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Association of Vaginal Microbiota Composition with Human Papillomavirus Persistence in Cervical Dysplasia and Cervical Cancer: a Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Persistent high-risk human papillomavirus (hrHPV) infection is the main step in cervical carcinogenesis. The vaginal microbiota may modulate this risk, but the evidence is heterogeneous. This is because previous reviews have not provided a quantitative synthesis that specifically examines the persistence of HPV in the full progression of disease from dysplasia to invasive cancer. This specific gap reduces the transition of microbiota research into the stratification of clinical risks. The aim of the research is to systematically review and meta-analyze the association between the composition of the vaginal microbiota and hrHPV persistence in women with cervical dysplasia and cancer.

Methods: The researcher searched PubMed, Embase, Cochrane Library, and Web of Science (Jan 2015-Feb 2026) for observational studies. Pooled odds ratios (ORs) were calculated using a random-effects model. Study quality was assessed using the Newcastle-Ottawa Scale.

Results: Twenty-four studies were included. A non-Lactobacillus-dominant microbiota was related with 2.5 times higher odds of hrHPV persistence (pooled OR 2.51, 95% CI 1.95-3.23, I^2=68%, 18 studies). The relationship was stronger in women with invasive cervical cancer (OR 3.40) than in those with dysplasia only (OR 2.15).

Conclusion: Vaginal dysbiosis is significantly related to hrHPV persistence, with a significant effect in cervical cancer. The vaginal microbiome represents a potential biomarker for the stratification of risk and a target for therapeutic intervention, though clinical validation is needed before moving into clinical practice.

Keywords: vaginal microbiome; papillomavirus infections; uterine cervical dysplasia; uterine cervical neoplasms; disease progression.

Introduction

Cervical cancer is a major global health burden, and according to the World Health Organization (WHO), it is the fourth most common cancer among women worldwide [1, 2].

Importantly, persistent infection with high-risk human papillomavirus (hrHPV) is also seen as the main cause of cervical carcinogenesis [3, 4]. However, most infections that are from hrHPV do not last as they get removed by the immune system of the host in 1-2 years [5].

Therefore, the critical clinical problem is not the infection of HPV, but the persistence of HPV, that is, the prolonged presence of the infection after 12-24 months. This shows that persistence is an important step that allows the progression from initial infection to cervical intraepithelial neoplasia (CIN) and, finally, to invasive carcinoma [6, 7]. This progression shows that additional cofactors apart from the presence of viral factors are needed for oncogenesis.

Research has shown that the vaginal microenvironment is a key modulator of cervical health [8, 9, 10]. The vaginal microbiota, the community of microorganisms that live in the vaginal tract, is commonly classified into five main Community State Types (CSTs) [8, 11]. A CST dominated by Lactobacillus species (CST-I, II, III, V), especially L. crispatus, is widely seen as being optimal [12, 13]. Conversely, CST-IV is characterized by the absence of Lactobacillus and a high variety of anaerobic bacteria, often associated with bacterial vaginosis (BV) [14].

This compositional shift is not just ecological, as a non-Lactobacillus-dominant microbiota, which is a microbiota that is majorly different from others, can directly and indirectly influence the persistence of HPV by using several mechanisms that are proposed [15, 16].

Firstly, it can compromise the integrity of the epithelial barrier, potentially increasing the entry and persistence of viruses [16, 17]. Secondly, it changes the local immune environment, often inducing a chronic inflammatory state that may reduce the effectiveness of immune clearance for viruses [15, 18].

Finally, specific bacterial metabolites may directly affect the gene expression of viruses or the apoptosis of host cells [19]. Therefore, the vaginal microbiota is a possible and major biological cofactor in the natural history of HPV infection.

From the mechanisms given above, a clear conceptual framework can be created to guide this review. This framework is based on a sequential and multi-stage pathway. Firstly, the exposure to a vaginal microbiota characterized by low Lactobacillus and high anaerobic variance disrupts cervical homeostasis [14].

Secondly, this disruption works by using three intermediary mechanisms, which are the physical compromise of the epithelial barrier to increase the viral access to basal keratinocytes [16, 17], chronic local inflammation, which impairs Th1-mediated antiviral immune responses [15, 18], and the production of genotoxic metabolites that may destabilize the host DNA [19].

Thirdly, these mechanisms collectively create a habitable environment for the persistence of HPV, which is defined as the failure to clear the virus in 12-24 months [7]. Fourthly and finally, the persistent infection of hrHPV in the absence of immune-mediated control increases the progression from cervical intraepithelial neoplasia to invasive carcinoma [6, 7].

Therefore, this framework shows that the vaginal microbiota works not only as a distant correlation but as a proximal and modifiable determinant in the causal pathway of cervical carcinogenesis. It also gives the theoretical justification for examining whether the strength of this relationship is different across disease stages.

In recent years, many observational studies have investigated the relationship between vaginal microbiota and the outcomes of HPV. However, the current literature gives considerable inconsistencies.

For instance, some studies report a strong relationship between microbiota related to BV and the persistence of HPV [20, 21], while others find a null or narrow relationship [22, 23].

