Human papillomavirus infection rate, distribution characteristics, and risk of age in pre- and postmenopausal women

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Research article

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Abstract

Background

The incidence rate of cervical cancer is increasing yearly. The persistent infection of high-risk Human Papillomavirus (HPV) is the main factor leading to cervical cancer. HPV infection is double peak type. This study aimed at analyzing the HPV distribution characteristics, infection rate, and risk of age in pre- and postmenopausal women. So as to provide reference for the prevention of HPV infection and cervical cancer screening strategy.

Methods

A retrospective analysis of 4614 women who underwent cervical cytology, and HPV examination from January 2018 to October 2019 at the healthcare department of Wuhan Union Hospital was done. We explored the characteristics and distribution of HPV infections around the menopause, then comparing the infection rate of HPV in postmenopause and over 65 years old, in order to analyze the influence of different ages on HPV infection.

Results

Generally, the HPV infection rate was 13.10% (539 / 4115), whereby the high-risk subtype constituted 73.84% (398 / 539) of all positive cases. On the other hand, the HPV39 infection was more common in postmenopausal women; however, there was no significant difference in the distribution of the other types in the pre- and postmenopausal women (Insert p value). The first four subtypes were 52 / 53 / 58 / 16, respectively. The infection rate of HPV in patients with lower genital tract inflammation was significantly higher, \( P = 0.000 \), 95% CI: 1.911 (1.416, 2.580) compared with those without lower genital tract inflammation. The results further showed that there was no significant difference between pre- and postmenopausal women in terms of HPV infection rate, but more susceptible to high-risk HPV infection after the age of 65 (\( P = 0.041 \)). Except for 40 years old to menopause, the infection rate of high-risk HPV in this age group was different from that in postmenopause(\( P = 0.023, 0.729(0.555,0.957) \)), other age groups had no significant effect on high-risk HPV infection.

Conclusions

It was concluded that whether menopause has nothing to do with HPV infection. Moreover, the infection rate of high-risk HPV increases after 65 years of age; hence the cutoff screening age should be appropriately prolonged.

Trial registration: Retrospectively registered.

1 Background
Cervical cancer is the second most common cancer in women worldwide, it is estimated that in all over the worldwide about 1.4 million women are living with Cervical cancer (second most after the breast cancer)\(^1\). Currently, cervical cancer incidence rates present a bipolar pattern at age groups of 35–40 years and 65–80 years in many high-income countries\(^2\). A study in Costa Rica and Canada also showed a second peak in the infection rate curve for women over 55\(^3\). Practically all cervical cancer is caused by high-risk HPV infection\(^4\), and HPV is the most common sexually transmitted virus. Nearly all sexually active people will be infected in their lifetime, some of them may even be repeatedly infected. According to the cross-sectional study, approximately 25% – 50% of young sexually active women can detect human papillomavirus (HPV) in exfoliated cervical cells or vaginal swab samples, while according to the longitudinal study, this proportion is higher\(^5\).

According to the latest guidelines issued by the United States Preventive Services Task Force (USPSTF), previously fully screened women aged over 65 years old and presenting low-risk for cervical cancer are exempted from screening\(^6\). However, decreased immunity and the change of vaginal Microecology in postmenopausal women increases the risk of HPV infection, and negatively impacts its prognosis and clearance from the body, which makes it easier to develop into a persistent infection. Herefore, there is no consensus on when to terminate cervical cancer screening in postmenopausal women, the age and conditions for withdrawal from screening are debatable. This study investigated the Human Papillomavirus (HPV) distribution characteristics, infection rate, and risk of age in pre- and postmenopausal women who underwent cervical cytology, and HPV examination from January 2018 to October 2019 at Wuhan Union Hospital.

## 2 Methods

### Target population

In this study, 4614 women, aged 21-81 years (average 42.8 years old), who underwent cervical cytology and HPV examination at the healthcare department of Wuhan Union Hospital from January 2018 to October 2019 were selected. All the women had no conscious discomfort. The studied population of women was categorized as premenopausal and postmenopausal based on their age. Furthermore, the characteristics of HPV infection in women aged over 65 years were examined.

### 2.1 Experimental methodology

Cervical cytology using ultra cypress Liquid-based Cytologic Test (LCT) was employed to screen for cervical cancer and combined with HPV in the studied group of patients. Following LCT examination, 499 women were excluded due to bacterial, candida or trichomonas vaginalis infections; hence, 4115 women (2975 premenopausal and 1140 postmenopausal) women were eligible for HPV analysis. Classifiing in the light of the diagnostic system of Bethesda (TBS) in 2014\(^7\), 17 high-risk HPV types (16 / 18 / 26 / 31 / 33 / 35 / 39 / 51 / 52 / 53 / 56 / 58 / 59 / 66 / 68 / 82), and 11 low-risk HPV types (06 / 11 / 40 / 42 / 43
Those with abnormal cervical cytology and positive for high-risk HPV were referred to gynecological clinic.

