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Associations of the gut, cervical, and vaginal microbiota with cervical cancer: a systematic review and meta-analysis

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Abstract

Background An increasing number of studies indicate that the gut, cervical, and vaginal microbiota may play crucial roles in the development of cervical cancer (CC). However, the interactions between the microbiota and the host are yet unknown. To address this gap, a systematic review and meta-analysis were conducted to assess the microbiota alterations in a variety of body locations, including the gut and genital tract.

Methods Electronic searches of PubMed, Embase, Web of Science, and the Cochrane Library were conducted to retrieve eligible papers published from January 1, 2014, to January 1, 2024 (PROSPERO: CRD42024554433). This study was restricted to English-language studies reporting on alpha diversity, beta diversity, and relative abundance, as well as on patients with CC whose microbiota had been analyzed via next-generation sequencing technologies. To assess the risk of bias (RoB), we utilized the Newcastle–Ottawa Quality Assessment Scale (NOS) and the ROBINS-I tool. For the meta-analysis, we employed Review Manager 5.4.

Results Thirty-six eligible studies were included in this review. The Chao1 index (SMD = 0.96, [95% CI: 0.71, 1.21], $I^2 = 0\%$) and the Shannon index (SMD = 1.02, [95% CI: 0.53, 1.50], $I^2 = 85\%$) values from vaginal samples were significantly greater in patients than in the controls. In the cervical samples, the Shannon index value (SMD = 1.29, [95% CI: 0.61, 1.97], $I^2 = 93\%$) significantly increased, whereas the Chao1 index value did not significantly differ (SMD = 0.50, [95% CI: -0.46, 1.46], $I^2 = 89\%$). The Shannon index value (SMD = 0.25, [95% CI: -0.22, 0.72], $I^2 = 38\%$) did not significantly differ across the gut samples. The majority of studies (19/25) indicated that the patients and noncancer controls differed significantly in terms of beta diversity. Cancer-associated changes were observed, with a dramatic decrease in the *Lactobacillus* genus and significant increases in pathogenic bacteria, including the *Anaerococcus*, *Peptostreptococcus*, *Porphyromonas*, *Prevotella*, and *Sneathia* genera. Additionally, the impact of antineoplastic therapies on microbial diversity was inconsistently reported across several studies.

Conclusion This systematic review elucidates the microbiota alterations associated with the prevalence of CC and its response to anti-tumor therapies, aiming to provide insights for future research directions and precision medicine strategies to enhance women's quality of life.

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Keywords Cervical cancer, 16S rRNA sequencing, Dysbiosis, Vaginal microbiota, Cervical microbiota, Gut microbiome, Meta-analysis

Background

Cervical cancer (CC) is the fourth most common malignancy in women worldwide, following breast cancer, lung cancer, and colorectal cancer [1]. Globally, there were estimated to be 342,000 deaths and 604,000 new cases in 2020, with considerably higher rates in transitioning countries than in transitioned countries [1]. CC is caused primarily by persistent high-risk human papillomavirus (HPV) infection [2]. Despite the promotion of the HPV vaccine, early screening, and standardized treatment of CC involving surgery, chemotherapy, radiotherapy, and immunotherapy, the outcomes of CC treatment are still not satisfactory [3]. In addition to HPV infection, numerous other factors contribute to CC progression. With rapid advancements in sequencing technologies, an increasing number of studies have explored the role of the human microbiota in carcinogenesis [4].

The human microbiota is defined as the various communities of beneficial and pathogenic microorganisms, including bacteria, archaea, fungi, protists, and viruses, that exist within the unique environment of the human body [5]. Owing to its anatomical location, the cervix is tightly connected to the genital and gut microbiota [6]. Anatomically, the female reproductive system consists of an upper section (uterus, fallopian canals, and ovaries) and a lower portion (cervix and vagina) with distinct microenvironmental compositions [7]. The vaginal microbiota comprises the majority of microorganisms in the female reproductive tract and is divided into five categories on the basis of the dominant species of the *Lactobacillus* genus: *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus iners*, anaerobic bacteria, and *Lactobacillus jensenii* [8]. Emerging evidence shows that the microbiota in the cervicovaginal tract plays a crucial role in the progression of CC [9–11].

The gut microbiota contains approximately 1000 species of microorganisms and is termed the "second genome" of the human body [12]. Emerging evidence indicates that the microorganisms in the gastrointestinal tract contribute to the development of cancers, such as gastric cancer, colorectal cancer, lung cancer, breast cancer, and CC [13–18]. The pathophysiological mechanisms of microbial carcinogenesis may involve failure of the epithelial barrier, chronic inflammation, immune dysregulation, and/or genotoxicity [19–21]. Moreover, research on preclinical mouse models and clinical cancer patients has demonstrated that gut microbial diversity and composition can influence antitumor immunity and affect the efficacy of immunotherapy in patients with melanoma and lung and kidney cancers [22].

Systematic reviews have focused on alterations in vaginal samples from patients with CC, indicating that *Lactobacillus iners* is a protective factor against carcinogenesis [23, 24]. However, further exploration is needed to focus simultaneously on microbiota alterations in both the genital tract and gut of CC patients. Therefore, we aimed to investigate the interaction between CC and the microbiota in the genital and gastrointestinal tracts and to evaluate treatment–microbiota interactions. Here, we present a systematic review and meta-analysis to characterize the composition of the microbiota in CC patients compared with that in non-CC controls and to explore the impact of treatment on the microbiota.

Methods

The systematic review was preregistered with PROSPERO (CRD42024554433) and was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [25].

Search strategy and information sources

Literature searches for inclusion in this systematic review were conducted in PubMed, Embase, Web of Science, and the Cochrane Library, as described in Appendix S1. The search was restricted to studies involving adults with a diagnosis of CC and to studies published in the English language within the last decade. Studies including only nonhuman subjects were excluded. We also manually examined the reference lists of the retrieved publications to identify additional appropriate studies that were missed during the primary search.

