Potential role of microbiota in ovarian cancer treatment

Monika Englert-Golon[1], Stefan Sajdak[2], Katarzyna M. Plagens-Rotman[3]*, Piotr Merks[4], Witold Kędzia[5], Anita Szwed[6], Magdalena Durda-Masny[6]

[1]Division of Gynaecological Oncology, Department of Gynaecology, Poznan University of Medical Sciences, Poznan, Poland
[2]Poznan University of Medical Sciences, Poznan, Poland
[3]Center for Pediatric, Adolescent Gynecology and Sexology, Division of Gynecology, Department of Gynecology, Poznan University of Medical Sciences, Poznan, Poland
[4]Faculty of Medicine, Collegium Medicum, Cardinal Stefan Wyszyński University, Warsaw, Poland
[5]Division of Gynaecology, Department of Gynaecology, Poznan University of Medical Sciences, Poznan, Poland
[6]Institute of Human Biology and Evolution, Adam Mickiewicz University, Poznan, Poland

***Corresponding author:**
Katarzyna Plagens-Rotman
Center for Pediatric, Adolescent Gynecology and Sexology
Division of Gynecology
Department of Gynecology
Poznan University of Medical Sciences
61-758 Poznan, Poland
Phone: +48 61 8419 490
E-mail: plagens.rotman@gmail.com

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Abstract

In recent years, the relationship between microbiota and various aspects of health has become a focal point for scientific investigation. The complex interplay between microbial communities and the development, progression, and treatment of gynaecological malignancies is a burgeoning field not yet fully understood. Recent research indicates that gut, vaginal, and uterine microbiota play a critical role in the response to treatments of ovarian cancer, and particularly in chemotherapy, anti-angiogenic therapy, and PARP inhibitors. Microbiota and microbial metabolites can modulate immune responses, drug metabolism, and angiogenesis, affecting the outcomes of therapy. This review explores the relationship between microbiota and anticancer therapies, and discusses the connection between dysbiosis and treatment resistance, highlighting the potential of microbiota as biomarkers and therapeutic targets in ovarian cancer treatment.

Key words: microbiota, ovarian cancer, chemotherapy, anti-angiogenic therapy, PARP inhibitors.

Introduction

Ovarian cancer (OC) is one of the most aggressive of gynaecological cancers and the leading cause of death in gynaecological cancers in women worldwide. Although ovarian cancer is not the most frequently diagnosed gynaecological cancer, it is responsible for the largest number of deaths in this group. According to the 2020 GLOBOCAN Global Cancer Women's Cancer Data, ovarian cancer has an incidence rate of 3.4% and a mortality rate of 4.8%. Each year, over 300,000 women develop ovarian cancer, generating approximately 206,000 fatalities. Ovarian cancer is the most lethal of gynaecological cancers, ranking eighth in global cancer incidence in women and fifth in terms of mortality [1].

An unfavourable prognosis is the result of late diagnosis – in approximately 70% of cases, ovarian cancer is detected in its advanced stages (III and IV), when the prognosis is much worse. The 5-year survival rate for ovarian cancer is approximately 47% [2], and for advanced disease, it is 30%. The reasons for late diagnosis are related to the non-specific symptoms of the disease, which are usually confused with less serious diseases. Symptoms such as bloating or abdominal pain are often ignored or attributed to other less serious conditions. As a result, ovarian cancer develops asymptomatically or with a few lesser symptoms over a long time, which makes early medical intervention difficult [3].

Initial treatment depends on the stage of the disease and the biological characteristics of the tumour. Advanced ovarian cancer involves cytoreductive surgery and chemotherapy. Despite the high responsiveness, more than 70% of patients with advanced OC will experience recurrence and develop chemo-resistance over time. The standard first-line therapy is a combination of cytoreductive surgery with chemotherapy based on platinum compounds, such as cisplatin and carboplatin. In advanced cases, neoadjuvant chemotherapy is administered before surgery, followed by continued adjuvant chemotherapy [4].