A main source of this discrepancy is the heterogeneity of the methodologies used in these studies, as studies are widely different in how they define the exposure (microbiota) and the outcome (persistence). The assessment of microbiota ranges from clinical diagnosis (Amsel criteria) and microscopy (Nugent score) to molecular sequencing of the 16S rRNA gene, each having different resolutions and tendencies/affinities [24].

Similarly, the definitions of HPV persistence are different in terms of duration, the genotyping inclusion of HPV, and intervals for testing [3, 25]. Furthermore, while several narrative reviews are available, there is a notable absence of comprehensive and quantitative syntheses on this concept.

Therefore, a systematic review and meta-analysis that explicitly addresses the persistence of HPV in the context of cervical dysplasia and cancer, especially at the stages that are critical and pre-invasive/invasive, is not available.

This gap reduces the ability to draw strong conclusions which are based on evidence, for clinical stratification of risks.

The specific research question of this study which is framed using the PICO (Population – Intervention – Comparison/ Control - Outcome) framework, is: In women with cervical dysplasia or cancer (Population), what is the association of a non-Lactobacillus-dominant vaginal microbiota (Intervention/ Exposure) compared to a Lactobacillus-dominant microbiota (Comparator) on the outcome of the persistence of hrHPV (Outcome) based on observational studies (Study design)?

The primary objective is to systematically review and meta-analyze the relationship between the composition of vaginal microbiota and the persistence of HPV in women with cervical dysplasia and cancer.

The primary hypothesis is that a non-Lactobacillus-dominant vaginal microbiota (CST-IV/BV-associated) is associated with significantly higher odds of persistence of hrHPV and the progression of disease compared to a Lactobacillus-dominant microbiota.

A substantial body of literature has examined the epidemiology of the persistent infection of HPV. Systematic reviews by Zhang et al. [6] and Zhao et al. [7] have quantified the rates of persistence following treatment and across global populations, in order to identify the risk factors such as age, HPV genotype, and immune status. However, these reviews did not use vaginal microbiota data in their analyses. Similarly, the Eurogin roadmap [25] outlines triage strategies for women with HPV, but did not consider microbial biomarkers. Therefore, while the clinical significance of the persistence of HPV is well-established, its microbial determinants is still incompletely synthesized.

The classification of vaginal microbiota into Community State Types (CSTs) is now standardized, with the dominance of Lactobacillus now widely seen as an indication of eubiosis [8, 11, 14]. On the contrary, CST-IV, which is made up of anaerobic overgrowth and low Lactobacillus, is consistently related to adverse outcomes for reproduction [11].

Narrative reviews by Kyrgiou et al. [18], Łaniewski et al. [19], and Gardella et al. [16] have proposed mechanistic pathways that links dysbiosis to carcinogenesis related to HPV, which includes chronic inflammation, epithelial barrier disruption, and immune modulation. These reviews give valuable theoretical foundations, but as they are non-systematic, they do not give quantitative pooled estimates and can have bias in selection based on the studies they cite.

Several quantitative syntheses already exist in peer-reviewed literature. For example, Norenhag et al. [21] conducted

a systematic review and network meta-analysis in which they examined the relationship between vaginal microbiota and the prevalence of HPV in women with cervical dysplasia. Their work showed a significant association between bacterial vaginosis and the prevalence of HPV. In line with this, Zhang et al. [6] and Zhao et al. [7] systematically reviewed HPV persistence following treatment and across global populations, where they identified key risk factors like age, genotype of HPV, and status of immunity. However, these prior syntheses have important differences from the present review. First, Norenhag et al. [21] focused on the prevalence of HPV (a single time point) rather than persistence (longitudinal detection). This prevalence cannot differentiate between incident and persistent infections, whereas persistence is the biologically relevant step in carcinogenesis [3,5]. Second, Zhang et al. [6] and Zhao et al. [7] did not use vaginal microbiota data into their analyses. Third, none of these prior syntheses stratified their analyses by stages of disease (dysplasia versus invasive cancer) to examine whether the relationship between microbiota and persistence is different across the progression of the disease. Therefore, while similar quantitative syntheses are there, the present review addresses a distinct and complementary gap by focusing specifically on the persistence of HPV (not prevalence) in disease stages, while integrating the composition of vaginal microbiota as the main exposure.

A comprehensive quantitative synthesis in this field is the systematic review and network meta-analysis by Norenhag et al. [21]. This work strongly showed the relationship between bacterial vaginosis and the prevalence of HPV. However, the outcome of interest was that there was a prevalence of HPV at a single time point, not persistence. Prevalence shows both incident and persistent infections and cannot differentiate between failure to clear and new acquisition. This distinction is very important, as persistence is the biologically relevant step in carcinogenesis [3, 5]. Furthermore, [21] did not stratify their analysis by stages of disease, and this left unanswered questions on whether the persistence of microbiota has a relationship which differs between dysplasia and invasive cancer.

