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Review

Microbiota Status and Endometrial Cancer: A Narrative Review About Possible Correlations in Affected Versus Healthy Patients

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Abstract: (1) Background: Microbiota could be related to tumorigenesis through the persistence of an inflammatory state, also at the endometrial level. Inflammation, in fact, is involved in the promotion of genetic instability and in a favorable microenvironment for tumor growth. One pathway could be the disruption of the epithelial/mucosal barrier, with the activation of cytokines. The microbiota also seem to favor other involved patterns, such as insulin resistance and increased adipose tissue. (2) Methods: The online search for this review was based on keywords such as "endometrial cancer" and "microbiota" on the main online scientific database. Our objective is a narrative up-to-date review of the current literature on gynecological microbiota; we analyze the possible correlations with known modifying and promoting oncological factors (i.e., Body Mass Index- BMI, menopause, pH), with particular attention to vaginal and uterine microorganisms respective to the development of endometrial cancer in comparison to healthy women. (3) Results: Various species and distributions of bacteria could be related to tumorigenesis and induce alterations in cell signaling and cycle pathways, including those in the gynecological field. (4) Conclusions: In the literature, the different composition of uterine and vaginal microbiota has been analyzed in the past years, and their diversity and actions seem to correlate with possible oncological effects.

Keywords: microbiota; microbiome; endometrial cancer; gynecology

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1. Introduction

Endometrial carcinoma (EC) is a malignant neoplasm that affects the endometrium [1]. It represents the most frequent gynecological cancer in industrialized countries, and the fourth in terms of mortality [2]. Among the risk factors, [1,3,4] the following are known: old age, ethnicity, hormonal deregulation, low parity, metabolic syndrome, genetic predisposition, and pro-inflammatory factors. In the past years, scientific attention has also focused on EC and the possible role of microbiota [5]. In the literature, in fact, it is described that microbial dysbiosis could be associated with several gynecological disorders, such as endometriosis, chronic endometritis, dysfunctional menstrual bleeding, infertility, and some tumors such as endometrial cancer [5]. The term "microbiota" indicates the living microorganisms found in a defined environment and varies from site to site [6]. The "microbioma" describes the collection of genomes from all the microorganisms in the environment, not only the community but also the microbial structural elements, metabolites, and the related environmental conditions. It has been estimated that the ratio between human cells and bacterial cells is 1:1/1:377 [7]. For the understanding of these microorganisms' complexity, α-diversity represents the abundance (number of taxa) and uniformity (relative presence of taxa) of a sample within a habitat type; β-diversity measures the variability in the composition of the bacterial community between samples of a habitat [7]. The microbioma begins to form from birth, different species rapidly accumulate, and its composition changes over time until it becomes relatively stable in adulthood [8]. Each

person has different bacterial species and subspecies: the microbiome is unique for each individual and becomes more diverse in the elderly. Its composition varies depending on the body location, but also several other exogenous and endogenous factors [9] can influence its structure, as in the case of cancer [10–12]. Pollution could also act on the microbiota and correlate with endometrial tumors. Chao et al. [13] conducted a study to analyze the microbiota composition of endometrial lavage samples from women with EC or endometrial hyperplasia (EH), versus benign endometrial conditions [14]. The study highlighted the prevalence of two types of bacteria known for their ability to degrade plastics: *Bacillus pseudofirmus* and *Stenotrophomonas rhizophila*. *Bacillus pseudofirmus*, a facultative aerobic bacterium, could degrade polyethylene-based plastics like low-density polyethylene [15]. Similarly, *Stenotrophomonas rhizophila* has been identified for its efficacy in breaking down polyvinyl alcohol and removing heavy metals from polluted water [16]. These plastic-degrading bacteria in the uterine microbiota might reflect an increased exposure to environmental pollutants, particularly plastics, which could potentially contribute to the carcinogenic processes in the endometrium [14–16].

Moreover, the microbiota of the female reproductive organs are site-specific (Table 1); even though bacteria are in a continuum between the upper and lower tract, there are significant differences between their diversity and proportions [17]. Changes in this equilibrium could alter the local homeostasis, in different situations such as modifications in the endometrial pH value, temperature, humidity and menstruation or pregnancy [18–21].

