Review Article

Breast Cancer and Microbiota: A Literature Review

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Abstract

Breast cancer is the most frequent type of cancer in women. It is the second greatest cause of cancer-related deaths among women in high-income countries. The objective of this current review is to elucidate the role of gut microbiota in cancer in general, with a specific focus on breast cancer. The dysbiosis of gut microbiota is a crucial component that has recently come to light, possibly altering the development, treatment, and prognosis of breast cancer through numerous molecular pathways. This review study investigates the relationships between gut microbiota and breast cancer, with an emphasis on how gut microbiota impacts the microenvironment of breast cancer. Final views on improving breast cancer prognosis and risk assessment may be influenced by new data from clinical trials on the breast-microbiome axis and the ability of immunotherapy to modify the microbiome associated with breast cancer.

Keywords: Breast cancer, cancer therapeutics, metabolomics, microbiota

Introduction

The most prevalent disease in women globally is breast cancer, which has a variety of causes. The likelihood of survival can be considerably increased by early cancer identification and therapy. It is predicted that 287,850 women would receive a breast cancer diagnosis, in 2022. Breast cancer is the second leading cause of cancer-related death in women and the most prevalent kind of cancer overall in high-income nations.[1] Breast cancer has recently risen to previously unheard-of levels, making it the most common illness affecting women in many parts of the world.

Since known genetic and epigenetic connections cannot often account for the beginning of breast cancer, the specific etiology of the illness remains unknown despite intensive investigation. Therefore, there must be some undiscovered mechanism influencing the emergence of breast cancer. Microorganisms have a role in the development of cancer in 15%–20% of instances, according to studies on cancer risk factors.[2] There are many connections between the gut microbiota and various illnesses, and these connections are associated with the composition of the microbiota and the particular types of bacteria that are believed to play a role in the onset of diseases, cancer, and the gut microbiome are intricately connected.[2]

Our bodies harbor 100 trillion microorganisms, distributed throughout various parts of the body, including the gastrointestinal system. These microorganisms form extensive colonies of bacteria with genomes 150 times larger than those of host cells, they are crucial to both health and disease.[3] In addition to the presence of certain bacteria, the microbiome's makeup and regulation can promote the formation and progression of tumors.[4]

Some individuals, even those who are genetically identical and lead similar lifestyles, develop cancer while others do not. Each person's chance of contracting the illness is

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influenced by a combination of genetic and environmental variables. The occurrence of DNA replication mistakes at random, which result in different kinds of mutations, contributes to the explanation. The makeup and function of the microbiota seem to be related to this DNA modification process. Both local gastrointestinal malignancies and other tumor types have been linked to interactions between the microbiota and cancer.[5] The aim of this review is to shed light on the involvement of the gut microbiota in cancer, with a specific emphasis on breast cancer.

Human Immune System and Microbiota

Microbiota is the term used to describe the group of microorganisms found in a certain biosphere, which includes bacteria, viruses, fungus, archaea, and protists, the term "microbiome" refers to the collective genome of these living entities, microbes live in various microbiota habitats across the human body, these natural communities and the human body have a long-standing relationship that has developed to benefit both sides concurrently and create a symbiotic balance.[6,7] The ability to tolerate commensal bacteria and identify potentially contagious pathogenic germs is made possible by the relationship between the host's immune system and microbiota, the lamina propria, the intestinal mucosa is made up of a layer that includes immune cells like T and B lymphocytes as well as antigen-presenting cells.

Gut-associated lymphoid tissue is a subset of lymphoid tissue that affects both systemic and local immune responses.[8] Sensors called pattern recognition receptors (PRRs), such as Toll-like receptors, which are produced by intestinal epithelial cells and innate immune cells, are responsible for facilitating communication between the host and microorganisms.[8]

These PRRs identify molecular patterns linked to microbes or pathogens by recognizing the microbiota through these PRRs, immune responses are influenced both locally and systemically. Also, the identification of the microbiota can trigger a memory response, which is mediated by transcriptional changes in genes or a specific locus and epigenetic rewiring of these cells after the initial exposure.[7,9]

