, making it impossible to attribute the data to individuals. The activities undertaken in the analysis were carried out by applicable law and the ethics of the research profession. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Shanghai Eighth People's Hospital (No. 2023-061-21) and individual consent for this retrospective analysis was waived.

Results

Prevalence of HPV subtypes and age

A total of 6,779 samples were classified by gender, detection results, and methods (*Figure 1A*). For many female subjects, the HPV-positive rate was 24.5%, which was also higher than that in 2015 (22.6%). Compared with physical examination or hospitalization, outpatient clinics are still the most important method of HPV detection. Considering the scarcity of male samples, our subsequent work involved statistical analysis of the female samples (*Figure 1B*).

We divided the samples into five age groups with 10-year intervals, namely <20, 20–29, 30–39, 40–49, and ≥50 years. The positivity rate varied widely among groups, especially the younger age group, which contributed to a higher positivity rate and more diverse infection subtypes (*Figure 1C*). These results suggest that the infection situation showed the characteristics of a younger HPV-positive population. We then analyzed the age changes in the number of HPV infection subtypes. The results showed that with the diversification of HPV infection subtypes, the age of the patients exhibited a decreasing trend (*Figure 1D*).

We also compared the ages of patients infected with each specific subtype of HPV with that of healthy donors (Figure S1). The results indicated that eight HPV types had a significant negative correlation with age, namely 16, 18, 43, 51, 56, 59, 6, and 73 (*Figure 1E*). Together, the above data indicate that HPV tends to appear in younger individuals and that teenagers are more likely to be infected with more HPV types.

The nine-valent vaccine

The nine-valent vaccine is currently the most effective in China and can induce memory immunity against nine HPV subtypes. As shown in *Figure 2A*, the Venn diagram indicated that only three of the nine HPV subtypes are younger HPV, this indicates that these three subtypes are more likely to occur in young people, namely HPV6, 16, and 18. However, HPV43, 51, 56, 59, and 73 cannot be targeted by the nine-valent vaccine.

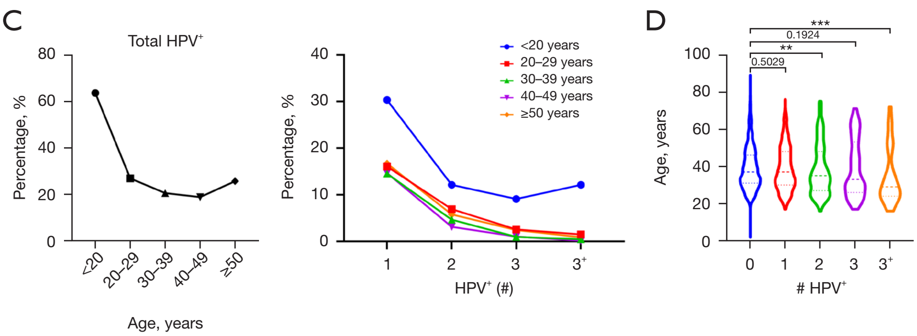
We then listed the number of 23 HPV-positive populations in descending order (*Figure 2B*). The nine-valent vaccine protects against some high-incidence subtypes, but HPV51, 59, 43, and 56 were missed. We also counted the cross-infection of HPV with different subtypes (*Figure 2C*). People with one of these four types of HPV are also susceptible to other types of HPV. Patients under the age of 30 years infected with HPV43, 51, 56, and 59 also exhibited characteristics of cross-infection with each other (*Figure 2D*). Together, these data suggest that the HPV43, 51, 56, and 59 subtypes are more common in teenagers and escape protection from the nine-valent vaccine.

A

Gender	Number / rate	Positive	Methods of positive samples detected		
			Outpatient clinic	Physical examination	Hospitalized
Male	19 (0.28%)	4 (21.05%)	4 (100%)	–	–
Female	6,760 (99.72%)	1,657 (24.50%)	1,592 (96.08%)	15 (0.91%)	50 (3.01%)

B

Age (years)	Total	The number of types of HPV⁺ (#)				
		0	1	2	3	3^+
<20	33	12	10	4	3	4
20–29	1,420	1,037	228	98	36	21
30–39	2,384	1,893	346	111	23	11
40–49	1,469	1,191	215	46	15	2
≥50	1,247	926	208	72	30	11