When the microbiota are in equilibrium and physiological conditions, it stimulates the regeneration of epithelial cells and the production of mucus and antimicrobial peptides [22–24], with protective effects that inhibit the passage of toxins and bacteria into the bloodstream and could prevent cancer, obesity, chronic inflammation, and metabolic syndrome [22–25]. Dysbiosis appears when a bacteria imbalance is persistent, the stability and diversity of colonies diminish, and opportunistic microorganisms overgrow [26–28], causing inflammation. In fact, the microbiota could be correlated with the development and subsequent persistence of an inflammatory state, also fundamental in carcinogenesis [29–31]. It is involved in tumor development also through different mechanisms, including the promotion of genetic instability and of a favorable microenvironment for tumor growth [32], both local and systemic [33,34]. Genital microbiota are interconnected with all the abdominal organs, and the metabolic, immunological, and hormonal perturbations of intestinal microorganisms can contribute to carcinogenesis of the genital tract [23,35]. Moreover, alterations of microbiota may affect the level of circulating estrogens, related to the development of obesity, metabolic syndromes, cognitive dysfunction, fertility problems, polycystic ovary syndrome, and cancer [23,36–39]. This is possible through intermediaries such as pattern recognition receptors, as toll-like receptor 4 (TLR-4) and its ligands, and the upregulation of pro-inflammatory cytokines (including IL17, TNF-α, and IFN-γ) [40]. TNF-α and IL6 promote the expression of aromatases, 17β-hydroxysteroid dehydrogenase, and estrone sulfatase (enzymes involved in ovarian steroidogenesis) [41]. In the case of gynecologic cancers, estrogen levels could influence the endometrium through the gut–vaginal microbiome axis [38,42], and the intestinal microbiota could also regulate the level of circulating estrogen through the secretion of β-glucuronidases, which activates estrogen action [38]. Furthermore, the microbiome also seems to favor other conditions involved in the carcinogenesis process, such as insulin resistance and the increase in adipose tissue [32,43]. The microbiome could contribute to tumor development by disrupting the epithelial/mucosal barrier of organs, allowing bacteria and their metabolites to access compartments with which they are not normally in contact. This stimulates a chronic local inflammatory response, and acts as growth factors, activating repair processes, inducing the migration of tumor cells, and promoting angiogenesis [44–46]. The normal microbiome are altered, with an incremented production of pro-inflammatory metabolites such as NOS2 (nitric oxide synthetase), RNS (reactive nitrogen species), and other reactive species of oxygen. Different bacteria can induce carcinogenesis through the alteration of cellular signaling pathways and the cell cycle [47,48], leading to reduced apoptosis, the

promotion of cell migration and invasion, cell proliferation, and reduced DNA stability. Many microorganisms can cause chronic infections and produce toxins that alter the cell cycle and cell growth. This chronic infection, through the activation of Cyclin D1 and MAPK (Mitogen-Activated Protein Kinase) pathway, activates cell proliferation and DNA replication with the activation of oncogenes and an increase in genetic mutations [48]. Another studied mechanism in chronic infection is in fact the reduction in apoptosis through the inactivation of the RB protein (Retinoblastoma Protein) and the modulation of the expression of proteins of the Bcl2 family. In this way, the atypical cells avoid the destruction processes and continue the neoplastic transformation [48]. These numerous mechanisms can cause or implement endometrial carcinogenesis [49], which is why it is essential to investigate which species are present at a gynecological level, and which alterations are most connected to EC. All these mechanisms favor a shift of the microbiome to a pathological state, such as the metabolization of carcinogenic substances [48]. The role of inflammation in the development of EC is known, but the contribution of genital microbiota is not yet completely clear [41,50–52].

2. Materials and Methods

The preliminary analysis was carried out based on information gathered from PubMed, Scholar, Embase, Scopus, etc. The identification of the articles was based on a keyword search for "endometrial cancer" and "microbiota". Articles in the English language were filtered according to the relevance of the scientific research. Data on other gynecological cancers or only on gut microbiota were excluded. Citation searching provided 145 articles about the uterine or vaginal microbiome for our narrative review (Prisma flow-chart, Figure 1).

