A Review of the Role of Microbiomes in Breast Cancer: Challenges and Opportunities

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Abstract:

This paper explores the impact of the microbiome on breast cancer (BC), one of the most prevalent and dangerous types of cancer in women. While factors such as obesity and family history are recognized as risk factors, the microbiome has emerged as a novel and potential contributor to the onset and prevention of BC. The microbiomes of the breast, gut, and oral cavity can influence estrogen metabolism and inflammation, potentially facilitating the development of cancer. Additionally, research indicates that probiotics may play a role in inhibiting BC development. Given that the microbiome can affect treatment response and its side effects, monitoring microbiome composition and developing new therapeutic strategies could aid in the prevention and improvement of BC treatment outcomes. Due to the sensitivity and complexity of this topic, further research is necessary to gain a more precise understanding of the microbiome's role in BC.

Keywords:* *Breast cancer, microbiome, dysbiosis, estrogen

Background and Objective

Breast cancer (BC) is one of the most common and deadly types of cancer among women, presenting significant challenges in diagnosis and treatment.[1] According to statistics published in 2020, approximately 2.3 million new cases of BC were reported globally, accounting for 11.7% of all cancer cases; consequently, BC has become the second leading cause of cancer-related deaths among women.[2] The increasing incidence of this disease has prompted researchers and specialists to investigate the factors influencing its onset.

Various risk factors, including age, gender, obesity, family history, genetic mutations, estrogen levels, and sedentary lifestyle, are recognized as influential in the development of BC.[3] However, recent developments in scientific research have indicated that the microbiome may also play a significant role as a new and potential contributor to the initiation and progression

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of BC.[4] Microbiomes, which comprise a diverse population of microorganisms such as bacteria, fungi, viruses, and single-celled organisms, naturally inhabit the human body and can have substantial effects on human health.[5]

Microbiomes are typically regarded as regulators of disease risk. This microbial community maintains a balanced presence in the human host under normal conditions and influences various organs. In other words, microbiomes fulfill multiple roles, including regulating metabolism, enhancing the immune system, and influencing hormonal balance.[6] However, in states of imbalance, known as "dysbiosis," harmful microorganisms can outcompete beneficial ones, leading to health issues, including cancer and inflammation.[7] Recent research has demonstrated a correlation between microbiome composition in various body regions and the occurrence of BC. Specifically, the gut, oral, and breast microbiomes have been investigated in this context.[8] For example, evidence suggests that the oral microbiome may affect overall health and immune system status, thereby contributing to the progression or prevention of cancers.[9] Furthermore, recent studies emphasize the importance of the breast microbiome; however, more information is needed regarding the precise composition of this microbiome and its impact on health and the incidence of breast-related diseases.[10]

Therefore, the aim of this study was to review and evaluate the role of the microbiome as a significant factor in the prevention and onset of BC, as well as to examine the influence of changes in the composition of the breast, gut, and oral microbiomes on the physiological state of breast tissue and cancerous lesions.

Microbiome and Immune System

1. Interaction of the Microbiome with the Immune System

Microbiomes in the human body are recognized as a diverse ecosystem of microorganisms that have profound effects on the immune system. This microbiota, particularly in the gut, not only enhances natural immune responses but also supports overall health by regulating inflammation.[11] The microbiome helps prevent chronic inflammation and immune disorders through the production of metabolites. For instance, short-chain fatty acids such as butyrate and propionate, produced by gut bacteria, play a critical role in enhancing cell membrane permeability and function, and can assist in the regulation and balance of immune cells such as T lymphocytes and macrophages.[12,13] Interactions between the microbiome and immune cells contribute significantly to maintaining immune homeostasis through pathogen recognition and cytokine production, which is especially important in responses to infections and tumors.[14]

2. Role of the Microbiome in Generating Immune Responses to Tumors

In addition to regulating the immune system, microbiomes significantly influence immune responses against tumors. Evidence suggests that specific compositions of the microbiome can affect the efficacy of immunotherapy and the overall immune response to tumors.[15] For example, studies have shown that certain bacterial species, such as Bifidobacterium and Lactobacillus, can enhance immune responses to cancer treatments and increase antitumor activity by boosting the activity of immune cells.[16] Additionally, alterations in microbiome composition can lead to dysbiosis, which may, in turn, influence genetic editing and tumor progression.[17]

Ultimately, investigating the interactions between the microbiome and immune responses may provide deeper insights into their roles in the onset and progression of BC and open new avenues for the development of microbiome-based therapeutic strategies.

