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Gut Microbiota in Breast Cancer

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Abstract
The purpose of the study: To study the changed microbiota population in the intestines and breast tissue of breast cancer patients, as well as the mechanisms of microbiota modulation and their interaction with breast cancer.
Materials and methods: Literature analysis was conducted based on various textbooks and literature. The data of the last 10 years were analyzed. The statistical data of the last 10 years on the etiology, epidemiology and clinic of the disease were taken into account.
Analysis and Discussion of results: Recent studies have shown that healthy people and breast cancer patients have different microflora composition, which suggests that microflora is a new risk factor for breast cancer. Changes in gut and breast microflora are associated with breast cancer prognosis. Dietary supplements such as probiotics and prebiotics are commonly used to mitigate the side effects of cancer treatment. They also shape the population of the human gut microbiome. This article presents novel means of modulating the microbiota through feeding probiotics and prebiotics as novel and promising strategies for breast cancer prevention and treatment.
Conclusion: Breast cancer occurs in both women and men, but it is more common among women. The wide spread of the disease, the severity of the treatment process, the long duration, and in most cases even the ineffectiveness and death of this disease indicate the great social importance of this disease. proves and shows that the fight against it should be conducted on a global scale.

Keywords: breast cancer, cancer, intestinal microflora, microbiota, microorganism, estrogen, probiotic, prebiotic, breast microflora, estrogen metabolism, microbiota modulation, systemic immunity, epigenetic regulation.

Introduction

Breast cancer (BC) affects more than 2 million women each year and became the most frequently diagnosed cancer in the U.S. in 2021. According to recent studies, ‘dysbiosis’, or the alteration in gut or breast tissue microbiota diversity, is frequently associated with BC. While microbiota in breast tissue have direct impact on tumor development, dysbiosis, or reduced alpha diversity of gut bacteria, can also affect tumor

development by the production of metabolites that can elicit altered immune response, manipulate estrogen level, or induce epigenetics effects.

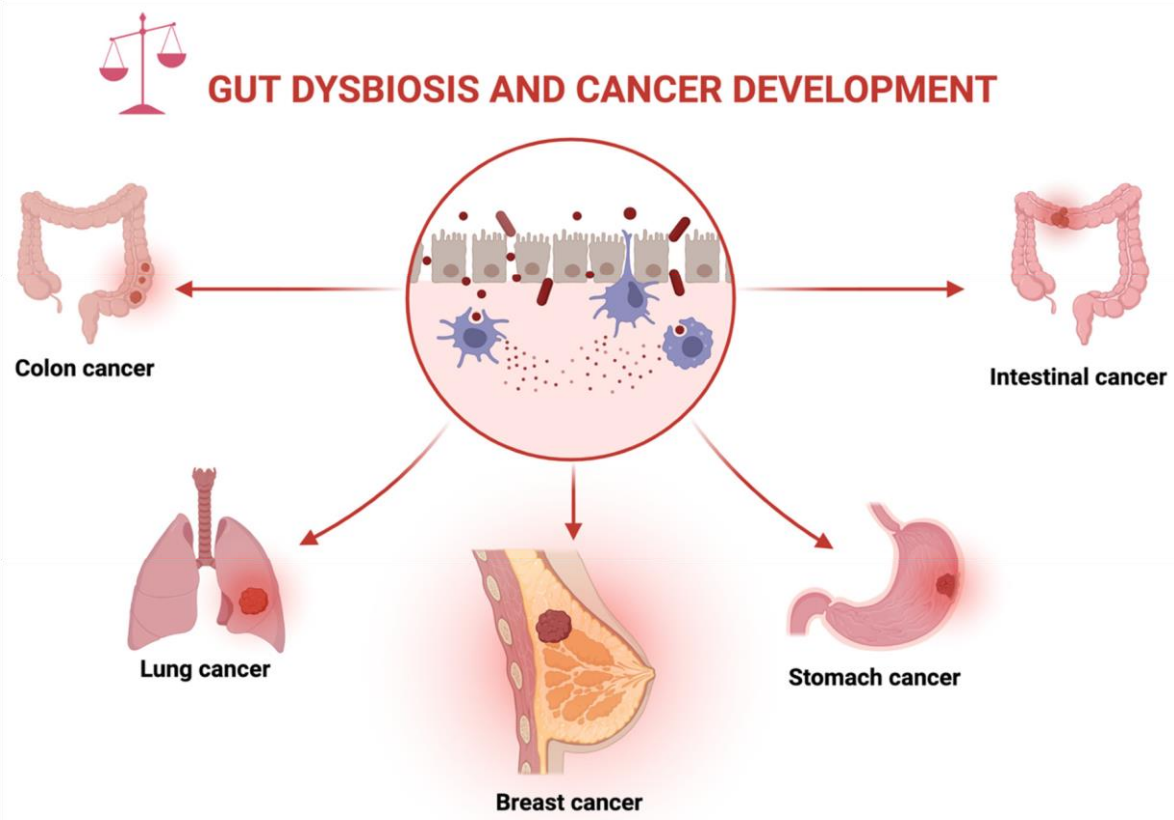

Figure 1. Dysbiosis (imbalance of the health gut microbial population) can lead to the development of different cancer types, including breast, colon, lung, stomach, and intestinal cancers.

