II. DIAGNOSTIC AND TREATMENT

OPTIMIZATION OF DIET THERAPY OF CANCER-PROTECTIVE CONTENT IN THE CLINICAL MANAGEMENT OF PATIENTS WITH BREAST CANCER. (REVIEW)

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The authors declare that they have no conflicts of interest

Abstract

Breast cancer (BC) is the most common cancer in the world and the most common malignancy in women. There is growing evidence that lifestyle factors, including diet, body weight, and physical activity, may be associated with a higher risk of breast cancer. Patients with breast cancer undergoing chemotherapy and / or radiotherapy experience various symptoms that impair the patient's quality of life. Research on dietary interventions during the treatment of breast cancer has shown that certain diets and the addition of certain nutritional components can be useful for reducing side effects caused by medication, increasing therapeutic effectiveness, and preventing the development of primary tumors. Thus, nutritional intervention in patients with breast cancer can be considered an integral part of a multi-modal therapeutic approach. However, further research using dietary interventions in large clinical trials is needed to definitively establish effective interventions in these patients, improve long-term survival and quality of life.

The article purpose is to generalize the role of dietary natural products and their biologically active compounds in the prevention and treatment of breast cancer, the clinical study of synthetic and natural anti-carcinogenic substances, the selection of effective and safe food products, as well as the choice of diet and lifestyle, as it is determined as a priority in breast cancer research.

Сүт безі қатерлі ісігі бар науқастарды клиникалық жүргізудегі қатерлі ісіктен қорғайтын диетотерапияны оңтайландыру (Әдебиет шолуы)

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Мүдделер қақтығысы
Авторлар мүдделер қақтығысының жоқтығын мәлімдейді

Аңдатпа

Сүт безі қатерлі ісігі - әлемдегі ең көп таралған қатерлі ісік және көбінде әйелдерде кездесетін қатерлі ісік. Өмір салты факторлары, оның ішінде диета, салмақ және физикалық белсенділік сүт безі қатерлі ісігінің жоғары қаупімен байланысты болуы мүмкін деген дәлелдер артып келеді. Химиотерапия және / немесе сәулелік терапиядан өтіп жатқан сүт безі қатерлі ісігі бар пациенттер өмір сапасын нашарлататын әртүрлі белгілерді сезінеді.

Сүт безі қатерлі ісігін емдеу барысындағы диеталық араласуды зерттеуге арналған бақылаулар бойынша, арнайы диеталар мен кейбір тағам компоненттерін қосу емдік препараттарды қолданудан болған теріс әсерлерді азайту үшін пайдалы болуы мүмкін екенін көрсетті. Дегенмен, осы клиникалық зерттеулерде диеталық араласуды қолдана отырып, осы пациенттерге тиімді араласуды нақты құру және ұзақ мерзімді өмір сүру мен өмір сапасын жақсарту үшін қосымша зерттеулер қажет.

Осылайша, сүт безі қатерлі ісігі бар науқастарға тағамдық қосу мультимодальды терапевтік тәсілдің ажырамас бөлігі ретінде қарастыруға болады.

Бұл мақаланың мақсаты сүт безі қатерлі ісігін емдеу мен алдын алу шараларында диеталық табиғи өнімдер мен олардың биологиялық белсенді қосындыларының маңызын жалпылау, табиғи және синтетикалық антиканцерогенді заттарды клиникалық зерттеу , тиімді және қауіпсіз тағам өнімдерін таңдау , және де өмір сүру салты мен диета түрін таңдау, себебі бұл сүт безі қатерлі ісігін зерттеудегі тиімді басты бағыт ретінде есептеледі.

Оптимизация диетотерапии онкопротективного содержания в клиническом ведении пациентов с раком молочной железы. (Обзор литературы)

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Ключевые слова
рак молочной железы, диета, продукты питания, питательные вещества, профилактика, антиканцерогены, биологически активные природные соединения.