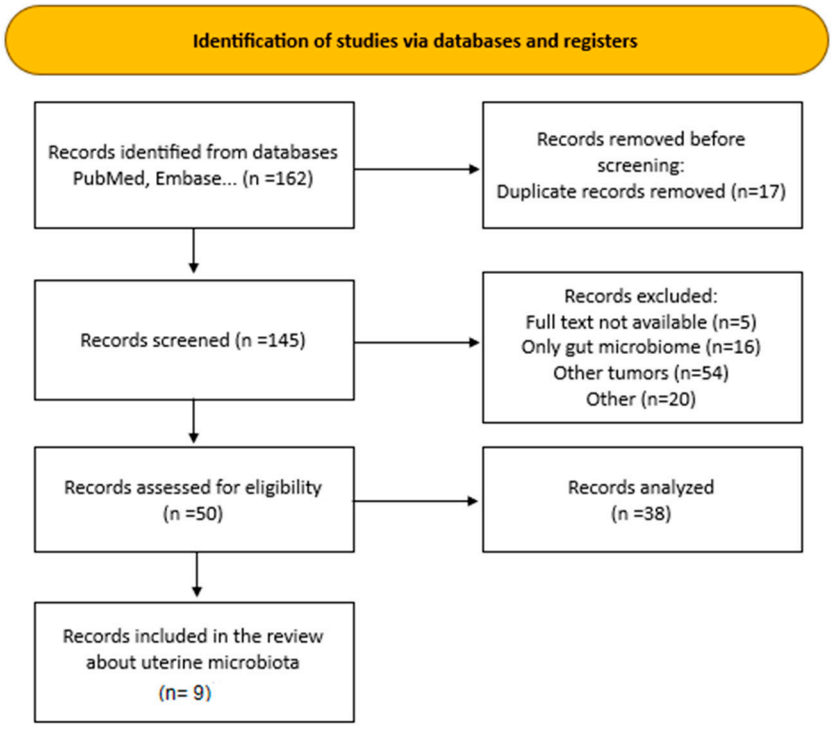

Figure 1. PRISMA flow-chart.

In Table 2, we analyzed in detail nine articles about uterine microbiota and EC, considering the possible direct association of uterine microbiota and the site of the tumor.

3. Results

3.1. Vaginal Microbiota

The vaginal microbiota are characterized by the predominance of *Lactobacillus*, followed by *Gardnerella*, *Vibrio*, and *Atopobium* genera [53–55] (Table 1). *Lactobacillus* is a facultatively anaerobic and microaerophilic Gram-positive bacteria. Physiologically, the vaginal microbiota are characterized not only by the presence of the *Lactobacillus*, but also by a low variability of microorganisms. In women of a reproductive age, five main bacterial community state types (CSTs) have been identified [56]: CST-1 with a prevalence of *L. crispatus*; CST-2 dominated by *L. gasseri*; CST-3 with *L. iners*; CST-4 with a greater microbial variability spp. [57]; and CST-5 with *L. jensenii* predominance. Under normal conditions, the vaginal microbiota are represented by one of these four CSTs dominated by *Lactobacillus*, which protects the host from pathogens through bacteriocins, hydrogen peroxide, lactic acid, and th competitive exclusion of the growth of other bacteria [57,58]. *Lactobacilli* produce lactic acid by glycogen degradation. This production of lactic acid leads to a vaginal pH of 2.8–4.2: a low vaginal pH prevents the growth of pathogenic bacteria [59–63]. Another mechanism through *Lactobacilli* have a protective role against possible pathogens is by adhering to vaginal epithelial cells, therefore occupying space, and producing toxic compounds to other bacteria [64]. Vaginal microbiota protect the reproductive tract against bacterial vaginosis, fungal infections, sexually transmitted infections (such as HIV), and urinary infections [65]. It is influenced by several factors, such as ethnicity, geographical and sociodemographic background, genetic and behavioral factors, contraception, and sexual activity [66–69]. Hormonal changes also influence the composition of the microbiome, although menstrual fluctuations do not appear to particularly modify its structure [70]. During puberty, a change in the microbiota is observed from anaerobic bacteria to *Lactobacilli* [70]. With menopause, then, we observe a return to a composition of anaerobic bacteria, with a reduction in *Lactobacilli* [71,72]. Estrogen is responsible for this change; in fact, a positive correlation with estradiol has been demonstrated in postmenopausal women taking estrogen-based hormone replacement therapy [71–73]. Furthermore, with advanced women's age, there is an increase in the α-diversity of the vaginal microbiome, contrary to what happens in the uterus [74]. In particular, Brotman et al.'s study in 2014 described a prevalence of *Lactobacilli* in the premenopausal period; during perimenopausal age, it described the presence of *Atopobium*; and in the postmenopausal phase, it highlighted a shift towards *Streptococcus* and *Prevotella* [72]. A decrease in female estrogen levels throughout years is known. These data have been correlated to possible differences in the nutrients that support the growth of the vaginal microbiota, creating an unfavorable microenvironment for *Lactobacilli*. In fact, the local administration of low-dose estrogen leads to an increase in this population [72]. Another typical characteristic of the vaginal microbiota is the presence of biofilm, colonies of microorganisms that cover solid surfaces, also on the vaginal epithelial cells [75]. The overgrowth of species such as *Candida spp.* and *G. vaginalis* can lead to the formation of negative biofilms, resulting in dysbiosis [75–77]. Differences in the vaginal microbiome have also been observed based on ethnicity: African women have a greater α-diversity; however, European women have a greater presence of *Lactobacilli* [78,79]. Another aspect that influences the vaginal microbiome is obesity [80]. The predominance of *Lactobacilli* in healthy weight women is 48.2%, while in overweight or obese women, it has been reported as 40.1%. In African women, the different prevalence of *Lactobacilli* between healthy weight and overweight/obese women is statistically significant, whereas in European women, it is not. The dominance of *Lactobacillus* is still greater in healthy weight European women than in African women. Overweight/obese women present greater α-diversity than healthy weight ones. Interestingly, in obese women with significant weight loss after bariatric surgery, there is an increase in *Lactobacilli* [81]. Also, diet could influence vaginal microbiota: poor intake of micronutrients, such as vitamin A, C, D, and E, and β-carotene, folate, and calcium, seems to increase the risk of bacterial vaginosis [82]. Furthermore, a diet high in fat has also been shown to increase the risk of vaginosis [82,83]. A diet rich in high levels of glycogen promotes the proliferation of