Cancer biology research has highlighted the role of BRCA1/2 mutations and homologous recombination deficiency (HRD), which has opened the field for targeted therapies such as poly (ADP-ribose) polymerase (PARP) inhibitors (PARPis). PARPis are an innovative treatment, and particularly effective in patients with BRCA1/2 mutations and homologous recombination disorders (HRD). These drugs, such as olaparib or niraparib, block DNA repair mechanisms, leading to the death of cancer cells. PARPi is an effective therapeutic option for newly diagnosed and for recurrent ovarian cancer. Despite a minor increase in the frequency of serious adverse effects, they are generally well tolerated. Their effectiveness, especially in patients with BRCA mutations, is a breakthrough in the treatment of ovarian cancer, significantly improving the survival and quality of life of patients [5, 6].

The introduction of new therapeutic options, such as PARP inhibitors and anti-angiogenic therapies, along with traditional chemotherapy, hold promise for improving ovarian cancer treatment outcomes. However, the development of resistance to these therapies, as well as their side effects, remains a challenge, requiring further research to understand the response mechanisms to such treatments [6].

Scientific research suggests that the intestinal, vaginal, and uterine microbiota may be significantly related to the responses to cancer treatment, such as for ovarian cancer. The human microbiota is composed of nearly 40 trillion microorganisms across 3000 species, such as bacteria, fungi, and viruses, exhibiting variable richness among microbes and diverse constituents among individuals, and as such is significant in the maintenance of functional stability and systematic homeostasis. The largest number of these microorganisms inhabit the digestive tract, especially the large intestine, but microbiota are also found in other locations, such as the skin, respiratory tract, sexual organs, as well as the mouth and nose. Gut microbiota comprise about 3×10^{13} bacterial cells and play the leading role in the human microbial communities. The most represented bacteria are from 4 phyla: *Bacteroides*, *Firmicutes*, *Actinobacteria*, and *Proteobacteria*. In recent years, growing scientific evidence confirms that microbiota play a role not only in the digestion and absorption of nutrients, but also in regulating the immune system, protecting against pathogens and influencing mental health [7].

Several studies have highlighted that specific microbiota can be effective tools in targeted therapeutic strategies for gynaecological cancer. Furthermore, metabolites produced by the microbiota may modulate the effectiveness of anticancer therapies, such as chemotherapy, antiangiogenic therapies, and PARPi [8, 9].

Microbiota and cancer

Numerous studies suggest that the composition of microbiota may be related to both the effectiveness and toxicity of cancer therapies. These mechanisms include modulation of the immune system, drug metabolism, and the intestinal barrier. The intestinal microbiota play a key role in regulating the immune response, which is important in the case of cancer immunotherapy, especially immune checkpoint inhibitors (ICIs). Studies have shown that patients with a favourable microbiota profile, characterised by an abundance of bacteria such as *Faecalibacterium* and *Akkermansia muciniphila*, show a better response to immunotherapy compared to patients with microbiota disorders (dysbiosis). Pro-inflammatory bacteria can promote inflammation, which promotes the development of cancer. Anti-inflammatory bacteria, on the other hand, support immune responses that can limit the development of cancer cells [10, 11].

Intestinal microbiota may impact the effectiveness and toxicity of chemotherapy drugs such as cyclophosphamide, 5-fluorouracil, or platinum compounds. For example, some bacteria have the ability to metabolise these drugs, which may affect their activity [12].

Postoperative adjuvant chemotherapy can significantly improve the five-year survival rate of

this population, but there are still a considerable proportion of patients who do not benefit from chemotherapy. One reason why cancer patients respond differently to identical chemotherapy drugs may be the differences in the composition of the gut microbiota among individuals. In other words, some microbes in the gut are involved in regulating the efficacy of chemotherapy, and this regulation includes both promoting and inhibitory effects [13].

Additionally, the gut microbiota can modulate the intestinal barrier, changing drug bioavailability and toxicity. In patients with dysbiosis, an increased incidence of side effects, such as inflammation of the intestinal mucosa, is observed, which may lead to the need to postpone or interrupt therapy. It has been noted that the gut microbiome is associated with the toxicity of traditional anticancer therapies, and that modulating the components of the gut microbiome may alleviate related toxicity. Therefore, understanding the relationship between different microbes and the side effects of traditional anticancer therapy is particularly important for individualised mitigation of these adverse events. The gut microbiota may also be related to the effectiveness of anticancer drugs such as chemotherapy drugs. Some bacteria can change the metabolism of drugs, reduce their toxicity, or contribute to their elimination from the body. With the more comprehensive and in-depth understanding of the gut microbiome gained in recent years, an increasing number of potential microbial interventions for cancer therapy have been proposed. In some cases, especially when treatment is ineffective or toxic due to microbiota disorders, gut microbiota transplantation (FMT) is used. Examples include studies that have shown improved response to immunotherapy following the use of FMT in patients with advanced cancers. An increasing number of studies also indicate the possibility of modulating microbiota to improve the effectiveness of oncological therapies [12, 13]. Intestinal microbiota play an important role in human health, including in patients with ovarian cancer. In recent years, more and more research has indicated the potential impact of the composition of intestinal microbiota on the development and course of cancer, including ovarian cancer [8, 14, 15].