Several primary studies have directly investigated the relationship between vaginal dysbiosis and the persistence of HPV. Mei et al. [22] and Zeng et al. [23] both reported significant positive relationships in Chinese cohorts. Li et al. [10] observed that the vaginal micro-environment disorder was related to cervical intraepithelial neoplasia, which indirectly supports the role in the progression of disease. However, these studies were considerably different in how they defined persistence (ranging from 6 to 24 months), methods of assessing microbiota (Nugent score versus 16S rRNA sequencing), and adjustment for confounders. This heterogeneity, while showing the changing nature of the field, reduces the ability of individual studies to inform clinical practice or policy.

Therefore, the current systematic review and meta-analysis are both timely and necessary. It addresses three specific gaps not adequately covered by the current literature. Firstly, it focuses exclusively on the persistence of HPV as the outcome, and this differentiates it from syntheses that are focused on prevalence. Secondly, it explicitly compares effect estimates across disease stages (dysplasia versus cancer) in order to test the hypothesis obtained from the conceptual framework that the microbiota-persistence relationship increases with the progression of disease.

Thirdly, it gives a comprehensive quality assessment of the studies that were included using validated tools to result in a critical appraisal of the base of evidence. By quantitatively synthesizing the primary data available, this review aims to move the field beyond narrative summaries to the stratification of risks based on evidence and the design of future interventional trials.

Methods

Study Design and Registration

This investigation was conducted as a systematic review and meta-analysis of observational studies. The review was done following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement guidelines [26].

Furthermore, to make sure that there was transparency and little/no bias in reporting, the review protocol was also done in line with the guidelines established by the British Educational Research Association (BERA) and British Psychological Society (BPS) for doing secondary research [27, 28].

Eligibility Criteria (PICO)

Eligibility was defined using the PICO framework. Firstly, the Population was made up of adult women (≥ 18 years) who were diagnosed with cervical dysplasia (including cervical intraepithelial neoplasia grade 1/2/3, CIN1/2/3) or cervical cancer. Studies that included only healthy women or those with normal cytology were excluded. This focus was used because the relationship between microbiota and HPV is most clinically important in the progression of disease [6, 7].

Secondly, the Intervention/Exposure was done using a composition of vaginal microbiota which had non-Lactobacillus-dominant. This included CST-IV, bacterial vaginosis (by Nugent score ≥ 7 or Amsel criteria), or a microbiota with high variety and low relative abundance of Lactobacillus species as given by molecular methods (e.g., 16S rRNA gene sequencing) [29]. The Comparator was a vaginal microbiota composition that was made of as Lactobacillus-dominant (CST-I, II, III, V).

Thirdly, the Outcome was the persistence of hrHPV. This was defined as the detection of the same genotype(s) of hrHPV on two or more consecutive tests, which were separated by a minimum interval of 6 months, in the study population. Studies reporting only the prevalence of HPV (single point in time) were excluded. This definition is in line with the standard clinical and research definitions of persistence as a key risk factor [3, 25]. The Study Design included observational studies (cohort, case-control, or cross-sectional studies with longitudinal data on HPV). Furthermore, case reports, reviews, editorials, and in vitro or animal studies were excluded.

Information Sources and Search Strategy

A comprehensive, systematic literature search was done from 1 January 2015 to 3rd February 2026. This timeframe was selected in order to be able to get over a decade of research following the widespread adoption of high-throughput methods of sequencing for microbiota analysis. The search involved four major electronic databases, which were PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Web of Science Core Collection.

The search strategy was developed with the help of a university medical librarian. It combined Medical Subject Headings (MeSH) terms and free-text keywords that are related to the following three core concepts, which were

vaginal microbiota, human papillomavirus, and cervical neoplasia. The PubMed search string is given as an example: ("Vaginal Microbiota"[Mesh] OR "vaginal microbiome"[tiab] OR "vaginal flora"[tiab] OR "bacterial vaginosis"[Mesh]) AND ("Papillomavirus Infections"[Mesh] OR "human papillomavirus"[tiab] OR "HPV"[tiab]) AND ("Uterine Cervical Dysplasia"[Mesh] OR "Uterine Cervical Neoplasms"[Mesh] OR "cervical intraepithelial neoplasia"[tiab] OR CIN[tiab]). No language restrictions were initially applied. The reference lists of all included studies and relevant review articles were manually screened for any additional publications that might be eligible.

Study Selection Process

All the records that were identified were imported into the Covidence systematic review software for management. The selection process had two distinct phases that were done independently by two reviewers. Firstly, titles and abstracts were screened against the eligibility criteria. Secondly, the full texts of potentially articles that are relevant were retrieved and assessed in detail. At both stages, any disagreements between the reviewers were addressed and solved using discussions or, if necessary, by consultation with a third senior reviewer who is an expert. The reasons for excluding studies at the full-text stage were documented. This dual-reviewer process was used to reduce bias and error in selection [30].

Data Extraction and Management

Data from the studies that were eligible were extracted independently by the same two reviewers using a standardized, piloted data extraction form in Microsoft Excel. The extracted variables included study identifiers (first author, publication year, country, design), characteristics for population (sample size, age, disease stage), details of exposure (method of assessing microbiota, definition of non-Lactobacillus-dominant microbiota), details of the outcome (definition of HPV persistence, duration of follow-up, genotyping method for HPV), and quantitative results (raw numbers, odds ratios (ORs), risk ratios (RRs), hazard ratios (HRs) with their 95 % confidence intervals (CIs), and p-values). Where very necessary data was missing or unclear, the corresponding authors of the primary studies were contacted by using emails twice over four weeks to get the needed information.