Lactobacilli: glycogen is used by bacteria to produce lactic acid. Lactic acid contributes to maintaining low vaginal pH and this, with the secretion of antimicrobial products (such as lactocidin, acidolin, lactacin B, and H_2O_2), prevents colonization by other bacteria [84,85].

Altered microbiota are not only linked to infections, but also to EC [86]: *Lactobacillus iners* [87] was found to be more frequent in patients with a benign condition, whereas *Dialister pneumosintes* and *Mobiluncus curtisii* were more frequent in oncological patients. *Mobiluncus curtisi* and *Dialister pneumosintes*, in particular, are more common in vaginal samples of affected women, and could be described as potential endometrial cancer co-factors. In fact, scientific research affirmed that vaginal sampling is an accurate surrogate of the microbiome within the uterus, and *Porphyromonas* and *Atopobium* species are also linked to endometrial carcinoma [52,88–90].

Moreover, α- and β-diversity also correlate with the tumor grade in the case of EC [89]. Four vaginal CSTs were associated with variations within tumor grades and histology. Benign disease is associated to CST1, while low-grade disease to CST2, and high-grade disease to both CST3 and CST4, considering the most abundant phyla as *Firmicutes*, *Actinobacteria*, and *Bacteroidetes.* The vaginal microbiome can segregate not just a benign gynecologic condition from EC, but also correlates with the cancer grade and histology. Despite this valuable information, the correlations between endometrial cancer and vaginal microbiota are still scarcely deepened [89].

3.2. Uterine Microbiota

The pathogenic influences of uterine microbiota on endometrial carcinogenesis remain not completely clear [91]. In the past, the feminine upper reproductive tract was considered sterile [55]. One hypothesized mechanism was the presence of the cervical mucus plug, which was believed to prevent the ascent of bacteria into the uterus, according to Henry Tissier's assumption in 1900 [92]. Uterus has instead been found to be inhabited by several bacterial species [92] (Table 1). The cervical mucus plug is not entirely resistant to the passage of microorganisms from the vaginal microbiota [93]. Furthermore, peristaltic uterine contractions can also contribute to the movement of bacteria towards the uterus, from the cervix or from the bloodstream or through retrograde transmission in the Fallopian tubes, trough the insertion of an intrauterine device, or gynecological procedures (e.g., assisted reproductive technology) [65,94–100]. The uterine microbiota are mainly composed of the genera *Lactobacillus*, *Gardnerella*, *Prevotella*, and *Bacteroides*, and also *Firmicutes* and *Actinobacteria*, being in common with the vaginal microbiota [101,102]. Mitchell et al.'s study [103] described the presence of uterine microbiota consisting mainly of *Lactobacilli*, with few bacterial variabilities; furthermore, it also confirmed the presence of *Gardnerella*, *Atopobium*, *Prevotella*, and *Sneathia* in the normal endometrial microbiota [103]. Moreno et al. described the presence of *Lactobacillus*, followed by *Gardnerella*, *Bifidobacterium*, *Streptococcus*, and *Prevotella* [102]. However, it has been observed that in the endometrium, there is a great variety of microorganisms compared to the vaginal microbiota [104,105], with a lower bacterial biomass [103]. Endometrial microbiota contain 10,000 fewer bacteria than the vaginal canal [58,106]. The *Lactobacillus* sp. has been predominantly identified in the endometrium, in a significantly reduced quantity compared to the vagina (30.6% versus 99.97%) [58]. Published data described a higher microbial diversity in the upper reproductive tract than in the lower one (vagina and cervix), with different compositions [58,105,107–116], variable in different conditions and diseases [117]. Moreover, EC seems to be more correlated with taxa *Firmicutes* (*Anaerostipes*, *Dialister*, *Peptoniphilus*, *Ruminococcus*, and *Anaerotruncus*), *Spirochaetes* (*Treponema*), *Actinobacteria* (*Atopobium*), *Bacteroidetes* (*Bacteroides* and *Porphyromonas*), and *Proteobacteria* (*Arthrospira*) [90]. *Atopobium vaginae* and *Porphyromonas* sp. (99% *P. somerae*) were significantly related to endometrial cancer, and also a higher vaginal pH (>4.5) [90]. *Micrococcus* sp. was identified as specific to EC. Higher mRNA pro-inflammatory levels and oncogenic IL6 and IL17 are associated with these microorganisms [118]. Effects of different colonization are known to act on cancerogenesis, fertility, pregnancy outcomes, or the stimulation of the immune system [102,103].

