REVIEW

DOI: 10.4274/hamidiyemedj.galenos.2025.98700

Hamidiye Med J 2025;6(2):67-77

The Role of Microbiota in Ovarian Cancer: Implications for Diagnosis, Prognosis, and Treatment

Yumurtalık Kanserinde Mikrobiyotanın Rolü: Teşhis, Prognoz ve Tedaviye Etkileri

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ABSTRACT

Ovarian cancer remains one of the most lethal gynaecological malignancies due to late diagnosis and poor prognosis. Recent studies highlight the potential role of microbiota in the development, progression, and management of ovarian cancer. The female reproductive tract hosts diverse microbial communities, with the lower tract dominated by Lactobacillus species and the upper tract containing a low-biomass microbiome. Dysbiosis in these microbial populations has been linked to chronic inflammation, immune dysregulation, and tumour progression. Notably, altered levels of specific taxa, such as elevated *Fusobacterium* and decreased *Lactobacillus*, have been associated with ovarian cancer. Advances in microbial profiling, particularly 16S rRNA sequencing, and machine learning offer novel approaches for improving ovarian cancer diagnosis and prognosis by identifying microbial biomarkers. Furthermore, microbiota may influence treatment outcomes through its interaction with chemotherapeutic agents and immune responses. This growing body of evidence suggests that targeting the microbiome could provide innovative strategies for ovarian cancer management, including personalized therapies aimed at restoring microbial balance. Further research is essential to fully clarify the role of microbiota in ovarian cancer and harness its potential for early detection and effective treatment.

Keywords: Microbiome, microbiota, ovarian cancer, biomarkers, therapeutics

ÖZ

Yumurtalık kanseri, geç teşhis ve kötü prognoz nedeniyle en ölümcül jinekolojik malignitelerden biri olmaya devam etmektedir. Son çalışmalar, mikrobiyotanın yumurtalık kanserinin gelişimi, ilerlemesi ve yönetimindeki potansiyel rolünü vurgulamaktadır. Kadın üreme yolu, Lactobacillus türlerinin baskın olduğu alt yol ve düşük biyokütleli bir mikrobiyom içeren üst yol ile çeşitli mikrobiyal topluluklara ev sahipliği yapar. Bu mikrobiyal popülasyonlardaki disbiyoz kronik enflamasyon, immün düzensizlik ve tümör progresyonu ile ilişkilendirilmiştir. Özellikle, yüksek *Fusobacterium* ve azalmış *Lactobacillus* gibi belirli taksonların değişen seviyeleri yumurtalık kanseri ile ilişkilendirilmiştir. Mikrobiyal profilleme, özellikle 16S rRNA dizileme ve makine öğrenimindeki gelişmeler, mikrobiyal biyobelirteçleri tanımlayarak yumurtalık kanseri teşhisini ve prognozunu iyileştirmek için yeni yaklaşımlar sunmaktadır. Ayrıca mikrobiyota, kemoterapötik ajanlar ve immün yanıtlarla etkileşimi yoluyla tedavi sonuçlarını etkileyebilir. Giderek artan bu kanıtlar, mikrobiyomun hedeflenmesinin, mikrobiyal dengeyi yeniden sağlamayı amaçlayan kişiselleştirilmiş tedaviler de dahil olmak üzere yumurtalık kanseri yönetimi için yenilikçi stratejiler sağlayabileceğini göstermektedir. Mikrobiyotanın yumurtalık kanserindeki rolünü tam olarak açıklığa kavuşturmak ve erken teşhis ve etkili tedavi potansiyelinden yararlanmak için daha fazla araştırma yapılması gerekmektedir.

Anahtar Kelimeler: Mikrobiyom, mikrobiyota, yumurtalık kanseri, biyobelirteçler, terapötikler

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Received: 07.02.2025 **Accepted:** 12.06.2025 **Publication Date:** 04.07.2025

Cite this article as: Akçeşme B, Berilo A, Islam N. The role of microbiota in ovarian cancer: implications for diagnosis, prognosis, and treatment. Hamidiye Med J. 2025;6(2):67-77

Introduction

The Role of Microbiota in Ovarian Cancer: Implications for Diagnosis, Prognosis, and Treatment

Ovarian cancer is a significant concern for women's health worldwide, primarily because it often goes undetected until reaching an advanced stage. This asymptomatic progression leads to approximately 75% of ovarian cancer cases being diagnosed only in later stages of the disease, critically impacting survival rates (1). Globally, ovarian cancer ranks as the eighth most common cancer among women and is the eighth leading cause of cancer-related deaths, with an incidence rate of about 6.6 per 100,000 women annually (2). In Türkiye, the situation mirrors global trends, with ovarian cancer accounting for a substantial portion of gynecological cancer diagnoses. According to Ugurlu et al. (3), ovarian cancer ranks as the third most common gynecological cancer in Türkiye, with 12,186 women diagnosed with gynecological cancer that year. This is reflected in advanced-stage diagnoses and high mortality rates, underscoring the need for increased awareness and early detection efforts.