Аннотация

Рак молочной железы (РМЖ) является наиболее распространенным раком в мире и наиболее часто встречающимся злокачественным новообразованием у женщин. Появляется все больше доказательств того, что факторы образа жизни, включая диету, массу тела и физическую активность, могут быть связаны с более высоким риском РМЖ. Пациенты с РМЖ, проходящие химиотерапию и / или радиотерапию, испытывают различные симптомы, которые ухудшают качество жизни пациента. Исследования, посвященные изучению диетических вмешательств во время лечения РМЖ, показали, что определенные диеты и добавление некоторых пищевых компонентов, могут быть полезны для снижения побочных эффектов, вызванных приемом лекарств, для повышения терапевтической эффективности а так же профилактики развития первичной опухоли. Таким образом, нутритивное вмешательство у пациентов с РМЖ может рассматриваться как неотъемлемая часть мультимодального терапевтического подхода. Тем не менее, необходимы дальнейшие исследования с использованием диетических вмешательств в крупных клинических испытаниях, чтобы окончательно установить эффективные вмешательства у этих пациентов, улучшить долгосрочную выживаемость и качество жизни.

Целью данной статьи является обобщение роли диетических натуральных продуктов и их биологически активных соединений в профилактике и лечении рака молочной железы, клиническое изучение синтетических и природных антиканцерогенных веществ, отбор эффективных и безопасных пищевых продуктов, а так же выбор диеты и образа жизни, так как это определяется в качестве приоритетного направления в исследований рака молочной железы.

The World Health Organization (WHO) has predicted that 24 million people will be affected by cancer deaths by 2035. Breast cancer is one of the most common cancers and the leading cause of cancer death among women. The incidence of breast cancer annually increases worldwide by 1.8-2.0%. Between 2005 and 2020, there was an almost 26% increase in breast cancer incidence, and this increase is expected to be higher from year to year [21]. Of all types of cancer diagnosed in women under the 40 age, 40% are in breast cancer. Of these, approximately 6.6% of cases are diagnosed in women aged 40 and younger. The average risk of developing breast cancer is one in 173 [1,8,22].

The American Cancer Society has identified exogenous factors that include reproductive, environmental, and life factors such as age, family history, infertility and absence of children, history of chest irradiation, early menarche, oral contraceptive use, lactation (never breastfeeding or short duration of breastfeeding) , use of hormone replacement therapy, alcohol consumption, diabetes, obesity, disturbed circadian rhythm.

Genetic risk factors, such as mutations in the breast cancer susceptibility genes 1 (BRCA1) and BRCA2, account for only about 5-10% of all breast cancer cases [2,5,21].

Breast cancer is classified by histology, TNM, and phenotype. The latter is described as one of the following types: Hormone-positive (estrogen and / or progesterone receptor) or hormone-negative (estrogen and / or progesterone negative); HER2 / neu positive or HER2 / neu negative; Triple negative (negative estrogen receptor, progesterone receptor and HER2 / neu). [1.6].

These different subtypes of breast cancer respond differently to treatment, making breast cancer extremely difficult to treat. Currently, the main treatment options for breast cancer are surgical resection, adjuvant chemotherapy, radiation therapy, and hormone therapy. However, the development of drug resistance and major side effects has weakened the effectiveness of these treatments. Also TNBC is now the most unfavorable prognostic form of the disease [24].

Therefore, the prevention of breast cancer is of the utmost importance. This situation urgently requires research to find more effective strategies for the prevention and treatment of breast cancer with fewer side effects [1,5]. Systemic chemotherapy, hormone therapy is the standard treatment for breast cancer. Therapy usually lasts 3-6 months and is often accompanied by drug-resistant side effects, which are common causes of chemotherapy failure and relapse, including nausea, vomiting, loss of appetite, dry mouth, changes in taste or smell, weight gain [3,4,5].