Eligibility criteria and study selection

An initial screening for compliance was carried out by two independent reviewers who read the titles and abstracts of the literature before moving on to a full-text reading screen. After careful reading of any literature that met the inclusion requirements, data extraction was performed. The following inclusion criteria were used: (1) the target population included adult patients with CC; (2) sequencing was performed via high-throughput sequencing and assessment of α-diversity, β-diversity, and relative abundance; and (3) a control group was included for the following comparisons: comparing nontumor patients to assess the changes in the microbiota with or without cancer or comparing patients before and after antineoplastic

treatment to assess the effects of such treatment on the microbiota; or (4) there were subgroups with different microbiota characteristics used to assess the effects of microbiota on treatment measures. Consensus and group discussion were the main methods used to resolve disagreements.

Data extraction and assessment of RoB

Two authors employed a preestablished template to extract data and then cross-checked for the following: authors, published year, nation, number of participants in each group, age, ethnicity, HPV status, smoking or drinking, sequencing technology, 16 S rRNA variable region, and sequencing platform, among others. The main areas of focus of this analysis were the microbiota composition at the community level (α and β diversity) and taxonomic discoveries at the phylum, family and genus levels (relative abundance).

We performed a quality assessment of the case–control studies and nonrandomized trials on the basis of the Newcastle–Ottawa Scale (NOS) [26] and ROBINS-I stool [27], respectively. A score of 0 was assigned for a "no" or "unclear" answer, whereas a score of 1 was assigned for a "yes" answer. The NOS is scored on a scale of 9, with studies receiving a score of 6 or higher considered to be of good quality [28, 29]. Therefore, studies with an NOS score between 6 and 9 were included in our meta-analysis to enhance the reliability of the findings. Two researchers separately assessed the RoB, and when there was dispute, it was settled by consensus and group discussion.

Data synthesis

Data were extracted from text, tables, and figures for analysis. For those studies lacking original data, the WebPlotDigitizer online tool was used to extract and estimate data from the box plot as previously described [30–32]. Means (M) and standard deviations (SD) were calculated via a web tool (http://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html) by converting medians, interquartile ranges, minimum values, and maximum values [33]. The meta-analysis employed bacterial diversity indices, a random effects model, and standardized mean difference (SMD) calculations to generate forest plots depicting microbiome variations between patients and controls. The I^2 statistic was used to assess heterogeneity levels, which were categorized as low (25%), moderate (50%), or high (75%), and funnel plots were used to detect publication bias. Subgroup analyses were conducted on different samples. Review Manager version 5.4 was utilized for all the statistical analyses to synthesize the data and evaluate the outcomes.

Results

Study selection

The search yielded 1613 published articles from PubMed, Embase, Web of Science, and the Cochrane Library. After 456 duplicate records were removed, 1157 articles were screened for exclusion on the basis of non-English language or inappropriateness assessed after the titles and abstracts were read. In total, this systematic review and meta-analysis involved a detailed evaluation of 113 full-text articles, with 36 studies ultimately included (Fig. 1). These included 31 case–control studies and 9 nonrandomized intervention studies, with four studies included in both the case–control and nonrandomized intervention categories.

Study characteristics

The included studies spanned from 2014 to 2024 and were conducted across 12 countries, predominantly (21 [58.33%]) in East Asia (China, Korea), 12 (33.33%) in westernized populations (USA, Mexico, UK, Germany, Russia, Poland, Romania), and 3 (8.33%) in Africa (Nigeria, Ethiopia, Botswana) (Table S1). In total, 3333 participants were included in the studies; these participants included 929 patients, 1179 cervical intraepithelial neoplasia (CIN) controls, and 1225 healthy controls (HCs), with sample sizes ranging from 4 to 124. The participants' average age was 43.39 years, with a standard deviation of 11.46 years. In addition, the mean BMI was 24.32, with a standard deviation of 4.46. The participants were divided into three groups according to their HPV infection status: HPV16/18, other HPVs, and uninfected, with 89.6% of the CC patients being infected with HPV. (Table S2).

Various methodologies were adopted for analyzing the composition and sequencing of samples (Table S3). Thirty-three studies employed 16 S rRNA sequencing techniques on the Illumina platform, whereas four studies employed shotgun metagenomic sequencing. The hypervariable region V3-V4 was the most frequently sequenced region (14/33), followed by region V4 alone (12/33) and other regions (7/33). The Illumina MiSeq, Illumina HiSeq, IonPGM and 454 GS platforms were primarily used for these sequencing analyses. The SILVA database (13/36) and the Greengenes database (8/36) were the most widely used databases.

Assessment of RoB

The RoB was determined on the basis of the type of research. The NOS scale was employed to evaluate the case–control studies (Figure S1), with scores ranging from 6 to 8 (mean = 7.39). The nonresponse rate score was set to zero for all the studies since it was not described in the text. The ROBINS-I stool was utilized to assess the RoB in nonrandomized trials (Figure S2), with

