BREAST CANCER AND THE MICROBIOME

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Abstract

Breast cancer affects one in eight women. The causes of breast cancer are not fully known. Regarding breast cancer, one of the most important roles of the human microbiome is to regulate the metabolism of steroid hormones, because endogenous estrogens are the most important risk factor in the development of breast cancer, especially in menopausal women.

Recent research has shown a correlation between the patient's microbiome and the presence of breast cancer. Risk factors are genetic predisposition, high-fat diet, alcohol consumption, age. According to recent studies, the alteration of the microbiome is both a risk factor for breast cancer and a possible explanation for the various responses to therapy.

This paper reveals the potential etiological role of the gastrointestinal microbiome in the occurrence of breast cancer, highlighting how the intestinal bacterial microbiome and, in particular, how the "estroboloma" (all enteric bacterial genes capable of metabolizing estrogens) could influence the risk the appearance of "estrogen receptor positive" breast cancer after menopause.

Keywords:

breast cancer, stroboloma, intestinal microbiota, inflammation, lifestyle

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In recent decades, the microbial composition of the human body (microbiota) has attracted attention in various medical fields, including cancer biology. The interaction between the human microbiome and cancer is called the „oncobiome". Moreover, the human host can modify the microbiota and its mechanisms.

The survival rate in breast cancer has increased, and the number of deaths associated with this disease is steadily declining, due to early diagnosis, personalized treatment approach and better understanding of the disease.

Researchers have identified hormonal, lifestyle and environmental factors that increase the risk of breast cancer. Most likely, breast cancer can be caused by an interaction between genetic and epigenetic factors.

It is estimated that about 5-10% of cases of breast cancer are related to genetic mutations. A number of mutant genes have been identified that may increase the risk of breast cancer, and the most common are the BRCA1 and BRCA2 genes - both of which significantly increase the risk of both breast and ovarian cancer.

The etiology of breast cancer is complex and several risk factors have been described for different subtypes of breast cancer (1-5). In postmenopausal women, an increased level of circulating estrogen is associated with an increased risk of breast cancer.

The gastrointestinal microbiome can modulate systemic estrogens, and intestinal dysbiosis has been linked to postmenopausal breast cancer by interacting with higher levels of circulating estrogen. However, there are few studies based on the association of the microbiome with breast cancer compared to other cancers.

This article aims to reveal the role of the microbiome as a risk factor for breast cancer. A decrease in the bacterial biodiversity of the faecal microbiota has been shown to increase the risk of breast cancer. About 70% of breast cancer patients express estrogen receptor cells and are affected by the concentration of estrogen.

The ovaries are the main source of estrogen. Estrogen production from androgen precursors is catalyzed by aromatase. Breast cancer is frequently diagnosed after menopause, when circulating levels of this hormone decrease (6).

Breast cancer is the most common malignancy in women worldwide, with more than half of women that develop the disease having known risk factors.

Scientific research advances have identified a subset of the intestinal microbiota - estroboloma (which consists of those bacteria that have the genetic ability to metabolize estrogen) that plays a key role in breast cancer.

Recent research provides evidence that the intestinal microbiome plays a substantial role in the regulation of estrogens. Compared with controls, postmenopausal patients with breast cancer had significant direct associations of estrogens concentration with the intestinal microbiota IgA + / IgA-, suggesting that the intestinal microbiome influences the risk of breast cancer by altering metabolism, estrogen recycling and immune response. .

The author of this article presents the potential role of the gastrointestinal microbiome in the development of breast cancer by medi-

ating the metabolism of steroid hormones and the synthesis of biologically active estrogens. The intestinal microbiome is one of the main regulators of circulating estrogens. Intestinal dysbiosis disrupts homeostasis by disrupting estrogen metabolism.

It is suggested that estroboloma, the total number of bacterial genes in the human gut, along with their products, which are involved in estrogen metabolism, increases the risk of developing after menopause the type of breast cancer with estrogen receptors.

The microbiome is undoubtedly the second genome of the human body and has various roles in the periods of health and of disease. Intestinal microbes encode enzymes capable of deconjugating conjugated estrogen metabolites for excretion, reaching the enterohepatic circulation in the biologically active form (4).