The secretion of immunoglobulins (like IgA), the stimulation of lymphocyte differentiation into regulatory T-lymphocytes and T helper 17 (Th17), the production of immunomodulatory cytokines, and even the epigenetic regulation of histone deacetylase enzymes are all directly impacted by the bacterial metabolites. Immunity is enhanced by plasma cells' generation of IgA, which prevents germs from adhering to epithelial cells. Furthermore, pathogen-associated molecular patterns (PAMPs) originating from microorganisms enhance dendritic cell development. The T cells can circulate throughout the body after being activated by APC, enabling an immune response against the same organism.[7] Certain metabolites produced by bacteria, such as lipopolysaccharide (LPS), stimulate the innate immune system, which in turn increases antitumor CD8 T cells that spread from the gut to the periphery [Figure 1].[6,10]

Epidemiology of infection associated cancers

Patients with cancer are at substantial risk of death and morbidity from infections brought on by harmful bacteria and viruses. These infections encompass a range of conditions, such as human papillomavirus (HPV) infections in individuals with cervical and oropharyngeal cancer, *Helicobacter pylori* infections in those with stomach cancer, and hepatitis B and C virus infections in patients with hepatocellular carcinoma. Additionally, infection with human herpesvirus 8 (HHV8) or Kaposi sarcoma-associated herpesvirus (KSHV) is associated with Kaposi sarcoma, Hodgkin's and non-Hodgkin's lymphoma, and nasopharyngeal carcinoma.[12] Bacterial infections are prevalent among cancer patients, especially those caused by drug-resistant pathogens. In a comprehensive prior study of bacteremia in cancer cases, it was found that 12% of cancer patients were afflicted by *Staphylococcus aureus* infections.[13] Among Asian cancer patients without neutropenia, *S. aureus* infections made up approximately 27% of skin and soft tissue infections and 25% of pneumonia cases. In various cancer types, other common Gram-positive bacteria associated with bacteremia include streptococcus and enterococci. In Italy, Gram-positive and Gram-negative infections accounted for 33% and 57% of bacteremia cases in cancer patients, respectively.[14] Notably, the most frequent bacteremia incidents in Japanese cancer patients were linked to infections caused by *Pseudomonas aeruginosa* (14.7%), *Escherichia coli* (18.6%), and various *Staphylococcus* species (33%).[15]

Gut microbiota and their relationship with different form of cancer

Researchers looked at seven different solid tumors, including breast, lung, ovary, pancreas, bone, skin, and brain cancers, and identified some surprising results. Bacteria were detected in all seven cancer types, encompassing DNA, RNA, and lipopolysaccharide (a constituent of Gram-negative bacteria's cell walls). Furthermore, skin cancer and, to a lesser extent, breast cancer were discovered to include lipoteichoic acid, a chemical prevalent in Gram-positive bacteria cell walls. It has long been understood that bacteria may be found in human cancers, but what distinguishes this study is the discovery that these tumor-associated bacteria are found within the cancer cells themselves.[16]

Both Gram-positive and Gram-negative bacteria were identified within tumor cells, as well as immune cells like

