



# Understanding the role of microbiomes in the development of HPV-cervical cancer

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Received: 02 March 2020; Accepted: 07 May 2020; Published: 25 June 2020.

doi: 10.21037/gpm-2020-hpv-02

View this article at: <http://dx.doi.org/10.21037/gpm-2020-hpv-02>

Cervical cancer (CC) is the fourth most common female cancer worldwide. Despite the popularized international vaccination efforts against human papillomavirus (HPV)—the primary causative agent of CC—it remains a significant global problem. Indeed, it is the 4<sup>th</sup> and the 2<sup>nd</sup> most common cancer in women globally and developing countries (1,2). In the United States, disparities in CC incidence also exist, with higher rates and presentation at more advanced disease (3) observed among Hispanics/Latinos compared to non-Hispanics whites. Additionally, in the US, underserved white populations, such as those of Appalachia, known for its geographic isolation and high rates of poverty (4,5), also show high rates of CC (6).

The factors associated with viral persistence and progression to CC are not yet apparent, however, recent work has shown a possible role of the epithelial microbiome in viral infections and cancer progression. With the advent of the human microbiome discoveries—we now know that microbes supply essential ecosystem services that contribute to homeostasis (7) and that microbiomes play a role in the susceptibility to HPV and neoplasia (8).

The female reproductive tract is characterized by low microbial diversity and dominance of one or a few species of *Lactobacillus*, who are believed to be the significant element needed to maintain healthy genital homeostasis (9). *Lactobacillus* is the dominant bacterial genus, with a protective role of the lactic acid product of fermentation, which maintains a low pH <4.5 (10), restricting colonization of other anaerobic species (11). Any perturbations to the vaginal flora results in an increase in bacterial diversity (12-14). The high diversity profile can also be associated with inflammatory diseases (15), transmitted sexual infections such as *Chlamydia* (16), HIV (17), or HPV (14).

Vaginal infections such as those by HPV also apparently increase bacterial diversity by yet unknown mechanisms.

HPV infections are a major etiologic agent for CC (18,19). For the virus to enter the basal cells of the stratified squamous epithelium (20), direct skin to skin contact is required. Among the oncogenic high-risk HPV subtypes associated with CC progression 16, 18, 31, 33, 45, 52, and 58 are included in the HPV 9-valent vaccine (21). Low-risk subtypes such as 6, 11, 40, 42, 43, 44, and 54, are associated with genital warts (22). The most important high-risk subtypes are 16 and 18 which cause 70% of cervical lesions and tumors.

Among the pap test results (cytology classification) there are mainly four categories: (I) negative for squamous intraepithelial lesion (NSIL); (II) atypical squamous cells of undetermined significance (ASC-US); (III) low-grade squamous intraepithelial lesion (LSIL); and (IV) high-grade squamous intraepithelial lesion (HGSIL). Results of cervical biopsy are reported as cervical intraepithelial neoplasia (CIN) of grades 1, 2 and 3 for severity (23).

Microbial infections in the context of HPV infections and cervical lesions remain largely unexplored. Ethnicity has been associated with changes in bacterial community composition, with Caucasians and Asians having a significantly higher prevalence of *Lactobacillus* spp and compared to Hispanics or African Americans (14,24).

The study of the bacterial communities associated with dysbiosis in different human populations will be essential for the appropriate translational development of probiotic and early detection methods for HPV-related cancer prevention.

Women in Appalachia—a US region with the highest annual rate of CC mortality in the United States (25), were

recruited and their cervical microbiomes studied.

In the study by McKee *et al.* (26), women with abnormal cervical cytology or who were HPV+ were more likely to have a diverse vaginal microbiota characterized by higher *Gardnerella vaginalis* relative abundance and reduced relative abundance of *L. iners* and *L. gasseri*, compared to women without either condition. This study adds to the current knowledge of cervicovaginal microbiome dynamics, highlighting the importance of using microbiomes for early detection of cancers.

### Acknowledgments

*Funding:* None.

### Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Gynecology and Pelvic Medicine* for the series “The Role of Microbiomes in the Development of HPV-cervical Cancer”. The article did not undergo external peer review.

*Conflicts of Interest:* The author has completed the ICMJE uniform disclosure form (available at <https://gpm.amegroups.com/article/view/10.21037/gpm-2020-hpv-02/coif>). The series “The Role of Microbiomes in the Development of HPV-cervical Cancer” was commissioned by the editorial office without any funding or sponsorship. FGV served as the unpaid Guest Editor of the series, and serves as an unpaid editorial board member of *Gynecology and Pelvic Medicine* from Sep 2019 to Aug 2021. The author has no other conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that the questions related to the accuracy and integrity of any part of the work are thoroughly investigated and resolved.

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doi: 10.21037/gpm-2020-hpv-02

**Cite this article as:** Godoy-Vitorino F. Understanding the role of microbiomes in the development of HPV-cervical cancer. *Gynecol Pelvic Med* 2020;3:7.