Ovarian tumours are broadly classified into three major categories according to cell of origin: epithelial tumours, germ cell tumours, and sex cord-stromal tumours. The World Health Organization 2020 classification further refines the categorization of epithelial tumours, which account for over 90% of malignant ovarian neoplasms (4). Epithelial tumours are subdivided based on cell type into high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous carcinoma (MC). There are also less common types such as seromucinous and Brenner tumours, with a rare category of mixed carcinomas, now reintroduced (5).

Epithelial ovarian cancers are the most frequently diagnosed subtype and the leading cause of gynaecological cancer death worldwide, accounting for roughly 3.7% of all new female cancer cases and 4.7% of cancer deaths in 2020 (6). Globally, 313,959 new cases and 207,252 deaths from ovarian cancer are estimated to occur each year (7). Most cases present at an advanced stage, with overall survival rates remaining low at approximately 40% for stage III disease and 20% for stage IV disease (8).

Ovarian cancer encompasses five principal histological subtypes: high-grade serous carcinoma (HGSC), low-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma (CCC), and MC, each considered distinct diseases with specific cells of origin, molecular alterations, and clinical behaviors (9). For instance, HGSC, the most common subtype, is primarily associated with BRCA1 and BRCA2 mutations (10), while CCC may be linked to endometriosis (11).

The pathogenesis of ovarian cancer, despite extensive research, remains partially understood, with gaps in understanding the precise origins of some subtypes and the heterogeneous nature of tumours, which make prevention and treatment challenging. The human microbiome is now emerging as a potential key in unraveling this complexity, as recent studies suggest it may play a role in cancer development and progression by modulating immune responses, influencing inflammation, and interacting with host and microbial metabolites (12-14). The trillions of microorganisms that inhabit the different parts of the human body form intricate, habitat-specific ecosystems uniquely adapted to the host's dynamic and ever-changing physiology. Changes in the microbiome composition, known as dysbiosis, have been linked to a wide range of diseases, including cancer (15). The rapid pace of global transformations significantly affects individuals' physiological and psychological well-being, disrupting the homeostasis of the microbiota (16). The human microbiome exhibits a high level of complexity due to its intricate interactions with other microorganisms and its surrounding environment. Several factors, including host genetics, gender, age, diet, lifestyle, and antibiotic exposure, influence it (17).

Recent studies have demonstrated a link between estrogenic metabolism and host recognition receptors in microorganisms, which influence changes in the gut and pelvic microbiomes. Understanding the composition of the microbiota involved in the progression of ovarian cancer could provide valuable insights for developing diagnostic and prognostic methods, as well as effective treatments (18). In this review, we aimed to summarize the research conducted on microbiota associated with ovarian cancer. The alterations in microbial species associated with ovarian cancer, highlighting both increased and decreased abundance, as well as etiological factors and mechanistic roles, in ovarian cancer are illustrated in Figure 1.

The aim of this paper is to comprehensively review current research regarding the relationship between human microbiota and ovarian cancer, with a focus on the potential impact of microbiome alterations in the development, progression, and management of epithelial ovarian cancer. By examining key studies and presenting current evidence, this review seeks to highlight both the clinical significance and future therapeutic implications of microbiome research in the context of ovarian cancer.

Bacterial Composition in Female Reproductive Tract

The female reproductive tract (FRT), plays a critical role in fertility, pregnancy, sexual activity, and childbirth. Its interconnected anatomy facilitates the migration of various