1. Etiology

Breast cancer is the most common cause of cancer-related deaths in women. Breast cancer is still a major cause of morbidity and mortality among women despite all the available diagnostic and treatment modalities. The gut microbiota has drawn keen interest as an additional environmental risk factor in breast cancer, especially in sporadic cases. Gut microbiota dysbiosis has been shown to play a role in the development of breast cancer via estrogen-dependent mechanisms and non-estrogen-dependent mechanisms involving the production of microbial-derived metabolites, immune regulation, and effects on DNA. The gut microbiota influence estrogen metabolism hence estrogen levels. The metabolites that have demonstrated anticancer properties inclue lithocholic acid, butyrate, and cadaverine.

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2. Epidemiology

Breast Cancer New cases: Breast cancer is the most frequently diagnosed cancer in women worldwide with more than 2 million new cases expected to be diagnosed in 2018, accounting for 25% of all new cancer cases in women. A little less than half (44%) of these cases will occur in very high-HDI countries, which represent about 19% of the world female population. Deaths: An estimated 626,700 breast cancer deaths will occur in women in 2018. Breast cancer is the leading cause of cancer death among women worldwide and in medium HDI countries and ranks second for other HDI levels

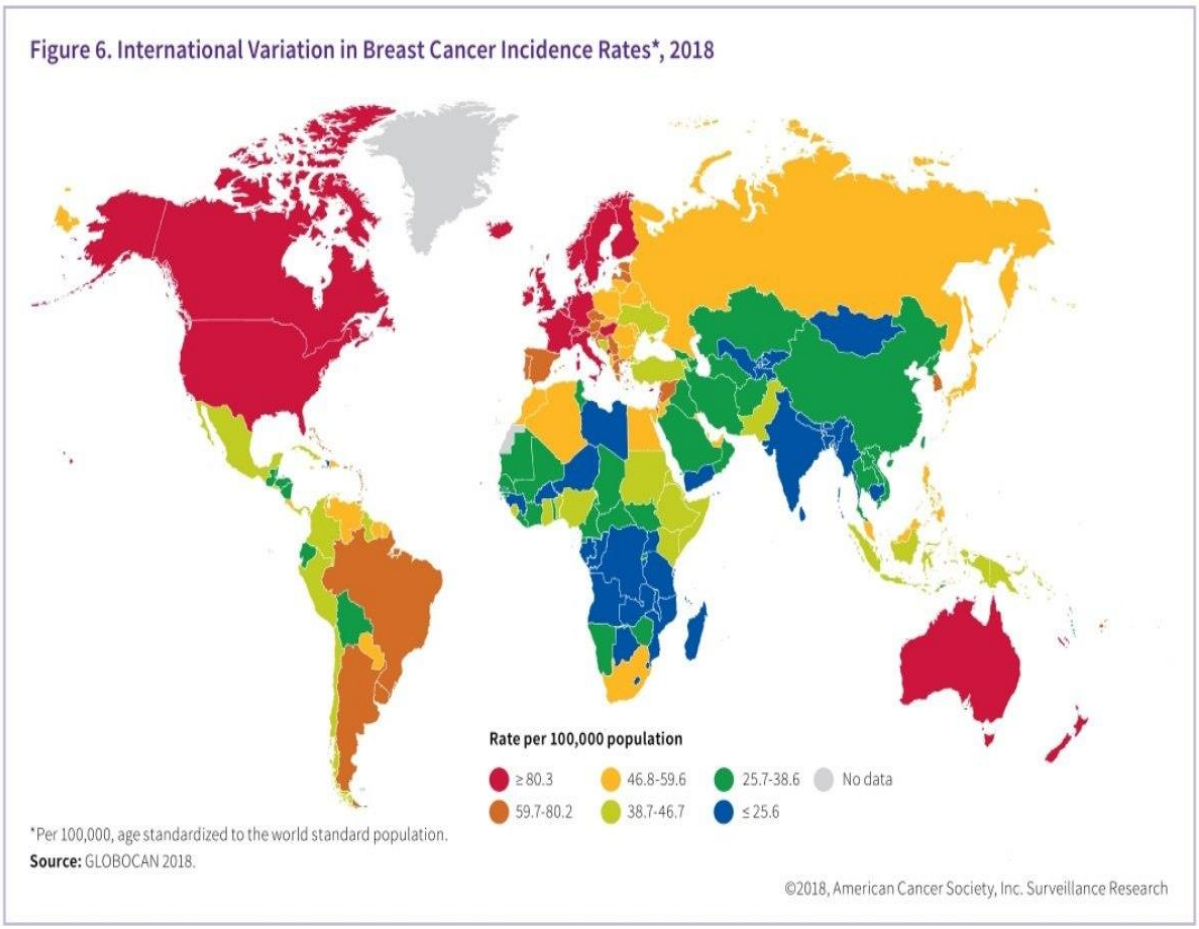

Figure 2. International Variation in Breast Cancer Incidence Rates (2018)