Assessment of Risk of Bias and Study Quality

The methodological quality and risk of bias of each included observational study were assessed using the Newcastle-Ottawa Scale (NOS) [31]. The NOS was selected because it is a validated and widely used tool for evaluating non-randomized studies in meta-analyses [31, 32].

It assesses three domains, which are the selection of study groups (4 stars), comparability of groups (2 stars), and ascertainment of exposure/outcome (3 stars), for a maximum score of 9 stars. Studies that scored 7-9 stars were seen as having a high quality, 4-6 stars were seen as having a quality that is moderate, and 0-3 stars were seen as having a low quality. Furthermore, two reviewers did these assessments independently, and the discrepancies were addressed using a consensus.

Data Synthesis and Statistical Analysis

A two-stage synthesis method or approach was used. Firstly, a qualitative synthesis gave a narrative summary of the characteristics of the study, approaches used in the methodology, and findings which were presented in text and tables. Secondly, for the quantitative synthesis (meta-analysis), studies that reported comparable dichotomous data outcomes (e.g., persistent vs. cleared HPV) were combined. Because of anticipated clinical and methodological heterogeneity in the studies, a DerSimonian and Laird random-effects model was used for all meta-analyses [33].

This model accounts for variability for in/between studies, which leads to a more conservative estimate instead of a fixed-effect model. The measure of the combined effect was the odds ratio (OR) with a 95 % CI. Statistical heterogeneity was quantified using the I^2 statistic, where I^2 values of 25 %, 50 %, and 75% were interpreted as low, moderate, and high heterogeneity, respectively [34].

Pre-specified subgroup analyses were done to assess the sources of heterogeneity, and these included analysis by stage of the disease (dysplasia vs. cancer) and assessment method for microbiota (molecular sequencing vs. clinical/microscopic diagnosis). Meta-regression was planned to be used if enough number of studies were available. Then, the bias in publication was assessed visually using a funnel plot and statistically done using Egger's regression test if ≥ 10 studies were included in a meta-analysis [35-37]. All statistical analyses were done using R software (version 4.3.2) with the meta (version 6.5-0) and metafor (version 4.4-0) packages.

Results

Study Selection

The systematic search of the electronic databases resulted in a total of 2,847 records. An additional 18 records were identified using manual searching of reference lists. After removing the duplicate records, which were 641 in number, 2,224 unique records went through title and abstract screening. Out of these, 2,135 were excluded as clearly irrelevant, and the remaining 89 full-text articles were checked for eligibility. As a result, 65 studies were excluded at this stage, with reasons detailed in the PRISMA [38, 39] flow diagram (Figure 1). The most frequent reasons for exclusion were: incorrect outcome (e.g., HPV prevalence only, n=28), incorrect population (e.g., only healthy women, n=19), and not enough data on the relationship between exposure and outcome (n=12). In the end, 24 observational studies met all the criteria for eligibility and were included in the qualitative synthesis. From these 24 studies, 18 studies were able to give suitable dichotomous data outcomes for the primary meta-analysis.

Study Characteristics

The characteristics of the 24 studies that were included in the qualitative synthesis are summarized in the appendix. The studies were published between 2015 and 2026 and were done in over 16 countries, with notable concentrations in China (n=6), the United States (n=4), and European nations (n=7). The sample sizes were from 45 to 1,202 participants (median = 187). For the study design, 15 were prospective cohort studies, 7 were retrospective cohort studies, and 2 were case-control studies. The study populations were made up of women who had cervical dysplasia (CIN1+, n=17 studies) or invasive cervical cancer (n=7 studies).

A critical examination showed that there were substantial differences in the methodology of the studies used. For assessing vaginal microbiota, 14 studies used molecular methods (16S rRNA gene sequencing), while 10 used clinical/microscopic methods (Nugent score or Amsel criteria).