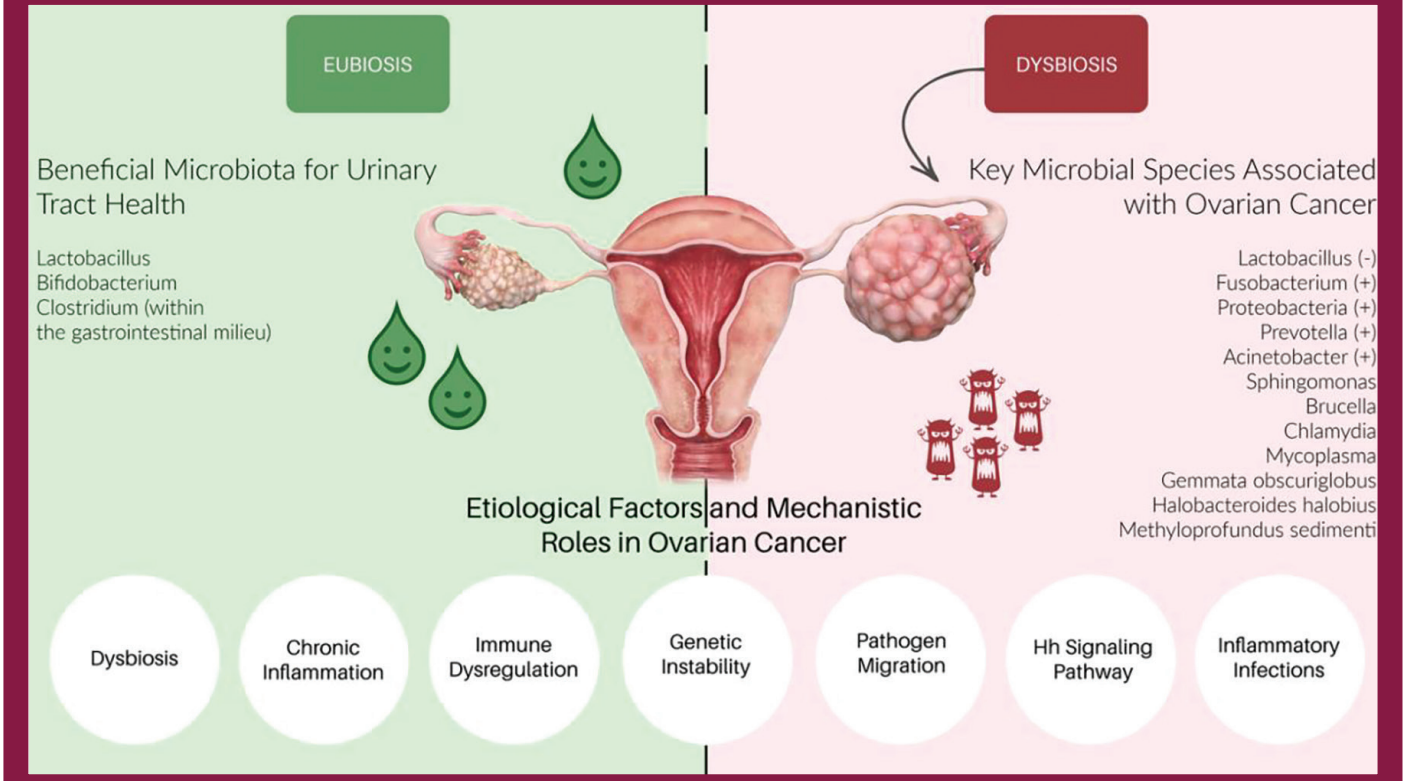

Figure 1. Microbial alterations in ovarian cancer and their implications for urinary tract health; the symbol (-) indicates a decrease in abundance in ovarian cancer, while the symbol (+) indicates an increase in abundance in ovarian cancer

substances between the lower and upper reproductive tracts (URTs). For instance, the dynamic nature of this system is highlighted by the passage of menstrual fluid, bacterial infections, and sperm through the vagina. Contrary to previous beliefs, the ovaries and fallopian tubes are not sterile structures, which makes them more susceptible to certain diseases, including infections and cancers (19). This susceptibility necessitates a deeper understanding of the microbiome's impact on reproductive health.

Bacteria are not inherently harmful to the human body, and certain bacterial species play a crucial role in maintaining health. The majority of the microbiota contributes to regulating the pH and acidity of the vagina, which is essential for maintaining reproductive health (20). Among these beneficial bacteria, *Lactobacillus* stands out as the predominant species in healthy ovaries. *Lactobacillus* is particularly significant as it prevents the invasion of pathogenic bacteria, thereby reducing the risk of reproductive tract infections (21). This protective role underscores the importance of maintaining a healthy microbiome.

Ravel et al. (22) discovered that the vaginal microbiota in reproductive-aged women can be divided into five distinct community state types (CSTs). CSTs I, II, III, and V are primarily characterized by relatively simplistic microbial communities dominated by various Lactobacillus species, specifically, *Lactobacillus crispatus, Lactobacillus gasseri*, *Lactobacillus iners*, and *Lactobacillus jensenii*, respectively. In contrast, CST IV is marked by increased microbial diversity and includes a range of bacterial species aside from *Lactobacillus*. This group largely consists of anaerobic bacteria, including *Prevotella*, *Dialister*, *Atopobium*, and *Gardnerella*. A thorough understanding of these differences is crucial for developing targeted interventions for microbiome-related health issues. Brewster et al. (19) examined microbiota variations within different regions such as the ovary, fallopian tube, and fimbriae, in healthy individuals. They found significant differences in the abundance of certain bacterial species between these sites. For instance, species like *Actinoplanes*, *Arthrobacter*, *Bradyrhizobium*, *Gemmatimonas*, *Limnobacter*, *Roseobacter*, *Saccharopolyspora*, and *Mycobacterium* were more prevalent in the ovary, compared to the fallopian tube. Additionally, comparisons between the fallopian tube and the fimbriae revealed significant differences in the abundance of *Acidovorax*, *Bradyrhizobium*, *Mesorhizobium*, *Mycobacterium*, and *Ralstonia*.

Previous research has largely focused on gynaecological tumours, often linking microbiome alterations to disease progression (23). This focus reflects the potential for microbiome analysis to serve as a diagnostic tool or therapeutic target. However, there remains a significant knowledge gap regarding the microbiome of healthy ovaries, primarily due to the limited availability of samples for study. This gap presents an opportunity for future research to enhance our understanding of reproductive health.