Another oncological pattern is a decrease in *Lactobacillus* or *Firmicutes* and an increase in *Proteobacteria* (*Staphylococcus*, *E. coli*, etc.), *Bacteroidetes* (*Bacteroides fragilis*, *Prevotella*, *Bacteroides*, etc.), and *Actinobacteria* (*Gardnerella*, *Bifidobacteria*, etc.) [117]. Bacteria profiles of the female genital tract change over the course of a woman's age, depending on several factors [119]. The composition of the uterine microbiome and the development of cancer could be influenced by menopause, BMI, and increased vaginal pH, which are also known as independent risk factors for EC [120]. Menopause is a phase of a woman's life that can be subjected to various hormonal, physiological, and non-physiological changes [121]. A reduction in uterine α-diversity was observed at this age, unlike the vaginal microbiota, where menopause causes an augmented α-diversity. During this period, an increase in *Anaerococcus*, *Peptoniphilus*, and *Porphyromonas* species is observed at the endometrial level [52]. Another studied factor is the possible correlation with the increased vaginal pH. This parameter could cause an increase in the α- and β-diversity of the vaginal microbiota; meanwhile, no statistically significant difference was observed in the uterus [52,103]. Chen et al.'s study also analyzed the uterine microbiota in relation to the BMI [51]: no statistically significant difference was observed, only an increase in α-diversity in the lower reproductive tract. Kaakoush et al.'s study looked for a possible correlation between changes in the endometrial microbiota in the case of obesity and the development of EC [122]. An increase in *Sphingomonas*, *Methylobacterium*, and *Brevundimonas* was found both in women with obesity and EC, suggesting that obesity could influence the composition of the uterine microbiota in a pro-carcinogenic sense. *Lactobacilli*, instead, were influenced by the presence of carcinoma, but not by obesity [122]. Moreover, microbiota of obese women affected by EC presented a greater variability compared to that of non-obese patients. This study also found a greater abundance of *Firmicutes* in EC in non-obese patients, compared to obese women [122]. It is evident that there is an important interplay between uterine microbiota, obesity, and endometrial cancer [123], which has to be more understood.

Table 1. Microbiota distributions in female genital tract [124].

Lower Third of the Vagina, Posterior Vault, and Cervical Mucus	**Endometrium**	**Fallopian Tubes**	**Pouch of Douglas**
Lactobacillus Others	*Lactobacillus* *Pseudomonas* *Acinetobacter* *Vagococcus* *Sphyngobium* *Comamondaceae* *Arthrobacter* *Dysgonomonas* *Shewanella* *Pseudomonadaceae* *Delitia* *Tissierellaceae* *Sphingomonas* *Erysipelotrichaceae* *Erysipelothrix* Others	*Acinetobacter* *Comamonas* *Pseudomonas* *Pseudomonadaceae* *Dysgonomonas* *Vagococcus* *Comamondaceae* *Delitia* *Arthrobacter* *Sphingobium* *Shewanella* *Sphingomonas* *Facklamia* *Stenotrophomonas* *Lactobacillus* *Erysipelotrichaceae* *Tissierellaceae* *Micrococcoceae* *Staphylococcus* *Oxalobacteriacea* *Erysipelothrix* Others	*Pseudomonas* *Vagococcus* *Acinetobacter* *Sphyngobium* *Comamondaceae* *Shewanella* *Dysgonomonas* *Delitia* *Tissierellaceae* *Pseudomonadaceae* *Arthrobacter* *Erysipelotrichaceae* *Sphingomonas* *Erysipelothrix* Others

Table 2. Review of Uterine Microbiota and Endometrial Cancer (EC).

