Review / Revisão

Breast cancer and nutrition: interplay between diet and prevention

Câncer de mama e nutrição: interação entre dieta e prevenção

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Abstract
Breast cancer (BC) is one of the main causes of morbidity and mortality worldwide, and several factors are being studied to identify the determinants of BC, as well as the protective factors and the therapeutic approach. The literature suggests that dietary factors may contribute to breast carcinogenesis, so the progression and control of this disease seem to be related to eating habits, consumption of fats, meats, dairy products, fruits and vegetables, fiber, phytoestrogens and other dietary components. Obesity, carbohydrates, folate, vitamin D, phytoestrogens, carotenoids and fatty acids may bring information and possible mechanisms that associate nutrition and risk of BC. Further investigation is needed to better understand the pathobiology of breast tumor and the nutrition related tumor microenvironment, focusing on molecular subtypes of BC. Therefore, this review highlights some components associated with nutrition and risk in this disease, aiming at its clinical and prophylactic importance.
Keywords: carbohydrates; vitamin D; carotenoids; fatty acids.

Resumo
O câncer de mama é uma das principais causas de morbidade e mortalidade em todo o mundo, e vários esforços estão sendo feitos para identificar os determinantes do câncer de mama, bem como os fatores de proteção e abordagem terapêutica apropriada. A literatura sugere que fatores alimentares podem contribuir para a carcinogênese da mama, portanto a progressão e o controle dessa doença parecem estar relacionados a hábitos alimentares, consumo de gorduras, carnes, laticínios, frutas e vegetais, fibras, fitoestrogênios e outros componentes da dieta. Obesidade,

carboidratos, folato, vitamina D, fitoestrogênios, carotenoides e ácidos graxos podem trazer informações e possíveis mecanismos que associam nutrição e risco de câncer de mama. Investigações adicionais são necessárias para entender melhor a patobiologia do tumor da mama ou o microambiente do tumor relacionado à nutrição, com foco nos subtipos moleculares do câncer de mama. Portanto, esta revisão destaca alguns componentes associados a nutrição e ao risco nesta doença, visando sua importância clínica e profilática.
Palavras-chave: carboidratos; vitamina D; carotenoides; ácidos graxos.

INTRODUCTION

Breast cancer (BC) is characterized as the second leading type of cancer among women, comprising a worldwide public health problem. Despite the fact that BC incidence is higher in developed countries, it continues spreading globally for women in other continents such as Asia, Africa and South America [1].

Although some researchers demonstrate the potential relation among diet/nutrition and cancer prevention into epidemiological, clinical, and laboratory contexts, the misconception between public opinion and scientific literature remains evident [2].

Research has shown that certain risk factors may increase a person's chances of developing cancer, like age (crescent), smoking, impaired glucose metabolism and over consumption of energy [3]. Besides that, other factors have been suggested, such as ethnicity, menopausal status, onset of puberty and the number of pregnancies and lifestyle in humans, generally as confounding factors [4].

The large increase in BC incidence and certain cases of mortality have been signaled by World Health Organization for actions to support research toward cancer prevention and to develop strategies that involve nutrition. Some nutrients as fatty acids, carbohydrates, vitamins B and D, carotenoids and phytoestrogens have been linked tumor microenvironment in animal experiments and populations studies [5, 6]. Intake of antioxidants-rich foods, including vitamins C and E seems to prevent tumor development, interfering in estrogen metabolism and inhibiting tumor cells growth [7, 8].

Nutrition are shown to play contentious role in the etiology of BC, although there are biological evidences of its involvement in inflammation, deoxyribonucleic acid (DNA) repair, stimulation of growth factors and epigenetic influences, modifying gene expression [9, 10]. Thus, it is imperative to gather information on the importance of some nutrients in BC pathogenesis concerning the potential health benefits of different foods.

In this context, this review aimed to demonstrate the relation between nutrition and BC, focusing on some nutrients that might be associated with comprehension of tumor development and how their use could be applied to prevention-directing nutrition strategies, in view of decreasing risk factors for new cases of BC in women.