E

Incidence ↔ age	Types of HPV
Positive	2; HPV53, 81
No correlation	13; HPV11, 31, 33, 35, 39, 42, 45, 52, 58, 66, 68, 82, 83
Negative	8; HPV16, 18, 43, 51, 56, 59, 6, 73

Figure 1 The HPV infection rate and number of infected subtypes are higher in the younger population. (A) Chart of gender, positivity rate, and sample collection method of the subjects. (B) Positive rate and number of infected subtypes by age group. (C) Dynamic curve of the HPV-positive rate and number of infection types in different age groups. (D) Violin plot of the number of HPV infection subtypes. (E) Chart of the age relationships for different HPV infection subtypes. **, P<0.01; ***, P<0.001. HPV, human papillomavirus.

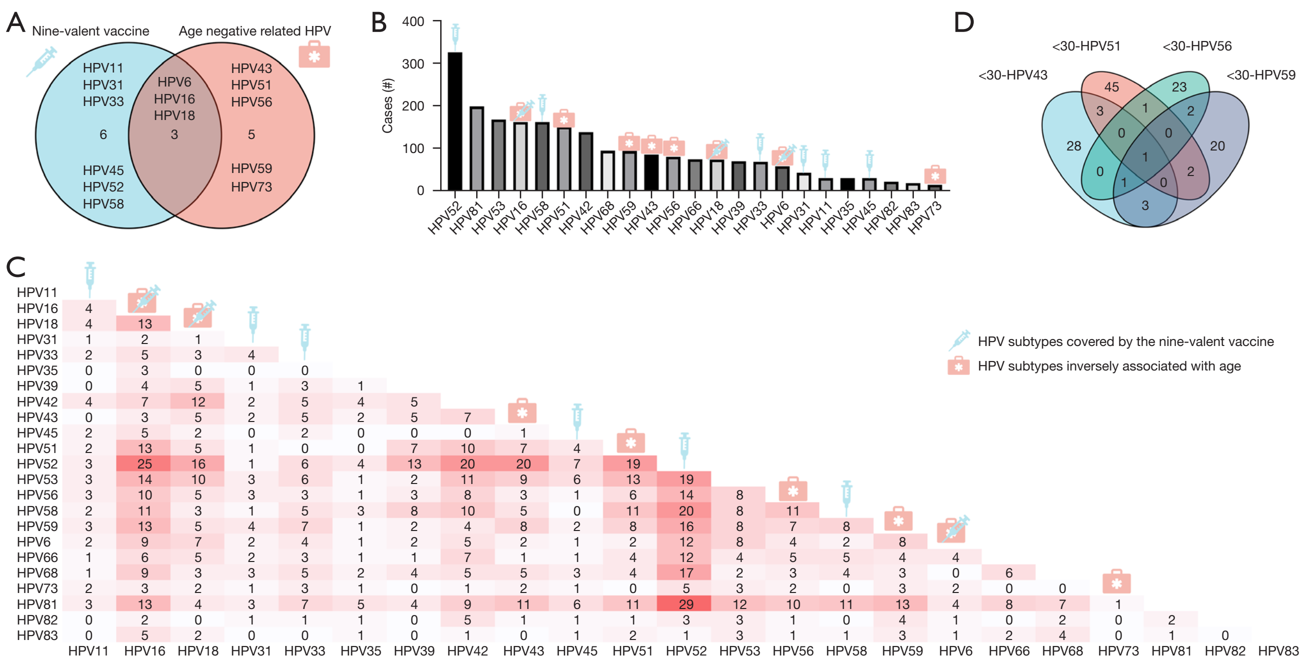


Figure 2 Analysis of HPV subtypes prevalent in the young population. (A) Venn diagram of the nine-valent vaccine and eight subtypes of HPV; (B) column of the number of cases of HPV infection by different subtypes; (C) chart of the number of HPV subtype cross-infection cases; (D) Venn diagram of HPV43, 51, 53, and 59 infection in people under 30 years old. HPV, human papillomavirus.

