Correlation between the diversity of vaginal microbiota and the risk of high-risk human papillomavirus infection

Xiao-Pei Chao, Ting-Ting Sun, Shu Wang, Qing-Bo Fan, Hong-Hui Shi, Lan Zhu, Jing-He Lang

HIGHLIGHTS
- The composition of the vaginal microbiota was analyzed separately at the genus and species level.
- Bacteroides plebeius, Acinetobacter Iwoffii, and Prevotella buccae occurred more frequently in the HPV-positive group.
- Specific microbiota species may serve as sensors for high-risk HPV infection.

ABSTRACT

Objectives Since other genital infections enhance HIV susceptibility by inducing inflammation and evidence suggests that the vaginal microbiome plays a functional role in the persistence or regression of high-risk human papillomavirus (HPV) infections, we investigated the relationship between the composition of the vaginal microbiota and the risk of high-risk HPV infection.

Methods The study included 151 healthy women (65 HPV-positive and 86 HPV-negative) aged 20–65 at enrollment. Total genome DNA from samples was extracted using the hexadecyltrimethylammonium bromide (CTAB) CTAB method. The vaginal microbiota composition was determined by sequencing barcoded 16S rDNA gene fragments (V4) on Illumina HiSeq2500.

Results Of the 30 most abundant bacteria at the genus level, we found only six bacteria with a statistical difference between HPV-positive and HPV-negative women: Bacteroides, Acinetobacter, Faecalibacterium, Streptococcus, Finegoldia, and Moryella. Bacteroides was the predominant genus and was detected in all women, but there was no significant difference between the two groups for L. iners, L. jensenii, and L. gasseri. Furthermore, we found 26 types of bacteria with a statistical difference at the species level between the two groups. Anaerobic bacteria such as Bacteroides plebeius, Acinetobacter Iwoffii, and Prevotella buccae were found significantly more frequently in HPV-positive women, which is the most important finding of our study.

Conclusion Our findings suggest a possible role for the composition of the vaginal microbiota as a modifer of high-risk HPV infection, and specific microbiota species may serve as sensors for changes in the cervical microenvironment associated with high-risk HPV infection. The exact molecular mechanism of the vaginal microbiota in the course of high-risk HPV infection and cervical neoplasia should be further explored. Future research should include intervention in the composition of the vaginal microbiota to reverse the course of high-risk HPV infection and the natural history of cervical neoplasia.

BACKGROUND

Cervical cancer is the fourth most common cancer among women worldwide, and over 500 000 new cases are diagnosed each year, leading to more than 200 000 deaths.1 Persistent infection with oncogenic human papillomavirus (HPV) is necessary but not sufficient for the development of cervical cancer.2 Additional factors correlated with persistent HPV infection include immunodeficiency caused by HIV, smoking, oral contraceptives and, more recently reported, vaginal dysbiosis.3 The classically-defined normal cervicovaginal microbiota is dominated by one or more Lactobacillus species (L. crispatus, L. gasseri, L. iners, or L. jensenii), and others. However, in a state of dysbiosis there is a marked reduction of Lactobacillus and a high diversity of bacteria, with an increased abundance of anaerobic bacterial species.4–6 The female genital tract is a relatively confined space and the vaginal flora mainly consists of anaerobic bacterium, so the cultivation and nutrition conditions are demanding. Isolating, culturing, and identification of a high proportion of bacteria is difficult. As a result of the rapid developments in molecular biology and related techniques, the non-culture-dependent technology invention, such as denaturing gradient gel electrophoresis and fluorescence in situ hybridization, there have been significant breakthroughs in the awareness of the vaginal flora. However, these traditional molecular biology techniques also have restrictions and limitations, such as time-consuming, heavy workload, and important information missed. Barcoded Paired-End Illumina Sequencing is a new sequencing method, which is based on the Illumina Solexa high-throughput sequencing platform and combined with the 16S rRNA tag sequence. This method is a simple, highly efficient, and low cost operation which enables us to obtain information about the overall structure and
composition of vaginal microbial communities rapidly. In order to explore the association between high-risk HPV infection and vaginal flora, we investigated the vaginal microbiota in HPV-infected and non-infected women using the Illumina sequencing platform. In the future it is hoped that persistent high-risk HPV infection and the natural course of cervical lesions caused by high-risk HPV can be suppressed by interfering with microorganisms in the vagina.