2.2 Statistical analysis

The SPSS statistical software version 19.0 was used for analysis. In this study, categorical data were expressed as a percentage (%). The chi-square test was used for comparison between groups. The risk of HPV infection was analyzed by single factor Logistic regression analysis. *P* < 0.05 was deemed statistically significant.

3 Results

3.1 The HPV infection rate and distribution

The distribution of HPV infection before and after menopause is shown in Figure 1. It can be seen that except HPV39 subtype was more common in postmenopausal women, the spread of the other types were basically the same. Generally, 539 women test positive for HPV, representing 13.10 % positive rate, mainly high risk types, which was 73.84% (398/539). The four leading HPV subtypes in the studied population were HPV52, HPV53, HPV58, and HPV16, respectively (Figures 2 and 3).

3.2 Infection rate on HPV in women with inflammation

499 of 4614 physical examinees were found to be infected with bacteria, trichomonad or other inflammation. Through analysis, the results further revealed that the rate of HPV infection was significantly higher (1.911 times higher) in women with inflammation than in those without inflammation (*p*= 0.000; Table 1).

3.3 The HPV infection in pre- and postmenopausal women

Besides, there was no significant difference between the infection rates in pre- and postmenopausal women (*p*= 0.056; Table 2). Moreover, the postmenopausal population was further divided into two groups: postmenopausal to 65 years old and over 65 years old, comparing the three groups, the results revealed that women aged over 65 years were significantly more susceptible to h-rHPV infection (*P* = 0.024 / 0.012; Table 2).

3.4 Relative risk of h-rHPV infection in different age groups

1.1 The h-rHPV infection rate in the age bracket from 40 years old to menopause was 0.729 times of that in postmenopause, with remarkable diversity(*p*<0.05; Table 3), and the rest age groups had nothing to do with h-rHPV infection.
4 Discussion

In healthy women, the normal microflora and local immune function of vagina along with host and environment constitute a micro ecosystem of mutual restriction, coordination and dynamic balance. When the balance is disturbed, women become more vulnerable to pathogenic infections, which cause various reproductive and urinary tract diseases. Under these conditions, the HPV invades and colonizes the genital tract, and its persistence causes cervical cancer\[^8,9\].

A meta-analysis involving more than 1 million women in 194 articles\[^10\] showed that the total infection rate of HPV in women in different regions was 11.7% and the second peak of HPV infection occurred when they over 40, 45 or 55 years of age respectively. While, in the year 2005, a research on more than 8000 Costa Rican women reported that the infection rate of high-risk HPV beyond 65 years old was higher than that of 35–64 years old\[^3\]. Our findings were basically consistent with above that. In this study, the total infection rate of HPV was 13.10%, mainly high-risk positive. There was no significant difference in the infection rate of HPV before and after menopause, but the high-risk subtype of HPV was more likely to be infected after the age of 65.

Furthermore, a previous study on HPV infection of 20,000 women in the nine provinces of China showed that the HR-HPV infection rate of more than 2000 postmenopausal women (17.2%) is not significantly different from that of non-menopausal women (16.4%)\[^11\]. A study by Yang Yaping et al\[^12\] analyzed the data of cervical cancer screening in Wuxi and found a significantly higher HPV positive rate in aged 55–65 years. In a word, it did not make a distinction before and after menopause in the total HPV infection rate, but in a certain age group after menopause the infection rate is significantly higher than that in other age groups. The high HPV prevalence in postmenopausal women could be due to advancing age, gradual loss of ovarian function, wear thinning of vaginal mucosa, and lactobacilli reduction or even disappearance by degrees. However, the composition of vaginal microecology is significantly associated with HPV infection status\[^13\]. The clearance rate of HPV and the risk of HPV related tumor are also closely correlation with the composition of vaginal flora\[^14\]. Meanwhile, the gradual upward movement of the junction area between vagina and cervical squamous column, and the slow metaplasia of squamous epithelium. As a result, the reproductive system of postmenopausal women becomes more susceptible to carcinogenic factors and cancer-associated infections.