The terms "microbiome" and „microbiota" are, in fact, distinct. Since the early 2000s, the role of the human gut microbiota and its relationship to breast cancer has become a major area of interest in the medical scientific community (7, 8), (Fig,1).

Regarding breast cancer, one of the most important roles of the human microbiome is to regulate the metabolism of steroid hormones, because endogenous estrogens are the most important in the development of breast cancer, especially after menopause (4).

The development of breast cancer is closely linked to changes in estrogen levels. Plottel and Blaser define "estroboloma" as "the totality of enteric bacterial genes whose products are capable of metabolising estrogen" (9).

Recent research indicates that the intestinal microbiome plays a substantial role in the regulation of estrogen. Intestinal dysbiosis is associated with dysfunctions of the enterogastric circulation of estrogen, alteration of host inflammation and immunity (TLR toll-like receptors, cytokines).

Scientific advances have identified a subset of the intestinal microbiota: estroboloma, those bacteria that have the genetic ability to metabolize estrogen, which play a key role in most breast cancers (7).

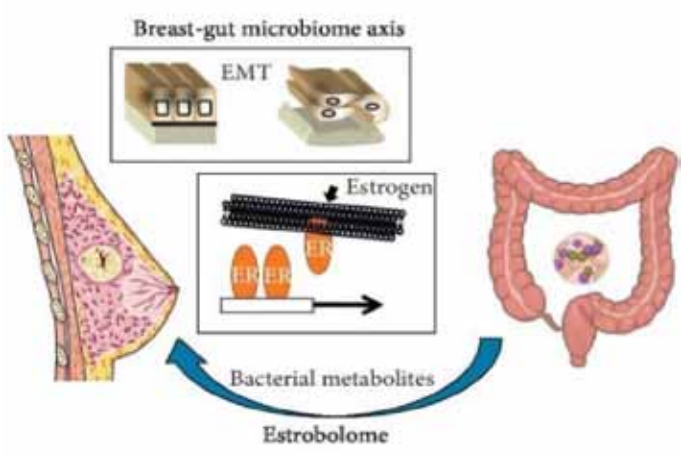

Fig. 1 The importance of the microbiota in breast cancer, EMT= epithelial-mesenchymal transition (8)

Recent research provides evidence that the intestinal microbiome plays a substantial role in the regulation of estrogen. An important role of the intestinal microbiome is the modulation of systemic estrogens, because it affects the enterohepatic circulation of estrogens and their reabsorption.

It has long been assumed that the intestinal microbiome contributes to breast carcinogenesis by altering systemic estrogen levels (10). The source of estrogen involved in breast cancer with positive estrogen-receptors metastasizing is less clear (6). Estroboloma/microbiome influences circulating estrogens levels and, consequently, the endogenous hormonal environment, which increases the risk of hormonal malignancies, including breast and endometrial cancer, directly or indirectly, for example by immunomodulation.

Several epidemiological studies have suggested a possible association of antibiotic use and breast cancer risk (11). The gastrointestinal microbiome acts as a symbiote that provides protection against external pathogens, helps the development of the immune system, the recovery and absorption of nutrients, and the breakdown of molecules (12,13), (Fig.2).

The human microbiome can influence the development of prostate cancer. Studies have shown that viral and bacterial infections of the prostate are risk factors associated with the development of prostate cancer (9, 12).

Several previous studies have reported an abundance of proteobacteria associated with dysbiosis-related conditions, including cancer (13 - 16).