3. Gut microbiome

According to data of Oncotarget journal about 10^{14} microorganisms are living in the gastrointestinal track, participating in physiological processes, and interacting with each other and the host [49]. Microorganisms comprise a 'forgotten organ' in the human body [44]. The ratio of bacteria cells to human cells is approximately 1:1 [54]. The human gastrointestinal tract supports the growth of beneficial microbiota owing to their ability to protect the body against pathogens [65]. Their contribution to immune system development and maintenance[38] ,the fermentation of indigestible fibers into

short-chain fatty acids (SCFAs) [60], production of essential amino acids [43] and vitamins (Hill M. Intestinal flora and endogenous vitamin), absorption of minerals[68], and deactivation of toxins [61] and carcinogens [36] are among their benefits. Animal model studies showed associations between the microbiome and the development of many diseases, including cancer [63]. Diet can contribute to the development of various diseases, including cancer[40], since it has a direct role in controlling the composition of the microbial community. Accordingly, a plant-based diet stimulates bacterial diversity[40], while animalbased regimen decreases the Firmicutes population (the common bacterial phylum in breast tissue) in digestive system. Shifting to a plant-based diet would increase Firmicutes population [9]. Thus, changes to the diet might contribute to the development of diseases through alternation in microbial metabolism and production of toxic metabolites.

4. Gut Dysbiosis

A symbiotic relationship (referred to as normobiosis) between host and microbiota is critical to maintaining a balance (homeostasis) in the gut. This symbiotic relationship confers benefits to the host in many key aspects of life. However, any perturbation of the normal microbiome content that disrupts this relationship, the so-called “dysbiosis”, may result in detrimental consequences for the host, and promote different diseases. Moreover, it is known that differential abundances of certain microorganisms in the composition of the microbial community, and/or a discrete presence of some bacterial species can exert pathogenic effects that encourage disease development. Thus, Helicobacter pylori infection is known to promote gastric cancer and gastric mucosal-associated lymphoid tissue (GALT) lymphoma [53], although H. pylori-mediated protection against extra-gastric immune and inflammatory disorders has been described[50]. This pathogen bacterium is classified as a carcinogen by the International Agency for Research on Cancer (IARC).Moreover, to modulating inflammation and influencing genomic stability of host cells through the deregulation of different signals and pathways, gut microbiota has also been related with cancer progression by affecting metabolic pathways of estrogens through enterohepatic circulation [48].In this regard, it has been proposed that certain gut microbes may play a role in breast carcinogenesis by promoting antitumor immunity and immune surveillance, and/or by modulating systemic estrogen levels [71,67]. BC associations with estrogen levels could reflect differences among individuals in their intestinal microbial communities [33], as shown 50 years ago by Adlercreutz and collaborators, who demonstrated one of the fundamental roles of the gut microbiota [1]. More recently, Fuhrman and co-workers demonstrated that postmenopausal estrogen metabolism is associated with microbial diversity [19]. In comparison with other human organs, the microbial load and its variety are increased in the digestive system, especially in the large intestine [42].This complex intestinal microbiome plays a

significant role in both local and distal areas of the body through the production of metabolites, hormonal intermediates, and immunologic cytokines. It was shown that higher phylogenetic diversity in the intestinal microbiome raises hydroxylated estrogen metabolites in the urine of a healthy female[17].In postmenopausal females, an increased level of circulating estrogen is associated with increased risk of BC [30].Intestinal microbiome is one of the major regulators of circulating estrogens [5]. Therefore, dysbiosis in the gut microbiome potentially disrupts homeostasis through the disruption of estrogen metabolism[5].It is suggested that estrobolome, the bacterial gene mass in the human intestine, the products of which take part in estrogens metabolism, may increase the risk of estrogen receptor-positive BC in postmenopausal females [47,31]

6. The Correlation between Gut Metabolites and Breast Cancer Development

Breast feeding, consumption of solid food, and changes in hormone levels all contribute to major establishment of gut microbiota [48]. Different bacterial genera colonize at different locations, such as the ileum, stomach, and colon, and actively regulate the intestinal immune system [49]. BC occurrence and development are affected by multiple factors, such as age, hormone level, menopausal stage, inflammation and immunity, and cancer development stage and severity, as well as other factors. Gut microbial species can directly modulate breast cancer risk via alterations to host metabolism, estrogen hormone recycling, and immune pressure[3]. For example: when ovarian function stops, small amounts of estrogen are **produced by converting adrenal precursors and adipose tissues,** or body fat, into estrone and estradiol, two of the three types of estrogens.However, because postmenopausal levels of hormones are normally lower than those of premenopausal levels, it is not uncommon for postmenopausal women to **fall into a state of estrogen deficiency**. This deficiency can provoke various **hormonal imbalance symptoms**, including hot flashes, mood swings, vaginal dryness, and more. If a deficiency is not addressed promptly, long-term health complications can arise as the years pass, including osteoporosis, incontinence, or dyspareunia. On the other end of the spectrum, postmenopausal women **may also suffer from estrogen dominance**, especially those whose accumulated body fat produces excessive levels of hormones. Estrogen dominance **produces similar symptoms** to those of a deficiency, such as hair loss, depression, water retention, and migraines. If left unattended, estrogen-dependent breast cancer or ovarian cancer as well as uterine fibroids can develop. Additionally, it has been reported that gut microbial species can translocate to the breast tissue via the skin, which may play a significant role in the maintenance of breast health [2**]**. This translocation is believed to occur via multiple pathways,including sexual contact, nipple-oral contact via lactation, or nipple-areolar orifices [2**]**. The possibility of translocation of bacterial species from the gut to breasts through systematic circulation has also been proposed