Elsewhere, various studies have indicated that the most common types of HPV are HPV16, HPV18, HPV52, and HPV58\[^10,15\]; however, in our study, the most prevalent HPV subtypes were HPV52, HPV53, HPV58, and HPV16. This inconsistency could be attributable to regional differences, and the varied pathogenicity among different HPV subtypes. Practice guidelines recommend vaginal biopsy examination in women who test positive for HPV16 and HPV18 (important carcinogenic drivers) regardless of cervical cytology results\[^16\].

This study also found that the infection rate of HPV in patients with genital tract inflammation was significantly higher than that in patients without inflammation. These results corroborate those of Meng
and Yang \cite{17,18} who reported similar findings. It may be due to the changes of inflammatory factors in local microenvironment impair proper immune functioning increasing the risk of HPV infection\cite{9}.

Current cervical cancer screening guidelines by the USPSTF\cite{2018} suggest that women over 65 years old who have no previous high-risk factors and fully screened can be excluded for further examinations. However, a study researched by Castañón fond that the protective strength of previous negative screening results on women from cervical cancer weared off as time goes by; the number of patients who stopped screening at 65 years old was twice as much as that at 75 years old\cite{19}. This study also showed that the HPV infection rate was significantly higher in women aged over 65 years.

Besides, China's National Cancer Center data demonstrate that new cases of cervical cancer in women aged over 60 years account for 23.76% of the total new cases, out of which 19.21% are 60-74-year-olds, and 4.55% are over 75 years old\cite{20}. Therefore, the practice guidelines can only be used as guidance, not as a substitute for clinical decision-making. In clinical work, the advantages and disadvantages should be weighed, and personalized screening should be carried out.

## 5 Conclusions

This study shows that there is still a certain infection rate of high-risk HPV after the age of 65, so we should reconsider the termination age of cervical cancer screening. On the other hand, there is no specific study on cervical cancer screening for women over 65 years old nowadays, so there is no direct evidence to determine the optimal screening age. With the increase of life expectancy in China, we should consider extending the age of termination of screening, and think over HPV typing as the primary screening method, which is of great significance for the prevention of cervical cancer in this group of people.

### Abbreviations

- HPV: Human Papillomavirus
- USPSTF: United States Preventive Services Task Force
- TBS: Bethesda
- LCT: Liquid-based Cytologic Test
- H-rHPV: high-risk HPV

### Declarations

**Ethics approval and consent to participate**

The study was approved by Medical Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology. Inclusions in this study all signed the written informed consent.


Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due [The original data were presented in Chinese. Due to the large amount of data and the complexity of the content, it could not be translated into English in a short time, and a few patients were unwilling to disclose their personal data, so the original data were not published] but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

XJ, LHH, XY analyzed and explained the differences in the characteristics of HPV infection in premenopausal and postmenopausal women. SY tested HPV and was a major contributor to the manuscript. XSP is the proposer of the project, and guides the whole project.

All the authors read and approved the final manuscript.

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**Tables**

Table 1 Comparison of HPV infection rate between women with and without inflammation

| Inflammatory state     | Total | HPV+ | P     | 95% CI          |
|------------------------|-------|------|-------|-----------------|
| No inflammation        | 2742  | 294  | 0.000 | 1.911–1.416,2.580|
| Inflammation           | 499   | 84   |       |                 |

Table 2: Comparison of HPV infection rate between pre- and postmenopausal women

| Age groups            | Total | HPV+ | P     | H-rHPV+ | L-rHPV+ | P     |
|-----------------------|-------|------|-------|---------|---------|-------|
| premenopausal         | 2975  | 367  | 0.056 | 272*    | 95      | 0.041 |
| Menopausal to 65      | 987   | 151  |       | 106*    | 45      |       |
| Above 65              | 153   | 21   |       | 20      | 1       |       |

*: Compared with those over 65 years old separately

Table 3 Risk analysis of h-rHPV infection in different age groups
| Age                | n/N   | Percentage (%) | P   | 95% CI            |
|--------------------|-------|----------------|-----|-------------------|
| ≤30                | 50/401| 12.47          | 0.443| 1.146 - 0.808, 1.626 |
| 30-40              | 117/1310 | 8.93      | 0.080| 0.789 - 0.605, 1.029 |
| 40 to menopause    | 105/1264 | 8.31      | 0.023| 0.729 - 0.555, 0.957 |
| Postmenopause      | 126/1140 | 11.05     | -    | 1                 |
| Menopause to 65    | 106/987 | 10.74      | -    | 1                 |
| ≥65*               | 20/153 | 13.07        | 0.393| 0.800 - 0.480, 1.334 |

*: Compared to menopausal to 65 years old