Bacterial Composition Changes in Ovarian Cancer

In women of reproductive age, the lower FRT, encompassing the vagina and cervix, is mainly dominated by *Lactobacillu*s species. These bacteria engage in mutually beneficial interactions that support the host. Conversely, the upper FRT, including the uterus, fallopian tubes, and ovaries, houses a low-biomass microbiome characterized by a diverse range of microorganisms. An imbalance in this area, known as dysbiosis, can interfere with immune and metabolic signaling pathways, affecting crucial cancer-related mechanisms such as chronic inflammation, epithelial barrier breaches, changes in cellular growth and death, genetic instability, angiogenesis, and metabolic disruptions. Such pathological alterations may play a role in the onset of gynecological cancers (24). A study comparing healthy women with women with ovarian cancer identified notable differences in microbial populations. Specifically, there was a rise in Aquificae and Planctomycetes, and a reduction in Crenarchaeota among the ovarian cancer groups (18). At the species level, Zhao et al. (25) reported that in healthy individuals, the predominant bacteria in the ovarian microbiome were *Halobacteroides sediment* at 14.53%, followed by *Gemmata obscuriglobus* at 11.07%, and *Methyloprofundus sediment* at 10.69%. In contrast, among those with cancer, *Gemmata obscuriglobus* was most prevalent at 13.89%, with *Halobacteroides sediment* at 11.99% and *Methyloprofundus sediment* at 11.12%. Importantly, *Lactobacilli*, typically abundant in healthy ovaries, were significantly reduced in cancer patients, suggesting a decreased ability to prevent bacterial invasion and emphasizing the protective function of *Lactobacilli*. Additionally, bacterial genera like *Prevotella* and *Proteobacteria*, typically associated with healthy ovaries, were found to be elevated in ovarian cancer cases (26). According to Brewster et al. (19), a noticeable reduction in the abundance of certain microbial taxa was observed in the URT tissues of ovarian cancer patients compared to healthy controls. Specifically, in cancer patients, species such as *Acidovorax*, *Acinetobacter*, *Aeromonas*, Cloacibacterium, *Conexibacter*, *Mariomonas*, *Methylobacterium*, *Propionibacterium*, *Pseudoalteromonas*, *Vibrio*, and *Xanthomonas* were significantly less common in URT tissues. In contrast, species like *Bosea*, *Mesorhizobium*, *Mycobacterium*, *Ralstonia*, and *Variovorax* showed increased prevalence in these tissues. Researchers found a significant increase in the ratio of *Proteobacteria* to *Firmicutes* in ovarian cancer, indicating that changes in microbial composition might be associated with the disease's development. Notably there was an increase of *Proteobacteria*, *Acinetobacter*, *Sphingomonas*, and *Methylobacterium species* in samples derived from normal distal fallopian tube tissues in ovarian cancer patients. In contrast, the composition of firmicutes, *Acidobacteria, Lactococcus* spp., *Acinetobacter lwoffii*, and *Lactococcus piscium* was decreased. They suggested that microbial dysbiosis might influence the onset or advancement of ovarian cancer by dampening the host's inflammatory and immune reactions, effectively forming an immunosuppressive microenvironment around the tumour (27).

The Role of Bacterial Metabolites in Ovarian Cancer

In a comprehensive study, researchers examined a unique collection of viral, bacterial, fungal, and parasitic markers that have a strong association with ovarian cancer. This research identified the presence of *Brucella*, *Chlamydia*, and *Mycoplasma* in 76%, 60%, and 74% of ovarian cancer samples, respectively (28). The potential involvement of lipopolysaccharides (LPS), lysophosphatidic acid, and tryptophan metabolites in the development of ovarian cancer through bacterial metabolism was reviewed (29). LPS, lipoglycans, and endotoxins are components that are found in Gram-negative bacteria which protect them from toxins, antibiotics, and bile acids.

In ovarian cancerous tissues, a notable shift occurs in the balance of Gram-negative bacteria, resulting in increased levels of LPS in the tissue (30). LPS is crucial in driving inflammation related to ovarian cancer, as it stimulates cancer cells and tumour-associated macrophages, thus facilitating disease progression. According to Zheng et al. (31), lysophospholipids, metabolic by-products of bacterial membrane homeostasis abundant in Gram-negative bacteria, are produced both by these bacteria and the host. These molecules are important for various physiological processes, including reproduction, vascular development, cancer, and nervous system functions. Lysophospholipids activate G protein-coupled receptors, which are essential for the binding of water-soluble hormones. Unfortunately, ovarian cancer patients exhibit significantly higher lysophospholipid levels in their plasma compared to individuals with benign ovarian conditions. The levels of lysophospholipids align with the expression of metastasis-promoting factors critical to ovarian cancer progression. Additionally, Ness et

al. (32) found that women with *Chlamydia* infections face a 90% increased risk of developing ovarian cancer. This association is explained by the inflammation hypothesis, which posits that inflammation or infection is responsible for one in four cancer cases. Factors such as cytokines, free radicals, prostaglandins, and growth factors contribute to inflammation by inducing point mutations and DNA methylation and posttranslational modifications (33,34).

In another comprehensive investigation into ovarian cancer, researchers employed Mendelian randomization to explore causal relationships between gut microbiota and their influence on ovarian cancer risk. The analysis identified 24 gut bacteria involved in the pathogenesis of ovarian cancer, categorized into 10 risk factors such as *Dorea phocaeense* and *Pseudomonas aeruginosa*, and 14 protective factors, such as Enorma massiliensis and *Turicibacter sp001543345*. These bacteria demonstrated causal links to lipoproteins, lipids, and amino acids, impacting ovarian cancer risk by modulating cholesterol and fatty acid ratios within various lipoprotein subtypes. Specifically, *Enorma massiliensis* and *Turicibacter sp001543345* showed potential protective roles by adjusting lipid profiles, thereby influencing ovarian cancer risk. This research highlights the genetic and metabolic interplay mediating the role of the gut microbiota in ovarian cancer, enhancing our understanding of its pathogenesis (35).