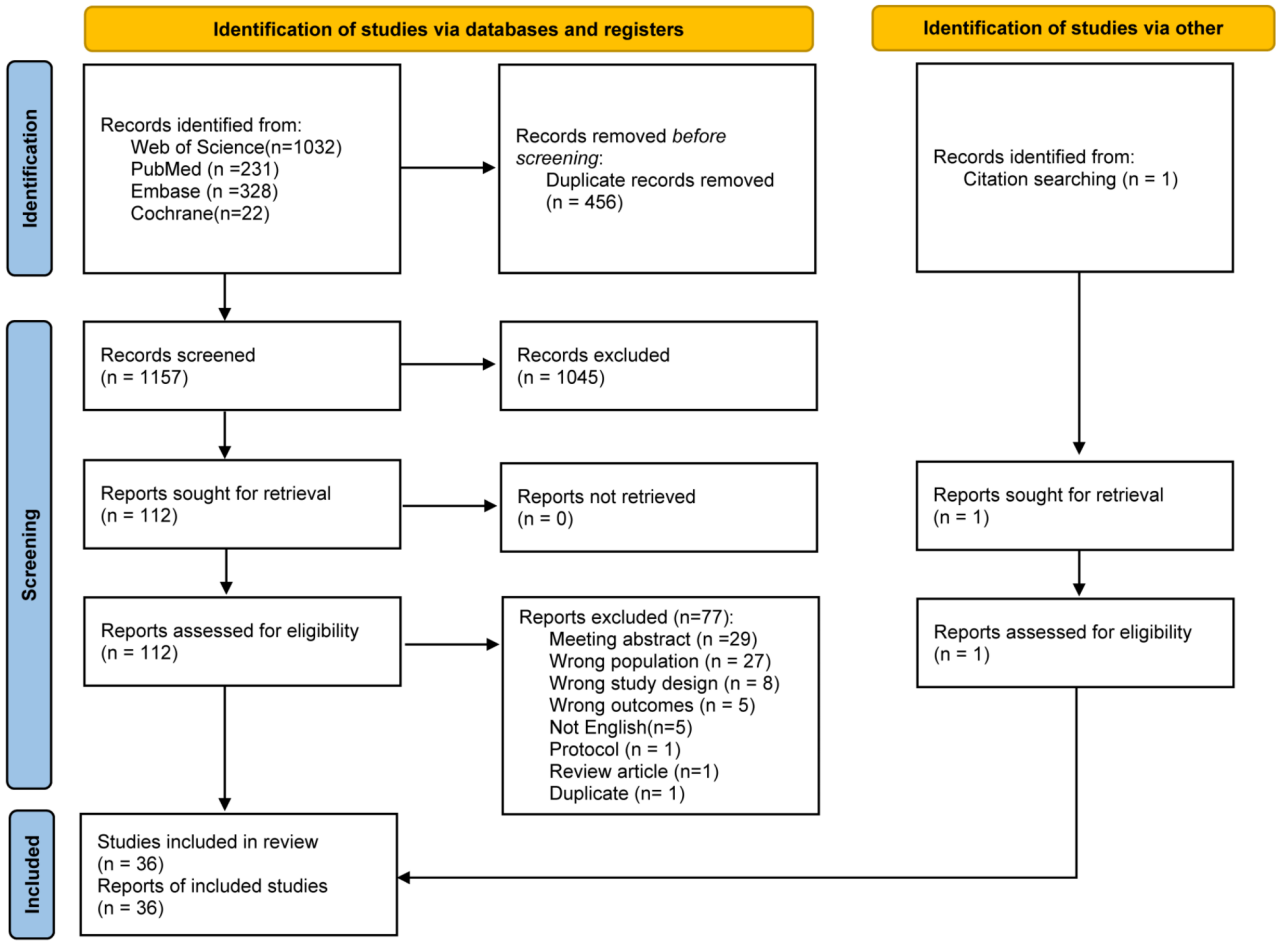

Fig. 1 Flow Diagram of the Study Selection in the Systematic Literature Review

each study graded as low risk. No articles were excluded from this systematic review due to RoB.

Alpha diversity

The alpha diversity of microbiota communities was assessed in 27 of 31 case–control studies and 8 of 9 non-randomized studies, all of which provided precise data or statistical plots. The most commonly used index was the Shannon index, followed by the Simpson index, Chao1, and observed species. None of the funnel plots showed evidence of publication bias upon visual inspection (Figure S3).

On the basis of an analysis of studies comparing genital microbiome richness among CC patients, HCs, and CIN controls, ten studies revealed Chao1 indices in patients ($n = 225$), HCs ($n = 474$) and CIN controls ($n = 356$) (Figs. 2A and 3A) [18, 34–42]. The microbiota of the vaginal samples tended to significantly increase (HC control: SMD = 0.96 [95% CI: 0.71, 1.21], $I^2 = 0\%$; CIN control: SMD = 0.81 [95% CI: 0.55, 1.08], $I^2 = 0\%$), whereas in the cervical samples, no significantly different results were observed (HC control: SMD = 1.08 [95% CI: -0.28, 2.44], $I^2 = 95\%$; CIN control: SMD = 0.12 [95% CI: -0.16, 0.39], $I^2 = 0\%$). The observed species indices were reported in nine studies with patients ($n = 211$), HCs ($n = 408$) and CIN controls ($n = 480$) (Figs. 2B and 3B) [10, 37–39, 41–45]. The cervical sample indices did not significantly differ between patients and HCs (SMD = 0.50, [95% CI: -0.46, 1.46], $I^2 = 89\%$) or between patients and CIN controls (SMD = 0.15, [95% CI: -0.12, 0.43], $I^2 = 2\%$). In contrast, a notable increase was observed in the vaginal sample comparisons (HC control: SMD = 0.93, [95% CI: 0.61, 1.25], $I^2 = 30\%$; CIN control: SMD = 0.92, [95% CI: 0.52, 1.32], $I^2 = 52\%$).

Regarding the assessment of genital microbiome diversity, the Shannon index value was reported in 26 studies involving patients ($n = 516$), HCs ($n = 996$), and CIN controls (Figs. 2C and 3C) ($n = 940$) [10, 11, 18, 34, 36–57]. Both comparisons revealed a significant increase in cervical samples (HC control: SMD = 1.29 [95% CI: 0.61, 1.97], $I^2 = 93\%$; CIN control: SMD = 0.82 [95% CI: 0.19, 1.45], $I^2 = 91\%$) and vaginal samples (HC control: SMD = 1.02 [95% CI: 0.53, 1.50], $I^2 = 85\%$; CIN control: SMD = 0.84 [95% CI: 0.55, 1.13], $I^2 = 52\%$). The Simpson index value

