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# The Interplay between Cervicovaginal Microbiota Diversity, Lactobacillus Profiles and Human Papillomavirus in Cervical Cancer: A Systematic Review

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## ADMINISTRATIVE INFORMATION

**Support -** None.

**Review Stage at time of this submission -** Completed but not published.

**Conflicts of interest -** None declared.

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**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 6 March 2025 and was last updated on 6 March 2025.

## INTRODUCTION

**Review question / Objective** To explore the association between cervicovaginal microbiota diversity, Lactobacillus profiles, and HPV in invasive cervical cancer.

**Rationale** In recent years, the study of cervicovaginal microbiota (CVM) has gained significant attention due to the growing body of evidence highlighting its crucial role in women's health. Among women of reproductive age, it is predominantly dominated by Lactobacillus species, with four primary species commonly identified: Lactobacillus crispatus, Lactobacillus gasseri, Lactobacillus iners, and Lactobacillus jensenii. These Lactobacillus species utilize carbohydrates from the host's mucosal epithelial cells to produce lactic acid, which inhibits the adhesion, colonization, and growth of pathogenic bacteria, thereby ensuring the stability and resilience of the microbial ecosystem. The importance of a Lactobacillus-dominated environment as a hallmark of women's health is underscored by the classification system proposed by Ravel et al., which categorizes vaginal microbial profiles into five distinct community state types (CSTs) based on hierarchical taxonomic clustering. CSTs I, II, III, and V are characterized by the dominance of Lactobacillus crispatus, Lactobacillus gasseri, Lactobacillus iners, and Lactobacillus jensenii, respectively. However, in some women, the microbiota is not Lactobacillus-dominant and is instead characterized by a diverse mixture of anaerobic and microaerophilic bacteria, such as Gardnerella, Atopobium, Prevotella, and Sneathia, which corresponds to CST IV. This particular community type is associated with a state of dysbiosis, which has significant implications for women's health. Microbiota disorders compromise cervicovaginal barrier function, facilitating the adhesion, invasion, and colonization of pathogenic flora. This disruption also alters the metabolic profile of the vaginal environment, leading to an increased risk of inflammation. Importantly, high genital inflammation has been linked to the persistence of Human Papillomavirus (HPV), a known critical

factor in the progression from infection to cervical dysplasia and malignancy. Laboratory techniques for profiling Lactobacillus and other cervicovaginal micro-flora have been crucial in understanding these microbial ecosystems. The most widely used method in recent studies is 16S rRNA gene sequencing, which allows for identifying and quantifying bacterial species. This method amplifies conserved regions of the bacterial ribosomal RNA gene, providing a comprehensive overview of the microbial diversity. Whole-genome sequencing (WGS) has also been used in some studies to gain deeper insights into the genetic and functional characteristics of both dominant and minor microbial populations. In addition, quantitative polymerase chain reaction (qPCR) has been employed to specifically quantify certain bacterial species, including Lactobacillus and key pathogens involved in dysbiosis. In addition to the Lactobacillus profile, microbial diversity may play a significant role in determining women's health. The concepts of CVM α-diversity (within a single microbial community) and β-diversity (between different microbial communities) are critical in understanding the complexity of the genital ecosystem. Higher α-diversity has been associated with dysbiosis and increased susceptibility to infections, including HPV. In contrast, lower β-diversity, indicating less variation between different microbial communities, may reflect a more stable and healthier microbiota. Therefore, differences in the CVM compared to its physiological state may underlie the pathogenic mechanisms of various genital disorders. Among these, invasive cervical cancer (ICC) is one of the most prevalent and lethal gynecological malignancies worldwide. There is increasing interest in defining the characteristics of the CVM in ICC, as evidence indicates that these may differ in affected women and potentially interact with HPV infection, acting as cofactors. Additionally, some studies suggest that ICC itself may disrupt the balance between commensal and pathogenic microbes, further complicating the relationship between the microbiota and disease progression. Understanding these correlations is essential not only for early detection and prevention but also for optimizing treatment strategies. However, despite the growing interest in this field, the evidence regarding these characteristics of CVM in ICC remains limited and often conflicting.

**Condition being studied** All studies evaluating the cervicovaginal microbiota of patients affected by cervical cancer —in terms of CSTs, Lactobacillus profiles, α-diversity, and β-diversity— compared with healthy patients have been included in the final analysis.

## METHODS

**Search strategy** The literature search was systematically performed across the following databases: Medline, Embase, Scopus, the Cochrane Database of Systematic Reviews, and Clinical-Trials.gov., evaluating the available articles from inception to August 2024. For each database, we retrieved all articles using the following search strategy: ((microbio-ta[Title/Abstract] OR microbiome[Title/Abstract]) AND (cervical cancer[Title/Abstract] OR cervical carcinoma[Title/Abstract])).

**Participant or population** Patients affected by cervical cancer compared with healthy patients.

**Intervention** Not applicable.

**Comparator** Not applicable.

**Study designs to be included** We excluded non-original studies, preclinical trials, animal trials, and abstract-only publications.

**Eligibility criteria** Inclusion criteria were: (1) studies that included patients with full information about the profile of cervicovaginal microbiota and at least one group with HPV infection; (2) studies with full information about methods of profiling (3) peer-reviewed articles published originally.

**Information sources** The literature search was systematically performed across the following databases: Medline, Embase, Scopus, the Cochrane Database of Systematic Reviews, and Clinical-Trials.gov. If possible, the authors of studies that were only published as congress abstracts were tried to be contacted via email and asked to provide their data.

**Main outcome(s)** CSTs, Lactobacillus profiles, α-diversity, and β-diversity.

**Quality assessment / Risk of bias analysis** Data analysis was conducted first by an author and then by blinding by another author, who was unaware of the study's objective. No missing data were present in the outcomes of interest.

**Strategy of data synthesis** All the variables were previously graphical as histograms and examined for parametric or non-parametric distribution. Continuous variables were expressed as median and interquartile range and compared using the Kruskal-Wallis test due to the non-parametric distribution. Dichotomous and Ordinal variables were expressed as absolute numbers and

percentages and compared using Fisher's exact test. The statistical significance level was set at 0.05, and all statistical investigations were performed using R software and R Studio vers. 2023.12.1 + 402.

**Subgroup analysis** No subgroup analysis was performed.

**Sensitivity analysis** None.

**Language restriction** We excluded articles in a language other than English.

**Country(ies) involved** Italy.

**Keywords** cervical cancer; microbiota; human papillomavirus; cancerogenesis; gynecological cancer.

**Contributions of each author**

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