[2]. Gut microbial dysbiosis can cause the breakdown of mucosal barriers enabling the gut microbial species to translocate into the peripheral circulation and the mesenteric lymph nodes (MLN) which leads to altered immune responses [2]. Dysbiosis is believed to accelerate cancer development by damaging host DNA, producing metabolites to induce inflammation, and causing dysregulation of the host immune system [21]. For example, an antibiotic treatment using cephalosporin (usually 1st and 4th Generation of Cephalosporins are used as anti-cancer drug for BC) induced BC and reduced microbiota diversity [66]. An EGFR/Her2 tyrosine kinase inhibitor, lapatinib, can induce diarrhea, decrease microbiota delivery, and, possibly, lead to dysbiosis [39]. Besides some negative impacts of pathogenic bacteria, however, microbiota populations can catalyze chemical reactions to accelerate anti-cancer drug biotransformation [51]

7. The Microbiota of Healthy Breast Versus Breast Tumour Microenvironment

The breast tissue microbiome is constituted by a multitude of lifestyle and biological factors, including the translocation of bacterial species from the gut to the breast, sexual activity, and breastfeeding, therefore, the microbiota can be altered by changes to these factors [27]. Despite some controversy, current evidence supports that microbiota of human BC tissue is different from normal paired tissue. It is not known whether these findings reflect local dysbiosis, creating an environment that favours breast tumour formation (oncogenic trigger), or the natural selection of microorganisms adapted to a microenvironment rich in fatty acids and other local metabolites. One study implemented next-generation sequencing to investigate the potential difference in microbial composition between breast tumour tissue and paired normal adjacent tissue from one patient [71]. This study identified high concentrations Methylobacterium radiotolerans in the breast tumour tissue, in comparison to the paired normal tissue, which presented with high concentrations of Sphingomonas yanoikuyae [71]. The reduction in the Sphingomonas species in the tumour tissue implied a potential probiotic role within the host, and this bacterium was also found to activate invariant NKT (iNKT) cells [71]. The iNKT cells have been observed to play a significant role in the modulation of breast carcinogenesis as a cancer immunosurveillance agent, which could implicate the importance of Sphingomonas yanoikuyae in the regulation of breast cancer development [71]. In an Asiatic cohort of patients, an increased representation of genus Propionicimonas and the families Micrococcaceae, Caulobacteraceae, Rhodobacteraceae, Nocardioidaceae, and Methylobacteriaceae was observed in BC tissues. Nevertheless, caution should be taken on extrapolation for a Western population (Meng et al., 2018). In a Canadian study, it was reported that adjacent normal tissue of women with BC had a higher relative abundance of Bacillus, Enterobacteriaceae, and Staphylococcus, compared to normal breast tissue of healthy controls (Urbaniak et al., 2016). The different β-diversity between BC and healthy

controls was also confirmed in nipple aspirate fluid (NAF), which may have a potential role in carcinogenesis. It was noticed that there were differences in the composition of microbiota and in functional properties associated with identified bacteria (Chan et al., 2016). A later study assessed potential pathogenic biomarkers in breast cancer patients, and observed that the Methylbacterium bacterial species was in higher concentrations in more advanced breast cancer cases, however, did not differ amongst tumour grades [73]. As the relative concentrations of each bacterial species inversely correlated with the tissue type, these studies were among the first few to acknowledge the link between microbial dysbiosis and the onset of carcinogenesis, indicating its clinical relevance in the diagnosis and staging of breast cancer [71, 72]. Figure 2 depicts the gut microbiota and mammary microbiota present in healthy individuals, compared to individuals with cancer.