	Article	Year of Publication	Sample	Ethnicity and/or Study Place	Results
1	Mikamo H, et al. [125]	1993	20 EC vs. 20 benign uterine disease participants	Japanese Department of Obstetrics and Gynecology, School of Medicine, Gifu University, Japan	EC: *Streptococcus agalactiae*, *E. coli*, *Klebsiella pneumoniae*, *Bacteroides distasonis*, and *Prevotella bivia*. Controls: *Staphylococcus epidermidis*, *L. acidophilus*, and *E. faecalis*.
2	Walther-Antonio MR et al. [90]	2016	17 EC, 4 hyperplasia, 10 benign uterine disease patients	Gynecologic Division, Mayo Clinic, Rochester, MN, USA	EC: *Firmicutes* (*Anaerostipes*, *ph2*, *Dialister*, *Peptoniphilus*, *Ruminococcus*, *and Anaerotruncus*), *Spirochaetes* (*Treponema*), *Actinobacteria* (*Atopobium*), *Bacteroidetes* (*Bacteroides* and *Porphyromonas*), *and Proteobacteria* (*Arthrospira*). Controls: *Staphylococcus*, *Blautia* (*Firmicutes*), and *Parabacteroides* (*Bacteroidetes*). *Atopium vaginae* and *Porphyromonas* sp. coexistence is more associated with cancer.
3	Walsh et al. [52]	2019	66 EC (56 type 1; and 10 type 2) cases; 7 atypical hyperplasia patients; 75 benign uterine disease controls	Division of Gynecologic Surgery at Mayo Clinic in Rochester, MN, USA	EC: *Porphyromas somerae*. Significant β-diversity in the lower reproductive tract, but this difference is not significant in the uterus.
4	Gressel GM et al. [88]	2021	14 EC, 11 serous tumors cases vs. 10 controls	Caucasian, Hispanic Division of Gynecologic Oncology, Department of Obstetrics and Gynecology and Women's Health, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY, USA	α-Diversity is greater in endometrioid EC than serous carcinomas. There was a reduction in *Lactobacillus* at the cervical-vaginal level and an increase in *Pseudomonas* at the uterine level in serous cancers.
5	Lu W et al. [118]	2021	25 EC cases vs. 25 controls	Chinese First Affiliated Hospital of Fujian Medical University, China	EC: *Micrococcus* (*Actinobacteria*). Controls: *Pseudoramibacter*, *Megamonas*, *Eubacterium* (*Firmicutes*), *Rhodobacter*, *Vogesella*, *Bilophila*, and *Rheinheimera* (*Proteobacteria*). EC: reduction in α-diversity compared to controls, differences in β-diversity between patients with EC and controls.
6	Li C. et al. [126]	2021	30 EC cases vs. 10 controls	Chinese Shanghai First Maternity and Infant Hospital affiliated with Tongji University, China	EC: prevalence of *Pelomonas* and *Prevotella*, reduction in bacteria variability.
7	Chen P. et al. [127]	2022	9 EC patients vs. 8 controls	Reproductive Medicine Center, Sun Yat-sen University, Guangzhou, China.	Description of more than 5000 functionally active microorganisms and of host–microbiota crosstalk in case of EC.
8	Chao A. et al. [13]	2022	35 endometrial lavage specimens (hyperplasia, n = 18; EC, n = 7; metastaticEC, n = 2; benign endometrial lesions, n = 8) vs 13 control women	Linkou Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taoyuan, Taiwan	EC/EH: over-represented *Bacillus Pseudofirmus* and *Stenotrophomonas Rhizophila*.
9	Wang L. et al. [128]	2022	28 EC (an analysis of the affected and the non-oncologic tissue for the same patient) cases	Chinese Department of Obstetrics and Gynecology of a comprehensive tertiary hospital in Taiyuan, China	EC: *Prevotella*, *Atopobium*, *Anaerococcus*, *Dialister*, *Porphyromonas*, and *Peptoniphilus*, with increased α-diversity. *Lactobacillus* and *Gardnerella* were present in both EC and adjacent non-EC.

4. Discussion

To consider the multiple elements related to EC, it is important to start from the inner uterine endometrial organization [129], typically with a basal and functional cell layer, wrapped by the myometrium and externally by the serosa. The endometrium undergoes modifications during menstruations, with proliferation, differentiation, and shedding [129]. Hormonal levels influence this cycle, and the microbiota actively participate in a not clear

way, this also occurs in pregnancy, menopause, and carcinogenesis [9,130]. A possible explanation could be linked to the immunological answer, with a key role in microenvironment maintenance, endometrial remodeling, embryo implantation, and protection against infection [131]. Microbial ligands can trigger and modulate the production of chemokines, inflammatory cytokines, and antibacterial substances with the elimination of pathogens and the induction of immune tolerance in pregnancy [131]. This interplay is possible through the toll-like receptors (TLRs), the complement system, antimicrobial peptides (AMPs), bacterial DNA, proteins, and lipopolysaccharides (LPSs) [132].

