

Breast Cancer and Intestinal Microbiota Transplantation

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Abstract

Breast cancer has been studied relating it to the intestinal microbiota and its own microbiota. Giving a primary role to the dysbiosis that occurs in both the mammary gland and the intestine. Likewise, metabolic processes and immunological eventualities have been considered as determining factors; By the way, many of them are determined by the intestinal microbiota itself, which is given the deserved name of endocrine gland, because it acts at a distance, and it is not only the super-organ or the new organ, but the multiple studies have generated this honorable new consideration.

We break down breast cancer, in order to determine the usefulness of the Intestinal Microbiota Transplant and we observe the importance of Resilience in the Intestinal Microbiota. The clinical significance of Dysbiosis, both breast and intestinal, in the genesis of the condition is emphasized and the importance, which it has, is given to Apoptosis.

Generally, the pattern of the breast microbiota, in descending order, is: Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes. The breast microbiota can be used as a potential biomarker.

The importance of the different axes that influence the process are analyzed, such as the Gut-microbiota-brain Axis, the breast-brain axis, the cancer-microbiome-gut axis and the cancer-microbiota-immunity axis.

It is pointed out how chemo and radiotherapy affect the intestinal microbiota and breast cancer, as well as antibiotics. Finally, the effect ofiotics and Fecal Microbiota Transplant are determined.

Keywords: breast cancer; fecal microbiota transplantation; mammary microbiota; intestinal microbiota; microbiota modulation; dysbiosis

Introduction

Breast cancer (BC) being the most common process among women and the second cause of death in developed countries [1], it has been addressed in numerous articles relating it to the Intestinal microbiota (IM), since this, through dysbiosis (Dys) (aberrant composition of the (IM) [2], it influences the evolution, management and prognosis of BC, through various biological mechanisms, alterations of the immune system, inflammatory process and, impact on hormonal pathways. Determining that BC could be related to the functionality and composition of both microbiota: breast and intestinal [3].

Alterations in bacterial diversity have been detected in post-menopausal patients with BC, which again links these two protagonists [4]. It is noted that β -bacteria Glucuronidases affect the transit and reabsorption of estrogens in the enterohepatic circulation, increasing

the possibility of this type of cancer [5], along with bacterial metabolites such as Lithocholic acid and short-chain fatty acids [6]. After the age of 65, IM is less stable, which leads to the onset of diseases [7]. Due to this, it is convenient to know the alpha diversity, defined as the richness of the microorganisms present and can be calculated by the Shannon index, which determines their uniformity, distributed in the intestine [8]. β -diversity is useful, which compares samples and determines how different the microbial community is from one environment to another [9].

Resilience. It is the capacity that IM has for self-regulation [10]. This characteristic depends on three variables; stability over time, taxonomic groups and functional groups [11]. Likewise, Resilience has four components: resistance, latitude, precariousness and

panarchy (how the microbiota can cope with stress) [12].

Resilience is not always stable, since it can develop dysbiosis, which describes a disease of the bacterial communities, due to their imbalance [13]. Both alpha and β diversity expel the potential of Resilience which has four elements related to its capacity: dispersal, diversification, drift and selection [14].

Now, how the IM and the breast microbiota interact with the BC. It does so through intestinal dysbiosis, as it is associated with the risk of autoimmune, inflammatory and malignant diseases [15]. For this reason, the IM is considered a paracrine and systemic gland; by transforming dysplasia into carcinoma and the distant effect, similar to hormonal action on effector organs [16].

Mammary Microbiota (MM). The microbiota of breast tissue is diverse and different from those of other areas of the body; It is determined by age, pregnancies and geographic area. The pattern consists, in decreasing order, of Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes [17]. An interesting study demonstrates that host MM could modulate the risk of BC, based on 16S Ames amplifier sequencing, by detecting those bacterial profiles are different between those affected and those without BC. In the former, there is a relative abundance of Bacillus, Enterobacteriaceae, Staphylococcus, Escherichia coli and Staphylococcus epidermidis [18]. The MM has enriched species, and in the nipple aspirate they are observed in the BC. These can be used as potential biomarkers [19]. Hieken TJ and his group point out that IM not only affects skin, stomach, colon, liver and lung cancer, but also in breast cancer [20], as MM does in BC, when evaluating the phylos bacteria obtained in surgery, through 16S rDNA sequencing. They demonstrated enrichment in taxa of Fusobacterium, Atopobium, Gluconacetobacter, Hydrogenophaga and Lactobacillus.