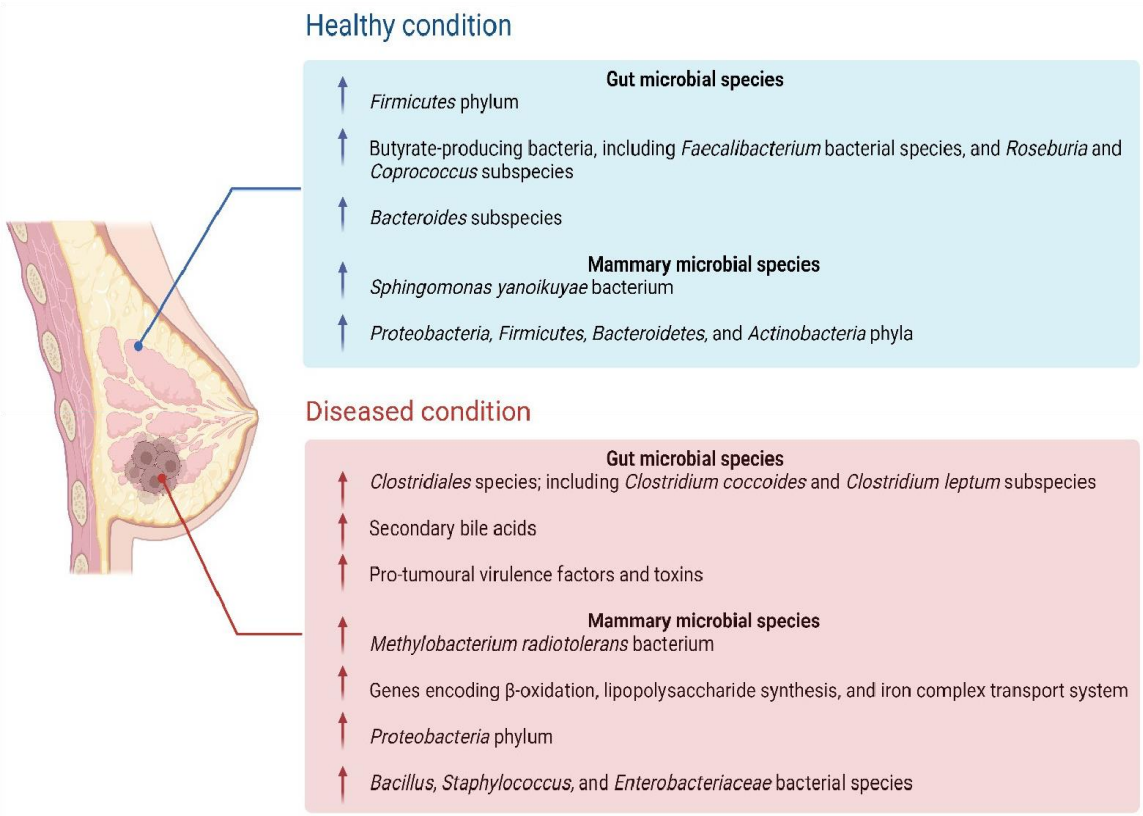

Figure 3 The differences in gut microbiota and mammary microbiota present in healthy individuals, in comparison to a diseased (cancerous) state. This includes increases or decreases in the abundance of protective or pro-tumoural bacterial species and subspecies between the two states.

These findings may reflect the influence of bacteria and/or their components in local immune microenvironment, highlighting unrecognised links between breast dysbiosis and BC that might exist.

8. Clinical Studies on Gut Microbiota in Breast Cancer

Studying microbiota in BC has translational and clinical significance as the breast microbiota colonize normal and cancerous breast tissue and the gut microbiota and their metabolites are closely related to host immune responses and have been associated with BC progression. Various factors, such as BC stages, subtypes of BC, and therapies, including neoadjuvant therapy, chemotherapies, and antibiotics treatments, can affect the therapeutic outcome as well as microbiota composition . In vitro and in vivo studies of gut and breast microbiota in BC have been actively investigated during the past two decades. Clinical trials are needed for understanding the association of microbiota composition with the risk of BC in humans and to bring scientific research to publicly available supplements and treatments for BC patients[29]. Several ongoing clinical trials focus on the impact of drugs, diet, and probiotics on gut microbiota in BC patients undergoing chemotherapy treatments. The abundance of Akkermansia, a promising probiotics candidate, has been evaluated in a presurgical weight-loss trail of overweight and obese BC women. Microbiome alphadiversity and the abundance of Akkermansia decreased while pro-inflammatory marker interleukin-6 increased [16]. Another innovative clinical trial explored the immune-boosting function of probiotics in BC.

9. Antibiotics usage in Breast Cancer

Antibiotics usage can alter the gut microbiota composition depending on the class of antibiotic, dose, period of exposure, and target bacteria from the mode of action. Some studies showed that antibiotic consumption (especially prolonged use) was associated with an increased risk of breast cancer development and recurrence, possibly by reducing the diversity of gut microbiota, with one of the studies, describing only a weak correlation. In contrast, two studies by Sorensen et al. and Garcia Rodriguez et al. found no increase in the risk of breast cancer with antibiotic use. Given the inconclusive evidence, a cause-and-effect relationship cannot be established, and some uncontrolled confounding factors may be involved, such as hormone-related diseases that the antibiotics were used for, like acne. Despite the conflicting studies, there is still a cause for prudent use of antibiotics, especially for long-term purposes. Further studies are needed to establish whether an association exists between antibiotic use and breast cancer and this would strengthen the hypothesized relationship between gut microbiota perturbation and breast cancer.