Indeed, therapy-induced nausea has a significant impact on the pleasure of eating, leading to inadequate intake of energy and essential nutrients, as well as malnutrition, decreased adherence to
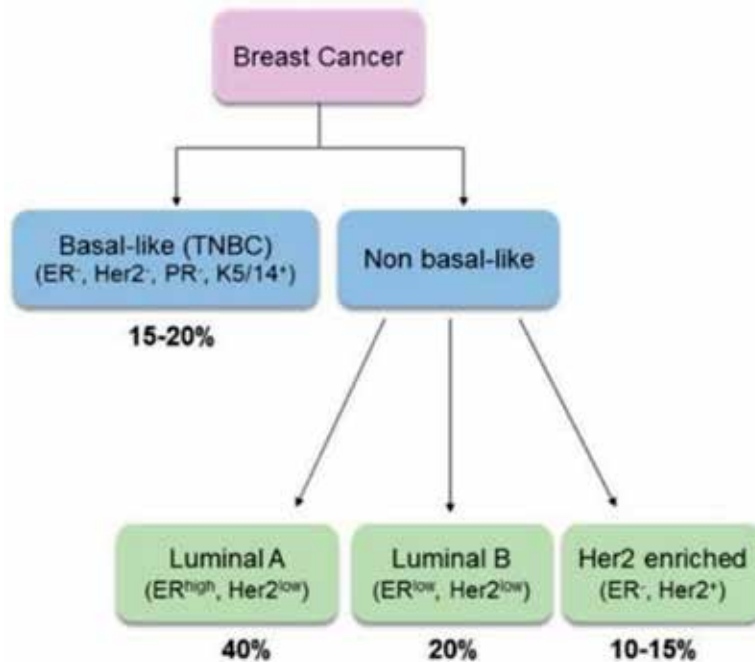
Picture 1.
Breast cancer subtypes and relative prevalence. TNBC: triple negative breast cancer [2]

treatment, decreased immunity, emotional distress and negative quality of life [6].

During chemotherapy, women report changes in food preferences. Cognitive side effects and mental activity are also common in women undergoing chemotherapy [3, 9].

There are also violations of attention, speed of information processing, executive functions and working memory with varying degrees of severity depending on the drugs used, the intensity and duration of treatment, as well as predisposing factors [2, 27].

Also, persistent fatigue is one of the most common and burdensome late effects of breast cancer treatment [18]. Even ten years after completing breast cancer treatment, one third of surviving patients have moderate to severe persistent fatigue. Persistent fatigue is also often associated with depression, poor sleep and a reduced quality of life [9]. Women with a history of breast cancer often use certain diets and supplements (such as multivitamins and antioxidants) to treat the typical symptoms and side effects of conventional cancer therapies. However, these products may not always have positive effects and therefore more clinical studies are needed regarding safety and efficacy, as well as timing and dosage. Studies examining nutritional interventions during breast cancer treatment have shown that nutritional counseling and the addition of some tested and proven dietary components may be beneficial in reducing drug-induced side effects as well as increasing therapeutic efficacy [2, 12].

The fact that morbidity is growing in parallel with economic development suggests that environmental factors may play a role in the causation of breast cancer [6]

Among these risk factors, diet is attracting significant attention, since it is a modifiable risk factor and, thus, opens up opportunities for the development of preventive strategies [3]. Based on the most recent data, the World Cancer Research Foundation / American Institute for Cancer Research (WCRF / AICR) has compiled guidelines for lifestyle. According to these guidelines, (1) maintaining a healthy body weight, (2) being physically active, (3) following a diet rich in fiber and soy, and (4) limiting fat intake (particularly saturated fatty acids) may improve overall survival after breast cancer diagnosis. Much evidence also supports the clinical relevance of nutritional intervention in cancer patients to ensure adequate energy and nutrient intake during chemotherapy, as well as the potential for improved response to pharmacological cancer therapy and reduced toxicity. In addition, lifestyle changes, including diet and exercise, can reduce long-term side effects of treatment and promote long-term overall health by reducing co-morbid conditions (eg, obesity, hypertension, hyperlipidemia, and diabetes mellitus) . Indeed, there is a potential new role for nutrition as an arsenal of modern cancer therapy [6,17]. At present, cancer chemoprophylaxis is recognized as one of the topical areas of anticancer control, and a large number of studies in developed countries are devoted to this area [22]. Given all these data, there is a need to understand that cancer prevention drugs must meet the following basic requirements: 1) proven effectiveness - the ability to prevent the occurrence of malignant tumors; 2) the possibility of using for a

long time; 3) lack of toxic properties or minimal toxicity; 4) the desired additional beneficial properties; 5) dosage forms - only oral or for topical use [25].

Thus, nutritional intervention in patients with breast cancer can be considered as an integral part of a multimodal therapeutic approach. Some evidence suggests that dietary intervention is a key factor in determining cancer prognosis, patient quality of life, and, in particular, the effectiveness of cancer therapy. Since BC is clinically a heterogeneous disease, there is growing evidence that lifestyle factors primarily include diet [2].

The role of diet in tumorigenesis was a popular area of research during the 1940s and early 1950s. Currently, there is a revival of interest due to the increasing role of environmental influences on the development of cancer and mortality in human populations in general [17]. For decades, researchers have viewed diet as the most important environmental factor. Some scientists report that the influence of diet is more important in the development of breast cancer than the influence of genetics [3].