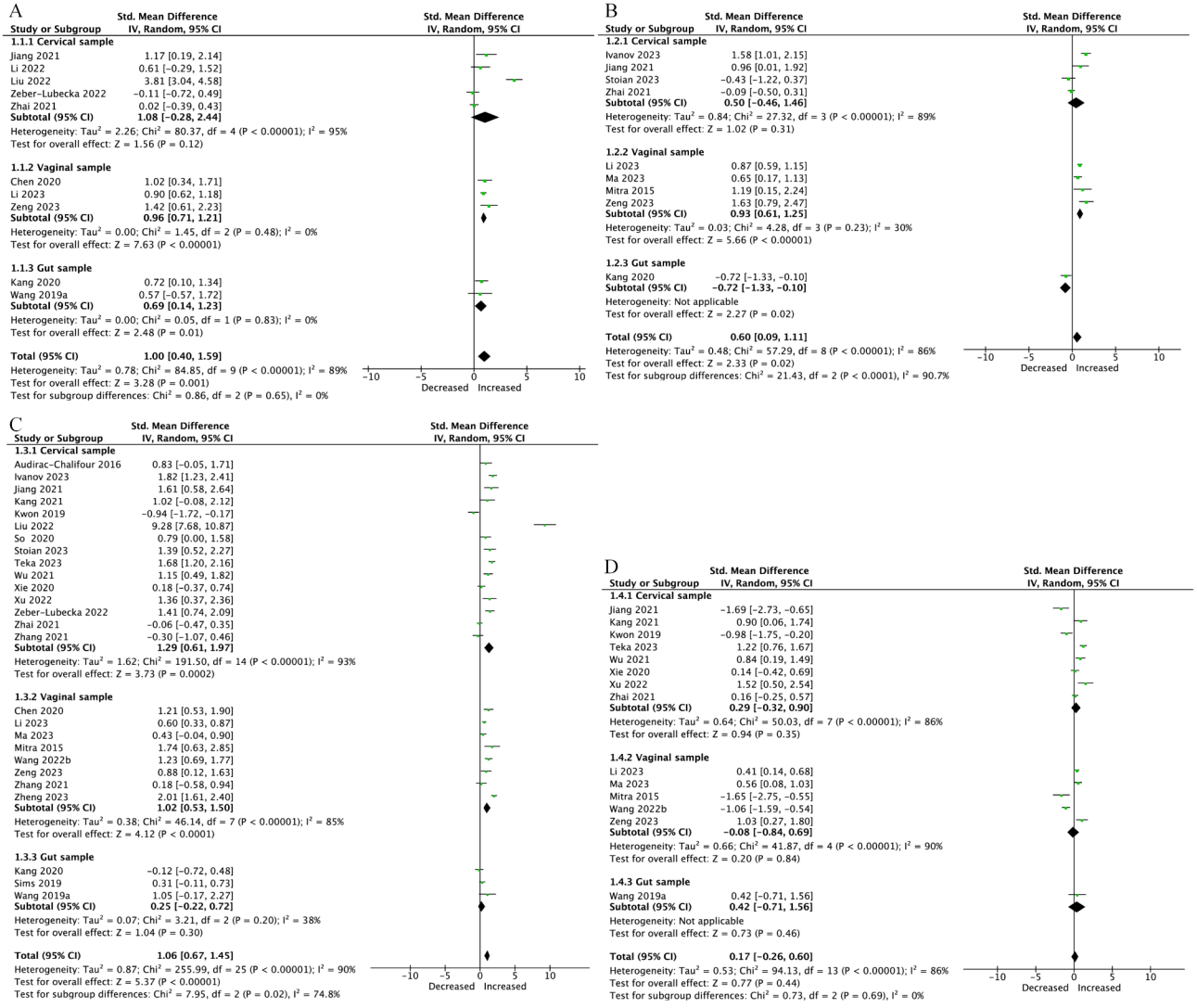

Fig. 2 Forest Plots of Alpha Diversity in the Microbiota of Patients with CC Compared with HC. (**A**) Chao1 (**B**) Observed species (**C**) Shannon index (**D**) Simpson index

was reported in 14 studies involving patients ($n = 337$), HCs ($n = 504$), and CIN controls ($n = 540$) (Figs. 2D and 3D) [10, 18, 37, 39, 41, 42, 44, 47–49, 53–56]. Both comparisons revealed no significant difference in the cervical samples (HC control: SMD = 0.29 [95% CI: -0.32, 0.90], $I^2 = 86\%$; CIN control: SMD = 0.27 [95% CI: -0.29, 0.82], $I^2 = 82\%$), whereas the indices for the vaginal samples presented different results (HC control: SMD = -0.08 [95% CI: -0.84, 0.69], $I^2 = 90\%$; CIN control: SMD = 0.41 [95% CI: 0.01, 0.82], $I^2 = 58\%$).

With respect to the gut microbiota, only three studies evaluated the microbial alterations between patients ($n = 67$) and HCs ($n = 80$) (Fig. 2). The Shannon index value was reported in 3 studies (SMD = 0.25, [95% CI: -0.22, 0.72], $I^2 = 38\%$]), the Chao1 index value was reported in 2 studies (SMD = 0.69, [95% CI: 0.14, 1.23], $I^2 = 0\%$]), the number of observed species was reported in 1 study (SMD = -0.72, [95% CI: -1.33, -0.10]), and the Simpson index value was reported in 1 study (SMD = 0.42, [95% CI: -0.71, 1.56]).

To better understand the heterogeneity among studies, we conducted a subgroup analysis based on geographic region, age group, sample collection techniques, and sequencing methods (Table S4). In the subgroup of participants aged ≤ 50 years, heterogeneity significantly decreased, as indicated by the I^2 value dropping to 0, suggesting that age variations likely contributed to the observed heterogeneity. However, heterogeneity remained high in the swab sampling group, the studies from China group, and the 16 S rRNA sequencing group. A downward trend was noted in these groups, indicating that these factors may influence the results. Further investigation is warranted to confirm these findings.