10. Probiotic Therapies

Correlations between the human microbiome and BC open up new horizons for the prognosis and treatment of cancer. Hence, researchers focus on the therapeutic application of microbiome (Figure 3). Several in vitro and in vivo studies investigated the effect of probiotics on BC; for instance, significant inhibition of cell proliferation, induction of apoptosis, and cell cycle arrest of Enterococcus faecalis and Staphylococcus hominis are proved [23]. Lakritz et al. studied two groups of mice: a group manipulated to develop human breast tumors and the other group fed by a Western-style diet (high fat and sugar, low vitamin D3, vitamin C, and fiber) to develop mammary tumors. The two groups were treated with oral intake of probiotic lactic acid microbes. The results showed that the probiotic Lactobacillus reuteri inhibited early-stage carcinogenesis and raised breast cell sensitivity to apoptosis[34].Additionally, it was confirmed that oral administration of L. acidophilus represents anticancer activity in mice bearing breast tumors [72]. Another in vivo study showed that drinking milk fermented with Lactobacillus helveticus R389 elevated IL10 and decreased IL-6 levels both in serum and mammary cells of mice, which lead to breast tumor cell inhibition [10]. Moreover, anticancer effects of probiotics on cancer cell lines are well gathered in the review by Mendoza et al. They showed anti-proliferative activity, apoptosis, cytotoxicity, and cell cycle arrest of probiotics [41]. Long-term exposure to probiotics such as L. casei Shirota and soy isoflavones in Japanese females demonstrated their chemopreventive effect on cancer development [64]. Although the mentioned studies provided the evidence that probiotics display activity against BC, there are still essential questions on the use of probiotics in BC. The strains, dosage, and regimen of probiotics should be determined based on the clinical feature of BC and probiotics interaction with the conventional treatment. Probiotics are already used in the treatment of a wide range of diseases; however, their application to BC is in its infancy. There are also some clinical trials on probiotics and BC. A study demonstrated that two species of Lactobacillus can treat mastitis[4]. Thus, probiotics might be good alternatives for antibiotics to treat breast infections during breastfeeding[4]. In the (NCT03358511) clinical trial, the role of probiotics on the number of CD8+ T-cells at stages 1–3 BC in post-menopausal patients is under investigation. Twenty post-menopausal females with BC took probiotics (15 billion colony-forming units of 13 beneficial bacterial species) for 2–4 weeks, three times a day. Another trial (NCT03760653) determined the effect of probiotics supplementation (Lactobacillus rhamnosus, Lactobacillus paracasei, Lactobacillus acidophilus, and Bifidobacterium bifidum) and physical exercise on the bacterial balance of gut, immune system, and the quality of life in BC survivors.

11. The Mechanistic Role of Breast Microbiota in Breast Cancer

Though researchers have found a strong correlation between microbiome and BC at different stages and ages, the mechanism of action is in need of further study. Firmicutes and Bacteroidetes are the most prevalent phyla found in feces in early-stage BC cancer patients.

Stage II and III cancer patients had significantly more Bacteroidetes, Clostridium coccoides, Clostridium leptum, F. prausnitzii, and Blautia spp. compared to stage 0 and I patients. Moreover, Blautia spp. increased as the prognostic grades increased [37]. Sheetal et al investigated a pro-carcinogenic colon microbe Bacteroides fragilis that promotes breast tumorigenesis and metastasis. Mammary gland or gut colonized with enterotoxigenic B. fragilis induced mammary gland epithelial cell proliferation. Toxins released by B. fragilis increased metastasis and invasion in BC cell lines and xenografts. This biological effect in vitro was mediated by toxin activated Notch1 and beta-catenin axes [46].Regulating tumor infiltrating lymphocyte (TIL) is another means by which gut microbiota can influence BC. Shi et al., classified TIL as three groups based on the proportion of filtrated area in tumor and adjacent areas. High TIL individuals had better chemotherapy outcomes and had statistically different beta diversity distribution of gut microbiota compared to the low TIL group. Higher abundance of Methanosphaera and Anaerobiospirillum and lower abundance of Mycobacterium, Rhodococcus, etc., were identified in the high TIL group compared to the low TIL group [57]. Moreover, species Barnesiae, that is known to regulate estrogen metabolism, had higher abundance in the low TIL group, indicating Barnesiae may be a potential risk factor promoting cancer development in low TIL cases [57].TLRs respond to pathogen-associated molecular patterns to induce the production of cytokines and chemokines [75]. For example, TLR2 expression is higher in MDA-MB-231 compared to less aggressive MCF-7 BC cells. The mechanism of higher aggressiveness seen in the MDA-MB-231 cell line is partially mediated by induced NF-kB, interlukin-6, and MMP9 levels [7]. These results suggest that immunity is closely related to carcinogenesis. Since gut microbiota modulate both lymphocytes and neutrophils, immune-related responses to gut microbiota can have a great impact on mammary carcinogenesis. Lakritz et al., showed neutrophiles-depleted mice were more susceptible to H. hepaticus-triggered tumor development [35,11]. Hormone metabolism is another important way for gut microbiota to affect their host, while the microbiota is, in turn, affected by host menopausal stage and hormone levels. Pre- and post-menopausal status is known to have significantly different hormone levels. Ming-Feng et al., showed alpha-diversity significantly decreased in premenopausal BC patients compared to control. Bacteroides fragilis was found in premenopausal individuals, while Klebsiella pneumoniae was found in aged post-menopausal individuals [26]. In studies focused on post-menopausal cases, Jia et al., found BC patients had higher microbial diversity compared to controls, although the diversity has been found to decrease in BC patients in most cases. Within

multiple species that were enriched in cancer patients, some species were positively correlated with estradiol levels and negatively correlated with CD3+ CD8+ T cells [77]. Moreover, gut metagenome showed enriched genes participating in lipopolysaccharide biosynthesis and the carbohydrate phosphotransferase system in cancer patients. Post-menopausal BC patients harbor significantly reduced alpha diversity especially in IgA-coated and Ig-A noncoated taxa. Species belonging to IgAcoated Proteobacteria and Firmicutes, and genus belonging to IgA-noncoated Firmicutes, such as Ruminococcus and Clostridium, are associated with BC cases [22].According to these previous studies, the difference in gut microbiota composition is more distinct comparing post-menopausal BC patients to controls.