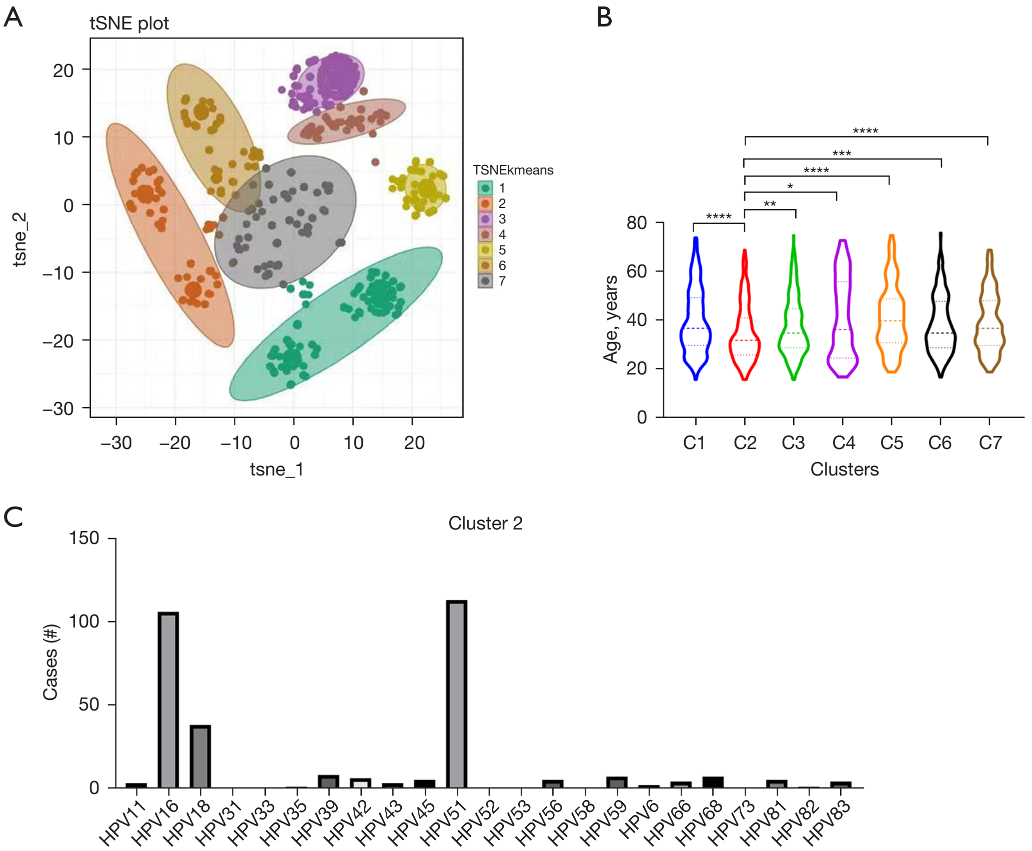


Figure 3 TSNE analysis of HPV-infected population. (A) TSNE cluster map for the HPV-infected population; (B) violin plot of the age distribution of different subclusters; (C) characteristic HPV subtypes of subcluster 2 infection. *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001. TSNE, t-Distributed Stochastic Neighbor Embedding; HPV, human papillomavirus.

Effectiveness of TSNE cluster analysis

The various HPV subtypes are classified into two main categories: high-risk and low-risk. However, due to the influence of geography, culture, and economy, the incidence of HPV subtypes and their impact on clinical outcomes are complex. We scaled HPV-negative to 0 and HPV-positive to 1. TSNE cluster analysis was performed on 1,657 HPV-positive patients (*Figure 3A*). The results indicated that HPV patients were divided into seven subclusters in the TSNE graph. We analyzed the age distribution of the different subclusters, and the data showed that the mean age of subcluster 2 was significantly lower than that of the other groups (*Figure 3B*). We also counted the HPV infection subtypes in the different subclusters (*Figure 3C* and Figure S2). For subcluster 2, HPV16, 18, and 51 are the characteristic HPV infection subtypes. Among them, HPV16 and 18 are covered by the nine-valent vaccine but HPV51 is not. HPV51, 16, and 18 are the hallmark subtypes of the young population.

TCT results

We collected the TCT results from some HPV patients and obtained their clinical status to display the data in descending order of age (*Figure 4*). These four HPV infections (HPV43, 51, 56, and 59) can still cause pathological symptoms such as vaginitis, irregular menstruation, and abnormal bleeding in younger people. Collectively, these diagnoses indicate that HPV43, 51, 56, and 59 can trigger inflammation and damage health.