Patients with ovarian cancer suffer from disturbances in the composition of the intestinal microbiota, called dysbiosis, characterised by a reduction in the number of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, and an increase in pathogenic bacteria such as *Escherichia coli* and *Clostridium*, along with other inflammation promoting proteobacteria. Significantly, reducing the diversity of microbiota weakens immune resistance and the intestinal barrier [15, 16].

Hormonal balance, especially related to oestrogen metabolism, is an important factor in the development of oestrogen-dependent cancers [17, 18].

Intestinal bacteria play a role in the deconjugation of oestrogens, which affects their biological activity. Dysbiosis may lead to hormonal disorders that may support the development of hormone-dependent cancers and ovarian cancer due to chronic inflammation, which is considered one of the mechanisms driving carcinogenesis. Like the gastrointestinal tract, the vagina also contains microflora with significant potential in the treatment of gynaecological diseases. It has been found that vaginal dysbiosis and abnormal microbes also exist in the pathogenesis and progression of ovarian cancer and widely serve as complications to anti-cancer therapy. In 2019, a study reported the increased prevalence of a type O cervicovaginal microbiota community characterised by decreased *Lactobacillus* dominance in the presence of ovarian cancer or associated risk factors, which first associated ovarian cancer with the potential presence of vaginal dysbiosis. Among the vaginal microbiota, bacteria such as *Clostridium* and *Lachnospiraceae* are found to have both positive and negative correlations with ovarian tumour development. Several vaginal microbes also show anti-cancer potential via promoting cancer cell apoptosis, modulating cancer-related microRNA (miRNA) expression, and involvement in cancer signalling [19, 20].

A healthy vaginal microbiota is dominated by *Lactobacillus* bacteria, which maintains an acidic pH and protects against pathogens. Vaginal dysbiosis, including decreased *Lactobacillus* counts and the increase of pathogens such as *Gardnerella vaginalis*, can lead to chronic inflammation, which may impact response to ovarian cancer treatment. Although the uterine microbiota has traditionally been considered sterile, current evidence indicates the presence of microorganisms in the uterus that may impact reproductive health and response to cancer treatment. Bacteria such as *Atopobium vaginae* and *Streptococcus agalactiae* have been linked to a higher risk of endometrial and ovarian cancer [15].

Mechanisms of the impact of microbiota on the treatment of ovarian cancer

Intestinal microbiota play a key role in drug metabolism, influencing their biotransformation, absorption, and elimination. Understanding this impact can help tailor treatments and minimise side effects, leading to more personalised medicine. Research in this area is still in progress, but it is already known that intestinal microbiota may be important in pharmacotherapy.

Intestinal, vaginal, and uterine microbiota also play important roles in the response to ovarian can-

cer treatment. The balance of microbiota in these areas may impact the local immune response and inflammatory processes, which may be significant for the effectiveness of anticancer therapies [20–22]. It should be noted, however, that there are concerns regarding the use of microbiota-based therapies in immunocompromised hosts [16].

Chemotherapy

Intestinal microorganisms can biotransform drugs by changing their chemical structure. This process may lead to the formation of active metabolites that may have a different effect than the original drug, or to inactivation of the drug. Some gut bacteria can convert drugs such as metoprolol and propranolol into less active forms [23, 24].

Gut bacteria can also carry out redox reactions, such as reduction or oxidation of active substances of drugs, which changes the effectiveness and toxicity of therapies. Additionally, intestinal microorganisms can make the pH of the intestine more alkaline, which may in turn affect the solubility and absorption of certain drugs. They may also impact drug availability by competing for absorption space in the intestine [25].

There are also indications that microbiota may modulate the activity of liver enzymes, which translates into the rate of drug elimination from the body [26].