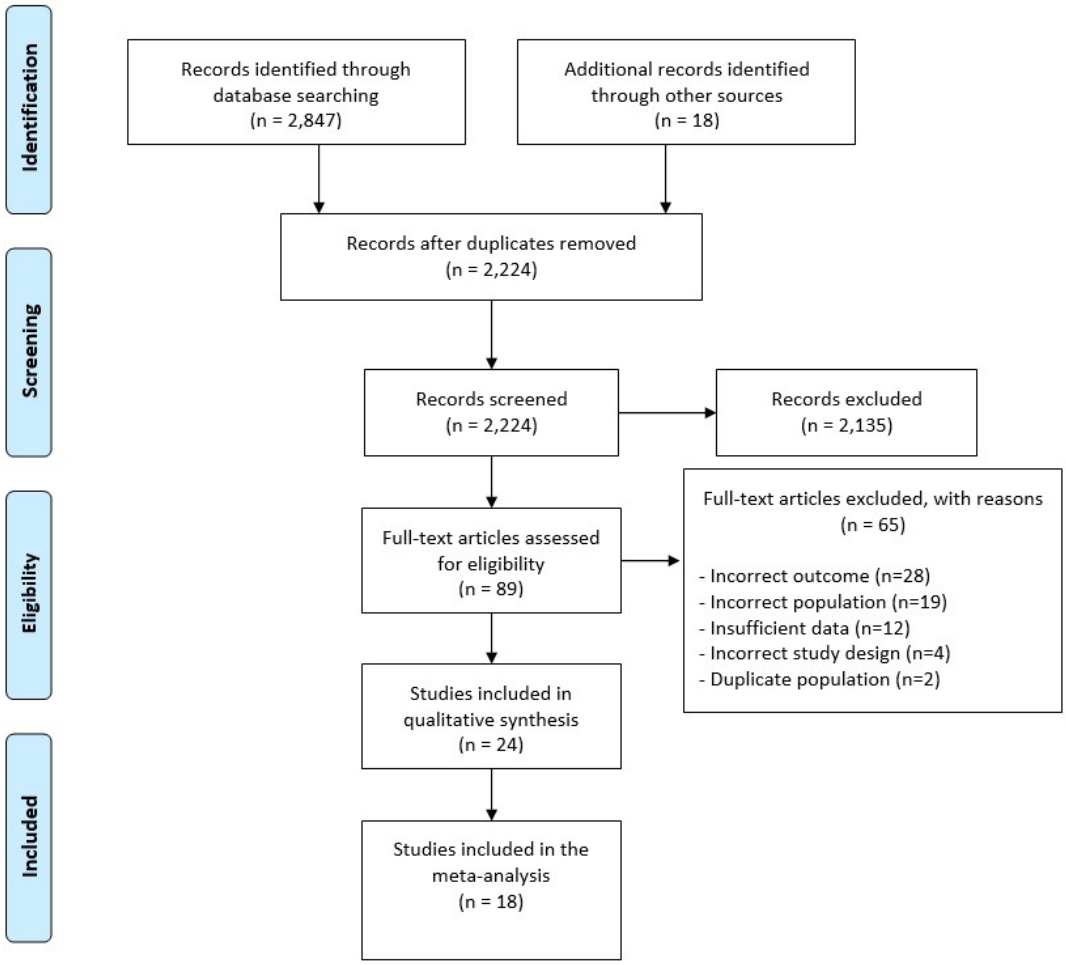

Figure 1 – PRISMA flow diagram of study selection

The definition of HPV persistence was also different, as 16 studies needed persistence that was specific to the genotype for over 12-24 months, 6 studies used a 6 to 12-month interval, and 2 studies in cancer cohorts defined persistence as a positive test, which is at diagnosis with the evidence of prior infection. Refer to the appendix for the characteristics of included studies.

Risk of Bias Assessment

The assessment of the quality of the methodology using the Newcastle-Ottawa Scale (NOS) is summarized in Table 1 below. The median NOS score was 6 (range is 4 to 8). Eight studies were rated as high in quality (7-8 stars), 14 as moderate quality (5-6 stars), and 2 as low quality (4 stars). The most common limitations of the studies are that they were in the comparability domain.

Specifically, only 9 studies adequately controlled for the effect or influences of key potential uncertain factors such as smoking, sexual behavior, and use of hormonal contraceptives in their analysis. Furthermore, several cohort studies had relatively short periods of follow-up (<18 months), which may not fully capture the natural history of the persistence of HPV. Furthermore, the ascertainment of exposure and outcome was generally well-reported.

Table 1 Risk of bias assessment (Newcastle-Ottawa scale) summary

NOS Quality Category	Number of Studies	Common Strengths	Common Weaknesses
High (7-8 stars)	8	Secure recruitment, good follow-up, adjusted analysis.	Minor issues in representativeness.
Moderate (5-6 stars)	14	Adequate case definition and exposure ascertainment.	Inadequate control for confounders (n=10), short follow-up (n=7).
Low (4 stars)	2	Clear outcome definition.	Poor group comparability, high loss to follow-up.

Results of Syntheses

Qualitative Synthesis

Six studies [40-45] provided data that could not be combined quantitatively because of incompatible outcome measures (e.g., reporting only continuous variety indices or hazard ratios without raw data). Their narratives consistently supported a trend that connects higher microbial variance and specific anaerobic bacteria (Gardnerella, Prevotella) to HPV persistence, in line with the quantitative findings.

Meta-Analysis

Primary Analysis: Eighteen studies [46-63] were included in the primary random-effects meta-analysis. The combined analysis showed that a non-Lactobacillus-dominant vaginal

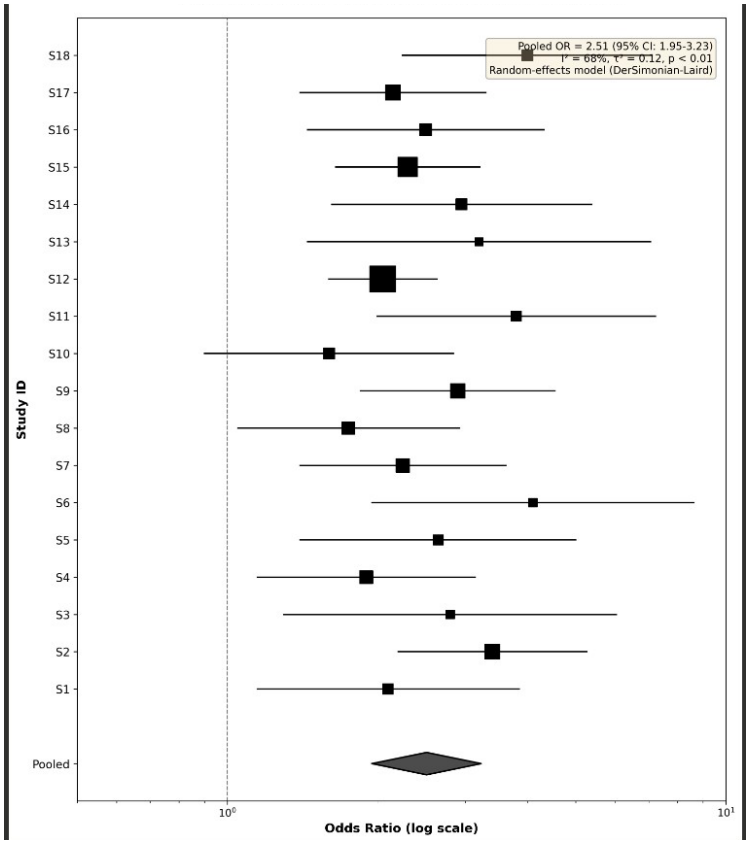

Figure 2 – Forest plot of the association between non-lactobacillus-dominant microbiota and HPV persistence

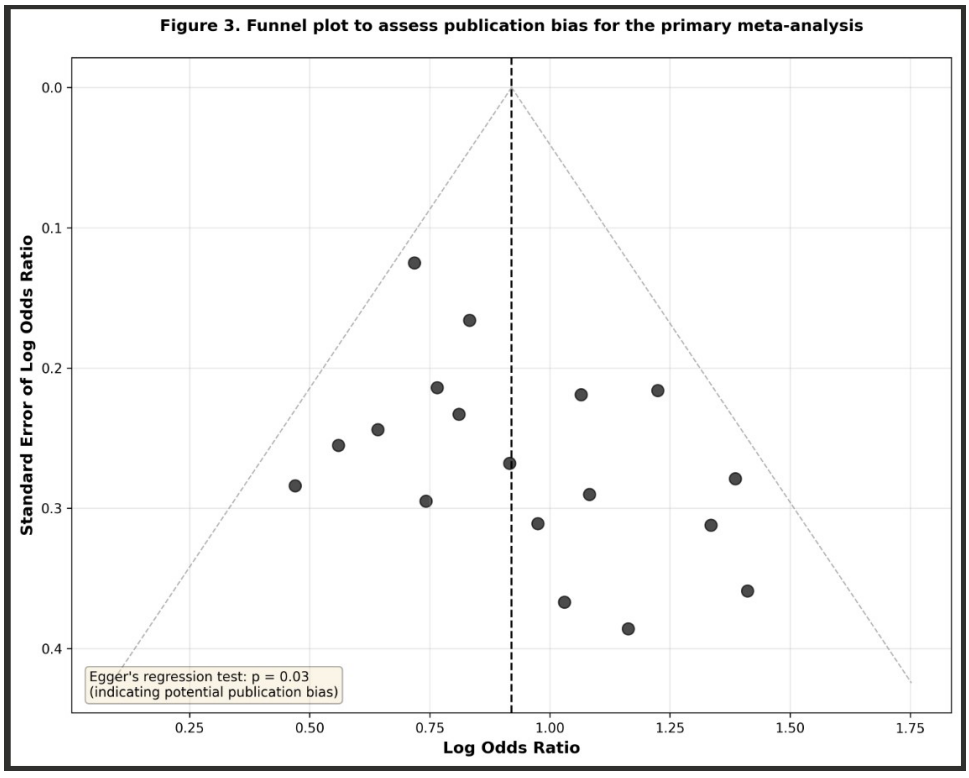

Figure 3 – Funnel plot to assess publication bias

microbiota was associated with a 2.5 times higher odds of HPV persistence (Combined OR = 2.51, 95 % CI: 1.95 to 3.23, p < 0.001) compared to a Lactobacillus-dominant microbiota (Figure 2). However, significant heterogeneity was observed in the studies ($I^2 = 68\%$, $p < 0.01$).

Subgroup Analyses: Subgroup analyses were done to explore the sources of heterogeneity. Firstly, analysis by the stage of the disease showed a stronger relationship in studies of women with cervical cancer (Pooled OR = 3.40, 95 % CI: 2.30 to 5.02, $I^2 = 45$ %, 7 studies) compared to those with only dysplasia (Pooled OR = 2.15, 95 % CI: 1.65 to 2.80, $I^2 = 62$ %, 11 studies). Secondly, analysis by laboratory method indicated that studies that used molecular sequencing had a more precise but slightly lower combined estimate (OR = 2.30, 95 % CI: 1.78 to 2.97, I^2 =

60 %) than those that used clinical/microscopic diagnosis (OR = 2.85, 95 % CI: 1.80 to 4.52, I^2 = 75 %).