Discussion

In this study, we collected and analyzed HPV detection data in Xuhui District, Shanghai from 2020 to 2022. The results

HPV43

Number	Age (years)	Symptoms
Case #1	46	Lower abdominal pain
Case #2	45	Cervical intraepithelial neoplasm, grade I
Case #3	38	No obvious symptoms, need further investigation
Case #4	35	No obvious symptoms, need further investigation
Case #5	34	Human papillomavirus infection
Case #6	32	Irregular menstruation
Case #7	32	No obvious symptoms, need further investigation
Case #8	29	Irregular menstruation; vaginitis
Case #9	29	Vaginitis
Case #10	29	Vaginitis
Case #11	26	No obvious symptoms, need further investigation
Case #12	25	Vaginitis; chronic cervicitis
Case #13	24	Vaginitis
Case #14	24	Vaginitis
Case #15	20	Irregular menstruation
Case #16	17	Vaginitis

HPV53

Number	Age (years)	Symptoms
Case #1	74	Uterine prolapse degree I
Case #2	64	Vaginitis
Case #3	64	Cervical intraepithelial tumor grade I
Case #4	54	No obvious symptoms, need further investigation
Case #5	50	Abnormal uterine bleeding; cervical polyps
Case #6	45	Menopause and perimenopausal disorders
Case #7	42	Vaginitis
Case #8	41	No obvious symptoms, need further investigation
Case #9	40	No obvious symptoms, need further investigation
Case #10	39	Abnormal uterine bleeding
Case #11	37	Vaginitis
Case #12	35	No obvious symptoms, need further investigation
Case #13	33	No obvious symptoms, need further investigation
Case #14	31	No obvious symptoms, need further investigation
Case #15	30	Human papillomavirus infection
Case #16	29	Vaginitis; with intrauterine contraceptive device
Case #17	28	Vaginitis
Case #18	28	Irregular menstruation
Case #19	27	Vaginitis
Case #20	27	Vaginitis; chronic cervicitis
Case #21	25	Irregular menstruation
Case #22	17	Vaginitis

HPV51

Number	Age (years)	Symptoms
Case #1	59	Cervical inflammatory disease; abdominal pain
Case #2	57	Vulvar pus
Case #3	55	Lower abdominal pain
Case #4	50	Stomach ache
Case #5	41	Abnormal uterine bleeding
Case #6	41	Chronic cervicitis; vaginitis
Case #7	41	Cervical inflammatory disease
Case #8	38	No obvious symptoms, need further investigation
Case #9	37	No obvious symptoms, need further investigation
Case #10	35	Vaginitis
Case #11	35	Abnormal uterine bleeding
Case #12	34	Gynecological examination; with intrauterine contraceptive device
Case #13	34	Cervical intraepithelial neoplasm, grade I
Case #14	34	Stomach ache
Case #15	32	Pelvic inflammatory disease in women
Case #16	32	Vaginal intraepithelial neoplasia grade III [VAIN grade III]; vaginal mediastinal surgery
Case #17	29	Vaginitis
Case #18	27	Vaginitis
Case #19	27	No obvious symptoms, need further investigation; pregnancy status
Case #20	26	Vaginitis
Case #21	24	Abnormal uterine bleeding
Case #22	21	No obvious symptoms, need further investigation

HPV59

Number	Age (years)	Symptoms
Case #1	64	Cervical intraepithelial tumor grade I
Case #2	52	Lower abdominal pain; high blood pressure
Case #3	46	Irregular menstruation
Case #4	39	No obvious symptoms, need further investigation
Case #5	37	Human papillomavirus infection
Case #6	37	Abnormal uterine bleeding; having a contraceptive device in the uterus
Case #7	37	Endometrial polyps; human papillomavirus infection; uterine diverticulum
Case #8	35	Vaginitis
Case #9	32	Vaginitis; chronic cervicitis
Case #10	31	Vaginitis
Case #11	31	No obvious symptoms, need further investigation
Case #12	31	Scarred uterus; with intrauterine contraceptive device
Case #13	29	Irregular menstruation
Case #14	28	Cervical intraepithelial tumor grade I
Case #15	26	Vaginitis
Case #16	25	Vaginitis; cervical inflammatory disease
Case #17	23	No obvious symptoms, need further investigation
Case #18	22	No obvious symptoms, need further investigation

Figure 4 TCT results of some HPV43, 51, 53, and 59 patients. TCT, Thinprep cytology test; HPV, human papillomavirus.

showed that HPV infection exhibits a younger trend, and the infection subtypes of younger patients are more diverse. Some HPV subtypes that occur in young patients, such as HPV43, 51, 56, and 59, have a high infection rate and lack effective vaccine protection.

