



## Risk factors for human papillomavirus infection in Shanghai suburbs: A population-based study with 10,000 women



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### ABSTRACT

**Background:** High risk human papillomavirus (HPV) infection is the major cause of cervical cancer. Several epidemiological studies have performed HPV screening in Chinese women, but no report was for Shanghai suburb women.

**Objectives:** To understand the prevalence of HPV infection and risk factors in Shanghai suburbs.

**Study design:** Between March 2011 and May 2011, 10,000 female volunteers lived in Fengxian District of Shanghai were recruited for the detection of 21 HPV types using PCR and fast flow hybridization of gene chip array. For the 508 HPV-positive patients, we performed the liquid-based ThinPrep cytology test (TCT) and histological examination for the diagnosis of local cervical lesions. The questionnaire surveyed demographic and behavioral indicators for the evaluation of risk factors of HPV infection.

**Results:** We found that the HPV-positive rate was 12.6%. The five top HPV types were as follows (in descending order): HPV52, 16, 58, 18 and 33. Moreover, HPV-positive rates were higher in women with older age, lower educational level, younger age of the first sexual intercourse, multiple sexual partners, no usage of condom for contraception, multiple deliveries, vaginal delivery, menopause, vaginal inflammation, cervical erosion and no regular cervical cytological examination. We also found that an HPV genotyping in combination with TCT and histological examination could improve early diagnosis for local cervical lesions.

**Conclusion:** HPV infection was associated with age, sexual behavior and chronic inflammation of the cervix and vagina. We recommend popularizing HPV genotyping in women with high risk factors for the early diagnosis and prevention of cervical cancer.

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## 1. Background

Human papilloma virus (HPV) is a small, double-stranded DNA virus, and it can specifically infect squamous epithelial cells of human skin and mucous membranes, causing a variety of benign and malignant lesions [1]. People found more than 100 HPV types, in which exceed 40 types are associated with reproductive tract infection and are divided into high-risk (HR) and low-risk (LR) types according to their pathogenicity [1]. The LR HPV types mostly induce genital wart-like lesions; while the repeated and persistent HR HPV types are found to be a major cause of cervical cancer and cervical intraepithelial neoplasia (CIN) III [1,2]. The distribution of HPV type varies among different regions and populations. Accumulated epidemiological surveys have found that young age of first

**Abbreviations:** HPV, human papilloma virus; HR, high-risk; LR, low-risk; CIN, cervical intraepithelial neoplasia; FCHS, Fengxian Central Hospital, Shanghai; TCT, ThinPrep cytology test; ASC-US, atypical squamous cells of unknown significance; LSIL, low-grade squamous intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion.

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sexual intercourse and multiple sexual partners are important risk factors for HPV infection [3].

To date, there were some reports on HPV prevalence and the distribution of HPV types in women in some areas (including Shanghai) in China [4–8]. However, we still lacked data for the assessment of HPV infection and its risk factors in the suburbs of Shanghai with a large migrating population and relatively poor education and economy.

## 2. Objectives

We aimed to assess the prevalence of HPV infection, HPV types and risk factors associated with HPV infection among Shanghai suburbs' women and then provided a theoretical basis for the development of appropriate preventive care and strategies of disease diagnosis through a comparison of the diagnostic value of different cervical histological examination methods for cervical lesions.

## 3. Study design

This study was reviewed and approved by the Institutional Review Board of Fengxian Central Hospital, Shanghai (FCHS). A written informed consent was obtained from all recruited individuals, and each clinical investigation was conducted according to the principles expressed in the Declaration of Helsinki consent.

The FCHS is located in the central of the Fengxian District, the southern suburb of Shanghai. Between March 08 to May 30, 2011, 10,000 volunteers who lived in this area were enrolled for HPV detection in the Outpatient Department of Obstetrics and Gynecology at FCHS. The median age of the individuals was 41 years (range from 17 to 89 years). All individuals had a history of sexual intercourse and no history of uterus resection or/and cervical surgery. During an in-person interview, an epidemiological questionnaire was conducted and all potential individuals provided information about their demographics, behavioral [9,10] and other risk factors with an approximate response rate of 75%. For each woman, a gynecologist with more than 5 years of clinical experience conducted a routine gynecological examination and collected exfoliated cervical cell samples for HPV genotyping.