Diet-related Risk factors in breast cancer

Obesity

The meaning of obesity would be an excess of fat, determined through the body mass index (BMI), derived from the body weight and height which has been emerged as the accepted clinical standard measure of overweight and obesity from children up to 2 years to adults [11]. It affects the physiological role of the adipocyte in energy homeostasis, culminating in inflammation and alteration of adipokine signaling. That said, it seems that the metabolic changes in obesity may be related to BC development [12].

The status of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor type 2 (HER2) and proliferation index Ki-67 has been used as predictive markers to identify high-risk phenotypes and for selection of most efficient therapies [13]. It has been showed an increased risk of triple-negative (TN) BC in obese premenopausal women patients [14] and Jeronimo and Weller [15] reported that obesity was positively associated with TNBC in BC patients from North-eastern Brazil. In this context, Sun, Zou [16] also verified that obesity can to contribute to the incidence of TNBC.

However, the relationship between obesity and BC prognosis could be dependent by subtypes of BC, which includes ER, PR, HER2, luminal A or B, basal-like and TN. Obesity was linked to differences in the distribution of BC subtypes, with more aggressive Luminal B cancers observed to be more prevalent in obese individuals, potentially contributing to the poor outcomes seen in this population [17].

Interestingly, some studies has shown the role of leptin on BC. Leptin is considered an adipocyte-secreted protein that plays a role in satiety, energy expenditure and thermogenesis, and can be involved in controlling hematopoiesis and immunity [18]. Moreover, leptin was associated with BC development by enhancing the janus kinase/signal transducer (JAK) and activator of transcription-3 (STAT3), extracellular signal-related kinases 1 and 2 (ERK1/2) and phosphoinositide 3-kinase (PI3K) pathways that leads to proliferation and cell survival in vitro studies [19].

Other authors revealed that gene and protein expression of leptin were higher in tissue of BC samples from obese patients than overweight and control patients, enhancing BC progression by inducing the expression of JAK-STAT3, ERK1/2 and estrogen pathways in obese patients with BC [20]. Therefore, it has been demonstrated that leptin presented capacity to increase the invasiveness of ER-positive MCF-7 BC cells. After analyzing the anti-proliferative effect of tamoxifen, 5-fluorouracil, taxol and vinblastine on BC cells treated with leptin, for the first time, it was showed that leptin at high doses appears to reduce the effectiveness of different cancer treatments [21], indicating that, depending of obesity level, these treatments cannot be sufficient to control tumor proliferation.

Although specific molecular pathways on how obesity increases the risk of BC are not completely defined, the balance between leptin and adiponectin must be investigated with intention to include like monitoring-form in obese BC patients. They do not have necessary to serve as biomarker, but it can control properly feeding.

Carbohydrate and intake

The carbohydrate intake and its quality might influence in BC risk by affecting insulin resistance and plasma levels of insulin and glucose [22]. In accordance to

European Prospective Investigation into Cancer and Nutrition (EPIC study), it was observed that high carbohydrate and glycose load would be related with an increase in negative hormonal receptors (ER and PR) BC between postmenopausal women patients [23]. On the same group in similar analysis, it was observed elevated consumption of carbohydrates in BC patients from Mexico [24].

Although it was verified that there was no association with ER+ or ER- BC subtypes in the Danish population regarding the ingestion of different carbohydrates [25], in Swedish women, a significant association of carbohydrate intake, glycemic index and glycemic pathway with risk of ER+/PR- BC was observed [26], which means that epidemiological studies have shown results conflicting.

An experiment has been shown that lactate, one of end-products of anaerobic glycolysis, displayed as a chemo-attractant driving metastasis-characterized migration and tumor growth on MDA-MB-231 BC cells [27]. Therefore, the population should be aware during carbohydrates consumption, because depending of the doses, these macronutrients can become risk of BC.

