**OVARIAN CANCER AND THE MICROBIOME - Review**

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**Abstract**

Cancer is one of the most serious public health issues in the world. Ovarian cancer is the most lethal malignancy among gynecological cancers worldwide. Ovarian cancer is a major threat to female health, ranking seventh in the most commonly diagnosed cancer among women worldwide.

There is a complex association between cancers and microbes. There are few studies explored the alterations of gut microbiota in ovarian cancer patients. Recent studies have indicated that many microorganisms are involved in the development of ovarian cancer. The gut microbiome has many roles in maintenance of human health, and has been increasingly linked with many disease states, including cancer.

Microbiome abnormalities are increasingly associated with diseases, including cancer development, and response to therapies. Some studies have shown the relationship between microbiome changes and ovarian cancer.

The purpose of this review was to analyze the complex associations between ovarian cancer, and the microbiota, specifically bacterial microbes. We discuss the possible roles of vaginal microbiota in carcinogenesis, highlighting the relationship of micro-organisms in ovarian cancer.

Therapeutic strategies targeting the gut microbiota may be beneficial for the clinical treatment of ovarian cancer.

**Keywords:**

vaginal microbiome, ovarian cancer, intestinal microbiota
Breast, ovarian and uterine cancer are the most common neoplasms among women.

Ovarian cancer is the fifth leading cause of cancer death among women in western countries and is the most lethal gynecologic malignancy, especially high-grade serous ovarian cancer.

Various factors—including age, family history, inflammation, reproductive factors, and tubal ligation—modulate the risk of ovarian cancer (1-3).

Abnormal estrogen synthesis and metabolism may be related to the occurrence and development of ovarian cancer. One prospective study showed that women with the highest levels of circulating estradiol had three times higher risk of developing ovarian cancer than women with the lowest estradiol levels.

One of the principal regulators of circulating estrogens is the gut microbiome. After using menopausal hormone therapy for five or more years, the risk of developing ovarian cancer becomes high for at least five years, even after ceasing the treatment.

Recent studies indicate that perturbations in the microbiome may be implicated in a number of diseases, including cancer. The composition of the cervicovaginal microbiome may have a key role in ovarian carcinogenesis.

Microbiota can significantly influence many aspects of host physiology, such as activating the immune system, regulating metabolism and promoting cancer progression. The interplays between microbiota and the initiation and progression of cancer are numerous and complex (4). The fact that the cervicovaginal microbiota was deficient in protective lactobacilli species in women with or at risk for ovarian cancer suggests that low prevalence could be causal.

A large set of neoplastic diseases are characterized by changes to microbiome compartment(s) that is termed oncobiosis, the opposite of which is eubiosis. Oncobiosis has a role in the pathogenesis of neoplastic diseases.

The oncobiome has different effects on the immune system than the eubiome. Women at high risk of developing ovarian cancer have lower levels of protective “friendly” vaginal bacteria. More specifically, changes in the gut and vaginal microbiomes may be associated with a variety of gynecologic cancers, including cervical cancer, uterine cancer, and ovarian cancer.

Vaginal infections (e.g. Neisseria gonorrhoeae or Chlamydia trachomatis) increase the risk of developing ovarian cancer (14). The dysbiotic microbiome drives local inflammation upon pathological colonization, such as in ovarian carcinoma. Bacterial colonization of the upper genital tract is a risk factor for ovarian cancer. Probiotics are frequently used to treat banal vaginal infections.

In oncobiosis accompanying ovarian cancer, the proportions of Gram-negative bacteria and, therefore, lipopolysaccharides (LPS) quantity increases in the cancer tissue. LPS plays a pivotal role in driving inflammation in ovarian cancer.

Currently, serous ovarian cancer can be classified into two groups, Type I and Type II based on the clinical behavior, pathology, molecular genetics and tumor precursors. Type I cancers are considered low-grade serous cancers, whereas Type II cancers are considered high-grade and constitute the majority of epi-
thelial ovarian cancers, lack well-defined precursor lesions and are characterized by highly aggressive neoplasms (2).

However, the origins and molecular pathogenesis of high-grade serous ovarian cancers are still largely unknown. Over the past decade, new evidence has challenged the theory that serous ovarian cancer originates from the ovarian surface epithelium (5).

Present researches have focused on the relationship between microbiota and gynecologic malignancy, with little regard for cause and effect. The term microbiome was first used at the turn of the 20th and 21st centuries by the Noble prize winner, Joshua Ladeberg, and should be understood not only as a description of a simple set of organisms occurring in a given environment, but above all as a set of their genomes interacting with each other and the place where are located.

Originally, the term microbiota was intended to describe an ecological community of symbionts, commensals, and pathogenic microbes living within the human body.

The totality of microbiota including bacteria, fungi, archaea, protists, and viruses colonize the human body at birth, where they establish a mutually beneficial host-microbiome relationship. Sex hormones have been reported to affect the gut microbiota in adolescence and this impact is sustained into adulthood.

A new study looked at the link between levels of lactobacilli species found in the cervicovaginal microbiome and the presence or risk of ovarian cancer. A lower percentage of certain kinds of cervicovaginal bacteria are associated with having ovarian cancer or risk factors for the malignancy.