The Role of Breast, Oral, and Gut Microbiomes in BC

1. Breast Microbiome

1.1. Exploring the Diversity and Characteristics of the Breast Microbiome

The breast microbiome is a complex and diverse ecosystem composed of various microorganisms, including bacteria, fungi, and viruses. This microbiome is distinct from those found in other tissues, such as the gut, and plays a crucial role in breast health.[18] Historically, breast tissue was considered sterile; however, recent research has shown that it harbors a unique microbial community that can vary significantly among individuals.[19] Factors influencing the diversity of the breast microbiome include age, hormonal status, nutrition, and developmental processes. For instance, hormonal fluctuations during different life stages such as puberty, pregnancy, and menopause can lead to changes in the microbial composition of breast tissue.[20]

Recent studies have identified key bacterial genera, such as Staphylococcus, Corynebacterium, and Propionibacterium, as dominant members of the breast microbiome.[21] Furthermore, emerging evidence suggests that pathogenic viruses, including human papillomavirus (HPV) and Epstein-Barr virus (EBV), may also be present in breast tissue and could be linked to the development of BC.[22] For example, research has shown that approximately 32% of breast tumors are associated with EBV or human herpesvirus 4 (HHV-4).[23,24] Additionally, the unique anatomical structure of the breast, characterized by adipose tissue and extensive vascular and lymphatic networks, creates an ideal environment for microbial growth. However, dysbiosis can increase the risk of breast diseases, including BC, highlighting the importance of understanding the composition and dynamics of the breast microbiome.[25]

1.2. Potential Mechanisms by which the Microbiome Influences BC Development

The breast microbiome may affect BC growth through several interconnected mechanisms. One important pathway involves the production of specific metabolites by the microbiome, which can influence hormonal metabolism and inflammatory processes. For example, the breast microbiome plays a significant role in estrogen metabolism, and alterations in this metabolism can lead to increased estrogen levels, thereby raising the risk of BC.[26] Certain bacteria are known to modulate the levels of hormones such as estrogen and progesterone, which are critical in the pathogenesis of BC.

Moreover, microbiome dysbiosis can create a pro-inflammatory environment in breast tissue that promotes tumor development. Dysbiosis can lead to increased production of inflammatory cytokines, such as interleukin-17 (IL-17), which is associated with the activation of the STAT3 signaling pathway.[27] When activated by factors such as HPV infection, this pathway can further enhance inflammatory responses in breast tissue, contributing to cancer progression.[28] Therefore, the interplay among microbial metabolites, hormonal regulation, and inflammation represents a complex network through which the breast microbiome may influence cancer growth.

1.3. The Relationship between the Breast Microbiome and Inflammation, Hormones, and Tumor Behavior

Research indicates a significant association between the breast microbiome and various inflammatory and hormonal factors that can affect tumor behavior.[29,30] Chronic inflammation is recognized as a major factor in the initiation and progression of cancer, and the microbiome can promote or inhibit inflammation by regulating cytokine production and immune responses. For instance, certain beneficial bacteria can help modulate immune responses and create a balanced inflammatory state that protects against tumorigenesis.[31] Conversely, a lack of diversity in the microbiome may disrupt the immune system's ability to respond effectively to tumor cells, potentially facilitating tumor progression.

Furthermore, the impact of the microbiome extends to hormonal regulation, as it can influence levels of hormones such as estrogen and progesterone, thereby modulating the risk of BC.[32] The complex interactions between the microbiome, hormones, and the immune system create a multifaceted environment that can either support or inhibit tumor growth. Understanding these intricate relationships is essential for elucidating the microbiome's role in BC and may pave the way for innovative therapeutic strategies. For example, targeting specific microbial populations or their metabolites could present a promising approach for the prevention or treatment of BC, ultimately enhancing patient outcomes and quality of life.[33]

2. Oral Microbiome

2.1. Relationship Between the Oral Microbiome and Cancers

Recent studies have highlighted a potential link between the oral microbiome and various types of cancer, including colorectal, lung, pancreatic, and head and neck cancers. Findings from a 2024 study on East Asian populations indicate a significant relationship between the oral microbiome and BC.[34] This suggests that changes in the composition of the oral microbiome may be associated with the risk of developing BC.