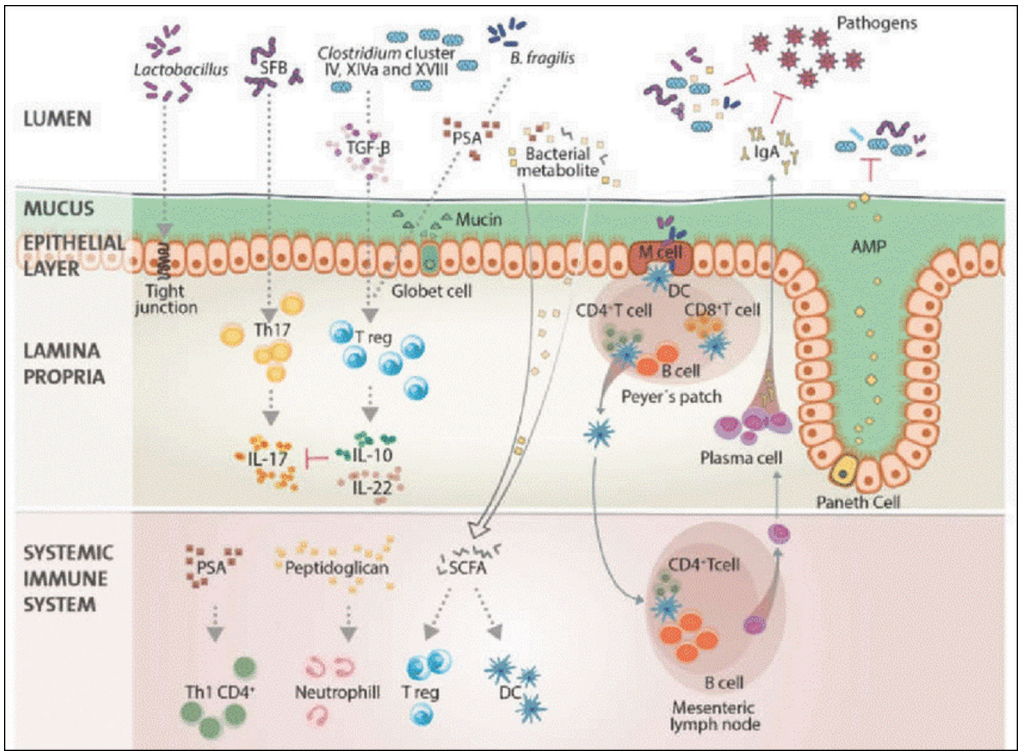

Figure 1: Gut microbiota and immune system[11]

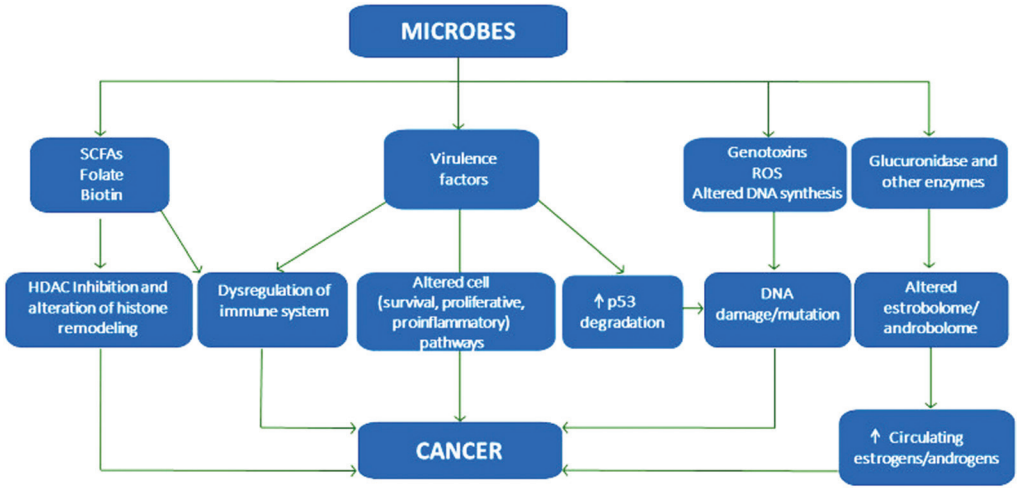

Figure 2: Several theories have been put out to explain how bacteria may affect cancer[17]

macrophages and CD45+ leukocyte, bacteria were devoid of a cell wall and consistently located in the cytoplasm near the nucleus; they were never observed inside the nucleus. The microbiomes of each tumor were distinct, with breast cancer having the most varied and abundant microbiota when compared to other cancer forms. Breast cancer has a high concentration of mycothiol-producing bacteria, which are known to help in the removal of reactive oxygen species. This finding is particularly significant because breast cancer is characterized by substantial oxidative stress.[16] To comprehend how bacteria affect cancer, several possible processes have been put forth [Figure 2].

Breast cancer has been closely linked to several bacterial genera. Each subtype of histologic tumor shows a unique microbial composition. Tepidiphilus, Alkanindiges, and Stenotrophomonas were found in invasive ductal cancer samples, whereas Peptostreptococcus, Micromonospora, Faecalibacterium, and Stenotrophomonas were found in invasive lobular carcinoma samples.[18] *Fusobacterium nucleatum*, an oral infection, has been shown by Parhi, *et al.*[19] to move through the circulation and concentrate in breast tumors, with its abundance rising in connection to the stage of breast cancer.