We performed the HybriBio HPV GenoArray test (Cat# 110101/101201/110301, HybriBio, Hong Kong) to simultaneously identify 21 HPV types, including 13 HR types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68), five LR types (HPV 6, 11, 42, 43 and 44) and three Chinese common types (HPV 53, 66 and cp8304). According to the manufacturer's protocol, the test is an L1 consensus primer-based PCR assay that is followed by flow-through hybridization technology. A positive control was provided within the kit, and we used the HPV-negative C33-A cell line as a negative control. Any of HPV types detected were defined as HPV-positive, and the others were HPV-negative. HPV-positive samples with two or more HPV types were defined as double or multiple HPV infection, respectively. In addition, a positive result for HR HPV types alone or both HR and LR HPV types were defined as HR HPV-positive, and a positive result for LR HPV types alone was defined as LR HPV-positive.

For HPV-positive patients who consented for a further examination and treatment, the liquid-based ThinPrep cytology test (TCT) and multiple punch biopsy under colposcopy were also performed. TCT results were categorized according to the Bethesda System [11], and abnormal TCT results were defined as follows: atypical squamous cells of unknown significance (ASC-US), low-grade squamous intraepithelial neoplasia (LSIL), high-grade squamous intraepithelial lesion (HSIL) and atypical glandular cells. For multiple punch biopsy under colposcopy, all biopsy samples were histopathologically evaluated by two gynecologic pathologists as

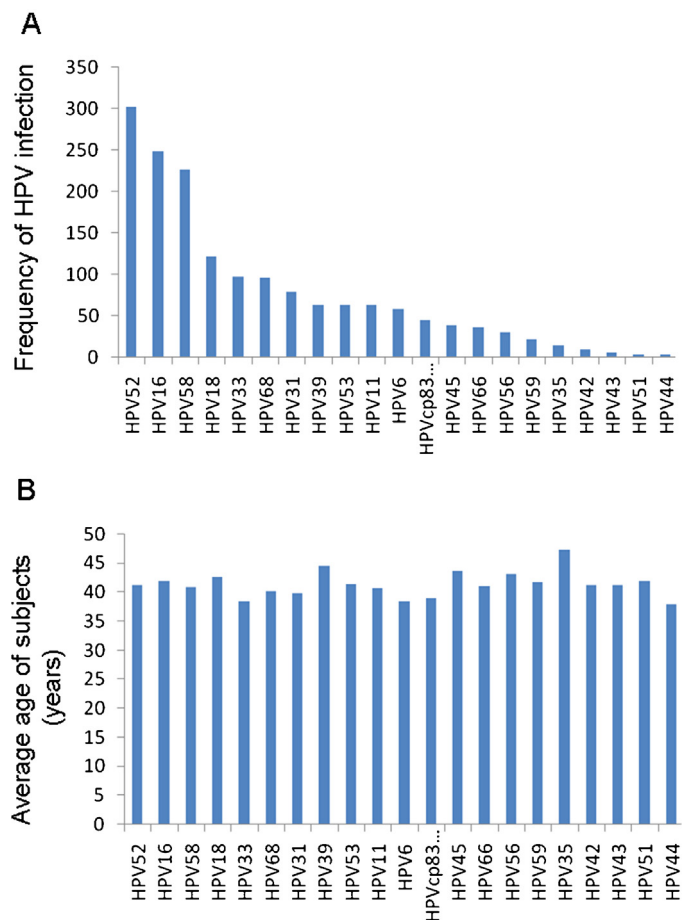


Fig. 1. Distributions of HPV type infection in 10,000 women. (A) The frequency of HPV infection; (B) average ages for women infected with different HPV types.

routine diagnosis at the Department of Pathology in FCHS. Cervical lesions were defined as follows: cervicitis, CIN grading (I, II and III) and cervical cancer.

### 3.1. Statistical analysis

The differences in selected variables between the HPV-negative and HPV-positive groups were evaluated by the Pearson's  $\chi^2$ -test. We performed Student's *t* test or Wilcoxon test to compare continuous variables between two groups, and we used an ANOVA or Kruskal–Wallis test to compare continuous variables among three or four groups. All statistical analyses were performed with SAS software (version 9.1; SAS Institute, Cary, NC), unless stated otherwise. All *P* values were two-sided with a significance level of  $P < 0.05$ .

## 4. Results

### 4.1. The prevalence of HPV infection

Among the 10,000 women who underwent the test and examination, an HPV gene chip array detected a total of 21 HPV types with 1257 patients being HPV-positive. The overall HPV infection rate was 12.6%. As shown in Fig. 1A, among the 13 HR HPV types, HPV52 was the first leading type among both single and multiple infection, which was followed by HPV16, 58, 18, 33, 68, 31, 39, 45, 56 and 59 (in descending order); while HPV35 and HPV51 were relatively rare. We found that the two most common types (i.e., HPV52 and 16) were accounted for 43.83% (551/1257) of all the

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