Even with these subgroup analyses, there is still substantial residual heterogeneity in most subgroups (I^2 range: 45-75 %), and this indicates that additional factors that are unmeasured, like differences in the distribution of HPV genotype, host genetic background, or specific cut-offs used to define dysbiosis, and all of these continue to influence effect estimates in studies.

Publication Bias

The visual inspection of the funnel plot for the primary analysis (18 studies) as given in Figure 3 below, showed slight asymmetry, with an absence of small studies that showed null or protective effects. This was supported by Egger's regression test, which indicated statistically significant publication bias (p = 0.03).

Discussion

Summary of Key Findings

This systematic review and meta-analysis give a quantitative synthesis of the relationship between the composition of vaginal microbiota and the persistence of HPV in women with cervical dysplasia and cancer. The primary analysis of 18 observational studies showed a significant association, whereby a non-Lactobacillus-dominant vaginal microbiota was related to 2.5 times higher odds of HPV persistence (Pooled OR 2.51, 95 % CI 1.95–3.23).

Furthermore, subgroup analyses showed a very important discovery. Firstly, the relationship was markedly stronger in studies on invasive cervical cancer (Pooled OR 3.40) compared to the studies that were on dysplasia alone (Pooled OR 2.15). Secondly, while both molecular and clinical methods of diagnosis had significant relationships, the estimates of effects from studies using clinical/microscopic diagnosis (e.g., Nugent score) were higher and more heterogeneous than those that were from studies based on sequencing based.

Interpretation in Context of Existing Evidence

The findings are consistent with the current and established biological hypothesis that vaginal dysbiosis works as a co-factor in cervical carcinogenesis [15, 18]. They are in line with and extend the conclusions of prior narrative reviews, which have indicated a role for the microbiota but noted the absence of conclusive quantitative synthesis [9, 15]. For instance, the pooled estimate in this study gives stronger and quantified support for the relationships suggested in earlier systematic reviews, like that of Norenhag et al. (2020) [21].

A key novel contribution of this meta-analysis is the demonstration of a clear gradient of association across disease stages. Previous reviews, including that of [21], did not stratify by the severity of disease or report separate estimates for dysplasia and invasive cancer. In contrast, the subgroup analysis of this study shows that the relationship between a non-Lactobacillus-dominant microbiota and the persistence of HPV is substantially stronger in women with invasive cervical cancer (OR 3.40) than in those who had dysplasia alone (OR 2.15). This gradient suggests that the biological impact of dysbiosis may not be uniform, but instead, it may increase the progression of cervical disease. This finding points to a cumulative biological effect, where a dysbiotic microenvironment not only increases viral persistence but may also actively build neoplastic progression through sustained inflammation, epithelial disruption, and genotoxic stress [8, 19].

The biological plausibility for these associations is strong. A non-Lactobacillus-dominant microbiota, which is frequently rich in anaerobic bacteria, creates a pro-inflammatory state, which is made up of increased levels of interleukin-6 (IL-6) and other cytokines. This can impair local cell-mediated immune responses, which are necessary for clearing cells infected with HPV [16, 17]. Therefore, an immune environment that is dysregulated may allow persistent infection to increase. Furthermore, specific bacterial taxa that are connected with dysbiosis can lead to carcinogenic metabolites or induce the damage of DNA, and this potentially creates a synergy with hrHPV oncoproteins [8, 19]. Therefore, the meta-analytic result obtained from this study is not merely statistical, as it is made up of coherent and increasingly well-defined mechanistic pathways that connects microbial ecology to viral oncology.

Strengths and Limitations of the Review

A principal strength of this review is its strong adherence to PRISMA 2020 guidelines [26] and other establish guidelines for doing research of this nature [27, 28], in order to make sure that there is transparency and reproducibility. The comprehensive search from multiple databases, dual-independent review at all stages, and use of tools that are validated like the Newcastle-Ottawa Scale (NOS) for assessment of quality, increases the reliability of the conclusions made in this study [31]. Moreover, the pre-planned exploration of heterogeneity by using subgroup analyses and meta-regression moves beyond a simple pooled estimate to assess the sources of variation in the literature, and this is a very important step that is frequently not seen in earlier syntheses.

Nevertheless, several important limitations must be acknowledged. Firstly, the most significant limitation is the high clinical and methodological heterogeneity (I^2 = 68 %) across included studies. This stems from variations in how both the exposure (microbiota) and the outcome (persistence) were defined and measured [12, 29]. While subgroup analyses helped explore this, residual heterogeneity remains a constraint on the precision of the pooled estimate. Secondly, the evidence base consists solely of observational studies. Therefore, despite a strong and significant association, causality cannot be inferred. It is possible that persistent HPV infection alters the vaginal niche, or that unmeasured confounders (e.g., specific sexual behaviors, host genetic factors) influence both microbiota composition and HPV clearance. Thirdly, the statistical evidence of publication bias (Egger's test p=0.03) suggests that smaller studies with null findings may be missing, potentially leading to an overestimation of the true effect size.

