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 deadly cancers affecting women. While factors such as obesity and family history are well-established risk factors, the microbiome has recently emerged as a novel and potential contributor to both the onset and prevention of BC. The microbiomes of the breast, gut, and oral cavity can influence estrogen metabolism and inflammation, potentially promoting cancer development. Additionally, research suggestes that probiotics may play a role in inhibiting BC progression. Since the microbiome can affect treatment response and associated side effects, monitoring its composition and developing new therapeutic strategies could improve prevention and treatment outcomes for BC. Due to the sensitivity and complexity of this topic, further research is necessary to achieve a more precise understanding of the microbiome's role in BC.

Keywords: Neoplasm cancer; Neoplasms, microbiology; dysbiosis; estrogens

Background and Objective

Breast cancer (BC) is one of the most common and deadly cancers among women, posing 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 rising 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 novel and potential contributor to the initiation and progression of BC[4]. Microbiomes, which comprise a diverse population of microorganisms - including 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. Under normal conditions, this microbial community

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maintains a balanced presence within the human host under normal conditions and influences various organs. In other words, microbiomes perform multiple functions, including regulating metabolism, enhancing the immune system, and modulating hormonal balance[6]. However, in states of imbalance, known as "dysbiosis," harmful microorganisms can outcompete beneficial ones, leading to health issues such as 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 function, thereby contributing to the progression or prevention of cancers[9]. Furthermore, recent studies highlight the importance of the breast microbiome; however, more information is needed regarding its 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 the Immune System

1. Interaction Between the Microbiome and the Immune System

Microbiomes in the human body are recognized as a diverse ecosystems of microorganisms that profoundly affect 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 assist in regulating and balancing 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 play a crucial role in modulating immune responses against tumors. Evidence suggests that specific microbiome compositions 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 stimulating the function 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 developing 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 key pathway involves the production of specific metabolites by the microbiome, which can affect hormonal metabolism and inflammatory processes. For example, the breast microbiome plays a significant role in estrogen metabolism, and alterations in this process can lead to elevated estrogen levels, thereby increasing the risk of BC[26]. Certain bacteria are known to modulate hormone levels, 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 may 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, Inflammation, Hormones, and Tumor Behavior

Research indicates a significant association between the breast microbiome and various inflammatory and hormonal factors that influence tumor behavior [29,30]. Chronic inflammation is recognized as a major contributer to cancer initiation and progression, and the microbiome can either promote or inhibit inflammation by regulating cytokine production and immune responses. For example, certain beneficial bacteria help modulate immune responses and maintain a balanced inflammatory state that protects against tumorigenesis [31]. Conversely, reduced microbiome diversity may impair 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 among the microbiome, hormones, and the immune system create a multifaceted environment that can either promote 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 offer a promising approach for the prevention or treatment of BC, ultimately improving patient outcomes and quality of life[33].

2. Oral Microbiome

2.1. Relationship Between the Oral Microbiome and Cancer

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 involving East Asian populations indicate a significant association between the oral microbiome and BC [34]. This suggests that a 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 triggers the release of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-**α**) and interleukin-6 (IL-6), thereby promoting the proliferation and survival of cancer cells [36]. These events illustrate a complex interplay between the oral microbiome and the body's inflammatory and immune responses, which can directly affect breast tissue health and influence 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 microbial community 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 hormone levels. These metabolic and hormonal interactions can contribute to overall health and may help prevent diseases such as 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 immune cell activity . 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 influence estrogen levels by facilitating hormone metabolism, which subsequently exerts significant effects on BC risk [40]. Specifically, the liver can reabsorb estrogen following its microbial metabolism, a process that directly affect BC risk. Additionally, the production of SCFAs by the gut microbiome promotes 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 microorganisms. 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

reduces bacterial diversity. Furthermore, a study by Knekt et al.[44] showed that excessive antibiotic use can lower plasma levels of enterolactone lignans, thereby directly impacting microbiome populations and increasing BC risk. However, it has been emphasized that antibiotic selection 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 gastrointestinal system- particularly the large intestine- harbors a higher microbial load and greater microbial diversity. The gut microbiome plays a crucial role both locally and systematically by producing metabolites, hormonal mediators, and immune cytokines [46]. Research has demonstrated that increased phylum-level microbial diversity in the gut microbiome correlates with elevated levels of hydroxylated estrogen metabolites in the urine of healthy women [47] In postmenopausal women, elevated blood estrogen levels are associated with an increased risk of BC. The gut microbiome is a key regulator of blood estrogen levels [47]. Recent studies have shown that postmenopausal women recently diagnosed with BC exhibit higher urinary estrogen levels compared to controls. Furthermore, postmenopausal BC patients display significant correlations between blood estrogen levels and IgA+/IgA– gut microbiota, suggesting that the gut microbiome may influence BC risk by modulating metabolism, estrogen recycling, and immune pathways [48, 49].