Furthermore, the link between obesity and sugar consumption has been questioned through years [28]. On the other hand, rising obesity has promoted the growth of added fruit juice concentrates in food supply as an alternative to other sugars [29], and this way have helped high-income countries to slow down BMI increase [30]. However, it may not reflect the continuous increase in other parts of the world. Though, it is reasonable that if current trends in overweight and obesity prevalence persist, we would expect cancer incidence rise further [31].

Prevention-directing nutrition to breast cancer

Carotenoids

Carotenoids are natural compounds classified into carotenes, composed only by atoms of carbon and hydrogen, and xanthophylls, which also have oxygen in a functional group. They are found in free form, as carotenes, or esterified with fatty acids, as hydroxylated xanthophylls [32].

Carotenoids have been shown protective influence in humans. They are present in yellow and orange vegetables, fruits and in dark green leafy vegetables [33], being a-carotene, b-carotene, b-cryptoxanthin, lutein, zeaxanthin and lycopene the most prevalent, comprising 90% of circulating carotenoids [34]. Despite presenting antiproliferative, antioxidant and cell differentiation properties [35, 36], dietary carotenoids seem to inhibit tumor progression and reduce proliferative action in both positive and negative ER BC cells in experimental studies [37].

In a pooled analysis involving circulating carotenoids and subsequent risk, it was observed significant reduced risks of total BC and 48% decreased risk of ER-negative tumors for β-carotene [38]. Recently, in large prospective analysis with 20 years of follow-up, the same group observed that women with high plasma concentration carotenoids were at reduced BC risk [39], highlighting the essence of these micronutrients as BC protectors.

A meta-analysis relating blood concentrations of carotenoids and BC risk was performed by Aune, Chan [40]. Of the six dietary carotenoids assessed (α-carotene, β-cryptoxanthin, lycopene, lutein/zeaxanthin, lutein, zeaxanthin**)**, just β-carotene was significantly associated with a reduced BC risk.

In experimental study, Gloria, Soares [41] have shown the capacity of lycopene and β-carotene to inhibit significantly cell proliferation, arrest the cell cycle in different

phases, and increase apoptosis in human breast adenocarcinoma cell lines, MCF-7, MDA-MB-231 and MDA-MB-235. In other research, Takeshima, Ono [42] showed the predominant anticancer activity of lycopene by apoptosis induction presumably through activation of Bax in triple-negative MDA-MB-468 cells, indicating possible prevention for this type of BC. This would represent a landmark once this subtype of cancer, besides being aggressive, has no specific treatment.

Folate, B vitamin: a dual role in cancer development

Folates belong to group of B vitamin which share a common vitamin activity based on the tetrahydrofolate structure, acting in important metabolic pathways including the biosynthesis of nucleotides and methionine [43, 44], and they may be related with cancer prevention due to the fact that excess folate increase DNA repair in healthy tissues [44].

Some studies have suggested that high folate intake or high concentration of blood folate level may reduce the risk of BC, presenting possible preventive effects against this type of cancer [45, 46]. Conversely, two studies related that high plasma folate concentrations might increase BC risk (positive association between plasma folate and ERbeta- BC) [47, 48]. The observed positive associations of folate status with risk of developing premenopausal BC and ER-positive or PR-positive tumors are unexpected [48] and other study was observed that elevated plasma folate concentrations may be associated with increased risk of BC in women with a BRCA1/2 mutation[49].

One interesting information was observed regarding high expression of HER2. The last observation needed to confirm and explain possible mechanisms and how folate may upregulate HER2 [50]. It is known that folate act on DNA methylation through DNA methyltransferases came from folate and homocysteine metabolism [51]. Knowing this, Terada, Okochi-Takada [52] group showed involvement of frequent methylation of cytosine-guanidine dinucleotide (CpG) islands highly associating with HER2 amplification in BC patients, suggesting that CpG DNA hypermethylation may be upregulated HER2 by folic acid intake, which can be poor prognosis.

These results desire to investigate detailly the effect of folate in human BC, trying to understand the mechanisms of folate into general cancers.