Liver-conjugated estrogens are deconjugated by the intestinal microbiota as "free" estrogens; these are reabsorbed through the enterohepatic circulation. Reabsorption causes an increased concentration of „estrogen-

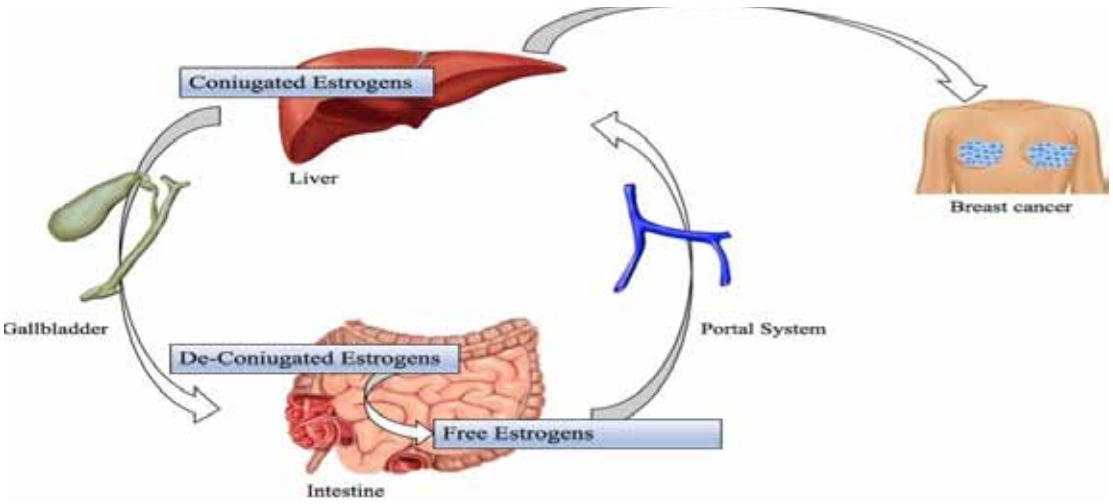

Fig. 2 Possible mechanisms of gastrointestinal microbiome in the development of breast cancer (13))

like substances" that leads to the synthesis of "estrogen-induced growth factors (estromedines)", polypeptides with carcinogenic potential with breast tropism.

The role of β-glucuronidase and bacterial β-glucosidase activity in breast cancer risk is currently unknown.

Estrogens are determinants of hormone receptor-positive breast cancer and play an important role in initiating and maintaining neoplastic growth (14). Adiposity has been associated with high levels of circulating estrogens in postmenopausal women, as well as an increased risk of breast cancer. In postmenopausal women, obesity and excess adipocytes can lead to increased circulating estrogens by peripheral aromatization of androgens (Fig.3).

Lifestyle recommendations also contribute to long-term survival. Such recommendations generally focus on diet and exercise.

A healthy diet could regulate the structure and function of the intestinal microbiota by interacting with the commensal microbiota and by expressing microbial enzymes and metabolites.

It is known that dietary changes affect the composition and function of the intestinal microbiome. Vegetarians showed an increase in the excretion of conjugated estrogens in feces compared to non-vegetarians, leading to decreased plasma estrogen concentrations. (Fig.4).

Diet plays a key role in the complex relationship between the human gut microbiota, estrogen metabolism and its influence on breast cancer recurrence, as well as on the metastatic potential. Diet is also an important factor in immunotherapy, as it may influence the gut microbiota.

A high-fiber diet increases the diversity of the intestinal microbiota, with a positive effect on the response to immunotherapy.

Diet may contribute to the development of various diseases, including cancer, because it has a direct role in controlling the microbial composition.

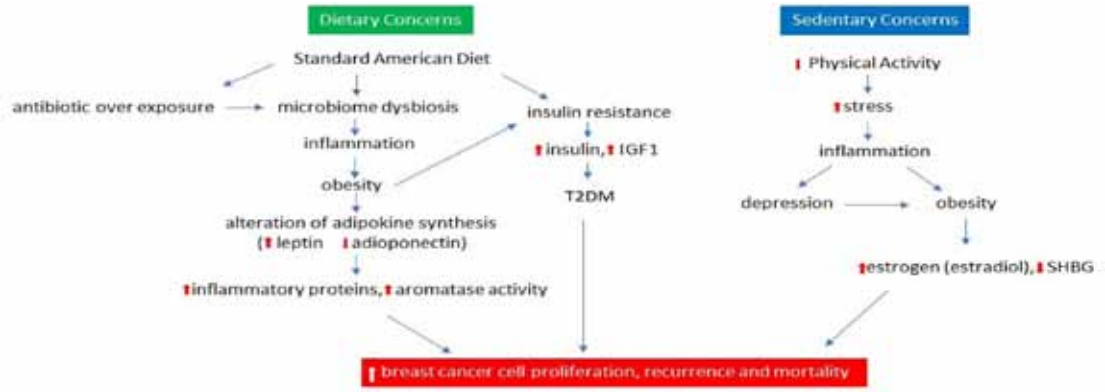

Fig. 3 The impact of lifestyle on breast cancer (7)

