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CLINICAL ARTICLE

Distribution of various types of low-risk human papillomavirus according to cervical cytology and histology in northern Chinese women

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ABSTRACT

Objective: To describe the distribution of specific types of low-risk (LR) human papillomavirus (HPV) among a general population of northern Chinese women. **Methods:** Between 2007 and 2012, 118 096 women were tested with the HPV Geno-Array Test Kit (HybriBio) at China Medical University's Shengjing Affiliated Hospital, Shenyang, China. Among these women, 80 418 underwent cervical cytology and colposcopic examination, and 30 961 of these had a cervical biopsy. The prevalence of HPV infection among the women was analyzed according to age, and cytologic and histologic findings. **Results:** CP8304 was the most common type of LR-HPV overall, and was most prevalent in the youngest age group. The overall prevalence of LR-HPV (averaged across all types) was 1.7% in women with normal cytology, 8.8% in those with atypical squamous cells of undetermined significance (ASCUS), 8.0% in those with low-grade squamous intraepithelial lesions (LSIL), and 5.8% in those with high-grade squamous intraepithelial lesions (HSIL). LR-HPV alone, without any high-risk (HR)-HPV, was most common among women with ASCUS and cervical intraepithelial neoplasia (CIN) not otherwise specified (CINNOS) together. Co-infections of LR-HPV and HR-HPV were most common among women with LSIL and CIN1. **Conclusion:** These data will facilitate modeling of the cost-effectiveness of a prophylactic LR-HPV vaccination in China.

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1. Introduction

Worldwide, cervical cancer is the second most common malignant neoplasm affecting women. In 2008, there were an estimated 529 500 new cases of and 275 000 deaths from this disease. Cervical cancer is also the most common cause of cancer-associated death among women aged 15–44 years in low-resource countries [1].

Although cervical cancer is preventable, its incidence is increasing, especially in low-income countries including China. This is possibly because China's economic development and medical resources are so unevenly distributed. China has the largest number of women with cervical cancer in the world [2].

Human papillomavirus (HPV) is one of the most frequent sexually transmitted infections found among women worldwide. An estimated 291 million women have detectable HPV DNA [3]. HPV infection can be the first step in cervical oncogenesis. There are over 200 genotypes of HPV, approximately 40 of which are known to infect the anogenital region. The genotypes of HPV are classified as high risk (HR) or low risk (LR) on the basis of their oncogenic potential.

In female populations, HR-HPV is more common than LR-HPV. In low-risk countries, there are twice as many sexually active women aged 15–74 years with HR-HPV than with LR-HPV [4]. Cervical carcinoma and high-grade lesions are frequently correlated with HR-HPV. However, benign lesions (genital warts) are more closely associated with LR-HPV (HPV6 and HPV11). Only a few studies have focused on LR-HPV and the lesions that it causes [4–8].

Quadrivalent vaccines containing both HR-HPV and LR-HPV are available. Before they can be implemented as part of a preventive program, however, more information must be gathered regarding the prevalence and the disease burden of HPV6 and HPV11. Furthermore, the prevalence and disease burden of other LR-HPV genotypes not included in the vaccine should be assessed.

The aim of the present study was, therefore, to obtain data on the distribution of specific types of LR-HPV by age, cervical cytology, and histology among a general population of northern Chinese women. These data that might serve as a baseline for the design of HPV vaccination programs.

2. Materials and methods

The present descriptive, cross-sectional study enrolled healthy Chinese women who underwent cervical cancer screening at the Health Check Center or Department of Obstetrics and Gynecology of China

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Medical University's Shengjing Affiliated Hospital, Shenyang, Liaoning Province, China, between January 1, 2007, and December 31, 2012. The study protocol was approved by the ethical review boards of the participating institutions. Because no identifying information was collected, informed consent was not necessary.

The study women were aged between 18 and 81 years and were permanent residents of northeast China. Data were collected from the medical records of all participants. All study women were screened for HPV, and the results were used to analyze associations between HPV infection and abnormal cervical cytology and histology. Cytology was performed on cervical specimens from 80 418 of the enrolled women, and cervical histology was evaluated in 30 961 of the enrolled women at a subsequent visit.

The HPV tests were performed blind. Testers had no knowledge of the expected cytologic or histologic findings. HPV DNA was amplified by using L1 consensus HPV primers. Internal controls included biotinylated primers, which amplified a 268-bp fragment of a human A-globin gene as a positive control [9]. Biotin served as a negative control.

HPV genotyping was performed by using an HPV GenoArray Test Kit (HybriBio, Hong Kong, China). The HPV blot was found to contain 21 genotypes, including 6 LR genotypes (HPV6, HPV11, HPV42, HPV43, HPV44, and CP8304) and 15 HR genotypes (HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV53, HPV59, HPV66, and HPV68). HPV L1 and the internal control, human A-globin, confirmed that no HPV DNA contamination had taken place.

Cells were classified via the 2001 revised Bethesda system [10]. Pathology experts interpreted the results as follows: absence of intraepithelial lesion or malignancy (NILM); atypical squamous cells of undetermined significance (ASCUS); atypical squamous cells, high-grade intraepithelial lesions cannot be excluded (ASC-H); atypical glandular cells of undetermined significance (AGC); adenocarcinoma in situ; low-grade squamous intraepithelial lesion (LSIL, including those caused by HPV infection); high-grade squamous intraepithelial lesion (HSIL, including those caused by HPV infection); and squamous cell carcinoma (including those caused by HPV infection). All classifications except NILM are cytologic abnormalities.

