

Review Article



Potential of the Microbiome as a Biomarker for Early Diagnosis and Prognosis of Breast Cancer

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Conflict of Interest

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ABSTRACT

Breast cancer affects 1 in 8 women globally, and is the leading cause of cancer-related deaths in female patients. The majority of breast cancer cases are of unknown cause; few are linked to genetic predisposition, and some arise sporadically. Finding the cause of these sporadic cases is an important area in cancer research. Investigations into the microbiome show links between microbiome dysbiosis and breast cancer, with possible mechanisms in the association of the microbiome and breast cancer, including estrogen metabolism and the 'oestrobolome,' immune regulation, propensity for obesity, and the regulation of the tumor microenvironment. This paper reviews the literature and discusses the potential implications of links between the microbiome and breast cancer, and concludes that the microbiome may have significant applications as a biomarker for breast cancer diagnosis, prognosis, and management. Further investigation is crucial, since modification of the microbiome can, at the most basic level, be achieved via dietary modification.

Keywords: Breast; Carcinoma; Microbiota

INTRODUCTION

Over the last few decades, global breast cancer cases in women have risen substantially, making it the most frequently diagnosed cancer in women, after non-melanoma skin cancer. Breast cancer is the leading cause of cancer-related deaths in females, affecting 1 in 8 women worldwide [1].

While mortality rates have declined owing to advances in diagnostics and treatment, the etiology of many breast cancers remains undetermined. While many genetic, epigenetic, and environmental risk factors have been identified, sporadic cases occur in women classified as low to average risk. Chen et al. [2] suggested that these cases point to the possibility of undiscovered risk factors, Fernández et al. [1] pointed out that as many as 70% of all breast cancer cases have an unknown cause, and Yang et al. [3] reported that only 10% of breast cancers are linked to a genetic predisposition. Among women with high-risk factors, only a small subset develops breast cancer. Therefore, finding a cause for sporadic cases is paramount in cancer research.

In most Western countries, screening exists for women between 40 and 65 years of age, and this consists of bi-annual mammography followed by ultrasonography and needle biopsies, if indicated [4]. Further, as outlined by Kalia [5] screening programs have substantially contributed to the knowledge of breast cancer biomarkers, and understanding of the molecular and cellular mechanisms that drive the initiation, maintenance, and progression of cancer cells, tumors, and their microenvironments. These biomarkers have aided diagnosis, and facilitated the development of chemotherapy with novel targets to personalize breast cancer treatment.

Microbiome diversity is closely associated with human health [6]. This paper aims to review the current knowledge available in the literature, to investigate how microbiome abnormalities, such as microbial dysbiosis, can be potential biomarkers for breast cancer risk, diagnosis, prognosis, and treatment response.

THE MICROBIOME

Parida and Sharma [7] noted that the gastrointestinal (GI) tract contains 99% of the human microbial mass that exists in a mutually beneficial relationship with the host. The host's digestive tract provides a home for the microbiota while they perform various essential tasks, including helping to develop the host's immune system, reclaiming nutrients from the host's food, and production of vitamins and essential amino acids [8].

Parida and Sharma [7] explained that the microbiome underpins several metabolic functions of the body, and that the dynamic interaction between microbes and their host affects cellular metabolism and inflammatory, neurologic, and immunologic functions. New evidence suggests that these interactions have remote effects via hormonal intermediates, metabolites, and mediators of immunological mechanisms. Fernández et al. [1] added that the microbiome also plays a crucial role in innate and adaptive immunity, ensuring that appropriate immune responses are mounted against pathogens.

Shapira et al. [8] outlined how the microbiota of the human GI tract is inherited from the mother during vaginal birth and subsequent breastfeeding, later modified by genetics, age, and lifestyle. Although previously thought of being sterile, the breast tissue itself also has a particular microbiome, unique from other microbial populations, such as the GI microbiota. Being made up of fatty tissue, abundant vasculature and lymphatic systems make it an ideal environment for bacterial growth. The breast tissue microbiome is acquired and altered via routes, such as breastfeeding, sexual activity, and bacterial translocation from the gut to the breast [9].