In addition, experimental studies have also shown that many dietary natural foods can be a potential source of prevention and treatment for breast cancer [18]. Comprehensive reviews of numerous studies have shown the specific protective role of various foods and their constituents and considered them as an effective cancer prevention strategy. [5,11,13]. Also, numerous environmental analytical epidemiological studies and laboratory studies have shown that dietary factors can influence the risk of developing breast cancer, as a useful factor for cancer prevention, in addition, to reduce the risk of cancer progression and thereby improve treatment outcomes and reduce human suffering, improve outcome in surviving breast cancer patients, contributing to weight loss and obesity reduction [8,10,20]. In addition, certain dietary components can also enhance therapeutic efficacy, thereby improving the quality of life of cancer survivors [2,4].

Since people consume not only single foods, but also their combinations, the assessment of dietary patterns can provide valuable information in determining the relationship between diet and cancer risk [3]. And a deeper understanding of the relationship between healthy eating and reduced cancer rates has prompted many researchers to focus on natural foods for cancer prevention. A variety of different terms are used to describe the many natural products currently being developed with the aim of obtaining health benefits. These include nutraceuticals, functional foods, pharmaceuticals, designer foods, nutritional supplements, and phytochemicals. Nutraceuticals and functional foods include many biologically active phytochemicals that act as a defense system against a number of diseases, have beneficial effects with good safety profiles for many types of cancer [12, 15]. A variety of dietary natural foods have shown potential roles in cancer prevention and treatment. A recently published meta-analysis that included 93 studies found that breast cancer outcomes were one of the few that achieved strong evidence of a protective effect of healthy eating habits, and this effect was particularly noticeable in postmenopausal women who were negative for the hormone receptor. In addition, various epidemiological studies have shown that consumption of soy products, fruits and vegetables (especially cruciferous vegetables) is associated with a reduced risk of breast cancer, and high consumption of certain dietary natural foods can reduce relapse and increase breast cancer survival [16, 21, 23].

Experimental studies have also shown that many dietary natural products and their biologically active components have an inhibitory effect on breast cancer, reducing expression and activity, inhibiting proliferation, metastasis and angiogenesis of breast tumor cells, inducing apoptosis and stopping the cell cycle, as well as sensitizing breast cancer cells to radiation therapy and chemotherapy [5,16].

The following natural products and related bioactives should be noted, including soy (genistein and daidzein), pomegranate (ellagitannins), mangosteen (mangosteen), citrus fruits (naringin), apple (2α-hydroxyursol), grapes, mangoes, cruciferous vegetables (isothiocyanates), ginger (gingerols and segaols), garlic (organosulfur compounds), black cumin (thymoquinone), edible macro-mushrooms (polysaccharides), as well as other useful substances and more flakes [5,11,26]. Therefore, the use of natural dietary substances can become a practical approach to the prevention and treatment of breast cancer [16]. In particular, women with the highest dietary adherence category (i.e. 6-9 points) had an approximately 20% lower risk of developing cancer, compared with women with the lowest category (i.e. 0-3 points). [11,13]. Nutritional enhancement interventions have led to significant dietary changes towards improvement, increased amounts of plant foods and decreased amounts of dietary fats. This, in turn, leads to changes in body composition, heart rate, BMI [7]. In addition, current evidence suggests that greater adherence of surviving breast cancer patients to the Mediterranean diet can reduce breast cancer recurrence, overall cancer mortality and other comorbidities, including cardiovascular disease, which has a beneficial effect on health and life expectancy [2]. The scientific literature has also reported a positive associa-

tion between postmenopausal breast cancer and obesity. The results of this study indicate changes in weight and body composition that occur in response to a diet high in vegetables and low in fat in breast cancer [7]. Numerous dietary components and vitamins have been found to inhibit molecular and signaling pathways associated with different stages of breast cancer development, and therefore may represent potential strategies in the field of breast cancer chemoprevention [19]. Some dietary products and their biologically active components have shown a synergistic effect with chemotherapy or radiation therapy, enhancing their therapeutic effect or reducing side effects [5]. It has been hypothesized that diets high in antioxidants and other specific micronutrients may help counteract the heightened inflammatory condition and thus relieve fatigue.