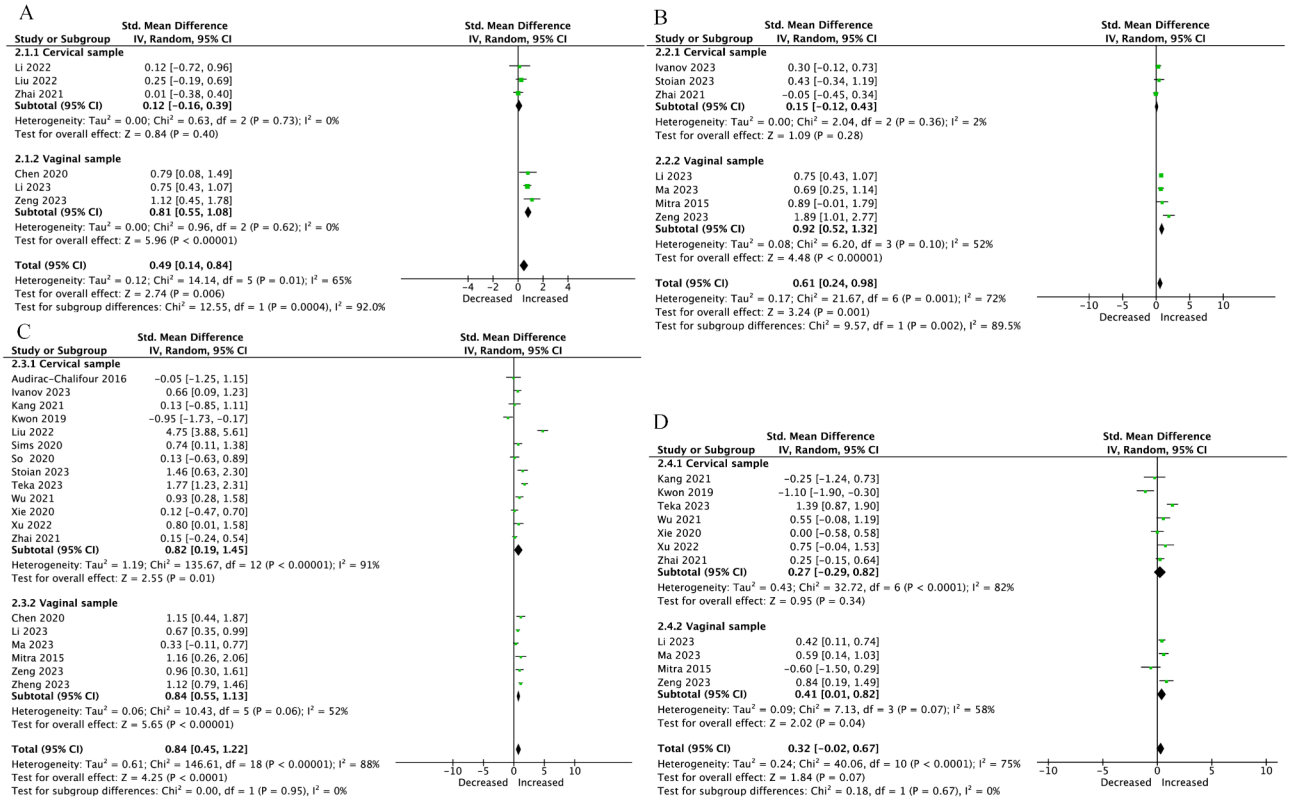

Fig. 3 Forest Plots of Alpha Diversity in the Microbiota of Patients with CC Compared with Patients with CIN. (**A**) Chao1 (**B**) Observed species (**C**) Shannon index (**D**) Simpson index

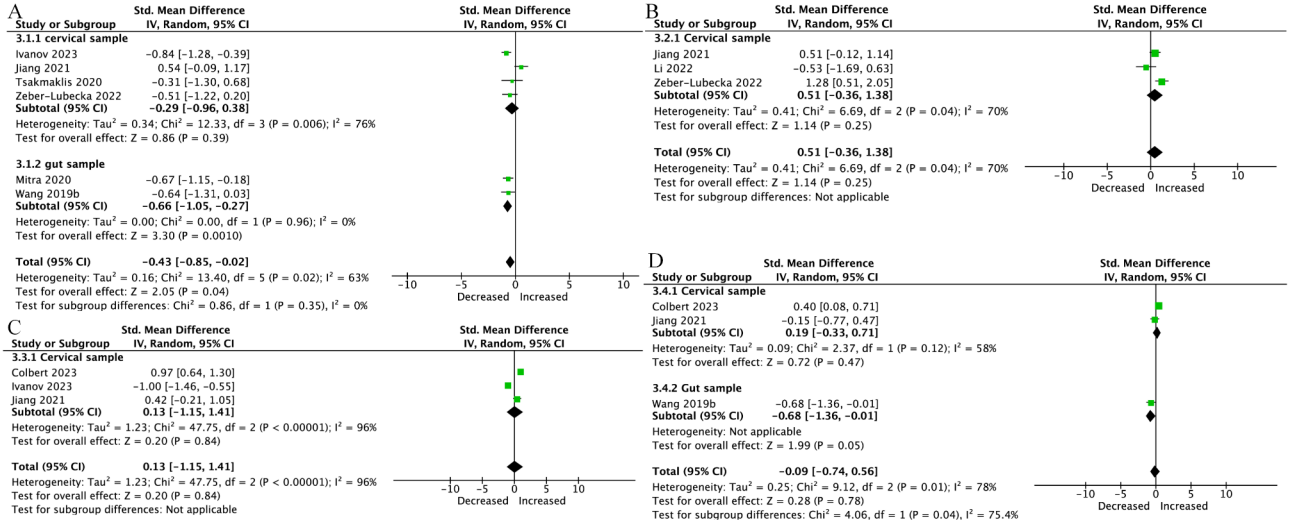

Fig. 4 Forest Plots of Alpha Diversity in the Microbiota of Post-treatment Patients Compared with Pre-treatment Patients. (**A**) Shannon index (**B**) Chao1 (**C**) Observed species (**D**) Simpson index

In nonrandomized trials, the impact of treatments on the microbiome has been the subject of attention. Data on the Shannon index in patients (posttreatment, $n = 126$) compared with controls (pretreatment, $n = 169$) were obtained from six studies [37, 40, 43, 58–60]. A significant decrease in posttreatment patients was shown by the pooled estimate (SMD = -0.43, [95% CI: -0.85, -0.02], $I^2 = 63\%$) (Fig. 4A). Only three publications reported the Chao1 estimator [33, 35, 38] (Fig. 4B), observed species [35, 41, 59] (Fig. 4C), and Simpson index [37, 60, 61] (Fig. 4D), and none of these values demonstrated statistically significant differences.