A disturbed or changed microbiome ecology is referred to as dysbiosis. It can eventuate from a disease, excessive hygiene practices, medications, or diet, as well as some genetic conditions—particularly changes in the expression of genes involved in immune functioning. Fernández et al. [1] added that dysbiosis could result in unfavorable outcomes for the host, and lead to various diseases due to the lack or abundance of certain microorganisms. According to Yang et al. [3] one of these pathological processes can be tumorigenesis.

DYSBIOSIS AND BREAST CANCER

Disruption of the delicate balance between a host and the resident microbiota has recently been reviewed with regard to its contribution to pathological processes, including tumorigenesis, and its role in averting carcinogenesis through its myriad of biological activities. Possible mechanisms involved in the association of the microbiome and breast cancer include estrogen metabolism, immune regulation, and propensity for obesity. There is also evidence that in the breast tissue itself, microorganisms may play a role in regulating the tumor microenvironment [9].

Chen et al. [2] described studies indicating that the GI microbiome of breast cancer patients differs from that of non-sufferers or healthy subjects. More specifically, Goedert et al. [10] found that the fecal microbiota of postmenopausal women with pretreated breast cancer differed from that of control subjects with normal mammography. Their study reported that breast cancer patients had different levels of specific bacterial phyla as compared to normal control patients; the cancer patients showed higher numbers of *Clostridiaceae*, *Faecalibacterium*, and *Ruminococcaceae*, and lower numbers of *Dorea* and *Lachnospiraceae*. The overall diversity of the microbiome was also reported to be lower in cancer patients.

Eslami et al. [9] described the breast microbiome studies that indicate lack of diversity and abundance in breast cancer patients, with relative increases in *Enterobacteriaceae*, *Bacillus*, and *Staphylococcus* species. It is worth noting here that some of these species contain members that can cause double-stranded DNA breaks in cells that make up breast cancers. The authors also pointed out that there is a considerable distinction between the microbial populations of malignant and benign breast tissue samples, malignancy being associated with an increase in certain bacteria that are usually less abundant.

Attraplsi et al. [11] demonstrated that the GI microbiome of cancer patients was similar to that of healthy control patients, with a first-degree family member diagnosed with breast cancer, suggesting that microbiome composition may be linked to the risk factors for breast cancer. Bard et al. [12] showed a correlation between GI microbiome composition and cancer grade, suggesting a relationship between the microbiome and breast cancer development and progression.

Studies have shown that the microbiome of women with breast cancer differs from that of healthy women, in quantity, types, and abundance of species and quality, i.e., at metabolic and immunological levels. Therefore, the microbiome, or rather an imbalance, or dysbiotic state of the microbiome, has the potential to be an additional risk factor and prognosticator of breast cancer. Furthermore, the microbiome can influence treatment options, as it is documented that the intestinal microbiota plays a role in the efficacy of immunotherapeutic treatment options in breast cancer. It has been suggested that actively shifting a microbial dysbiotic state to a state of homeostasis can be used in an intervention in the treatment of breast cancer [13].

THE MICROBIOME, DIET, AND ESTROGEN METABOLISM

Apart from traditional risk factors, it is reported that elevated levels of endogenous and circulating estrogens have a direct association with increased risk of breast cancer in women post-menopause [3].

Estrogen synthesis occurs in the ovaries, using endogenous or dietary lipids, and estrogens circulate in the blood either bound to carrier proteins or as free unconjugated molecules. The liver carries out conjugation and subsequent inactivation of estrogen, and once conjugated, the inactive estrogen is transported into the intestinal lumen. In the intestinal lumen, the microbiota plays a role in the fate of this inactive estrogen. If an individual has a microbiome capable of deconjugating estrogen, the freed estrogen is reabsorbed, increasing free estrogen levels. The individuals whose microbiome is less able to perform this estrogen deconjugation have a greater estrogen excretion in feces and, therefore, lower circulating estrogen levels [8].

The diversity of the GI microbiome has been shown to influence estrogen levels. The dysregulation of sex hormones is reported to be one of the primary risk factors for developing breast cancer, manifesting as the distinct subtypes of triple-negative, human epidermal growth factor receptor 2-positive, and estrogen receptor-positive [3]. Thompson et al. [14] reported that postmenopausal estrogen metabolism seems to be influenced by the diversity of the microbiome, and higher circulating estrogen levels were found to be associated with microbiome dysbiosis in patients with a history of breast cancer.

Plottel and Blaser [15] proposed the ‘oestrobolome’—the collection of all enteric bacterial genes involved in estrogen metabolism, particularly species that possess enzymes involved in the deconjugation and conjugation of estrogen. They suggested that a woman's oestrobolome can influence the burden of estrogen over her lifetime and can, in turn, influence the development of estrogen-driven neoplasia. The authors hypothesized that analysis of the oestrobolome could be used as a biomarker to assess the risk of estrogen receptor-positive breast cancer, among others. Moreover, modification of the oestrobolome via the right mix of antimicrobials, prebiotics, and probiotics can reduce the risk of estrogen-related cancers [15].

OBESITY, THE MICROBIOME, AND BREAST CANCER

Changes in the GI microbiome are related to the risk of obesity, and obesity is a risk factor for breast cancer development, particularly in postmenopausal women. *Firmicutes* and *Bacteroidetes* species are heavily involved in the breakdown of dietary fibers and polyphenols in the large intestine. Fernández et al. [1] and Shapira et al. [8] found that obesity caused by a diet high in saturated fats and low in fiber changed the proportions of these 2 bacterial phyla. A study on twins, one obese and the other lean, showed a smaller amount of *Bacteroidetes* in the obese twin, a finding that changed when the obese twin lost weight. This change in the ratio of these 2 bacterial populations, whether caused by obesity or a factor that helps promote obesity, resulted in the growth of detrimental bacterial species, culminating in dysbiosis of the microbiome [16]. Diets high in calories and saturated fats are a significant cause of obesity, and obesity, coupled with dysbiosis, also results in increased estrogen levels. Together, these 3 factors may contribute to the higher risk of breast cancer observed in women with a high body mass index. Kwa et al. [17] confirmed that growing evidence links diet, the microbiome, and estrogen-driven breast cancer. Interventional techniques using prebiotics and probiotics target certain bacterial species (resulting in modulating estrogen levels) that could lower the risk.

IMMUNE REGULATION, THE MICROBIOME, AND BREAST CANCER

The microbiome—commensal microorganisms that have co-evolved with the host— elicits an effect on various host immune functions. The microbiota can regulate the host's immune responses to infection and the presence of tumor cells. Thus, dysbiosis can result in an inability to control pathogens and a misguided immune response to commensals, leading to chronic tissue damage and inflammation, which is conducive to developing some cancers. Dysbiosis affects immune regulation and hampers the host's immune response to the progression and invasion of tumor cells. Inflammation and immunity are fundamental physiognomies of cancer, and 2 hallmarks of cancer are the ability to avoid immune destruction and the ability to cause tumor-promoting inflammation [18].

Previously, it was noted that poor dietary choices and obesity could lead to dysbiosis, favoring the growth of particular bacterial species, such as *Fusobacterium nucleatum*, which decrease the host's lymphocytes by killing mature lymphocytes directly in the M cells of the Peyer's Patches. It has been noted that a low lymphocyte count in patients with cancer is related to poor disease-related outcomes [8]. Concerning breast cancer, a study by Noh et al. [19] showed that changes in neutrophil-to-lymphocyte ratios were associated with the risk of relapse, and a higher risk of mortality within 5 years of diagnosis.

BREAST MICROBIOME AND THE TUMOR MICROENVIRONMENT

There is a growing body of evidence suggesting that microorganisms are involved in regulating the tumor microenvironment, and that bacteria may help support breast tissue health via stimulation of inflammatory responses in the host. Reduction of or lack of diversity in the microbiome of breast tissue may, therefore, increase the risk of breast cancer. It is known that many pathogens have carcinogenic effects, therefore, a better understanding of the effects of microbial agents within breast tissue may build upon the use of the microbiome as a biomarker in breast cancer. Studies are in preliminary stages, and the link between breast tissue dysbiosis and breast cancer is still not fully understood; however, given the potential implications of the current findings, further investigation is warranted [9].

MICROBIOME AND THERAPY

Evidence is emerging that the microbiome affects the patient's response to therapy via the metabolism of drugs, pharmacokinetics, anti-tumor actions, and toxicity. The interactions between the microbiome and anti-cancer treatments include the metabolism of chemotherapeutic agents and the modulation of the host's immune system and its anti-cancer activities [4]. Conversely, therapies can also be used to modulate the microbiome. The bioavailability of most chemotherapeutic agents and the body's ability to absorb them requires exposure of these agents to enzymes in the GI tract before they enter the systemic blood circulation. The bacteria that make up the microbiome are the factories that synthesize the enzymes; therefore, microbiome composition can alter the mode of action of certain therapies. Over 40 drugs are known to be metabolized by the microbiome [7].

The way a patient responds to the myriad of treatment options for breast cancer depends on their anti-tumor immune response. The most accurate indicator of anti-tumor response, as well as a useful prognosticator, is the number of tumor-infiltrating lymphocytes (TILs) [6]. The authors found that the greater the quantity and diversity of the microbiome, the greater the expression of TILs, which can positively affect the efficacy of immunotherapy treatment regimes in breast cancer.

In addition to the response to therapy, management of the microbiome can be considered pre-diagnosis to reduce cancer risk. Plottel and Blaser [15] hypothesized that establishing and maintaining an oestrobolome that has reduced deconjugation activity and errs towards estrogen excretion can reduce the risk of developing a malignancy that is propelled by estrogen. Mikó et al. [4] supported this hypothesis and suggested that dietary choices may exist that maintain a cytostatic microbiome pre-cancer, which would prove vital post-cancer to aid in the successful completion of chemotherapeutic treatment. Stringent hygiene practices and the overuse of antibiotics in specific demographics may predispose some patients to develop cancer associated with chronic inflammation. While antibiotics can increase the risk of breast cancer, they can also be utilized to balance a dysbiotic microbiome, either before or after a cancer diagnosis. Furthermore, dietary changes can be beneficial, including increased consumption of lignin-rich foods, which have anti-estrogenic characteristics [8].

There have been several studies on the use of probiotics in breast cancer, with one in particular by Lakritz et al. [20] showing that in mice with western/fast food diet-induced neoplasms, the probiotic *Lactobacillus reuteri* inhibited the early stages of carcinogenesis and raised the sensitivity of breast cells to apoptosis, reducing hyperplastic and neoplastic features in the test subjects. Furthermore, it was found that the mice that received *L. reuteri*, in addition to the western diet, were leaner than their counterparts that only received the western diet.

Some of the mechanisms considered in the effectiveness of probiotics in breast cancer include inhibition of cell proliferation, induction of apoptosis, and cell cycle arrest. In addition to mouse studies, human clinical trials have been carried out concerning probiotic therapy in breast cancer. In one trial (NCT03358511), probiotics were administered to 20 postmenopausal women with breast cancer, to observe the effect of probiotics on the number of CD8+ T cells [9]. Another trial (NCT03760653) studied how a combination of probiotics and exercise affected microbiome composition, immune function, and quality of life in patients who have survived breast cancer.

MICROBIOME AS A BIOMARKER FOR BREAST CANCER

The launch of the Human Microbiome Project (HMP) in 2007 set out to determine the associations between changes in the microbiome in health and disease and establish a standardized resource [21]. The HMP shows that human health can be improved by studying, monitoring, or manipulating the human microbiome. Much of what has been learned about the microbiome has been achieved using 16S ribosomal RNA technology, revealing significant diversity of normal microbiome flora among individuals. However, there are limitations to this technology, and efforts have involved the compilation of genomic libraries made from extracted DNA samples, a process termed metagenomics [21].

Rajpoot et al. [22] noted that since 2007, innovations in high-throughput sequencing have provided cost-effective ways of investigating the components of the human microbiome, when combined with bioinformatics. With regard to breast cancer, microbiomics and metagenomics will build knowledge on tumor development and the differences in the microbiome of cancer and cancer-free patients. Therefore, the human microbiome has a strong potential to be used as an early detection biomarker and prognostic indicator in cancer treatment.

Zhu et al. [23] used shotgun metagenomic analysis to study the microbiome of pre- and postmenopausal cancer patients and controls, concluding that the composition and functions of the gut microbiota differed between postmenopausal cancer patients and healthy controls. However, it was unclear whether the alterations in the gut metagenome were involved in the pathogenesis of the disease or were a consequence of it.

Methods used for testing noninvasive and invasive biological samples by Plaza-Diaz et al. [13] included DNA quantification, metagenomic library construction, sequencing, data processing, and metabolomics. Based on these tests, the study concluded that microbial composition in women with breast cancer differs from that of healthy women, confirming that the microbiome can be used as a biomarker in breast cancer investigation.

In addition to studies of the GI tract microbiota, studies have been performed on the microbiota of the breast tissue, and a study by Xuan et al. [24] found changes in the microbiota of breast tissue from cancer sufferers, based on DNA sequencing. When measured quantitatively via quantitative polymerase chain reaction, it was found that total bacterial DNA load was reduced in the tumor tissue when compared to normal breast tissue, which correlated inversely with disease advancement. These findings show a strong link between dysbiosis and breast cancer, and demonstrate the use of the microbiome as a biomarker, using noninvasive and invasive samples.

An interesting observation by Joice et al. [25] was that at least 50% of the genes that make up the human microbiome are still uncharacterized, meaning that there is a vast amount of information to be discovered regarding the microbiome and its potential applications as a biomarker for breast cancer diagnosis, prognosis, and treatment.

However, Ingman [26] cautions that care must be taken in over-interpretation of preliminary findings, and that further studies need to look more deeply into the physiologic function of the proteins and metabolites produced as part of the microbiome, current antibiotic and probiotic practices, how they impact breast cancer occurrence and recurrence, and the actual mechanisms the microbiome uses to act on breast cancer cells.

CONCLUSION

While still in its relative infancy at the molecular stage, the microbiome study and its correlation with breast cancer is a promising area in breast cancer research. It has significant potential as a biomarker for diagnostic and prognostic purposes, when making treatment choices, and even as a treatment option—both pre-cancer (in terms of risk management) and post-cancer as adjuvant therapy in its own right, or a way of optimizing currently employed therapies. Preliminary studies regarding the microbiome's role concerning the risk

factors of estrogen levels and obesity have proved promising, as are studies that associate the microbiome with the host's immune response to cancer, and the link between the microbiome, cell cycles, chronic inflammation, and cancer development. There is growing evidence that modification of the human microbiome may play a role in the treatment of diseases, such as breast cancer, and their prevention. Recent advancements in high-throughput sequencing, metabolomics, metagenomics, and culture-independent studies make this an area of great opportunity, and as Ni et al. [27] pointed out, the most proven method for modifying the microbiome of the GI tract is neither invasive nor costly, but merely diet. To this end, the microbiome study as a biomarker in breast cancer deserves further consideration and attention.

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