In exploring the potential role of metabolites from the vaginal microbiome in ovarian cancer, a cross-sectional study investigated how these compounds might contribute to racial disparities in cancer progression. Researchers found significant differences in the concentration of certain metabolites in vaginal fluids from Black and White patients, highlighting the biological role these metabolites may play in cancer-related inflammation. Among 99 metabolites analyzed, arachidonoylcarnitine, a derivative of arachidonic acid known for its inflammation-inducing properties, consistently appeared at lower levels in Black patients compared to their White counterparts. This metabolite, involved in eicosanoid signaling pathways, plays a critical role in inflammatory responses that may facilitate ovarian cancer progression (36). This study also revealed that more than one-third of the vaginal metabolites analysed were correlated with systemic inflammation markers, suggesting that bacterial metabolites might influence inflammatory processes relevant to cancer development. The research pointed to the involvement of pathways related to mitochondrial dysfunction and sphingolipid metabolism, which can affect the proliferation and apoptosis of cancer cells. Specifically, sphingolipids and their metabolites, such as ceramides and sphingomyelins, were found to interact with inflammatory pathways, indicating potential roles in either promoting or inhibiting tumour growth.

Building on this understanding, recent research further supports the emerging role of the gut microbiome and its metabolites in shaping the tumour microenvironment in ovarian cancer. Metabolites such as lactic acid, produced by certain bacterial species like *Ruminococcus* and *Leuconostoc mesenteroides*, have been found in greater abundance in patients who respond well to immunotherapy. Lactic acid is known to enhance the effectiveness of T-cell responses by boosting cytokine production, which can improve both chemotherapy and immunotherapy outcomes. Additionally, metabolic pathways involving tryptophan, amino acids, and glycerophospholipids are increasingly recognized for their contribution to immune modulation. Furthermore, metabolites such as trimethylamine N-oxide, associated with bacteria like *Desulfovibrio fastidiosa*, have shown potential in modulating immune responses within the tumour microenvironment, offering insights into dietary interventions that could enhance immunotherapy effectiveness (37). These bacterial metabolites not only interact with immune cells but also have a direct impact on cellular metabolism and the tumour's ability to grow and metastasize. For instance, changes in lipid and amino acid metabolism, potentially mediated by gut microbiota, can support cell survival and proliferation, or conversely, promote cancer cell apoptosis.

Influence of Gut Microbiota on Ovarian Cancer Development

Several studies have indicated that the microbiota present in both the FRT and other body regions may play a significant role in ovarian cancer. Since the most diverse microorganisms are found in the abdomen, we have focused on examining the gut microbiota in this review. Some of the research mentions that the following bacteria interact with the human intestinal tract: *Bacteroides, Clostridium*, *Bifidobacterium*, and *Lactobacillus*. The mention of all these bacteria indicates that *Lactobacillu*s is present in the ovaries, demonstrating a strong connection. One of the studies reveals that the gynaecologic malignancies have changes in their intestinal flora proving another connection (38).

In studies, it is often mentioned that Hedgehog (Hh) signalling pathways play an important role in the occurrence of ovarian cancer. This pathway and gut microbiota play a crucial role in maintaining the homeostasis of physiological processes (39).

Abnormally active Hh signaling pathway raises the risk of cancer by promoting cell proliferation, invasion, and migration. The pathway indicating activation in ovarian cancer patients can be decreased by introducing Gli antagonist v61 in vitro or in vivo, or insulin-like growth

factor 1 as an epidermal growth factor. All of these agents can be regulated by the gut microbiota. In addition, this can be a potential biomarker for ovarian cancer (40). Dysbiosis is a bacterial infection of the gut or the gastrointestinal tract, which is observed in cancers related to the female population such as breast, cervical, and ovarian cancer (41).

The connection of gut microbiota is still being studied in a variety of diseases because the gut microbiota is very complex, and the healthy gut microbiome composition is not yet known due to inter-individual variation. It is only known that gastrointestinal microbiota is connected to many diseases like obesity, diabetes, cardiovascular disorder, cancer, hypertension, and inflammatory bowel disease. Microbiome alterations in gut, cervicovaginal, and different compartments from patients with ovarian cancer are summarized in Table 1.