Eslami SZ and his group consider MM as a new risk factor for BC and point out how the ups and downs of its microorganisms block chemotherapeutic treatment [21].

Gut Microbiota. IM produces and metabolizes hormone-like bio-active substances that modulate the risk of BC, so it is advisable to maintain a healthy microbiota [22]. It is known that IM not only modifies intestinal tumor processes but also affects extra-intestinal ones; Therefore, its manipulation (bio-therapeutics) has become a reality [23]. For all these

reasons, MI can determine the risk of the malignant process, provide diagnostic information, as well as limit the evolution and treatment [24]. Possibly the bacterial integration of the strobolome is affected by multiple circumstances in life, such as alcohol, the use of antibiotics, diet and environmental factors [25]. Publications on Microbiota have multiplied and forced funding groups to focus on this new super organ. At the level there are already clear objectives for the immediate future such as: developing diverse tools, searching for new drugs, using the microbiota as a therapeutic target and as biotherapeutics with live microorganisms [26]. Some gut bacteria are capable of metabolizing phyto-estrogens and making them active metabolites, which protect against the risks of BC [27]. Inflammation of the IM generates a countless number of conditions, which fortunately has forced the implementation of numerous strategies to modulate its balance, for the benefit of health, even though many of its functions are unknown [28]. Lower Firmicutes / Bacteroidetes ratio and lower relative abundance of Lachnospira and Roseburia spp. have been reported. In postmenopausal women [29]. Finally, the great potential that IM has as immunotherapy in cancer, as well as the optimization it generates in the therapeutic effect and the reduction of complications, have made it be seen as an enormous help in oncological disorders and many other conditions. [30]. In summary, the healthy Microbiota is made up of Bacteroidetes, Firmicutis, Actinobacteria, Proteobacteria, Verrucomicrobia, Cyanobacteria and Tenericutes [31].

MM dysbiosis and its relationship with IM. Dysbiosis is defined as an imbalance in bacterial communities [32]. There is a possibility of an undetected relationship between BC and Dys, which has diagnostic and therapeutic links. Likewise, the relationship between intestinal and breast microbiota should be considered [33]. Furthermore, environmental pollution possibly alters both microbiotas [34]. It has been shown that IM hinders BC through its own microbiota [35]. IM can be considered broad-spectrum, maintaining host metabolism [36].

Breast dysbiosis, in cases of BC, can be determined by the local microbiota; predisposing oncological development, through genetic inconsistency [37]. IM can improve the prognosis of BC or enhance its risk [38]. Among the symptoms of dysbiosis we find: halitosis, nausea, abdominal and chest pain, constipation, dysuria, anxiety and even depression;

and based on them request: hydrogen breath test, organic acids, complete stool analysis, air balloon analysis, or biopsies [39].

Dysbiosis of the Intestinal Microbiota in the BC. Although there are numerous studies of intestinal bacteria, little has been written about intestinal viruses (Mycobiome) in cancer. Perhaps, because these microorganisms are rarer. Although we must delve deeper into them since the impact on health is significant. We see their significance when they are involved in head and neck, esophageal, gastric, colorectal, hepatocellular, and pancreatic cancer. Melanoma, lung cancer and the one we studied: breast cancer [40]. Viruses are components of the microbiome, in addition to bacteria, fungi, protozoa and parasites.

BC is the most common cancer worldwide, with 11.7% of cases (2020) and recent analyzes show that it is impacted by IM, by increasing or decreasing the risk of the disease, through the regulation of the steroid hormones, regulating energy intake and use, synthesizing metabolites, and modulating the immune system [41].