In several observational studies in breast cancer survivors, diets high in fiber, low in total fat, high in fruits and vegetables, and high in omega-3 fatty acids have been associated with a lower likelihood of persistent fatigue, depression in surviving patients breast cancer [9,18]. Similarly, significant experimental studies have also shown that many dietary natural foods can influence the development of breast cancer by providing a protective effect in general. Their anti-cancer effects include various mechanisms of action, such as decreased expression and activity of ER-α, inhibition of proliferation, migration, metastasis and angiogenesis of breast tumor cells, inducing apoptosis and cell cycle arrest, and sensitizing breast tumor cells to radiation therapy. and chemotherapy [5,7]. In addition, diets high in antioxidant micronutrients found in whole foods, including fish, fruits, and vegetables, have significantly lower concentrations of circulating inflammatory biomarkers [9, 18].

It is well known that many bioactive natural products have a beneficial effect on estrogen-induced breast cancer. These natural products have shown promise for preventive and therapeutic purposes [12,15]. However, some data indicate that, for the prevention of breast cancer, the consumption of active foods (eg, cereals, soy, ginger) should be at an early age, that is, during childhood and / or adolescence [14,16].

In addition, it was found that some food additives exhibit positive activity at the concentration of a certain chemotherapy drug (for example, quercetin enhances the effects of doxorubicin and reduces its cytotoxic side effects) [19].

At the same time, over the past decades, diets in many countries have changed towards a sharp increase in the consumption of ultra-processed foods. After going through numerous physical, biological and / or chemical processes, these foods are considered microbiologically safe, convenient, delicious and affordable. Several surveys (in Europe, USA, Canada, New Zealand and Brazil) assessing individual food consumption, household food expenditure, and supermarket sales have shown that ultra-processed foods account for 25% to 50% of total daily consumption. energy.This dietary trend can be worrisome and worth investigating. Several characteristics of ultra-processed foods may be implicated in causing disease, in particular cancer [23,27]. First, ultra-processed foods are often higher in total fat, saturated fat, and added sugar and salt, as well as lower fiber and vitamin dens.

In addition to the nutrient components, unformed contaminants are present as a result of the reaction in cooked foods, some of which are carcinogenic (for example, acrylamide, heterocyclic amines and polycyclic aromatic hydrocarbons). Second, the packaging of ultra-processed foods

Fig. 2
Dietary natural foods that have been shown to inhibit breast cancer [5]

Table 1.
Summary of evidence on key nutritional interventions to improve breast cancer treatment

	Research	Outcome
Fruits and vegetables	Meta-analysis (15 prospective studies) • Prospective study (75 929 women, 24 years of follow-up) • Prospective study (31,000 women, 11 years of follow-up)	Great antioxidant activity; anti-inflammatory properties; induction of cell cycle arrest in the G2 / M and G0 / G1 phases, increased cell adhesion, cell migration suppress the invasion and motility of breast cancer, suppressing the expression of RhoC and RhoA proteins; arrest of cell apoptosis and the G1 cycle in TNBC cell lines.
Red meat	Meta-analysis (13 cohorts, 3 case-control, 2 clinical trials) • Cohort study (262 195 women, 7 years of follow-up) meta-analysis	Downregulation of oncogenes and upregulation of suppressor genes
Products from soybeans, Isoflavones	Meta-analysis (14 control cases + 7 cohort studies) • Meta-analysis (1 cohort + 7 case-control study) • Meta-analysis (18 prospective studies)	Inhibition of proliferation, migration, metastasis and angiogenesis of tumor cells; sensitization of tumor cells to radiation and chemotherapy; increasing the effectiveness of tamoxifen;
Milk products	Pooled Analysis (8 prospective cohort studies: 351,041 women, 15 years of follow-up) • Meta-analysis (18 prospective cohort studies • Meta-analysis (22 cohorts + 5 case control studies)	Anti-inflammatory, antioxidant and anti-cancer properties; antiproliferative effect, inhibiting cell growth; a proapoptotic effect that stimulates the natural death of breast cancer cells.
Fats	Randomized controlled trial (48,835 postmenopausal women 8.1 years of follow-up) • Meta-analysis (cohort + case control studies) • Systematic review (18 studies) • Epic Exploration (337,327 women, 11.5 years of follow-up) • Meta-analysis (6 cohorts study + 3 case control studies)	Inhibition of molecular and signaling pathways; enhancement of the chemotherapeutic effect of doxorubicin on breast cancer cells and reduction of its cytotoxic side effects.

may contain certain food contact materials that have been postulated to be carcinogenic and destructive, such as bisphenol A. Finally, ultra-processed foods contain permitted but controversial food additives such as sodium nitrite or titanium dioxide, where carcinogenicity is very high [23].

Thus, the prevention, treatment, and support of the general condition of patients with breast cancer with the help of dietary means relies on an individually selected approach rich in staple foods and traditional methods of food production and preparation. [6]. There are a number of recent studies that provide data on what changes in dietary habits and diet have occurred since the diagnosis.

The results of the study showed that 60% of women increased their portions of fruits and veg-

etables and 80% reported a decrease in fat intake since diagnosis [8].

Based on these findings, it is necessary to propose a "healthy" dietary model, and patients with breast cancer should be motivated to improve their lifestyle and dietary habits before, during and after treatment in order to have better long-term survival and quality of life. [2].

Evidence suggests that efforts are needed to stimulate increased consumption of healthy foods. Armed with this knowledge, women will be highly motivated to learn about cancer prevention and lifestyle changes [8,9,18].

This confirms that the study of the relationship between diet and breast cancer is of great interest, given that cancer prevention through diet and life-
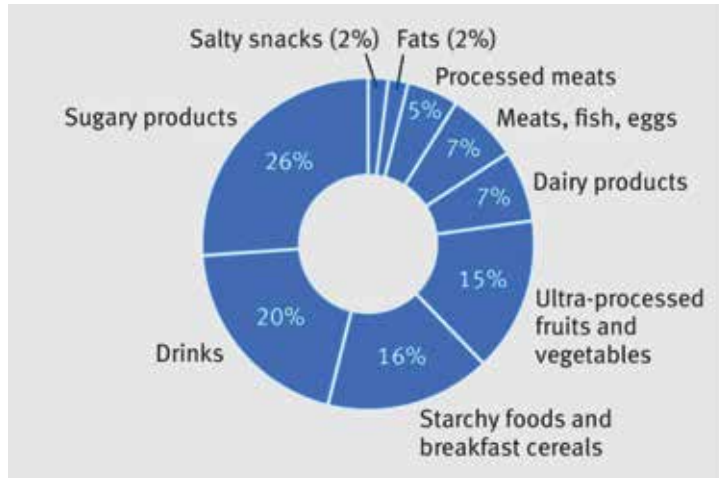
Fig. 3
The relative contribution
of each food group to the
consumption of ultrafood
in the diet [23]

style choices has been identified as a priority area of cancer research. [13].

In addition, the clinical efficacy of dietary natural products and their biologically active components in patients with breast cancer requires further study [9, 18]. It should be noted here that the rapidly growing consumption of ultra-processed foods may lead to an increased burden of cancer and other noncommunicable diseases. Thus, policies aimed at restructuring foods, taxing and marketing restrictions on ultra-processed foods, and promoting fresh or minimally processed foods can contribute to primary cancer prevention. Therefore, it is imperative to raise awareness and disseminate information about healthy eating and how to change unhealthy diets [2,13,24].

Key actions to strengthen cultural support for healthy food consumption that would lower the risk of breast cancer include taking responsibility by political leaders from the capital to the most remote villages and funding initiatives to promote healthy eating.

Additional local measures including national and subnational campaigns such as community-based organic food initiatives; educational ses-sions; development of brochures, posters and banners and their distribution in towns and villages; as well as an expression of gratitude to medical professionals who are actively working in this direction [3, 21].

It can be assumed that the potential impact on reducing relapse and improving survival in breast cancer may be significant. Additional research in this area will provide directions for lifestyle and clinical interventions that support beneficial behavior change to improve outcomes in women diagnosed with breast cancer. Future research should aim to maximize the integration of factors so that the relative effects of different lifestyle factors can be assessed independently or in combination [10,22].

It should also be recognized that reducing the risk of breast cancer requires a holistic approach, but in order to obtain high-quality scientific evidence, we must consider the various components individually [2, 20]. Dietetic cancer is an emerging field that has the potential to uncover the effects of nutrition on gene expression, and it integrates the science of dietetics, nutritional science, bioinformatics, epigenetics, genomics, epidemiology, and molecular medicine [5,20].

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