Little is known about the clinical applications of the microbiome, such as probiotics, modulation of the microbiome genome, and the use of microbiome enzymes in breast cancer therapy.

This diet results in decreased production of short-chain fatty acids (butyrate, propionate, acetate), which play a major role in preventing "permeable bowel syndrome". This syndrome is responsible for the flow of harmful inflammatory products in the circulatory system, influencing the evolution of breast cancer.

The microbiome could also decrease the risk of breast cancer by modulating functional estrogens. The correlations between the microbiome and breast cancer create new opportunities for the stratification of the prognosis and, respectively, for the treatment of cancer.

Unhealthy lifestyle negatively affects breast cancer by impacting the gastrointestinal microbiota and microbial and digestive products. Lifestyle medicine, in terms of survival after breast cancer, is based on 3 major pillars: diet, physical activity and stress management.

Lifestyle changes focused on diet and exercise have been shown to influence overall survival in breast cancer (7).

Obesity increases the risk of breast cancer, especially after the onset of menopause.

Thus, it is recommended to eat vegetables and fruits, whole grains and to give up, as much as possible, fats and carbonated drinks; it is also ideal to stop drinking alcohol or drinking it in moderation, to quit smoking and to exercise every day.

Alcohol increases the risk of breast cancer. Increased use of antibiotics has also been linked to an increased risk of breast cancer.

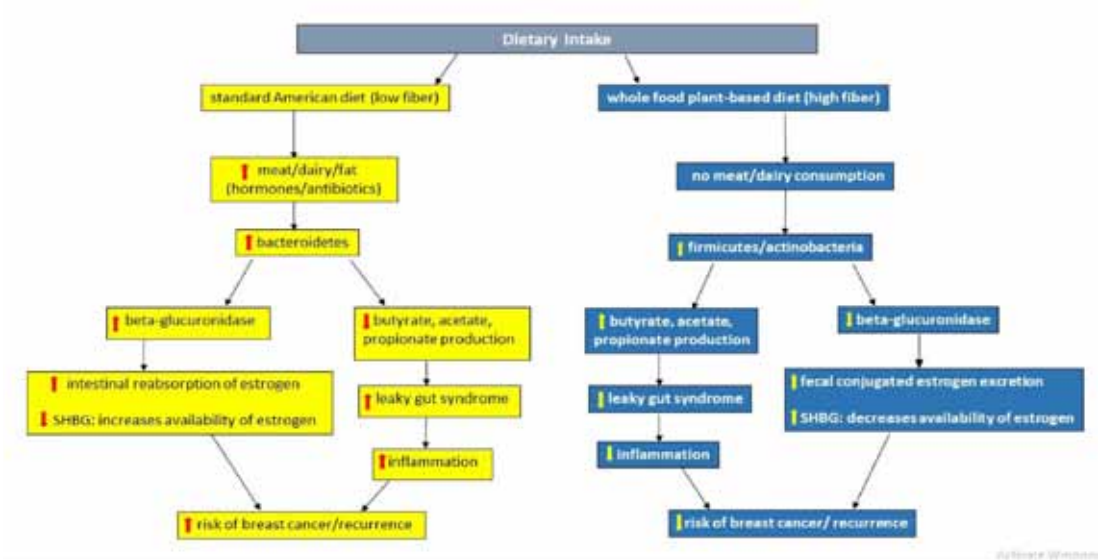

Fig. 4 Influence of diet on intestinal microbiota/microbiome and estrogen metabolism (7)