The topic of microbiota and cancer is arousing great interest in the scientific world. There are already articles that demonstrate the correlation of some dysbiosis with oncogenesis. For example, recent studies have identified a notable *Micrococcus* abundance associated with various cancers, including cervical cancer [133], colorectal cancer [134], and tongue tumors [135]. Lu and colleagues [118] conducted a study to investigate potential differences in the endometrial microbiome between EC and benign uterine lesions: EC samples also exhibited an increased *Micrococcus* presence, whereas benign samples showed enrichment in genera such as *Pseudoramibacter*, *Eubacterium*, *Rhodobacter*, *Vogesella*, *Bilophila*, *Rheinheimera*, and *Megamonas*, with notable differences in IL-6 protein levels and mRNA expressions of IL-6, IL-8, and IL-17; and a positive correlation between *Micrococcus* abundance and mRNA levels of IL-6 and IL-17. This emerging evidence suggests a potential role for *Micrococcus* in cancer development, highlighting the importance of understanding microbial distributions to oncogenesis [136].

Moreover, chronic conditions like diabetes [137] and inflammatory bowel diseases [138] seem to be related to a lower α-diversity, as is applicable for EC. Decreased diversity often results in the dominance of a few microbial species, and diminished ecosystem resilience, which can negatively impact health [139]. These findings highlight the importance of maintaining microbial diversity for preventing chronic and oncological diseases and promoting overall well-being. In the specific context of endometrial cancer, science is still debating on possible microbial correlations. Moreover, data about the impact of microbiota on EC identified a link between hormonal dysfunction [140], such as elevated estrogen levels and an imbalance between progesterone and estrogen [141,142], and the distribution of *Prevotella* and *Lactobacillus* in the vagina and cervix, while Shigella and *Barnesiella* are prevalent in the uterus. Certain bacteria, such as *A. vaginae* and *Porphyromonas* sp., heightened the risk of EC by prolonged inflammation and immune dysregulation [141,142]. Additionally, their presence in the gynecologic tract, along with a higher pH (>4.5), was linked to increased susceptibility to EC, with involvement in early disease stages. Chronic inflammation, driven by specific bacterial species, was shown to promote free radical formation, leading to DNA damage, cell proliferation, and angiogenesis, thereby contributing to cancer development [143]. The uterine microbiota could impact on genomic stability of the uterine epithelium, hindering apoptosis and promoting cell proliferation [144].

There is evidence on the genital species correlation, and on the possible related dysbiosis linked to tumors. The distributions of the different species at the vaginal and/or uterine level are of particular interest for EC. Moranska et al.'s review aimed to characterize the composition of the uterine microbiome and explore potential pathways involved in endometrial carcinogenesis, describing distinct alterations in the uterine microbiome composition compared to healthy environments [9]. Various bacterial taxa belonging to *Firmicutes*, *Spirochaetes*, *Actinobacteria*, *Bacteroidetes*, and *Proteobacteria* were identified as associated with EC. Specifically, genera like *Anaerostipes*, *Dialister*, *Peptoniphilus*, *Ruminococcus*, *Anaerotruncus*, *Treponema*, *Atopobium*, *Bacteroides*, *Porphyromonas*, and *Arthrospira* were implicated in EC pathogenesis [90]. The co-occurrence of *Atopobium vaginae* and *Porphyromonas* sp. was notably linked to EC, particularly in the presence of increased vaginal pH (>4.5). Wang et al. [128] described the uterine prevalence of *Prevotella*, *Atopobium*, *Anaerococcus*, *Dialister*, *Porphyromonas*, and *Peptoniphilus* in the EC group. These findings highlight the potential role of the uterine microbiome in influencing the physiological processes of the endometrial epithelium and immune response, potentially contributing to

malignant transformation. Another study also revealed a positive correlation between *Prevotella*, elevated serum D-dimer, and fibrin degradation products, indicative of significant tumor burden [126]. Additionally, the presence of endometrial *Porphyromonas* emerged as a potentially accurate microbial marker of EC in high-risk, asymptomatic women [126]. These examples of research illustrate that postmenopausal women exhibit distinct microbial populations in both an EC-affected and unaffected endometrium, highlighting specific bacteria that may play significant roles in tumor behavior.

Moreover, microbiota could also have other characteristics at the vaginal level. Hakimjavadi et al. [89] conducted a research study investigating the association between the vaginal microbiome and characteristics of EC. Distinct patterns in microbial diversity and CSTs correlated with the grade of EC. An α-diversity analysis showed a significant increase from benign to high-grade disease, suggesting that a more diverse vaginal microbiome may be associated with higher-grade tumors [89].

β-Diversity significantly varied with the tumor grade, indicating distinct microbial communities influenced by tumor-related factors rather than demographic variables like race, ethnicity, age, or BMI, and suggesting that the vaginal microbiome not only distinguishes between benign and malignant conditions but also differentiates between low-grade and high-grade tumors [89]. Machine learning models using microbial species abundance could accurately predict the tumor grade and histology, underscoring the vaginal microbiome's potential as a significant biomarker [89]. This could enhance the early detection and personalized management of EC. Such advancements may revolutionize cancer screening strategies, deepen our understanding of disease mechanisms, and improve patient-centered outcomes in gynecologic oncology.