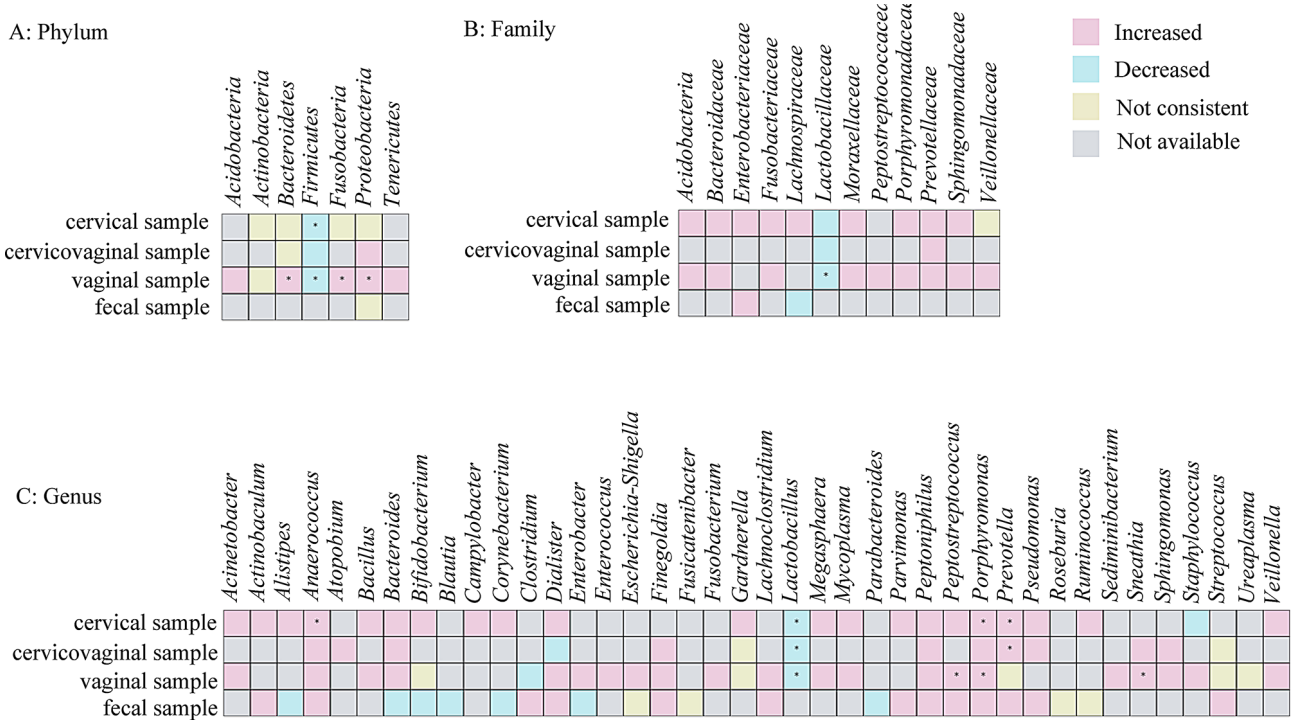

Fig. 5 Summary of Changes in the Relative Abundance of Microbial Taxa from a Sample Category

Beta diversity

The microbial community compositions of the patient and control samples were compared using beta diversity. Twenty-five of the 36 studies reported beta diversity using various measures, with two studies comparing patients to controls as well as comparing the pre- to post-treatment conditions (Table S4). In 19 studies, significant differences in beta diversity were detected in 11 cases involving cervical samples, 4 cases involving vaginal samples, and 4 cases involving fecal samples compared with noncancer controls. However, four studies reported that the cancer patients did not differ significantly from the noncancer controls. While Łaniewski et al. [9] found no differences between cancer patients and controls, they did observe significant differences when participants were clustered on the basis of vaginal PH. Four studies compared the microbial communities of patients before and after antineoplastic therapy. Among them, two studies reported significant differences before and after radiation treatment, whereas the other two reported no significant differences.

Differential abundance of microbial taxa

All the investigations evaluated the relative abundance of microorganisms, and 23 of them reported significant differences between the patient and control groups [9, 18, 34–36, 38, 39, 41–45, 47–49, 51–57, 62]. Overall, seven phyla, 12 families, and 40 genera were identified from four samples: cervical sample, cervicovaginal sample, vaginal sample, and fecal sample.

The within-disorder comparison is illustrated below, with inconsistent findings categorized as "not consistent" (Fig. 5). The majority of consistently observed changes within disorders were replicated by only two studies, indicating a need for further investigation.

Cancer-associated alterations

Cancer specificity was defined as consistent alterations observed in the same direction across three or more studies. Our findings revealed several cancer-associated alterations, including enrichment of the genera *Anaerococcus*, *Peptostreptococcus*, *Porphyromonas*, *Prevotella*, and *Sneathia* as well as depletion of the *Lactobacillus* genus (Figure S4). However, there is limited evidence for consistent enrichment of pathogenic bacteria such as *Anaerococcus*, *Peptostreptococcus*, *Porphyromonas*, *Prevotella*, and *Sneathia*, as the findings were not consistent across more than three studies. Regarding the *Lactobacillus* genus, CST I and CST III, dominated respectively by *Lactobacillus crispatus* and *Lactobacillus iners*, were positively associated with healthy microbiota, as demonstrated in seven and six publications, respectively. Overall, 18 out of 23 studies reported a significant decrease in *Lactobacillus* species in the cervical, cervicovaginal, and vaginal samples of CC patients, providing robust evidence of cancer specificity.

Treatment-associated alterations

In this meta-analysis, none of the patients in the 28 studies used either antibiotics or probiotics before sample collection. A total of 9 studies provided data on how antineoplastic treatment influences the relative abundance of the microbiota [35, 37, 40, 43, 58–61, 63], including 6 studies on chemoradiotherapy (CRT), 1 on pelvic radiotherapy, 1 on radical hysterectomy and 1 encompassing various antineoplastic treatments. Among these, only six studies assessed changes in the microbiota before and after therapy. At the genus level, one study reported a significant increase in the genera *Varibaculum*, *Bosea*, *Actinotignum*, and *Propionimicrobium* and a decrease in *Cutibacterium*, *Acinetobacter*, *Rhodococcus*, *Amaricoccus*, and *Paracoccus* in patients receiving antineoplastic treatments. Additionally, there was evidence of enrichment of *Desulfovibrio* and *Turicibacter* in patients undergoing radical hysterectomy and depletion of the genera *Atopobium* and *Aerococcus* in patients with CRT. However, these treatment-associated alterations have been reported in only single studies, indicating limited evidence and the need for further investigation.

Discussion

This systematic review included data on the cervical, vaginal, or gut microbiota in patients with CC. The present meta-analysis evaluated microbiological alterations by comparing CC patients with nontumor controls and examined changes before and after antineoplastic therapy. The findings are summarized as follows: [1] There was a slight increase in the effect size of the Chao1 and Shannon indices comparing CC with CIN; a moderate increase in this effect size in patients versus HCs; and a slight increase in the Shannon index value was compared between patients before and after treatment; [2] significant differences in beta diversity were consistently observed in the majority of studies (19/25); [3] cancer-associated alterations included a significant decrease in *Lactobacillus* species in all samples, identified in the majority of studies (18/23); and [4] treatment-associated alterations were noted, but evidence was limited and requires further verification.