Researchers studied whether ovarian cancer may be associated with imbalances in the cervicovaginal microbiome. Ovarian cancer is the leading cause of death in gynecologic malignancies. Growing evidences demonstrate that a complicated relationship exists between the gut microbiota and cancer. Importantly, Lactobacilli are protective species against ovarian cancer. Vaginal communities that are poor in Lactobacillus are more prevalent in ovarian cancer patients compared to controls (6), (Fig,1).

Accumulating evidence indicates that microbiota plays a pivotal role in the occurrence and development of cancer, and microbiota dysbiosis is associated with cancer therapies. Antibiotic use can disturb the normal states of some microorganisms in the human body and may increase the risk and promote the growth of ovarian cancer. Estrogen can promote the growth of ovarian cancer by disturbing the metabolism of estrogen in the liver and intestines. The disease is often diagnosed late mainly because of the lack of specific symptoms.

The term “human microbiome” can be defined as the total of all microorganisms and their genomes residing in the human body and how they interact with the environment (3). The intestinal bacteria are of three types: beneficial, harmful, and neutral. The effect of the intestinal microbiome on the body’s immune system is not just limited to the intestinal tract but is spread across the entire body.

The microbiome plays a crucial role in maintaining the health of the human body, and abnormalities in the microbiome have been associated with a variety of diseases, including ovarian cancer (8). Recent studies have indicated that many microorganisms are involved in the development of ovarian cancer.
Most ovarian cancer patients are diagnosed at an advanced stage because of non-specific clinical symptoms (9). Abnormal estrogen synthesis and metabolism may be related to the occurrence and development of ovarian cancer.

One prospective study showed that women with the highest levels of circulating estradiol had higher risk of developing ovarian cancer. In addition, this study showed that after using menopausal hormone therapy for five or more years, the risk of developing ovarian cancer becomes high for at least five years, even after ceasing the treatment (10).

The gut microbiome may influence the level of estrogen produced. Antibiotic use can disturb the normal states of some microorganisms in the human body and may increase the risk of developing ovarian cancer.

Estrogen can promote the growth of ovarian cancer by disturbing the metabolism of estrogen in the liver and intestines. However, the microbiome can also stimulate the immune system and increase anti-tumor activity. The gut microbiome disturbs the enterohepatic circulation of estrogen, or interferes with the secretion of β-glucuronidase, an enzyme that degrades the active forms of estrogen (7). (Fig.2).

Microbiome compositional alterations in both ovarian and cervicovaginal microenvironment have been shown to correlate with the occurrence of ovarian cancer. The cervicovaginal microbiota dysbiosis may play a role in ovarian cancer tumorigenesis. Abnormal estrogen synthesis and metabolism may be related to the occurrence and development of ovarian cancer.

We discuss the applicability of nutrients, antibiotics, and probiotics to harness the microbiome and support ovarian cancer the-
A growing body of literature indicates that the microbiota plays a significant role in the development and curability of cancer, essentially due to the microbial ability to modulate immune and inflammatory responses to cancer and therapeutic treatments. Gut microbiota represents a new player in the regulation of a patient’s response to cancer therapies, including chemotherapy and immunotherapy. A growing interest in diet impact on health and disease has been fueled by the blooming of microbiota studies following the disclosure of the so-called “our other genome,” a gene catalog of the human gut microbiome (11,12).

Therapeutic strategies targeting the gut microbiota may be beneficial for the clinical treatment of ovarian cancer. Recent evidence suggests that the gut microbiome may modulate responses to cancer treatment, including traditional chemotherapy and immunotherapy (13).

Despite progress in understanding the role of the microbiomes in cervical cancer, investigations regarding the role of microbiome in ovarian cancers are limited. Despite the high prevalence and public health significance, the etiology of this disease remains largely elusive.

Fig. 2 Interactions between female reproductive tract microbiota and the development of ovarian cancer (6)
The microbial composition change, as a novel risk factor, may be involving the initiation and progression of ovarian cancer via influencing and regulating the local immune microenvironment of fallopian tubes except for regular pathways (5).

Nutrition modulates the composition of the microbiome along with other lifestyle elements. Obesity is a risk factor for ovarian cancer and the ketogenic diet was shown to reduce central obesity and reduce insulin levels in ovarian cancer patients.

A better understanding of how the microbiome composition is altered at these sites and its interaction with the host may aid in prevention, optimization of current therapies, development of new therapeutic agents and/or dosing regimens, and possibly limit the side effects associated with cancer treatment.

Conclusions

Vaginal infections and the colonization of the upper genital tract seem to play important roles in the development of ovarian cancer. In recent years, there has been growing evidence demonstrating a link between the gut microbiome, carcinogenesis and response to cancer therapy. It should be noted that further studies are needed to define the involvement of metabolite signaling in ovarian cancer.

Women with, or at risk of developing, ovarian cancer have an imbalanced cervico-vaginal microbiome. The microbiome could offer a new treatment strategy for ovarian cancer by stimulating the immune system and increasing anti-tumor activity.

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Bibliographical references: