Breast Cancer Research and Treatment (2019) 178:493–496
https://doi.org/10.1007/s10549-019-05407-5

REVIEW

The microbiome and breast cancer: a review

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Received: 31 May 2019 / Accepted: 10 August 2019 / Published online: 27 August 2019

Abstract

The human microbiome plays an integral role in physiology, with most microbes considered benign or beneficial. However, some microbes are known to be detrimental to human health, including organisms linked to cancers and other diseases characterized by aberrant inflammation. Dysbiosis, a state of microbial imbalance with harmful bacteria species outcompeting benign bacteria, can lead to maladies including cancer. The microbial composition varies across body sites, with the gut, urogenital, and skin microbiomes particularly well characterized. However, the microbiome associated with normal breast tissue and breast diseases is poorly understood. Collectively, studies have shown that breast tissue has a distinct microbiome with particular species enriched in the breast tissue itself, as well as the nipple aspirate and gut bacteria of women with breast cancer. More importantly, the breast and associated microbiomes may modulate therapeutic response and serve as potential biomarkers for diagnosing and staging breast cancer.

Keywords Breast cancer · Microbiome · Immune response · Flora · Gut

Introduction

Breast cancer remains the most common form of cancer in the United States. Among women, breast cancer alone accounts for nearly 30% of all cancer diagnoses, with 267,000 expected new cases and nearly 41,000 estimated deaths in 2018 [1]. Though mortality rates have steadily declined over the past two decades due to advancements in detection and treatment, the etiology of the majority of breast cancer cases remains unknown. Given the emphasis on microbiota composition and its supportive role in human diseases in recent years, the question arises as to how an individual's distinct microbiome, which contain the same magnitude of bacterial cells as cells in the human body, 3×10^{13} cells [2], may influence breast cancer risk and subsequent response to therapy.

While there are well characterized genetic risk factors (e.g., BRCA1/2 mutations) and environmental risk factors (e.g., sedentary lifestyle, obesity, alcohol, and hormone replacement therapy) for breast cancer, most sporadic cases occur in women of average risk. This suggests the possibility of other undetermined risk factors. The cancer microenvironment, composed of tumor cells, stromal, and immune cells in a milieu of cytokines and extracellular proteins, is characterized by a state of chronic inflammation and elevated immune responses. Studies show that the immune system surveys for nascent transformed cells and plays a key role in cancer prevention as well as tumor immunoediting [3, 4]. Given the role of microbial dysbiosis in chronic inflammation, inflammation-mediated carcinogenesis processes, and immune evasion, it is not surprising that particular microbes

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are associated with the development of particular cancers. Such relationships have been reported with the role of *H. pylori* in gastric cancer and *Fusobacterium* in colorectal cancers [5–7]. However, relatively little is known about the connection between the microbiome and breast cancer.

Dysbiosis and the gastrointestinal microbiome

The microbial environment in the human body plays an essential role in health maintenance by interacting with the nutrient absorption, the immune system, and various metabolic processes. In a symbiotic state, host-microbe interactions counteract invading pathogens and prevent tumorigenesis [8]. However, disruptions in the microbiota composition may shift homeostasis toward a state of dysbiosis. Such imbalances in the local microbial environment could modulate the host immune responses and inflammation to favor disease pathogenesis and progression [8, 9].

Beyond the adaptive nature of the microbiome, several studies have demonstrated that the gut microbiome of patients with breast cancer is altered relative to that of healthy matched controls [10]. An increasing amount of evidence also implicates involvement of the microbiome environment in the metabolism of estrogen, which has a strong correlation with breast cancer development. One study showed that patients that received ampicillin had increased fecal excretion of conjugated estrogens, emphasizing the active involvement of the gut microbiota in estrogen metabolism [11]. This suggests gut microbes may be involved in the metabolism of estrogen, thus modifying one's microbiome may have some effects on breast cancer pathogenesis. In addition, sex hormones can also impact the gut microbiome composition [12].

One case–control study showed that the fecal microbiota of postmenopausal breast cancer patients exhibited less diversity and overall different composition compared to matched controls [10]. Another study reported similar findings with enrichment of *Methylobacterium radiotolerans* in breast tumor tissue versus *Sphingomonas yanoikuyae* in matched healthy tissues. Importantly, quantification of total bacterial DNA load demonstrated an inverse correlation between bacterial load and breast cancer disease stage. Stage 1 patients contained the highest copy numbers of bacterial DNA compared to both stage 2 and 3 patients. This discrepancy in bacterial load was further linked to reduced expression of antibacterial response genes among advanced stage breast cancer patients. These findings suggest dysbiosis may play a role in breast cancer tumorigenesis, where a reduction or alteration of bacterial composition can lead to downstream aberrant immune system functioning permitting tumor development. Furthermore, these findings suggest that bacterial load can serve as a biomarker for diagnosis and staging, thus warranting further investigation [13].

Breast tissue and skin microbiome

Breast tissue and milk, once thought to be sterile, are now known to contain a diverse and unique microbial community [14, 15]. A study comparing the microbial composition of nipple aspirate fluid in women with a history of breast cancer versus normal controls demonstrated a relatively higher incidence of the genus *Alistipes* and lower incidence of a genus from the *Sphingomonadaceae* family [16]. Other studies demonstrate the microbiome of breast skin swabs and breast tissue from patients with breast cancer relative to health controls is enriched in particular microbes, including *Fusobacterium*, *Atopobium*, *Gluconacetobacter*, *Hydrogenophaga*, *Bacillus*, *Enterobacteriaceae*, *Staphylococcus*, *Comamonadaceae*, and *Bacteroidetes* [15, 17].