Steroid hormones play important roles in BC. For example, in gastrointestinal lumen, conjugated estrogen is deconjugated by beta-glucuronidase bacteria that supply free estrogen to breast tissue through the circulatory system [20]. A higher estrogen level has been linked to increased risk of BC. Estrogen level is affected by intestinal microbiota because they produce beta-glucuronidase enzymes that deconjugate estrogen metabolites. Estrogen metabolites can remain in the circulation to raise the estrogen level. Gut microbial beta-glucuronidase and estrogen level are regulated bidirectionally. Beta-glucuronidase is structurally specific for reactivating estrogen. Ervin et al., confirmed in vitro that certain members in beta-glucuronidase enzymes with distinct structure can reactivate estrogen glucuronidases [12]Estrogen level is also affected by bacterial estrobolome in host intestine that increases the risk of estrogen-receptor positive BC among post-menopausal patients [32] Decreasing diversity of bacteria and dysbiosis of gut microbiome resulted in excreted estrogen and higher risk of BC [5]. Bacteria that produce beta-glucuronidase include Clostridia, Ruminococcaceae, and Eschherichia. Potential beta-glucuronidase inhibitors include the probiotics Bifidobacterium longum, flavonoids, and silybin, as well as others [59]. The relative abundance of B. longum positively correlated with docosahexaenoic acid, an essential nutrient that has beneficial effects in BC survivors [25]. This study reinforced the important relationship among gut microbiota, metabolites, and BC prognosis. Estrogen level can also be manipulated by dietary fiber consumption and gut microbiota digestion[74]. In addition to circulating estrogen levels, hormone receptor level is another important factor in BC development. A pilot study that explored the association between gut microbiome and BC risk factors, including receptor status, stage, and grade of BC, showed that women with Her2+ BC had 12–23% lower alpha diversity, higher abundance of Bacteroidetes and lower abundance of Firmicutes compared to Her2- patients [69]. On the other hand, gut microbiota can also have a positive impact on estrogen signaling. Intestinal microbes can break down polyphenols and plant-derived phytochemical compounds to form estrogen-like compounds [45].Phytoestrogens and plant-derived xenoestrogens compete with estrogen for its receptor; therefore, they can act as anti- estrogen agents [55]. Bacteria ferment plant

lignans into enterodiol and enterolactone which was shown to serve as an anti-estrogen agent that can lower the risk of BC [52,13]. Furthermore, gut microbiota can modulate estrogen metabolism. The ratio of estrogen metabolites, such as estradiol and hydroxylated estrogen, to parent estrogen are positively related to higher risk of BC. This effect has been evaluated on post-menopausal BC patients with higher levels of circulating estrogen [14,18]. These studies indicate that bacteria that have positive or negative impacts on BC partially depended on their roles in estrogen metabolism for these effects.

12. Diagnosis of Breast Cancer

The following tests may be used to diagnose breast cancer or for follow-up testing after a breast cancer diagnosis.

1.Imaging tests

Imaging tests show pictures of the inside of the body. They can show if cancer has spread. The following imaging tests of the breast may be done to learn more about a suspicious area found in the breast during screening. In addition to these, there are other new types of tests that are being studied.

Diagnostic mammography. Diagnostic mammography is similar to screening mammography except that more pictures of the breast are taken. It is often used when a person is experiencing signs, such as a new lump or nipple discharge. Diagnostic mammography may also be used if something suspicious is found on a screening mammogram.

Ultrasound. An ultrasound uses sound waves to create a picture of the breast tissue. An ultrasound can distinguish between a solid mass, which may be cancer, and a fluid-filled cyst, which is usually not cancer.

Magnetic resonance imaging (MRI). An MRI uses magnetic fields, not x-rays, to produce detailed images of the body. A special dye called a contrast medium is given before the scan to help create a clear picture of the possible cancer. This dye is injected into the patient's vein. A breast MRI may be used after a person has been diagnosed with cancer to find out how much the disease has grown throughout the breast or to check the other breast for cancer. Breast MRI may also be a screening option, along with mammography, for someone with a very high risk of developing breast cancer and for some women who have a history of breast cancer (Risk Factors and Prevention). MRI may also be used if locally advanced breast cancer is diagnosed or if chemotherapy or endocrine therapy is being given first, followed by a repeated MRI for surgical planning (Types of Treatment). Finally, MRI may be used as a surveillance method following breast cancer diagnosis and treatment.

1) *2.Biopsy*

A biopsy is the removal of a small amount of tissue for examination under a microscope. Other tests can suggest that cancer is present, but only a biopsy can make a definite diagnosis. A pathologist then analyzes the sample(s). A pathologist is a doctor who specializes in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease. There are different types of biopsies, classified by the technique and/or size of needle used to collect the tissue sample.

Fine needle aspiration biopsy. This type of biopsy uses a thin needle to remove a small sample of cells.

Core needle biopsy. This type of biopsy uses a wider needle to remove a larger sample of tissue. This is usually the preferred biopsy technique. If a tumor is identified, the cancer biomarkers, such as hormone receptor status (ER, PR) and HER2 status, will be tested to help guide treatment options. These biomarkers are found on the tumor cells. Additional types of biomarkers can be found in the blood or other fluids, although these are not commonly used to establish a breast cancer diagnosis. They are made by the tumor or by the body in response to the cancer. This information will help the doctor recommend a treatment plan. Local anesthesia, which is medication to block pain, is used to lessen the patient's discomfort during the procedure.