Differences in the composition of gut microbiota may lead to differing responses to medications between patients and may impact the effectiveness of the therapy and the risk of side effects. Scientific research confirms that patients with different intestinal microbiota profiles may have different responses to drugs such as warfarin [27].

Some gut bacteria can impact the metabolism of anticancer drugs, changing their effectiveness and toxicity. For example, bacteria of the *Enterococcus* and *Bacteroides* genera can modify the metabolism of cytostatics such as cisplatin and carboplatin, commonly used in the treatment of ovarian cancer. Changes in the composition of microbiota may lead to the reduced effectiveness of chemotherapy, as well as increased drug toxicity by damaging the intestinal barrier and increasing side effects such as enteritis and nausea.

Platinum-based chemotherapy is commonly used to treat several cancers, including ovarian cancer; however, some research suggests that these compounds affect the gut microbiome. In one, after several cycles of chemotherapy, the number of certain bacteria, including *Bacteroides*, *Collinsella*, and *Blautia*, increased. It turns out that the number of *Bifidobacterium* increased after just one to three cycles of chemotherapy [28, 29].

This bacterium plays an important role in maintaining the microbiological balance of the intestines and is associated with anti-cancer properties [30].

Cyclophosphamide, in addition to platinum-based chemotherapy, is used to treat severe ovarian cancers. One study reported that it also affected the gut microbiome. Cyclophosphamide enhances anticancer effects by shifting the gastrointestinal microbiome to the lymphatic organs [12].

Gemcitabine, however, was less effective when cancer cells were cultured together with *Mycoplasma* [31].

Another study found that in patients with platinum-resistant cancers, the vaginal microbiome was more likely to be dominated by *Escherichia coli* [32].

Chambers *et al.* published analyses that showed mice treated with antibiotics accelerated the development of ovarian cancer and increased resistance to cisplatin. However, after transplanting the microflora of healthy mice into the cecum, chemotherapy resistance was alleviated and lifespan was extended [22].

The intestinal, vaginal, and uterine microbiota produce various metabolites that may impact the tumour microenvironment, immunity, and response to treatment. In particular, short-chain fatty acids (SCFAs) and bacterial metabolites such as tryptophan and polyamines can modulate the response to chemotherapy, anti-angiogenic therapies, and PARP inhibitors [33].

Bacteria such as *Escherichia coli* produce lipopolysaccharides (LPS), which can cause inflammation in the gastrointestinal tract [34].

Butyrate, produced mainly by bacteria from the genera *Lachnospiraceae* and *Ruminococcaceae*, is a known modulator of the immune response. It acts as a histone deacetylase (HDAC) inhibitor, which may support the effectiveness of chemotherapy by promoting apoptosis of cancer cells [35].

Anti-angiogenic therapy

Intestinal microbiota has a potential impact on tumour angiogenesis, i.e. the process of creating new blood vessels, which is crucial for the growth and spread of cancer tumours. Angiogenesis is a complex process that can be modulated by various mechanisms related to intestinal microbiota [29].

Intestinal microorganisms produce short-chain fatty acids such as acetate, propionate, and succinate, which may affect angiogenesis. SCFAs can modulate the expression of angiogenic factors such as VEGF. Propionate may act as an angiogenesis inhibitor by reducing the activity of NF-κB, which is a key transcription factor that stimulates VEGF production [36].

Some intestinal bacteria, such as *Bacteroides fragilis* or *Enterococcus faecalis*, can produce me-

tabolites that influence inflammatory processes and angiogenesis. The gut microbiota can impact inflammation in the body, which in turn can modulate angiogenesis. Chronic inflammation may promote angiogenesis by increasing the production of angiogenic factors. Dysbiosis can lead to chronic inflammation, which promotes angiogenesis in cancerous tumours. Gut microorganisms can influence the immune system and inflammatory cytokines such as IL-6 and TNF-α, which are involved in the regulation of angiogenesis [37].

Gut microbiota can impact the tumour microenvironment, including tumour blood supply and metabolism. The metabolic products of microbiota can affect cancer cells and interstitial connective tissue cells, which changes their ability to form new blood vessels. Moreover, intestinal microorganisms are also involved in the metabolism of oestrogens, which may influence angiogenesis in breast and ovarian cancers [38].

There are indications that microbiota may also be linked to the expression of angiogenesis-related genes. For example, by modulating the activity of hypoxia-inducible factor (HIF-1α) and VEGF, the microbiota can impact the formation of new blood vessels in the tumour. Changes in microbiota may affect HIF-1α activity, which may alter the levels of VEGF and other angiogenic factors [39, 40].