With respect to alpha diversity (within samples), specific indices, such as the Chao1 estimator for richness, the Simpson index, and the Shannon index for community diversity (both richness and evenness), were used to assess the diversity and abundance of the bacterial microbiota. In the vaginal microbiota, both richness (Chao1 and observed species) and diversity (Shannon index) significantly increased in CC patients compared with HCs or CIN patients. Furthermore, in the cervical microbiota, all richness and diversity indices showed no differences except for a significant increase in the Shannon index value in CC patients compared with HCs. Overall, greater microbiota diversity in the genital tract was observed in more severe pathological conditions, suggesting that microbial dysbiosis of the genital tract, typified by the replacement of *Lactobacillus* species with diverse anaerobic bacteria, may be a contributing factor to CC progression [6, 10]. Previous studies have demonstrated that some intestinal bacteria in colorectal cancer can promote carcinogenesis by modulating inflammatory factors such as NF-κB and IL-6 [19, 64]. Moreover, several cross-sectional studies have shown correlations between IL-4 and *Fusobacterium spp.* [11], as well as between proinflammatory (IL-36γ) and non-*Lactobacillus* dominance [9]. Thus, chronic inflammation may be one of the possible mechanisms by which bacteria associated with CC contribute to cancer progression.

The gut microbiome interacts with the reproductive tract microbiota through direct or estrogen-mediated mechanisms. The proximity of the vagina and anus results in a shared microbiota, with over 30% of bacterial species in common, including *Firmicutes* and *Bacteroidetes* [65]. The gut microbiota may partially function as a reservoir for the vagina microbiota. Furthermore, gut microbial diversity has been shown to influence the composition of vaginal microbiota through the estrogen-mediated gut–vaginal axis. This process is primarily mediated by intestinal bacteria capable of metabolizing estrogen and promoting the growth of *Lactobacillus spp.* through estrogen degradation and reabsorption [66–69]. Microbe-secreted β-glucuronidase and β-glucosidase contribute to the deconjugation of estrogens, thereby facilitating their reabsorption into the circulation. In the female reproductive tract, free estrogen binds to receptors and transmits intracellular signals that increase gluconeogenesis and induce other physiological changes, such as mucus production and epithelial thickening. Enhanced glycogen synthesis facilitates the proliferation of *lactobacilli*, which are essential for maintaining vaginal homeostasis [67, 69].

In addition to linking with the gut-vaginal and gut-brain axes, the gut microbiota also impacts systemic diseases, including cancer, through its physiological activities in the gastrointestinal system, which regulates immune function and metabolic processes. Alterations in gut microbiota significantly influence disease through the production of metabolites such as short-chain fatty acids (SCFA), tryptophan (Trp), and bile acid (BA) metabolites, which are synthesized by diverse microorganisms [70, 71]. These metabolites can promote the differentiation and function of immunosuppressive cells, such as regulatory T cells, while inhibiting inflammatory cells, thereby contributing to the maintenance of both intestinal and systemic immune homeostasis [72, 73]. Additionally, dysbiosis of the gut microbiota can compromise the intestinal barrier and enhance lipopolysaccharide-induced

inflammation, allowing harmful molecules from gut microorganisms to enter the bloodstream through capillaries, thus contributing to the development of distant diseases [74, 75]. However, this review highlights contentious conclusions regarding diversity indices in a small number of studies, showing no significant variations in the Shannon and Simpson indices, a decline in observed species, and an increase in Chao1, thus calling for further research to explore the potential role of gut microbiome in the progression of cervical cancer.

Beta diversity measures are widely employed to assess the similarity between communities, with the majority of studies demonstrating significant differences between patients and controls. Although some studies have shown no significant difference, beta diversity may still serve as a promising diagnostic biomarker.

Although there is limited evidence demonstrating differences between patients before and after treatment in terms of treatment-associated alterations, available studies suggest that antitumor therapy may negatively impact the microbiota composition. However, the treatment-related alterations in microbial communities exhibited inconsistencies across studies in our meta-analysis. Differences in treatment regimens may substantially contribute to this variability. Prior studies indicated that therapies for CC, such as radiotherapy, chemotherapy, and immunotherapy, can compromise the intestinal epithelial barrier, thus facilitating the proliferation of opportunistic pathogenic bacteria [76–78]. Furthermore, radiotherapy can directly influence the microbiota in the gut or vagina, particularly in areas exposed, such as the cervix [79]. Chemotherapy, owing to its systemic toxic effects, leads to immunosuppression and modifies various metabolic pathways, causing significant dysbiosis and the selective enhancement of specific drug-resistant pathogens [80–82]. Immunotherapy might affect the composition of the microbiota by altering microbe-related signaling or metabolic functions controlled by host immunity [83]. Combination therapy, such as concurrent chemoradiotherapy, may affect the microbiota through intricate mechanisms, leading to diverse changes in microbial composition. Additionally, microbial diversity typically diminishes with the progression of antitumor therapy [63]. The variability in microbial sampling time points among the studies analyzed may have contributed to the observed inconsistencies. Dysbiosis during antineoplastic treatments may serve as a mechanism potentially influencing both the response and toxicity to therapies [84, 85].

Additionally, our results suggest that CC may lead to cancer-associated alterations in the microbiota. Consistently, the abundance of the *Lactobacillus* species decreased markedly with the progression of cervical lesions, whereas the abundances of pathogenic bacteria, including *Anaerococcus*, *Peptostreptococcus*, *Porphyromonas*, *Prevotella*, and *Sneathia*, increased significantly. Notably, the *Lactobacillus* species were found to be favorably associated with a healthy state, preventing pathogen invasion in the microenvironment by inhibiting pathogen adherence and producing antimicrobial agents, among other mechanisms [66, 86, 87]. A reduction in *lactobacilli* can disturb the balance of the vaginal ecosystem, promoting the overgrowth of pathogenic bacteria. Specific species linked to a high diversity of microbiome composition, such as *Prevotella*, bacterial vaginosis-associated bacteria (BVAB), and *Sneathia*, are capable of producing sialidases, resulting in mucus breakdown and rendering the cervical epithelium susceptible to tissue damage [88]. BVAB, including *Gardnerella vaginalis*, exhibits proteomic characteristics associated with immune activation, apoptosis, epithelial integrity disruption, and impaired wound healing [89]. Conversely, pathogenic bacteria trigger chronic inflammation and secrete bacterial genotoxins, which contribute to the persistence of inflammation and establish conditions conducive to cancer progression, including cellular and DNA damage [90, 91]. Tissue damage and the establishment of an inflammatory environment increase the susceptibility of tissues to HPV infection [92]. HPV persistence is a known causative factor of CC through the integration of viral nucleic acid into host genomes and the induction of mutations in host cells [19, 93, 94]. Previous studies have shown that bacteria such as *Prevotella* and *Sneathia* are linked to persistent HPV infection [88, 95–97], although the precise mechanism of interaction between the two remains unclear and warrants further investigation.