Fatty acids – focusing on n-3 series as protector agent

The humans are surrounded by different foods, containing different amounts of fat and distinct types of fatty acids, and these are dependent by processing, storage, and cooking methods. Depending of their availability, they can synthesize either nonlipid precursors such as glucose or other fatty acids that are called essential fatty acids [53].

Inside of fatty acids, polyunsaturated fatty acids (PUFAs) are considered as subclass of bioactive components divided in two groups, omega-6 (n-6) and omega-3 (n-3) fatty acids. The n-6 series are included by a precursor, linoleic acid, present in food of animal origin, in vegetables and in oils such as sunflower, soybean and grape seed. Moreover, these include the arachidonic acid and gamma-linolenic acid found in some vegetable sources. Now, the n-3 series are included essential fatty acid, the alpha-linolenic acid found in green vegetables and in some oils, and highly unsaturated derivatives present in seafood and marine products like the eicosapentaenoic acid (EPA) and the docosahexaenoic acid (DHA) [54].

The balance of n-6/n-3 series can be greater importance than the absolute levels of a particular fatty acid [55] because it may serve as control of consumption, and, n-3 series evidently become the protector of our organism, acting against breast tumor development.

In study conducted by Patterson, Flatt [56] in BC survivors to indicate that consumption of marine fatty acids is associated with improved BC prognosis. Specifically, in a cohort of 3081 BC survivors, higher intakes of EPA plus DHA from food were associated with a reduction in additional BC events and all-cause mortality.

Vitamin D

Vitamin D is derived dietary sources such as oil fish and eggs and exposure to sunlight. The natural form of vitamin D from animal sources is cholecalciferol (vitamin D_3), when vitamin D derives from 7-dehydrocholesterol found in the skin and it is exposed to ultraviolet B radiation to produce calcitriol [57]. One of the major physiological role of calcitriol is to maintain calcium and phosphorus homeostasis, which is regulated by parathyroid hormone and fibroblast growth factor [58]. When calcitriol interacts and activates vitamin D receptor, although the main function is to maintain extracellular calcium levels, vitamin D receptor influences up to 200 genes that mediate cellular growth, differentiation and apoptosis [59]. The current growing body of research supports vitamin D deficiency as a risk factor for BC [60].

Preclinical studies had shown the effect of vitamin D inhibiting cell proliferation, inducing differentiation and apoptosis, and anti-angiogenesis effects in normal as well as malignant breast cells [61]. Study realized by Ooi, Zhou [62] evidenced that maintenance of adequate vitamin D levels may reduce the ability of BC cells to grow in the bone environment.

Some studies report that high vitamin D levels at early BC diagnosis correlate with lower tumor size and improved BC outcomes, especially in postmenopausal patients [63]. Interestingly, low vitamin D concentrations were associated with advanced tumor stage and TN subtype among premenopausal women [64]. At same time, vitamin D deficiency might be associated with poor outcomes and significantly lower disease-free survival times in patients with luminal A and luminal B subtypes BC [65].

Vitamin D that comes from the skin or diet is biologically inert and requires a first hydroxylation in the liver by 25-hydroxylase, 25-hydroxyvitamin D (25 (OH) D), partially water-soluble form with a short half-life circulating binding proteins). This requires further hydroxylation at the renal level by 1α-hydroxylase (CYP27B1) to form 1, 25-dihydroxyvitamin D (1, 25 [OH] 2D), the biologically active form of vitamin D. This form circulates in lower concentrations 25 (OH) D but has a much higher affinity for the receptor and is biologically more potent [66].

In a joint analysis of two studies with 880 cases of BC and 880 cases of the control group, women with serum 25 (OH) D levels of about 52 ng/mL had a 50% lower risk of developing BC compared to those with levels <13 ng/mL [67]. An analysis of 1,394 postmenopausal women with BC and 1,365 control cases demonstrated that the serum concentration of 25 (OH) D is inversely associated with the risk of the disease, especially at levels <20 ng/mL [68].

Previous epidemiological data suggest an association between vitamin D deficiency and increased risk of BC development, as well as a poor prognosis [69].