**METHODS**

**Study population**
Participants in this study were women who visited the Department of Obstetrics and Gynecology at Peking Union Medical College Hospital between May 2017 and May 2018. All of the participants were healthy women (65 HPV-positive and 86 HPV-negative, total 151) at enrollment.

Inclusion and exclusion criteria
Women aged 20–65 years, have had vaginal intercourse for more than 3 years, and were not in their menstrual cycle, pregnant or in the puerperium period were included in the study.

Those aged more than 65 years, having no vaginal intercourse, and not able to cooperate with the examiner were excluded from the study. Women who were HIV or hepatitis B/C positive, had autoimmune disorders and systemic disease (eg, diabetes mellitus, hormone treatment diseases, severe liver and kidney dysfunction), or had severe mental illness and malignant tumors were also excluded. At the same time, all the participants should meet the following requirements: no vagina douching within the last 2 days, no vaginal intercourse within the last 3 days, no systemic application of antifungal agents or antibiotics or pessaries within the last 14 days of sampling.

According to the results of the HPV test, the participants were divided into two groups. Group A consisted of 65 women with high-risk HPV infection (all infected with high-risk HPV and not treated with antiviral drugs such as α2b-recombinant human interferon, physiotherapy such as laser therapy and cryotherapy, or surgical treatment such as loop electrosurgical excision and cold knife conization). Group B comprised 86 cases without high-risk HPV infection (all the participants came to visit just for physical examination).

Clinical data collection
Ethical approval was obtained from the ethics committee of Peking Union Medical College Hospital, Beijing, China. Written informed consent was obtained from all participants. Women were included irrespective of their parity, phase in their cycle, and contraception. The type of contraception and the time of their menstrual cycle were documented.

**Specimen collection**
A sterile disposable speculum was inserted, without lubricant, and a sterile swab sample was taken from the posterior vaginal fornix and stored immediately at −80°C for DNA extraction. At the same time, these women had received ThinPrep Pap testing (Hologic, Massachusetts, USA) and the Cobas 4800 System HPV Genotyping Test (Roche Molecular Diagnostics, California, USA), which is based on real-time qualitative PCR.

DNA extraction and amplification of the bacterial 16S rRNA V4 gene region and Illumina sequence ares shown in the supplementary material (Annex I).

**Data analysis**
SPSS 23.0 software (SPSS, Chicago, Illinois, USA) was used for statistical analysis of the clinical data. Continuous variables were

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**Table 1  Patient characteristics.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HPV-positive group (n=65)</th>
<th>HPV-negative group (n=86)</th>
<th>Total (n=151)</th>
<th>P value</th>
<th>χ² value</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
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<td></td>
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</tr>
<tr>
<td>Mean (SD, range)</td>
<td>37.63 (10.3, 20–65)</td>
<td>38.03 (9.84, 23–60)</td>
<td>37.86 (9.99, 20–65)</td>
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<td>Parity, n/N (%)</td>
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<td></td>
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<td>0.819</td>
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<td>Nulliparous</td>
<td>25/65 (38.5)</td>
<td>27/86 (31.4)</td>
<td>52/151 (34.4)</td>
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<tr>
<td>Parous</td>
<td>40/65 (61.5)</td>
<td>59/86 (68.6)</td>
<td>99/151 (65.6)</td>
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<tr>
<td>Phase of menstrual cycle, n/N (%)</td>
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<td>7.015</td>
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<td>Follicular</td>
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<td>61/151 (40.4)</td>
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<td>Luteal</td>
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<td>35/86 (40.1)</td>
<td>58/151 (38.4)</td>
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<td></td>
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<td>Menopausal</td>
<td>12/65 (18.5)</td>
<td>15/86 (17.4)</td>
<td>27/151 (17.9)</td>
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<td>Contraception, n/N (%)</td>
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<td>47/86 (54.7)</td>
<td>85/151 (56.3)</td>
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<td>Condoms</td>
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<td>45/151 (29.8)</td>
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<td>Copper IUD</td>
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<td>12/86 (14.0)</td>
<td>20/151 (13.2)</td>
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<td>Vaginal ring</td>
<td>1/65 (1.5)</td>
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<td>1/151 (0.7)</td>
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</table>

P value is calculated using Pearson χ² and t-test. IUD, intrauterine device.