The Impact of Environmental Factors on Microbiota Linked to Ovarian Cancer

The investigation into the role of environmental factors in microbiota associated with ovarian cancer, illustrates a significant interface between the human microbiome and cancer. Current research predominantly focuses on the gut microbiome and its connection to gastrointestinal cancers, yet the influence of the vaginal microbiome on ovarian cancer remains inadequately explored beyond the established link between human papillomavirus and cervical cancer. The retrospective study delves into the relationship between ovarian cancer, platinum-free interval durations, and both vaginal and gut microbiomes (42). Findings indicate that *Lactobacillus*-dominated vaginal communities are less prevalent among women with ovarian cancer compared to similarly aged women without cancer. Notably, the absence of *Lactobacillus* and presence of *Escherichia*, in

Table 1. Microbiome alterations in ovarian cancer tissues

Location	Microbiome/Relative abundance		References
Ovarian cancer tissues	*Brucella*	+	(28)
	Chlamydia	+	
	Mycoplasma	+	
	Proteobacteria/Firmicutes	+	(18,27)
	Fusobacteria/Bacteroides	+	(59)
	Acinetobacter	+	(28)
	Lactococcus	_	
	Gram-negative bacteria	+ (high LPS)	(18)
Gut	*Bacteroides*	-	(60)
	Prevotella	+	(26)
	Proteobacteria	+	
	Ruminococcus	-	
	Actinobacteria	-	
	Gram-positive bacteria	+	(60)
Cervicovagina	*Mobiluncus curtisii*	+ → -	(61)
	Eubacterium rectale	+ → -	
	Fusobacterium nucleatum	+ → -	
	Porphyromonas	+ → -	
	Lactobacilli	- (protective)	(17,62)
Other compartments	Gram-negative bacteria in the peritoneal microbiome	+	(54)
	No α/β diversity interference observed in serum	0 (no interference observed in diversity)	(63)
	Increased risk related to genital pathogens like Neisseria gonorrhoeae and Chlamydia trachomatis	+	(32,64)

LPS: Lipopolysaccharide. The plus (+) denotes greater abundance, while the minus (-) signifies reduced abundance in ovarian cancer patients or ovarian cancer cells compared to the control group

the vaginal microbiome correlates with platinum-resistant ovarian cancer, where patients show higher rates of disease recurrence and reduced survivability. Women with platinum-resistant tumours display lower phylogenetic diversity than their platinum-sensitive counterparts. This reduced diversity aligns with trends observed in other inflammatory conditions, suggesting that unique environmental exposures impacting the gut microbiota may influence cancer progression and treatment resistance. The presence of *Escherichia*-dominated profiles in these patients could be linked to immune system modulation, which affects the effectiveness of platinum-based chemotherapies, potentially through alterations in reactive oxygen species production.

Diet, a fundamental environmental factor, plays a crucial role in determining gut microbiota composition. Diets high in processed foods, red meats, and sugars can lead to dysbiosis, characterized by a loss of beneficial microbes and an increase in potentially pathogenic bacteria. Conversely, diets rich in fibre, fruits, and vegetables promote the growth of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, which can produce short-chain fatty acids with anti-inflammatory and anti-carcinogenic properties (43). The Western diet, characterized by high-fat and low-fibre intake, has been linked to an increased risk of various cancers, including ovarian cancer, through mechanisms involving chronic inflammation and immune modulation. Obesity, a condition often resulting from dietary choices and sedentary lifestyles, is another critical environmental factor affecting gut microbiota composition (44). Obesity is associated with reduced microbial diversity and a higher prevalence of pro-inflammatory bacteria, which can lead to systemic inflammation a known contributor to cancer progression. Increased adipose tissue in obese individuals can alter hormone levels, further affecting cancer risk (45). Additionally, changes in gut microbiota can influence the metabolism of oestrogens and other hormones, potentially impacting ovarian cancer development (46).

Lifestyle factors such as physical activity also play a role in modulating the gut microbiome. Regular exercise has been shown to increase microbial diversity and promote the abundance of beneficial bacteria, potentially enhancing immune function and reducing cancer risk. Conversely, sedentary behaviour is associated with dysbiosis and a higher risk of inflammatory diseases (47). Alcohol consumption can lead to dysbiosis by selectively increasing harmful bacteria and reducing beneficial species. It can impair gut barrier function, allowing microbial endotoxins such as LPS to enter circulation and promote systemic inflammation. This inflammatory state is linked to an increased cancer risk (48).

Antibiotic use is another significant environmental factor affecting gut microbiota. While antibiotics can be lifesaving, overuse or misuse can lead to a drastic reduction in microbial diversity and the proliferation of antibiotic-resistant bacteria. This alteration can result in a disrupted gut ecosystem and an inflammatory environment conducive to cancer development (49). The impact of probiotics and prebiotics as potential interventions to restore microbial balance and mitigate cancer risk is an area of ongoing research. Probiotics may enhance the gut's barrier function, promote anti-inflammatory pathways, and modulate immune responses. Emerging evidence suggests that specific strains of probiotics could exert protective effects against cancer progression.

Smoking is recognized as an environmental risk factor that significantly affects the composition of the gut microbiome. Exposure to cigarette smoke is associated with decreased microbial diversity and an increase in harmful bacteria, creating a pro-inflammatory state that may facilitate carcinogenesis. The toxic substances found in cigarette smoke, such as polycyclic aromatic hydrocarbons and heavy metals, can modify the gut environment, leading to dysbiosis, a condition of microbial imbalance (50). This imbalance in the gut microbiome can trigger systemic inflammation and oxidative stress, processes that are closely linked to cancer development, including ovarian cancer. While smoking's negative impact on ovarian function and menopause is well established, its effect on the gut microbiome represents an additional pathway through which it may influence cancer risk. Altered microbial composition can impact the metabolism of oestrogens and other hormones, potentially affecting cancer susceptibility. Specifically, the pro-inflammatory environment caused by smoking can activate pathways that promote tumour growth and progression. In a study using two-sample Mendelian randomization analysis, researchers showed that environmental factors like smoking can incite changes in the gut microbiome that may contribute to ovarian cancer risk, highlighting the necessity for further investigation into these complex interactions. The environmental factors contributing to microbiota disruption and their potential link to ovarian cancer are summarized in Figure 2.