Phytoestrogens

Phytoestrogens are plant-derived polyphenolic compounds that are structurally like estradiol. There are composed by flavonoids (apigenin, quercetin, narigenin, catechins), isoflavonoids (genistein, biochanin A, daidzein), lignans (enterodiol, enterolactone), coumestans (coumesterol) and stilbenes (resveratrol) [70, 71]. In these

classes, the most consumed and investigated are isoflavonoids, found in soy products and highly consumed by Asian populations [72]. When analyzing in Asiatic habit, soy exposure and BC risk revealed that some studies showed a significant trend of a reduced risk with elevated soy intake in both pre- and postmenopausal Asian women, but, it was not observed association in low soy consuming Western populations, indicating that soy intake may have protective benefits [73, 74]. Women who consumed a high amount of soy foods consistently during adolescence and adulthood had a substantially reduced risk of BC and no significant association with soy food consumption was found for postmenopausal BC (75).

In the other context, the effect of phytoestrogens in BC cells has been brought relevant results. Phytoestrogens like genistein exhibited the growth of estrogen-dependent (MCF-7) cells, and biochanin A and coumestrol seem to inhibit the growth and proliferation of cancer cells at low pharmacologic concentrations [76, 77].

For other types of phytoestrogens, genistein, resveratrol and quercetin inhibited MCF-7 (ERa+/HER2-) cell proliferation and induced apoptosis significantly when compared to MCF-10A cells, demonstrating antiproliferative effects on BC cells via an ER-dependent mechanism [78]. Besides those phytoestrogens mentioned above, apigenin related also antiproliferative activity in either human BC cells MCF-7 or SKBR3 (ERa-/HER2+), evidencing this effect in other subtypes of breast tumors, particularly in HER2+ BC women patients [79]. Interestingly, the study showed that arctigenin, phenylpropanoid dibenzyl butyrolactone lignan [80], exhibited anti-metastatic effects in ER-negative MDA-MB-231 cells, suggesting these effects were not via the ER. Taken together, arctigenin was presented anti-metastatic effect by inhibiting matrix metalloproteinase-9 (MMP-9) and urokinase plasminogen activator (uPA) via the Akt, NF-kB and MAPK signaling pathways on BC, regardless of ER expression [81].

The research on phytoestrogens has brought relevant results, trying to exert effects in some mechanisms, mainly proliferation, apoptosis and to affect in cell signaling pathways.

Concluding remarks and trends to research

Study realized in 2014 from the World Cancer Research Fund on diet and women with a history of BC did not demonstrate a major effect on BC prognosis. The studied diets were categorized: macronutrients, micronutrients, and selective foods. For macronutrients, a low-fat diet was associated with better survival. With regard to micronutrients, a diet rich in phytoestrogens reduced the risk of cancer recurrence and the adoption of a healthy diet was not associated with an improved prognosis for BC but with an improvement in overall survival and risk of death from cardiovascular disease [82].

Non-communicable diseases (like cancer, diabetes, obesity, and heart disease) are multifactorial illnesses, and diet, although related, is only one of the risk factors (together with lifestyle choices, genetics and environmental factors) accounting for the pathology [83]. Based on a small explanation on the risk or prevention of BC and nutrition, we can suggest the control of food intake, respecting the custom of each geographic region. BC patients should be encouraged to improve their lifestyle and dietary habits before, during and after treatment, in order to have better long-term survival and quality of life [83]. However, it is important to consider the molecular subtypes of BC that possesses different characteristics and could be induced by nutrients related to receptors and cell signaling pathways.

Interlinking studies between diet/nutrition and subtypes of BC remain scarce and deserves to be clarified in literature. This conception may possibly induced various favorable mechanisms to homeostasis of organism, like to induce apoptosis and antiproliferative effect. Further investigation is needed to understand the pathobiology of BC or the diet/nutrition related tumor microenvironment, focusing on molecular subtypes such as HER2, ER, PR, luminal A and B, normal, basal, and TN, and prognosis.

Declarations

The authors declare that there is no conflict of interests regarding the publication of this paper.

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