In addition to the attention on the various species and their distribution in the genital context, it also seems necessary to highlight the correlation between hormonal factors and genital and intestinal microbiota. The gut–vaginal microbiome axis linking intestinal microbiota with the upper genital tract is crucial. The transformation of endometrial tissue into malignancy involves a complex interplay of factors including hormonal imbalances, chronic inflammation, and microbiome composition [124]. Hormonal imbalance, such as elevated estrogen levels in obesity, where aromatase activity in adipose tissue converts androgens to estrogen, can drive an uncontrolled proliferation of endometrial tissue. Chronic inflammation [124], a hallmark of cancers, is influenced significantly by the microbiome in both the uterus and gut. Bacterial components trigger inflammatory cytokine and chemokine production, fostering a pro-tumor environment [117]. The microbiome's interaction with the immune system regulates cancer development through pattern recognition receptor activation and antimicrobial peptide production, influencing immune response integrity and cancer cell detection and destruction [117,145]. Moreover, microbiome-induced genetic mutations and epigenetic alterations of EC are modulated by bacterial metabolites affecting DNA methylation, histone modification, and gene expression [145]. The intestinal microbiome's substantial influence on the metabolic pathway is essential in endometrial carcinogenesis [146]. Microbiota-mediated estrogen metabolism, facilitated by certain bacteria producing β-glucuronidase [38], increases circulating estrogen, a known EC risk factor. Gut microbiota dysbiosis enhances inflammatory responses via molecular patterns recognized by TLR-4, upregulating pro-inflammatory cytokines [24]. Furthermore, healthy microbiota-produced short-chain fatty acids (SCFAs), from fermenting indigestible carbohydrates [22,23], maintain gut pH, promote beneficial bacteria, inhibit pathogens, and support gut barrier integrity. Decreased SCFAs due to dysbiosis creates a cancer-prone environment. Bacterial metabolites such as chenodeoxycholic acid and butyrate influence cancer dynamics, promoting cell proliferation [39]. Alternative pathways also alter the vaginal microbiota, impacting the uterine environment and contributing to cancer [23]. The dysregulation of the intestinal microbiota increases endometrial cancer susceptibility, highlighting potential microbiome-targeted therapies [23].

Related to gut equilibrium, another topic of great relevance in daily practice is the use of probiotics: these substances have interesting influences on the microbiota, including the

genital tract. Probiotics, encompassing *Lactobacillus* and others, are living microorganisms found in food products like supplements and infant formula [147]. They exert diverse effects such as reducing inflammation and oxidative stress and promoting apoptosis: all crucial in tumorigenesis processes [148–150]. Notably, *Lactobacillus* strains like *L. crispatus* and *L. gasseri* have demonstrated anticancer properties by inhibiting cell proliferation and metastasis in cervical cancer models. These strains also modulate immune responses, enhance chemotherapy efficacy, and potentially prevent bacterial vaginosis [151]. Moreover, studies highlight the therapeutic potential of probiotics in enhancing radiotherapy outcomes [151] and improving survival rates among cervical cancer patients; further research is essential to fully understand their mechanisms and possible clinical applications also for EC.

Limitations

The complexity of the genital tract causes difficulties in tissue sampling; the different organs are spatially close, and contamination is possible with not trustworthy results.

The sample size of different studies is often not sufficient, and the understanding of results is not univocal. Microecological variability further complicates interpretation, necessitating extensive research into these intricate interactions. Further studies are necessary to limit the existent bias and deepen the field of microbiota and EC.

5. Conclusions

Significant alterations in microbial composition were observed between individuals with EC vs those with benign conditions, suggesting distinct microbial profiles characterized by genera such as *Prevotella*, *Atopobium*, and *Porphyromonas*, which could potentially play a role in the pathogenesis of endometrial tumors.

The presence of specific bacteria in the gynecologic tract, with their possible alteration and consequent chronic inflammation, was linked to processes such as DNA damage and immune dysregulation, critical in tumor initiation and progression. Additionally, other risk factors have to be studied (as the role of the environment) after the identification of plastic-degrading bacteria within the endometrial microbiom, suggesting a plausible link between pollution and increased EC. Understanding these microbial influences is crucial not only for unraveling the etiology of EC, but also for developing targeted therapeutic strategies. Future research efforts should focus on elucidating the precise mechanisms by which microbial dysbiosis contributes to carcinogenesis, exploring microbial biomarkers for early detection and prognoses, and investigating microbiome-targeted interventions to modulate disease outcomes.

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