In this study, observations revealed higher levels of certain bacteria, particularly from the families Pasteurellaceae and Streptococcic, in the saliva of BC patients compared to healthy individuals.[34] These microbial changes may influence cancer development through mechanisms that induce inflammation and modulate immune responses. Specifically, certain oral microbiomes, such as Porphyromonas gingivalis , produce pro-inflammatory metabolites like lipopolysaccharides (LPS), which can be transported via the bloodstream to distant breast tissues.[35]

2.2. Mechanisms by which the Oral Microbiome Influences BC

In breast tissue, LPS binds to Toll-like receptor 4, activating the NF-kB signaling pathway.[35] This activation leads to the release of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), thereby facilitating the proliferation and survival of cancer cells.[36] These events represent a complex chain of interactions between the oral microbiome and inflammatory and immune responses within the body, which can directly impact breast tissue health and the risk of cancer development.

3. Gut Microbiome

The gut microbiome plays a fundamental role in regulating the body's metabolism and immune response. This diverse microbiome influences host metabolism through the production of metabolites such as vitamins, short-chain fatty acids (SCFAs), and other bioactive compounds.[37] These metabolites not only help regulate blood sugar and lipid levels but also affect hormonal levels. Such metabolic and hormonal interactions can contribute to overall health and help prevent diseases like cancer. Furthermore, the gut microbiome is recognized as a key regulator of the immune system.[38]

Gastrointestinal microorganisms enhance immune responses against infections and tumors by stimulating and modulating the activity of immune cells. These interactions between the microbiome and the immune system help maintain immune homeostasis and reduce the risk of chronic diseases and cancer.[39] The gut microbiome can influence the onset of BC in several ways, with its impact on estrogen metabolism being one of the primary mechanisms.[40]

The gut microbiome can lead to changes in estrogen levels by aiding in the metabolism of hormones, which subsequently imposes significant pressure on BC risk.[40] Specifically, the liver can absorb estrogen after its microbial metabolism, and this process can directly affect BC risk. Additionally, the production of SCFAs by the gut microbiome can help promote anti-inflammatory responses.[41] SCFAs such as butyrate, propionate, and acetate possess anti-inflammatory properties and can positively influence tumor growth by increasing the production of anti-inflammatory cytokines and reducing the activity of pro-inflammatory cytokines.[41]

The use of antibiotics can impact both target pathogens and beneficial pathogens. The extent of the effect on non-target microbial populations depends on the type of antibiotic used, its mechanism of action, and the level of microbial resistance present.[42] Research by Kaye et al.[43] indicated that irregular antibiotic use increases the likelihood of microbiome disruption and reduced bacterial diversity. Furthermore, a study by Knekt et al.[44] showed that excessive antibiotic use could lower plasma levels of enterolactone lignans, thereby directly impacting microbiome populations and increasing BC risk. However, it has been emphasized that the selection of antibiotics leads to antimicrobial resistance, and it is believed that the symbiotic microbiota returns to a normal state a few weeks after treatment cessation.[45]

Compared to other human organs, the microbial load and its diversity in the gastrointestinal system, particularly in the large intestine, are higher. The gut microbiome plays a significant role in local and distant areas of the body through the production of metabolites, hormonal mediators, and immune cytokines.[46] Research has demonstrated that higher phylum-level microbial diversity in the gut microbiome increases the levels of hydroxylated estrogen metabolites in the urine of healthy women.[47] In postmenopausal women, elevated blood estrogen levels are linked to an increased risk of BC. The gut microbiome is one of the main regulators of blood estrogen levels.[47] Recent analyses have shown that postmenopausal women recently diagnosed with BC have higher urinary estrogen levels compared to others. Compared to the control group, postmenopausal BC patients exhibited significant correlations between blood estrogen levels and IgA+/IgA− gut microbiota, suggesting that the gut microbiome may influence BC risk by modifying metabolism, estrogen recycling, and immune pathways.[48, 49]

In another study[39], the composition of the gut microbiome was examined in 32 BC patients with various clinical features. Most of these patients were at advanced stages and before aggressive BC treatment. Results showed that patients with grade III cancer had a higher number of Blautia species compared to those with grade I cancer. Additionally, the absolute counts of Bifidobacterium and Blautia, as well as the ratio of F. prausnitzii to Blautia, were significantly associated with the clinical stage of the patients. These findings emphasize the impact of the gut microbiome in the development and progression of BC.