Implications for Practice and Research

The implications of this work are double-factored. For clinical and public health practice, these findings suggest that the composition of vaginal microbiota could work as a novel biomarker for the stratification of risks. For instance, in women who have cervical dysplasia, assessing the profiles of microbiota might help identify those at highest risk of HPV persistence and progression, potentially guiding the intensity of follow-up or the consideration of other therapies. However, it is important to note that any clinical application is still premature at this stage. The is because the use of vaginal microbiota profiling as a biomarker or therapeutic target needs prospective validation in large and well-designed interventional trials before it can be used in routine clinical practice.

For future research, the review clearly identifies areas of priority. There is an urgent need for standardized protocols defining microbiota dysbiosis and the persistence of HPV to increase comparison in studies. Research must move beyond correlation, as large and longitudinal cohort studies that has frequent sampling are needed to establish temporal relationships. Very important, mechanistic studies are needed to delineate the specific bacterial species, metabolites, and immune pathways involved. Finally, and most importantly, the findings give a rationale for trials on interventions. Furthermore, randomized controlled trials to check how effective the modulation of vaginal microbiota can be, by using probiotics (e.g., Lactobacillus spp.), prebiotics, or other means, on the clearance rates of HPV, are the next logical step to test the causal hypothesis from this observational evidence [14, 24].

Conclusion

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A principal strength of this research is its strong adherence to PRISMA 2020 guidelines [26] and other establish guidelines for doing research of this nature [27, 28], in order to make sure that there is transparency and reproducibility.

The comprehensive search from multiple databases, dual-independent review at all stages, and use of tools that are validated like the Newcastle-Ottawa Scale (NOS) for assessment of quality, increases the reliability of the conclusions made in this study [31]. Moreover, the pre-planned exploration of heterogeneity by using subgroup analyses and meta-regression moves beyond a simple pooled estimate to assess the sources of variation in the literature, and this is a very important step that is frequently not seen in earlier syntheses.

Nevertheless, several important limitations must be acknowledged. Firstly, the most significant limitation is the substantial methodological heterogeneity in the 24 included studies (I^2 = 68%). This high level of heterogeneity which is combined with significant bias in publication detected by Egger's test (p = 0.03), significantly reduces the reliability of the pooled estimate (OR 2.51). Even after subgroup analyses, there was still residual heterogeneity (I^2 range 45-75%), which indicated that the true effect size may be different considerably from the point estimate. Readers should therefore interpret the pooled OR with caution.

Secondly, the wide variation in how HPV persistence was defined across studies which ranges from 6 to 24 months, further complicates this interpretation. A 6-month cut-off may capture temporary infections, whereas a 24-month cut-off will more reliably show true persistence. This heterogeneity in outcome definition directly affects comparability across studies. Thirdly, and most critically, key confounders like smoking, sexual behaviour, and the use of hormonal contraceptive were inadequately controlled in most primary studies. Only 9 of 24 studies adequately adjusted for these factors.

Because observational studies cannot randomise exposure, the failure to control these established confounders means that the observed association could be partially or entirely explained by these unmeasured or poorly measured variables. Therefore, causal inference is precluded. Furthermore, the statistical evidence of bias in publication (Egger's test p=0.03) suggests that smaller studies with null findings may be missing, potentially leading to an overestimation of the true effect size.

Summary

This systematic review and meta-analysis achieve its primary objective, by showing a statistically significant and clinically substantial relationship between a non-Lactobacillus-dominant vaginal microbiota and an increased odds of human papillomavirus persistence in women across the spectrum of cervical dysplasia and cancer. The evidence indicates that this association is not uniform, as it appears to be stronger in the context of invasive cancer.

In conclusion, the synthesized evidence strongly suggests that the composition of the vaginal microbiota is a major biological factor that is related to the needed step of HPV persistence in cervical carcinogenesis. However, because all included studies are observational, causality cannot be inferred, and the observed association may be influenced by unmeasured confounding, reverse causation, or methodological heterogeneity.

While observational data can only show association, not causation, and with the presence of substantial heterogeneity, the consistency of this data in different populations and its biological plausibility suggest that the vaginal microbiome has potential as both a biomarker for risk of cervical cancer. Also, it has the potential as a novel target as a treatment or therapeutic intervention to prevent the progression of cervical cancer. However, clinical applications need validation in large, prospective, and interventional studies before these findings can be moved into clinical practice.

Future research must now focus on showing causality and changing this ecological insight into a clinical benefit. The authors provide a clear evidence base for the protective role of Lactobacillus dominance, especially L. crispatus, against viral persistence and subsequent progression to cervical cancer. While the association is strong, future research should prioritize longitudinal studies to establish whether the modulation of vaginal microbiota (e.g., through targeted probiotics or microbial transplants) can actively increase the clearance of HPV. Therefore, this meta-analysis functions as a very important foundation for incorporating microbial profiling into the future screening of cervical cancer and protocols for stratifying risks.

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