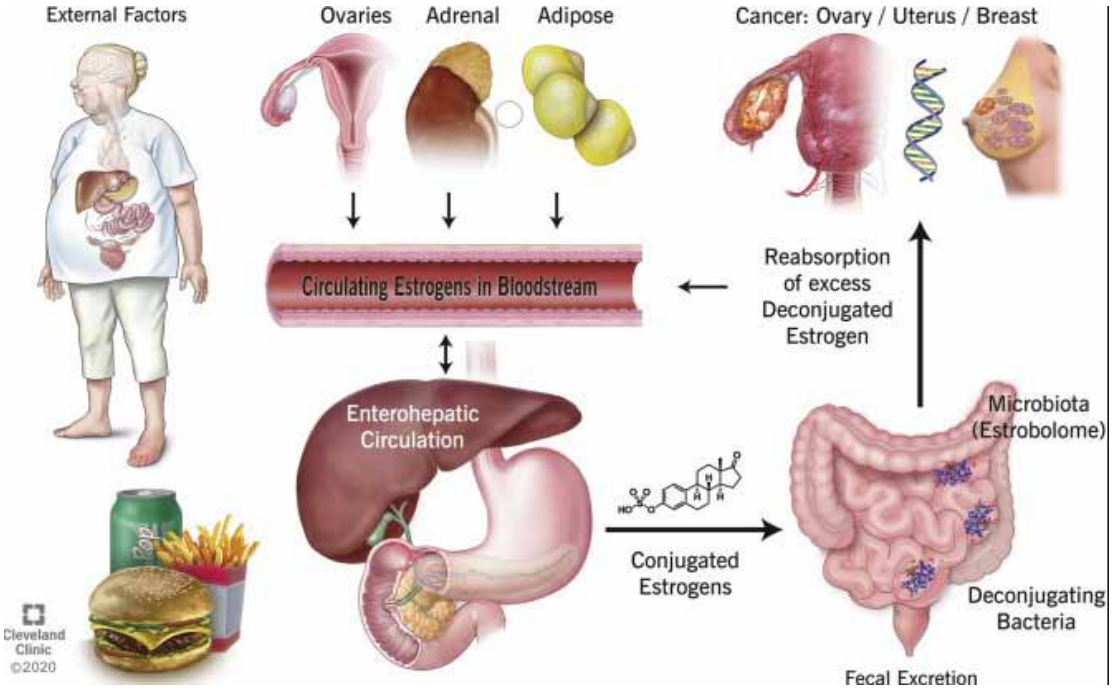

Fig. 5 Diet and interactions of intestinal microbiome in breast cancer (15)

Exposure to antibiotics (clarithromycin, metronidazole, ciprofloxacin) has been observed to decrease biodiversity and the abundance of bacterial communities, disrupting the balance of the intestinal microbiome associated with an increased risk of breast cancer.

Pre-existing intestinal dysbiosis induced by antibiotic treatment has been reported as a possible intrinsic host-tissue inflammation regulator and tumor cell dissemination in hormone-positive breast cancer.

Probiotics and fermented foods containing lactic acid bacteria have been explored for anti-carcinogenic properties, which may involve modulation of the intestinal microbiome and the host's immune response, (Fig.5).

There is a dynamic and complex relationship between the human host and the microbiota. Individuals who took oral supplements of Lactobacillus acidophilus showed a reduction in faecal enzyme activity, including β-glucuronidase (16 - 19)..

Micronutrients are essential elements for life in small quantities. These include micro-minerals and vitamins.

Dietary micronutrients are essential for human health.

Further studies are needed to find the exact relationship between the microbiome, micronutrients and cancer.

Conclusion

Based on recent studies, the changes in the microbiome are a risk factor for breast cancer. It is expected that the association between the intestinal microbiome and the breast neoplasm will help to specify the analyzes that will be performed in the future in order to assess the clinical importance of this correlation.

Further studies are needed to assess the hypothesis of the role of the stroboloma and to define the impact of the metabolic capacity of the microbiome on estrogen metabolism and host physiology.

Declaration of conflict of interest:

Competing interests: The author stated that there are no competing interests.

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