TSNE dimensionality reduction analysis of the ages and infection subtypes of infected patients revealed that young HPV patients present a subtype characterized by HPV16, 18, and 51. The seven subclusters resolved have their own characteristic subtypes, which may be used as a guideline for the typing of HPV patients. This indicates that the seven clusters in the TSNE graph have their own characteristic HPV subtypes. For example, the characteristic subtype of sub-cluster 2 is HPV16, 51, while the characteristic subgroup of subcluster 5 is HPV53.

Infection with the HPV43, 51, 53, and 59 subtypes can also result in pathological manifestations such as inflammation and abnormal bleeding, which highlights the urgency and necessity of studying vaccines against these HPV subtypes threatening teenagers.

The prevalence and spread of HPV involve various factors such as the regional economy, customs, religion, and geography (8-14). In some previous reports, it is generally believed that middle-aged and elderly women contributed the highest number of HPV cases (33-35). However, with the prevalence of sexually open lifestyles among young people, HPV infections appear to be increasing in teenagers. Teenagers are also more likely to be infected with multiple subtypes of HPV, possibly due to the lack of awareness of protection and the frequent switching of sexual partners (35,36). We observed that patients with the most subtypes were as young as 24 years old, and many patients younger than 20 years old also had five subtypes. The protection of teenagers requires a variety of medical technologies supported by sociological measures and education.

Normally, the risk of exposure to multiple HPV pathogens among women increases with age. However, our results revealed that there are already some HPV subtypes that are inversely associated with age. Although the idea that the nine-valent vaccines protect against multiple HPV infections is well-established, subtypes such as HPV43, 51, 53, and 59 that affect teenagers cannot be targeted by vaccines. Additionally, HPV51 is also recognized as a high-risk subtype. Notably, these HPV infections also cause inflammation, which may lead to cervical cancer in patients. It is widely recognized that the various subtypes of HPV are divided into two categories: high- and low-risk. However, these classification criteria are mainly based on clinical investigations from a decade ago or even earlier. With economic and social development, the threat of HPV to young people has also increased, and the standards and rules of the past may not be fully applicable to today's risks (37,38).

TSNE is a common dimensionality reduction algorithm that maps each data point to a corresponding probability distribution through a mapping transformation (39). We digitized the detection results and performed TSNE analysis with the digitized results and age as variables. Clustering results revealed seven distinct subclusters, each of which also had its own characteristic HPV subtypes. For example, the characteristic subtypes of subcluster 1 are HPV56, 58, and 81; subcluster 3 is HPV52; and subcluster 5 is HPV53. These characteristic subtypes can serve as an important reference for HPV classification. It is foreseeable that there must also be new features to be discovered in the populations of different subclusters and subclusters. This indicates that different clusters have potential characteristics that need to be further studied and discovered. For example, one of the characteristics of cluster 2 is the age of the infected population. Furthermore, this analytical approach also demonstrates that dimensionality reduction analysis commonly applied in bioinformatics can be used to classify numerous HPV patient samples to find therapeutic strategies targeting characteristic populations. Therefore, obtaining more patient information and adding additional variables to the sample is a prerequisite for precision medicine by classifying patients more accurately.

Conclusions

Some HPV subtypes, such as HPV43, 51, 53, and 59, seriously endanger the health of adolescents, and existing vaccines do not target these subtypes. Dimensionality-reduced clustering analysis of patient data information also revealed a trend of HPV subtypes among younger patients. In addition, the use of big data algorithms for digital management and accurate clustering of detection results may be the direction of HPV precision medicine. Moreover, it seems that HPV51 should be urgently targeted by next-generation vaccines.

The results indicated that HPV infection exhibits a younger trend, and some HPV subtypes that occur in young people are not protected by the nine-valent vaccine. TSNE analysis also indicated that HPV51 may be a new HPV subtype that harms the health of young people, and thus, research on vaccines for this subtype is urgently needed. Also, HPV43, 51, 53, and 59 triggered a variety of pathological symptoms. TSNE analysis technology can be used for the classification of big HPV data samples, which is expected to provide the basis for precision medicine. This study highlights the importance of youth protection and provides reflections on the analysis and management of big HPV data samples.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1491/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1491/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1491/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1491/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Shanghai Eighth People's Hospital (No. 2023-061-21) and individual consent for this retrospective analysis was waived.

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