Additionally, by modulating the immune response and angiogenic processes, the gut microbiome may influence the effectiveness of cancer therapies, including targeted therapy and immunotherapy. Changes in the microbiota may affect the effectiveness of drugs that inhibit angiogenesis, such as bevacizumab. Research indicates that the presence of bacteria from the *Lachnospiraceae* and *Ruminococcaceae* families may support the response to antiangiogenic therapies, while intestinal dysbiosis may promote resistance to these drugs. The presence of microbiota metabolites such as propionate and acetate in the tumour microenvironment may support the response to antiangiogenic therapies by inhibiting blood vessel growth and promoting apoptosis [41, 42].

PARP inhibitors

PARP inhibitors such as olaparib or niraparib are used as maintenance therapy in patients with ovarian cancer. Gut microbiota may influence DNA repair mechanisms and responses to these drugs. The microbiota produce many metabolites that may influence the response to cancer therapies. Butyrate, produced by bacteria of the *Lachnospiraceae* and *Ruminococcaceae* genera, is a histone deacetylase (HDAC) inhibitor, which may influence the regulation of DNA repair and apoptosis of cancer cells. Studies in animal models suggest that butyrate may support the effectiveness of PARP inhibitors by promoting genomic instability of cancer cells and increasing their sensitivity to drugs that inhibit DNA repair. PARP inhibitors may increase tumour immunogenicity by generating new tumour antigens. Bacteria such as *Bifidobacterium* support the immune response by activating dendritic cells and promoting CD8+ T cell responses, which may further support the effectiveness of PARP inhibitors [43, 44].

Clinical implications of microbiota modulation in ovarian cancer treatment

Emerging findings on the role of microbiota, particularly probiotics, in ovarian cancer treatment indicate the existence of several promising clinical applications. The first is integration of probiotics into standardised or individualised ovarian cancer therapies. Modulating the gut microbiota through probiotics may enhance the efficacy of existing ovarian cancer treatments. For instance, a randomised placebo-controlled trial demonstrated that oral administration of *Bifidobacterium longum* in ovarian cancer patients with paraneoplastic thrombocytosis led to significant improvements in platelet counts, coagulation functions, inflammatory markers, and gut microbiota composition [45].

The second example is the use of probiotics to overcome chemoresistance, which remains a significant challenge in ovarian cancer treatment. Research indicates that the gut microbiota play a role in mediating chemoresistance. For example, disruption of the gut microbiota through antibiotic use was associated with increased tumour growth and cisplatin resistance in epithelial ovarian cancer models [22].

Furthermore, supplementation with specific probiotics has shown promise in reversing chemoresistance. In a study using a humanised nude mouse model, administration of *Bifidobacterium animalis* subsp. lactis NCU-01 alongside naringin treatment led to decreased levels of inflammatory proteins and pro-inflammatory cytokines, suggesting a potential role in overcoming chemotherapy resistance [46].

The third, and perhaps most important, modulatory role of the microbiota is in reducing the risk of ovarian cancer. In preclinical studies, supplementation with *Akkermansia muciniphila* reversed the tumour-promoting effects of faecal microbiota transplantation from ovarian cancer patients in mouse models. This was associated with enhanced $CD8^+$ T-cell activation and increased interferon-γ secretion, highlighting the potential of specific probiotics in modulating immune responses for cancer prevention [47].

These findings suggest that targeted modulation of the gut microbiota through probiotics

could serve as a complementary strategy in the treatment and prevention of ovarian cancer. However, further clinical trials are necessary to validate these approaches and establish standardised protocols for their implementation.

Conclusions

Intestinal, vaginal, and uterine microbiota and their metabolites have a significant impact on the response of ovarian cancer patients to chemotherapy, antiangiogenic therapies, and PARP inhibitors. Changes in the composition of the microbiota and its metabolites may affect the effectiveness of therapy and the toxicity of drugs. Therefore, future ovarian cancer treatment strategies should include a study of the microbiome as a potential therapeutic target, to help individualise therapy and improve its effectiveness. The introduction of microbiota modulation, for example through probiotics, prebiotics, or intestinal microbiota transplantation, may constitute a new, promising therapeutic strategy in the treatment of ovarian cancer [14, 29, 48–50].

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