In another study, 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 had not yet undergone aggressive BC treatment. The results showed that patients with grade III cancer had a higher abundance 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 underscore the impact of the gut microbiome on 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, potentially having a significant impact on patients' quality of life.

Effects of Treatments on the Microbiome

1. Effects of Chemotherapy and Hormonal Treatment Effects on the Microbiome

Chemotherapy and hormonal therapies significantly affect the composition and function of the gut microbiome. As a common cancer treatment, chemotherapy can reduce microbial diversity and cause dysbiosis due to its toxic effects on gut bacteria [51]. This alteration in microbiota composition can lead to side effects such as diarrhea, secondary infections, and impaired immune responses, all of which negatively affect treatment outcomes [52]. Furthermore, hormonal treatments, frequently used in BC therapy, can induce substantial changes in estrogen and progesterone levels, which may also significantly affects 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 widely recognized as effective tools for managing the microbiome and improving overall health [54]. Probiotics, defined as live microorganisms that confer health benefits to the host , play a significant role in mitigating the side effects associated with chemotherapy and hormonal treatments by increasing microbial diversity and enhancing microbiome function [55]. Research has shown that probiotic intake can alleviate gastrointestinal symptoms,

strengthen immune responses, and even improve tolerance to cancer therapies [56].

On the other hand, prebiotics- typically indigestible fibers- serve as nourishment for the microbiome, promoting 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 stimulate the production of anti-inflammatory cytokines, thereby helping to reduce inflammation and improve gastrointestinal health[58]. Overall, the use of probiotics and prebiotics can serve as complementary strategies for managing the microbiome and enhancing treatment outcomes in BC patients. These approaches not only help maintain microbial balance but can also enhance patients' quality of life and reduce the risk of adverse side effects.

Opportunities and Challenges

Research into the role of the microbiome in BC faces several challenges. One major challenges is the high diversity of microbiomes among individuals, which significantly hinders the ability to obtain generalizable results in studies [59]. Variations in diet, lifestyle, age, and genetic factors contribute to rapid changes and diversity within the microbiome, complicating data analysis. Moreover, microbiome sampling methods and analyses are often time-consuming and costly due to their complexity and the requiement for advanced techniques [31]. Additionally, a comprehensive understanding of the molecular mechanisms through which microbiomes influence BC remains limited, with existing information frequently insufficient. This gap is especially pronounced regarding the interplay between the microbiome, hormonal metabolism, and the immune system.

Despite these challenges, research in the field of microbiomes presents unique opportunities for developing new and effective therapies. A deeper understanding of the role of microbiomes in the onset and progression of BC could lead to 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 effectively enhance quality of life and reduce side effects associated with conventional treatments[31].

Moreover, there is potential to develop microbiome-based therapies that target specific compounds or microbial metabolites associated with the progression or recurrence of BC. Effective microbial compounds could serve as novel therapeutic agents or even supplements to existing treatment modalities. Further research in this area may also contribute to strategies for BC prevention through dietary modifications 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 becoming increasingly feasible.

Conclusion

The correlations between the human microbiome and BC open new avenues for disease prediction and treatment, prompting researchers to explore the therapeutic potential of the microbiome. On one hand, the microbiome can significantly influence treatment responses in BC patients by affecting drug metabolism, immune system regulation, and the management of side effects. On the other hand, an imbalance in the microbiome- where harmful microbes outcompete beneficial ones- can initiate or accelerate cancer progression. Given these effects, monitoring the microbiome composition and developing targeted therapeutic strategies can aid in cancer prevention and control, improve treatment outcomes, and enhance patients' quality of life . Furthermore, considering the direct impact of diet, lifestyle, and antibiotics on maintaining microbiome balance, there is a pressing need for further research to deepen our understanding of the microbiome's role in BC treatment.

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