Another study by Mahno et al.[50] indicated that alpha and beta diversities of the microbiome could serve as predictors for the early detection of BC, which could significantly influence the quality of life for patients.

Effects of Treatments on the Microbiome

1. Chemotherapy and Hormonal Treatment Effects on the Microbiome

Chemotherapy and hormonal therapies significantly impact the composition and function of the gut microbiome. As a common cancer treatment, chemotherapy can reduce microbial diversity and lead to dysbiosis due to its toxic effects on gut bacteria.[51] This alteration in the microbiota composition can result in side effects such as diarrhea, secondary infections, and diminished immune responses, all of which negatively affect treatment outcomes.[52] Furthermore, hormonal treatments, which are frequently used in BC therapy, can induce substantial changes in estrogen and progesterone levels, which may also have significant effects on the microbiome. Specifically, hormonal fluctuations can alter the production and metabolism of microbial compounds and may be associated with an increased risk of adverse effects or disease progression.[53]

2. The Role of Probiotics and Prebiotics in Microbiome Management

Probiotics and prebiotics are considered effective tools for managing the microbiome and enhancing overall health.[54] Probiotics, defined as live microorganisms beneficial to host health, can play a significant role in reducing the side effects associated with chemotherapy and hormonal treatments by increasing microbial diversity and strengthening microbiome function.[55] Research has shown that probiotic intake can improve gastrointestinal symptoms, bolster immune responses, and even enhance tolerance to cancer therapies.[56]

On the other hand, prebiotics, which are typically indigestible fibers, serve as food for the microbiome and promote the growth and activity of beneficial gut bacteria, contributing to the balance and maintenance of microbiome health.[57] These compounds can positively influence metabolic processes and the production of anti-inflammatory cytokines, helping to reduce inflammation and improve gastrointestinal health.[58] Overall, the use of probiotics and prebiotics can serve as complementary strategies in managing the microbiome and improving treatment outcomes in BC patients. These strategies not only help maintain microbial balance but can also enhance patients' quality of life and reduce the potential for adverse side effects.

Opportunities and Challenges

Research into the role of the microbiome in BC faces several challenges. One of the main challenges is the high diversity of microbiomes among different individuals, which poses a significant barrier to achieving generalizable results in studies.[59] Individual variations in diet, lifestyle, age, and genetic factors can lead to rapid changes and diversity within the microbiome, complicating the analysis of data. Furthermore, the sampling methods and analyses of microbiomes can be time-consuming and costly due to their complexity and the need for advanced techniques.[31] Additionally, a thorough understanding of the molecular mechanisms by which microbiomes influence BC is still lacking, and existing information is often insufficient. This is particularly true in the context of the relationship between the microbiome, hormonal metabolism, and the immune system.

Despite these challenges, research in the field of microbiomes also presents unique opportunities for the development of new and effective therapies. A deeper understanding of the role of microbiomes in the onset and progression of BC could lead to the development of personalized treatment approaches. For instance, the use of probiotics and prebiotics as complementary therapies may help improve the condition of patients undergoing chemotherapy or hormonal treatments. These therapies could be effective in enhancing quality of life and reducing side effects associated with conventional treatments.[31]

Moreover, there is potential to design microbiome-based therapies targeting specific compounds or microbial metabolites associated with the progression or recurrence of BC. Effective microbial compounds could serve as new therapeutic agents or even supplements to existing treatment modalities. Further research in this area could also contribute to strategies for BC prevention through dietary changes and improvements in microbiome health. Finally, with advancements in data analysis technologies and enhanced interdisciplinary collaborations, the discovery of new aspects of microbiome-host interactions and the development of more effective treatments in this field are increasingly feasible.

Conclusion

The correlations between the human microbiome and BC open up new horizons for prediction and treatment of the disease, prompting researchers to focus on the therapeutic applications of the microbiome. On one hand, the microbiome can significantly influence treatment responses in BC patients, including drug metabolism, immune system regulation, and management of side effects. On the other hand, an imbalance in the microbiome, with harmful microbes outcompeting beneficial ones, can lead to the initiation or acceleration of cancer progression. Given these effects, monitoring the microbiome

composition and developing targeted therapeutic strategies can aid in the prevention and control of cancer, improving treatment outcomes and enhancing the quality of life for patients. Furthermore, considering the direct impact of diet, lifestyle, and antibiotics on maintaining microbiome balance, there is a pressing need for further research and studies in this area to gain a deeper understanding of the role of the microbiome in BC treatment.

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