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RESULTS

Sociodemographic and clinical baseline characteristics

The age of both groups met normal distribution; the mean age and median age of the 65 cases with high-risk HPV infection were 37.63 years and 35.00 years, while the mean age and median age of the 86 cases without high-risk HPV infection were 38.03 years and 35.50 years. No difference in the mean age of the population was determined (p=0.807). Table 1 shows the characteristics of the two groups. No category showed systematic bias with respect to the two groups after adjustment for multiple hypothesis testing.

Diversity of microbiome community

Identification of vaginal microbiota

A total of 56 phyla were detected. Figure 1 shows that Firmicutes was the most predominant phylum in the HPV-negative group, accounting for 73.99%. The remaining phyla whose relative abundance was more than 1%, included the Actinobacteria, Proteobacteria, Bacteroidetes, and the Fusobacteria. Their relative abundances were 9.5%, 5.7%, 6.2%, and 1.9%, respectively. The relative abundance of Firmicutes, Actinobacteria, Proteobacteria, Bacteroidetes, Fusobacteria, and Tenericutes were analyzed with the t-test and categorical variables were analyzed with the χ² test. P values <0.05 were considered to be statistically significant.

Alpha diversity analysis within the group

Of the top 30 most abundant genera, Lactobacillus_aridus and Prevotella_oris were the most abundant species in group A, and Lactobacillus_crustorum, Bifidobacterium_psychrobacter, Shuttleworthia_sativa, Bacteroidetes_bacterium_enrichment_culture_clone_AP-FeEnrich3, Bacteroides_salitrois, Prevotella_zoogleiformans, Tissierella_sp._feline_oral_taxon_025, Clostridiales_bacterium_oral_clone_MCE3_9_Rhodococcus_corynebacterioides, and Lachnospiraceae_oral_clone_MCE9_173 were the most abundant species in group B.

Beta diversity analysis between the two groups

Based on the unweighted_unifrac distance, analysis of the principal components of the vaginal microbiota was carried out by QIIME software (Version 1.7.0). The t-test and two-sample Wilcoxon test both showed that there was a significant difference between the two groups (p<0.05).

A t-test analysis showed that there was no statistical difference between the two groups for the 30 most abundant genera. However, meta-state analysis and linear discriminant analysis effect size (LEfSe) found that six types of bacteria had statistical differences in the 30 most abundant bacteria at the genus level (Table 2)—namely, Bacteroides, Acinetobacter,
Faecalibacterium, Streptococcus, Finegoldia, and Moryella—of which aerobic bacteria Acinetobacter had significantly higher frequency in the HPV-positive group. Lactobacillus, including L. iners, L. jensenii, and L. gasseri, was the predominant genus and was detected in all women, but there was no significant difference between the two groups for these three species. We found a statistical difference at the species level between the two groups for 26 types of bacteria (Table 2). Anaerobic bacteria such as Bacteroides plebeius, Acinetobacter lwoffii, and Prevotella buccae occurred significantly more frequently in HPV-positive women, which is the most important finding of our study. Lactobacillus agilis and Lactobacillus sanfranciscensis occurred significantly less frequently in HPV-positive women than in the HPV-negative group. Figure 3 shows the differences at the species level between the two groups for 26 types of bacteria (Table 2). 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Figure 3  Statistically different genus/species of the 30 most abundant genera between the two groups by meta-state analysis.
DISCUSSION

It has been shown that reduction of Lactobacillus spp combined with increased diversity of cervicovaginal microbiota are risk factors for HPV acquisition, persistence, development of cervical intraepithelial neoplasia, and cervical cancer. However, we did not find a statistical difference in Lactobacillus spp between the two groups or a statistical difference in vaginal microbiota diversity. At the genus level, however, we found six types of bacteria with a statistical difference between the two groups among the 30 most abundant bacteria. The aerobic bacteria Acinetobacter occurred significantly more frequently in the HPV-positive group. Although there was no statistical difference for Lactobacillus spp, we carried out an analysis at the species level and did find some difference.