Accumulating evidence indicates that microbial dysbiosis is linked to cancer progression, as well as the efficacy and side effects of anti-cancer treatments, suggesting that microbial-targeted therapy holds significant clinical promise. Microbial dysbiosis is associated with persistent HPV infection and the advancement of CIN during tumor progression [88]. However, the diverse proinflammatory environment in women with CIN cannot be entirely rectified through surgical resection or HPV clearance. The inability to restore the *Lactobacillus*-rich CST may elucidate the persistently elevated risk of recurrence of pre-invasive and invasive disease in women [98]. The vaginal probiotic *Lactobacillus*, specifically the *L. crispatus* strain CTV-05 (administered as a vaginal suppository, LACTIN-V), is primarily utilized for treating bacterial vaginosis and is currently in clinical trials, indicating the potential of vaginal probiotics in modulating the vaginal microbiome [99, 100]. The microbiome can simultaneously influence the efficacy of anti-cancer therapies through various mechanisms, including translocation, immune modulation, metabolism, and enzymatic degradation [101, 102]. The composition of the

gut microbiota affects the efficacy of chemotherapeutic agents, such as irinotecan, by modifying drug metabolism and modulating the host immune response [103]. This modulation also influences radiotherapy and immunotherapy, including PD-1/PD-L1 blockade, primarily by mediating T cell activation, enhancing T cell priming, and facilitating T cell accumulation at tumor sites [22, 104–106]. Utilizing antibiotics or other inhibitors to reduce gut microbiota, supplementation through fecal microbiota transplantation (FMT) or vaginal microbiota transplantation (VMT), and enhancement with prebiotics or probiotics may serve to prevent or alleviate cervical cancer and improve responses to cancer therapy.

Overall, the relationship between the microbiota (cervical, vaginal and gut) and CC, as well as its relationship with treatment, is relatively poorly understood. Dysbiosis may affect the development of CC through mechanisms such as chronic inflammation and persistent HPV infection. Local dysbiosis caused by antitumor therapies may influence treatment side effects. However, these mechanisms are still unclear and need to be explored in more appropriate mechanistic studies.

This meta-analysis has several limitations. First, the majority of studies contained modest sample sizes, which indicates that our analysis may be preliminary and that larger sample sizes are necessary. Additionally, inadequate data prevented the inclusion of variables such as the Pielou index, Good's coverage, and the ACE index in this meta-analysis. Second, our study utilized multiple sequencing technologies, specifically 16 S rRNA gene sequencing, 16 S rDNA gene sequencing, and shotgun metagenomic sequencing [107–109]. Although 16 S rRNA gene sequencing serves as the standard approach for microbial community analysis and yields important bacterial taxonomic data, it predominantly depends on the amplification of specific regions of the 16 S rRNA gene, which may restrict its resolution in distinguishing certain species or subspecies [107]. Shotgun metagenomic sequencing provides a more comprehensive analysis of microbial communities and offers functional insights into microorganisms [109]. However, it exhibits greater vulnerability to sample contamination, biases, and difficulties in data processing. The heterogeneity among studies resulting from varying sequencing technologies may have introduced bias into our results. Moreover, differences in technical platforms result in variations in sequencing depth, coverage, and error rates, which can impact microbiota diversity estimation and lead to discrepancies in species classification, potentially affecting the analysis outcomes [110].

Third, this systematic review included several nonrandomized trial studies, offering preliminary insights into the impact of antineoplastic treatments on the microbiota. However, these studies were limited in number and exhibited inconsistencies in their findings, thus providing insufficient evidence to draw firm conclusions on how anticancer treatments affect the microbiota, thereby necessitating additional research. Finally, we did not emphasize the functional impact of the microbiota on the progression of cancer, although previous studies have demonstrated associations between the microbiota (e.g., *Fusobacterium spp.*, non-*Lactobacillus* dominance) and mediators such as proinflammatory (IL-36γ), chemotactic (MIP1β), hematopoietic (FLT3 ligand) and adaptive immune response cytokines (IL-2, IL-4 and soluble CD40 ligand) [9, 11]. This finding emphasizes how vital functional analysis is a crucial tool for comprehending how host–microbiome interactions contribute to CC.

Conclusion

In conclusion, our study highlights distinct changes in the genital and gut microbiota among patients with CC. These alterations are characterized by a notable increase in alpha diversity, a substantial decrease in the relative abundance of *Lactobacillus spp.* and an increase in the relative abundance of pathogenic microbes compared with those of the controls. Furthermore, treatment-associated microbiota alterations have also been incipient, which may provide a cornerstone for the interaction of antitumor therapies with the microbiota. Therefore, more clinical studies are warranted to investigate treatment–microbiome interactions and host–microbiome interactions in the context of CC and in vivo and in vitro experiments to explore the mechanism behind this phenomenon. Finally, a clearer understanding of the role of microorganisms in the progression of CC and their interactions with anticancer therapies may lead to new opportunities for cancer prevention, precision therapy, and improved quality of life for women.

Supplementary Information

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Supplementary Material 1

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Author contributions
Conceptualization, J.L. and Q.W.; methodology, Q.W. and M.C.; screening and assessment of eligible studies, M.C. and S.W.; data extraction, S.W., Y.M., X.L., and J.F.; quality assessment, Y.M. X.L., and J.F.; original draft preparation, Q.W.; supervision and funding acquisition, J.L. and M.C. All the authors reviewed and agreed to the final version of the manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author, [MHC], upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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