Non-malignant breast diseases

Most of the studies on microbiome and its influence on breast diseases have focused on understanding connections to invasive cancers; however, non-malignant breast diseases are very common and can negatively impact quality of life including increasing one's risk of cancer [18]. Such non-malignant breast diseases include Atypical Ductal Hyperplasia (ADH), Ductal Carcinoma In Situ (DCIS), and mastitis/breast abscesses. While particular organisms, most notably *S. aureus*, have long been implicated as causative in mastitis, recently a study showed that milk from mastitis patients demonstrated microbiota disruptions including lower microbial diversity with increased opportunistic pathogens and reduced commensal organisms [19]. ADH and DCIS, characterized by abnormal, neoplastic cell growth and possibly associated with or leading to invasive breast cancer, have some known risk factors but their etiology is largely unknown. Given data suggesting that microbial differences in other tissues can be associated with neoplastic non-malignant growth [20], the question is whether the breast and gut microbiomes could influence non-malignant breast diseases such as ADH and DCIS.

Chemotherapy

Growing evidence indicates that the gut microbial composition impacts the efficacy of chemotherapy by modulating the translocation, metabolism, and immune response to such drugs [21]. It is possible that the local microbiome in the breast may play a distinct role in modulating

chemotherapeutic efficacy in addition to the known role of the gut microbiome in modulating the efficacy of particular chemotherapeutics [22].

Antibiotics have been shown to disrupt the microbiota leading to a decreased response to platinum-based chemotherapies as well as immunotherapies [23]. This study suggests that an intact microbiome is necessary for optimal responses to anti-cancer therapies. Other studies arrived at similar conclusions regarding the importance of the gut microbiome in determining drug response [24].

Radiotherapy

Radiation therapy (RT) is another important therapeutic modality in the treatment of breast cancer. RT can be used in both the breast conservation and post-mastectomy settings to reduce local recurrence and improve overall survival. However, up to 95% of patients experience acute or chronic dermatitis in response to the ionizing RT. Acute radiation dermatitis can include pain, erythema, epilation, blistering, and ulceration, and can interrupt cancer treatment. Chronic dermatitis, occurring months to years after RT, consists of progressive and irreversible skin changes such as fibrosis, atrophy, or pigmentation alterations, negatively impacting reconstruction and quality of life. While proper skin hygiene and topical steroids can mitigate radiation dermatitis, many patients still experience significant post-RT skin sequela. While the exact mechanism of RT-induced dermatitis is unknown, an aberrant proinflammatory response is strongly implicated [25, 26]. One study demonstrated that bacterial superantigens, particularly those from *S. aureus*, can exacerbate RT-induced inflammation by further activating T cells and preventing epidermal repair [27].

Active clinical trials

New active clinical trials are studying the impact of the microbiome upon breast cancer in a variety of ways. One particular study is investigating how probiotics may increase the immune system's ability to recognize cancer cells in patients with breast cancer [28]. This particular trial is measuring the number of cytotoxic T cells in the tumor after 4 weeks of probiotic treatment. Another study is testing a hypothesis that dominance of specific microbiome organisms is associated with complete pathologic response in breast cancer patients receiving neoadjuvant chemotherapy [29]. A third study is investigating whether the gut microbiome plays a role fighting cancer by impacting the efficacy of immune cells [30].

Immunotherapy

Increasing evidence suggest involvement of the gut microbiota in the degree of clinical response to immune checkpoint inhibitors. Findings from one study indicate the potential role of *Bacteroides* species, particularly *B. thetaiotaomicron* and *B. fragilis,* in improving therapeutic efficacy of the immune checkpoint inhibitor, anti-CTLA-4 antibodies [31]. Likewise, melanoma patients categorized as responders to anti-PD-1 treatment exhibit more diverse fecal microbiome samples with enrichment of *Ruminococcaceae* bacteria. More importantly, patients with a greater diversity of fecal microbiome experienced significantly longer progression-free survival when compared to those with only low or moderate microbiota diversity. The microbiota of immunotherapy responders may upregulate the immune response through enhancing antigen presentation or increasing T cell recruitment in the local tumor environment [32]. Additional studies have reported that certain bacterial species, including *Bifidobacterium* and *Akkermansia muciniphila* [33, 34] correlated with increased anti-PD-L1 therapeutic response. While no studies to date have characterized the impact of microbiome composition on therapeutic response in breast cancer, the above findings indicate that one's microbiome may be used to provide targeted, patient-centered treatments. In addition, manipulation of the microbial ecosystem may provide a means to overcome resistance to certain breast cancer immunotherapies.

Conclusion

Given the vast number of potential connections between the microbiome and various breast diseases, both benign and malignant, we seek to better understand the microbiome in the context of breast disease pathogenesis and treatment. The microbiome can affect drug responsiveness to systemic chemo- and hormonal therapies and can modulate the immune system with regard to response and side effects associated with radiotherapy and immunotherapy.

Author contributions JC, JD, and VP collected and analyzed relevant literature. JC, JD, VP, and MH drafted the manuscript. JC, JD, VP, MN, SA, MM, SS, and MH critically revised the manuscript for content. All authors read and approved the final manuscript.

Funding None.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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