Gut-Brain Axis. Our intestinal microorganisms produce metabolites, which protect us, they are also capable of generating molecules that develop inflammatory and carcinogenic processes, all detected through metagenomic studies [42]. The influential factor of the Microbiota-Brain Axis has been demonstrated in BC [43].

Sinus-gut axis. Also known as the axis of the intestinal estrogen microbiome, it is extraordinarily significant, establishing bidirectional communication between the breast and the intestine, IM regulating the volumes of estrogens, especially when these are scarce and generate various conditions such as alterations in the reproductive system, intestinal health and brain cognition processes [44]. It has been considered a factor that enhances the breast microbiota through dendritic mediation in the endogenous route, influencing the potential for bacterial uptake in the intestinal mucosa. This is carried out by β -glucuronidases (intestinal microbial enzymes) [45].

Cancer-microbiome-gut axis. The tumor microbiome is considered as part of the tumor microenvironment, in addition to other components. And through clinical studies the bacteria existing in this environment have been determined. For this reason, the presence of the microbiome in the affectation of cells has been highlighted as being of utmost importance. And, therefore, the different phylos of

bacteria that appear in the process, where the cancer-microbiome-intestine Axis plays a determining role in the evolution of BC [46].

Cancer-microbiota-immunity axis. Another of the numerous axes cited in the literature, as a component of tumor biology, involved with IM, since it triggers and involves the tumor process, by activation of the immune system, impacting tumor cells [47]. Modulation can also increase the effect of immunotherapy and reduce its toxicity.

Therefore, there is a reciprocal and indissoluble communication between IM and cancer. Immuno-onco-microbiotherapy is in full development [48].

Immunity. Cytotoxic T cells are able to destroy cancer cells, while regulatory T cells are not and suggest a poor prognosis [49]. Treg cells increase according to the status of ductal cancer in situ and increase more in invasive carcinoma [50]. It has been considered that the richness or decrease of some specific bacteria in IM could generate a greater number of Treg cells or decrease the differentiation of pathogenic T cells [51], therefore playing a crucial role in the immune response. oncology. Likewise, a link, independent of estrogen, between IM IgA + and IgA - was found in patients with BC [52]. As the above occurred in menopausal women, it can be seen that the microbial DNA of the breast and its metabolites could affect the immune status, helping tumor processes by influencing inflammation with its metabolic capacity of immune cells [53].

Apoptosis. Greek word (apo - separation and ptosis - fall) means "Falling of leaves from trees." "It is a set of cytoplasmic and nuclear changes that cause the destruction of cells within tissues without affecting neighboring cells, caused by the activation of a genetically determined cell suicide program" [54]. These changes are very significant, since current research focuses on it. And, there is a balance of control between apoptosis and cell proliferation. Furthermore, reduced apoptosis appears in BC [55].

Intestinal microbiota and anticancer. Chemotherapy has increased substantially, currently there are countless products, among which the following stand out: Antimetabolites (5-fluorouracil, gemcitabine, capecitabine) and navelbine; Anthracyclines; Cyclophosphamides and Taxane. And as mentioned, IM can bi-directionally modulate the effectiveness and complications of these products [56].

BC, Radiotherapy and Intestinal Microbiota. IM may or may not act beneficially in radiotherapy. There are phylos that have a protective impact such as:

Lactobacillus sakei, L. acidophilus, L. casei and Bifidobacterium spp [57]. Meanwhile, Robrobacter radiotolerans is resistant [58].

Antibiotics and BC. Antibiotics decrease diversity, increasing the risk of BC, with a causal relationship existing [59]. It is proven that these medications, especially penicillin, tetracycline and nitrofurans, generate intestinal dysbiosis and compromise the evolution of BC [60]. Therefore, it is necessary to maintain excellent IM so that the therapies used give their best response.

It has been observed that the tumor grows when antibiotics are administered and there is a reduction in butyrate in the feces, as Odoribacter and Anaerotruncus are affected and Bacteroides increases [61]. In the case of BC, it is inappropriate to prescribe antibiotics, only if the elderly person presents infections, and especially recurrent *C. difficile*.