Surgical biopsy. This type of biopsy removes the largest amount of tissue. Because surgery is best done after a cancer diagnosis has been made, a surgical biopsy is usually not the recommended way to diagnose breast cancer. Most often, non-surgical core needle biopsies are recommended to diagnose breast cancer in order to limit the amount of tissue removed. Since many people who are recommended to undergo breast biopsy are not diagnosed with cancer, using a needle biopsy for diagnosis reduces the number of people who have surgery unnecessarily.

Sentinel lymph node biopsy. When cancer spreads through the lymphatic system, the lymph node or group of lymph nodes the cancer reaches first is called the "sentinel" lymph node. In breast cancer, these are usually the lymph nodes under the arms called the axillary lymph nodes. The sentinel lymph node biopsy procedure is a way to find out if there is cancer in the lymph nodes near the breast.

2) *3. Analyzing the biopsy sample*

Tumor features. Examination of the tumor under the microscope is used to determine if it is invasive or non-invasive (in situ); ductal, lobular, or another type of breast cancer; and whether the cancer has spread to the lymph nodes. The margins or edges of the tumor are also examined, and the distance from the tumor to the edge of the tissue that was removed is measured, which is called margin width.

Estrogen receptors (ER) and progesterone receptors (PR). Testing for ER and PR helps determine both the patient's risk of recurrence and the type of treatment that is

most likely to lower the risk of recurrence. Generally, hormonal therapy, also called endocrine therapy or hormone-blocking therapy,reduces the chance of recurrence of ER-positive and/or PR-positive cancers. Guidelines recommend that the ER and PR status should be tested on the breast tumor and/or areas of spread for everyone newly diagnosed with invasive breast cancer or when there is a breast cancer recurrence. For those with ductal carcinoma in situ (DCIS), testing for ER status is recommended to find out if hormone therapy may reduce the risk of future breast cancer.

Human epidermal growth factor receptor 2 (HER2). The HER2 status of the cancer helps determine whether drugs that target the HER2 receptor, such as trastuzumab (Herceptin) and pertuzumab (Perjeta), might help treat the cancer. This test is only done on invasive cancers. Guidelines recommend that HER2 testing be done when you are first diagnosed with an invasive breast cancer. In addition, if the cancer has spread to another part of your body or comes back after treatment, testing should be done again on the new tumor or areas where the cancer has spread.

HER2 tests are usually clearly positive or negative, meaning that cancer has either a high or low level of HER2. If test results are not clearly positive or negative, additional testing may need to be done, either on a different tumor sample or with a different test. Sometimes, even with repeated testing, the results may not be conclusive, so patientand doctor will have to discuss the best treatment option. If the cancer is HER2 positive, HER2-targeted therapy may be a recommended treatment option for patients.

Grade. The tumor grade is also determined from a biopsy. Grade refers to how different the cancer cells look from healthy cells and whether they appear slower growing or faster growing. If the cancer looks similar to healthy tissue and has different cell groupings, it is called "well differentiated" or a "low-grade tumor." If the cancerous tissue looks very different from healthy tissue, it is called "poorly differentiated" or a "high-grade tumor." There are 3 grades: grade 1 (well differentiated), grade 2 (moderately differentiated), and grade 3 (poorly differentiated).

Results of these tests can help determine patient's treatment options.

12. Prevention

There are some ways to prevent from breast cancer. Firstly, staying at a healthy weight and avoiding from overweightness. Secondly, being physically active and avoiding time spent sitting. Moreover,following a healthy eating pattern or diet on a daily basis and healthy lifestyle without bad habits including smoking, drinking alcohol or drug addiction. And besides, thinking carefully about using hormone replacement therapy (HRT).These methods are especially useful for women who in postmenopaual condition. Among several factors that significantly alter gut microbiota in BC, such as diet, obesity, alcohol consumption, hormone levels, and antibiotic treatment, diet and gut microbiota are closely related because the presence of bacteria is constantly

modulated by our daily dietary patterns [62]. A diet rich in red meat and animal fat has been associated with increased risk of BC. Among post-menopausal patients, western diets had a negative impact on hormone receptor-positive patients. However, the significant effect of a healthy diet (i.e., vegetable, fruit, and fish) was only significant among premenopausal patients, indicating that diet may greatly affect the health of individuals at younger ages [70].Decreasing proinflammatory cytokines and inflammation can also prevent tumor development during the early stages of BC [76]. Furthermore, effector CD8+ T cells inhibited the growth of Her-2/neu tumor cells in anti-cancer immunotherapy. Calories intake is another factor affecting BC treatment outcome. Restricting calories intake during TNBC radiotherapy treatment greatly decreased tumor development in mice compared to normal diet supplying a normal amount of calories. The mechanism was mediated by down-regulation of a well-known metastasis-driving pathway, insulin-like growth factor, and Akt pathway [56,58]

Conclusion

The microbiota plays a crucial role in preserving the health status of the human body, and their impairment causes pathobiological changes, including BC. Although the association between microbiome and development of BC has been studied in the past decade, there are many remaining questions about the mechanistic role of specific bacterial strains in carcinogenesis progression. Serving as supplements for conventional treatments, probiotics strains and dosage and the mechanism for facilitating conventional treatments have not been studied in depth. Further studies are needed to reveal cause and effect mechanisms between microbiota and BC.

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