Among the women diagnosed with abnormalities, a 5% acetic acid and iodine solution was used to diagnose lesions in the transformation zone. When a colposcopy produced indefinite results, the endocervix was further evaluated.

Data were analyzed via SPSS version 13.0 (IBM, Armonk, NY, USA). The overall and type-specific prevalence of LR-HPV together with 95% confidence intervals (CIs) were estimated across all participants. These data were also stratified by cytologic results (normal, ASCUS, LSIL, and HSIL), age group (≤ 25 years, 26–30 years, 31–35 years, 36–40 years, 41–45 years, 46–50 years, 51–55 years, 56–60 years, ≥ 61 years), and cervical cancer status. An age-adjusted logistic regression was used to evaluate the role of infection with LR-HPV alone and that of infection with LR + HR-HPV in the development of different of cytologic and histologic abnormalities of different levels of severity.

3. Results

Among the 118 096 study women, HPV tests were positive (HR- and/or LR-HPV) for 21 589 women (18.28%; 95% CI, 17.77–18.80) (Fig. 1). Overall, 2803 of these HPV-positive women (12.98%; 95% CI, 12.53–13.43) were positive for LR-HPV types (Table 1). LR-HPV was most common among the youngest women (≤ 25 years; 3.33%; 95% CI, 2.94–3.73). The prevalence of LR-HPV among the oldest women (≥ 61 years) was 1.67% (95% CI, 1.23–2.11). In Table 1, the relative frequency of LR-HPV types is shown by age group.

Table 2 shows the prevalence of specific types of LR-HPV stratified by cytologic findings. Among women with normal cytology, there was an overall LR-HPV prevalence of 1.67% (95% CI, 1.57–1.76). Women diagnosed with ASCUS, LSIL, or HSIL had an LR-HPV prevalence of 8.84% (95% CI, 8.19–9.49), 7.98% (95% CI, 6.93–9.02), and 5.75% (95% CI, 4.95–6.54), respectively. LR-HPV was most prevalent among women with ASCUS.

Among women with only LR-HPV and no HR-HPV, single infections were significantly more common than multiple infections for both women with normal cytology and women with cytologic abnormalities. Women infected with a single type of LR-HPV were most likely to have ASCUS cytology (5.42%; 95% CI, 4.90–5.94). LSIL was the most common abnormality detected among those infected with multiple types of LR-HPV (0.12%; 95% CI, 0–0.25) and those infected with both LR-HPV and HR-HPV (4.12%; 95% CI, 3.36–4.89). CP8304 was the most common type of LR-HPV (3.49%; 95% CI, 3.07–3.91) among women with ASCUS.

Table 3 shows the prevalence of different types of LR-HPV stratified by histologic diagnosis. The highest prevalence of LR-HPV infection was detected among women with CINNOS (13.61%; 95% CI, 11.16–16.05).

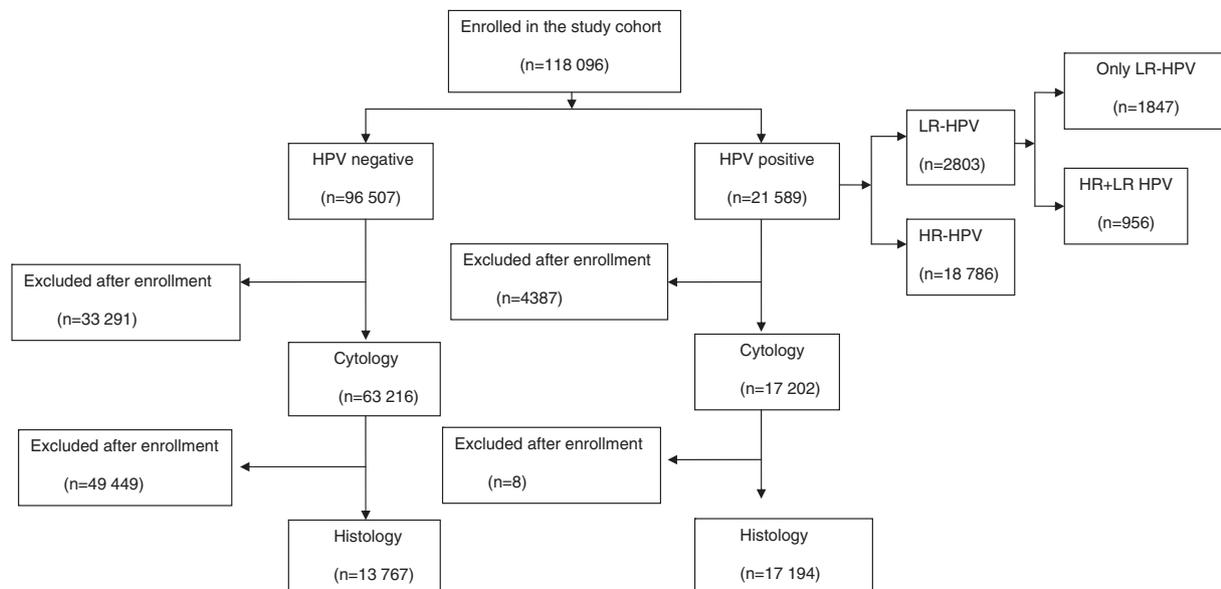


Fig. 1. Flow of participants through the study. Abbreviations: HPV, human papillomavirus; HR-HPV, high-risk HPV; LR-HPV, low-risk HPV.

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