The use of antibiotics in rats that are powerful producers of apoptosis (thiazole, etc.) has been considered; However, they do not metagenomically indicate the impact that is made on IM, since as we know antibiotics damage it [62].

Probiotics, prebiotics and synbiotics. The use of probiotics, prebiotics and synbiotics is more widespread and can be used rationally, depending on the status of the cancer, without leaving aside the complications, which exist and can be fatal. These elements improve intestinal diversity and regulate the immune system [63]. Lactobacillus with Bifidobacterium have been reported to have positive effects in BC survivors, especially with regard to the reduction of obesity, dyslipidemia or lymphedema [64].

There are reviews that indicate that probiotics, based on modulating intestinal bacteria and the immune system, could be effective as preventives in BC. The conclusion is that larger studies are required to confirm this possible evidence [65]. Duan D, and his group point out that synbiotics can modulate IM, by inhibiting the production of pro-inflammatory cytokines, improving the incidence of anti-oxidant enzymes and, thereby, alleviating lymphedema [66].

Fecal Microbiota Transplantation. It has been noted that Fecal Microbiota Transplantation (FMT) restores Intestinal Dysbiosis, through metabolites generated by microorganisms. This has been transferred to the oncological area, probably guiding new therapies [67]. It has also been determined that pathogenic microorganisms are overabundant in patients with

BC, being modulated by chemotherapy, and may influence weight gain and neurological effects [68].

There is a relationship between intestinal dysbiosis and some bacteria and cancer. It is also known that IM can modulate therapeutic efficacy in cancer. Likewise, improvement of bile acid metabolism [69]. On the other hand, overabundant microorganisms in the BC affect the prognosis [70]. These data give rise to and we consider helpful to that group that is considering specific FMT studies in BC, which is in its infancy.

Future. It has been noted that IM modulates not only the immune response but also estrogen levels, as well as the release of metabolites. This has repercussions on the development of BC. And given that specific bacterial species have been identified, which are strengthened by BC, actions could be determined based on this. In the future, interventions involving the use of probiotics, prebiotics, synbiotics, paraprobiotics, psychobiotics, antimicrobial agents, etc. May be considered. These therapeutic strategies can be specifically designed to modulate intestinal bacterial populations, to decrease the risk of estrogen-related BC, or after cancer diagnosis, become adjunctive treatments [71].

We must consider that the treatment of BC in initial status is not the same as the process with metastasis; in any case, there are components that we can use to support the process. Good support from Computer Engineering, in metagenome studies, helps, although it does not completely define the management. Other considerations are menopause, diet, postmenopausal status. Likewise, it is cautious not to consider patients with no more than three months of use of antibiotics, biotics and Chinese medicinal herbs in this treatment [72].

Although we are already in the territory of the breast axes, there is a lack of complete understanding regarding two-way communication. With all of the above, we will soon be able to know what happens in so-called "brain cancer" or "chemo brain." With its favorable consequences [73].

Conclusions

- ✚ The microbiota, that "unknown organ", seems to have a notable collision in our body [74].
- ✚ Dysbiosis, both intestinal and breast, help in the oncological process of the breast [75].

- ✚ Advancement in multiomics will demonstrate more obligatory links between BC and microbiota [76].
- ✚ The microbiota can be prognostic or predictive of treatment in CAMA [77].
- ✚ There is a balance of control between apoptosis and cell proliferation.
- ✚ More progress must be made in the management of biotics, to recommend these products.
- ✚ Although Fecal Microbiota Transplantation modulates, more studies are required to recommend it in BC.

Likewise, in established CAMA, the microbiota can be a prognostic and predictive factor of response to treatment and/or its side effects. Furthermore, modulation of the microbiota can be used to improve outcomes in breast cancer patients.

Declarations

Conflicts of interest

The authors declare that do NOT have affiliation or participation in organizations with financial interests.

Ethical approval

This report does not contain any study with human or animal subjects carried out by the authors.

Informed consent

The authors obtained informed written consent from the patients, in order to develop this article.

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