Gut microbiome and breast cancer

Numerous bacterial species may be found in a healthy human gut, which is where vital physiological processes including energy absorption, immunological control, and xenobiotic metabolism predominately occur and are greatly aided by gut microorganisms.[20,21] The production of enzymes that deconjugate conjugated estrogen metabolites by a variety of gut microbe strains is known to block the excretion of these compounds and regulate the levels of active estrogens in the blood—a crucial component in the development of breast cancer. Additionally, it is known that a number of bacterial species may convert dietary lignans into estrogen mimics such secoisolariciresinol, enterolactone, and enterodiol.[22] The conversion of conjugated estrogen to deconjugated estrogen by gut microbial beta-glucuronidases is crucial for controlling breast dysbiosis. This procedure can result in long-lasting inflammation, which damages DNA and causes increased angiogenesis, proliferation, metastasis, and invasion [Figure 3].

Gut bacteria can exert an influence through PAMPs that interact with and modulate Toll-like receptors which initiate signaling pathways that activate immune and inflammatory genes, allowing the host to protect itself against invasive pathogens. PAMPs are also implicated in T cell, B cell, and CD4 T cell development into Treg and Th17 cells. These cells may either return to the stomach or circulate throughout the body, impacting immunity on several levels.[23]

A symbiotic connection known as normobiosis is fostered by the gut microbiota and is essential for sustaining digestion, metabolism, and host immunological responses. Conversely, dysbiosis occurs when there is a shift in the microbiome, accompanied by a decrease in microbial diversity. This diminishes the microbiota's capacity to combat harmful microorganisms, ultimately contributing to the development of both localized and systemic disorders.[24]

Gut dysbiosis is directly related to obesity, a major breast cancer risk factor. Numerous studies have shown distinct variations in the gut microbiota of breast cancer patients and healthy women, with some results suggesting a similarity to the microbiome seen in obese people.[25]

Gut microbiota and its impact on breast cancer treatment

The efficiency and side effects of breast cancer chemotherapy, hormone treatment, targeted therapy, immunotherapy, and radiation may be influenced by the microbiome. In recent years, it has become obvious that the gut microbiota may impact the efficacy and adverse effects of cancer therapy. On the other hand, there can be a two-way interaction between the gut microbiota and both cancer and anticancer treatments.[24,26]

Hormone therapy, also known as endocrine therapy, is a common treatment for hormone-sensitive breast cancer. Some forms of breast cancer rely on the hormone's progesterone and estrogen for proliferation.[27-29] Considering the crucial role of gut bacteria in estrogen metabolism, this fact becomes highly significant. diverse persons have diverse gut microbiota compositions based on factors such as race, ethnicity, diet, body mass index, antibiotic exposure, and the presence of diseases. It plays a pivotal role in the development of breast cancer. The gut microbiota is instrumental in estrogen regulation as it produces β-glucuronidase, an enzyme responsible for converting estrogens into their active forms.[30]