Microbiome as Biomarker and Therapeutic in Ovarian Cancer

The use of microbiomes as a biomarker for the diagnosis and prognosis of ovarian cancer holds significant importance due to their potential to address critical challenges in the management of this deadly disease. Ovarian cancer is often diagnosed at advanced stages due to the lack of specific early symptoms and reliable biomarkers. The microbiome, particularly the changes in microbial diversity and composition, could serve as a non-invasive biomarker for early detection. Specific

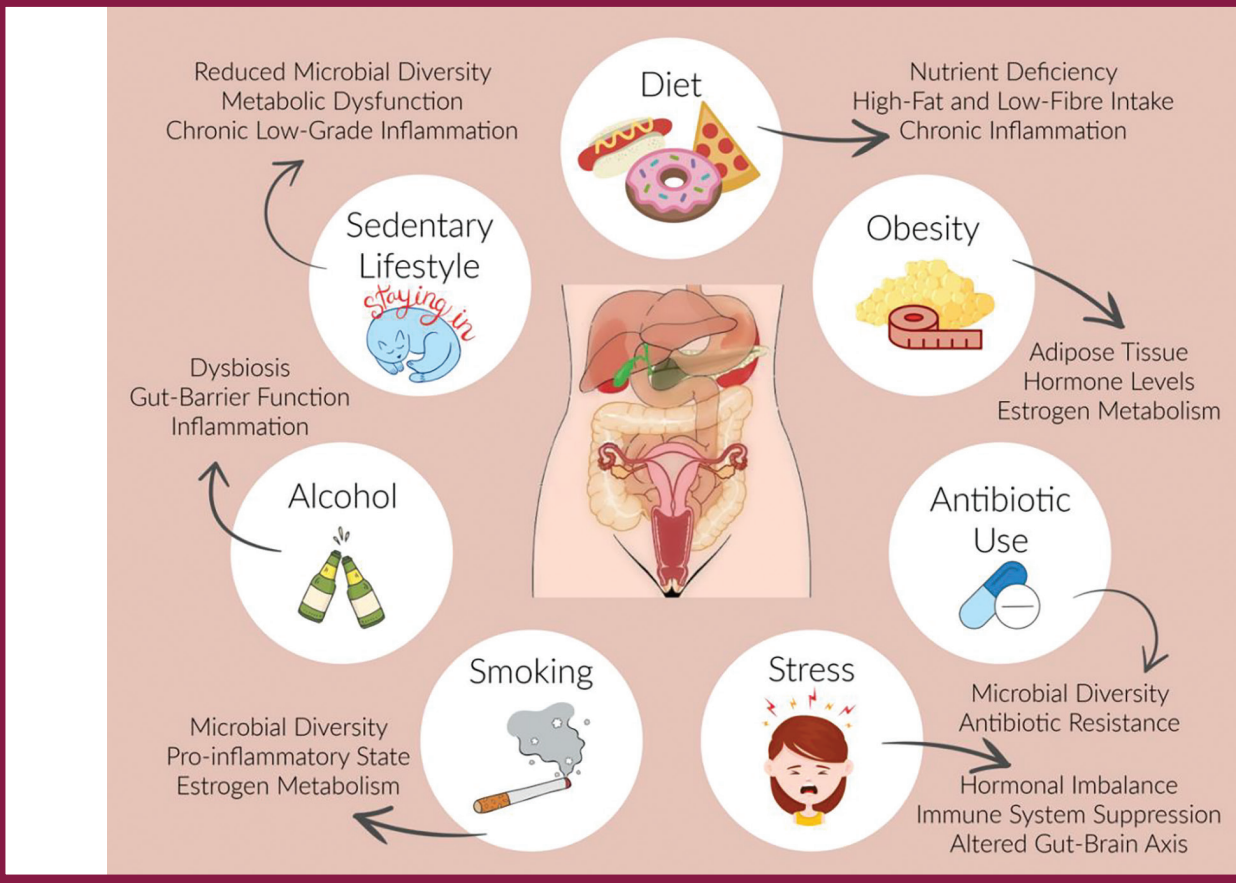

Figure 2. Environmental factors contributing to microbiota disruption and their potential link to ovarian cancer (Drawing of abdominal organs taken from Shutterstock©)

microbial signatures in the reproductive tract, gut, or blood may indicate disease development before conventional clinical symptoms appear (51). As mentioned above, this study revealed an increase in *Bacteroides*, *Prevotella*, and *Proteobacteria*, along with a decrease in *Ruminococcus* and *Actinobacteria,* in gut samples from patients with ovarian cancer (26). Research has consistently shown reduced levels of *Lactobacilli* in the cervicovaginal microbiome of ovarian cancer patients (26,52). The composition of *Proteobacteria* and *Firmicutes* and *Acinetobacter* was observed to increase, whereas *Lactococcus* decreased in ovarian cancer tissues. A decrease in *Lactococcus* in ovarian cancer likely contributes to microbial dysbiosis, inflammation, immune dysregulation, and the loss of protective antimicrobial activity. These changes collectively create an environment that facilitates tumour initiation, progression, and immune escape, emphasizing the importance of maintaining a balanced microbiome for ovarian health.