A study conducted with Korean women with and without cervical intraepithelial neoplasia showed that those carrying Atopobium vaginae, Gardnerella vaginalis, and L. iners in the absence of L. crispatus had an almost six times higher risk for cervical intraepithelial neoplasia. The study also showed the synergistic effect of this microbial pattern and oncogenic HPV infection on a very high risk (OR 34.1) of cervical intraepithelial neoplasia. In a longitudinal study with samples collected over a 16-week period, women with highly diverse or L. iners-dominated cervicovaginal microbiota were more likely to be HPV-positive, while a microbiota dominated by L. gasseri was associated with more rapid clearance of HPV infection. Our study showed that the abundance of L. iners (36.01% vs 33.29%), Atopobium vaginae (25.36% vs 22.33%), and Gardnerella vaginalis (0.14% vs 0.02%) was higher in the HPV-positive group than in the HPV-negative group, which was consistent with the findings of previous studies. Furthermore, the abundance of L. gasseri (0.41% vs 0.46%) was lower in the HPV-positive group than in the HPV-negative group. However, a previous study using quantitative PCR showed a higher prevalence of L. gasseri and Gardnerella vaginalis among HPV-positive women. At the species level of vaginal microbiota, we also found a significant reduction in Lactobacillus agilis and Lactobacillus sanfranciscensis in HPV-positive women. Anaerobic bacteria such as Bacteroides plebeius, Acinetobacter lwoffii, and Prevotella buccae were found significantly more frequently in HPV-positive women, which is a new finding of our study. The results of this study may provide new ideas for the treatment of vaginal microbes in the future.

This study analyzed the different bacterial species between HPV-positive and HPV-negative Chinese women based on the sequencing of barcoded 16S rDNA gene fragments (V4) on Illumina HiSeq2500. Our findings suggest that the presence and prevalence of specific vaginal microbiome may be involved in the persistence of high-risk HPV, and even in the pathogenesis of cervical intraepithelial neoplasia. Because this was a cross-sectional study, we were unable to determine whether a change in vaginal microbiota preceded HPV infection or whether HPV infection preceded a change in vaginal microbiota. Environmental and hormonal factors are also known to modulate the vaginal microbiome. Smoking has previously been correlated with persistent HPV infection and cervical intraepithelial neoplasia, as well as Lactobacillus spp depletion and dysbiosis. Future research should include studies of vaginal microbiome in a more complex assessment of hormonal changes and lifestyle.

At present, HPV vaccines are the main prevention strategy for cervical cancer. Microbiome modulation with pre- and pro-biotics towards stable Lactobacillus-dominant vaginal community structure that promotes HPV clearance could represent low-cost future therapeutic strategies. Future therapeutic strategies permitting the modulation of the vaginal microbiome with oral or vaginal regimes to a Lactobacillus spp-dominant microbiome may be able to promote HPV clearance or even reverse the process of tumorigenesis, reducing the morbidity resulting from these conditions and their treatment. Pro-biotics have been used in a similar manner to reduced recurrence of bacterial vaginitis through accurate targeted modification of the bacterial community. Further research is required to understand the molecular mechanisms involved in the complex role that bacterial communities can play in the development of cancer and the persistence of HPV infection. An understanding of the functional properties of the community state types is required in order to complement what we already know about their structure. Further longitudinal studies are needed to investigate the changes and stability of the microbiome during transition from acute HPV infection to persistent infection through to development of cervical intraepithelial neoplasia and cancer.

CONCLUSION

Six types of bacteria among the 30 most abundant bacteria at the genus level and 26 types of bacteria at the species level were found to be statistically different between the two groups in our study. Anaerobic bacteria such as Bacteroides plebeius, Acinetobacter lwoffii, and Prevotella buccae were detected significantly more frequently in HPV-positive women. These findings suggest that the vaginal microbiota composition can be a modifier of high-risk HPV infection, and specific microbiota species may serve as sensors for changes in the cervical microenvironment associated high-risk HPV infection. Abnormal vaginal microbiota may be a co-factor for the acquisition of HPV. Further study will focus on the synergic effect of the vaginal microbiota and HPV acquisition on cervical lesions. The exact molecular mechanism of the vaginal microbiota in the course of high-risk HPV infection and cervical neoplasia should also be further explored. Future research should include intervention in the composition of the vaginal microbiota to reverse the course of high-risk HPV infection and the natural history of cervical neoplasia.

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Provenance and peer review Not commissioned; externally peer reviewed.
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