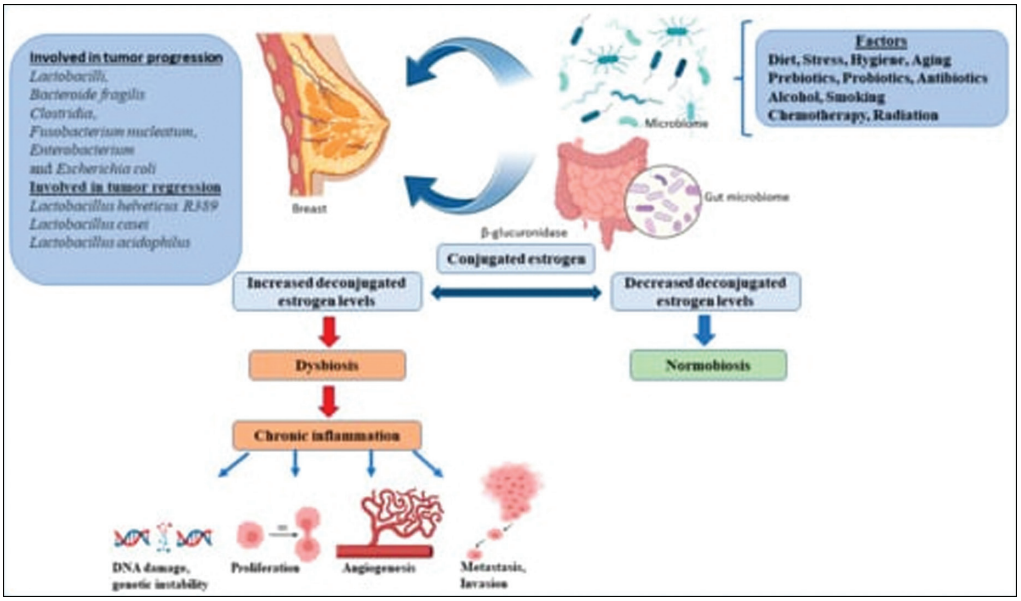

Figure 3: Estrogen regulation and the microbiota in breast cancer. Figures created with BioRender.com

Several *in vitro* and *in vivo* studies have indicated that probiotics can help reduce the progression of breast cancer by boosting the Th1 response and boosting cellular immunity, for instance, *Lactobacillus acidophilus* has demonstrated anticancer properties in mice with breast cancer when given orally. In another study, it was found that *L. helveticus* R389 increased the levels of interleukin (IL)-10 in both blood and mammary cells while decreasing IL-6 levels. This resulted in the suppression of mammary tumor cells by enhancing the local immune response. Additionally, *L. casei* treatment stimulated the production of IL-12 and IFN-γ, further bolstering the immune response in mice with invasive ductal carcinoma.[31] Furthermore, a population-based case–control study revealed that frequent consumption of probiotics like *L. casei Shirota* and soy isoflavones was associated with a reduced incidence of breast cancer among Japanese women.[32]

Thanks to advancements in imaging techniques like fluorescent *in situ* hybridization and improved PCR procedures, we can now detect the spatial distribution of microbial inhabitants within tumors. These methods offer valuable insights into how these bacteria may impact the tumor microenvironment. Nejman, *et al.*[16] examined nine different tumor types, which included breast, lung, ovarian, pancreatic, melanoma, bone, and brain tumors. They demonstrated the presence of immune cells and tumor-specific microorganisms inside tumors in an intracellular state lacking a cell wall. Notably, of the nine tumor types examined, breast tumors were shown to have the highest variety and biodiversity.

Another noteworthy study conducted by Cai, *et al.*[33] demonstrated that the internal tumor environment played a role in the metastatic spread of breast cancers. Intratumor bacteria were found to induce cytoskeletal rearrangement in circulating breast cancer cells. Consequently, this alteration made cancer cells more resilient to fluid shear stress in the circulation, thereby aiding their proliferation in distant locations.[34]

A probiotic beverage containing *L. casei Shirota* has been shown to have an inverse connection with breast cancer incidence when mixed with soy isoflavones.[32] Soy isoflavones with estrogenic and antiestrogenic qualities, such as genistein and daidzein, may be responsible for soy's potential to prevent breast cancer. Breast tumors that are estrogen receptor-positive are less common, according to research on the probiotic bacteria genus Lactobacillus. It does this by boosting the anticancer effects of medications that target the endocrine system, including tamoxifen.[35] The microbiota has the potential to influence the host's immune system and inflammation, which play pivotal roles in the advancement of cancer.

Conclusion

Breast cancer continues to pose a significant global health threat, and existing methods for treating breast cancer face limitations in their therapeutic efficacy, often due to issues such as drug resistance. The gut microbiota has been associated to the onset, growth, progression, and metastasis of breast cancer.

Combining probiotics or prebiotics with traditional treatments such as immunotherapy and chemotherapy has the potential to enhance the effectiveness of breast cancer treatment. Numerous elements, including as diet, medicine, age, genetics, ethnicity, and way of life, have a significant impact on the makeup of the gut microbiota. Utilizing the protective potential of gut commensals as diseases develop will need an understanding of how these parameters might be regulated.

Even more importantly, the microbiome of the breast and its surrounding environment may impact therapeutic response and serve as potential biomarkers for breast cancer detection and staging.

Ethical approval

Not applicable.

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Conflicts of interest

There are no conflicts of interest.

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