Another phenomenon that may serve as a potential biomarker is the predominant origin of microorganisms within the reproductive tract. The connection between the upper and lower reproductive tracts enables the migration of pathogens from the lower to the upper regions. This complicates the identification of a specific target for potential biomarkers. However, the upper genital tract in women with ovarian cancer differs significantly from that of healthy women, a finding supported by the observed increase in *Fusobacterium* levels in affected individuals (53). In a study, they combined microbial analysis with machine learning techniques that represent a promising and powerful approach for the diagnosis and prognosis of ovarian cancer. They revealed 18 microbial features that were unique for ovarian cancer by performing ensemble modeling and machine learning pathways method (54).

The microbiome is increasingly recognized as a critical target for cancer therapies due to its impact on cancer initiation, progression, and the effectiveness of treatments. Researchers highlight the microbiome's therapeutic importance in various areas: modulation of the tumour microenvironment, enhancement of responses

to immunotherapy, chemotherapy, and radiotherapy, and the development of probiotics and microbiome engineering strategies (55). Researchers also found that *Lactobacillus reuteri* engineered to secrete IL-22 (LR-IL-22) can safeguard intestinal tissues during whole abdomen irradiation in mouse models of ovarian cancer, indicating its potential as an intestinal radioprotector that could be used in future treatment protocols (56). In a later study, researchers showed that this genetically modified probiotic could transform the tumour microenvironment, which may improve irradiation outcomes in ovarian cancer (57). Meanwhile, Qin et al. (58) observed that changes in the microbiota, caused by ovarian cancer, enhance their potential as a biotherapeutic option not only for ovarian cancer but possibly for other malignancies and conditions as well. They suggest that the microbiota could be analysed and harnessed within a predictive, preventive, and personalized medicine framework for treating ovarian cancer (58). Additionally, it was noted that restoring the disrupted gut microbiota following surgery and chemotherapy can lead to improved survival rates in ovarian cancer patients. A summary of these findings and their implications can be found in Table 2, which outlines the role of the microbiome as both a biomarker and therapeutic in ovarian cancer.

Conclusion

The human body is a highly interconnected system, including the microorganisms that reside within. These microorganisms are dynamic and can adapt to various factors such as lifestyle, diet, environment, gender, age, ethnicity, and stress exposure. However, the alteration of the microbiota may sometimes lead to severe diseases, including ovarian cancer. The high diversity of microorganisms in the female body poses challenges for the treatment of reproductive diseases. Researchers have investigated the microbiota present in diseased individuals and compared it to that of healthy individuals to explore the molecular and genetic mechanisms underlying the connection between microorganisms and the host. This review has highlighted the complex relationship between human microbiota and ovarian cancer, summarizing recent findings that alterations in microbial communities may contribute to the development, progression, and prognosis of ovarian malignancy. Studies comparing the microbiota of healthy individuals and ovarian cancer patients have revealed distinctive microbial signatures, and suggest that dysbiosis may play a significant role in tumour biology.

Looking forward, understanding these microbial patterns opens promising avenues for early diagnosis, prognostic assessment, and the development of novel microbiome-based therapies. Future clinical studies investigating targeted modulation of microbiota may provide new strategies to improve outcomes and reduce treatment-related side effects for ovarian cancer patients.

Table 2. Role of microbiome as a biomarker and therapeutic in ovarian cancer

Aspect	Findings	References
Early detection	Changes in microbial diversity in reproductive tract, gut and blood as potential biomarkers for early detection	(26,51)
Microbial signatures	Increase in *Bacteroides Prevotella Proteobacteria* decrease in *Ruminococcus* and *Actinobacteria* in ovarian cancer patients	(26)
Reproductive tract microbiota	Increase in *Fusobacterium* in the upper genital tract of ovarian cancer patients	(53)
Machine learning for diagnosis/ Prognosis	18 unique microbial features for ovarian cancer identified through machine learning	(54)
Therapeutic impact	Modulation of tumour microenvironment enhancement of responses to immunotherapy chemotherapy and radiotherapy	(55)
Probiotics and microbiome engineering	Lactobacillus reuteri engineered to secrete IL-22 to protect intestinal tissues during irradiation	(56,57)
Predictive and personalized medicine	Potential of microbiota as a biotherapeutic option and within personalized treatment frameworks	(58)
Post-treatment microbiota restoration	Restoring gut microbiota post-surgery and chemotherapy can improve survival rates	(24)

Ethics

Informed Consent: The retrospective study delves into the relationship between ovarian cancer, platinum-free interval durations, and both vaginal and gut microbiomes.

Footnotes

Authorship Contributions

Concept: B.A., A.B., N.I., Design: B.A., A.B., N.I., Literature Search: B.A., A.B., N.I., Writing: B.A., A.B., N.I.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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